C4XD solves Class B GPCR ligand solution-structure in one week

Structure provides new insights into binding mechanism and future design

Manchester, UK, August 20 2013 – C4X Discovery (C4XD), a leader in conformational drug discovery and design, has used its proprietary NMR-based technology to solve the dynamic solution-structure of a small molecule antagonist of the Class B GPCR corticotropin-releasing factor receptor (CRF-1R) in just seven days. The results add to the recent co-crystal structure of the same antagonist bound to CRF-1R, providing new insights into its binding properties and illustrating the invaluable role that C4XD's technology can play in rational drug design.

CRF is a critical hormone involved in the body's stress response and the recent publication of an X-ray co-crystal structure of a small molecule antagonist, CP-376395[1], bound to CRF-1R represents the first ever co-crystal structure of a Class B GPCR and a major scientific breakthrough[2]. Here, C4XD solved the free solution structure of CP-376395, revealing a dynamic 'ensemble' of conformations that the ligand occupies when not bound to the receptor. Amongst these, the most populated or 'dominant' conformations are highly predictive of the bound, or bioactive, conformation of CP-376395 observed in the co-crystal structure. These data explain CP-376395's high binding affinity and reveal new routes for design of CRF-1R antagonists.

This result is consistent with those generated by C4XD for a wide range of ligands (small molecule drugs, peptides, macrocycles and cofactors) that show that free solution-structures can be used to accurately predict the bioactive conformation. Moreover, by measuring the behaviour of ligands in solution, C4XD can understand the binding interaction in a way that is unavailable from the static, single-conformation view provided by X-ray co-crystallography. For targets that are not amenable to co-crystallography - which include many important GPCRs and ion channels - C4XD's technology provides a new means of driving the medicinal chemistry design cycle.

In the case of CP-376395, C4XD used the latest version of its proprietary analysis suite, MolGyrate, to solve the structure in seven days from delivery of the compound. C4XD is now routinely able to solve the structures of small molecule drugs in this timeframe and, for the second or third compound in a hit or lead series, one or two days. Its approach relies purely on experimental data generated from conventional NMR experimentation and is not based on either computational chemistry or molecular modelling. Full details on this and other case studies can be found on our **website**.

Dr Charles Blundell, CSO of C4X Discovery, said, 'These results demonstrate how our technology can be used to gain a full understanding of ligand behaviour and binding dynamics, thereby representing both a complementary and alternative method to X-ray co-crystallography for rational drug design.'

--ENDS—

[1] The molecule was originally reported by Pfizer. Chen, Y. L., Obach, R. S., Braselton, J., Corman, M. L., Forman, J., Freeman, J., Schulz, D. W. (2008). 2-aryloxy-4-alkylaminopyridines: discovery of novel corticotropin-releasing factor 1 antagonists. *Journal of medicinal chemistry*, ***51*** (5), 1385–92. doi:10.1021/jm070579c.

[2] Hollenstein, K., Kean, J., Bortolato, A., Cheng, R. K. Y., Doré, A. S., Jazayeri, A., Marshall, F. H. (2013). Structure of class B GPCR corticotropin-releasing factor receptor 1. *Nature*, ***499*** (7459), 438–43. doi:10.1038/nature12357.

For further information please contact:

C4X Discovery Ltd
Sam Williams, CEO +44 (0)7881 588947
Emma Palmer Foster, Strategic Communications Consultant +44 (0)7880 787185
communications@c4xdiscovery.com

About C4X Discovery Ltd

C4X Discovery is a Manchester-based company focused on optimising drug discovery and design. It was founded in 2008 as a spin-out from the University of Manchester. The company uses its NMR-based technology to solve the dynamic 3D structures of a broad range of biomolecules, including peptides, cofactors, oligonucleotides and carbohydrates. Since C4X Discovery's NMR technology shows what shapes active molecules prefer to adopt, it provides high-quality templates for drug discovery and design, and valuable information for drug candidate optimisation. In addition, the data is generated faster and more reliably than standard techniques such as X-ray co-crystallography or molecular modelling. C4X Discovery has solved ligand structures for large pharmaceutical companies, is developing proprietary drug programmes and has a strategic R&D collaboration with AstraZeneca signed in 2012. It has been funded since inception by life science investor Aquarius Equity Partners. www.c4xdiscovery.com.

About C4X Discovery's technology

C4X Discovery’s NMR technology determines accurate 3D structures of drug molecules in solution without the need for structural information for the target. These structures are predictive of the bioactive conformation and thereby provide researchers with valuable information on how to improve development-stage compounds. This new information should improve the efficiency and quality of the lead identification, lead optimisation and candidate selection stages of drug discovery programmes.