Sebastiaan Kuhne

Design and synthesis of tool compounds to probe GPCRs

Many existing drugs exert their action via so-called G protein-coupled receptors (GPCRs). During his PhD research at Vrije Universiteit Amsterdam and the University of Copenhagen, Medicinal Chemist Sebastiaan Kuhne developed a variety of new '*tool compounds*' to probe various GPCRs on a molecular level.

At the University of Copenhagen, Kuhne and colleagues studied an orphan GPCR. After screening many compounds, they identified a first ligand that binds to the protein target. Subsequently, they synthesized series of related molecules (analogs) in order to reveal the first structural elements which were key for activity. The identified tool compounds represent a first important step in unravelling the role of this GPCR and to explore the possible clinical use of ligands that bind to this receptor.

At Vrije Universiteit Amsterdam, Sebastiaan Kuhne developed new tool compounds to study the histamine H_1 receptor, as part of the European IMI-K4DD program (Innovative Medicines Initiative – Kinetics for Drug Discovery). Although this GPCR has already been thoroughly investigated, and H1 receptor ligands are very successfully used as medicines, important molecular features such as ligand-receptor binding kinetics (e.g., residence time) are not yet understood. To this end, Sebastiaan Kuhne designed and synthesized series of tool compounds. The ligands were pharmacologically evaluated, revealing remarkable differences in binding kinetics of the compounds. The molecular features that govern binding kinetics were systematically investigated to come to a better understanding of this important property that has been shown to play an important role in the clinical efficacy of drug molecules.