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Review article

# The selectivity and bioavailability improvement of novel oral anticoagulants: An overview

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ABSTRACT

Anticoagulants have exhibited a critical role in the prevention and/or treatment of thrombotic diseases. Up to now, kinds of novel oral anticoagulants, inhibiting plasma serine proteases in the coagulation cascade, have been developed to overcome the clinical limitations of classical anticoagulants (like warfarin and heparins). Some of them, such as Apixaban, Rivaroxaban, Edoxaban, and Dabigatran, have been approved by FDA in recent years. This review summarizes the discovery and optimization of representative novel oral anticoagulants with the aim to improve selectivity and bioavailability of compounds. The impact of different targets in the cascade on bleeding risk also is discussed. We hope some more effective, selective, and safer anticoagulants can be developed in the future on the basis of these design experiences.



**Contents**



## 1. Introduction

Thromboembolic events such as arterial and venous thrombosis,

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heart attacks, strokes, and peripheral vascular diseases, have been the leading causes of death worldwide. Its death rate has reached the death rates caused by cancer formations in recent years [1]. Dysregulation of blood coagulation is one of critical reasons for various thrombotic diseases with the abnormal formation of clots that occlude vessels (thrombosis), producing tissue ischemia. Therefore, anticoagulant drugs have displayed an important role in the treat or prevent thromboembolism in clinical practice [2].

Blood coagulation is the coordinated activation of plasma proteases, plasma cofactors, and platelets. Normally, blood coagulation is related to the repair and maintenance of the circulatory system (hemostasis) with a vital host defense mechanism. Protease thrombin is the end product among the coagulation, cleaving fibrinogen to generate a fibrin clot (thrombosis) [3]. The coagulation cascade has been classically divided into the extrinsic, intrinsic and common pathways (Fig. 1). In the extrinsic pathway, vessel injury initiates the process by converting factor VII (FVII) to factor VIIa (FVIIa). Tissue factor/FVIIa (TF/FVIIa) complex catalyzes the formation of factor Xa (FXa), which in turn cleaves prothrombin to generate thrombin. In the intrinsic pathway, factor XIIa (FXIIa), formed by contact activation, catalyzes the formation of FXIa, which leads to the sequential activation of factor IX (FIX) and factor X (FX). In addition, Thrombin can also activate factor XI (FXI) to FXIa by feedback activation. In the cascade, the formation of factor Xa and conversion of prothrombin to thrombin belong to the common pathway [4].

As classical anticoagulants, warfarin [5] (vitamin K antagonist, blocking the biosynthesis of vitamin K-dependent coagulation factors) and heparins [6] (antithrombin activators, binding to the enzyme inhibitor antithrombin III (AT), causing a conformational change that results in its activation and then inactivating thrombin, factor Xa and other proteases) have been used for treating thrombotic disease for many years, possessing high efficacy and low cost to benefit ratio. However, they suffer from many agent-specific adverse effects (mainly bleeding risks and narrow therapeutic index), in addition to the patient-to-patient response variations and the need for laboratory adjusted dosing [7]. Furthermore, for heparins, the side effects also include osteoporosis, thrombocytopenia and high risk of contamination, and for warfarin, they have drug-drug and drug-food interactions [8]. To satisfy requirement for patients in clinic, many new oral anticoagulants, targeting key serine proteases in coagulation cascade have been developed in the last decade. Some of them, such as FXa inhibitor Apixaban [9], Rivaroxaban [10], Edoxaban [11], and thrombin inhibitor Dabigatran [12] have been entered to the market with improved efficacy and bleeding safety profile in comparison with the classical anticoagulants.

In this review, we discuss the rational design, optimization and modification of representative anticoagulants targeting key serine proteases including FXa, FIXa, FVII/TF and thrombin, mainly viewing on the improvement of the selectivity, bioavailability and impact on bleeding risk. The review will provide useful experiences to further develop novel oral anticoagulants (FXIa or FXIIa inhibitors) or other targeted drugs.

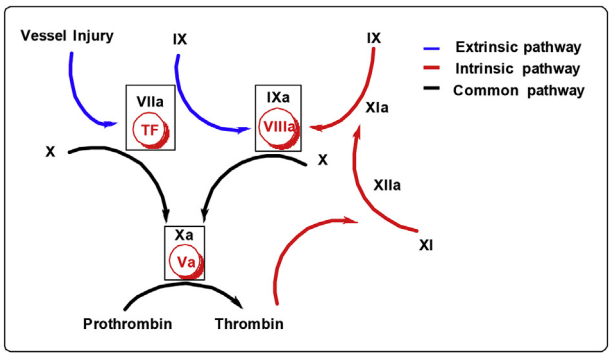


**Fig. 1.** The intrinsic, extrinsic, and common pathways of coagulation cascade.

## 2. Factor Xa inhibitors

Factor X is one of the vitamin K dependent serine proteases involved in blood coagulation cascade, which displays an important role in the coagulation network at the common pathway that connects both the tissue factor-activated extrinsic pathway and the surface-activated intrinsic pathway [13]. It is a glycoprotein dimer (the only one in a prothrombin group with dimeric structure) with a molecular weight of 59 000 Da. The active part is in the heavy chain, which acquires the function of factor Xa after cleavage of low molecular weight fragment [14]. Activated FX (FXa) forms the prothrombinase complex with calcium ion, phospholipid and factor Va, converting prothrombin to thrombin. In turn, thrombin intervenes in proteolytic formation of fibrin from fibrinogen, thereafter hemostatic clotting is trigged. The prothrombinase complex also can amplify the procoagulant action of FXa [4]. Since FXa doesn't directly act on platelet function, it is believed to have less impact on bleeding risk [24].

A number of small molecule FXa inhibitors have been reported to date. They are classified as amidine derivatives exemplified by DX-9065a [15], or nonamidine derivatives exemplified by Apixaban.

### 2.1. Discovery and optimization of ASP8102

Compound **1**, a hit obtained by high-throughput screening (HTS) was a potent FXa inhibitor ($IC_{50} = 6.2\ \mu M$) [16]. In strategic intention to improve selectivity and bioavailability, the first step was introduction of cationic group which could bind Asp189 residue of S1 pocket and a group that could interact with S4 aryl binding site. Groups of 3-amidino and 1-methyl-1,4-diazepan-1-yl were found to be responsible for improved activity of compound **2**, $IC_{50} = 5.8$ nM (Fig. 2).

Since the HN group of the amide between phenyldiazepanyl and central benzenic ring forms hydrogen bond with Gly216, the isosteric modifications of other amide functional groups were carried out in compounds **3-7**. Oxymethyl contained **4** and aminomethyl contained **5** showed stronger activity than corresponding methoxyl contained **3,** methylamino contained **6** and ethylene contained **7**. However, all of them were less potent than compound **2**. The reason was that the isosteric groups could not favor the orientation of benzamidine moiety towards S1 pocket like amide group. Moreover, carboxyl group on the central phenyl in compounds **8-11** caused 1.8–3.4-fold more potency than corresponding compounds **2-7** [16]. This activity improvement can be explained by improved hydrophilicity of **8-11**. Despite the good *in vitro* potency of benzamidino analogues, highly polar P1 motif was responsible for lower oral absorption and deleterious effect on pharmacokinetic profile [17]. Therefore, it was wise to search another way to enhance FXa binding affinity and reintegration of 4-methoxyphenyl in compounds **12-16** was tolerated.

Compound **12** was 5-fold more potent than its retroisosteric amide analogue **13** which lacks H-bond with Gly216, whereas compound **14** with reversed amide between 4-methoxyphenyl and central benzenic core showed only about 1.4-fold less activity compared to compound **12**. The 3-hydroxyphenyl **15** (named **Darexaban** which discontinued in phase III, $IC_{50} = 54.6$ nM) showed 2-fold more potent *in vitro* anticoagulant activity than