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Design and Synthesis of Orexin Receptor Selective Ligands

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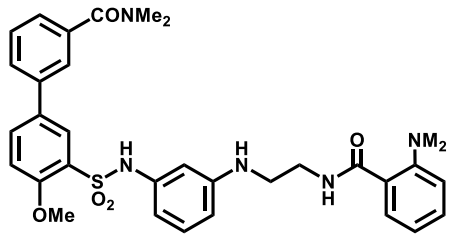
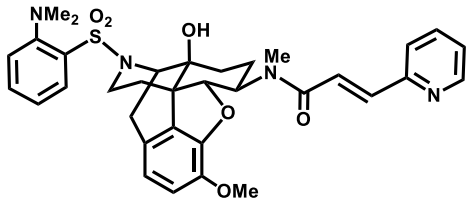
Orexin is a pair of lateral hypothalamic neuropeptides for orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R). An essential role of orexin system is regulation of sleep and wakefulness. Many researchers have attempted to develop non-peptide orexin antagonists to evaluate the role of orexin receptors (OXRs), especially focused on sleep indications. Many selective OX1R and OX2R antagonists have been reported. Quite recently, Merck released suvorexant in Japan and United State for insomnia. However, no orexin agonist has been reported until recently. In 2015, we reported the design and synthesis of the first non-peptide OX2R agonist, YNT-185 which showed potent and selective agonistic activity for OX2R (EC_{50} = 28 nM, OX1R/OX2R ratio = 100).[1] The icv and ip injection of YNT-185 increased wake time to 53 min and showed improvement of narcoleptic symptom in mouse narcolepsy model. Furthermore, we discovered the antagonistic activity of nalfurafine (κ opioid agonist) for OX1R (*K*i = 250 nM). The *K*i value was improved by the modification of the 3-hydroxy, 6-amide and 17-alkyl groups in nalfurafine to afford YNT-1310 (*K*i = 1.36 nM for OX1R, >10,000 nM for OX2R). YNT-1310 attenuated the physical dependence of morphine.[2]

We will report the design, synthesis and pharmacological effects of OX2R selective agonist YNT-185 and OX1R selective antagonist YNT-1310.



YNT-185



YNT-1310

References

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2) Nagase, H.; Yamamoto, N.; Yata, M.; Ohrui, S.; Okada, T.; Saitoh, T.; Kutsumura, N.; Nagumo, Y.; Irukayama-Tomobe, Y.; Ishikawa, Y.; Ogawa, Y.; Hirayama, S.; Kuroda, D.; Watanabe, Y.; Gouda, H.; Yanagisawa, M. *J. Med. Chem.* **2017**, *60*, 1018.