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Terauchi et al.

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(54) **CYCLOPROPANE COMPOUND**

(75) Inventors: **Taro Terauchi**, Tsukuba (JP); **Ayumi Takemura**, Tsukuba (JP); **Takashi Doko**, Tokyo (JP); **Yu Yoshida**, Tsukuba (JP); **Toshiaki Tanaka**, Tsukuba (JP); **Keiichi Sorimachi**, Tsukuba (JP); **Yoshimitsu Naoe**, Tsukuba (JP); **Carsten Beuckmann**, Tsukuba (JP); **Yuji Kazuta**, Tsukuba (JP)

(73) Assignee: **Eisai R&D Management Co., Ltd.**, Tokyo (JP)

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(30) **Foreign Application Priority Data**

Sep. 22, 2010 (JP) 2010-211629

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A61K 31/505 (2006.01)

(52) **U.S. Cl.** **514/269**; 544/298

(58) **Field of Classification Search** 514/269; 544/298

See application file for complete search history.

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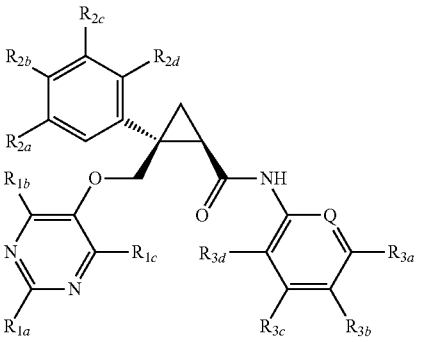
Primary Examiner — James O Wilson
Assistant Examiner — Alexander R Pagano
(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(57) **ABSTRACT**

A cyclopropane compound represented by the following formula (A) or a pharmaceutically acceptable salt thereof has orexin receptor antagonism, and therefore has a potencial of usefulness for the treatment of sleep disorder for which orexin receptor antagonism is effective, for example, insomnia:

(A)



wherein Q represents —CH— or a nitrogen atom, R_{1a} and R_{1b} each independently represent a C_{1-6} alkyl group and the like, R_{1c} represents a hydrogen atom and the like, R_{2a}, R_{2b}, R_{2c} and R_{2d} each independently represent a hydrogen atom, a halogen atom, a C_{1-6} alkyl group and the like, R_{3a}, R_{3b} and R_{3c} each independently represent a hydrogen atom, a halogen atom and the like, and R_{3d} represents a hydrogen atom and the like

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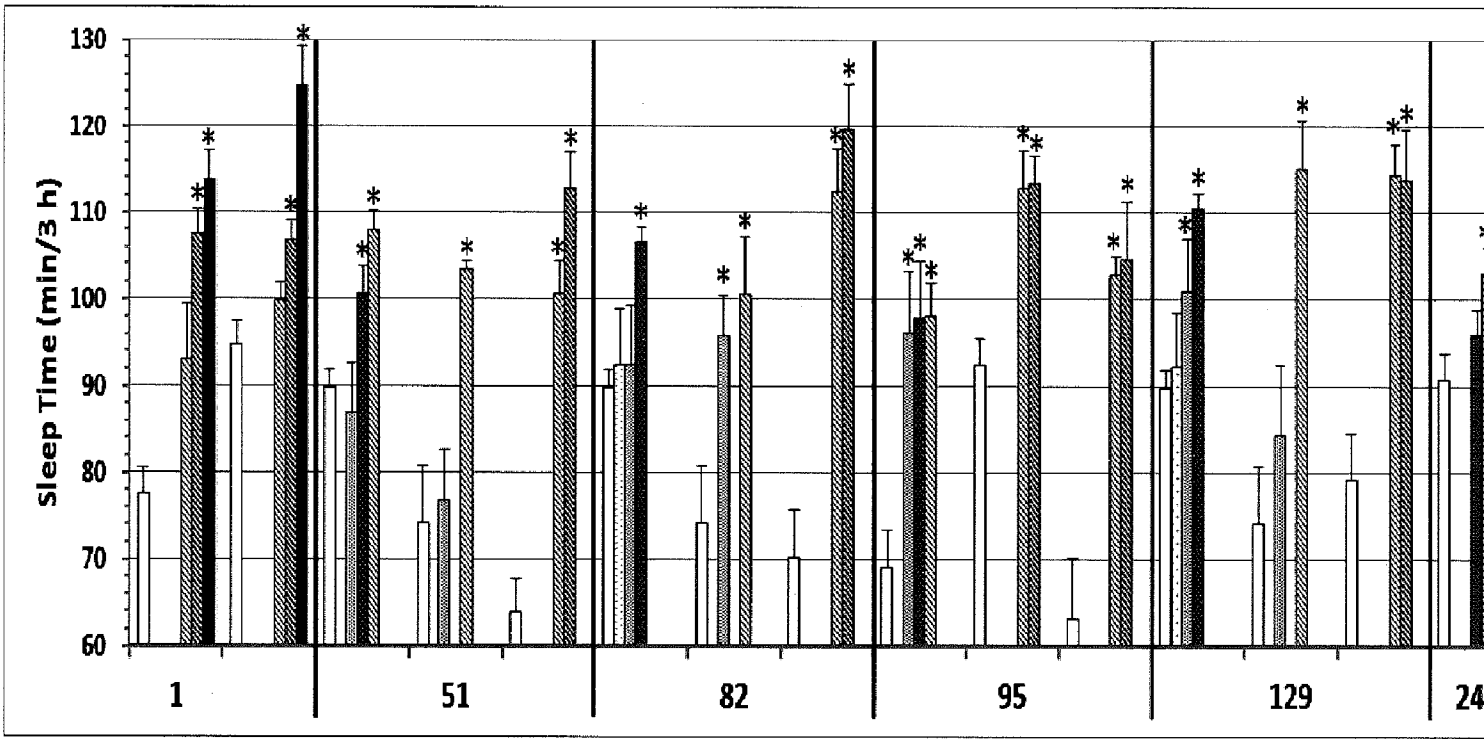

* : indicating significance compared to vehicle group (P <= 0.05).

CYCLOPROPANE COMPOUND

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims priority from U.S. Provisional Application No. 61/385,342 filed Sep. 22, 2010 and Japanese Patent Applicaton No. 2010-211629 filed Sep. 22, 2010, all of the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

(1) Field of the Invention

The present invention relates to a cyclopropane compound having orexin receptor antagonism or a pharmaceutically acceptable salt thereof, and a medicinal use thereof. The present invention also relates to a pharmaceutical composition comprising the above-mentioned compound as an active ingredient.

(2) Description of Related Art

Orexin-A (OX-A, consisting of 33 amino acid peptides) and orexin-B (OX-B, consisting of 28 amino acid peptides), two types of intracerebral neuropeptides, which are expressed by neurons localized at the hypothalamus in the brain, have been discovered (Patent Document 5 and Non-Patent Document 1) as endogenous ligands of G protein-coupled receptors mainly existing in the brain, namely, orexin receptors (Patent Documents 14). It has been known that such orexin receptors include two subtypes, namely, an OX_1 receptor (OX1) as a type 1 subtype and an OX_2 receptor (OX2) as a type 2 subtype. OX1 binds OX-A more selectively than OX-B, and OX2 is able to bind OX-A as well as OX-B. Orexin has been found to stimulate the food consumption of rats, and thus, it has been suggested that orexin would play a physiological role as a mediator in a central feedback mechanism for controlling feeding behavior (Non-Patent Document 1). On the other hand, it has been observed that orexins control sleep-wake conditions. Thus, it is considered that orexins will potentially lead to new therapies for narcolepsy, as well as for insomnia and other sleep disorders (Non-Patent Document 2). In addition, it has been suggested that orexin signals in the ventral tegmental area regarding neural plasticity associated with opioid dependence and nicotine dependence play an important role in vivo (Non Patent Document 3 and Non Patent Document 4). It has been also reported that OX2 receptor was selectively inhibited to alleviate ethanol dependence in experiment using rats (Non Patent Document 5). Moreover, it has been reported that corticotropin-releasing factor (CRF), whichinvolved in depression and anxiety disorder, is involved in orexin-induced behaviors in rats, and that orexin may play an important role in some stress reactions (Non Patent Document 6).

Orexin receptors are found in the mammalian brain and may have numerous implications in pathologies such as depression; dysphoria; anxiety; addictions, obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; eating disorders; sleep disorders; cardiovascular diseases, diabetes; appetite/taste disorders; vomiting/nausea; asthma; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyper-

gastric dyskinesia; gastric ulcers; Froehlich's syndrome; hypophysis diseases, hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep apnea; narcolepsy; insomnia; parasomnia; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-pontonigral degeneration epilepsy; seizure disorders and other diseases related to general orexin system dysfunction.

(2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide (ACT-078573; almorexant), a compound that functions as an orexin receptor antagonist, had been clinically developed as a therapeutic agent for insomnia (Patent Document 6). This compound causes a decrease in wakefulness in rats, which is characterized by decreased functions of awakening and spontaneous locomotor activity, and it dose-dependently increases both rapid eye movement (REM) sleep time and non-REM sleep time, and this compound, when administered to normal humans, exhibits dose-dependently a reduction of sleep latency, sleep efficacy and extension of total sleep time (Non Patent Document 7). Thereis is also an article reporting that the compound, when administered to patients with insomnia, exhibits improvement of sleep efficacy, shortness of sleep latency, increase of REM sleep and improvement of REM sleep ratio (Non Patent Document 8). Furthermore, it has also been described that this compound improves the memory function of model rats (Patent Document 7), and that the compound is effective for posttraumatic stress disorder (Patent Document 8). On the other hand, 5-chloro-2-{(5R)-5-methyl-4-[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]-1,4-diazepan-1-yl}-1,3-benzoxazole (MK-4305; suvorexant, Patent Document 9) and MK-6096, which have dual orexin antagonisms against OX1 and OX2, have been clinically developed as a medicine for insomnia.

RELATED ART DOCUMENTS

Patent Documents

Patent Document 1: International Publication No. WO1996/34877

Patent Document 2: JP 10-327888 A

Patent Document 5: JP 10-229887 A

Patent Document 6: International Publication No. WO2005/118548

Patent Document 7: International Publication No. WO2007/105177

Patent Document 8: International Publication No. WO2009/047723

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Non Patent Document 4: C. J. Winrow et al., Neuropharmacology, 2010, 58, 185-194

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Non Patent Document 6: T. Ida et al., Biochemical and Biophysical Research Communications, 2000, 270, 318-323

Non Patent Document 7: F. Jenck et al., Nature Medicine 2007, 13, 150-155

Non Patent Document 8: G Dorffner et al., European Neuropsychopharmacology, Vol. 20, Supplement, 3, 2007, S252-S253

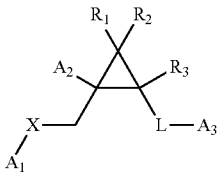
BRIEF SUMMARY OF THE INVENTION

It is an object of the present invention to provide a cyclopropane compound or a pharmaceutically acceptable salt thereof having orexin receptor antagonism, and a pharmaceutical composition comprising the same.

The present invention relates to the following [1] to [20]:

[1] A compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:

[Formula 1]



(I)

wherein

A_1 represents a pyrimidinyl group or a N-oxide pyrimidinyl group, each of which may optionally have substituents selected from Substituent Group α,

A_2 and A_3 each independently represent an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent Group α, or a heterocyclic group selected from group 3, which may optionally have 1 to 3 substituents selected from Substituent Group β,

R_1, R_2 and R_3 each independently represent a hydrogen atom, a halogen atom, a C_{1-6} alkyl group which may optionally have 1 to 3 substituents selected from Substituent Group β, or a C_{3-8} cycloalkyl group which may optionally have 1 to 3 substituents selected from Substituent Group β,

X represents an oxygen atom, a C_{1-6} alkylene group, a formula —NR_4— wherein R_4 represents a hydrogen atom or

Substituent Group a: a cyano group, a halogen atom, a hydroxyl group, an oxo group, a formula —NR_5R_6 wherein R_5 and R_6 each independently represent a hydrogen atom or a C_{1-6} alkyl group, a C_{1-6} alkyl group which may optionally have 1 to 3 substituents selected from Substituent Group β, a C_{1-6} alkoxy group which may optionally have 1 to 3 substituents selected from Substituent Group β, a C_{1-6} alkylcarbonyl group which may optionally have 1 to 3 substituents selected from Substituent Group β, a C_{1-6} alkylsulfonyl group which may optionally have 1 to 3 substituents selected from Substituent Group β, an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent Group β, and a heteroaryl group selected from Group 2, which may optionally have 1 to 3 substituents selected from Substituent Group β;

Substituent Group β: a cyano group, a halogen atom, a hydroxyl group, a C_{3-8} cycloalkyl group, and a C_{1-6} alkoxy group;

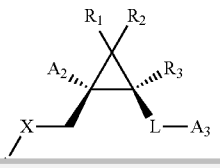
Group 1: a phenyl group, a naphthyl group, an azulenyl group, an anthryl group, and a phenanthryl group;

Group 2: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a triazinyl group, an indolyl group, an isoindolyl group, an indazolyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a quinolyl group, and an isoquinolyl group; and

Group 3: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a triazinyl group, a 2-pyridonyl group, a 4-pyridonyl group, a pyridazidonyl group, a pyrimididonyl group, a purinyl group, a pteridinyl group, a quinolyl group, an isoquinolyl group, a naphthylidyl group, a quinoxalyl group, a cinnolyl group, a quinazolyl group, a phthalazyl group, an imidazopyridyl group, an imidazothiazolyl group, an imidazoxazolyl group, a benzimidazolyl group, an indolyl group, an isoindolyl group, an indazolyl group, a pyrrolopyridyl group, a thienopyridyl group, a fluoropyridyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a pyridopyrimidinyl group, an oxodihydropyridopyrimidinyl group, a benzofuryl group, a benzothienyl group, a benzothiadiazolyl group, a benzo[1,3]dioxolyl group, a thienofuryl group, a dihydrousobenzofuranyl group, a chromanyl group, an isochromanyl group, a 1,3-dioxaindanyl group, a 1,4-dioxatetralinyl group, and a dihydrobenzo[1,4]oxazinyl group.

[2] The compound according to [1] above, which is represented by the following formula (II), or a pharmaceutically acceptable salt thereof:

[Formula 2]



(II)

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