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(54) **Title**: COMPOSITIONS AND METHODS FOR TREATING INSOMNIA

(57) **Abstract**: In the present invention, compound such as (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide have been found to be potent orexin receptor antagonists, and may be useful in

DESCRIPTION

COMPOSITIONS AND METHODS FOR TREATING INSOMNIA

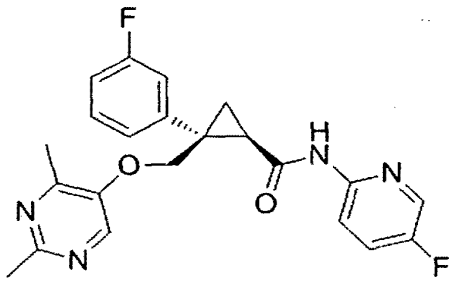
FIELD OF THE INVENTION

[0001] The present invention is directed to compositions and methods for treating insomnia. The present application claims priority on the basis of US Patent Application No. 62/067,443, filed in the United States on October 23, 2014, the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Orexin receptors are G-protein coupled receptors found predominately in the brain. Their endogenous ligands, orexin-A and orexin-B, are expressed by neurons localized in the hypothalamus. Orexin-A is a 33 amino acid peptide; orexin-B consists of 28 amino acids (Sakurai T. et al., Cell, 1998, 92 573-585). There are two subtypes of orexin receptors, orexin receptor 1 (hereinafter referred to as OX1) and orexin receptor 2 (hereinafter referred to as OX2); OX1 binds orexin-A preferentially, while OX2 binds both orexin-A and -B. Orexins stimulate food consumption in rats, and it has been suggested that orexin signaling could play a role in a central feedback mechanism for regulating feeding behavior (Sakurai et al., supra). It has also been observed that orexins control wake-sleep conditions (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Orexins may also play roles in brain changes associated with opioid and nicotine dependence (S.L. Borgland et al., Neuron, 2006, 49, 598-601; C.J. Winrow et al., Neuropharmacology, 2010, 58, 185-194), and ethanol dependence (J.R. Shoblock et al., Psychopharmacology, 2011, 215, 191-203). Orexins have additionally been suggested to play a role in some stress reactions (T. Ida et al., Biochem. Biophys. Res. Commun., 2000, 270, 318-323). Compound such as
(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide (hereinafter referred to as Compound A) have been found to be potent orexin receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.

[0003] The Formula of Compound A



[0004] Regarding the hypnotic agent, when an active pharmaceutical ingredient (hereinafter referred to as API) in a pharmaceutical formulation to be taken a once-a-night dosing is too high a dose, it has the potential to cause the next-day residual sleepiness, while the single insufficient dose may cause the patient to wake up during normal sleep period even if the patients are able to fall sleep with the hypnotic. Therefore, it is difficult to set the proper dose with considering the sensitive balance between easy of sleep onset and the avoidance of the residual sleepiness, as compared with the considering only the balance between side effects and efficacy. Furthermore, even if the dose of a certain drug for insomnia, the physiochemical properties of the API and the pharmacokinetic (hereinafter referred to as PK) profile after administration of the drug were known, such information would not be applicable to other APIs for insomnia because it would be likely effected by a number of factors, including the mechanism of action, the route of administration, the rate of absorption, the physiochemical property such as the solubility and the stability in plasma or other factors of each API. Indeed, the relationship between the residual sleepiness and the characteristics of the hypnotic agents is not always consistent (CNS Drugs 2004; 18 (5): 297-328). The relation between PK profile and the sleepiness effect such as the sleep onset or the residual sleepiness has been unknown yet for compound A.

[0005] There exists a need in the art for more effective methods of treating insomnia to achieve rapid sleep onset as well as sleep maintenance, throughout the sleep period, but avoid residual sleepiness and/or the next-day impairment, comprising administrating orally a solid dosage form of a hypnotic agent. Further, there exists a need in the art for a pharmaceutical composition comprising a hypnotic agent and at least one pharmaceutically acceptable excipient for the treatment of insomnia to achieve rapid sleep onset as well as sleep maintenance, throughout the sleep period, but avoid residual sleepiness and/or next-day impairment.

SUMMARY OF THE INVENTION

[0006] It is an object of the present invention to provide methods of treating insomnia comprising administrating orally a solid dosage form of the drug compound A.

[0007] It is further an object of the present invention to provide a pharmaceutical composition, comprising a therapeutically effective amount of compound A

[0008] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg.

[0009] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 2 mg to about 15 mg.

[0010] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 2 mg to about 10 mg.

[0011] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose chosen from about 2, 2.5, 4, 5, 8, 10, or 15 mg.

[0012] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose providing a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0013] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0014] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single dose achieves a mean

maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 5.3 ng/ml, after single dose administration to human subjects.

[0015] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 16 ng/ml, after single dose administration to human subjects.

[0016] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) of within the range of about 80% to about 125% of 23 ng/ml, after single dose administration to human subjects.

[0017] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 36 ng/ml, after single dose administration to human subjects.

[0018] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0019] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml, after single dose administration to human subjects.

[0020] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a

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