In silico discovery of small molecule ligands with tailored affinity and efficacy profiles

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Small molecules are frequently used both in Nature and therapeutically to modulate the activity of the protein they bind to. This is attractive for altering protein activity in a time-resolved manner. It might seem straightforward to identify such ligands, either by their complementarity to a binding pocket on a protein surface or by similarity to already known ligands. Yet, there are 10^{60} small molecules to choose from (the "chemical space").

We have identified novel ligands with chemotypes unprecedented for the respective targets by docking to G protein-coupled receptors,[1-3] the pharmacologically most relevant protein family. Furthermore, we have attempted to open up new regions of chemical space for ligands of the β_2-adrenergic receptor by expanding experimentally determined fragment ligands, which led to affinity improvements and non-obvious extensions. I will also describe our strategy to make chemical space more accessible by calculating databases of easily synthesizable molecules, the current version of which is called SCUBIDOO[4]. By exploiting semi-automatic synthesis strategies of highly-designed libraries, we were able to obtain and optimize 141 new ligands for this highly investigated target in just a few weeks.

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