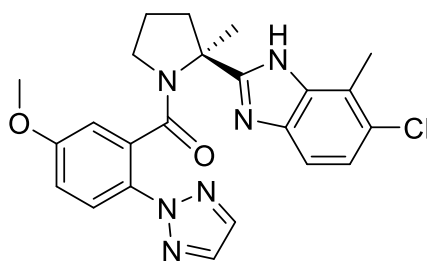


Discovery and Characterization of ACT-541468, an Orally Available, Brain Penetrant Dual Orexin Receptor Antagonist with Potent Sleep Promoting Properties

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The orexins are wake-promoting neuropeptides which bind to the two distinct and differentially expressed excitatory G protein coupled receptors (GPCRs), orexin receptor type 1 (OXR-1) and orexin receptor type 2 (OXR-2). [1] Blockade of both receptors reduces wakefulness in rats, dogs and humans. [2] This resulted in the development of dual orexin receptor antagonists as novel treatments for insomnia. The dual orexin receptor antagonist suvorexant was the first in class to be approved by the FDA in 2014 for the treatment of insomnia. [3]



ACT-541468

We will describe our efforts to identify a new potent dual orexin receptor antagonist with an appropriate PK profile for the treatment of insomnia and devoid of next day residual effects. The medicinal chemistry, starting from ACT-462206 [4] and culminating in the selection of ACT-541468 [5] will be detailed. Pharmacology and pharmacokinetics will be shown to explain the profile of ACT-541468 as a potentially optimal combination for the treatment of insomnia.

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