GPCR Library

ASINEX

G-Protein Coupled Receptors (GPCRs) have historically been the most successful of all the classes of drug targets in terms of creation of approved drugs. Even within this protein family, however, there remain substantial opportunities for further discovery. Particular examples of this are the lipid receptors, of which there are ~50 in humans. Whilst there are some marketed drugs targeti ng such receptors, including the leukotriene receptor antagonists (montelukast, zafirlukast, pranlukast) and various prostaglandins and prostaglandin analogues (dinoprostone, epoprostenol, alprostadil, travoprost, misoprostol, bimatoprost), the majority of the receptors are currently unexploited. The emerging importance of such targets is demonstrated by the recent regulatory approval of fingolimod for the treatment of Multiple Sclerosis and reports of the biological significance of numerous other receptors in a wide range of diseases.

Finding ligands for Lipid GPCRs remains a challenging area in Drug Discovery, possibly due to the importance of an acidic group in the pharmacophore for most targets and the relative shortage of such moieties in screening collections to date. Based on analysis of known hits, we have designed a library of natural product-like lipophilic molecules possessing a carboxylic acid group. Most of the molecules have 22 - 27 heavy atoms which is consistent with natural lipid GPCR binders. Such molecules are very rare in synthetic compound libraries available for screening, due to lack of synthetic methods which allow synthesis of large numbers of carboxylic acids.

Leveraging our efforts around the synthesis of trans-decalin related poly-oxygenated scaffolds, we have developed a library of non-nitrogenous compounds for screening at GPCR targets which have traditionally required basic compounds. In addition to the mu, kappa and delta opioid receptors, these include the various aminergic GPCRs such as serotonin, dopamine, histamine, adrenergic and muscarinic receptors and certain other peptide GPCRs including somatostatin receptors, the urotensin-II receptor (UT2R, GPR14) and the melanin-concentrating hormone receptors (MCHR1, MCHR2). Many of these receptors have well-established interest in diseases of the central and peripheral nervous system, although there are a number of additional possible non-CNS/PNS applications.