Ligand NMR: a Tool for Rational Drug Design Highly Synergistic with Computational Chemistry and Crystallography Data

Thorsten Nowak
C4X Discovery, 53 Portland Street, Manchester, M1 3LD, UK
eMail: Thorsten.Nowak@C4XDiscovery.com

Drug design is greatly facilitated by the use of small molecule conformational data, which allows a detailed, mechanistic contextualisation of the binding interaction. While 3D-data for the target protein in both free and bound states is often accessible through X-ray crystallography, experimental 3D-data for the ligand in the unbound solution state is often harder to obtain at high resolution. Since the free ligand's 3D-shape is an integral part of the binding equation, it also provides crucial information for understanding and controlling the interaction. One technique that excels in providing this information is solution Nuclear Magnetic Resonance (NMR).

Solution NMR offers a highly versatile tool to access information on small molecules under physiologically relevant conditions. Free ligand conformational states in particular can be measured and often readily assessed for changes across a series by diagnostic spectral features that can be easily measured. Even small amounts of easy-to-measure ligand data can greatly aid *in silico* ligand conformational analysis and SAR interpretation. The availability of experimentally validated ligand conformational data greatly ameliorates docking and pharmacophore searching and provides opportunities for improving the accuracy of analysis, prediction and design. The use of quantitative ligand NMR data can be very useful to contextualise protein crystallographic information and the interpretation of molecular recognition events.

The presentation will demonstrate the use of ligand NMR 3D-data as a vital tool for rational drug design, highlighting its synergy with X-ray crystallography and computational modelling. Taking examples from the literature [1] in addition to ones from our in-house programmes, I will illustrate how solution NMR data from both routine and advanced methods [2] have been used to guide docking studies, the description of pharmacophore data and produce better compounds by rational design.

References:

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2. Blundell, C. D., Packer, M. J., & Almond, A. (2013). Quantification of free ligand conformational preferences by NMR and their relationship to the bioactive conformation. Bioorganic & Medicinal Chemistry, 21(17), 4987–4976.