The Impact of Synthetic Chemistry in Validating Novel Targets for Drug Discovery: The Histamine H_4 Receptor

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Among the various ways to "validate" new drug discovery targets, nothing beats having human clinical data on a potent, highly selective ligand for that target. Given that clinical data can be a long time in coming, a close runner-up is pharmacological data for a highly selective ligand in appropriate models. For many targets, such as G-protein coupled receptors (GPCRs), that ligand is almost assuredly a small molecule. Identifying potent small molecule leads, optimizing their pharmaceutical properties, and developing ways to make them on the appropriate scale, are just a few of the challenges facing synthetic chemists in drug discovery.

The histamine H_4 receptor is the newest member of the histamine receptor family and was disclosed by several laboratories in 2000-2001. Found primarily on eosinophils, mast cells, and dendritic cells, the histamine H_4 receptor is distinct from the other histamine receptors not only in sequence but also expression pattern.

In this presentation will be described the discovery of non-imidazole antagonists of the histamine H_4 receptor, how those initial leads were optimized as potential drug candidates, and the chemistry required to enable critical experiments. Key synthetic and medicinal chemistry questions will be addressed, and important pharmacological results that challenge the current dogma concerning the clinical utility of "anti-histamines" will be highlighted.