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Arylsulfonamidopiperidone derivatives as a novel class of factor Xa inhibitors

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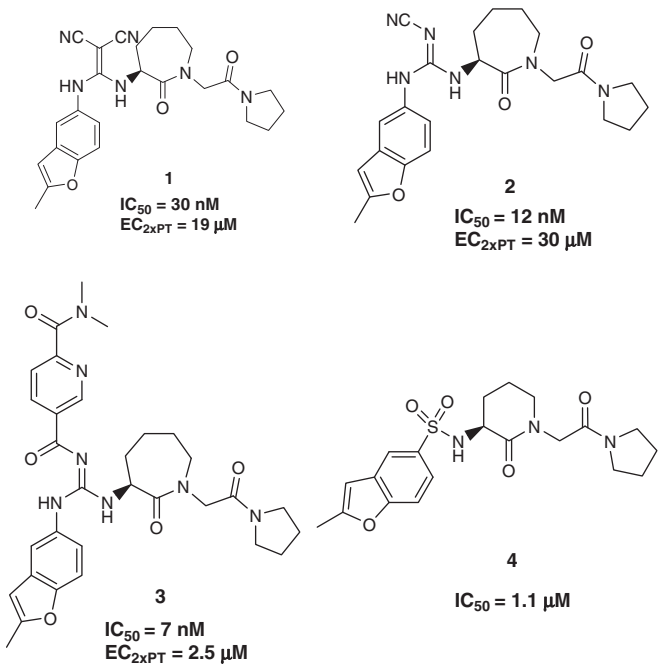
ABSTRACT

The design, synthesis and SAR of a novel class of valerolactam-based arylsulfonamides as potent and selective FXa inhibitors is reported. The arylsulfonamide–valerolactam scaffold was derived based on the proposed bioisosterism to the arylcyanoguanidine-caprolactam core in known FXa inhibitors. The SAR study led to compound **46** as the most potent FXa inhibitor in this series, with an IC_{50} of 7 nM and $EC_{2\times PT}$ of 1.7 μM. The X-ray structure of compound **40** bound to FXa shows that the sulfonamide–valerolactam scaffold anchors the aryl group in the S1 and the novel acylcytisine pharmacophore in the S4 pockets.

Thromboembolic events are a leading cause of mortality worldwide.[1] Inhibition of the trypsin-like serine protease factor Xa (FXa) has emerged as a key point of intervention in the blood coagulation cascade for the development of antithrombotic agents for some time.[2] Selective factor Xa inhibitors may effectively block coagulation, since factor Xa is positioned at the start of the common pathway of the extrinsic and intrinsic coagulation systems.[3] Currently, rivaroxaban[4] and apixaban[5] have been approved in the EU for the prevention of venous thromboembolism (VTE) in adults undergoing elective knee or hip replacement surgery; edoxaban[6] has been approved in Japan for prevention of venous thromboembolic events in patients undergoing major orthopedic surgery; other oral and direct factor Xa inhibitors such as betrixaban[7] and darexaban (YM150)[8] are in late stages of clinical development.

Factor Xa contains a deep S1 and a box-like S4 recognition site at the enzyme's active site. Potent FXa inhibitors generally require both an S1 and an S4 binding element which are connected through L-shaped or other 'bent' scaffolds.[2] We have previously reported several series of caprolactam based FXa inhibitors containing a ketene aminal **1**,[9] a cyanoguanidine **2**,[10] and an aroylguanidine **3**[11] as linkers of the P1 and P4 pharmacophores. To identify suitable backups for these initial series, we have focused on



Scheme 1. The ketene aminal **1**, cyanoguanidine **2**, aroylguanidine **3** and benzofuran-5-sulfonamide **4**.

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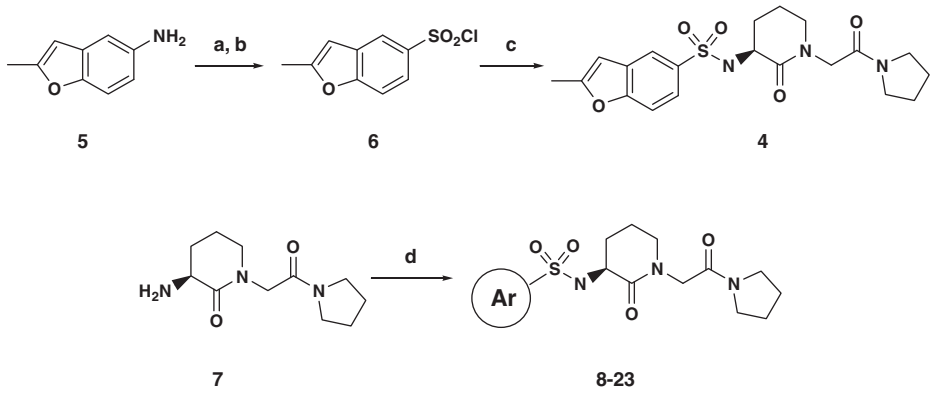
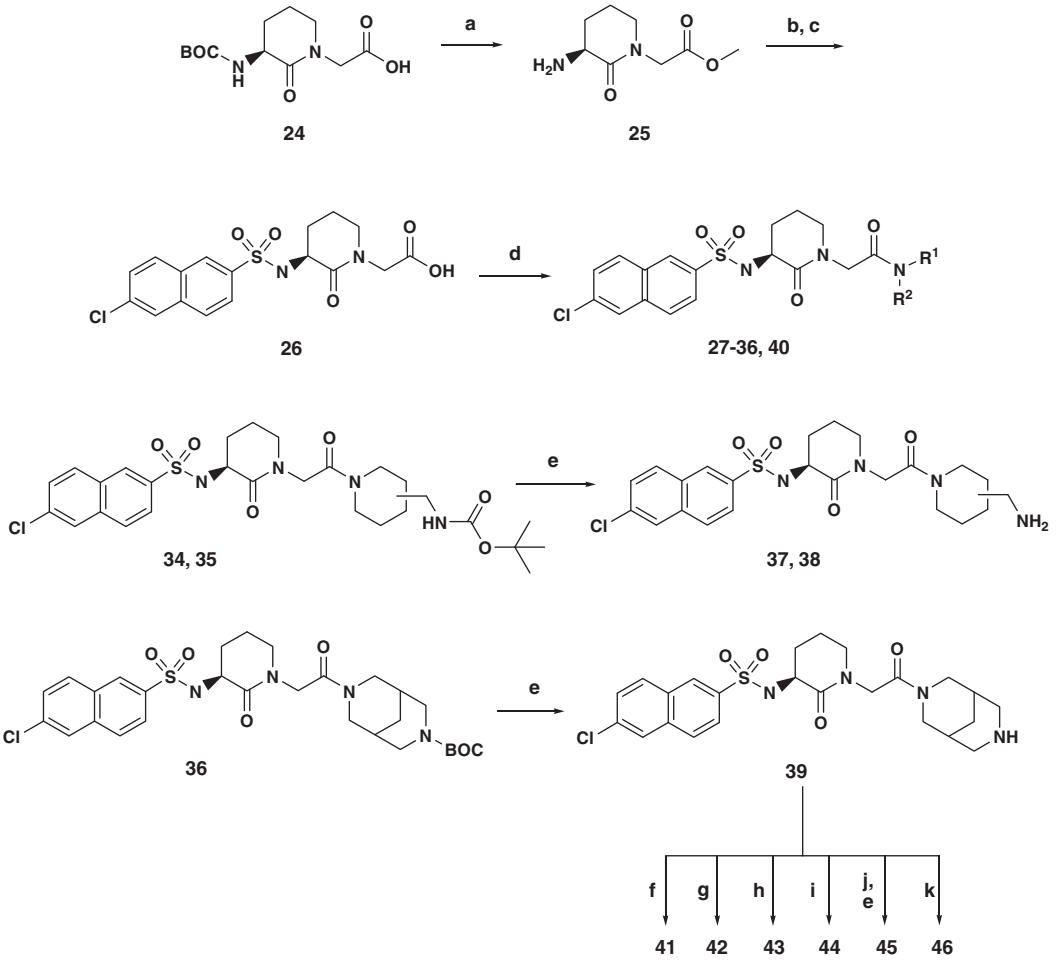


Scheme 2. The synthesis of **4** and **8–23**. Reagents and conditions: (a) $NaNO_2$, HCl/HOAc, −10 °C to −5 °C. (b) SO_2, CuCl, 29% yield for 2 steps. (c) **7**, EtOAc/$NaHCO_3$ (sat.), 83% yield. (d) Arylsulfonyl chloride, EtOAc/$NaHCO_3$ (sat.), 65–93% yield.

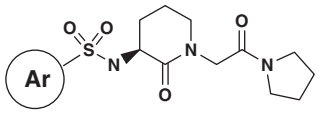


Scheme 3. The synthesis of **27–46**. Reagents and conditions: (a) MeOH, HCl, 0 °C to rt, 96%. (b) 6-Chloronaphthalene-2-sulfonyl chloride, EtOAc/$NaHCO_3$ (sat.). (c) LiOH.$2H_2O$, THF-H_2O, 85% yield for 2 steps. (d) HNR^1R^2, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrchloride (EDCI), Et_3N, CH_2Cl_2, 25–90% yield. (e) TFA, CH_2Cl_2, 60–98% yield. (f) Acetic anhydride, Et_3N, CH_2Cl_2, 85% yield. (g) TMSNCO, CH_2Cl_2, 93% yield. (h) (1) Ethyl 2-chloro-2-oxoacetate, Et_3N, CH_2Cl_2; (2) NH_4OH, 32% for 2 steps. (i) Methylsulfonyl chloride, Et_3N, CH_2Cl_2, 63% yield. (j) 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid, EDCI, Et_3N, CH_2Cl_2, 91% yield. (k) 3-Amino-1*H*-pyrazole-4-carboxylic acid, Et_3N, CH_2Cl_2, 23% yield.

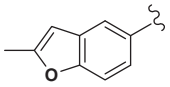
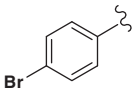
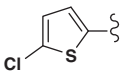
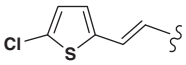
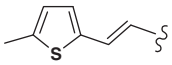
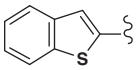
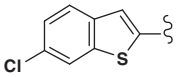
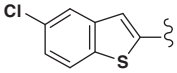
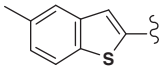
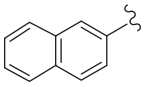
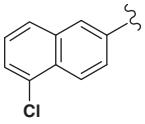
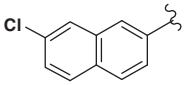
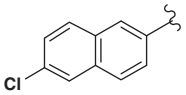
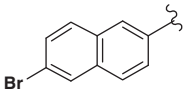
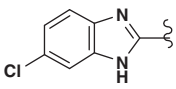
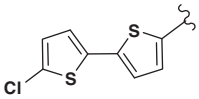
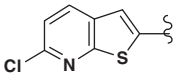
preparing structurally diverse compounds that would address potential issues in the parent series. To this end, targets were designed to maintain the key interactions in the S1 and S4 pockets of FXa by modifying the central scaffold and the linker region to eliminate the possibility of generating an aniline-type metabolite.

Inspection of the X-ray crystal structures of **2**[10] and a compound closely related to **3**[11] bound to FXa suggested that the benzofuran-guanidine moiety may be replaced with an arylsufonamide,[12] whilst maintaining the proper projection of the aryl group into the deep S1 pocket. To test this hypothesis, we synthesized three

Table 1
SAR of the aromatic binding element

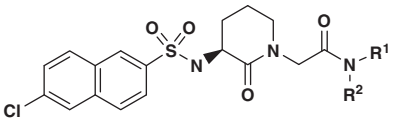


4, 8-23

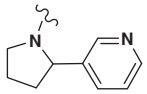
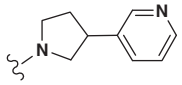
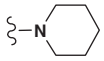
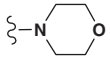
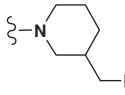
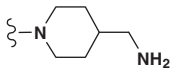
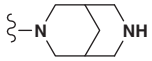
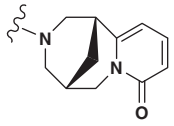
Compound	Ar	IC_{50}[a] (nM)	$EC_{2\times PT}$[b] (μM)
4		1110	–
8		9750	–
9		11750	–
10		61	11
11		1015	–
12		2794	–
13		122	34
14		60	20
15		1948	–
16		1708	–
17		2218	–
18		1010	–
19		32	12
20		19	11
21		32	50
22		51	29
23		14	13

[a] IC_{50} values are measured against human factor Xa utilizing the cleavage of a synthetic substrate S-2222.
[b] Concentration of inhibitor required to double the prothrombin based clotting time in human plasma; data are the average of two independent determinations.

Table 2
SAR of the amide pharmacophore



19, 27-33, 37-40

Compound	NR^1R^2	IC_{50}[a] (nM)	$EC_{2\times PT}$[b] (μM)
19		32	12
27		130	38
28		129	>50
29		337	>50
30		58	26
31		121	40
32		674	–
33		1957	–
37		209	17
38		1330	–
39		22	3.5
40		13	4.1

[a] IC_{50} values are measured against human factor Xa utilizing the cleavage of a synthetic substrate S-2222.
[b] Concentration of inhibitor required to double the prothrombin based clotting time in human plasma; data are the average of two independent determinations

benzofuran-5-sulfonamide compounds with different ring sizes in the central lactam core. While the 7-membered caprolactam-containing compound is not active, both 5- and 6-membered lactam compounds showed weak activity against human FXa, with the benzofuran sulfonamidopiperidine-2-one **4** having an IC_{50} of 1.1 μM (Scheme 1). Based on this lead, we initiated SAR studies to further improve the potency. This communication describes the in vitro SAR of this novel series of sulfonamidopiperidine-2-one based FXa inhibitors.[13]

Compounds **4** and **8–23** were synthesized by the reaction of various aryl- or alkyl-sulfonyl chlorides and the valerolactam amine **7** in 65–93% yields as shown in Scheme 2. For example, the 2-methylbenzofuran-5-amine **5** was treated with $NaNO_2$/HCl/HOAc and the corresponding diazonium was sulfonylated with SO_2/CuCl to give 2-methylbenzofuran-5-sulfonyl chloride **6** in 29% yield. Further reaction of **6** with lactam amine **7** afforded the corresponding sulfonamides **4** in 83% yield.

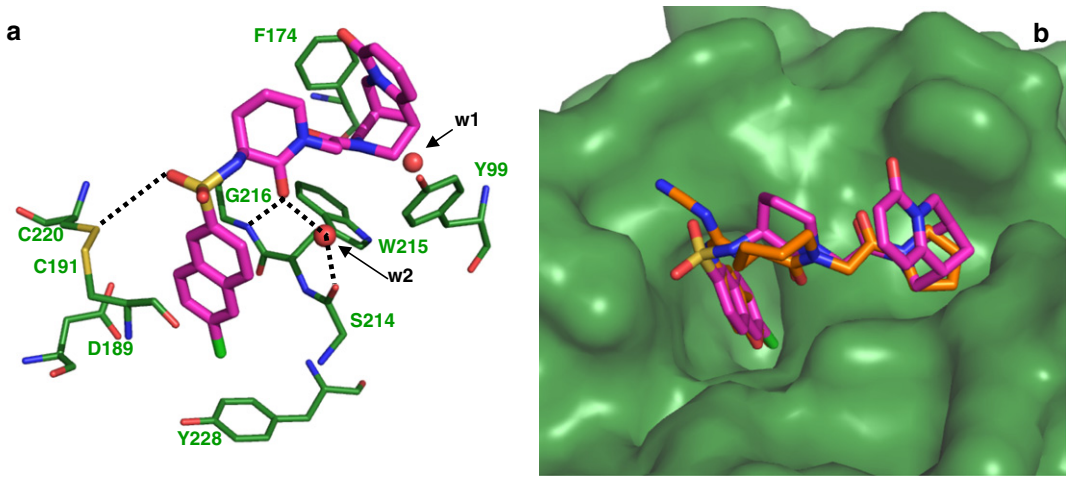


Figure 1. (a) X-ray crystal structure of **40** bound in FXa. The direct hydrogen bond between the ligand's lactam carbonyl and Gly216 backbone amide N*H* (3.3 Å) and the interaction between the ligand's lactam carbonyl and Ser214 backbone carbonyl via water w2 (2.8 Å, 2.6 Å) are highlighted, in addition to the contact between one of the sulfonamide oxygens and FXa's Cys220 sulfur (3.7 Å). Conserved P4 water w1 is also shown. (b) The overlay of cyanoguanidine–caprolactam **2** (orange carbons) with **40** (magenta carbons) bound in FXa. Figures were created using PyMol (http://www.pymol.org).

Synthesis of compounds **27–46** are outlined in Scheme 3. The lactam acid **24** was synthesized following Friedinger's protocol.[14] Simultaneous esterification and deprotection afforded the intermediate ester **25**, which was reacted with the 6-chloronaphthalene-2-sulfonyl chloride to give the sulfonamide. Further hydrolysis with lithium hydroxide provided the common intermediate acid **26**. EDC mediated amide formation furnished the compounds **27–36** and **40**. Deprotection of the BOC group in **34–36** afforded compounds **37–39**. Further derivatization of the amine function in **39** provided compounds **41–46**.

Early efforts in this study focused on analogs of **4** where the aryl group was varied. Selected analogs are shown in Table 1 to illustrate the SAR. The monocyclic arylsulfonamide compounds are generally weak FXa inhibitors (compounds **8** and **9**), with the 5-chloro-2-yl-thiophene analog **9** having an IC_{50} of 11.8 μM. Adding an ethylene spacer between the thiophene and sulfonyl group increases activity dramatically. Both compounds **10** and **11** are significantly more potent than **9**. The (*E*)-2-(5-chlorothiophen-2-yl)ethylene derivative **10** (IC_{50} = 61 nM) is 192-fold more potent than **9**, and 16-fold more potent than its 5-methylthiophene analog **11** (IC_{50} = 1015 nM). An activity difference between chloro- and methyl-substitution is also found in the benzothiophene series. The 5-chlorobenzo[*b*]thiophene-2-sulfonamide **14** (IC_{50} = 60 nM) is 46-fold more active than unsubstituted benzo[*b*]thiophene-2-sulfonamide **12** (IC_{50} = 2792 nM), and is 32-fold more potent than its 5-methylbenzo[*b*]thiophene-2-sulfonamide analog **15** (IC_{50} = 1948 nM). This is consistent with the previously noted preference for chloro- versus methyl-substituted P1 groups in FXa and can be explained by the stronger hydrophobic nature of chloro- versus methyl-substituted aromatic rings, Cl-π interactions, and by enhanced electrostatic interactions with FXa's Asp189 due to Cl-induced polarization of the P1 aryl ring.[15]

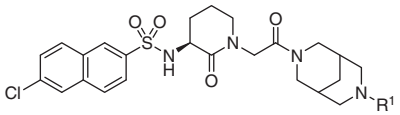
Replacement of the 2-methyl-2-yl-benzofuran group in **4** with a 2-naphthyl group provides **16**, which is slightly less active (IC_{50} = 1708 nM). A survey of chloro-substitution on the 2-naphthyl group leads to the 6-chloro-2-naphthyl compound **19**, which has an IC_{50} of 32 nM ($EC_{2\times PT}$ = 12 μM).[16] The 6-bromo-2-naphthyl compound **20** (IC_{50} = 19 nM) has similar FXa activity to **19**. Other chloro-substituted bicyclic aryl sulfonamides **21–23** also showed good anti-FXa activity, with compound **23** having an IC_{50} of 14 nM ($EC_{2\times PT}$ = 13 μM).

With an optimized P1 pharmacophore and central lactam ring in hand, we next turned our attention to the SAR of the P4 binding group. Selected analogs are shown in Table 2. Similar to the thiourea and cyanoguanidine series,[10] the replacement of the pyrrolidine with non-cyclic amines led to significant losses in potency (data not shown). Substitutions at the C-2 and C-3 positions on the pyrrolidine ring were tolerated with the C-2 substituted analogs slightly more potent than the C-3 substituted ones. For example, compound **27** with a 2-methylpyrrolidine has an IC_{50} of 130 nM. The 2-(3-pyridyl) substituted pyrrolidine **28** (IC_{50} = 129 nM) is slightly more potent than the 3-substituted analog **29** (IC_{50} = 337 nM), although both show diminished $EC_{2\times PT}$ (>50 μM). Modest changes to the ring size (thiazolidine, piperidine, morpholine and 4-methylpiperazine) also provided compounds less active than **19**. While the thiazolidine compound **30** (IC_{50} = 58 nM) is only slightly less potent than **19**, the piperidine compound **31** (IC_{50} = 121 nM) is about 4-fold less potent than **19**, and compounds with a morpholine (**32**, IC_{50} = 674 nM) and 4-methylpiperazine (**33**, IC_{50} = 1957 nM) are significantly less active.

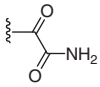
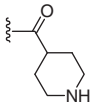
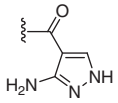
Among the substituted piperidine analogs **37–40**, the 3-aminomethyl substituted piperidine compound **37** (IC_{50} = 209 nM) is only slightly less active than the unsubstituted piperidine compound **31**, but it is about 6-fold more potent than its 4-substituted analog **38** (IC_{50} = 1330 nM). Finally, replacement of the pyrrolidine group in **19** with a 3,7-diazabicyclo[3.3.1]nonane or a cytisine provide the bicyclic analogs **39** and **40**, both of them are more potent FXa inhibitors than **19** with FXa IC_{50}s of 22 nM ($EC_{2\times PT}$ = 3.5 μM) and 13 nM ($EC_{2\times PT}$ = 4.1 μM), respectively.

To elucidate the binding mode of this arylsulfonamide–valerolactam series, an X-ray crystal structure of compound **40** bound to FXa was determined at a resolution of 2.42 Å. The resulting complex is shown in Figure 1.[17] As expected, the arylsulfonamide creates the needed L-shaped turn seen in many FXa inhibitors, allowing the 6-chloro-2-naphthyl group to fit deep into the S1 pocket where the chlorine atom fills a key hydrophobic interaction site above Tyr228 (3.4 Å from *Cl* to *C*-OH). The cytisine occupies the hydrophobic S4 pocket with the piperidine ring bound by Tyr99, Trp215 and Phe174. One of the sulfonyl oxygens contacts the disulfide bond between Cys191 and Cys220, and the valerolactam carbonyl forms an elongated hydrogen bond with N*H* of Gly216 (3.3 Å); the valerolactam carbonyl also interacts with Ser214 backbone carbonyl via a crystallographic water (2.8 Å and 2.6 Å between the water–valerolactam C=*O* and the water–Ser214 C=*O*, respectively). The structure of **40** in FXa has many features in common with the previously reported X-ray crystal complex structures

Table 3
SAR of the 3,7-diazabicyclo[3.3.1]nonane P4 pharmacophore



39, 41-46

Compound	R^1	IC_{50}[a] (nM)	$EC_{2\times PT}$[b] (μM)	Pc[c] nm/s)
39	H	22	3.5	<15
41		11	2.5	73
42		14	5	<15
43		32	3.2	<15
44		10	9	<15
45		13	2	<15
46		7	1.7	<15

[a] IC_{50} values are measured against human factor Xa utilizing the cleavage of a synthetic substrate S-2222.
[b] Concentration of inhibitor required to double the prothrombin based clotting time in human plasma; data are the average of two independent determinations.
[c] Caco-2 cell permeability (apical to basolateral) measured at 3 μM of compound.

Table 4
Selectivity profile of **40**

Hman enzymes	Ki[a] (nM)
Fctor Xa	4.71
Kallikrein	6218
Thrombin	3280
Tryptase	4979
Activated protein C	22500
Factor XIa	13330
FVIIa	3684
u-PA	15100
Plasmin	15780
t-PA	1279
Chymotrypsin	9359

[a] K_i values are calculated from the IC_{50} values assuming competitive inhibition versus the low molecular weight synthetic substrates using the relationship, $K_i = IC_{50}/(1 + [S]/K_m)$, where S is the substrate concentration in the assay and K_m is the Michaelis constant for that substrate. Data are the average of two independent determinations.

between FXa and **2**[10] and a compound closely related to **3**[11], indicating that the linkers between the P1 and P4 groups are for the most part interchangeable. It appears that the distal pyridone ring in **40** is largely solvent exposed and modification of this portion of the ligand may provide compounds with improved physicochemical properties without strongly impacting their FXa inhibitory activity (IC_{50}). Thus, further SAR investigation was concentrated on the derivatization of the P4 NH group in compound **39** and results are summarized in Table 3 (compounds **41–46**).

Among the 7-acetyl-, 7-carboxamide, 7-oxalamide-, and 7-methylsufonyl- substituted analogs **41–44**, only the acetyl compound **41** is more potent than **39** both in IC_{50} and $EC_{2\times PT}$. Although both the 7-carboxamido- and 7-methylsulfonyl-compounds **42** and **44** showed improved IC_{50} values, they are less active in $EC_{2\times PT}$. The more polar oxalamide compound **43** is less potent in IC_{50} but maintains equipotent $EC_{2\times PT}$. Further improvements in potency are seen in compounds **45** and **46**, with compound **46** having an IC_{50} of 7 nM and $EC_{2\times PT}$ of 1.7 μM.

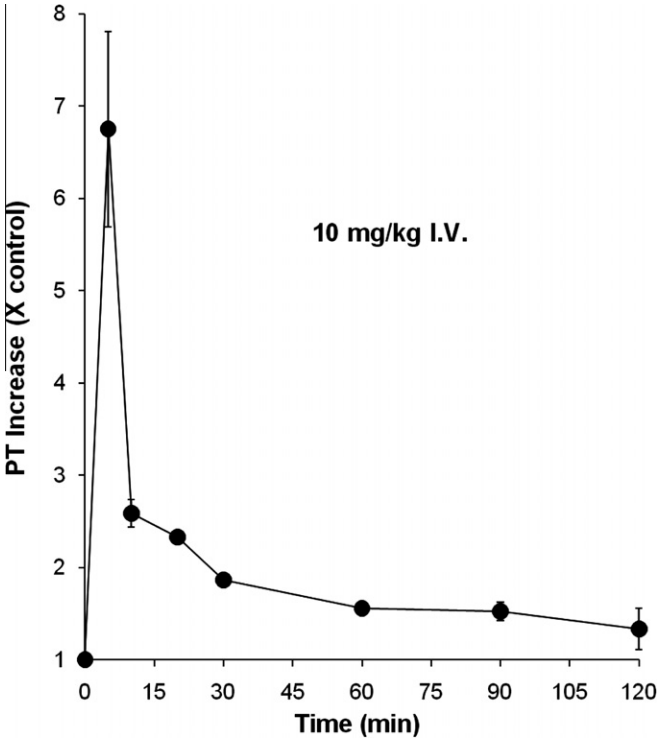


Figure 2. The i.v. dosing of **40** in rat.

Similar to the lead compounds **2**[10] and **3**,[11] the arylsulfonamidopiperidone derivatives described above are selective FXa inhibitors relative to related trypsin-like serine proteases. Table 4 shows the selectivity profile of compound **40**. Furthermore, compound **40** showed activity in rats after intravenous administration and measurement of ex vivo clotting time.[18] As shown in Figure 2, intravenous bolus injection of 10 mg/kg of **40** led to an 1.34-fold increase in prothrombin time (PT) after 2 h. Unfortunately, despite their other favorable properties, compounds containing a 7-substituted-3,7-diazabicyclo[3.3.1]nonan-3-yl or a cytisine as the P4 pharmacophore generally have limited Caco-2 cell permeability and a short metabolic half life in liver microsomes.[19] Further work is necessary to address these issues before this series can furnish acceptable antithrombotic drug candidates.

In summary, we have discovered a novel series of FXa inhibitors, which contain an arylsulfonamidopiperidone P1 and a novel cytisine or 7-substituted-3,7-diazabicyclo[3.3.1]nonan-3-yl P4 pharmacophore. These compounds exhibit potent and highly selective anti-FXa activity. The SAR demonstrates that sulfonamidopiperidones are excellent bioisosteres for the cyanoguanidine–caprolactam core in previously reported series; both anchor the P1 and P4 pharmacophores in an L-shaped conformation. The SAR is consistent with the binding conformation revealed by the X-ray structure of compound **40** bound to FXa, where the 6-chloro-2-naphthyl group resides in the S1 pocket and the bulky cytisine or 7-substituted-3,7-diazabicyclo[3.3.1]nonan-3-yl group is bound to the S4 pocket of FXa.

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References and notes

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16. IC_{50}s are measured against human factor Xa utilizing the cleavage of a synthetic substrate S-2222. The $EC_{2\times PT}$ is the concentration of inhibitor required to double the prothrombin based clotting time in human plasma. For detailed assay methods, see Ref.15
17. The X-ray crystal structure coordinates of **40** in human Factor Xa have been deposited in the Protein Data Bank (PDB code 3SW2).
18. Compound testing protocol: male Sprague–Dawley rats (320–390 g) were fasted overnight and then anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The trachea was cannulated with PE-205 tubing to assure airway patency. Catheters (PE-50) were placed in the right carotid artery for blood withdrawal and in the left jugular vein for saline infusion (25 μL/min throughout the experiment) and for i.v. dosing of test compound. Animals received compound by i.v. (10 mg/kg) route in a 1 mg/mL volume of saline vehicle followed by a 0.3 mL saline flush. Arterial blood samples (0.5 mL) were withdrawn into 3.8% Na-citrate (1/10; v/v) for ex vivo prothrombin time (PT) determination before (0 min control), and at 30, 60, 90 and 120 min after test compound dosing. The PT was measured using a Amelung KC4A micro coagulation analyzer (Heinrich Amelung GmbH, Lemgo, Germany) and the standard procedure described for Dade Thromboplastin-C reagent (Baxter Healthcare Corp., Miami, FL).
19. For example, compounds **40** and **41** have Caco-2 cell permeability (apical to basal) of 25 and 73 nm/s at pH 6.5 respectively; both compounds have half lives of less than 2 min in liver microsomes (human, rat, mouse, dog, cynomulgus monkey). Assay conditions: 0.5 μM of compound is incubated with liver microsomal protein (1.0 mg/mL) in the presence of NAPDH (1.0 mM), NaPi (100 mM), $MgCl_2$ (5.0 mM) at pH 7.4 at 37 °C.