[SC10] Frags2Drugs: Discovery of new kinase inhibitors from 3D fragment network

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Over the past twenty years, Fragment-Based Drug Design (FBDD) approach has been widely developed and used in academic laboratories and pharmaceutical companies[1]. Today, several drugs approved by the FDA or advanced in clinical trials were discovered from FBDD[2] as example, vemurafenib, a drug targeting the mutated protein kinase BRAF V600E, developed by Plexxikon and approved by the FDA in 2011[3].

Here, we present an innovative *in silico* FBDD tool, Frags2Drugs, which uses fragments to design new kinase inhibitors into the ATP binding site. Positions of the fragments within the cavity were extracted from co-crystallized ligands or obtained by molecular docking. Then, we calculate all the relations (excluded or linked) between these hundreds of thousands of fragments and store them in a graph-oriented database. That allows us to rapidly retrieve all possible connections between the fragments for a desired target and to use a network-based algorithm to build all possible molecules fitting this cavity. The first positioned fragment, the seed, is usually proposed by a medicinal chemist as the scaffold of interest. During automatic fragment growing, specific molecular filters are applied to create novel ligands with desired molecular properties. Using kinase inhibitors under development, we also developed an *in-house* kinase like filters[4] to retrieve most interesting molecules. Finally, each newly identified molecule is docked into the cavity to validate its conserved binding mode.

Frags2Drugs was recently applied successfully on several kinase targets (figure 1) such as BRAF and ABL and new kinase inhibitors were identified.

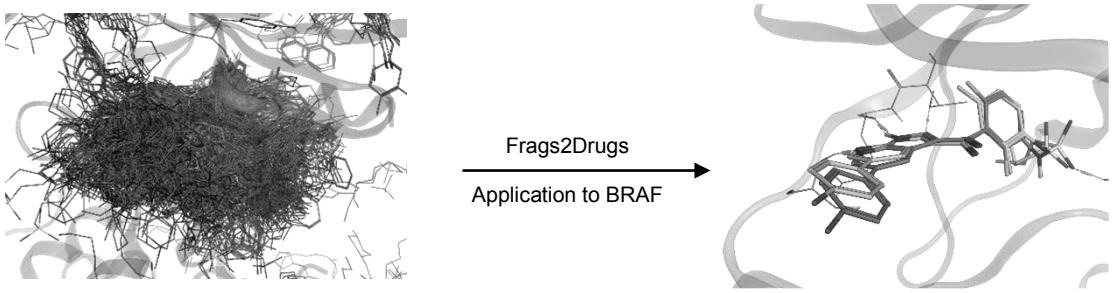

Figure 1: Validation of the Frag2Drugs tool by reconstructing existing inhibitors

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