Fragment linking combined to graph-based approach in the discovery of novel kinase inhibitors

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Fragment-based ligand design has been widely used across both pharmaceutical industries and academic laboratories. Its use led to several drugs either in clinical trial or approved and its efficiency against different targets is now proven [1].

Here, we present the latest improvements of Frags2Drugs, a tool developed within the SB&C team at the ICOA, which aims at identifying novel potent and selective kinase inhibitors from fragments. How to transform crystallographic data into a large fragment-based network? How to quickly and efficiently link fragments together to design new compounds? These two questions will be answered in the presentation.

Frags2Drugs is able to build thousands of compounds from a large library of 3D fragments within the active site of the target. The protein kinase family is used as example, it represents a large protein family involved in various diseases such as cancer and many drugs targeting protein kinases were already approved [2-3]. Frags2Drugs was successfully applied on several kinases and original and selective Abl and B-Raf inhibitors with nanomolar activity were discovered.

Bibliography :

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