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# Anthranilamide inhibitors of factor Xa

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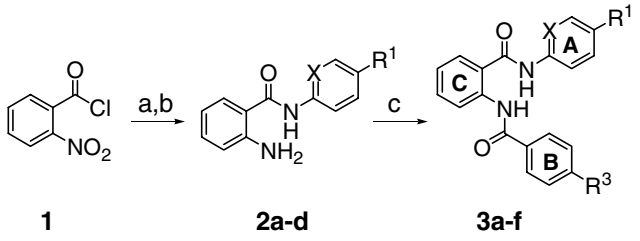
**Abstract**—SAR about the B-ring of a series of $N^2$-aroyl anthranilamide factor Xa (fXa) inhibitors is described. B-ring *o*-aminoalkylether and B-ring *p*-amine probes of the S1′ and S4 sites, respectively, afforded picomolar fXa inhibitors that performed well in in vitro anticoagulation assays.


Thromboembolic diseases are well known as a major cause of morbidity and mortality throughout the world. Standard therapeutics against these diseases such as coumadin and heparin are limited by narrow therapeutic windows and/or parenteral routes of administration,[1,2] hence there is a major need to provide orally active agents with a high safety margin suitable for both acute and chronic treatment. Because of its central role in the coagulation cascade, factor Xa (fXa) is a key target for therapeutic intervention in diseases such as DVT and PE.[3] Numerous efforts to produce an orally active fXa inhibitor are described in several reports and reviews.[4,5]

We previously described anthranilamide[6] and 1,2-dibenzamidobenzene[7] inhibitors of fXa bearing amidine[8] or neutral probes[9] of the fXa S1 pocket. Others[10,11] also utilized the anthranilamide scaffold to produce potent fXa inhibitors. Here we describe further SAR results with anthranilamides. Scheme 1 depicts the general synthetic route to $N^2$-aroyl anthranilamides such as **3a**, which inhibits fXa with a $K_i$ of about 1 μM.[6] 2-Nitrobenzoyl chloride was coupled with a 4-substituted aniline or heterocyclic amine of choice in DCM–pyridine and the resulting nitro amide reduced with Raney nickel and hydrogen to provide amines **2a**–**d**, typically 65% for the two steps. Intermediates **2a**–**d** were then coupled with the indicated 4-substituted benzoyl chlorides in DCM–pyridine to furnish $N^2$-aroyl anthranilamides **3a**–**f** (Table 1).




**Scheme 1.** Reagents and conditions: (a) DCM, pyridine, and *p*-methoxy aniline (**2a**), *p*-Cl aniline (**2b**), 2-amino-5-Cl-pyridine (**2c**), or 4-*t*-Bu aniline (**2d**), rt; (b) Raney Ni, 4.1 bar $H_2$, 1:1 THF/EtOAc, rt 16 h; (c) DCM, pyridine, and 4-OMe-, 4-*i*-Pr-, or 4-*t*-Bu-benzoyl chloride, rt.

The A-ring $R^1$ group of anthranilamides **3a**–**f** likely interacts with the fXa S1 pocket.[6] Inhibitors equipped with small $R^1$ substituents such as methoxy and chloro (**3a**–**d**) inhibit fXa with modest affinity, whereas bulky groups are not well tolerated (Table 1). The $R^1$ methoxy to *tert*-butyl replacement (**3a** → **3f**) results in a thirtyfold activity loss versus fXa. The 5-chloropyridin-2-yl derivative **3e** is significantly more potent than the anilino derivatives and serves as the prototype for further SAR results. Based on modeling studies[7] of **8b**, we

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**Table 1.** Activity of $N^2$-aroyl anthranilamides **3a**–**f** versus fXa

| Compound | X | $R^1$ | $R^3$ | fXa $K_{assoc}$[a] (in $10^6$ L/mol) |
|---|---|---|---|---|
| **3a** | CH | OMe | OMe | 1 |
| **3b** | CH | OMe | *i*-Pr | 7 |
| **3c** | CH | OMe | *t*-Bu | 5 |
| **3d** | CH | Cl | *t*-Bu | 0.5 |
| **3e** | N | Cl | *t*-Bu | 42 |
| **3f** | CH | *t*-Bu | OMe | 0.03 |

[a] $K_{assoc}$ represents the apparent association constant between enzyme and inhibitor and represents the average of at least two separate runs. $K_i$ may be approximated[6] by $1/K_{assoc}$.

perceived that the fXa S1′ site could possibly be reached from the anthranilamide B-ring *o*-position (Fig. 1). Accordingly, a series of B-ring *o*-aminoalkylether probes was prepared according to Scheme 2.

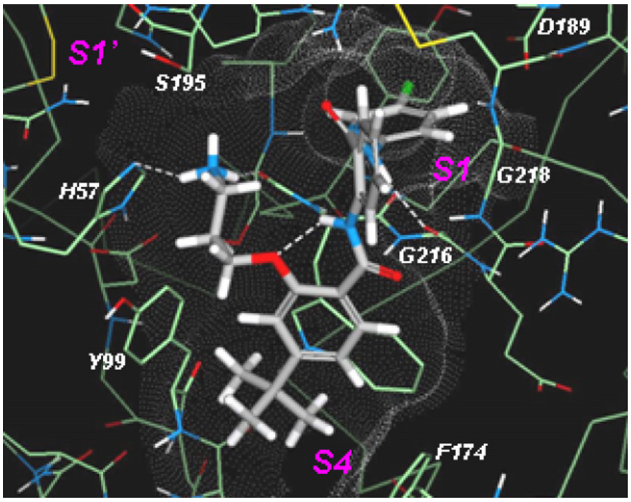



**Figure 1.** Molecular model of **8b** docked into the fXa active site. In this potential binding mode, the B-ring *o*-aminoalkylether chain is directed toward the S1′ region and hydrogen bonds to His57 and Ser214.

Phenol **4** was protected with methyl chloromethyl ether in DCM at 0 °C. Lithiation of the ether followed by carbonylation gave benzoic acid **5** in 65% yield. Treatment of **5** with methanolic HCl provides methyl salicylate **6a** in 87% yield. Mitsunobu[12] coupling of linear or cyclic *N*-boc-protected aminoalcohols to **6a** proceeded in good yield, even for secondary alcohol *N*-boc-4-hydroxypiperidine **6d** (73%). Esters **6b**–**e** were then saponified, converted to their acid chlorides, and coupled with **2c** in DCM–pyridine to give $N^2$-aroyl anthranilamides **7b**–**e**. Compound **7a** was prepared by coupling **5** and **2c** followed by acidic removal of the MOM ether protecting group. Compounds **7b**–**e** were treated with acid, then base, to afford free amines **8b**–**e.**

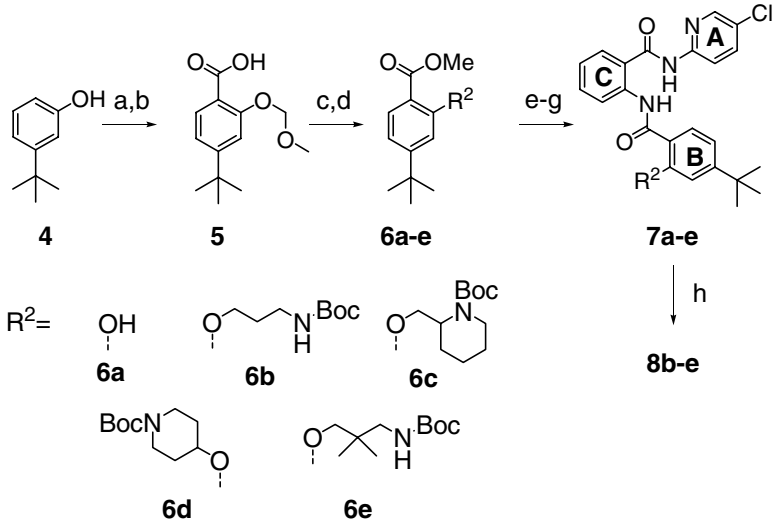
Potency versus fXa in the anthranilamide series is not greatly affected by addition of a B-ring *o*-phenol, **3e** → **7a**, 42 versus $23 \times 10^6$ L/mol, respectively (Table 2). Whereas *N*-boc aminoethers **7b** and **7d** inhibit fXa to a similar degree as proteo reference **3e**, compounds

**Table 2.** Performance of compounds **7a**–**8e** versus fXa, thrombin (fIIa), and in in vitro anticoagulation assays

| Compound | fXa $K_{assoc}$[a] (in $10^6$ L/mol) | fIIa $K_{assoc}$[b] (in $10^6$ L/mol) | APTT[c] (μM) | PT[d] (μM) |
|---|---|---|---|---|
| **7a** | 23 | 0.02 | >100 | >100 |
| **7b** | 54 | 0.2 | >70 | >70 |
| **8b** | 1440 | 152 | 0.85 | 0.79 |
| **7c** | 3.1 | 3.9 | >70 | >70 |
| **8c** | 219 | 67 | 1.4 | 1.4 |
| **7d** | 69 | 6 | 55 | 64 |
| **8d** | 1112 | 114 | 0.85 | 0.88 |
| **7e** | 2.9 | 0.14 | >70 | >70 |
| **8e** | 76 | 1102 | 2 | 1.6 |

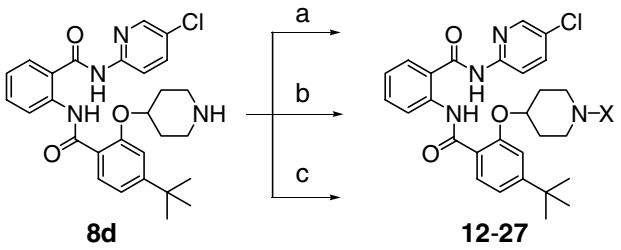
[a,b] $K_{assoc}$ represents the apparent association constant between enzyme and inhibitor.[6]

[c,d] APTT and PT are defined as the concentration of compound required to double clotting times in activated partial thromboplastin or prothrombin clot formation assays, respectively.[13]




**Scheme 2.** Reagents and conditions: (a) DIEA, DCM, methyl chloromethyl ether, 0 °C (54%); (b) *t*-BuLi, $CO_2$, 0 °C (65%); (c) MeOH, HCl, 0 °C (87%); (d) *N*-boc-aminoalcohol, $PPh_3$, THF, DIAD, rt (73% for **6d**); (e) LiOH, THF–water, 60 °C (90%); (f) oxalyl chloride, DCM, pyridine, cat. DMF; (g) **2c**, DCM, pyridine, 0 °C to rt (54%); (h) HCl dioxane, then $K_2CO_3$ in DCM–$H_2O$ (90%).

**7c** and **7e** lose about 10-fold potency versus **3e**. Factor Xa inhibition improves when the *N*-boc groups of **7b–e** are removed to reveal amines **8b–e**. For example, racemate **8c** is about 5- to 10-fold more active than **3e** and **7a**, respectively. Greater improvement is observed for amines **8b** and **8d** which inhibit fXa in the 1 nM range, about 50 times more potent than **7a**. Translation of enzyme inhibitory activity to in vitro anticoagulant activity is good for **8b** and **8d**, each of which double APTT and PT clotting times when present at less than 1 μM concentration.[13] This result contrasts with the performance of **7a–e** that each requires more than 50 μM concentration to double clotting times. Compound **8e** differs from **8b** by the presence of two methyl groups in the middle of the aminoalkylether sidechain. The added methyl groups neutralize most of the fXa potency gains realized with the aminopropyl ether chain and produce potent thrombin inhibitor **8e**, thus fXa-fIIa selectivity may be tuned by varying B-ring *ortho* substituents.

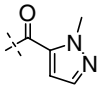
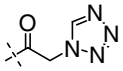
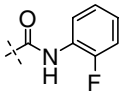
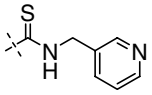



**Scheme 3.** Reagents and condition: (a) XCHO or acetone (>2 equiv), $NaCNBH_3$ (3 equiv), 95:5 MeOH/AcOH; (b) XCOCl, piperidinomethyl polystyrene, $CHCl_3$ (amylenes stabilized), or XCOOH, resin-bound carbodiimide, 4:1 $CHCl_3$/*t*-BuOH, rt, or succinic anhydride, $CHCl_3$ (**22**); (c) XNCO or XNCS, $CHCl_3$ (amylenes stabilized).

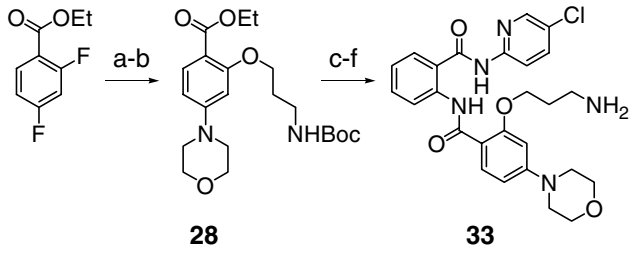
Compounds **8b–e** show that adding aminoalkylethers to the B-ring *o*-position produces very potent fXa and/or fIIa inhibitors that perform well in anticoagulation assays using human plasma.[13] Further SAR in this region is illustrated by elaboration of **8d** via reductive amination or acylation according to Scheme 3. Reductive amination of **8d** with $NaCNBH_3$ and aldehydes or acetone in 95:5 MeOH/AcOH provides tertiary amines **12–20** (Table 3). Acylation of **8d** was performed either with acid chlorides and resin-bound base or with acids and polymer-supported carbodiimide to provide **21–24**. Reaction of **8d** with isocyanates or isothiocyanates in chloroform provides urea and thiourea derivatives **25–27**.

Table 3 summarizes the SAR of substitution of the amine of **8d**. For alkyl derivatives **12–20**, fXa inhibitory activity changes slightly, increasing for isopropyl (**13**) and methoxyethyl (**15**) derivatives, and decreasing for thien-3-yl-methyl (**18**) and benzyl (**19**) derivatives. The more polar alkyl derivatives **12–17** and **20** perform similarly to unmodified **8d** in in vitro anticoagulation assays, whereas **18** and **19** are much less potent in these assays than would be expected based on their fXa

**Table 3.** Enzyme activity and anticoagulant performance of alkyl (**12–20**) and acyl (**21–27**) derivatives of amine **8d**

| Compound | X | fXa $K_{assoc}$[a] (in $10^6$ L/mol) | fIIa $K_{assoc}$[b] (in $10^6$ L/mol) | APTT[c] (μM) | PT[d] (μM) |
|---|---|---|---|---|---|
| **8d** | H | 1112 | 114 | 0.85 | 0.88 |
| **12** | Me | 1630 | 61 | 0.93 | 1.1 |
| **13** | *i*-Pr | 3440 | 25 | 1.2 | 1.8 |
| **14** | *n*-Pr | 1940 | 30 | 3.1 | 3.3 |
| **15** | Methoxyethyl | 3080 | 24 | 2.1 | 2.1 |
| **16** | Cyclopropylmethyl | 1370 | 37 | 2.4 | 2.5 |
| **17** | Imidazo-2-yl-methyl | 2160 | 54 | 1.8 | 2.6 |
| **18** | Thien-3-yl-methyl | 450 | 23 | 14.8 | 20 |
| **19** | Bn | 488 | 20 | 28.1 | 44.6 |
| **20** | 2-Carboxybenzyl | 1160 | 72 | 0.57 | 1.0 |
| **21** | $-COCH_2NMe_2$ | 176 | 60 | n.t. | n.t. |
| **22** | $-CO(CH_2)_2COOH$ | 714 | 4 | 6.1 | 5.3 |
| **23** |  | 513 | 21 | 5.7 | 7.6 |
| **24** |  | 448 | 134 | 8 | 10 |
| **25** |  | 307 | 27 | 21.5 | 30.2 |
| **26** | $-CSNH(CH_2)_3NMe_2$ | 170 | 145 | 2.9 | 2.9 |
| **27** |  | 733 | 34 | 13.4 | 21.8 |

[a,b] $K_{assoc}$ represents the apparent association constant between enzyme and inhibitor.[6]
[c,d] APTT and PT are defined as in Table 2.[13]




**Scheme 4.** Reagents and conditions: (a) $HO(CH_2)_3NHBoc$, *t*-BuOK, THF, −65 °C to rt (4:1 *o*/*p* isomers); (b) morpholine, >80 °C (56%); (c) LiOH, dioxane-$H_2O$, 60 °C (91%); (d) oxalyl chloride, DCM, pyridine, cat. DMF; (e) **2c**, DCM, pyridine, 0 °C to rt (55%); (f) HCl-dioxane, then $K_2CO_3$ in DCM–$H_2O$.

inhibition. This observation may reflect increased binding to proteins and/or phospholipids by these more lipophilic derivatives. Of the acyl analogs **21**–**27**, none are as potent versus fXa as **8d** and their anticoagulation performance lags both **8d** and the simpler alkyl derivatives.

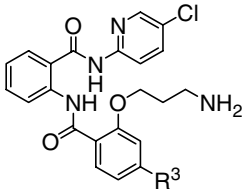
Replacing the *p*-*tert*-butyl group of **8b** with more polar amino groups affords further SAR results related to the fXa S4 binding site. In general, amines were installed at the B-ring *p*-position according to the route illustrated for morpholine in Scheme 4.

Potassium *N*-boc-*n*-aminopropoxide was condensed with ethyl 2,4-difluorobenzoate in THF at −65 °C, then warmed to room temperature to give a 4:1 mixture of *o*/*p* adducts. The *o*-substituted product was isolated in 65% yield after flash chromatography, then subjected to a second round of nucleophilic substitution in neat morpholine to provide ester **28**. Ester **28** was saponified, converted to its acid chloride, then condensed with **2c** and deprotected to give amine **33**.

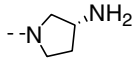
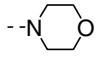
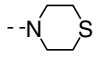
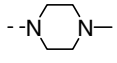
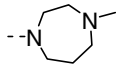
The SAR for B-ring *p*-amines is shown in Table 4. Replacing *tert*-butyl with pyrrolidine (**8b** → **30**) increases fXa affinity and in vitro anticoagulant potency, but a further increase in ring size to piperidine **32** and homopiperidine **37** diminishes both activities. Morpholine derivative **33** is slightly less potent versus fXa than its *tert*-butyl comparator **8b**, but **33** is a slightly more potent anticoagulant, consistent with reduced protein or phospholipid binding. Remarkably, *N*-methylpiperazine **35** loses significant fXa affinity, but ring expansion to *N*-methylhomopiperazine **36** increases potency one hundredfold versus **35**. Compound **36** is a picomolar fXa inhibitor with nanomolar in vitro anticoagulation potency.

In summary, relative to the prototypical $N^2$-aroyl anthranilamides such as **3a**, we describe SAR for the

**Table 4.** $R^3$ group SAR: enzyme activity and anticoagulant performance of compounds **30**–**37** versus comparator **8b**




**8b**, **30-37**

| Compound | $R^3$ | fXa $K_{assoc}$[a] (in $10^6$ L/mol) | fIIa $K_{assoc}$[b] (in $10^6$ L/mol) | APTT[c] (μM) | PT[d] (μM) |
|---|---|---|---|---|---|
| **8b** | *t*-Bu | 1440 | 152 | 0.85 | 0.79 |
| **30** |  | 3010 | 40 | 0.41 | 0.41 |
| **31** |  | 874 | 7.3 | 0.4 | 0.45 |
| **32** |  | 323 | 17 | 1.0 | 0.93 |
| **33** |  | 516 | 5.8 | 0.26 | 0.34 |
| **34** |  | 709 | 17 | 0.69 | 0.61 |
| **35** |  | 82 | 2 | n.t. | n.t. |
| **36** |  | 8970 | 24 | 0.1 | 0.14 |
| **37** |  | 130 | 25 | 3.1 | 2.7 |

[a,b] $K_{assoc}$ represents the apparent association constant between enzyme and inhibitor.[13]
[c,d] APTT and PT are defined as in Table 2.[13]

B-ring which provides more potent fXa inhibitors. Elaboration of the B-ring *o*-position with a series of aminoalkylethers produces several ~1 nM fXa inhibitors that perform well in in vitro anticoagulation assays. Additional modification of the B-ring *p*-position with various amines affords pM fXa inhibitor **36** with in vitro anticoagulant potency in the 100–140 nM range.

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