3. Aims and Objectives

Thrombosis is a leading contributor to global diseases like ischemic heart diseases, stroke, and venous thromboembolism (VTE). Conventional antithrombotic drugs have been reported to have several disadvantages and limitations like inconvenience in oral administration, bleeding risks (heparin analogs), narrow therapeutic window, and certain undesirable interactions with food and drugs (vitamin K antagonist-warfarin). The unmet medical demand for orally-active safe anticoagulant agents has generated widespread interest among the medicinal chemists in this field.

To prevent blood coagulation, various enzymes involved in the coagulation process have received great attention as potential targets by various research groups for the development of oral anticoagulants. Among these enzymes, factor Xa (FXa) has remained at the center of attention in the last two decades. Intensive research efforts have been made by various research groups for the development of small, safe, and orally bioavailable FXa inhibitors.

The active site of FXa is identified as S1 and S4 subsites and the surrounding residues. The S1 subsite is a narrow pocket formed by Trp215-Gly216 on one side of the wall and Ala190-Cys191-Gln192 on the other side. The bottom of S1 pocket is lined by Asp189 and the side chain of Tyr228. The S4 binding pocket is an aromatic box formed by the side chains of Tyr99, Phe174 and Trp215 (**Figure 3.1**).

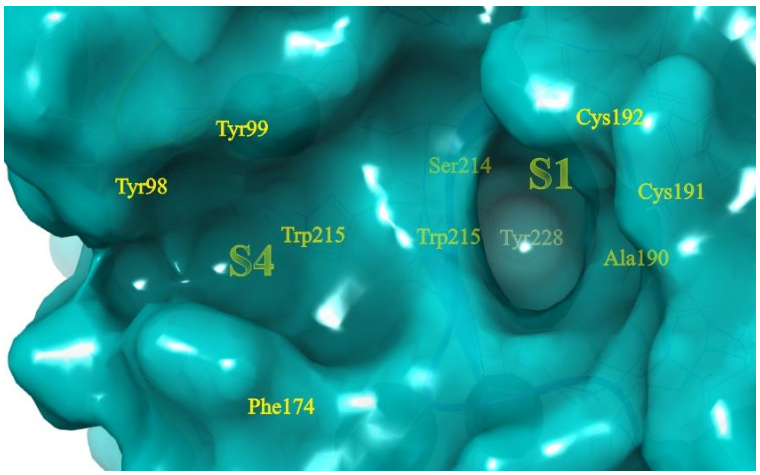

Figure 3.1. Active site of FXa enzyme.

The review of the literature reveals that for selective FXa inhibitory activity, the following structural features are required in any molecule:

- S1 subsite binding ligand
- S4 subsite binding ligand
- A basic scaffold (linker) that connects the S1 subsite binding ligand with the S4 subsite binding ligand and offers a final U or V shaped structure of the molecule that can be best accommodated into the active site.

So designing the ligands in such a way that they fulfill all the above-mentioned requirements was our primary goal. Synthesis of these designed ligands and biological evaluations were the other objectives of this work. It was decided to use three scaffolds 2-aminobenzamide, 1,3,4-thiadiazole, and carbazole to connect them to the two different hydrophobic arms (S1 binding ligand and S4 binding ligand) independently.

In 2-aminobenzamide series, it was contemplated to introduce alkyls, benzyls, biphenyls or substituted piperazines as S4 binding ligands in the anthranilamide scaffold as the replacements of highly basic amidine group of betrixaban (**10**) and maintain the 5-chloro-2-pyridyl group as such, as the S1 binding ligand, as represented in **Figure 3.2**.

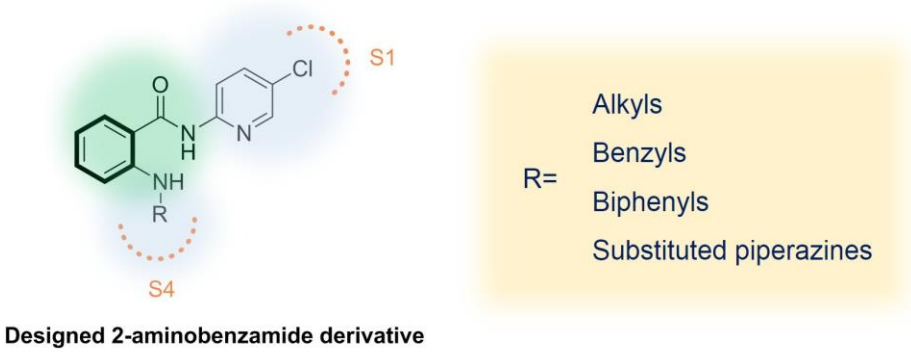

Figure 3.2. Designing of 2-aminobenzamide-based FXa inhibitors.

A multi-receptor based virtual screening approach was employed to identify 1,3,4-thiadiazole derivatives as novel FXa inhibitors. Substituted benzyls, biaryls, or amidoalkyls were incorporated as S4 binding ligands in the

novel 1,3,4-thiadiazole scaffold and maintain the chloroaromatic group as such, as the S1 binding ligand, as represented in **Figure 3.3 (Series 1-3)**. Further modifications were carried out to explore favorable P1 motifs with pyridinone as the optimal P4 substituent **(Series 4)**.

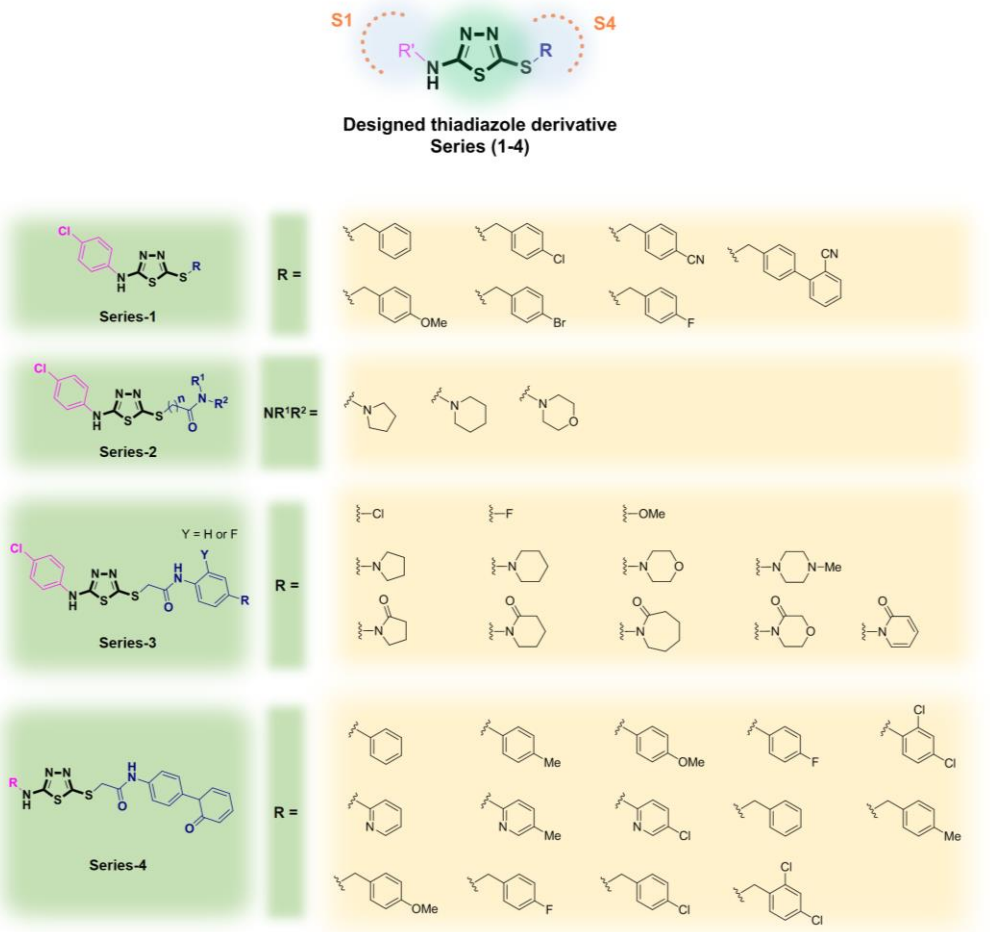

Figure 3.3. Structures of 1,3,4-thiadiazole compounds (**Series 1-4**).

Antiplatelet and anticoagulant activities of the carbazole derivatives suggested that a carbazole ring is an important privileged scaffold for the development of multitarget directed antithrombotic agents. Introduction of monoaryls or biaryls as S4 binding ligands in the carbazole scaffold and the chloroaromatic group as the S1 binding ligand resulted in a novel series of carbazole derivatives as FXa inhibitors (**Figure 3.4**).

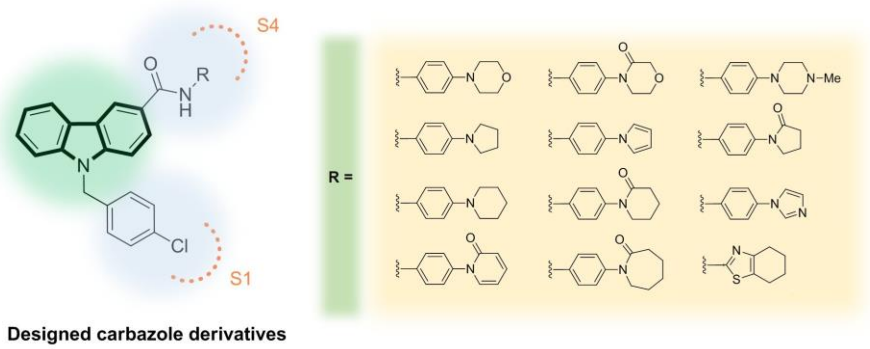

Figure 3.4. Structures of designed carbazole derivatives.