Protein Structure-Based Organic Chemistry-Driven Ligand Design from Ultralarge Chemical Spaces

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The chemically accessible space for synthesis is growing exponentially year after year. With the advent of "on-demand" chemical libraries, suppliers can now offer trillions of readily accessible molecules with a high synthesis success rate (e.g., Enamine xREAL Space, 4.4 trillion). With the continuous expansion of this chemical space, novel methods need to be developed to navigate in ultra-large chemical libraries while considering target 3D constraints.

We herewith introduce "SpaceDock" [1], a computational method designed to screen make-on-demand libraries in a structure-based manner. SpaceDock relies on docking to pose chemical reagents (~150 000) within a target binding site. Reagent pairs or triplets with compatible distances and orientations are directly assembled in the three-dimensional coordinates of the binding site to enumerate complete molecules, based on 43 robust one- or two-step organic chemistry reactions. This approach enables the exploration of a chemical space of 758 billion molecules, all being synthesizable with a success rate of ~ 80-85%.

The approach described above was first applied to the rapid identification of dopamine D3 receptor antagonists. It successfully retrieved close analogs and proposed new chemical entities with nanomolar potencies and a very high hit rate. The approach was further applied to a more challenging target, chitinase-3-like-1, a flexible protein involved in various cellular processes and overexpressed in several cancers. It successfully identified novel chemical structures, including one compound that inhibited tumor cell growth in a glioblastoma spheroid-based assay[2].

Bibliography :

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