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Design, Synthesis and Structure–Activity Relationships of Benzoxazinone-Based Factor Xa Inhibitors

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Abstract—A series of benzoxazinone derivatives was designed and synthesized as factor Xa inhibitors. We demonstrated that the naphthyl moiety in the aniline-based compounds **1** and **2** can be replaced with benzene-fused heterobicycles and biaryls to give factor Xa inhibitors with improved trypsin selectivity. The P4 modifications lead to monoamidines which are moderately active. The benzoxazinones **41**–**45** are potent against factor Xa, retain the improved trypsin selectivity of the corresponding aniline-based compounds, and show strong antithrombotic effect dose responsively.
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Factor Xa is a trypsin-like serine protease positioned at the convergence of the intrinsic and extrinsic blood coagulation pathways.[1] The prothrombinase complex formed by factor Xa on the phospholipid surface with factor Va and calcium catalyzes the conversion of prothrombin to thrombin(IIa), which is the last enzyme in the coagulation cascade leading to fibrin formation and eventually thrombosis. Inhibition of factor Xa has been actively pursued to develop novel anticoagulants to replace existing therapies in the treatment or prevention of thromboembolic disorders.[2] Previously reported small molecule, direct factor Xa inhibitors include a variety of diamidines as represented by DX-9065a[3] and YM60828 (**1**, Fig. 1) and its analogue 2.[4] DX-9065a is currently under clinical investigation as an intravenous agent. Even though the diamidines are highly efficacious in animal thrombosis models, they are poorly absorbed following oral administration due to the presence of the strongly basic amidino groups.[2]

Compounds **1** and **2** were quite attractive to us when our factor Xa inhibitor medicinal chemistry efforts started several years ago due to their structure simplicity, ease of synthesis and opportunities for chemical diversification. A stepwise design strategy was employed. First, it was highly desired to substitute the P1 naphthylamidine group with bicyclic heteroaromatic and/or biaryl amidines to expand the chemical diversity as well as to probe the selectivity of a factor Xa inhibitor over other serine proteases including thrombin and trypsin. Structure–activity relationship studies around the P4 moiety were planned because replacement of the P4 amidino group with less basic functional groups might result in monoamidines which can potentially display improved oral bioavailability. Finally, compound **2** exhibited an extended L-shaped conformation when docked in the active site of factor Xa. The P1 amidine binds to the S1 specificity site of factor Xa, while the iminoethylpiperidine moiety occupies the aryl binding site. This binding conformation is very similar to that of DA-9065a co-crystallized with factor Xa.[5] It was envisioned that substituting the sulfonyl group with a carbonyl followed by tethering the methyl group to the aniline template with an oxygen atom would yield the benzoxazinones (structure **3** in Fig. 1) as structurally novel, bicyclic factor Xa inhibitors.[6,7] This sequential introduction of new P1 benzamidines, P4 modifications and aniline template cyclization is reported here.

Our studies started with the synthesis of compound **2** according to Scheme 1 (Ar = naphthyl). The IC_{50} values

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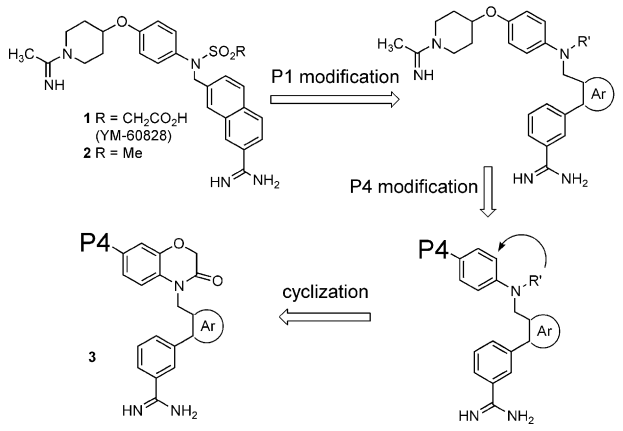
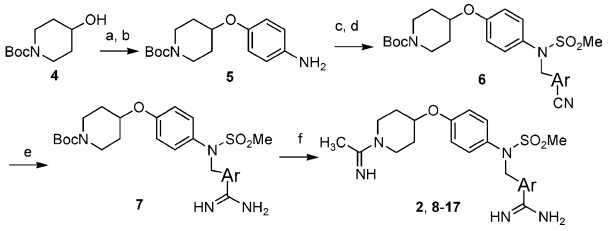


Figure 1. Design of benzoxazinone derivatives as factor Xa inhibitors.



Scheme 1. (a) 1-Fluoro-4-nitrobenzene, NaH, THF; (b) Pd/C (10%), H_2 (1 atm), MeOH; (c) MsCl, Py; (d) XCH_2–Ar–CN, Cs_2CO_3, DMF (X = Br, Cl); (e) (1) NH_2OH, EtOH; (2) Ac_2O, AcOH; (3) Pd/C (10%), H_2 (1 atm), MeOH; (f) (1) TFA, CH_2Cl_2; (2) ethyl acetimidate/HCl, Et_3N, EtOH.

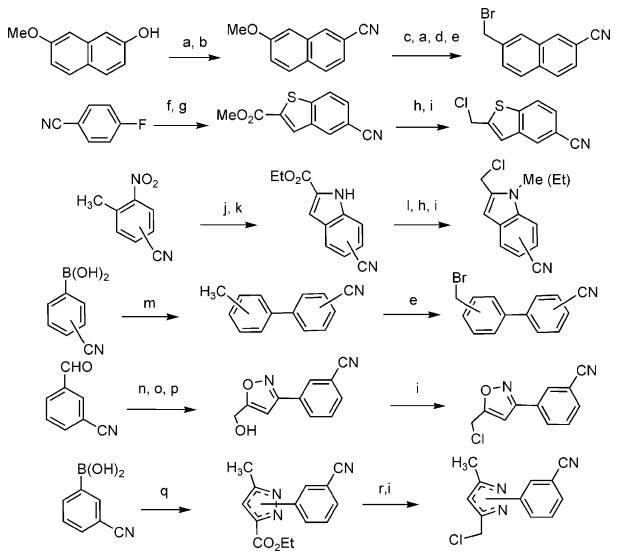
of compound **2** for factor Xa, thrombin and trypsin were determined as 6 nM, >10 μM and 95 nM, respectively, in our in-house assay. It is noted that compound **2** has a rather low trypsin selectivity ($IC_{50,\ trypsin}/IC_{50,\ Xa}$ = 15).

To synthesize the analogues of compound **2** with P1 aryl variations, a variety of the halide intermediates were prepared according to Scheme 2. The halides were utilized in the alkylation step of Scheme 1 to obtain compounds **8**–**17**.

Table 1 shows that replacing the naphthyl moiety with a benzothiophene unit affords the equipotent compound **8**. While the 5-amidinoindole compound **9** is less active than compound **2**, a 40-fold improvement in potency was observed with the 6-isomer (**10**, IC_{50} = 0.8 nM).

The replacement of the naphthyl moiety with a biaryl substructure was then investigated. Compound **11**, which contains a *para–meta* substituted biphenyl group, has an IC_{50} = 25 nM. The survey of the regio-isomers of compound **11** demonstrates the importance of the *meta–meta* substitution (**14**).[8] Further studies on the P1 moiety involve replacement of the distal phenyl ring in compound **14** with heteroaromatic structures. Compound **15**, which bears an isoxazole moiety,[9] shows a minor (2-fold) decrease in potency. Compounds **16** and **17** incorporating a pyrazole ring[10] are substantially less active.

Table 1 also shows that compounds **8**–**17** are all highly selective for factor Xa over thrombin(IIa). On the other



Scheme 2. (a) Tf_2O, Py; (b) KCN, DPPF, $(dba)_3Pd_2(CHCl_3)$, acetone; (c) BBr_3, CH_2Cl_2; (d) $SnMe_4$, LiCl, $PdCl_2(PPh_3)_2$, DMF; (e) NBS, $(PhCO_2)_2$, CCl_4; (f) LDA, DMF, THF; (g) $HSCH_2CO_2Me$, TEA, DMSO; (h) $NaBH_4$, CaI_2, $NaHCO_3$, THF; (i) TsCl, Py, CH_2Cl_2; (j) NaOEt, $(CO_2Et)_2$, EtOH; (k) Zn, HOAc; (l) MeI or EtI, Cs_2CO_3, DMF; (m) bromotoluene, $Pd(PPh_3)_4$, NaOH, H_2O, ^{i}PrOH; (n) NH_2OH/HCl, TEA, EtOH; (o) NCS, DMF; (p) propargyl alcohol, TEA; (q) ethyl 3-methylpyrazole-5-carboxylate, $Cu(OAc)_2$, Py, CH_2Cl_2; (r) $LiAlH_4$, THF.

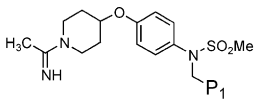
hand, the P1 moieties have a marked effect on trypsin selectivity (trypsin/Xa in Table 1). For example, compounds **8**, **9**, and **16** are less selective than the lead compound **2**. Interestingly, moving the amidino group from the 5-position of the indole ring as in compound **9** to the 6-position as in compound **10** improves potency as well as trypsin selectivity. Increased trypsin selectivity was also observed for compounds **11**, **14**, and especially **15**, which has a trypsin/Xa >700.

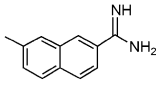
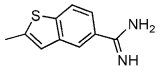
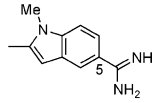
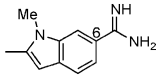
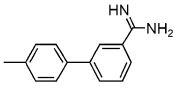
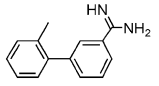
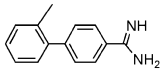
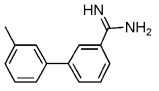
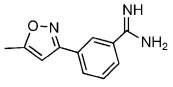
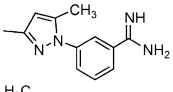
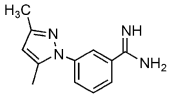
The benzothiophene compound **8** and biphenyl compound **14** were selected for the attachment of a carboxyl group to evaluate its effect on in vitro potency and enzyme selectivity. Scheme 3 describes the syntheses of compounds **19**–**23** as well as YM60828 (**1**). The aldehydes used in the amination reactions were prepared according to Scheme 4.

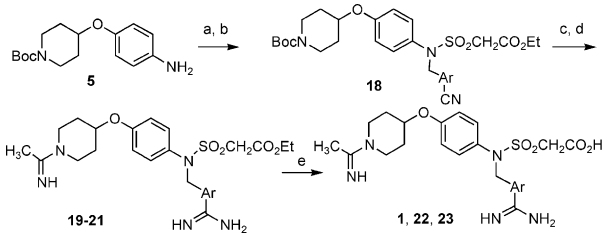
Table 2 shows that the acids **22** and **23** are more potent than the parent compounds **8** and **14**, as well as the ethyl esters **20** and **21**. This trend is similar to that observed with the naphthyl compounds **1**, **2**, and **19**. The esters (**19**, **20**, and **21**) have trypsin selectivity comparable to that of the methylsulfonyl compounds **2**, **8**, and **14**. A slight increase in trypsin selectivity was observed with the carboxyl containing compounds **1**, **22**, and **23** (the in vitro IC_{50} assays were repeated at least three times). Interestingly, the improved trypsin selectivity of **14** over **2** is retained by the ester **21** and acid **23**. All the compounds have thrombin IC_{50}s >10 μM.

The replacement of the P4 amidino group in the diamidines with less basic functional groups would result in monoamidine compounds which may improve the poor

Table 1. SARs of aniline-based dibasic factor Xa inhibitors: P1 modifications

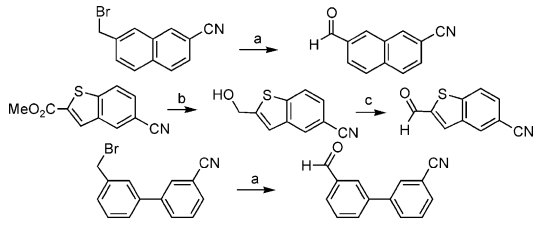


Compd	P1	IC_{50}s (nM)			
		Xa	IIa	Trypsin	Trypsin/Xa
2		6	>10,000	94	15
8		6	>10,000	21	<5
9		31	>10,000	167	5
10		0.8	>10,000	25	30
11		25	>10,000	769	30
12		7000	>10,000	>10,000	—
13		>10,000	>10,000	>10,000	—
14		7	>10,000	360	50
15		14	>10,000	>10,000	>700
16		934	>10,000	2110	<5
17		6920	>10,000	>10,000	—



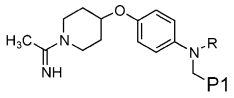
Scheme 3. (a) CHO–Ar–CN, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (b) $ClSO_2CH_2CO_2Et$, Py; (c) (1) NH_2OH, EtOH; (2) Ac_2O, AcOH; (3) Pd/C (10%), H_2 (1 atm), MeOH; (d) (1) TFA, CH_2Cl_2; (2) ethyl acetimidate/HCl, Et_3N, EtOH; (e) 4 N HCl.

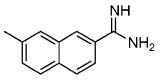
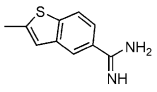
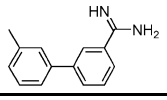
oral bioavailability of the diamidines due to the decrease of overall basicity.[2] Scheme 5 shows the synthesis of compounds **26–29**, which incorporate a S4 binding biphenylsulfonamide moiety.[11] Compounds **26** and **27** with an amidinonaphthyl or amidinobiphenyl as P1 motifs, respectively, are only moderately potent (Table 3). Further decrease of potency was observed with pyrazoles **28** and **29.**



Scheme 4. (a) Trimethylamine *N*-oxide, $CHCl_3$; (b) $NaBH_4$, CaI_2, $NaHCO_3$, THF; (c) IBX, THF.

Table 2. In vitro potency of dibasic factor Xa inhibitors: modification of the methylsulfonyl group by introduction of an ester or acid functionality

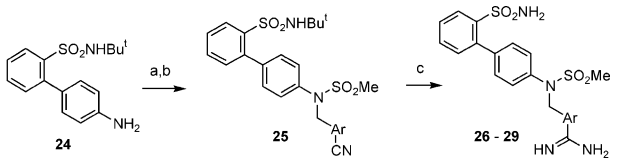


Compd	P1	R	IC_{50}s (nM)		
			Xa	Trypsin	Trypsin/Xa
2		SO_2Me	6	94	15
19		$SO_2CH_2CO_2Et$	6	83	15
1		$SO_2CH_2CO_2H$	2	63	30
8		SO_2Me	6	21	<5
20		$SO_2CH_2CO_2Et$	9	86	10
22		$SO_2CH_2CO_2H$	3	63	20
14		SO_2Me	7	360	50
21		$SO_2CH_2CO_2Et$	7	292	40
23		$SO_2CH_2CO_2H$	3	269	90

Compounds **33–35** containing a pyrrolidinylcarbonyl group[12] were synthesized from the commercially available compound **30** according to Scheme 6. Compound **31** also served as the starting material to afford **36**.

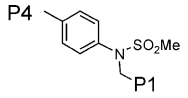
Compound **33** is, unfortunately, a poor factor Xa inhibitor (Table 3). Compounds **34** and **35** possess an amide group on the pyrrolidine ring to mimic the sulfonamide functionality in **26**. However, both compounds have insignificant potency. The low activity of compound **36** with a reinstalled P4 amidino group clearly indicates the importance of the ether linkage in the P4 region probably due to its rotational flexibility which allows optimal interaction with factor Xa. Further studies on substituting the P4 amidine with a neutral group were discontinued due to the difficulties in achieving good potency.

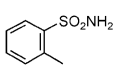
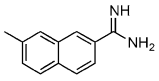
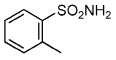
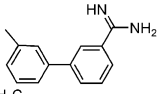
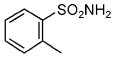
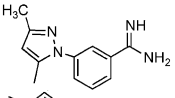
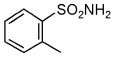
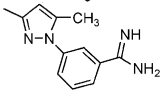
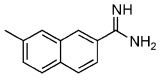
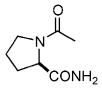
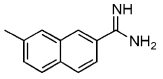
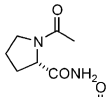
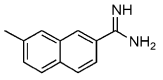
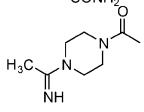
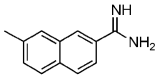
After mapping out the SAR profile of the P1 and P4 moieties, attention was focused on bicyclic factor Xa inhibitors. Benzoxazinone is among a variety of the heterobicyclic templates we have designed.[6] The naphthyl, indole, biphenyl and phenylisoxazole moieties were selected as the P1 groups based on the factor Xa potency and trypsin selectivity in the aniline series. Scheme 7 describes the syntheses of benzoxazinone-based factor Xa inhibitors.

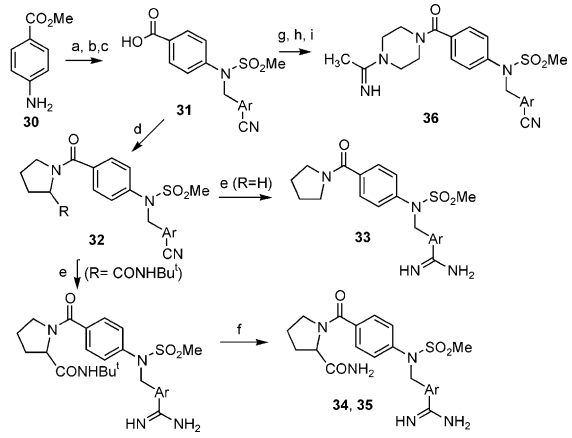


Scheme 5. (a) MsCl, Py; (b) XCH_2–Ar–CN, Cs_2CO_3, DMF (X = Br, Cl); (c) (1) HCl(g), MeOH; (2) NH_4OAc, MeOH.

Table 3. SARs of aniline-based factor Xa inhibitors: P4 modifications



Compd	P4	P1	IC_{50} (nM)
26			153
27			191
28			500
29			3933
33			1050
34			14,900
35			4060
36			1570

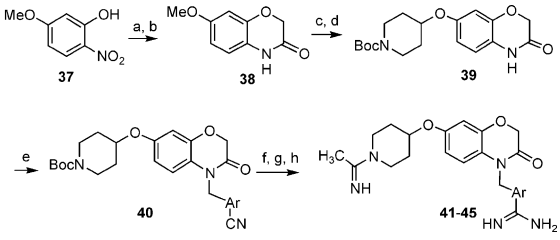


Scheme 6. (a) MsCl, Py; (b) XCH_2–Ar–CN, Cs_2CO_3, DMF (X = Br, Cl); (c) LiOH; (d) BOP, pyrrolidine(s), TEA, DMF; (e) (1) HCl(g), MeOH; (2) NH_4OAc, MeOH; (f) TFA, reflux (for compounds **34** and **35**); (g) BOP, *N*-Boc-piperazine, TEA, DMF; (h) (1) HCl(g), MeOH; (2) NH_4OAc, MeOH; (i) ethyl acetimidate/HCl, Et_3N, EtOH.

The high potency of the compounds shown in Table 4 validated the design of bicyclic compounds as factor Xa inhibitors even though no significant activity enhancing effect by the rotation constraint was observed. Interestingly, replacing the *N*-methyl in the indole compound **42** with an ethyl group resulted in the equipotent compound **43**.

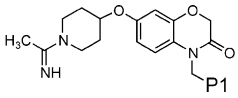
While the good thrombin selectivity is retained by compounds **41**, **44**, and **45**, the indoles (**42** and **43**) have IC_{50}s against thrombin in the sub-micromolar range. The trypsin selectivity of the benzoxazinones is similar to that of the aniline series, with the naphthyl- containing compound **41** the least selective and compound **45** which has an isoxazole moiety the most selective.

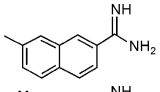
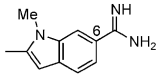
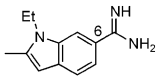
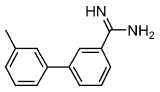
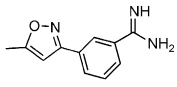
The difference in selectivity noted between compounds **41** and **45** is supported by molecular modeling. Docking studies using Gold[13] suggest both compounds bind to factor Xa (Fig. 2a) in a manner consistent with published and in-house crystallography data.[5] The P1-benzamidine moiety clearly interacts with the Asp189 side



Scheme 7. (a) Pd/C (10%), H_2 (1 atm), MeOH; (b) chloroacetyl chloride, satd $NaHCO_3$; (c) BBr_3, CH_2Cl_2; (d) *N*-Boc-4-hydroxypiperidine, PPh_3, DEAD, THF; (e) XCH_2–Ar–CN, Cs_2CO_3, DMF (X = Br, Cl); (f) (1) NH_2OH, EtOH; (2) Ac_2O, AcOH; (3) Pd/C (10%), H_2 (1 atm), MeOH; (g) TFA, CH_2Cl_2; (h) ethyl acetimidate/HCl, Et_3N, EtOH.

Table 4. In vitro potency of benzoxazinone-based dibasic factor Xa inhibitors



Compd	P1	IC_{50}s (nM)			
		Xa	IIa	Trypsin	Trypsin/Xa
41		6	> 10,000	28	5
42		2	882	76	40
43		2	877	58	30
44		4	> 10,000	143	35
45		52	> 10,000	250,000	5000

chain carboxylate. The P4-amidine is held in the S4 binding pocket by pi-cation interaction with Tyr99, Phe174, and Trp215. However, contrary to the docking results with factor Xa, the best binding conformation of compound **45** predicted by Gold displays an *inverted* binding mode, with the benzamidino group in the S4 site of trypsin (Fig. 2b). A less favorable conformer does indeed show *normal* binding (not shown here); however, this conformation of **45** is significantly different from that of compound **41** in both the S1 and S4 binding pockets. This observation may explain why compound **45** is a poor trypsin inhibitor.

Selected compounds were subjected to more detailed in vitro and in vivo tests. For example, the K_i value of compound **41** is 0.78 nM. It doubles the thrombin generation time of rabbit plasma at a concentration of 0.5 μM. The half lives of compound **41** are 0.5 h in rats and 0.9 h in rabbits following intravenous administration at 2 mg/kg. The bioavailability in rats is 4.6% at an oral dose of 2 mg/kg in 0.5% methylcellulose. This low oral bioavalibility is characteristic of diamidine compounds. The antithrombotic effect of compound **41** in our rabbit deep vein thrombosis model is dose responsive.[14] It shows a 7, 44, and 99% inhibition of thrombosis at the dose of 25, 50, and 100 μg/kg, respectively. The rabbit bleeding time is prolonged by 1.7-fold and the plasma concentration of compound **41** is 200 nM at the 100 μg/kg dose.

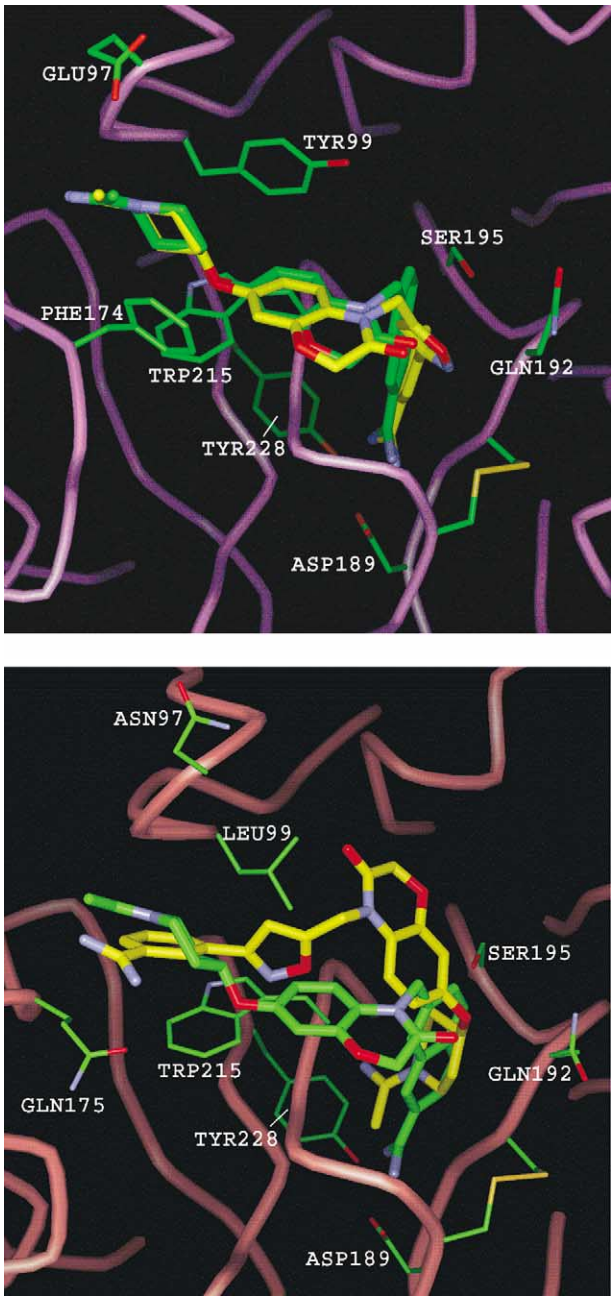


Figure 2. Compounds **41** (green) and **45** (yellow) docked in the factor Xa active site (a, top) and trypsin active site (b, bottom).

In summary, starting with the aniline-based lead compound **2**, we have demonstrated that the naphthyl moiety is tolerant of replacement with a variety of benzene-fused heterobicycles or biaryls. Compounds **10**, **14**, and especially **15** which contain an indole, biphenyl or phenylisoxazole moiety as P1, respectively, display improved trypsin selectivity. Improvements in potency and trypsin selectivity were observed when a carboxyl group was attached to the aniline nitrogen as in the biphenyl and benzothiophenyl compounds **22** and **23**, similar to that observed for YM-60828. Considerable potency drop was observed in compounds with a biphenylsulfonamide moiety or a pyrrolidinylcarbonyl phenyl group as the P4 motifs. The benzoxazinone-based compounds **41**–**45** are active factor Xa inhibitors. The improved trypsin selectivity profile of the aniline series of compounds is retained by the corresponding benzoxazinones. Compound **41** shows strong antithrombotic effect in a dose responsive manner. The compounds with an amidinobiaryl group as the P1 moiety paved the way to the convenient introduction of benzamidine surrogates such as aminoisoquinolines and aminobenzoisoxazoles, which offer possibility to achieve good oral bioavailability.[15] The details will be reported in due course.

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