Articles

Discovery of 1-(2-Aminomethylphenyl)-3-trifluoromethyl-*N*-[3-fluoro-2′-(aminosulfonyl)[1,1′-biphenyl)]-4-yl]-1*H*-pyrazole-5-carboxyamide (DPC602), a Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor[1]

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Factor Xa, a serine protease, is at the critical juncture between the intrinsic and extrinsic pathways of the coagulation cascade. Inhibition of factor Xa has the potential to provide effective treatment for both venous and arterial thrombosis. We recently described a series of meta-substituted phenylpyrazoles that are highly potent, selective, and orally bioavailable factor Xa inhibitors. In this paper we report our efforts to further optimize the selectivity profile of our factor Xa inhibitors with a series of ortho- and/or para-substituted phenylpyrazole derivatives. The most potent compounds display sub-nanomolar inhibition constants for factor Xa and show greater than 1000-fold selectivity against other serine proteases. These compounds are also effective in a rabbit model of arteriovenous shunt thrombosis. Optimization of this series led to the preclinical development of DPC602, a 2-(aminomethyl)phenylpyrazole analogue, as a highly potent, selective, and orally bioavailable factor Xa inhibitor.

Introduction

Two classes of antithrombotic agents are used in the treatment and prevention of thromboembolic diseases, antiplatelet agents and anticoagulants. Antiplatelet agents block platelet activation and aggregation. Anticoagulants inhibit thrombin generation and fibrin formation. The limitations of current anticoagulant therapies, such as unfractionated heparin, warfarin, and low-molecular weight heparins, have led to the research and development of new anticoagulants.[2] Warfarin, the only marketed oral anticoagulant, is prescribed for a growing number of indications but takes several days to reach therapeutic levels and has a narrow therapeutic index.[3] It has been our desire to develop safe and efficacious orally active anticoagulants that require less rigorous patient monitoring.

The coagulation cascade provides many opportunities to intervene and therefore expand current anticoagulant therapies. Factor Xa, a trypsin-like serine protease, is situated at the critical juncture between the intrinsic and extrinsic pathways, catalyzing the conversion of prothrombin to thrombin, and hence plays a pivotal role in the final common pathway of the cascade[4] and has become an important target in the discovery and development of new anticoagulants. As factor Xa (fXa) precedes thrombin in the coagulation cascade, inhibitors of fXa could be more effective in attenuating thrombotic disorders. Additionally, since fXa inhibitors affect coagulation specifically, but not platelet function, this mechanism should have less propensity to increase abnormal bleeding.[5]

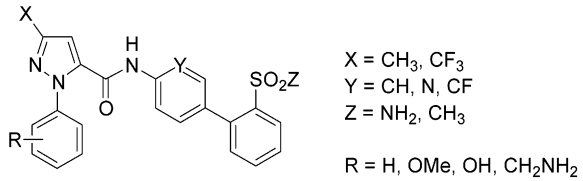

Figure 1. Structural scaffold for SAR.

Selectivity has been one of the key issues in the design of small molecule inhibitors of serine proteases. Historically, the substrate specificity of the S1 subsite of the trypsin-like serine proteases of the coagulation cascade for the cationic arginine has presented a significant problem for the development of therapeutically useful inhibitors of this class of enzyme.[6] In addition, the early cationic inhibitors had poor oral absorption and relatively short duration of action.[7] The effort to develop selective thrombin and fXa inhibitors with good oral bioavailability and useful duration of action in vivo has evolved from the use of charged compounds incorporating cationic guanidine and amidine functionality as ligands to compounds using neutral or less basic aryl or heteroaryl functionality at P1.[8,9] Initial success at replacing the benzamidine with a benzylamine, while

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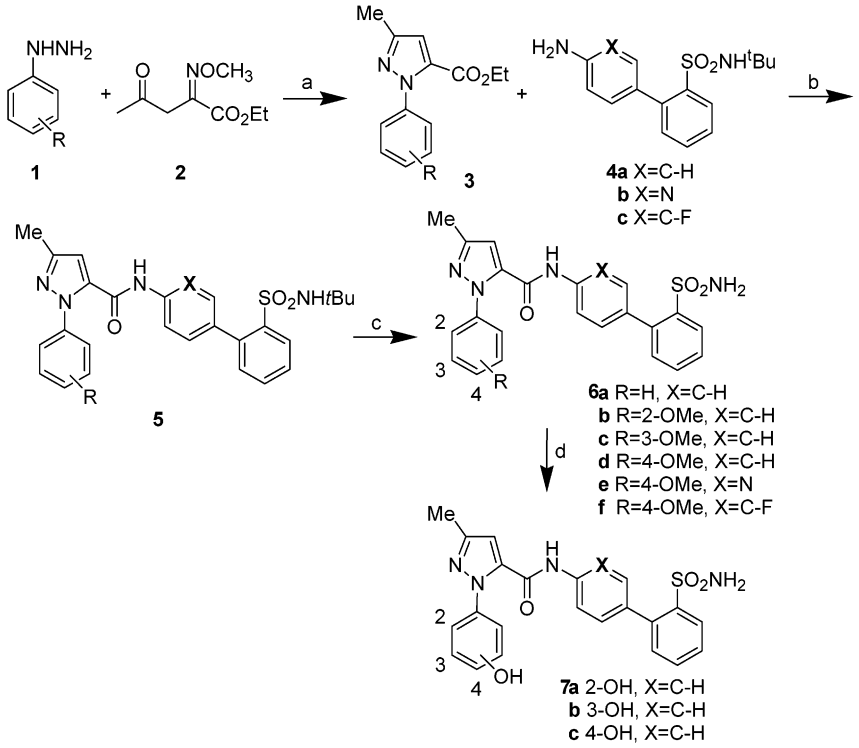
Scheme 1. Synthesis of the 1-(Methoxyphenyl)-3-methylpyrazole Analogues[a]



[a] Reagents: (a) AcOH, reflux; (b) $Al(Me)_3/CH_2Cl_2$; (c) TFA, reflux; (d) BBr_3/CH_2Cl_2.

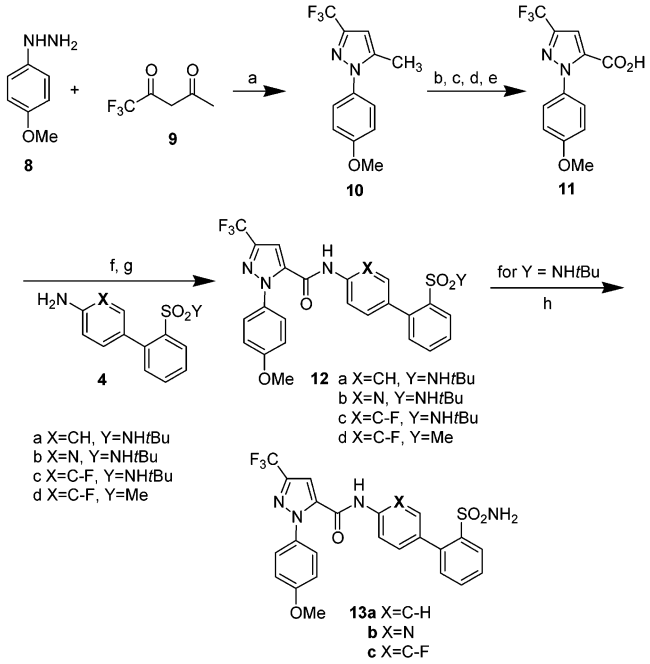
maintaining fXa potency and enhancing the PK profile, was accomplished in our laboratories with DPC423.[10] Our laboratories[10,11] and others[12] have reported on less basic surrogates for benzamidines such as 2-aminoisoquinoline and 3-aminobenzisoxazole and neutral inhibitors[13,14] of fXa. In this paper we report on our continuing efforts to discover benzamidine surrogates with improved selectivity over trypsin and other serine proteases and with good ADME properties. Specifically as shown in Figure 1, we sought to build on the structural–activity relationships already discovered with the DPC423 scaffold[10] and scan for non-amidino P1 groups. This work resulted in the discovery of DPC602, a 2-(aminomethyl)phenylpyrazole analogue as, a potent, selective and orally bioavailable inhibitor of factor Xa.

Chemistry

The required ethyl-1-phenyl-3-methyl-5-carboxypyrazoles (**3**, Scheme 1) were prepared regioselectively from a condensation of the appropriate phenylhydrazine **1** and ethyl 2-(*N*-methoxyimino)-4-oxopentanoate **2**.[10,15] Coupling of ester **3** with the known amines **4** by pretreatment of **4** with trimethylaluminum[16] and heating the mixture in toluene gave good yields of the amide **5.** Deprotection of the *tert*-butylsulfonamide moiety, by treatment with trifluoroacetic acid, afforded compounds **6a**–**f.** Treatment of the methoxy-substituted precursor compounds **6b**–**d** with excess boron tribromide[17] afforded the phenolic analogues **7a**–**c**.

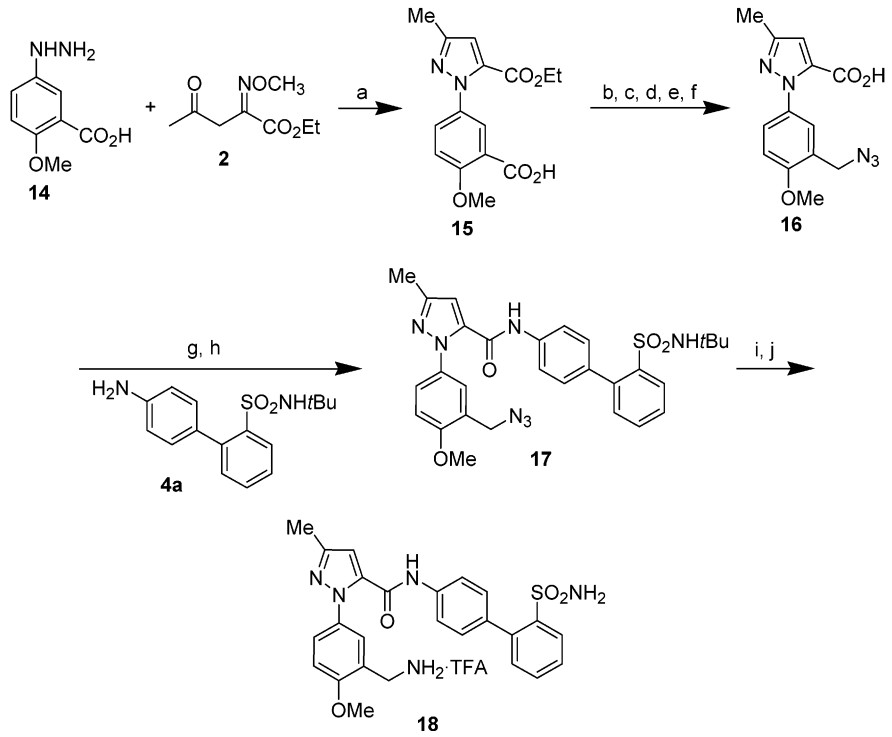
The 3-trifluoromethylpyrazole analogues **13a**–**c** were prepared by the method outlined in Scheme 2. Condensation of 4-methoxyphenylhydrazine **8** with 1,1,1-trifluoro-2,4-pentanedione **9**[10] in refluxing methoxyethanol afforded the 5-methylpyrazole **10**. The 5-methyl group was oxidized in four steps to the corresponding carboxylic acid. This was achieved via a NBS-mediated bromination to the bromomethyl group, followed by transformation to the *O*-acetyl derivative by displacement of the bromine with potassium acetate (activated by 18-crown-6) in acetonitrile. Conversion of the acetate derivative to the alcohol with acidic resin followed by

Scheme 2. Synthesis of the 1-(4-Methoxyphenyl)-3-(trifluoromethyl)Pyrazole Analogues[a]



[a] Reagents: (a) $MeOCH_2CH_2OH$, AcOH, reflux; (b) NBS, benzoyl peroxide, CCl_4; (c) KOAc, 18-crown-6, MeCN; (d) IR400 resin, MeOH; (e) $NaIO_4$, cat. $RuCl_3$, MeCN, 0 °C; (f) oxalyl chloride; (g) cat. DMAP, pyridine, CH_2Cl_2; (h) TFA, reflux.

Scheme 3. Synthesis of the 1-[3-(Aminomethyl)-4-methoxyphenyl]-3-methylpyrazole **18**[a]



[a] Reagents: (a) AcOH, H_2O, reflux; (b) ^{i}BuOCOCl, NMM, THF; (c) $NaBH_4$, THF, H_2O; (d) MsCl, Et_3N, $CHCl_3$; (e) NaN_3, DMSO; (f) 50% aq NaOH, EtOH, H_2O; (g) oxalyl chloride; (h) cat. DMAP, Et_3N, $CHCl_3$; (i) $SnCl_2$ dihydrate, MeOH; (j) TFA, reflux.

oxidation with ruthenium chloride/sodium periodate afforded the carboxylic acid derivative **11**. Compound **11** was converted to the acyl chloride by treatment with oxalyl chloride and coupled with amines **4a**−**d** in the presence of *N*,*N*-dimethylaminopyridine and pyridine in dichloromethane to afford compounds **12a**−**d**. Further treatment of **12a**−**c** with trifluoroacetic acid provided sulfonamide compounds **13a**−**c**.

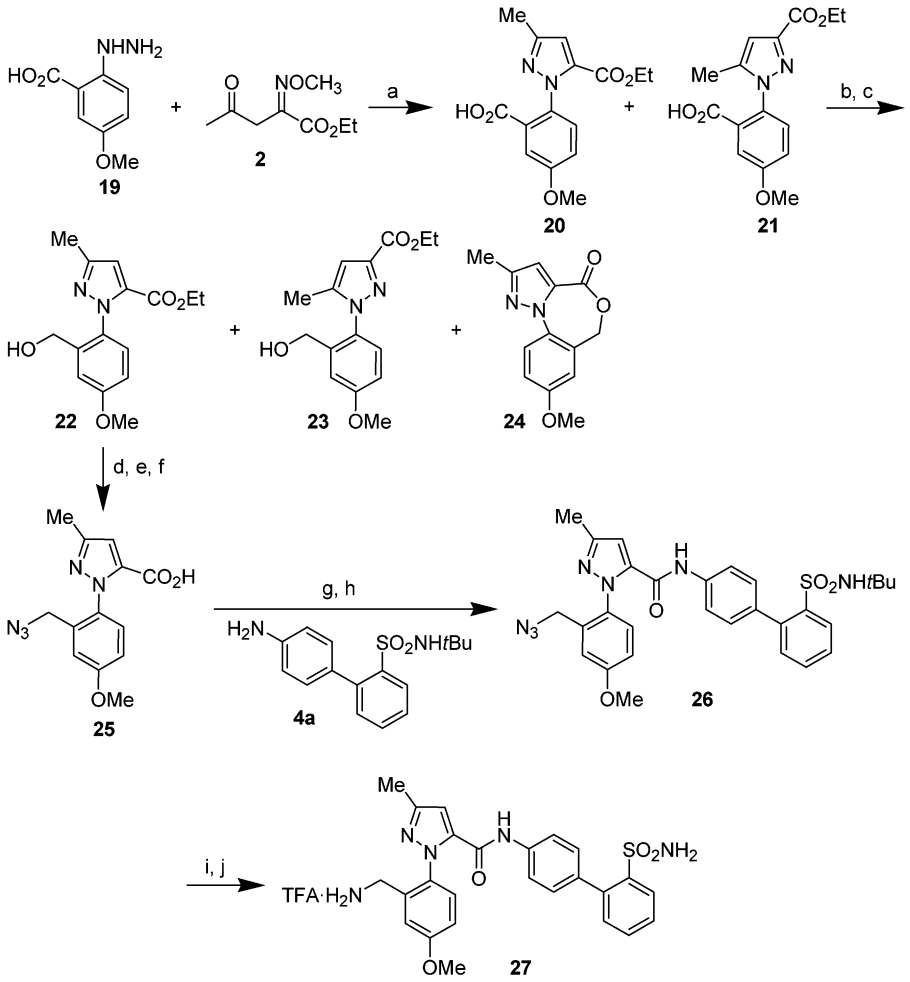
Compound **18** was prepared by the reaction of 3-carboxy-4-methoxyphenylhydrazine **14** with ethyl 2-(*N*-methoxyimino)-4-oxopentanoate **2** to afford the carboxy-functionalized phenylpyrazole ester **15** (Scheme 3). Transformation of this benzoic acid to the benzylic azide **16** was accomplished by sequential sodium borohydride reduction of the mixed anhydride and mesylation of the resulting alcohol with methansulfonyl chloride followed by treatment with sodium azide. Pyrazole ester saponification, acid chloride formation, and subsequent coupling to biphenylamine **4a** afforded compound **17**. Reduction of the benzylic azide **17** with stannous chloride[18] and final deprotection of the *tert*-butylsulfonamide with trifluoroacetic acid provided compound **18**.

Refluxing a mixture of the 2-carboxy-4-methoxyphenylhydrazine **19** with ethyl 2-(*N*-methoxyimino)-4-oxopentanoate **2** in a mixture of acetonitrile and acetic acid afforded a mixture (1:1) of pyrazole derivatives **20** and **21** (Scheme 4). Formation of the mixed anhydrides of compounds **20** and **21**, followed by sodium borohydride reduction, afforded the benzylic alcohols compounds **22** and **23.** A small amount (10%) of the ring-closed lactone derivative **24** was also isolated. The desired phenyl pyrazole **22** was isolated by flash chromatography and then transformed to a benzylic azide by mesylation of the alcohol and azide displacement. Saponification of the pyrazole ester afforded compound **25**, which was transformed to the acid chloride and coupled with the phenyl aniline derivative **4a** to afford compound **26**. The azide functionality of **26** was reduced to the benzylic amine with tin(II) chloride dihydrate and then refluxed with TFA to afford sulfonamide compound **27**.

Analogues **33a**,**b** and **34a**,**b** were prepared according to the route outlined in Scheme 5. A mixture of 5-methoxy-2-hydrazinobenzoic acid **19** and 1,1,1-trifluoro-4-(furan-2-yl)-2,4-butanedione **28** was heated at reflux in acetic acid to afford the 5-furanylpyrazole compound **29a** in good yield. The benzoic acid functionality from compound **29a** was transformed to the benzylic azide compound **30a.** Oxidation of the furan moiety of compound **30a** to the carboxylic acid, followed by the acid chloride formation and coupling with the appropriate biphenylamine **4a**,**c**−**e** afforded the azide compounds **32a**−**d**. Subsequent reduction with tin(II) chloride afforded compounds **33a**,**b**. The sulfonamide analogues **32c**,**d** were similarly reduced and deprotected with TFA to afford compounds **34a**,**b**.

DPC 602 was also synthesized via the methodology outlined in Scheme 5. Other analogues lacking the 4-methoxyphenyl P1 substituent were similarly synthesized via a modified approach outlined in Scheme 6. 2-Hydrazinobenzoic acid compound **35** and 1,1,1-trifluoro-4-(furan-2-yl)-2,4-butanedione **28** were condensed at reflux in acetic acid. The resulting carboxylic acid was transformed into the acyl chloride and quenched with aqueous ammonia to afford amide derivative **36**. Dehydration of **36** with trichloroacetyl chloride in the presence of excess triethylamine afforded the nitrile intermediate, which was reduced to the amine with cobalt(II) chloride and sodium borohydride,[19] and protected to afford compound **37**. The furan moiety of compound **37** was oxidized with potassium permanganate[20a,b] to afford

Scheme 4. Synthesis of the 1-[2-(Aminomethyl)-4-methoxyphenyl]-3-methylpyrazole **27**[a]



[a] Reagents: (a) AcOH, MeCN, reflux; (b) ^{i}BuOCOCl, NMM, THF; (c) $NaBH_4$, THF, H_2O; (d) MsCl, Et_3N, $CHCl_3$; (e) NaN_3, DMSO; (f) 50% aq. NaOH, EtOH, H_2O; (g) oxalyl chloride; (h) cat. DMAP, Et_3N, $CHCl_3$; (i) $SnCl_2$ dihydrate, MeOH; (j) TFA, reflux.

the carboxylic acid derivative **38**. Subsequent acyl chloride formation and coupling with amines **4a**,**c**−**e** and deprotection with TFA afforded the desired benzylamine analogues **40a**−**d**.

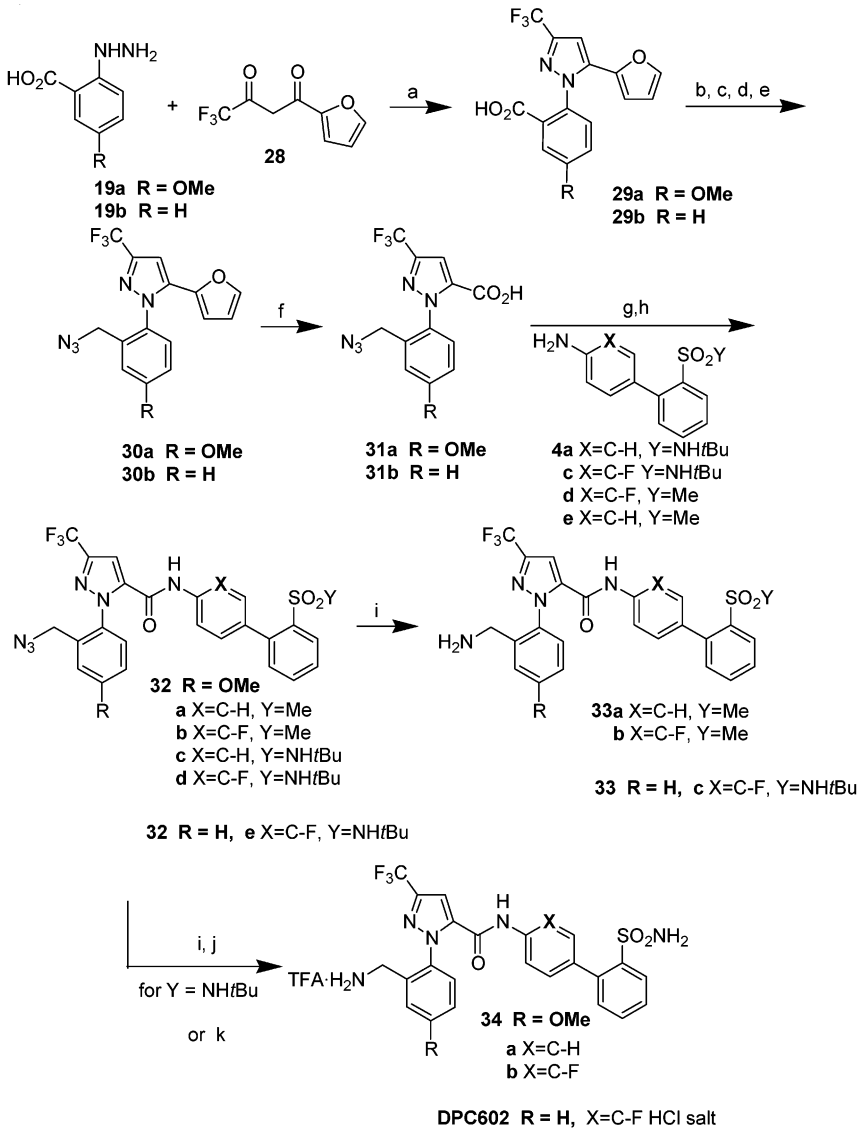
The alkylated benzylamine analogues **45a**−**d** were prepared following the sequence outlined in Scheme 7. The 2-(2-methoxycarbonyl-phenyl)-5-trifluoromethyl-2*H*-pyrazole-3-carboxylic acid (**42)** was obtained via a sequence of reactions as described previously for intermediate **36** (Scheme 5). In this particular case 2-hydrazinobenzoic acid was condensed with trifluoromethyl intermediate **28** to afford the pyrazolyl intermediate **41** which was immediately converted to the ester via the acid chloride/methanol methodology. Oxidation of the furyl functonality as previously described afforded the desired carboxylic derivative **42**. This was then was coupled to the biphenylamine **4d** via the acyl chloride to afford the compound **43**. Saponification of the ester moiety, mixed anhydride formation, reduction to the benzylic alcohol, and subsequent MnO_2 oxidation afforded key aldehyde intermediate **44**. The alkylated amines **45a**−**d**, were obtained via the reductive amination of **44** with methylamine, dimethylamine, isopropylamine, or benzylamine. A Horner−Emmons reaction of **44** with diethylphosphonoacetonitrile followed by hydrogenation of the acrylonitrile side chain in the presence of TFA afforded the propylamine compound **46**.

To prepare the two-carbon homologue side chain (Scheme 8), the mixed anhydride of carboxylic acid **41** was reduced to the alcohol, converted to the mesylate, and displaced with cyanide to give the nitrile **47.** The furan moiety of **47** was oxidized to the carboxylic acid with buffered sodium chlorite, converted to the acyl chloride, and coupled with amine **4d** to afford compound **48**. Catalytic reduction of the nitrile of **48** gave the desired amine analogue **49**.

Results and Discussion

The discovery of DPC423 (fXa K_i = 0.15 nM) from these laboratories had successfully shown that it was possible to replace the more polar *meta*-benzamidine (pK_a ∼ 10.7) with a less basic *meta*-benzylamine (pK_a ∼ 8.8) in the P1 position. Although DPC423 was selective (>1000-fold) against thrombin and other serine proteases, the selectivity against trypsin was only 400-fold (DPC423 trypsin K_i = 60 nM). While this was not a concern for us in the development of DPC423, the potential concern about long-term inhibition of trypsin made it necessary for us to identify a DPC423 follow-on with a much improved trypsin selectivity profile. To achieve greater fXa selectivity while maintaining a good pharmacokinetic profile, we chose to modify the P1 moiety of our existing series of 1-phenylpyrazole-5-carboxamides. As a starting point, in these modifications

Scheme 5. Synthesis of the 1-[2-(Aminomethyl)-phenyl-3-(trifluoromethyl)Pyrazole Analogue. Synthesis of DPC602[a]

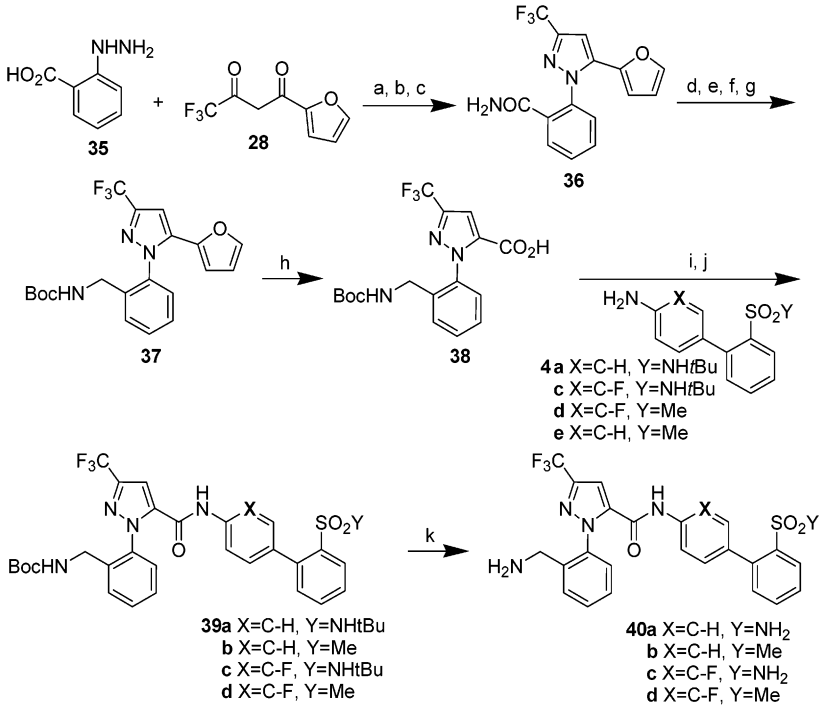


[a] Reagents: (a) AcOH, reflux; (b) ^{i}BuOCOCl, NMM, THF; (c) $NaBH_4$, THF, H_2O; (d) MsCl, Et_3N, $CHCl_3$; (e) NaN_3, DMSO; (f) $KMnO_4$, H_2O, acetone; (g) oxalyl chloride; (h) cat. DMAP, Et_3N, CH_2Cl_2; (i) $SnCl_2$ dihydrate, MeOH; (j) TFA, reflux; (k) 10%Pd/C, MeOH, HCl.

we compared the fXa bound X-ray structures of DPC423 with TAP (tick anticoagulant protein, Figure 2). The TAP structure reveals a hydrogen bond interaction of the tyrosyl (hydroxyl) moiety of TAP with Asp189 of fXa.[21] In contrast, the highly optimized DPC423 has the benzylamine P1 substituent interacting with Asp189 in fXa, just as we had previously seen in the trypsin bound complex,[10] and the benzylamine is within hydrogen bonding distance with the carbonyl of Gly218. Both compounds are potent inhibitors of factor Xa. Intrigued by the differences in binding modes for these two different, yet potent fXa molecules, we reasoned that either replacing our benzylamine with a 4-methoxy- or 4-hydroxyphenylpyrazole substituent or repositioning of the methylamine P1 moiety might afford potent factor Xa inhibitor. To test the first part of this hypothesis, we incorporated a hydroxyl or a methoxyl functionality on the P1 phenyl ring of the pyrazole template and compared it with the highly potent benzamidine analogues SN429 and DPC423 (Table 1).

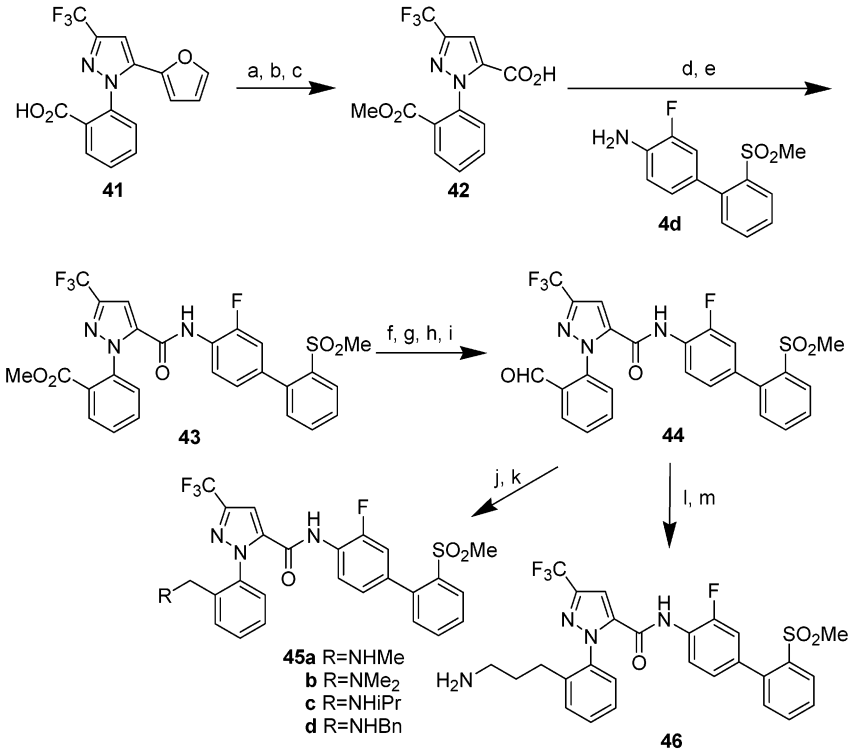
The data in Table 1 shows the 4-methoxyphenyl P1 analogue **6d** (fXa K_i = 11 nM) as the most potent compound when compared to other methoxyphenyl P1 regioisomers. Additionally, these compounds are weak inhibitors of serine protease enzymes thrombin and trypsin. Compound **6d** is a considerably weaker inhibitor of fXa (K_i = 11 nM) when compared to the benzamidine compound SN429 (fXa K_i = 0.01 nM) and the *m*-benzylamine compound DPC423 (fXa K_i = 0.15 nM). The loss in fXa potency for **6d** relative to SN429 and DPC423 may be due to a weak hydrogen bond interaction of the 4-methoxy functionality of **6d** with Asp189. The importance of the 4-methoxy moiety is further evident by the significant loss in fXa potency for the unsubstituted phenylpyrazole compound **6a** (fXa K_i = 198 nM). While compound **6a** is not as potent as compound **6d**, it still elicits binding affinity to the fXa enzyme. This result is a further illustration of the optimized conformation of our rigid pyrazole molecules in the fXa enzyme active site. Also in contrast to compound **6d**, the other methoxyphenyl regioisomers, compounds **6b** (fXa K_i > 30 000 nM) and **6c** (fXa K_i = 110 nM), along with the 2-hydroxyphenyl analogue **7a** (fXa K_i = 1200 nM), the 3-hydroxyphenyl analogue **7b**

Scheme 6. Synthesis of the 1-[2-(aminomethyl)Phenyl]-3-(trifluoromethyl)Pyrazole Analogues[a]



[a] Reagents: (a) AcOH, reflux; (b) $SOCl_2$; (c) aq. NH_3; (d) Cl_3CCOCl, Et_3N, CH_2Cl_2; (e) $NaBH_4$, $CoCl_2$; (f) aq HCl; (g) Boc_2O; (h) $KMnO_4$; (i) oxalyl chloride; (j) DMAP; (k) TFA.

Scheme 7. Synthesis of the Alkylated 2-(Aminoalkyl) Analogues[a]

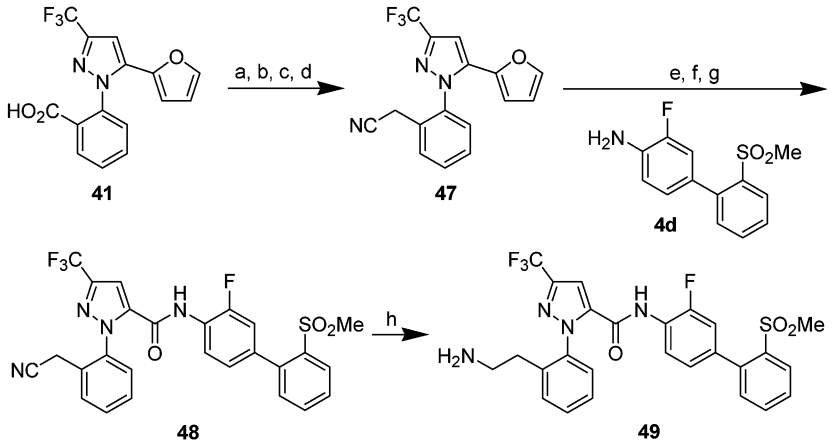


[a] Reagents: (a) oxalyl chloride; (b) MeOH; (c) $KMnO_4$, H_2O, acetone; (d) oxalyl chloride; (e) cat. DMAP, Et_3N, CH_2Cl_2; (f) NaOH, MeOH; (g) ^{i}BuOCOCl, NMM, THF; (h) $NaBH_4$, H_2O; (i) MnO_2, CH_2Cl_2; (j) HNR_2, MeOH; (k) $NaBH_4$, MeOH; (l) NaH, $EtO_2P(O)CH_2CN$, DMF; (m) H_2, 10% Pd−C, 2% TFA, MeOH.

(fXa K_i = 164 nM), and 4-hydroxyphenyl analogue **7c** (fXa K_i = 900 nM), are weak inhibitors of fXa. This suggests that these weak inhibitors do not effectively interact with Asp189 but maintain other important interactions with the protein.

To further optimize compound **6d**, we employed the strategy of modifications on the pyrazole template and the biphenyl portion of the compound, that was successfully used to identify our earlier compound DPC423[10] (Table 2). As we had previously observed with the *meta*-

Scheme 8. Synthesis of the 2-(aminoethyl) Analog 49[a]



[a] Reagents: (a) ^{i}BuOCOCl, NMM, THF; (b) $NaBH_4$, MeOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) KCN, Et_4NBr, H_2O, toluene; (e) $NaClO_2$, NaH_2PO_4, MeCN, H_2O; (f) oxalyl chloride; (g) cat. DMAP, Et_3N, CH_2Cl_2; (h) H_2, 10% Pd−C, 2% TFA, MeOH.

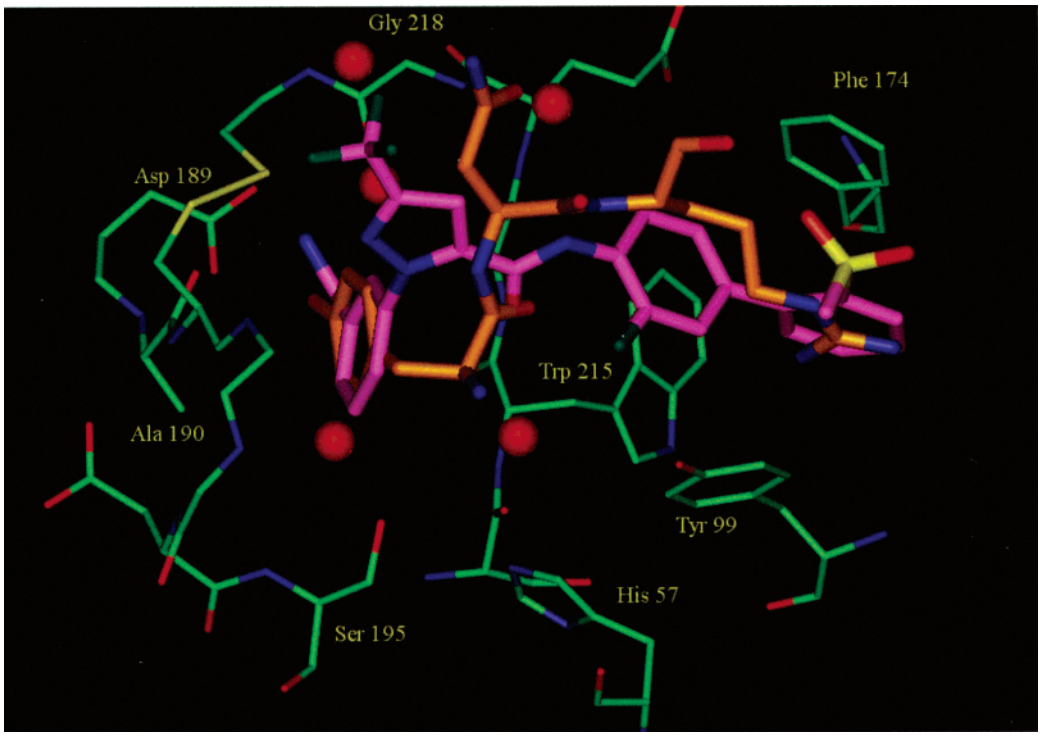


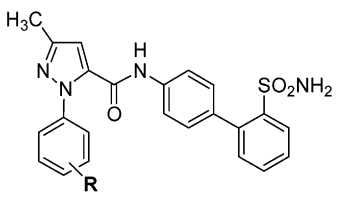
Figure 2. X-ray structure of N-terminal tripeptide sequence of Tick Anticoagulant Protein (orange) in fXa with an overlay of a structure of DPC423 (magenta).

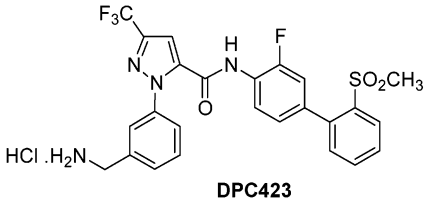
benzylamine series of DPC423, incremental fXa potency increases was seen in the *p*-methoxyphenyl P1 pyrazole series in going from the C-3 methyl analogue **6d** to the C-3 trifluoromethylpyrazole analogue **13a**. In the case of the P4 substitution, compound **6f** showed a 2-fold improvement over **6d**. However in the C-3 trifluoromethylpyrazole series, the changes in the P4 substituent did not further improve binding affinity. In addition, in the clotting assay (APTT, activated partial thromboplastin time), compounds **13a** ($IC_{2x} = 103.7\ \mu M$), **13b** ($IC_{2x} = 18.8\ \mu M$) and **12d** ($IC_{2x} = 64.9\ \mu M$) were poor when compared to SN429 ($IC_{2x} = 0.44\ \mu M$) and DPC423 ($IC_{2x} = 4.86\ \mu M$). This may be attributable to the high protein binding (>98%) exhibited by these molecules.

The above not withstanding, we evaluated the pharmacokinetics for a select set of neutral compounds (Table 3). The data shows an overall improvement in pharmacokinetics for the neutral compounds when compared to highly basic benzamidine SN429 ($pK_a \sim 10.7$). The hallmark feature for compounds **6d** and **6e** was the decreased clearance (Cl) and low volume of distribution (V_{dss}). In addition, the good Caco-2 permeability for neutral compound **6d** (Papp $= 51 \times 10^{-6}$ cm/s) was predictive of its good oral bioavailability ($F =$ 48%). In terms of half-life, compound **13b** was best; however, the oral bioavailability for this compound was not determined but was expected to be poor based on its low Caco-2 P_{app} value.

In the SAR development of the *m*-benzylamine pyrazole series which led to the clinical compound DPC423,[10] we had previously found that the 3-aminomethylphenylpyrazole P1 substituent was an effective ligand for S1 binding interaction with Asp189.[10] This is exemplified by the fXa activity for compound **51** (Table 4, fXa $K_i = 2.7$ nM). In our desire to achieve further enhancement of fXa potency in our *p*-methoxyphenyl pyrazole

Table 1. In Vitro fXa Activity of Substituted Phenyl P1 Pyrazole Analogues



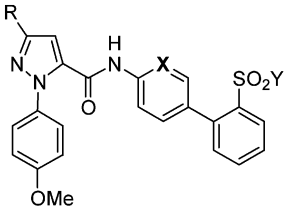


DPC423

compd	R	human fXa[a] K_i (nM)	human thrombin[a] K_i (nM)	human trypsin[a] K_i (nM)
6a	H	198	>21000	>1500
6b	2-OMe	>30000	>21000	>1500
6c	3-OMe	110	>21000	>1500
6d	4-OMe	11	>21000	>1500
7a	2-OH	1200	>21000	>1500
7b	3-OH	164	>21000	>1500
7c	4-OH	900	>21000	>1500
DPC423	−	0.15	6000	60
SN429	3-(C=N)NH_2	0.013	300	16

[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$), and the standard deviations are <30% of the mean. K_i's were measured as in refs 10 and 22.

Table 2. In Vitro Factor Xa Activity of *p*-Methoxyphenyl Pyrazole Analogues



compd	R	X	Y	human fXa[a] K_i (nM)	human thrombin[a] K_i (nM)	human trypsin[a] K_i (nM)	human APTT[b] IC_{2x} (μM)
6d	CH_3	C−H	NH_2	11	>21000	>1500	NT
6e	CH_3	N	NH_2	16	>21000	>1500	NT
6f	CH_3	C−F	NH_2	5.3	>21000	>1500	NT
13a	CF_3	C−H	NH_2	3.5	>21000	>1500	103.7
13b	CF_3	N	NH_2	2.8	>21000	>1600	18.8
13c	CF_3	C−F	NH_2	4.2	>21000	NT	NT
12a	CF_3	C−F	CH_3	3.6	>21000	>2500	64.9
SN429 (amidine)	CF_3	C−H	NH_2	0.013	300	16	0.44
DPC423 (benzylamine)	CF_3	C−F	CH_3	0.15	6000	60	4.86

[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$) and the standard deviations are <30% of the mean. K_i's were measured as in refs 10 and 22. [b] APTT measurements were performed as in ref 26a,b. NT = not tested.

Table 3. In Vivo Dog Pharmacokinetics of Neutral and Basic Factor Xa Inhibitors

compd	Cl[a] (L/h/kg) iv	$t_{1/2}$[a] (h) iv	C_{max}[a] (μM) iv	V_{dss}[a] (L/kg) iv	Caco-2[c] $P_{app} \times 10^{-6}$ cm/s	%F[b] po
6d	0.09	4.46	3.86	0.52	51	48
6e	0.08	4.33	3.96	0.4	1.1	ND
13b	0.12	6.0	0.73	1.8	< 0.1	ND
SN429	0.67[d]	0.82[d]	2.9[d]	0.29[d]	0.3	4.4

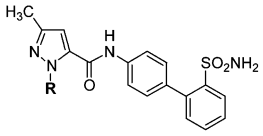
[a] IV dose 1 mg/kg/h. [b] Oral dose 4 mg/kg. IV dose 0.5 mg/kg/hr. ND = not determined. [c] Caco-2 was measured as in ref 27. [d] Reference 10.

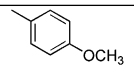
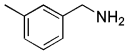
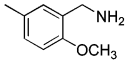
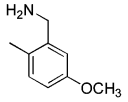
series, we sought to combine the P1 phenyl substituents from **6d** and **51** into a molecule such as compound **18**. Unfortunately, compound **18** was found to be a considerably weaker inhibitor (fXa $K_i = 270$ nM). With this result, we reasoned that an internal H-bond between the vicinal 3-aminomethyl moiety and the oxygen atom of the 4-methoxyphenyl substituent precluded an effective interaction of the P1 with Asp 189 in the S1 pocket. This hypothesis was confirmed by the repositioning of the aminomethyl P1 moiety to the 2-position of the P1 phenyl ring. Compound **27** produced a 3-fold improvement in fXa K_i ($K_i = 3.8$ nM) when compared to compound **6d** and a 70-fold improvement over its regioisomer **18.** The high serine protease selectivity was also maintained. A further benefit was also evident in the improved in vitro potency in the clotting assay (APTT $IC_{2x} = 12$ μM).

The discovery of the 2-aminomethyl-4-methoxyphenyl P1 group, allowed us to explore C-3 modifications on the pyrazole core and the P4 biphenyl group in an effort to further improve potency (Table 5). Incremental improvements in binding affinity were observed for changes made with the trifluoromethyl group at R_1, compound **34a**; the addition of a fluorine atom at R_3, compound **34b**; and the choice of an *o*-sulfonylmethylphenyl P4 substituent (compound **33a)**. Combining the best features from these compounds produced subnanomolar inhibtors **34b** (fXa $K_i = 0.88$ nM) and **33b** (fXa $K_i = 0.54$ nM) with good overall selectivity for fXa.

Noteworthy is the data for pyrazole analogues **40a**−**d** lacking the *p*-methoxy substituent which were shown

Table 4. In Vitro fXa Activity of Benzylamine P1 Analogues



Compound	R	human fXa[a] K_i (nM)	human thrombin[a] K_i (nM)	human trypsin[a] K_i (nM)	human APTT[b] IC_{2x} (μM)
6d		11	> 21000	>1500	NT
50[10]		2.7	> 21000	250	2.3
18		270	> 13000	NT	NT
27		3.8	> 21000	> 1600	12

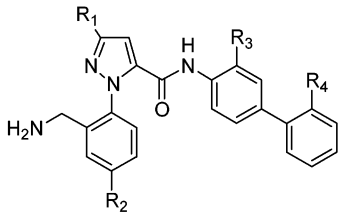
[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$) and the standard deviations are <30% of the mean. K_i's were measured as in refs 10 and 22. [b] APTT measurements were performed as in ref 26a,b. NT = not tested.

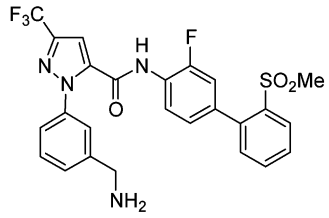
to be equipotent with analogous compounds **33a** and **34a**,**b** which contain the 4-methoxy moiety. These data suggest that the 2-aminomethyl P1 ligand binds strongly to the S1 region of the enzyme, essentially negating the contribution from the 4-methoxyl substituent. We were gratified to observe that for compounds **40a**−**d**, high selectivity for fXa relative to trypsin was maintained. Although 3-fold less potent than DPC423, the selectivity of compounds **40a**−**d** was viewed as an asset. Extension of the 2-aminoalkyl moiety as in **46** and **49** (Table 6) significantly decreased the fXa potency. Alkylamino compounds **45a**−**d** were less active. It therefore appears that the 2-aminomethylphenyl P1 pyrazole substitution was optimal for binding to factor Xa.

To better understand the differences in binding interactions of the *o*-benzylamine and the *m*-benzylamine inhibitors of factor Xa, we compared the X-ray structure of compound **40c** complexed to human factor Xa to that of DPC423 in fXa (Figure 3). The crystal structure of DPC423 in fXa was resolved to a 2.15 Å resolution with a crystallographic *R*-factor of 0.222. The crystal structure of **40c** in fXa was resolved to a 1.9 Å resolution with a crystallographic *R*-factor of 0.224. The overall binding mode of the inhibitors was quite similar to the mode observed in trypsin pyrazole-based inhibitor complexes that were studied previously.[10] Outside of the S1 pocket, the interactions between DPC423 and those of **40c** and factor Xa are essentially identical. For the pyrazole template, a close contact is observed between the N2 nitrogen on the pyrazole ring and the backbone amide nitrogen of Gln192. This pyrazole nitrogen is also in close proximity to the disulfide bond between residues 191 and 220. In the linker region, the amide carbonyl interacts with Gly216 directly and also through a water molecule. The amide proton interacts in a similar manner with Gly218. The biphenyl P4 moieties of both these inhibitors are neatly tucked between Tyr99, Phe174, and Trp215 in the S4 region. No direct interaction is observed between the inhibitor and Ser195 of the catalytic triad.

Although the benzylamine P1 of both inhibitors interacts with the carboxylate of Asp189, they do so in a slightly different manner. A small rotation is observed for the phenyl ring in compound **40c**. The P1 *o*-aminomethyl moiety in compound **40c** fits in the S1 pocket and interacts with Asp189. The carbon of the aminomethyl moiety is close to the wall of the S1 pocket near residue Gly218. In contrast, the *m*-benzylamine binds with the carbon of the aminomethyl moiety near the center of the S1 pocket. The trajectory of the *m*-benzylamine P1 substituent shows a water molecule interacting with the benzylamine nitrogen and the second side-chain oxygen of Asp189. The benzylamine moieties of both inhibitors interact via hydrogen bonds with the carbonyl of the Gly218 backbone.

Table 5. In Vitro fXa Activity of Benzylamine P1 Analogues with Varied P4 Substituents **27**





DPC423

compd	R_1	R_2	R_3	R_4	human fXa[a] K_i (nM)	human thrombin[a] K_i (nM)	human trypsin[a] K_i (nM)	human APTT[b] IC_{2x} (μM)	rabbit fXa[a] K_i(nM)	rabbit APTT[b] IC_{2x} (μM)	rabbit A−V shunt ID_{50}[c] (μmol/ kg/h)
27	CH_3	OMe	H	SO_2NH_2	3.8	>21000	>1600	12	NT	NT	NT
34a	CF_3	OMe	H	SO_2NH_2	2.4	14000	>1600	14.5	NT	NT	NT
33a	CF_3	OMe	H	SO_2CH_3	1.7	9100	>1600	7.3	NT	NT	NT
34b	CF_3	OMe	F	SO_2NH_2	0.88	15000	>1600	6.4	NT	4.4	3.4
33b	CF_3	OMe	F	SO_2CH_3	0.54	6500	>1600	2.4	NT	3.4	5.5
40a	CF_3	H	H	SO_2NH_2	1.8	4100	>1600	7.1	4.6	4.8	NT
40b	CF_3	H	H	SO_2CH_3	1.0	1400	>1600	3.8	2.6	2.6	NT
40c	CF_3	H	F	SO_2NH_2	0.91	3600	3500	4.8	2.9	10.6	4.2
40d	CF_3	H	F	SO_2CH_3	0.46	1500	>2500	26	4.3	6.6	3.2
DPC423	−	−	−	−	0.15	6000	60	4.9	0.3	1.7	1.1

[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$) and the standard deviations are <30% of the mean. K_i's were measured as in refs 10 and 22. [b] APTT measurements were performed as in ref 26a,b. [c] AV-shunt measurements were done as in refs 10 and 22.

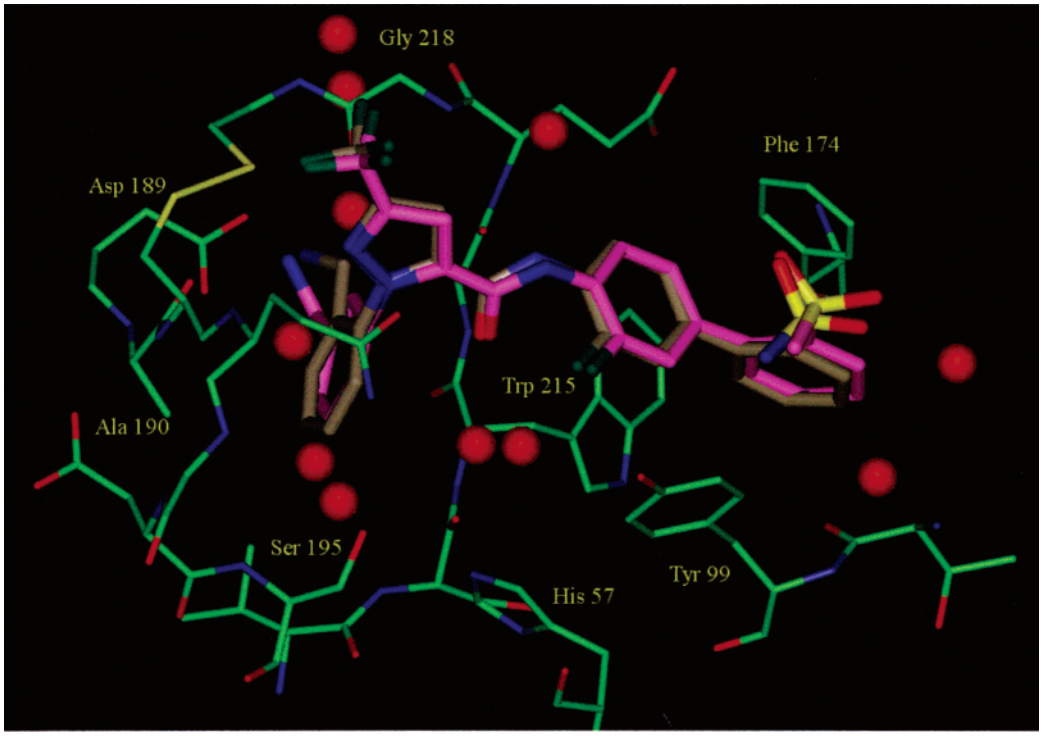
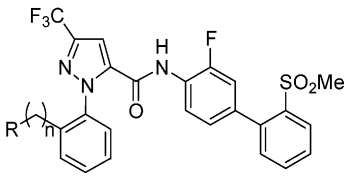


Figure 3. Superposition of the coordinates of DPC423(purple) from the DPC423-factor Xa complex on the coordinates of the **40c**−factor Xa complex.

Table 6. In Vitro Factor Xa Activity of 2-(Aminoalkyl)phenyl P1 Pyrazole Derivatives



compd	R_1	n	human fXa[a] K_i (nM)	human thrombin[a] K_i (nM)	human trypsin[a] K_i (nM)
40d	NH_2	1	0.46	1500	>2500
49	NH_2	2	110	>21000	>2500
46	NH_2	3	600	>21000	NT
45a	NHMe	1	28	>21000	>2500
45b	NMe_2	1	800	>21000	NT
45c	NHiPr	1	38	>21000	>2500
45d	$NHCH_2Ph$	1	61	>21000	NT

[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$) and the standard deviations are <30% of the mean. K_i's were measured as in refs 10 and 22.

Table 7. In Vivo Dog Pharmacokinetics and Cell Permeability of Aminomethyl P1 Analogues

compd	Cl[a] (L/h/kg) iv	V_{dss}[a] (L/kg) iv	$t_{1/2}$[b] (h) iv	F %[b] po	Caco-2[c] $P_{app} \times 10^{-6}$ cm/s	human protein binding[d] (% bound)
33a	1.29	8.0	6	NT	NT	NT
33b	1.51	5.4	2.84	NT	NT	98
40c	0.14	1.2	7.1	100	6.5 ± 0.4	89
DPC423	0.24	0.9	7.5	57	4.9 ± 0.3	89

[a] IV dose 0.5 mg/kg. [b] Oral dose 0.2 mg/kg. [c] Reference 27. [d] Reference 28.

In the human APTT in vitro clotting assay, the potent *p*-methoxy analogue **33b** was ~2-fold better when compared to DPC423. With the exception of compound **33b**, the *p*-methoxy compounds (**27**, **33a**, **34a**, and **34b**) shown in Table 5 were slightly weaker than DPC423 in the clotting APTT assay. The compounds lacking the *p*-methoxy functionality (**40a**−**c**) were comparable to DPC423 in the same assay. Interestingly, the more potent compound **40d** (APTT IC_{2x} = 26 μM) was considerably weaker than its counterpart **33b** (APTT IC_{2x} = 2.4 μM) and DPC423 (APTT IC_{2x} = 4.9 μM). To get a full understanding of the in vivo efficacy for these compounds, we examined them in the rabbit arteriovenous shunt (AV-shunt) thrombosis model. In that model, anesthetized rabbits have a shunt device connected to the femoral artery and vein. Inside the Tygon shunt, a silk thread induces formation of a thrombus. After 40 min the thrombus is recovered and weighed. The dose required to reduce the thrombus weight by 50% is designated the ID_{50}.[10] Compounds **33b**, **34b**, **40c**, and **40d** (Table 5) show good potency in the rabbit AV-shunt thrombosis model.

On the basis of the excellent in vitro and in-vivo efficacy profile of the 4-methoxy-2-(aminomethyl)phenyl compounds **33a** and **33b**, and with 2-(aminomethyl)-phenyl pyrazole compound **40c** (Table 7), we evaluated their pharmacokinetics in dog. Upon intravenous administration in beagle dogs, moderately high clearance and volumes of distribution were observed for compounds **33a** and **33b**. The best overall PK profile was achieved with compound **40c**, which showed 10-fold lower clearance and a long terminal half-life ($T_{1/2}$). Excellent oral bioavailability (F% = 100) was observed for compound **40c** which was consistent with the high Caco-2 permeability observed for this compound. The human plasma protein binding via equilibrium dialysis for **40c** was 89%. The selectivity profile for compound **40c** (Table 8) was excellent except for plasma kallikrein (>60-fold). This profile compared favorably to that

Table 8. Selectivity Profile of **40c** versus DPC423

human enzymes	K_i (nM) **40c**	DPC423
factor Xa	0.91	0.15
trypsin	3500	60
thrombin	3600	6000
plasma kallikrein	58	61
activated protein C	4600	1800
factor IXa	>12000	2200
factor VIIa	>15000	>15000
chymotrypsin	6800	>17000
urokinase	>13000	>19000
plasmin	>15000	>35000
tPA	>33000	>45000

previously determined for DPC423.[10] Thus combining the in vitro and in vivo efficacy and the excellent in vivo pharmacokinetic profile, compound **40c** emerged as a leading candidate for further evaluation. **DPC602**, the crystalline hydrochloride salt form of **40c**, was selected for preclinical development.

Conclusions

Optimization of the substituents on the P1 phenylpyrazole portion of our fXa inhibitors led to a potent and selective *p*-methoxy analogue **27.** Further optimization led to potent, selective *o*-aminomethyl pyrazole derivatives. By careful selection of appropriate substituents on the pyrazole core and the biphenyl P4 region of the molecule, a highly potent, selective, and orally active bioavailable fXa inhibitor compound **40c** was discovered. On the basis of a balanced review of the selectivity, in vitro potency, antithrombotic properties, and pharmacokinetic profile, **DPC602**, a crystalline hydrochloride salt form of **40c**, was selected for further preclinical evaluation.

Experimental Section

All reactions were run under an atmosphere of dry nitrogen or argon. All solvents were used without purification as acquired from commercial sources. NMR spectra were obtained with a Varian VXR-300a spectrometer. Microanalyses were performed by Quantitative Technologies Inc. and were within 0.4% of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP particle beam interface. Flash chromatography was done using EM Science silica gel 60. HPLC purifications were done on a Rainin Dynamax SD200 or an Agilent 1100 instrument using a C18 reverse phase column with acetonitrile/water (containing 0.05% TFA) as a mobile phase. HPLC purity in most cases was >95%. Various P4 starting materials such as 4′-amino[1,1′-biphenyl]-2-*tert*-butylsulfonamide, 4′-amino-3′-fluoro[1,1′-biphenyl]-2-*tert*-butylsulfonamide, 3-fluoro-2′-(methylsulfonyl)[1,1′-biphenyl]-4-amine, and 2-(6-amino-3-pyridinyl)benzene-*tert*-butylsulfonamide substituted aminobiaryls and aminopyridylphenylsulfonamides were obtained as per procedures described by Quan et al.[22a,b]

The DPC423 factor Xa 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 to 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 overnight and concentrated to 6 mg/mL using a Vivaspin 6 mL concentrator with a 5000 MWCO membrane. The crystals were grown using hanging drop vapor diffusion, at 4 °C, with from 14% to 24% PEG 6000 buffered with 100 mM Na phosphate 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.

For the **40c** structure, preexisting crystals of factor Xa were soaked in 5 mM **40c**, 22% PEG 6000, 200 mM Na acetate pH 5.5 and 5% DMSO for 17 days at 4 °C to replace a 15 nM proprietary inhibitor.

For both factor Xa inhibitor crystals, 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 6000, 200 mM Na acetate pH 5.5, and 20% ethylene glycol. After about 1 min, the crystals were frozen.

Data for the fXa DPC423 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 one degree rotation were collected. Data were 99% complete. Data for the fXa−**40c** complex were collected at the IMCA beamline 17 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 was processed with the program Denzo.[23] The program EPMR[24] 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 (Accelerys) program was used for crystallographic refinement. Simulated annealing (at a maximum temperature of 3000°) was followed by *B*-factor refinement. The inhibitors were built with the program QUANTA (Accelerys). Peaks in the difference electron density map which were greater than 3σ which 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 all enzyme inhibitor structures will be deposited with the Protein Data bank.[25]

Ethyl 2-*N*-(Methoxyimino)-4-oxopentanoate (2). Ethyl 2,4-dioxopentanoate (39.5 g, 250 mmol) and *N*-methoxylamine hydrochloride (13.9 g, 167 mmol) in EtOH (150 mL) was left to stand over molecular sieves (3 Å, 100 g) for 18 h. CH_2Cl_2 (100 mL) was added, the sieves were removed by filtration, and the solvent was evaporated. The crude product was applied to a column of flash silica gel and eluted with 20:1 hexane:EtOAc. There was obtained 12.3 g of ethyl 2-(*N*-methoxyimino)-4-oxopentanoate (66.2 mmol, 40%). ^{1}H NMR ($CDCl_3$) δ: 4.3 (q, J = 8 Hz, 2H), 4.0 (s, 3H), 3.65 (s, 2H), 2.2 (s, 3H) and 1.3 (t, J = 8 Hz, 3H) ppm; LRMS $(M + H)^+$ m/z: 187.

Ethyl 3-Methyl-1-phenyl-1*H*-pyrazolecarboxylate (3a). Ethyl 2-(*N*-methoxyimino)-4-oxopentanoate (0.5 g, 2.67 mmol) and phenylhydrazine (0.58 g, 5.35 mmol) in acetic acid (10 mL) and 2-methoxyethanol (5 mL) were heated at 105 °C for 5 h. The reaction was evaporated, dissolved in ethyl acetate, and washed with 0.2 N HCl and then water. The solution was dried (Na_2SO_4) and evaporated and the residue applied to a silica gel column. Elution with a gradient of 10:1 to 5:1 hexane:ethyl acetate gave 160 mg (26%) of ethyl 3-methyl-1-phenyl-1*H*-pyrazolecarboxylate. ^{1}H NMR ($CDCl_3$) δ: 7.5−7.3 (m, 5H), 6.8 (s, 1H), 4.2 (q, J = 7 Hz, 2H), 2.35 (s, 3H), 1.25 (t, J = 3 Hz, 3H) ppm; LRMS $(M + H)^+$ m/z: 231.

3-Methyl-1-phenyl-1*H*-pyrazole-5-(*N*-(2′-*N*-*tert*-butylaminosulfonyl-[1,1′]-biphen-4-yl))carboxamide (5a). To a solution of 4-(2-*N*-*tert*-butylaminosulfonyl)phenyl)aniline[22a,b] (0.22 g, 0.73 mmol) in dichloromethane (10 mL) at 0 °C was added a solution of trimethylaluminum (2.0 M in hexane, 5 equiv, 1.75 mL). This mixture was stirred for 15 min, and then ethyl 3-methyl-1-phenyl-1*H*-pyrazolecarboxylate (0.16 g, 0.69 mmol) in dichloromethane (5 mL) was added. The reaction was allowed to warm to ambient temperature and stirred for 18 h. This mixture was carefully quenched with water and then diluted with ethyl acetate, and the layers were separated, dried, and evaporated. The residue was applied to a silica gel

column and the title compound isolated by gradient elution with mixture of 3:1 to 1:1 hexane:ethyl acetate. There was obtained 150 mg (44%) of 3-methyl-1-phenyl-1*H*-pyrazole-5-(*N*-(4-(2′-*N*-*tert*-butylaminosulfonyl-[1,1′]-biphen-4-yl)carboxamide. ^{1}H NMR ($CDCl_3$) δ: 8.15, (d, J = 7 Hz, 1H), 7.75 (s, 1H), 7.6−7.4 (m, 12H), 6.75 (s, 1H), 2.4 (s, 3H), 1.0 (s, 9H) ppm; HRMS $(M + H)^+$ for $C_{27}H_{28}N_4O_3S$, calcd *m*/*z*: 489.196038, obs: 489.194346.

3-Methyl-1-phenyl-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl))carboxamide (6a). A solution of 150 mg of 3-methyl-1-phenyl-1*H*-pyrazole-5-(*N*-(4-(2′-*N*-*tert*-butylaminosulfonyl-[1,1′]-biphen-4-yl)carboxamide in trifluoroacetic acid (15 mL) was heated at reflux for 1 h. The reaction was evaporated, taken up in ethyl acetate and washed with 1 N sodium hydroxide solution. The organic solution was dried and evaporated to give 140 mg of product. Further purification of 3-methyl-1-phenyl-1*H*-pyrazole-5-(*N*-(4-(2′-aminosulfonyl-[1,1′]-biphen-4-yl)carboxamide was effected by hplc utilizing gradient elution with a mixture of water: acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave 130 mg (98%) of a white solid. mp: > 260 °C (decomposes). ^{1}H NMR (CD_3OD) δ: 8.1 (d, J = 7.7 Hz, 1H), 7.7−7.3 (m, 13H), 6.8 (s, 1H), 2.15 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{23}H_{20}N_4O_3S$, calcd *m*/*z*: 433.133438, obs: 433.131005.

3-Methyl-1-(4-methoxyphenyl)-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl))carboxamide (6d). This compound was prepared by the same methodology described for **6a** with 4-methoxyphenyl hydrazine·HCl substituted for phenyl hydrazine. There was obtained 750 mg (84%) of 3-methyl-1-(2-methoxyphenyl)-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl)carboxamide. mp: 116−122 °C. ^{1}H NMR (CD_3OD) δ: 8.0 (d, J = 7.2 Hz, 1H), 7.6−7.2 (m, 9H), 6.9 (d, J = 8.7 Hz, 2H), 6.7 (s, 1H), 3.75 (s, 3H), 2.3 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{24}H_{22}N_4O_4S$, calcd *m*/*z*: 463.144002, obs: 463.141980. Anal. Calcd for $C_{24}H_{22}N_4O_4S \cdot 0.5H_2O$: C, 61.13, H, 4.92, N, 11.88; found, C, 61.56, H, 4.88, N, 11.80.

3-Methyl-1-(2-hydroxyphenyl)-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl))carboxamide (7a). Compound **6b** (0.245 g, 0.53 mmol) in dichloromethane (20 mL) was cooled to 0 °C, and a solution of boron tribromide in dichloromethane (1.0 M, 6 equiv, 3.2 mL) was added. The reaction was allowed to warm to ambient temperature and stirred for 18h. The reaction was evaporated and the residue applied to a small plug of silica gel and eluted with ethyl acetate. The ethyl acetate solution was dried and evaporated. This material was purified by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the 103 mg (43%) of title compound. mp: 207−210 °C. ^{1}H NMR (DMSO-d_6) δ: 10.4 (s, 1H), 10.0 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 7.7 (d, J = 10 Hz, 2H), 7.65−7.5 (m, 2H), 7.4−7.3 (m, 6H), 7.2 (t, J = 10 Hz, 1H), 6.9 (t, J = 7.5 Hz, 2H), 6.8 (s, 1H), 2.2 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{23}H_{20}N_4O_4S$, calcd *m*/*z*: 449.128352, obs: 449.129006.

5-Methyl-1-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole (10). A mixture of 1,1,1-trifluoro-2,4-pentanedione **9** (0.08 mol, 9.8 mL) and 4-methoxyphenylhydrazine·HCl **8** (0.09 mol, 16.3 g, 1.1 equiv) in 2-methoxyethanol (50 mL) and acetic acid (100 mL) was refluxed for 18 h. The reaction mixture was evaporated and then poured into 10% NaOH (300 mL). The product was extracted with CH_2Cl_2 (3 × 200 mL), dried, and evaporated to give 18.8 g of crude product. This was filtered through a plug column of flash silica gel (500 g) by eluting with 5:1 hexane:ethyl acetate in three 1 L fractions. These fractions were combined and evaporated to give to give 17.3 g of product (84%) with the 2-phenyl isomer as a minor contaminant (<10:1). ^{1}H NMR ($CDCl_3$) δ: 7.35 (d, J = 9 Hz, 2H), 7.05 (d, J = 9 Hz, 2H), 6.4 (s, 1H), 3.85 (s, 3H), 2.3 (s, 3H) ppm.

1-(4-Methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic Acid (11). A mixture of 5-methyl-1-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole (0.067 mol, 17.3 g), *N*-bromosuccinimide (14.4 g, 0.081 mol.), and benzoyl peroxide (0.4 g) in carbon tetrachloride (500 mL) was illuminated with a sunlamp and heated at reflux for 18 h. The reaction mixture was filtered through Celite to remove solid impurity and washed with carbon tetrachloride (200 mL) and evaporated to give 28.5 g of product [partial ^{1}H NMR ($CDCl_3$) δ: 4.4 ppm (s, CH_2Br, 2H)] with some unreacted starting material remaining. This material was treated with potassium acetate (0.134 mol, 13.2 g) and 18-crown-6 (3.0 g) in acetonitrile (400 mL) at ambient temperature for 18 h. The reaction mixture was evaporated, filtered, dissolved in EtOAc (500 mL), and washed with water (3 × 200 mL). The solution was dried and evaporated to give 17.4 g of the acetate. ^{1}H NMR ($CDCl_3$) δ: 7.4 (d, J = 9 Hz, 2H), 7.0 (d, J = 9 Hz, 2H), 6.75 (s, 1H), 5.05 (s, 2H), 3.85 (s, 3H), 2.1 (s, 3H) ppm. The acetate from above was dissolved in MeOH (250 mL), and IR400 (OH^-) resin (17.7 g) was added. After 3 h at ambient temperature, the reaction was filtered and evaporated to give 16.43 g of product. Recrystallization from a mixture of benzene:hexane gave an analytically pure sample; mp: 79.0 °C. ^{1}H NMR ($CDCl_3$) δ: 7.5 (d. J = 9 Hz, 2H), 7.1 (d. J = 9 Hz, 2H), 6.05 (s, 1H), 4.6 (d, J = 7 Hz, 2H), 3.85 (s, 3H), 2.0 (broad, 1H) ppm. To the solution of 5-hydroxymethyl-1-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole (22.7 mmol, 6.2 g) in acetonitrile (100 mL) at 0 °C were added sodium periodate (47.6 mmol, 10.2 g) and several crystals of ruthenium(III) chloride. This reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite to remove white solid impurity and the filter cake washed with 1:1 acetonitrile: water. The filtrate was evaporated in vacuo, and the residue was taken up in water and made basic with 1 N NaOH (30 mL, pH = 10). The basic aqueous solution was washed with Et_2O (3 × 50 mL). The aqueous solution was made acidic (pH 3) by the dropwise addition of concentrated HCl at 0 °C and then extracted with ethyl acetate (3×); the ethyl acetate extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 3.03 g of product (48%). This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ: 7.4 (d, J = 9.1 Hz, 2H), 7.3 (s, 1H), 7.0 (d, J = 9.1 Hz, 2H), 3.9 (s, 3H) ppm.

1-(4-Methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl)carboxamide (13a). To 300 mg of 1-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid (1.05 mmol) in dichloromethane (10 mL) at 0 °C was added a solution of oxalyl chloride in dichloromethane (2 M, 1.5 equiv, 1.58 mmol, 0.8 mL) and a drop of dimethylformamide. After 4 h the reaction was complete, the solvent was evaporated and the acid chloride carried on to the next reaction. The acyl chloride was dissolved in dichloromethane (20 mL) and then added over a period of 15−20 min to a 0 °C solution of 4-(2-N-*tert*-butylaminosulfonyl)phenyl)-aniline (1.2 equiv, 1.25 mmol, 0.365 g), pyridine (10 equiv, 12.5 mmol, 0.99 g, 1.0 mL) and *N*,*N*-dimethylaminopyridine (1.2 equiv, 1.25 mmol, 0.155 g) in dichloromethane (20 mL). The reaction was maintained at 0 °C until thin-layer chromatography indicated that all of the starting acid chloride was consumed. The reaction was evaporated and then the residue suspended in 1 N hydrochloric acid solution. The suspension was extracted with ethyl acetate; the extracts were washed with 1 N hydrochloric acid solution twice and then dried and evaporated. There was obtained 660 mg of the desired product.^{1}H NMR ($CDCl_3$) δ: 8.2−8.1 (m, 2H), 7.7−7.4, (m, 9H), 7.3 (d, J = 1 Hz, 1H), 7.2 (s, 1H), 7.0 (d, J = 9 Hz, 2H), 3.85 (s, 3H), 1.0 (s, 9H) ppm; LRMS $(M + Na)^+$ *m*/*z*: 594.5. 1-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(2′-*N*-*tert*-butylaminosulfonyl-[1,1′]-biphen-4-yl)carboxamide (0.66 g) was dissolved in trifluoroacetic acid (20 mL) and heated at reflux for 30 min. The reaction was evaporated and then dissolved in ethyl acetate and washed with 1 N sodium hydroxide solution twice and brine. This solution was dried and evaporated to 0.48 g of crude product. This material was made analytically pure by first subjecting it to flash chromatography with a 200 g column of silica gel and elution with 2:1 hexane: ethyl acetate and finally recrystallizing the homogeneous chromatography product from chloroform. There was obtained 0.262 g (48%) of the title compound. mp: 237.3 °C. ^{1}H NMR

(DMSO-d_6) δ: 10.8 (s, 1H), 8.0 (d, J = 7 Hz, 1H), 7.7−7.2 (m, 12 H), 7.1 (d, J = 9 Hz, 2H), 3.8 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{24}H_{19}F_3N_4O_2S$, calcd *m/z*: 517.116712, obs: 517.115737. Anal. Calcd for $C_{24}H_{19}F_3N_4O_2S$: C, 55.81, H, 3.72, F, 11.03, N, 10.85, S, 6.22; found, C, 56.02, H, 3.77, F, 11.29, N, 10.51, S, 5.84.

1-(4-Methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methanesulfonyl-[1,1′]-biphen-4-yl)carboxamide (12c). This material was prepared according to the methods described for **13a** with the exception that during the coupling step 3-fluoro-4-(2-methanesulfonyl)phenyl)aniline was substituted for 4-(2-*N*-*tert*-butylaminosulfonyl)phenyl)aniline. The subsequent trifluoroacetic acid cleavage step was omitted. Purification of the final product by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave 155 mg (47%) of the title compound. mp: 242.3 °C. ^{1}H NMR (DMSO-d_6) δ: 10.7 (s, 1H), 8.1 (dd, J = 7 and 1 Hz, 1H), 7.8−7.5 (m, 4H), 7.5−7.3 (m, 4H), 7.2 (dd, J = 9 and 1.5 Hz, 1H), 7.05 (d, J = 9 Hz, 2H), 3.8 (s, 3H) and 2.9(s, 3H) ppm; HRMS $(M + H)^+$ for $C_{25}H_{19}F_4N_3O_4S$, calcd *m/z*: 534.1111, obs: 534.1114. Anal. Calcd for $C_{25}H_{19}F_4N_3O_4S \cdot 0.5\ H_2O$: C, 55.35, H, 3.72, N, 7.75; found, C, 55.66, H, 3.33, N, 7.52.

Ethyl 1-(2-carboxy-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (20) and Ethyl 1-(2-Carboxy-4-methoxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (21). 2-Amino-5-methoxybenzoic acid (4.2 g, 25.1 mmol) in concentrated hydrochloric acid (50 mL) was cooled to 0 °C, and sodium nitrite (2.08 g, 30.2 mmol) in cold water (20 mL) was added dropwise. This mixture was stirred at 0 °C for 30 min and then tin(II)chloride dihydrate (17.0 g, 75.4 mmol) in cold concentrated hydrochloric acid (25 mL) was added dropwise. This mixture was allowed to thaw to ambient temperature over 3 h and then filtered and air-dried overnight. The filter cake was broken up and dried further in a vacuum oven at 60 °C overnight. There was obtained 8.76 g of 2-carboxy-4-methoxyphenylhydrazine **19** contaminated with tin salts. Ethyl 2-(*N*-methoxyimino)-4-oxopentanoate **2** (1.0 g, 5.35 mmol) and crude 2-carboxy-4-methoxyphenylhydrazine **19** (2.33 g, ca. 10.7 mmol) in acetonitrile (40 mL) and acetic acid (5 mL) were stirred at ambient temperature for 3 h and then heated at reflux for an additional 3 h. The reaction was cooled to ambient temperature, diluted with methylene chloride (150 mL), and filtered. The filtrate was evaporated and the product isolated by flash chromatography by elution with 10% methanol in chloroform. This material (1.28 g, 4.2 mmol, 79%) coeluted as a mixture of regiosiomers as evident by proton NMR. ^{1}H NMR ($CDCl_3$) δ: 7.7 (broad d, J = 7 Hz, 1H), 7.65−7.5 (m), 7.4−7.25 (m), 7.2−7.1 (m), 6.8 (s, major regioisomer), 5.3 (s, minor regioisomer), 4.35 (broad q, J = 7 Hz, minor regioisomer), 4.15 (q, J = 8 Hz, major regioisomer), 3.9 (s, major regioisomer), 3.85 (s, minor regioisomer), 2.35 (s, minor regioisomer), 2.1 (s, major regioisomer), 1.35 (broad t, J = 7 Hz, minor regioisomer), 1.2 (t, J = 8 Hz, major regioisomer) ppm; LRMS $(M + H)^+$ *m/z*: 306.

Ethyl 1-(2-Hydroxymethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (22) and Ethyl 1-(2-Hydroxymethyl-4-methoxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (23). A mixture compounds **20** and **21** (1.28 g, 4.2 mmol) was dissolved in tetrahydrofuran (60 mL) and cooled to 0 °C. To the cold solution were added *N*-methylmorpholine (0.42 g, 4.2 mmol) and isobutyl chloroformate (0.57 g, 4.2 mmol). The reaction was stirred for 30 min at 0 °C, the precipitate removed by filtration, and the cold solution poured immediately into a cold (5 °C) solution of sodium borohydride (0.48 g, 12.6 mmol) in water (20 mL) and tetrahydrofuran (20 mL). The reaction was allowed to thaw to room temperature over 18 h. The reaction mixture was evaporated, partitioned between ethyl acetate (100 mL) and 1 N hydrochloric acid (50 mL) and then washed with 5% sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried and evaporated; three products were isolated by elution of the crude mixture from a silica gel column with 2:1 hexane:ethyl acetate. The first product to elute was a ring closed lactone **24** (0.14 g, 0.6 mmol). ^{1}H NMR ($CDCl_3$) δ: 7.3 (t, J = 7.5 Hz, 1H), 7.0−6.9 (m, 2H), 6.85 (d, J = 7.5 Hz, 1H), 4.85 (s, 2H), 3.8 (s, 3H) ppm; LRMS $(M + H)^+$ *m/z*: 245. The second product isolated was the desired material, **22** (0.18 g, 0.62 mmol) as determined by proton NMR NOE experiments. ^{1}H NMR ($CDCl_3$) δ: 7.15 (d, J = 7.5 Hz, aromatic H6), 7.05 (d, J = 1 Hz, aromatic H3), 6.85 (dd, J = 7.5 and 1 Hz, aromatic H5), 6.8 (s, pyrazole H, NOE), 4.3 (s, benzylic H), 4.2 (q, J = 7.5 Hz, $-OCH_2CH_3$), 3.85 (s, $-OCH_3$), 2.35 (s, pyrazole $-CH_3$, NOE), 1.25 (t, J = 7.5 Hz, $-OCH_2CH_3$) ppm; LRMS $(M + H)^+$ *m/z*: 291. The third product to elute was the regioisomer **23** (0.14 g, 0.5 mmol). ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, J = 7.5 Hz, aromatic H6, NOE), 7.1 (d, J = 1 Hz, aromatic H3), 6.9 (dd, J = 7.5 and 1 Hz, aromatic H5), 6.9 (s, pyrazole H, NOE), 4.4 (q, J = 7.5 Hz, OCH_2CH_3), 4.25 (s, benzylic H), 3.85 (s, OCH_3), 2.2 (s, pyrazole CH_3, NOE), 1.38 (t, J = 7.5 Hz, OCH_2CH_3) ppm; LRMS $(M + H)^+$ *m/z*: 291.

1-(2-Azidomethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid (25). Ethyl 1-(2-hydroxymethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (0.18 g, 0.62 mmol) was dissolved in chloroform (20 mL) and then methanesulfonyl chloride (0.3 g, 2.6 mmol) and triethylamine (0.26 g, 2.6 mmol) were added. The reaction was complete in 6 h; it was evaporated, dissolved in ethyl acetate (100 mL), washed with 1 N hydrochloric acid (50 mL) and brine (50 mL), dried, and evaporated to give 0.22 g of product (0.6 mmol, 97%). The resulting mesylate and sodium azide (0.12 g, 1.8 mmol) were dissolved in dimethylformamide (15 mL) and heated for 1.5 h at 60 °C and then diluted with brine (50 mL), extracted with ethyl acetate (100 mL), dried, and evaporated. There was obtained 0.11 g of ethyl 1-(2-azidomethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (0.35 mmol, 58%). ^{1}H NMR ($CDCl_3$) δ: 7.2 (d, J = 7.5 Hz, 1H), 7.0 (d, J = 1 Hz, 1H), 6.9 (dd, J = 7.5 and 1 Hz, 1H), 6.8 (s, 1H), 4.2 (q, J = 7.5 Hz, 2H), 4.1 (s, 2H), 3.85 (s, 3H), 2.35 (s, 3H), 1.2 (t, J = 7.5 Hz, 3H) ppm; LRMS $(M + H)^+$ *m/z*: 316. The ester (0.11 g, 0.35 mmol) in ethanol (2 mL) and water (2 mL) was stirred with 50% sodium hydroxide (3 drops) at 45 °C and followed by TLC (1:1 hexane:ethyl acetate). When all of the ester was consumed, the reaction was cooled, diluted with brine, and washed with ethyl ether (25 mL). The aqueous layer was acidified with 1 N hydrochloric acid (pH = 1), extracted with ethyl acetate (2 × 30 mL), dried, and evaporated. There was obtained 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1*H*-pyrazole-5-carboxylic acid (0.06 g). LRMS $(M - H)^-$: 285 *m/z*.

3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1*H*-pyrazole-5-(*N*-(4-(2-*N*-*tert*-butylsulfamido)phenyl)phenyl)-carboxamide (26). 3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1*H*-pyrazole-5-carboxylic acid (0.60 g, 0.21 mmol) in dichloromethane (5 mL) was cooled to 0 °C, and oxalyl chloride (0.21 mL of a 2 M solution in dichloromethane) and dimethylformamide (1 drop) were added. The reaction was complete inside of 1 h; it was evaporated to remove residual HCl. The acid chloride (0.17 g, 0.50 mmol) in dichloromethane (3 mL) was added dropwise to an ice-cold solution of 4-(2-*N*-*tert*-butylsulfonamido)phenylaniline **4a** (0.15 g, 0.51 mmol), pyridine (0.39 g, 4.4 mmol), and 4,4-(dimethylamino)pyridine (0.09 g, 0.7 mmol) in dichloromethane (15 mL). The reaction was allowed to warm to ambient temperature over 18 h and then evaporated, dissolved in ethyl acetate (30 mL), washed with 1 N hydrochloric acid (20 mL), and dried. Silica gel flash chromatography, eluting with a gradient of 2:1 to 1:1 hexane: ethyl acetate, gave 0.09 g of the title compound (0.16 mmol, 76%). ^{1}H NMR ($CDCl_3$) δ: 8.15 (d, J = 9 Hz, 1H), 7.78 (broad s, 1H), 7.6−7.4 (m, 6H), 7.35−7.2 (m, 2H), 7.05 (d, J = 1 Hz, 1H), 6.92 (dd, J = 7.5 and 1 Hz, 1H), 6.75 (s, 1H), 4.3 (s, 2H), 3.85 (s, 3H), 3.55 (s, 1H), 2.4 (s, 3H), 1.0 (s, 9H) ppm; LRMS $(M - H)^-$: 572 *m/z*.

1-(2-Aminomethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-(*N*-(2′-aminosulfonyl-[1,1′]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (27). 1-(2-Azidomethyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-(*N*-(2′-*N*-*tert*-butylaminosulfonyl-[1,1′]-biphen-4-yl))carboxamide (0.09 g, 0.16 mmol) was stirred with tin(II) chloride dihydrate (0.11 g, 0.47 mmol) in methanol (10 mL). When the reaction was complete

by TLC (1:1 hexane:ethyl acetate), it was evaporated to give a crude mixture of the aminomethyl product and tin salts weighing 0.39 g. The material was heated at reflux in trifluoroacetic acid (10 mL) for 45 min and then evaporated. The residue was partitioned between 1 N sodium hydroxide (30 mL) and ethyl acetate (30 mL). The ethyl acetate solution was dried and evaporated to give 0.04 g of crude product. This material was purified further by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 0.010 g of the title compound (0.02 mmol, 13%). mp 184.3 °C. ^{1}H NMR (DMSO-d_6) δ: 10.55 (s, 1H), 8.2 (broad s, 2H), 8.0 (dd, J = 9 and 1 Hz, 1H), 7.7−7.5 (m, 4H), 7.4−7.1(m, 6H), 7.0 (m, 2H), 3.85 (s, 3H), 3.8 (m, 2H), 2.3 (s, 3H) ppm; HRMS (M + H)$^+$ calcd m/z: 492.170551, obsd m/z: 492.17155

1-(2-Carboxy-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1*H*-pyrazole (29a). Crude 2-carboxy-4-methoxyphenylhydrazine **19** (8.88 g, ca. 23.9 mmol) and 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione **28** (7.4 g, 35.9 mmol) in acetic acid (150 mL) was heated at 100 °C for 4 h. The hot reaction mixture was evaporated and the residue stirred in a biphasic mixture of water (150 mL) and chloroform (150 mL). The layers were filtered, separated, the solid precipitate was washed several times with additional chloroform (3 × 50 mL), and the chloroform layer and washings were combined, dried, and evaporated. There was obtained 3.55 g of 3-trifluoromethyl-1-(2-carboxy-4-methoxyphenyl)-5-(furan-2-yl)-1*H*-pyrazole; LRMS (M − H)$^-$ m/z: 351.

1-(2-Azido-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1*H*-pyrazole (30a). Compound **29** (3.55 g, 10.1 mmol) was dissolved in tetrahydrofuran (100 mL) and cooled to 0 °C. *N*-Methylmorpholine (1.02 g, 10.1 mmol) and isobutyl chloroformate (1.38 g, 10.1 mmol) were added. The reaction mixture was stirred for 30 min at 0 °C, filtered, and added immediately to a cold solution of sodium borohydride (1.15 g, 30.2 mmol) in water (50 mL) and tetrahydrofuran (50 mL). The reaction mixture was evaporated, partitioned between ethyl acetate (100 mL) and 1 N hydrochloric acid (50 mL) and then washed with 5% sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried and evaporated and then purified further by flash chromatography using 4:1 hexane: ethyl acetate as the eluent. There was obtained 1.5 g of 1-(2-hydroxymethyl-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1*H*-pyrazole. ^{1}H NMR ($CDCl_3$) δ: 7.4 (d, J = 1 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.18 (d, J = 1,5 Hz, 1H), 6.95 (s, 1H), 6.9 (dd, J = 8 and 1 Hz, 1H), 6.3 (m, 1H), 5.75 (d, J = 1.5 Hz, 1H), 4.3 (broad s, 2H), 3.9 (s, 3H) ppm; LRMS (M + H)$^+$ m/z: 339. To a cooled chloroform (50 mL) solution of 1-(2-hydroxymethyl-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1*H*-pyrazole (1.5 g, 4.44 mmol) and triethylamine (1.79 g, 17.7 mmol) was added a chloroform solution (10 mL) of methanesulfonyl chloride (2.03 g, 17.7 mmol). The reaction was complete in 4 h. It was evaporated and dissolved in ethyl acetate (100 mL), and the ethyl acetate solution was washed with cold 5% $NaHSO_4$ (50 mL) and cold saturated $NaHCO_3$ (50 mL). The organic layer was dried and evaporated to give 2.1 g of the mesylate which was used immediately in the next reaction; LRMS (M + H)$^+$ m/z: 417.

A mixture of the mesylate prepared above (2.1 g, 5.05 mmol) and sodium azide (0.98 g, 15.1 mmol) in dimethylformamide (40 mL) was heated at 60 °C for 2 h. The reaction mixture was cooled, diluted with brine (100 mL), and extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water (5 × 50 mL) and then dried and evaporated. There was obtained 1.43 g (78%) of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-5-(furan-2-yl)-1*H*-pyrazole. ^{1}H NMR ($CDCl_3$) δ: 7.4 (d, J = 1 Hz, 1H), 7.3 (d, J = 8 Hz, 1H), 7.1 (d, J = 1.5 Hz, 1H), 6.95 (dd, J = 8 and 1 Hz, 1H), 6.3 (m, 1H), 5.7 (d, J = 1.5 Hz, 1H), 4.1 (broad s, 2H), 3.9 (s, 3H) ppm; LRMS (M + H)$^+$ m/z: 364.

1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic Acid (31a). To 1.43 g of 1-(2-azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1*H*-pyrazole (3.9 mmol) in acetone (60 mL) was added potassium permanganate (5.0 g, 27.5 mmol) in water (60 mL). The reaction was heated at 60 °C for 3 h and then cooled to ambient temperature, and isopropyl alcohol (60 mL) was added. This mixture was stirred for 18 h and then filtered through a Celite pad and washed with copious amounts of isopropyl alcohol. The combined filtrates were evaporated, and the residue was dissolved in 1 N NaOH (50 mL) and washed with ethyl ether (2 × 50 mL). The basic layer was acidified with 1 N HCl (75 mL) and solid NaCl added. The suspension was extracted with EtOAc (3 × 100 mL), and the extracts were dried and evaporated. There was obtained 0.91 g (68%) of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1*H*-pyrazole-5-carboxylic acid. ^{1}H NMR ($CDCl_3$) δ: 7.3 (s, 1H), 7.25 (d, J = 8 Hz, 1H), 7.1−7.0 (broad, 1H), 7.05 (d, J = 1 Hz, 1H), 6.95 (dd, J = 8 and 1 Hz, 1H),4.05 (broad s, 2H), 3.9 (s, 3H) ppm; LRMS (M − H)$^-$ m/z: 340.

1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(2-fluoro-4-(2-*N*-*tert*-butylaminosulfonyl-[1,1]-biphen-4-yl))carboxamide (32d). 1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid (1.09 g, 3.2 mmol) in dichloromethane (50 mL) was stirred at 0 °C with oxalyl chloride from 3.2 mL of a 2 M dichloromethane solution of the reagent and a catalytic amount of DMF (3 drops). The reaction was complete in 3 h and then evaporated to remove residual reagent. There was obtained 1.04 g (2.9 mmol) of the acid chloride. A portion of the acyl chloride (0.52 g, 1.45 mmol) in dichloromethane (10 mL) was added dropwise to an ice-cold solution of 2-fluoro-4-(2-*N*-*tert*-butylsulfonamido)phenylaniline (0.56 g, 1.74 mmol), pyridine (1.14 g, 14.5 mmol), and 4,4- (dimethylamino)pyridine (0.21 g, 1.74 mmol) in dichloromethane (30 mL). The reaction was allowed to warm to ambient temperature over 18 h and then evaporated, dissolved in ethyl acetate (100 mL), washed with 1 N hydrochloric acid (50 mL), and dried. Silica gel flash chromatography, eluting with 4:1 hexane:ethyl acetate, gave 0.28 g (30%) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 8.5 (t, J = 8 Hz, 1H), 8.3 (t, J = 11.3 Hz, 1H), 8.25 (s, 1H), 8.15 (t, J = 11.3 Hz, 2H), 7.95 (s, 1H), 7.6−6.9 (m, 6H), 4.25 (s, 2H), 3.9 (s, 3H), 1.05 (s, 9H) ppm; HRMS (M + Na)$^+$ calcd m/z: 668.167907, obsd m/z: 668.166000.

1-(2-Aminomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(2′-methylsulfonyl-[1,1]-biphen-4-yl))-carboxamide, Trifluoroacetic Acid Salt (33a). 1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid chloride and 4-(2-methylsulfonylphenyl)aniline were treated in the manner described for **33b** to give 98 mg (42%) of the title compound. mp 133 °C. ^{1}H NMR (CD_3OD) δ: 8.15 (dd, J = 11 and 1 Hz, 1H), 7.8−7.65 (3H, m), 7.6 (t, J = 11 Hz), 7.45 (s, 1H), 7.4−7.3 (4H, m), 7.25 (d, J = 1.2 Hz, 1H), 7.1 (dd, J = 11 and 1.2 Hz, 1H), 3.95 (s, 2H), 3.9 (s, 3H), 2.7 (s, 3H) ppm; HRMS (M + H)$^+$ for $C_{26}H_{23}F_3N_4O_4S$, calcd m/z: 545.147037, obsd m/z: 545.145700. Anal. Calcd for $C_{26}H_{23}F_3N_4O_4S$·1.3 $C_2HF_3O_2$: C, 49.58, H, 3.54, N, 8.09; found, C, 49.72, H, 3.39, N, 7.65.

1-(2-Aminomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-4-(2-aminosulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (34b). Compound **32d** (0.28 g, 0.43 mmol) and tin(II) chloride dihydrate (0.29 g, 1.3 mmol) was stirred in methanol (30 mL) for 18 h. The reaction was evaporated, and the reduction product (0.60 g) was refluxed in trifluoroacetic acid (20 mL) for 30 min and then evaporated. The residue was suspended in 1 N NaOH (30 mL), extracted with EtOAc (3 × 50 mL), dried, and evaporated. This material was purified further by hplc utilizing gradient elution with a mixture of water: acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 0.18 g (80%) of the title compound. mp 103.2 °C. ^{1}H NMR (DMSO-d_6) δ: 10.7 (s, 1H), 8.0 (dd, J = 7.5 and 1 Hz, 1H), 7.8 (s, 1H), 7.7−7.55 (m, 3H), 7.45 (d, J = 1 Hz, 1H), 7.4 (s, 1H), 7.35−7.25 (m, 3H), 7.2 (dd, J = 7.5 and 1 Hz, 1H), 7.05 (dd, J = 9 and 1.5 Hz, 1H), 3.85 (s, 3H), 3.75 (broad s, 2H) ppm; HRMS (M + H)$^+$ for $C_{25}H_{21}F_4N_5O_4S$, calcd m/z: 564.132864, obsd m/z: 564.131700. Anal. Calcd for

$C_{25}H_{21}F_4N_5O_4S \cdot C_2HF_3O_2$: C, 47.86, H, 3.27, N, 10.34; found, C, 47.98, H, 3.22, N, 10.20.

1-(2-Aminomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (33b). 1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid chloride (0.52 g, 1.45 mmol) in dichloromethane (10 mL) was added dropwise to an ice-cold solution of 2-fluoro-4-(2-methylsulfonylphenyl)aniline (0.52 g, 1.74 mmol), pyridine (1.14 g, 14.5 mmol), and 4,4- (dimethylamino)pyridine (0.21 g, 1.74 mmol) in dichloromethane (30 mL). The reaction was allowed to warm to ambient temperature over 18 h and then evaporated, dissolved in ethyl acetate (100 mL), washed with 1 N hydrochloric acid (50 mL), and dried. Silica gel flash chromatography, eluting with a gradient of 5:1 to 1:1 hexane: ethyl acetate, gave 0.46 g (0.78 mmol, 54%) of the desired amide. LRMS $(M + H)^+$ *m/z*: 587. This azide (0.46 g, 0.78 mmol) and tin(II) chloride dihydrate (0.53 g, 2.35 mmol) was stirred in methanol (25 mL) for 18 h. The reaction was evaporated, and the residue was suspended in 1 N NaOH (50 mL), extracted with EtOAc (3 × 100 mL), dried, and evaporated to give 0.29 g of crude product. The crude product was purified further by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 157 mg (36%) of the title compound. mp 101.5 °C. ^{1}H NMR (600 MHz, CD_3OD) δ: 8.15 (dd, J = 8 and 1 Hz, 1H), 7.78 (m, 1H), 7.73 (m, 1H), 7.65 (m, 1H), 7.45 (s, 1H), 7.39 (m, 1H), 7.31 (m, 2H), 7.2 (m, 2H), 7.04 (m, 1H), 3.89 (s, 3H), 3.76 (broad s, 2H), 2.76 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{26}H_{22}F_4N_4O_4S$, calcd *m/z*: 563.137615, obsd *m/z*: 563.138100. Anal. Calcd for $C_{26}H_{22}F_4N_4O_4S \cdot 1.5C_2HF_3O_2$: C, 47.48, H, 3.23, N, 7.64; found, C, 47.71, H, 3.06, N, 7.65.

1-(2-(Aminomethyl)phenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-aminosulfonyl-[1,1′]-biphen-4-yl))-carboxamide, Trifluoroacetic Acid Salt (40c). Oxalyl chloride (300 μl, 3.4 mmol) and DMF (3 drops) were added to compound **38** (888 mg, 2.3 mmol) in CH_2Cl_2 (30 mL), and the resulting solution was stirred for 65 min at room temperature. The solvents were evaporated, and the resulting compound was placed briefly under high vacuum before redissolving in CH_2Cl_2 (30 mL). 4-Amino-3-fluoro-2′-(*tert*-butylamino)sulfonyl-[1,1′]-biphenyl (890 mg, 2.8 mmol), and 4-(dimethylamino)-pyridine (420 mg, 3.4 mmol) were added, and the resulting solution was stirred for 22 h at room temperature. The reaction was concentrated and chromatographed on silica gel (20−30% EtOAc/hexanes). The fractions containing product were combined and concentrated to half the original volume and then extracted 3× with ice-cooled 1 M HCl, 2× with room temperature 1 M HCl, sat. $NaHCO_3$, 2 M HCl, and sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated to yield the desired product (600 mg, 38%). TFA (9 mL) was added to {2-[5-(3-fluoro-2′-*N*-*tert*-butylaminosulfonyl-biphenyl-4-ylcarbamoyl)-3-trifluoromethyl-pyrazol-1-yl]benzylcarbamic acid *tert*-butyl ester (600 mg, 0.87 mmol) in CH_2Cl_2 (3 mL) and stirred at room temperature for 18 h. The reaction was evaporated and purified by reverse phase prep HPLC (10−70% MeCN/H_2O/0.5% TFA) to yield impure product (349 mg). This material was again purified by reverse phase HPLC (5−70% MeCN/H_2O/0.5% TFA) to yield clean product (162 mg, 35%). Any impure fractions containing product were combined and purified by reverse phase HPLC (20−60% MeCN/H_2O/0.5% TFA) to yield additional product (119 mg, 26%). ^{1}H NMR (DMSO-d_6) δ 8.25 (bs, 2H), 7.85 (s, 1H), 7.67 (dd, 2H, J = 7.0, J' = 2.2), 7.68−7.55 (m, 4H), 7.51 (s, 2H), 7.41 (s, 2H), 7.33−7.28(m, 2H), 7.21 (dd, 1H, J = 8.4, J' = 2.1), 3.81 (s, 2H) ppm; ^{19}F NMR (DMSO-d_6 δ −61.26, −74.29, −122.79 ppm; HRMS calcd $C_{24}H_{20}F_4N_5O_3S$: 534.1223; found, 534.1216. Anal. Calcd for $C_{24}H_{20}F_4N_5O_3S \cdot C_2HF_3O_2$: C, 48.15, H, 3.26, N, 10.80; found, C, 48.01, H, 3.02, N, 10.68.

2-(5-Furan-2-yl-3-trifluoromethyl-pyrazol-1-yl)benzoic Acid (41). 2-Hydrazinobenzoic acid (12.5 g, 66.3 mmol) and 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (13.65 g, 66.3 mmol) in acetic acid (100 mL) and water (30 mL) were heated at 100 °C for 1 h. The hot reaction was stirred at for another 1 h and then diluted with 1-chlorobutane (300 mL) and water (300 mL). The layers were separated, and the water layer was extracted with 1-chlorobutane (6 × 50 mL). The combined organic layers were extracted with water (4 × 100 mL) and then the product was extracted into a solution of saturated $NaHCO_3$ (5 × 100 mL). The combined basic extracts were acidified with concentrated HCl (pH ca. 2), and the resulting gum was isolated by decanting off the aqueous layer. This material was purified by trituration with benzene to give 16.2 g (50.3 mmol, 76%) of product. ^{1}H NMR ($CDCl_3$) δ: 8.15 (dd, J = 7.7 and 1.8 Hz, 1H), 7.74 (td, J = 7.7 and 2.2 Hz, 1H), 7.65 (td, J = 7.7 and 2.2 Hz, 1H), 7.5 (dd, J = 7.7 and 1.1 Hz, 1H), 7.3 (d, J = 1.4 Hz, 1H), 6.9 (s, 1H), 6.3 (m, 1H), 5.75 (d, J = 3.7 Hz, 1H) ppm.

2-(2-Methoxycarbonylphenyl)-5-trifluoromethyl-2*H*-pyrazole-3-carboxylic Acid (42). Compound **41** (16.1 g, 50 mmol) in CH_2Cl_2 (160 mL) was stirred with oxalyl chloride (7.61 g, 60 mmol) and 5 drops of DMF for 4 h. The mixture was evaporated to give a solid which was redissolved in MeOH, and this was stirred at ambient temperature for 2 h and then evaporated. There was obtained 16.65 g (50 mmol, 100%) of the desired product as a syrup. ^{1}H NMR ($CDCl_3$) δ: 8.15 (dd, J = 7.3 and 1.5 Hz, 1H), 7.8−7.6 (m, 2H), 7.5 (dd, J = 8.1 and 2.2 Hz, 1H), 7.4 (d, J = 1.1 Hz, 1H), 6.9 (s, 1H), 6.3 (m, 1H), 5.77 (d, J = 3.3 Hz, 1H), 3.6 (s, 3H) ppm.

To 2-(5-furan-2-yl-3-trifluoromethyl-pyrazol-1-yl)benzoic acid methyl ester (16.65 g, 50 mmol) in acetone (1200 mL) was added 40 g of $KMnO_4$ in 800 mL of water dropwise over 1 h. This mixture was heated at reflux for 4 h and then cooled to ambient temperature. To this solution was added isopropyl alcohol (263 mL), and the mixture was stirred at ambient temperature for 18 h. This material was filtered through a pad of Celite and washed with acetone and the acetone removed by evaporation. The aqueous suspension was acidified with concentrated H_2SO_4 (pH 2) and then extracted with EtOAc (2 × 200 mL), dried ($MgSO_4$), and evaporated. There was obtained 17 g of crude material as a syrup. Trituration with 1-chlorobutane gave the title compound (5.45 g, 17.35 mmol, 35%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.12 (dd, J = 7.7 and 1.4 Hz, 1H), 7.75−7.6 (m, 3H), 7.42 (dd, J = 7.7 and 1.1 Hz, 1H), 7.2 (s, 1H), 7−6.7 (broad, 1H), 3.7 (s, 3H) ppm.

1-(2-Methoxycarbonyl-phenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide (43). To compound **42** (2.7 g, 8.9 mmol) in CH_2Cl_2 (25 mL) were added oxalyl chloride (1.24 g, 9.8 mmol) and 4 drops of DMF. The reaction was stirred at ambient temperature for 2 h and then evaporated and placed under high vacuum. This material was combined with 2-fluoro-4-(2-methylsulfonylphenyl)aniline **4d** (2.97 g, 9.8 mmol) and DMAP (3.6 g, 29.4 mmol) in CH_2Cl_2 (25 mL) and stirred at ambient temperature for 18 h. The reaction was evaporated, dissolved in EtOAc (120 mL), washed with 1 N HCl (3 × 50 mL) and then dried ($MgSO_4$) and evaporated. This material was triturated with 1-chlorobutane and there was obtained 3.34 g of product (6 mmol, 67%) with a purity of 97% by HPLC. ^{1}H NMR ($CDCl_3$) δ: 8.3 (t, J = 8.4 Hz, 1H), 8.2 (dd, J = 7.7 and 1.7 Hz, 1H), 8.18 (broad s, 1H), 8.1 (dd, J = 7.7 and 1.8 Hz, 1H), 7.8−7.5 (m, 5H)7.35−7.25 (m, 2H), 7.17 (s, 1H), 3.8 (s, 3H), 2.7 (s, 3H) ppm; LRMS $(M + NH_4)^+$: 579 *m/z*.

3-Trifluoromethyl-1-(2-formylphenyl)-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide (44). Compound **43** (3.5 g, 6.2 mmol) in MeOH (30 mL) was stirred with water (4 mL) and 50% NaOH (2 mL) at ambient temperature for 5 h. The basic mixture was diluted with water (100 mL) and concentrated HCl added until acidic (pH 1). The product was isolated by filtration, air-dried, and triturated with 1-chlorobutane to give the carboxylic acid (3 g, 5.5 mmol, 89%). ^{1}H NMR ($CDCl_3$) δ: 8.3−8.1 (m, 4H), 7.8−7.5 (m, 5H), 7.3 (m, 1H), 7.2−7.1 (m, 2H) and 2.7 ppm (s, 3H) ppm; LRMS $(M-H)^-$: 546.1 *m/z*. The carboxylic acid (1.66 g, 3.0 mmol) and NMM (0.37 g, 3.66 mmol) in THF (10 mL) was cooled to −10 °C (MeOH/ice bath). To the cold solution, isobutyl chloroformate (0.5 g, 3.66 mmol) was added. The reaction was

stirred for 1 h at −10 °C. The solution was filtered then added to a 0 °C solution of $NaBH_4$ (0.17 g, 4.57 mmol) in 1:1 THF:water (6 mL: 6 mL). The reaction was left to thaw to ambient temperature and stirred 18 h. The reaction was quenched by the addition of 1 N HCl (18 mL), and EtOAc (30 mL) was added. The solution washed with 5% $NaHCO_3$ and brine and then dried ($MgSO_4$) and evaporated. Chromatography on a column of flash silica with a mixture of EtOAc:hexane as the elutent gave the desired product (0.56 g, 1.1 mmol, 37%). mp: 101.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.33 (broad s, 1H), 8.26 (t, J = 8 Hz, 1H), 8.2 (dd, J = 7.7 and 1.4 Hz, 1H), 7.7−7.5 (m, 4H), 7.45 (td, J = 7.3 and 1.8 Hz, 1H), 7.4−7.22 (m, 3H), 7.2 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 4.55 (d, J = 4.1 Hz, 2H), 2.7 (s, 3H) ppm; LRMS $(M + Na)^+$: 556.1 *m/z*. 1-(2-Hydroxymethylphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide (0.88 g, 1.65 mmol) and MnO_2 (activated, 2.5 g, 28.8 mmol) in $CHCl_3$ was stirred at ambient temperature for 48 h. The reaction was filtered through a pad of Celite, washed with chloroform then evaporated to give 0.711 g of the aldehyde **44** (1.34 mmol, 81%). ^{1}H NMR ($CDCl_3$) δ: 9.3 (s, 1H), 8.4−8.0 (m, 3H), 7.8−7.3 (m, 8H), 7.2 (s, 1H), 2.7 (s, 3H) ppm.

1-(2-Methylaminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (45a). Compound **44** (0.025 g, 0.05 mmol) was stirred in THF (3 mL) with 40% methylamine in water (2 mL) for 18 h. This was evaporated and added to $NaBH_4$ (0.2 mmol, 0.008 g) in MeOH (2 mL). After 18 h, the reaction was evaporated and the product purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound as 10 mg of a colorless syrup (0.018 mmol, 36%). mp 100.8 °C. ^{1}H NMR (DMSO-d_6) δ: 10.6 (s, 1H), 8.8−8.7 (broad, 1H), 8.1 (dd, J = 7.7 and 1.4 Hz, 1H), 7.81 (s, 1H), 7.8−7.5 (m, 7H), 7.48 (d, J = 8 Hz, 1H), 7.42−7.3 (m, 2H), 7.21 (dd, J = 7.7 and 1.4 Hz, 1H), 3.95 (broad, 2H), 2.9 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{26}H_{22}N_4O_3SF_4$, calcd *m/z*: 547.1427, obsd *m/z*: 547.1441.

1-(2-Dimethylaminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (45b). Prepared from compound **44** (100 mg, 0.19 mmol) by the method reported for **45a** with 40% dimethylamine in water substituted for 40% methylamine solution. The product was a white solid (35 mg, 0.063 mmol, 33%). mp 136.7 °C. ^{1}H NMR (DMSO-d_6) δ: 10.7 (s, 1H), 8.1 (dd, J = 7.7 and 1.4 Hz, 1H), 7.85 (broad s, 1H), 7.82−7.64 (m, 4H), 7.62−7.58 (m, 2H), 7.5 (d, J = 8 Hz., 1H), 7.43−7.3 (m, 2H), 7.22 (dd, J = 8.3 and 1.4 Hz, 1H), 4.18 (broad s, 2H), 2.92 (s, 3H), 2.7 (broad s, 6H) H ppm; RMS $(M + H)^+$ for $C_{27}H_{24}N_4O_3SF_4$, calcd *m/z*: 561.1584, obsd *m/z*: 561.1584.

1-(2-Isopropylaminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (45c). Prepared from compound **44** (100 mg, 0.19 mmol) by the method reported for **45a** with isopropylamine substituted for 40% methylamine solution. The product was a white solid (42 mg, 0.073 mmol, 38%). ^{1}H NMR (DMSO-d_6) δ: 10.73 (s, 1H), 8.15 (dd, J = 7.8 and 1.5 Hz, 1H), 7.93 (broad s, 1H), 7.80−7.68 (m, 4H), 7.63−7.57 (m, 2H), 7.45 (d, J = 8 Hz., 1H), 7.43−7.25 (m, 2H), 7.20 (dd, J = 8 and 1.5 Hz, 1H), 4.31 (broad s, 2H), 2.92 (s, 3H), 2.78 (m, 1H), 2.06 (d, J = 8 Hz, 6H) ppm; HRMS $(M + H)^+$ for $C_{28}H_{27}F_4N_4O_3S$, calcd *m/z*: 574.1662, obsd *m/z*: 574.1666.

1-(2-Benzylaminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (45d). Prepared from compound **44** (100 mg, 0.19 mmol) by the method reported for **45a** with benzylamine substituted for 40% methylamine solution. The product was a white solid (45 mg, 0.072 mmol, 38%). ^{1}H NMR (DMSO-d_6) δ: 10.80 (s, 1H), 8.12 (dd, J = 7.7 and 1.5 Hz, 1H), 7.90 (broad s, 1H), 7.82−7.67 (m, 4H), 7.65−7.60 (m, 2H), 7.52 (d, J = 7.9 Hz., 1H), 7.43−7.25 (m, 7H), 7.22 (dd, J = 8.1 and 1.5 Hz, 1H), 4.25 (broad s, 2H), 3.72 (s, 2H), 2.93 (s, 3H) ppm; HRMS $(M + H)^+$ for $C_{32}H_{27}F_4N_4O_3S$, calcd *m/z*: 622.1662, obsd *m/z*: 622.1659.

1-(2-(3-Aminopropyl)phenyl)-3-trifluoromethyl-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1′]-biphen-4-yl))carboxamide, Trifluoroacetic Acid Salt (46). To a solution of diethyl (cyanomethyl)phosphonate (0.123 g, 0.7 mmol) in DMF (10 mL) was added NaH (25 mg of 60% suspension in mineral oil). This mixture was stirred for 30 min and then cooled to 0 °C, and a solution of 3-trifluoromethyl-1-(2-formylphenyl)-1*H*-pyrazole-5-(*N*-(3-fluoro-2′-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide **44** (prepared in SZ738, 0.71 g, 0.63 mmol) in DMF (10 mL) was added dropwise. The reaction was stirred for 30 min with cooling and then the ice bath was removed and the reaction stirred for 3 h at ambient temperature. After this time, 1 N HCl (20 mL) and water (20 mL) were added. This mixture was extracted with EtOAc (3 × 10 mL), and the EtOAc extract was washed with water (4 × 10 mL) and brine (15 mL) and then dried ($MgSO_4$) and evaporated to give 588 mg of the crude unsaturated nitrile. This material was then taken up in MeOH (50 mL) with TFA (1 mL) and placed in a Parr bottle, and 10% Pd−C catalyst (300 mg) was added under a N_2 blanket. The suspension was shaken on a Parr apparatus under 50 psi of H_2 gas for 18 h. The catalyst was removed by filtration through a pad of Celite under a N_2 blanket. The product was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound as 71 mg of a white solid (0.13 mmol, 21%); mp 102.1 °C. ^{1}H NMR (CD_3OD) δ: 8.14 (dd, J = 8 and 1.4 Hz, 1H), 7.8−7.6 (m, 3H), 7.58−7.45 (m, 3H), 7.4−7.25 (m, 4H), 7.2 (dd, J = 7.3 and 1.1 Hz, 1H) 2.81 (broad t, J = 7.9 Hz, 2H), 2.76 (s, 3H), 2.57 (broad t, J = 8 Hz, 2H) and 1.88 (5 line pattern, J = 7.7 Hz, 2H) ppm; HRMS $(M + H)^+$ for $C_{27}H_{24}N_4O_3SF_4$, calcd *m/z*: 561.1584, obsd *m/z*: 561.1590.

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Supporting Information Available: Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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