From small molecules investigated as Factor XIIIa Inhibitors to biological target diversity

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Activated Factor XIIIa (FXIIIa) is a key enzyme in the final stage of the blood coagulation cascade. It catalyses the crosslinking of γ-glutamyl and ε-lysyl residues on adjacent fibrin strands and as a result the formed fibrin mesh becomes more stable and resistant to fibrinolytic degradation. While physiological hemostasis is essential to prevent bleeding, excessive or inappropriate clot formation can lead to vascular obstruction, and in some cases can cause life-threatening situations such as heart attack or stroke. Inhibition of FXIIIa represents an interesting anticoagulant strategy, as reduced fibrin crosslinking is expected to produce mechanically weaker clots that are more susceptible to fibrinolysis and also having lower risk of side-effect bleeding.[1] Despite reported FXIIIa inhibitors, to date, there is no medically approved drug specifically targeting this enzyme. The main focus of this study is on the computational identification and characterization of small-molecule compounds with peptide-mimicking structure as virtually active towards diverse biological targets, initially investigated for their inhibitory potential against FXIIIa (Figure 1). Structure-based molecular docking was combined with ligand-based target prediction approaches to evaluate reference and query drug sets against selected biological target.

Ligand-based target prediction tools were employed to investigate potential secondary biological targets and off-target activities based on chemical similarity principles. The investigated compounds are comprised of two sets: (i) a reference set of molecules with documented physicochemical and biological relevance, including the approved drugs **donepezil**, **safinamide**, **galantamine**, and the investigational drugs **NTZ-1091**, and (ii) a drug test set derived from novel scaffolds as well as previously synthesized and characterized by our group.[2, 3] Based on target prediction results obtained from target-prediction sources, additional docking experiments were performed against biologically relevant enzymes, including human monoamine oxidase A and B (MAO-A/B) as a starting point of our investigations. The identification of MAO as a potential secondary target (off-target) is supported further by literature evidence demonstrating that structurally optimized small molecules can achieve high potency and selectivity toward MAO-B. In particular, indazole-5-carboxamide inhibitors with slight modifications enhance MAO-B affinity, selectivity, and drug-like properties.[2, 3] These findings reinforce the applicability of structure and ligand-based target prediction approaches, having higher score rates when investigating structurally related analogues, and providing a good starting point for subsequent compound optimization and experimental validation.

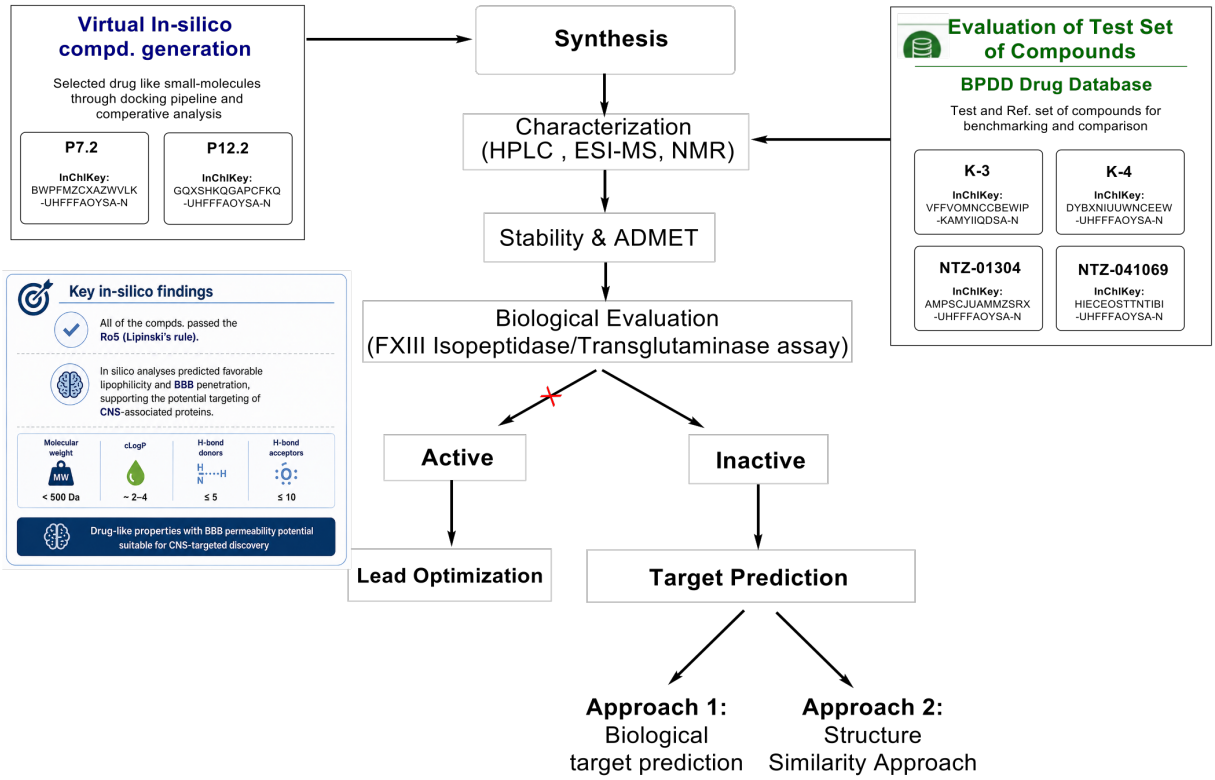


Figure 1. Workflow for generating small molecules as FXIIIa inhibitors and their further evaluation development as biologically active compounds.

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