Allosteric GPCRs Library

We are delighted to offer a library of carefully selected compound sets as prospective allosteric GPCR modulators:
General Library comprises over **13,000** off-the-shelf available **compounds**
Pharmacophore based allosteric GPCR set: 6,200 compouunds
The library is a utile starting point for the drug discovery in the field of allosteric GPCR modulators

In spite of the proven success of GPCRs as drug targets, many intense efforts to develop orthosteric selective drug candidates for GPCRs have failed. Thus, numerous studies to discover selective *allosteric* GPCR modulators are of great interest in this area. The small molecule allosteric modulation of GPCRs can promote a conformational change in the receptor that often alone produces no noticeable downstream effects, but in the presence of an orthosteric ligand can significantly increase efficacy and have a strong impact on changing of signaling pathway. Another advantage is that undruggable GPCRs that are actuated by intractable stimuli can be modulated allosterically by synthetically accessible small molecules, opening a new opportunity to target unassailable. Two allosteric GPCRs modulators that have been introduced in the clinic (Cinacalcet and Maraviroc) are excellent evidence of prospects of investigation in this area. Additionally, benefit of development of such modulators is that allosteric site can be targeted with low molecular weight ligands that have high potential for oral bioavailability in contrast to structural features of most orthosteric ligands. Besides, allosteric sites are generally less conserved enabling development of actives with greater subtype selectivity than drugs targeting the conserved binding site.

Pharmacophore based Library was created using 3D Pharmacophore search to the reference set of known ligands with high activity values (>200 compounds from ChEMBL, Bindingdb). The main emphasis has been done on allosteric modulators of class B GPCRs that are well established in drug development. Two pharmacophore models were created basing on the reference compounds sets and then validated with the training sets of actives and non-active ligands. Finally, over 6,000 small molecules from Enamine MedChem subset (710 K) were included in the Library.

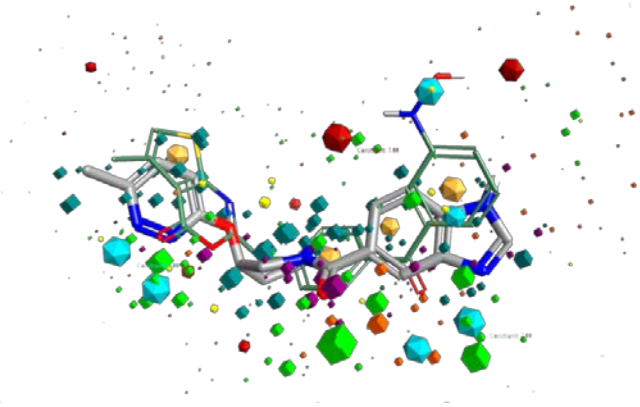
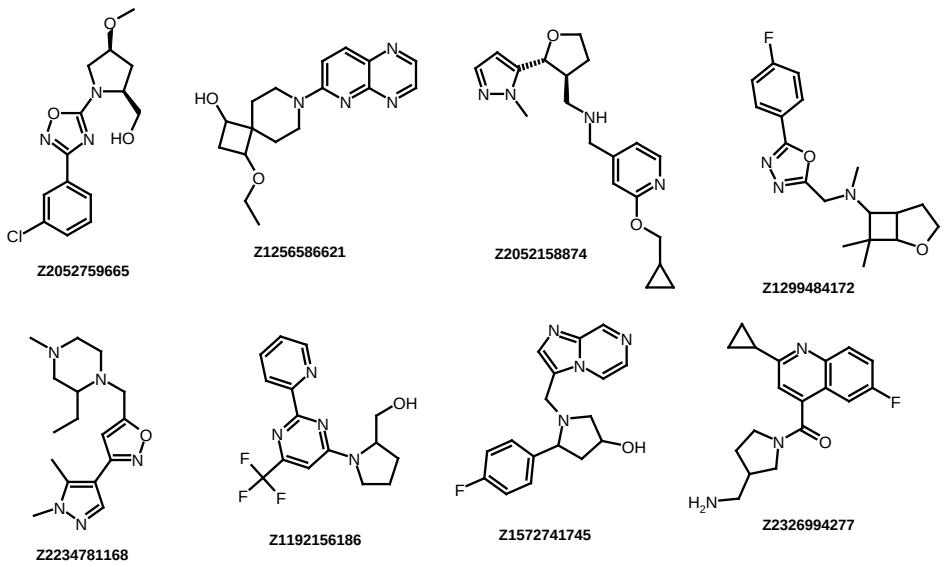


Fig. 1. Pharmacophore superposition of a reference active compound (carbons in green lines) and a hit compound from the Library (in stick representation).



Examples of the molecules from Pharmacophore based allosteric GPCR library

Targeted Sets of GPCR allosteric modulators

h-Glucagon receptor (GCGR) targeted set: 200 compounds
h-Corticotropin-releasing factor 1 receptor (CRF1R) targeted set: 7,200 compounds

The sets of small molecules were created using *in silico* screening against promising targets with reported structural data. The docking calculations were carried out on *h*-Glucagon receptor (GCGR) and *h*-Corticotropin-releasing factor 1 receptor (CRF1R) validated models. Corresponding protein structures recorded in 5EE7 and 4K5Y PDB entry were optimized and used for the docking calculation with Glide (Schrödinger software). Compounds with scores of at least 50% efficacy of the scoring results obtained for co-crystallized ligands were selected as hits and included in the targeted sets.

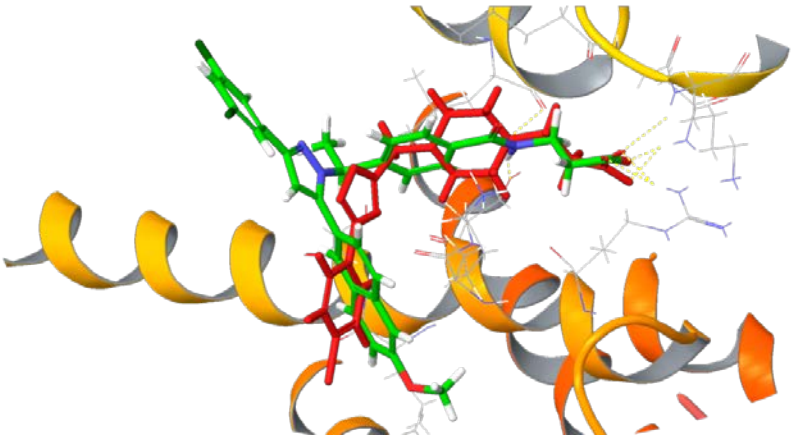


Fig. 3. Example of the binding mode of hit (in red) obtained from the docking and co-crystallized ligand (in green) of *h*-Glucagon receptor.

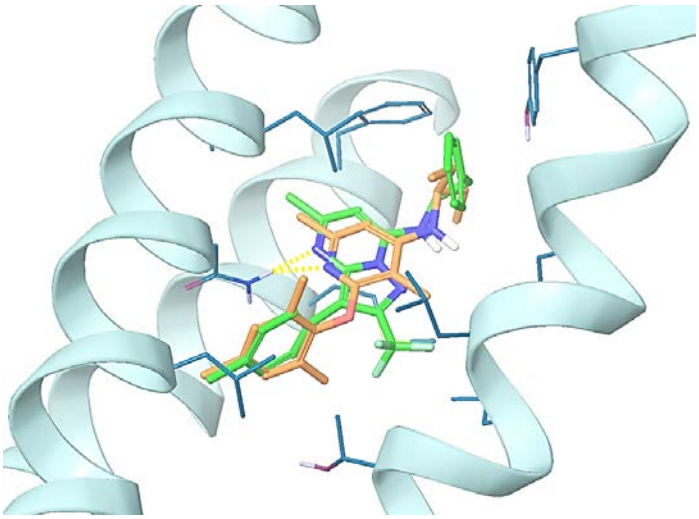


Fig. 3. Superposition of a hit (colored in green) compound and co-crystallized ligand CP-376395 (in orange stick representation) obtained after docking of CRF1R allosteric site with Enamine MedChem compounds subset.