

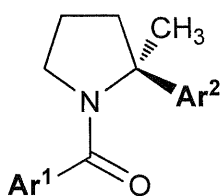
Neuronal afferences and efferences connect hypothalamic orexin neurons to brain areas involved in circadian rhythm regulation (receiving day-night signals) and in cortical activation (inducing and maintaining alertness); orexin neurons also receive afferent physiological and emotional inputs of limbic and metabolic origin. Activated orexin neurons thus regulate alertness for adapting the organism to environmental and circadian requirements and for accurate maintenance of homeostatic balance (Saper et al., Nature 437: 1257, 2005). The Ventro Lateral Pre-Optic area (VLPO) and the Supra-Chiasmatic Nucleus (SCN) are important brain clock regions that exert major inhibition on activity of orexin neurons during the nocturnal phase. It is hypothesized that abnormally hyperactive orexin neurons significantly contribute to cortical overdrive mediating hyperalertness at a given time point in the circadian cycle. Pathological orexin hyperactivity may result from deficient inhibitory input from VLPO and SCN that should start to gradually establish in late afternoon.

Caffeine administration increases orexin levels in rat brain. Caffeine may be used as a tool to experimentally simulate deficient inhibitory VLPO-SCN input to hypothalamic orexin neurons. The pharmacological action of caffeine, an adenosine A1 and A2A receptor antagonist, is to block adenosinergic inhibition exerted by adenosinergic neurons upon orexin neurons.

The orexin receptor antagonists of the present invention may reverse late-day agitation simulated in animals by afternoon caffeine administration. Electroencephalographic recordings confirm the behavioral symptoms of agitation which were reduced by two of the exemplified compounds when administered orally to rats and / or dogs.

Summary

In one aspect of the present disclosure, there is provided the use of a compound of the

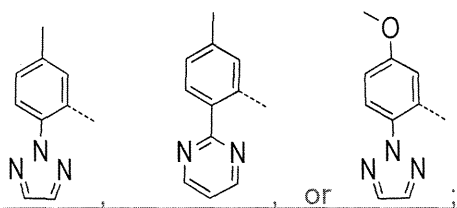


formula (I): **Ar¹** **Formula (I)**, or of a pharmaceutically acceptable salt thereof,

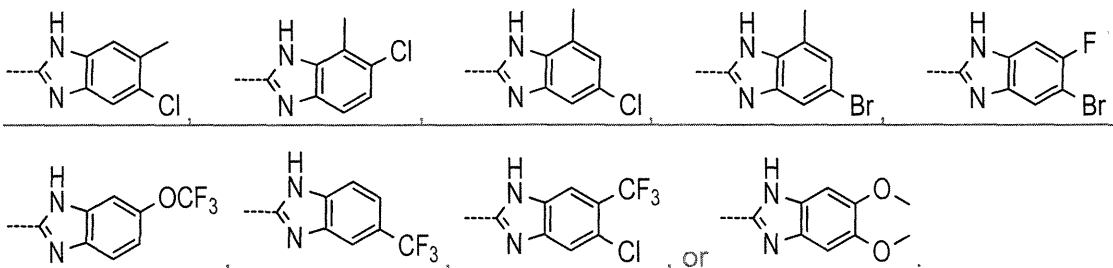
In the preparation of a medicament for the prevention or treatment of sundown syndrome;

wherein the compound of formula (I) is in absolute configuration (S);

Ar¹ represents



and Ar² represents



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Short description of the figures:

Figure 1 shows the effect of the compound of example 7 in a coffein-induced agitation model in the rat.

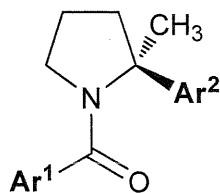
- 10 Figure 2 shows the effect of the compound of example 11 in a coffein-induced agitation model in the rat.

Figure 3 shows the effect of the compound of example 7 in a coffein-induced agitation model in the dog.

- 15 Orexin receptor antagonists comprising a 2-substituted saturated cyclic amide derivatives (such as 2-substituted pyrrolidine-1-carboxamides) are known for example from WO2008/020405, WO2008/038251, WO2008/081399, WO2008/087611, WO2008/117241, WO2008/139416, WO2009/004584, WO2009/016560, WO2009/016564, WO2009/040730, WO2009/104155, WO2010/004507, WO2010/038200, WO2001/096302, WO2002/044172, WO2002/089800, WO2002/090355, WO2003/002559, WO2003/032991, WO2003/041711, 20 WO2003/051368, WO2003/051873, WO2004/026866, WO2004/041791, WO2004/041807,

Claims

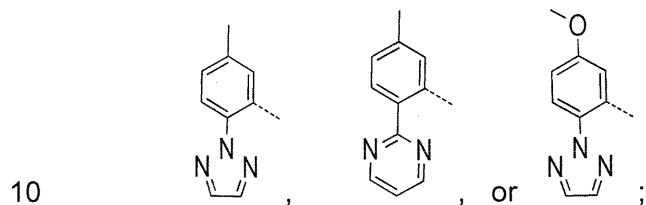
1. Use of Aa compound of the formula (I):

**Formula (I)**

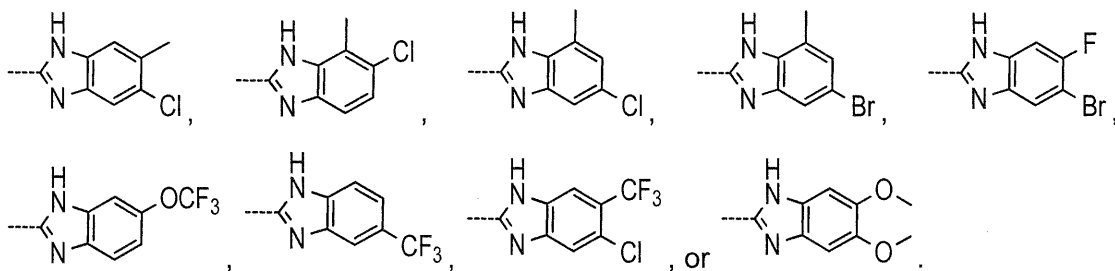
5 or of a pharmaceutically acceptable salt thereof,
for the preparation of a medicament ~~for use in~~ the prevention or treatment of sundown syndrome;

wherein the compound of formula (I) is in absolute configuration (S);

Ar¹ represents



and **Ar²** represents



15 2. The use ~~The compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use according to claim 1,~~ wherein the compound is:

[(S)-2-(5-Chloro-4-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-pyrimidin-2-yl-phenyl)-methanone;

[(S)-2-(5-Bromo-7-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

20 [(S)-2-(5-Bromo-7-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-pyrimidin-2-yl-phenyl)-methanone;

[(S)-2-(5-Chloro-4-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methoxy-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(S)-2-(6-Bromo-5-fluoro-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(S)-2-(5,6-Dimethoxy-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

5 [(S)-2-(5,6-Dimethoxy-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;

[(S)-2-(5,6-Dimethoxy-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methoxy-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

10 [(S)-2-(6-Chloro-5-trifluoromethyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(S)-2-methyl-2-(5-trifluoromethyl-1H-benzimidazol-2-yl)-pyrrolidin-1-yl]-methanone; or

(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(S)-2-methyl-2-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-pyrrolidin-1-yl]-methanone; or a pharmaceutically acceptable salt thereof.

15 **3.** ~~The compound use according to claim 1, or a pharmaceutically acceptable salt thereof, for use according to claim 1,~~ wherein the compound is:

[(S)-2-(5-Bromo-7-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methyl-2-pyrimidin-2-yl-phenyl)-methanone; or a pharmaceutically acceptable salt thereof.

20 **4.** ~~The compound use according to claim 1, or a pharmaceutically acceptable salt thereof, for use according to claim 1,~~ wherein the compound is:

[(S)-2-(5-Chloro-4-methyl-1H-benzimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methoxy-2-[1,2,3]triazol-2-yl-phenyl)-methanone; or a pharmaceutically acceptable salt thereof.

25 **5.** ~~The compound use according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use according to claim 1,~~ wherein the compound medicament is used for the prevention or treatment of sundown syndrome in a patient who has a dementia of Alzheimer's type.

6. ~~The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use according to claim 5,~~ wherein said patient has middle stage Alzheimer dementia.

30 **7.** ~~The use compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 4, 5, or 6;~~ wherein said sundown syndrome is afternoon sundown syndrome.

~~8. A compound as defined in to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for use in the prevention or treatment of sundown syndrome.~~

5 ~~9. A method to treat sundown syndrome; comprising administering to a patient in need thereof, the compound defined in any one of claims 1 to 4, in free or pharmaceutically acceptable salt form.~~

8. The use according to any one of claims 1 to 7, wherein what is treated is increased agitation.