Frags2Drugs: Discovery of kinase inhibitors from a fragment network

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Over the last 20 years, Fragment-Based Drug Design (FBDD) approach has been widely developed in academic laboratories and pharmaceutical companies [1]. Today, several drugs approved by the FDA or in advanced clinical trials have been discovered from FBDD. For instance, erdafitinib was developed by Janssen and Astex and approved by the FDA in 2019.

Fragments are molecules with low molecular weight (< 300 Da). Frags2Drugs (F2D) is an *in silico* FBDD tool based on a graph network built from more than 50,000 fragments and targets where they can be placed in. Fragments were extracted from co crystallized ligands. Relations between each of them are divided in two categories, inclusion or exclusion (Figure 1).

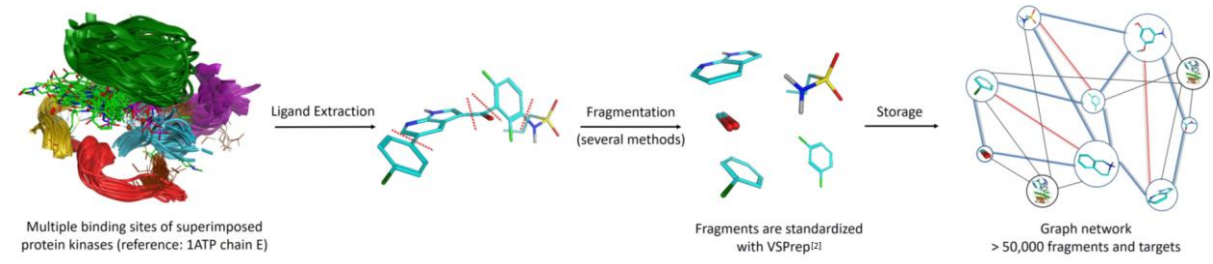

Figure 1: Simplified workflow of graph network creation from PDB structures.

Starting from a seed (the initial fragment), F2D will find all the connections with other fragments in given targets. The seed is chosen by a medicinal chemist as a molecular scaffold. The growing is achieved by linking two fragments if they respect certain distances and angles. At the end, in-house kinase-like filters, extracted from PKIDB (Protein Kinase Inhibitor Database) [3], are applied to the proposed molecules in order to target only the kinase chemical space.

F2D was successfully applied on several protein kinases implicated in cancer and neurodegenerative diseases. 6 molecules were synthesized for each of the 3 new chemical series. These new molecules were also evaluated experimentally and excellent kinase activity (nM range) and selectivity S(10)=0.011@1µM [4] (i.e. 1 kinase inhibited on a panel of 93) were obtained in vitro.

The database is now automatically updated and F2D was rewritten in order to speed up execution time.

In a near future, F2D will be applied on several projects to discover protein kinase inhibitors on untargeted protein kinases. A web interface is under development and will be available in our web platform (http://sbc.icoa.fr).

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