Design and Structure−Activity Relationships of Potent and Selective Inhibitors of Blood Coagulation Factor Xa

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The discovery of a series of non-peptide factor Xa (FXa) inhibitors incorporating 3-(*S*)-amino-2-pyrrolidinone as a central template is described. After identifying compound **4**, improvements in in vitro potency involved modifications of the liphophilic group and optimizing the angle of presentation of the amidine group to the S1 pocket of FXa. These studies ultimately led to compound RPR120844, a potent inhibitor of FXa (K_i = 7 nM) which shows selectivity for FXa over trypsin, thrombin, and several fibrinolytic serine proteinases. RPR120844 is an effective anticoagulant in both the rat model of $FeCl_2$-induced carotid artery thrombosis and the rabbit model of jugular vein thrombus formation.

Introduction

Initiation of the blood coagulation cascade by activation of either the intrinsic or extrinsic pathway ultimately leads to the conversion of the zymogen factor X to its activated form, factor Xa (FXa). Once produced, FXa in the presence of factor Va and calcium ions on a phospholipid membrane forms the prothrombinase complex. The prothrombinase complex converts prothrombin to thrombin 300 000-fold more efficiently than FXa alone.[1] Once generated, thrombin converts fibrinogen to fibrin leading to clot formation.[1] The efficiency with which the prothrombinase complex produces thrombin suggests that the inhibition of FXa would represent an effective approach to controlling thrombin levels.[2] Current antithrombotic therapies have limitations such as the need for clinical monitoring, failure to inhibit thrombin generation at the site of thrombus formation, and lack of effectiveness for inactivating clot-bound thrombin.[3] Further studies have suggested that inhibitors of FXa may have a reduced effect on abnormal bleeding when compared to direct or indirect inhibitors of thrombin.[4] Inhibition of FXa may offer a safety advantage over currently available antithrombotic agents.[4]

FXa belongs to the trypsin class of serine proteinases. The X-ray crystal structure of human des(1−45) FXa was solved by Tulinsky and co-workers.[5] The S1 specificity pocket of FXa is homologous to that found for thrombin. The aryl binding pocket or S4 of FXa is formed by the residues Phe174, Tyr99, and Trp215. This pocket is more aromatic in nature than the corresponding region in thrombin which contains the residues Leu99 and Ile174. Another recognition element, located in the back of the aryl binding pocket, has been termed the "cation hole".[6] The carbonyl functions of Glu97 and Lys96, together with a structural water molecule, form the "cation hole", which can bind basically charged groups. The S2 site of FXa is small compared to the same region in thrombin. Recently, the crystal structures of two non-peptide inhibitors, Daiichi's DX-9065a[6] and Banyu's FX-2212,[7] bound to the active site of FXa have been reported.

Our design of FXa inhibitors focused on developing molecules with subunits that interacted with the lipophilic S4 pocket and the S1 specificity pocket of FXa. These two subunits were to be presented via a central scaffold meeting the distance requirements needed for interaction with S1 and S4. The P1 group was chosen based on literature precedent which demonstrated that generally *m*-benzamidines have higher affinity for FXa than *p*-benzamidines.[8] For the P4 group, naphthalene was chosen as modeling studies suggested this group could fill the highly aromatic S4 pocket. The first scaffold identified that accommodated these two groups was 1,3-disubstituted indole **1**. Compound **1** was found to be a modest inhibitor of FXa (K_i = 0.9 μM) with selectivity over thrombin and trypsin. Several attempts to improve on the activity of indole **1** by introducing H-bonding groups to potentially interact with Gly216 or Gly218 of the β-sheet or by replacing the naphthalene with other lipophilic groups were not successful. A search for alternative scaffolds, which possessed better solubility, synthetic flexibility, and the possibility of interacting with the β-sheet, led to the identification of a novel series of FXa inhibitors, incorporating 3-(*S*)-amino-2-pyrrolidinone as the central scaffold.

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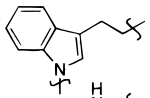
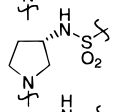
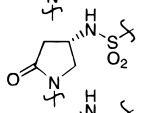
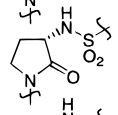
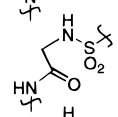
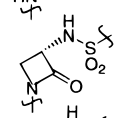
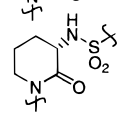
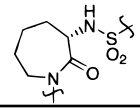
Table 1. Central Scaffolds

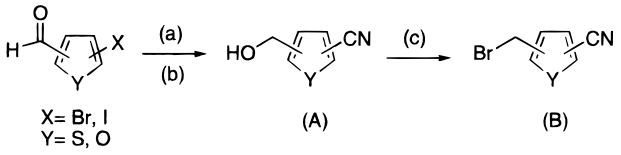
compound #		(Ki's in μM) factor Xa	thrombin	trypsin
1		0.9	>4.0	~2.9
2		>10	>4.0	>2.9
3		9.8	>4.0	>2.9
4		0.23	>4.0	~2.9
5		0.34	0.63	0.08
6		9.9	>4.0	>2.9
7		1.3	>4.0	>2.9
8		7.0	>4.0	>2.9

Chemistry

The enantiomerically pure 3-amino lactam scaffolds (Table 1) were prepared from either direct methods or known literature procedures.[9] Both enantiomers of the 3-amino-2-pyrrolidinone and 4-amino-2-pyrrolidinone were originally derived from the appropriately protected aspartic acid derivatives. As an example, the template used for compound **3** was prepared from N-Boc-L-Asp-(O-*t*-Bu)-OH. The α-acid functionality was reduced to the alcohol via its isobutyl mixed anhydride and then oxidized under Swern conditions to the aldehyde.[10] Under reductive amination conditions,[11] Boc-L-Asp-(O-*t*-Bu)-H was condensed with *m*-cyanobenzylamine hydrochloride[12] to give the secondary amine. The product was then cyclized to Boc-4-(*S*)-amino-2-pyrrolidinone under acidic conditions. The other scaffolds were easily obtained by a combination of similar techniques or from commercial sources.

The various sulfonyl chlorides used to prepare compounds listed in Tables 2 and 3 were synthesized from arylsulfonic acids or via a lithiation/sulfonation procedure[13] from the corresponding aryl bromide or arylstannane precursors.[9b] Several of the naphthalene-derived sulfonic acids were converted directly to their sulfonyl chlorides using phosphorus oxychloride or thionyl chloride.[14] Many of the naphthyl and biphenyl/biarylsulfonyl chlorides were obtained from the bromide or stannane intermediate using butyllithium followed by a sulfur dioxide quench and subsequent reaction with sulfuryl chloride.

Scheme 1. Synthesis of Heteroaryl Nitriles[a]



[a] (a) $NaBH_4$, THF; (b) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF; (c) CBr_4, PPh_3.

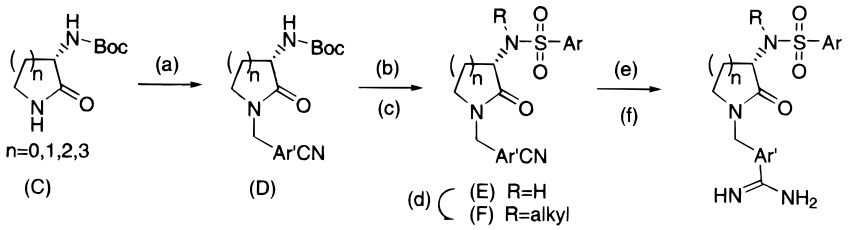
The heteroaryl amidines (Table 6) were prepared from their respective heteroaryl nitrile methyl halides **B** as illustrated in Scheme 1. Thiophene-3-carboxaldehyde serves as an illustrative example in its conversion to the 4-(bromomethyl)thiophene-2-carbonitrile. A three-step procedure involves reduction of the aldehyde, cyanation via a palladium-mediated cross-coupling with zinc cyanide[15] to generate nitrile intermediate **A**, and conversion of the alcohol to the methyl bromide (CBr_4/PPh_3).

The synthesis of target compounds proceeded via a modular approach. Boc-3-(*S*)-aminopyrrolidin-2-one (**C**, $n = 1$), exemplified in Scheme 2, was readily obtained by cyclization of commercially available N-α-Boc-L-2,4-diaminobutyric acid. N-Alkylation of the lactam ring nitrogen (NaH or NaHMDS) with the requisite heteroaryl halide electrophiles provided intermediates **D** and allowed for incorporation of the various P1 units.[16] A typical reaction sequence involves deprotection (HCl/EtOAc or TFA/CH_2Cl_2), sulfonylation, and imidate formation under Pinner conditions[17] (HCl/EtOH) followed by ammonolysis (NH_3/MeOH). Amidine formation could also be achieved using an alternate method via a thioamide intermediate (H_2S/MeI/NH_4OAc).[18] Additionally, prior to nitrile conversion, the sulfonamide nitrogen of intermediates **E** could be alkylated with various electrophiles (**E** → **F**) (Table 5).

Results and Discussion

Figure 1 shows inhibitor **1** docked in the active site of FXa. In this model, the scaffold lies near the β-sheet but does not appear to have interactions in this region. Additionally from this model, the phenyl ring of the indole does not have contacts with the active site. We began to search for monocyclic templates to replace indole with functional groups which could potentially form H-bonds with the β-sheet of FXa. Table 1 shows a scan of templates which contain H-bond donor and acceptor groups (sulfonamides and carbonyl groups). Replacement of indole with a pyrrolidine, **2,** results in a 10-fold loss (comparison of K_i's) in FXa activity. To remove the basic center from compound **2**, two pyrrolidinone regioisomers **3** and **4** were synthesized. Sulfonamide **3**, derived from 4-(*S*)-amino-2-pyrrolidinone, was 10-fold less potent than indole **1**. The 3-(*S*)-amino-2-pyrrolidinone **4** resulted in an improvement in potency ($K_i = 0.23$ μM) relative to the indole **1**. Comparing the activity of the two pyrrolidinones suggests that the location of the ring carbonyl plays an important role in activity. Analogues containing lactams of other ring sizes, compounds **6**−**8**, were also investigated. None of these had better activity than the five-membered ring

Scheme 2. Synthesis of Final Compounds[a]



[a] (a) NaH, THF:DMF (10:1), 0 °C; (b) HCl, EtOAc; (c) $ArSO_2Cl$, Et_3N, CH_2Cl_2; (d) K_2CO_3, DMF, R-Br; (e) HCl, EtOH; (f) NH_3, MeOH.

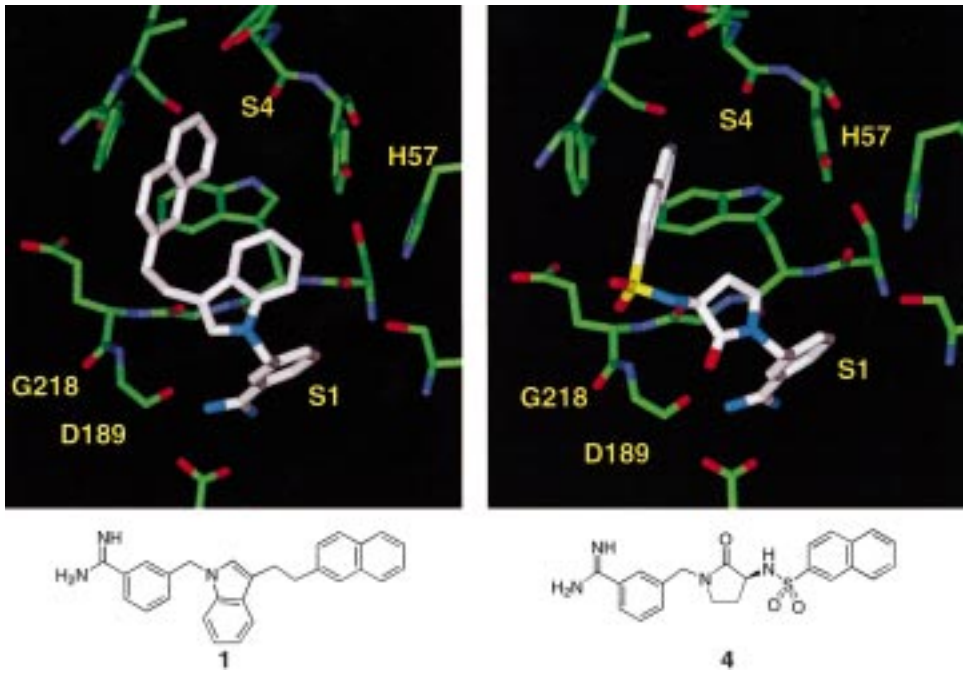


Figure 1. Binding model of indole **1** (left) in the FXa active site compared with pyrrolidinone **4** (right) in the FXa active site. FXa coordinates[5] available on the Brookhaven database: 1HCG.

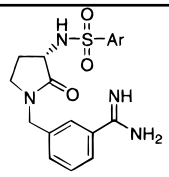
analogue. Additionally, the pyrrolidinone was compared to glycine **5**. While the potency of these two derivatives is similar, the glycine analogue lacked selectivity for FXa over thrombin and trypsin.

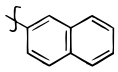
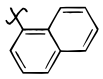
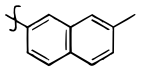
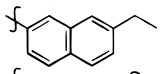
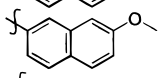
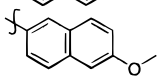
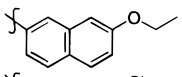
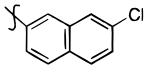
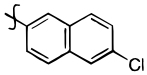
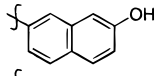
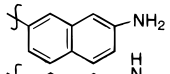
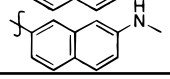
One of the shortcomings reported for some direct inhibitors of thrombin is the lack of selectivity against serine proteinases involved in fibrinolysis.[19] Inhibition of the fibrinolytic enzymes (plasmin and tPA) and activated protein C (aPC) has been identified as a potential liability resulting in the compromise of hemostasis. To further assess the 3-amino-2-pyrrolidinones as FXa inhibitors, compound **4** was assayed against several serine proteinases. Pyrrolidinone **4** was found to display selectivity for FXa over thrombin (K_i > 4 000 nM), trypsin (K_i = 2 900 nM), aPC (K_i = 7 000 nM), plasmin (K_i = 4 700 nM), and tPA (K_i > 10 000 nM). With the potency and selectivity profile observed for compound **4**, further optimization studies were undertaken.

Figure 1 shows the proposed binding model of compound **4** docked into the active site of FXa.[5] In this model, the pyrrolidinone carbonyl oxygen is within H-bonding distance of the Gly218 NH. The orientation of the sulfonamide oxygens suggests that they are pointing away from the β-sheet and facing out toward the solvent. A primary role of the sulfonamide linkage may be to direct the naphthalene group into the aryl binding pocket.

The docked structure, Figure 1, also suggests that the naphthalene group does not completely fill the aryl binding pocket. Initial SAR studies focused on substituted naphthalenes or biaryl ring systems. Table 2 depicts several attempts to improve the potency of compound **4** with substituted naphthalene groups. A preference for the 2-naphthalene moiety was established by the relative loss in potency observed for the 1-naphthalene **9**. Compounds **10**−**19** were synthesized to probe the effect of increasing the size of the naphthalene group in the aryl binding pocket. The methyl derivative **10** was found to be 2-fold more potent than the parent compound **4**. Incorporating a methoxy group showed a preference for the 7-position over the 6-position. The 7-methoxy **12** exhibited a 5-fold improvement in potency (K_i = 0.047 μM) relative to compound **4,** maintaining selectivity over thrombin and trypsin. The corresponding 6-methoxy analogue was 20-fold less active than compound **12**. Increasing the length of the alkoxy group by one carbon, compound **14**, resulted in a considerable loss in potency. Compounds **15** and **16** show the effect on activity of substituting the 6- and 7-positions with chlorine. In contrast to the methoxy substitutions, both chloro compounds were found to be essentially equipotent. Several polar groups were also examined on the naphthalene ring. The 7-hydroxyl analogue **17** was 10-fold less active than compound **12**. The 7-aniline **18** retained good activity for FXa with a K_i = 0.12 μM,

Table 2. Naphthalene Optimization



compound #	Ar	(Ki's in μM) factor Xa	thrombin	trypsin
4		0.23	>4.0	~2.9
9		0.75	>4.0	>2.9
10		0.10	1.34	1.1
11		0.37	1.6	1.6
12		0.047	1.4	0.85
13		1.0	0.9	>2.9
14		0.28	1.9	>2.9
15		0.078	1.2	2.0
16		0.070	1.5	>2.9
17		0.50	>4.0	>2.9
18		0.12	2.6	1.3
19		0.25	>4.0	1.5

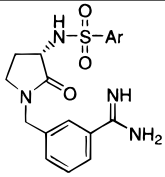
whereas the methylanilino **19** resulted in a drop in FXa potency of $K_i = 0.25$ μM.

Another approach to improving the potency of compound **4** involves replacement of naphthalene with biphenyl ring systems (Table 3). Compounds **20** and **21** were prepared to find the preferred location of the second phenyl ring. Of the two regioisomers, the 1,4-biphenyl analogue **21** exhibited better activity. Substitution of the distal ring with either methyl (**22**) or methoxy (**23** and **24**) offered only modest potency enhancements, with compound **23** exhibiting a $K_i = 0.10$ μM for FXa. Linking the two aryl groups with either a carbon (**25**) or oxygen (**26**) did not lead to improved FXa activity. From the SAR studies shown in Tables 2 and 3, the 7-methoxynaphthalene analogue **12** was identified as the lead structure for further optimization. Compound **12** has selectivity for FXa over thrombin (K_i > 1 400 nM), trypsin (K_i = 853 nM), aPC (K_i = 1 200 nM), plasmin (K_i = 4 700 nM), and tPA (K_i > 10 000 nM).

During the course of our research effort, the relationship between the stereochemistry of the 3-amino-2-pyrrolidinone scaffold and FXa activity was investigated (Table 4). When the sulfonamide nitrogen is unsubstituted, both the (*S*)- and (*R*)-3-amino-2-pyrrolidinones **12** and **27** were equipotent. However, when the sulfonamide nitrogen was alkylated with a methyl group, a clear stereochemical preference for FXa activity was observed. Methylation of the (*S*)-isomer **28** increased FXa potency 2-fold, whereas methylation of the (*R*)-isomer **29** resulted in a 10-fold loss in potency. From these results, the (*S*)-isomer was chosen for further optimization studies.

A series of N-alkylated analogues was prepared based on the results found for methylsulfonamide **28** (Table 5). This region was probed with small aromatic and alkyl groups. A set of aryl rings was examined, compounds **31**−**35**, which contained neutral H-bond-donating or H-bond-accepting groups. The most potent from

Table 3. Biaryl Ring System Optimization



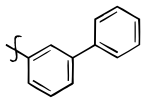
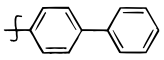
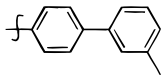
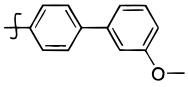
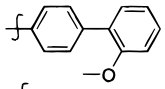
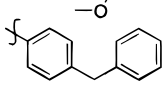
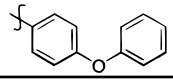
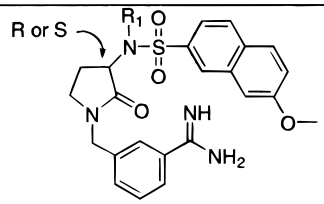
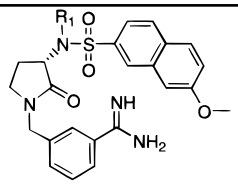
compound #	Ar	(Ki's in μM) factor Xa	thrombin	trypsin
20		0.44	>4.0	>2.9
21		0.16	>4.0	>2.9
22		0.12	>4.0	>2.9
23		0.10	2.5	>2.9
24		0.19	>4.0	>2.9
25		1.1	>4.0	>2.9
26		0.38	>4.0	>2.9

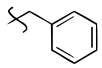
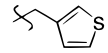
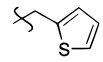
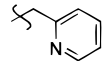
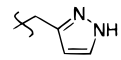
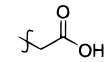
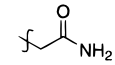
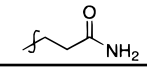
Table 4. Effect of Stereochemistry on Activity



compound #	stereochem.	R_1	(Ki's in μM) factor Xa
12	S	H	0.047
27	R	H	0.047
28	S	CH_3	0.022
29	R	CH_3	0.440

Table 5. N-Alkylation of the 3-Sulfonamide Group

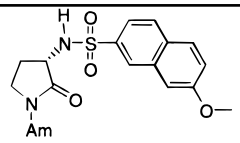


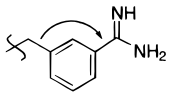
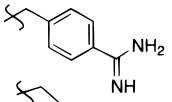
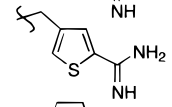
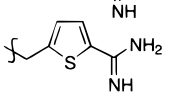
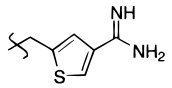
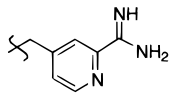
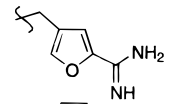
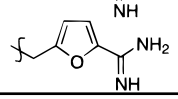
compound #	R_1	(Ki's in μM) factor Xa	thrombin	trypsin
28		0.022	1.1	0.7
30		0.043	0.88	1.4
31		0.041	0.44	1.8
32		0.019	0.36	1.08
33		0.034	0.97	1.94
34		0.031	1.16	1.94
35		0.021	1.08	1.39
36		0.12	>4.0	>2.9
37		0.025	1.44	1.0
38		0.056	1.5	2.0

this set was compound **32** containing a 3-thiophene moiety. Amide and carboxylic acid derivatives were also investigated (compounds **36**−**38**). The acetamide **37** had a K_i = 0.025 μM. No analogue was found which improved on in vitro potency over the *N*-methyl derivative **28**. The role of small groups such as methyl and acetamide or small heterocycles is most likely conformational, stabilizing the bound conformation of the inhibitor rather than forming additional interactions with the FXa active site.

In an effort to optimize the amidine interaction with Asp189 in the S1 pocket, the angle of presentation of the P1 group was varied between 120° and 180° using the heterocyclic amidines as shown in Table 6.[20] The angles listed represent the calculated angle between the amidine carbon and the benzylic carbon of the side chain.[21] Placing the amidine group in the para position, **39**, resulted in a 20-fold loss in FXa activity. Compounds **40**−**42** contain thiophene amidine regioisomers. The calculated angle shows that compound **41** is more "para-like", while **40** and **42** are closer to "meta". Compound **40** (K_i = 0.011 μM) had the best activity, a 4-fold improvement over the *m*-benzamidine **12**. The calculated angle between the methylene bearing the side chain and the amidine carbon for compounds **40** and **42** is similar. Despite this, the activity for these two analogues differs by nearly 1 order of magnitude. One possible explanation for the enhanced activity seen for compound **40** is favorable van der Waals contacts between the sulfur atom and Val213 side chain in the S1 pocket. Other heteroaryl amidines were also explored. Attempts to form complementary hydrogen bonds near Asp189 were probed using pyridine and furan rings (**43**−**45**). Again factors other than angle play a role in activity for these heterocycles as furan **45** offered no improvement in FXa potency.

Table 6. Heterocyclic Amidines

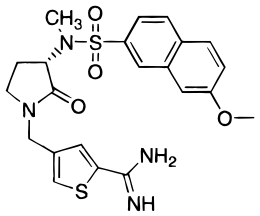


compound #	Am	angle*	(Ki's in μM) factor Xa	thrombin	trypsin
12		120	0.047	1.4	0.85
39		180	0.97	>4.0	2.3
40		140	0.011	1.3	0.5
41		147	0.22	n.d.	n.d.
42		140	0.083	2.4	0.94
43		120	0.11	2.04	2.84
44		153	0.18	>4.0	>2.9
45		126	0.57	>4.0	>2.9

From the SAR investigated, several structural modifications were found which enhanced FXa activity. The indole scaffold was replaced by a 3-(*S*)-sulfonamido-2-pyrrolidinone resulting in a more potent FXa inhibitor with good selectivity. The 7-methoxynaphthalene group was found to bind optimally in the S4 binding pocket. N-Methylation of the sulfonamide nitrogen improved potency for analogues containing the (*S*)-enantiomer of the scaffold. Finally, FXa activity was further enhanced by replacing the *m*-benzamidine with an appropriately substituted thiophene amidine. Combination of the optimal groups from the inhibitor design process described above resulted in RPR120844 (Table 7). RPR-120844 is a potent inhibitor of FXa (K_i = 0.007 μM). Additionally, RPR120844 is selective for FXa over thrombin and trypsin and displays high selectivity for FXa versus plasmin, tPA, and aPC.

Inhibitor RPR120844 was docked into the FXa active site as shown in Figure 2. The proposed binding models for inhibitors **4** and RPR120844 are quite similar. The P1 amidine group forms twin−twin hydrogen bonds with the Asp189 side chain carboxyl group and one additional hydrogen bond with the Gly218 oxygen. The pyrrolidinone carbonyl oxygen and one of the two sulfonamide oxygens form weak hydrogen bonds with

Table 7. Activity and Selectivity of RPR120844



RPR120844

enzyme	Ki (nM)	selectivity enzyme/FXa
Xa	7	
thrombin	1,000	140
trypsin	530	76
aPC	2,400	342
plasmin	4,400	630
tPA	8,600	>1,200

the Gly218 NH. The remaining oxygen of the sulfonamide group as well as the sulfonamide methyl group are oriented away from the protein surface. Although the pyrrolidinone ring lies directly over Gly216, hydrogen-bonding contacts with this residue are not formed. The naphthyl group lies deep within the S4 binding pocket with the methoxy group oriented favorably toward the face of Trp215 side chain.

RPR120844 was cocrystallized with trypsin (Figure 3) and confirmed several of the observations found from the modeling study with FXa. Trypsin has been used as a surrogate for FXa to determine binding conformations.[22] The inhibitor is tightly bound in the P1 pocket forming a salt bridge between the amidine group and Asp189 carboxylate group. The amidine also forms H-bonds with Gly219 carbonyl oxygen atom, Ser190 hydroxyl oxygen, and a water molecule. The sulfur atom makes a van der Waals contact with the Val213 side chain in the P1 pocket. The carbonyl oxygen of the pyrrolidinone ring is oriented toward Gly219 but lies 3 Å away and does not appear to form a strong H-bond. One of the sulfonamide oxygens is pointing toward Ser217 but also does not H-bond to this residue. The 7-methoxynaphthalene is in the lipophilic pocket with the methoxy group pointing toward Trp215. The greater potency of RPR120844 for FXa over trypsin can be explained by a better fit of the methoxynaphthalene group in the aryl binding pocket of FXa as compared with the same domain in trypsin. In FXa, the methoxynaphthalene can π-stack with the Phe174 and Try99, whereas in trypsin the group is near Ile174 and Leu99.

RPR120844 was found to double-activate partial thromboplastin time (APTT) in vitro at concentrations of 1.45, 1.48, and 0.74 μM in plasma obtained from humans, dogs, and rats, respectively. Antithrombotic efficacy of intravenously administered RPR120844 was assessed in arterial (rat) and venous (rabbit) thrombosis models. At 0.1 and 0.3 mg/kg iv bolus administration, RPR120844 maximally increased APTT 1.7- and 2.4-fold above control values, respectively. When administered iv to rats, RPR120844 (3 mg/kg iv bolus + 300 μg/kg/min constant infusion) increased time to occlusion from 18 to 60 min in a rat model of $FeCl_2$-induced carotid artery thrombosis.[23] In this study, thrombus mass was reduced from 5.5 mg (vehicle) to 1.4 mg. In a rabbit model of venous thrombosis, RPR120844, dose-dependently inhibited jugular vein thrombus formation.[24] At a dose of 100 μg/kg/min, RPR120844 decreased thrombus mass from 42 mg (vehicle) to 12 mg. At this dose, peak plasma levels of 2.4 μM were obtained. RPR120844 was also tested orally in rats. At a dose of 50 mg/kg, inhibitor RPR120844 obtained plasma levels of 500 and 260 nM, respectively.

Conclusion

The 3-(*S*)-amino-2-pyrrolidinone scaffold has been identified for the design of noncovalent inhibitors of FXa. The 2-pyrrolidinone scaffold supported a number of structural modifications to the P1 and P4 groups while maintaining activity for FXa. These inhibitors also displayed good selectivity for FXa over related serine proteinases. RPR120844, resulting from this research, was effective in both rat and rabbit models of thrombosis. Further optimization studies with this scaffold are under investigation in these laboratories.

Experimental Section

Enzyme Assays. Human FXa, thrombin, and activated protein C (aPC) were obtained from Enzyme Research Laboratories, Inc. (South Bend, IN). Bovine trypsin was obtained from Sigma Chemical Co. (St. Louis, MO). Plasmin was purchased from Pharmacia Hepar (Franklin, OH). Tissue-plasminogen activator (tPA; Actives) was obtained from Genentech (San Francisco, CA). The chromogenic substrates used were Spectrozyme fXa (American Diagonostica Inc., Greenwich, CT) for FXa; Pefachrome TH (Centerchem, Inc., Stamford, CT) for thrombin; S-2765 (Diapharma Group Inc., Franklin, OH) for trypsin; Pefachrome-tPA (Centerchem Inc.) for tPA. The chromogenic substrate S-2366 (Diapharma Group Inc.) was used for assay of both plasmin and aPC.

FXa, thrombin, and plasmin were assayed in a buffer containing 0.05 M Tris, 0.15 M NaCl, 0.1% PEG-8000, pH 7.5. Trypsin and aPC were assayed in the aforementioned buffer with addition of 0.02 M $CaCl_2$. tPA was assayed in the first buffer, but the PEG-8000 was replaced with 0.1% (w/v) BSA (bovine serum albumin; Sigma).

The final substrate concentrations in the reactions were 200, 50, 250, and 500 μM for Spectrozyme fXa, Pefachrome TH, S-2765, and Pefachrome-tPA, respectively. The final concentrations of S-2366 for the plasmin and aPC assays were 300 and 500 μM, respectively. All enzyme assays were carried out at room temperature in 96-well microtiter plates with a final enzyme concentration of 1 nM. Compound dilutions were added to the wells containing buffer and enzyme and preincubated for 30 min. The enzyme reactions were initiated by the addition of substrate, and the color developed from the release of *p*-nitroanilide from each chromogenic substrate was monitored continuously for 5 min at 405 nm on a Thermomax microtiter plate reader (Molecular Devices, Sunnyvale, CA). Under the experimental conditions, less than 10% of the substrate was consumed in all assays. The initial velocities measured were used to determine the amount of inhibitor required to diminish 50% of the control velocity, which was defined as IC_{50} of the inhibitor. Assuming the kinetic mechanisms were all competitive, the apparent K_i values were then calculated according to the Cheng−Prusoff equation: $K_i = IC_{50}/1 + [S]/K_m$.

Coagulation Assay. Activated partial thromboplastin time (APTT) was measured with a MLA Electra 800 automatic coagulation timer (Orthodiagnostics, NJ). Citrated human (George King Biomedical Inc., Overland Park, KS), dog (mongrel; Covance Research Product, Alice, TX), and rat (Sprague−Dawley; Charles River) plasma were used in the assays. One hundred microliters of freshly thawed plasma was mixed with 100 μL of compound dilutions followed by automatic addition of 100 μL of actin-activated cephaloplastin reagent (Dade, Miami, FL) and 100 μL of 0.035 M calcium chloride to start the clot formation. Anticoagulant activity of a compound was evaluated with the concentration required for doubling the plasma clotting time.

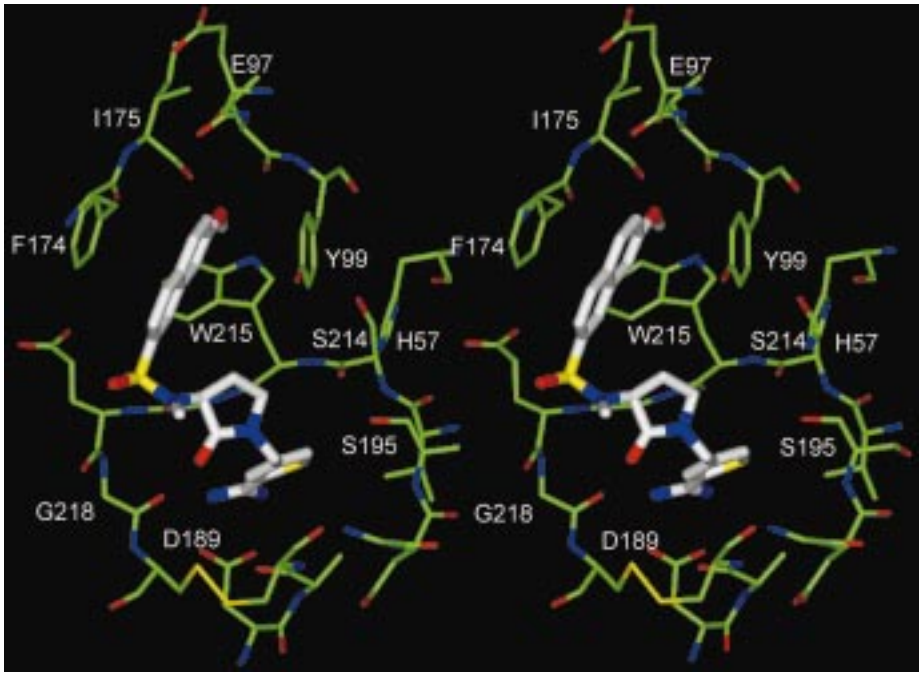


Figure 2. Proposed binding model of RPR120844 in the FXa active site. FXa coordinates[5] available on the Brookhaven database: 1HCG.

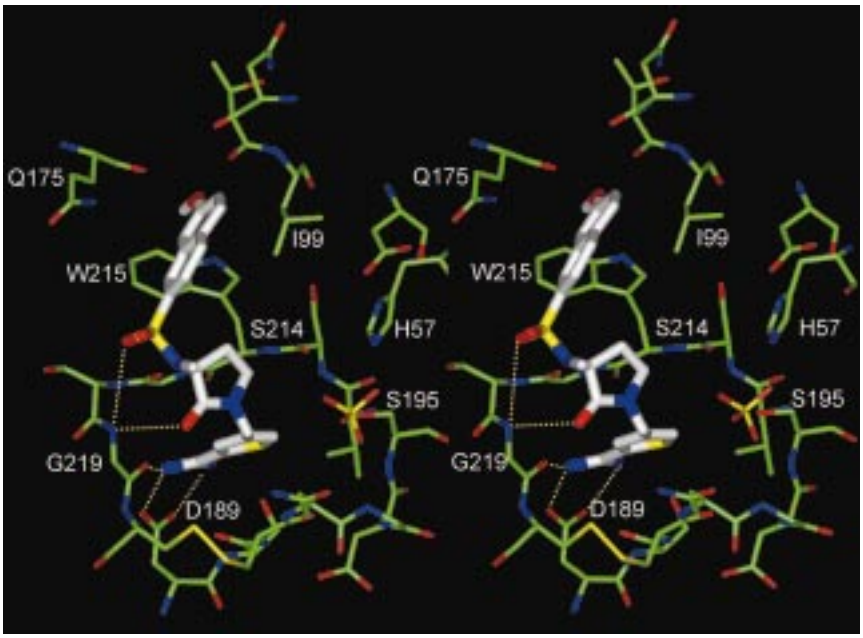


Figure 3. X-ray of the RPR120844/trypsin complex at 1.9 Å.

Molecular Modeling. The inhibitor RPR120844 was flexibly docked into the FXa active site using an automated protocol developed in-house.[20] In this method, lower-energy conformations of the ligand are generated on the fly using a modifed version of a rule-based method implemented in ChemX. Using ChemDBS-3D with in-house customization, an attempt is made to fit each conformation in turn onto a predefined, minimal pharmacophore model using a steric shell of the active site as an added constraint. Matching conformations are then passed to the program DISCOVER for optimization in a partially relaxed active site model using the CFF97 force field. The resulting docked complexes are scored on the basis of total force field energy. This method has been validated against several known protein/ligand systems, having reproduced the correct bound conformation of the ligand within 0.7 Å rms.[20]

Trypsin/Inhibitor RPR120844 Crystal Structure Determination. Crystallization and inhibitor soaking: Bovine pancreatic trypsin (Sigma T8003) was solubilized in 1 mM $CaCl_2$, 60 mM benzamidine, 50 mM Mes-NaOH (pH 6.0) buffer to a final concentration of 30 mg/mL. The hanging drops crystallization method was used at 19 °C. Single crystals were obtained with ammonium sulfate (1.4−1.8 M), pH 6.0, in the "open" form ($P2_12_12_1$, a = 63.6 Å, b = 63.7 Å, c = 68.9 Å) for which the binding site is free of any contact with crystallographic symmetry-related molecules.

RPR120844 is scarcely soluble in water or ammonium sulfate solution, but it was still possible to prepare a 100 μM solution in 2.5 M ammonium sulfate, 50 mM Mes-NaOH, pH 6.0. The crystals were soaked in 50 μL of this solution for a couple of days to allow proper exchange of the benzamidine by the "low"-affinity inhibitor RPR120844.

Data collection and processing: The crystal was mounted in a glass capillary and exposed to X-ray radiation at room temperature on a FR591 rotating anode generator (Nonius, The Netherlands) equipped with a DIP2020K image plate

detector (Mac Science, Japan). Data images were processed using DENZO and SCALEPACK (Otwinowski & Minor, 1997), and structure refinement was performed using X-PLOR (Brünger, 1992). The trypsin structure used as a starting point is the uncomplexed 1.55 Å form (2ptn Protein Data Bank entry) (Walter et al., 1982).

Chemistry. All starting materials, reagents, and solvents were used as received from commercial sources except for *N*-bromosuccinimide which was recrystallized from water and dried under vacuum. In general, reactions were performed under an inert atmosphere such as nitrogen or argon. Workup means drying over sodium or magnesium sulfate, filtering, and concentrating in vacuo. Flash column chromatography of intermediates was performed using 230−400 mesh silica gel 60 (E. Merck). Proton NMRs were recorded on a Bruker ARX 300 MHz or ACF 300 spectrometer, and mass spectra were obtained using a Varian VG-70SE spectrometer. Elemental analyses were performed by Quantitative Technologies of Whitehorse, NJ.

Final products were generally purified by preparative reverse-phase HPLC. Purification was performed on a Rainin SD-1 Dynamax system with a 2-in. C-18 reverse-phase Dynamax 60 Å column using a gradient of about 5−30% acetonitrile/0.1% TFA water to 70−100% acetonitrile/0.1% TFA water over a 20−40-min period at a flow rate of 40−50 mL/min. Fractions containing the desired material were concentrated and lyophilized to obtain the final products as white solids.

Preparation of [1-(3-Cyanobenzyl)-2-oxopyrrolidin-4-(*S*)-yl]carbamic Acid *tert*-Butyl Ester (benzonitrile precursor to compound 3). Boc-L-Asp(O-*t*-Bu)-OH (18.7 g, 64.8 mmol) is dissolved in 65 mL of THF and cooled to −10 °C. The solution is treated with *N*-methylmorpholine (7.48 mL, 68.0 mmol) and stirred for 5 min. To the solution is added dropwise isobutyl chloroformate (8.82 mL, 68.0 mmol). After the addition is completed, the solution is stirred for 30 min and then filtered through a pad of Celite. The collected solution is cooled to −10 °C. To the solution is added sodium borohydride (3.80 g, 100 mmol) predissolved in 100 mL of water. The solution is stirred at 0 °C for 1 h and then at room temperature for 1 h. The solution is poured into a separatory funnel and diluted with 800 mL of EtOAc. The organic layer is washed with 1 N HCl solution, water, saturated $NaHCO_3$ solution, and saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (20% EtOAc/hexanes to 33% EtOAc/hexanes), and the alcohol (12.2 g, 44.3 mmol) is isolated as an oil: ^{1}H NMR ($CDCl_3$) δ 5.26 (bs, 1H), 3.98 (m, 1H), 3.68 (bs, 2H), 2.82 (bs, 1H), 2.54 (m, 2H), 1.45 (bs, 18H).

To a solution of oxalyl chloride (6.63 mL, 76 mmol) in 110 mL of CH_2Cl_2 at −65 °C is added a solution of methyl sulfoxide (12.4 mL g, 175 mmol) in 25 mL of CH_2Cl_2 dropwise over 20 min. The alcohol intermediate (12.2 g, 44.3 mmol) in 50 mL of CH_2Cl_2 is added dropwise to the mixture over 20 min. The reaction mixture is stirred at −65 °C for 15 min; then triethylamine (40.5 mL, 290 mmol) in 110 mL of CH_2Cl_2 is added over 20 min. The reaction mixture is stirred at −70 °C for 40 min. The solution is poured into 400 mL of Et_2O and 150 mL of 0.5 N $KHSO_4$ solution. The resulting mixture is poured into a separatory funnel, and the layers are separated. The organic layer is washed with 150 mL of 0.5 N $KHSO_4$ solution (2×), then concentrated to one-half volume, diluted with Et_2O, and washed again with water and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude aldehyde (12.5 g) is used in the next step without purification: ^{1}H NMR ($CDCl_3$) δ 9.63 (s, 1H), 5.60 (bs, 1H), 4.32 (m, 1H), 2.92 (dd, 1H), 2.74 (dd, 1H), 1.46 (s, 9H), 1.44 (s, 9H).

To a solution of Boc-L-Asp(O-*t*-Bu)-H (6.25 g) dissolved in 50 mL of methanol over 4 Å molecular sieves are added *m*-cyanobenzylamine hydrochloride[12] (8.5 g, 50.4 mmol) and NMM (5.6 mL, 50.4 mmol). The solution is stirred for 40 min. After this time, a solution of zinc chloride (1.55 g, 11.4 mmol) in 25 mL of MeOH is added followed by portionwise addition of sodium cyanoborohydride (1.43 g, 22.8 mmol). The mixture is stirred overnight. After this time, the mixture is filtered through a pad of Celite, washed with MeOH, and concentrated in vacuo. The residue is diluted with EtOAc and 20 mL of 1 N NaOH, 100 mL of water is added, and the layers are separated. The aqueous layer is washed with EtOAc (2×). The combined organic layers are washed with water and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes), and the secondary amine product (4.60 g, 11.8 mmol) is obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.56 (m, 2H), 7.40 (m, 1H), 5.14 (bs, 1H), 4.05 (m, 1H), 3.86 (m, 2H), 2.72 (m, 2H), 2.47 (m, 2H), 1.62 (bs, 1H), 1.42 (bs, 18H).

To a solution of the secondary amine (9.55 g, 24.5 mmol) in 220 mL of toluene is added 24 mL of HOAc. The resulting mixture is heated at reflux for 1.5 h, then cooled, and concentrated in vacuo. The residue is purified by column chromatography (30% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2), and the [1-(3-cyanobenzyl)-2-oxopyrrolidin-4-(*S*)-yl]carbamic acid *tert*-butyl ester (6.30 g, 20.0 mmol) is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.59 (m, 1H), 7.51 (m, 1H), 7.46 (m, 2H), 4.92 (bs, 1H), 4.49 (s, 2H), 4.27 (m, 1H), 3.60 (dd, 1H), 3.17 (dd, 1H), 2.82 (dd, 1H), 2.35 (dd, 1H), 1.43 (s, 9H).

General Procedures for the Preparation of Central Scaffolds (Table 1) as Boc-Protected 3-Amino Lactam Ring Systems (intermediates C and D). Boc-3-(*S*)-Aminoazetidin-2-one (C, *n* = 0; template for compound 6). To a solution of Boc-L-serine (10.3 g, 50 mmol) in 75 mL of H_2O:*t*-BuOH (2:1) are added methoxyamine hydrochloride (23 g, 75 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.6 g, 50 mmol). After 2 h, the solution is saturated with NaCl and extracted with EtOAc. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The resulting crude amide is dissolved in 50 mL of pyridine and cooled to 0 °C. To the solution is added methanesulfonyl chloride (7.44 g, 65 mmol). After 1 h, the solution is poured into 100 mL of cold 1 N HCl and diluted with EtOAc. The layers are separated, and the organic layer is washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated.

The crude mesylate intermediate is dissolved in 50 mL of acetone and added dropwise to a solution of K_2CO_3 (20.7 g, 150 mmol) in 900 mL of acetone at reflux. After 1 h, the solution is cooled to room temperature. The solution is filtered through Celite and then washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The resulting solid is dissolved in 20 mL of THF and added dropwise to an ammonia solution containing sodium (2.6 g, 113 mmol) at −78 °C. After the blue color has dissipated, the solution is stirred for an additional 10 min. To the reaction mixture is added NH_4Cl (13.4 g, 250 mmol), and the solution is allowed to warm to room temperature. The solution is filtered and concentrated. The residue is recrystallized from EtOAc to give the Boc-3-(*S*)-aminoazetidin-2-one (2 g, 11 mmol) as a white solid: ^{1}H NMR (acetone-d_6) δ 6.96 (bs, 1H), 6.63 (bs, 12H), 4.81 (bs, 1H), 3.40 (m, 1H), 3.21 (m, 1H),1.40 (s, 9H).

Boc-3-(*S*)-Aminopyrrolidin-2-one (C, *n* = 1; template for compounds 4, 9−26, 28, 30−45, and RPR120844). To a solution of *N*-α-Boc-L-2,4-diaminobutyric acid (25 g, 115 mmol), Et_3N (35 g, 344 mmol), and hydroxybenzotriazole (19.3 g, 143 mmol) in 0.5 L of THF is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (27.4 g, 143 mmol). The solution is heated to 60 °C over 15 min. A white precipitate forms, and the solution is kept at 60 °C for 4 h. After this time, the solution is filtered and concentrated in vacuo. The crude product is purified by column chromatography (1% MeOH/CH_2Cl_2 to 3% MeOH/CH_2Cl_2) to afford Boc-3-(*S*)-aminopyrrolidin-2-one (19.6 g, 98 mmol) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.17 (bs, 1H), 5.08 (bs, 1H), 4.12 (m, 1H), 3.33 (m, 2H), 2.65 (m, 1H), 2.00 (m, 1H), 1.42 (s, 9H).

[1-(3-Cyanobenzyl)-2-oxopiperidin-3-(*S*)-yl]carbamic Acid *tert*-Butyl Ester (D, *n* = 2; template for compound

7). A mixture of *N*-α-Boc-L-ornithine (1.5 g, 6.45 mmol) and 3-cyanobenzaldehyde (0.42 g, 3.23 mmol) is suspended in 20 mL of MeOH. A solution of anhydrous zinc chloride (0.24 g, 1.79 mmol) and sodium cyanoborohydride (0.22 g, 3.5 mmol) in 5 mL of MeOH is added. The mixture is stirred for 16 h at room temperature. After this time, 20 mL of 1 N NaOH is added. The solution is concentrated, and the residue is partitioned between EtOAc and water. The organic layer is washed with saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated to give *N*-α-Boc-*N*-δ-(3-cyanobenzyl)-L-ornithine.

A portion of the crude residue (0.75 g, 2.16 mmol), BOP reagent (1.05 g, 2.38 mmol), and potassium hydrogen carbonate (1.08 g, 10.8 mmol) are dissolved in 20 mL of DMF. The reaction mixture is stirred for 16 h and then diluted with 300 mL of EtOAc. The organic layer is washed with 1 N HCl, 10% Na_2CO_3, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (15% EtOAc/CH_2Cl_2 to 35% EtOAc/CH_2Cl_2) to give the [1-(3-cyanobenzyl)-2-oxopiperidin-3-(*S*)-yl]-carbamic acid *tert*-butyl ester (0.26 g, 0.76 mmol) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 4H), 5.50 (bs, 1H), 4.59 (s, 2H), 4.08 (m, 1H), 3.21 (m, 2H), 2.48 (m, 1H), 1.89 (m, 2H), 1.62 (m, 1H), 1.45 (s, 9H).

Boc-3-(*S*)-Amino-ϵ-caprolactam (C, $n = 3$; template for compound 8). l-(−)-α-Amino-ϵ-caprolactam (5 g, 39 mmol) and Et_3N (4.9 g, 49 mmol) are dissolved in 100 mL of CH_2Cl_2. To the solution is added Boc anhydride (8.5 g, 39 mmol) and (dimethylamino)pyridine (0.1 g). The reaction mixture is stirred for 16 h at room temperature. After this time, the solution is washed with 1 N HCl, 10% Na_2CO_3, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated to give Boc-3-(*S*)-amino-ϵ-caprolactam (6.23 g, 27 mmol) as a solid: ^{1}H NMR ($CDCl_3$) δ 6.15 (bs, 1H), 5.90 (bs, 1H), 4.24 (m, 1H), 3.21 (m, 2H), 2.05 (m, 2H), 1.79 (m, 2H), 1.45 (m, 11H).

General Procedure for the Synthesis of Arylsulfonyl Chlorides from Arylsulfonic Acids. 7-Methoxynaphthalene-2-sulfonyl Chloride. To a suspension of 7-hydroxynaphthalene-2-sulfonic acid, sodium salt (15.0 g, 60.9 mmol) in 150 mL of 2:1 H_2O/ethanol is added solid NaOH (2.68 g, 67.0 mmol) at room temperature. The mixture is stirred until a homogeneous solution forms, and dimethyl sulfate (6.34 mL, 67.0 mmol) is then added. A precipitate eventually forms, and the mixture is stirred over a period of 16 h. The crude mixture is concentrated in vacuo, and the residue is stirred in 100 mL of absolute EtOH as a slurry for 2 h. The precipitate is filtered and dried. The solid is heated at reflux in 100 mL of 95% EtOH for 2 h, allowed to cool to room temperature, filtered, and dried to give 12.6 g of crude 7-methoxynaphthalene-2-sulfonic acid, sodium salt. A mixture of the sulfonic acid, sodium salt (12.6 g, 48.6 mmol) in 20 mL of phosphorus oxychloride and phosphorus pentachloride (13.2 g, 63.2 mmol) is heated slowly to 60 °C until a homogeneous solution forms and then is heated at 120 °C for 4 h. The resulting mixture is cooled in an ice bath, and a mixture of ice/ice water is added slowly with stirring. The mixture is diluted with water and extracted with $CHCl_3$ (2 × 100 mL). The combined organic layers are washed successively with water, saturated $NaHCO_3$ solution, and saturated NaCl. The organic phase is dried over anhydrous $MgSO_4$, filtered, and concentrated to give 10.0 g of a crude oil. The crude product is purified by column chromatography (5% EtOAc/hexanes to 30% EtOAc/hexanes) to afford 7-methoxynaphthalene-2-sulfonyl chloride (3.80 g, 14.8 mmol) as a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 8.49 (d, 1H), 7.96 (d, 1H), 7.85 (d, 2H), 7.39 (dd, 1H), 7.29 (d, 1H), 3.99 (s, 3H); EI MS $[M]^+ = 256$.

General Procedure for the Synthesis of Arylsulfonyl Chlorides from Aryl Bromides and Arylstannanes. 2′-Methoxybiphenyl-4-sulfonyl Chloride. To a solution of 2-bromoanisole (3.5 g, 18.7 mmol) in 40 mL of THF at −78 °C is added *n*-butyllithium (11.7 mL of a 1.6 M solution in THF, 18.7 mmol). The solution is stirred for 15 min after which $ZnCl_2$ (20 mL of a 1 M solution in Et_2O, 20 mmol) is added. The solution is allowed to warm to ambient temperature and stirred for 3 h. At this time, a solution of 4-iodobromobenzene (5.6 g, 19.8 mmol) and tetrakis(triphenylphospine)palladium-(0) (1.1 g, 1 mmol) in 30 mL of THF is added. The reaction mixture is stirred for 16 h, and then the solution is poured into 100 mL of H_2O. The solution is diluted with EtOAc, and the organic layer is washed with 2 N NH_4OH, H_2O, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography (10% CH_2Cl_2/hexanes to 20% CH_2Cl_2/hexanes) to give 4-(2-methoxyphenyl)bromobenzene as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 2H), 7.51 (d, 2H), 7.38 (m, 2H), 7.08 (m, 2H), 3.85 (s, 3H).

To a solution of 4-(2-methoxyphenyl)bromobenzene (0.82 g, 3.2 mmol) in 15 mL of THF at −78 °C is added *n*-butyllithium (2.0 mL of a 1.6 M solution in hexanes, 3.2 mmol). After 30 min, the solution is transferred via cannula to a flask containing 10 mL of SO_2 in 40 mL of Et_2O at −78 °C. The solution is stirred at −78 °C for 30 min and then at ambient temperature for 2 h. After this time, the solution is concentrated. The residue is dissolved in 20 mL of hexanes. The solution is cooled to 0 °C, and sulfuryl chloride (3.2 mL of a 1 M solution in CH_2Cl_2) is added. The solution is stirred for 1 h. After this time, the solution is concentrated. The crude product is purified by column chromatography (2% EtOAc/hexanes) to afford 2′-methoxybiphenyl-4-sulfonyl chloride (0.34 g, 2.6 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 2H), 7.81 (d, 2H), 7.44 (m, 2H), 7.02 (m, 2H), 3.88 (s, 3H).

7-Methylnaphthalene-2-sulfonyl Chloride. To a solution of 7-methoxy-2-naphthol (5.00 g, 28.7 mmol) in 150 mL CH_2Cl_2 at 0 °C are added Et_3N (5.95 g, 58.8 mmol), trifluoromethanesulfonic anhydride (10.1 g, 35.6 mmol), and DMAP (0.36 g, 2.94 mmol). The brown solution is stirred for 1 h at 0 °C and then concentrated in vacuo to remove most of the CH_2Cl_2. The residue is diluted with EtOAc and washed with 1 N aqueous HCl, water, 10% Na_2CO_3 solution, and saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered, and concentrated to provide crude material which is purified by column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes) to give 2-methoxy-7-(trifluoromethylsulfonyl)naphthalene (8.44 g, 27.5 mmol) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H), 7.78 (d, 1H), 7.65 (d, 1H), 7.22 (m, 2H), 7.15 (d, 1H), 3.95 (s, 3H).

2-Methoxy-7-(trifluoromethylsulfonyl)naphthalene (10.0 g, 32.6 mmol) is dissolved in 300 mL of DMF and treated with lithium chloride (7.20 g, 170 mmol) and tetramethyltin (12.4 g, 69.3 mmol). Bis(triphenylphosphine)palladium(II) chloride (1.44 g, 2.00 mmol) is added, and the resulting heterogeneous mixture is heated at 80 °C for 18 h. The reaction mixture is cooled to room temperature, filtered through a Celite pad, and washed with EtOAc. The filtrate is washed with water, and the layers are separated. The aqueous layer is extracted twice with EtOAc, and the combined organic layers are washed with water and saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered, and concentrated to give crude material which is purified by column chromatography (2% EtOAc/hexanes to 5% EtOAc/hexanes) to yield 2-methoxy-7-methylnaphthalene (5.34 g, 31.0 mmol) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2H), 7.52 (s, 1H), 7.19 (d, 1H), 7.10 (m, 2H), 3.93 (s, 3H), 2.50 (s, 3H).

A suspension of 2-methoxy-7-methylnaphthalene (5.30 g, 30.8 mmol) in 90 mL of 48% aqueous HBr is heated at reflux for a period of 2 h. The resulting mixture is allowed to cool to room temperature, diluted with water, and partially neutralized with saturated $NaHCO_3$ solution. The aqueous mixture is extracted with EtOAc twice, and the combined organic layers are washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and concentrated to provide crude material which is purified by column chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes) to afford 7-methyl-2-naphthol (3.05 g, 19.3 mmol) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2H), 7.47 (s, 1H), 7.18 (m, 1H), 7.03 (m, 2H), 5.01 (m, 1H), 2.50 (s, 3H).

7-Methyl-2-naphthol (3.05 g, 19.3 mmol) is converted to 7-methyl-2-(trifluoromethylsulfonyl)naphthalene using Tf_2O and DMAP as described above. The crude product is purified by column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes) to give an oil (4.74 g, 16.3 mmol): ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H), 7.80 (d, 1H), 7.69 (m, 2H), 7.40 (m, 1H), 7.30 (m, 1H), 2.59 (s, 3H).

7-Methyl-2-(trifluoromethylsulfonyl)naphthalene (1.50 g, 5.17 mmol) is dissolved in 30 mL of *p*-dioxane and treated with lithium chloride (0.66 g, 15.5 mmol) and hexamethylditin (1.86 g, 5.68 mmol). Bis(triphenylphosphine)palladium(II) chloride (0.30 g, 0.26 mmol) is added, and the resulting heterogeneous mixture is heated at reflux for 1 h. The reaction mixture is cooled to room temperature, diluted with 10% NH_4OH solution and CH_2Cl_2, and stirred for 45 min. The layers are separated, and the aqueous layer is extracted twice with CH_2Cl_2. The combined organic layers are washed with saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered, and concentrated to give crude material which is purified by column chromatography (2% EtOAc/hexanes to 5% EtOAc/hexanes) to yield 7-methyl-2-(trimethylstannyl)naphthalene (0.60 g, 1.97 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.60 (s, 1H), 7.51 (d, 1H), 7.30 (d, 1H), 2.54 (s, 3H), 0.34 (m, 9H).

7-Methyl-2-(trimethylstannyl)naphthalene is converted to 7-methylnaphthalene-2-sulfonyl chloride as described above. The crude product is purified by column chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to give a solid: ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.01 (d, 1H), 7.92 dd, 1H), 7.89 (d, 1H), 7.80 (s, 1H), 7.58 (d, 1H), 2.58 (s, 3H).

General Procedures for the Synthesis of Heteroaryl Nitriles (intermediates B). 4-(Bromomethyl)thiophene-2-carbonitrile. To a solution of thiophene-3-carboxaldehyde (36 g, 321 mmol) in 80 mL of CCl_4 and 60 mL of H_2O is added 2.5 mL of concentrated H_2SO_4 in 160 mL of acetic acid. To the resulting solution are added HIO_3 (14 g, 80 mmol) and I_2 (38 g, 150 mmol). The solution is refluxed for 6 h. After this time, the reaction is cooled to ambient temperature, and 200 mL of $CHCl_3$ is added. The layers are separated, and the aqueous layer is extracted with $CHCl_3$. The organic layers are combined and washed with 0.5 M $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography (2% EtOAc/hexanes to 5% EtOAc/hexanes) to afford 5-iodothiophene-3-carboxaldehyde (20 g, 84 mmol) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 8.10 (s, 1H), 7.69 (s, 1H).

To a solution of 5-iodothiophene-3-carboxaldehyde (42 g, 176 mmol) in 800 mL of THF is added $NaBH_4$ (7 g, 185 mmol). After 1 h, the reaction is quenched by the addition of 100 mL of saturated NH_4Cl. The resulting solution is diluted with 1 L of EtOAc, and the layers are separated. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. (5-Iodothiophene-3-yl)methanol (42 g, 176 mmol) is obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 2H), 4.63 (s, 2H), 1.92 (bs, 1H).

To a solution of (5-iodothiophene-3-yl)methanol (42 g, 176 mmol) in 150 mL of DMF are added zinc cyanide ($Zn(CN)_2$) (12.4 g, 106 mmol) and $Pd(PPh_3)_4$ (8.13 g, 7.04 mmol). The solution is heated to 80 °C. After 6 h, the solution is diluted with 3 L of EtOAc. The resulting solution is washed with 1 N NH_4OH, H_2O, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography (20% EtOAc/hexanes to 30% EtOAc/hexanes) to give 4-(hydroxymethyl)thiophene-2-carbonitrile (10 g, 72 mmol) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.46 (s, 1H), 4.67 (s, 2H), 2.42 (bs, 1H).

To a solution of 4-(hydroxymethyl)thiophene-2-carbonitrile (10 g, 72 mmol) in 360 mL of THF are added triphenylphosphine (18.3 g, 76 mmol) and CBr_4 (25 g, 76 mmol). After 3 h, the solution is filtered and concentrated. The crude product is purified by column chromatography (5% EtOAc/hexanes to 10% EtOAc/hexanes) to afford the 4-(bromomethyl)thiophene-2-carbonitrile (14 g, 69 mmol) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.49 (s, 1H), 4.42 (s, 2H).

5-(Bromomethyl)thiophene-2-carbonitrile. Prepared from 5-bromothiophene-2-carboxaldehyde: ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H), 7.09 (d, 1H), 4.66 (s, 2H).

5-(Bromomethyl)thiophene-3-carbonitrile. Prepared from 4-bromothiophene-2-carboxaldehyde: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1H), 7.27 (d, 1H), 4.65 (s, 2H).

2-Cyano-4-(bromomethyl)pyridine. A solution of 2-cyano-4-[{(*tert*-butyldimethylsilyl)oxy}methyl]pyridine[25] (10.1 g, 40.5 mmol) in 200 mL of anhydrous MeOH is stirred over 12 g of Dowex-50W-H^+ ion-exchange resin (prewashed with MeOH) for a period of 18 h. After this time, the mixture is filtered and washed with MeOH twice. The combined filtrates are concentrated in vacuo. The crude residue is purified by column chromatography (50% EtOAc/hexanes) to afford 2-cyano-4-(hydroxymethyl)pyridine (4.82 g, 35.9 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.70 (m, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 4.87 (d, 2H), 2.31 (bs, 1H).

Bromine (6.88 g, 43.1 mmol) is added dropwise to a solution of triphenylphosphine (11.3 g, 43.1 mmol) in 280 mL of CH_2Cl_2 at 0 °C. The mixture is stirred for 30 min at 0 °C. At this time, 2-cyano-4-(hydroxymethyl)pyridine (4.82 g, 35.9 mmol) is added, and the resulting mixture is stirred for 2 h at room temperature. The reaction mixture is diluted with CH_2Cl_2 and washed with water (2×) and saturated NaCl solution. The organic layer is dried with $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography eluting (20% EtOAc/hexanes to 30% EtOAc/hexanes) to give the 2-cyano-4-(bromomethyl)pyridine (6.40 g, 32.5 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.75 (d, 1H), 7.79 (s, 1H), 7.60 (d, 1H), 4.49 (s, 2H).

4-(Bromomethyl)furan-2-carbonitrile. A solution of furan-3-ylmethanol (9.68 g, 98.7 mmol) in THF (150 mL) at −78 °C is treated with *n*-butyllithium (65 mL of 1.6 M solution) for 1 h followed by *s*-butyllithium (86 mL of 1.3 M solution) for 4 h. A solution of iodine (29 g, 114 mmol) in THF (250 mL) is added, and the solution is slowly warmed to room temperature. After stirring overnight, the reaction mixture is diluted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated. The crude residue is purified by column chromatography (30% EtOAc/hexanes) to give (5-iodofuran-3-yl)methanol as a dark red oil (13.7 g, 61.2 mmol) contaminated with furan-3-ylmethanol.

The crude material is converted to 4-(bromomethyl)furan-2-carbonitrile as described above: ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.12 (s, 1H), 4.30 (s, 2H); EI MS M^+ = 185/187.

5-(Bromomethyl)furan-2-carbonitrile. 5-(Hydroxymethyl)furan-2-carbonitrile[26] (1.12 g, 9.1 mmol) is dissolved in THF (75 mL), treated with triphenylphosphine (2.9 g, 11.06 mmol) and carbon tetrabromide (3.78 g, 11.4 mmol), and stirred at room temperature for 18 h. Standard workup yields 5-(bromomethyl)furan-2-carbonitrile (1.45 g, 7.8 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.04 (d, 2H), 6.50 (d, 1H), 4.43 (s, 2H).

General Procedure for N-Alkylation of Boc-Protected 3-Amino Lactam Ring Systems (intermediates D). [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]carbamic Acid *tert*-Butyl Ester (D, *n* = 1). To a solution of Boc-3-(*S*)-aminopyrrolidin-2-one (**C, *n* = 1**) (9 g, 45 mmol) and α-bromo-*m*-toluyl nitrile (9.3 g, 47 mmol) in 225 mL of THF/DMF (10:1) at 0 °C is added a 60% mineral oil dispersion of sodium hydride (1.8 g, 46 mmol). The reaction mixture is stirred at 0 °C for 0.5 h and then allowed to warm to ambient temperature. After 3 h, the reaction mixture is quenched by the addition of saturated NH_4Cl and diluted with EtOAc. The layers are separated, and the organic layer is washed with 1 N HCl, H_2O, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes) to afford [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]carbamic acid *tert*-butyl ester (12.7 g, 40 mmol) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 4H), 5.18 (bs, 1H), 4.47 (AB, 2H), 4.18 (dd, 1H), 3.21 (m, 2H), 2.60 (m, 1H), 1.42 (s, 9H).

[1-(3-Cyanobenzyl)-2-oxoazetidin-3-(*S*)-yl]carbamic Acid *tert*-Butyl Ester (D, *n* = 0). Prepared from Boc-3-(*S*)-aminoazetidin-2-one (**C, *n* = 0**): ^{1}H NMR ($CDCl_3$) δ 7.59 (m, 2H), 7.41 (m, 2H), 5.18 (bs, 1H), 4.72 (m, 1H), 4.41 (AB, 2H), 3.41 (m, 1H), 3.23 (m, 1H), 1.41 (s, 9H).

[1-(3-Cyanobenzyl)-2-oxoazepan-3-(*S*)-yl]carbamic Acid *tert*-Butyl Ester. (D, *n* = 3). Boc-3-(*S*)-amino-ϵ-caprolactam (**C, *n* = 3**) (1.07 g, 4.7 mmol) is dissolved in 45 mL of THF and cooled to 0 °C. To the solution is added a 1 M solution of lithium hexamethyldisilyl azide (4.7 mL, 4.7 mmol) in THF. The mixture is stirred for 30 min at 0 °C. To the resulting solution is added α-bromo-*m*-toluyl nitrile (0.9 g, 4.7 mmol). The reaction mixture is stirred for 4 h. The solution is diluted with 100 mL of EtOAc and washed with 1 N HCl, 10% Na_2CO_3, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (20% EtOAc/CH_2Cl_2) to give [1-(3-cyanobenzyl)-2-oxoazepan-3-(*S*)-yl]carbamic acid *tert*-butyl ester (1.05 g, 3.1 mmol) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 4H), 5.95 (d, 1H), 4.85 (AB, 1H), 4.35 (AB, 1H), 4.40 (m, 1H), 3.48 (m, 1H), 3.15 (dd, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.70 (m, 2H), 1.49 (m, 1H), 1.45 (s, 9H), 1.20 (m, 1H).

General Procedures for the Synthesis of 3-Sulfonamido Lactam Ring Systems (intermediates E). Naphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (E, *n* = 1). To a solution of [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]carbamic acid *tert*-butyl ester (**D, *n* = 1**) (9.1 g, 29 mmol) in 150 mL of EtOAc at 0 °C is bubbled HCl gas for 10 min. After this time, the solution is stirred at room temperature for 4 h. The solution is then concentrated in vacuo and dried to give 3-(3-(*S*)-amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (7.3 g, 29 mmol) as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.71 (bs, 3H), 7.85 (m, 2H), 7.70 (m, 2H), 4.58 (AB, 2H), 4.13 (m, 1H), 3.32 (m, 2H), 2.44 (m, 1H), 2.18 (m, 1H).

3-(3-(*S*)-Amino-2-oxopyrrolidin-1-ylmethyl)benzonitrile hydrochloride (0.4 g, 1.6 mmol) is suspended in 10 mL of CH_2Cl_2. To the solution is added triethylamine (0.49 g, 4.8 mmol) followed by 2-naphthalenesulfonyl chloride (0.4 g, 1.8 mmol). After stirring for 2 h, the solution is diluted with CH_2Cl_2. The solution is washed with 1 N HCl, 10% Na_2CO_3, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is triturated with Et_2O to give naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (0.46 g, 1.13 mmol) as a solid: ^{1}H NMR (DMSO-d_6) δ 8.56 (d, 1H), 8.32 (d, 1H), 8.20 (m, 3H), 8.09 (m, 1H), 7.93 (d, 1H), 7.74 (m, 3H), 7.48 (d, 2H), 4.38 (AB, 2H), 4.17 (m, 1H), 3.05 (m, 2H), 2.02 (m, 1H), 1.57 (m, 1H).

Naphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopyrrolidin-4-(*S*)-yl]amide (sulfonamide precursor to compound 3). Prepared from [1-(3-cyanobenzyl)-2-oxopyrrolidin-4-(*S*)-yl]carbamic acid *tert*-butyl ester: ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H), 7.95 (m, 4H), 7.68 (m, 2H), 7.46 (m, 4H), 5.00 (m, 1H), 4.53 (d, 1H), 4.46 (d, 1H), 4.36 (d, 1H), 3.68 (dd, 1H), 3.36 (dd, 1H), 3.07 (dd, 1H), 2.58 (dd, 1H).

Naphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxoazetidin-3-(*S*)-yl]amide (E, *n* = 0). Prepared from [1-(3-cyanobenzyl)-2-oxoazetidin-3-(*S*)-yl]carbamic acid *tert*-butyl ester (**D, *n* = 0**): ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 7.95 (m, 2H), 7.90 (d, 1H), 7.83 (d, 1H), 7.60 (m, 3H), 7.46 (m, 3H), 5.81 (d, 1H), 4.57 (m, 1H), 4.46 (AB, 2H), 3.41 (dd, 1H), 3.17 (dd, 1H).

Naphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopiperidin-3-(*S*)-yl]amide (E, *n* = 2). [1-(3-Cyanobenzyl)-2-oxopiperidin-3-(*S*)-yl]carbamic acid *tert*-butyl ester (**D, *n* = 2**) (0.25 g, 0.76 mmol) is dissolved in 5 mL of CH_2Cl_2. To the solution is added 1 mL of trifluoroacetic acid. The mixture is stirred for 3 h at room temperature and then concentrated. The residue is reconcentrated from toluene to give 3-(3-amino-2-oxopiperidin-1-ylmethyl)benzonitrile trifluoroacetate (0.23 g, 0.76 mmol) as a solid. The crude product is then sulfonylated as above to give naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopiperidin-3-(*S*)-yl]amide: ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 7.94 (m, 4H), 7.51 (m, 6H), 6.10 (s, 1H), 4.47 (AB, 2H), 3.56 (m, 1H), 3.20 (m, 2H), 2.52 (m, 1H), 1.83 (m, 3H).

Naphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxoazepan-3-(*S*)-yl]amide (E, *n* = 3). Prepared from [1-(3-cyanobenzyl)-2-oxoazepan-3-(*S*)-yl]carbamic acid *tert*-butyl ester (**D, *n* = 3**): ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.95 (m, 3H), 7.83 (d, 1H), 7.64 (m, 2H), 7.46 (d, 1H), 7.29 (s, 1H), 7.04 (m, 1H), 6.93 (d, 1H), 6.40 (d, 1H), 4.78 (AB, 1H), 4.10 (AB, 1H), 4.03 (m, 1H), 3.18 (dd, 1H), 3.00 (dd, 1H), 2.18 (m, 1H), 1.93 (m, 1H), 1.67 (m, 3H), 1.20 (m, 1H).

General Procedures for the N-Alkylation of 3-Sulfonamido Lactam Ring Systems (intermediates F). 7-Methoxynaphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]methylamide (F, *n* = 1; *N*-methyl sulfonamide precursor to compound 28). 7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (0.34 g, 0.76 mmol) is dissolved in 7 mL of THF and cooled to 0 °C. Sodium hydride (30 mg of a 60% dispersion in mineral oil, 0.76 mmol) is added, and the solution is stirred for 20 min. To the mixture is added methyl iodide (0.32 g, 2.27 mmol). The cooling bath is removed, and the solution is stirred at room temperature for 2 h. The solution is poured into a separatory funnel and diluted with 100 mL of EtOAc. The organic layer is washed with 1 N HCl, dried over $MgSO_4$, and concentrated. The residue is purified by column chromatography (10% EtOAc/CH_2Cl_2) to give 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]-methylamide (0.25 g, 0.54 mmol) as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.44 (d, 1H), 7.92 (d, 1H), 7.82 (m, 2H), 7.61 (m, 1H), 7.47 (m, 3H), 7.28 (m, 2H), 4.97 (m, 1H), 4.53 (AB, 1H), 4.39 (AB, 1H), 3.96 (s, 3H), 3.13 (m, 2H), 2.83 (s, 3H), 2.37 (m, 1H), 2.06 (m, 1H).

7-Methoxynaphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl](thiophene-3-ylmethyl)-amide (F, *n* = 1; precursor to compound 32). To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (0.19 g, 0.44 mmol) in 20 mL of acetone are added K_2CO_3 (0.12 g, 0.88 mmol) and thiophen-3-ylmethyl bromide[27] (0.30 g, 1.68 mmol). The resulting mixture is stirred for 48 h, then diluted with CH_2Cl_2, and washed with saturated $NaHCO_3$, H_2O, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The crude product is triturated with hexane/ether to give 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl](thiophene-3-ylmethyl)amide and used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.94 (AB, 2H), 7.80 (d, 1H), 7.06 (d, 1H), 7.40−7.65 (m, 2H), 7.18−7.32 (m, 4H), 7.05−7.13 (m, 2H), 4.4−4.6 (m, 3H), 4.38 (AB, 2H), 3.93 (s, 3H), 3.07 (m, 2H), 2.27 (m, 1H), 1.99 (m, 1H); FAB MS $[M + H]^+ = 532$.

7-Methoxynaphthalene-2-sulfonic Acid [1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl](*N*-*tert*-butyloxycarbonylpyrazol-3-ylmethyl)amide (F, *n* = 1; precursor to compound 35). 3-Methylpyrazole (2.04 g, 2.49 mmol) is dissolved in 25 mL acetonitrile under nitrogen, cooled in a ice bath, and treated with BOC anhydride (6.5 g, 2.98 mmol) followed by DMAP (0.303 g, 2.48 mmol). The reaction is warmed to room temperature over about 2 h and diluted with ethyl acetate. The organic solution is washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to obtain *N*-*tert*-butyloxycarbonyl-3-methylpyrazole (2.5 g, 13.7 mmol): EI MS $[M]^+ = 182$.

A portion of this material (1 g, 5.8 mmol) is dissolved in CCl_4 (20 mL), treated with *N*-bromosuccinimide (1.47 g, 8.26 mmol) and benzoyl peroxide (0.2 g, 0.83 mmol), and heated to reflux. After 4 h, the solution is diluted with EtOAc washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue is purified by column chromatography (10% EtOAc/hexanes) to yield *N*-*tert*-butyloxycarbonylpyrazol-3-ylmethyl bromide (0.74 g, 2.85 mmol): EI MS $[M]^+ = 259/261$.

7-Methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl](*N*-*tert*-butyloxycarbonylpyrazol-3-ylmethyl)amide is prepared as described

above using *N-tert*-butyloxycarbonylpyrazol-3-ylmethyl bromide: ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 7.90−8.02 (m, 3H), 7.79 (d, 1H), 7.46−1.60 (m, 4H), 7.30 (dd, 1H), 7.27 (s, 1H), 6.50 (d, 1H), 4.62 (t, 1H), 4.47 (AB, 2H), 4.45 (AB, 2H), 3.94 (s, 3H), 3.24 (m, 1H), 3.14 (m, 1H), 2.26 (m, 2H), 1.63 (s, 9H); FAB MS $[M + H]^+ = 616$.

2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-acetic Acid (F, *n* = 1; precursor to compound 36). Prepared from 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-acetic acid *tert*-butyl ester using *tert*-butyl bromoacetate: ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 2H), 7.81 (m, 3H), 7.50 (m, 1H), 7.44 (m, 3H), 7.22 (m, 2H), 4.61 (t, 1H), 4.42 (AB, 2H), 3.90 (s, 3H), 3.74 (AB, 1H), 3.20 (m, 2H), 2.58 (m, 1H), 2.41 (m, 1H), 1.42 (s, 9H).

2-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-acetic acid *tert*-butyl ester is dissolved in 25 mL of a 5:1 mixture of CH_2Cl_2/trifluoroacetic acid. After 3 h, the solution is concentrated in vacuo to give 2-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-acetic acid as a white foam: ^{1}H NMR ($CDCl_3$) δ 9.45 (bs, 1H), 8.41 (s, 2H), 7.91 (d, 1H), 7.80 (d, 1H), 7.71 (m, 1H), 7.62 (m, 1H), 7.59 (m, 3H), 7.20 (m, 1H), 4.81 (t, 1H), 4.50 (AB, 2H), 3.90 (s, 3H), 3.89 (AB, 2H), 3.28 (m, 2H), 2.41 (m, 1H), 2.16 (m, 1H).

3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]propionamide (F, *n* = 1; precursor to compound 38). To a solution of 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (0.82 g, 1.9 mmol) in 10 mL of DMF are added K_2CO_3 (0.52 g, 3.8 mmol) and *tert*-butyl acrylate (0.48 g, 3.8 mmol). The solution is heated at 60 °C and stirred for 24 h. After this time, the solution is cooled to room temperature and diluted with EtOAc. The solution is washed with 1 N HCl and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated to afford 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-propionic acid *tert*-butyl ester (0.64 g, 1.1 mmol) as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1H), 7.89 (m, 2H), 7.80 (m, 1H), 7.56 (m, 4H), 7.23 (m, 2H), 4.71 (t, 1H), 4.50 (AB, 2H), 3.92 (s, 3H), 3.63 (m, 4H), 3.37 (m, 1H), 3.36 (m, 4H), 2.78 (m, 2H), 2.41 (m, 1H), 2.20 (m, 1H) 1.42 (s, 9H).

3-[{1-(3-Cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-propionic acid *tert*-butyl ester is dissolved in 25 mL of a 5:1 mixture of CH_2Cl_2/trifluoroacetic acid. After 3 h, the solution is concentrated in vacuo to give 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-propionic acid as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1H), 7.89 (d, 1H), 7.80 (m, 2H), 7.56 (m, 4H), 7.22 (m, 2H), 4.74 (t, 1H), 4.50 (AB, 2H), 3.92 (s, 3H), 3.56 (m, 1H), 3.37 (m, 1H), 3.22 (m, 2H), 2.89 (m, 2H), 2.39 (m, 2H), 2.10 (m, 1H).

To a solution of 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]-*N*-propionic acid (0.51 g, 1.0 mmol) and Et_3N (0.12 g, 1.2 mmol) in 10 mL of THF at −20 °C is added ethyl chloroformate (0.11 g, 1.0 mmol). The solution is stirred for 15 min. After this time, 14.8 N ammonium hydroxide (0.1 mL, 1.5 mmol) is added. The solution is allowed to warm to room temperature, and the reaction is stirred for 16 h. After this time, the solution is diluted with EtOAc. The organic layer is washed with 1 N HCl, 10% Na_2CO_3, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered, and concentrated to afford 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}-7-methoxynaphthalen-2-ylsulfonylamino]propionamide (0.39 g, 0.77 mmol) as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1H), 7.85 (m, 2H), 7.50 (m, 4H), 7.26 (m, 3H), 5.94 (bs, 1H), 5.34 (bs, 1H), 4.75 (t, 1H), 4.45 (AB, 2H), 3.92 (s, 3H), 3.51 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 2.78 (m, 2H), 2.32 (m, 1H), 2.09 (m, 1H).

General Procedure for the Preparation of Heteroaryl Amidines (compounds 3, 4, 6−29, 30−34, 36−42, 44−45, and RPR120844). Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (4). Naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide (0.46 g, 1.13 mmol) is dissolved in 50 mL of ethanol. The solution is cooled to 0 °C, and HCl gas is bubbled through the solution for 10 min. The ice bath is removed, and the reaction mixture is stirred at room temperature for 6 h. After this time, the solution is concentrated. The residue is dissolved in 50 mL of methanol. The solution is cooled to 0 °C, and ammonia gas is bubbled through the solution for 10 min. The reaction mixture is stirred for 24 h. After this time, the solution is concentrated. The crude residue is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA). The appropriate fractions are lyophilized to give naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide trifluoroacetate (**4**) (0.33 g, 0.61 mmol) as an amorphous solid: ^{1}H NMR (DMSO-d_6) δ 9.30 (bs, 2H), 9.14 (bs, 2H), 8.50 (s, 1H), 8.28 (d, 1H), 8.13 (m, 3H), 8.04 (d, 1H), 7.91 (d, 1H), 7.80 (m, 3H), 7.62 (d, 2H), 4.42 (AB, 2H), 4.18 (m, 1H), 3.10 (m, 2H), 2.00 (m, 1H), 1.57 (m, 1H); FAB MS $[M + H]^+ = 423$. Anal. ($C_{22}H_{22}N_4O_3S\cdot TFA\cdot 1.5H_2O$) C, H, N.

Naphthalene-1-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (9). Anal. ($C_{22}H_{22}N_4O_3S\cdot TFA\cdot H_2O$) C, H, N.

7-Methylnaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (10). The imidate intermediate is formed in a 2:1 $EtOH/CH_2Cl_2$ solvent mixture. Anal. ($C_{23}H_{24}N_4O_3S\cdot TFA\cdot 1.7H_2O$) C, H, N.

7-Ethylnaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (11). Anal. ($C_{24}H_{26}N_4O_3S\cdot TFA\cdot 1.6H_2O$) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (12). ^{1}H NMR (DMSO-d_6) δ 9.41 (bs, 2H), 9.29 (bs, 2H), 8.33 (d, 1H), 8.19 (d, 1H), 7.96 (d, 1H), 7.87 (d, 1H), 7.68 (dd, 1H), 7.64 (m, 1H), 7.50 (m, 4H), 7.27 (dd, 1H), 4.36 (AB, 2H), 4.16 (dd, 1H), 3.48 (s, 3H), 3.04 (m, 2H), 1.93 (m, 1H), 1.59 (m, 1H); FAB MS $[M + H]^+ = 453$. Anal. ($C_{23}H_{24}N_4O_4S\cdot TFA\cdot 1.7H_2O$) C, H, N.

6-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (13). Anal. ($C_{23}H_{24}N_4O_4S\cdot TFA\cdot 2.5H_2O$) C, H, N.

7-Ethoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (14). Anal. ($C_{24}H_{26}N_4O_4S\cdot TFA\cdot 1.9H_2O$) C, H, N.

7-Chloronaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (15). ESI HMRS $[M + H]^+$ calcd for $C_{22}H_{21}ClN_4O_3S$ 457.1101, found 457.1104; RP-HPLC analysis (C18, 20-min linear gradient; elution 10−100% CH_3CN/0.1% TFA H_2O; flow rate 1.0 mL/min) indicated that the product was 95.0A%.

6-Chloronaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (16). Anal. ($C_{22}H_{21}ClN_4O_3S\cdot TFA\cdot 1.35H_2O$) C, H, N.

7-Hydroxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (17). Prepared from 7-benzyloxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide. Anal. ($C_{22}H_{22}N_4O_4S\cdot TFA\cdot 2.6H_2O$) C, H, N.

7-Aminonaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Bistrifluoroacetate (18). Prepared from *N*-Cbz-7-aminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl]amide. Anal. ($C_{22}H_{23}N_5O_3S\cdot 2TFA\cdot 0.8H_2O$) C, H, N.

7-(Methylamino)naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Bistrifluoroacetate (19). Prepared from N-Cbz-7-methylaminonaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-

2-oxopyrrolidin-3-(*S*)-yl]amide. Anal. ($C_{24}H_{24}N_4O_3S$·TFA·1.25H_2O) C, H, N.

Biphenyl-3-sulfonic Acid {1-[3-(Aminoiminomethyl)-benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (20). Anal. ($C_{24}H_{24}N_4O_3S$·TFA·1.25H_2O) C, H, N.

Biphenyl-4-sulfonic Acid {1-[3-(Aminoiminomethyl)-benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (21). Anal. ($C_{24}H_{24}N_4O_3S$·TFA·0.25H_2O) C, H, N.

3′-Methylbiphenyl-4-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (22). Anal. ($C_{25}H_{26}N_4O_3S$·TFA·2.0H_2O) C, H, N.

3′-Methoxybiphenyl-4-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (23). Anal. ($C_{25}H_{26}N_4O_4S$·TFA·H_2O) C, H, N.

2′-Methoxybiphenyl-4-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (24). Anal. ($C_{25}H_{26}N_4O_4S$·2.0TFA·0.5NH_4Cl) C, H, N.

Benzylbenzene-4-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (25). Anal. ($C_{25}H_{26}N_4O_3S$·TFA·1.75H_2O) C, H, N.

Phenoxybenzene-4-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (26). Anal. ($C_{24}H_{24}N_4O_4S$·TFA·0.5H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*R*)-yl}-amide Trifluoroacetate (27). Prepared from 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*R*)-yl]amide which is derived from [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*R*)-yl]carbamic acid *tert*-butyl ester according to the above procedures. The [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*R*)-yl]carbamic acid *tert*-butyl ester is obtained from Boc-D-Asp(OH)-OBn in a manner analogous to procedure for the preparation of [1-(3-cyanobenzyl)-2-oxopyrrolidin-4-(*S*)-yl]carbamic acid *tert*-butyl ester. Spectroscopic data is identical to that reported for compound **12.** Anal. ($C_{23}H_{24}N_4O_4S$·TFA·H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}methylamide Trifluoroacetate (28). ^{1}H NMR (DMSO-d_6) δ 9.28 (bs, 2H), 9.07 (bs, 2H), 8.38 (s, 1H), 8.01 (d, 1H), 7.93 (s, 1H), 7.68 (m, 2H), 7.54 (m, 4H), 7.33 (d, 1H), 4.90 (m, 1H), 4.40 (AB, 2H), 3.88 (s, 3H), 3.12 (m, 2H), 2.66 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H); FAB MS $[M + H]^+ = 467$. Anal. ($C_{24}H_{26}N_4O_4S$·TFA·2.5H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*R*)-yl}methylamide Trifluoroacetate (29). Prepared from 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*R*)-yl]amide according to the above procedures. Spectroscopic data is identical to that reported for compound **28.** Anal. ($C_{24}H_{26}N_4O_4S$·TFA·2.0H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}ethylamide Trifluoroacetate (30). Anal. ($C_{25}H_{28}N_4O_4S$·TFA·1.75H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}-benzylamide Trifluoroacetate (31). Anal. ($C_{30}H_{30}N_4O_4S$·TFA·2.5H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}-(thiophene-3-ylmethyl)amide Trifluoroacetate (32). Anal. ($C_{28}H_{28}N_4O_4S_2$·TFA·H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}-(thiophene-2-ylmethyl)amide Trifluoroacetate (33). Anal. ($C_{28}H_{28}N_4O_4S_2$·TFA·2.0H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}(pyridin-2-ylmethyl)amide Trifluoroacetate (34). Anal. ($C_{29}H_{29}N_5O_4S$·TFA·0.35H_2O) C, H, N.

[{1-[3-Aminoiminomethyl)benzyl]-2-oxopyrroldin-3-(*S*)-yl}(7-methoxynaphthalen-2-ylsulfonyl)amino]-acetic Acid Trifluoroacetate (36). Anal. ($C_{25}H_{26}N_4O_6S$·TFA·2.0H_2O) C, H, N.

3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}(7-methoxynaphthalen-2-ylsulfonyl)amino]acetamide Trifluoroacetate (37). Anal. ($C_{25}H_{27}N_5O_5S$·1.5TFA) C, H, N.

3-[{1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}(7-methoxynaphthalen-2-ylsulfonyl)amino]propionamide Trifluoroacetate (38). Prepared from 3-[{1-(3-cyanobenzyl)-2-oxopyrrolidin-3-(*S*)-yl}(7-methoxynaphthalen-2-ylsulfonyl)amino]propionamide. Anal. ($C_{26}H_{29}N_5O_5S$·TFA·2.25H_2O) C, H, N.

7-Methoxynaphthalene-2-sulfonic Acid {1-[4-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}amide Trifluoroacetate (39). Anal. ($C_{23}H_{24}N_4O_4S$·TFA·1.2H_2O) C, H, N.

4-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine Trifluoroacetate (40). Anal. ($C_{21}H_{22}N_4O_4S_2$·2.5TFA·H_2O) C, H, N.

5-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-2-carboxamidine Trifluoroacetate (41). ESI HMRS $[M + H]^+$ calcd for $C_{21}H_{22}N_4O_4S_2$ 459.1160, found 459.1174; RP-HPLC analysis (C18, 20-min linear gradient; elution 10−100% CH_3CN/0.1% TFA H_2O; flow rate 1.0 mL/min) indicated that the product was >95A%.

5-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]thiophene-3-carboxamidine Trifluoroacetate (42). Anal. ($C_{21}H_{22}N_4O_4S$·1.5TFA·1.0H_2O) C, H, N.

4-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]furan-2-carboxamidine Trifluoroacetate (44). Anal. ($C_{21}H_{22}N_4O_5S$·TFA·0.35H_2O) C, H, N.

5-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]furan-2-carboxamidine Trifluoroacetate (45). Anal. ($C_{21}H_{22}N_4O_5S$·TFA·1.5H_2O) C, H, N.

4-{3-(*S*)-[(7-Methoxynaphthalen-2-ylsulfonyl)methylamino]-2-oxopyrrolidin-1-ylmethyl}thiophene-2-carboxamidine Trifluoroacetate (RPR120844). ^{1}H NMR (DMSO-d_6) δ 9.24 (bs, 2H), 8.97 (bs, 2H), 8.39 (s,1H), 8.02 (d,1H), 7.95 (d, 1H), 7.91 (s, 1H), 7.80 (s, 1H), 7.68 (dd, 1H), 7.55 (s, 1H), 7.32 (dd, 1H), 4.86 (t, 1H), 4.37 (AB, 2H), 3.87 (s, 3H), 3.46 (m, 1H), 3.14 (m, 1H), 2.46 (s, 3H), 1.95 (m, 1H), 1.74 (m, 1H); FAB MS $[M + H]^+ = 473$. Anal. ($C_{22}H_{24}N_4O_4S_2$·TFA·1.5H_2O) C, H, N.

Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-4-(*S*)-yl}amide Trifluoroacetate (3). ^{1}H NMR (CD_3CN) δ 10.05 (bs, 4H), 8.45 (s, 1H), 8.12 (m, 1H), 8.00 (m, 1H), 7.93 (m, 1H), 8.05 (m, 2H), 7.78 (m, 3H), 7.55 (m, 1H), 6.18 (m, 1H), 2.32 (m, 2H), 1.91 (m, 1H); FAB MS $[M + H]^+ = 423$. Anal. ($C_{22}H_{22}N_4O_3S$·1.5TFA) C, H, N.

Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxoazetidin-3-(*S*)-yl}amide Trifluoroacetate (6). ^{1}H NMR (DMSO-d_6) δ 9.28 (bs, 2H), 8.98 (bs, 2H), 8.84 (m, 1H), 8.47 (m, 1H), 8.12 (m, 2H), 8.02 (m, 1H), 7.83 (m, 1H), 7.65 (m, 3H), 7.581 (m, 3H), 4.75 (m, 1H), 4.28 (AB, 2H), 3.28 (m, 1H), 2.87 (m, 1H); FAB MS $[M + H]^+ = 409$; RP-HPLC analysis (C18, 20-min linear gradient; elution 10−100% CH_3CN/0.1% TFA H_2O; flow rate 1.0 mL/min) indicated that the product was 98.5A%.

Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopiperidin-3-(*S*)-yl}amide Trifluoroacetate (7). ^{1}H NMR (DMSO-d_6) δ 9.29 (bs, 2H), 9.19 (bs, 2H), 8.48 (s, 1H), 8.04 (m, 4H), 7.90 (d, 1H), 7.60 (m, 6H), 4.48 (s, 2H), 3.95 (m, 1H), 3.18 (s, 2H), 1.86 (m, 1H), 1.69 (m, 3H); FAB MS $[M + H]^+ = 437$. Anal. ($C_{23}H_{24}N_4O_3S$·TFA·H_2O) C, H, N.

Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxoazepan-3-(*S*)-yl}amide Trifluoroacetate

(8). ^{1}H NMR (DMSO-d_6) δ 9.22 (bs, 2H), 9.06 (bs, 2H), 8.40 (s, 1H), 8.05 (m, 3H), 7.85 (m, 2H), 7.63 (m, 2H), 7.48 (m, 1H), 7.15 (m, 1H), 7.02 (m, 1H), 4.70 (d, 1H), 4.22 (m, 1H), 4.18 (d, 1H), 3.40 (m, 1H), 3.10 (m, 1H), 1.72 (m, 2H), 1.48 (m, 3H), 1.17 (m, 1H); FAB MS $[M + H]^+ = 423$. Anal. ($C_{24}H_{26}N_4O_3S\cdot TFA\cdot 1.25H_2O$) C, H, N.

Naphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]pyrrolidin-3-(*S*)-yl}amide Bistrifluoroacetate (2). Prepared from naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)pyrrolidin-3-(*S*)-yl]amide which is obtained from 3-(*S*)-aminopyrrolidine by selective Boc protection,[28] sulfonylation with 2-naphthalenesulfonyl chloride, Boc deprotection, and alkylation with α-bromo-*m*-toluyl nitrile: ^{1}H NMR (DMSO-d_6) δ 9.32 (bs, 4H), 8.45 (s, 1H), 8.14 (m, 2H), 8.05 (d, 1H), 7.72 (m, 8H), 4.35 (s, 2H), 3.85 (m, 1H), 3.25 (m, 4H), 1.95 (m, 2H); FAB MS $[M + H]^+ = 409$. Anal. ($C_{22}H_{24}N_4O_2S\cdot 2.0TFA\cdot 1.25H_2O$) C, H, N.

Alternate Conversion of Heteroaryl Nitriles to Heteroaryl Amidines (compounds 35, 43, 1, and 5). 7-Methoxynaphthalene-2-sulfonic Acid {1-[3-(Aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}(pyrazol-3-ylmethyl)-amide Hydrochloride (35). Hydrogen sulfide gas is bubbled for 5 min through a solution of 7-methoxy-2-naphthalenesulfonic acid {1-[3-cyanobenzyl]-2-oxo-3-(*S*)-pyrrolidin-3-yl}-(pyrazol-3-ylmethyl)amide (0.37 g, 0.6 mmol) in 10 mL of a 10:1 mixture of pyridine/triethylamine. After the pale green solution is stirred for a period of 18 h, the reaction mixture is concentrated in vacuo. The residue is diluted in acetone and concentrated to give the crude thioamide. To a solution of thioamide in 20 mL of acetone is added methyl iodide (2 mL, 32 mmol). The resulting mixture is heated at reflux for 2 h, allowed to cool to room temperature, and concentrated in vacuo to provide the crude thioimidate hydroiodide. To a solution of thioimidate hydroiodide in 20 mL of MeOH is added ammonium acetate (0.24 g, 3.17 mmol). The resulting mixture is heated at reflux for 3 h and then allowed to cool to room temperature. The resulting mixture is concentrated in vacuo, and the crude product is converted to the hydrochloride salt with methanolic HCl then purified by RP-HPLC eluting with a gradient of 5% CH_3CN/H_2O to 50% CH_3CN/H_2O; the appropriate product fractions are lyophilized to provide the 7-methoxynaphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)benzyl]-2-oxopyrrolidin-3-(*S*)-yl}(pyrazol-3-ylmethyl)amide hydrochloride (0.045 g, 0.08 mmol) as an amorphous white solid: ^{1}H NMR (DMSO-d_6) δ 9.35 (bs, 2H), 9.07 (bs, 2H), 8.46 (s, 1H), 8.03 (d, 1H), 7.98 (d, 1H), 7.72 (d, 1H), 7.58 (d, 1H), 7.55−7.64 (m, 5H), 7.36 (dd, 1H), 6.12 (s, 1H), 4.80 (t, 1H), 4.40 (two AB, 4H), 3.90 (s, 3H), 3.14 (m, 1H), 3.03 (m, 1H), 2.12 (m, 1H), 1.69 (m, 1H); FAB MS $[M + H]^+ = 533$. Anal. ($C_{27}H_{28}N_6O_4S\cdot HCl\cdot 1.6H_2O$) C, H, N.

4-[3-(*S*)-(7-Methoxynaphthalen-2-ylsulfonylamino)-2-oxopyrrolidin-1-ylmethyl]pyridine-2-carboxamidine Trifluoroacetate (43). Prepared from 7-methoxynaphthalene-2-sulfonic acid [1-(2-cyanopyridin-4-ylmethyl)-2-oxopyrrolidin-3-(*S*)-yl]amide. Anal. ($C_{22}H_{23}N_5O_4S\cdot TFA\cdot 1.5H_2O$) C, H, N.

1-[3-(Aminoiminomethyl)benzyl]-3-(2-β-naphthylethyl)-indole Trifluoroacetate (1). Prepared from 1-(3-cyanobenzyl)-3-(2-β-naphthylethyl)indole which is obtained from indole-3-carboxaldehyde by alkylating with α-bromo-*m*-toluyl nitrile, aldehyde homologation with (naphthalen-2-ylmethyl)phosphonic acid diethyl ester cf. Nagarathnam,[29] followed by olefin reduction under hydrogenation conditions: ^{1}H NMR (DMSO-d_6) δ 9.32 (bs, 2H), 9.10 (bs, 2H), 7.84 (m, 4H), 7.75 (s, 1H), 7.64 (m, 2H), 7.42 (m, 5H), 7.28 (s, 1H), 7.22 (d, 1H), 7.10 (m, 1H), 7.02 (m, 1H), 5.40 (s, 2H), 3.11 (bs, 4H); FAB MS $[M + H]^+ = 404$; RP-HPLC analysis (C18, 30-min linear gradient; elution 10−100% CH_3CN/0.1% TFA H_2O; flow rate 1.0 mL/min) indicated that the product was 97.9A%.

***N*-[3-(Aminoiminomethyl)benzyl]-2-(naphthalen-2-ylsulfonylamino)acetamide Trifluoroacetate (5).** Prepared from *N*-(3-cyanobenzyl)-2-(naphthalen-2-ylsulfonylamino)acetamide which is obtained from glycine methyl ester hydrochloride by sulfonylation with 2-naphthalenesulfonyl chloride, ester hydrolysis, and amide formation with *m*-cyanobenzylamine hydrochloride:[12] ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 2H), 9.08 (s, 2H), 8.50 (t, 1H), 8.42 (s, 1H), 8.12 (m, 3H), 8.03 (d, 1H), 7.81 (d, 1H), 7.56 (m, 4H), 7.46 (m, 2H), 4.26 (d, 2H), 3.52 (d, 2H); FAB MS $[M + H]^+ = 397$. Anal. ($C_{20}H_{20}N_4O_3S\cdot TFA$) C, H, N.

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