Novel factor Xa inhibitors: a patent review

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**Importance of the field.** New oral anticoagulants with favorable safety profiles and fixed doses are required for the management of thromboembolism and stroke prevention in patients with atrial fibrillation. Among them, fXa inhibitors (the so-called xabans) are attractive options that can overcome limitations (e.g., bleeding) of the current oral antithrombotic therapy. The rational design of small-molecule direct fXa inhibitors, whose importance is testified by the growing number of publications and patents recently registered, has been fully supported by the X-ray crystallography of enzyme–ligand complexes.

**Areas covered in this review.** Pubmed, SciFinder® Scholar, ISI web of knowledgeSM, http://ep.espacenet.com/ and Google websites were used as the main sources for literature retrieving, and > 100 patents filed between 2006 and April 2009, reviewed and discussed herein, highlight the variety among the P1 and P4 moieties on suitable scaffolds.

**What the reader will gain.** The replacement of the benzamidine P1 moiety, which characterizes the first generation, with less basic bioisosteric or nonpolar neutral P1 groups led to the disclosure of numerous fXa inhibitors with high potency, selectivity and oral bioavailability. Novel selective fXa inhibitors with stable pharmacokinetics, better therapeutic windows and ease-of-use than the existing anticoagulants are currently under advanced stage clinical trials.

**Take-home message.** Available data from Phase II and Phase III studies reflect the drive towards fXa inhibitors as potentially more effective and safer antithrombotic drugs. Their development is expected to address two major needs for anticoagulation, namely safety and ease-of-use, and to significantly affect the anticoagulant market.

Keywords: acute coronary syndrome, anticoagulant, antithrombotic, factor Xa inhibitor, venous thromboembolism, xabans

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1. Introduction

Thromboembolic diseases are leading causes of cardiovascular-associated morbidity and death [1-3]. Prevention and treatment of arterial thrombosis in patients with cardiovascular diseases (e.g., atherosclerotic vascular disease, acute coronary syndrome or ACS) are achieved using antiplatelet drugs [4], whereas venous thrombosis illnesses, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), are treated with anticoagulant drugs that directly or indirectly inhibit various factors, mainly thrombin (thr) and factor Xa (fXa), in the blood coagulation cascade [5,6].

Vitamin K antagonists (e.g., warfarin) and heparins have been the most prescribed anticoagulants for > 50 years in a variety of conditions, including venous thromboembolism (VTE) and long-term prevention of ischemic stroke in patients with atrial fibrillation (AF) [7]. Nonetheless, despite their proven efficacy, they share several limitations. Warfarin carries the risk of serious bleeding, requires continuous monitoring for accurate dosing and its activity is affected by food and drug interactions [8]. It has a narrow therapeutic window and unpredictable pharmacokinetics, with marked inter- and intra-individual variability. Warfarin
can also induce skin necrosis as a specific adverse reaction [9].

As for heparins, which are administered by injection, complications include the need of laboratory monitoring for dose adjustment and heparin-induced thrombocytopenia (reduced with low molecular weight heparins, LMWHs) [10]. Because of these limitations, new anticoagulants, with stable pharmacokinetics, better therapeutic windows and ease-of-use than the existing ones, have been developed and are currently under advanced stages of clinical trials [7,11]. The combined use of antiplatelet and anticoagulant agents showed additional benefits over anticoagulants alone in patients with prosthetic heart valves [12] and in patients with AF [13,14]. Indeed, compounds combining anticoagulant and platelet antiaggregatory activities in the same molecule are believed to be promising drugs [15,16].

Among the novel anticoagulant drugs, orally administered direct inhibitors of thrombin and FXa display better efficacy and improved safety profile (e.g., bleeding). Ximelagatran (exanta, AstraZeneca, Södertälje, SE), the first approved orally bioavailable direct thrombin inhibitor (DTI), was unfortunately withdrawn from the market owing to its hepatotoxicity [19], whereas in 2008 a second DTI, dabigatran etexilate (pradaxa, Boheringer Ingelheim; Ingelheim am Rhein, DE) [20], which proved to be as effective as the LMWH enoxaparin in reducing the risk of VTE following joint-replacement surgery [21], gained approval in the European Union and Canada and is undergoing review by the US FDA [22].

FXa: Factor Xa; LMWHs: Low molecular weight heparins; UFHs: Unfractionated heparins.

**Figure 1. Scheme of the blood coagulation cascade with potential targets of selected anticoagulants.** Several proteases in both the extrinsic (tissue factor, factor VIIa) and intrinsic (factors XIIa, Xla, IXa) pathways converge upon activation of FXa in a common pathway, in which thrombin plays a central role in either procoagulant (i.e., generation of fibrin from fibrinogen, stimulation of platelet aggregation through activation of thrombin receptors, auto-amplification of its production through activation of factors V, VIII and X) or anticoagulant (i.e., thrombomodulin-assisted activation of protein C, which in turn slows down its conversion from prothrombin) actions. Drugs are shown in boxes; the new oral anticoagulants (right boxes) include direct inhibitors of thrombin and FXa; the currently used vitamin K antagonist warfarin and heparins are reported on the left side.
During the past 10 years, the number of publications dealing with drug design and medicinal chemistry of small molecule, selective and orally active fXa inhibitors has progressively increased, becoming higher than that of publications pertaining to DTIs in the past 5 years (Figure 2). The growing interest in these compounds is demonstrated by the active participation of several pharmaceutical companies, and documented by many patents published between 2006 and April 2009, which are reviewed and discussed herein.

2. Structure-based drug design of small molecule factor Xa inhibitors

The design of selective small molecule fXa inhibitors has profited from X-ray crystallography of several enzyme–inhibitor complexes, molecular modeling and three-dimensional QSAR studies [26]. Factor Xa contains a serine protease domain in a trypsin-like closed β-barrel fold encompassing the catalytic triad Ser195-His57-Asp102 and two essential subsites S1 and S4. The search for ligands providing optimal interactions within S1 and S4 pockets, combined with suitable scaffolds, has been a major focus in structure-based design of selective fXa inhibitors. Early fXa inhibitors contained benzamidine, naphtylamidine or other basic groups [27], thought to be necessary for binding in the S1 pocket, but the poor bioavailability often associated with the amidine group directed efforts to replace this functionality with less basic or nonpolar neutral groups [28,29]. Examples of benzamidine-containing fXa inhibitors are DX-9065a (1), developed by Daiichi Pharmaceutical Co. (Tokyo, JP) [30], and otamixaban (2), developed at Sanofi-Aventis (Frankfurth aM, DE) [31]. DPC-423 (3), disclosed by DuPont Pharmaceuticals (Newark, Delaware, US), was the first orally active fXa inhibitor that went into the clinic [32,33]. A range of potent and orally bioavailable fXa inhibitors has since emerged, which include compounds containing either less basic amidine isosters, such as razaxaban (DPC-906, 4) [34], or neutral P1 substituents, such as rivaroxaban (BAY 59-7939, 5) [35] and apixaban (BMS-562247-1, 6) [36].

X-Ray crystal structures of potent inhibitors in complex with fXa (Figure 3) revealed that inhibitors bearing amidine or less basic isoster (2 and 4) and neutral (5 and 6) P1 substituents adopt L-shaped binding conformations. The chlorothiophene substituent in rivaroxaban (5) is buried inside the S1 pocket, with chlorine pointing towards the center of the Tyr228 aromatic ring. The gain in binding energy due to this hydrophobic contact, that is, the so-called chloro binding mode, could compensate the lack of electrostatic/H-bond interactions between amidine and Asp189. Interestingly, even in the presence of a benzamidine plus a chlorothiophene or chlorobenzothiophene, the molecules interact by directing the neutral group into the S1 pocket [37], thus demonstrating that electrostatic interactions in S1 are not mandatory for high affinity inhibitors. The chloro binding mode has been reported for fXa inhibitors bearing other P1 substituents, such as...
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1 DX-9065a
2 Otamixaban (FXV-673)
3 DPC-423
4 Razaxaban (DPC-906)
5 Rivaroxaban (BAY 59-7939)
6 Apixaban (BMS-562247-1)
Figure 3. X-ray crystal structures of otamixaban (A, pdb entry 1ksn), razaxaban (B, pdb entry 1z6e), rivaroxaban (C, pdb entry 2w26) and apixaban (D, pdb entry 2p16) in complex with human fXa. Only key amino acids of the essential S1 and S4 pockets are displayed. H-bonds are shown as dashed lines; structural water molecules within 4 Å around the ligand are displayed with the symbol ×.

fXa: Factor Xa.

as, for example, chlorophenyl [38,39] and chloropyridine [40]. Apixaban (6), which instead bears 4-methoxyphenyl as P1 substituent, adopts a similar binding mode, with the para-methoxyphenyl group located in the S1 pocket [36].

3. Therapeutic applications

Several oral fXa inhibitors are currently under various stages of clinical development [11]. Among them, rivaroxaban 5 (Xarelto; Bayer Healthcare/Johnson & Johnson, Leverkusen, DE), apixaban 6 (in co-development by Bristol-Myers Squibb, Princeton, New Jersey, US, and Pfizer, Groton, US) and edoxaban 9 (DU-176b, Daiichi Sankyo) [41] are in the most advanced stages of development [42].

Rivaroxaban (5) has shown a favorable safety/efficacy balance for preventing VTE after major orthopedic surgery [43]. It exhibited 60 – 80% oral bioavailability, achieving peak plasma level in 3 h and half-lives of 9 and 12 h in healthy young and elderly subjects, respectively. Phase II clinical trials for VTE prophylaxis following total knee replacement (TKR) [44] showed that each single dose of rivaroxaban is well tolerated, with predictable pharmacokinetics and pharmacodynamics at doses ≤ 40 mg, whereas adverse effects were somewhat elevated in the 50 mg group [45,46]. Compared to enoxaparin in Phase III studies examining VTE prevention following orthopedic surgery, rivaroxaban revealed higher effectiveness [11].

Apixaban (6) is currently undergoing Phase III trials in VTE prevention [11]. Displaying > 50% oral bioavailability and half-life as between 9 and 14 h, it showed promising benefit-risk profile compared with the current standard of care in patients following TKR [47]. The ADVANCE-1 study failed to show non-inferiority to enoxaparin, whereas the results of the ADVANCE-2 study, that is, a randomized, double-blind, multicenter trial comparing the efficacy of apixaban (2.5 mg orally b.i.d.) with enoxaparin (40 mg/day s.c.) for thromboprophylaxis after TKR, have been presented in July 2009 [48]. Taken together, the results of the ADVANCE studies indicate a favorable risk-benefit profile of apixaban relative to approved enoxaparin regimens. Moreover, it entered Phase III trials for stroke prevention and Phase II studies for ACS [42].

Edoxaban (DU-176b, 9), a potent and highly selective fXa inhibitor built up on cis-2-aminocyclohexylamine scaffold, significantly reduced both venous and arterial ex vivo thrombus formation, ≤ 5 h post-dose [49-51]. The Phase II program has been successfully completed for orthopedic and cardiological indications, and a dose-ranging study provided crucial insight with regard to optimal dosage of edoxaban for a Phase III study (ENGAGE-AF TIMI 48) aimed at seeking approval for AF [52].
Other fXa inhibitors in earlier stages of clinical development include YM-150 (Astellas Pharma, Inc., Tokyo, JP; formerly Yamanouchi), LY-517717 (8, Eli Lilly & Co., Indianapolis, Indiana, US), betrixaban (PRT-054021, 10; in co-development by Merk, Dormstadt, DE, and Portola Pharm., Inc., San Francisco, California, US) and TAK-442 (Takeda Pharm. Co., Osaka, JP) [7,11,53].

YM-150, whose structure is not known, is most likely a compound representing the second generation class of compounds that replaced YM-60828 (7) (54,55). The compound has a $K_I$ for fXa of 31 nM. In a randomized, open-label, dose-escalation Phase IIa study for the prevention of VTE in patients undergoing THR ($H$ is for ‘hip’), a significant dose–response relationship was observed and no major bleeding events were reported. Oral administration at doses of 10 – 60 mg was shown to be well tolerated and effective. Further investigation reported in the continuing large-scale Phase Ib study (ONYX-2). YM-150 also entered into Phase II dose-finding trials for stroke prevention in patients with AF.

LY-517717 (8), an indole caboxamide derivative of D-phenyl-Gly, which selectively inhibits fXa with a $K_I$ of 4.6 – 6.6 nM, achieves plasma peak concentration within 0.5 – 4 h after oral administration and elimination half-life of about 27 h in healthy volunteers. In a randomized, double-blind, dose-escalation Phase II study in patients undergoing TKR and THR, it exhibited dose-dependent efficacy with a similar incidence of bleeding to enoxaparin for the VTE prevention.

Betrixaban (10) inhibits fXa with a $K_I$ of 0.1 nM. It has an oral bioavailability of 47% and half-life of 19 h (excreted almost unchanged in bile). The completed Phase II clinical trials in patients undergoing TKR surgery provided proofs for efficacy and safety of betrixaban (15 or 45 mg b.i.d.) compared with enoxaparin (30 mg b.i.d.) in > 200 patients. Further Phase II studies have also been planned for investigating betrixaban in VTE prevention and treatment, stroke prevention in AF and secondary prevention of stroke and myocardial infarction.

The Takeda’s novel fXa inhibitor TAK-442 (structure not reported) for venous and arterial TE treatment has entered into Phase II clinical stage in the US and in Europe. Recently reported preclinical findings [56] suggest that TAK-442 may be more effective than fondaparinux in preventing arterial thrombosis in patients undergoing percutaneous coronary interventions.

4. Survey of the patent literature

An overview of the patents filed during the period 2000 – 2005 has been reported [29]. Herein, we review advances published in the patent literature between 2006 and April 2009. During this period, > 100 patents on novel fXa inhibitors, claimed by ~ 30 companies, have been published. Bayer HealthCare contributed for 20% out of the total number of the filed patents, followed by Boehringer Ingelheim (11%), Hoffmann-La Roche (Basel, CH) (10%), Bristol-Myers Squibb (8%), Millennium Pharmaceuticals (Cambridge, Massachusetts, US) (6%) and others. The key players in the area were Bayer, Bristol-Myers Squibb, Daiichi and Eli Lilly. Almost all other contributors highlighted new structure–activity relationships pertinent to scaffolds and/or P1 and P4 moieties.

A few patents deal with compounds bearing benzamidine or its mimics as P1 groups, whereas the majority describes fXa inhibitors containing neutral lipophilic groups as S1 binding moieties. Data on inhibitory activity (e.g., IC$_{50}$, $K_I$, $K_{\text{act}}$), selectivity and other biological properties will be presented as reported in the original publications.

4.1 Amidine-based factor Xa inhibitors and less basic analogues

Bis-amidine derivatives, built up using 2-phenoxethyl benzoate as scaffold, were disclosed by Ajinomoto Co. (Tokyo, JP) and claimed as inhibitors of fXa with good in vitro anticoagulant properties [57]. The most potent inhibitor 11 (IC$_{50}$ = 3 nM) proved to be selective versus thr. Alkylation, and not acylation, of the phenol OH, as well as the replacement of the S4 binding moiety imino(pyridinylidinyl)methyl with the imino-ethytlperidinylloxoy group (12, $K_I$ = 63 nM), resulted in a significant decrease of the inhibitory activity.

Curacyte Chemistry GmbH (Jena, DE) has patented a series of highly potent and selective fXa inhibitors, designed as substrate analogues. They include either 4-amidino- (13, 14) or 2-(aminomethyl)-5-chloro-benzylamide (15 – 17) derivatives [58-60]. Compound 13, containing a residue of D-homophenylalanine (D-hPhe), exhibited high inhibition potency ($K_I$ = 0.6 nM), but low selectivity versus thr and very short plasma half-life (< 20 min). In an effort to improve potency, selectivity and pharmacokinetic profile, D-hPhe was replaced by other aromatic homo amino acids, and better inhibition potency and selectivity were achieved by introducing D-homo-2-pyriddylalanine or its pyridine $N$-oxide analogue [58]. Compound 14 was designed taking into account that incorporation of the $\pi$-deficient pyridine $N$-oxide may reinforce aromatic interactions with the aryl binding site (S3/S4 pocket). Substitution of the N-terminal benzylsulfonyl group with alkylsulfonyl groups led to less potent inhibitors. Compound 14 exhibited excellent in vitro anticoagulant potency and high selectivity, but proved to have poor oral bioavailability and to be rapidly eliminated after intravenous administration. To overcome these problems, 4-aminobenzylamide was replaced with less basic residues, such as 2-(aminomethyl)-5-chloro-benzamide. Compounds 15 – 17 retained high fXa affinity, but moderate selectivity against thrombin, and compound 15 emerged as a more potent inhibitor than the corresponding benzamidine derivative 14, showing good anticoagulant activity, as assessed in clotting assays as the concentration that doubles activated partial tromboplastin time (2 $\times$ aPTT $=$ 0.16 $\mu$M). The replacement of the Gly with Pro led to increase of fXa selectivity, whereas D-hTyr in compound 17 did increase affinity for thrombin.

Morphochem Chemie Co. (München, DE) has registered a number of 3-benzamidino derivatives of phenylglycine.
In these compounds, the α-NH$_2$ group of the PhGly scaffold is connected to 3-amidinophenyl group (18 and 20) or 5-amidino-2-hydroxyphenyl group (19) as P1 moieties, and the α-COOH to 4-methyl-piperazinyl (18), 4-methyl-1,4-diazepan-1-yl (19) and 1-(2-methoxyphenyl) piperazinyl (20) groups as P4 moieties.

An unusual feature of these inhibitors is represented by β-D-glucose linked at the ortho position of the PhGly. Derivatives belonging to both S and R series inhibited fXa at nanomolar concentrations and showed good ex vivo anticoagulant properties (S-enantiomers were slightly more active than R-enantiomers). In general, a suitable dose ranging from 0.1 μg to 10 mg/kg/day has been established. As tumor cells express several procoagulant activities, which may be involved in hemostasis disturbances and metastasis mediated by the action of serine proteases on the protease activated receptor, some of these derivatives have been assayed for their ability to interfere with cellular proliferation in different cancer cell lines. Interestingly, compound 20 (MCM-09) was found to inhibit melanoma lung cancer colonies in mice in a dose-dependent manner [63].

Janssen Pharmaceutical Co. (Beerse, BE) disclosed a high-affinity 7-fluoroindazole-based fXa inhibitor (21, fXa $K_i = 1$ nM) [64]. Application of 1,2-benzisoxazol-3-amine as a bioisosteric replacement for the benzamidine moiety and
diverse P4 groups gave compounds (22 – 24) that exhibited fXa $K_i$ values in the low nanomolar range.

The 7-fluoroindazole scaffold seems to reduce the in vivo metabolic susceptibility [65]. Moreover, 7-F substituent, as well as the addition of a second fluorine on the 6-phenyl group, enhanced potency. A significant increase in potency was achieved by introducing 3-CONH$_2$ group (and not 3-CH$_3$ or 3-CF$_3$), as exemplified by compound 22 (fXa $K_i$ = 6.5 nM), which displayed good selectivity against tth and trypsin, but a low in vitro anticoagulant activity (2 x aPTT > 90 μM). The investigation on basic P4 moieties led to the pyridine-containing derivative 23 (fXa $K_i$ = 4 nM), and optimization studies led to the identification of compound 24, endowed with good in vitro anticoagulant properties and Caco-2 cell permeability.

7-Fluoroindazole derivatives bearing benzylamine as P1 element (25, 26) were also reported, which showed lower fXa inhibition potency and poorer selectivity versus trypsin.

In two very recent patents, mainly dealing with oxazolidinone-based fXa inhibitors [66,67], Schebo Biotech AG (Giessen, DE) has also described a number of amidine-based compounds (e.g., 27 – 31), including potential prodrugs (29, 30) and glycosyl derivatives (31), but no biological data have been provided.

Bristol Myers Squibb disclosed razaxaban (DPC-906, 4) in 2005 [34]. Then, a series of 3-trifluoromethyl pyrazole-5-carboxamide derivatives were patented [68,69], in which 1,1'-biphenyl-2-sulfonamide (32 – 36) group is fixed as
P4 element and different arginine-mimetic fused heterocycles, such as quinazolin-4-amine (32), phtalazin-1-amine (33), 1H-isindol-4-amine (34) and 1,2-benzisoxazol-3-amine (35, 36), investigated as P1 moieties. The most promising compounds were claimed for exhibiting fXa Ki values ≤ 1 nM.

4.2 Factor Xa inhibitors bearing neutral P1 binding moieties

Privileged neutral substituents, which interact with the S1 pocket through the ‘chloro binding mode’ and improve oral bioavailability, are 2-chlorothiophene, 3-chloropyridine, chlorobenzene, methoxybenzene, 2-chloronaphthalene and 5-chloro-1H-indole. While the molecular scaffolds may largely vary, there are a number of recurrent P4 substituents, among which pyridine-2(1H)-one, piperidin-2-one, morpholin-2-one, benzenesulfonamide, variously fused piperidines and benzazepines are the most privileged ones.

In the past 3 years, Bayer HealthCare company has registered the greatest number of patents in the area. Most of their disclosures deal with new rivaroxaban-like compounds, their administration forms and use in prevention and treatment of thromboembolic disorders. A series of 2-iminooxazolidine derivatives, structurally related to rivaroxaban 5 (fXa Ki = 0.4 nM), has been reported. Compound 37, exhibiting IC50 = 5.4 nM and ∼ 2,000-fold selectivity versus thr, is a representative example [70].
In other series, the morpholinone P4 moiety was replaced with 2-iminooxazolidine \[71\], morpholine \[72,73\] and 2-aminoethoxyacetic acid \[74\]. Compounds 38 (fXa IC\(_{50}\) = 1.1 nM), 39 (IC\(_{50}\) = 43 nM) and 40 (IC\(_{50}\) = 32 nM) shed light on structure–activity relationships of P4 elements. Replacing Cl in chlorothiophene with Br led to a twofold increase of fXa inhibition potency (41, IC\(_{50}\) = 0.3 nM; rivaroxaban, IC\(_{50}\) = 0.7 nM) \[75\]. In vivo data from the AV shunt model in rat were reported along with results from thrombin generation assay in human platelet rich plasma (PRP), in which compound 41 has been tested alone and in combination with aspirin or clopidogrel. One patent \[76\] covered a number of compounds bearing fluorine at the ortho position of the phenyl ring, two representative potent fXa inhibitors being compounds 42 and 43. Irrespective of their diverse P4 elements, they displayed the same inhibition potency (fXa IC\(_{50}\) = 0.9 nM). Bayer laboratories have reported other series of oxazolidinone-based compounds, which vary either for substituents on the phenyl ring or P4 moieties. Compounds 44 – 47 exemplify these series, but the enzyme data showed that none of them achieved inhibition potency and selectivity close to rivaroxaban. Indeed, compounds 44 and 45 \[77\] were both reported with IC\(_{50}\) values of 11 nM for fXa, but 10 and 34 nM, respectively, for thr. Compound 46 \[78\] inhibited fXa and thr with IC\(_{50}\) values of 21 and 198 nM, respectively, whereas, as shown by compound 47 \[79\], the introduction of the cyclopropyl group at the meta position of the P3 phenyl group and ring expansion of the P4 moiety...
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resulted in a marked decrease of fXa/thr selectivity (fXa IC$_{50}$ = 25 nM; thr IC$_{50}$ = 34 nM).

As for oxazolidinone derivatives, Bayer has also registered a few patents pertaining to methods for treating thromboembolic disorders (e.g., dosage) [80], controlled-release oral administration form [81], formulation for prophylaxis and treatment of pulmonary hypertension [82] and therapeutic use in prevention and treatment of disseminated intravascular coagulation, septic shocks, septic organ dysfunction and failure [83].

Other disclosed potent fXa inhibitors are exemplified by the 4,5-dihydroisoxazole derivative 48 (IC$_{50}$ = 7.9 nM) and pyrazole derivative 49 (IC$_{50}$ = 1.4 nM) [84].

Bayer has reported further potential anticoagulants that incorporate indolin-1-one as central core. Two isomer compounds, namely 50 and 51, exhibited fXa IC$_{50}$ values of 1.2 and 5.3 nM, respectively [85]. Compound 52 was found to inhibit fXa with an IC$_{50}$ of 1.1 nM [86,87]. Compounds 53 – 56 are four further potent fXa inhibitors, representative of series reported in as many recent patents, which exhibited subnanomolar IC$_{50}$ values. The pyrazole-related derivative 53 displayed IC$_{50}$ of 0.8 nM [88], and even more potent inhibitors resulted in the pyrazine dicarboxamide derivative 54 (IC$_{50}$ = 0.16 nM) [89], the 2-methylthiazol dicarboxamide derivative 55 (IC$_{50}$ = 0.30 nM) [90] and the anthranilamide-based compound 56 (IC$_{50}$ = 0.66 nM) [91].

Boehringer Ingelheim has reported several derivatives bearing 2-chlorotripheny1 as P1 element. As exemplified by structure 57, some of them incorporate 1-aminocyclopropanecarboxylic acid as the central template [92] and 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine as S4 binding motif. Other patents disclosed compounds with pyrrolidin-2-one and other five-membered rings, including imidazole and oxadiazole, as central templates, and either basic or neutral P4 moieties, as illustrated by structures 58 – 62 [93-96].

A variety of fXa inhibitors, containing 3-chloropyridine (63, 64), chlorobenzene (65) and 5-chloro-1H-benimidazole (66, 67) as the P1 moieties, and 2-methyl-1,2,3,4-tetrahydroisquinoline, 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and morpholin-2-one as suitable P4 substituents, has been reported [97-101]. In addition, one patent deals with fXa inhibitors bearing 2-ethenylthiophene as P1 element (68) [102], whereas a more recent patent described azetidine dicarboxamide derivatives bearing bromobenzene as P1 moiety (e.g., 69) [103]. All these compounds were claimed for inhibiting fXa with IC$_{50}$ values < 100 μM.

Recent papers reported 1,2- cis-(1R,2S)-cyclopyridinylamide and cyclohexylamine derivatives [104,105]. A series of nonbasic selective fXa inhibitors, built up using a central cycloalkyl dicarboxylic acid scaffold [106,107], has been patented from Hoffman-La Roche. In an attempt to improve activity and oral bioavailability, the dicarboxylic acid moiety was replaced by different aliphatic cyclic amino acids, affording compounds 70 – 72 [108], which bear 5-chlorothiophen-2-carboxamide as P1 moiety. The most potent fXa inhibitor 70 exhibited fXa Ki value of 6 nM. An important feature was shown to be the alkoxy side chain at C-4 of the cyclopentane ring, the ethoxy group providing the most favorable effect. The hydroxy congener of 70 and compound 71 had been found to be 3 times less potent than 70. Moreover, alkyl groups longer and more sterically hindered than the ethyl group did not enhance the activity, as well as the replacement of the ethoxy side chain with 2-oxopropyl group (72, Ki = 30 nM) [108].

A focused screen on the Roche compound collection allowed the 2-aminothiazole-based fXa inhibitor 73 to be identified (Ki = 112 nM) [109,110]. Unfortunately, it failed to display optimal anticoagulant activity in vitro (2 × aPTT = 70.1 μM), most likely because of its high lipophilicity. Hence, N-substituted piperazines were investigated as P4 elements, and compounds 74 (Ki = 442 nM, 2 × aPTT = 32 μM) and 75 (Ki = 32 nM, 2 × aPTT = 4.4 μM) resulted by far superior with respect to fXa inhibition potency and in vitro clotting assays [109]. The thiazole core was also replaced by various 5-membered nitrogen heterocycles, such as pyrazole, 1,3,4-triazole (76) and tetrazole. Compound 76 displayed excellent in vitro activity (fXa Ki = 6 nM, 2 × aPTT = 2 μM) [109]. Finally, 3-aminopyrrolidine derivatives (77 – 79), in R-configuration, exhibited excellent Ki values [111], and compound 77 emerged as the most potent compound in this series (fXa Ki = 3 nM). Removal of the methoxy group or introduction of larger substituents led to a loss of activity [111]. Unfortunately, compound 77 is rapidly metabolized by human and rat microsomes, whereas the corresponding hydroxy derivative showed better microsomal stability. A good fXa inhibitory potency was achieved by the trifluoromethyl derivative 78 (Ki = 8 nM), in which curiously chlorothiophene was replaced by the -butoxy carbonyl group [111]. A recent disclosure is represented by compound 79 (Ki = 23 nM). Other patents deal with compounds containing various cycloalkyl dicarboxylic acids as central scaffolds [106,107]. Among them, compound 1,5,2R,8R exhibited Ki value of 3 nM, and improvements were claimed for a number of derivatives (e.g., 81 – 84) [106,107].

Promising results were obtained with the spirocyclic derivative 55,65S-82 (Ki = 8 nM), tac-83 (Ki = 9 nM) and 1,5,2S,4S-84 (Ki = 8 nM). In vitro anticoagulant assays showed good efficacy (2 × aPTT values in the 0.5 – 10 μM range). The patented synthesis of cyclopentan-1,2-dicarboxamides is illustrated in Figure 4. Oxidation of the exocyclic methylene group by periodate cleavage or epoxidation afforded the cyclopentanones or the corresponding spirocyclic epoxides as useful starting materials for subsequent reactions.

In 2007, Hoffman-La Roche filed two patents on compounds bearing 4-chlorophenyl and pyridine-2(1H)-one as P1 and P4 moieties, respectively, exemplified by compounds 85 – 90 [112,113], which contain fused azaheterocyclic nuclei as central cores. These compounds exhibited good in vitro anticoagulant properties, as assessed by concentrations doubling prothrombin time (PT) and aPTT, ranging from 0.5 to 10 μM, and nanomolar fXa Ki values. Pyridine fused cyclic amine derivatives 86 (Ki = 51 nM) and 87 (Ki = 12 nM) resulted
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in less potent compounds than corresponding benzene fused analogues 89 (3,4-dihydro-1H-isoquinoline series) and 90 (2,3-dihydroisoindole series), both displaying $K_i$ of 2 nM.

In several patents, Bristol-Myers Squibb disclosed a family of anthranilamide-based fXa inhibitors, bearing chloropyridine and pyridine-2(1H)-one as P1 and P4 binding moieties, respectively [114,115]. Specific biological data were not reported, whereas a recent publication provided information on compounds 91 and 92, which exhibited fXa $K_i$ values in the picomolar range ($\leq 0.06$ nM), good oral bioavailability, low- to moderate clearance and half-life shorter than apixaban [116].

In another application, Bristol-Myers Squibb claimed cyclic $\beta$-amino acids based derivatives, such as compounds 93 – 95 [117]. The most potent inhibitors showed fXa inhibition constants $< 1$ nM.

As reported earlier, in 2005 Bristol-Myers Squibb disclosed razaxaban (4, DPC-906) and investigated a series of its analogues. These studies revealed that compounds belonging to pyrazole carboxamide series may undergo in vivo hydrolysis with liberation of potentially mutagen biarylaniline compounds [34]. Then, a great deal of efforts was made to find more in vivo stable fXa inhibitors, pursuing several strategies, which mainly consist in incorporating the amide group into a bicyclic lactam structure and replacing anilines with cycloalkamines. A lot of new compounds, including carboxamide and dione derivatives of pyrazolo[3,4-c]pyridine (96, 97), pyrazolo[4,3-d]pyrimidinone (98), pyrazolo[3,4-d]pyridazinone (99) and pyrazolo[3,4-c]azepinone (100), were synthesized and patented [118-123].

Compounds bearing 4-methoxyphenyl and biphenyl-2'-sulfonamido as P1 and P4 residues, respectively, proved to be potent fXa inhibitors, with $K_i$ values in the range of 1 – 40 nM. Unfortunately, aPTT clotting assay revealed poor anticoagulant properties in compounds containing pyrazolo [3,4-d]pyridazinone, pyrazolo[3,4-c]azepinone and pyrazolo [4,3-d]pyrimidin-5,7(4H, 6H)-dione as bicyclic core, because of their high binding to plasma proteins. Promising results were instead obtained with derivatives of pyrazolo[3,4-c]pyridinone and pyrazolo[4,3-d]pyrimidinone, the most active compounds showing $2 \times$ aPTT values in the low micromolar range [118,119]. In the development of bicyclic lactam derivatives belonging to the pyrazolo[3,4-c]pyridinone-7-one family (general structure 101), diverse P4 moieties and substituents at C-3 of pyrazole ring have been introduced (general...
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Chemical structures:

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Compounds 105 ($K_i = 0.3$ nM) and 106 ($K_i = 0.03$ nM, $2 \times PT = 1.2$ μM) exhibited promising anticoagulant activity and good pharmacokinetic profile in dogs [120-124]. In order to reduce the potential risk of releasing in vivo mutagenic biarylanilines, the 6-phenyl group was replaced with a piperidine one, leading to derivatives such as compound 107 [125]. The introduction of pyridin-2(1H)-one led to apixaban (6, BMS-562247-1, $K_i = 0.08$ nM, $2 \times PT = 3.8$ μM) [36], which proved to be effective in inhibiting both free and clot-bound fXa and is currently undergoing advanced stages of clinical trials [126-128].

Most of the patents registered by Millennium Pharmaceuticals reported fXa inhibitors incorporating various 5-membered heterocycle rings as central cores and 5-chlorothiophene-2-carboxamide as constant P1 moiety. Compound 108 [129] exhibited fXa IC$_{50}$ at concentration < 100 nM. A series of imidazole derivatives, exemplified by compounds 109 and 110 [130], both bearing pyridine-2(1H)-one as P4 group, proved to be in vitro inhibitors of fXa (IC$_{50} \leq 100$ nM), but the impact of 2-oxopiperazine at the ortho position of the P3 phenyl group cannot be assessed (no specific biological data provided). For compound 111, pharmacokinetic data in rat, dog and monkey after oral or intravenous administration were given. 1,2,3-Triazole derivatives, exemplified by compounds 111 and 112 [131,132], have been also reported and the respective in vitro fXa IC$_{50}$ values claimed to be ≤ 100 nM. Methods for preparing suitable pharmaceutical salts and polymorphs of the anthranilamide derivative betrixaban (10) have been described [133,134]. As reported in recent publications [135,136], compounds belonging to this series are highly potent and orally bioavailable fXa inhibitors. In thrombin generation assay in human platelet rich plasma (PRP), combination of compound 10 (15.6 nM) with aspirin proved to be successful (26.9% inhibition versus 5.1% inhibition without aspirin) [137].

The pyrrolidinone series of fXa inhibitors disclosed by GlaxoSmithKline (Greenford Middlesex, GB) was already discussed in previous patent review [29]. Further reported compounds incorporate various benzofused cyclic amines as S4 binding moiety. Compound 113, representative of this series [138], has been claimed as active principle in modified pharmaceutical composition for oral administration [139,140].

Some Glaxo patents reported introduction of diverse polar groups on the sulfonamide nitrogen or in P4-position [141,142]. Specific biologic data were not reported, but in medicinal chemistry literature compound 114 (fXa $K_i = 4$ nM), which exhibited appreciable selectivity versus thr ($K_i = 367$ nM) and oral bioavailability (%F = 75% in Sprague-Dawley rats), as well as reduced binding to human serum albumin and good anticoagulant effects ($1.5 \times PT = 1.2$ μM), was identified as one of the most attractive candidates for further developments [143]. Interestingly, small modifications at the double bond led to different selectivity ratios [144]. Thus, the saturated
Figure 4. Synthetic pathway for a series of cyclopentan-1,2-dicarboxamide derivatives patented by Hoffman-La Roche as fXa inhibitors.

fXa: Factor Xa.
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[Chemical structures of various factor Xa inhibitors are shown.]
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derivative reverted the selectivity ratio (FXa $K_i = 154 \text{ nM}$, thr $K_i = 17 \text{ nM}$) and the propenyl derivative 115 resulted in a potent dual inhibitor ($K_i$ values for both FXa and thr = 2 nM) endowed with good in vitro anticoagulant activity (1.5 × PT = 0.54 μM) and oral bioavailability. 2-Chloronaphthalene was also introduced as P1 neutral moiety (e.g., 116) [145,146].

Edoxaban 9 (DU-176b, Daiichi Sankyo) is an oral FXa inhibitor showing $K_i$ value of 0.6 nM, 10,000-fold more selective for FXa than for thr. Daiichi Pharmaceuticals reported several series of FXa inhibitors incorporating chlorothiophene, chlorobenzene, chloropyridine and chloroindole as P1 binding moieties and, in most cases, 5-methyl(or isopropyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine as P4 group. One patent reported $N$-formyl (or acetyl) piperidine-3,4-diamide derivatives [147]. The water-soluble compound 117 exhibited good FXa inhibitory potency (IC$_{50}$ = 0.9 nM) and anticoagulant properties (2 × PT in human plasma = 0.14 μM), as well as oral bioavailability in monkeys (AUC = 899 ng·h/ml).

Using diversely substituted 3-aminobenzoic acid as central scaffold, a wide series of FXa inhibitors was obtained [148], the most active compound in this series being 118 (FXa IC$_{50}$ = 0.51 nM). Change in the fluorine atom position led to marked loss of activity, and the carboxylic group emerged as important element. As for compounds bearing chloropyridine as the P1 moiety, in vitro IC$_{50}$ values were reported only for 119 and 120 (2.2 and 1.6 nM, respectively). These compounds displayed good anticoagulant properties (2 × PT in human plasma = 0.26, 0.25 and 0.50 μM, respectively) and pharmacokinetics after oral administration in monkey.

Among FXa inhibitors of Daiichi Sankyo, compound 121 (IC$_{50}$ = 2.2 nM) [149] deserves mention. Substitution of chloropyridine with chlorobenzene moiety causes 60% loss of the inhibitory activity. The replacement of chlorine atom in the central ring with a methoxy group did not produce any significant biological effect. In contrast, fluorination at 3-position of the piperidine ring slightly increased potency, as shown by the IC$_{50}$ value of compound 122 (1.8 nM), whereas a carboxyl group on the central phenyl ring doubled the inhibitory potency (123, FXa IC$_{50}$ = 1.1 nM). Novel FXa inhibitors were identified among compounds built up using 3-amino-4-(2-carboxyethyl)benzoic acid as the central scaffold, such as 124 and 125 (FXa IC$_{50}$ = 0.38 and 0.39 nM, respectively) [150].

Very recently, Daiichi Sankyo Co. filed a patent describing synthesis of orally available potent factor Xa inhibitors [151]. Their disclosures include compounds bearing 5-chloroindole and 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine groups as suitable P1 and P4 moieties, respectively. A series of (piperazin-1-yl)sulfonyl derivatives were provided, which displayed high FXa inhibition potency, as exemplified by

![Chemical structures](image-url)
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compound 126 ($K_i = 5$ nM), but with unsatisfactory oral bioavailability [152]. The replacement of piperazine with 1,2-cyclohexyldiamine led to less potent fXa inhibitors, whereas better results were achieved with the diamide derivatives cis-127 ($K_i = 41$ nM) and trans-128 ($K_i = 13$ nM). Ring size showed significant effect on potency [153]. Although less potent than the trans isomer 128, cis-127 showed better anticoagulant activity. Even more the dimethylcarbamoyl derivative 129, with a given stereochemistry, enhanced fXa inhibition and anticoagulant activity ($K_i = 5.1$ nM, $2 \times PT = 0.9$ μM).

AstraZeneca contributed to the discovery of novel fXa inhibitors with four patents. Two patents disclosed compounds 130 (fXa IC$_{50} = 18$ nM) and 131 (fXa IC$_{50} = 0.5$ nM) [154,155]. Another series incorporates piperidine instead of the phenyl ring; this is exemplified by compounds 132 (IC$_{50} = 2.3$ nM) [156] and 133 (IC$_{50} = 4.8$ nM) [157].

Three patents from Merck described pyrazole carboxamide derivatives bearing benzylamine (134) or benzamide (135 – 137) groups as P1 moieties, and various basic and nonbasic pyrrolidine-, imidazolidine- and 1,3,4-thiadiazole-containing P4 moieties [158-160]. These compounds were shown to serve as dual fXa/TF:FVIIa inhibitors, as specified by compound 134 (fXa IC$_{50} = 9.6$ nM; TF:FVIIa IC$_{50} = 23$ nM). One patent claimed disclosure of proline derivatives, exemplified by compounds 138 and 139 [161], without furnishing the respective biological data. Further developments of previously registered glycine-based fXa inhibitors were also described [162].

In previous patents, Eli Lilly & Co. disclosed LY-517717 (8) as a clinical candidate [29]. Further patents claimed a stable crystalline salt of LY-517717 [163], additional modifications to anthranilamide-based fXa inhibitors, as exemplified by compound 140 (fXa $K_{ass} = 407 \times 10^6$ l/mol) [164] and novel pyridine-3,4-diamine derivatives, such as compound 141 [165].

Takeda Pharmaceutical Co. reported several fXa inhibitors containing piperidine as central scaffold and 2-chloronaphtalene as S1 binding moiety. A recent disclosure deals with sustained
release preparations containing fXa inhibitors like compound 142 [166-168]. Additional modifications were accomplished by replacing piperidine with piperazine; compound 143 (fXa IC$_{50}$ = 2.1 nM) exemplifies this series.

Among the anthranilamide-based compounds, betrixaban (PRT-054021, 10) was found to be an orally available fXa inhibitor (K$_i$ = 0.117 nM), which has been selected as clinical candidate [135]. Portola Pharmaceuticals has filed two previous patents claiming preparation of amino acid (e.g., glycine, phenylglycine), urea [169] and thiourea [170] derivatives. Most of their disclosures include compounds bearing chlorophenyl or bromophenyl groups as P1 elements, as exemplified by compounds 144 and 145, respectively (fXa IC$_{50}$ ≤ 100 nM). Sulfonyl urea derivatives, specified by compound 146, were claimed as agents effective in inhibiting ADP-dependent human blood platelet aggregation [171].

Pfizer has registered a patent reporting preparation of the chiral 5-methyl-4,5-dihydropyrazole-based fXa inhibitor 147 [172], in which the S enantiomer (IC$_{50}$ = 0.982 nM) was claimed as much more potent inhibitor than the R enantiomer (0.141 μM). Preparation of polymorphic crystalline forms of the (2R,4R)-1,2-pyrrolidine carboxamide fXa inhibitor (148), known as eribaxaban [173], has been described by Warner-Lambert (Morris Plains, New Jersey, US) in a patent [174] that additionally reports suitable pharmaceutical dosage.

Aventis Pharma, which merged with Sanofi in 2004, has contributed to the development of novel fXa inhibitors during the period 2000 – 2005 [29]. A major outcome of the efforts of the Aventis group was the discovery of otamixaban (2, fXa K$_i$ = 0.4 nM). A recent patent [175] deals with aminosulfonylhexyl-based compounds, as exemplified by compound 149 (K$_i$ = 5 nM).
Other companies have contributed to the advances in the field in recent years. Among them, Legochem Biosciences (Daejeon, KR) has reported various rivaroxaban-like compounds (e.g., 150 with \( K_i = 0.39 \text{ nM} \)) [176,177]. Tanabe Seiyaku Co. (Osaka, JP) has used, among others, benzofuran as central scaffold (151, \( IC_{50} = 0.8 \text{ nM} \)) [178] and described 3-chloroanthranilamide derivatives (152, \( IC_{50} = 2.5 \text{ nM} \)) [179]. Astellas Pharma disclosed anthranilamide derivatives, exemplified by compound 153 (fXa \( IC_{50} = 6.7 \text{ nM} \)) and the glucuronic acid derivative 154 [180]. Mochida Pharmaceutical Co. (Gotemba, Shizuoka, JP) investigated two different families of spiro-tricyclic and tetracyclic perhydroimidazo[1,2-a]pyrazine derivatives with general structure 155 [181-184]. Compound 156 (fXa \( K_i = 0.4 \text{ nM} \)) is representative of this family. Schebo Biotech has described preparation and suitable pharmaceutical compositions of new fXa inhibitors belonging to oxazolidinone (157), pyrazolo[3,4-c]pyridine (158), anthranilamide (159) and salicylamide (160) series [66,67]. The preparations of deuterated rivaroxaban and related pharmacokinetic study in rats [185], as well as deuterium-enriched apixaban [186], have been also reported in the patent literature.

5. Expert opinion

New anticoagulants that do not need frequent monitoring or dose adjustment are required for VTE treatment and stroke prevention in patients with AF. Among them, drugs that inhibit fXa are attractive options. As fXa inhibitors prevent the generation of new thrombin, without affecting its basal level that ensures primary haemostasis, their use may overcome bleeding, that is, a limitation of current oral antithrombotic therapy.

The first generation of direct fXa inhibitors (the so-called xabans), which relied upon a benzamidine group as S1 binding moiety, exhibited high clearance and limited oral bioavailability. These limitations have been successfully addressed through the replacement of the benzamidine moiety with less basic bioisoster or nonpolar neutral P1 elements. Indeed, fXa inhibitors under the most advanced stage clinical trials, namely rivaroxaban, apixaban and edoxaban, bear different lipophilic non-amidine groups as P1 substituents.

Numerous oral, direct fXa inhibitors are currently at various stages of clinical development. The selective inhibitors that
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recently reached the clinic no longer contain highly charged groups, such as amidine and carboxylic acid groups. They incorporate neutral (e.g., rivaroxaban, apixaban) or less basic amidine mimics (e.g., edoxaban, betrixaban), which lead to significant improvement in oral bioavailability. Rivaroxaban, apixaban and edoxaban are the furthest advanced in their development programs, but other low molecular weight direct Xa inhibitors, such as YM-150, LY-517717, betrixaban, TAK-442, entered Phase II clinical trials. Pivotal Phase III studies and several Phase II trials have established the efficacy and safety of these Xa inhibitors for the prevention of VTE after orthopedic surgical interventions and/or for the treatment of VTE, supporting on the other hand the potential for stroke prevention in patients with AF. The clinical development of new anticoagulants, including the direct Xa inhibitors, follows the well-established strategy of dose-ranging and registration studies in major orthopedic surgery, prior to development in arterial indications. Based on data from clinical trials, the availability of new oral Xa inhibitors is expected to have a great impact on the AF-related stroke prevention segment of the market, in which the use of warfarin should become obsolete [42].

Besides novel selective Xa inhibitors, direct thrombin inhibitors, such as dabigatran etexilate, with better therapeutic windows and ease-of-use than the existing anticoagulants, which can conveniently replace heparins and vitamin K antagonists (i.e., warfarin) in the prophylaxis and treatment of thrombotic disorders, are currently being developed. It remains to be established which is a better target between Xa and thr. To address this question direct comparison trials are needed. Although the new anticoagulants exhibited favorable safety profiles, there is, however, the need of monitoring them for unexpected adverse effects.

As far as the future developments are concerned, > 100 patents filed between 2006 and April 2009, examined in this review, highlight the variety among the P1 and P4 moieties, showing that the majority of the newly synthesized Xa inhibitors contains neutral lipophilic groups as P1 moieties. Privileged non-amidine P1 groups are 2-chlorothiophene,
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3-chloropyridine, chlorobenzene, methoxybenzene and 5-chloro-1H-indole. While the central core may largely vary, including oxazolidine, pyrazole, piperazine, anthranilamide, indole, indazole, cyclic diamine and others, there are a number of recurrent P4 substituents, among which pyidine-2(1H)-one, piperidin-2-one, morpholin-2-one, fused piperidines and benzazepines emerge as the most preferred ones. Many combinations of P1 and P4 groups on suitable scaffolds have led to the disclosure of a number of FXa inhibitors with high potency, selectivity and oral bioavailability, and the results from Phase II and Phase III studies reflect the drive towards FXa inhibitors as potentially more effective and safer antithrombotic drugs. The development of these drugs is expected to address two major unmet needs for anticoagulation, namely safety and ease-of-use, and to significantly affect the anticoagulant market.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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** An excellent review that highlights the current pharmacology and the most recently published data from clinical trials with the new anticoagulants, including factor Xa inhibitors.

• This paper reports a systematic study aimed at improving antithrombotic efficacy and oral bioavailability of factor Xa inhibitors, by replacing the benzamide in the P1 position with less basic benzamidine mimics or neutral residues.

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