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Structure–activity relationships of anthranilamide-based factor Xa inhibitors containing piperidinone and pyridinone P4 moieties

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Abstract—Introduction of the phenyl piperidinone and phenyl pyridinone P4 moieties in the anthranilamide scaffold led to potent, selective, and orally bioavailable inhibitors of factor Xa. Anthranilamide **28** displayed comparable efficacy to apixaban in the rabbit arteriovenous-shunt (AV) thrombosis model.

Thromboembolic disorders, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke, are the leading cause of mortality and disability in the industrialized world. Warfarin (Coumadin®), the only oral anticoagulant on the market, is effective for the prevention and treatment of thromboembolic disorders. However, due to the narrow therapeutic window and highly variable dose response among individuals (food interactions, drug–drug interactions, genetic polymorphisms), careful monitoring is required to provide an antithrombotic effect while minimizing the risk of severe bleeding.[1] There is a need for safer, more efficacious oral anticoagulants.

One approach to address this unmet medical need has focused on selective factor Xa (fXa) inhibitors. Factor Xa, a trypsin-like serine protease, is a key enzyme located at the junction between the intrinsic and extrinsic pathways of the coagulation cascade. Experimental evidence suggests that selective fXa inhibitors may offer a safe profile by preventing thrombus formation without causing a significant increase in bleeding.[2] As a result, research on small molecule fXa inhibitors is a major area of interest for the pharmaceutical industry.[3]

Work from our laboratories led to the discovery of the clinical candidate apixaban (BMS-562247, Fig. 1).[4] This potent, selective, and orally bioavailable fXa inhibitor contained the novel, neutral, phenyl piperidinone P4 group. As part of our research program to explore structurally diverse fXa inhibitors as potential back-up candidates, we introduced the phenyl piperidinone P4 moiety into the anthranilamide scaffold which gave **2**, a single digit nanomolar fXa inhibitor (Fig. 1). Next,

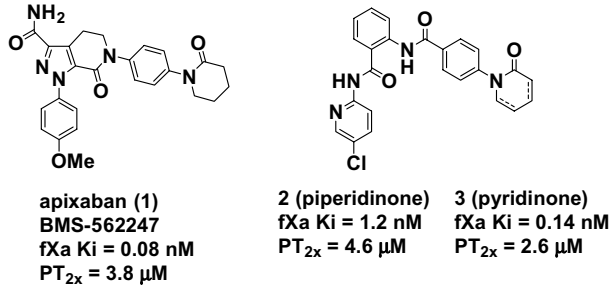

Figure 1. Apixaban and anthranilamides **2** and **3**.

Keywords: Factor Xa; Anthranilamide.
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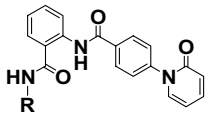
we discovered that incorporation of the unsaturated version of this P4 group, the phenyl pyridinone,[5] gave **3**, a potent fXa inhibitor with similar in vitro activity to apixaban. In this letter, we describe the SAR of anthranilamide-based fXa inhibitors containing these piperidinone and pyridinone P4 moieties. Subsequent to this work, other fXa inhibitors containing phenyl piperidinone and phenyl pyridinone P4 groups were described in the literature.[6] It should also be noted that anthranilamide-based fXa inhibitors have been previously reported by several groups.[7–10]

Since the phenyl pyridinone moiety proved to be a viable P4 group in the anthranilamide core, we decided to explore the remaining regions of the molecule in order to optimize the in vitro and in vivo properties of this series. Our initial efforts focused on the exploration of the P1 group (Table 1). The position of the chlorine substituent was very important for binding in the S1 pocket. The removal of the chlorine gave the unsubstituted pyridine **4** which resulted in >20-fold loss in activity. Replacing the chloro with fluoro (**6**) led to a 7-fold loss in fXa activity. Though the isosteric methyl derivative (**7**, fXa K_i=0.58 nM) showed a minor drop in activity, the trifluoromethyl derivative (**8**) exhibited a significant (>2500-fold) loss. The 5-Cl-Pyrimidin-2-yl (**9**) exhibited a 9-fold loss in fXa K_i activity, however, the 4-Cl-phenyl (**10**) was equivalent to **3**, both in terms of inhibitory activity in the fXa assay and potency in the in vitro clotting assay. We recognized that the P1 amide bond may be hydrolyzed in vivo generating potentially mutagenic aniline metabolites. Since the 2-amino-5-chloropyridine fragment was inactive in our Ames and MTT cytotoxicity assays,[12] it became our preferred P1 group for this series.

As an alternative strategy to address the potential hydrolysis of the P1 amide, we investigated additional P1 linkers (Table 2). Reducing the carbonyl to a methylene (**12**) led to only a 5-fold drop in activity but unfortunately the $EC_{2\times}$ value in the clotting assay was high. Branching at the benzylic position (**13**) resulted in a more dramatic loss in fXa activity. Even though the sulfonamide linker (**14**) led to a 40-fold loss in activity, it was still a single digit nanomolar fXa inhibitor.

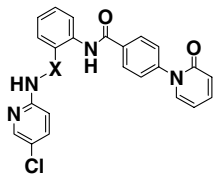
Table 1. P1 modifications



Compound	R	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
3	5-Cl-Pyridin-2-yl	0.14	2.6
4	Pyridin-2-yl	3.0	—[c]
5	Pyridin-3-yl	43	—[c]
6	5-F-Pyridin-2-yl	1.0	2.8
7	5-Me-Pyridin-2-yl	0.58	2.7
8	5-CF_3-Pyridin-2-yl	1560	—[c]
9	5-Cl-Pyrimidin-2-yl	1.3	3.2
10	4-Cl Phenyl	0.21	3.5
11	3-Cl Phenyl	4.2	—[c]

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations (n = 2), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.
[c] Not tested.

Table 2. P1 linker modifications



Compound	X	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
12	$–CH_2–$	0.62	6.7
13	$–CH(CH_3)–$	59	—[c]
14	$–SO_2–$	5.5	—[c]

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations (n = 2), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.
[c] Not tested.

An X-ray structure of **14** bound to fXa (1.6 Å resolution, R-value = 0.26, Fig. 2) was obtained.[13] The overall P1–P4 trajectory is similar to that described previously.[9] The P1 chloro is positioned above Y228, and there is a weak to moderate hydrogen bond (3.2 Å) between the P1 sulfonamide N–H and the carbonyl of G218 and a strong hydrogen bond (2.7 Å) between the P4 amide N–H and the carbonyl of G216. The pyridinone, which is orthogonal to the inner phenyl ring, forms an edge to face interaction with W215 and is appropriately sandwiched between Y99 and F174.

The SAR of the P4 linker moiety is highlighted in Table 3. As was observed in the P1 amide linker, the conversion of the P4 amide carbonyl to methylene (**15**) resulted in a 7-fold loss in fXa activity and a significant drop in the in vitro clotting assay. Surprisingly, the introduction of sulfonamide (**16**) led to a significant loss in activity.

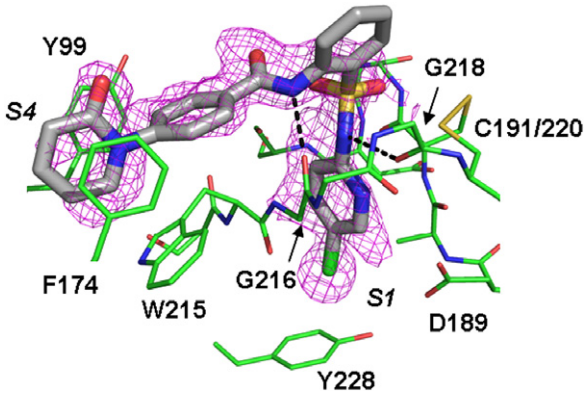
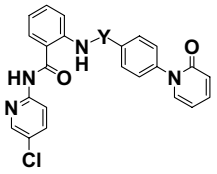


Figure 2. X-ray crystal of **14** in factor Xa.

Table 3. P4 linker modifications



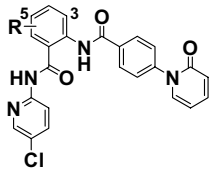
Compound	Y	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
3	–C(O)–	0.14	2.6
15	$–CH_2–$	1.1	>20
16	$–SO_2–$	7670	—[c]

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.
[c] Not tested.

Next, we modified the anthranilamide scaffold.[14] Our earlier work in the pyrazole-5-carboxamide series revealed that a methyl substituent at the C3 position of the pyrazole provided a 10-fold increase in fXa binding by interacting with a small lipophilic pocket above the S1 pocket near the C191–220 disulfide bridge.[11,15] Modeling suggested that substitution at C5 of the phenyl core could access this pocket. A number of C5-substituted phenyl cores containing the phenyl pyridinone P4 group were synthesized (Table 4).

Small groups like 5-Cl (**19**) and 5-Me (**20**) gave a 2-fold and 5-fold increase in potency, respectively. Introduction of the 3-OMe, 5-Cl phenyl core, which was originally developed by researchers at Berlex,[9] gave **22** as a 13-pM fXa inhibitor with an excellent PT value. We observed a similar enhancement in potency when these substituted phenyl cores and the phenyl piperidinone P4 were combined (Table 5). Groups like 5-Cl (**25**) and 5-Me (**27**) gave a 4-fold and 6-fold increase in potency, respectively. Gratifyingly, the 3-OMe, 5-Cl phenyl (**28**) provided an additional enhancement in potency giving a 57-pM fXa inhibitor. Since the conversion of the 3-OMe (**28**) to 3-OH (**29**) did not affect fXa activity, we used the phenol as a handle to introduce solubilizing groups. For example, the 5-chloro-3-*N*,*N*-dimethyl ethyl derivative (**30**) was equipotent to **28** and showed a >45-fold improvement in aqueous solubility (cf. compound **30**, amorphous, 912 μg/mL, with compound **28**, amorphous, 19 μg/mL; measured by a thermodynamic equilibrium aqueous solubility assay at pH 6.5 in a 25-mM potassium phosphate buffer).

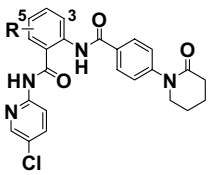
Table 4. Substituted anthranilamide cores with phenyl pyridinone P4



Compound	R	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
3	H	0.14	2.6
17	$5\text{-MeSO}_2\text{NH}$	0.12	—[c]
18	5-CN	2.2	>20
19	5-Cl	0.060	6.4
20	5-Me	0.028	2.0
21	3-OMe	0.14	2.6
22	3-OMe, 5-Cl	0.013	1.4

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.
[c] Not tested.

Table 5. Substituted anthranilamide cores with phenyl piperidinone P4

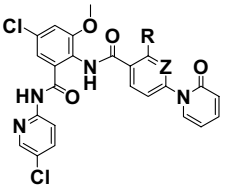


Compound	R	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
2	H	1.2	4.6
23	$5\text{-MeSO}_2\text{NH}$	2.0	9.6
24	5-CN	0.45	3.8
25	5-Cl	0.33	1.3
26	5-Br	0.14	11
27	5-Me	0.19	2.8
28	3-OMe, 5-Cl	0.057	1.5
29	3-OH, 5-Cl	0.047	4.0
30	$3\text{-O(CH}_2)_2\text{NMe}_2$, 5-Cl	0.065	1.0

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.

A brief investigation of the phenyl portion of the phenyl pyridinone group was undertaken (Table 6). Replacing the phenyl ring with the pyridine analogue (**31**) showed

Table 6. P4 modifications



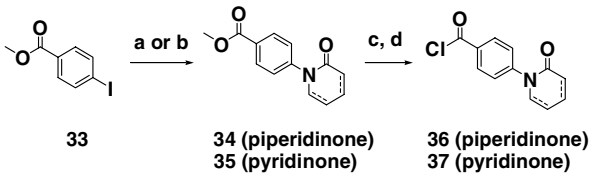
Compound	R	Z	fXa K_i[a] (nM)	PT[b] ($EC_{2\times}$, μM)
31	H	N	0.24	3.0
32	F	CH	0.005	1.6

[a] Ki values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11.
[b] PT (prothrombin time) in vitro clotting assay was performed in human plasma as described in Ref. 11.

Table 7. Dog pharmacokinetic profile[a]

Compound	Cl (L/h/kg)	$t_{1/2}$ (po) (h)	Vdss (L/kg)	F (%)
Apixaban (**1**)	0.02	5.8	0.2	58
22	0.67	0.70	0.62	99
28	0.70	1.5	1.3	44
31	0.30	1.6	0.81	74
32	0.80	0.70	2.6	18

[a] Compounds were dosed in an *N*-in-1 format as described in Ref. 4. Doses ranged from 0.02 to 0.5 mg/kg for iv and po.



Scheme 1. Reagents and conditions: (a) δ-valerolactam, CuI, K_2CO_3, *N*,*N*′-dimethyl ethylene diamine, toluene, 100 °C, 70%; (b) pyridine-2-one, CuI, K_2CO_3, 1,10-phenanthroline, DMSO, 110 °C, 17–82%; (c) NaOH, MeOH, H_2O, 84–96%; (d) $SOCl_2$, cat. DMF, 1,2-dichloroethane, reflux, quantitative.

a 20-fold loss in activity. Previously, we have shown that the substitution of a fluoro substituent on the phenyl ring in the P4 group enhanced fXa activity in the pyrazole 5-carboxamide series.[15] Thus, the introduction of the 3-fluoro substituent on the P4 phenyl ring led to **32** (fXa K_i = 5 pM), the most potent anthranilamide derivative in our study.

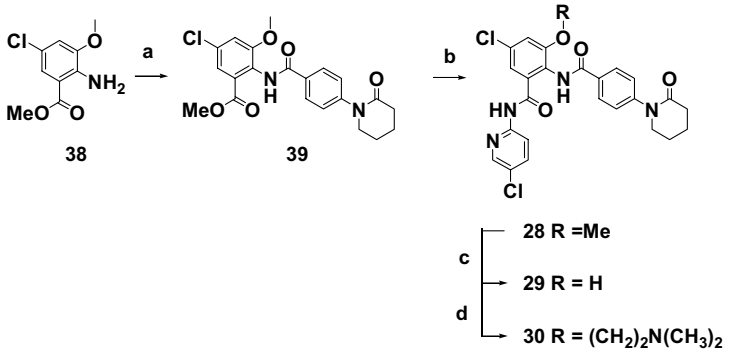
The pharmacokinetics of compounds **22**, **28**, **31**, and **32** were investigated in dogs and the data for apixaban are included for comparison (Table 7). These anthranilamides have low to moderate clearance and good oral bioavailability. However, due to higher clearance than apixaban, these compounds have a shorter half-life.

Based on good in vitro potency in the fXa assay, good oral bioavailability, and excellent selectivity against related serine proteases (>10,000-fold against trypsin, plasma kallikrein, activated protein C, factor IXa, factor XIa, thrombin, factor VIIa, chymotrypsin, urokinase, plasmin, and tPA), compound **28** was chosen for further evaluation in mechanistic[16a] and in vivo studies. As expected for reversible, active site inhibitors, **28** was competitive versus a tripeptide substrate (37 °C K_i is 0.2 nM)[16b] with a rapid onset of inhibition,[17] but exhibited mixed-type inhibition versus the physiological substrate, prothrombin, which interacts with fXa primarily at exosites.[18] An advantage of this mechanism is that **28** is a potent inhibitor at both low (prothrombinase 37 °C K_i for free E is 0.6 nM) and saturating (K_i for ES is 1.7 nM) physiological levels of prothrombin. In the rabbit arteriovenous-shunt (AV) thrombosis model,[19] compound **28** at 0.3, 1.0, and 3.0 mg/kg/h inhibited thrombus formation by 34%, 70%, and 80%, respectively. The calculated ID_{50} of **28** was 0.97 μmol/kg/h and it was comparable to that of apixaban (ID_{50} = 2.4 μmol/kg/h) in this model.

Representative examples of the synthesis of the piperidinone and pyridinone P4 groups are described in Scheme 1. Copper-catalyzed amidation of phenyl iodide **33** with either δ-valerolactam or pyridin-2-one, according to Buchwald's protocol,[20] yielded piperidinone **34** and pyridinone **35**. The esters were hydrolyzed to the carboxylic acids which were then converted to the acid chlorides **36** and **37**.

The preparation of the anthranilamide analogues is exemplified by the synthesis of **28** (Scheme 2). Reacting the substituted aniline **38** with the P4 acid chloride **36** followed by the introduction of the 2-amino-5-chloropyridine, according to Weinreb's procedure,[21] gave **28**. Cleavage of the methyl ether with BBr_3 provided **29** and subsequent alkylation with 2-chloro-*N*,*N*-dimethylethyl amine under basic conditions afforded **30**.

Introduction of either the phenyl piperidinone or the phenyl pyridinone P4 groups into the anthranilamide scaffold led to potent fXa inhibitors. Optimization of this series led to compound **28**, a potent, selective, and orally bioavailable fXa inhibitor which displayed comparable efficacy to apixaban in the rabbit arteriovenous-shunt (AV) thrombosis model. However, compound **28** had a shorter half-life compared to apixaban.



Scheme 2. Reagents and conditions: (a) acid chloride **36**, pyridine, dichloromethane, 0 °C–rt, 83%; (b) 5-Cl-2-NH_2-pyridine (10 equiv), $AlMe_3$ (9.8 equiv), 1,2-dichloroethane, then **39**, rt–40 °C, 26–59%; (c) BBr_3, dichloromethane, 0 °C–rt, 29%; (d) KOH, DMSO (or NaH, DMF), $Cl(CH_2)_2N(CH_3)_2$·HCl, 75°C,8%.

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