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Sulfonamidolactam inhibitors of coagulation factor Xa

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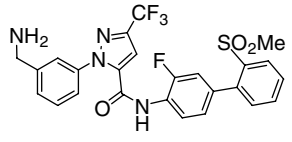
Abstract—As part of an effort to identify novel backups for previously reported pyrazole-based coagulation Factor Xa inhibitors, the pyrazole 5-carboxamide moiety was replaced by 3-(sulfonylamino)-2-piperidone. This led to the identification of a structurally diverse chemotype that was further optimized to incorporate neutral or weakly basic aryl and heteroaryl P1 groups while maintaining good potency versus Factor Xa. Substitution at the sulfonamide nitrogen provided further improvements in potency and as did introduction of alternate P4 moieties.

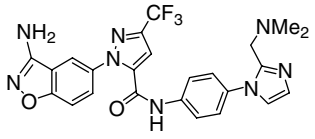
Safer and more efficacious oral anticoagulants that eliminate the need for the patient monitoring remain an unmet medical need in the treatment of thromboembolic disorders. Therapeutic agents that target specific coagulation serine proteases are a major focus of ongoing antithrombotic drug research. In particular, selective inhibitors of Factor Xa (fXa) have been shown in animal models to offer a greater safety margin and better efficacy when compared with heparin, LMWH, warfarin, or direct thrombin inhibitors.[1] Numerous potent and selective small molecule Factor Xa inhibitors have been reported, several of which have progressed into human clinical trials.[2]

Previous reports from our laboratories have described various pyrazole-based inhibitors of fXa including clinical candidates DPC423 (**1**)[3] and razaxaban (**2**).[4] In a phase II clinical trial, **2** was shown to prevent deep vein thrombosis in patients undergoing total knee replacement, displaying increased efficacy, and similar safety to the LMWH, enoxaparin.[5]

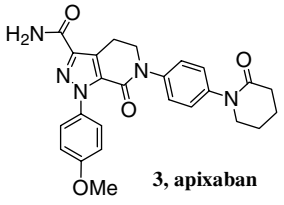
The identification of suitable backups for these initial clinical candidates focused on preparing structurally diverse compounds that would address potential issues in the parent series. To this end, targets were designed to maintain the key interactions in the S1 and S4 pockets of fXa by modifying the central scaffold, which provides the conformational constraint necessary to present the P1 and P4 groups in the appropriate orientation for binding to the enzyme. Various strategies were investigated for the modification and/or the removal of the pyrazole amide linkage to eliminate the potential for metabolic cleavage. Non-cleavable amide bond replacements were prepared,[6] as well as a number of alternate



1, DPC423



2, razaxaban



3, apixaban

Keywords: Factor Xa inhibitors; Anticoagulant; Serine protease inhibitors; Antithrombotic.
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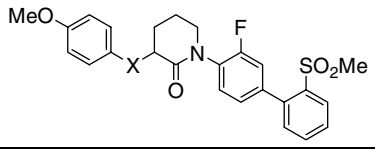
scaffolds resulting from cyclization of the amide nitrogen back to either the central aromatic ring[7] or the pyrazole.[8] The latter strategy culminated in the design and synthesis of apixaban (**3**),[9] which is currently undergoing clinical trials. In the work presented here, we incorporated the amide linkage into a monocyclic piperidone ring and removed the pyrazole ring to give compounds of formula **4**–**7** in Table 1, where X is an ether, amine, amide, or sulfonamide linker.[10] As can be seen from the fXa K_i data for these compounds, there was a clear difference in potency seen between the linkers, and sulfonamide **7** was 4- to 10-fold more potent compared to compounds **4**–**6**.

Further optimization of **7** via a library of P1 sulfonamides was therefore carried out. Among the substituted phenyl sulfonamides, a *para* substituent was generally preferred over the same substitution at the *meta* position, with the *p*-chlorophenyl compound **10** having the best potency at 23 nM. Both the 6-chloronapthyl (**22**) and the 5-chloro-2-thienyl (**25**) compounds were single digit nanomolar inhibitors of fXa. Analogs with 7-chloronaphthyl (**23**), 3-aminobenzisoxazolyl (**24**), 6-indazolyl (**28**), and 3-quinolinyl (**29**) P1 groups also showed promising potency in this series.

Despite relatively good affinity for fXa, the chloronaphthyl compound **22** had poor potency in the prothrombin time (PT) assay[13] used for assessing the in vitro anticoagulation efficacy of these compounds (See Table 3). In view of the highly lipophilic nature of this compound ($c\log P = 5.63$), this is most likely due to high plasma protein binding.[14] Substitution of polar groups on the sulfonamide nitrogen as a means to lower protein binding and increase aqueous solubility was therefore investigated. Introduction of carboxymethyl, (methoxycarbonyl)methyl or 3-hydroxypropyl groups in this position provided compounds **31**–**33** with similar or slightly improved fXa affinity, but did little to improve PT. In contrast, acetamide compounds **34**–**39**, which incorporated a terminal tertiary amine, were both 2- to 4-fold more potent inhibitors of fXa and provided approximately 5-fold improvement in PT as compared to **22**.

Further reduction in overall lipophilicity was achieved by replacing the terminal phenylsulfone P4 group in the parent compound with more polar heterocyclic groups such as the *N*,*N*-(dimethylaminomethyl)-imidazole P4 group of **2** (See Table 4). Similar potency versus fXa was observed for this analog (**40**) with ~10-fold improvement in PT as compared to **22**. Quaternary compounds **41** and **42** which were obtained from attempted alkylation of the sulfonamide nitrogen of **40** were ~10-fold more potent fXa inhibitors with similar potency in the PT assay to **40**. A loss in potency as compared to the 2-methylsulfonyl-phenyl and *N*,*N*-dimethylamino-methylimidazole compounds was observed with 4-pyridine, **43**, 1-piperidine, **44**, and 2-oxo-1-piperidine analogs, **45**, although most of this potency loss could be regained in the latter analog by the introduction of the *N*-methyl, *N*-(2-*N*,*N*-dimethylaminomethyl)acetamide substitution on the sulfonamide nitrogen (**46**). As previously observed in the pyrazole-based series,[15] the replacement of the saturated lactam P4 group of **45** with a 2-pyridone moiety results in enhanced affinity for fXa. Pyridone P4 analog **47** was indeed the most potent in this group with fXa K_i of 0.11 nM, however, the translation to the PT assay was poor as compared to imidazole **40**. Again substitution at the nitrogen of the sulfonamide nitrogen resulted in a 5-fold increase in fXa potency over **47** in *N*-methyl, *N*-(2-*N*,*N*-dimethylaminoethyl)-acetamide analog **48**, along with a 10-fold improvement in the PT assay. The (*S*)-enantiomer of **48**[16] was evaluated in a PK study in dogs. The compound had clearance of 1.19 L/h/kg, a 6.45 h half-life and low oral bioavailability ($F\% = 4\%$),

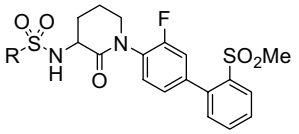
Table 1. SAR of linkers



Compound[11]	X	fXa K_i[a] (nM)
4	O	200
5	NH	450
6	CONH	560
7	SO_2NH	53

[a] K_i's obtained from purified human enzymes and are averaged from two experiments ($n = 2$).[12]

Table 2. P1 sulfonamide SAR



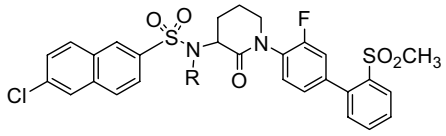
Compound[8]	R	fXa K_i[a] (nM)
7	4-MeO-phenyl	53
8	Phenyl	370
9	4-F-phenyl	44.5
10	4-Cl-phenyl	23
11	4-Et-phenyl	78
12	4-Cyanophenyl	420
13	3-Cl-phenyl	380
14	3-MeO-phenyl	100
15	3,4-diF-phenyl	270
16	3,4-diCl-phenyl	61
17	2,5-Cl-phenyl	650
18	3,5-diCl-phenyl	730
19	3-Pyridyl	2600
20	2-NH_2-5-pyridinyl	260
21	Benzyl	3200
22	6-Cl-naphthyl	2.2
23	7-Cl-naphthyl	18
24	3-NH_2-5-benzisoxazolyl	19
25	5-Cl-2-thienyl	5.3
26	5-Cl-3-Me-2-benzothienyl	160
27	5-(3-Isoxazolyl)-2-thienyl	26
28	6-Indazolyl	19
29	3-Quinolinyl	28
30	6-Quinolinyl	73

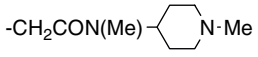
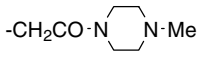
[a] K_i's obtained from purified human enzymes and are averaged from two experiments ($n = 2$).

consistent with its lack of permeability in a Caco-2 assay.[17]

An additional improvement in potency versus fXa in compounds with the pyridone P4 group was realized by replacing the 6-chloronaphthyl P1 with a 6-chlorothieno[2,3-b]pyridinyl moiety to provide the compounds in Table 5. This allowed the replacement of the basic sulfonamide substituent in analog **50** with the neutral *N*-methylamide of compound **51**, which maintained good potency and anticoagulant activity, but still had poor Caco-2 permeability. Removal of the *o*-fluoro substitution from the phenyl of **49** provided **52** with better translation to the PT assay. Des-fluoro analog **53** with a primary amide substituent on the sulfonamide linker also showed good PT potency, but no Caco-2 permeability. Acid **54** was similar in fXa affinity to amide **53** but had a ~3-fold drop off in vitro anticoagulant actvity. Improved permeability over amides **50**, **51**, and **53** was achieved with methyl ester **55**, which had a similar fXa affinity and potency in the PT assay to **51**. These results suggest that further optimization could provide additional potent compounds with improved oral bioavailability in this series. The compounds described herein are highly selective for fXa with >10000-fold selectivity over thrombin, trypsin, and fVIIa. Compounds (*S*)-**48** and **55**, were selected for evaluation in mechanistic studies.[18] As predicted for reversible inhibitors binding in the active site, both compounds were competitive inhibitors with a chromogenic tripeptide substrate,[19] but exhibited mixed-type inhibition versus the physiological substrate, prothrombin, which interacts with FXa primarily at exosites.[20] This mechanism is advantageous since these compounds are potent inhibitors at both low and high physiological levels of prothrombin.

Table 3. SAR of substituted sulfonamide analogs

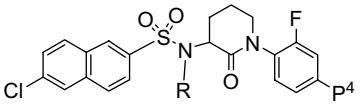


Compound[8]	R	fXa K_i[a] (nM)	PT[b] EC_{2x} (μM)
22	H	2.2	102
31	CH_2CO_2H	1.0	250
32	CH_2CO_2Me	0.88	89
33	$(CH_2)_3OH$	2.3	208
34	$CH_2CONH(CH_2)_2NMe_2$	2.2	ND[c]
35	$CH_2CON(Me)(CH_2)_2NMe_2$	0.84	17
36	$CH_2CON(Me)(CH_2)_2NEt_2$	1.1	19.5
37	$CH_2CON(Me)(CH_2)_2OH$	2.7	ND[c]
38		0.43	19.5
39		0.71	24.4

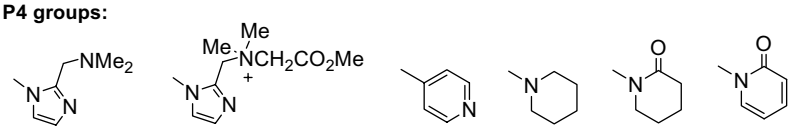
[a] K_is are obtained from purified human enzymes and are averaged from two experiments ($n = 2$).
[b] PT values were measured according to Refs. 3 and 4.
[c] ND, not determined.

The racemic compounds in Tables 1–5 were synthesized from commercially available 2-tetrahydrofuran carboxylic acid as outlined in Scheme 1. The acid was converted to the acid chloride which was coupled with 2-fluoro-4-[2-(methylsulfonyl)-phenyl]aniline[3] in the presence of DMAP to provide amide **56**. Treatment of **56** with BBr_3 led to the open chain bromoalcohol, which was acetylated and then cyclized by treatment with

Table 4. P4 heterocycle SAR



P4 groups:



A **B** **C** **D** **E** **F**

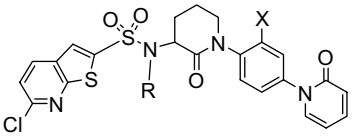
Compound	R	P4	fXa K_i[a] (nM)	PT[b] EC_{2x} (μM)
40	H	A	2.4	13
41	H	B	0.35	13
42	CH_2CO_2Me	B	0.21	12
43	H	C	28	ND[c]
44	H	D	16	ND[c]
45	H	E	10	ND[c]
46	$CH_2CON(Me)(CH_2)_2NMe_2$	E	1.7	12
47	H	F	0.11	35
48	$CH_2CON(Me)(CH_2)_2NMe_2$	F	0.02	3.3
(***S***)-**48**	$CH_2CON(Me)(CH_2)_2NMe_2$	F	0.016	1.7

[a] K_is are obtained from purified human enzymes and are averaged from two experiments ($n = 2$).
[b] PT values were measured according to Refs. 3 and 4.
[c] ND, not determined.

Hunig's base to give the 3-acetoxylactam. Hydrolysis of the acetate and treatment of the resulting alcohol with PBr_3 provide the key bromolactam intermediate **57**. The bromide was displaced with *p*-methoxyaniline or the corresponding phenol in the presence of sodium hydride to give the N and O linked analogs **58** and **60**, respectively, or converted into the corresponding primary amine **59** by displacement with sodium azide followed by reduction either by catalytic hydrogenation or by triphenylphosphine in ether. Amide analogs **61** were prepared by condensation of **59** with carboxylic acids in the presence of TBTU and TEA, and sulfonamide analogs **62** by reaction of **59** with the corresponding sulfonylchlorides which were either commercially available or prepared as described by Becker et al.[21] Bis-sulfonylation was avoided by use of a two phase reaction mixture consisting of 1 M K_2CO_3 and EtOAc, and the excess sulfonylchloride was scavenged with PS-trisamine resin. The sulfonamide products could then be alkylated with the appropriate alkyl bromides or iodides in the presence of K_2CO_3 in DMF to provide compounds of formula **63**. To prepare the acetamide analogs, **62** was first alkylated using *tert*-butyl bromoacetate followed by the cleavage of the *tert*-butyl ester with TFA in CH_2Cl_2. Amides were prepared from the resulting acids by reaction with amines in the presence of BOP, TEA, and DMAP at 50°C. Analogs with heterocyclic P4 groups were similarly prepared from amine intermediates **66**, **67**, and **68**, which were obtained as outlined in Scheme 2 from aryliodide intermediate **65** using copper mediated N-arylation chemistry.

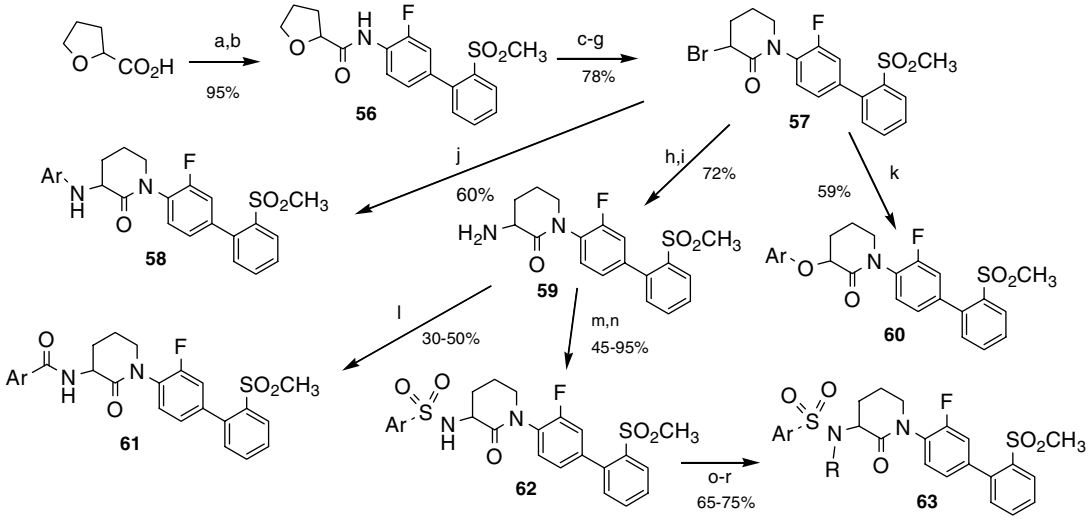
A model of (*S*)-**48** overlaid with the crystal structure of **1**[22] is shown in Figure 1. The biaryl P4 fits as expected into the hydrophobic box formed by residues Phe174, Trp215, and Tyr99. The carbonyl of the central lactam core is within H-bonding distance of the backbone NH of Gly216. The chlorine at the 6-position of the naphthyl P1 moiety extends deeper into the S1 pocket to displace a structural water molecule and engage in a hydrophobic interaction with Tyr228. Similar close hydrophobic contact between aromatic chloride moie-

Table 5. 6-Chlorothieno[2,3-b]pyridinyl analogs

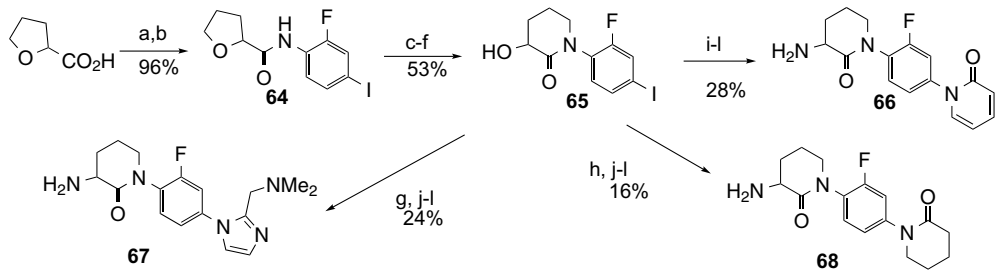


Compound	R	X	fXa K_i[a] (nM)	PT[b] EC_{2X} (μM)	Caco-2[b] Papp $\times 10^{-6}$ (cm/s)
49	H	F	0.02	32	8.3
50	$CH_2CON(Me)(CH_2)_2NMe_2$	F	0.013	2.1	0
51	$CH_2CONHMe$	F	0.037	4.2	0.1
52	H	H	0.05	15	2.0
53	CH_2CONH_2	H	0.1	4.8	0
54	CH_2CO_2H	H	0.13	16	ND
55	CH_2CO_2Me	H	0.043	4.4	3.5

[a] K_is are obtained from purified human enzymes and are averaged from two experiments ($n = 2$).
[b] PT and Caco-2 values were measured according to Ref. 3 and 4.



Scheme 1. Reagents and conditions: (a) oxalyl chloride, DMF, CH_2Cl_2; (b) CH_2Cl_2, DMAP, 2-fluoro-4-(2-methylsulfonylphenyl)aniline; (c) BBr_3, CH_2Cl_2; (d) Ac_2O, heptane; (e) DIPEA, DMF, reflux; (f) K_2CO_3, $MeOH/H_2O$; (g) PBr_3, CH_2Cl_2; (h) NaN_3, DMF, 50 °C; (i) H_2, Pd/C MeOH; (j) $ArNH_2$, NaH, THF; (k) ArOH, NaH THF; (l) $ArCO_2H$, TBTU, TEA, DMF; (m) $ArSO_2Cl$, 1 M K_2CO_3, EtOAc; (n) PS-trisamine; (o) *tert*-butyl bromoacetate, K_2CO_3, DMF; (p) TFA, CH_2Cl_2; (r) RNHR′, BOP, TEA, DMAP, DMF, 50 °C.



Scheme 2. Reagents and conditions: (a) oxalyl chloride, DMF, CH_2Cl_2; (b) CH_2Cl_2, DMAP, 2-fluoro-4-iodoaniline; (c) BBr_3, CH_2Cl_2; (d) Ac_2O, heptane; (e) DIPA, DMF, reflux; (f) K_2CO_3, MeOH/H_2O; (g) 2-(*N*,*N*-dimethylamino)methylimidazole, CuI, K_2CO_3, DMSO, 140 °C, 3 h; (h) piperidinone, K_3PO_4, CuI, 1,2-diaminocyclohexane, dioxane, 85 °C (i) 2-hydroxypyridine, CuI, K_2CO_3, DMSO, 140 °C, 3 h; (j) PBr_3, CH_2Cl_2; (k) NaN_3, DMF, 50°C; (l) $SnCl_2$, MeOH.

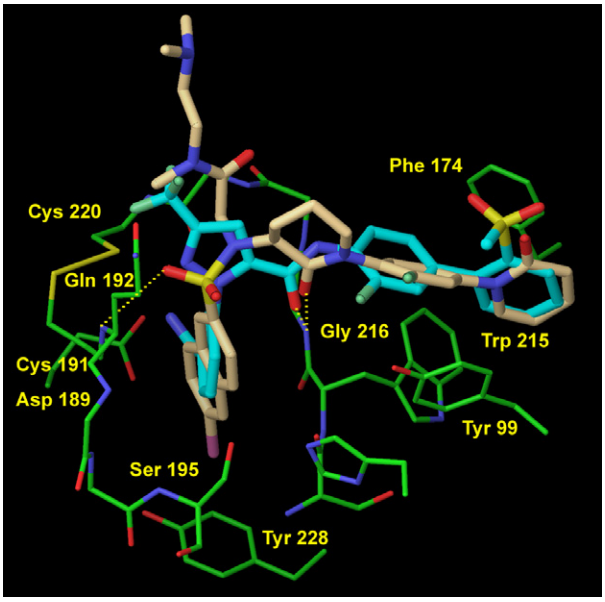


Figure 1. Model of Compound (*S*)-**48** in white overlaid on crystal structure of **1** (DPC423) in blue complexed with fXa (in green).

ties and the aromatic ring of Tyr228 has been observed in several recently reported fXa-inhibitor crystal structures.[23] One of the oxygens of the sulfonamide linker is directed toward the backbone NH of Gln192 similar to the N2 of the pyrazole ring of **1** while the other sulfonamide oxygen points toward the oxyanion hole. The *N*-methyl of the acetamide substituent at the sulfonamide nitrogen extends toward the Cys191–Cys220 disulfide bridge occupying a similar position as the trifluoromethyl moiety of **1**, while the basic dimethylamine group is most likely solvent exposed.

In summary, highly potent inhibitors of fXa which combine biaryl P4 groups with chloronaphthylsulfonyl and chlorothienylpyridinesulfonyl P1 moieties linked by an aminopiperidone conformational constraint have been identified. Potency and molecular properties can be fine-tuned by introduction of appropriate functionality at the sulfonamide nitrogen in these molecules. The best combination of fXa potency, in vitro anticoagulant activity and permeability was obtained with compound **55**.

Acknowledgment

We thank Dr. Philip Stein for providing the 6-chlorothienopyridine-2-sulfonylchloride used in the synthesis of compounds **49**–**55**.

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