Articles

Discovery of 1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-dimethylaminomethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide Hydrochloride (Razaxaban), a Highly Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor

Mimi L. Quan,*,§ Patrick Y. S. Lam,§ Qi Han,§ Donald J. P. Pinto,§ Ming Y. He,§ Renhua Li,§ Christopher D. Ellis,§ Charles G. Clark,§ Christopher A. Teleha,§ Jung-Hui Sun,§ Richard S. Alexander,§ Steve Bai,† Joseph M. Luettgen,‡ Robert M. Knabb,‡ Pancras C. Wong,‡ and Ruth R. Wexler§

Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., P.O. Box 5400, Princeton, New Jersey 08543-5400

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Modification of a series of pyrazole factor Xa inhibitors to incorporate an aminobenzisoxazole as the P_1 ligand resulted in compounds with improved selectivity for factor Xa relative to trypsin and plasma kallikrein. Further optimization of the P_4 moiety led to compounds with enhanced permeability and reduced protein binding. The SAR and pharmacokinetic profile of this series of compounds is described herein. These efforts culminated in 1-(3′-aminobenzisoxazol-5′-yl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-dimethylaminomethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (**11d**), a potent, selective, and orally bioavailable inhibitor of factor Xa. On the basis of its excellent in vitro potency and selectivity profile, high free fraction in human plasma, good oral bioavailability, and in vivo efficacy in antithrombotic models, the HCl salt of this compound was selected for clinical development as razaxaban (DPC 906, BMS-561389).

Introduction

Thromboembolic disorders including acute myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism, and ischemic stroke continue to be the leading cause of morbidity and mortality in the U.S. and other Western countries. Current therapies for the treatment and prevention of thrombotic disorders are inadequate because they require parenteral administration or careful monitoring of clotting time to achieve desired efficacy and dose titration to minimize excessive bleeding.[1] Therefore, there is a significant medical need for safer and more effective orally active anticoagulants to combat these diseases.

Factor Xa is a key serine protease in the coagulation cascade and is a promising target enzyme for the design of new therapeutic agents with potential for the treatment and prevention of arterial and venous thrombosis.[2] Factor Xa is essential in the formation of thrombin, a key mediator of both fibrin formation and platelet activation. It plays an important role in the coagulation network at the common pathway that connects both the tissue factor-activated extrinsic pathway and the surface-activated intrinsic pathway.[3] Factor Xa, together with calcium and factor Va, forms the prothrombinase complex, which amplifies the procoagulant action of factor Xa. Factor Xa acts at an earlier level in the coagulation cascade than thrombin. Inactivation of factor Xa by specific inhibitors does not influence preformed thrombin but does effectively prevent the generation of thrombin. Extensive preclinical and clinical proof-of-principle data show that inhibition of factor Xa is effective in both venous and arterial thrombosis.[2] In animal models a better therapeutic index (antithrombotic efficacy vs antihemostatic effects) has been shown for direct factor Xa inhibitors compared with that for direct thrombin inhibitors.[4,5] On the basis of these data, a cleaner side effect profile would be expected for a factor Xa inhibitor relative to a thrombin inhibitor in the clinical setting.[2]

Previous reports from our laboratories have detailed several approaches to the design of small-molecule factor Xa inhibitors.[6] These efforts resulted in the discovery of clinical candidate DPC423, which showed potent antithromobotic efficacy in animal models of thrombosis and excellent pharmacokinetics in preclinical and clinical studies.[5,7,8] Simultaneously, we evaluated the pharmacokinetic profile of an extensive series of compounds containing benzamidine P_1 mimics and found that the aminobenzisoxazole moiety showed an excellent balance of potency, selectivity, and oral bioavailability.[9] Therefore, a series of pyrazole derivatives containing an aminobenzisoxazole in the P_1 position was explored. Optimization of this series of compounds has culminated in the discovery of clinical candidate razaxaban (DPC 906, BMS-561389), a highly potent, selective, and orally bioavailable factor Xa inhibitor.

* To whom correspondence should be addressed. Phone: (609) 818-5301. Fax: (609) 818-3331. E-mail: mimi.quan@bms.com.
§ Discovery Chemistry.
† Clinical Discovery.
‡ Discovery Biology.

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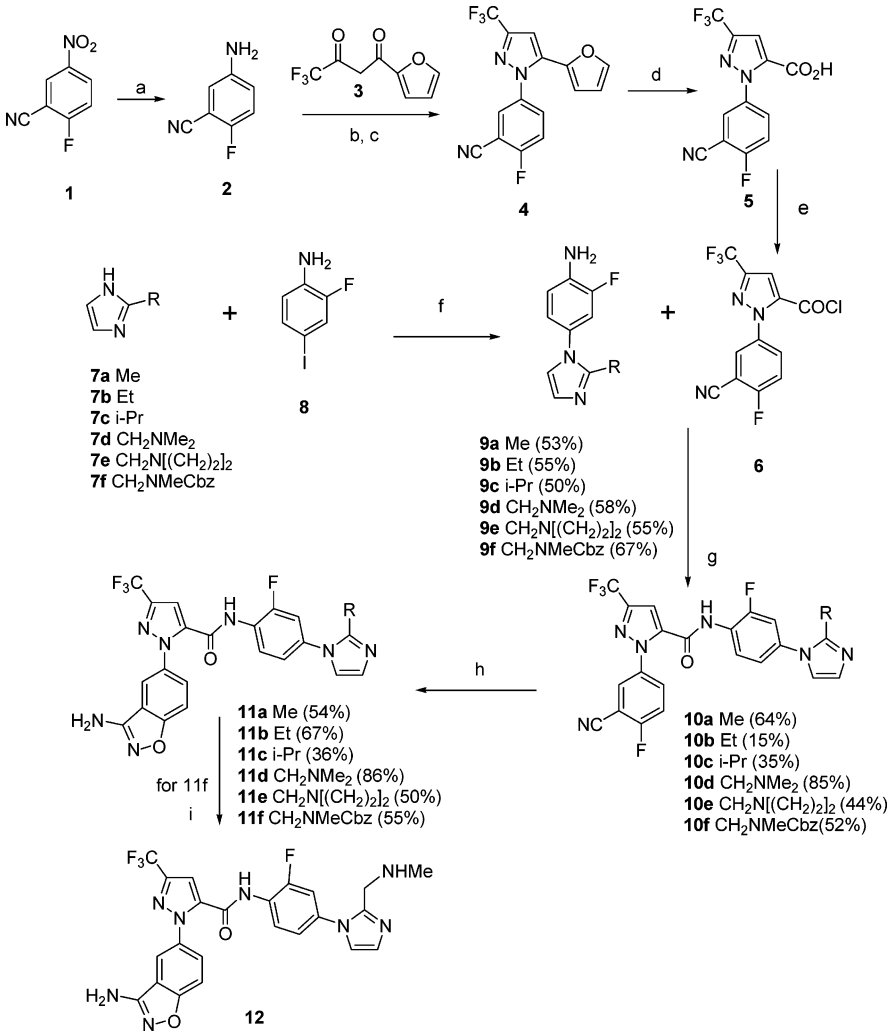
Scheme 1. Synthesis of **11d** (Razaxaban) and Related Analogues[a]



[a] Reagents: (a) $SnCl_2$, EtOAc, reflux, 85%; (b) $NaNO_2$, concentrated HCl; $SnCl_2$, HCl; (c) HOAc, reflux, 31% for steps b and c; (d) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 64%; (e) $(COCl)_2$, CH_2Cl_2, reflux, quantitative; (f) K_2CO_3, CuI, DMSO, 120 °C, 50−67%; (g) DMAP, CH_2Cl_2, 15−85%; (h) MeCONHOH, *t*-BuOK or K_2CO_3, DMF, 36−86%; (i) TFA, reflux, 67%.

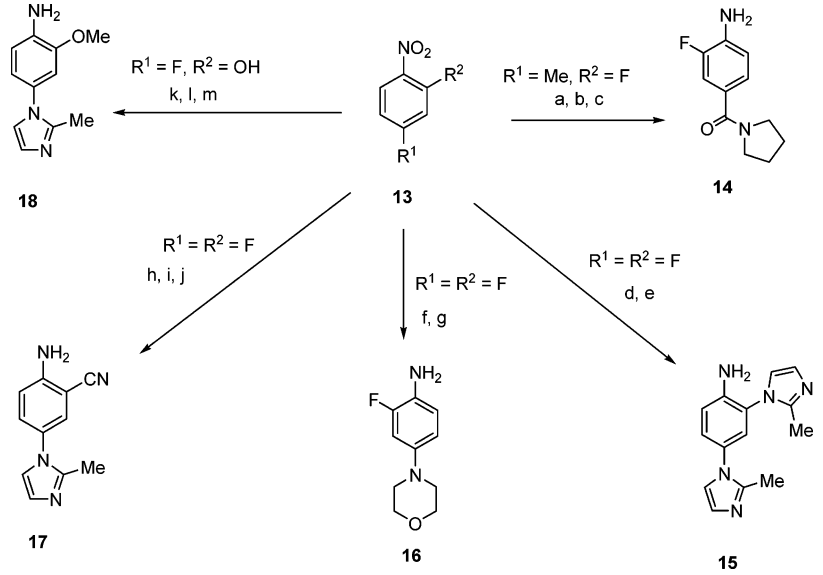
Chemistry

The syntheses of **11d** and related analogues were prepared as shown in Scheme 1. Reduction of commercially available 2-fluoro-5-nitrobenzonitrile **1** afforded aniline **2**. Diazotization and reduction with stannous chloride gave the hydrazine as the tin salt, which was reacted with commercially available 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione **3** in situ to give pyrazole **4**. The furan ring was then oxidized with sodium periodate to give acid **5**,[5b] which was converted to the acyl chloride **6** with oxalyl chloride. Anilines **9a**−**f** were prepared via Ullmann[10] coupling of imidazoles **7a**−**f** with 2-fluoro-4-iodoaniline **8**. Imidazoles **7a**−**c** were obtained commercially, and **7d**−**e** were obtained from reductive amination of 2-imidazolecarboxaldehyde with dimethylamine or pyrrolidine. Compound **7f** was prepared similarly by reductive amination of 2-imidazolecarboxyaldehyde with monomethylamine, followed by protection with CbzCl/Et_3N in CH_2Cl_2. Anilines **9a**−**f** were coupled with acyl chloride **6** with DMAP in CH_2Cl_2 to give amides **10a**−**f**. Reaction of **10a**−**f** with acetohydroxamic acid and potassium *tert*-butoxide or potassium carbonate in DMF gave aminobenzisoxazoles **11a**−**f**.[9] Cleavage of the Cbz group in **11f** was accomplished with TFA at reflux to afford the monomethyl compound **12**. Compounds **38** and **39** were prepared using 3-fluoro-2′-methanesulfonylbiphenyl-4-ylamine[7,11] and 4′-amino-3′-fluorobiphenyl-2-sulfonic acid amide[7,11] instead of aniline **9** following the procedures described in Scheme 1. Similarly, compounds **40**, **41**, **42**, **44**, and **45** were prepared from anilines **14**, **16**, **17**, **15**, and **18**, respectively. The syntheses of these anilines are shown in Scheme 2.

The pyridyl analogue **23** was prepared as shown in Scheme 3. Acyl chloride **6** was coupled with 4-iodo-2-fluoroaniline **8** to give amide **19**. Conversion of the iodo intermediate to boronic ester **20**, followed by coupling with bromide **21**, afforded biaryl compound **22**. Aminobenzisoxazole formation using the same methods described for **11d** resulted in compound **23**.

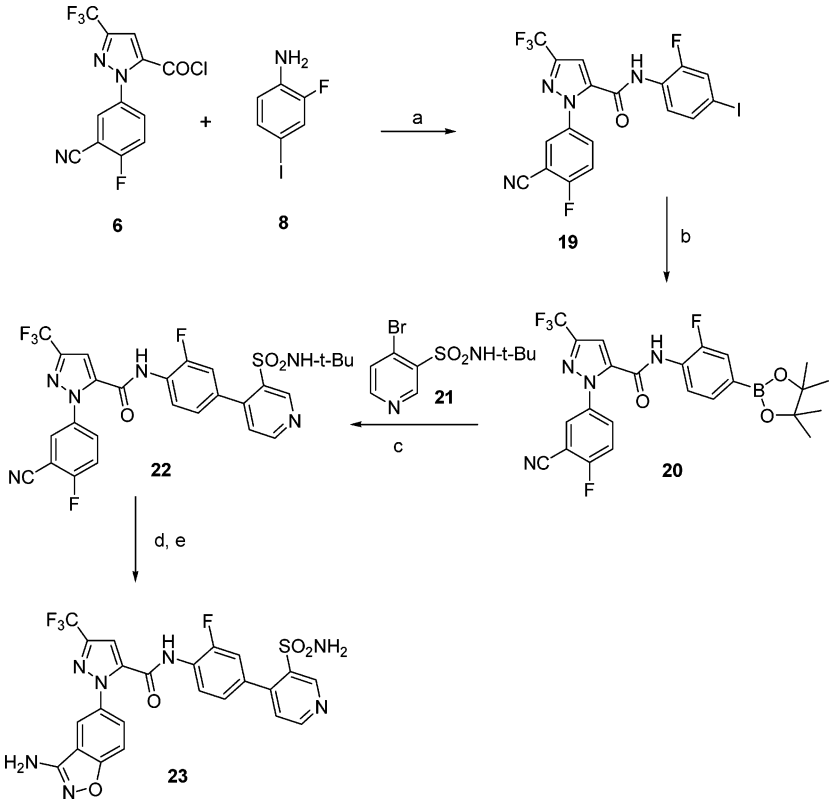
The synthesis of compound **28** is shown in Scheme 4. 2-Fluoro-4-bromoaniline was protected with a Boc group and then coupled with tin intermediate **25**, which was prepared via lithiation of 1-methylimidazole with *n*-BuLi, followed by reaction with Bu_3SnCl. Removal of the Boc group with HCl resulted in aniline **26**. Acid **5** was esterified with sulfonyl chloride and methanol. The resulting product was converted to aminobenzisoxazole

Scheme 2. Syntheses of 4-Substituted Anilines[a]



[a] Reagents: (a) $K_2Cr_2O_7$, 82%; (b) $(COCl)_2$, CH_2Cl_2; pyrrolidine, Et_3N, CH_2Cl_2; (c) H_2, 5% Pd/C, 55% for steps b and c; (d) 2-methylimidazole, CH_3CN, K_2CO_3, reflux, 90%; (e) H_2, 10% Pd/C, 56%; (f) morpholine, THF, 8%; (g) H_2, 10% Pd/C, 95%; (h) NaCN, DMF, 31%; (i) 2-methylimidazole, CH_3CN, 96%; (j) H_2, 10% Pd/C, 98%; (k) 2-methylimidazole, CH_3CN, 78%; (l) MeI, K_2CO_3, 20%; (m) H_2, 10% Pd/C, quantitative.

Scheme 3. Synthesis of Compound **23**[a]

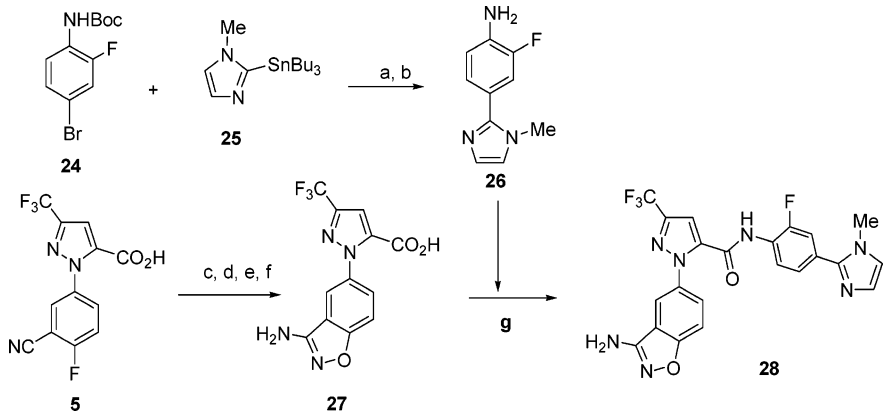


[a] Reagents: (a) DMAP, CH_2Cl_2, 45%; (b) KOAc, pinacol diborane, $PdCl_2$(dppf), DMSO, 80 °C; (c) $Pd(PPh_3)_4$, EtOH, toluene, reflux; (d) MeCONHOH, K_2CO_3, DMF; (e) TFA, 15% for the steps b−e.

with acetohydroxamic acid and potassium *tert*-butoxide, followed by reaction with 18% aqueous HCl in methanol and dichloromethane. Hydrolysis of the ester group resulted in acid **27**, which coupled with aniline **26** using DMAP and PyBrop to give compound **28**.

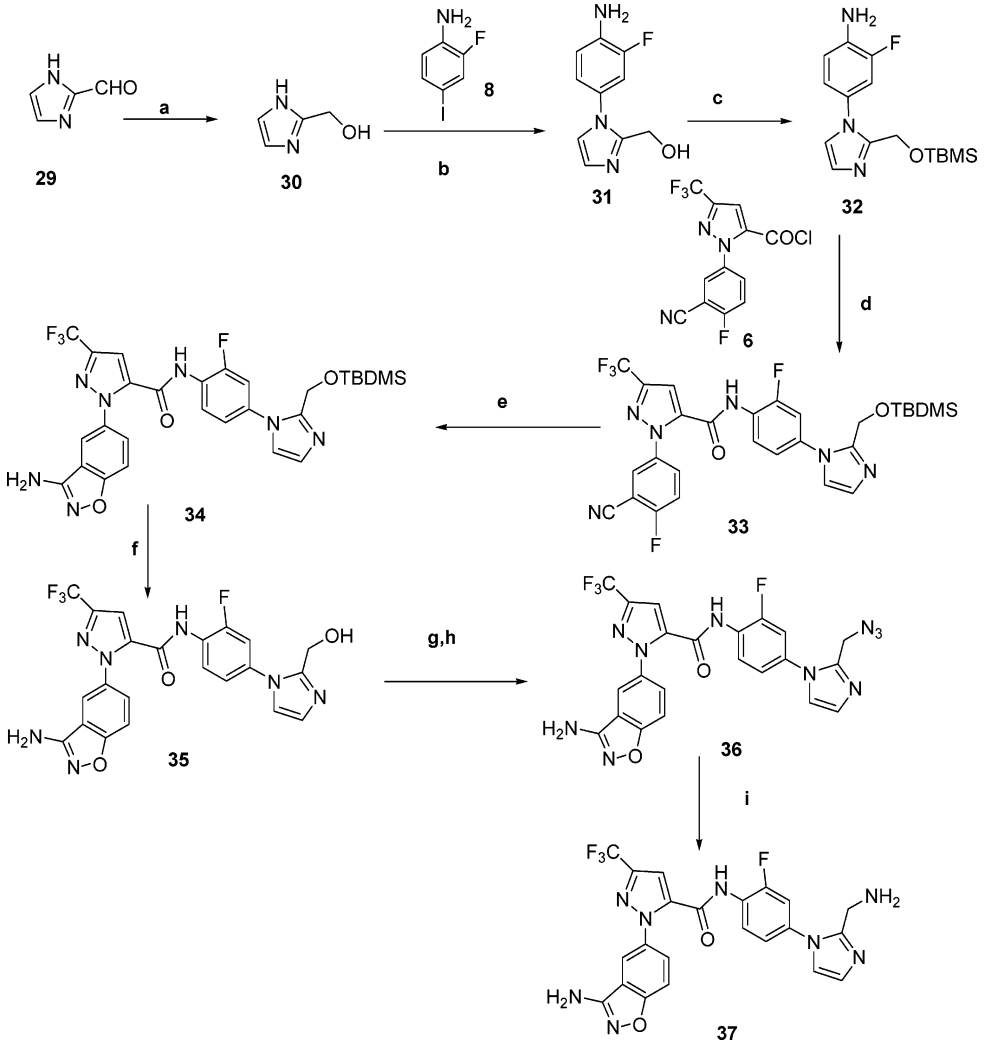
The synthesis of aminomethylimidazole **37** is shown in Scheme 5. 2-Imidazolecarboxaldehyde **29** was reduced to the corresponding alcohol **30** with sodium borohydride. Aniline **31** was prepared via the coupling of alcohol **30** with 2-fluoro-4-iodoaniline **8** using Ullmann conditions as described above. The alcohol group was protected as the TBDMS ether and then coupled with acyl chloride **6** in DMAP to afford amide **33**. Compound **33** was converted to aminobenzisoxazole **34** by reaction with acetohydroxamic acid and potassium carbonate. Removal of the TBDMS group with

Scheme 4. Synthesis of Compound **28**[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, THF, reflux, 60%; (b) HCl, EtOAc, 83%; (c) $SOCl_2$, MeOH, 92%; (d) MeCONHOH, *t*-BuOK, DMF, 68%; (e) 18% aqueous HCl, MeOH/CH_2Cl_2, reflux, 65%; (f) NaOH, THF, 96%; (g) PyBrop, (*i*-Pr)$_2$NEt, DMF, 60 °C, 41%.

Scheme 5. Synthesis of Compound **37**[a]



[a] Reagents: (a) $NaBH_4$, MeOH, 45%; (b) K_2CO_3, CuI, DMSO, 120 °C, 10%; (c) TBDMSCl, Et_3N, DMF, 67%; (d) DMAP, CH_2Cl_2, 53%; (e) MeCONHOH, K_2CO_3, DMF; (f) Bu_4NF (1 N in THF), THF, 90% for steps e and f; (g) PBr_3, CH_2Cl_2; (h) NaN_3, DMF; (i) $SnCl_2$, MeOH, reflux, 15% for steps g−i.

n-Bu_4NF in THF (1 N) afforded the alcohol functionality, which was then converted to the bromide with PBr_3. Reaction of the bromide with sodium azide afforded azide **36**, which was reduced with $SnCl_2$ to provide aminomethylimidazole **37**.

Results and Discussion

Our first clinical candidate, DPC423, a potent and orally active factor Xa inhibitor (Figure 1),[5,7,8] showed excellent selectivity over thrombin and many other

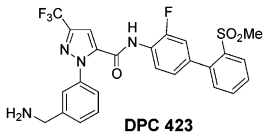
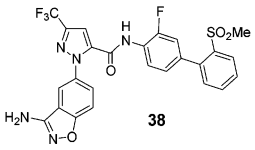
Human Enzyme K_i[21] (nM)	 DPC 423	 38
Factor Xa	0.15	0.09
Trypsin	60	>5200
Kallikrein	61	>2300
Thrombin	6000	6300
Factor IXa	2200	3500
Factor VIIa	>15000	>15000
Chymotrysin	>17000	2300
Urokinase	>17000	16000
Activated Protein C	1800	28000

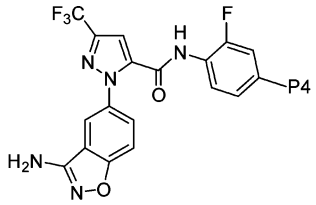
Figure 1. Comparison of benzylamine and aminobenzisoxazole P_1.

serine proteases (>10000-fold) with the exception of trypsin and plasma kallikrein in which selectivity was approximately 400-fold. We have previously demonstrated that selectivity for factor Xa over other trypsin-like serine proteases was significantly improved by replacement of the benzamidine P_1 moiety with a larger P_1 ligand such as aminobenzisoxazole.[9] We believe this increased selectivity is due to the larger S_1 pocket in factor Xa relative to other serine proteases such as trypsin (Ala190 at the bottom of the S_1 pocket in factor Xa compared to Ser190 in trypsin). Indeed, replacement of the benzylamine in DPC423 with an aminobenzisoxazole P_1 moiety (**38**, Figure 1) greatly improved the selectivity for factor Xa relative to trypsin and plasma kallikrein from approximately 400-fold to >25000-fold while maintaining the factor Xa potency and selectivity over other key serine proteases. Albeit highly selective, aminobenzisoxazole **38** had several limitations including poor permeability (Caco-2 Papp is $<0.1 \times 10^{-6}$ cm/s)[12] and poor solubility (<0.0001 mg/mL).[13] As predicted by the poor permeability, compound **38** was found to have only 2% bioavailability when administered orally to dogs (0.2 mg/kg, $n = 2$). These issues precluded compound **38** from further advancement.

In an effort to address the permeability issue, we investigated the replacement of the terminal phenyl ring with heterocycles (Table 1). Pyridylsulfonamide **23** maintained factor Xa inhibitory potency and improved Caco-2 permeability slightly compared with phenylsulfonamide **39**. Incorporation of solubilizing heterocycles such as 1-methylimidazol-2-yl and 2-methylimidazol-1-yl groups greatly improved Caco-2 permeability (**28** and **11a**) but showed a 3-fold decrease in factor Xa inhibitory potency. Employing less lipophilic neutral moieties such as pyrrolidinylamide **40** also improved the permeability, but at a greater expense of factor Xa inhibitory potency (5-fold loss). Replacement of the terminal ring with a morpholino group resulted in compound **41** with a 40-fold reduction in factor Xa inhibitory potency. Although improved permeability was obtained by replacing the terminal phenyl ring with solubilizing groups with reduced lipophilicity, protein binding was high for **11a**, **28**, and **40** (98.0%, 97.5%, and 97.0% bound to human plasma, respectively),[14] which resulted in low anticoagulant activity as shown by their aPTT values[15] (Table 1). Therefore, reducing protein binding was necessary in order to improve anticoagulant activity of these compounds. Since solubility was lower for compound **40** and since the 1-methylimidazol-yl **28** was less selective for factor Xa versus thrombin (thrombin $K_i = 34$ nM) compared to the 2-methylimidazol-1-yl analogue **11a**, further optimization focused on the 2-methylimidazol-1-yl series.

We have previously observed that substitution at the 2′-position on the proximal phenyl ring favorably affects both the factor Xa affinity and the pharmacokinetic profile of the compounds.[6−7,11] Therefore, a series of 2-methylimidazol-1-yl containing compounds were explored with a variety of substituents at the "ortho" position of the proximal phenyl ring (Table 2). The 2-fluoro analogue **11a** provided the best combination of potency and permeability. Cyano-substituted analogue **42** maintained factor Xa inhibitory potency; however, the permeability was decreased. Other "ortho"-substituted compounds such as imidazole **44**, methoxy **45**, and amide **46** reduced factor Xa inhibitory affinity by 3-, 5-, and 13-fold, respectively. All the compounds listed in Table 2 have a trypsin K_i value greater than 2500 nM, and they are very selective over thrombin except for **45** with a thrombin K_i of 200 nM. After determining that fluoro substitution improved Caco-2 permeability significantly (**11a**), this substituent was maintained while

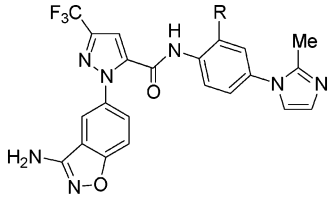
Table 1. Effect of P_4 Substitution on Caco-2 Permeability



Compd#	P4	fXa K_i	Thrombin K_i	Trypsin K_i	Caco-2 Papp[12] (cm/sec) x 10^{-6}	aPTT[15] (IC2x μM)
39		0.16	2300	>1600	< 0.1	12.3
23		0.10	740	>4200	0.54	15.5
28		0.51	34	>2500	4.69	9.4
11a		0.70	900	>2500	7.41	24.4
40		0.92	8000	>5200	24.9	13.8
41		6.30	20000	>5200	nd	nd

[a] K_i values in nM were obtained using human purified enzymes.[21]

Table 2. Effect of "Ortho" Substitution on Caco-2 Permeability



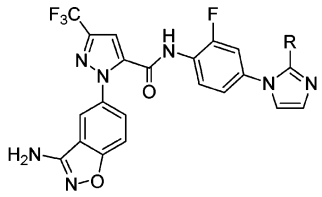
Compd#	R	fXa K_i	Thrombin K_i	Caco-2 Papp[12] (cm/sec) x 10^{-6}
42	CN	0.52	900	<0.1
43	H	0.60	1100	0.82
11a	**F**	**0.70**	**900**	**7.41**
44		1.60	800	nd
45	OMe	2.80	200	nd
46	$CONH_2$	7.70	>21000	nd

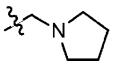
[a] K_i values in nM were obtained using human purified enzymes.[21] Trypsin K_i > 2500 nM for all compounds.

further optimization of the heterocyclic portion of the P_4 moiety was investigated.

Further modification of the substituent at the 2-position of the imidazole was explored in an attempt to further improve S_4 binding and to decrease protein binding (Table 3). Replacement of the methyl group with an ethyl group at the 2-position of the imidazole resulted in **11b** with similar factor Xa activity, while a decrease in factor Xa inhibitory potency was observed for the isopropyl analogue **11c**. Introduction of a hydroxymethyl or an aminomethyl moiety at the 2-position of the imidazole resulted in decreased Caco-2 permeability (**35**) and in decreased potency (**37**). However, alkylation of this aminomethyl group resulted in improved factor Xa inhibitory affinity as observed in compounds **12**, **11d**, and **11e**. The dialkylated compounds **11d** and **11e** showed good Caco-2 permeability relative to the monomethylated compound **12**. Furthermore, human plasma protein binding was reduced for the dimethylated and the monomethylated compounds **11d** and **12** (90.5% and

Table 3. Effect of 2-Imidazole Substitution on Permeability and Human Plasma Protein Binding



Compd #	R	fXa K_i	Thrombin K_i	Caco-2 Papp[12] (cm/sec) x 10^{-6}	Human Plasma Protein Binding[14]	aPTT[15] (IC2x μM)
11a	Me	0.70	900	7.41	98.0 %	24.4
11b	Et	0.73	900	3.32	95.0 %	14.3
11c	i-Pr	1.60	900	nd	nd	nd
35	CH_2OH	1.00	1700	0.10	nd	nd
37	CH_2NH_2	3.00	3500	nd	nd	nd
12	**CH_2NHMe**	**0.17**	**1700**	**0.20**	**85.6 %**	**5.9**
11d	**CH_2NMe_2**	**0.19**	**600**	**5.56**	**90.5 %**	**6.1**
11e		0.37	600	23.00	nd	nd

[a] K_i values in nM were obtained using human purified enzymes.[21]

Table 4. Dog Pharmacokinetics Profile[a]

Comp d#	fXa K_i (nM)	Caco-2 Papp[12] (cm/sec) x 10^{-6}	Cl L/h/kg	t1/2 h	Vdss L/kg	F %
12	0.17	0.2	1.1	3.7	4.6	27
11d	**0.19**	**5.56**	**1.1**	**3.4**	**5.3**	**84**

[a] Compounds were dosed as TFA salts in an *N*-in-1 format[24] at 0.4 mg/kg iv and 0.2 mg/kg po. ($n = 2$).

85.6%, respectively).[14] The lower protein binding resulted in higher anticoagulation activity observed in the aPTT assay for **11d** and **12** (Table 3).

As a result of the excellent in vitro profiles of compounds **12** and **11d**, the pharmacokinetic profiles of these compounds were studied in dogs (Table 4). While the clearance values of the mono- and dimethylaminomethylimidazole compounds **12** and **11d** were determined to be similar, dimethylaminomethylimidazole **11d** showed significantly better oral bioavailability (*F* is 84% compared to 27%) as predicted by the observed Caco-2 permeability for these two compounds.

An X-ray crystal structure of **11d** in the human factor Xa active site was obtained at 1.8 Å resolution with a crystallographic *R* factor of 0.207 (Figure 2). The overall binding mode was found to be similar to what was observed for DPC423.[16] The inhibitor was shown to bind to the active site through interactions with the S_1 and S_4 pockets with no major reorientation of the protein upon inhibitor binding. As anticipated, the aminobenzisoxazole group was bound in the S_1 pocket. The amino group formed hydrogen bonds with Asp189 (2.7 Å) and the carbonyl group of Gly218 (3.5 Å). As indicated earlier, the specificity of this series of inhibitors over trypsin can be attributed to the binding mode in the S_1 pocket. The aminobenzisoxazole is observed to bind in close contact with the side chain of Ala190 (3.4 Å) in factor Xa. This orientation would lead to unfavorable interactions in trypsin (Ser190) if a similar binding mode was employed. The pyrazole ring was optimally oriented for the N-2 nitrogen to interact with the backbone NH of Gln192 (3.4 Å). The pyrazole 3-trifluoromethyl group partially fit in the small lipophilic pocket above the S_1 pocket near the Cys191−220 disul-

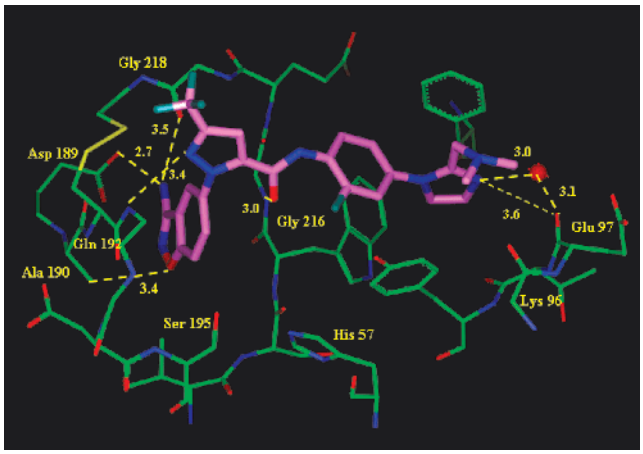
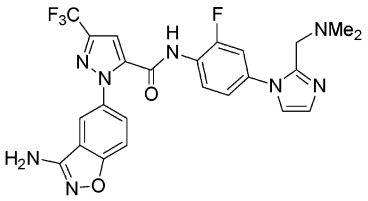


Figure 2. X-ray structure of **11d** (razaxaban) in the factor Xa active site. The amino group formed hydrogen bonds with Asp189 (2.7 Å) and the carbonyl group of Gly218 (3.5 Å). The pyrazole N-2 nitrogen interacts with the backbone NH of Gln192 (3.4 Å). The 5-carboxamide carbonyl showed a strong interaction with the NH of Gly216 (3.0 Å). The N-3 nitrogen of the imidazole P_4 group formed a direct H bond (3.6 Å) and indirect H bonds through an H_2O molecule (3.0 and 3.1 Å) with Glu97.

Table 5. Human Enzyme Selectivity Profile for Razaxaban



Human Enzyme	K_i (nM)
Factor Xa	0.19
Trypsin	>10000
Plasma Kallikrein	>2300
Activated Protein C	19700
Factor IXa	9000
Factor XIa	>12000
Thrombin	540
Factor VIIa	>15000
Chymotrypsin	8500
Urokinase	>13000
Plasmin	>15000
tPA	>33000

[a] All K_i values were obtained using human purified enzymes.[21]

fide bridge. The 5-carboxamide carbonyl showed a strong interaction with the NH of Gly216 (3.0 Å). The orientation of the 5-carboxamide functionality allowed the phenylimidazole P_4 moiety to nicely fit into the S_4 region of the enzyme. The N-3 nitrogen of the imidazole P_4 group formed a direct hydrogen-bonding interaction with Glu97 (3.6 Å) as well as an indirect hydrogen-bonding interaction to the same residue through an H_2O molecule (3.0 and 3.1 Å). It is not clear from the X-ray structure how the dimethyl group contributes to the factor Xa potency. Overall, the inhibitor was highly constrained and fit into the enzyme active site in a complementary manner.

Compound **11d** exhibited excellent selectivity (>5000-fold) against related serine proteases (Table 5). The anticoagulant activity of **11d** was evaluated in the in vitro human plasma aPTT and human prothrombin time (PT) assays.[15] In these assays, **11d** showed a doubling of aPTT and PT at 6.1 and 2.1 μM, respectively. The human and rabbit plasma protein binding were found to be 90.5% and 93.4%, respectively, using equilibrium dialysis.[14] Compound **11d** was found to have similar affinity in the rabbit factor Xa assay with a K_i of 0.16 nM. Upon intravenous dosing in the rabbit arterio-venous shunt thrombosis model,[17a] compound **11d** inhibited thrombus formation in a dose-dependent manner with an ID_{50} of 1.6 μmol kg^{-1} h^{-1} (Figure 3).[17b] Compound **11d** has an ID_{50} comparable to that for DPC423 (ID_{50} = 1.1 μmol kg^{-1} h^{-1})[5,7] in this model. On the basis of its factor Xa inhibitory affinity, selectivity over other enzymes, bioavailability, and in vivo antithrombotic efficacy, the HCl salt of compound **11d** (razaxaban, DPC 906, BMS-562389) was selected for clinical trials.

Conclusion

Replacement of the benzylamine P_1 moiety of DPC423 with an aminobenzisoxazole afforded compounds with improved selectivity over trypsin and plasma kallikrein.

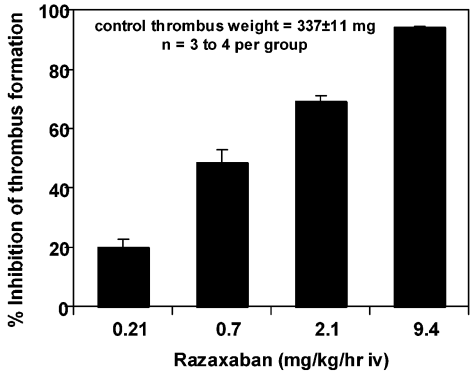


Figure 3. Antithrombotic effect of razaxaban in the rabbit arterio-venous shunt thrombosis model.

However, the resulting compounds were poorly soluble, poorly permeable, and highly protein-bound. Employing solubilizing and less lipophilic heterocycles at the terminal ring of the P_4 moiety led to the identification of phenylimidazole analogues with increased permeability. Substitution of the 2-position of the imidazole with a dimethylaminomethyl moiety reduced protein binding and provided the best balance of potency, selectivity, and pharmacokinetic profile. These efforts culminated in the discovery of clinical candidate razaxaban, a potent, selective, and orally active factor Xa inhibitor that shows antithrombotic efficacy in the rabbit arterio-venous shunt thrombosis model.

Experimental Section

All reactions were run under an atmosphere of dry nitrogen unless otherwise noted. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used without further purification unless otherwise indicated. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on VXR or Unity 300 MHz instruments (Varian Instruments, Palo Alto, CA) with chemical shift in ppm downfield from TMS as an internal reference standard. ^{1}H assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). Elemental analyses were performed by Quantitative Technologies, Inc. (Whitehouse, NJ 08888) and were within 0.4% of the theoretical values. Mass spectra were measured with an HP 5988A mass spectrometer with a particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 ionization. Flash chromatography was done using EM Science silica gel 60 (230−400 mesh). Preparative thin-layer chromatography was done on EM Science 60 plates F_{254} (2 mm; 20 cm × 20 cm). HPLC purification was performed on a Jasco 900 series instrument or a Rainin Dynamax SD200 using a C18 reverse-phase column with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase. All compounds were found to be >95% pure by HPLC analysis unless otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

The factor Xa−**11d** crystals were obtained from GLA-domainless β-factor Xa (Haematologic Technologies) that had been fractionated on a Pharmacia mono-Q 10/10 column equilibrated with 50 mM Tris, pH 8.0, 100 mM NaCl, and 1 mM $CaCl_2$ and eluted with a 20-bed volume, 0−500 mM NaCl gradient. Inhibitor was added to the fractions as they were collected. The protein eluted at about 100 mM NaCl. This solution was incubated for 12 h and concentrated to 6 mg/mL using a Vivaspin 6 mL concentrator with a 5000 molecular weight cut-off (MWCO) membrane. The crystals were grown using hanging drop vapor diffusion at 4 °C with 18% PEG 6000

buffered with 200 mM NaOAc (pH 5.5) in the reservoir. The drops contain 4 μL of protein solution and 4 μL of reservoir solution. The drops were microseeded with a crushed crystal from a previous crystal growth. The cryoprotectant was introduced to the factor Xa crystals by first transferring the crystals to a 2 μL drop of the soaking solution. This drop was then bridged into a 20 μL drop of a solution of 22% PEG with 200 mM sodium acetate, pH 5.5, and 20% ethylene glycol. After about a minute, the crystals were frozen. Data for the Xa−**11d** complex were collected at the DND beamline 4 ID at the Advanced Photon Source using a marCCD detector. Data were collected at 100 K using an Oxford cryosystems cooling device with a wavelength of 1.0 Å. Data frames of 1° rotation were collected. Data were 99% complete. Raw data were processed with the program Scalepack/Denzo.[18]

The program EPMR[19] was used to determine the initial model for refinement using the PDB coordinates 1fjs (minus the inhibitor and solvent molecules) as the search model. The CNX (Accelrys) program was used for crystallographic refinement. Simulated annealing (at a maximum temperature of 3000 °C) was followed by B-factor refinement. The inhibitors were built with the program QUANTA (Accelrys). Peaks in the difference electron density map that were greater than 3σ and were less than 4 Å away from the protein were built in as solvent molecules. No major adjustments to the protein model were needed during the course of the refinements. Final *R* factors as well as other relevant data collection statistics are found in the supporting data. Coordinates for the enzyme inhibitor structure will be deposited with the Protein Data Bank.[20]

2-Fluoro-5-aminobenzonitrile (2). To a solution of 2-fluoro-5-nitrobenzonitrile (2.0 g, 12 mmol) in ethyl acetate (50 mL) was added stannous chloride dihydrate (27.0 g). The mixture was brought to reflux for 1.5 h and allowed to cool. The mixture was partitioned between EtOAc and saturated sodium bicarbonate. The aqueous phase was extracted with EtOAc four times. The combined organic phases were washed with 4 × H_2O, dried over sodium sulfate, filtered, and concentrated to give 1.4 g (85%) of **2**. ^{1}H NMR (DMSO-d_6) δ 7.16 (t, J = 3.1 Hz, 1H), 6.87 (m, 2H), 5.49 (bs, 2H); MS m/z 137 $(M + H)^+$.

1-(4′-Fluoro-3′-cyanophenyl)-3-trifluoromethyl-5-furyl-1*H*-pyrazole (4). 2-Fluoro-5-aminobenzonitrile **2** (1.4 g, 10 mmol) was added to 10 mL of concentrated hydrochloric acid at 0 °C. Sodium nitrite (0.71 g) was dissolved in H_2O (3 mL), cooled to 0 °C, and added dropwise. The reaction mixture was stirred at 0 °C for 30 min. Stannous chloride dihydrate (6.95 g) was dissolved in HCl (concentrated, 4 mL) and cooled to 0 °C. It was then added dropwise to the reaction mixture. The reaction mixture was placed in the refrigerator for 12 h. The precipitate was isolated by filtration and washed with ice-cold brine (30 mL) followed by a 2:1 petroleum ether/ethyl ether (30 mL) solution. The yellow solid was dried under vacuum for 12 h to give 4-fluoro-3-cyanophenylhydrazine tin chloride (2.5 g).

To a suspension of 4-fluoro-3-cyanophenylhydrazine tin chloride (17 g, 50 mmol) in acetic acid (200 mL) was added 4,4,4-trifluoro-1-(2-furyl)-2,4-butanedione **3** (10.3 g, 50 mmol). The reaction mixture was heated to reflux for 12 h. The acetic acid was evaporated, and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with 1 N HCl, H_2O, and brine. It was then dried over sodium sulfate, filtered, and concentrated. Flash chromatography gave 7.0 g (44%) of **4**. ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.44 (d, J = 0.5 Hz, 1H), 7.34 (t, J = 2.8 Hz, 1H), 6.90 (s, 1H), 6.46 (m, 1H), 6.32 (d, J = 1.1 Hz, 1H); MS m/z 322 $(M + H)^+$.

1-(4′-Fluoro-3′-cyanophenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic Acid (5). To a solution of **4** (4.0 g, 12.5 mmol) in acetonitrile (30 mL) was added carbon tetrachloride (30 mL), ruthenium chloride (0.4 g), and a solution of sodium periodate (11.9 g, 56.1 mmol) in H_2O (45 mL). The reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was filtered through Celite. The filtrate was concentrated and partitioned between EtOAc and 1 N aqueous HCl. The organic phase was washed with H_2O, dried over sodium sulfate, filtered, and concentrated to give 2.4 g of acid **5** (64%). ^{1}H NMR(DMSO-d_6) δ 8.31−8.29 (m, 1H), 8.04−7.99 (m, 1H), 7.67 (t, J = 3.0 Hz, 1H), 7.47 (s, 1H); MS m/z 298 $(M - H)^-$.

2-Dimethylaminomethylimidazole (7d). To a 5 L three-neck round-bottomed flask equipped with a reflux condenser, pressure-equalizing addition funnel, and an internal temperature probe was added 2-imidazolecarboxaldehyde (100 g, 1.04 mol) in MeOH (1000 mL). To this suspension (ambient temperature) was added a solution of dimethylamine (40% aqueous, 1000 mL) at a fast dropping rate (20 min). After the addition was complete, solid sodium borohydride (118 g, 3.12 mol, 2.99 equiv) was CAUTIOUSLY added portionwise over 45 min. Foaming occurred after each portion, and the internal temperature was allowed to reach 54 °C without external cooling. The reaction mixture was then heated to 65 °C for 3 h and allowed to cool to ambient temperature for 12 h. The reaction contents were concentrated in vacuo and added to a 12 L separatory funnel containing brine (2 L). The contents were extracted with EtOAc (2 × 500 mL) and with $CHCl_3$ (4 × 1600 mL). The EtOAc extract was discarded. The $CHCl_3$ extract was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 99.0 g of the desired product **7d** as a waxy solid (76%): mp 58−59 °C; ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 2H), 3.62 (s, 2H), 2.30 (s, 6H); MS m/z 126 $(M + H)^+$.

2-(Pyrrolidin-1-ylmethyl)imidazole (7e). This compound was prepared following the same procedures described for **7d** using pyrrolidine instead of dimethylamine (56%). ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 2H), 6.33 (bs, 2H), 3.78 (s, 2H), 2.60 (m, 4H), 1.81 (m, 4H); MS m/z 152.2 $(M + H)^+$.

Benzyl 1*H*-Imidazol-2-ylmethyl(methyl)carbamate (7f). 2-Imidazolecarboxyaldehyde (5.0 g, 52.0 mmol) was suspended in 200 mL of methanol. Methylamine (20 mL of 33% solution in methanol) was added. After the mixture was stirred for 15 min, $NaBH_4$ (3.95 g, 0.10 mol) was added portionwise. The reaction mixture was then heated at 50 °C for 2 h under N_2. The solvent was removed. The solid was washed with CH_2Cl_2 and filtered. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, concentrated, and dried under vacuum to give 2-methylaminomethylimidazole as a yellow oil. This oil was dissolved in a 1:1 solution of CH_2Cl_2 and THF. To it was added Et_3N (7.94 mL, 57.0 mmol) and benzyl chloroformate (7.4 mL, 52.0 mmol). The mixture was stirred at ambient temperature under N_2 for 1 h. The solvent was removed, and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The mixture was heated to reflux with 15 mL of TFA for 30 min to convert most of the bis-acylated byproduct to the desired product. The TFA was removed. The mixture was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica gel, eluting with 1:1 EtOAc/hexane to give 6.56 g of benzyl 1*H*-imidazol-2-ylmethyl(methyl)carbamate **7f** (51.4% yield). ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 6H), 6.90 (s, 1H), 5.14 (s, 2H), 4.48 (s, 2H), 3.00 (s, 3H); MS m/z 246.3 $(M + H)^+$.

2-Fluoro-4-[(2-dimethylaminomethyl)imidazol-1-yl]aniline (9d). To a 500 mL round-bottomed flask equipped with a reflux condenser and an internal temperature probe was added 2-fluoro-4-iodoaniline **8** (9.8 g, 0.042 mol), K_2CO_3 (11.5 g, 0.083 mol, 2 equiv), Cu(I) (1.58 g, 0.0083 mol, 0.2 equiv), and **7d** (7.8 g, 0.023 mol, 1.5 equiv), followed by DMSO (300 mL). The reaction contents were heated to 120 °C for 12 h. After cooling to ambient temperature, the reaction mixture was partitioned between brine (1 L) and EtOAc (2 × 500 mL). The aqueous layer was extracted with additional $CHCl_3$ (500 mL) and kept separate. Both organic extracts were washed separately with brine, dried ($MgSO_4$), and filtered. They were then combined and concentrated. The crude black oil was purified on silica gel, eluting first with (a) $CHCl_3$, then (b) $CHCl_3$ (1 L with 8 drops of concentrated ammonia), (c) 5% MeOH in $CHCl_3$ (1 L with 8 drops of concentrated ammonia), and (d) 5% MeOH in $CHCl_3$ (5 L with 40 drops concentrated ammonia). The product was isolated (5.6 g) as a tan waxy solid

(58%): mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (dd, J = 11.7, 2.2 Hz, 1H), 7.09−7.01 (m, 2H), 6.81 (t, J = 8.6 Hz, 1H), 3.92 (bs, 2H), 3.36 (s, 2H), 2.25 (s, 6H); MS *m/z* 235 $(M + H)^+$.

2-Fluoro-4-[2-methylimidazol-1-yl]aniline (9a). This compound was prepared following the same procedures described for **9d** using 2-methylimidazole instead of 2-dimethylaminomethylimidazole (53%). ^{1}H NMR ($CDCl_3$) δ 6.99−6.80 (m, 5H), 3.92 (bs, 2H), 2.33 (s, 3H); MS *m/z* 192.0 $(M + H)^+$.

2-Fluoro-4-[2-ethylimidazol-1-yl]aniline (9b). This compound was prepared following the same procedures described for **9d** using 2-ethylimidazole instead of 2-dimethylaminomethylimidazole (55%). ^{1}H NMR ($CDCl_3$) δ 7.02−6.96 (m, 5H), 3.98 (bs, 2H), 2.64 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); MS *m/z* 206.1 $(M + H)^+$.

2-Fluoro-4-[2-isopropylimidazol-1-yl]aniline (9c). This compound was prepared following the same procedures described for **9d** using 2-isopropylimidazole instead of 2-dimethylaminomethylimidazole (50%). ^{1}H NMR ($CDCl_3$) δ 7.04−6.81 (m, 5H), 4.10 (bs, 2H), 2.95 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H); MS *m/z* 220.2 $(M + H)^+$.

2-Fluoro-4-(2-pyrrolidin-1-ylmethylimidazol-1-yl)-aniline (9e). This compound was prepared following the same procedures described for **9d** using **7e** instead of 2-dimethylaminomethylimidazole (55%). ^{1}H NMR ($CDCl_3$) δ 7.23 (dd, J = 12.6, 2.2 Hz, 2H), 7.05−6.68 (m, 4H), 3.89 (bs, 2H), 3.49 (s, 2H), 2.50 (m, 4H), 1.66 (m, 4H); MS *m/z* 261.2 $(M + H)^+$.

[1-(4-Amino-3-fluorophenyl)-1*H*-imidazol-2-ylmethyl]-methylcarbamic Acid Benzyl Ester (9f). This compound was prepared following the same procedures described for **9d** using **7f** instead of 2-dimethylaminomethylimidazole (67%). ^{1}H NMR ($CDCl_3$): δ 7.40−7.10 (m, 5H), 7.05 (s, 1H), 7.00−6.70 (m, 4H), 5.00 (m, 2H), 4.68 (m, 2H), 3.83 (s, 2H), 2.89 (s, 3H); MS *m/z* 355.2, $(M + H)^+$.

1-(3′-Cyano-4′-fluorophenyl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-dimethylaminomethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (10d). To a suspension of the acid **5** (38.31 g, 0.128 mol) in 1 L of dichloromethane was added oxalyl chloride (32.5 g, 0.256 mol) and DMF (0.5 mL). The mixture was stirred at ambient temperature for 1 h and then heated to reflux for 1 h. The solvent and excess reagent in the solution were evaporated to give the acid chloride **6** as a yellow solid. The solid was dissolved in 1 L of dichloromethane and cooled with an ice bath. To this was added aniline **9d** (30 g, 0.128 mol) and (dimethylamino)pyridine (31.3 g, 0.256 mol). The solution was stirred at ambient temperature for 12 h. The solution was washed with H_2O (3 × 200 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography (gradient of 0−5% MeOH in CH_2Cl_2) gave 56.1 g (85%) of **10d**. ^{1}H NMR ($CDCl_3$) δ 8.27 (t, J = 8.5 Hz, 1H), 8.17 (bs, 1H), 7.86−7.79 (m, 2H), 7.74 (dd, J = 9.5, 2.5 Hz, 1H), 7.40−7.34 (m, 2H), 7.20 (s, 1H), 7.10−7.08 (m, 2H), 3.37 (s, 2H), 2.26 (s, 6H); MS *m/z* 561.2 $(M + H)^+$.

1-(3′-Cyano-4′-fluorophenyl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-methyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (10a). This compound was prepared following the same procedures described for **10d** using **9a** instead of **9d** (64%). ^{1}H NMR ($CDCl_3$) δ 8.31 (m, 1H), 8.17 (bs, 1H), 7.82 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.18 (m, 2H), 7.20 (s, 1H), 7.00 (m, 2H), 2.38 (s, 3H); MS *m/z* 473.0 $(M + H)^+$.

1-(3″-Cyano-4′-fluorophenyl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-ethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (10b). This compound was prepared following the same procedures described for **10d** using **9b** instead of **9d** (15%). ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H), 8.17 (t, J = 8.5 Hz, 1H), 7.80 (m, 2H), 7.38 (m, 1H), 7.12 (m, 2H), 7.06−6.83 (m, 3H), 2.64 (q, J = 7.3 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H); MS *m/z* 487.2 $(M + H)^+$.

1-(3′-Cyano-4′-fluorophenyl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-isopropyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (10c). This compound was prepared following the same procedures described for **10d** using **9c** instead of **9d** (35%). ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 2.2 Hz, 1H), 8.27 (t, J = 8.4 Hz, 1H), 7.82 (m, 2H), 7.38 (m, 1H), 7.26−7.08 (m, 3H), 7.05 (d, J = 2.5 Hz, 3H), 6.92 (d, J = 2.5 Hz, 3H), 2.96 (m, J = 6.9 Hz, 2H), 1.23 (d, J = 6.9 Hz, 3H); MS *m/z* 501.2 $(M + H)^+$.

1-(3′-Cyano-4′-fluorophenyl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-pyrrolidin-1-ylmethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (10e). This compound was prepared following the same procedures described for **10d** using **9e** instead of **9d** (44%). ^{1}H NMR ($CDCl_3$) δ 8.28 (t, J = 8.8 Hz, 1H), 8.12 (s, 1H), 7.82 (m, 2H), 7.72 (dd, J = 2.6, 12.1 Hz, 1H), 7.40 (m, 2H), 7.20 (s, 1H), 7.08 (s, 2H), 3.04 (s, 2H), 2.57 (bs, 4H), 1.77 (bs, 4H); MS *m/z* 542.2 $(M + H)^+$.

Benzyl {1-[4-({[1-(3-Cyano-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]carbonyl}amino)-3-fluorophen-yl]-1*H*-imidazol-2-yl}methyl(methyl)carbamate (10f). This compound was prepared following the same procedures described for **10d** using **9f** instead of **9d** (52%). ^{1}H NMR ($CDCl_3$) δ 7.85−7.76 (m, 2H), 7.30 (m, 8H), 7.15 (m, 2H), 7.00 (m, 2H), 5.02 (m, 2H), 4.56 (s, 2H), 2.93 (s, 3H); MS *m/z* 636.1 $(M + H)^+$.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-dimethylaminomethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide (11d), Hydrochloride Salt (Razaxaban). Into a 2 L flask with mechanical stirrer was added potassium *tert*-butoxide (19.5 g, 0.157 mol), acetohydroxamic acid (11.77 g, 0.157 mol), and 500 mL of DMF. This mixture rapidly produced a thick white precipitate. After 40 min, **10d** (26.93 g, 0.052 mol) was added all at once as a solid. The mixture turned brown and became very fluid. Stirring was continued at ambient temperature for 12 h. The mixture was poured into a separatory funnel containing 500 mL of aqueous ammonium chloride and 500 mL of EtOAc. After the mixture was shaken, the lower aqueous phase separated rapidly. This was drawn off, and the organic phase was washed again with 500 mL of H_2O. A solid formed at the interface, which was filtered off to give 8.5 g of the desired product **11d**. The organic solution was evaporated to 100 mL, and another 6.5 g of product was precipitated. The aqueous washing was extracted again with EtOAc. The EtOAc solution was washed with H_2O and was then evaporated to give 8.6 g of the desired product. All fractions were combined to give 23.6 g (86%) of the free base (**11d**) with 99% HPLC purity. ^{1}H NMR (DMSO-d_6) δ 8.10 (d, J = 1.8 Hz, 1H), 7.73−7.68 (m, 4H), 7.59 (d, J = 8.4, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 1.1 Hz, 1H), 7.00 (d, J = 1.1 Hz, 1H), 6.59 (s, 2H), 3.34 (s, 2H), 2.13 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.00, 159.14, 157.11, 156.64, 153.35, 144.87, 141.63, 141.14, 138.86, 136.51, 136.38, 134.24, 128.01, 126.74, 124.25, 124.14, 123.23, 122.02, 120.93, 119.50, 117.50, 1132.23, 112.91, 110.05, 108.23, 54.89, 44.92; ^{19}F NMR (282 MHz, DMSO-d_6) δ −61.243 (s), −119.571 (t, J = 6.8 Hz); MS *m/z* 529.2 $(M + H)^+$. The free base (20.78 g, 0.039 mol) was dissolved in 105 mL of methanol with gentle heating. Once dissolved, the solution was cooled in an ice bath, with stirring. To this was added 1 N HCl/ether (85 mL, 0.085 mol, 2.18 equiv) all at once. After the mixture was stirred for 10 min, 25 mL of ether was added. The hydrochloride salt crystallized out over the next 10 min. Cooling was continued for an additional 90 min. Product was collected on a filter, washed with ether (2 × 50 mL), and dried under house vacuum for 12 h to give 20.67 g (92%) of a crystalline solid of the HCl salt (razaxaban) with 99% purity by HPLC. ^{1}H NMR (DMSO-d_6) δ 8.12 (d, J = 1.8 Hz, 1H), 7.83−7.78 (m, 2H), 7.70−7.67 (m, 1H), 7.61−7.57 (m, 2H), 7.741 (dd, J = 8.8, 1.8 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H), 4.41 (s, 2H), 2.78 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.97, 159.14, 157.03, 156.64, 153.30, 141.53, 141.03, 138.68, 137.84, 134.28, 133.27, 133.14, 128.11, 127.15, 126.66, 126.49, 125.01, 123.23, 122.99, 119.75, 117.49, 115.38, 115.07, 111.06, 109.97, 108.57, 49.66, 48.98, 43.04; ^{19}F NMR (282 MHz, DMSO-d_6) δ −56.458 (s), −113.218 (t, J = 9.6 Hz); IR (KBr) 1687, 1625, 1528, 1235, 1172, 1140, 975 cm^{-1}. Anal. ($C_{24}H_{20}N_8F_4O_2$·HCl) C, H, N, Cl, F. HRMS calcd for ($C_{24}H_{21}N_8F_4O_2$) $(M + H)^+$ 529.1724, found 529.1715.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[4′-(2″-methylimidazol-1″-yl)-2′-fluorophenyl)aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (11a). This

compound was prepared following the same procedures described for **11d** using **10a** instead of **10d**. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (54%). ^{1}H NMR (CD_3OD) δ 8.09 (t, J = 8.4 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.66 (dd, J = 8.8, 2.2 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 9.1, 2.1 Hz, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.46 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (CD_3OD) δ 163.76, 160.43, 159.05, 157.17, 154.67, 146.80, 143.78, 139.61, 135.74, 129.10, 127.30, 124.48, 123.35, 121.03, 120.08, 119.77, 118.23, 115.47, 115.23, 110.92, 108.65, 11.33; ^{19}F NMR (CD_3OD) δ −64.21, −77.62 (TFA), −121.45; MS m/z 486.2 $(M + H)^+$. Anal. ($C_{22}H_{15}N_7O_2F_4 \cdot 1.3TFA \cdot 1H_2O$) C, H, N, F.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[4-(2′-ethylimidazol-1′-yl)-2-fluorophenyl]aminocarbonyl]-pyrazole, Bis(trifluoroacetic acid) Salt (11b). This compound was prepared following the same procedures described for **11d** using **10b** instead of **10d**. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (67%). ^{1}H NMR (acetone-d_6) δ 9.99 (s, 1H), 8.27 (t, J = 8.8 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.80−7.57 (m, 7H), 3.04 (q, J = 7.7 Hz, 2H), 1.30 (t, J = 7.7 Hz, 3H); ^{19}F NMR (acetone-d_6) δ −63.17, −76.65 (TFA), −122.91; HRMS calcd for $C_{23}H_{18}F_4O_2N_7$ (M + H) 500.1458, found 500.1471.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[4-(2′-isopropylimidazol-1′-yl)-2-fluorophenyl]aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (11c). This compound was prepared following the same procedures described for **11d** using **10c** instead of **10d**. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (36%). ^{1}H NMR (acetone-d_6) δ 10.02 (s, 1H), 8.28 (t, J = 8.5 Hz, 1H), 8.11 (d, J = 1.9 Hz, 1H), 7.82−7.56 (m, 7H), 3.33 (m, 1H), 1.40 (d, J = 7.3 Hz, 6H); ^{19}F NMR (acetone-d_6) δ −63.16, −76.72 (TFA), −122.56; HRMS calcd for $C_{23}H_{19}F_3O_3N_7$ (M + H) 514.1615, found 514.1634.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-pyrrolidinylmethyl)imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxyamide, Bis(trifluoroacetic acid) Salt (11e). This compound was prepared following the same procedures described for **11d** using **10e** instead of **10d**. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (50%). ^{1}H NMR (acetone-d_6) δ 9.42 (bs, 1H), 8.15 (t, J = 8.8 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 2.2, 8.8 Hz, 1H), 7.58 (m, 3H), 7.48 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.25 (s, 1H), 4.68 (s, 2H), 3.58 (m, 4H), 2.08 (m, 4H); ^{19}F NMR (acetone-d_6) δ −63.16, −76.772 (TFA), −123.08; HRMS calcd for $C_{26}H_{23}F_4O_2N_8$ (M + H) 555.1880, found 555.1898.

***N*-[4-(2-{[Methylamino]methyl}-1*H*-imidazol-1-yl)-2-fluorophenyl]-1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide, Bis(trifluoroacetic acid) Salt (12).** Acetohydroxamic acid (0.40 g, 5.34 mmol) was dissolved in 10 mL of DMF. K_2CO_3 (0.98 g, 7.12 mmol) was added, followed by 1 mL of H_2O. The mixture was stirred at room temperature under N_2 for 30 min, and a solution of benzyl {1-[4-({[1-(3-cyano-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]carbonyl}amino)-3-fluorophenyl]-1*H*-imidazol-2-yl}methyl(methyl)carbamate **10f** (1.13 g, 1.78 mmol) in 10 mL of DMF was added. The resulting mixture was stirred at ambient temperature under N_2 for 12 h. H_2O was added to the reaction mixture. The precipitate formed was filtered and dried to give **11f**. MS (ES^+) m/z 647.1, $(M - H)^-$.

The above solid was heated to reflux with 20 mL of TFA under N_2 for 30 min. The TFA was removed. The residue was purified by reverse-phase HPLC (C18 reverse-phase column, eluted with a H_2O/CH_3CN gradient with 0.05% TFA) to give 0.61 g of **12** as the bis-TFA salt (67%). ^{1}H NMR (acetone-d_6) δ 8.16 (t, J = 8.4 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.55 (m, 4H), 7.40 (m, 2H), 4.64 (bs, 2H), 2.92 (s, 3H); ^{19}F NMR (acetone-d_6) δ −63.16, −76.72 (TFA), −123.07; HRMS calcd for $C_{23}H_{19}F_4O_2N_8$ (M + H) 515.1567, found 515.1577.

(4-Amino-3-fluorophenyl)pyrrolidin-1-ylmethanone (14). To a suspension of potassium dichromate (128 g, 0.430 mol) in glacial acetic acid (400 mL) was added 2-fluoro-4-methyl-1-nitrobenzene (50.0 g, 0.323 mol) portionwise followed by stirring for 15 min. Concentrated sulfuric acid (340 g) was added slowly (CAUTION: strong exothermic reaction occurs!) followed by heating to 120 °C for 1.5 h. The flask was allowed to cool to ambient temperature, and 1.5 L of H_2O was added with vigorous stirring to precipitate straw-colored crystals. The solid was isolated by filtration and air-dried to give 3-fluoro-4-nitrobenzoic acid (49 g, 82%). ^{1}H NMR (DMSO-d_6) δ 13.93 (bs, 1H), 8.23 (t, J = 7.7 Hz, 1H), 7.99−7.94 (m, 2H). The above acid (18.8 g, 0.10 mol) was dissolved in 200 mL of dichloromethane. The mixture was cooled in an ice bath, and to it was added oxalyl chloride (18.2 mL, 0.20 mol), followed by a few drops of DMF. The mixture was stirred at 0 °C for 5 h, and it was evaporated to dryness. After the mixture was dried under vacuum, the solid was dissolved in 200 mL of dichloromethane. Triethylamine (21.3 mL, 0.15 mol) was added, followed by pyrrolidine (9.3 mL, 0.20 mol). The reaction mixture was stirred at ambient temperature under N_2 for 48 h. The mixture was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to 24.5 g of yellow solid. The solid (15.0 g) was dissolved in 200 mL of methanol, and Pd/C (1.5 g of 5%) was added. The mixture was hydrogenated at 30 psi for 30 min. It was filtered through Celite, concentrated, and chromatographed with EtOAc to give 7.0 g of **14** (55%). ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H), 6.74 (t, J = 8.8 Hz, 1H), 3.93 (bs, 2H), 3.59 (m, 4H), 1.90 (m, 4H); MS m/z 209 $(M + H)^+$.

2,4-Bis-(2-methylimidazol-1-yl)phenylamine (15). 2,4-Difluoronitrobenzene (5.0 g, 31.4 mmol) was dissolved in 50 mL of acetonitrile. 2-Methylimidazole (5.15 g, 62.8 mmol) and K_2CO_3 (8.69 g, 63.0 mmol) were added. The mixture was heated to reflux for 12 h. It was cooled and poured into 500 mL of H_2O and then extracted with EtOAc. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. It was dissolved in 20 mL of dichloromethane, and hexane (200 mL) was added. The precipitate was filtered and dried to give 7.98 g of 2,4-bis(2-methylimidazol-1-yl)nitrobenzene (90%). ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 1H), 7.60 (dd, J = 2.2, 8.2 Hz, 1H), 7.40 (d, J = 2.2, 8.2 Hz, 1H), 7.10 (m, 3H), 6.95 (d, J = 1.5 Hz, 1H), 2.49 (s, 3H), 2.29 (s, 3H); MS m/z 284.2 $(M + H)^+$. The nitro intermediate (1.12 g) was dissolved in 80 mL of MeOH. Pd/C (42 mg of 10%) was added. The mixture was hydrogenated at 40 psi for 12 h. It was filtered through Celite and concentrated to give 0.60 g of **15** (56%). ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 1H), 8.01(s, 1H), 7.36 (t, J = 8.4 Hz, 1H), 7.26 (d, J = 1.5 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 6.88 (d, J = 1.5 Hz, 1H), 3.37 (bs, 2H), 2.27 (s, 3H), 2.17 (s, 3H); MS m/z 254.2 $(M + H)^+$.

2-Fluoro-4-morpholinoaniline (16). A solution of 2,4-difluoronitrobenzene (10.0 mL) and morpholine (17.4 mL) in THF (100 mL) was stirred at ambient temperature under N_2 for 2 h. The solvent was removed, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting solid was purified by chromatography on silica gel with 20−50% EtOAc in hexane to give 18.1 g of 4-fluoro-2-morpholinonitrobenzene and 1.81 g of 2-fluoro-4-morpholinonitrobenzene. 2-Fluoro-4-morpholinonitrobenzene (1.80 g) was dissolved in methanol (100 mL), and 10% Pd/C (94 mg) was added. The mixture was placed in a hydrogenator (45 psi) for 2.5 h. The reaction mixture was filtered through Celite and washed with methanol. The filtrate was concentrated to give 1.51 g of **16** (8.4%). ^{1}H NMR ($CDCl_3$) δ 6.76−6.54 (m, 3H), 3.84 (t, J = 4.7 Hz, 4H), 3.45 (bs, 2H), 3.02 (t, J = 4.7 Hz, 4H); MS m/z 197.1 $(M + H)^+$.

2-Amino-5-(2-methylimdazol-1-yl)benzylnitrile (17). To a solution of 2,4-difluoronitrobenzene (1.98 g, 12.6 mmol) in

20 mL of DMF was added NaCN (0.63 g, 12.9 mmol). The mixture was stirred at ambient temperature for 12 h. It was poured into H_2O and extracted with EtOAc. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography with 0−20% EtOAc in hexane to give 0.65 g of 5-fluoro-2-nitrobenzylnitrile (31%). ^{1}H NMR ($CDCl_3$) δ 8.41 (m, 1H), 7.62 (m, 1H), 7.53 (m, 1H); ^{19}F NMR ($CDCl_3$) δ −100 (s); MS *m/z* 167.0 $(M + H)^+$.

5-Fluoro-2-nitrobenzylnitrile(0.64 g, 3.85 mmol) and 2-methylimidazole (0.66 g, 8.04 mmol) were dissolved in CH_3CN (25 mL) and heated to reflux under N_2 for 12 h. The solvent was removed, and the residue was purified by chromatography on silica gel with 2−5% MeOH in CH_2Cl_2 to give 0.84 g (96%) of 5-(2-methylimdazol-1-yl)-2-nitrobenzylnitrile. ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.76 (dd, J = 2.6, 8.8 Hz, 1H), 7.11 (dd, J = 1.4, 12.1 Hz, 2H), 2.49 (s, 3H); MS *m/z* 246.2 $(M + NH_4)^+$.

To a suspension 5-(2-methylimdazol-1-yl)-2-nitrobenzylnitrile (0.40 g, 1.75 mmol) in methanol (50 mL) was added 10% Pd/C (50 mg). The mixture was placed on a hydrogenator at 47 psi for 3 h. It was filtered through Celite and concentrated to give 0.34 g of **17** (98%). ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 2.2 Hz, 1H), 7.14 (dd, J = 2.6, 8.8 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 6.92 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.93 (br s, 2H), 2.26 (s, 3H).

2-Methoxy-4-(2-methylimidazol-1-yl)aniline (18). A solution of 5-fluoro-2-nitrophenol (2.03 g) and 2-methylimidazole (2.14 g) in CH_3CN (50 mL) was stirred at reflux under N_2 for 16 h. The solvent was removed, and the residue was purified by chromatography on silica gel with 0−10% MeOH in CH_2Cl_2 to give 2.21 g (78%) of 5-(2-methylimdazol-1-yl)-2-nitrophenol. ^{1}H NMR ($CDCl_3$) δ 10.78 (bs, 2H), 8.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.07 (dd, J = 1.5, 4.3 Hz, 2H), 6.97 (dd, J = 2.2, 9.1 Hz, 1H), 5.30 (s, 1H), 2.48 (s, 3H); MS *m/z* 220.1 $(M + H)^+$.

5-(2-Methylimdazol-1-yl)-2-nitrophenol (1.16 g) was dissolved in DMF (30 mL). To this solution was added K_2CO_3 (0.92 g) and iodomethane (0.33 mL). The reaction mixture was stirred at ambient temperature under N_2 for 6 h. The reaction mixture was poured into 100 mL of H_2O and extracted with EtOAc (4 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.25 g (20%) of 2-methoxy-4-(2-methylimidazol-1-yl)nitrobenzene. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 9.2 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.00 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 4.01 (s, 3H), 2.44 (s, 3H); MS *m/z* 234.2 $(M + H)^+$.

2-Methoxy-4-(2-methylimidazol-1-yl)nitrobenzene (0.25 g) was dissolved in methanol (20 mL), and 10% Pd/C (29.3 mg) was added. The mixture was placed on a hydrogenator (40 psi) for 4 h. The reaction mixture was filtered and washed with methanol. The filtrate was concentrated to give 0.27 g (quantitative) of **18**. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.86 (s, 3H), 3.95 (bs, 2H, NH_2), 6.68 (t, 1H, J = 1.8 Hz, 1H), 6.72 (m, 2H), 6.95 (d, J = 1.4 Hz, 1H), 6.99 (d, J = 1.1 Hz, 1H); MS *m/z* 204.2 $(M + H)^+$.

2-(3-Cyano-4-fluorophenyl)-5-trifluoromethyl-2*H*-pyrazole-3-carboxylic Acid (2-Fluoro-4-iodophenyl)amide (19). To a dichloromethane suspension of 1-(4′-fluoro-3′-cyanophenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid (**5**) (3.21 g, 11.27 mmol) was added oxalyl chloride (1.48 mL, 16.90 mmol) and a catalytic amount of DMF. The reaction mixture was stirred at ambient temperature for 3 h and then concentrated to a pale-yellow solid. The crude mixture was redissolved in dichloromethane, and to this solution was added 2-fluoro-4-iodoaniline **8** (2.67 g, 11.27 mmol), followed by DMAP (3.44 g, 28.17 mmol). The reaction mixture was stirred at ambient temperature for 12 h and concentrated. The crude product was taken in EtOAc(100 mL), and the reaction was quenched with HCl (3 N, 50 mL). The mixture was shaken in a separatory funnel and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to afford pure **19** (2.61 g, 45%). ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 1H), 7.23 (t, J = 8.5 Hz, 1H), 7.49−7.58 (m, 2H), 7.75−7.99 (m, 4H); MS *m/z* 517 $(M - H)^-$.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[4-(2′-aminosulfonyl-4-pyridinyl)-3-fluorophenyl]aminocarbonyl]pyrazole, Trifluoroacetic Acid Salt (23). The iodo intermediate **19** obtained above (0.18 g, 0.35 mmol) was dissolved in dry and degassed DMSO (5 mL). To this solution was added KOAc (0.10 g, 1.05 mmol) and pinacol diborane (0.1 g, 0.38 mmol), followed by $PdCl_2$(dppf) (9 mg, 0.01 mmol). The reaction mixture was heated at 80 °C for 2 h, and then the reaction was quenched with H_2O (100 mL). The organic mixture was extracted with EtOAc (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to a brownish oil (0.26 g). The oil was redissolved in an ethanol/toluene mixture (4:1, 50 mL), and to this solution was added 4-bromopyridine-3-sulfonic acid *tert*-butylamide **21** (0.168 g, 0.49 mmol), followed by a catalytic amount of tetrakistriphenylphosphine palladium (spatula, tip). The reaction mixture was heated to reflux for 12 h. It was cooled, filtered over Celite, and concentrated in vacuo. The crude mixture without purification was redissolved in dry DMF (1 mL) and converted to the desired compound **23** via reaction with acetohydroxamic acid and K_2CO_3 (see compound **35** for detailed procedure) followed by deprotection with TFA. The final product was purified by reverse-phase HPLC (C18 reverse-phase column), eluted with an H_2O/CH_3CN gradient with 0.05% TFA, and isolated as the TFA salt (15%). ^{1}H NMR (DMSO-d_6) δ 10.7 (s, 1H), 9.14 (s, 1H), 8.80 (d, J = 5.1 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.75−7.65 (m, 4H), 7.60 (d, J = 8.8 Hz, 1H), 7.48−7.40 (m, 2H), 7.42−7.27 (dd, J = 8.8 Hz, 2H), 3.80 (bs, 2H); ^{19}F NMR (DMSO-d_6) δ −61.21, −75.19; HRMS calcd for $C_{23}H_{16}F_4N_7O_4S$ 562.0921, found 562.0911.

2-Fluoro-4-(1-methylimidazol-2-yl)aniline (26). To a solution of 4-bromo-2-fluoroaniline (19.2 g, 100 mmol) in THF (100 mL) at 0 °C was slowly added LiN(TMS) $_2$ (1 M in THF, 200 mL) over 30 min. After the resulting solution was warmed to ambient temperature, a solution of di-*tert*-butyl dicarbonate (21.8 g, 100 mmol) in THF (50 mL) was slowly added. The mixture was stirred for 15 min and filtered through a pad of silica gel. The filtrate was concentrated and recrystallized from hexane to give 4-bromo-2-fluoro-1-*tert*-butoxycarbonylaniline **24** (27.7 g, 95%). ^{1}H NMR ($CDCl_3$) δ 8.00 (t, J = 8.8 Hz, 1H), 7.25−7.20 (m, 2H), 6.66 (bs, 1H), 1.52 (s, 9H); ^{19}F NMR ($CDCl_3$) δ −130.42; MS *m/z* 290/292 $(M + H)^+$.

To a solution of 1*N*-methylimidazole (1.64 g, 20 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (2.5 M, 9.6 mL), and the resulting solution was stirred at −78 °C for 30 min. After Bu_3SnCl (7.18 g, 22 mmol) was added, the resulting mixture was slowly warmed to ambient temperature over 2 h and was stirred for an additional 16 h. To the reaction mixture was added 4-bromo-2-fluoro-1-*tert*-butoxycarbonylaniline **24** (0.58 g, 2 mmol) and $Pd(PPh_3)_4$ (92 mg, 0.08 mmol). The resulting mixture was degassed and filled with nitrogen three times. The mixture was heated to reflux under N_2 for 18 h and then cooled to ambient temperature. After saturated aqueous KF (10 mL) was added, the resulting mixture was stirred for 1 h and filtered through a pad of Celite. The filtrate was washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography with EtOAc to give 2-fluoro-4-(1′-methylimidazol-2′-yl)-1-*tert*-butoxycarbonylaniline (0.35 g, 60%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.19 (t, J = 8.0 Hz, 1H), 7.42 (dd, J = 12.1, 1.8 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.10 (d, J = 1.1 Hz, 1H), 6.96 (s, 1H), 6.80 (bs, 1H), 3.75 (s, 3H), 1.54 (s, 9H); ^{19}F NMR ($CDCl_3$) δ −132.59; MS *m/z* 292.2 $(M + H)^+$.

To a solution of 2-fluoro-4-(1′-methylimidazol-2′-yl)-1-*tert*-butoxycarbonylaniline (0.33 g, 1.13 mmol) in EtOAc (10 mL) was added 3 M HCl (5 mL), and the resulting solution was stirred at ambient temperature for 30 min. The solution was cooled to 0 °C, neutralized with 50% NaOH to pH 8, and extracted with EtOAc (50 mL × 3). The EtOAc layer was concentrated and purified by silica gel chromatography and eluted with 5% MeOH in EtOAc to give 2-fluoro-4-(1′-methylimidazol-2′-yl)aniline **26** (0.18 g, 83%). ^{1}H NMR (CD_3OD) δ 7.54 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 11.8, 2.2 Hz, 1H), 7.27 (dd, J = 8.4, 2.2 Hz, 1H), 6.97 (t, J

= 8.8 Hz, 1H), 3.88 (s, 3H); ^{19}F NMR (CD_3OD) δ −136.77 (dd, J = 90.1 Hz, J = 9.1 Hz); MS *m/z* 192 $(M + H)^+$.

1-(3′-Aminobenzisoxozol-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic Acid (27). To a solution of 1-(4′-fluoro-3′-cyanophenyl)-3-trifluoromethyl-5-pyrazolecarboxylic acid **5** (2.0 g, 6.39 mmol) in CH_3CN (30 mL) was added $SOCl_2$ (5.1 g, 42.8 mmol), and the resulting solution was heated to reflux for 2 h. The mixture was concentrated on an evaporator, and the residue was dissolved in MeOH (20 mL). The resulting solution was heated to reflux for 30 min and then concentrated and purified by silica gel chromatography with CH_2Cl_2 to give methyl 1-(4′-fluoro-3′-cyanophenyl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (1.93 g, 92%). ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, J = 5.6, 2.6 Hz, 1H), 7.73 (dd, J = 8.4, 3.4 Hz, 1H), 7.36 (t, J = 8.4 Hz, 1H), 7.30 (s, 1H), 3.88 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −63.01, −104.60; MS *m/z* 331 $(M + NH_4)^+$.

To a solution of acetone oxime (0.67 g, 9.2 mmol) in DMF (20 mL) was added potassium *tert*-butoxide (1.0 M in THF, 9.2 mL), and the mixture was stirred at ambient temperature for 15 min. To it was added a solution of methyl 1-(4′-fluoro-3′-cyanophenyl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (1.92 g, 6.15 mmol) in DMF (20 mL), and the resulting mixture was stirred at ambient temperature for 20 h. The reaction was then quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (100 mL). The EtOAc layer was washed with brine (10 mL × 5), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography, eluting with 80% CH_2Cl_2 in hexane to give methyl 1-(4′-isopropylideneaminooxy-3′-cyanophenyl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (1.53 g, 68%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.69 (d, J = 9.1 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 9.1, 2.5 Hz, 1H), 7.26 (s, 1H), 3.85 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −62.88; MS *m/z* 367 $(M + H)^+$. To a solution of methyl 1-(4′-isopropylideneaminooxy-3′-cyanophenyl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (1.53 g, 4.18 mmol) in MeOH (13 mL) and CH_2Cl_2 (6 mL) was added 18% HCl (13 mL), and the mixture was heated to reflux for 3 h. It was then concentrated to remove organic solvents. The resulting aqueous solution was neutralized with 2 N NaOH to pH 7 and extracted with EtOAc. The EtOAc layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give methyl 1-(3′-aminobenzisoxozol-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (1.32 g, 65%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.89 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 8.8, 2.2 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 3.79 (s, 3H); ^{19}F NMR (CD_3OD) δ −64.36; MS *m/z* 327 $(M + H)^+$.

A solution of methyl 1-(3′-aminobenzisoxozol-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic ester (260 mg, 0.8 mmol) in THF (10 mL) was treated with 2 N NaOH (10 mL) at ambient temperature for 16 h. The mixture was acidified with concentrated HCl to pH 3 and extracted with EtOAc. The EtOAc layer was dried over Na_2SO_4 and concentrated to give 1-(3′-aminobenzisoxozol-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic acid **27** (240 mg, 96%). ^{1}H NMR (CD_3OD) δ 7.90 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H); ^{19}F NMR (CD_3OD) δ −64.32; MS *m/z* 311 $(M - H)^-$.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[4′-(1-methylimidazol-2-yl)-2′-fluorophenyl)aminocarbonyl]-pyrazole, Bis(trifluoroacetic acid) Salt (28). To a solution of 1-(3′-aminobenzisoxozole-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic acid **27** (30 mg, 0.096 mmol) in DMF (2 mL) was added 2-fluoro-4-(1-methylimidazol-2-yl)aniline **26** (20.4 mg, 0.106 mmol), diisopropylethylamine (0.2 mL), and PyBrop (49.4 mg, 0.106 mmol). The resulting mixture was stirred at 60 °C for 16 h and quenched with EtOAc (75 mL) and H_2O (5 mL). The EtOAc layer was washed with 1 N HCl (5 mL), 1 N NaOH (5 mL), and brine (5 mL × 4), dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel TLC plates with 10% MeOH in EtOAc, followed by further purification by HPLC (CH_3CN/H_2O/0.05% TFA) to give **28** as the TFA salt (19 mg, 40.8%). ^{1}H NMR (CD_3OD) δ 8.21 (t, J = 8.1 Hz, 1H), 7.99 (dd, J = 2.2, 0.6 Hz, 1H), 7.70−7.66 (m, 3H), 7.64 (d, J = 2.2 Hz, 1H), 7.57 (dt, J = 8.3 Hz, 1.0 Hz, 1H), 7.52 (dd, J = 8.8, 0.5 Hz, 1H), 7.48 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (CD_3OD) δ 163.78, 160.43, 159.02, 156.71, 154.22, 144.84, 143.78 (CF_3), 139.64, 135.73, 129.09, 127.05, 126.51, 126.08, 120.52, 120.08, 118.23, 117.99, 110.93, 108.71, 36.16; ^{19}F NMR (CD_3OD) δ −64.21, −77.58 (TFA), −123.46; HRMS calcd. for $C_{22}H_{16}F_4N_7O_2$ 486.1302, found 486.1323.

2-Hydroxymethyl-1*H*-imidazole (30). 2-Imidazolecarboxyaldehyde (5.0 g, 52.0 mmol) was suspended in 200 mL of methanol, and $NaBH_4$ (3.95 g, 0.10 mol) was added portionwise. The reaction mixture was stirred at ambient temperature for 1 h under N_2. It was quenched with 10 mL of brine, and the solvent was removed. The solid was washed with 5% MeOH in CH_2Cl_2, and the inorganic solid was filtered off. The filtrate was concentrated and chromatographed with 5% MeOH in CH_2Cl_2 to give 2.32 g of 2-hydroxymethyl-1*H*-imidazole **30** (45.2%). ^{1}H NMR (DMSO-d_6) δ 6.86 (s, 2H), 4.40 (s, 2H).

1-(4-Amino-3-fluorophenyl)-2-hydroxymethylimidazole (31). 2-Hydroxymethyl-1*H*-imidazole **30** (2.30 g, 23.47 mmol), 2-fluoro-4-iodoaniline **8** (5.56 g, 23.47 mmol), K_2CO_3 (1.56 g, 25.82 mmol), 1,10-phenanthroline (0.42 g, 2.35 mmol), CuI (0.45 g, 2.35 mmol), and DMSO (50 mL) were added together and degassed. The mixture was then heated at 130 °C under N_2 for 12 h. The mixture was cooled, and 14% aqueous NH_4OH (200 mL) and EtOAC (200 mL) were added. The mixture was filtered through Celite and washed with EtOAc. The filtrate was extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was filtered, concentrated, and purified by chromatography on silica gel with 5% MeOH in CH_2Cl_2 to give 0.48 g of 1-(4-amino-3-fluorophenyl)-2-hydroxymethylimidazole **31** (10%). MS *m/z* 208.2 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 7.27 (m, 2H), 7.06 (dd, J = 2.2, 8.5 Hz, 1H), 6.94 (s, 1H), 6.83 (t, J = 8.4 Hz, 1H), 5.41 (s, 2H), 5.34 (t, J = 5.5 Hz, 1H), 4.36 (d, J = 5.5 Hz, 2H).

1-(4-Amino-3-fluorophenyl)-2-(*tert*-butyldimethylsilyloxymethyl)imidazole (32). 1-(4-Amino-3-fluorophenyl)-2-hydroxymethylimidazole **31** (0.48 g, 2.32 mmol), TBDMSCl (0.52 g, 3.48 mmol), and Et_3N (0.65 mL, 4.64 mmol) were dissolved in 20 mL of DMF. The mixture was stirred at ambient temperature under N_2 for 12 h. It was diluted with H_2O and extracted with EtOAc, and the combined organic solution was washed with brine and dried over $MgSO_4$. It was filtered, concentrated, and purified by chromatography on silica gel with 5% MeOH in CH_2Cl_2 to give 0.50 g of 1-(4-amino-3-fluorophenyl)-2-(*tert*-butyldimethylsilyloxymethyl)imidazole **32** (67%). ^{1}H NMR ($CDCl_3$) δ 7.20 (dd, J = 2.6, 11.8 Hz, 1H), 7.02 (m, 3H), 6.78 (t, J = 9.1 Hz, 1H), 4.56 (s, 2H), 3.84 (bs, 2H), 0.82 (s, 9H), 0.00 (s, 6H).

***N*-[4-[(2-*tert*-Butyldimethylsilyloxymethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl]-1-(3-cyano-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (33).** 1-(3-Cyano-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic **5** (0.45 g, 1.50 mmol) was stirred in 20 mL of CH_2Cl_2 at ambient temperature under N_2. Oxalyl chloride (0.20 mL, 2.25 mmol) was added, followed by a few drops of DMF. The mixture was stirred for 2 h. The solvent was removed, and the resulting solid (**6**) was dried under vacuum. This solid was then dissolved in 20 mL of CH_2Cl_2, and 1-(4-amino-3-fluorophenyl)-2-(*tert*-butyldimethylsilyloxymethyl)imidazole **32** (0.48 g, 1.50 mmol) was added followed by DMAP (0.50 g, 4.25 mmol). The mixture was stirred at ambient temperature under N_2 for 12 h. It was diluted with CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel with 50% hexane in EtOAc to give 0.48 g of *N*-[4-[(2-*tert*-butyldimethylsilyloxymethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl]-1-(3-cyano-4-fluoropheyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide **33** (53%). ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.18 (m, 1H), 7.78 (m, 2H), 7.50, 4.56 (s, 2H), 3.84 (bs, 2H), 0.82 (s, 9H), 0.00 (s, 6H); MS *m/z* 603.31 $(M + H)^+$.

***N*-[4-(2-[Hydroxymethyl]-1*H*-imidazol-1-yl)-2-fluorophenyl]-1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (35).** Acetohydrox-

amic acid (0.18 g, 1.80 mmol) was dissolved in 5 mL of DMF. K_2CO_3 (0.44 g, 3.20 mmol) was added, followed by a few drops of H_2O. The mixture was stirred at ambient temperature under N_2 for 30 min, and a solution of *N*-[4-[(2-*tert*-butyldimethylsilyloxymethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl]-1-(3-cyano-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide **33** (0.48 g, 0.80 mmol) was added. The resulting mixture was stirred at ambient temperature under N_2 for 12 h, and then H_2O was added to the reaction mixture. The precipitate formed was filtered and dried to give **34**. MS (ES^+) *m/z* 616.3 $(M + H)^+$. This solid was dissolved in 20 mL of THF. Tetrabutylammonium fluoride (1.66 mL of a 1 M solution) was added, and the mixture was stirred at ambient temperature under N_2 for 1 h. The THF was removed. The residue was partitioned between EtOAc and H_2O. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to give 0.36 g of a light-yellow solid (90%). This solid was approximately 95% pure by analytical HPLC and was taken into the next step without further purification. A small amount was purified by reverse-phase HPLC (C18 reverse-phase column, eluted with a H_2O/CH_3CN gradient with 0.05% TFA) to give *N*-[4-(2-[hydroxymethyl]-1*H*-imidazol-1-yl)-2-fluorophenyl]-1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide as the TFA salt (**35**). ^1H NMR (DMSO-d_6) δ 10.86 (s, 1H), 8.10 (d, $J = 1.9$ Hz, 1H), 7.90 (m, 2H), 7.70 (m, 4H), 7.58 (d, $J = 9.1$ Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 6.62 (bs, 1H), 4.68 (s, 2H); MS *m/z* 502.2 $(M + H)^+$.

***N*-[4-(2-[Aminomethyl]-1*H*-imidazol-1-yl)-2-fluorophenyl]-1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide, Bis(trifluoroacetic acid) Salt (37).** *N*-[4-(2-[Hydroxymethyl]-1*H*-imidazol-1-yl)-2-fluorophenyl]-1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide **35** (0.21 g, 0.42 mmol) was dissolved in 20 mL of CH_2Cl_2, and PBr_3 (0.18 mL, 1.76 mmol) was added. The mixture was stirred at ambient temperature under N_2 for 12 h. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to give 0.18 g of the desired bromide. MS (ES^+) *m/z* 567.3 $(M + H)^+$. The bromide was dissolved in 5 mL of DMF, and NaN_3 (62.0 mg, 1.26 mmol) was added. The mixture was heated at 50 °C under N_2 for 2 h. The reaction mixture was cooled, and H_2O was added. It was extracted with EtOAc. The organic solution was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 0.08 g of the desired azide **36** as colorless oil. MS (ES^+) *m/z* 529.4 $(M + H)^+$. This oil was heated to reflux with $SnCl_2$ (240 mg) in 10 mL of MeOH for 1 h. It was cooled, the reaction was quenched with saturated sodium bicarbonate, and the mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated and purified by reverse-phase HPLC (C18 reverse-phase column, eluted with a H_2O/CH_3CN gradient with 0.05% TFA) to give the desired product **37** as the TFA salt (38.2 mg, 15%). ^1H NMR (DMSO-d_6) δ 10.80 (s, 1H), 8.38 (bs, 2H), 8.05 (s, 1H), 7.76 (t, $J = 8.4$ Hz, 1H), 7.68−7.50 (m, 5H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.16 (s, $J = 1.4$ Hz, 1H), 4.10 (s, 2H); HRMS calcd for $C_{22}H_{17}F_4O_2N_8$ (M + H) 501.1404, found 501.1410.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[(2′-methylsulfonyl-3-fluoro[1,1′]biphen-4-yl)aminocarbonyl]-pyrazole, Trifluoroacetic Acid Salt (38). This compound was prepared following the same procedures described for **11d** using 3-fluoro-2′-methanesulfonylbiphenyl-4-ylamine[7,8,11] to couple with acid **5** (87%). The resulting amide was converted to the aminobenzisoxazole by reaction with acetohydroxamic acid and potassium *tert*-butoxide, followed by heating in HCl/EtOH at 80 °C. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (64%). ^1H NMR (DMSO-d_6) δ 10.66 (s, 1H), 8.09 (d, $J = 1.8$ Hz, 1H), 8.07 (d, $J = 1.3$ Hz, 1H), 7.76 (td, $J = 7.5$, 1.8, 1H), 7.71−7.66 (m, 4H), 7.58 (d, $J = 8.8$ Hz, 1H), 7.41 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.36 (dd, $J = 11$, 1.8 Hz, 1H), 7.22 (dd, $J = 8.4$, 1.8 Hz, 1H), 6.58 (s, 2H), 2.91 (s, 3H); ^{19}F NMR (DMSO-d_6) δ −60.67, −121.90. HRMS calcd for $C_{25}H_{18}F_4N_5O_4S$ 560.1016, found 560.1020.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[(2′-aminosulfonyl-3-fluoro[1,1′]biphen-4-yl)aminocarbonyl]-pyrazole, Trifluoroacetic Acid Salt (39). 1-(3′-Aminobenzisoxozole-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic acid **27** was coupled with 4′-amino-3′-fluorobiphenyl-2-sulfonic acid amide[7,8,11] following the same procedures described in the synthesis of compound **28** (20%). The coupling product was heated to reflux in TFA for 0.5 h to remove the *tert*-butyl group. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (47%). ^1H NMR ($CDCl_3$) δ 8.09 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.91 (t, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 2.1$ Hz, 1H), 7.67−7.45 (m, 4H), 7.31−7.16 (m, 3H); ^{19}F NMR ($CDCl_3$) δ −62.79, −126.65; HRMS calcd for $C_{24}H_{17}F_4N_6O_4S$ 561.0968, found 561.0978.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[2-fluoro-4-(*N*-pyrrolidinocarbonyl)phenylaminocarbonyl]-pyrazole Trifluoroacetate, Trifluoroacetic Acid Salt (40). This compound was prepared following the same procedures described for **11d** using aniline **14** to couple with acid **5** (87%). The resulting amide was converted to the aminobenzisoxazole by reaction with acetohydroxamic acid and potassium *tert*-butoxide, followed by heating in HCl/EtOH at 80 °C. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (72%). ^1H NMR ($CDCl_3$) δ 9.59 (s, 1H), 7.69−7.40 (m, 5H), 7.07−6.99 (m, 2H), 4.71 (bs, 2H), 3.62 (t, $J = 6.6$ Hz, 2H), 3.32 (t, $J = 6.6$ Hz, 2H), 2.00−1.84 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −62.68, −123.82; HRMS calcd for $C_{23}H_{19}F_4N_6O_3$ 503.1455, found 503.1469.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[(2-fluoro-4-morpholinophenyl)aminocarbonyl]pyrazole, Trifluoroacetic Acid Salt (41). This compound was prepared following the same procedures described for **11d** using aniline **16** to couple with acid **5** (45%). The resulting amide was converted to the aminobenzisoxazole by reaction with acetohydroxamic acid and potassium *tert*-butoxide, followed by heating in HCl/EtOH at 80 °C. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (22%). ^1H NMR (DMSO-d_6) δ 9.39 (s, 1H), 8.06 (d, 1H), 7.77−7.48 (m, 4H), 6.81−6.75 (m, 2H), 3.77 (t, 4H), 3.15 (t, 4H); HRMS calcd for $C_{22}H_{19}F_4N_6O_3$ 491.1455, found 491.1454.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[(2-cyano-4-(2′-methylimidazol-1′-yl)phenyl]aminocarbonyl]-pyrazole, Bis(trifluoroacetic acid) Salt (42). This compound was prepared following the same procedures described for **11d** using aniline **17** to couple with acid **5** (31%). The resulting amide was converted to the aminobenzisoxazole by reaction with acetohydroxamic acid and potassium *tert*-butoxide, followed by heating in HCl/EtOH at 80 °C. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (20%). ^1H NMR (DMSO-d_6) δ 11.32 (bs, 1H), 8.23 (d, $J = 2.6$ Hz, 1H), 8.12 (d, $J = 2.6$ Hz, 1H), 7.95 (dd, $J = 8.8$, 2.6 Hz, 1H), 7.88 (d, $J = 2.6$ Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.71 (m, 2H), 7.55 (d, $J = 8.8$ Hz, 1H), 6.57 (bs, 2H), 2.53 (s, 3H); HRMS calcd for $C_{23}H_{16}F_3N_8O_2$ 493.1348, found 493.1342.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[4′-(2″-methylimidazol-1″-yl)phenyl)aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (43). To a suspension of NaH (4.8 g, 120 mmol, prewashed with THF) in THF (100 mL) was added a solution of 1-fluoro-4-nitrobenzene (14.1 g, 100 mmol) and 2-methylimidazole (8.2 g, 100 mmol) in THF (50 mL) at 0 °C. The mixture was heated to reflux for 16 h and cooled to ambient temperature. To it were added EtOAc (200 mL) and H_2O (100 mL). The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to give the crude nitro compound. A solution of the nitro intermediate in MeOH (200 mL) was placed under a balloon filled with hydrogen gas in the presence of 5% Pd on

carbon (1.5 g) at ambient temperature for 24 h. The mixture was filtered through Celite, and the filtrate was concentrated to give 4-(2-methylimidazol-1-yl)aniline (16.5 g, 95.4% for the two steps) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.05 (dd, J = 6.4, 2.1 Hz, 2H), 6.98 (d, J = 1.1 Hz, 1H), 6.93 (d, J = 1.1 Hz, 1H), 6.73 (dd, J = 6.4, 2.1 Hz, 2H), 3.85 (bs, 2H), 2.31 (s, 3H); MS *m/z* 174 $(M + H)^+$.

To a solution of 1-(3′-aminobenzisoxozol-5-yl)-3-trifluoromethyl-5-pyrazolecarboxylic acid **27** (240 mg, 0.77 mmol) in DMF (5 mL) was added 4-(2′-methylimidazol-1′-yl)aniline (133 mg, 0.77 mmol), DMAP (99.5 mg, 0.79 mmol), and PyBrop (372 mg, 0.79 mmol). The resulting mixture was stirred at 60 °C for 16 h, and then the reaction was quenched with EtOAc (100 mL) and H_2O (20 mL). The EtOAc layer was washed with 1 N HCl (10 mL), 1 N NaOH (10 mL), H_2O (10 mL), and brine (10 mL × 3). It was dried over $MgSO_4$, filtered, and concentrated. The final product **43** was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (281 mg, 63%). ^{1}H NMR (CD_3OD) δ 7.97 (d, J = 0.8 Hz, 1H), 7.89 (d, J = 9.1 Hz, 2H), 7.65 (dd, J = 9.1, 2.2 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 2.54 (s, 3H); ^{19}F NMR (CD_3OD) δ −64.21, −77.51 (TFA); HRMS calcd 468.1396, found 468.1381.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[(2,4-bis-(2′-methylimidazol-1′-yl)phenyl]aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (44). The title compound was prepared in a two-step sequence by coupling 2,4-bis-(2-methylimidazol-1-yl)phenylamine **15** with pyrazole-5-carboxylic acid **5** followed by aminobenzisoxazole formation via the methods described for the synthesis of **11d**. The final product **44** was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (5%). ^{1}H NMR (DMSO-d_6) δ 11.15 (bs, 1H), 8.08 (s, 1H), 8.05 (d, J = 4.5 Hz, 1H), 7.96−7.93 (m, 4H), 7.79 (dd, J = 2.7, 8.9 Hz, 3H), 7.61−7.55 (m, 2H), 7.48 (dd, J = 2.5, 9 Hz, 1H), 6.60 (bs, 1H), 2.89 (s, 3H), 2.60 (s, 3H); ^{19}F NMR (DMSO-d_6) δ −60.75, −60.94; HRMS calcd for $C_{26}H_{21}F_3O_2N_9$ (M + H) 548.1770, found 548.1790.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[(2-methoxy-4-(2′-methylimidazol-1′-yl)phenyl]aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (45). This compound was prepared following the same procedures described for **11d** using aniline **18** to couple with acid **5** (34%). The resulting amide was converted to the aminobenzisoxazole by reaction with acetohydroxamic acid and potassium *tert*-butoxide, followed by heating in HCl/EtOH at 80 °C. The final product was purified by reverse-phase HPLC with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase and isolated as a TFA salt (46%). ^{1}H NMR (DMSO-d_6) δ 10.15 (bs, 1H, CF_3CO_2H), 8.11 (d, J = 1.4 Hz, 1H), 7.90 (bs, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.60 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.17 (dd, J = 10.0, 1.5 Hz, 1H), 3.82 (s, 3H), 2.53 (s, 3H); HRMS calcd for $C_{23}H_{19}F_3O_3N_7$ (M + H) 498.1501, found 498.1505.

1-(3′-Aminobenzisoxazol-5′-yl)-3-trifluoromethyl-5-[[(2-aminocarbonyl-4-(2′-methylimidazol-1′-yl)phenyl]aminocarbonyl]pyrazole, Bis(trifluoroacetic acid) Salt (46). This compound was isolated as a byproduct during the preparation of **42**. ^{1}H NMR (DMSO-d_6) δ 12.91 (bs, 1H), 8.51 (bs, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.15 (bs, 1H), 8.09 (dd, J = 2.2, 9.2 Hz, 2H), 7.86 (d, J = 1.8 Hz, 1H), 7.79 (m, 1H), 7.77 (m, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.51 (s, 1H), 6.57 (bs, 2H), 2.55 (s, 3H); HRMS calcd for $C_{23}H_{18}F_3N_8O_3$ 511.1454, found 511.1464.

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five to seven different concentrations of inhibitor. Determinations at each plasma concentration were done in duplicate. The clotting time at each concentration was compared with the control clotting time for each pooled plasma. The prothrombin time test was performed using Dade Thromboplastin C Plus according to the reagent instructions. Plasma (50 μL) was warmed to 37 °C for 3 min before adding thromboplastin (100 μL). The activated partial thromboplastin time (aPTT) was performed using AlexinTM (Sigma Diagnostics) according to the reagent instructions. Plasma (50 μL) was warmed to 37 °C for 1 min before adding aPTT reagent (50 μL). Three minutes later, calcium chloride (50 μL) was added.

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