

## **Conformetrix and its application to drug discovery**

*Thorsten Nowak*

C4X Discovery Ltd.

Manchester One, 53 Portland Street, Manchester M1 3LD

Understanding the conformational behaviour of small molecules in free solution, “Conformetrix<sup>1</sup>” and its relationship to biological activity is of fundamental importance to drug discovery. How the free ligand’s conformational envelope changes upon binding to its target to adopt the bound (bioactive) conformation is central to the compatibility of pharmacophoric feature between target and ligand, resulting in the the observed binding affinity. Rational manipulation of ligand conformations is crucial for optimal affinity and functional activity of drug molecules. Therefore conformational analysis in concert with elucidation of the molecular drivers that control conformational preferences are fundamental considerations if drug ligands are to be rationally designed.

This presentation describes/introduces a NMR based methodology that enables experimentally led conformational analysis independent of computational chemistry input. The relevance of the method to modern drug discovery is highlighted using working examples targeting the Orexin-1 receptor, Nrf-2 activation and inhibition of IL-17.

1) Blundell, C. D., Nowak, T., & Watson, M. J. (2016). Measurement, Interpretation and Use of Free Ligand Solution Conformations in Drug Discovery. *Progress in Medicinal Chemistry*, 55, 45–147.