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COMPUTER MODELING OF DIRECT FACTOR Xa INHIBITORS

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Introduction. The vast mortality proportion in the developed countries is caused by cardiovascular related diseases. Hence, biological investigations of blood coagulation cascade and inhibition of related key enzymes should be taken into consideration. Factor Xa (FXa) is the calcium-binding gamma carboxyglutamyl(Gla)-containing vitamin K-dependent glycoprotein, that is directly involved in inhibition of prothrombin conversion into the active thrombin, which provokes clot formation. Thus, FXa inhibitors could be used as potential active treatment for certain thrombotic disorders. Furthermore, it is important to search for direct inhibition compounds due to their more accurate and precise effect on target.

Methods. Structural compounds from ChEMBL (FXa inhibitors) were used in this research, previously filtered according to ADME requirements: molecular weight range (350-650), QlogP (0-6), rotation bonds (3-9), H-bond acceptor (0-10), H-bond donor (0-5). Of 2.5m Enamine compounds, filters have passed more than 1.75m. The structures were translated into a format suitable for docking.

A Schrodinger program was used to prepare binding site of the FXa from crystal structure (PDB entry 1KSN). Initially, all water molecules within 10 Å from the ligand were removed, missing atoms and chains were added and overall protein' structure was optimized and minimized. Docking was performed after posing four main constraints within S1 and S4.

This resulted in a library of approximately 3000 compounds, this sample went through a visual inspection. Selected series for each model were tested using a modified RVV test (RVVT) and inhibitor activity.

Results. Based on all aforementioned criteria, it was noticed that 59 substances reached 70% inhibitor activity. Further biological screening on purified FXa within selected compounds demonstrated activity ranging 40-60%. Seventeen selected compounds inhibited FXa by 60-100%, among which 2 demonstrated the highest activity.

Conclusions. As a result of our investigation we have obtained a virtually generated library of 1200 compounds, within which several revealed high active inhibitors of FXa could be applied as potential cures.

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