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Factor Xa Inhibitors: Next-Generation Antithrombotic Agents

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1. Introduction

Thrombosis is the underlying cause of a host of common, debilitating, and often fatal cardiovascular disorders. Formation of thrombi in the arterial circulation can lead to acute myocardial infarction (MI[a]) or ischemic stroke. In the venous circulation, deep vein thrombosis (DVT) may result in chronic leg pain, swelling, and ulceration and can, if partially or fully dislodged, be followed by life-threatening pulmonary embolism (PE). The public health consequences of thromboembolic disease are vast. For example, approximately 2.5 million people in the United States are affected by atrial fibrillation (AF), a cardiac arrhythmia associated with a 4- to 5-fold increase in the risk of stroke of primarily cardioembolic origin.[1] Another group at elevated risk of ischemic stroke, as well as recurrent acute MI, is the large and growing population of patients with acute coronary syndrome (ACS).[2] Furthermore, it has been estimated that DVT and PE, which together comprise venous thromboembolism (VTE), afflict up to 600 000 individuals in the United States each year and are implicated in at least 100 000 deaths.[3]

Despite the continued morbidity and mortality caused by thromboembolic disease, recent advances in drug development provide cause for optimism that we are about to enter a new era in antithrombotic therapy. One of the most important advances has been the development, and recent introduction into clinical practice, of a new class of anticoagulants, the direct factor Xa (FXa) inhibitors.[4,5] In this Perspective, we provide a detailed insight into the development of these important new agents, describe how structure-based design played a pivotal role in this process, and review the wealth of preclinical and clinical data that have emerged to date. Finally, we consider the issues that will determine the future impact of the direct FXa inhibitors on clinical practice. We begin by briefly highlighting the limitations of the current standards of care in antithrombotic therapy, reviewing some key concepts in hemostasis and thrombosis, and explaining the rationale for targeting FXa.

1.1. Current Antithrombotic Therapy. Numerous clinical trials have confirmed the efficacy of traditional anticoagulants, including vitamin K antagonists (VKAs), unfractionated heparin (UFH), and low-molecular-weight heparins (LMWHs, fractionated heparin with reduced activity toward thrombin compared to UFH), in the prevention and treatment of a range of arterial and venous thromboembolic diseases.[1,6−8] Despite the fact that these drugs are the current standard of care and despite their proven efficacy, these anticoagulants all possess significant limitations that restrict their usefulness in the clinic and have created the need for new therapies. Use of warfarin and other VKAs is especially problematic, even though these anticoagulants offer the convenience of oral administration.[9] For example, warfarin is associated with numerous drug and food interactions, an unpredictable pharmacokinetic (PK) and pharmacodynamic (PD) profile, and considerable intra- and interpatient variability in drug response.[9] As a result, the appropriate therapeutic dose varies, necessitating monitoring and frequent dose adjustment. Monitoring of warfarin therapy is critical because of this variability and relatively narrow therapeutic index, which often leads to subtherapeutic anticoagulation and a higher risk of thromboembolism or to excessive anticoagulation and an increased risk of bleeding.[9] Furthermore, the delayed onset of action of warfarin means that in critical situations therapy must be initiated with a rapid-acting, parenteral anticoagulant. Urgent surgical or invasive procedures may also be complicated by the fact that the anticoagulant effects of warfarin are retained for several days after discontinuation of treatment.

Agents for short-term anticoagulation include UFH, LMWHs, the indirect FXa inhibitor fondaparinux, and the direct thrombin inhibitors (DTIs) argatroban, bivalirudin, and hirudin. These anticoagulants all require parenteral administration, which makes their use outside the hospital problematic and which can also be associated with injection-site hematomas. UFH and, to a lesser extent, LMWHs carry the risk of thrombocytopenia, and since they are produced from animal tissue, they are sometimes associated with serious side effects.[10] In addition, UFH has an unpredictable PK profile and anticoagulant response that necessitate monitoring.[5] The limitations of parenteral anticoagulants, particularly the need for injection, mean that warfarin and other VKAs, which in many countries are still the only orally administered anticoagulants approved for

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[a]Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; aPTT, activated partial thromboplastin time; ATIII, antithrombin III; AV, arteriovenous; DTI, direct thrombin inhibitor; DVT, deep vein thrombosis; ECAT, electric-current-induced arterial thrombosis; FVa, factor Va; FVIIa, factor VIIa; FVIII, factor FVIII; FVIIIa, factor FVIIIa; FIX, factor IX; FX, factor X; FXa, factor Xa ; FXIa, factor XIa; GPIIb/IIIa, glycoprotein IIb/IIIa; HLM, human liver microsomes; hERG, human ether-a-go-go related gene; HTS, high-throughput screen; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PD, pharmacodynamic; PDB, Protein Data Bank; PE, pulmonary embolism; PK, pharmacokinetic; PT, prothrombin time; SAR, structure−activity relationship; TAFI, thrombin-activatable fibrinolysis inhibitor; TAP, tick anticoagulant peptide; TF, tissue factor; TG, thrombin generation; THR, total hip replacement; TKR, total knee replacement; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism; vWF, von Willebrand factor.

use, represent the sole viable option for long-term anticoagulation therapy.

As discussed below, hemostasis and thrombosis are interrelated processes, and it is not surprising that anticoagulant and antiplatelet agents may have hemorrhagic complications. Dose selection, therefore, is primarily influenced by the maximum dose that can be safely administered rather than the dose providing greatest efficacy. Although this will remain true for new antithrombotic agents on the horizon, benefit-to-risk profiles do vary.[11] These limitations result in the underutilization of existing therapies in the very patients who are at highest risk of serious thrombotic events. For example, use of antithrombotic drugs is often avoided in the very elderly, despite the fact that advanced age is a major risk factor for both arterial and venous thromboembolism.[12,13] Concerns over bleeding have also restricted long-term use of warfarin and other anticoagulants in combination with antiplatelet drugs in patients with ACS and AF.[4]

All of these factors have been the driving force for the development of new anticoagulants, including the direct FXa inhibitors. For any new anticoagulant to be considered ideal, it would need to possess a predictable PK profile that allows fixed oral dosing without routine monitoring and to possess a relatively wide therapeutic index with low peak-to-trough plasma concentrations to provide high levels of efficacy and low rates of bleeding. Since the target is in the central compartment, the ideal PK profile also features a low volume of distribution (to reduce the potential for off-target liabilities) and low systemic clearance (to minimize drug−drug interactions). Other key features of the "ideal" new anticoagulant include a rapid onset of action and an ability to bind clot-bound coagulation factors.[14]

1.2. Hemostasis and Thrombosis. Hemostasis is the physiologic process during which bleeding is antagonized, and possibly stopped, in order to minimize blood loss.[15] Unlike hemostasis, which is a necessary physiologic response to bleeding, thrombosis is a pathological process involving an exaggerated hemostatic response and is often ascribed to the combined influence of a triad of causative factors, namely, prothrombotic vascular endothelial changes or injury, stasis of blood flow, and/or other causes of hypercoagulability.[16]

Primary hemostasis begins immediately after endothelial damage and involves localized vasoconstriction and the activation and adhesion of platelets to form a soft aggregate plug. In contrast, secondary hemostasis comprises a complex series of reactions during which several trypsin-like serine proteases, including FXa, are formed from their respective proenzymes. Figure 1A depicts how the "coagulation cascade" has classically been viewed, with two parallel and largely independent pathways, the extrinsic and intrinsic pathways, converging at the point of factor X (FX) activation.[4] Upon the formation of FXa, the common pathway is initiated, leading to the activation of prothrombin to thrombin and the subsequent conversion of fibrinogen to fibrin (described in more detail in section 1.3). Polymerized fibrin strands, together with activated platelets, then form stable clots that seal the breach at the site of injury. While this classic view of the coagulation cascade aids understanding of some of the key processes involved in secondary hemostasis, recent advances have led to the development of a cell-based model that may describe the time course and physiology of thrombogenesis more accurately, including the roles of tissue-factor (TF)-bearing cells and platelets. In this model,

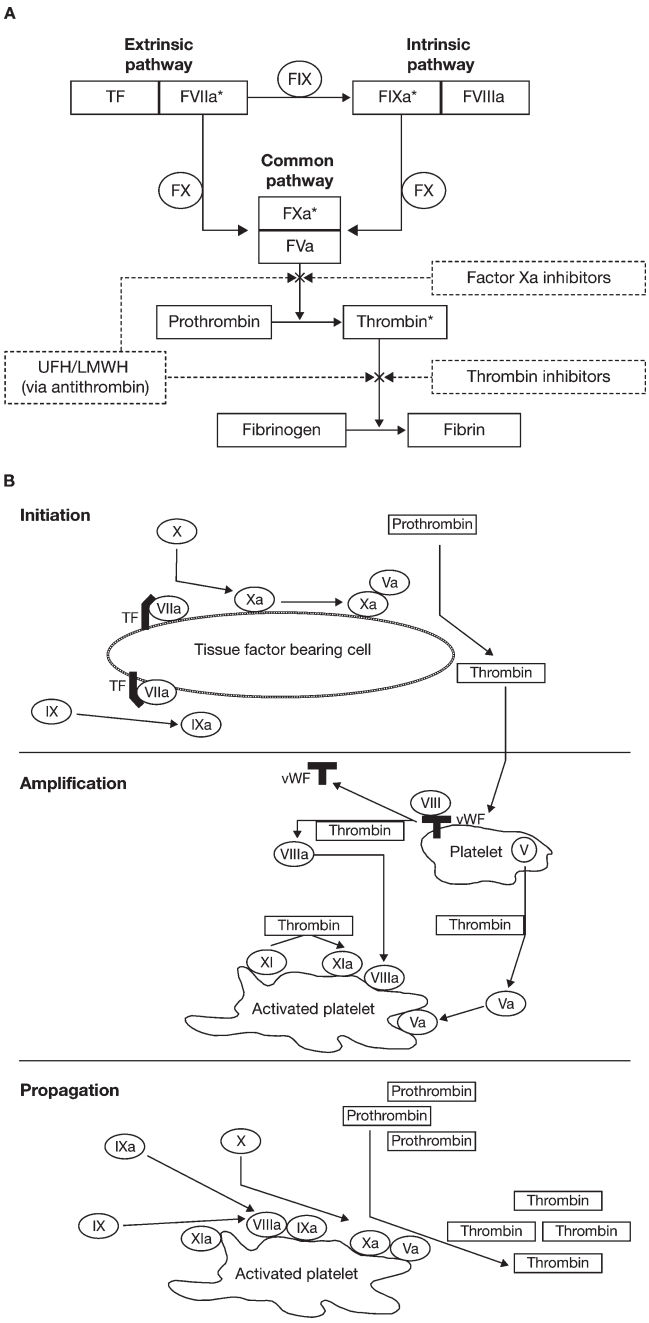

Figure 1. (A) Classic view of the coagulation cascade. Sites of action of traditional and new anticoagulants are also depicted (coagulation factors affected by VKAs are indicated by an asterisk). Adapted by permission from Macmillan Publishers Ltd.: *Clinical Pharmacology & Therapeutics* (http://www.nature.com/clpt/index.html) (Gross, P. L.; Weitz, J. I. New antithrombotic drugs. *Clin. Pharmacol.Ther.* **2009,** *86*, 139−146),[4] Copyright 2009. (B) Cell-based model of coagulation. Adapted by permission from Wolters Kluwer Health/Lippincott, Williams & Wilkins: *Journal of Cardiovascular Pharmacology* (Hammwöhner, M.; Goette, A. Will warfarin soon be passé? New approaches to stroke prevention in atrial fibrillation. *Journal of Cardiovascular Pharmacology* **2008,** *52*, 18−27),[17] Copyright 2008, and *Arteriosclerosis, Thrombosis and Vascular Biology* (Monroe, D. M.; Hoffman, M.; Roberts, H. R. Platelets and thrombin generation. *Arterioscler., Thromb., Vasc. Biol.* **2002,** *22*, 1381−1389),[18] Copyright 2002.

three overlapping phases (initiation, amplification, and propagation) and is critically dependent on the contribution

phase, TF−factor VIIa (FVIIa) complexes activate factor IX (FIX) and FX; subsequently formed FXa−factor Va (FVa) complexes then generate small amounts of thrombin. During the amplification phase, thrombin generated in the initiation phase activates platelets, leading to release of factor VIIIa (FVIIIa) from factor VIII (FVIII)−von Willebrand factor (vWF) complexes on the platelet surfaces and also generation of FVa and factor XIa (FXIa). In the final propagation phase, factor XIa (FXIa) generates more FIXa; this FIXa, together with that generated in the amplification phase, activates FX, leading to the formation of numerous FXa−FVa complexes and a burst of thrombin generation.

The inhibitory activity of anticoagulants can be assessed by a number of methods. Assays that employ purified coagulation proteases and synthetic substrates are most commonly used for the initial characterization of the affinity of synthetic inhibitors toward their target enzyme. Modifications of these methods can also be used to measure the activity of inhibitors in blood samples as, for example, the anti-Xa assay that can be used with the LMWHs, fondaparinux, or synthetic inhibitors. Anticoagulants can be further characterized using clotting assays (including prothrombin time (PT) and activated partial thromboplastin time (aPTT)) that measure the time for formation of a fibrin clot after addition of an activator of coagulation to whole blood or plasma.[19] Clotting assays can be used for either in vitro characterization of the potency of compounds or for ex vivo assessments in laboratory animals or in humans. In vitro potency is conventionally reported as the concentration of inhibitor required to produce a doubling of the uninhibited clotting time ($PT_{2\times}$ or $aPTT_{2\times}$). Other useful laboratory methods include the thrombin generation (TG) assay, which measures time-dependent changes in thrombin concentration.[20]

1.3. Targeting FXa. FXa plays a critical role in coagulation. Together with FVa and calcium ions on a phospholipid surface, FXa forms the prothrombinase complex, which is responsible for the conversion of prothrombin to thrombin, the final effector of coagulation. Regulation of thrombin generation is the primary physiologic function of FXa, and few other roles have been identified.[21] FXa is therefore an attractive and potentially specific target for new anticoagulant agents. As will be discussed, experience with indirect inhibitors of FXa has helped to validate FXa inhibition as an effective and safe anticoagulant strategy. However, indirect FXa inhibitors possess two significant limitations. First, these agents require parenteral administration; second, they rely on the activity of antithrombin and are therefore not able to inhibit FXa bound within the prothrombinase complex.[22] Development of orally administered direct inhibitors of FXa that can effectively inhibit prothrombinase-associated and clot-bound FXa, and thereby offer potentially greater anticoagulant activity, is therefore a highly significant advance.

Once formed via the actions of FXa, thrombin plays key roles in both coagulation and platelet activation. Within the coagulation cascade, thrombin directly cleaves fibrinopeptides from fibrinogen, participates in positive feedback reactions via activation of FV and FVIII, promotes the cross-linking of fibrin through activation of factor XIII (FXIII), and renders fibrin resistant to fibrinolysis through activation of thrombin-activatable fibrinolysis inhibitor (TAFI).[23] Oral anticoagulant drug discovery efforts initially focused on the thrombin directly, the oral DTIs. Although the rationale for targeting thrombin is clear, there is some evidence to suggest that inhibition earlier in the coagulation cascade at the level of FXa may have greater antithrombotic potential.[21] Furthermore, preclinical studies suggest that FXa inhibitors may possess a wider therapeutic index than DTIs.[24] Therefore, it is not surprising that the oral anticoagulant drug discovery efforts of many pharmaceutical companies ultimately focused aggressively on small-molecule, direct FXa inhibitors. Differences between the direct FXa inhibitors and DTIs, and the potential consequences of these differences for clinical practice, are discussed in more detail in section 5.

Before we begin our review of the development of the direct FXa inhibitors, it is worth briefly considering some important molecular features of the target protein. FXa belongs to the family of trypsin-like serine proteases, the catalytic domain of which consists of two similar antiparallel β-barrel folds that together form the catalytic triad and substrate binding site.[25] Schechter and Berger have developed a useful nomenclature to describe the prototypical binding site of a serine protease that has been widely adopted and that we will use herein.[26] Accordingly, each protein subsite, labeled S_i, binds the corresponding substrate amino acid labeled P_i, with "i" increasing toward the substrate N-terminus. Similarly, the corresponding subsites and substrate amino acids to the left of the scissile amide bond in Figure 2 are designated as S_i' and P_i', respectively, increasing toward the substrate C-terminus. Substrate cleavage occurs at the P1′−P1 amide bond. As the discovery of small-molecule protease inhibitors has advanced, this convention has been extended to denote drug substructures that bind in a manner similar to substrate amino acids.[27] Figure 2A depicts the serine protease subsites primarily responsible for the recognition and binding of substrate and druglike molecules. It is noteworthy that all reported small-molecule serine protease inhibitors for which structural data exist bind in the S1 and one or more of the remaining subsites.

The FXa binding site is defined by the S1 and S4 subsites and surrounding residues (Figure 2B and Figure 2C). S1 is a deep, largely hydrophobic cleft at the bottom of which lies the Asp189 and Tyr228 side chains. S4 is a strongly hydrophobic pocket defined principally by the side chains of Tyr99, Phe174, and Trp215. The most potent ligands reported in the literature invariably engage both sites. Other features include the catalytic triad consisting of His57, Asp102, and Ser195 and the β-strand region defined by the 214−217 backbone.

Selectivity is a significant issue in the development of factor Xa inhibitors, since, as discussed above, several trypsin-like serine proteases play key regulatory roles in the coagulation cascade, among them FVIIa, FIXa, FXa, FXIa, and thrombin. Trypsin itself is an important enzyme for digestion of proteins in the gastrointestinal tract. Although the consequences of trypsin inhibition in humans have not been well-studied, results in laboratory animals could be problematic in preclinical toxicity testing that is required of any new drug.[30] Orally administered drugs can reach concentrations many-fold higher within the GI tract compared to concentrations within blood; therefore, a high degree of selectivity for the target coagulation enzyme over trypsin is important. In addition, selectivity over trypsin may be considered as a surrogate determination for achieving selec-

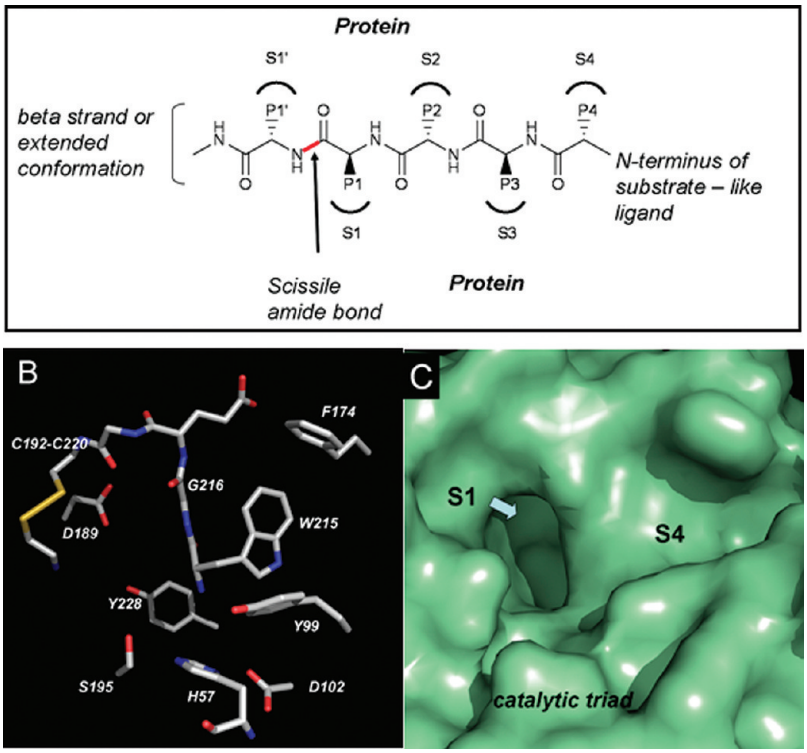

Figure 2. Serine protease and factor Xa structure and nomenclature. (A) Depiction of substrate/protease nomenclature based on the convention of Schechter and Berger.[26] This figure is based on that of Leung et al.[28] (B, C) Overview of the factor Xa binding site,[29] with subsites and several residues important for ligand binding labeled.

As will be discussed in section 3 in more detail, a differentiating feature that can be exploited for selectivity among serine proteases is the nature of the S1 pocket, being smaller and lipophilic in some such as trypsin, or larger and more hydrophobic such as in FXa.

2. Development of Direct FXa Inhibitors

2.1. Precedence for FXa Inhibition as an Effective and Safe Anticoagulant Therapy. Proof of principle for the effectiveness of direct FXa inhibition was established in preclinical animal models of thrombosis with naturally occurring FXa inhibitors of the prothrombinase complex such as tick anticoagulant peptide (TAP)[31] and antistasin.[32,33] Both are highly potent inhibitors of FXa (K_i = 0.59 and 0.3−0.6 nM, respectively), with > 50 000-fold selectivity for FXa over other related serine proteases.[34,35] Compound **1** (Figure 3), a synthetic pentasaccharide, is selective for FXa but acts indirectly via binding to antithrombin and has demonstrated improved or similar clinical benefit over LMWHs in venous thrombotic indications.[36] Superiority in ACS patients with unstable angina/non-ST-segment elevation MI for reducing risk of death or recurrent heart attack was also demonstrated.[37,38] The safety and efficacy of **1** provided the first clinical proof of principle that targeting FXa would be an important advancement in the area of anticoagulation therapy.[36]

More recently, Sanofi-Aventis advanced a hypermethylated derivative of **1** with a high affinity for antithrombin III (ATIII), in which the amino functional groups were replaced with hydroxyl or methoxy groups.[39] This compound, idraparinux (**2a**, K_d = 1 nM, Figure 3), interacts more strongly with ATIII than **1** (K_d = 50 nM) and in patients has a longer half-life ($t_{1/2} \approx$ 80 h), allowing for once-weekly dosing. The

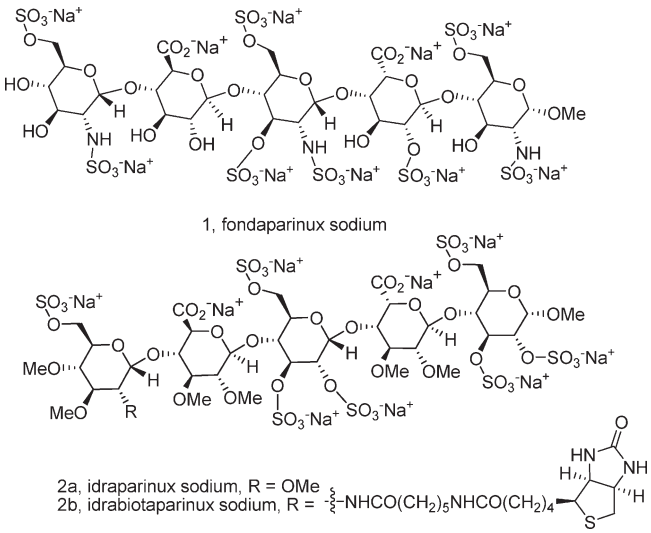

Figure 3. Structures of the pentasaccharide indirect FXa inhibitors.

did not demonstrate a clear advantage over **1**.[40] In a phase III trial, long-term treatment with **2a** (once weekly) for the prevention of stroke and systemic embolism in patients with AF was noninferior to warfarin but caused more bleeding.[41] Development of **2a** has since been discontinued. A second-generation synthetic pentasaccharide, idrabiotaparinux (**2b**, SSR126517E), is in late-stage clinical trials for treatment of VTE and for stroke prevention in patients with AF,[4,42] although the company recently announced discontinuation of development of the drug for the latter indication.[43] Compound **2b** incorporates a biotin moiety that enables the selective reversal of anticoagulant activity by intravenous

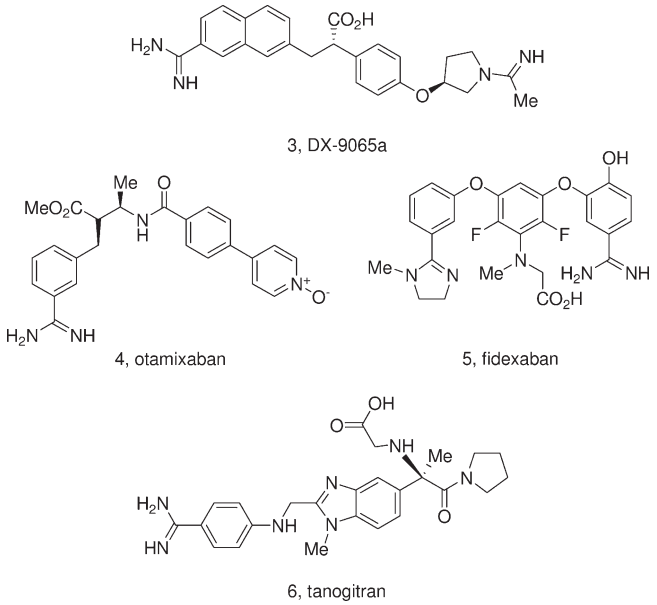

Figure 4. Parenteral direct FXa inhibitors **3**, **4**, and **5** and the dual FXa/thrombin inhibitor **6**.

2.2. Early Prototype Direct FXa Inhibitors: Parenteral Agents. The shortcomings of the LMWHs (e.g., indirect activity, limited ability to inhibit fibrin-bound FXa, parenteral use only) provided great impetus for the discovery of synthetic, small-molecule direct FXa inhibitors. The first generation of these were iv agents, and several small-molecule, nonpeptidic, direct inhibitors of FXa were advanced to phase II clinical trials as parenteral agents.[44,45] DX-9065a (**3**, Daiichi Sankyo, Figure 4, FXa K_i = 41 nM, thrombin K_i > 2000 μM, trypsin K_i = 620 nM) was clearly one of the first potent and selective FXa inhibitors identified, with good clotting activity (activated partial thromboplastin time twice the control [$aPTT_{2\times}$] = 0.97 μM, prothrombin time twice the control [$PT_{2\times}$] = 0.52 μM).[46,47] The compound was studied extensively in preclinical models; found to be efficacious in animal models of thrombosis after iv, subcutaneous, and oral administration; and did not show prolongation of bleeding time.[48] Because of its very low human oral bioavailability (F = 2−3%), **3** was advanced clinically as a parenteral agent.[49] The compound was well tolerated, with no increase in bleeding over the dose range. Human PK for **3** showed a long half-life ($t_{1/2}$ > 20 h), low clearance (120 mL/min), and low plasma protein binding (60% bound). Plasma concentrations correlated well with PD markers. In a phase II study in patients with non-ST-elevation ACS, dose-related trends toward reductions in ischemic events with high-dose **3** compared with heparin were observed.[50] Safety parameters such as bleeding increased dose proportionally.

Otamixaban (**4**, FXV-673, Sanofi-Aventis, Figure 4), a 2,3-disubstituted β-aminoester derivative, is a potent, reversible FXa inhibitor (K_i = 0.5 nM) with good in vitro anticoagulant activity ($aPTT_{2\times}$ = 0.41 μM, $PT_{2\times}$ = 1.1 μM).[51,52] Like **3**, compound **4** belongs to the benzamidine class of molecules, and its polarity precludes significant oral absorption. In vivo, **4** was efficacious in canine models of thrombosis and demonstrated minimal effect on bleeding at effective doses.[53,54] In phase I/II studies, **4** was administered intravenously and was found to be well tolerated in healthy

was rapidly distributed in the plasma and rapidly eliminated with a half-life of 1.5−2 h.[55] In a phase II trial setting, **4** significantly reduced prothrombin fragment 1 + 2, a marker of thrombin generation, when compared with UFH and a glycoprotein (GPIIb/IIIa) antagonist, eptifibatide.[56] Two phase II clinical trials for the management of ACS and patients with ACS undergoing percutaneous coronary intervention have also been completed and showed the potential for reduced ischemic events with bleeding rates similar to those of UFH plus eptifibatide.[56,57] A third parenteral agent that was advanced to human clinical trials was fidexaban (**5**, ZK-807834, Berlex-Pfizer; Figure 4),[58] a compound that contains two amidine groups and a polar carboxylic acid moiety.[59] The dihydrochloride salt of **5** (ZK-807191) is a potent inhibitor of FXa (K_i = 0.10 nM) and exhibits nearly 20 000-fold selectivity over thrombin and 2500-fold selectivity over trypsin; it has been shown to be efficacious in several in vivo animal models of thrombosis.[60−62] In human clinical trials, infusion of **5** was found to be well tolerated.[63] Phase II trials were underway in unstable angina in 2001; however, no results from these studies were published.[64] In addition to the above direct FXa parenteral compounds, a dual thrombin/Xa inhibitor, tanogitran (**6**, BIBT 986, Boehringer Ingelheim, FXa K_i = 26 nM, thrombin K_i = 2.7 nM, Figure 4), was evaluated more recently in a phase II clinical trial involving a human model of endotoxin-induced coagulation.[65] In this study, **6** prolonged plasma aPTT, reduced in vivo thrombin generation in a dose-dependent manner, and was safe and well tolerated. No further development has been reported.

Clinical success of indirect FXa inhibitors such as **1** and the improved therapeutic index with the early direct FXa inhibitors such as the parenteral inhibitors described above fueled an intense effort to discover and develop safer and more effective oral FXa inhibitors. The discovery and advancement of orally bioavailable, direct-acting FXa inhibitors that progressed to clinical studies, including a brief survey of some of the early inhibitors that led up to these agents, are now discussed.

2.3. Approach to Oral FXa Inhibitors. 2.3.1. Transition State and Peptidomimetic Approach: Covalent Inhibitors. Early efforts to identify inhibitors of FXa stemmed from the prior discoveries of thrombin inhibitors that contained "serine traps", such as aldehyde or ketothiazole moieties, which are capable of interacting covalently with the catalytic Ser195 hydroxyl group to mimic a tetrahedral transition state in a reversible manner. Compounds **7** (FXa IC_{50} = 15 nM),[66] **8** (FXa K_i = 0.13 nM),[67] and **9** (FXa IC_{50} = 0.83 nM)[68] are examples of early FXa inhibitors that contain a "serine trap" (Figure 5). As with the thrombin inhibitors in this class, several of the first transition-state FXa inhibitors also contained arginine or constrained arginine P1 residues that would interact strongly with the acidic Asp189 S1 residue, flanked by aromatic residues designed to fit into the hydrophobic S1 pocket of FXa.[44] In the design of these inhibitors, it also became apparent that basic substituents could be tolerated in both the S1 and S4 regions, with a basic P4 moiety interacting in a π−cation manner with the hydrophobic residues in the S4 subsite. These peptide-like inhibitors eventually evolved to incorporate heterocyclic amide-bond replacements,[69] such as pyridone (**10**, FXa IC_{50} = 3 nM), ketopiperazine (**11**, FXa IC_{50} = 2 nM), and caprolactam (**12**, FXa IC_{50} = 3 nM), while maintaining

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