EUROPEAN PATENT SPECIFICATION

INHIBITOR OF ANALGESIC TOLERANCE

INHIBITOR DER ANALGETIKA-TOLERANZ

INHIBITEUR DE LA TOLÉRANCE AUX ANALGÉSIQUES

Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK TR

Designated Extension States:
AL BA RS

Priority:
29.05.2008 JP 2008141178
27.11.2008 JP 2008302783

Date of publication of application:

Proprietor:
Kyowa Hakko Kirin Co., Ltd.
Tokyo 100-8185 (JP)

Inventors:
• OUCHI, Jun
  Shizuoka 411-8731 (JP)
• KUNORI, Shunji
  Shizuoka 411-8731 (JP)
• KOJIMA, Yozo
  Shizuoka 411-8731 (JP)
• SHINODA, Katsumi
  Chiyoda-ku
  Tokyo 100-8185 (JP)
• SASAKI, Katsutoshi
  Shizuoka 411-8731 (JP)

Representative:
Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München (DE)

References cited:
WO-A1-00/17201
WO-A1-01/92264
WO-A1-99/13799
WO-A1-02/05583
WO-A1-02/055524
WO-A1-03/011864
WO-A1-2005/063743
WO-A1-2006/032273
WO-A2-03/09289


• LEDENT,C. ET AL.: ‘Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A2a receptor.’ NATURE vol. 388, 1997, pages 674 - 8, XP008141533

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
• BAILEY, A. ET AL.: 'Quantitative autoradiography of adenosine receptors and NBTI-sensitive adenosine transporters in the brains and spinal cords of mice deficient in the mu-opioid receptor gene.' BRAIN RES. vol. 943, 2002, pages 68 - 79, XP008141537

Description

Technical Field

[0001] The present invention relates to an agent for suppressing an undesirable effect (for example, analgesic tolerance, hyperalgesia, dependence, constipation, drowsiness, etc.) of an opioid-type analgesic (opioid), which comprises a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient, and the like.

Background Art

[0002] An opioid is widely used for serious acute pain and chronic pain. It is known that an opioid shows a strong analgesic effect and also exhibits undesirable effect such as analgesic tolerance, hyperalgesia, constipation, dependence, and drowsiness (The Medical Clinics of North America, 2007, Vol. 91, p. 199). Conventionally, as a main method for treating and/or preventing analgesic tolerance or hyperalgesia, caused by an opioid, increase in the dose of the opioid, opioid rotation, change of administration route, or the like has been performed. However, the increase in the dose of the opioid has a problem that the side effects of the opioid itself such as constipation, nausea, drowsiness, respiratory depression, confusion, and immunosuppression also become severe, and the critical effectiveness is decreased from the overall viewpoint. Further, as for the opioid rotation or change of administration route, there are not a few cases where the option to be taken is limited due to the site of pain or the past history of a patient (for example, nephropathy, hepatopathy, etc.).

[0003] As a method for reducing the undesirable effect of an opioid such as dependence, for example, there are reports as described below: (1) Oxytrex ("The Journal of Pain", 2005, Vol. 6, p. 392) or Embeda ("Annual Meeting of The American Society of Anesthesiologists", 2007, Abstract A1370), both of which are a mixed preparation of an opioid and an ultra-low dose of an opioid antagonist, reduces opioid physical dependence as compared with the single administration of an opioid; (2) methylaltrexone improve constipation induced by the administration of an opioid ("The Annals of Pharmacotherapy", 2007, Vol. 41, p. 984); (3) aminoguanidine suppresses analgesic tolerance and physical dependence of morphine ("European Journal of Pharmacology", 2006, Vol. 540, pp. 60-66); (4) finasteride suppresses analgesic tolerance and physical dependence of morphine ("Hormones and Behavior", 2007, Vol. 51, p. 605); (5) an N-methyl-D-aspartic acid (NMDA) receptor antagonist suppresses analgesic tolerance and dependence of opioid ("Naunyn-Schmiedeberg's Archives of Pharmacology", 2000, Vol. 361, p. 425; "The Clinical Journal of Pain", 2000, Vol. 16, pp. S73-9); (6) a GM1 ganglioside inhibitor suppresses analgesic tolerance and physical dependence of morphine and the like (US 2004-0087607); (7) 3,7-dimethyl-1-propargylxanthine (DMPX), which is an adenosine receptor antagonist, suppresses psychological dependence of morphine (see Non-patent document 1); (8) DMPX suppresses psychological dependence of heroin (see Non-patent document 2 and Patent document 1); (9) 8-(3-chlorostyryl) caffeine (CSC) suppresses psychological dependence of morphine (see Non-patent document 3); (10) ZM241385, which is an adenosine receptor antagonist, affects an excitatory postsynaptic current induced by DAMGO, which is one of the opioid peptides (see Non-patent document 4); and (11) SCH59261 and CSC, both of which are an adenosine receptor antagonist, suppress physical dependence of morphine (see Non-patent document 8).

[0004] On the other hand, it is known that adenosine is widely distributed in the body and exhibits various physiological effects on the central nervous system, cardiac muscle, kidney, smooth muscle, and the like via its receptors (see Non-patent document 5).

[0005] For example, it is known that an adenosine A1 receptor antagonist has defecation promoting activity (see Non-patent document 6). It is also known that the adenosine A2A receptors are involved particularly in the central nervous system, and an adenosine A2A receptor antagonist is known to be useful as a therapeutic agent for, for example, Parkinson’s disease and the like (see Non-patent document 7). Further, a composition comprising an adenosine A2A receptor antagonist and an opioid for treating restless legs syndrome (RLS) and the like are also known (see Patent documents 2 and 3). Further, a method for alleviating chronic consumption of abused drugs such as ethanol or an opioid using an adenosine A2A receptor antagonist (see Patent documents 1 and 4), a method for treating a disease with chronic musculoskeletal pain (see Patent document 5) and the like are known. Furthermore, it is also known that an adenosine A2B receptor antagonist is useful as a therapeutic agent for constipation (see Patent document 6).

[0006] As a compound having an adenosine A2A receptor antagonistic activity, for example, compounds represented by the following formulae (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), (VIII), and the like are known (see Patent documents 7 to 13, and Non-patent documents 9 to 11).
Prior Art Documents

Patent Documents

[0007]

Non-Patent Documents

[0008]

Non-patent document 3: "Research Communications in Alcohol and Substances of Abuse”, 1997, Vol. 18, p. 141
Non-patent document 8: "Naunyn-Schmiedeberg’s Archives of Pharmacology", 2003, Vol. 368, p. 113
Non-patent document 9: "European Journal of Pharmacology”, 1994, Vol. 267, p. 113

Summary of the Present Invention

Problems that the Present Invention is to Solve

[0009] An object of the present invention is to provide an agent for suppressing an undesirable effect (for example, analgesic tolerance, hyperalgesia, constipation, dependence, drowsiness, etc.) of an opioid, which comprises a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient, and the like. Means for Solving the Problems

[0010] The present application discloses the following (1) to (93).

(1) An agent for suppressing an undesirable effect of an opioid, which comprises a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient.
(2) The agent according to (1), wherein the undesirable effect is analgesic tolerance, hyperalgesia, constipation, dependence, or drowsiness.
(3) The agent according to (1), wherein the undesirable effect is analgesic tolerance or constipation.
(4) The agent according to (1), wherein the undesirable effect is analgesic tolerance.
(5) The agent according to any one of (1) to (4), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

[Chemical 2]
Wherein, \( R_1 \) represents a hydrogen atom or methyl; \( R_2 \) and \( R_3 \) may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; \( R_4, R_5, \) and \( R_6 \) may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; \( R_7 \) represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted by hydroxy; \( R_8 \) represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted by 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; \( R_9 \) represents pyridyl or tetrahydropyranyl; \( R_{10} \) and \( R_{11} \) may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and \( R_{12} \) represents methyl, ethyl, propyl, or butyl.

(6) The agent according to any one of (1) to (4), wherein the compound having adenosine \( A_{2A} \) receptor antagonistic activity is a compound represented by the following formula (I).

(Wherein, \( R_1, R_2, R_3, R_4, R_5, \) and \( R_6 \) have the same definitions as described above, respectively.)

(7) The agent according to any one of (1) to (4), wherein the compound having adenosine \( A_{2A} \) receptor antagonistic activity is a compound represented by the following formula (II).
(Wherein, $R^7$ has the same definition as described above.)

(8) The agent according to any one of (1) to (4), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (III).

(Wherein, $R^8$ and $R^9$ have the same definitions as described above, respectively.)

(9) The agent according to any one of (1) to (4), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).
(10) The agent according to any one of (1) to (4), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA) or (IB).

[Chemical 7]
(11) The agent according to any one of (1) to (4), wherein the compound having adenosine A\textsubscript{2A} receptor antagonistic activity is a compound represented by the following formula (IIA), (IIIA), (IIIB), or (IIIC).

(12) The agent according to any one of (1) to (11), wherein the opioid is selected from the group consisting of anileridine, opium, ampramide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphor, diamorphor, dioxaphetylbutyrate, dizecotine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimeheptanol, sufentanil, tildine, dextromoramide, desomorphor, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxyperidine, hydromorphone, pimindodine, piriramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, propethidine, propoxyphene, propheptazine, promedol, heroin, bezitramide, berzymorphine, pentaizocine, myrophyne, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenalfentanil, levorphanol, and remifentanil.

(13) The agent according to any one of (1) to (11), wherein the opioid is morphine, fentanyl, or oxycodone.

(14) The agent according to any one of (1) to (11), wherein the opioid is morphine.

(15) A therapeutic and/or preventive agent for pain, which comprises (a) a compound having adenosine A\textsubscript{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an opioid in combination.

(16) A therapeutic and/or preventive agent for pain, which comprises the following (a) and (b) as active ingredients, both of which are to be administered simultaneously or separately at an interval: (a) a compound having adenosine A\textsubscript{2A} receptor antagonist activity or a pharmaceutically acceptable salt thereof; and (b) an opioid.

(17) The agent according to (15) or (16), wherein the pain is selected from the group consisting of nociceptive pain, cancer pain, dorsolumbar pain, postoperative pain, herpes zoster pain, osteoarticular pain, dorsolumbar pain, rheumatic joint pain, pain accompanying osteoarthitis, fibromyalgia, myofascial pain, visceral pain, inflammatory pain, neuropathic pain, entrapment neuropathy, postherpetic neuralgia, diabetic pain, neurological low back pain, pain after infection with AIDS virus, post-spinal cord injury pain, and trigeminal neuralgia.

(18) The agent according to any one of (15) to (17), wherein the compound having adenosine A\textsubscript{2A} receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

[Chemical 8]

(11) The agent according to any one of (1) to (4), wherein the compound having adenosine A\textsubscript{2A} receptor antagonistic activity is a compound represented by the following formula (IIA), (IIIA), (IIIB), or (IIIC).
(wherein, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, and R12 have the same definitions as described above, respectively.)

(19) The agent according to any one of (15) to (17), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (I).

(Wherein, R1, R2, R3, R4, R5, and R6 have the same definitions as described above, respectively.)

(20) The agent according to any one of (15) to (17), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (II).

(Wherein, R7 has the same definition as described above.)

(21) The agent according to any one of (15) to (17), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (III).
(Wherein, R⁸ and R⁹ have the same definitions as described above, respectively.)

(22) The agent according to any one of (15) to (17), wherein the compound having adenosine A₂A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).

[Chemical 13]
(23) The agent according to any one of (15) to (17), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA) or (IB).
(24) The agent according to any one of (15) to (17), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IIA), (IIIA), (IIIB), or (IIIC).

(25) The agent according to any one of (15) to (24), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphan, diamorphine, dioxaphethylbutyrate, diezocine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepethanol, sufentanil, tilidine, dexromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, piminodine, pirritramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, propoxyphene, propheptazine, promedol, heroin, bezitramide, bezylmorphine, pentazocine, myrophine, methadone, metazocine, meptazinol, meperidine, morphine, levallorphan, levophenalanofentanil, levormethanol, and remifentanil.

(26) The agent according to any one of (15) to (24), wherein the opioid is morphine, fentanyl, or oxycodone.

(27) The agent according to any one of (15) to (24), wherein the opioid is morphine.

(28) A kit, which comprises (a) a first component containing a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) a second component containing an opioid.

(29) The kit according to (28), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).
(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, and $R_{12}$ have the same definitions as described above, respectively.)

(30) The kit according to (28), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (I).

(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, and $R_6$ have the same definitions as described above, respectively.)

(31) The kit according to (28), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (II).
(Wherein, $R^7$ has the same definition as described above.)

(32) The kit according to (28), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (III).

![Chemical 19]

(Wherein, $R^8$ and $R^9$ have the same definitions as described above, respectively.)

(33) The kit according to (28), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).

![Chemical 20]
(34) The kit according to (28), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA) or (IB).

[Chemical 21]
(35) The kit according to (28), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IIA), (IIIA), (IIIB), or (IIIC).

(36) The kit according to any one of (28) to (35), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethynorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphan, diamorphone, dioxaphetylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepethanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypropylene, hydromorphone, piminozine, piritramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, properidine, propoxyphene, proprazocine, promedol, heroin, bezitramide, benzylmorphine, pentazocine, myphrine, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenalfentanyl, levorphanil, and remifentanil.

(37) The kit according to any one of (28) to (35), wherein the opioid is morphine, fentanyl, or oxycodone.

(38) The kit according to any one of (28) to (35), wherein the opioid is morphine.

(39) A pharmaceutical composition, which comprises (a) a compound represented by any one of the following formulae (I) to (VIII) or a pharmaceutically acceptable salt thereof and (b) an opioid.
(Wherein, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, and R12 have the same definitions as described above, respectively.)

(40) A pharmaceutical composition, which comprises (a) a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof and (b) an opioid.

(Wherein, R1, R2, R3, R4, R5, and R6 have the same definitions as described above, respectively.)

(41) A pharmaceutical composition, which comprises (a) a compound represented by the following formula (II) or a pharmaceutically acceptable salt thereof and (b) an opioid.
EP 2 308 509 B1

(Wherein, $R^7$ has the same definition as described above.)

(42) A pharmaceutical composition, which comprises (a) a compound represented by the following formula (III) or a pharmaceutically acceptable salt thereof and (b) an opioid.

[Chemical 26]

(III)

(Wherein, $R^8$ and $R^9$ have the same definitions as described above, respectively.)

(43) A pharmaceutical composition, which comprises (a) a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII) or a pharmaceutically acceptable salt thereof and (b) an opioid.
A pharmaceutical composition, which comprises (a) a compound represented by the following formula (IA) or (IB) or a pharmaceutically acceptable salt thereof and (b) an opioid.
A pharmaceutical composition, which comprises (a) a compound represented by the following formula (IIC), (IIIA), (IIIB), or (IIIC) or a pharmaceutically acceptable salt thereof and (b) an opioid.

The pharmaceutical composition according to any one of (39) to (45), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylpromine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cylmophan, diamorphine, dioxaphethylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepethanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxyethylidene, hydromorphone, piminodine, piritaclidine, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, properidine, propoxyphene, proheptazine, promedol, heroin, bezitramide, berzylmorphine, penta- zocine, myrophyne, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallophan, levophenylalanil, levorphanol, and remifentanil.

The pharmaceutical composition according to any one of (39) to (45), wherein the opioid is morphine, fentanyl, or oxycodone.

A method for suppressing an undesirable effect of an opioid, which comprises administering an effective amount of a compound having adenosine A<sub>2A</sub> receptor antagonistic activity or a pharmaceutically acceptable salt thereof.

The method according to (49), wherein the undesirable effect is analgesic tolerance or constipation.

The method according to any one of (49) to (51), wherein the compound having adenosine A<sub>2A</sub> receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).
(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, and $R_{12}$ have the same definitions as described above, respectively.)

(53) The method according to any one of (49) to (51), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (I), (II), or (III).

(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, and $R_9$ have the same definitions as described above, respectively.)

(54) The method according to any one of (49) to (51), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).
The method according to any one of (49) to (54), wherein the opioid is selected from the group consisting of anileridine, opium, amparemine, allylprodine, alfaprodine, alfentanil, isomethadone, ethylmethylythiambutene, ethylmorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphin, diamorphine, dioxaphetylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, diperpanone, dimethylthiambutene, dimenoxadol, dimephentanol, sufentanil, tidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, pimidodine, piramidim, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorph, butorphanol, buprenorphine, propyridine, propoxyphene, proheptazine, promedol, heroin, bezitramide, berzylmorphine, pentazocine, myrophine,
methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenolofentanil, levophen-anol, and remifentanil.

(56) The method according to any one of (49) to (54), wherein the opioid is morphine.

(57) A method for treating and/or preventing pain, which comprises administering an effective amount of (a) a compound having adenosine A<sub>2A</sub> receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an effective amount of an opioid in combination.

(58) A method for treating and/or preventing pain, which comprises administering an effective amount of (a) a compound having adenosine A<sub>2A</sub> receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an effective amount of an opioid simultaneously or separately at an interval.

(59) The method according to (57) or (58), wherein the compound having adenosine A<sub>2A</sub> receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

---

[Chemical 33]

(Wherein, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> have the same definitions as described above, respectively.)

(60) The method according to (57) or (58), wherein the compound having adenosine A<sub>2A</sub> receptor antagonistic activity is a compound represented by the following formula (I), (II), or (III).

---

[Chemical 34]

---
(Wherein, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, and $R^9$ have the same definitions as described above, respectively.)

(61) The method according to (57) or (58), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).

(62) The method according to any one of (57) to (61), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethyl-
morphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cylmorphan, diamorphine, dioxaphetylbutyrate, didezocine, dinorphine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepethanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, pimindine, piracetam, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, propoxiphene, proheptazine, promedol, heroin, bezitramide, bezylmorphine, pentazocine, myphine, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenyalofentanil, levophenylalan, and remifentanil.

(63) The method according to any one of (57) to (61), wherein the opioid is morphine.

(64) Use of a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof for the manufacture of a suppressant of an undesirable effect of an opioid.

(65) The use according to (64), wherein the undesirable effect is analgesic tolerance or constipation.

(66) The use according to (64), wherein the undesirable effect is analgesic tolerance.

(67) The use according to any one of (64) to (66), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

[Chemical 36]

(Wherein, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² have the same definitions as described above, respectively.)

(68) The use according to any one of (64) to (66), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (I), (II), or (III).
(Wherein, R₁, R₂, R₃, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ have the same definitions as described above, respectively.)

(69) The use according to any one of (64) to (66), wherein the compound having adenosine A₂₅ receptor antagonistic activity is a compound represented by the following formula (I), (II), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VIA), or (VIII).
The use according to any one of (64) to (69), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cylmophan, diamorphone, dioxaphethylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, dipanalone, dimethylthiambutene, dimenoxadol, dimepethanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, naltbuphene, nicomorphine, norlevorphanol, normeth-
adone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, pimino
dine, piriramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, prop
eridine, propoxyphene, propheptazine, promedol, heroin, bezitramide, berzyllmorphine, pentazocine, myrophine,
methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenalofentanil, levorph
anol, and remifentanil.

(71) The use according to any one of (64) to (69), wherein the opioid is morphine.
(72) Use of (a) a compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an opioid in combination for the manufacture of a therapeutic and/or preventive agent for pain.  
(73) Use of the following (a) and (b) for the manufacture of a therapeutic and/or preventive agent for pain: (a) a compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof; and (b) an opioid, both of which are to be administered simultaneously or separately at an interval.  
(74) The use according to (72) or (73), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

![Chemical 39](image)
(Wherein, R₁, R₂, R₃, R₄, R₅, R, R₇, R₈, and R⁰ have the same definitions as described above, respectively.)

(76) The use according to (72) or (73), wherein the compound having adenosine Aₐ_A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).
(Wherein, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, and R12 have the same definitions as described above, respectively.)

(77) The use according to any one of (72) to (76), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethyliambutene, ethylmorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cybmorphan, diamorphine, dioxapheptylbutyrate, didezocile, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepheptanol, sufentanil, tilidine, dex-
tromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, nomethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypropidol, hydromorphine, pimindine, pirritramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenorphine, propyridine, propoxyphene, propheptazine, promedol, heroin, bezitramide, berzylmorphine, pentazocine, myrophine, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophanol, levorphanol, and remifentanil.

(78) The use according to any one of (72) to (76), wherein the opioid is morphine.

(79) A compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof for use in suppressing an undesirable effect of an opioid.

(80) The compound or a pharmaceutically acceptable salt thereof according to (79), wherein the undesirable effect is analgesic tolerance or constipation.

(81) The compound or a pharmaceutically acceptable salt thereof according to (79), wherein the undesirable effect is analgesic tolerance.

(82) The compound or a pharmaceutically acceptable salt thereof according to any one of (79) to (81), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, and $R_{12}$ have the same definitions as described above, respectively.)

(83) The compound or a pharmaceutically acceptable salt thereof according to any one of (79) to (81), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (I), (II), or (III).
(Wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R⁹ have the same definitions as described above, respectively.)

(84) The compound or a pharmaceutically acceptable salt thereof according to any one of (79) to (81), wherein the compound having adenosine A₂A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IC), (ID), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (VII), or (VIII).
The compound or a pharmaceutically acceptable salt thereof according to any one of (79) to (84), wherein the opioid is selected from the group consisting of anileridine, opium, amprolude, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphin, diamorphine, dioxaphethylbutyrate, didezocine, dinorhine, dihyrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepheptanol, sufentanil, tildine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydroco-
done, hydroxypethidine, hydromorphone, pimino dine, piriram ide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorph an, butorphanol, buprenorphine, pro peridine, propoxyphene, propephtazine, promedol, heroin, bezitramide, bezylmorphine, pentazocine, myrophine, methadone, metazocine, metopon, metazinol, meperidine, morphine, levallorphan, levophenalofentanil, levorphanol, and remifentanil.

(86) The compound or a pharmaceutically acceptable salt thereof according to any one of (79) to (84), wherein the opioid is morphine.

(87) A combination of (a) a compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an opioid for use in treating and/or preventing pain.

(88) A combination of (a) a compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) an opioid for simultaneous or separate-at-an-interval use in treating and/or preventing pain.

(89) The combination according to (87) or (88), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by any one of the following formulae (I) to (VIII).

Wherein, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, and $R^{12}$ have the same definitions as described above, respectively.

(90) The combination according to (87) or (88), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (I), (II), or (III).
(Wherein, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_7$, $R_8$, and $R_9$ have the same definitions as described above, respectively.)

(91) The combination according to (87) or (88), wherein the compound having adenosine $A_{2A}$ receptor antagonistic activity is a compound represented by the following formula (I), (II), (III), (IVA), (IIIA), (IIIB), (IIIc), (IVA), (IIIA), (VIA), (IIA), or (VIII).
(92) The combination according to any one of (87) to (91), wherein the opioid is selected from the group consisting
of anileridine, opium, ampromide, allylprodine, alpaprodine, alfentanil, isomethadone, ethylmethylthiambutene,
ethylmorphine, ethoheptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene,
ketobemidone, cocaine, codeine, cylmphan, diamorphine, dixaphethylbutyrate, didezocine, dinorphine,
dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepheptanol, sufentanil, tildine,
dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol,
normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, pimino-
odine, piritramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphan, butorphanol, buprenor-
phine, propridine, propoxyphene, propheptazine, promedol, heroin, bezitramide, berzymorphine, pentazocine,
myrophyne, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenalofen-
tanil, levorphanol, and remifentanil.

(93) The combination according to any one of (87) to (91), wherein the opioid is morphine.

[0011] The present invention provides the following (a) to (o) as cited in claims 1 to 15 attached herewith:

(a) A pharmaceutical composition which comprises (a) a compound represented by the following formula (II), (III),
(VI), (VII) or (VIII) or a pharmaceutically acceptable salt thereof and (b) an opioid:

wherein $R^7$ represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy;
$R^8$ represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyrdylmethyl, or any of these groups substituted with
1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; $R^9$ represents pyridyl or
tetrahydropyranyl; and $R^{12}$ represents methyl, ethyl, propyl, or butyl.

(b) The pharmaceutical composition according to (a), wherein (a) is a compound represented by the following formula
(IIA), (IIIA), (IIIB), (IIIC), (VIA), (VII), or (VIII) or a pharmaceutically acceptable salt thereof:
(c) The pharmaceutical composition according to (a), wherein (a) is a compound represented by the following formula (IIIc) or a pharmaceutically acceptable salt thereof:

(d) The pharmaceutical composition according to any one of (a) to (c), wherein the opioid is selected from the group consisting of anileridine, opium, amprofide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethyldiambutene, ethylmorphine, ethoheptazine, etonitazene, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphon, diamorphine, dioxaphetylbutyrate, dizecine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepethantanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphene, niconorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxyphedidine, hydromorphone, pimindone, piritramide, fentanyl, phenazocine, phenoxydine, phenoperidine, phenomorphan, butorphanol, buprenorphine, properidine, propoxyphene, prophenaztine, promedol, heroin, bezitramide, bezylmorphine, pentazocine, myrophine, methadone, metazocine, meclofen, metazazinol, meperidine, morphine, levallophan, levophenalofen, levorphanol, and remifentanil.

(e) The pharmaceutical composition according to any one of (a) to (c), wherein the opioid is morphine.

(f) The pharmaceutical composition according to any one of (a) to (e), in the form of a kit.

(g) Use of a compound having adenosine A<sub>2A</sub> receptor antagonistic activity or a pharmaceutically acceptable salt thereof for the manufacture of a suppressant of an undesirable effect of an opioid, wherein the undesirable effect is analgesic tolerance, and the compound having adenosine A<sub>2A</sub> receptor antagonistic activity is a compound represented by the following formula (I), (II), (III), (IV), (VI), (VII) or (VIII):
wherein R₁ represents a hydrogen atom or methyl; R₂ and R₃ may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; R⁴, R⁵, and R⁶ may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; R⁷ represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R⁸ represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R⁹ represents pyridyl or tetrahydropyranyl; R¹⁰ and R¹¹ may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and R¹² represents methyl, ethyl, propyl, or butyl.

(h) The use according to (g), wherein the compound having adenosine A₂a receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII) or (VIII):
(i) The use according to (g), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IIIC):

(j) The use according to any one of (g) to (i), wherein the opioid is morphine.

(k) A compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof for use in suppressing an undesirable effect of an opioid, wherein the undesirable effect is analgesic tolerance, and the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (I), (II), (III), (IV), (VI), (VII) or (VIII):
wherein R1 represents a hydrogen atom or methyl; R2 and R3 may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; R4, R5, and R6 may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; R7 represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R8 represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R9 represents pyridyl or tetrahydropyranyl; R10 and R11 may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and R12 represents methyl, ethyl, propyl, or butyl.

(i) The compound or a pharmaceutically acceptable salt thereof for use according to (k), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IIA), (IIIB), (IIIC), (IVA), (VIA), (VII), or (VIII):

wherein R1 represents a hydrogen atom or methyl; R2 and R3 may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; R4, R5, and R6 may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; R7 represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R8 represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R9 represents pyridyl or tetrahydropyranyl; R10 and R11 may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and R12 represents methyl, ethyl, propyl, or butyl.
(m) The compound or a pharmaceutically acceptable salt thereof for use according to (k), wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IIIC):

(n) The compound or a pharmaceutically acceptable salt thereof for use according to any one of (k) to (m), wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, ketobemidone, cocaine, codeine, cymorphin, diamorphine, dioxaphetylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimepheptanol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, naceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, piminodine, piroramide, fentanyl, phanazocine, phendadoxone, phenoperidine, phenomorphin, butorphanol, buprenorphine, properidine, propxyphene, propheptazine, promedol, heroin,
bezitramide, berzylmorphine, pentazocine, myrophine, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levallorphan, levophenalofentanil, levorphanol, and remifentanil.

(o) The compound or a pharmaceutically acceptable salt thereof for use according to any one of (k) to (m), wherein the opioid is morphine.

The Effects of the present invention

[0012] According to the present invention, an agent for suppressing an undesirable effect (for example, analgesic tolerance, hyperalgesia, constipation, dependence, drowsiness, etc.) of an opioid, which comprises a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient, and the like can be provided.

Brief Description of the Drawings

[0013] Fig. 1 is a graph showing the effect of Compound (IA) on analgesic tolerance of morphine according to Test Example 1 of the present invention. The vertical axis represents response latency (sec) and the horizontal axis represents time (h) after administration.

Fig. 2 is a graph showing the effect of Compound (IA) on morphine-induced constipation according to Test Example 2 of the present invention. The vertical axis represents the amount (number) of stools. The bars from left to right represent the results of normal group, morphine administration group, Compound (IA) administration group, and combination administration group, respectively.

Description of Embodiments

[0014] The compound having adenosine A2A receptor antagonistic activity of the present invention or to be used in the present invention is defined in the claims. Specifically, for example, a compound represented by any one of the following formulae (I) to (VIII) or a pharmaceutically acceptable salt thereof is preferred:
wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁¹, and R₁² have the same definitions as described above, respectively.

More specifically, for example, a compound represented by the following formula (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (V), (VIA), (IIA), or (VIII), or a pharmaceutically acceptable salt thereof is preferred. Further more preferably, for example, a compound represented by the following formula (IA) or (IB), or a pharmaceutically acceptable salt thereof is illustrated.

Further more preferably, for example, a compound represented by the following formula (IA) or (IB), or a pharmaceutically acceptable salt thereof is illustrated.
Further, for example, a compound represented by the following formula (IIA) or a pharmaceutically acceptable salt thereof is also preferred.

Still further, for example, a compound represented by the following formula (IIIA), (IIIB), or (IIIC) or a pharmaceutically acceptable salt thereof is also preferred.

The compounds having adenosine A2A receptor antagonistic activity or pharmaceutically acceptable salts thereof of the present invention or to be used in the present invention can be produced according to conventionally known methods, respectively. For example, Compound (I) can be produced by the method described in WO 94/01114, US 5587378, J. Med. Chem. 1993, 36, 1333-1342, or the like. Compound (II) can be produced by the method described in WO 00/17201 or the like. Compound (III) can be produced by the method described in WO 2005/063743 or the like. Compound (IV) can be produced by the method described in WO 2001/092264 or the like. Compound (V) can be produced by the method described in WO 2005/063743 or the like.
produced by the method described in WO 2002/055524 or the like. Compound (VI) can be produced by the method described in WO 2003011864 or the like. Compound (VII) can be produced by the method described in WO 2006/032273 or the like. Compound (VIII) can be produced by the method described in WO 2002/055083 or the like.

[0022] Some compounds having adenosine $A_{2A}$ receptor antagonistic activity of the present invention or to be used in the present invention may exist in the form of stereoisomers such as geometric isomers and optical isomers, tautomers, or the like. In the agent for suppressing an undesirable effect of an opioid, therapeutic and/or preventive agent for pain, the kit, the pharmaceutical composition, the method for suppressing an undesirable effect of an opioid, the method for treating and/or preventing pain, the use for the manufacture of an agent for suppressing an undesirable effect of an opioid, the use for the manufacture of a therapeutic and/or preventive agent for pain, and the combination of the present invention, any of all possible isomers including the above-mentioned isomers and mixtures thereof can be used, and the compounds having adenosine $A_{2A}$ receptor antagonistic activity of the present invention include all possible isomers including the above-mentioned isomers and mixtures thereof.

[0023] In the case where the salt of the compound having adenosine $A_{2A}$ receptor antagonistic activity of the present invention or to be used in the present invention is desired to be obtained, when the respective compounds are obtained in the form of a salt, the compounds may be purified as it is, and when the respective compounds are obtained in the free form, the salt may be obtained by dissolving or suspending each compound in an appropriate solvent and adding an acid or a base thereto, followed by isolation and purification.

[0024] Further, some compounds having adenosine $A_{2A}$ receptor antagonistic activity or pharmaceutically acceptable salts thereof of the present invention may exist in the form of an adduct with water or any of various solvents. Any of these adducts can also be used in the agent for suppressing an undesirable effect of an opioid, the therapeutic and/or preventive agent for pain, the kit, the pharmaceutical composition, the method for suppressing an undesirable effect of an opioid, the method for treating and/or preventing pain, the use for the manufacture of an agent for suppressing an undesirable effect of an opioid, the use for the manufacture of a therapeutic and/or preventive agent for pain, and the combination of the present invention.

[0025] Examples of the opioid to be used in the present invention include drugs which act on the opioid receptor to exhibit analgesic activity, and specific examples thereof include anileridine, opioid, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethohpeptazine, etonitazene, eptazocine, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymorphin, diamorphine, dioxaphethylurate, didezocine, dinorphine, dihydrocodeine, dihydroxymorphone, dipipanone, dimethylthiambutene, dimenoxadol, dimorphetanephantol, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, narceine, nalorphine, nalbuphine, nicomorphine, norlevorphan, normethadone, normorphine, norpipanone, papaveretum, hydrocodone, hydroxypropylene, hydroxymorphone, pinimidine, piritramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorph, butorphanol, buprenorphine, propionephrine, propoxyphene, propheptazine, promедол, heroin, bezitramide, benzylmorphone, pentazocine, myrophine, methadone, metazocine, metopon, meptazinol, meperidine, morphine, levorphorane, levophenalofentanil, levorphanol, remifentanil, and the like. Preferred examples thereof include morphine, fentanyl, oxycodone, and the like, and more preferred examples thereof include morphine and the like. These may be used alone or in combination.

[0026] Some of these opioids may exist in the form of a pharmaceutically acceptable salt (the pharmaceutically acceptable salt includes pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, and the like, and examples thereof include inorganic acid salts such as hydrochloride, sulfate, hydrobromide, nitrate, and phosphate; organic acid salts such as cetate, mesilate, succinate, maleate, fumarate, citrate, and tartrate; alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as magnesium salts and calcium salts; metal salts such as aluminum salts and zinc salts; ammonium salts such as ammonium salts and tetramethylammonium salts; organic amine addition salts of morpholine, piperidine, and the like; amino acid addition salts of glycine, phenylalanine, lysine, aspartic acid, glutamic acid, and the like; and the like), a hydrate thereof, or the like. Any of these can also be used in the therapeutic and/or preventive agent for pain, the kit, the pharmaceutical composition, the method for treating and/or preventing pain, the use for the manufacture of a therapeutic and/or preventive agent for pain, and the combination of the present invention.

[0027] Further, the opioids illustrated above can be obtained as commercially available products or by producing them according to conventionally known methods.

[0028] The agent for suppressing an undesirable effect of an opioid and a compound having adenosine $A_{2A}$ receptor antagonistic activity of the present invention can be used, for example, in combination with any of the above-mentioned opioids, and also, the agent for suppressing an undesirable effect of an opioid, the kit, the pharmaceutical composition, the method for suppressing an undesirable effect of an opioid, and the combination of the present invention can be used for, for example, the treatment and/or prevention of pain. The pain for which the agent for suppressing an undesirable effect of an opioid, the therapeutic and/or preventive agent for pain, the kit, the pharmaceutical composition, the method for suppressing an undesirable effect of an opioid, the method for treating and/or preventing pain, the compound having adenosine $A_{2A}$ receptor antagonistic activity, and the combination of the present invention can be used is not particularly
administration, in general, a dose of 0.001 to 1000 mg, preferably 0.01 to 100 mg is administered to an adult patient once or several times a day. In the parenteral administration such as intravenous solution. Also, a suppository, a patch, and the like can be produced by conventionally known methods. using a diluent, a solvent, etc. such as a salt solution, a glucose solution, or a mixed solution of brine and a glucose hydroxypropyl cellulose, or the like.

Suitable dosage form for oral administration, for example, a tablet and the like can be produced by using an excipient such as lactose, a disintegrator such as starch, a lubricant such as magnesium stearate, a binder such as excipient such as lactose, a disintegrator such as starch, a lubricant such as magnesium stearate, a binder such as hydroxypropyl cellulose, or the like. The undesirable effect of an opioid of the present invention refers to symptoms, side effects, and the like, which are problematic when an opioid such as morphine, fentanyl, or oxycodone is administered, and examples thereof include symptoms caused by administering an opioid such as analgesic tolerance, hyperalgesia, dependence, constipation, vomiting, anorexia, drowsiness, wobble, respiratory depression, anxiety, pruritus, paralytic ileus, yawning, sneezing, lacrimation, perspiration, nausea, stomachache, mydriasis, headache, insomnia, delirium, tremor, general myalgia, general joint pain, respiratory distress, withdrawal syndrome, shortness of breath, slow respiration, irregular respiration, abnormal respiration, confusion, pulmonary atelectasis, bronchial spasm, laryngeal edema, toxic megacolon, arrhythmia, change in blood pressure, facial flushing, dizziness, restlessness, excitement, visual accommodation disorder, dry mouth, rash, urination disorder, and intracranial hypertension. By the agent for suppressing an undesirable effect of an opioid or the method for suppressing an undesirable effect of an opioid of the present invention, for Example, the above-mentioned symptom or the like caused by administrating an opioid can be treated and/or prevented. Among them, analgesic tolerance, hyperalgesia, dependence, constipation, vomiting, anorexia, drowsiness, wobble, respiratory depression, anxiety, pruritus, paralytic ileus, and the like, preferably analgesic tolerance, hyperalgesia, dependence, constipation, vomiting, anorexia, drowsiness, and the like, more preferably analgesic tolerance, hyperalgesia, dependence, constipation, and the like, further more preferably analgesic tolerance, hyperalgesia, dependence, constipation, and the like, still further more preferably analgesic tolerance, constipation, and the like can be treated and/or prevented.

As for the compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof to be used in the agent for suppressing an undesirable effect of an opioid and the method for suppressing an undesirable effects of an opioid of the present invention, the above-mentioned compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof can be administered alone as it is, however, in general, it is preferably provided as any of various pharmaceutical preparations. Further, such a pharmaceutical preparation is used for animals or humans.

The pharmaceutical preparations related to the agent for suppressing an undesirable effect of an opioid and the method for suppressing an undesirable effect of an opioid of the present invention can contain a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient alone or as a mixture with any other active ingredients for any other treatments. Further, these pharmaceutical preparations are produced by mixing the active ingredient with one or more pharmaceutically acceptable carriers (for example, a diluent, a solvent, an excipient, etc.) and then subjecting the mixture to any method well known in the technical field of pharmaceutics.

As for the administration route, it is preferred to use the most effective administration route for the treatment, and examples thereof include oral administration and parenteral administration such as intravenous administration, and transdermal administration.

Suitable dosage form for oral administration, for example, a tablet and the like can be produced by using an excipient such as lactose, a disintegrator such as starch, a lubricant such as magnesium stearate, a binder such as hydroxypropyl cellulose, or the like. Suitable dosage form for parenteral administration, for example, an injection and the like can be produced by using a diluent, a solvent, etc. such as a salt solution, a glucose solution, or a mixed solution of brine and a glucose solution. Also, a suppository, a patch, and the like can be produced by conventionally known methods.

The doses and the frequencies of administration of the compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof may vary depending on its dosage form; type; potency; dose and/or dosage form of an opioid used; age and body weight of a patient; nature or seriousness of the symptom to be treated; and the like. However, in the oral administration, in general, a dose of 0.01 to 1000 mg, preferably 0.05 to 100 mg is administered to an adult patient once or several times a day. In the parenteral administration such as intravenous administration, in general, a dose of 0.001 to 1000 mg, preferably 0.01 to 100 mg is administered to an adult patient.
once or several times a day. However, these doses and frequencies of administration vary depending on the various conditions described above.

[0037] The (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid to be used in the pharmaceutical composition, the therapeutic and/or preventive agent for pain, the method for treating and/or preventing pain, the use for the manufacture of a therapeutic and/or preventive agent for pain, or the combination of the present invention can be used or administered as a single preparation (combination preparation) or as a combination of a plurality of preparations as long as, for example, the formulation is performed along with a pharmaceutically acceptable carrier so that these respective active ingredients are incorporated therein. In particular, a combination of two or more preparations is preferred. When these active ingredients are used or administered as a combination of a plurality of preparations, these active ingredients can be used or administered simultaneously or separately at an interval. Incidentally, these preparations are preferably used in the form of, for example, a tablet, an injection, a suppository, a patch, or the like.

[0038] The ratio of the doses (weight/weight) of the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid may be appropriately adjusted according to the combination of the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid used, the respective potencies of the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid, or the like, however, specifically, the ratio is between 1/100000 ((a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof)/(b) opioid) and 1000/1, preferably between 1% 50000 and 500/1, more preferably between 1/6000 and 100/1, further more preferably between 1/4000 and 15/1, still further more preferably between 1/1000 and 10/1, and most preferably between 1/100 and 1/1.

[0039] When these active ingredients are administered as a combination of a plurality of preparations, for example, (a) a first component containing a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) a second component (containing an opioid are separately formulated into preparations and prepared as a kit, and the respective components can be administered simultaneously or separately at an interval to the same subject through the same administration route or different administration routes using this kit.

[0040] As the kit, for example, a kit comprising contents and two or more containers (for example, vials, bags, etc.) whose material, shape, and so on are not particularly limited as long as the containers do not cause degeneration of the components which are the contents due to external temperature or light nor cause elution of chemical components from the containers during storage, and having a form which enables the administration of the above first and second components which are the contents through separate routes (for example, tubes, etc.) or the same route is used. Specific examples thereof include tablet kits, injection kits, and the like.

[0041] As described above, the pharmaceutical composition, the therapeutic and/or preventive agent for pain, or the combination of the present invention can be used, administered, or produced as a single preparation or a combination of a plurality of preparations as long as it is obtained by formulating the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid into a preparation so that the respective active ingredients are incorporated therein. The therapeutic and/or preventive agent for pain and the like are preferably in a unit dosage form suitable for oral administration such as a tablet or parenteral administration such as an injection, a suppository, or a patch.

[0042] These preparations are produced by mixing the respective active ingredients with one or more pharmaceutically acceptable carriers (for example, a diluent, a solvent, an excipient, etc.) other than these active ingredients, and then subjecting the mixture to any method well known in the technical field of pharmaceutics.

[0043] Suitable for oral administration, for example, tablets and the like can be produced by using an excipient such as lactose, a disintegrator such as starch, a lubricant such as magnesium stearate, a binder such as hydroxypropyl cellulose, and the like.

[0044] Suitable for parenteral administration, for example, an injection and the like can be produced by using a diluent, a solvent, etc. such as a salt solution, a glucose solution, or a mixed liquid of brine and a glucose solution. Also, a suppository, a patch, and the like can be produced by conventionally known methods.

[0045] In the case where the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are used or administered as a combination of a plurality of preparations for the above-mentioned purpose, the doses and the frequencies of administration of the respective active ingredients may vary depending on potencies of the respective active ingredients, dosage form, age, body weight, and symptom of a patient, and the like. However, in general, the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are preferably administered at the following doses per day, respectively.

[0046] In the case of oral administration, in the form of, for example, tablets, the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are administered at doses of 0.1 to 1000 mg and 0.1 to 10000 mg, preferably 0.1 to 500 mg and 0.1 to 5000 mg, more preferably 0.5 to 500 mg
and 1 to 3000 mg, further more preferably 0.5 to 300 mg and 1 to 2000 mg, respectively, to an adult patient generally once or several times a day simultaneously or separately at an interval.

[0047] In the case of parenteral administration in the form of, for example, an injection and the like, the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are administered at doses of 0.1 to 1000 mg and 0.1 to 1000 mg, preferably 0.1 to 500 mg and 0.1 to 500 mg, more preferably 0.5 to 500 mg and 1 to 3000 mg, further more preferably 0.5 to 300 mg and 1 to 2000 mg, respectively, to an adult patient generally once or several times a day simultaneously or separately at an interval.

[0048] Further, in the case where the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are administered at doses of 0.1 to 1000 mg and 0.1 to 1000 mg, preferably 0.1 to 500 mg and 0.1 to 500 mg, more preferably 0.5 to 500 mg and 1 to 3000 mg, further more preferably 0.5 to 300 mg and 1 to 2000 mg, respectively, to an adult patient generally once or several times a day simultaneously or separately at an interval.

[0049] In the case of parenteral administration in the form of, for example, an injection and the like, the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are administered at doses of 0.1 to 1000 mg and 0.1 to 1000 mg, preferably 0.1 to 500 mg and 0.1 to 500 mg, more preferably 0.5 to 500 mg and 1 to 3000 mg, further more preferably 0.5 to 300 mg and 1 to 2000 mg, respectively, to an adult patient generally once or several times a day simultaneously or separately at an interval.

[0049] However, these doses and frequencies of administration vary depending on the above-mentioned various conditions.

[0050] Further, in the case where the (a) compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof and the (b) opioid are administered at doses of 0.1 to 1000 mg and 0.1 to 1000 mg, preferably 0.1 to 500 mg and 0.1 to 500 mg, more preferably 0.5 to 500 mg and 1 to 3000 mg, further more preferably 0.5 to 300 mg and 1 to 2000 mg, respectively, to an adult patient generally once or several times a day simultaneously or separately at an interval.

Test Example 1: Suppressing Activity of Compound (I) on Morphine Analgesic Tolerance

Experimental Materials and Methods

1. Used Animals

[0051] Male ddy mice (3 to 4 weeks old, Japan SLC, Inc.) having a body weight of 19 to 25 g were used, and the animals were maintained under the following conditions: 19 to 25°C room temperature, 30 to 70% humidity, and 12-h light and dark cycle (light period: from 7 a.m. to 7 p.m., dark period: from 7 p.m. to 7 a.m.) until they were subjected to the experiment. Food and water were provided ad libitum.

2. Used Agents and Preparation Methods

[0052] Hereinafter, the test was performed under the instructions of narcotics researchers in accordance with the narcotic handling rule each time morphine was used. Morphine was dissolved in physiological saline at a concentration of 0.6 mg/mL and subcutaneously administered at a dose of 6 mg/kg. Compound (IA) was suspended in 0.5% methyl cellulose (0.5% MC) at a concentration of 1 mg/mL and orally administered at a dose of 10 mg/kg.

3. Determination of Analgesic Activity

[0053] Nociceptive pain was determined by a hot plate method. Each mouse was placed on a hot plate apparatus (35100, Ugo Basile, Comerio, VA, Italy) set to 53°C, and the time (latency) until an escape response (paw-licking, -biting, -shaking, or jumping) was evoked was determined to be a pain threshold. In the experiment, animals having a response latency of 6 to 16 seconds before the first drug administration were used. Further, in order to minimize the damage to the site of stimulation, the cut-off time was set to 45 seconds. The analgesic activity was evaluated by determining the response latency at 30, 60, and 120 minutes after drug administration on the last day of repeated drug administration (on day 7).

4. Statistical Processing

[0054] The experimental results were expressed as mean ± standard error. The statistical analysis was performed using a statistical analysis software SAS (SAS Institute Inc., Cary, NC, USA). Comparison between two groups was performed using a Wilcoxon rank sum test. A p-value of less than 0.05 was considered to be a significant difference.

5. Experimental Results

[0055] The results are shown in Fig. 1. In the group in which morphine was repeatedly administered for 7 days (repeated
morphine administration group: twice a day, one-time administration only on day 7), the response latency was significantly
and markedly decreased as compared with that of the single morphine administration group (physiological saline was
repeatedly administered twice a day for 6 days, and morphine was administered only on day 7), and the development
of analgesic tolerance was observed. In the repeated combination administration group in which Compound (IA) was
orally administered at 30 minutes before administration of morphine, a decrease in analgesic activity was not observed
as compared with the single morphine administration group, and the development of analgesic tolerance was prevented.
Incidentally, in the group in which Compound (IA) was repeatedly administered alone (repeated Compound (IA) admin-
istration group), the effect on the response latency was not observed.

[0056] From the above test, it was confirmed that Compound (IA) has a suppressing effect on morphine analgesic
tolerance. From this, it was considered that the development of analgesic tolerance following chronic opioid administration
can be prevented by using Compound (I) and an opioid in combination.

Test Example 2: Suppressing Activity of Compound (I) on Morphine-Induced Constipation

Experimental Materials and Methods

1. Used Animals

[0057] Male ddY mice (5 weeks old, Japan SLC, Inc.) having a body weight of 23 to 27 g were used, and the animals
were maintained under the following conditions: 19 to 25°C room temperature, 30 to 70% humidity, and 12-h light and
dark cycle (light period: from 7 a.m. to 7 p.m., dark period: from 7 p.m. to 7 a.m.) until they were subjected to the
experiment. Food and water were provided ad libitum. At the time of collection of fecal pellets, food and water were not
provided.

2. Used Agents and Preparation Methods

[0058] Morphine was dissolved in physiological saline at a concentration of 0.3 mg/mL and subcutaneously adminis-
tered at a dose of 3 mg/kg. Compound (IA) was suspended in 0.5% MC at a concentration of 1 mg/mL and orally
administered at a dose of 10 mg/kg.

3. Determination of Suppressing Activity on Constipation

[0059] On the day of the test, the tails of the mice were numbered for identification, and the body weight of each mouse
was measured. On the basis of the measured body weight, 0.5% MC or Compound (IA) was orally administered. At 30
minutes after administration of 0.5% MC or Compound (IA), physiological saline or morphine was subcutaneously ad-
ministered, and collection of fecal pellets was started. The fecal pellets were collected at 3 hours after administration of
morphine. The amount of feces was evaluated by counting the number of the fecal pellets.

4. Statistical Processing

[0060] The experimental results were expressed as mean ± standard error. The statistical analysis was performed
using a statistical analysis software SAS (SAS Institute Inc., Cary, NC, USA). Comparison between two groups was
performed using a Wilcoxon rank sum test. A p-value of less than 0.05 was considered to be a significant difference.

5. Experimental Results

[0061] The results are shown in Fig. 2. In the morphine administration group, the number of fecal pellets was significantly
decreased as compared with the normal group, and constipation was observed. In the combination administration group
in which Compound (IA) was orally administered at 30 minutes before administration of morphine, the number of fecal
pellets was significantly increased as compared with the morphine administration group, and a suppressing activity on
constipation was observed. Further, in the Compound (IA) administration group in which only Compound (IA) was
administered and the combination administration group in which morphine and Compound (IA) were administered,
diarrhea was not induced.

[0062] From the above test, it was confirmed that Compound (IA) has a suppressing effect on morphine-induced
constipation. That is, it was considered that Compound (I) improves morphine-induced constipation and that constipation
caused by administration of an opioid can be improved by using Compound (I) and an opioid in combination.
Test Example 3: Suppressing Activity of Compound (III) on Morphine Analgesic Tolerance

Experimental Materials and Methods

1. Used Animals

[0063] Male ddY mice (3 to 4 weeks old, Japan SLC, Inc.) having a body weight of 19 to 25 g were used, and the animals were maintained under the following conditions: 19 to 25°C room temperature, 30 to 70% humidity, and 12-h light and dark cycle (light period: from 7 a.m. to 7 p.m., dark period: from 7 p.m. to 7 a.m.) until they were subjected to the experiment. Food and water were provided ad libitum.

2. Used Agents and Preparation Methods

[0064] Hereinafter, the test was performed under the instructions of narcotics researchers in accordance with the narcotic handling rule each time morphine was used. Morphine was dissolved in physiological saline at a concentration of 0.6 mg/mL and subcutaneously administered at a dose of 6 mg/kg. Compound (IIIB) was suspended in 0.5% MC at a concentration of 0.3 mg/mL and orally administered at a dose of 3 mg/kg. Compound (IIIC) was suspended in 0.5% MC at a concentration of 0.1 mg/mL and orally administered at a dose of 1 mg/kg.

3. Determination of Analgesic Activity

[0065] Nociceptive pain was determined by a hot plate method. Each mouse was placed on a hot plate apparatus (35100, Ugo Basile, Comerio, VA, Italy) set to 53°C, and the time (latency) until an escape response (paw-licking, -biting, -shaking, or jumping) was evoked was determined to be a pain threshold. In the experiment, animals having a response latency of 6 to 16 seconds before the first drug administration were used. Further, in order to minimize the damage to the site of stimulation, the cut-off time was set to 45 seconds. The analgesic activity was evaluated by determining the response latency before drug administration, and at 30, 60, and 120 minutes after drug administration, on the last day of repeated drug administration (on day 7).

4. Statistical Processing

[0066] The experimental results were expressed as mean ± standard error. The statistical analysis was performed using a statistical analysis software SAS (SAS Institute Inc., Cary, NC, USA). Comparison between two groups was performed using a Wilcoxon rank sum test. A p-value of less than 0.05 was considered to be a significant difference.

5. Experimental Results

[0067] The results are shown in Tables 1 and 2.

[0068] [Table 1]

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td>Single morphine administration group</td>
<td>11.4 ± 0.8</td>
<td>21.9 ± 1.9</td>
</tr>
<tr>
<td>Repeated morphine administration group</td>
<td>9.3 ± 0.6</td>
<td>11.4 ± 1.3 **</td>
</tr>
<tr>
<td>Repeated combination administration group</td>
<td>9.6 ± 0.3</td>
<td>18.2 ± 1.2 ###</td>
</tr>
<tr>
<td>Repeated Compound (IIIB) administration group</td>
<td>10.7 ± 0.7</td>
<td>0.1 ± 0.5</td>
</tr>
</tbody>
</table>

**P<0.01, *P<0.05 [Single morphine administration group vs. Repeated morphine administration group]  
##P<0.01 [Repeated morphine administration group vs. Repeated combination administration group]
In the group in which morphine was repeatedly administered for 7 days (repeated morphine administration group: twice a day, one-time administration only on day 7), the response latency was significantly and markedly decreased as compared with that of the single morphine administration group (physiological saline was repeatedly administered twice a day for 6 days, and morphine was administered only on day 7), and the development of analgesic tolerance was observed. In the repeated combination administration group in which Compound (IIIB) or (IIIC) was orally administered at 30 minutes before administration of morphine (repeated combination administration group: Compound (IIIB) or (IIIC) was administered at 30 minutes before each administration of morphine in repeated morphine administration group), a decrease in analgesic activity was not observed as compared with the single morphine administration group, and the development of analgesic tolerance was prevented. Incidentally, in the group in which Compound (IIIB) or (IIIC) was repeatedly administered alone (repeated Compound (IIIC) administration group), the effect on the response latency was not observed.

From the above test, it was confirmed that Compounds (IIIB) and (IIIC) have a suppressing effect on morphine analgesic tolerance. From this, it was considered that the development of analgesic tolerance following chronic opioid administration can be prevented by using Compound (III) such as Compound (IIIB) or (IIIC) and an opioid in combination.

Test Example 4: Suppressing Activity of Compounds (IC) and (ID) on Morphine Analgesic Tolerance

The effect of Compounds (IC) and (ID) on morphine analgesic tolerance was studied. The experiment was performed in the same manner as in Test Example 3. Compounds (IC) and (ID) were used at a dose of 10 mg/kg, respectively. The results are shown in Table 3. In the statistical analysis, comparison between two groups was performed using a Wilcoxon rank sum test, and comparison among multi-groups was performed using a Kruskal-Wallis test.

**Table 2: Effect of Compound (IIIC) on Morphine Analgesic Tolerance (Response Latency (sec))**

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td>Single Morphine administration group</td>
<td>10.7 ± 0.7</td>
<td>20.2 ± 1.9</td>
</tr>
<tr>
<td>Repeated morphine administration group</td>
<td>10.8 ± 0.7</td>
<td>7.7 ± 1.3**</td>
</tr>
<tr>
<td>Repeated combination administration group</td>
<td>10.9 ± 0.7</td>
<td>16.1 ± 2.4 #</td>
</tr>
<tr>
<td>Repeated Compound (IIIC) administration group</td>
<td>12.4 ± 1.0</td>
<td>-2.2 ± 1.3</td>
</tr>
</tbody>
</table>

**P<0.01 [Single morphine administration group vs. Repeated morphine administration group]

#P<0.05 [Repeated morphine administration group vs. Repeated combination administration group]

**Table 3: Effect of Compounds (IC) and (ID) on Morphine Analgesic Tolerance (Response Latency (sec))**

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td>Single morphine administration group</td>
<td>12.8 ± 1.5</td>
<td>19.5 ± 2.0</td>
</tr>
<tr>
<td>Repeated morphine administration group</td>
<td>10.5 ± 1.4</td>
<td>7.5 ± 1.3**</td>
</tr>
<tr>
<td>Repeated combination administration group (Compound (IC) and morphine)</td>
<td>11.4 ± 1.2</td>
<td>16.0 ± 1.8 ##</td>
</tr>
</tbody>
</table>
In the group in which morphine was repeatedly administered for 7 days (repeated morphine administration group: twice a day, one-time administration only on day 7), the response latency was significantly and markedly decreased as compared with the single morphine administration group (physiological saline was repeatedly administered twice a day for 6 days, and morphine was administered only on day 7), and the development of analgesic tolerance was observed.

In the repeated combination administration group in which Compound (IC) or (ID) was orally administered at 30 minutes before administration of morphine (repeated combination administration group: Compound (IC) or (ID) was administered at 30 minutes before each administration of morphine in repeated morphine administration group), the degree of the decrease in response latency was smaller as compared with that of the repeated morphine administration group, and the development of analgesic tolerance was prevented. Incidentally, in the group in which Compound (IC) or (ID) was repeatedly administered alone (repeated Compound (IC) administration group, repeated Compound (ID) administration group), the effect on the response latency was not observed.

From the above test, it was confirmed that Compounds (IC) and (ID) have a suppressing effect on morphine analgesic tolerance. From the results of this test and Test Example 1, it was considered that the development of analgesic tolerance following chronic opioid administration can be prevented by using Compound (I) such as Compound (IA), (IB), (IC), or (ID) and an opioid in combination.

Test Example 5: Suppressing Activity of Compounds (IIA), (VIA), and (VII) on Morphine Analgesic Tolerance

The effect of Compounds (IIA), (VIA), and (VII) on morphine analgesic tolerance was studied. The experiment was performed in the same manner as in Test Example 3. Compounds (IIA), (VIA), and (VII) were used at doses of 100 mg/kg, 30 mg/kg, and 60 mg/kg, respectively. The results are shown in Table 4. In the statistical analysis, comparison between two groups was performed using a Wilcoxon rank sum test, and comparison among multi-groups was performed using a Kruskal-Wallis test.

Table 4: Effect of Compounds (IIA), (VIA), and (VII) on Morphine Analgesic Tolerance (Response Latency (sec))

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td>Single morphine administration group</td>
<td>8.8 ± 0.6</td>
<td>16.8 ± 2.7</td>
</tr>
<tr>
<td>Repeated morphine administration group</td>
<td>9.1 ± 0.9</td>
<td>7.3 ± 1.2</td>
</tr>
<tr>
<td>Repeated combination administration group (IIA and morphine)</td>
<td>8.2 ± 0.5</td>
<td>12.8 ± 1.9</td>
</tr>
<tr>
<td>Repeated combination administration group (VIA and morphine)</td>
<td>8.6 ± 1.1</td>
<td>13.0 ± 2.4</td>
</tr>
<tr>
<td>Repeated combination administration group (VII and morphine)</td>
<td>8.2 ± 0.5</td>
<td>12.8 ± 2.1</td>
</tr>
</tbody>
</table>

**P<0.01 [Single morphine administration group vs. Repeated morphine administration group]

#P<0.01, #P<0.05 [Repeated morphine administration group vs. Repeated combination administration group]
In the group in which morphine was repeatedly administered for 7 days (repeated morphine administration group: twice a day, one-time administration only on day 7), the response latency was significantly and markedly decreased as compared with that of the single morphine administration group (physiological saline was repeatedly administered twice a day for 6 days, and morphine was administered only on day 7), and the development of analgesic tolerance was observed. In the repeated combination administration group in which Compound (IIA), (VIA), or (VII) was orally administered at 30 minutes before administration of morphine (repeated combination administration group: Compound (IIA), (VIA), or (VII) was administered at 30 minutes before each administration of morphine in repeated morphine administration group), the degree of the decrease in response latency was smaller as compared with that of the repeated morphine administration group, and the development of analgesic tolerance was prevented. Incidentally, in the group in which Compound (IIA), (VIA), or (VII) was repeatedly administered alone (repeated Compound (IIA) administration group, or repeated Compound (VIA) administration group, repeated Compound (VII) administration group), the effect on the response latency was not observed.

From the above test, it was confirmed that Compounds (IIA), (VIA), and (VII) have a suppressing effect on morphine analgesic tolerance. From the results of this test, it was considered that the development of analgesic tolerance following chronic opioid administration can be prevented by using Compound (II) such as Compound (IIA), Compound (VI) such as Compound (VIA), or Compound (VII) and an opioid in combination.

Test Example 6: Suppressing Activity of Compounds (IVA) and (VIII) on Morphine Analgesic Tolerance

The effect of Compounds (IVA) and (VIII) on morphine analgesic tolerance was studied. The experiment was performed in the same manner as in Test Example 3. Compounds (IVA) and (VIII) were used at a dose of 30 mg/kg, respectively. The results are shown in Table 5. In the statistical analysis, comparison between two groups was performed using a Wilcoxon rank sum test, and comparison among multi-groups was performed using a Kruskal-Wallis test.

Table 5: Effect of Compounds (IVA) and (VIII) on Morphine Analgesic Tolerance (Response Latency (sec))

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value) each time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td>Single morphine administration group</td>
<td>12.4 ± 1.0</td>
<td>18.0 ± 2.2</td>
</tr>
<tr>
<td>Repeated morphine administration group</td>
<td>12.0 ± 1.1</td>
<td>6.8 ± 1.3*</td>
</tr>
<tr>
<td>Repeated combination administration group</td>
<td><strong>Compound (IVA) and morphine</strong></td>
<td>11.7 ± 0.9</td>
</tr>
<tr>
<td>Repeated combination administration group</td>
<td><strong>Compound (VIII) and morphine</strong></td>
<td>12.3 ± 0.8</td>
</tr>
<tr>
<td>Repeated Compound (IVA) administration group</td>
<td>12.6 ± 1.2</td>
<td>0.5 ± 0.6</td>
</tr>
</tbody>
</table>
In the group in which morphine was repeatedly administered for 7 days (repeated morphine administration group: twice a day, one-time administration only on day 7), the response latency was significantly and markedly decreased as compared with that of the single morphine administration group (physiological saline was repeatedly administered twice a day for 6 days, and morphine was administered only on day 7), and the development of analgesic tolerance was observed. In the repeated combination administration group in which Compound (IVA) or (VIII) was orally administered at 30 minutes before administration of morphine (repeated combination administration group: Compound (IVA) or (VIII) was administered at 30 minutes before each administration of morphine in repeated morphine administration group), the degree of the decrease in response latency was smaller as compared with that of the repeated morphine administration group, and the development of analgesic tolerance was prevented. Incidentally, in the group in which Compound (IVA) or (VIII) was repeatedly administered alone (repeated Compound (IVA) administration group, or repeated Compound (VIII) administration group), the effect on the response latency was not observed.

From the above test, it was confirmed that Compounds (IVA) and (VIII) have a suppressing effect on morphine analgesic tolerance. From the results of this test, it was considered that the development of analgesic tolerance following chronic opioid administration can be prevented by using Compound (IV) such as Compound (IVA) or Compound (VIII) and an opioid in combination.

Test Example 7: Suppressing Activity of Compound (IA) on Oxycodone Analgesic Tolerance

Experimental Materials and Methods

1. Used Animals

Male ddY mice (3 to 4 weeks old, Japan SLC, Inc.) having a body weight of 18 to 23 g were used, and the animals were maintained under the following conditions: 19 to 25°C room temperature, 30 to 70% humidity, and 12-h light and dark cycle (light period: from 7 a.m. to 7 p.m., dark period: from 7 p.m. to 7 a.m.) until they were subjected to the experiment. Food and water were provided ad libitum.

2. Used Agents and Preparation Methods

Hereinafter, the test was performed under the instructions of narcotics researchers in accordance with the narcotic handling rule each time oxycodone was used. Oxycodone was prepared at a concentration of 2 mg/mL using distilled water for injection and orally administered at a dose of 20 mg/kg. Compound (IA) was suspended in 0.5% MC at a concentration of 1 mg/mL and orally administered at a dose of 10 mg/kg.

3. Determination of Analgesic Activity

Nociceptive pain was determined by a hot plate method. Each mouse was placed on a hot plate apparatus (MK-350B, MUROMACHI KIKAI CO., LTD.) set to 53°C and the time (latency) until an escape response (paw-licking, -biting, -shaking, or jumping) was evoked was determined to be a pain threshold. In the experiment, animals having a response latency of 6 to 16 seconds before the first drug administration were used. Further, in order to minimize the damage to the site of stimulation, the cut-off time was set to 45 seconds. The analgesic activity was evaluated by determining the response latency at 30, 60, and 120 minutes after drug administration on the last day of repeated drug administration (on day 4).
4. Statistical Processing

[0087] The Experimental results were expressed as mean ± standard error. The statistical analysis was performed using a statistical analysis software SAS. Comparison between two groups was performed using a Wilcoxon rank sum test. A p-value of less than 0.05 was considered to be a significant difference.

5. Experimental Results

[0088] The results are shown in Table 6.

[0089] Table 6: Effect of Compound (IA) on Oxycodone Analgesic Tolerance (Response Latency (sec))

<table>
<thead>
<tr>
<th>Latency (sec)</th>
<th>Pre value (before drug administration on last day)</th>
<th>ΔChange (Latency at each time point - Pre value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>Single oxycodone administration group</td>
<td>11.7 ± 1.0</td>
<td>17.5 ± 4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.8 ± 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.9 ± 2.4</td>
</tr>
<tr>
<td>Repeated oxycodone administration group</td>
<td>12.4 ± 1.1</td>
<td>5.9 ± 3.4 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7 ± 2.3 **</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 ± 1.3 **</td>
</tr>
<tr>
<td>Repeated combination administration group</td>
<td>11.9 ± 0.7</td>
<td>13.5 ± 2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 ± 1.6</td>
</tr>
<tr>
<td>Repeated Compound administration group</td>
<td>11.9 ± 1.2</td>
<td>-0.2 ± 1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.4 ± 2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.1 ± 2.2</td>
</tr>
</tbody>
</table>

**P<0.01, *P<0.05 [Single oxycodone administration group vs. Repeated oxycodone administration group]

[0090] In the group in which oxycodone was repeatedly administered for 4 days (repeated oxycodone administration group: twice a day, one-time administration only on day 4), the response latency was significantly and markedly decreased as compared with that of the single oxycodone administration group (distilled water for injection was repeatedly administered twice a day for 3 days, and oxycodone was administered only on day 4), and the development of analgesic tolerance was observed. In the repeated combination administration group in which Compound (IA) was orally administered at 30 minutes before administration of oxycodone, the degree of the decrease in response latency was smaller as compared with that of the repeated oxycodone administration group, and the development of analgesic tolerance was prevented. Incidentally, in the group in which Compound (IA) was repeatedly administered alone (repeated Compound (IA) administration group), the effect on the response latency was not observed.

[0091] From the above test, it was confirmed that Compound (IA) has a suppressing effect on oxycodone analgesic tolerance.


[0093] Accordingly, from Test Examples 1 and 3 to 7, it was considered that a compound having adenosine A_{2A} receptor antagonistic activity (for example, Compounds (I) to (VIII)) or a pharmaceutically acceptable salt thereof has a suppressing effect on opioid analgesic tolerance.

[0094] Further, from the above Test Example 2, it was considered that a compound having adenosine A_{2A} receptor antagonistic activity (for example, Compounds (I) to (VIII)) or a pharmaceutically acceptable salt thereof can suppress constipation induced by an opioid such as morphine, and that constipation caused by administration of an opioid can be improved by using a compound having adenosine A_{2A} receptor antagonistic activity (for example, Compounds (I) to (VIII)) or a pharmaceutically acceptable salt thereof and an opioid in combination.

[0095] That is, from the above Test Examples 1 to 7, it is considered that the undesirable effect (for example, analgesic tolerance, constipation, etc.) of an opioid can be prevented by using a compound having adenosine A_{2A} receptor antagonistic activity (for example, Compounds (I) to (VIII)) or a pharmaceutically accept-
able salt thereof and an opioid in combination, and as a result, it is considered that the undesirable effect (for example, drowsiness, wobble, respiratory depression, hallucination, anxiety, pruritus, etc.) of an opioid due to an increase in the dose of the opioid can be suppressed. That is, it is considered that use of a compound having adenosine $A_{2A}$ receptor antagonistic activity or a pharmaceutically acceptable salt thereof and an opioid in combination is useful for the treatment and/or prevention of pain in which an undesirable effect of an opioid is reduced. Accordingly, the therapeutic and/or preventive agent for pain and the method for treating and/or preventing pain of the present invention are effective particularly in patients in which the useful effect of an opioid itself cannot be sufficiently achieved due to the undesirable effect (for example, analgesic tolerance, constipation, etc.) of an opioid such as morphine.

Hereinafter, the aspects of the present invention will be more specifically described with Examples, however, the scope of the present invention is not limited to these Examples.

Example 1

Tablets having the following composition are prepared according to the conventional manner. Compound (IA) (40 g), lactose (286.8 g), and potato starch (60 g) are mixed, and then a 10% aqueous solution of hydroxypropyl cellulose (120 g) is added thereto. The resulting mixture is kneaded, granulated, dried, and sized according to the conventional manner, whereby granules for tableting are prepared. Magnesium stearate (1.2 g) is added thereto and mixed therewith, and the resulting mixture is tableted using a tableting machine (RT-15, manufactured by Kikusui Seisakusho Ltd.) with a punch having a diameter of 8 mm, whereby tablets (containing 20 mg of the active ingredient per tablet) are obtained.

Table 7

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IA)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 2

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 8

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IB)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 3

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 9

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IIA)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
</tbody>
</table>
Example 4

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 10

<table>
<thead>
<tr>
<th>Formulation</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
</tbody>
</table>

Example 5

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 11

<table>
<thead>
<tr>
<th>Formulation</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IIIA)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
</tbody>
</table>

Example 6

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 12

<table>
<thead>
<tr>
<th>Formulation</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IIIC)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
</tbody>
</table>

Example 7

Tablets having the following composition are prepared in the same manner as in Example 1.
Example 8

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 13

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IVA)</td>
<td>20 mg</td>
<td>Lactose</td>
<td>143.4 mg</td>
<td></td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 9

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 14

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (V)</td>
<td>20 mg</td>
<td>Lactose</td>
<td>143.4 mg</td>
<td></td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 10

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 15

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (VIA)</td>
<td>20 mg</td>
<td>Lactose</td>
<td>143.4 mg</td>
<td></td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 10

Tablets having the following composition are prepared in the same manner as in Example 1.

Table 16

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (VII)</td>
<td>20 mg</td>
<td>Lactose</td>
<td>143.4 mg</td>
<td></td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 11

[0117] Tablets having the following composition are prepared in the same manner as in Example 1. **[Table 17]**

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 12

[0119] Tablets having the following composition are prepared according to the conventional manner. Compound (IA) (40 g), morphine (40 g), lactose (246.8 g), and potato starch (60 g) are mixed, and then a 10% aqueous solution of hydroxypropyl cellulose (120 g) is added thereto. The resulting mixture is kneaded, granulated, dried, and sized according to the conventional manner, whereby granules for tableting are prepared. Magnesium stearate (1.2 g) is added thereto and mixed therewith, and the resulting mixture is tableted using a tableting machine RT-15, manufactured by Kikusui Seisakusho Ltd.) with a punch having a diameter of 8 mm, whereby tablets (containing 20 mg of Compound (VII) and 20 mg of morphine per tablet) are obtained. **[Table 18]**

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IA)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>123.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 13

[0121] Tablets having the following composition are prepared in the same manner as in Example 12. **[Table 19]**

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IB)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>123.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 14

[0123] Tablets having the following composition are prepared in the same manner as in Example 12.
Example 15

Tablets having the following composition are prepared in the same manner as in Example 12.

Table 20

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IIA)</td>
<td>20 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>123.4 mg</td>
</tr>
<tr>
<td>Potato starch</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>6 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td></td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Example 16

An injection having the following composition is prepared according to the conventional manner. Compound (IB) (1 g) is added to distilled water for injection and mixed therewith. Hydrochloric acid and an aqueous solution of sodium hydroxide are further added thereto to adjust the pH of the mixture to 7, and distilled water for injection is added thereto to make the total amount 1000 mL. The obtained mixed liquid is aseptically filled in glass vials in an amount of 2 mL per vial, whereby injections (containing 2 mg of the active ingredient per vial) are obtained.

Table 22

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IB)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td></td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
<td></td>
</tr>
<tr>
<td>Distilled water for injection</td>
<td>2.00 mL</td>
</tr>
</tbody>
</table>

Example 17

An injection having the following composition is prepared in the same manner as in Example 16.

Table 23

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IVA)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td></td>
</tr>
</tbody>
</table>
Example 18

[0131] An Injection having the following composition is prepared in the same manner as in Example 16.

[0132] [Table 24]

Table 24

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>2 mg</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Distilled water for injection</td>
<td>appropriate amount</td>
</tr>
<tr>
<td></td>
<td><strong>2.00 mL</strong></td>
</tr>
</tbody>
</table>

Example 19

[0133] An injection having the following composition is prepared according to the conventional manner. Compound (IB) (1 g) and morphine (1 g) are added to distilled water for injection and mixed therewith. Hydrochloric acid and an aqueous solution of sodium hydroxide are further added thereto to adjust the pH of the mixture to 7, and distilled water for injection is added thereto to make the total amount 1000 mL. The obtained mixed liquid is aseptically filled in glass vials in an amount of 2 mL per vial, whereby injections (containing 2 mg of Compounds (IB) and 2 mg of morphine per vial) are obtained.

[0134] [Table 25]

Table 25

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IB)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>2 mg</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Distilled water for injection</td>
<td>appropriate amount</td>
</tr>
<tr>
<td></td>
<td><strong>2.00 mL</strong></td>
</tr>
</tbody>
</table>

Example 20

[0135] An injection having the following composition is prepared in the same manner as in Example 19.

[0136] [Table 26]

Table 26

<table>
<thead>
<tr>
<th>Formulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (IB)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Heroin</td>
<td>2 mg</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>Distilled water for injection</td>
<td>appropriate amount</td>
</tr>
<tr>
<td></td>
<td><strong>2.00 mL</strong></td>
</tr>
</tbody>
</table>
Example 21

[0137] An injection having the following composition is prepared in the same manner as in Example 19.
[0138] [Table 27]

<table>
<thead>
<tr>
<th>Table 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Compound (IVA)</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
</tr>
<tr>
<td>Distilled water for injection</td>
</tr>
<tr>
<td>2.00 mL</td>
</tr>
</tbody>
</table>

Example 22

[0139] An injection having the following composition is prepared in the same manner as in Example 19.
[0140] [Table 28]

<table>
<thead>
<tr>
<th>Table 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Compound (V)</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>Aqueous solution of sodium hydroxide</td>
</tr>
<tr>
<td>Distilled water for injection</td>
</tr>
<tr>
<td>2.00 mL</td>
</tr>
</tbody>
</table>

Industrial Applicability

[0141] According to the present invention, an agent for suppressing an undesirable effect of an opioid-type analgesic (opioid), which comprises a compound having adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof as an active ingredient, and the like can be provided.

Description of Reference Numerals and Signs

1. Fig. 1

[0142] - ● - Single morphine administration group
- ▲ - Repeated morphine administration group
- O - Repeated combination administration group
- ■ - Repeated Compound (IA) administration group
** : P < 0.01 [Single morphine administration group vs. Repeated morphine administration group (Wilcoxon rank sum test)]
### : P < 0.01 [Repeated morphine administration group vs. Repeated combination administration group (Wilcoxon rank sum test)]
# : P < 0.05 [Repeated morphine administration group vs. Repeated combination administration group (Wilcoxon rank sum test)]
2. Fig. 2
** P < 0.01 (Wilcoxon rank sum test)
Claims

1. A pharmaceutical composition which comprises (a) a compound represented by the following formula (II), (III), (VI), (VII) or (VIII) or a pharmaceutically acceptable salt thereof and (b) an opioid:

\[
\text{Chemical Structures}
\]

wherein R\textsuperscript{7} represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R\textsuperscript{8} represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R\textsuperscript{9} represents pyridyl or tetrahydropyranyl; and R\textsuperscript{12} represents methyl, ethyl, propyl, or butyl.

2. The pharmaceutical composition according to claim 1, wherein (a) is a compound represented by the following formula (IIA), (IIIA), (IIIB), (IIIC), (VIA), (VII), or (VIII) or a pharmaceutically acceptable salt thereof:
3. The pharmaceutical composition according to claim 1, wherein (a) is a compound represented by the following formula (IIIC) or a pharmaceutically acceptable salt thereof:

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the opioid is selected from the group consisting of anileridine, opium, amphoprodine, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethy whole 

5. The pharmaceutical composition according to any one of claims 1 to 3, wherein the opioid is morphine.

6. The pharmaceutical composition according to any one of claims 1 to 5, in the form of a kit.

7. Use of a compound having adenosine A2A receptor antagonistic activity or a pharmaceutically acceptable salt thereof for the manufacture of a suppressant of an undesirable effect of an opioid, wherein the undesirable effect is analgesic tolerance, and the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (I), (II), (III), (IV), (VI), (VII) or (VIII):
wherein R1 represents a hydrogen atom or methyl; R2 and R3 may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; R4, R5, and R6 may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; R7 represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R8 represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R9 represents pyridyl or tetrahydropyranyl; R10 and R11 may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and R12 represents methyl, ethyl, propyl, or butyl.

8. The use according to claim 7, wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII) or (VIII):
9. The use according to claim 7, wherein the compound having adenosine A₂A receptor antagonistic activity is a compound represented by the following formula (IIIc):

10. The use according to any one of claims 7 to 9, wherein the opioid is morphine.

11. A compound having adenosine A₂A receptor antagonistic activity or a pharmaceutically acceptable salt thereof for use in suppressing an undesirable effect of an opioid, wherein the undesirable effect is analgesic tolerance, and the compound having adenosine A₂A receptor antagonistic activity is a compound represented by the following formula (I), (II), (III), (IV), (VI), (VII) or (VIII):
wherein R1 represents a hydrogen atom or methyl; R2 and R3 may be the same or different, and each represents methyl, ethyl, propyl, butyl, or isopropyl; R4, R5, and R6 may be the same or different, and each represents a hydrogen atom, methyl, ethyl, methoxy, ethoxy, a fluorine atom, a chlorine atom, or a bromine atom; R7 represents methyl, ethyl, propyl, butyl, or 3-methylbutyl, or any of these groups substituted with hydroxy; R8 represents phenyl, pyridyl, pyrimidinyl, or 5,6-dihydro-2H-pyridylmethyl, or any of these groups substituted with 1 to 3 substituents selected from a chlorine atom, methyl, ethyl, methoxy, and ethoxy; R9 represents pyridyl or tetrahydropyranyl; R10 and R11 may be the same or different, and each represents a hydrogen atom, a fluorine atom, or 2-methoxyethoxy; and R12 represents methyl, ethyl, propyl, or butyl.

12. The compound or a pharmaceutically acceptable salt thereof for use according to claim 11, wherein the compound having adenosine A2A receptor antagonistic activity is a compound represented by the following formula (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII), or (VIII):

\[
\begin{align*}
\text{(IA)} & \quad \text{(IB)} \\
\text{(IIA)} & \quad \text{IIIA} \\
\text{(IIIB)} & \quad \text{(IIIC)}
\end{align*}
\]
13. The compound or a pharmaceutically acceptable salt thereof for use according to claim 11, wherein the compound having adenosine A$_{2A}$ receptor antagonistic activity is a compound represented by the following formula (IIIC):

14. The compound or a pharmaceutically acceptable salt thereof for use according to any one of claims 11 to 13, wherein the opioid is selected from the group consisting of anileridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isomethadone, ethylmethylthiambutene, ethylmorphine, ethoheptazine, etonitazene, endorphin, enkephalin, oxycodone, oxymorphone, clonitazene, ketobemidone, cocaine, codeine, cymophan, diamorphine, dioxaphetylbutyrate, didezocine, dinorphine, dihydrocodeine, dihydromorphine, dipipanone, dimethylthiambutene, dimenoxadol, dimethoanal, sufentanil, tilidine, dextromoramide, desomorphine, tramadol, nartceine, nalorphine, nalbuphene, nicomorphine, norlevorphanol, normethadone, normorphine, normorphan, papaveretum, hydrocodone, hydroxypethidine, hydromorphone, pimindine, piriramide, fentanyl, phenazocine, phenadoxone, phenoperidine, phenomorphin, butorphanol, butroporphine, properidine, propoxyphene, propheptazine, promedol, heroin, bezitramide, benzylmorphine, pentazocine, myrophine, methadone, metazocine, metopon, meptazinol, meperidine, morphone, levallorphan, levophenadifenitran, levorphanol, and remifentanil.

15. The compound or a pharmaceutically acceptable salt thereof for use according to any one of claims 11 to 13, wherein the opioid is morphine.

**Patentansprüche**

1. Arzneimittel, welches (a) eine Verbindung dargestellt durch die folgende Formel (II), (III), (VI), (VII) oder (VIII) oder ein pharmaceutisch verträgliches Salz davon und (b) ein Opioid umfasst:
wobei R\textsuperscript{7} Methyl, Ethyl, Propyl, Butyl oder 3-Methylbutyl oder eine beliebige dieser Gruppen mit Hydroxy substituiert darstellt; R\textsuperscript{8} Phenyl, Pyridyl, Pyrimidinyl oder 5,6-Dihydro-2H-pyridylmethyl oder eine beliebige dieser Gruppen substituiert mit 1 bis 3 Substituenten ausgewählt aus einem Chloratom, Methyl, Ethyl, Methoxy und Ethoxy darstellt; R\textsuperscript{9} Pyridyl oder Tetrahydropyranyl darstellt; und R\textsuperscript{12} Methyl, Ethyl, Propyl oder Butyl darstellt.

2. Das Arzneimittel gemäß Anspruch 1, wobei (a) eine Verbindung dargestellt durch die folgende Formel (IIA), (IIIA), (IIIB), (IIIC), (VIA), (VII) oder (VIII) oder ein pharmazeutisch verträgliches Salz davon ist:
3. Das Arzneimittel gemäß Anspruch 1, wobei (a) eine Verbindung dargestellt durch die folgende Formel (IIIC) oder ein pharmazeutisch verträgliches Salz davon ist:


5. Das Arzneimittel gemäß einem der Ansprüche 1 bis 3, wobei das Opioid Morphin ist.

6. Das Arzneimittel gemäß einem der Ansprüche 1 bis 5 in Form eines Kits.

7. Verwendung einer Verbindung, welche eine Adenosin-A2A-Rezeptorantagonisten-Aktivität aufweist oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Medikaments, welches eine unerwünschte Wirkung eines Opioids unterdrückt, wobei die unerwünschte Wirkung Analgetikatoleranz ist, und die Adenosin-A2A-Rezeptorantagonisten-Aktivität aufweisende Verbindung eine Verbindung dargestellt durch die folgende Formel (I), (II), (III), (IV), (VI), (VII) oder (VIII) ist:
wobei $R_1$ ein Wasserstoffatom oder Methyl darstellt; $R_2$ und $R_3$ gleich oder verschieden sein können und jeweils Methyl, Ethyl, Propyl, Butyl oder Isopropyl darstellen; $R_4$, $R_5$ und $R_6$ gleich oder verschieden sein können und jeweils ein Wasserstoffatom, Methyl, Ethyl, Methoxy, Ethoxy, ein Fluoratom, ein Chloratom oder ein Bromatom darstellen; $R_7$ Methyl, Ethyl, Propyl, Butyl oder 3-Methylbutyl oder eine beliebige dieser Gruppen substituiert mit Hydroxy darstellt; $R_8$ Phenyl, Pyridyl, Pyrimidinyl oder 5,6-Dihydro-2H-pyridylmethyl oder eine beliebige dieser Gruppen substituiert mit 1 bis 3 Substituenten ausgewählt aus einem Chloratom, Methyl, Ethyl, Methoxy und Ethoxy darstellt; $R_9$ Pyridyl oder Tetrahydropyryl darstellt; $R_{10}$ und $R_{11}$ gleich oder verschieden sein können und jeweils ein Wasserstoffatom, ein Fluoratom oder 2-Methoxyethoxy darstellen; und $R_{12}$ Methyl, Ethyl, Propyl oder Butyl darstellt.

8. Die Verwendung gemäß Anspruch 7, wobei die Verbindung, welche eine Adenosin-A$_{2A}$-Rezeptorantagonisten-Aktivität aufweist, eine Verbindung dargestellt durch die folgende Formel (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII) oder (VIII) ist:
9. Die Verwendung gemäß Anspruch 7, wobei die Verbindung, welche eine Adenosin-A\(_{2A}\) Rezeptorantagonisten-Aktivität aufweist, eine Verbindung dargestellt durch die folgende Formel (IIIC) ist:

![Chemical Structure (IIIC)](image)

10. Die Verwendung gemäß einem der Ansprüche 7 bis 9, wobei das Opioid Morphin ist.

11. Eine Verbindung, welche eine Adenosin-A\(_{2A}\)-Rezeptorantagonisten-Aktivität aufweist oder ein pharmazeutisch verträgliches Salz davon zur Verwendung beim Unterdrücken einer unerwünschten Wirkung eines Opioids, wobei die unerwünschte Wirkung Analgetikatoleranz ist, und die Adenosin-A\(_{2A}\)-Rezeptorantagonisten-Aktivität aufweisende Verbindung eine Verbindung dargestellt durch die folgende Formel (I), (II), (III), (IV), (VI), (VII) oder (VIII) ist:

![Chemical Structures (I), (II), (III)](image)
wobei $R^1$ ein Wasserstoffatom oder Methyl darstellt; $R^2$ und $R^3$ gleich oder verschieden sein können und jeweils Methyl, Ethyl, Propyl, Butyl oder Isopropyl darstellen; $R^4$, $R^5$ und $R^6$ gleich oder verschieden sein können und jeweils ein Wasserstoffatom, Methyl, Ethyl, Methoxy, Ethoxy, ein Fluoratom, ein Chloratom oder ein Bromatom darstellen; $R^7$ Methyl, Ethyl, Propyl, Butyl oder 3-Methylbutyl oder eine beliebige dieser Gruppen substituiert mit Hydroxy darstellt; $R^8$ Phenyl, Pyridyl, Pyrimidinyl oder 5,6-Dihydro-2H-pyridylmethyl oder eine beliebige dieser Gruppen substituiert mit 1 bis 3 Substituenten ausgewählt aus einem Chloratom, Methyl, Ethyl, Methoxy und Ethoxy darstellt; $R^9$ Pyridyl oder Tetrahydropyryanyl darstellt; $R^{10}$ und $R^{11}$ gleich oder verschieden sein können und jeweils ein Wasserstoffatom, ein Fluoratom oder 2-Methoxyethoxy darstellen; und $R^{12}$ Methyl, Ethyl, Propyl oder Butyl darstellt.

12. Die Verbindung oder ein pharmazeutisch verträgliches Salz davon zur Verwendung gemäß Anspruch 11, wobei die Verbindung, welche eine Adenosin-$A_2A$-Rezeptorantagonisten-Aktivität aufweist, eine Verbindung dargestellt durch die folgende Formel (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII) oder (VIII) ist:
13. Die Verbindung oder ein pharmazeutisch verträgliches Salz davon zur Verwendung gemäß Anspruch 11, wobei die Verbindung, welche eine Adenosin-A₂A-Rezeptorantagonisten-Aktivität aufweist, eine Verbindung dargestellt durch die folgende Formel (IIIC) ist:

![Chemical structure](image)


15. Die Verbindung oder ein pharmazeutisch verträgliches Salz davon zur Verwendung gemäß einem der Ansprüche 11 bis 13, wobei das Opioid Morphin ist.

Revendications

1. Composition pharmaceutique qui comprend (a) un composé représenté par la formule (II), (III), (VI), (VII) ou (VIII) suivante ou l’un de ses sels pharmaceutiquement acceptables et (b) un opioide:
dans laquelle R⁷ représente un groupe méthyle, éthyle, propyle, butyle, ou 3-méthylbutyle, ou l’un quelconque de ces groupes substitué par un groupe hydroxy ; R⁸ représente un groupe phényle, pyridyle, pyrimidinyle, ou 5,6-dihydro-2H-pyridyl-méthyle, ou l’un quelconque de ces groupes substitué par 1 à 3 substituants sélectionnés parmi un atome de chlore, un groupe méthyle, éthyle, méthoxy, et éthoxy ; R⁹ représente un groupe pyridyle ou tétrahydropyranyle ; et R¹² représente un groupe méthyle, éthyle, propyle, ou butyle.

2. Composition pharmaceutique selon la revendication 1, dans laquelle (a) est un composé représenté par la formule (IIA), (IIIA), (IIIB), (IIIC), (VIA), (VII), ou (VIII) suivante ou l’un de ses sels pharmaceutiquement acceptables :
3. Composition pharmaceutique selon la revendication 1, dans laquelle (a) est un composé représenté par la formule (IIIC) suivante ou l’un de ses sels pharmaceutiquement acceptables :

![Chemical structure image](image)

4. Composition pharmaceutique selon l’une quelconque des revendications 1 à 3, dans laquelle l’opioïde est sélectionné dans le groupe constitué par aniléridine, opium, ampromide, allylprodine, alphaprodine, alfentanil, isométhadone, éthylméthylthiambutène, éthylmorphine, éthoheptazine, étazocine, endorphine, enképhaline, oxycodeine, oxyméridine, clonitazène, kétobémidone, cocaïne, codéine, cymophane, diamorphine, butyrate de dioxa-phényle, didézocine, dinorphine, dihydrocodeïne, dihydromorphine, dipipanone, diméthylthiambutène, diménoxadrol, diméhéptanol, sufentanil, tildine, dextromoramide, désomorphine, tramadol, narcéine, nalorphine, nalbuphène, nicomorphine, norlédorphine, norméthadone, normorphine, norpipanone, papavérétum, hydrocodone, hydroxyphénythidine, hydromorphine, peméridine, piritramide, fentanyl, phénazocine, phénaxodone, phénopéridine, phénomorphine, butorphanol, buprénorphine, propéridine, propoxyphène, prophéptazine, proméndol, héroïne, bézitramide, berylholméphine, pentazocine, myphine, méthadone, métopazocine, métopon, meptazinol, mélépéridine, morphine, lévallorphane, levophénalofentanil, lévorphanol, et rémifentanil.

5. Composition pharmaceutique selon l’une quelconque des revendications 1 à 3, dans laquelle l’opioïde est la morphine.

6. Composition pharmaceutique selon l’une quelconque des revendications 1 à 5, sous la forme d’un kit.

7. Utilisation d’un composé doté d’une activité antagoniste du récepteur A2A de l’adénosine ou de l’un de ses sels pharmaceutiquement acceptables pour la fabrication d’un suppresseur d’un effet indésirable d’un opioïde, l’effet indésirable étant la tolérance aux analgésiques, et le composé doté d’une activité antagoniste du récepteur A2A de l’adénosine étant un composé représenté par la formule (I), (II), (III), (IV), (VI), (VII) ou (VIII) suivante :

![Chemical structure images]
dans laquelle $R^1$ représente un atome d'hydrogène ou un groupe méthyle ; $R^2$ et $R^3$ peuvent être identiques ou différents, et chacun représente un groupe méthyle, éthyle, propyle, butyle, ou isopropyle ; $R^4$, $R^5$, et $R^6$ peuvent être identiques ou différents, et chacun représente un atome d'hydrogène, un groupe méthyle, éthyle, méthoxy, éthoxy, un atome de fluor, un atome de chlorure, ou un atome de brome ; $R^7$ représente un groupe méthyle, éthyle, propyle, butyle, ou 3-méthyl-butyle, ou l'un quelconque de ces groupes substitué par un groupe hydroxy ; $R^8$ représente un groupe phényle, pyridyle, pyrimidinyle, ou 5,6-dihydro-2H-pyridylméthyle, ou l'un quelconque de ces groupes substitué par 1 à 3 substituants sélectionnés parmi un atome de chlorure, un groupe méthyle, éthyle, méthoxy, et éthoxy ; $R^9$ représente un groupe pyridyle ou tétrahydropyranyle ; $R^{10}$ et $R^{11}$ peuvent être identiques ou différents, et chacun représente un atome d'hydrogène, un atome de fluor, ou un groupe 2-méthoxyéthoxy ; et $R^{12}$ représente un groupe méthyle, éthyle, propyle, ou butyle.

8. Utilisation selon la revendication 7, dans laquelle le composé doté d'une activité antagoniste du récepteur $A_{2A}$ de l'adénosine est un composé représenté par la formule (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII) ou (VIII) suivante :
9. Utilisation selon la revendication 7, dans laquelle le composé doté d’une activité antagoniste du récepteur A$_{2A}$ de l’adénosine est un composé représenté par la formule (IIIC) suivante :

10. Utilisation selon l’une quelconque des revendications 7 à 9, dans laquelle l’opioïde est la morphine.

11. Composé doté d’une activité antagoniste du récepteur A$_{2A}$ de l’adénosine ou l’un de ses sels pharmaceutiquement acceptables pour son utilisation dans la suppression d’un effet indésirable d’un opioïde, l’effet indésirable étant la tolérance aux analgésiques, et le composé doté d’une activité antagoniste du récepteur A$_{2A}$ de l’adénosine étant un composé représenté par la formule (I), (II), (III), (IV), (VI), (VII) ou (VIII) suivante :
dans laquelle R1 représente un atome d’hydrogène ou un groupe méthyle ; R2 et R3 peuvent être identiques ou différents, et chacun représente un groupe méthyle, éthyle, propyle, butyle, ou isopropyle ; R4, R5, et R6 peuvent être identiques ou différents, et chacun représente un atome d’hydrogène, un groupe méthyle, éthyle, méthoxy, éthoxy, un atome de fluor, un atome de chlore, ou un atome de brome ; R7 représente un groupe méthyle, éthyle, propyle, butyle, ou 3-méthyl-butyle, ou l’un quelconque de ces groupes substitué par un groupe hydroxy ; R8 représente un groupe phényle, pyridyle, pyrimidinyle, ou 5,6-dihydro-2H-pyridylméthyle, ou l’un quelconque de ces groupes substitué par 1 à 3 substituants sélectionnés parmi un atome de chlore, un groupe méthyle, éthyle, méthoxy, et éthoxy ; R9 représente un groupe pyridyle ou tétrahydropyranyle ; R10 et R11 peuvent être identiques ou différents, et chacun représente un atome d’hydrogène, un atome de fluor, ou un groupe 2-méthoxyéthoxy ; et R12 représente un groupe méthyle, éthyle, propyle, ou butyle.

12. Composé ou l’un de ses sels pharmaceutiquement acceptables pour son utilisation selon la revendication 11, le composé doté d’une activité antagoniste du récepteur A2A de l’adénosine étant un composé représenté par la formule (IA), (IB), (IIA), (IIIA), (IIIB), (IIIC), (IVA), (VIA), (VII), ou (VIII) suivante :
13. Composé ou l'un de ses sels pharmaceutiquement acceptables pour son utilisation selon la revendication 11, le composé doté d'une activité antagoniste du récepteur A$_{2A}$ de l'adénosine étant un composé représenté par la formule (IIIC) suivante:

14. Composé ou l'un de ses sels pharmaceutiquement acceptables pour son utilisation selon l'une quelconque des revendications 11 à 13, l'opioïde étant sélectionné dans le groupe constitué par aniléridine, opium, ampromide, allylprodine, alphanptide, alfentanil, isométhadone, éthylméthylthiambutène, éthylmorphine, éthoheptazine, étonitazène, eptazocine, endorphine, enképhaline, oxycodone, oxymorpHEME, clonitazène, kétobémidone, cocaïne, codéine, cyromorphine, diamorphine, butyrate de dioxyphényle, didézocine, dinorphine, dihydrocodéine, dihydro-morphine, dipipanone, diméthylthiambutène, diméthoxadol, diméthepentanol, sufentanil, tilidine, dextromoramide, désomorphine, tramadol, narcéine, nalorphine, nalbuphène, nicomorphine, norfénfurphanol, norméthadone, normorphine, norpipanone, papavérétum, hydrocodone, hydroxypéthidine, hydromorphone, piminoïne, piritramide, fentanyl, phénazonine, phénadoxone, phénopéridine, phénomorphane, butorphanol, buprénorphine, propéridine, propoxyphène, propheptazine, promédoc, héroïne, bétamipidane, benzylmorphine, pentazocine, myrophine, méthadone, métopon, meptazinol, mépérindine, morphine, lévallorphane, levopéphénalofentanil, lévorfenthalphnorphine, et rémifentanil.

15. Composé ou l'un de ses sels pharmaceutiquement acceptables pour son utilisation selon l'une quelconque des
revendications 11 à 13, l'opioïde étant la morphine.
REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2006009698 A [0007]
- WO 2007047293 A [0007]
- WO 2007038212 A [0007]
- WO 2006059713 A [0007]
- WO 2005094885 A [0007]
- WO 01080893 A [0007]
- US 5587378 A [0021] [0092]
- WO 0017201 A [0007] [0021]
- WO 2005063743 A [0007] [0021] [0092]
- WO 2002055524 A [0007] [0021] [0092]
- WO 2003011864 A [0007] [0021] [0092]
- WO 2006032273 A [0007] [0021] [0092]
- WO 2002055083 A [0007] [0021] [0092]
- WO 9401114 A [0021]
- WO 2001092264 A [0021]
- WO WHO0017201 A [0092]

Non-patent literature cited in the description

- Proceedings of the National Academy of Sciences of the United States of America, 2006, vol. 103, 7877 [0008]
- Research Communications in Alcohol and Substance Abuse, 1997, vol. 18, 141 [0008]
- Neuroscience Letters, 2005, vol. 376, 102 [0008]
- Naunyn-Schmiedeberg's Archives of Pharmacology, 2003, vol. 368, 113 [0008]