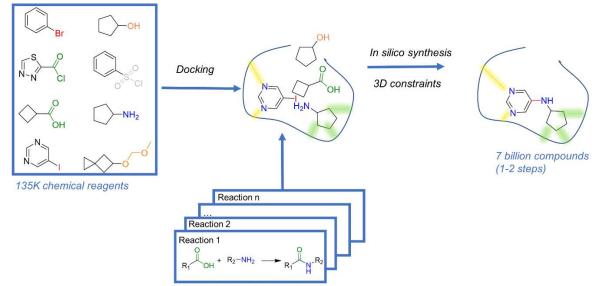# Protein structure-based organic chemistry-driven ligand design from billion-size chemical spaces.

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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 to ultra-large chemical space navigation in which commercial chemical reagents are first docked to the target of interest and then directly connected according to organic chemistry rules and topological constraints, 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 receptors of pharmaceutical interest, the computational method was able to quickly enumerate hits that were both known ligands or new chemical entities.