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The discovery and *in-vivo* profile of a potent and selective orexin-1 receptor antagonist

Thorsten Nowak and **Barrie Martin**
C4X Discovery Holdings PLC., UK

Highly selective Orexin-1 (OX1) antagonists have demonstrated pre-clinical proof of concept for ameliorating a range of "reward"-related disorders as well as alcohol and substance abuse. C4X utilized experimentally determined dynamic 3D-conformational analysis of a selection of literature known Ox1/Ox2 antagonists in guiding the definition of a sophisticated pharmacophore model. This model was validated against literature data and provided a firm geometrical description of the requirements for highly selective and potent OX1 antagonism, enabling the application of conformational design to de novo design potent and selective OX1 antagonist series. Moreover, the knowledge of structural features which influence the dynamic and conformational nature of the molecules provides additional powerful tools to address issues such as physical properties and metabolic liabilities. Thus facilitating the identification of a compound suitable for further *in-vivo* investigation. We will report how of the lead compound, following oral administration, attenuated OXA mediated grooming behavior in a dose dependant manner and how reversal of this pharmacological effect can be directly attributed to OX1 blockade through receptor occupancy studies.

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 joint AstraZeneca where he worked on all stages of drug discovery from target to candidate selection in medicinal chemistry as team leader and project manager. His keen interest in new technologies motivated a career move from big pharma to platform technology business in 2012 when he joint C4X Discovery. In his current role he is responsible for all internal drug discovery projects at C4X Discovery as well as continued development of the technology in the context of application to drug discovery.

thorsten.nowak@c4xdiscovery.com