CHAPTER NINE

Case History: Eliquis™ (Apixaban), a Potent and Selective Inhibitor of Coagulation Factor Xa for the Prevention and Treatment of Thrombotic Diseases

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1. INTRODUCTION

Despite substantial advances in the prevention and treatment of cardio-

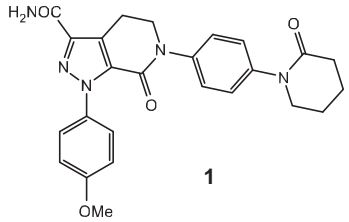

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Figure 9.1 Eliquis™ (Apixaban).

diseases involve multiple, complex mechanisms, a common component of the end stage of these diseases is thrombosis. Safe and effective antithrombotic drugs are therefore critical to effective treatment of cardiovascular diseases. Paradoxically, many patients who are at the highest risk for thromboembolic diseases, including the very elderly, are often less likely to be taking highly effective antithrombotic drugs due to risk of bleeding. Due to the large remaining unmet medical need, there has been intense activity to develop new antithrombotic therapies with improved efficacy and safety. In recent years, the strategy of targeting coagulation factor Xa (FXa) has received substantial clinical validation. Eliquis™ (Apixaban **1**, Fig. 9.1) is one of the first compounds acting by this mechanism to complete late-stage clinical studies and enter clinical practice. Along with other novel oral anticoagulants, it is poised to usher in a new era of antithrombotic therapy.

2. RATIONALE FOR TARGETING FXa

Vitamin K antagonists (VKAs), such as warfarin, are no longer the only available oral anticoagulants. Direct thrombin inhibitors, such as dabigatran etexilate, and FXa inhibitors, such as rivaroxaban and apixaban, have been developed and shown to be effective oral anticoagulants.[1–4] To date, there is no direct clinical evidence favoring one target over the other. However, there is some theoretical and preclinical evidence to support that the FXa mechanism may positively differentiate from thrombin as a preferred antithrombotic target.

First, as blood coagulation involves sequential steps of activation and amplification of coagulation proteins, generation of one molecule of FXa results

in vitro observation that inhibition of FXa produced a more effective sustained reduction of thrombus-associated procoagulant activity than inhibition of thrombin activity.[3] Second, inhibition of FXa is not thought to affect existing levels of thrombin and its activity. In addition, reversible FXa inhibitors might not completely suppress the production of thrombin. These small amounts of thrombin might be enough to activate high-affinity platelet thrombin receptors to preserve hemostasis. Early work from several laboratories provided experimental evidence from animal studies suggesting that the antithrombotic efficacy of FXa inhibitors is accompanied by a lower risk of bleeding when compared with thrombin inhibitors.[4–8] In summary, inhibition of FXa may represent an attractive approach compared with thrombin inhibition for effective and safe antithrombotic therapy. However, head-to-head clinical studies to validate this hypothesis have not been performed.

3. MEDICINAL CHEMISTRY EFFORTS CULMINATING IN APIXABAN

3.1. Factor Xa program objectives

As we believed that Factor Xa had the hallmarks of a target that would positively differentiate from anticoagulant standard of care, our discovery objective was to continuously deliver compounds until an optimal compound was in full development. This was driven by our strong belief that a high-quality factor Xa inhibitor would be transformational. The objective was to optimize for the right balance of efficacy and safety. The goal of the program was to identify potent, highly selective noncovalent FXa inhibitors with good oral bioavailability (> 20%) and a half-life suitable for either twice daily (BID) or once daily (QD) dosing with low peak/trough to minimize the potential for bleeding liabilities. *In vivo*, the compounds were required to demonstrate efficacy in preclinical thrombosis models. The ideal candidate would also not have drug–drug or food interactions, particularly given that these are issues with warfarin.

3.2. Early preclinical leads

When the medicinal chemistry program began in the mid-1990s, the only published FXa inhibitors were dibasic compounds which were not orally

the inhibitor with the S1 Asp189 residue, and a π-cation interaction between the hydrophobic residues in the S4 subsite and the remaining basic functionality.[10]

At the genesis of our program, homology models and the X-ray coordinates for the FXa dimer were used extensively to design a number of dibasic FXa inhibitors.[12,13] An initially designed compound, ketone **5**, though a weak inhibitor of FXa (K_i = 5100 nM) was rapidly improved to **6** (K_i = 34 nM), by the introduction of an ester group.[12] With the aid of molecular modeling, these compounds evolved into amidine-based benzimidazoles such as compound **7** (K_i = 140 nM, Fig. 9.3). The SAR was extended to include several additional scaffolds such as indole, indoline, and phenylpyrrolidine, all conferring improved FXa activity, albeit with poor selectivity over trypsin and no oral bioavailability.[13]

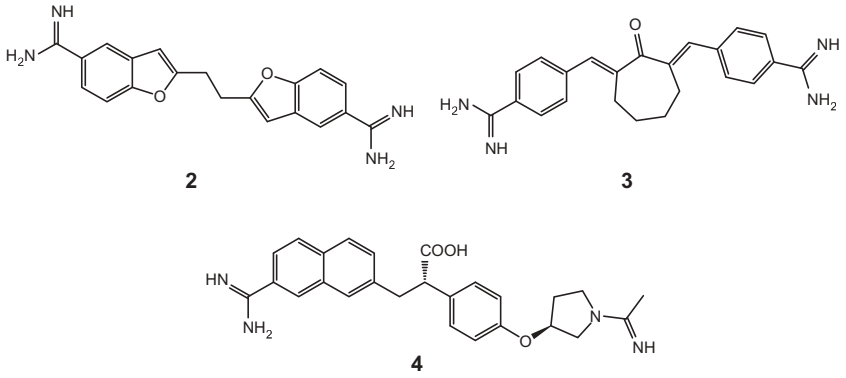
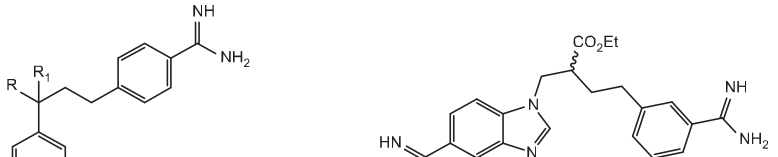


Figure 9.2 Published dibasic benzamidine FXa inhibitors.

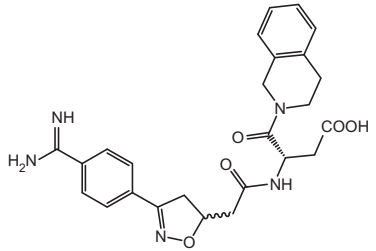


3.3. Screening library hits—The discovery of the isoxazoline scaffold

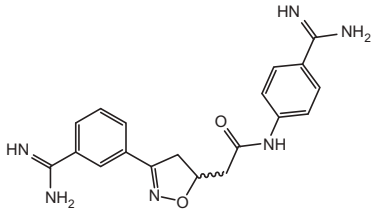
The second and more innovative approach resulted in a "focused screening" strategy which was coupled early with structure-based design to drive affinity. We recognized that the peptide sequence of ligands for the GPIIb/IIIa receptor Arg–Gly–Asp (RGD) and the two prothrombin cleavage sequences for FXa, namely, Glu–Gly–Arg (EGR), though reversed, shared some similarity. Based on these observations, and because known GPIIb/IIIa receptor antagonists contain a benzamidine group which is also found in FXa inhibitors such as **5**–**7**, our internal proprietary collection of small molecule GPIIb/IIIa antagonists was screened against FXa.[14]

This effort led to the identification of a weak isoxazoline inhibitor **8** ($K_i = 38.5$ μM; Fig. 9.4). Not discouraged by the weak affinity of **8**, lead optimization was jump-started by expeditiously improving affinity to subnanomolar levels by enhancing hydrophobic interactions in the S1 and S4 pockets.

Replacement of the aspartate residue in **8** with a second benzamidine afforded compound **9** ($K_i = 1.4$ μM), providing ~30-fold improvement in FXa affinity. Direct substitution of the carboxamide group onto the isoxazoline core, followed by substitution with a geminal carbonyl group designed to hydrogen bond to



8 (screening hit)



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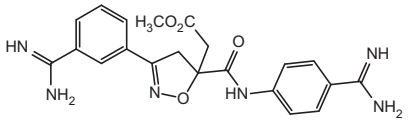

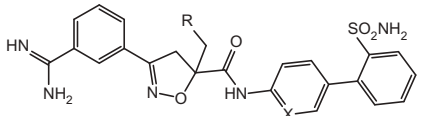

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