# 3. AIMS AND OBJECTIVES

Thromboembolic diseases involving the formation of blood clot in the veins or arteries of body are considered one of the major causes behind morbidity and mortality today and contributed in development of many cardiovascular ailments that impose a challenge to global healthcare because of total cost and intensive medical care involved. Rivaroxaban, apixaban and betrixaban are approved antithrombotic factor Xa inhibitors for the treatment of thrombosis related diseases while dabigatran is the only available orally acting direct thrombin inhibitor in the current market while few other thrombin inhibitors like heparin are given parenterally. All these drugs are associated with various drawbacks like bleeding tendencies, drug interactions, dose monitoring, low therapeutic indices hence which remain a challenge to antithrombotic therapies. Hence new antithrombotic agents with high efficacy and safety profile are urgent need of the time.

Factor Xa inhibitors have been developed from basic, nonselective to non-basic, highly selective, orally available potent small size antithrombotic agents. The chemical structures of these compounds have showed that these molecules are made up of mainly three units including central core scaffold and two hydrophobic P1 and P4 side chains that imparts a non-linear geometry required for suitable interactions with FXa enzyme. It has been reported that these compounds bind with FXa enzyme in L- or V-shaped conformation where P1 fragment is binding with S1 pocket and P4 motif with S4 pocket of the enzyme.

Numerous scaffolds have been explored for the development of selective FXa inhibitors. The recently US-FDA approved oral FXa inhibitor, betrixaban is reported to possess low bioavailability because of basic amidine P4 fragment present in it and also caused significant bleeding events. Therefore, we envisioned to modify the betrixaban molecule through structure-based design approach by replacing its amidine moiety with less basic piperazinyl moiety and reversing the connection order of carbonyl and amino groups of both P1 and P4 motifs present in its anthranilamide scaffold. Piperazinyl amides as P4 motif were successfully introduced in some FXa inhibitors in the past where they displayed excellent anti-FXa potency. Less basic piperazine moiety facilitates improvement in aqueous solubility and oral bioavailability.

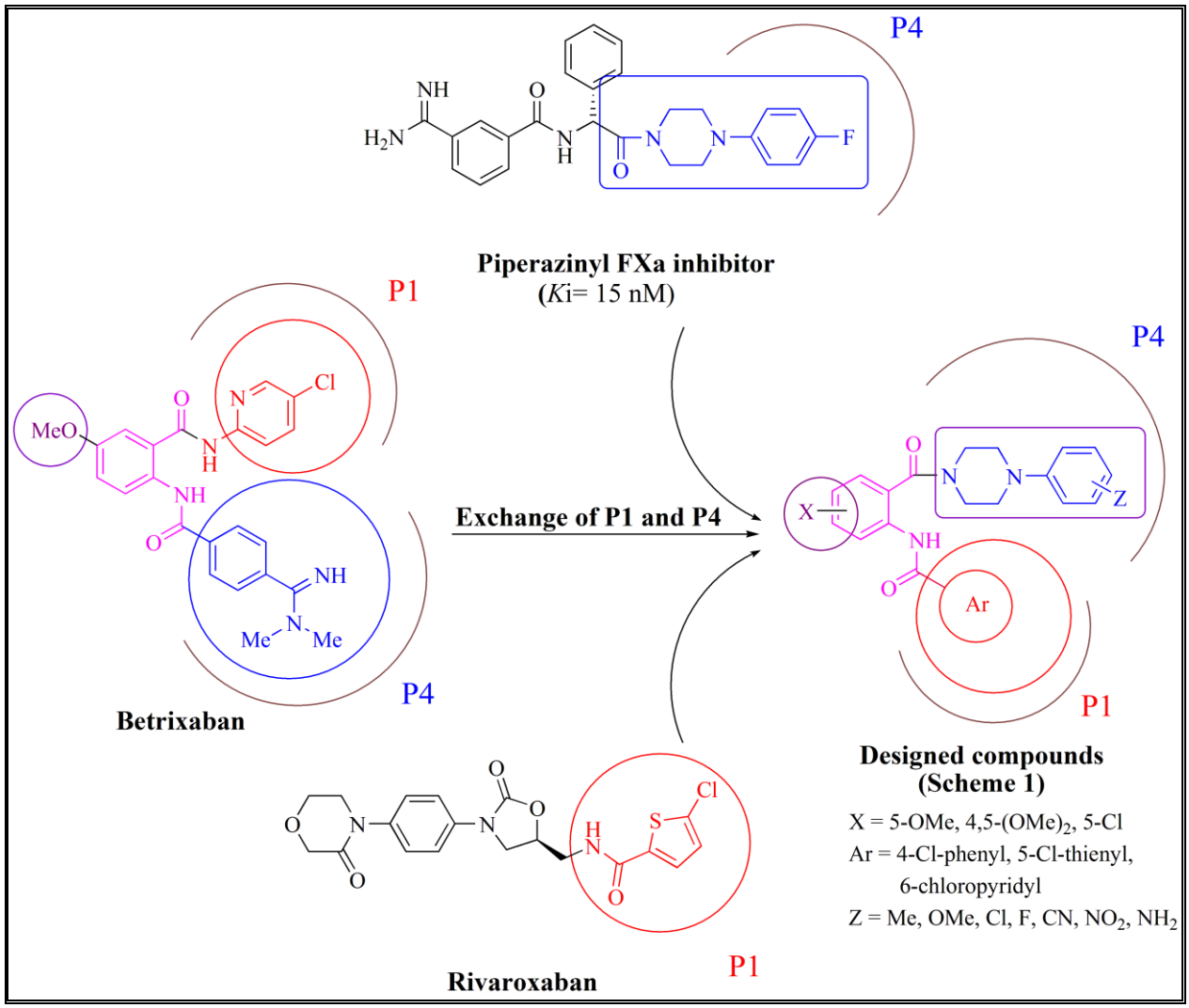


**Figure 3.1:** Designing of FXa inhibitory anthranilamide target compounds.

Different haloaromatic groups like 5-chlorothiophen-2-yl (rivaroxaban), 6-chloropyridin-3-yl (betrixaban isostere) and 4-chlorophenyl (eribaxaban) groups present in the reported FXa inhibitors have been employed to improve selectivity for the enzyme FXa. Taking these findings into consideration, a novel series of anthranilamide derivatives was designed (**Figure 3.1**) and where in piperazinyl amides as P4 fragment and different haloaromatic rings like 5-chlorothiophen-2-yl, 6-chloropyridin-3-yl and 4-chlorophenyl as P1 surrogates were used.

Direct thrombin inhibitors are an emerging class of antithrombotic drugs that can inhibit not only the thrombin but can also inhibit the activity of thrombin-mediated factors V, VIII, and XII, fibrinogen and platelets also they do not cause heparin-induced thrombocytopenia. In

addition, direct thrombin inhibitors can inhibit platelet aggregation and exert anti-inflammatory effects, suggesting broad application in the clinical treatment of thrombotic-related diseases.

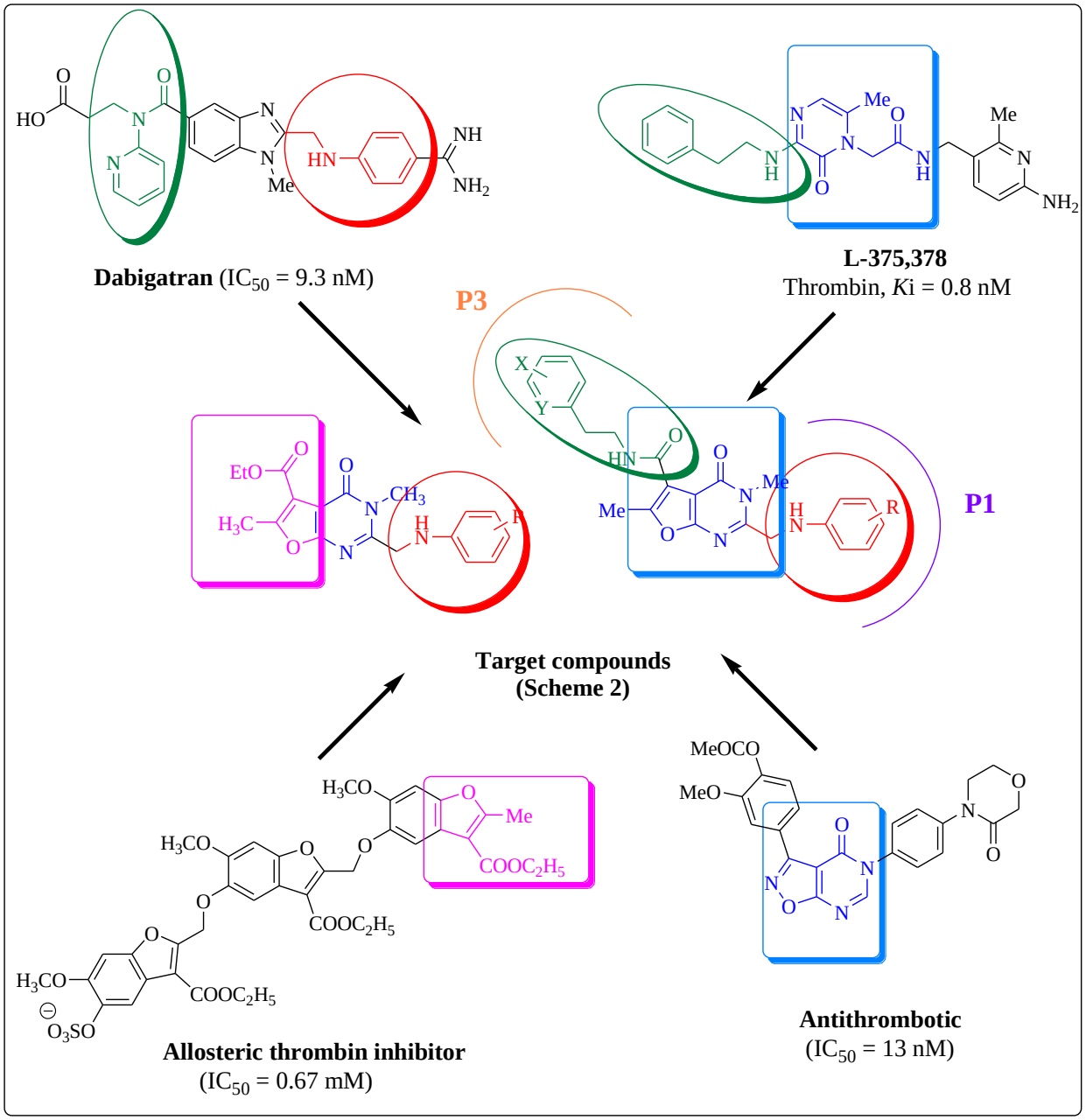


**Figure 3.2:** Designing of thrombin inhibitory furanopyrimidinone compounds

Several fused heterocycles like benzimidazoles, benzofurans, pyrazinones, pyrimidinones are explored as thrombin inhibitors. Benzofuran derivatives showed good allosteric inhibition of thrombin. Considering these reports, derivatives containing furanopyrimidinone as central

scaffold and S1 binding anilino side chains and S3 occupying ethylene linked aromatic fragments were designed to provide compounds having improved biological profile (**Figure 3.2**). Modifications on both P1 and P3 fragments were carried out to obtain novel compounds. Methyl substitution in central ring confers conformational stability and increases selectivity for thrombin over trypsin while ethylene bridge spacer also needed for thrombin inhibitor molecules to acquire S-or U-shaped binding conformation.