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 billions of readily-accessible molecules with a high synthesis success rate (e.g., Enamine REAL Space, 48 billion). 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 a novel method (SpaceDock)[1] relying first on the accurate docking of carefully selected chemical reagents and then on a one-step or two-steps in silico synthesis of full ligands according to topological and chemical reactivity rules, affording the identification of potential hits from billion-sized chemical spaces with limited resources and computing time. The method scales non-linearly with the size of the chemical space and permits the construction of up to 6 billion easily synthesizable compounds from 170,000 chemical reagents and 40 rules of organic chemistry two-component reactions.

The above-described approach was applied to the fast structure-based identification of dopamine D3 receptor antagonists and was able to recover very close analogs as well as propose new chemical entities with nanomolar potencies at a very high hit rate.

Recently, the methodology has been expanded to include three-component reactions, allowing us to explore chemical spaces on a trillion-scale. By applying the SpaceDock methodology to the Petasis reaction,[2] we were able to rapidly prioritize candidate inhibitors of human EP300/CBP Histone acetyltransferase from a chemical space of 360 billion molecules.

Bibliography :

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[2] Petasis, N. A.; Akritopoulou, I. The boronic acid mannich reaction: A new method for the synthesis of geometrically pure allylamines. Tetrahedron Lett., **(1993)**, 34, 583–586.