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5-Amidinobenzo[*b*]thiophenes as dual inhibitors of factors IXa and Xa

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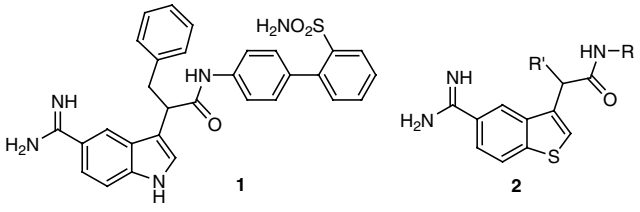
Abstract—Syntheses and SAR studies of 5-amidinobenzo[*b*]thiophene analogs provided compounds with low submicromolar factor IXa activity and equal or slightly better selectivity relative to factor Xa.

1. Introduction

Thromboembolic diseases, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and thromboembolic stroke, are the leading causes of morbidity and mortality in the developed countries. Conventional antithrombotic therapies using either heparin or warfarin have several limitations, including excessive bleeding, due to their targeting multiple factors within the coagulation cascade. To improve the benefit-to-risk ratio of antithrombotic drugs, small-molecule direct thrombin inhibitors and selective factor Xa (fXa) inhibitors are being extensively investigated.

The coagulation cascade is a proteolytic sequence of events, involving several serine proteases, leading to overall maintenance of hemostasis. The cascade consists of three systems: the intrinsic and extrinsic pathways that provide alternative routes for the generation of fXa, and a final common pathway that leads to thrombin formation. Factor IXa (fIXa) in the presence of cofactor fVIIIa and Ca^{2+} activates fX to fXa on the surface of platelets or endothelial cells via the intrinsic pathway.[1] FIXa seems to be essential for the amplification of coagulation, as indicated by the high bleeding tendency of hemophilia B patients (fIX deficiency). Inhibition of fIXa may provide 'upstream' inhibition of intrinsic coagulation and thrombus propagation, while leaving hemostasis intact via the fVIIa/tissue factor extrinsic pathway. It has been demonstrated that inhibition of fIXa either by active site-blocked fIXa or by fIX/fIXa antibody was effective in prevention of thrombus formation in animal models without increasing bleeding.[2]

These results suggested that potent and selective small-molecule fIXa inhibitors may have the potential to be viable therapeutic agents for the treatment of thromboembolic disorders with a reduced bleeding liability. Our initial goal was to identify a reversible, small-molecule, selective fIXa inhibitor as a tool molecule for animal studies.



fIXa K_i 0.66 μM
fXa K_i 0.00063 μM

High throughput screening of our proprietary fXa inhibitor collection identified amidinoindole **1**.[3] Compound **1** is a submicromolar lead for fIXa, however it is approximately 1000-fold more potent for fXa (fIXa K_i 0.66 μM, fXa K_i 0.00063 μM).[4] In this paper, we describe the

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syntheses and structure activity relationships developed in an effort to optimize **1**, which resulted in the 5-amidinobenzo[*b*]thiophene series **2** with both improved inhibitory activity for fIXa and improved selectivity relative to other relevant trypsin-like serine proteases.

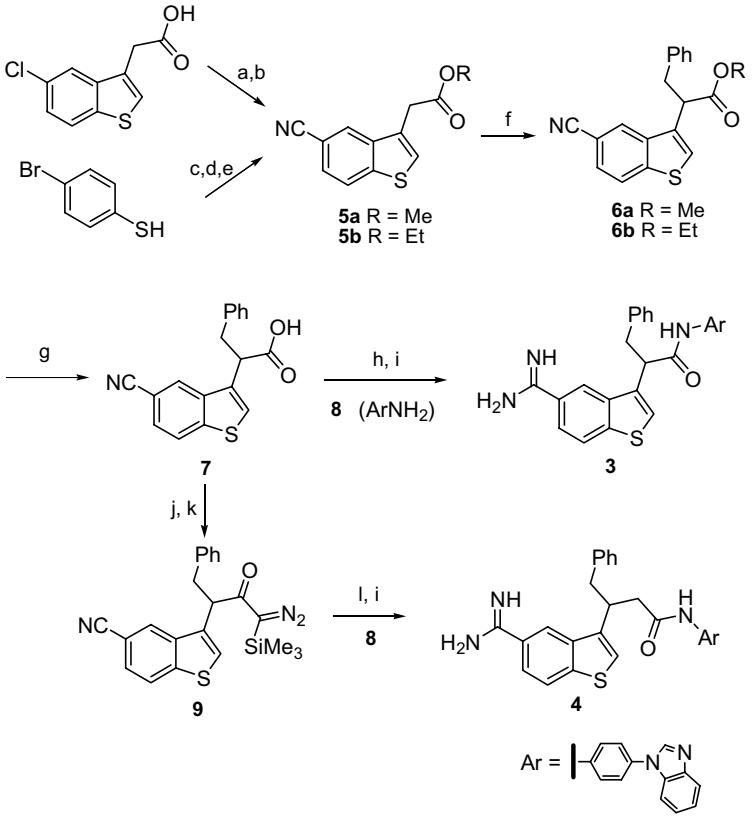
2. Chemistry

Scheme 1 depicts the preparation of 5-amidinobenzo[*b*]-thiophene analog **3** and its homolog **4**. Pd-catalyzed cyanation of methyl 5-cyano-3-benzothiophene acetate with zinc cyanide gave the methyl ester **5a**.[5] Alternately, a three-step sequence provided the ethyl ester **5b**, namely, alkylation of 4-bromothiophenol with ethyl chloroacetoacetate followed by cyclization with polyphosphoric acid using a modified literature method,[6] and then displacement of the bromide with copper cyanide. Alkylation of **5a** or **5b** with benzyl bromide led to the corresponding ester **6a** or **6b**, which was then hydrolyzed to give the acid **7**. Coupling of **7** with aniline **8** followed by Pinner chemistry/ammonolysis afforded **3**. Alternatively, the acid chloride of **7** reacted with TMS diazomethane gave the α-TMS diazoketone **9**. An Arndt–Eistert reaction of **9** with aniline **8** in 2,4,6-collidine at reflux provided **4**.

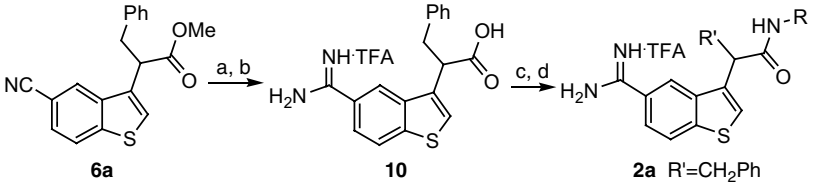
Solution phase parallel synthesis was utilized to prepare a range of amides (Scheme 2). Conversion of nitrile **6a** to the corresponding amidine followed by acid hydrolysis provided the common intermediate **10** as a TFA salt. Coupling of **10** with both aromatic and aliphatic amines using diisopropylcarbodiimide in pyridine/DMSO or pyridine/DMF afforded amides **2a** in moderate to high yields. A broad range of functional groups incompatible with the conditions of the Pinner reaction, such as ketones and nitriles, were introduced into the final products using this methodology.

Enantiomerically pure compounds of this series were prepared using either Evans' chiral auxiliary synthesis or chiral HPLC separation of the racemic amidine precursors. For instance, Scheme 3 illustrates the production of isomers of compound **11** using an oxadiazole as a masked amidine. Condensation of racemic acid **12** with enantiopure methyl 2-amino-1-cyclohexane carboxylate (1*R*,2*S*)-**13** or (1*S*,2*R*)-**13**[7] followed by hydrogenation gave the racemic mixture **11a** and **11b**, respectively. Compounds **11c** and **11d**, the two diastereomers of **11a**, were obtained by chiral HPLC separation of the racemic mixture **14** followed by hydrogenation.

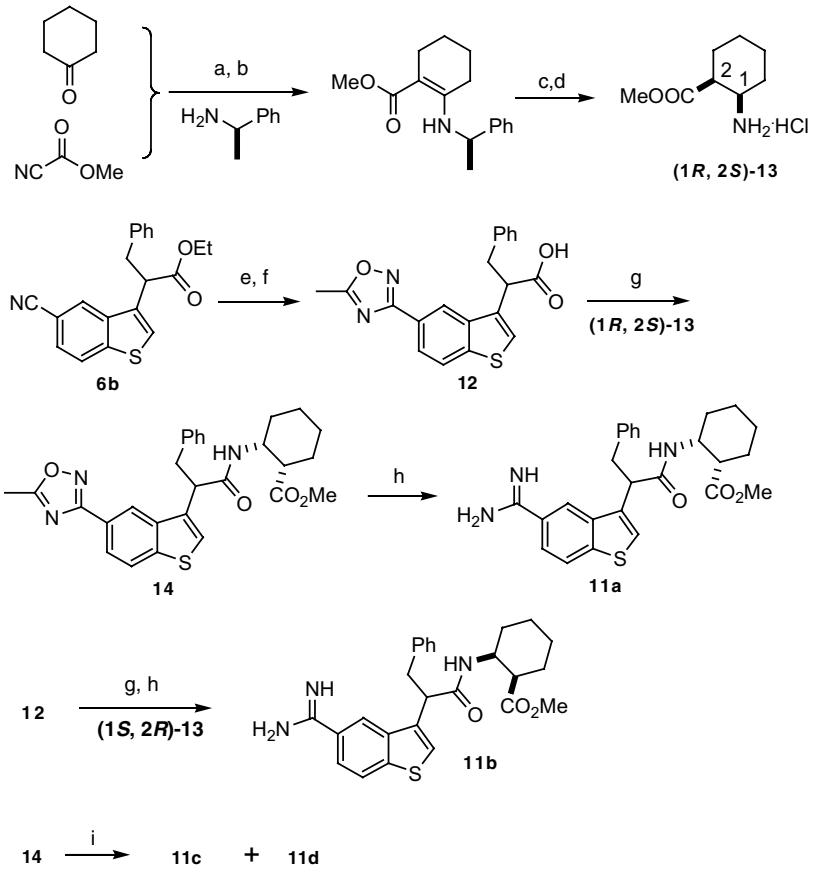
The preparation of 5-amidinobenzo[*b*]furan analog **15** was carried out using transformations similar to those described in the literature[8] and to those shown in Scheme 1 for the analogous benzo[*b*]thiophenes. The benzo[*b*]thiophene 1,1-dioxide **16** was prepared by oxidation of **10** with oxone® followed by coupling with racemic *cis*-**13**.



Scheme 1. Reagents and conditions: (a) MeOH, cat. H_2SO_4; (b) $Zn(CN)_2$ (1.5 equiv), $Pd_2(dba)_3$ (5 mol%), dppf (10 mol%), Zn (30 mol%), DMAC, 140 °C, 83% for two steps; (c) $ClCH_2COCH_2COOEt$, pyridine; (d) PPA, 65 °C; (e) CuCN, DMF, 140 °C, 35% for three steps; (f) $LiN(TMS)_2$, THF, then $PhCH_2Br$, −78 °C, 95%; (g) NaOH, EtOH, 100%; (h) BOPCl, NMM, **8**, DMF, 59%; (i) HCl, MeOH; then $(NH_4)_2CO_3$, MeOH, 38%; (j) $(COCl)_2$, CH_2Cl_2; (k) $TMSCHN_2$, THF/CH_3CN (1:1), 0 °C; (l) **8**, collidine, 180 °C, yield for j–l, 45%.



Scheme 2. *Solution phase syntheses of* **2a**. Reagents and conditions: (a) HCl, MeOH; then $(NH_4)_2CO_3$, MeOH; (b) 6 N HCl, reflux; (c) NH_2–R, DIC, pyridine/DMSO (1:4 v/v); (d) RP-HPLC or LC–MS purification, 30–75% overall yields.



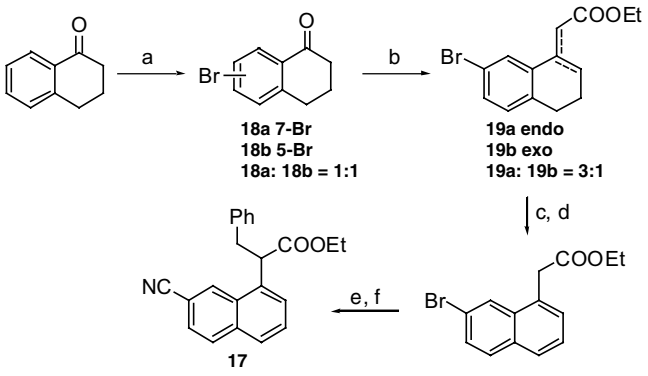
Scheme 3. Reagents and conditions: (a) LDA, THF, 75%; (b) YbOTf, PhH, 72%; (c) $NaBH(OAc)_3$, CH_3CN, 78%; (d) H_2, Pd–C (10%), HCl, MeOH, 82%; (e) NH_2OH·HCl, Et_3N, EtOH; then Ac_2O, HOAc, 78%; (f) NaOH, EtOH, 100%; (g) DIC, pyridine/DMSO (1:4 v/v), 78%; (h) H_2, Pd–C (5%), MeOH, 85–90%; (i) chiral HPLC separation, then H_2, Pd–C (5%), MeOH.

Using transformations similar to those described in the literature,[9] the 7-cyanonaphthalene derivative **17** was prepared from α-tetralone (Scheme 4).

3. Results and discussion

The 5-amidinoindole group has been demonstrated, both computationally and experimentally, to have higher potency and selectivity for fXa compared with several other amidino bicyclic P1 groups not containing an N–H.[10] This difference is presumably due to the ability to form the hydrogen bond between the indole NH and the oxygen atom of Ser195. In contrast, amidinoindole **1** showed weaker fIXa potency compared with fXa potency. This may be due to one or both of the following two possibilities. First, the amidine NH forms an extra hydrogen bond with Ser190 in fIXa, restricting the orientation of the inhibitor in the S1 pocket such that the geometrical requirement of hydrogen bond formation between the indole NH and Ser195 may not be optimal. Second, fIXa has a smaller S1 pocket due to amino acid residue differences (fIXa Ser190 vs fXa Ala190, and fIXa Ile213 vs fXa Val213). As a result, the 5-amidinoindole group may be too large to fit well into the S1 pocket of fIXa.

Initially, to eliminate the possibility of a hydrogen bond with Ser195, we replaced the indole ring with a benzo[*b*]thiophene ring. To our delight, 5-amidinobenzo[*b*]thiophene analogs **3** and **21** containing a *para* benzimidazole aniline P4 group[11] were found to be



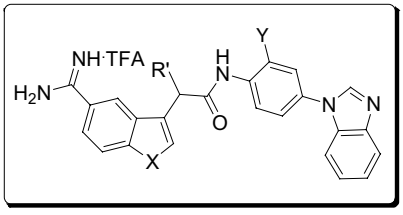
Scheme 4. Reagents and conditions: (a) $AlCl_3$, Br_2, 80 °C; column chromatography followed by crystallization from hexane, 46% for **18a**; (b) $(C_2H_5O)_2POCH_2COOC_2H_5$, NaH, THF, 0 °C reflux, 59%; (c) Br_2, CCl_4; (d) DBU, benzene, 90% for two steps; (e) CuCN, DMF, 140 °C, 65%; (f) $LiN(TMS)_2$, THF, then $PhCH_2Br$, −78 °C, 69%.

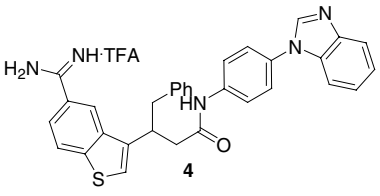
essentially equipotent for fIXa and fXa (Table 1). Relative to the corresponding indoles **20** and **22**, the fIXa potency was retained while the fXa potency decreased 10- to 20-fold. The decreased fXa K_i in the benzo[*b*]thiophene series confirms the important role of a hydrogen bond with Ser195 for fXa potency. The retained fIXa potency suggests that the structure around the S1 site of fIXa may be more 'plastic' than that around the S1 site of fXa. The hydrophobic interaction of the benzothiophene ring with the wall of the S1 pocket and the polarizable and sterically larger sulfur atom appear to be favorable in improving selectivity relative to fXa.

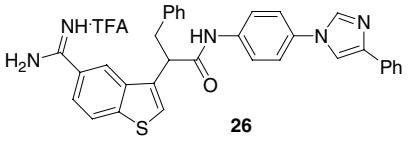
Compound **23** bearing a 1-naphthylmethyl group, compared to compound **24** with an ethyl group, though equipotent in fIXa, provided slightly better fIXa/fXa selectivity. On the other hand, cyclopropyl analog **25** had much decreased fIXa activity while retaining fXa potency. Compound **4**, a homolog of **3**, is 10-fold less potent for fIXa (fIXa $K_i = 1.25\,\mu M$) compared with **3**, while its fXa potency (fXa $K_i = 0.28\,\mu M$) remains similar to that of **3**. Compound **26** containing a 4-phenylimidazole P4 moiety, is less potent for fIXa compared with **3**; however, it is sixfold more selective for fIXa than for fXa. As previously demonstrated via the overlay of the Cα trace of the fIXa-bound and the fXa-bound crystal structures,[11] the conformation and geometry of the 99-loop of fIXa is quite different compared with fXa. The phenyl group on the imidazole ring in **26** might bump into the 99-loop of fXa, which resulted in a 20-fold decrease of fXa potency compared with **3**.

We anticipated that modification in the P4 region might provide further opportunity to improve selectivity. Combining the tools of computational library design and automated synthesis, 300 amines were selected via informative library design[14] and manually picked to allow for maximum spatial diversity of the P4 region. Several compounds showed submicromolar fIXa affinity and 6- to 10-fold selectivity for fIXa compared to fXa. However, none of the compounds were significantly more potent or more selective than **26**. Of the 300 compounds prepared, compounds **27** and **28** were the two most potent and selective fIXa inhibitors among compounds prepared with Ar–X–Ar type of P4 groups (Table 2). Compound **29**, containing a benzothiazole group, was the most potent and selective compound containing a 5,6-, or 6,6-fused heterocyclic P4 group. Because of the much decreased fXa potency observed with **29**, it is possible that this compound does not bind the same way as the earlier mentioned benzothiophenes such as **3**. Modeling of **29** suggests an alternate binding mode that places the benzothiazole ring system above the S1 pocket near the disulfide of Cys191–Cys220.

Table 1.





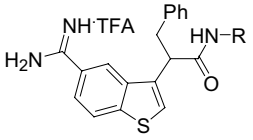


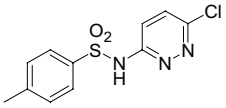
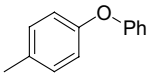
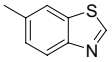
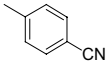
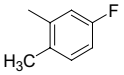
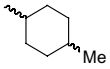
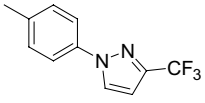
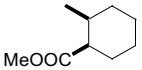
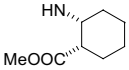
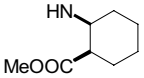
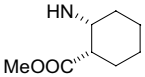
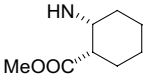
Compound	X	Y	R′ (+/−)	fIXa K_i, μM	fXa K_i, μM	fIXa/fXa	Trypsin K_i, μM	Thrombin K_i, μM
1				0.66	0.00063	1048	0.15	0.60
3	S	H	CH_2Ph	0.098	0.12	0.8	1.02	>6.3
20	NH	F	CH_2Ph	0.063	0.0025	25	0.34	13
21	S	H	CH_2Ph-*p*-NH_2	0.074	0.047	1.6	>4.2	4.2
22	NH	H	CH_2Ph-*p*-NH_2	0.075	0.004	19	>4.2	4.2
23	S	H	CH_2-1-naphthyl	0.23	0.74	0.3	3.90	>6.3
24	S	H	CH_2CH_3	0.22	0.071	3.1	0.27	0.27
25	S	H	–CH_2CH_2–	4.90	0.022	223	0.06	0.39
4				1.25	0.28	4.5	>4.2	4.2
26				0.39	2.02	0.2	>4.2	>6.3

All compounds were purified by either reverse phase HPLC or preparative LC/MS (water/acetonitrile gradient + 0.5% TFA). The basic compounds were isolated as TFA salts following lyophilization. All compounds gave satisfactory spectral and analytical data.

Human purified enzymes were used. Values are averages from multiple determinations ($n > 2$). K_i values were calculated based on the inhibition observed over a range of inhibitor concentrations (0.001–50 μM) as described in Ref. 12 and Ref. 13.

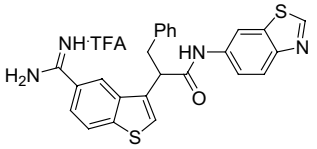
Table 2.



Compound	R (+/−)	fIXa K_i, μM	fXa K_i, μM	fIXa/fXa
27		0.93	5.36	0.2
28		0.25	0.45	0.6
29		0.78	>8	<0.1
30		1.73	>8	<0.2
31		0.96	>8	<0.1
32		0.58	3.24	0.2
33		0.13	0.41	0.3
11	 (*cis*)	0.14	0.12	1.2
11a	 (+/− at benzyl position)	0.31	0.3	1.0
11b	 (+/− at benzyl position)	0.50	0.09	5.6
11c	 (R at benzyl position)	0.28	0.27	1.0
11d	 (S at benzyl position)	41.3	>9.0	—

Unfortunately, a crystal structure of **29** complexed with fIXa has not been obtained. The two enantiomers of **29** had very different fIXa potency (Table 3). The *R* isomer (ee >98%, $[\alpha]_D = -80°$ (MeOH)) was the more potent fIXa inhibitor and showed fivefold selectivity for fIXa, similar to that observed with a related indole inhibitor.[4]

Table 3.



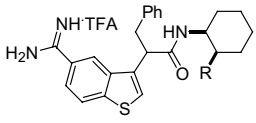
Compound	Stereochemistry	fIXa K_i, μM	fXa K_i, μM	fIXa/fXa
29	(+/−)	0.78	>8	<0.1
29-*R*	*R*-(−)	0.48	2.7	0.2
29-*S*	*S*-(+)	14.22	5.7	2.5

The simple substituted arylamides, **30** and **31**, although less potent for fIXa relative to benzimidazole phenylamides such as **3**, showed slightly enhanced fIXa selectivity relative to fXa. Compound **32** bearing a 4-methylcyclohexyl group demonstrated a sixfold fIXa/fXa selectivity. Compounds **33** and **11** were the most potent fIXa inhibitors synthesized in this library; however, they showed less selectivity than **29**. Compound **11**, containing a mixture of four diastereomers with a *cis*-cyclohexyl ring conformation, also had fIXa potency in the hundred nanomolar range although it had similar inhibitory activity against fXa. Molecular modeling suggests that the cyclohexyl group may interact with the Tyr99 region of fIXa, which is at the entrance of the S3/S4 pocket. Compound **11c**, the most potent single diastereomer of **11**, had similar fIXa potency and selectivity as **11**.

Efforts to modify the methyl ester group in **11** did not improve fIXa potency or selectivity (Table 4). Replacement of the methyl ester in **11** with a larger group such as benzylamide or hydrolysis of the ester to the acid resulted in compounds with decreased fIXa potency (**37**, **38**). On the other hand, the smaller ethyl ester, ethyl amide, and glycine amide were tolerated (**34**, **35**, **36**).

Variation of the heteroatoms in bicyclic P1 group (X = O, NH, SO_2) resulted in compounds with decreased fIXa potency (Table 5). Interestingly, compound **40** containing a 7-amidinonaphthalene P1 group showed potency and selectivity for fIXa similar

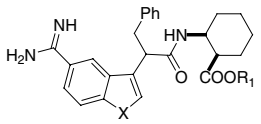
Table 4.



Compound	R[a]	fIXa K_i, μM	fXa K_i, μM	fIXa/fXa
11	COOMe	0.14	0.12	1.2
34	COOEt	0.12	0.18	0.7
35	CONHEt	0.43	0.13	3.3
36	$CONHCH_2CONH_2$	0.28	0.065	4.3
37	$CONHCH_2Ph$	>32	>9	—
38	COOH	3.50	0.20	18

[a] Stereochemistry of two substituents on the cyclohexyl is *cis*-racemic.

Table 5.



Compound	X	R_1	fIXa K_i, μM	fXa K_i, μM	Trypsin K_i, μM	fIXa/fXa
39	NH	Me	0.34	0.019	1.5	18
34	S	Et	0.12	0.18	2.5	0.7
15	O	Et	1.19	0.27	>4.2	4.4
16	SO_2	Et	8.53	>9.0	>4.2	—
40	–HC=CH–	Et	0.24	0.53	>4.2	0.5

to amidinobenzothiophene **34**. SAR studies with a variety of replacements for 5-amidinobenzo[*b*]thiophene demonstrated, once again, that the S1 pocket is a fingerprint region of serine proteases.[15]

In the above discussion, we did not test the second possibility: fIXa has a smaller S1 pocket, and the larger bicyclics may not fit well into it. Changing the bicyclic P1 groups to certain preferable monocyclic P1 groups may provide an opportunity for further improvement of fIXa potency and selectivity over fXa.

4. Conclusion

We identified a series of 5-amidinobenzo[*b*]thiophenes as low submicromolar fIXa inhibitors, some of which showed improved selectivity over fXa. The most selective compounds prepared herein were 6- to 10-fold more selective for fIXa relative to fXa (**26** and **29**-*R*); however, they were less potent (fIXa K_i 0.4–0.8 μM) than the compounds containing the benzimidazole phenylamide P4 group. Further varying the P4 substituents did not result in compounds with improved fIXa potency and selectivity. In addition, we have identified several compounds that are dual fIXa and fXa inhibitors, the therapeutic benefits of which are yet to be validated.

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13. Factor IXa inhibition was assayed using human fIXa with a chromogenic substrate in the absence (substrate S229) or presence (substrate S299) of ethylene glycol, as described by Sturzebecher, J.; Kopetzki, E.; Bode, W.; Hopfner, K.-P. *FEBS Lett.* **1997**, *412*, 295, FIXa substrate: S229 with a sequence of H-(D)Leu-Ph′Gly-Arg-pNA, K_m = 700 μM and a low K_{cat} can only be used for fIXa inhibitors K_i > 50 nM. The other fIXa substrate S299, has a sequence of $MeSO_2$-chGly-Gly-Arg-pNA, K_m = 1800 μM.
14. We employed an in-house protocol16 that generated millions of 2, 3, and 4 point pharmacophores from the entire fIXa dataset. Once the pharmacophores were

generated, the most 'informative' pharmacophores were selected based on activity versus inactivity as well as diversity. A library of amines were selected through 'infopicking' of the most informative pharmacophores, resulting in a diverse and informative set.

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