Thorsten Nowak et al., Med chem 2015, 5:10
http://dx.doi.org/10.4172/2161-0444.C1.015

OMICS International
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4th International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
November 02-04, 2015 Atlanta, USA

Discovery of novel orexin-1 selective antagonists using NMR guided conformational design

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Orexin-1 and orexin-2 are Class A GPCRs primarily found in the hypothalamus and locus coeruleus. These receptors have been linked to a range of different physiological functions, including the control of feeding, energy metabolism, modulation of neuroendocrine function, and regulation of the sleep-wake cycle. Importantly, they are also associated with dopaminergic neurons of the Ventral Tegmental Area (VTA) that are critical elements of the reward system. The presentation will detail the impact of a new NMR-enabled conformational design approach on the identification and optimization of novel highly selective orexin-1 antagonists which show significant *in vivo* activity. Moreover, it will be described how the detailed understanding of the experimentally determined conformational behavior of small molecule ligands when coupled with GPCR homology modeling and targeted mutagenesis (HGMP) provide novel insights into the likely pharmacophore as well as the origin of the exquisite selectivity of the described orexin-1 antagonists. The HGMP method has been developed by Evotec in conjunction with the Oxford University to support GPCR structure-based drug discovery programs.

Biography

Thorsten Nowak completed his PhD from the University of Cambridge (UK) in the areas of aldol methodology and natural product synthesis. In 1996, he joined AstraZeneca where he worked on all stages of drug discovery in medicinal chemistry as Team Leader and Project Manager. His keen interest in new technologies motivated a career move in 2012, when he joined C4X Discovery. Since he joined C4X, he has been instrumental in expanding the capabilities of C4X into applied drug discovery. In his current role as Head of Medicinal Chemistry, he is leading the chemistry group and is responsible for all internal drug discovery efforts conducted at C4X as well as program work with our pharmaceutical partners.

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