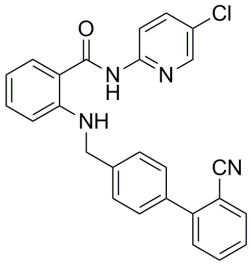
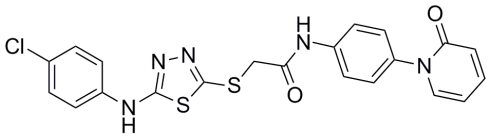
6. Conclusion

A total of twenty-eight 2-aminobenzamide derivatives having some novel S4 binding moieties such as alkyls, benzyls, biphenyls, and substituted piperazines were prepared and assessed to ascertain their effect on antithrombotic activity. Amongst the tested compounds, the benzyl substituted derivative (**71**) and the biphenyl derivatives (**104**, **105** and **107**) showed significant inhibition of the enzyme with IC_{50} values of 11.5 µM, 5.4 µM, 1.3 µM, and 0.7 µM respectively. The obtained results suggest that lipophilicity and aromaticity all alone do not play significant roles for good binding to the S4 pocket rather steric and electronic factors of the functional groups are responsible for higher binding affinity. Compound (**107**) is the 'best find' of the study offering a high selectivity for FXa over thrombin, with an IC_{50} value in the submicromolar range and causing a significant enhancement in the clotting time.



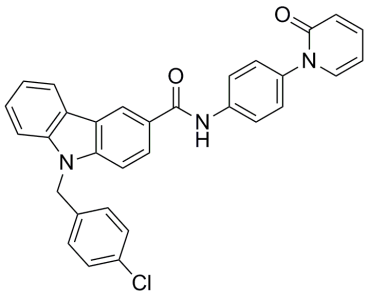
(107)



(237)

A multi-receptor based virtual screening approach was used for the identification of novel FXa inhibitors. Considering the activity observed for the lead compound (**158**), a novel 1,3,4-thiadiazole scaffold was used for the development of FXa inhibitors. Extensive modifications focusing on the P4 and P1 groups resulted in novel series of FXa inhibitors. Among these, compound (**237**) displayed potent FXa inhibitory activity with an IC_{50} value of 0.22 µM. Moreover, compound (**237**) exhibited good *in vitro* anticoagulant activity with its 2 × PT value of 25.9 µM and 2 × aPTT value of µM. Compound (**237**) displayed good *in vivo* antithrombotic activity in FeCl3 induced arterial thrombosis model (49 % and 32 % inhibition of thrombus formation at 30 mg/kg and 15 mg/kg in rats). These findings suggested that

compound (**237**) warrants further evaluation as a potential candidate for the development of antithrombotic agents.



(278)

A series of novel carbazole derivatives has been designed by incorporating monoaryls or biaryls as the S4 binding ligands and the chloroaromatic group as the S1 binding ligand in the carbazole scaffold. All the synthesized compounds were evaluated for *in vitro* FXa inhibitory and anticoagulant activities. Among these, Compound (**278**) showed the highest FXa inhibitory activity (IC_{50} value of 7.49 µM). Compound (**278**) also exhibited good anticoagulant activity with PT (39.4 sec) and aPTT (69.6 sec) time.