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Heptares collaboration with AstraZeneca yields new insights to drug discovery

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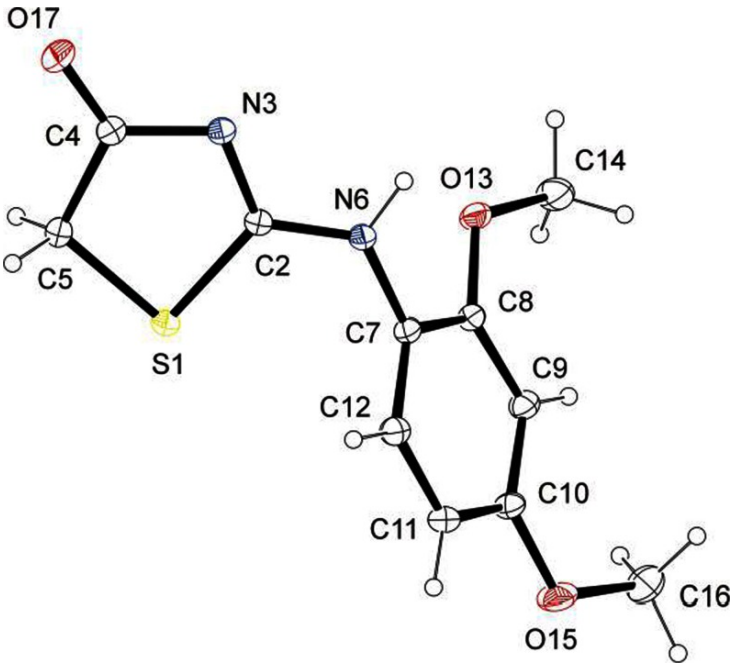

Heptares Therapeutics, the wholly-owned subsidiary of Sosei Group Corporation, described new insights for drug discovery from the first resolved high-resolution X-ray crystal structures of the Protease-Activated Receptor-2 (PAR2) in complex with antagonist molecules. The research reports on findings from PAR2 bound and inactivated by small molecule and antibody antagonists.

PAR2 is a G protein-coupled receptor (GPCR) that is a well-validated target for multiple indications in pain, cancer and inflammatory diseases, but which has previously proved to be intractable to conventional drug discovery approaches. PAR2 is an unusual GPCR that is activated by cleavage with a protease enzyme such that the cleaved part of the receptor acts as its own ligand. Because of this unusual mechanism of activation, it has been extremely difficult to identify PAR2 antagonists for development as new medicines.

The structures have provided Heptares and AstraZeneca with a unique understanding of the precise mechanisms of action of these antagonists, which bind at novel allosteric sites distant from the ligand-binding site. In turn, these structural insights are providing a basis for further development of the small molecule drug candidates for a range of therapeutic indications.

Access to the Heptares StaR technology enabled the team at AstraZeneca to progress available small molecule actives on PAR2 to credible lead series, where they earlier struggled to develop their chemistry.