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Case Study – Computational Chemistry

Structure-based Design and discovery of a clinical candidate for a challenging CNS target

Introduction and Problem Description

A challenging, well-trodden CNS target was taken up by the computational chemistry team at Jubilant, for the discovery of a small molecule CNS drug candidate, in collaboration with *in house* structural biology and medicinal chemistry teams, monitored by an external partner. Creating novel IP, while maintaining CNS drug-like characteristics, and achieving the targeted potency were the main challenges facing the project.

Fragment-based Drug Design (FBDD) Approach

Fig. 1 shows the work flow adopted in a FBDD approach, for this project. Using this approach, a core fragment was initially identified, followed by co-crystal structure determination, additional design, synthesis, and testing in an iterative fashion.

These efforts resulted in two novel, low MW scaffolds amenable to lead development, which were designed to attain desired property profile for a CNS drug (low MW, Log P, CNS penetration, potency and selectivity).

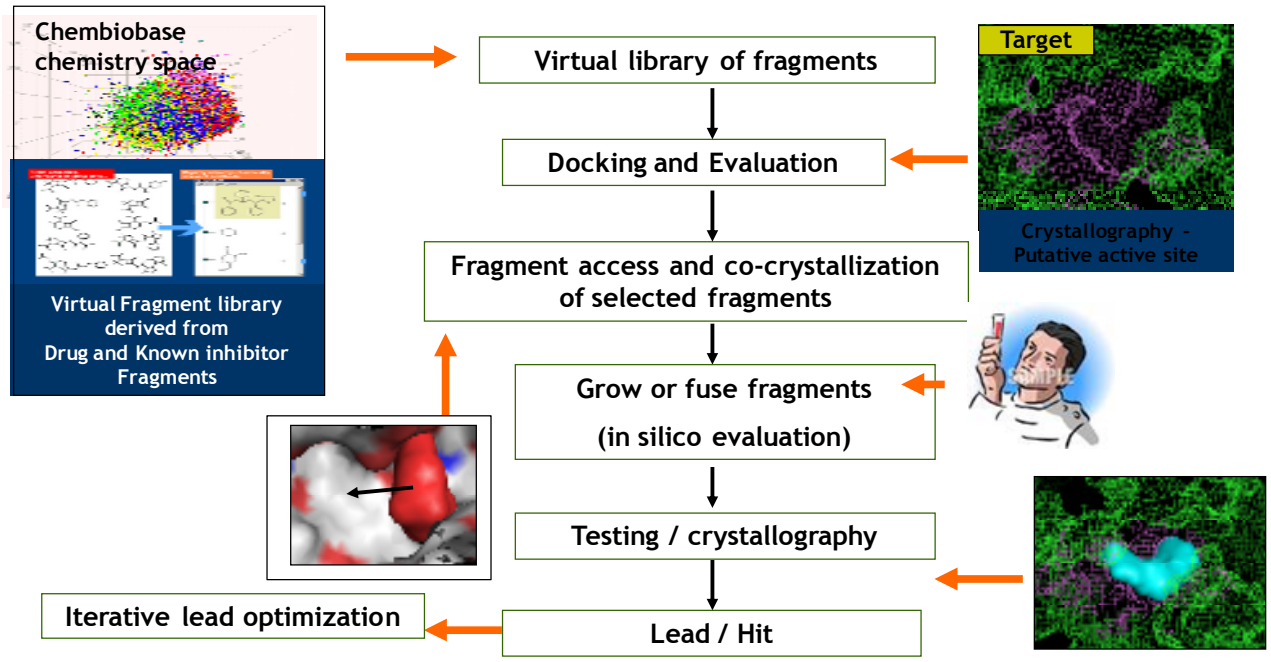

Fig. 1. Work flow of Fragment-based Drug Design (FBDD) Approach

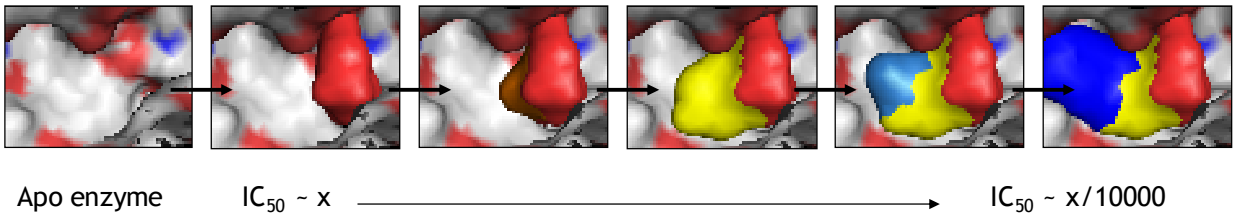

Fig. 2. Application of FBDD Paradigm: Active site is filled by sequentially added fragments, dramatically enhancing potency for the final molecule.

Design Solution

Fig. 2 shows the application of FBDD paradigm for obtaining a design solution. The active site pocket is filled by sequentially added fragments, each of which binds weakly, but the potency is

dramatically enhanced by joining carefully selected fragments satisfying property criteria set for the target. Designs focused on Lean efficiency, Clog P, MW and PSA in addition to potency.

Thus, starting from a weakly bound fragment, a highly potent, drug-like inhibitor series was designed, synthesized and delivered, in three iterations involving medicinal and computational chemistry, structural biology and biological testing. This is followed by successful identification of a compound with CNS drug-like characteristics, as a second generation clinical candidate.