# Structure-based organic chemistry-driven ligand design from ultra-large chemical spaces

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Ultra-large chemical spaces describing several billion compounds are revolutionizing hit identification in early drug discovery. Because of their size, such chemical spaces cannot be fully enumerated and requires ad-hoc computational tools to navigate them and pick potentially interesting hits. We here propose a structure-based approach [1] to ultra-large chemical space screening in which commercial chemical reagents are first docked to the target of interest and then directly connected according to organic chemistry and topological rules, to enumerate drug-like compounds under three-dimensional constraints of the target. When applied to bespoke chemical spaces of different sizes and chemical complexity targeting two receptors of pharmaceutical interest, the computational method was able to quickly enumerate hits that were either known ligands (or very close analogs) of targeted receptors as well as chemically novel candidates that could be experimentally confirmed by in vitro binding assays. The proposed approach is generic, can be applied to any docking algorithm and requires few computational resources to prioritize easily synthesizable hits from giant chemical spaces up to a trillion synthesizable compounds.

Bibliography:

[1] F. Sindt; A. Seyller; M. Eguida; D. Rognan. ACS Cent. Sci. (2024) in revision.