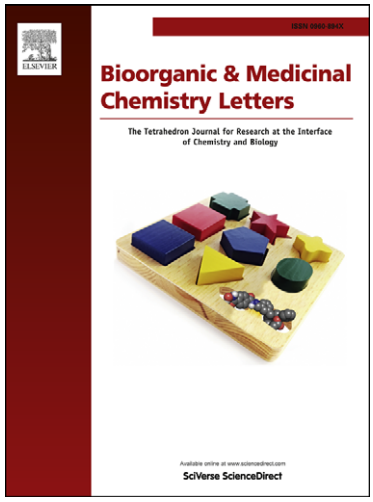

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Discovery, synthesis, selectivity modulation and DMPK characterization of 5-azaspiro[2.4]heptanes as potent orexin receptor antagonists.

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ABSTRACT

Starting from a orexin 1 receptor selective antagonist 4,4-disubstituted piperidine series a novel potent 5-azaspiro[2.4]heptane dual orexin 1 and orexin 2 receptor antagonist class has been discovered. SAR and Pharmacokinetic optimization of this series is herein disclosed. Lead compound **15** exhibits potent activity against orexin 1 and orexin 2 receptors along with low cytochrome P450 inhibition potential, good brain penetration and oral bioavailability in rats.

Orexins, also known as hypocretins, are hypothalamic neuropeptides secreted by a discrete number of neurons in the lateral and posterior hypothalamus. The orexin system is highly conserved across species and it is based on two hypothalamic peptides, orexin A (OXA) and orexin B (OXB), arising from a common 130 amino acids precursor protein named prepro-orexin peptide. Discovered in 1998 by independent research groups[1], the orexin peptides were found to bind at two previously identified orphan G-protein coupled receptors, which following this discovery were classified as orexin 1 (OX_1) and orexin 2 (OX_2) receptors. These receptors are widely distributed, though differentially, in the brain and periphery. In the central nervous system (CNS) OX_1 receptors are found mainly in the locus coeruleus, frontal cortex, ventral tegmental area and lateral hypothalamus while OX_2 receptors are mainly located into tuberomammillary nucleus[2,3,4]. Outside the central nervous system (CNS) orexin receptors are distributed in the gut, in adipose brown tissue and in pancreatic islets[5]. As shown in many studies, OXA binds with similar affinity to OX_1 and OX_2, whereas OXB displays higher affinity vs. OX_2. Neuronal OX_1 and OX_2 display a common signal transduction mechanism based on the activation of Gq proteins followed by the modulation of several ion channel activities to enhance synaptic transmission. Considerable evidences have been accumulated in literature regarding the utility of antagonizing the orexin receptors. Selective blockade of central OX_1 receptors has been reported to modulate addiction and craving to rewarding drugs such as alcohol, cocaine and morphine[6]. The modulation of binge eating episodes, induced by highly palatable food, has been recently observed in rats by using a centrally acting OX_1 antagonist[7]. Selective OX_1 receptor antagonists (SORA) also have been shown to be potentially useful in managing other disorders like

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