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Advanced in-house crystallography using the next generation D8 VENTURE

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Structure-based drug design (SBDD) organizations working on soluble protein targets continue to utilize and rely on in-house X-ray sources to generate structural information due to their convenience. However, membrane protein structural biology has remained almost exclusively reliant on synchrotron light sources. Diffraction data collection on-site can provide fast turnaround times to medicinal chemists, enabling key decisions to be made quickly and efficiently in real time.

Over 40% of prescription medications target G protein-coupled receptors (GPCR) a superfamily of protein receptors which are notoriously difficult to crystallize due to their instability when removed from the cell membrane, so remaining intractable to most SBDD platforms. The challenges are huge and yet so are the potential rewards. Heptares proprietary StaR® technology generates thermostabilized receptors containing a small number of point mutations, homogenous and in a natural pharmacologically relevant conformation (agonist or antagonist) that matches the drug product profile. These can then be readily crystallised in both classical vapour diffusion using harsh short-chain detergents and lipidic cubic phase (LCP) to drive SBDD even with weak early stage compounds / fragments.

Together, Heptares and Bruker have performed feasibility studies to asses if in-house sources have reached a level that would have a role in SBDD pipelines specifically dedicated to GPCRs. We find that Heptares StaR technology alongside Bruker's state-of-the-art instrumentation enables high resolution structures to be obtained in-house in a realistic timeframe using the D8 VENTURE. The D8 VENTURE x-ray diffractometer consists of state-of-the art technology; the METALJET source is the only source available that can deliver small, high intensity x-ray beams and is coupled with the newly launched PHOTON II CPAD detector.

Here, we present the results obtained using the combination of both technologies yielding a 2.8Å dataset for the human Orexin-1 StaR in under 120 minutes on the D8 VENTURE. To the best of our knowledge the structure represents the first atomic resolution GPCR structure to be determined without the use of synchrotron radiation. Human Orexin-1 has been strongly implicated in the treatment of cocaine addiction with potential broader applications in substance addictions (nicotine, alcohol) and compulsive disorders (binge eating, gambling).

Keywords: METALJET, D8 VENTURE, GPCR