Diamino Benzo[*b*]thiophene Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors. 5. Potency, Efficacy, and Pharmacokinetic Properties of Modified C-3 Side Chain Derivatives

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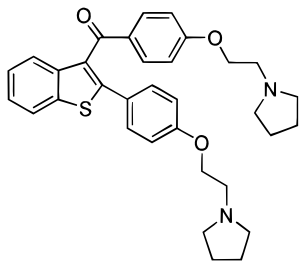
A systematic investigation of the structure−activity relationships of the C-3 side chain of the screening hit **1a** led to the identification of the potent thrombin inhibitors **23c**, **28c**, and **31c**. Their activities (1240, 903, and 1271 × 10^6 L/mol, respectively) represent 2200- and 2900-fold increases in potency over the starting lead **1a**. This activity enhancement was accomplished with an increase of thrombin selectivity. The in vitro anticoagulant profiles of derivatives **28c** and **31c** were determined, and they compare favorably with the clinical agent H-R-1-[4a*S*,-8a*S*]perhydroisoquinolyl-prolyl-arginyl aldehyde (D-Piq-Pro-Arg-H; **32**). The more potent members of this series have been studied in an arterial/venous shunt (AV shunt) model of thrombosis and were found to be efficacious in reducing clot formation. However, their efficacy is currently limited by their rapid and extensive distribution following administration.

Introduction

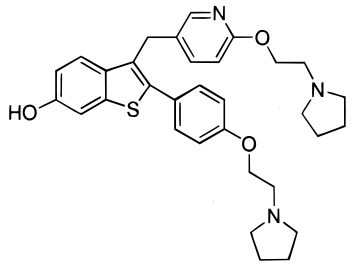
Thrombosis is one of the leading single causes of morbidity and mortality in developed societies. The most widely prescribed anticoagulants to treat thrombotic disorders, parenteral heparins and oral vitamin K antagonists (coumadin), are unfortunately less than ideal due to well-documented liabilities.[1,2] Accordingly, over the last 10 years there has been an intense search for novel anticoagulant agents with the most recent efforts being aimed at discovering an oral anticoagulant alternative to coumadin.

The most widely studied target for antithrombotic intervention has been the serine protease thrombin which performs a dual role in thrombogenesis, including fibrin formation and platelet activation.[3,4] Inhibitors of this enzyme would have the potential to produce an antithrombotic effect in both arterial and venous thrombosis.[5] Not surprisingly, the development of direct acting thrombin inhibitors has been the subject of extensive research. Recent efforts have been focused on small molecules possessing an arginine, benzamidine, or a surrogate of the same, leading to the identification of a number of potent and selective thrombin inhibitors.[6] To date however, none of these have successfully progressed through clinical trials as an oral anticoagulant.

As part of our effort to identify structurally novel, orally active thrombin inhibitors, we undertook a broad screening approach leading to the identification of the 2,3-disubstituted benzo[*b*]thiophene derivative **1a**.[7] Preliminary structure−activity relationship (SAR) studies provided a better understanding of the structural requirements necessary for thrombin inhibition, leading to the preparation of the more potent and selective inhibitor **1b**.[7] The compounds from this series are



1a
K_{ass} = 0.43 ± 0.07 L/mole



1b
K_{ass} = 24.3 ± 2.0 L/mole

distinguished from previously reported thrombin inhibitors by their structural novelty (i.e. they are not derived from arginine or benzamidine). Despite their unique structure, these derivatives still displayed competitive inhibition kinetics, indicating their interaction at the active site of the enzyme, a result later confirmed by X-ray crystallography. The promising bioavailability (up to 50%) of these early derivatives warranted the further development of this class of agents.

To expand our understanding of the SAR around this novel series of thrombin inhibitors, with an emphasis

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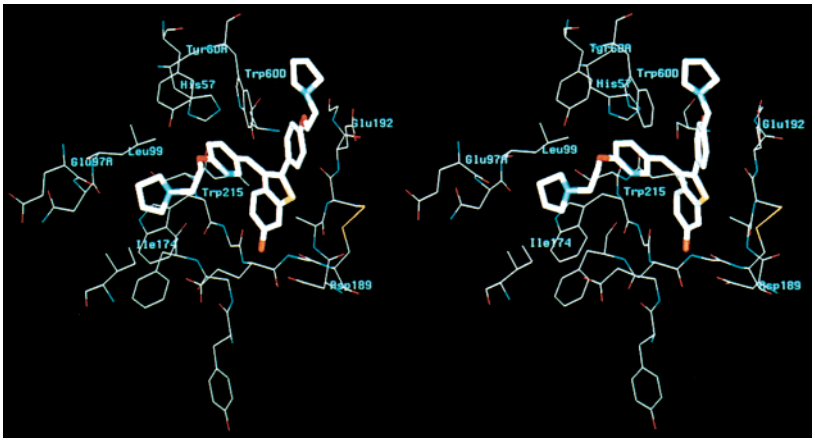
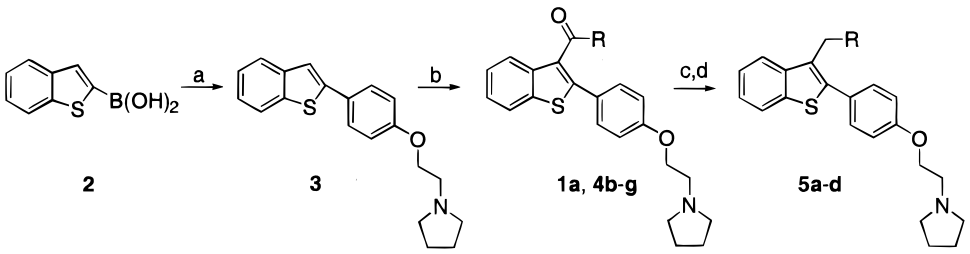
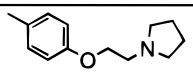
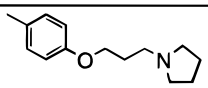
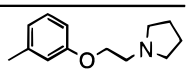
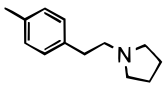
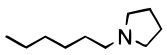
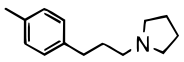
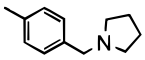


Figure 1. Stereoview of the X-ray crystal structure of inhibitor **1b** bound in the active site of human α-thrombin. The principal interactions between the inhibitor and the active site residues are shown. The proximal binding site (S_2) is formed by residues Trp215, Leu99, His57, Tyr60A, and Trp60D while the distal pocket (S_3) is composed of residues Trp215, Ile174, and Glu97A-Leu99.

Scheme 1[a]



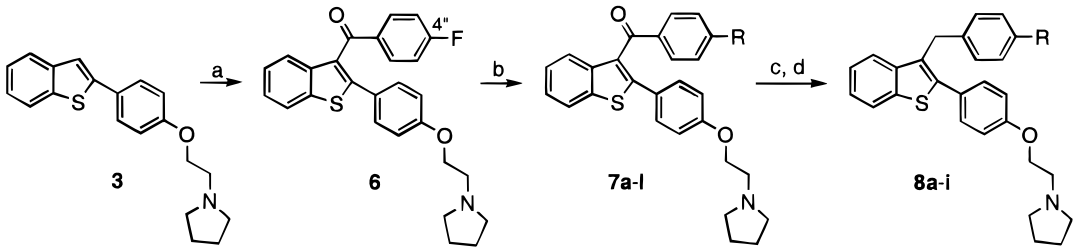
Compound #	R	Compound #	R	Compound #	R
1a, 5a		**4d, 5d**		**4f**	
4b, 5b		**4e**		**4g**	
4c, 5c					

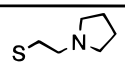
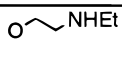
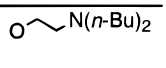
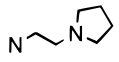
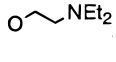
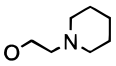
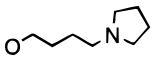
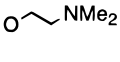
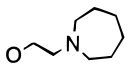
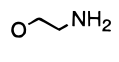
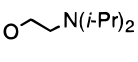
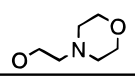
[a] Reagents: (a) Ph_3P_4Pd, 2 N aqueous Na_2CO_3, 1-[2-(4-bromophenoxy)ethyl]pyrrolidine; (b) aminoacyl chloride, $TiCl_4$ or $AlCl_3$; (c) DIBAL-H or $LiAlH_4$; (d) Et_3SiH, TFA.

on identifying more potent derivatives, we conducted a more systematic SAR study than previously described. X-ray crystallographic studies provided a clearer understanding of the interaction of compound **1b** in the active site of thrombin. While the hydrophobic benzo[*b*]thiophene nucleus binds in the specificity pocket (S_1) of the enzyme, the C-3 side chain spans the proximal and distal pockets of the active site (Figure 1).[7] In contrast, the interaction of the C-2 side chain with thrombin is not as well defined. However, X-ray analysis does indicate that the pyrrolidine ring is predominantly exposed to solvent. Since the interaction of the C-3 side chain within the active site of thrombin is better defined, we chose to study the SAR in this region of the molecule. This report represents the first detailed, comprehensive account of both the synthesis and systematic SAR studies surrounding the C-3 side chain, resulting in the discovery of inhibitors that are 2200- and 2800-fold more potent than the original screening hit **1a** and are efficacious in a rat model of thrombosis.[8] Also reported for the first time are the pharmacokinetic properties of this novel series of agents.

Chemistry. Two general synthetic routes were employed for the preparation of a majority of the compounds used in this study (Schemes 1 and 2). Derivatives **1a**, **4b**−**g**, and **5a**−**d** were prepared according to Scheme 1, beginning with the commercially available benzo[*b*]thiophene-2-boronic acid (**2**). Installation of the entire basic C-2 side chain was accomplished through a Suzuki coupling with 1-[2-(4-bromophenoxy)ethyl]-pyrrolidine to afford the 2-substituted benzo[*b*]thiophene **3**.[9] In the second step, the desired C-3 side chains were incorporated through Friedel−Crafts acylation[10] with the acid chlorides derived from a variety of amino benzoic acids to provide the 2,3-disubstituted benzo[*b*]-thiophene derivatives **1a, 4b**−**g**. While a variety of Lewis acids could be employed in the acylation step, including $AlCl_3$ and $SnCl_4$, $TiCl_4$ was the reagent of choice since it gave cleaner reactions and higher product yields. In those cases where the C-3 methylene deriva-

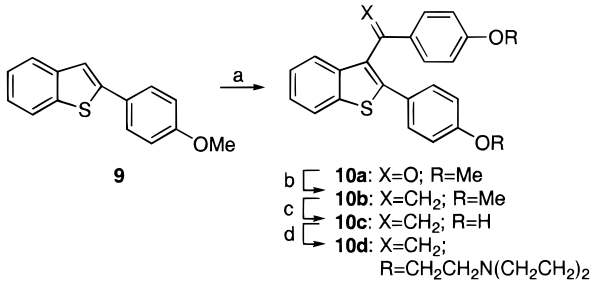
Scheme 2[a]



Compound #	R	Compound #	R	Compound #	R
7a, 8a		**7e, 8e**		**7i, 8i**	
7b, 8b		**7f, 8f**		**7j**	
7c, 8c		**7g, 8g**		**7k**	
7d, 8d		**7h, 8h**		**7l**	

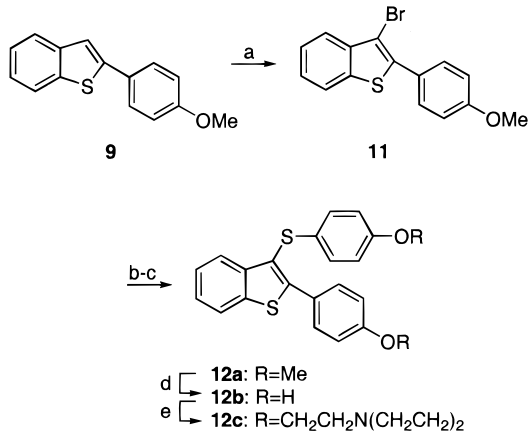
[a] Reagents: (a) *p*-fluorobenzoyl chloride, $TiCl_4$; (b) RH, NaH; (c) DIBAL-H or $LiAlH_4$; (d) Et_3SiH, TFA.

Scheme 3[a]



[a] Reagents: (a) *p*-anisoyl chloride, $AlCl_3$; (b) methyltriphenylphosphonium bromide, KO*t*-Bu; (c) pyridine hydrochloride; (d) 1-(2-chloroethyl)pyrrolidine, Cs_2CO_3.

Scheme 4[a]



[a] Reagents: (a) Br_2; (b) *n*-BuLi; (c) bis(4-methoxyphenyl)disulfide; (d) BBr_3; (e) 1-(2-hydroxyethyl)pyrrolidine, Ph_3P, DEAD.

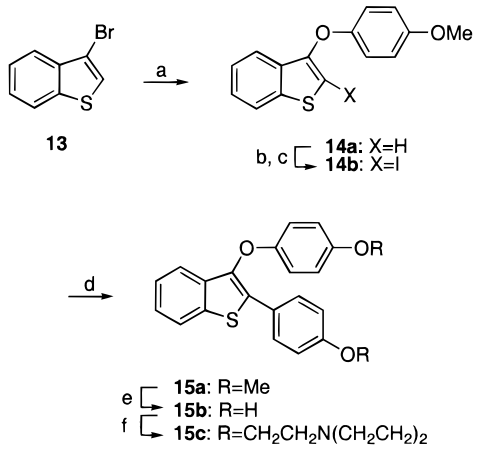
tives were required (**5a**−**d**), reductive deoxygenation was accomplished by a two-step procedure involving initial hydride reduction to the secondary benzylic alcohols (DIBAL-H or $LiAlH_4$), followed by a second reductive deoxygenation (TFA/Et_3SiH) to give the desired methylene products **5a**−**d**. Attempts to affect both the reduction and deoxygenation steps in a single transformation using $NaBH_4$/TFA were unsuccessful.

The second general synthetic approach that was employed also utilized benzo[*b*]thiophene **3** (Scheme 2). Acylation at the C-3 position with *p*-fluorobenzoyl chloride afforded the common intermediate **6**. Employing the methods of Schmid et al.,[11] a diverse set of basic C-4″ side chains was installed through displacement of the fluoride with a variety of oxygen-, sulfur-, and nitrogen nucleophiles to yield derivatives **7a**−**l**. Reductive deoxygenation to the C-3 methylene derivatives (**8a**−**i**) was accomplished in a manner similar to that described for the preparation of analogues **5a**−**d** in Scheme 1.

Scheme 3 depicts the synthesis of the C-3 olefin derivative **10d**. The starting 2-aryl benzo[*b*]thiophene **9** was conveniently prepared by a Suzuki coupling[9] of benzo[*b*]thiophene-2-boronic acid with *p*-bromoanisole. Acylation with *p*-anisoyl chloride afforded the 2,3-disubstituted derivative **10a** which was subjected to the Wittig reaction using a methyl phosphorane to give the desired olefin **10b**.[12] Unfortunately, attempts to add other Wittig or Horner−Wadsworth−Emmons reagents to the C-3 ketone were unsuccessful, presumably due to the steric congestion around this site. Deprotection of the two methyl ethers using pyridine hydrochloride afforded the corresponding diphenol (**10c**) which was alkylated with 1-(2-chloroethyl)pyrrolidine in the presence of cesium carbonate to give the desired diamine **10d**.

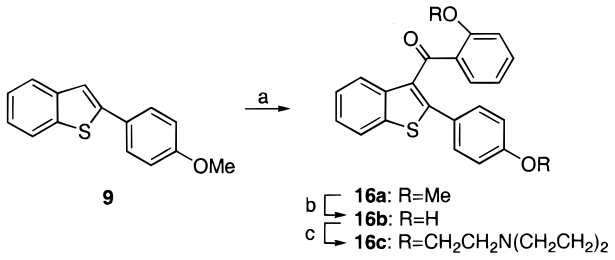
Thioether **12c** was prepared according to Scheme 4. Treatment of the 2-aryl benzo[*b*]thiophene derivative **9** with bromine afforded the 3-bromo intermediate **11**. Metal−halogen exchange gave the 3-lithio species which

Scheme 5[a]



[a] Reagents: (a) 4-methoxyphenol, CuI, K_2CO_3; (b) *n*-BuLi; (c) I_2; (d) 4-methoxyphenylboronic acid, $(Ph_3P)_4Pd$, 2 N aqueous Na_2CO_3; (e) pyridine hydrochloride; (f) 1-(2-chloroethyl)pyrrolidine, Cs_2CO_3.

Scheme 6[a]



[a] Reagents: (a) *o*-anisoyl chloride; $AlCl_3$; (b) $AlCl_3$, EtSH; (c) 1-(2-chloroethyl)pyrrolidine, Cs_2CO_3.

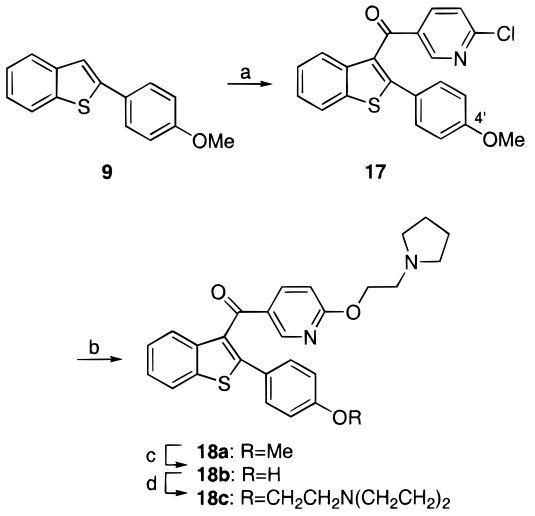
was quenched with commercially available bis(4-methoxyphenyl)disulfide to afford the thioether linked product **12a**. Deprotection of the methyl ethers using BBr_3 at room temperature followed by alkylation of the resulting diphenol (**12b**) gave the desired diamine **12c**.

The synthesis of the diaryl ether product **15c** began with 3-bromobenzo[*b*]thiophene (**13**; Scheme 5), which was readily prepared by the methods of Cherry et al.[13] Subjecting bromide **13** to Ullmann-type conditions employing 4-methoxyphenol/CuI with sonication afforded the C-3 ether derivative **14a**.[14] Lithiation at the 2-position and subsequent quench with iodine gave the 2-iodo-3-phenoxy product **14b**. Suzuki coupling[9] with 4-methoxyphenylboronic acid gave the 2,3-disubstituted derivative **15a**. Conversion to the desired diamine product **15c** was accomplished by employing conditions similar to those used in the preparation of analogue **10d** in Scheme 3.

Scheme 6 depicts the synthesis of isomer **16c** which possesses an ortho-substituted C-3 side chain. Initial attempts to install the entire C-3 side chain via acylation of compound **9** with 2-[2-(1-pyrrolidinyl)ethoxy]-benzoyl chloride failed, possibly due to steric congestion caused by the ortho substituent. Accordingly, the 2-aryl derivative **9** was acylated with *o*-anisoyl chloride/$AlCl_3$ to give the 2,3-disubstituted product **16a**. Bis deprotection of the methyl ethers using EtSH and $AlCl_3$ afforded the diphenol **16b** which could be alkylated to give the desired diamine **16c**.

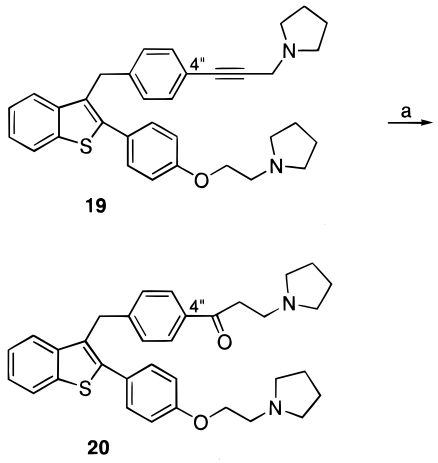
The C-3 pyridyl derivative **18c** was prepared from intermediate **9** according to Scheme 7. Acylation with

Scheme 7[a]



[a] Reagents: (a) 6-chloronicotinyl chloride, $AlCl_3$; (b) 1-(2-hydroxyethyl)pyrrolidine, Na; (c) $AlCl_3$, EtSH; (d) 1-(2-chloroethyl)pyrrolidine, Cs_2CO_3.

Scheme 8[a]



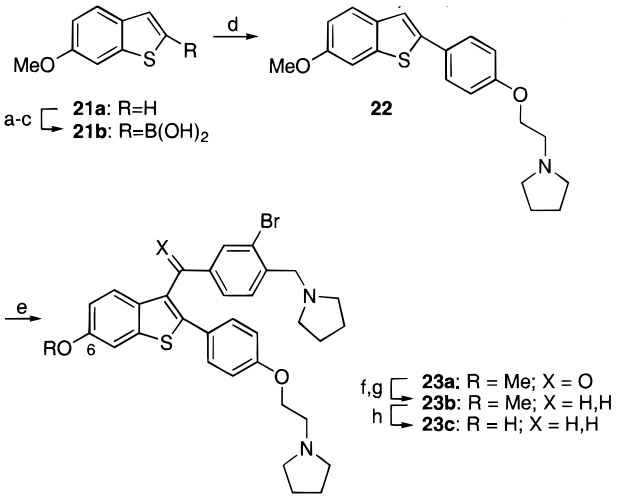
[a] Reagents: (a) TFA.

6-chloronicotinoyl chloride afforded the 3-pyridyl-substituted compound **17**. Installation of the remainder of the C-3 side chain was accomplished by displacement of the chloride with the sodium salt of 1-(2-hydroxyethyl)pyrrolidine to give compound **18a**. Deprotection of the C-4′ methyl ether and subsequent alkylation afforded the desired pyridyl product **18c**.

The preparation of the C-4″ ketone analogue **20** is shown in Scheme 8. Treatment of the previously reported acetylene **19**[15] with TFA afforded the desired ketone product **20** in a single step.

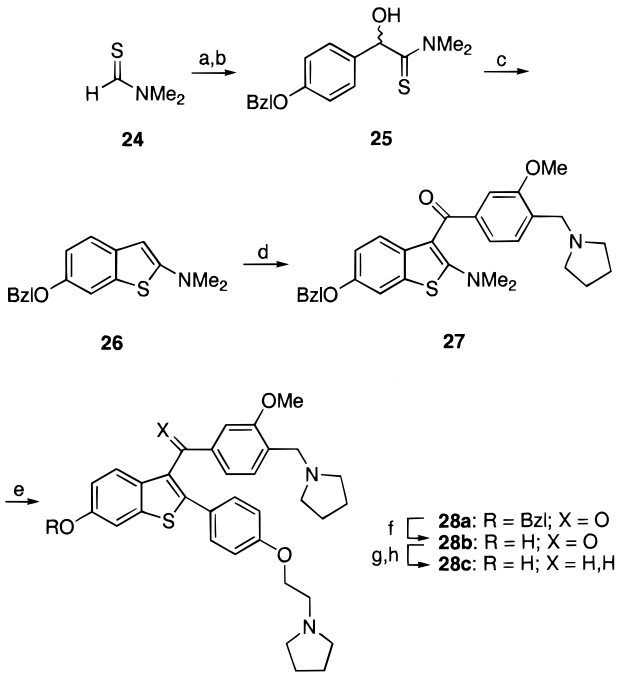
Hybrid analogues which possess the optimal structural elements identified in this and previous studies (**23c**, **28c**, and **31c**) were synthesized according to Schemes 9−11. Preparation of the C-3″ bromo-substituted derivative **23c** began with 6-methoxybenzo[*b*]-thiophene (**21a;** Scheme 9), which was prepared according to the methods of Graham et al.[16] Treatment of **21a** with *n*-BuLi followed by quench with triisopropylborate afforded the 2-boronic ester which was hydrolyzed under acidic conditions to give the 6-methoxybenzo[*b*]thiophene-2-boronic acid (**21b**). Coupling of **21b** to 4-[2-(1-pyrrolidinyl)ethoxy]-1-bromobenzene under Suzuki condi-

Scheme 9[a]



[a] Reagents: (a) *n*-BuLi; (b) i-PrO)$_3$B; (c) HCl; (d) [(Ph)$_3$P]$_4$Pd, 2 N aqueous Na_2CO_3, 4-[2-(1-pyrrolidinyl)ethoxy]-1-bromobenzene; (e) 3-bromo-4-[(1-pyrrolidinyl)methyl]benzoyl chloride, $AlCl_3$; (f) $LiAlH_4$; (g) Et_3SiH, TFA; (h) EtSH, $AlCl_3$.

Scheme 10[a]

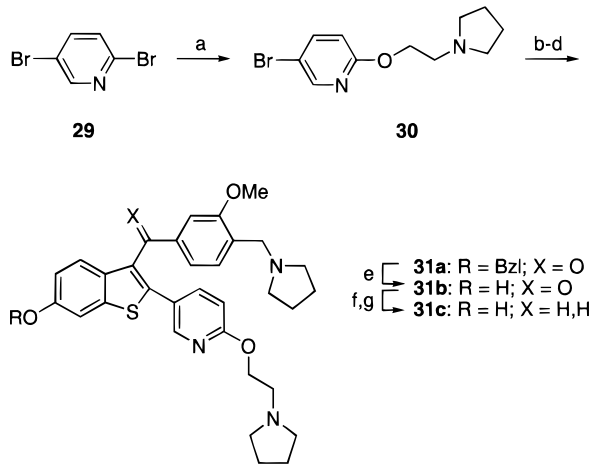


[a] Reagents: (a) LDA; (b) 4-benzyloxybenzaldehyde; (c) $MeSO_3H$; (d) 3-methoxy-4-[(1-pyrrolidinyl)methyl]benzoyl chloride, 135 °C; (e) 4-[2-(1-pyrrolidinyl)ethoxy]phenyl magnesium bromide; (f) 10% Pd-C, $NH_4^+HCO_2$; (g) $LiAlH_4$; (h) Et_3SiH, TFA.

tions[9] allowed installation of the entire C-2 side chain in a single step, affording product **22**. Acylation at the 3-position with 3-bromo-4-[(1-pyrrolidinyl)methyl]benzoyl chloride/$AlCl_3$ gave the 2,3-disubstituted derivative **23b**. Reductive deoxygenation of the C-3 ketone (1: $LiAlH_4$; 2: Et_3SiH, TFA) followed by cleavage of the methyl ether at C-6 (EtSH, $AlCl_3$) afforded target **23c**.

The C-3″ methoxy analogue **28c** was prepared using the methods of Godfrey et al.[17] (Scheme 10). Treatment of *N*,*N*-dimethylthioformamide with LDA and quench of the resulting anion with 4-benzyloxybenzaldehyde afforded condensation product **25**. Acid-catalyzed cyclization gave the 2-dimethylamino benzo[*b*]thiophene

Scheme 11[a]



[a] Reagents (a) NaH, 1-(2-hydroxyethyl)pyrrolidine; (b) *n*-BuLi; (c) $MgBr_2$; (d) compound **27**; (e) 10% Pd-C, 25% aqueous NH_4^+ HCO_2^-; (F) DiBAL-H; (g) Et_3SiH, TFA.

derivative **26**. Acylation with 3-methoxy-4-[(1-pyrrolidinyl)methyl]benzoyl chloride in the absence of a Lewis acid gave product **27** which possesses the entire C-3 side chain. Treatment of **27** with the Grignard reagent derived from 4-[2-(1-pyrrolidinyl)ethoxy]bromobenzene installed the requisite C-2 side chain of the 2,3-disubstituted benzo[*b*]thiophene **28a**. Reductive deoxygenation of the C-3 ketone and deprotection of the C-6 methoxy group gave the desired product **28c**.

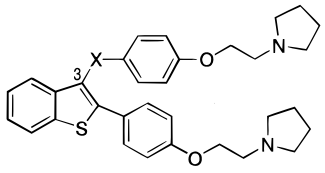
The final target of the study, the C-2 pyridyl derivative **31c**, was prepared from 2,5-dibromopyridine (**29**) according to Scheme 11. Treatment of pyridine **29** with the sodium alkoxide of 1-(2-hydroxyethyl)pyrrolidine afforded the incipient C-2 side chain **30**. Conversion of bromide **30** to the corresponding Grignard reagent and its addition to the 2-dimethylbenzo[*b*]thiophene intermediate **27** (Scheme 10) afforded the 2,3-disubstituted benzo[*b*]thiophene analogue **31a**. Conversion to the desired target **31c** was accomplished as discussed above in Scheme 10.

Results and Discussion

The thrombin inhibitory activities of the compounds in this study were measured as apparent association constants (K_{ass}).[7,18] The results of structure−activity relationship (SAR) studies in the C-3 side chain are shown in Tables 1−6, beginning at the C-3 linker and extending to the basic pyrrolidine terminus of the side chain. Conversion of the C-3 carbonyl to the corresponding olefin (**10d**) enhanced activity 2-fold while reductive deoxygenation down to the methylene analogue **5a** increased thrombin inhibition 8-fold. Replacement of the C-3 ketone with a sulfur or oxygen atom also increased thrombin inhibitory activity relative to ketone **1a** (**12c** and **15c**, respectively).

The data in Table 2 summarize a few of the structural requirements surrounding the C-3 phenyl ring. While the more conformationally flexible, acyclic analogue **4e** was significantly less potent than the parent **1a**, the pyridyl derivative **18c** retained comparable activity. Altering the substitution pattern of the C-3 aryl ring in the form of the 1,3- and 1,2-disubstituted derivatives **4f** and **16c**, respectively, led to diminished potency.

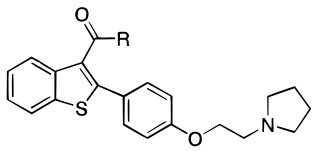
Table 1. Effects of the C-3 Linker on Thrombin Inhibition: Analogues **1a**, **5a**, **10d**, **12c**, and **15c**

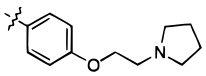
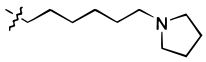
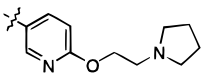
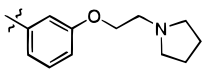
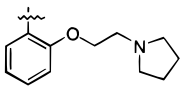


cmpd	X	K_{ass}[a] (L/mol × 10^6)
1a	C=O	0.43 ± 0.07
10d	C=CH_2	0.77 ± 0.07
5a	CH_2	3.43 ± 0.55
12c	S	3.08 ± 0.36
15c	O	2.07 ± 0.21

[a] Represents the apparent association constant as measured by the methods of Smith et al., ref 17.

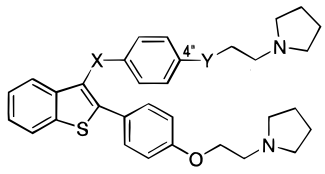
Table 2. Structure−Activity Relationships of the C-3 Aryl Ring: Derivatives **4e**, **4f**, **16c** and **18c**



cmpd	R	K_{ass}[a] (L/mol × 10^6)
1a		0.43 ± 0.07
4e		<0.005
18c		0.63 ± 0.19
4f		0.04 ± 0.002
16c		<0.005

[a] Represents the apparent association constant as meas-ured by the methods of Smith et al., ref 17.

Table 3. Effects of the C-4′ Linker on Thrombin Inhibition: Analogues **1a**, **5a**, **5d**, **8a**, **8b**, **20**

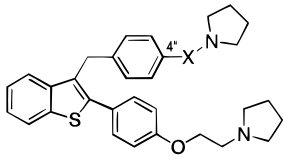


cmpd	X	Y	K_{ass}[a] (L/mol × 10^6)
1a	C=O	O	0.43 ± 0.07
3d	C=O	CH_2	0.84 ± 0.07
5a	CH_2	O	3.43 ± 0.55
8a	CH_2	S	2.27 ± 0.16
8b	CH_2	NH	3.04 ± 0.45
20	CH_2	C=O	0.97 ± 0.01

[a] Represents the apparent association constant as measured by the methods of Smith et al., ref 17.

The SAR studies progressed next to the linking group between the 2-(1-(pyrrolidinyl)ethyl side chain and the C-4″ position (Y; Table 3). Replacement of the ether oxygen of lead **1a** by carbon (**3d**) led to a 2-fold increase in activity, while incorporation of other heteroatoms such as sulfur and nitrogen (**8a** and **8b**, respectively) had only a modest impact on activity relative to compound **5a**. Ketone derivative **20** was 3-fold less active. Although the carbon analogue **3d** was more potent than its ether counterpart **1a**, subsequent SAR studies were conducted using ether linkages at C-4″ due to the ease of constructing aryl ether bonds relative to aryl alkyl bonds.

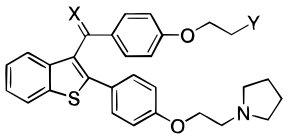
Table 4. Effects of Modifying the Length of the C-4″ Tether: Analogues **5a**−**d** and **8c**



cmpd	X	K_{ass}[a] (L/mol × 10^6)
5a	$O(CH_2)_2$	3.43 ± 0.55
5d	$O(CH_2)_3$	0.61 ± 0.13
8c	$O(CH_2)_4$	0.28 ± 0.02
5b	$(CH_2)_2$	6.19 ± 0.09
5c	CH_2	16.0 ± 2.30

[a] Represents the apparent association constant as measured by the methods of Smith et al., ref 17.

Table 5. Modification of the C-3 Terminal Amine: Derivatives **1a**, **5a**, **7j**−**l**, and **8d**−**i**



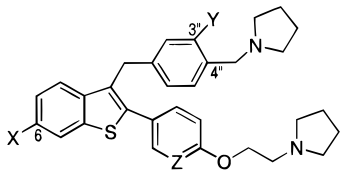
cmpd	X	Y	K_{ass}[a] (L/mol × 10^6)
1a	C=O	1-pyrrolidinyl	0.43 ± 0.07
7j	C=O	1-piperidinyl	0.16 ± 0.01
7k	C=O	1-hexamethyleneimino	0.20 ± 0.02
7l	C=O	1-morpholinyl	0.30 ± 0.10
5a	H, H	1-pyrrolidinyl	3.43 ± 0.55
8d	H, H	NH_2	0.24 ± 0.02
8e	H, H	NHEt	2.24 ± 0.13
8f	H, H	NEt_2	12.80 ± 1.66
8g	H, H	NMe_2	1.91 ± 0.12
8h	H, H	N(*i*-Pr)$_2$	6.75 ± 0.95
8i	H, H	N(*n*-Bu)$_2$	2.11 ± 0.46

[a] Represents the apparent association constant as measured by the methods of Smith et al., ref 17.

X-ray crystallography studies on benzo[*b*]thiophene **1b** show that the C-3 side chains of inhibitors **1a** and **5a** span the proximal (S_2) and distal sites of the thrombin active site (Figure 1).[7,19] The pyrrolidine ring appears to interact at the lipophilic, distal site which is composed of residues Trp215, Ile174, and Glu97A−Leu99. In an effort to enhance this interaction, the length of the tether between the pyrrolidine ring and the C-4″ site was varied (Table 4). While lengthening the tether decreased potency (**5d** and **8c**), shortening the distance between the pyrrolidine and the C-3 phenyl ring increased thrombin inhibitory activity (**5b** and **5c**). The greatest increase was observed for the pyrrolidinylmethyl derivative **5c** which was 5-fold more potent than parent **5a**.

The key structural elements of the pyrrolidine ring were also modified to investigate interactions at the

Table 6. Thrombin Inhibitory Activity and in Vitro Anticoagulant Profile of Hybrid Structures **23c**, **28c**, and **31c** as Well as **32**



cmpd	X	Y	Z	K_{ass}[a] (L/mol × 10^6)	2 × TT[b] (μg/mL)	2 × aPTT[b] (μg/mL)	2 × PT[b] (μg/mL)
23c	OH	Br	CH	1240 ± 249	0.48	1.45	1.26
28c	OH	OMe	CH	903 ± 99	0.02	0.42	0.40
31c	OH	OMe	N	1271 ± 145	0.02	0.23	0.34
1a				0.43 ± 0.07	>44.5	>44.5	>44.5
D-Piq-Pro-Arg-H[c] (**32**)				531 ± 198	0.02	0.60	1.42

[a] Represents the apparent association constant as measured by the methods of Smith et al. ref 17. [b] Represents the concentration of inhibitor necessary to double the thrombin time (TT), activated partial thromboplastin time (aPTT), and prothrombin time (PT) as measured by the methods of Smith et al. refs 17 and 20. [c] The full chemical name is(H-*R*-1-[4a*S*,8a*S*]-perhydroisoquinolyl-prolyl-arginyl aldehyde.

distal pocket. Expanding the size of the pyrrolidine ring to the six- and seven-membered analogues, as well as incorporation of an oxygen atom (**7j**−**l**, respectively), led to decreased activity relative to parent **1a**. Decreasing the lipophilic environment surrounding the amine, as in the primary or secondary amines **8d** and **8e**, respectively, also diminished potency relative to the pyrrolidine derivative (**5a**). The importance of lipophilicity is consistent with the interaction of the pyrrolidine with the lipophilic, distal pocket. Opening the pyrrolidine ring to the acyclic, tertiary diethylamine (**8f**) affected a 4-fold increase in potency. However, increasing the size of the nitrogen substituents to di-*i*-propyl (**8h**) or di-*n*-butyl (**8i**) reduced potency relative to the diethyl analogue, possibly due to unfavorable steric interactions at the distal site.

In past and present structure−activity relationships studies on the C-3 side chain,[7] a number of structural modifications which increase thrombin inhibitory activity have been made. Many of the optimal structural elements identified have been incorporated together into a single molecule in order to gauge the levels of thrombin inhibition that might be achieved within this series (**23c**, **28c**, and **31c**; Table 6). Each derivative contains the reduced C-3 methylene linker (from Table 1) as well as the contracted C-4″ side chain (from Table 4), both of which were discovered during the current study. In addition, they possess a C-6 hydroxyl which has been shown to increase thrombin inhibitory activity by 6-fold, presumably through the formation of a hydrogen bond with the carboxyl group of Asp189 in the S_1 specificity pocket of thrombin.[7] Finally, each is substituted at C-3″ with either a bromine or methoxy which have been reported to enhance potency by 8-fold and 3.5-fold, respectively, presumably through interaction at the lipophilic, proximal S-2 binding site of thrombin.[20] Analogue **31c** is distinguished from derivative **28c** by the fact that the C-2 aryl ring has been replaced by a pyridine. As the data in Table 6 indicate, combining the optimal structural elements into a single molecule, as in derivatives **23c**, **28c**, and **31c**, resulted in very potent thrombin inhibition. Relative to the screening hit **1a**, thrombin inhibition has been enhanced by 2800-, 2200-, and 2900-fold for derivatives **23c**, **28c**, and **31c**, respectively. On the basis of individual effects of the C-6 hydroxyl (6-fold),[7] the C-3″ substituents (Br, 8-fold; OMe, 3.5-fold),[20] the C-3 methylene (8-fold), and the contracted C-4″ side chain (4.5-fold), the activity of hit **1a** would be expected to be increased by 1700-fold in the case of **23c** and 750-fold in the case of **28c**.

The determination of the in vitro anticoagulant profiles for compounds **23c**, **28c**, and **31c** was accomplished using the methods of Smith et al.[17,21] (Table 6). Briefly, compounds **23c**, **28c**, and **31c** were added to human plasma over a range of concentrations to determine prolongation effects on the thrombin time (TT), activated partial thromboplastin time (aPTT), and prothrombin time (PT) assays. The concentrations of inhibitor that are required to double the clotting time for each assay are reported as 2 × TT, 2 × aPTT, and 2 × PT, respectively. Whereas derivative **23c** doubled the TT at a concentration of 0.48 μg/mL, only 0.02 μg/mL of both **28c** and **31c** were required. The activities of thrombin inhibitors **23c**, **28c**, and **31c** in the human plasma aPTT and PT assays are also reported in Table 6. Consistent with the TT assay, lower concentrations of **28c** (0.42 and 0.40 μg/mL, respectively) and **31c** (0.23 and 0.34 μg/mL, respectively) were required to double the aPTT and PT, relative to **23c** (1.45 and 1.26 μg/mL, respectively). However, in each case the concentrations of inhibitor necessary to double the aPTT and PT are significantly higher than those in the TT assay. This is consistent with the larger amounts of thrombin that are generated in both the aPTT and PT assays. The lower activity of the more lipophilic bromide **23c** in the anticoagulant assays, relative to **28c** and **31c**, may be due in part to the increased interaction with plasma lipids that are present in the assay.[22]

The thrombin inhibitory activity and in vitro anticoagulant profile of **23c**, **28c**, and **31c** were compared to the tripeptide arginal, *R*-1-Piq-Pro-Arg-H (H-*R*-1-[4a*S*,-8a*S*]-perhydroisoquinolyl-prolyl-arginyl aldehyde; **32**),[23] to assess the significance of the novel compounds from this study. This potent tripeptide thrombin inhibitor entered phase I clinical trials as an oral anticoagulant candidate, and therefore, its in vitro activity could serve as a benchmark for the current work. As reported in Table 6, the thrombin times (TT) of benzo[*b*]thiophenes **28c** and **31c** were identical to that of the arginal **32**, doubling the TT at concentrations of 0.02 μg/mL. In the aPTT and PT assays, however, thrombin inhibitors **28c** (0.42 and 0.40 μg/mL, respectively) and **31c** (0.23 and 0.34 μg/mL, respectively) were more potent than compound **32** (0.60 and 1.42 μg/mL, respectively), with the pyridyl analogue being approximately 3-fold more active. A number of factors could be responsible for the

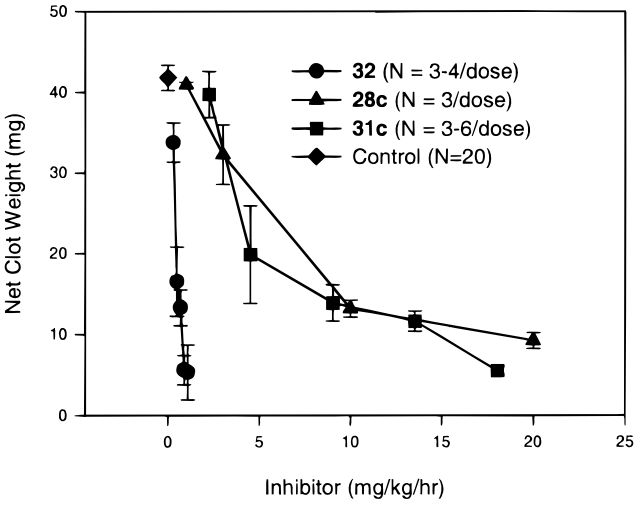


Figure 2. Effects of thrombin inhibitors **28c**, **31c**, and **32** on net clot weight in the rat arterial−venous (AV) shunt model.

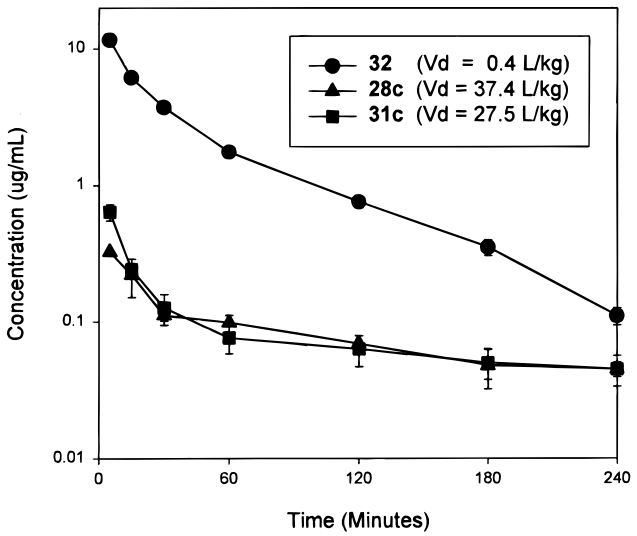


Figure 3. Plasma drug concentrations following intravenous administration of thrombin inhibitors **28c**, **31c** (5 mg/kg), and **32** (2.3 mg/kg) to Rats.

greater potency of derivatives **28c** and **31c** in the aPTT and PT assays, including a faster on-rate relative to the arginine aldehyde **32**, inhibition of alternate elements of the aPTT and PT pathways or, by affecting in a different fashion, a thrombin-mediated function in the aPTT and PT pathways.

Compounds **28c** and **31c** were next evaluated for their ability to inhibit in vivo blood clot formation in the rat arterial/venous (AV) shunt model of thrombosis (Figure 2).[24] The clinical agent **32** was also used as a benchmark in this model. The average clot weight of 20 vehicle-treated rats (control) was calculated to be 41.8 ± 1.6 mg (mean ± sem). Infusion of compound **32** (0.3−1.1 mg/kg/h for 30 min), beginning 15 min prior to opening the shunt, reduced the average clot size in a dose-related manner. The dose−response curve was steep with a calculated ED_{50} of 0.7 mg/kg/h. Infusion of compound **28c** (1−20 mg/kg/h) and compound **31c** (2.25−18 mg/kg/h) also reduced the average clot size in a dose-related manner. The dose−response curves for **28c** and **31c** were shallow, and the calculated ED_{50} values were 8.8 and 6.6 mg/kg/h, respectively. Despite the comparable in vitro anticoagulant profiles, derivatives **28c** and **31c** were approximately 10-fold less efficacious in this model than the tripeptide arginal **32**.

To better understand the discrepancy between the in vitro anticoagulant profile and the observed in vivo efficacy, rats were administered a single IV bolus dose of each thrombin inhibitor (**28c**, **31c**, and **32**) and the plasma levels of parent drug monitored over time (Figure 3). The pharmacokinetic properties that were calculated from these studies are reported in Table 8.[25] Following a 2.3 mg/kg dose of arginal **32**, maximal plasma concentrations (C_{max}) reached 11.57 μg/mL and decreased monoexponentially with a half-life of 0.8 h.[26] Area under the plasma concentration versus time curve (AUC) and volume of distribution were 7.18 μg·h/mL and 0.4 L/kg, respectively.[27] In contrast, a 2-fold higher dose (5 mg/kg) of benzo[*b*]thiophenes **28c** and **31c** resulted in significantly lower C_{max} and AUC values (C_{max}'s of 0.32 and 0.64 μg/mL and AUC's of 0.35 and 0.40 μg·h/mL for derivatives **28c** and **31c**, respectively) and moderate half-lives of 2−3 h. Perhaps the low observed plasma levels of analogues **28c** and **31c** relative to arginal **32** were due to the high volumes of distribution to which they undergo (volumes of 37.4 and 27.5 L/kg compared to 0.4 L/kg; Table 8). Since the majority of thrombin resides in the plasma component, the relatively high volumes of distribution and resulting low plasma levels of inhibitor may account for the efficacy differences of inhibitors **28c** and **31c** relative to arginal **32**, despite the comparable in vitro anticoagualnt profiles.

To better understand the nature of the high volumes of distribution observed for the benzo[*b*]thiophenes, tissue distribution studies were undertaken with benzo[*b*]thiophene **31c**. Samples of plasma, liver, kidney, lung, and heart were obtained from male rats at various times after a 5 mg/kg intravenous dose of **31c** and assayed for parent drug concentrations.[28] The results are shown in Figure 4. Only low levels of benzo[*b*]-thiophene **31c** were observed in the plasma from 15 min to 5 h following drug administration (−■−; plasma **31c** concentrations were multiplied by 10 in order to show them on the graph). In contrast, very high concentrations were detected in each of the tissues. Maximal tissue concentrations occurred 30 min posttreatment and declined slowly. The highest concentrations were found in the lung tissue (−●−; 77.7 μg/g), followed by the kidney (−○−; 36.4 μg/g), heart (−▼−; 21.3 μg/g), and liver (−▽−; 3.6 μg/g). Maximal plasma concentrations (at 10 min) were 0.73 μg/mL. Tissue-to-plasma ratios at 2 h posttreatment ranged from 30 for the liver to over 800 for the lung. The relatively low concentrations in liver were likely the result of its capacity to metabolize parent **31c**. Appreciable amounts of a component whose molecular weight corresponded to the glucuronide of **31c** were found in the liver extracts, but not in the kidney.[29] The data in Figure 4 suggest that following intravenous administration the benzo[*b*]thiophenes undergo both rapid and extensive distribution to various tissues, making them less available to inhibit thrombin in the plasma.

A number of structural modifications were necessary to achieve the high levels of thrombin inhibition displayed by derivatives **23c**, **28c**, and **31c**. To determine

Table 7. Serine Protease Selectivity of Derivatives **28c**, **1a**, **1b**, and **32**

cmpd	apparent K_{ass} values (L/mol × 10^6)[a]					
	human thrombin	bovine trypsin	human fXa	human plasmin	human ntPA	human urokinase
28c	903 ± 99	<0.009	<0.002	0.007	0.008	<0.009
1a	0.43 ± 0.07	0.003	0.01	0.003	0.03	<0.009
1b	24.3 ± 2.0	<0.009	0.015	0.009	0.009	<0.009
D-Piq-Pro-Arg-H[b] (**32**)	531 ± 198	27.0	2.70	1.51	0.03	0.018

[a] Represents the apparent association constant as measured by the methods of Smith et al., ref 17. K_{ass} values for each serine protease, except thrombin, are the average of two determinations where the variation in the assay is ±10%. K_{ass} values for thrombin are the mean of $n = 3$, showing the standard deviation. [b] The full chemical name is (H-*R*-1-[4a*S*,8a*S*]-perhydroisoquinolyl-prolyl-arginyl aldehyde.

Table 8. Summary of the Pharmacokinetic Parameters for Thrombin Inhibitors **28c**, **31c**, and **32** Following iv Administration to Rats

parameter	compound		
	32	**28c**	**31c**
dose (mg/kg)	2.3	5.0	5.0
C_{max} (μg/mL)	11.57	0.32	0.64
AUC_{0-4h} (μg·h/mL)	7.18	0.35	0.40
half-life (h)	0.8	2.7	2.0
volume (L/kg)	0.4	37.4	27.5

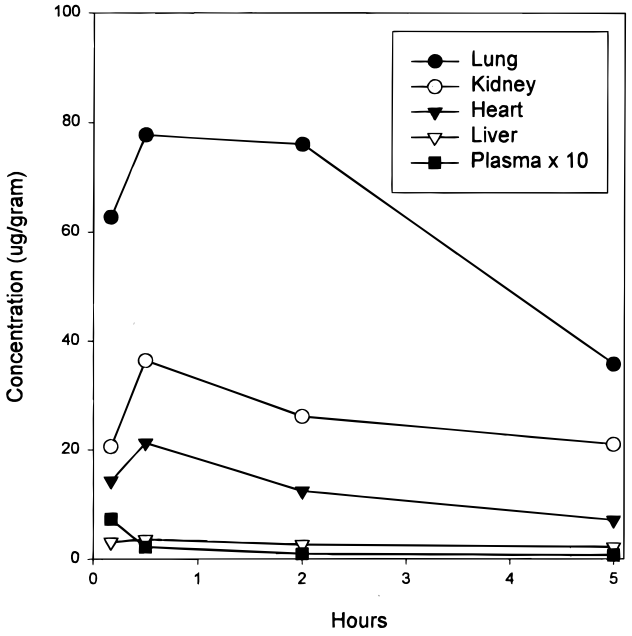


Figure 4. Concentrations of analogue **31c** in plasma and selected tissues following a 5 mg/kg dose to rats.

whether these analogues retain the same levels of thrombin specificity observed earlier for compounds **1a** and **1b**, derivative **28c** was tested for its ability to inhibit other serine proteases, including the fibrinolytic proteases as well as trypsin. As reported in Table 7, analogue **28c** is exceptionally selective for thrombin relative to the other serine proteases tested, even surpassing the high levels of specificity reported for compound **1b**.[7] This series of agents represents one of the most selective classes of thrombin inhibitors reported to date.

Conclusions

This report describes a systematic SAR study surrounding the C-3 side chain of a structurally novel class of diamino benzo[*b*]thiophene thrombin inhibitors, derived from the screening hit **1a**. Through a series of structural modifications, the inhibitory activity of the hit **1a** was enhanced by up to 2800-fold, achieving activities of $K_{ass} = 900-1200 \times 10^6$ L/mol. In addition, the levels of thrombin selectivity for this series are among the highest yet reported, being similar to that found with hirudin.[18] The observed levels of thrombin inhibition translated into potent in vitro anticoagulant effects in the thrombin time (TT), activated partial thromboplastin time (aPTT), and prothrombin time (PT) assays. The in vitro thrombin inhibition and anticoagulant activity achieved in derivatives **28c** and **31c** equals or surpasses the potency of the clinical thrombin inhibitor candidates, *R*-1-Piq-Pro-Arg-H and Efegatran.[18] In a rat model of arterial/venous thrombosis, compounds **28c** and **31c** were found to be efficacious in reducing blood clot formation. However, the efficacy of the current analogues is limited by their rapid and extensive distribution following administration.

Experimental Section

The experimental details for the synthesis and the physical chemical data for the amino acids used in the preparation of compounds **4**−**d**, **4f**, **4g**, **23a**, and **27** are included in the Supporting Information. The physical chemical properties of compounds **1a**, **4b**−**g**, **5a**−**d**, **7a**−**l**, **8a**−**i**, **10a**, **16a**, and **17** are reported in the Supporting Information.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus calibrated with known compounds and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on either a Varion Mercury-400 or General Electric QE-300 spectrometer using either deuterated dimethyl sulfoxide (DMSO-d_6), deuterated chloroform ($CDCl_3$), or deuterated methanol (CD_3OD) as the solvent, and chemical shifts are reported in parts per million (ppm) relative to dimethyl sulfoxide (DMSO; 2.49 ppm), chloroform ($CHCl_3$; 7.25 ppm), or methanol (CH_3OH; 3.30 ppm). Infrared spectra (IR) were run either as solutions in $CHCl_3$ or as pellets in KBr and were recorded on a Nicolet 510P spectrometer. Field desorption mass spectra (FDMS) were obtained on a VG Analytical VG70SE mass spectrometer. Fast atom bombardment high resolution mass spectra (FAB-HRMS) were obtained on a VG Analytical VGZAB-2SE mass spectrometer. Combustion analyses were performed on a Control Equipment Corporation 440 elemental analyzer and were within 0.4% of the calculated values. Medium pressure liquid chromatography (MPLC) was performed using PrepPak silica gel cartridges on a Waters Prep LC/System 500A. Flash chromatography was performed over silica gel 60 (230−400 mesh ASTM). Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison model 7924 chromatotron with Merck silica gel 60 PF_{254} containing $CaSO_4 \cdot 0.5H_2O$ binder. All reactions, regardless of the solvent used, were performed under a positive N_2 flow with anhydrous solvents.

Inhibitor activity against human α-thrombin and other serine proteases were measured as apparent association constants (K_{ass}) which were derived from inhibition kinetics, according to the methods of Smith et al.[18] Briefly, enzyme inhibition kinetics were performed in 96-well polystyrene plates, and reaction rates were determined from the rate of hydrolysis of appropriate *p*-nitroanilide substrates at 405 nm

using a Thermomax plate reader from Molecular Devices (San Francisco, CA). The same protocol was followed for all enzymes studied: 50 μL of 0.6 M Tris/0.15 M NaCl, pH 7.4, buffer was added in each well, followed by 25 μL of inhibitor solution and 25 μL enzyme solution; within two minutes, 150 μL chromogenic substrate was added to start the enzymatic reactions. The rates of benzoyl-Phe-Val-Arg-p-NA hydrolysis reactions provide a linear relationship with human α-thrombin such that free thrombin can be quantitated in reaction mixtures. Data were analyzed directly as rates by the Softmax program to produce [free enzyme] calculations for tight-binding K_{ass} determinations. For apparent K_{ass} determinations, 5.9 nM human thrombin or 1.4 nM bovine trypsin was used to hydrolyze 0.2 mM BzPheValArg-pNA, 3.4 nM human plasmin with 0.5 mM HD-Val-Leu-Lys-pNA, 1.2 nM human nt-PA with 0.81 mM HD-Ile-Pro-Arg-pNA, 0.37 nM urokinase with 0.30 mM pyro-gfsGlu-Gly-Arg-pNA, and 1.34 nM human factor Xa with 0.18 mM BzIle-Glu-Gly-Arg-pNA.

2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (3). To a solution of 2.53 g (9.4 mmol) of 1-(2-(4-bromophenoxy)ethyl)pyrrolidine in 65 mL of benzene was added 0.90 g (0.78 mmol) of tetrakis(triphenylphosphine)-palladium(0). After the mixture was stirred for 5 min, a solution of 1.40 g (7.90 mmol) of benzo[*b*]thiophene-2-boronic acid (**2**) in 26 mL of EtOH was added followed by 8.80 mL of 2 N aqueous Na_2CO_3. The reaction was heated to 50 °C for 3 h, allowed to cool, and diluted with H_2O and EtOAc (250 mL each). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo to give 3.26 g of an oil. Purification by flash chromatography (36:60:4 THF−hexanes−TEA) afforded 1.94 g (6.00 mmol; 76%) of product **3** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.38−7.26 (m, 3H), 6.97 (d, J = 8.8 Hz, 2H), 4.17 (t, J = 5.9 Hz, 2H), 2.96 (t, J = 5.9 Hz, 2H), 2.73−2.64 (m, 4H), 1.89−1.80 (m, 4H); IR (KBr) 2922, 1607, 1500, 1456, 1433, 1261, 1047, 822, 725 cm^{-1}; FDMS 324 (M + 1). Anal. ($C_{20}H_{21}NOS\cdot 0.1H_2O$) C, H, N.

General Procedure for the Acylation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (3) and 2-(4-Methoxyphenyl)benzo[*b*]thiophene (9). Preparation of Derivatives 1a, 4b−g, 10a, 16a, and 17. A mixture of the aminocarboxylic acid (1.1 equiv) in 1,2-dichloroethane (10 mL/mmol) was treated with a drop of DMF followed by $SOCl_2$ (5.5 equiv). The reaction was heated to mild reflux for 2 h and concentrated in vacuo. The residue was resuspended in 1,2-dichloroethane and reconcentrated to afford the corresponding acid chlorides. For the preparation of compounds **10a**, **16a**, and **17**, the required acid chlorides were commercially available.

The acid chlorides were dissolved or suspended in 1,2-dichloroethane (10 mL/mmol), and the mixture was cooled to 0 °C. Benzo[*b*]thiophene **3** (1 equiv) was added followed by the portionwise addition of $AlCl_3$ (8 equiv). The mixture was stirred at 0 °C until TLC analysis showed no further reaction (∼5 h) at which time it was carefully poured into a 0 °C solution of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the combined organic extracts were dried (K_2CO_3), filtered, and concentrated in vacuo. The crude material was purified by chromatography to yield the desired products. The free bases of the products were taken up in a minimal amount of EtOAc and were treated with a solution of 2.1 equiv of oxalic acid in EtOAc. The resulting solids were filtered and dried. The physical chemical properties of compounds **1a**, **4b−g**, **10a**, **16a**, **17** are reported in the Supporting Information.

General Procedure for the Reductive Deoxygenation of Ketones 1a, 4b−d and 7a−l. Preparation of Products 5a−d and 8a−i. A 0 °C slurry of $LiAlH_4$ (3 equiv) in 10 mL of THF was treated with a solution of the appropriate ketone (1 equiv) in THF (15 mL/mmol). The reaction was stirred at 0 °C until TLC showed complete consumption of starting material (∼2 h). The reaction was quenched by the sequential addition of H_2O (3 mL/mmol), 2 N aqueous NaOH (3 mL/mmol), and H_2O (3 mL/mmol). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (25 mL), dried, and concentrated in vacuo.

The residue was taken up in CH_2Cl_2 (30 mL/mmol). The mixture was cooled to 0 °C and was treated with triethylsilane (10 equiv). After being stirred at 0 °C for 0.5 h, the reaction mixture was treated with TFA (7 equiv) and stirred at 0 °C until no further reaction was occurring as monitored by TLC. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL/mmol), and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried, filtered, and concentrated in vacuo. The products were purified by chromatography. The physical chemical properties of compounds **5a−d** and **8a−i** are reported in the Supporting Information.

4-Fluorophenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl Ketone (6). A 0 °C solution of benzo-[*b*]thiophene **3** (3.54 g; 11.0 mmol) and 4-fluorobenzoyl chloride (2.60 g; 16.4 mmol) in 130 mL of CH_2Cl_2 was protected from light and treated with $TiCl_4$ (8.30 g; 43.80 mmol) in a dropwise manner. The mixture was stirred overnight while allowed to warm to room temperature. The mixture was poured rapidly into saturated aqueous $NaHCO_3$ (300 mL). After being stirred for 1 h, the mixture was diluted with H_2O (200 mL) and the mixture extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by MPLC (75% hexanes/20% THF/5% Et_3N) afforded 4.40 g (90%) of product **6**: ^{1}H NMR ($CDCl_3$) δ 7.95−7.89 (m, 1H), 7.87−7.77 (m, 3H), 7.46−7.32 (m, 4H), 7.01−6.93 (m, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.09 (t, J = 5.9 Hz, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.72−2.61 (m, 4H), 1.91−1.82 (m, 4H); IR ($CHCl_3$) 1649, 1598, 1505, 1499, 1435, 1237, 1153 cm^{-1}. FAB-HRMS: *m/e*, calcd for $C_{27}H_{25}FNO_2S$: 446.1590; Found: 446.1597 (M + 1). Anal. ($C_{27}H_{24}FNO_2S$) C, H, N.

General Procedure for the Displacement of Fluorine from 4-Fluorophenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone (6). Preparation of 7a−l. A slurry of NaH (2−5 equiv of 60% NaH in mineral oil) in DMF (3 mL/mmol NaH) was treated with a solution of the appropriate alcohol, amine, or sulfide (2−5 equiv) in DMF in a dropwise manner. After the mixture was stirred for 15 min and gas evolution had ceased, a solution of fluoride **6** (1 equiv) in DMF (2 mL/mmol) was added. The mixture was stirred at room temperature for 5 h, then poured into water. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered, and concentrated in vacuo. The crude products were purified by chromatography. The physical chemical properties of compounds **7a−l** are reported in the Supporting Information.

Methyl 4-[1-[2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl]ethenyl]phenyl Ether (10b). A slurry of methyltriphenylphosphonium bromide (1.20 g; 3.36 mmol) in THF (50 mL) was treated with potassium *tert*-butoxide (0.45 g; 4.01 mmol) and the mixture stirred at room temperature for 0.5 h. To this was added a solution of ketone **10a** (0.80 g; 2.14 mmol) in THF (10 mL) in a dropwise manner. The reaction was stirred at room temperature for 18 h and then heated at gentle reflux for 48 h. The reaction was quenched by the addition of brine (100 mL). The two layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentration in vacuo to give 1.36 g of an oil. Purification by PCTLC (10% EtOAc in hexanes) afforded product **10b** as an oil (0.61 g; 1.64 mmol; 77%): ^{1}H NMR (DMSO-d_6) δ 7.99 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.40−7.27 (m, 5H), 6.95 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 6.02 (s, 1H), 5.17 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H); IR ($CHCl_3$) 1607, 1511, 1435, 1251, 1179, 1036 cm^{-1}; FDMS 372 (M$^+$; 100). Anal. ($C_{24}H_{20}O_2S$) C, H.

4-[1-[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]ethenyl]phenol (10c). A mixture of dimethyl ether **10b** (0.50 g; 1.34 mmol) and pyridine hydrochloride (10.0 g) was heated to 160 °C for 5 h. The reaction was allowed to cool and at 145 °C

was treated with ice (20 g). The mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed sequentially with H_2O (25 mL), 1 N aqueous HCl (25 mL), and H_2O (25 mL) and were dried (Na_2SO_4), filtered, and concentrated in vacuo to a yellow solid. Purification by PCTLC (gradient of 20−40% EtOAc in hexanes) afforded 310 mg (0.90 mmol; 67%) of diphenol **10c**: ^{1}H NMR (DMSO-d_6) δ 9.70 (s, 1H), 9.53 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 6.9 Hz, 2H), 7.32−7.23 (m, 3H), 7.14 (d, J = 6.9 Hz, 2H), 6.71 (d, J = 6.9 Hz, 2H), 6.65 (d, J = 6.9 Hz, 2H), 5.89 (s, 1H), 5.06 (s, 1H); IR ($CHCl_3$) 3593, 3320, 1610, 1590, 1504, 1456, 1436, 1265, 1173, 838 cm^{-1}; FDMS 344 (M^+; 100). Anal. ($C_{22}H_{16}O_2S\cdot 0.5H_2O$) C, H.

1-[2-[4-[1-[2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thien-3-yl]ethenyl]phenoxy]ethyl]pyrrolidine (10d). A mixture of phenol **10c** (290 mg; 0.84 mmol) and Cs_2CO_3 (2.20 g; 6.75 mmol) in 10 mL of DMF was treated with 1-(2-chloroethyl)pyrrolidine hydrochloride (430 mg; 2.53 mmol). The mixture was heated to 80 °C for 16 h, cooled, filtered, and concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo to give an oil. Purification by PCTLC (gradient of 2 to 5 to 10% MeOH in CH_2Cl_2) afforded 301 mg (67%) of diamine **10d** as an oil. The free base of product **10d** was converted to the dioxalate salt: ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.38−7.16 (m, 5H), 6.95 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.99 (s, 1H), 5.14 (s, 1H), 4.32−4.10 (m, 4H), 3.54−3.36 (m, 4H), 3.29−3.12 (m, 8H), 1.98−1.72 (m, 8H); IR (KBr) 3425, 1719, 1606, 1510, 1404, 1245, 1181, 721 cm^{-1}; FDMS 539 (M + 1; 100). Anal. ($C_{34}H_{38}N_2O_2S\cdot 2C_2H_2O_4$) C, H, N.

3-Bromo-2-(4-methoxyphenyl)benzo[*b*]thiophene (11). A 0 °C slurry of 2-(4-methoxyphenyl)benzo[*b*]thiophene (**9**; 5.00 g; 20.8 mmol)[30] in $CHCl_3$ (400 mL) was treated slowly with Br_2 (1.60 mL; 31.0 mmol), resulting in a yellow solution. The reaction was stirred at 0 °C for 1 h and then washed sequentially with 1 N aqueous $Na_2S_2O_3$ (200 mL), 1 N aqueous $NaHCO_3$ (200 mL), and H_2O (200 mL). The solution was dried (Na_2SO_4), filtered, and concentrated in vacuo to give analytically pure product **11** as an off-white solid (6.24 g; 19.6 mmol; 94%): mp 84.5−86.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.50−7.37 (m, 2H), 7.02 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); IR ($CHCl_3$) 1610, 1540, 1498, 1435, 1255, 1179, 1035, 889, 836 cm^{-1}; FDMS 318 (100), 320 (M + 1). Anal. ($C_{15}H_{11}BrOS$) C, H.

Methyl4-[[2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenyl Ether (12a). To a −78 °C solution of bromide **11** (1.0 g; 3.1 mmol) in 20 mL of THF was added *n*-BuLi (2.90 mL; 1.6 M in hexanes; 4.7 mmol) in a dropwise manner. The mixture was stirred at −78 °C for 10 min and treated with solid bis(4-methoxyphenyl)disulfide (0.87 g; 3.13 mmol). The reaction was stirred at −78 °C for 0.5 h and was allowed to warm slowly to room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL) and MeOH (1 mL) and was concentrated in vacuo. The residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oily solid. Partial purification by flash chromatography (gradient of 1−5% EtOAc in hexanes) afforded 0.82 g of product **12a** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.94−7.85 (m, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.43−7.38 (m, 2H), 7.09−6.99 (m, 4H), 6.78 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H), 3.77 (s, 3H); IR ($CHCl_3$) 1609, 1528, 1494, 1288, 1248, 1177, 1034 cm^{-1}; FDMS 378 (M + 1; 100). Product **12a** was taken on without further purification.

4-[[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenol (12b). A 0 °C solution of dimethyl ether **12a** (0.82 g; 2.2 mmol) in dichloroethane (50 mL) was treated with BBr_3 (1.20 mL; 13 mmol). The reaction was stirred at 0 °C for 5 h and quenched by the careful addition of MeOH (15 mL). Concentration in vacuo gave a residue which was subjected to flash chromatography (1% MeOH in $CHCl_3$) to afford 0.47 g (1.34 mmol; 61%) of the diphenol **12b** as a solid: ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 9.47 (s, 1H), 7.86−7.78 (m, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.6 Hz, 2H); IR ($CHCl_3$) 3595, 3309, 1610, 1588, 1493, 1434, 1261, 1171, 827 cm^{-1}; FDMS 350 (M^+; 100). Anal. ($C_{20}H_{14}O_2S_2\cdot 0.5MeOH$) C, H.

1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]thio]phenoxy]ethyl]pyrrolidine (12c). A solution of diphenol **12b** (1.00 g; 2.90 mmol), tripenylphosphine (1.90 g; 7.10 mmol), and 1-(2-hydroxyethyl)pyrrolidine (0.82 g; 7.1 mmol) in THF (30 mL) was treated with DEAD (1.50 g; 8.60 mmol) in a dropwise manner. After complete addition, the reaction was stirred at ambient temperature for 16 h. Additional tripenylphosphine and 1-(2-hydroxyethyl)pyrrolidine (2.50 equiv each) as well as DEAD (3 equiv) were added, and stirring continued for 4 h. The mixture was concentrated in vacuo and the residue purified by PCTLC (60:37:3 hexanes:THF:TEA) to afford 0.72 g (1.33 mmol; 43%) of diamine **12c** as an oil. The free base of product **12c** was converted to the dioxalate salt: ^{1}H NMR (DMSO-d_6) δ 8.12−8.00 (m, 1H), 7.76−7.65 (m, 3H), 7.47−7.38 (m, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 4.36 (t, J = 5.0 Hz, 2H), 4.19 (d, J = 5.1 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 3.47 (t, J = 4.9 Hz, 2H), 3.42−3.18 (m, 8H), 2.03−1.82 (m, 8H); IR (KBr) 3467, 1722, 1607, 1493, 1238, 1180, 706 cm^{-1}; FDMS 545 (M + 1), 636 (M + 91, 100). Anal. ($C_{32}H_{36}N_2O_2S_2\cdot 2C_2H_2O_4\cdot 0.4H_2O$) C, H, N.

Benzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether (14a). A mixture of 3-bromobenzo[*b*]thiophene (4.00 g; 19.7 mmol),[12] 4-methoxyphenol (4.96 g; 40 mmol), K_2CO_3 (5.52 g; 40 mmol), and CuI (0.20 g; 1.0 mmol) was heated to 140 °C and sonicated at this temperature for 2 h. The reaction mixture was allowed to cool, taken up in CH_2Cl_2, and then washed several times with 0.5 N NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to an oil which was subjected to flash chromatography (gradient of 0−5% EtOAc in hexanes). The fractions containing the desired product were combined and evaporated in vacuo, and the residue was recrystallized from hexanes to afford 500 mg (1.95 mmol; 10%) of product **14a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84−7.78 (m, 2H), 7.42−7.37 (m, 2H), 7.11 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.45 (s, 1H), 3.82 (s, 3H); FDMS 256 (M^+). Anal. ($C_{15}H_{12}O_2S$) C, H.

2-Iodobenzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether (14b). A −78 °C solution of aryl ether **14a** (133 mg; 0.52 mmol) in THF (3 mL) was treated with *n*-BuLi (0.33 mL; 1.6 M in hexanes; 0.54 mmol). The mixture was stirred at −78 °C for 15 min and treated with a solution of I_2 (138 mg; 0.54 mmol) in THF (3 mL). The reaction was allowed to gradually warm to room temperature and then partitioned between brine and EtOAc/hexanes. The two phases were separated, and the organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized from hexanes to afford 143 mg (0.37 mmol; 72%) of iodide **14b** as a solid: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.34−7.19 (m, 2H), 6.91−6.78 (m, 4H), 3.78 (s, 3H); FDMS 382 (M^+). Anal. ($C_{15}H_{11}IO_2S$) C, H.

2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether (15a). Employing the methods used in the preparation of **3**, product **15a** was prepared from iodide **14b** and (4-methoxyphenyl)boronic acid in 70% yield following flash chromatography (5% EtOAc in hexanes): ^{1}H NMR ($CDCl_3$) δ 7.80−7.72 (m, 3H), 7.42−7.36 (m, 1H), 7.32−7.21 (m, 2H), 6.95−6.86 (m, 4H), 6.81−6.75 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H); FDMS 363 (M + 1). Anal. ($C_{22}H_{18}O_3S$) C, H.

4-[[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]oxy]phenol (15b). Employing the conditions described in the preparation of **10c**, diphenol **15b** was prepared from dimethyl ether **15a** in 87% yield following PCTLC (25% EtOAc in hexanes): ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 9.10 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.37−7.25 (m, 3H), 6.82−6.73 (m, 4H), 6.63 (d, J = 8.6 Hz, 2H); IR (KBr) 3394, 1611,

1504, 1438, 1356, 1202, 1183, 1054, 825, 752 cm^{-1}; FDMS 334 (M^+, 100). Anal. ($C_{20}H_{14}O_3S$) C, H.

1-[2-[4-[3-[4-[2-(1-Pyrrolidinyl)ethoxy]phenoxy]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine (15c). Employing the conditions described in the preparation of **10d**, diphenol **15b** was converted to diamine **15c** in 52% yield following PCTLC (gradient of 2−10% MeOH in CH_2Cl_2). The free base of product **15c** was converted to the dioxalate salt: ^{1}H NMR (DMSO-d_6) δ 7.96 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.40−7.23 (m, 3H), 7.04 (d, J = 8.5 Hz, 2H), 6.91−6.80 (m, 4H), 4.38−4.13 (m, 4H), 3.55−3.41 (m, 4H), 3.36−3.14 (m, 8H), 1.97−1.78 (m, 8H); IR (KBr) 1730, 1502, 1247, 1199, 833 cm^{-1}; FDMS 529 (M + 1; 100). Anal. ($C_{32}H_{36}N_2O_3S\cdot 2C_2H_2O_4$) C, H, N.

2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 2-Hydroxyphenyl Ketone (16b). A 0 °C solution of dimethyl ether **16a** (1.11 g; 2.97 mmol) in CH_2Cl_2 (100 mL) was treated with $AlCl_3$ (3.16 g; 23.7 mmol) followed by EtSH (2.63 mL; 35.6 mmol). The cold bath was removed and the reaction allowed to stir at ambient temperature for 2 h. The reaction was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (350 mL) and EtOAc (350 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (250 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 1.00 g of diphenol **16b** as a yellow foam. ^{1}H NMR (DMSO-d_6) δ 9.81 (s, 1H), 8.03 (d, J = 6.7 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.44−7.32 (m, 4H), 7.26−7.18 (m, 3H), 6.89 (d, J = 8.4 Hz, 1H), 6.72−6.63 (m, 3H); IR (KBr) 3594, 2977, 1625, 1611, 1501, 1484, 1437, 1267, 1237, 1175, 1155, 835, 808 cm^{-1}; FDMS 346 (M^+). Anal. ($C_{21}H_{14}O_3S$) C, H.

2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 2-[2-(1-Pyrrolidinyl)-ethoxy]phenyl Ketone (16c). Employing the conditions described in the preparation of **10d**, diphenol **16b** was alkylated to afford diamine **16c** in 97% yield following PCTLC (5% MeOH in CH_2Cl_2). The free base of product **16c** was converted to the dioxalate salt: ^{1}H NMR (DMSO-d_6) δ 8.08−8.03 (m, 1H), 7.95−7.90 (m, 1H), 7.49−7.42 (m, 2H), 7.36−7.24 (m, 4H), 6.90−6.78 (m, 4H), 4.21 (t, J = 4.9 Hz, 2H), 4.07 (t, J = 4.9 Hz, 2H), 3.47 (t, J = 4.9 Hz, 2H), 3.15 (t, J = 4.9 Hz, 2H), 3.08 (t, J = 6.3 Hz, 2H), 2.94−2.82 (m, 4H), 1.97−1.82 (m, 6H), 1.67−1.58 (m, 4H); IR (KBr) 3054, 1727, 1660, 1609, 1457, 1349, 1289, 1249, 756, 701 cm^{-1}; FDMS 541 (M + 1). Anal. ($C_{33}H_{36}N_2O_3S\cdot 1.4C_2H_2O_4\cdot 2H_2O$) C, H, N.

2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy]pyrid-3-yl Ketone (18a). A solution of 1-(2-hydroxyethyl)pyrrolidine (0.50 mL; 4.30 mmol) in xylenes (10 mL) was treated with Na (50 mg; 2.20 mmol). The mixture was heated to 50 °C until all the Na had disappeared. The mixture was cooled to room temperature and treated with a solution of chloride **17** (420 mg; 1.10 mmol) in xylenes (5 mL). The reaction was heated to 50 °C for 2 h and was concentrated in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo to give 810 mg of a yellow solid. Purification by PCTLC (gradient of 1−5% MeOH in CH_2Cl_2) gave 525 mg (1.09 mmol; 99%) of product **18a** as an amber oil: ^{1}H NMR (DMSO-d_6) δ 8.33 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.97−7.91 (m, 1H), 7.67−7.62 (m, 1H), 7.47−7.39 (m, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 1H), 4.31 (t, J = 5.8 Hz, 2H), 3.68 (s, 3H), 2.67 (t, J = 5.8 Hz, 2H), 2.49−2.38 (m, 4H), 1.68−1.57 (m, 4H); IR ($CHCl_3$) 2970, 1647, 1599, 1485, 1458, 1435, 1281, 1254, 1238, 1178, 1034 cm^{-1}; FDMS 459 (M^+; 100). Anal. ($C_{27}H_{26}N_2O_3S$) C, H, N.

2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy)pyrid-3-yl Ketone (18b). Employing the conditions described in the preparation of **16b**, phenol **18b** was prepared from methyl ether **18a** in 89% yield as a yellow solid following PCTLC (5% MeOH in CH_2Cl_2): ^{1}H NMR (DMSO-d_6) δ 9.81 (br s, 1H), 8.32 (s, 1H), 8.08−8.02 (m, 1H), 7.93 (dd, J = 2.2 and 8.8 Hz, 1H), 7.66−7.61 (m, 1H), 7.43−7.38 (m, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 8.6 Hz, 2H), 4.31 (t, J = 5.7 Hz, 2H), 2.78−2.67 (m, 2H), 2.48−2.41 (m, 4H), 1.67−1.58 (m, 4H); IR ($CHCl_3$) 2975, 1642, 1599, 1489, 1458, 1358, 1282, 1237 cm^{-1}. HRMS calcd for $C_{26}H_{24}N_2O_3S$: 445.1586. Found: 445.1569. Anal. ($C_{26}H_{24}N_2O_3S\cdot 0.2H_2O$) C, H, N.

1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thien-3-yl]methyl]phenoxy]ethyl]pyrrolidine (18c). Employing the conditions described in the preparation of **10d**, phenol **18b** was alkylated to provide diamine **18c** in 84% yield as an oil following PCTLC (gradient of 5−20% MeOH in THF). The free base of product **18c** was converted to the dioxalate salt. ^{1}H NMR (DMSO-d_6) δ 8.33 (d, J = 2.4 Hz, 1H), 8.09−8.04 (m, 1H), 7.94 (dd, J = 8.7 and 2.2 Hz, 1H), 7.66−7.62 (m, 1H), 7.47−7.38 (m, 2H), 7.29 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 6.1 Hz, 2H), 6.74 (d, J = 8.7 Hz, 1H), 4.29 (t, J = 4.8 Hz, 2), 4.02−3.95 (m, 2H), 2.74−2.66 (m, 4H), 2.53−2.38 (m, 8H), 1.69−1.58 (m, 8H); IR (KBr) 3434, 2966, 1729, 1644, 1599, 1458, 1239, 1051, 837, 698 cm^{-1}; FDMS 542 (M + 1). Anal. ($C_{32}H_{35}N_3O_3S\cdot 2C_2H_2O_4\cdot 1.5H_2O$) C, H, N.

4-[2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophenyl-3-yl]methylphenyl 2-(1-Pyrrolidinyl)ethyl Ketone (20). Acetylene **19**[14] (185 mg, 0.355 mmol) was dissolved in TFA (1 mL) and the solution heated to reflux in a sealed tube. After 2.5 h, the reaction mixture was cooled to 0 °C and poured into saturated aqueous $NaHCO_3$ (20 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by PCTLC (gradient of 85:10:5 to 65:30:5 hexanes:THF:TEA) afforded ketone **20** as a yellow oil (30 mg; 0.056 mmol, 16%): ^{1}H NMR ($CDCl_3$) δ 7.85−7.88 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 (, J = 8.6 Hz, 2H), 7.29−7.22 (m, 5H), 6.95 (d, J = 8.6 Hz, 2H), 4.31 (s, 2H), 4.13 (t, J = 5.9 Hz, 2H), 3.19 (t, J = 6 Hz, 2H), 2.95−2.90 (m, 4H), 2.71−2.58 (m, 8H), 1.88−1.76 (m, 8H). The free base of product **20** was converted to the dioxalate salt. IR (KBr) 1721, 1682, 1606, 1503, 1413, 1243, 1180, 1083, 720 cm^{-1}; FDMS 539 (M + 1). Anal. ($C_{34}H_{38}N_2O_2S_2\cdot C_2H_2O_4\cdot 0.5H_2O$) C, H, N.

6-Methoxybenzo[*b*]thiophene-2-boronic Acid (21b). To a −60 °C solution of 6-methoxybenzo[*b*]thiophene (**21a**; 18.13 g, 0.111 mol)[15] in THF (150 mL) was added *n*-BuLi (76.2 mL, 0.122 mol, 1.6 M solution in hexanes) in a dropwise manner. After the mixture was stirred for 30 min, triisopropyl borate (28.2 mL, 0.122 mol) was added dropwise. The resulting mixture was allowed to gradually warm to 0 °C and then partitioned between 1.0 N HCl and EtOAc (300 mL each). The layers were separated, and the organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The white solid was triturated from Et_2O/hexanes and filtered to provide 16.40 g (71%) of boronic acid **21b** as a white solid which was used without further purification: mp 200 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.36 (br s, 2H), 7.86−7.75 (m, 2H), 7.53 (dd, J = 8.1 and 2.0 Hz, 1H), 6.98 (m, 1H), 3.82 (s, 3H); FDMS 208 (M^+; 100).

6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (22). Employing the conditions described in the preparation of benzo[*b*]thiophene **3**, the coupled product **22** was prepared from boronic acid **21b** and 1-(2-(4-bromophenoxy)ethyl)pyrrolidine in 55% yield as an off-white solid following MPLC (53:35:2 THF:hexanes:TEA): mp 151−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 7.29 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.7 Hz, 3H), 4.18 (t, J = 5.9 Hz, 2H), 3.88 (s, 3H), 2.97 (t, J = 5.9 Hz, 2H), 2.71 (br t, 4H), 1.85 (m, 4H); IR ($CHCl_3$) 2941, 1610, 1501, 1479, 1250, 1176, 1059, 830 cm^{-1}; FDMS 353 (M^+). Anal. ($C_{21}H_{23}NO_2S$) C, H, N.

3-Bromo-4-[(1-pyrrolidinyl)methyl]phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone (23a). Employing the conditions described in the preparation of **1a** and **4b**−**g**, product **23a** was prepared from 3-bromo-4-[(1-pyrrolidinyl)methyl]benzoate[31] and benzo[*b*]-thiophene **22** in 55% yield following flash chromatography (95:5 EtOAc:Et_3N): ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.70 (d, J

= 9.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.26 (d, J = 8.3, 2H), 7.02 (d, J = 9.0 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 2H), 2.85 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.2 Hz, 4H), 2.51 (t, J = 6.2 Hz, 4H), 1.80 (m, 8H); FDMS 620 (M + 1). Anal. ($C_{33}H_{35}BrN_2O_3S$) C, H, N.

3-[3-Bromo-4-[(1-pyrrolidinyl)methyl]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (23b). Employing the conditions described in the preparation of **5a**−**d**, ketone **23a** was converted to product **23b** in 72% yield flash chromatography (gradient of 0−5% Et_3N in EtOAc). ^1H NMR ($CDCl_3$) δ 7.34 (m, 6H), 7.03 (d, J = 9.0 Hz, 1H), 6.95 (m, 3H), 4.16 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 2H), 2.95 (t, J = 6.0 Hz, 2H), 2.65 (br s, 4H), 2.60 (br s, 4H), 1.82 (m, 10H); IR (KBr) 3423, 1718, 1607, 1503, 1477, 1403, 1243, 1223, 1179, 1044, 1019, 834, 721 cm^{-1}; FDMS 605 (M^+). Product **23b** was taken on directly to the next step.

3-[3-Bromo-4-[(1-pyrrolidinyl)methyl]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (23c). Employing the conditions described in the synthesis of compound **16b**, methyl ether **23b** was deprotected to afford phenol **23c** as a white crystalline solid in 74% following flash chromatography (gradient of 100% EtOAc to 85% EtOAc:10% MeOH:5% Et_3N): ^1H NMR ($CDCl_3$) δ 7.34 (m, 5H), 7.14 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 1H), 4.12 (br t, J = 6.0 Hz, 2H), 3.78 (s, 2H), 3.02 (s, 2H), 2.95 (t, J = 6.0 Hz, 2H), 2.79 (br s, 4H), 2.63 (br s, 4H), 1.82 (m, 4H), 1.79 (m, 4H), no OH signal observed; FDMS 591 (M^+). The free base of product **23c** was converted to the dioxalate salt: mp 190−192 °C; IR (KBr) 1772, 1724, 1607, 1503, 1471, 1403, 1241, 1179 cm^{-1}. Anal. ($C_{32}H_{35}BrN_2O_2S\cdot C_2H_2O_4\cdot H_2O$) C, H, N.

***N*,*N*-Dimethyl-2-hydroxy-2-(4-benzyloxy)phenylthioacetamide (25).** A −78 °C solution of diisopropylamine (22.9 mL; 174 mmol) in THF (400 mL) was treated with *n*-BuLi (100 mL; 1.6 M in hexanes; 160 mmol). After complete addition, the mixture was stirred at −78 °C for 30 min then at 0 °C for 30 min. The mixture was cooled to −78 °C and treated with a solution of 4-benzyloxybenzaldehyde (30.9 g; 146 mmol) and *N*,*N*-dimethylthioformamide (**24**; 13.7 mL; 160.0 mmol) in THF (50 mL) over 1 h. The reaction mixture was allowed to stir at −78 °C for 16 h, poured into saturated aqueous NH_4Cl (500 mL), and extracted with EtOAc (4 × 400 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 23.0 g of a black oil which solidified on standing. Purification by MPLC (25% EtOAc in hexanes) afforded a solid which was recrystallized from hexanes/EtOAc to afford the product **25** as a tan solid (14.90 g; 49.4 mmol; 34%): ^1H NMR ($CDCl_3$) δ 7.57−7.41 (m, 7H), 6.96 (d, J = 8.6 Hz, 2H), 5.27 (s, 1H), 5.06 (s, 2H), 3.53 (s, 3H), 3.13 (s, 3H), no OH signal observed; IR ($CHCl_3$) 1609, 1508, 1386, 1245, 1230, 1176 cm^{-1}; FDMS 301 (M^+). Anal. ($C_{17}H_{19}NO_2S$) C, H, N.

2-Dimethylamino-6-benzyloxybenzo[*b*]thiophene (26). A solution of alcohol **25** (7.00 g; 23.2 mmol) in CH_2Cl_2 (925 mL) was treated with $MeSO_3H$ (7.50 mL; 116.1 mmol) over 5 min. The reaction was stirred at ambient temperature for 2 h and poured into saturated aqueous $NaHCO_3$ (200 mL). The two layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 7.25 g of a brown solid. Purification by MPLC (5% EtOAc in hexanes) afforded product **26** as a solid (4.15 g; 14.7 mmol; 63%): ^1H NMR ($CDCl_3$) δ 7.60−7.44 (m, 6H), 7.36 (d, J = 4.5 Hz, 1H), 6.95 (dd, J = 8.6 and 2.2 Hz, 1H), 5.96 (br s, 1H), 5.09 (s, 2H), 2.98 (s, 6H); IR ($CHCl_3$) 3008, 2877, 1600, 1566, 1550, 1476, 1436, 1262, 1052 cm^{-1}; FDMS 283 (M^+). Anal. ($C_{17}H_{17}NOS$) C, H, N.

6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone (27). A solution of dimethylamine derivative **26** (2.50 g, 8.80 mmol) and 3-methoxy-4-[(1-pyrrolidinyl)methyl]benzoyl chloride[31] (3.0 g, 1.3 equiv) in chlorobenzene (30 mL) was heated at 135 °C under nitrogen for 2 h. The cooled reaction mixture was diluted with brine (100 mL), neutralized with aqueous NaOH (5.0 M), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (5% Et_3N in EtOAc) afforded product **27** as a brown oil (3.70 g, 7.39 mmol; 84%): ^1H NMR ($CDCl_3$) δ 7.5−6.9 (m, 11H), 5.10 (s, 2H), 3.90 (s, 3H), 3.71 (s, 2H), 2.91 (s, 6H), 2.60 (m, 4H), 1.83 (m, 4H); IR (CHCl3) 1600, 1542, 1477, 1465, 1409, 1264 cm^{-1}; FDMS 500 (M^+). Product **27** was converted to the monooxalate salt. Anal. ($C_{30}H_{32}N_2O_3S\cdot 1C_2H_2O_4\cdot 0.1H_2O$) C, H, N.

6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]-phenyl Ketone (28a). Magnesium turnings (0.30 g; 12.3 mmol) were placed in a two-neck 100 mL round-bottom flask fitted with a reflux condenser and a magnetic stir bar. The whole apparatus was flame-dried and allowed to cool to ambient temperature. Dry THF (22 mL) and a small crystal of iodine were then introduced, followed by slow addition of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (2.75 mL; 3.59 g; 13.3 mmol) while stirring at ambient temperature. The reaction mixture was allowed to warm to a gentle reflux for 2 h or until the magnesium turnings were completely consumed to give a 0.5 M solution of the Grignard reagent. This freshly prepared Grignard solution (7 mL) was added slowly to a stirring solution of intermediate **27** (1.10 g, 2.20 mmol) in THF (5.0 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 2 h before quenching with saturated aqueous NH_4Cl (50 mL) and extraction with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (5:5:90 Et_3N:MeOH:EtOAc) afforded product **28a** as a colorless oil (1.33 g, 2.06 mmol): ^1H NMR ($CDCl_3$) δ 7.60 (d, 1H), 7.47−7.00 (m, 12H), 6.75 (d, 2H), 5.16 (s, 2H), 4.03 (t, 2H), 3.79 (s, 3H), 3.62 (s, 2H), 2.86 (t, 2H), 2.59 (m, 4H), 2.49 (m, 4H), 1.80 (m, 8H). Product **28a** was taken on without further purification.

6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]-phenyl Ketone (28b). Intermediate **28a** (105 mg, 0.16 mmol) in THF (5.0 mL) was treated sequentially with a solution of ammonium formate (25% in H_2O, 3 mL) and 10% Pd-C (50 mg). The resulting mixture was stirred at ambient temperature for 9 h and filtered, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (5:10:85 Et_3N:MeOH:EtOAc) afforded product **28b** as a yellow solid (80 mg, 0.15 mmol; 88%): ^1H NMR ($CDCl_3$) δ 7.56 (d, 2H), 7.32 (s, 1H), 7.24 (d, 1H), 7.20 (d, 1H), 7.15 (d, 2H), 6.98 (s, 1H), 6.79 (d,-1H), 6.60 (d, 2H), 4.08 (t, 2H), 3.80 (s, 2H), 3.75 (s, 3H), 3.01 (t, 2H), 2.99 (m, 4H), 2.82 (m, 4H), 1.87 (m, 8H); FDMS 557 (M + 1). Anal. ($C_{33}H_{36}N_2O_4S\cdot 1.7C_2H_2O_4\cdot 3H_2O$) C, H, N.

6-Hydroxy-3-[3-methoxy-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (28c). Employing the conditions described in the preparation of **5a**−**d**, ketone **28b** was converted to product **28c** in 76% yield following flash chromatography (5:10:85 Et_3N:MeOH:EtOAc): ^1H NMR ($CDCl_3$) δ 7.32 (d, 2H), 7.24 (d, 1H), 7.23 (d, 1H), 7.21 (s, 1H), 6.84 (d, 2H), 6.68 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 4.16 (s, 2H), 4.14 (t, 2H), 3.80 (s, 2H), 3.58 (s, 3H), 2.98 (t, 2H), 2.78 (m, 4H), 2.74 (m, 4H), 1.86 (m, 8H). The free base of product **28c** was converted to the dioxalate salt: IR (KBr) 1719, 1612, 1548, 1504, 1462, 1420, 1241, 1215, 1179, 1032, 721 cm^{-1}; FDMS 543 (M + 1). Anal. ($C_{33}H_{38}N_2O_3S\cdot 2C_2H_2O_4\cdot 0.5H_2O$) C, H, N.

5-Bromopyrid-2-yl 2-(1-pyrrolidinyl)ethyl Ether (30). A solution of 2,5-dibromopyridine (**29**; 20.0 g; 84.4 mmol) in DMF (400 mL) was treated with NaH (5.00 g; 60% in mineral oil; 126.6 mmol). The mixture was cooled to 0 °C and treated slowly with 1-(2-hydroxyethyl)pyrrolidine (10.0 mL; 85.5 mmol). The reaction was stirred for 16 h while warming to room temperature and was poured into brine (300 mL). The mixture was diluted with H_2O (150 mL) and EtOAc (200 mL). The two layers were separated, and the aqueous phase was extracted

with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 25.80 g of an oil. Purification by MPLC (5:15:80 TEA:THF: hexanes) afforded product **30** as a clear oil which solidified on standing (21.50 g; 79.30 mmol; 94%): ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 2.4 Hz, 1H), 7.62 (dd, J = 8.8 and 2.6 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.40 (t, J = 5.8 Hz, 2H), 2.86 (t, J = 5.9 Hz, 2H), 2.75−2.66 (m, 4H), 1.97−1.85 (m, 4H); IR ($CHCl_3$) 2967, 1586, 1472, 1460, 1371, 1351, 1302, 1282, 828 cm^{-1}; FDMS *m/e*: 270, 272 (M^+). Anal. ($C_{11}H_{15}BrN_2O$) C, H, N.

6-Hydroxy-2-[6-[2-(1-pyrrolidinyl)ethoxy]pyrid-3-yl]-benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)-methyl]phenyl Ketone Dioxalate (31b). A −78 °C solution of pyridyl bromide **30** (3.25 g, 12.0 mmol) in THF (40 mL) was treated with *n*-BuLi (1.6 M in hexanes; 8.10 mL, 13.00 mmol). After 1 h, a slurry of $MgBr_2$ [freshly prepared from Mg (365 mg, 15.0 mmol) and 1.3 mL of 1,2-dibromoethane] in THF (20 mL) was added. The reaction mixture was stirred at −78 °C for an additional 10 min, and then the cold bath was removed. After 45 min, the Grignard reagent was added dropwise via a cannula to a 0 °C solution of benzo[*b*]thiophene **27** (5.00 g, 10.00 mmol) in THF (50 mL). The resulting mixture was stirred for 2 h at 0 °C and then was allowed to warm to ambient temperature. After 5 h, the reaction mixture was poured into saturated aqueous NH_4Cl (200 mL). The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Partial purification was achieved by MPLC (gradient of 85:10:5 hexanes:THF: TEA to 75:20:5 hexanes:THF:TEA) to afford 2.90 g (4.48 mmol; 45%) of semi-pure product **31a** as a viscous orange oil: IR ($CHCl_3$) 2966, 1603, 1463, 1285, 1250 cm^{-1}. FAB-HRMS: *m/e*, calcd for $C_{39}H_{42}N_3O_4S$: 648.2896. Found: 648.2889 (M + 1). Product **31a** was taken on without further purification.

Intermediate ketone **31a** (2.90 g; 4.48 mmol) was deprotected using the conditions described in the preparation of compound **28b** to afford phenol **31b** as a yellow foam in 48% yield following PCTLC (gradient of 75:20:5 hexanes:THF:TEA to 60:35:5 hexanes:THF:TEA): ^{1}H NMR ($CDCl_3$) δ 8.12 (d, J = 2.3 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.47−7.39 (m, 2H), 7.20 (s, 2H), 6.77 (d, J = 2.0 Hz, 1H), 6.64 (dd, J = 8.9 and 2.1 Hz, 1H), 6.35 (d, J = 8.7 Hz, 1H), 4.44 (t, J = 5.3 Hz, 2H), 3.74 (s, 3H), 3.63 (s, 2H), 2.95 (t, J = 5.3 Hz, 2H), 2.87−2.79 (m, 4H), 2.69−2.58 (m, 4H), 2.00−1.84 (m, 8H), no phenolic OH observed. A sample of product **31b** was converted to the dioxalate salt: IR (KBr) 2967, 1718, 1602, 1525, 1466, 1413, 1285, 1271, 1207, 1029, 720 cm^{-1}; FDMS 558 (M + 1). Anal. ($C_{32}H_{35}N_3O_4S\cdot 2C_2H_2O_4$) C, H, N.

1-[2-[[5-[6-Hydroxy-3-[[3-methoxy-4-[(1-pyrrolidinyl)-methyl]phenyl]methyl]benzo[*b*]thiophen-2-yl]pyrid-2-yl]oxy]ethyl]pyrrolidine (31c). Employing the conditions described in the preparation of compounds **5a**−**d**, only using DIBAL-H as the reducing agent, product **31c** was prepared from ketone **31b** in 68% yield following PCTLC (gradient of 75:20:5 hexanes:THF:TEA to 60:35:5 hexanes:THF:TEA): ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.4 and 2.3 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 6.63 (d, J = 11.2 Hz, 1H), 6.62−6.58 (m, 2H), 6.45 (dd, J = 8.7 and 2.1 Hz, 1H), 4.49 (t, J = 5.7 Hz, 2H), 4.13 (s, 2H), 3.65 (s, 2H), 3.51 (s, 3H), 2.95 (t, J = 5.7 Hz, 2H), 2.69−2.61 (m, 8H), 1.86−1.78 (m, 8H), no phenolic OH observed. The free base of the product was converted to the dioxalate: IR (KBr) 1719, 1611, 1484, 1468, 1421, 1283, 1243, 1218 cm^{-1}; FDMS 544 (M + 1). Anal. ($C_{32}H_{37}N_3O_3S\cdot 2C_2H_2O_4$) C, H, N.

Supporting Information Available: Experimental details for the synthesis and the physical chemical data for the amino acids used in the preparation of compounds **4b**−**d**, **4f**, **4g**, **23a**, and **27**; physical chemical properties of compounds **1a**, **4b**−**g**, **5a**−**d**, **7a**−**l**, **8a**−**i**, **10a**, **16a**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Plasma pharmacokinetic studies were conducted in male Sprague−Dawley rats in which saline solutions of inhibitor **28c** and **31c** were administered intravenously at 5 mg/kg via tail vein injection. Serial blood samples were obtained from the orbital sinus at 5, 15, 30, 60, 120, 180, and 240 min post dose from 2 or 3 rats per time point. Plasma samples were extracted using Bond Elute C8 (Varian) cartridges and assayed for drug concentrations by an HPLC method using a methanol/30 mM ammonium acetate buffer (pH 4) gradient.
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