Rational Design, Synthesis, and Biological Activity of Benzoxazinones as Novel Factor Xa Inhibitors

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Received February 21, 2000

Inappropriate thrombus formation within blood vessels is the leading cause of mortality in the industrialized world. Factor Xa (FXa) is a trypsin-like serine protease that plays a key role in the blood coagulation cascade and represents an attractive target for anticoagulant drug development. From a high-throughput in vitro mass screen of our chemical library, we identified 4-[5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**1a**) as an inhibitor of FXa with an IC_{50} of 27 μM. Through a combination of SAR studies and molecular modeling, we synthesized 3-(4-[5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide (**1n**) which was a potent FXa inhibitor with an IC_{50} of 3 nM. This compound exhibited high selectivity for FXa over other related serine proteases and was efficacious when dosed intravenously in rabbit and dog antithrombotic models.

Introduction

Abnormal coagulation and inappropriate thrombus formation within blood vessels precipitates many acute cardiovascular disease states. The resulting clinical ramifications of occlusive thrombus development, including myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke, annually affect millions of people worldwide and are the leading causes of mortality and morbidity in the industrialized world.[1] While a variety of plasma proteins such as fibrinogen, serine proteases, and cellular receptors are involved in hemostasis, it is the abnormal regulation that disrupts the fine balance between hemostasis and thrombosis that leads to cardiovascular disease. Thrombin (factor IIa) is the final serine protease in the pathway to generate a fibrin clot and can be considered the principal regulatory enzyme in the coagulation cascade. It serves a pluralistic role as a positive and negative feedback regulator in normal hemostasis. However, in some pathologic conditions, the former is amplified through catalytic activation of cofactors required for thrombin generation such as factor Xa (FXa).

Factor Xa is a trypsin-like serine protease that plays a key role in the blood coagulation cascade by ultimately regulating the generation of thrombin by proteolysis of prothrombin. The catalytic activity of FXa is present in the prothrombinase complex, which is also composed of nonenzymatic cofactor Va and calcium ions assembled on the phospholipid membrane surface of activated platelets or inflammatory cells adhering to the site of vascular damage.[2] This prothrombinase complex is located at the convergence of both the intrinsic and extrinsic coagulation pathways, and because of this key position in the enzymatic cascade, FXa represents an attractive target for anticoagulant drug development.

Ample evidence exists for the role of FXa inhibitors as anticoagulants. Antistatin, a potent inhibitor of blood coagulation FXa isolated from the Mexican leech (*Haementeria offcinalis*), displayed antithrombotic activity in various models of arterial and venous thrombosis.[3] Other protein or polypeptide FXa inhibitors include recombinant tick anticoagulant peptide (rTAP), which exhibited potent antithrombotic efficacy in various experimental models and was equal or superior to herapin and hirudin in its action when administered parenterally.[4] In addition to these relatively high-molecular-weight proteins which are not suitable as oral antithrombotic agents, there also exist examples of low-molecular-weight FXa inhibitors.[5] In particular the bisamidine DX-9065a (Figure 1), a low-molecular-weight synthetic FXa inhibitor, has been shown to possess antithrombotic potential in various experimental thrombosis models.[6] In both arteriovenous shunt and venous stasis models, inhibition of thrombus formation was achieved at doses that had little effect on activated partial thromboplastin time (aPTT), indicating that DX-9065a was effective in preventing thrombosis and hence has therapeutic antithrombotic potential.[7]

We have designed and systematically synthesized a new class of low-molecular-weight benzoxazinone FXa inhibitors of structural type **1**, which originated from high-volume screening of our chemical library. In this report, we will describe the synthesis and in vitro and in vivo activity of this novel series of FXa inhibitors. [8]

Chemistry

The synthesis of the compounds in Table 1 proceeded by linear stepwise processes as shown in Schemes 1−3. Of the routes shown in Scheme 1 the alkylation of the *o*-nitrophenol or *o*-aminophenol by the α-bromoacetic acid derivatives **3** was the most favored approach.[9,10] In general for step b, the yields were modest (∼55%) when an excess of the sodium salt of the appropriate

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10.1021/jm000074l CCC: $19.00
Published on Web 09/27/2000

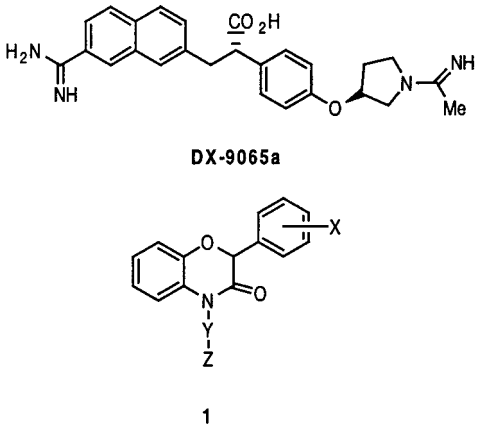
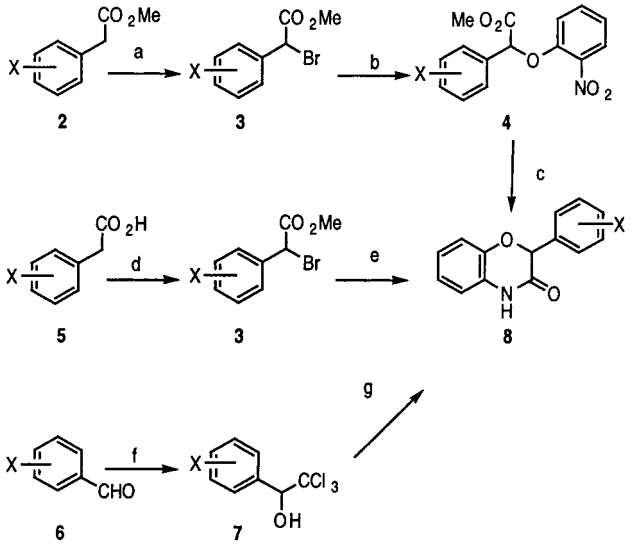


Figure 1. DX-9065a and structural formula for a new class of benzoxazinones.

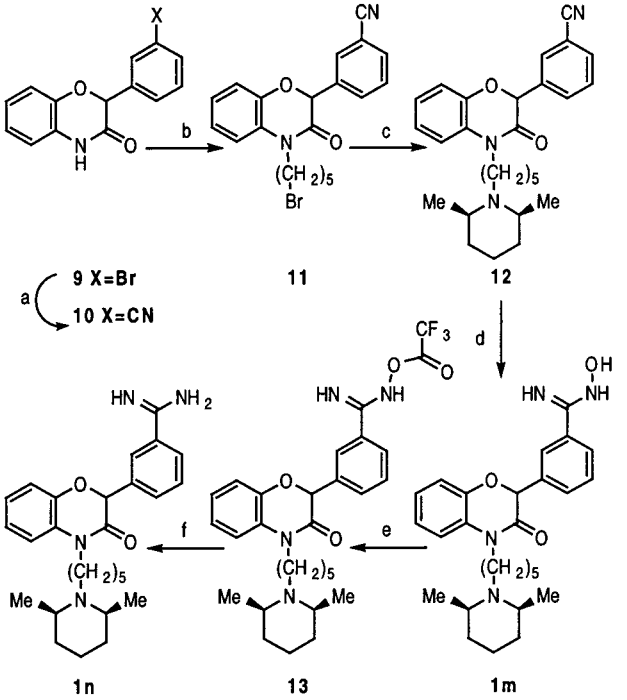
Scheme 1. Synthesis of Benzoxazinones[a]



[a] (a) NBS, VAZO52, CCl_4; (b) *o*-nitrophenol sodium salt, DMSO; (c) H_2, RaNi, MeOH; (d) PBr_3, Br_2, MeOH; (e) *o*-aminophenol hydrochloride, NaH, DMF; (f) CCl_4, $PbBr_2$, Al foil, DMF, rt; (*g*) *o*-aminophenol hydrochloride, NaH, DMF or DMSO.

o-nitrophenol was employed in DMSO, at a slightly elevated temperature (60−70 °C). These ethers were then reduced with hydrogen and Raney nickel in methanol which provided the corresponding aniline that underwent intramolecular cyclization to directly afford the benzoxazinone **8**. In some instances, as a slightly modified procedure, the *o*-aminophenol was treated directly with the α-bromoacetic acid derivative **3** such that the benzoxazinone **8** was generated directly, as shown by step e.[11] This sequence was particularly useful to circumvent undesirable overreduction, which resulted in debenzylation or in some situations dehalogenation, for some of the derivatives of Table 1. While an alternative approach of treating the trichloromethyl carbinol derivative **7** with *o*-aminophenol benefited from a large variety of aldehydes that could easily be converted to the carbinol, the route suffered from modest yields that were obtained upon formation of the benzoxazinone **8** and hence was not generally employed.[12] Interestingly, while a number of reaction conditions were attempted, the yields of the benzoxazinones never met those described for this transformation in the literature.[13]

Scheme 2. Synthesis of 3-(4-[5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxybenzenecarboximidamide (**1n**)[a]

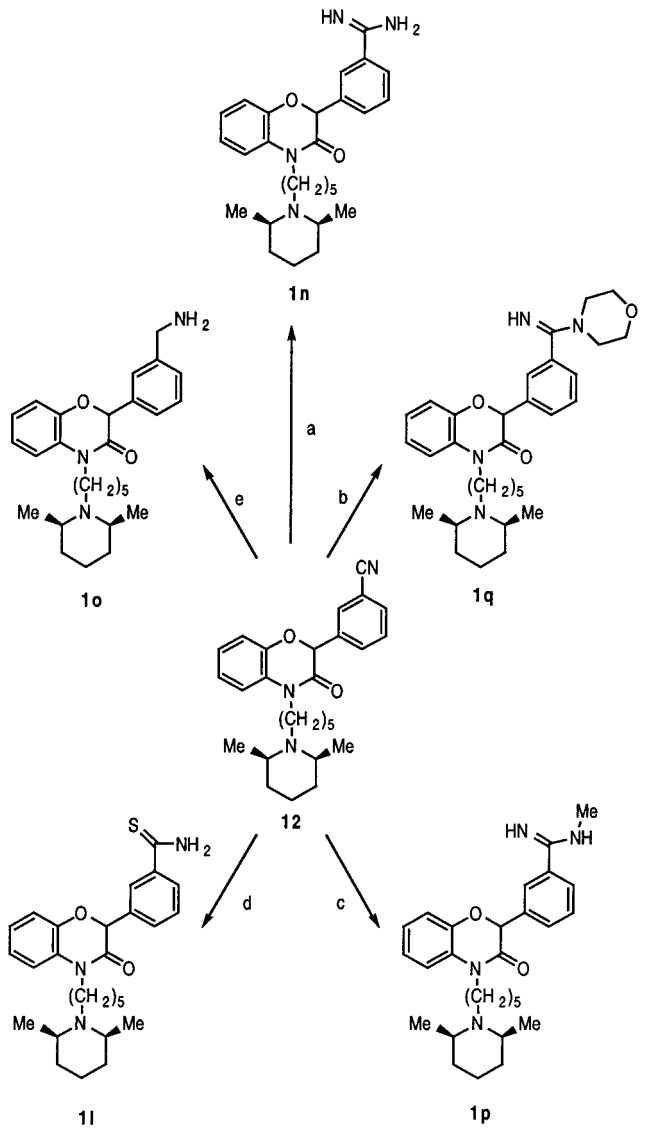


[a] (a) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 100 °C; (b) 1,5-dibromopentane, NaH, DMF; (c) *cis*-2,6-dimethylpiperidine, DMF, 70 °C; (d) $H_2NOH{\cdot}HCl$, *N*,*N*-diisopropylethylamine, MeOH; (e) trifluoroacetic anhydride; (f) H_2, trifluoroacetic acid, 20% Pd/C.

Scheme 2 depicts the subsequent steps that were employed to elaborate the intermediate benzoxazinone **9** to the final compounds **1m**−**1n**. The bromide **9** was converted to the nitrile **10** by treatment with a transition metal, such tetrakis(triphenylphosphine)palladium-(0) and zinc cyanide, in DMF, typically to a temperature of 100 °C for 24 h to afford the required product in 75% yield.[14] Alkylation of the lactam at N-1 proceeded in reasonably good yield by generating the sodium salt with sodium hydride in DMF and then treating with an excess of 1,5-dibromopentane to give **11**. Addition of *cis*-2,6-dimethylpiperidine and warming of the reaction mixture to 70 °C afforded the piperidine derivative after a period of 16 h. Conversion of the nitrile **12** to the amidine in **1n** was achieved by first generating the amidoxime **1m** with an excess of hydroxylamine at room temperature.[15] In situ activation of the amidoxime by formation of the trifluoroacetate ester **13** and then hydrogenation readily afforded the required compound **1n**. This route also demonstrates the alkylation of benzoxazinones and the further derivatization with amines which is applicable to the preparations of **1a**−**1h** and **1r**−**1y**.

While it is apparent that nitriles may be converted to a variety of functional groups, as depicted in Scheme 3, the generation of the imino ether with dry hydrogen chloride in methanol was the preferred procedure for preparing the substituted amidines **1p**−**1q**. The well-known methodology of proceeding to the amidine via the thioamide followed by alkylation and treatment with ammonia was not efficient in this series.[16]

Scheme 3[a]



[a] (a) (i) HCl, EtOH, (ii) NH_3/EtOH; (b) (i) HCl, EtOH, (ii) morpholine; (c) (i) HCl, EtOH, (ii) 2 M methylamine in toluene; (d) H_2S, pyridine; (e) H_2, RaNi, Et_3N, MeOH.

Results and Discussion

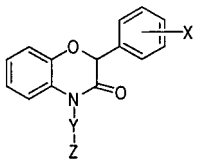
The discovery program oriented toward the identification of antithrombotic FXa inhibitors was initiated by conducting a high-throughput in vitro screen of our chemical library against FXa at fixed inhibitor concentrations of 10 and 100 μM. Although several active series of compounds emerged from this analysis, the benzoxazinone **1a** with an IC_{50} of 27 μM was selected for further chemical exploration. The compound had a relatively unique chemical structure that was readily amenable to SAR studies. It was also apparent that the compound did not contain a moiety capable of interacting with the FXa Asp189 (chymotrypsinogen numbering) in the S1 pocket. This is an interaction typical of known FXa inhibitors and suggested to us that the introduction of such a pharmacophore could be expected to improve activity. Thus, a systematic investigation of the lead (**1a**) was undertaken to determine substituents that would improve FXa inhibitory activity. These investigations were guided, in part, by the application of a molecular modeling program (GASP) which allowed comparison of the screening lead with a known FXa inhibitor, DX-9065a.[17]

Each of the analogues required multiple synthetic steps, which did not proceed through any common intermediates, severely restricting the number of analogues that could be prepared. Therefore, the selection of substituents was initially guided by the application of the Topliss tree approach with the goal of gaining as much information from the least numbers of analogues. The Topliss approach takes into account the electronic, lipophilic, and steric factors for substitution on a phenyl ring using basic Hansch principles in a noncomputerized manner.[18] Fortunately, when **1f** was synthesized among others (**1b**−**1h**), it displayed a modest improvement in inhibitory activity suggesting that substituents on this ring significantly affected in vitro FXa activity (IC_{50}'s 4.9−26 μM for **1a**−**1h**). Further analysis of the GASP generated overlays of **1f** and DX-9065a suggested that the 4-methoxyphenyl moiety may occupy the S1 pocket of FXa. In fact, the first disclosure of a lipophilic moiety which occupied the S1 pocket was described in the X-ray of rTAP (tyrosine).[19] More recently, a 4-methoxyphenyl moiety was described as an S1 element.[20] Therefore, given the fact that an amidine substituent was common to nearly all FXa inhibitors, we replaced the methoxy group to afford the amidine analogue **1k**. Surprisingly, this analogue was even less active than the parent compound **1a**. However, preparation of the *m*-amidine derivative **1n** resulted in an almost 200-fold increase in in vitro activity with good selectivity toward a variety of other serine proteases (Table 2).

We then modified the chemically most accessible 2,6-dimethyl-1-pentylpiperidine substituent of the benzoxazinone. With the goal of retaining the basic nature of the region, we introduced amines, alkylamines, and various heterocycles (**1t**−**1y**) but did not elicit any improvement in activity. We also varied the length of the alkyl chain (**1r** and **1s**) that attached this basic substituent to the benzoxazinone and observed a loss in activity, suggesting that the five-carbon chain was optimal and implying that the *cis*-2,6-dimethyl-1-pentylpiperidine afforded a rather unique pharmacophore.

Fortunately, **1n** displayed marginal affinity for trypsin, which allowed for the X-ray crystallographic determination of the binding mode of this compound. Trypsin was used as a surrogate protein for FXa due to its structural similarity and because crystals of FXa had previously been shown to be very difficult to obtain.[21] From the trypsin crystal structure it was observed that the amidino moiety binds in the S1 pocket making the classical twin−twin hydrogen bonds to Asp189 as shown schematically in Figure 2 and stereographically in Figure 3.[22] The carbonyl group of the benzoxazinone accepts a hydrogen bond from Gly216NH, and the aryl ring of the benzoxazinone stacks against Gly219 and makes van der Waals contact with the Cys191−Cys220 disulfide bridge. While the dimethylpiperidine substituent lacked any definitive interactions with trypsin, a minimal conformational change of the flexible pentyl chain and modeling with FXa orientated the dimethylpiperidine in the "aryl-binding site" of FXa.[23] It is presumed therefore that the piperidine ring makes a cationic−π interaction with the protein affording enhanced binding. It was apparent that the trypsin/

Table 1. Benzoxazinone Analogues[a]



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				IC_{50} (μM) or % inhibition at 100 μM			
compd	X	Y	Z	FXa	thrombin	trypsin	plasmin
1a	H	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	27	19%	2.8%	26%
1b	3,4-Cl	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	26	47%	14%	25%
1c	4-Cl	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	23	38%	46%	30%
1d	2-Cl	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	16	65	39	23%
1e	4-CH_3	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	28	33%	18%	13%
1f	4-OCH_3	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	4.9	29%	2.3%	19%
1g	3,4-OCH_3	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	31%	0%	0%	0%
1h	3,4,5-OCH_3	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	30%	30%	12%	20%
1i	4-C(=S)NH_2	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	34	32%	7.8%	44%
1j	4-C(=NH)NHOH	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	66	18%	8%	10%
1k	4-C(=NH)NH_2	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	7.9	1.7	13	80%
1l	3-C(=S)NH_2	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	1.7	20%	5.2%	29%
1m	3-C(=NH)NHOH	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	5.6	19%	21%	11%
1n	3-C(=NH)NH_2	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	0.0030	0.89	0.33	8.4
1o	3-CH_2NH_2	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	0.84	64%	7.8	25
1p	3-C(=NH)$NHCH_3$	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	2.8	68%	32%	32%
1q	3-C(=NH)NHmorpholinyl	$(CH_2)_5$	*cis*-2,6-diMe-piperidinyl	1.5	15%	58%	0%
1r	3-C(=NH)NH_2	$(CH_2)_6$	*cis*-2,6-diMe-piperidinyl	0.068	5.6	2.1	12
1s	3-C(=NH)NH_2	$(CH_2)_4$	*cis*-2,6-diMe-piperidinyl	0.012	1.1	0.30	38
1t	3-C(=NH)NH_2	$(CH_2)_5$	*cis*-2,5-diMe-pyrrolidinyl	0.048	0.91	0.76	85%
1u	3-C(=NH)NH_2	$(CH_2)_5$	piperidinyl	0.053	3.4	0.99	21
1v	3-C(=NH)NH_2	$(CH_2)_5$	morpholinyl	0.24	2.2	1.1	70%
1w	3-C(=NH)NH_2	$(CH_2)_5$	NH_2	6.3	60%	4.3	64%
1x	3-C(=NH)NH_2	$(CH_2)_5$	diisopropylamino	0.12	1.2	1.2	72%
1y	3-C(=NH)NH_2	$(CH_2)_5$	dihexylamino	1.6	1.9	2.5	2.2

[a] The in vitro FXa, thrombin, trypsin, and plasmin assays were performed typically in duplicate using 14 concentrations of test substance that bracketed the IC_{50}.

Table 2. Selectivity of Compound **1n** Against Various Serine Proteases[a]

serine protease	IC_{50} (μM) or % inhibition at 100 μM
FXa	0.0030
prothrombinase	0.0040
thrombin	0.89
trypsin	0.33
plasmin	8.4
activated protein c	23
chymotrypsin	24%
factor VIIa	32%

[a] The in vitro FXa, thrombin, trypsin, and plasmin assays were performed typically in duplicate using 14 concentrations of test substance that bracketed the IC_{50}.

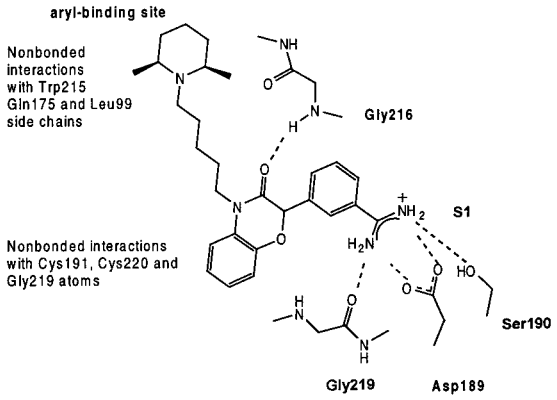

Figure 2. Schematic representation of the interaction of compound **1n** with the trypsin active site.

inhibitor crystal structure provided a conformation of the inhibitor that would be expected to make similar interaction with FXa, and thus the previously described interactions account for the observed in vitro activity.

To evaluate the potential efficacy of **1n**, in vitro tests were conducted using human, dog, and rabbit plasma to determine the effect of the compounds in the standard coagulation tests.[24] The anticoagulant status of patients on heparin is frequently monitored ex vivo using the aPTT assay, while the prothrombin time (PT) assay is used for patients on oral coumarins. Interestingly, **1n** is a more potent inhibitor of FXa in human rather than rabbit or dog plasma (Table 3). This species-dependent inhibition of FXa is a common observation that has been seen previously with the prototypical FXa inhibitors, such as DX9065a.[25]

The in vivo studies were conducted in anesthetized rabbits using a veno-venous shunt model which has previously been described.[26] In this thrombosis model the test compounds were administered intravenously as a bolus followed by a continuous infusion in the presence of a cotton thread thrombotic stimulus. The main endpoint of this study was the time to occlusion of the vessel containing the cotton threads, which is typically about 20 min in control animals. Clot weight was significantly reduced when the test compound **1n** was administered at the highest dose associated with plasma concentration of approximately 300 ng/mL, and only one out of five animals occluded within a 2-h time frame (Table 4). Thus, **1n** was effective at relatively low doses

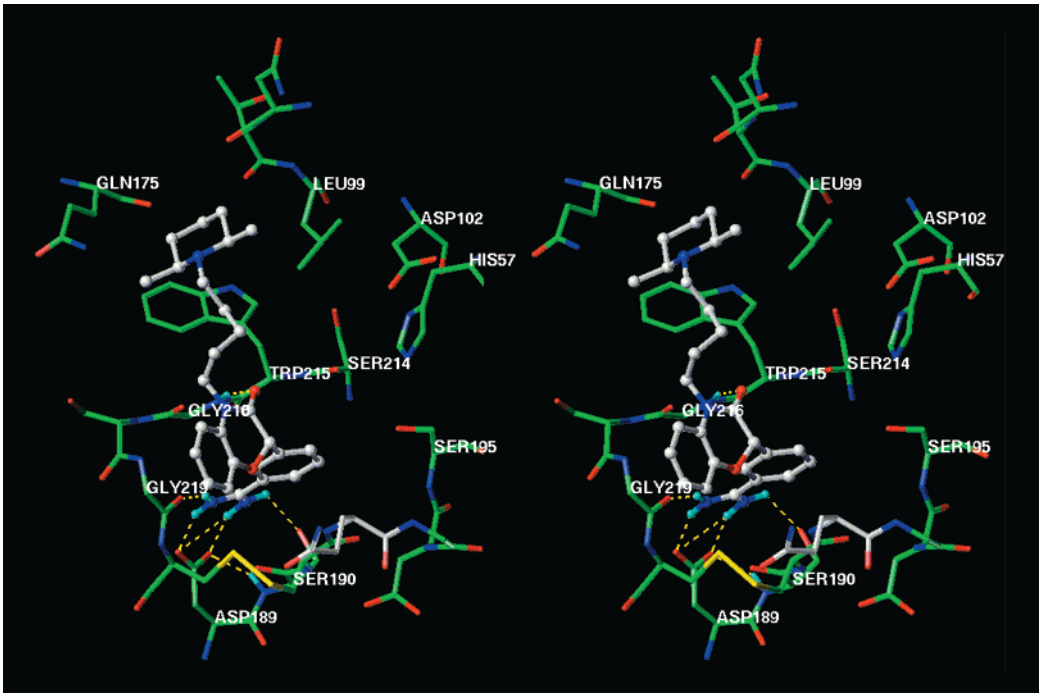

Figure 3. Stereographical representation of the interaction of compound **1n** with the trypsin active site.

Table 3. In Vitro aPTT and PT Assay[a]

species	concn (μM) of **1n** for 2-fold prolongation of PT and aPTT		ratio of PT/aPTT
	PT	aPTT	
rabbit	0.33	0.15	2.2
dog	0.57	0.19	3.0
human	0.17	0.34	0.5

[a] The in vitro PT and aPTT assays were done by using pooled plasma, and values were duplicated.

Table 4. Effect of Compound **1n** on the Time to Occlusion in the Rabbit Veno-Venous Shunt Model

dose of **1n** (iv bolus μg/kg + infusion μg/kg/min)	incidence (occluded/total)	time to occlusion[a] (min)
30 + 1	5/5	27 ± 7
60 + 2	4/5	37 ± 21
90 + 3	1/5	98 ± 22

[a] All numbers are mean ± SE where $n = 5$ for each of three dose groups.

supporting the potential utility of this agent as a parenteral antithrombotic.

Compound **1n** was also investigated in anesthetized dogs using an electrolytic injury to the endothelium as a thrombotic stimulus. In this model the efficacy of the test compound was assessed in both arteries and veins and was measured, in part, by recording the time to occlusion of the vessels under study (Table 5).[27] For example, when the compound was infused continuously at 1.25, 2.5, 5, and 10 μg/kg/min, the time to occlusion of the femoral artery varied in a dose-dependent manner from 150 min at the lowest dose to the maximal duration of 240 min at the higher dose. In the vein a similar dose response was observed. Administration of compound **1n** significantly extended the time to occlusion with the two highest doses in the vein (mean plasma concentration ≥ 400 ng/mL) and the three highest doses in the artery (mean plasma concentration ≥ 250 ng/mL). Most vessels occluded in the control and

Table 5. Effect of Compound **1n** on the Time to Occlusion in the Dog Electrolytic Injury Model[a]

dose of **1n** (μg/kg/min)	incidence (occluded/total)	time to occlusion (min)	
		artery	vein
0 (control)	24/24	87 ± 12	120 ± 15
1.25	7/8	148 ± 33	125 ± 12
2.5	9/10	167 ± 27	144 ± 22
5	1/10	240 ± 0	220 ± 18
10	0/10	240 ± 0	240 ± 0

[a] All numbers are mean ± SEM where $n = 12$ in the control group, $n = 4$ in the 1.25 μg/kg/min group, and $n = 5$ in the 2.5, 5, and 10 μg/kg/min groups for both artery and vein.

1.25 and 2.5 μg/kg/min groups. In the group treated with 5 μg/kg/min compound **1n**, 1 out of 10 vessels occluded, while all vessels remained patent in the 10 μg/kg/min group for the full duration of the study. Loss of blood from the surgical incisions was significantly elevated only at the highest dose of 10 μg/kg/min.

Pharmacokinetic data for an oral/intravenous crossover study with **1n** in rats or dogs indicated oral bioavailabilities were quite poor (≤6−13%, respectively) with terminal half-lives less than 0.5 h. While these characteristics are unfavorable for oral administration of an antithrombotic for chronic use, they are however suitable for development as a parenteral for the treatment of acute coronary syndromes. However, there is also interest in developing FXa inhibitors for the treatment or prevention of chronic maladies, such as deep-vein thrombosis. While there are a limited number of orally active FXa inhibitors, or even antithrombins, it is readily apparent from the published SAR that oral activity is limited in part by highly basic P1 substituents.[28] In an attempt to address this issue, we prepared a number of benzoxazinones (**1m** and **1o**−**1q**) containing P1 groups with modest pK_a (10 ± 2) as calculated from commercial software.[29] Unfortunately, we observed a substantial loss of in vitro activity with each replacement of the amidine moiety, and thus further work in this area represents a current area of focus.

It should also be noted that in addition to the low bioavailability, this class of agents also presents a chiral center. Throughout this work these compounds were prepared and analyzed as racemic mixtures, and it can be assumed that the potency of the pure enantiomer could potentially be twice that of the mixture. In fact, the trypsin crystal structure of **1n** revealed that the *S* isomer bound preferentially in the active site. Currently, several approaches are being assessed to prepare chiral benzoxazinones and will be described in detail in future publications.

In summary a high-throughput screening lead was optimized from approximately 27 μM to a low-nanomolar lead. Critical to the success of this process was the application of molecular modeling and the Topliss tree approach, which enabled us to rationally design a series of novel benzoxazinone inhibitors of FXa. While the molecular modeling tools were unable to uniquely place the amidine moiety, sufficient guidance was provided to ultimately synthesize the lead **1n**. This compound exhibits high selectivity for the target protein FXa over other related serine proteases such as trypsin. Finally this compound is efficacious in dog and rabbit antithrombotic models. Discovery of this novel, selective, potent, efficacious inhibitor of FXa incorporating the amidine moiety at S1 was a key step in our search for a clinical candidate. Subsequent publications will describe further results in this area.

Experimental Section

Biochemistry. Compounds were evaluated for their ability to inhibit the serine proteases, FXa, thrombin, trypsin, and plasmin. In vitro kinetic assays were conducted at 37 °C using a kinetic spectrophotometric plate reader. An optimized concentration of human enzyme in buffer (0.5 nM final concentration for thrombin and trypsin, and 1 nM for FXa and plasmin) was combined with 2 μL of inhibitor dilutions (creating a final concentration range of 1 nM to 100 μM) and preincubated for 1 h at room temperature. The assay was initiated by the addition of an appropriate synthetic substrate (S-2765 (Pharmacia Hepar) for FXa, CHROMOZYM TH (Boehringer Mannheim) for thrombin, S-2222 (Pharmacia Hepar) for trypsin, and S-2403 (Pharmacia Hepar) for plasmin), at predetermined $2 \times K_m$. Absorbance at 405 nm was determined over 10 min, and percent inhibition was calculated from the slope of the progress curves during the linear part of the time course at each concentration. The IC_{50} was defined as that concentration of test substance that inhibited 50% of the respective protease activity. Typically a $n = 2$ was performed on each compound such that data reported is an average of the two measurements.

Chemistry. All starting materials were obtained from commercial sources and used without further purification unless otherwise specified in the experimental. Proton NMR spectra were obtained on a Varian Unity 400- or 300-MHz spectrometer. Elemental analyses were determined by Robertson Microlit, Inc. (Madison, NJ), and the results were within 0.4% of the theoretical values for the elements indicated. Mass spectral data were obtained on a VG Analytical 7070 E/HF mass spectrometer. Flash column chromatography was performed on Merck silica gel 60, 230−400 mesh, purchased from Mallinckrodt. Reactions were monitored by thin-layer chromatography (TLC) on Merck glass plates precoated with 0.25 mm of silica gel.

Abbreviations: DIEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; EtOH, ethanol; MeOH, methanol; NBS, *N*-bromosuccinimide; RaNi, Raney nickel; TFA, trifluoroacetic acid.

Methyl 2-Bromo-2-(3-bromophenyl)acetate. To 3-bromophenylacetic acid (10 g, 47 mmol) under argon was added PBr_3 (11.2 mL, 118 mmol) and the suspension stirred at room temperature for 45 min. Bromine (11.1 mL, 216 mmol) was added dropwise over 5 min. The mixture was stirred at 100 °C for 3 h and then cooled. Anhydrous MeOH (35 mL) was added dropwise over 30 min and then the reaction mixture was diluted with Et_2O (400 mL), washed with 5% $NaHCO_3$ (800 mL), brine (200 mL), and then dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo to afford 13.9 g (96%) of pure material. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-(1H, m), 7.48(2H, m), 7.25(1H, m), 5.29(1H, s), 3.80(3H, s). CI MS M − 1 = 304/306/308. Anal. ($C_9H_8Br_2O_2$) C, H, N, Br.

2-(3-Bromophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (9). To *o*-aminophenol hydrochloride (4.25 g, 38.9 mmol) in DMF (30 mL) was added NaH (1.55 g, 38.9 mmol). After bubbling and evolution of heat ceased, a solution of methyl 2-bromo-2-(3-bromophenyl)acetate (3.00 g, 9.74 mmol) in DMF (10 mL) was added dropwise over 15 min. After evolution of heat ceased, the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried with $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% EtOAc in hexane. The product **9** was isolated 1.63 g (55%) as a solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76(1H, s), 7.63(1H, m), 7.43(2H, m), 7.23(1H, m), 7.01(3H, m), 6.81(1H, m), 5.66(1H, s). CI MS M + 1 = 306, M − 1 = 304. Anal. ($C_{14}H_{10}Br_1N_1O_2$) C, H, N.

2-(3-Cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (10). To a solution of 2-(3-bromophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (**9**) (3.00 g, 9.87 mmol) in DMF (20 mL) were added zinc cyanide (0.68 g, 5.79 mmol) and then tetrakis-(triphenylphosphine)palladium(0) (0.96 g, 8 mol %). The nitrogen-degassed solution was heated at 100 °C or 5 h, cooled to room temperature and treated with water (50 mL). The product was extracted into EtOAc (2 × 100 mL), washed with brine (50 mL), dried over $MgSO_4$, and then purified by silica gel chromatography, eluent 50% EtOAc in hexane. This process afforded the title compound (1.86 g, 76%) that was recrystallized from EtOH/water. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (1H, s), 7.80−7.72(2H, m), 7.64(1H, m), 7.49(1H, m), 7.11−6.97(3H, m), 6.82(1H, m), 5.70(1H, s). CI MS M + 1 = 251, M − 1 = 250. Anal. ($C_{15}H_{10}N_2O_2$) C, H, N.

4-(5-Bromopentyl)-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (11). To 2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (**10**) (0.72 g, 2.87 mmol) in DMF (5 mL) was added NaH (0.126 g, 3.15 mmol) and the solution was stirred at 70 °C for 15 min until bubbling stopped. To this solution was added 1,5-dibromopentane (1.57 mL, 11.5 mmol) and the solution was stirred at 70 °C for additional 3 h. The solution was cooled, diluted with water, and extracted with EtOAc (5 × 200 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried with $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified on a silica gel column eluted with 20% to 40% EtOAc in hexane. The product **11** was isolated 0.64 g (56%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71(2H, m), 7.61(1H, m), 7.46(1H, m), 7.12−7.03(3H, m), 6.97(1H, m), 5.69(1H, s), 3.98(2H, m), 3.41-(2H, m), 1.91(2H, m), 1.71(2H, m), 1.55(2H, m). CI MS M + 1 = 401/402. Anal. ($C_{20}H_{19}N_2O_2Br_1$) C, H, N.

4-[5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]-pentyl]-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (12). To 4-(5-bromopentyl)-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (**11**) (1.08 g, 2.70 mmol) was added *cis*-2,6-dimethylpiperidine (8 mL, 60 mmol). The solution was stirred at 70 °C for 16 h. The solution was cooled, diluted with water, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2 × 100 mL), washed with brine (2 × 100 mL), dried with $MgSO_4$, filtered, evaporated in vacuo, coevaporated with toluene, and dried under high vacuum to give 1.09 g (94%) of **12** as a yellow oil. An analytical sample was prepared by purification by preparative reverse phase HPLC (Vydac 218TP1022 C18,

eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid (TFA) in water and (ii) 0.1% TFA in CH_3CN, gradient profile 95:5 i:ii to 60:40 i:ii over 90 min, flow rate 20 mL/min, $\lambda = 214$ nm) and appropriate fractions were combined and lyophilized. The powder was then dissolved in CH_3CN (2 mL) and water (1 mL) was added Amberlite IRA-400(Cl) ion-exchange resin (5 g) and the mixture swirled for 30 min. The mixture was filtered through additional resin, and the filtrate was lyophilized to give 31 mg of the HCl salt **12**. ^{1}H NMR (DMSO, 300 MHz): δ 7.83(2H, m), 7.70(1H, m), 7.60-(1H, m), 7.26(1H, m), 7.08(3H, m), 5.93(1H, s), 3.97(2H, bs), 2.94(4H, bm), 1.74−1.32(12H, bm), 1.23(6H, m). HPLC: t_R = 13.8 min (Beckman 235328 C18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% TFA in water and (ii) 0.1% TFA in CH_3CN, gradient profile 80:20 i:ii to 10:90 i:ii over 23 min, flow rate 1.5 mL/min, $\lambda = 214$ nm). CI MS M + 1 = 432. Anal. ($C_{27}H_{33}N_3O_2$·HCl·1.5H_2O) C, H, N.

3-(4-[5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxybenzenecarboximidamide (1m). To 4-[5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-2-(3-cyanophenyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (**12**) (1.09 g, 2.53 mmol) in MeOH (30 mL) were added hydroxylamine hydrochloride (0.438 g, 6.30 mmol) and DIEA (0.44 mL, 2.53 mmol). The solution was stirred at room temperature for 16 h. The solvent was evaporated in vacuo and the oil was dried under high vacuum to give **1m** in quantitative yield, which was used without purification. HPLC: t_R = 8.4 min (Beckman 235328 C18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% TFA in water and (ii) 0.1% TFA in CH_3CN, gradient profile 80:20 i:ii to 10:90 i:ii over 23 min, flow rate 1.5 mL/min, $\lambda = 214$ nm).

3-(4-[5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxytrifluoroacetobenzenecarboximidamide (13). To 3-(4-[5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]-pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxybenzenecarboximidamide (**1m**) (0.53 g, 1.14 mmol) was added trifluoroacetic anhydride (7 mL) and the solution was stirred at room temperature for 2 h. The solvent was removed in vacuo to give **13** as a yellow oil in quantitative yield. HPLC: t_R = 17.4 min (Beckman 235328 C18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% TFA in water and (ii) 0.1% TFA in CH_3CN, gradient profile 80:20 i:ii to 10:90 i:ii over 23 min, flow rate 1.5 mL/min, $\lambda = 214$ nm).

3-(4-[5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide (1n). To 3-(4-[5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)-1-*N*-hydroxytrifluoroacetobenzenecarboximidamide (**13**) (0.57 g, 1.13 mmol) in TFA (16 mL) was added 20% palladium on carbon (0.1 g) and the mixture was hydrogenated at 23 °C for 48 h under 50 psi of hydrogen. The mixture was filtered and the filter pad washed with TFA. The combined filtrate and washings were evaporated in vacuo, and the residue was purified by preparative reverse phase HPLC (Vydac 218TP1022 C18, eluted with a mixture of solvents consisting of (i) 0.1% TFA in water and (ii) 0.1% TFA in CH_3CN, gradient profile 95:5 i:ii to 60:40 i:ii over 90 min, flow rate 20 mL/min, $\lambda = 214$ nm) and lyophilized to give 251 mg (50%) of the bis-TFA salt of **1n**. To **1n** in CH_3CN (2 mL) and water (2 mL) was added Amberlite IRA-400(Cl) ion-exchange resin (3.36 g) and the mixture swirled for 30 min. The mixture was filtered, and the filtrate was lyophilized to give 155 mg (26%) of the bis-HCl salt **1n**. ^{1}H NMR (DMSO, 300 MHz): δ 9.44(1H, s), 9.19(2H, s), 7.80(2H, m), 7.64(2H, m), 7.28(1H, m), 7.11−7.01(3H, m), 5.93(1H, s), 3.97(2H, m), 3.18(2H, bs), 3.03(2H, bs), 1.75−1.36(12H, bm), 1.23(6H, m). CI MS M + 1 = 449. HPLC: t_R = 8.3 min (Beckman 235328 C18 5 μm 4.6 mm × 25 cm, eluted with a mixture of solvents consisting of (i) 0.1% TFA in water and (ii) 0.1% TFA in CH_3CN, gradient profile 80:20 i:ii to 10:90 i:ii over 23 min, flow rate 1.5 mL/min, $\lambda = 214$ nm). Anal. ($C_{27}H_{38}N_4O_2$·2HCl·H_2O) C, H, N, Cl.

Supporting Information Available: Characterization data for compounds **1a**−**1y**, average IC_{50}, *N* size, standard deviation, and crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Vlasuk, G. P. Direct Factor Xa Inhibitors. In *New Therapeutic Agents in Thrombosis and Thrombolysis*, 1st ed.; Sasahara, A. A., Loscalzo, J., Eds.; Marcel Dekker: New York, 1997; pp 261−283.

(2) Rapaport, S. I.; Rao, L. V. Initiation and regulation of tissue factor-dependent blood coagulation. *Arterioscler. Thromb.* **1992**, *12*, 1111−1121.

(3) Lapatto, R.; Krengel, U.; Schreuder, H. A.; Arkema, A.; De Boer, B.; Kalk, K. H.; Hol, W. G. J.; Grootenhuis, P. D. J.; Mulders, J. W. M.; Dijkema, R.; Theunissen, H. J. M.; Dijkstra, B. W. X-ray structure of antistasin at 1.9.ANG. resolution and its modeled complex with blood coagulation factor Xa. *EMBO J.* **1997**, *16*, 5151−5161.

(4) (a) Schaffer, L. W.; Davidson, J. T.; Vlasuk, G. P.; Siegl, P. K. Antithrombotic efficacy of recombinant tick anticoagulant peptide. A potent inhibitor of coagulation of factor Xa in a primate model of arterial thrombosis. *Circulation* **1991**, *84*, 1741−1748. (b) Vlasuk, G. P.; Ramjit, D.; Fujita, T.; Dunwiddie, C. T.; Nutt, E. M.; Smith, D. E.; Shebuski, R. J. Comparison of the in vivo anticoagulant properties of standard heparin and the highly selective factor Xa inhibitors antistatin and tick anticoagulant peptide (TAP) in a rabbit model of venous thrombosis. *Thromb. Haemost.* **1991**, *65*, 257−262. (c) Sitko, G. R.; Ramjit, D. R.; Stabilito, I. I.; Lehman, D.; Lynch, J. J.; Vlasuk, G. P. Conjunctive enhancement of enzymatic thrombolysis and prevention of thrombotic reocclusion with the selective factor Xa inhibitor, tick anticoagulant peptide. Comparison to hirudin and heparin in a canine model of acute coronary artery thrombosis. *Circulation* **1992**, *85*, 805−815.

(5) Al-Obeidi, F.; Ostrem, J. A. Factor Xa inhibitors. *Exp. Opin. Ther. Pat.* **1999**, *9*, 931−953.

(6) Walenga, J. M.; Jeske, W. P.; Hoppensteadt, D.; Kaiser, B. Factor Xa inhibitors: Today and Beyond. *Curr. Opin. Cardiovasc., Pulm. Renal Invest. Drugs* **1999**, *1*, 13−27.

(7) Wong, P. C.; Crain, E. J.; Nguan, O.; Watson, C. A.; Racanelli, A. Antithrombotic actions of selective inhibitors of blood coagulation factor Xa in rat models of thrombosis. *Thromb. Res.* **1996**, *83*, 117−126.

(8) Berryman, K. A.; Downing, D. M.; Dudley, D. A.; Edmunds, J. J.; Narasimhan, L. S.; Rapundalo, S. T. Preparation of benzoxazinones and -thiazinones as serine protease inhibitors. International Patent Application WO 99/50257, 1999.

(9) Othman, M.; Decroix, B. Synthesis of phthalimidine-3-carboxylate and benzopyrroloindolizine from N-(pyrrol-2-yl)phthalimidine-3-carboxylate. *Synth. Commun.* **1996**, *26*, 2803−2809.

(10) Harwood, H. J. Reactions of the Hydrocarbon Chain of Fatty Acids. *Chem. Rev.* **1962**, *62*, 99−154.

(11) Olagbemiro, T. O.; Nyakutse, C. A.; Lajide, L.; Agho, M. O.; Chukwu, C. E. Synthesis and reactions of 3-phenyl-3,4-dihydro-1,4-quinoxalin-2(1H)-one and its heterocyclic analogues. *Bull. Soc. Chim. Belg.* **1987**, *96*, 473−480.

(12) Tanaka, H.; Yamashita, S.; Yamanoue, M.; Torii, S. Reductive addition of polyhalomethanes and their related compounds to aldehydes and 1,2-elimination of the coupling products in a palladium/aluminum bimetal redox system. *J. Org. Chem.* **1989**, *54*, 444−450.

(13) Gukasyan, A. Kh.; Galastyan, L. Kh.; Avetisyan, A. A. Investigations in the field of (trihalomethyl) carbinols. IV. Block-addition reaction of aromatic 1,4-dinucleophiles to gem-dichloro epoxides generated from aryl(trichloromethyl)carbinols. *Arm. Khim. Zh.* **1988**, *41*, 572−575.

(14) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. An improved procedure for aromatic cyanation. *Synth. Commun.* **1994**, *24*, 887−890.

(15) Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. A versatile synthesis of amidines from nitriles via amidoximes. *Synth. Commun.* **1996**, *26*, 4351−4367.

(16) Sall, D. J.; Afrsten, A. E.; Bastian, J. A.; Denney, M. L.; Harms, C. S.; McCowan, J. R.; Morin, J. M., Jr.; Rose, J. W.; Scarborough, R. M.; Smyth, M. S.; Um, S. L.; Utterback, B. G.; Vasileff, R. T.; Wikel, J. H.; Wyss, V. L.; Jakubowski, J. A. Use of Conformationally Restricted Benzamidines as Arginine Surrogates in the Design of Platelet GPIIb-IIIa Receptor Antagonists. *J. Med. Chem.* **1997**, *40*, 2843−2857.

(17) Jones, G.; Willett, P.; Glen, R. C. A genetic algorithm for flexible molecular overlay and pharmacophore elucidation. *J. Comput.-Aided Mol. Des.* **1995**, *9*, 532−549.

(18) (a) Topliss, J. G. Utilization of Operational Schemes for analogue synthesis in drug design. *J. Med. Chem.* **1972**, *15*, 1006−1011. (b) Topliss, J. G. A manual method for applying the Hansch approach to drug design. *J. Med. Chem.* **1977**, *20*, 463−469.

(19) Wei, A.; Alexander, R. S.; Duke, J.; Ross, H.; Rosenfeld, S. A.; Chang, C. H. Unexpected binding mode of tick anticoagulant peptide complexed to bovine factor Xa. *J. Mol. Biol.* **1998**, *283*, 147−154.

(20) Herron, D. K.; Goodson, T., Jr.; Wiley: M. R.; Weir, L. C.; Kyle, J. A.; Ying, K. Y.; Tebbe, A. L.; Tinsley, J. M.; Mendel, D.; Masters, J. J.; Franciskovich, J. B.; Sawyer, J. S.; Beight, D. W.; Ratz, A. M.; Milot, G.; Hall, S. E.; Klimkowski, V. J.; Wikel, J. H.; Eastwood, B. J.; Towner, R. D.; Gifford-Moore, D. S.; Craft, T. J.; Smith, G. F. 1,2-Dibenzamidobenzene Inhibitors of Human Factor Xa. *J. Med. Chem.* **2000**, *43*, 859−872.

(21) (a) Maignan, S.; Guilloteau, J.; Mikol, V.; Choi-Sledeski, Y. M.; Becker, M. R.; Klein, S. I.; Ewing, W. R.; Pauls, H. W.; Spada, A. P. Crystal structures of human factor Xa complexed with potent inhibitors. Presented at the 218th American Chemical Society National Meeting, New Orleans, LA, Aug 22−26, 1999; Abstr. #20. (b) Renatus, M.; Bode, W.; Huber, R.; Sturzebecher, J.; Stubbs, M. T. Structural and functional analyses of benzamidine-based inhibitors in complex with trypsin: implications for the inhibition of factor Xa, tPA, and urokinase. *J. Med. Chem.* **1998**, *41*, 5445−5456.

(22) (a) Bode, W.; Schwager, P. The refined crystal structure of bovine beta-trypsin at 1.8 A resolution. II. Crystallographic refinement, calcium binding site, benzamidine binding site and active site at pH 7.0. *J. Mol. Biol.* **1975**, *98*, 693−717. (b) Singh, J.; Thornton, J. M.; Snarey, M.; Campbell, S. F. The geometries of interacting arginine-carboxyls in proteins. *FEBS Lett.* **1987**, *224*, 161−171.

(23) Brandstetter, H.; Kuhne, A.; Bode, W.; Huber, R.; von der Saal, W.; Wirthensohn, K.; Engh, R. A.; X-ray structure of Active site-inhibited clotting Factor Xa. Implications for drug design and substrate recognition. *J. Biol. Chem.* **1996**, *271*, 29988−29992.

(24) Berryman, K. A.; Downing, D. M.; Dudley, D. A.; Edmunds, J. J.; Narasimhan, L. S.; Rapundalo, S. T. Preparation of benzoxazinones and -thiazinones as serine protease inhibitors. International Patent Application WO 99/50257, 1999.

(25) (a) Tidwell, R. R.; Webster, W. P.; Shaver, S. R.; Geratz, J. D. Strategies for anticoagulation with synthetic protease inhibitors. Xa inhibitors versus thrombin inhibitors. *Thromb. Res.* **1980**, *19*, 339−349. (b) Hara, T.; Yokoyama, A.; Morishima, Y.; Kunitada, S. Species differences in anticoagulant and anti-Xa activity of DX-9065a, a highly selective factor Xa inhibitor. *Thromb. Res.* **1995**, *80*, 99−104.

(26) Rogers, K. L.; Chi, L.; Rapundalo, S. T.; Kramer, J. B.; Gallagher, K. P. Effects of a factor Xa inhibitor, DX-9065a, in a novel rabbit model of venous thrombosis. *Basic Res. Cardiol.* **1999**, *94*, 15−22.

(27) (a) McClanahan, T. B.; Ignasiak, D. P.; Juneau, P.; Finkle, C.; Winocour, P. D.; Gallagher, K. P. Antithrombotic effects of BCH 2763, a new direct thrombin inhibitor, in a canine model of venous thrombosis. *J. Thromb. Thrombolysis* **1999**, *7*, 301−306. (b) Ignasiak, D. P.; McClanahan, T. B.; Bousley, R. E.; Juneau, P. L.; Gallagher, K. P. Effects of intravenous enoxaparin and intravenous inogatran in an electrolytic injury model of venous thrombosis in the dog. *J. Thromb. Thrombolysis* **1998**, *6*, 199−206.

(28) (a) Al-Obeidi, F.; Ostrem, J. A. Factor Xa inhibitors. *Exp. Opin. Ther. Pat.* **1999**, *9*, 931−953. (b) Kimball, S. D. Oral thrombin inhibitors: Challenges and progress. *Handbk. Exp. Pharmacol.* **1999**, *132*, 367−396. (c) Rewinkel, J. B. M.; Lucas, H.; Van Galen, P. J. M.; Noach, A. B. J.; Van Dinther, T. G.; Rood, A. M. M.; Jenneboer, A. J. S. M.; Van Boeckel, C. A. A. 1-aminoisoquinoline as benzamidine isostere in the design and synthesis of orally active thrombin inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 685−690. (d) Choi-Sledeski, Y. M.; Becker, M. R.; Green, D. M.; Davis, R.; Ewing, W. R.; Mason, H. J.; Ly, C.; Spada, A.; Liang, G.; Cheney, D.; Barton, J.; Chu, V.; Brown, K.; Colussi, D.; Bentley, R.; Leadley, R.; Dunwiddie, C.; Pauls, H. W. Aminoisoquinolines: design and synthesis of an orally active benzamidine isostere for the inhibition of factor Xa. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2539−2544.

(29) Williams, A.; Kulkov, V. Web-based access to structure-based prediction and databases for spectroscopy and physical properties. Presented at the 218th American Chemical Society National Meeting, New Orleans, LA, Aug 22−26, 1999; Abstr. #64.

JM000074L