Discovery and Evaluation of Potent P_1 Aryl Heterocycle-Based Thrombin Inhibitors

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In an effort to discover potent, clinically useful thrombin inhibitors, a rapid analogue synthetic approach was used to explore the P_1 region. Various benzylamines were coupled to a pyridine/pyrazinone P_2-P_3 template. One compound with an *o*-thiadiazole benzylic substitution was found to have a thrombin K_i of 0.84 nM. A study of ortho-substituted five-membered-ring heterocycles was undertaken and subsequently demonstrated that the *o*-triazole and tetrazole rings were optimal. Combination of these potent P_1 aryl heterocycles with a variety of P_2-P_3 groups produced a compound with an extraordinary thrombin inhibitory activity of 1.4 pM. It is hoped that this potency enhancement in P_1 will allow for more diversification in the P_2-P_3 region to ultimately address additional pharmacological concerns.

Introduction

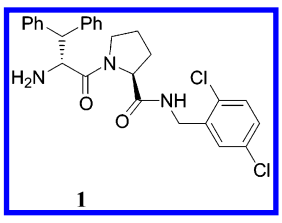
The thromboembolic occlusion of a blood vessel with resultant tissue ischemia can lead to heart attack, stroke, or pulmonary infarction. Predisposing conditions include atherosclerosis, atrial fibrillation, and venous pooling or inflammation.[1] These pathologies consequently trigger a coagulation cascade involving platelets and blood clotting factors, which leads to a stabilized fibrin clot.[2]

In an effort to block coagulation, the cascade lends itself to a number of strategies for chemotherapeutic intervention. Older anticoagulants still in current use, such as heparin and warfarin, interfere with the activity of many clotting factors. In contrast, the newer drugs, hirudin and melagatran, directly target thrombin, a serine protease involved in the conversion of fibrinogen to fibrin.[3,4] Other therapies include antiplatelet drugs[2] and clot lysis agents such as streptokinase and t-PA.[5]

Many of these agents suffer from various side effects and limitations, including increased rate of bleeding and the need for parenteral administration. Clinically, patients taking the oral anticoagulant warfarin have to be closely monitored to ensure safe therapeutic drug levels for the duration of treatment. In addition, warfarin interacts adversely with a large number of other drugs.

With the consideration that a direct thrombin inhibitor possessing oral bioavailability and predictable pharmacokinetics may help lessen the incidence of side effects, research was initiated in this field. The medicinal chemistry effort in these laboratories started with a tripeptide template, D-Phe-Pro-Arg-H.[6] This fragment interacts with three essential binding sites on the thrombin enzyme, the S_1 specificity pocket and two hydrophobic pockets, the proximal S_2 and distal S_3. The S_1 specificity pocket contains an aspartic acid residue (Asp 189) which forms a salt bridge to the guanidine functionality on Arg. To take advantage of this interaction, many initial inhibitors contained a guanidine or other highly basic groups, such as benzamidine and imidazole. Although this strategy often resulted in increased potency, a concomitant decrease in oral bioavailability and poor pharmacokinetics was noted.[7]

Thus, research focused on the discovery of weakly basic or neutral P_1 moieties as well as optimization of P_2-P_3.[8] Compound **1** retains a proline P_2 core and incorporates a neutral 2,5-dichlorobenzylamine in P_1.[9] This inhibitor is potent, with a K_i of 3 nM against



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thrombin, and shows an oral bioavailability of 45% in dogs, with a $t_{1/2}$ of 100 min.[10] Substitution of the P_2 proline with a pyrazinone ring and addition of a weakly basic P_1 aminopyridine produced compound **2**.

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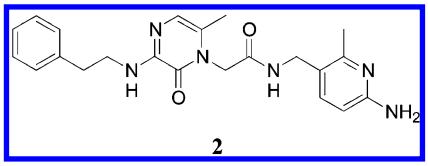
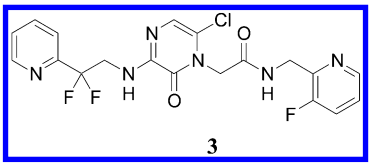


2

This compound has subnanomolar potency (K_i = 0.8 nM) and demonstrates excellent oral bioavailability in dogs, rats, and rhesus macaques of 91%, 42%, and 60%, respectively.[11] Further modification of compound **2**, taking into account metabolic considerations, led to compound **3**. This inhibitor has acceptable potency (K_i = 5.2 nM), good oral bioavailability in three species, and an improved $t_{1/2}$ in dogs of 4.5 h.[12]



3

The above results demonstrate that replacing the original highly basic P_1 groups with neutral or slightly basic moieties provided potent inhibitors with improved pharmacokinetic profiles. This article describes the discovery of a new series of potent P_1 groups and their evaluation when combined with various P_2-P_3 scaffolds.

Results and Discussion

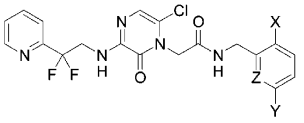
The neutral 2,5-dichlorobenzylamine P_1 fragment discussed above was discovered via the utilization of a rapid analogue approach.[9] We decided to employ this strategy also, using the P_2-P_3 template contained within compound **3** as a constant. Numerous benzylamines were coupled to [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid using standard procedures. The resulting compounds were assayed for thrombin (IIa) inhibitory potency and the ability to double the activated partial thromboplastin time (2× APTT) in human plasma.[13]

One compound which caught our attention with a K_i of 0.84 nM and 2× APTT of 0.60 μM displays an ortho-substituted thiadiazole ring (**6**) (Table 1). This inhibitor exhibits a 14-fold increase in potency over unsubstituted benzylamide **4**. Furthermore, the activity is outstanding, considering that the thiadiazole is a neutral moiety. This result prompted a systematic study of various five-membered heterocycles in the 2-position of benzylamine. Table 1 illustrates these results with comparisons to unsubstituted benzylamide **4** and 3-chlorobenzylamide **5**.

Compounds **7**−**13** and **16** all have improved potencies relative to benzylamide **4**. Pyrazoles and imidazoles **7**−**11** show only modest increases (1−3-fold), whereas 1,2,4-triazole **13** and tetrazole **16** exhibit marked improvement of 25- and 125-fold, respectively. A striking increase in inhibitory potency is generally seen with 5-chloro substitution. Triazole **14** and tetrazole **17** display picomolar K_i's and excellent 2× APTT results, with **17** showing a large increase in activity (300-fold) over chlorobenzylamide **5**. These data follow a general trend observed with addition of chloro in the 5-position and are exemplified by comparing **4** and **5**. The potency enhancement occurs as a result of the favorable interaction of the chlorine atom with Tyr 228 in the S_1 pocket of thrombin.[10] Substitution of pyridine for benzene, as in **15** and **18**, affords compounds with improved physical properties and potencies similar to **13** and **16**. Introduction of the corresponding acidic tetrazole (**19**) resulted in an 80-fold decrease in activity. As anticipated, however, potency is retrieved by substituting the acidic tetrazole NH with a methyl group (**20** and **21**).

X-ray crystallography and molecular modeling were utilized to help explain why these neutral/weakly basic P_1 groups are so potent despite the lack of a strong interaction with Asp 189 . Compound **34** (vide infra) was

Table 1. Comparison of P_1 Heterocycles with the P_2-P_3 Pyrazinone/Pyridine Template



Comp No.	X	Y	Z	K_i (nM)	2x APTT (μM)
4	H	H	CH	12	2.68
5	H	Cl	CH	0.44	0.79
6		H	CH	0.84	0.60
7		H	CH	5.6	2.08
8		H	CH	4.2	1.83
9		H	CH	7.2	2.88
10		H	CH	6.9	1.9
11		H	CH	6.3	1.29
12		H	CH	3.5	0.52
13		H	CH	0.45	0.23
14		Cl	CH	<0.01	0.17
15		H	N	0.66	0.33
16		H	CH	0.096	0.22
17		Cl	CH	0.0015	0.18
18		H	N	0.14	0.25
19		H	CH	940	-
20		H	CH	1.2	0.34
21		H	CH	5.8	1.72

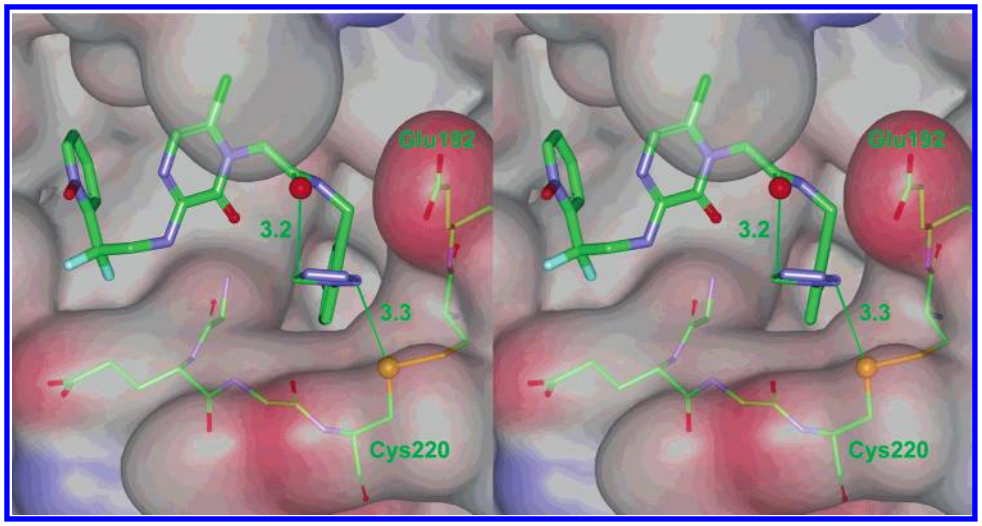


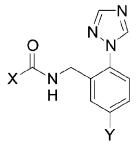
Figure 1. X-ray crystal structure of **34** bound in the thrombin active site.

soaked into thrombin crystals, and the structure of the complex was resolved to 1.8 Å (Protein Data Bank code 1SL3) (Figure 1). The chlorophenyl group occupies the S_1 pocket, and the tetrazole ring extends out of the S_1 pocket toward Glu 192. The tetrazole moiety fits snugly between the Glu 192 side chain and Gly 216. Additionally, the tetrazole ring contacts the sulfur atom of Cys 220, forming a donor-atom−π interaction similar to that observed in flavoenzymes between flavin and oxygen or sulfur atoms;[14,15] the observed tetrazole−S distance of 3.3 Å is consistent with that observed crystallographically for flavoenzymes (ca. 3.0−3.4 Å). Further stabilization of this binding mode is provided by the carbonyl oxygen of the P_1−P_2 linker, which forms a second donor-atom−π interaction on the opposite face of the tetrazole (tetrazole−O distance 3.2 Å), effectively forming a donor-atom−π−donor-atom sandwich. Additional electrostatic stabilization may come from the interaction of the tetrazole H with the backbone carbonyl oxygen of Gly216 (H−O distance 2.2 Å).

Triazole and tetrazole benzylamine P_1 groups impart a 25−300-fold increase in activity within the P_2−P_3 pyrazinone/pyridine template (**13**, **14**, **16**, and **17** vs **4** and **5**). Tables 2 and 3 confirm the value of these entities when coupled to a variety of P_2−P_3 scaffolds. Addition of a solubilizing N-oxide in P_3[16] results in small improvements in potency compared to the parent pyridines. Tetrazole **34**, with a K_i of 1.4 pM and 2× APTT of 0.13 μM, is one of the most potent thrombin inhibitors reported to date. Of interest is the observation that, while K_i's increase 20−65-fold when comparing the 5-chlorobenzylamides (**14**, **17**, **23**, and **34**) with the deschloro analogues (**13**, **16**, **22**, and **33**), very little difference is seen in the 2× APTT values. This functional assay, performed in plasma, reflects not only inherent enzyme potency but also inhibitor lipophilicity and associated plasma protein binding as well.[17] As this assay is a better indicator of potential clinical efficacy, 5-chloro does not seem to impart a large advantage in this series.

Compounds **24**−**27** and **35**−**38** lack substitution in the 6-position of the P_2 pyrazinone. A substituent in this position improves potency via interaction with the Tyr-Pro-Pro-Trp insertion loop near the S_2 pocket of thrombin. In the past, substituents such as methyl showed metabolic liabilities.[12] Chlorine addresses these concerns, but we were interested in seeing whether the new P_1's could offset the potency decrease from overall loss of this important binding interaction. Generally the results are encouraging, with the tetrazoles in particular showing acceptable K_i's and very good 2× APTT results.

Table 2. P_1 Triazole with Different P_2−P_3 Scaffolds



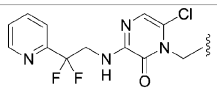
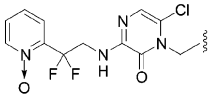
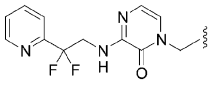
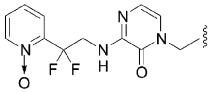
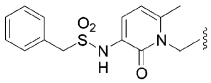
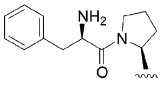
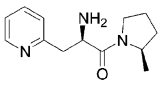
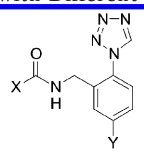
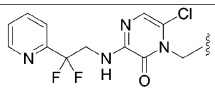
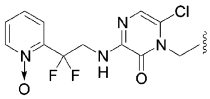
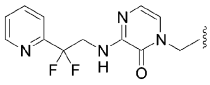
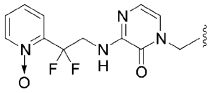
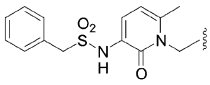
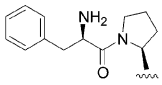
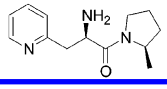
Comp No	X	Y	K_i (nM)	2xAPPT (μM)
13		H	0.45	0.23
14		Cl	<0.01	0.17
22		H	0.21	0.29
23		Cl	<0.01	0.2
24		H	16	2.06
25		Cl	0.24	0.33
26		H	7.2	0.98
27		Cl	0.085	0.26
28		H	7.3	1.06
29		Cl	0.16	0.36
30		H	106	-
31		Cl	1.8	0.43
32		Cl	2.0	0.39

Table 3. P_1 Tetrazole with Different P_2-P_3 Scaffolds

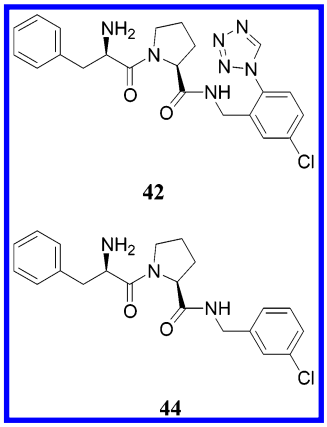


Comp No	X	Y	K_i (nM)	2xAPPT (μM)
16		H	0.1	0.22
17		Cl	0.0015	0.18
33		H	0.05	0.2
34		Cl	0.0014	0.13
35		H	2.7	0.52
36		Cl	0.033	0.2
37		H	1.1	0.42
38		Cl	0.013	0.12
39		H	1.4	0.37
40		Cl	0.018	0.23
41		H	14	1.94
42		Cl	0.33	0.23
43		Cl	0.4	0.2

Incorporation of the triazole or tetrazole benzylamine P_1 group in a P_2 pyridinone scaffold[11] was also well tolerated, as illustrated by inhibitors **28**, **29**, **39**, and **40**. In particular, tetrazole **40** (K_i = 0.018 nM) demonstrated a 390-fold increase in potency over the corresponding 2-unsubstituted-5-chlorobenzylamide analogue (K_i = 7 nM).[18]

The remaining compounds in Tables 2 and 3 evolved from the original D-Phe-Pro template from which inhibitor **1** was derived. Proline derivatives **30**, **31**, **41**, and **42** are all more potent than the corresponding unsubstituted and 3-chlorobenzylamide analogues. Indeed, compound **42** (K_i = 0.33 nM) afforded a 750-fold enhancement in potency over unsubstituted **44** (K_i = 250 nM).[19] Introduction of pyridyl in P_3 within the proline scaffold had little effect on either intrinsic potency or functional activity (**32** and **43**).

Thrombin inhibitors **4**−**43** were counterscreened for activity against various serine proteases, such as trypsin, involved in digestion, tPA, involved in fibrinolysis, and Factor Xa, an enzyme active in the latter half of the coagulation cascade. Selectivities for thrombin vs trypsin and tPA were deemed appropriate (>1000-fold). Interestingly, a few compounds in these series, **36**, **37**, **38**, and **40**, display moderate inhibition of Factor Xa, with



42

44

K_i = 10, 370, 5, and 11 nM, respectively. This finding could represent an added benefit to thrombin inhibition.[20]

The pharmacokinetic profiles of most inhibitors presented in Tables 1−3 were evaluated after PO administration in dogs, and a select few are shown in Table 4. These results were disappointing, as the majority of these compounds suffer from average to poor bioavailability, and none was superior to pyrazinone **3**.[12] Triazole derivative **13**, however, displayed the most encouraging profile, with a C_{max} of 1.1 μM and $t_{1/2}$ of 3.5 h after a 0.5 mg/kg po dose. Further structure refinement to improve the pharmacokinetic profile of triazole- and tetrazole-derived thrombin inhibitors is the subject of ongoing studies and will be presented in due time.

Chemistry

The syntheses of the heterocycle benzylamines are shown in Schemes 1−11. These schemes can be divided into two categories. The first includes syntheses where the heterocycle is formed by manipulation of functional groups already present on the benzene ring (Schemes 1, 3, 4, 5, 9, and 11). The second group encompasses syntheses where an aryl halide is displaced by the intact heterocycle (Schemes 2, 6, 7, 8, and 10).

In Scheme 1, thiadiazole **46** was synthesized via cyclization of hydrazine ester **45** with thionyl chloride. Conversion of the ortho methyl group to benzylamine **47** was accomplished via the methyl bromide and azide. Imidazoles **52** and **55** and pyrazole **57** were formed by cyclization of acyl bromide **51**, imidate ester **54**, and 2-hydrazinobenzoic acid, respectively (Schemes 3, 4, and 5). Tetrazoles **62**, **63**, and **66** were synthesized by reacting sodium azide with 2-aminobenzoic acid (R = H, Cl) and 2-(bromomethyl)benzonitrile (Schemes 9 and 11).

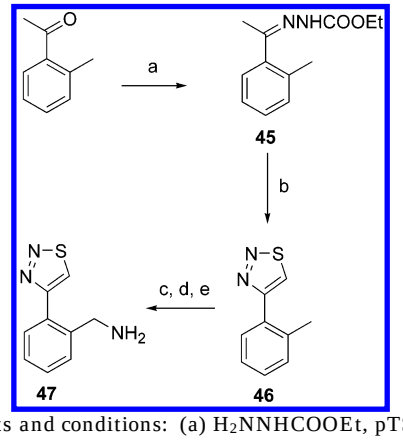
A Suzuki coupling of pyrazole boronic acid **48** with aryl bromide **49** gave benzylamine **50** after deprotection (Scheme 2). Nucleophilic displacement of aryl fluorine or chlorine with imidazole, 1,2,4-triazole, and tetrazole with subsequent ortho functional group manipulation gave compounds **58**, **59**, **60**, **61**, and pyridines **64** and **65** (Schemes 6, 7, 8, and 10).

The heterocyclic benzylamines were coupled to various P_2-P_3 acids using standard procedures, as depicted in the general Scheme 12. Experimental details for the pyridine/pyrazinone acids used to synthesize compounds **13**, **14**, **16**, **17**, **22**−**27**, and **33**−**38** are described by Burgey et al.[12,21] Pyridinones **28**, **29**, **39**, and **40** were

Table 4. Dog Pharmacokinetic Parameters

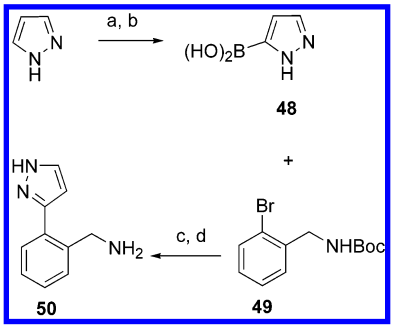
compd	dose (mg/kg)	C_{max} (μM)	$t_{1/2}$ (h), po
13	0.5	1.13	3.5
22	1.0	0.86	1.4
25	0.9	1.04	1.2
36	0.95	1.31	2.0

Scheme 1[a]



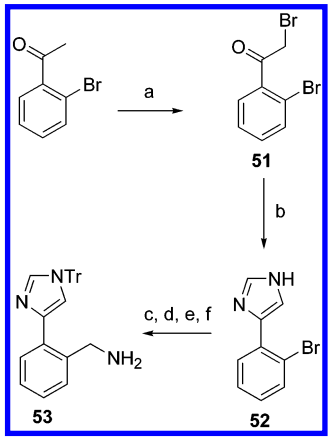
[a] Reagents and conditions: (a) $H_2NNHCOOEt$, pTSA, toluene, reflux; (b) $SOCl_2$, 60 °C; (c) NBS, AIBN, $CHCl_3$, reflux; (d) NaN_3, DMF; (e) PPh_3, H_2O, THF.

Scheme 2[a]



[a] Reagents and conditions: (a) 2,3-dihydropyran, CF_3COOH, reflux; (b) *n*-BuLi, $B(O\text{-}^iPr)_3$, HCl; (c) $[(C_6H_5)_3P]_4Pd$, Na_2CO_3, DMF, 100 °C; (d) HCl, EtOAc, 0 °C.

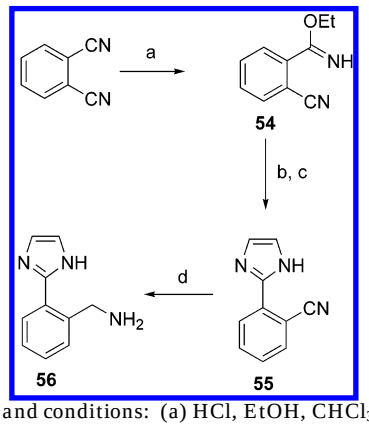
Scheme 3[a]



[a] Reagents and conditions: (a) $B(OMe)_3$, Br_2, MeOH; (b) formamide, 145 °C; (c) trityl chloride, Et_3N, DMF; (d) CuCN, DMF, 80 °C; (e) LAH, THF; (f) oxalic acid, THF.

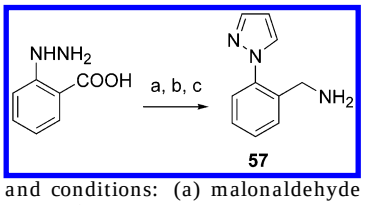
obtained from the acid intermediate described by Sanderson et al.[11] Commercially available Boc-D-Phe-Pro-OH was coupled and deprotected to ultimately give **30**, **31**, **41**, and **42**. Boc-D-Pyr-Pro-OH was synthesized via reaction of *N*-(*tert*-butoxycarbonyl)-3-pyridin-2-yl-L-alanine and methyl-L-prolinate hydrochloride with subsequent methyl ester hydrolysis (**32** and **43**).

Scheme 4[a]



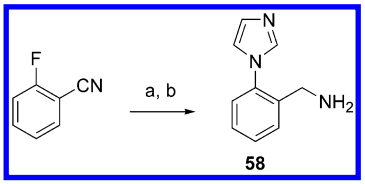
[a] Reagents and conditions: (a) HCl, EtOH, $CHCl_3$, 0 °C; (b) 2,2-diethoxyethylamine, MeOH, H_2SO_4, HCl; (c) NaOH, H_2O; (d) H_2, RaNi, $EtOH/NH_3$.

Scheme 5[a]



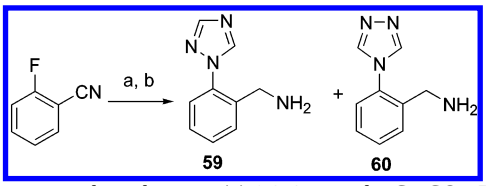
[a] Reagents and conditions: (a) malonaldehyde bis(dimethylacetal), HCl, H_2O, reflux; (b) NH_4Cl, EDC, HOAt, DIEA, DMF; (c) BH_3, THF, reflux.

Scheme 6[a]



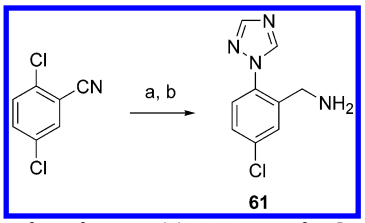
[a] Reagents and conditions: (a) 1*H*-imidazole, NaH, DMF; (b) H_2, RaNi, $EtOH/NH_3$.

Scheme 7[a]



[a] Reagents and conditions: (a) 1,2,4-triazole, Cs_2CO_3, DMF, 50 °C; (b) H_2, Pd/C, EtOH.

Scheme 8[a]

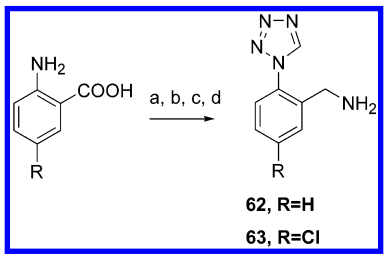


[a] Reagents and conditions: (a) 1,2,4-triazole, Cs_2CO_3, DMF, 85 °C; (b) H_2, RaNi, $EtOH/NH_3$.

Conclusion

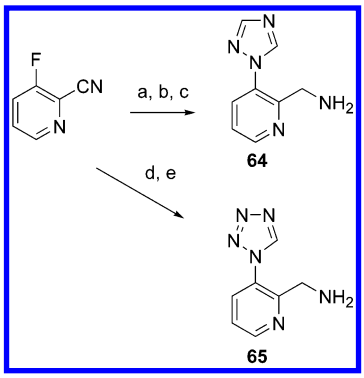
This article describes the discovery of a novel series of triazole and tetrazole benzylamine P_1 groups which

Scheme 9[a]



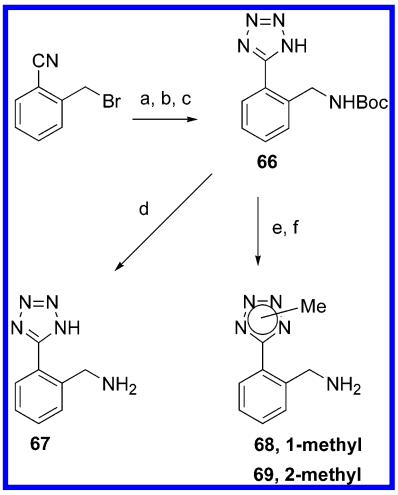
[a] Reagents and conditions: (a) NaN_3, $CH(OMe)_3$, MeCOOH; (b) NH_4Cl, EDC, HOAt, DIEA, DMF; (c) Burgess reagent, THF; (d) H_2, RaNi, EtOH/NH_3.

Scheme 10[a]



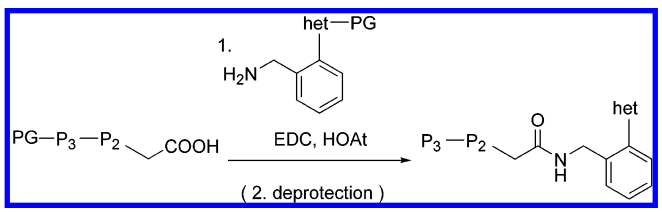
[a] Reagents and conditions: (a) 1,2,4-triazole, Cs_2CO_3, DMF, 65 °C; (b) H_2, RaNi, EtOH/NH_3, BOC_2O, CH_2Cl_2, MeOH; (c) HCl, CH_2Cl_2, MeOH; (d) tetrazole, $[CH_3(CH_2)_3]_4NOH$, DMF; (e) H_2, Pd/C, EtOH.

Scheme 11[a]



[a] Reagents and conditions: (a) NaN_3, DMF; (b) $SnCl_2$, BOC_2O, MeOH, THF; (c) NaN_3, NH_4Cl, DMF, 110 °C; (d) HCl, EtOAc; (e) MeI, K_2CO_3, DMF; (f) HCl, EtOAc.

Scheme 12



impart several-hundred-fold enhancements in thrombin inhibitory potency when coupled with pyrazinone, pyridinone, and proline P_2 scaffolds. This extraordinary potency increase now allows for extensive modifications of the P_2−P_3 area to improve pharmacokinetic profiles, since even a 1000-fold loss in potency from compounds such as **17** could be tolerated. Our work in this area continues.

Experimental Section

All nonaqueous reactions were carried out under a N_2 atmosphere with commercial grade reagents and solvents. The ^{1}H NMR spectra were recorded on Varian Unity Inova 300- and 400-MHz spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane. Flash column chromatography was performed using EM silica gel 60 (230−400 mesh) or Biotage silica gel cartridges. Reversed-phase preparative HPLC was performed using a Gilson 215 preparative HPLC unit. Analytical HPLC was performed using an Agilent Zorbax SB-C18 4.6- × 75-mm, 3.5-μm column with a 4-min linear gradient from 95:5 to 5:95 0.1% H_3PO_4:CH_3CN at a flow rate of 2 mL/min, with UV detection at 215 and 254 nm (system A), and a YMC PRO 3- × 50-mm, 5-μm column with a 3.7-min linear gradient from 92:8 to 0:100 0.05% TFA/H_2O:0.0425% TFA/CH_3CN at a flow rate of 1.5−2 mL/min, with UV detection at 215 nm (system B). Experimental procedures for 1*H*-pyrazol-3-yl-boronic acid **48** and 2-pyrazol-1-yl-benzoic acid supplied by ChemBridge Corp. Experimental procedures for 2-(1-trityl-1*H*-imidazol-4-yl)benzylamine oxalate salt **53** were supplied by J-Star Research, Inc. 2-(1*H*-Imidazol-2-yl)benzonitrile **55** was synthesized in 1962 (Merck, unpublished), and the procedure contained in this paper is original and unmodified.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-[1,2,3]thiadiazol-4-yl-benzyl)acetamide (6). A solution of [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] (70 mg, 0.16 mmol), 2-[1,2,3]thiadiazole-4-yl-benzylamine **47** (40 mg, 0.21 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (46 mg, 0.24 mmol), 1-hydroxy-7-azabenzotriazole (33 mg, 0.24 mmol), and diisopropylethylamine (42 μL, 0.24 mmol) in *N*,*N*-dimethylformamide (2 mL) was stirred at room temperature overnight. Water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave an oil; flash chromatography (silica gel, chloroform−2-propanol−ammonium hydroxide, 99:1:0.1−98:2:0.2) gave 2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-[1,2,3]thiadiazol-4-yl-benzyl)acetamide **6** (45 mg, 54%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, J = 4.1 Hz, 1H), 8.65 (s, 1H), 7.82 (td, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.64 (m, 1H), 7.53 (m, 1H), 7.48−7.38 (m, 3H), 6.92 (s, 1H), 6.47 (t, J = 6.3 Hz, 1H), 4.81 (s, 2H), 4.47 (d, J = 6.3 Hz, 2H), 4.36 (td, J = 14 Hz, J = 6.3 Hz, 2H). HRMS ES: calculated for $C_{22}H_{18}ClF_2N_7O_2S$, 518.0972; found, 518.0963.

***N*-Benzyl-2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetamide (4).** Compound **4** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and benzylamine using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.78 (t, J = 6.2 Hz, 1H), 8.71 (d, J = 4.8 Hz, 1H), 7.99 (td, J = 8 Hz, J = 2.2 Hz, 1H), 7.70 (m, 1H), 7.57 (m, 1H), 7.42 (t, J = 6.2 Hz, 1H), 7.32 (m, 2H), 7.26 (m, 3H), 6.94 (s, 1H), 4.77 (s, 2H), 4.32 (d, J = 6.2 Hz, 2H), 4.23 (td, J = 15.1 Hz, J = 6.2 Hz, 2H). HRMS ES: calculated for $C_{20}H_{18}ClF_2N_5O_2$, 434.1190; found, 434.1185.

***N*-(3-Chlorobenzyl)-2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetamide (5).** Compound **5** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 3-chlorobenzylamine using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.84 (t, J = 5.6 Hz, 1H), 8.71 (d, J = 4.5 Hz, 1H), 7.99 (t, J = 8.1 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.57 (m, 1H), 7.43 (t, J = 5.6 Hz, 1H), 7.38−7.30 (m, 3H), 7.23 (d, J =

6.1 Hz, 1H), 6.95 (s, 1H), 4.78 (s, 2H), 4.33 (d, J = 5.6 Hz, 2H), 4.24 (td, J = 14.5 Hz, J = 5.6 Hz, 2H). HRMS ES: calculated for $C_{20}H_{17}Cl_2F_2N_5O_2$, 468.0800; found, 468.0804.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1*H*-pyrazol-3-yl)-benzyl]-acetamide Trifluoroacetic Acid Salt (7). Compound **7** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-(1*H*-pyrazol-3-yl)benzylamine hydrochloride salt **50** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.64 (d, J = 4.4 Hz, 1H), 7.93 (m, 1H), 7.70 (m, 2H), 7.49−7.44 (m, 3H), 7.37−7.34 (m, 2H), 6.83 (s, 1H), 6.51 (d, J = 2.2 Hz, 1H), 4.84 (s, 2H), 4.51 (s, 2H), 4.28 (t, J = 13.9 Hz, 2H). HRMS ES: calculated for $C_{23}H_{20}ClF_2N_7O_2$, 500.1408; found, 500.1415.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1*H*-imidazol-4-yl)-benzyl]-acetamide Trifluoroacetic Acid Salt (8). 2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1-trityl-1*H*-imidazol-4-yl)-benzyl]acetamide was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-(1-trityl-1*H*-imidazol-4-yl)-benzylamine oxalate salt **53** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.11 (t, J = 6 Hz, 1H), 8.65 (d, J = 4.6 Hz, 1H), 8.02 (s, 1H), 7.80 (m, 1H), 7.61 (m, 1H), 7.47 (m, 1H), 7.38−7.15 (m, 18H), 6.99 (d, J = 1.2 Hz, 1H), 6.78 (s, 1H), 6.36 (t, J = 6 Hz, 1H), 4.78 (s, 2H), 4.43 (d, J = 6.4 Hz, 2H), 4.14 (m, 2H).

To a solution of 2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1-trityl-1*H*-imidazol-4-yl)-benzyl]acetamide (47 mg, 0.058 mmol) in trifluoroacetic acid (1.5 mL) was added triethylsilane (excess) until completion of the reaction. Concentration and purification by reversed-phase preparative HPLC (5% to 95% CH_3CN in water containing 0.1% TFA, C18 PRO YMC 20 × 150 mm) gave 2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1*H*-imidazol-4-yl)-benzyl]acetamide trifluoroacetic acid salt **8** (22 mg, 45%). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.95 (d, J = 1.4 Hz, 1H), 8.63 (d, J = 4.1 Hz, 1H), 7.94 (td, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.70 (m, 1H), 7.68 (d, J = 1.4 Hz, 1H), 7.51 (m, 6H), 6.83 (s, 1H), 4.80 (s, 2H), 4.46 (s, 2H), 4.28 (t, J = 14.1 Hz, 2H). HRMS ES: calculated for $C_{23}H_{20}ClF_2N_7O_2$, 500.1408; found, 500.1412.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1*H*-imidazol-2-yl)-benzyl]-acetamide (9). Compound **9** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-acetic acid[12] and 2-(1*H*-imidazol-2-yl)benzylamine **56** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.63 (d, J = 5.8 Hz, 1H), 7.93 (m, 1H), 7.90 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.51 (m, 3H), 7.38 (m, 2H), 7.11 (m, 1H), 6.83 (s, 1H), 4.83 (s, 2H), 4.52 (s, 2H), 4.27 (t, J = 14 Hz, 2H). HRMS ES: calculated for $C_{23}H_{20}ClF_2N_7O_2$, 500.1408; found, 500.1405.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-pyrazol-1-yl-benzyl)-acetamide (10). Compound **10** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-pyrazol-1-yl-benzylamine trifluoroacetic acid salt **57** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.63 (d, J = 4 Hz, 1H), 7.93 (m, 1H), 7.90 (m, 2H), 7.71 (m, 1H), 7.54−7.34 (m, 5H), 6.83 (s, 1H), 6.52 (m, 1H), 4.83 (s, 2H), 4.29 (s, 2H), 4.28 (t, J = 14 Hz, 2H). HRMS ES: calculated for $C_{23}H_{20}ClF_2N_7O_2$, 500.1408; found, 500.1410.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-imidazol-1-yl-benzyl)acetamide Trifluoroacetic Acid Salt (11). Compound **11** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-imidazol-1-yl-benzylamine **58** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.09 (s, 1H), 8.65 (m, 1H), 7.95 (t, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.61 (m, 2H), 7.52 (m, 3H), 7.36 (s, 1H), 7.30 (d, J = 8 Hz, 1H), 6.85 (s, 1H), 4.73 (s, 2H), 4.32 (t, J = 14.1 Hz, 2H), 4.25 (s, 2H). HRMS ES: calculated for $C_{23}H_{20}ClF_2N_7O_2$, 500.1408; found, 500.1404.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-[1,2,4]triazol-4-yl-benzyl)-acetamide Trifluoroacetic Acid Salt (12). Compound **12** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-[1,2,4]-triazol-4-yl-benzylamine **60** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.3 Hz, 1H), 8.48 (s, 2H), 7.85 (m, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.56 (m, 2H), 7.44 (m, 2H), 7.23 (m, 1H), 6.93 (s, 1H), 6.81 (m, 1H), 6.54 (m, 1H), 4.79 (s, 2H), 4.33 (m, 2H), 4.24 (d, J = 4.9 Hz, 2H). HRMS ES: calculated for $C_{22}H_{19}ClF_2N_8O_2$, 501.1361; found, 501.1358.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-[1,2,4]triazol-1-yl-benzyl)-acetamide (13). Compound **13** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-[1,2,4]triazol-1-yl-benzylamine **59** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.77 (s, 1H), 8.64 (d, J = 4.1 Hz, 1H), 8.20 (s, 1H), 7.93 (m, 1H), 7.70 (d, J = 8 Hz, 1H), 7.62−7.43 (m, 5H), 6.84 (s, 1H), 4.82 (s, 2H), 4.34 (s, 2H), 4.28 (t, J = 13.9 Hz, 2H). HRMS ES: calculated for $C_{22}H_{19}ClF_2N_8O_2$, 501.1361; found, 501.1363.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(5-chloro-2-[1,2,4]triazol-1-yl-benzyl)acetamide Trifluoroacetic Acid Salt (14). Compound **14** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.78 (s, 1H), 8.63 (d, J = 4.4 Hz, 1H), 8.20 (s, 1H), 7.93 (m, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.60 (m, 1H), 7.52−7.42 (m, 3H), 6.84 (s, 1H), 4.84 (s, 2H), 4.32 (s, 2H), 4.28 (t, J = 13.9 Hz, 2H). Elemental analysis ($C_{22}H_{18}Cl_2F_2N_8O_2$): C, H, N.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(3-[1,2,4]triazol-1-yl-pyridin-2-ylmethyl)acetamide Trifluoroacetic Acid Salt (15). Compound **15** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and *C*-(3-[1,2,4]triazol-1-yl-pyridin-2-yl)methylamine hydrochloride salt **64** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (m, 2H), 8.40 (s, 1H), 8.15 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.70 (m, 2H), 7.42 (m, 2H), 7.35 (m, 1H), 6.96 (s, 1H), 6.51 (t, J = 6.4 Hz, 1H), 4.89 (s, 2H), 4.57 (d, J = 4.8 Hz, 2H), 4.38 (td, J = 13.5 Hz, J = 6.4 Hz, 2H). HRMS ES: calculated for $C_{21}H_{18}ClF_2N_9O_2$, 502.1313; found, 502.1316.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-tetrazol-1-yl-benzyl)acetamide (16). Compound **16** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.52 (s, 1H), 8.64 (d, J = 4.5 Hz, 1H), 7.94 (m, 1H), 7.71 (m, 1H), 7.64 (m, 2H), 7.57−7.46 (m, 3H), 6.83 (s, 1H), 4.81 (s, 2H), 4.28 (m, 4H). Elemental analysis ($C_{21}H_{18}ClF_2N_9O_2$): C, H, N.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(5-chloro-2-tetrazol-1-yl-benzyl)-acetamide (17). Compound **17** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.52 (s, 1H), 8.63 (d, J = 4.7 Hz, 1H), 7.92 (td, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 7.56−7.47 (m, 3H), 6.83 (s, 1H), 4.82 (s, 2H), 4.28 (t, J = 13.8 Hz, 2H), 4.25 (s, 2H). Elemental analysis ($C_{21}H_{17}Cl_2F_2N_9O_2$): C, H, N.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(3-tetrazol-1-yl-pyridin-2-yl-

methyl)acetamide (18). Compound **18** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 3-(tetrazol-1-yl)-2-aminomethylpyridine **65** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.59 (s, 1H), 8.79 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H), 8.63 (d, J = 4.8 Hz, 1H), 7.96 (m, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.59 (m, 1H), 7.50 (m, 1H), 6.80 (s, 1H), 4.83 (s, 2H), 4.42 (s, 2H), 4.27 (t, J = 13.8 Hz, 2H). HRMS ES: calculated for $C_{20}H_{17}ClF_2N_{10}O_2$, 503.1266; found, 503.1268.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1*H*-tetrazol-5-yl)benzyl]-acetamide Trifluoroacetic Acid Salt (19). Compound **19** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-(1*H*-tetrazol-5-yl)-benzylamine hydrochloride salt **67** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.63 (d, J = 4.6 Hz, 1H), 7.93 (m, 1H), 7.71 (m, 2H), 7.57 (m, 2H), 7.50 (m, 2H), 6.82 (s, 1H), 4.84 (s, 2H), 4.67 (s, 2H), 4.27 (t, J = 13.9 Hz, 2H). HRMS ES: calculated for $C_{21}H_{18}ClF_2N_9O_2$, 502.1313; found, 502.1318.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]acetamide Trifluoroacetic Acid Salt (20). Compound **20** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-(1-methyl-1*H*-tetrazol-5-yl)-benzylamine hydrochloride salt **68** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.63 (m, 1H), 7.94 (td, J = 7.8 Hz, J = 1.7 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (m, 2H), 7.53−7.47 (m, 3H), 6.82 (s, 1H), 4.78 (s, 2H), 4.32−4.24 (m, 4H), 4.01 (s, 3H). HRMS ES: calculated for $C_{22}H_{20}ClF_2N_9O_2$: 516.1470; found, 516.1466.

2-[6-Chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-[2-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]acetamide Trifluoroacetic Acid Salt (21). Compound **21** was prepared from [6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-(2-methyl-2*H*-tetrazol-5-yl)benzylamine hydrochloride salt **69** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.64 (d, J = 4.1 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.94 (m, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.56−7.42 (m, 4H), 6.83 (s, 1H), 4.83 (s, 2H), 4.76 (s, 2H), 4.43 (d, J = 2 Hz, 3H), 4.28 (t, J = 13.8 Hz, 2H). HRMS ES: calculated for $C_{22}H_{20}ClF_2N_9O_2$, 516.1470; found, 516.1465.

2-{6-Chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(2-[1,2,4]triazol-1-yl-benzyl)-acetamide Trifluoroacetic Acid Salt (22). Compound **22** was prepared from {6-chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 2-[1,2,4]-triazol-1-yl-benzylamine **59** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (s, 1H), 8.42 (t, J = 4.2 Hz, 1H), 8.10 (s, 1H), 7.70 (dd, J = 6.1 Hz, J = 4.2 Hz, 1H), 7.63 (dd, J = 7.5 Hz, J = 2.3 Hz, 1H), 7.52−7.42 (m, 4H), 7.32 (dd, J = 7.5 Hz, J = 2.3 Hz, 1H), 7.14 (t, J = 6.5 Hz, 1H), 6.84 (s, 1H), 6.40 (m, 1H), 4.78 (s, 2H), 4.64 (td, J = 13.8 Hz, J = 5.9 Hz, 2H), 4.31 (d, J = 6.3 Hz, 2H). HRMS ES: calculated for $C_{22}H_{19}ClF_2N_8O_3$, 517.1309; found, 517.1306.

2-{6-Chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(5-chloro-2-[1,2,4]triazol-1-yl-benzyl)acetamide Trifluoroacetic Acid Salt (23). Compound **23** was prepared from {6-chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.77 (s, 1H), 8.36 (d, J = 6.2 Hz, 1H), 8.19 (s, 1H), 7.69 (dd, J = 8 Hz, J = 2.4 Hz, 1H), 7.59−7.43 (m, 5H), 6.69 (s, 1H), 4.79 (s, 2H), 4.55 (t, J = 13 Hz, 2H), 4.31 (s, 2H). HRMS ES: calculated for $C_{22}H_{18}Cl_2F_2N_8O_3$, 551.0920; found, 551.0925.

2-[3-(2,2-Difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-[1,2,4]triazol-1-yl-benzyl)acetamide (24). Compound **24** was prepared from [3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-[1,2,4]-triazol-1-yl-benzylamine **59** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.90 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 8.62 (m, 1H), 8.24 (s, 1H), 7.98 (t, J = 6.9 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.57−7.46 (m, 5H), 7.10 (m, 1H), 6.79 (d, A of AB, J = 3.4 Hz, 1H), 6.72 (d, B of AB, J = 3.4 Hz, 1H), 4.52 (s, 2H), 4.20 (m, 4H). HRMS ES: calculated for $C_{22}H_{20}F_2N_8O_2$, 467.1750; found, 467.1747.

***N*-(5-Chloro-2-[1,2,4]triazol-1-yl-benzyl)-2-[3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-acetamide (25).** Compound **25** was prepared from [3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 8.71 (m, 2H), 8.26 (s, 1H), 7.99 (m, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.54 (m, 4H), 7.04 (t, J = 6.6 Hz, 1H), 6.81 (d, A of AB, J = 4.6 Hz, 1H), 6.74 (d, B of AB, J = 4.6 Hz, 1H), 4.54 (s, 2H), 4.21 (m, 4H). HRMS ES: calculated for $C_{22}H_{19}ClF_2N_8O_2$, 501.1361; found, 501.1370.

2-{3-[2,2-Difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(2-[1,2,4]triazol-1-yl-benzyl)-acetamide (26). Compound **26** was prepared from {3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 2-[1,2,4]triazol-1-yl-benzylamine **59** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.89 (s, 1H), 8.60 (m, 1H), 8.35 (d, J = 6.3 Hz, 1H), 8.24 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.54−7.40 (m, 5H), 7.37 (t, J = 6.4 Hz, 1H), 7.25 (t, J = 6.4 Hz, 1H), 6.73 (d, A of AB, J = 4 Hz, 1H), 6.58 (d, B of AB, J = 4 Hz, 1H), 4.48 (m, 4H), 4.20 (d, J = 5.5 Hz, 2H). HRMS ES: calculated for $C_{22}H_{20}F_2N_8O_3$, 483.1699; found, 483.1698.

***N*-(5-Chloro-2-[1,2,4]triazol-1-yl-benzyl)-2-{3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetamide (27).** Compound **27** was prepared from {3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.77 (s, 1H), 8.36 (d, J = 6 Hz, 1H), 8.18 (s, 1H), 7.69 (dd, J = 7.8 Hz, J = 2.2 Hz, 1H), 7.61 (m, 1H), 7.58−7.42 (m, 4H), 6.61 (d, A of AB, J = 3.8 Hz, 1H), 6.60 (d, B of AB, J = 3.8 Hz, 1H), 4.56 (t, J = 13.1 Hz, 2H), 4.48 (s, 2H), 4.30 (s, 2H). HRMS ES: calculated for $C_{22}H_{19}ClF_2N_8O_3$, 517.1310; found, 517.1303.

2-(6-Methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)-*N*-(2-[1,2,4]triazol-1-yl-benzyl)acetamide (28). Compound **28** was prepared from (6-methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)acetic acid[11] and 2-[1,2,4]-triazol-1-yl-benzylamine **59** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H), 8.09 (s, 1H), 7.60 (m, 1H), 7.48−7.39 (m, 3H), 7.36 (t, J = 6.4 Hz, 1H), 7.31−7.21 (m, 6H), 6.03 (d, J = 7.5 Hz, 1H), 4.72 (s, 2H), 4.33 (d, J = 6.4 Hz, 2H), 4.28 (s, 2H), 2.32 (s, 3H). HRMS ES: calculated for $C_{24}H_{24}N_6O_4S$, 493.1653; found, 493.1654.

***N*-(5-Chloro-2-[1,2,4]triazol-1-yl-benzyl)-2-(6-methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)-acetamide (29).** Compound **29** was prepared from (6-methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)acetic acid[11] and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 8.10 (s, 1H), 8.02 (br s, 1H), 7.86 (br s, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.48 (t, J = 6.2 Hz, 1H), 7.33 (m, 1H), 7.21 (m, 5H), 6.04 (d, J = 7.7 Hz, 1H), 4.63 (s, 2H), 4.30 (d, J = 6.2 Hz, 2H), 4.27 (s, 2H), 2.37 (s, 3H). HRMS ES: calculated for $C_{24}H_{23}ClN_6O_4S$, 527.1263; found, 527.1251.

1-(2(*R*)-Amino-3-phenylpropionyl)pyrrolidine-2(*S*)-carboxylic Acid 2-[1,2,4]Triazol-1-yl-benzylamide (30). A solution of Boc-D-Phe-Pro-OH (60 mg, 0.16 mmol), 2-[1,2,4]-triazol-1-yl-benzylamine **59** (37 mg, 0.21 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (46 mg, 0.24 mmol), 1-hydroxy-7-azabenzotriazole (33 mg, 0.24 mmol), and

diisopropylethylamine (42 μL, 0.24 mmol) in *N*,*N*-dimethylformamide (2 mL) was stirred at room temperature overnight. Water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave an oil; flash chromatography (silica gel, hexanes−ethyl acetate, 75:25−0:100) gave {1(*R*)-benzyl-2-oxo-2-[2-(2-[1,2,4]triazol-1-yl-benzylcarbamoyl)pyrrolidin-1(*S*)-yl]-ethyl}carbamic acid *tert*-butyl ester (44 mg, 53%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H), 8.14 (s, 1H), 7.53 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30−7.24 (m, 4H), 7.21 (m, 2H), 5.29 (d, *J* = 6.2 Hz, 1H), 4.48 (m, 2H), 4.37 (dd, A of ABX, *J* = 15.6 Hz, *J* = 6.6 Hz, 1H), 4.23 (dd, B of ABX, *J* = 15.6 Hz, *J* = 5.8 Hz, 1H), 3.56 (t, *J* = 8.3 Hz, 1H), 2.98 (d, *J* = 7.7 Hz, 2H), 2.56 (m, 1H), 2.14 (m, 1H), 1.84 (br s, 1H), 1.73 (m, 1H), 1.56 (m, 2H), 1.31 (s, 9H).

Through a solution of {1(*R*)-benzyl-2-oxo-2-[2-(2-[1,2,4]triazol-1-yl-benzylcarbamoyl)pyrrolidin-1(*S*)-yl]ethyl}carbamic acid *tert*-butyl ester (44 mg, 0.08 mmol) in ethyl acetate (20 mL), cooled to 0 °C, was bubbled HCl(g) for 5 min. The reaction was stirred at room temperature for 1 h. Nitrogen was bubbled through the reaction mixture. Concentration from ethyl acetate gave 1-(2(*R*)-amino-3-phenylpropionyl)pyrrolidine-2(*S*)-carboxylic acid 2-[1,2,4]triazol-1-yl-benzylamide **30** (42 mg). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 8.58 (t, *J* = 5.8 Hz, 1H), 8.48 (m, 2H), 8.24 (s, 1H), 7.49 (d, *J* = 2 Hz, 2H), 7.43 (d, *J* = 2 Hz, 2H), 7.37−7.30 (m, 3H), 7.23 (d, *J* = 6.8 Hz, 2H), 4.28 (m, 1H), 4.15 (m, 3H), 3.58 (m, 1H), 3.10 (dd, A of ABX, *J* = 13.1 Hz, *J* = 5.8 Hz, 1H), 2.96 (dd, B of ABX, *J* = 13.1 Hz, *J* = 9.4 Hz, 1H), 2.56 (m, 1H), 1.76−1.63 (m, 3H), 1.43 (m, 1H). HRMS ES: calculated for $C_{23}H_{26}N_6O_2$, 419.2190; found, 419.2194.

1-(2(*R*)-Amino-3-phenylpropionyl)pyrrolidine-2(*S*)-carboxylic Acid 5-Chloro-2-[1,2,4]triazol-1-yl-benzylamide (31). Compound **31** was prepared from Boc-D-Phe-Pro-OH and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **30**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (s, 1H), 8.75 (t, *J* = 5.8 Hz, 1H), 8.56 (m, 2H), 8.26 (s, 1H), 7.49 (m, 3H), 7.37−7.30 (m, 3H), 7.24 (d, *J* = 6.9 Hz, 2H), 4.25 (m, 1H), 4.18 (m, 1H), 4.12 (m, 2H), 3.59 (m, 1H), 3.11 (dd, A of ABX, *J* = 12.8 Hz, *J* = 5.6 Hz, 1H), 2.97 (dd, B of ABX, *J* = 12.8 Hz, *J* = 9.7 Hz, 1H), 2.50 (m, 1H), 1.75−1.59 (m, 3H), 1.43 (m, 1H). HRMS ES: calculated for $C_{23}H_{25}ClN_6O_2$, 453.1801; found, 453.1808.

1-(2(*R*)-Amino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic Acid 5-Chloro-2-[1,2,4]triazol-1-yl-benzylamide (32). A solution of *N*-(*tert*-butoxycarbonyl)-3-pyridin-2-yl-L-alanine (1 g, 3.8 mmol), methyl-L-prolinate hydrochloride (0.62 g, 3.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1 g, 5.7 mmol), 1-hydroxy-7-azabenzotriazole (0.51 g, 3.8 mmol), and triethylamine (0.52 mL, 3.8 mmol) in *N*,*N*-dimethylformamide (7 mL) was stirred at room temperature for 3 h. Ethyl acetate was added, and the reaction mixture was washed with saturated sodium bicarbonate, water, and brine. Drying and solvent evaporation gave an oil; flash chromatography (silica gel, hexanes−ethyl acetate, 50:50−0:100, followed by ethyl acetate−methanol, 98:2−90:10) gave 1-(2(*R*)-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid methyl ester (0.9 g, 64%). To a solution of 1-(2(*R*)-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid methyl ester (0.44 g, 1.2 mmol) in methanol (7 mL) was added lithium hydroxide (1 M in water, 1.2 mL, 1.2 mmol). The reaction was stirred at room temperature for 6 h. Additional lithium hydroxide (1 M in water, 0.12 mL, 0.12 mmol) was added, and the reaction was stirred at room temperature for 16 h. Hydrochloric acid (12 M, 0.12 mL, 1.44 mmol) was added, and the mixture was concentrated to give 1-(2(*R*)-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid (∼0.44 g). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.47 (m, 1H), 7.78 (m, 1H), 7.34 (m, 2H), 4.31 (dd, *J* = 8.8 Hz, *J* = 4.2 Hz, 1H), 3.78 (br m, 1H), 3.54 (br m, 1H), 3.17 (dd, *J* = 13.5 Hz, *J* = 6.2 Hz, 1H), 3.02 (m, 2H), 2.30−1.80 (br m, 4H), 1.35 (s, 9H).

1-(2(*R*)-Amino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid 5-chloro-2-[1,2,4]triazol-1-yl-benzylamide **32** was prepared from 1-(2(*R*)-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid and 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** using a procedure similar to that described for the preparation of **30**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.95 (s, 1H), 8.66 (t, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 4.4 Hz, 1H), 8.47 (br s, 3H), 8.27 (s, 1H), 7.92 (t, *J* = 7.9 Hz, 1H), 7.55−7.43 (m, 5H), 4.56 (br s, 1H), 4.28−4.11 (m, 3H), 3.37−3.20 (m, 4H), 2.00−1.93 (br s, 1H), 1.88−1.72 (m, 3H). HRMS ES: calculated for $C_{22}H_{25}ClN_7O_2$, 454.1753; found, 454.1754.

2-{6-Chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(2-tetrazol-1-yl-benzyl)-acetamide (33). Compound **33** was prepared from {6-chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.50 (s, 1H), 8.37 (d, *J* = 6.5 Hz, 1H), 7.69 (m, 1H), 7.64 (m, 2H), 7.59−7.51 (m, 2H), 7.47 (m, 2H), 6.68 (s, 1H), 4.76 (s, 2H), 4.55 (t, *J* = 13 Hz, 2H), 4.27 (s, 2H). HRMS ES: calculated for $C_{21}H_{18}ClF_2N_9O_3$, 518.1262; found, 518.1256.

2-{6-Chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(5-chloro-2-tetrazol-1-yl-benzyl)acetamide (34). Compound **34** was prepared from {6-chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.51 (s, 1H), 8.69 (m, 1H), 8.36 (d, *J* = 5.8 Hz, 1H), 7.69 (dd, *J* = 7.9 Hz, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.59−7.47 (m, 4H), 6.68 (s, 1H), 4.77 (s, 2H), 4.55 (t, *J* = 12.8 Hz, 2H), 4.24 (m, 2H). HRMS ES: calculated for $C_{21}H_{17}Cl_2F_2N_9O_3$, 552.0872; found, 552.0878.

2-[3-(2,2-Difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-*N*-(2-tetrazol-1-yl-benzyl)acetamide Trifluoroacetic Acid Salt (35). Compound **35** was prepared from [3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.84 (s, 1H), 8.71 (m, 2H), 7.99 (t, *J* = 7.7 Hz, 1H), 7.72 (m, 1H), 7.65−7.55 (m, 5H), 7.21 (m, 1H), 6.80 (d, A of AB, *J* = 4.7 Hz, 1H), 6.74 (d, B of AB, *J* = 4.7 Hz, 1H), 4.51 (s, 2H), 4.24 (m, 2H), 4.15 (d, *J* = 5.5 Hz, 2H). HRMS ES: calculated for $C_{21}H_{19}F_2N_9O_2$, 468.1703; found, 468.1699.

***N*-(5-Chloro-2-tetrazol-1-yl-benzyl)-2-[3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetamide (36).** Compound **36** was prepared from [3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]acetic acid[12] and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.54 (s, 1H), 8.64 (m, 1H), 7.94 (m, 1H), 7.72 (m, 2H), 7.50 (m, 3H), 6.76 (d, A of AB, *J* = 4.7 Hz, 1H), 6.68 (d, B of AB, *J* = 4.7 Hz, 1H), 4.52 (s, 2H), 4.26 (m, 4H). HRMS ES: calculated for $C_{21}H_{18}ClF_2N_9O_2$, 502.1313; found, 502.1318.

2-{3-[2,2-Difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-*N*-(2-tetrazol-1-yl-benzyl)acetamide Trifluoroacetic Acid Salt (37). Compound **37** was prepared from {3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetic acid[21] and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.82 (s, 1H), 8.66 (m, 1H), 8.36 (d, *J* = 6.5 Hz, 1H), 7.64−7.54 (m, 4H), 7.38 (m, 2H), 6.73 (d, A of AB, *J* = 4.7 Hz, 1H), 6.60 (d, B of AB, *J* = 4.7 Hz, 1H), 4.46 (m, 4H), 4.13 (d, *J* = 5.6 Hz, 2H). HRMS ES: calculated for $C_{21}H_{19}F_2N_9O_3$, 484.1652; found, 484.1653.

***N*-(5-Chloro-2-tetrazol-1-yl-benzyl)-2-{3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-yl}acetamide (38).** Compound **38** was prepared from {3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)ethylamino]-2-oxo-2*H*-pyrazin-1-

yl}acetic acid[20] and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.51 (s, 1H), 8.36 (d, J = 6.2 Hz, 1H), 7.69 (m, 2H), 7.58−7.46 (m, 4H), 6.60 (d, A of AB, J = 4.8 Hz, 1H), 6.58 (d, B of AB, J = 4.8 Hz, 1H), 4.56 (t, J = 13.2 Hz, 2H), 4.45 (s, 2H), 4.23 (s, 2H). Elemental analysis ($C_{21}H_{18}ClF_2N_9O_3$): C, H, N.

2-(6-Methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)-*N*-(2-tetrazol-1-yl-benzyl)acetamide (39). Compound **39** was prepared from (6-methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)acetic acid[11] and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.54 (s, 1H), 7.70 (m, 1H), 7.64 (m, 1H), 7.54 (m, 1H), 7.48 (m, 1H), 7.28 (m, 6H), 6.14 (d, J = 7.4 Hz, 1H), 4.76 (s, 2H), 4.43 (s, 2H), 4.32 (s, 2H), 2.31 (s, 3H). Elemental analysis ($C_{23}H_{23}N_7O_4S$): C, H, N.

***N*-(5-Chloro-2-tetrazol-1-yl-benzyl)-2-(6-methyl-2-oxo-3-phenylmethane sulfonylamino-2*H*-pyridin-1-yl)acetamide (40).** Compound **40** was prepared from (6-methyl-2-oxo-3-phenylmethanesulfonylamino-2*H*-pyridin-1-yl)acetic acid[11] and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **6**. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.55 (s, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.54 (m, 1H), 7.48 (m, 1H), 7.33−7.23 (m, 6H), 6.14 (d, J = 7.9 Hz, 1H), 4.77 (s, 2H), 4.43 (s, 2H), 4.29 (s, 2H), 2.31 (s, 3H). Elemental analysis ($C_{23}H_{22}ClN_7O_4S$): C, H, N.

1-(2-Amino-3-phenyl-propionyl)pyrrolidine-2-carboxylic Acid 2-Tetrazol-1-yl-benzylamide (41). Compound **41** was prepared from Boc-D-Phe-Pro-OH and 2-tetrazol-1-yl-benzylamine **62** using a procedure similar to that described for the preparation of **30**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.87 (s, 1H), 8.53 (t, J = 5.6 Hz, 1H), 8.35 (s, 2H), 7.61−7.53 (m, 3H), 7.37−7.22 (m, 4H), 4.30 (m, 1H), 4.16 (d, J = 7.5 Hz, 1H), 4.08 (m, 2H), 3.53 (m, 2H), 3.07 (m, 1H), 2.97 (m, 1H), 2.63 (m, 1H), 1.70 (m, 3H), 1.43 (m, 1H). HRMS ES: calculated for $C_{22}H_{25}N_7O_2$, 420.2143; found, 420.2149.

1-(2(*R*)-Amino-3-phenylpropionyl)pyrrolidine-2(*S*)-carboxylic Acid 5-Chloro-2-tetrazol-1-yl-benzylamide (42). Compound **42** was prepared from Boc-D-Phe-Pro-OH and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **30**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.92 (s, 1H), 8.58 (m, 1H), 8.32 (br s, 2H), 7.61 (m, 2H), 7.36−7.22 (m, 3H), 4.30 (m, 1H), 4.27−3.99 (m, 2H), 3.52 (m, 1H), 3.27−2.95 (m, 2H), 2.56−2.45 (m, 2H), 1.76−1.66 (m, 3H), 1.44 (m, 1H). HRMS ES: calculated for $C_{22}H_{24}ClN_7O_2$, 454.1753; found, 454.1751.

1-(2(*R*)-Amino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic Acid 5-Chloro-2-tetrazol-1-yl-benzylamide (43). Compound **43** was prepared from 1-(2-(*R*)-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionyl)pyrrolidine-2(*S*)-carboxylic acid and 5-chloro-2-tetrazol-1-yl-benzylamine **63** using a procedure similar to that described for the preparation of **32**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.89 (s, 1H), 8.73 (t, J = 5.6 Hz, 1H), 8.62 (d, J = 4.0 Hz, 1H), 8.59−8.48 (m, 3H), 7.95 (t, J = 9.5 Hz, 1H), 7.61 (br s, 2H), 7.51−7.43 (m, 3H), 4.55 (br s, 1H), 4.20 (d, J = 7.7 Hz, 1H), 4.15−3.97 (m, 2H), 3.41−3.20 (m, 4H), 2.00−1.91 (br s, 1H), 1.83−1.71 (m, 3H). HRMS ES: calculated for $C_{21}H_{24}ClN_8O_2$, 455.1705; found, 455.1707.

***N*′-(1-*o*-Tolyl-ethylidene)hydrazinecarboxylic Acid Ethyl Ester (45).** A solution of 2′-methylacetophenone (0.98 mL, 7.4 mmol), ethyl carbazate (0.81 g, 7.8 mmol), and *p*-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol) in toluene (30 mL) was heated at reflux temperature with a Dean−Stark apparatus for 2 h. Solvent evaporation and flash chromatography (silica gel, hexanes−ethyl acetate, 80:20) gave *N*′-(1-*o*-tolyl-ethylidene)hydrazinecarboxylic acid ethyl ester **45** (1.0 g, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (br s, 1H), 7.21 (m, 4H), 4.31 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.17 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

4-*o*-Tolyl-[1,2,3]thiadiazole (46). To thionyl chloride (1 mL), cooled to 0 °C, was added *N*′-(1-*o*-tolyl-ethylidene)-hydrazinecarboxylic acid ethyl ester **45** (100 mg, 0.45 mmol). The reaction mixture was heated to 60 °C for 1 h. Solvent evaporation gave 4-*o*-tolyl-[1,2,3]thiadiazole **46** (78 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.36 (m, 3H), 2.46 (s, 3H).

2-[1,2,3]Thiadiazole-4-yl-benzylamine (47). A solution of 4-*o*-tolyl-[1,2,3]thiadiazole **46** (100 mg, 0.57 mmol), *N*-bromosuccinimide (100 mg, 0.57 mmol), and 2,2′-azobisisobutyronitrile (9.4 mg, 0.057 mmol) in chloroform (10 mL) was heated at reflux temperature for ∼18 h. Additional chloroform was added, and the mixture was washed with water, sodium thiosulfate solution (5% in water), and brine. Drying and solvent evaporation gave 4-(2-(bromomethyl)phenyl)-[1,2,3]-thiadiazole (125 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 7.67−7.39 (m, 4H), 4.71 (s, 2H).

A solution of 4-(2-(bromomethyl)phenyl)-[1,2,3]thiadiazole (7.0 g, 0.027 mol) and sodium azide (5.3 g, 0.081 mol) in DMF (200 mL) was stirred at room temperature overnight. Ethyl acetate was added, and the reaction mixture was washed with water and brine. Drying and solvent evaporation gave an oil; flash chromatography (silica gel, hexanes−ethyl acetate, 96:4) gave 4-(2-(azidomethyl)phenyl)-[1,2,3]thiadiazole (4.0 g, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.74 (s, 1H), 7.76 (m, 1H), 7.53 (m, 3H), 4.54 (s, 2H).

A solution of 4-(2-(azidomethyl)phenyl)-[1,2,3]thiadiazole (1.0 g, 4.6 mmol), triphenylphosphine (1.4 g, 5.5 mmol), and water (0.12 mL, 6.9 mmol) in THF (20 mL) was stirred at room temperature overnight. Solvent evaporation and flash chromatography (silica gel, chloroform−2-propanol, 95:5−92:8) gave 2-[1,2,3]thiadiazole-4-yl-benzylamine **47** (0.59 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.45 (m, 3H), 3.88 (s, 2H).

1*H*-Pyrazol-3-yl-boronic acid (48). A mixture of pyrazole (14.3 g, 0.21 mol), 3,4-dihydro-2*H*-pyran (29 mL, 0.32 mol), and trifluoroacetic acid (0.1 mL, 0.0013 mol) was refluxed for 5 h. Addition of sodium hydride (0.2 g, 0.008 mol) and distillation (∼60−65 °C, 0.5−1 Torr) gave 1-(tetrahydropyran-2-yl)-1*H*-pyrazole (30.8 g, 96%).

To a solution of 1-(tetrahydropyran-2-yl)-1*H*-pyrazole (7.6 g, 0.052 mol) in THF (50 mL), cooled to −70 °C, was added *n*-butyllithium (1.6 M in hexane, 33 mL, 0.052 mol) dropwise. Triisopropyl borate (12.7 mL, 0.055 mol) was added over 10 min, and the reaction mixture was stirred at −70 °C for 1 h. The reaction was quenched with hydrochloric acid (2 M in water, 0.104 mol, 52 mL), and the resultant precipitate was filtered and washed with water and benzene to give 1*H*-pyrazol-3-yl-boronic acid **48** (∼2.3 g, 40%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.23 (br s, 1H), 7.48 (s, 1H), 6.68 (d, J = 1.6 Hz, 1H).

2-(1*H*-Pyrazol-3-yl)benzylamine Hydrochloride Salt (50). To a solution of 1*H*-pyrazol-3-yl-boronic acid **48** (156 mg, 1.4 mmol), tetrakis(triphenylphosphine) palladium(0) (242 mg, 0.21 mmol), and sodium carbonate (222 mg, 2.1 mmol) in DMF (2 mL) was added (2-bromobenzyl)carbamic acid *tert*-butyl ester **49**[22] (200 mg, 0.70 mmol). The reaction mixture was heated to 100 °C for 2 h, cooled to room temperature, and quenched with saturated sodium bicarbonate. The reaction was extracted with ethyl acetate, and the combined organic layers were washed with brine. Drying, solvent evaporation, and flash chromatography (silica gel, hexanes−ethyl acetate, 100:0−70:30) gave [2-(1*H*-pyrazol-3-yl)benzyl]carbamic acid *tert*-butyl ester (60.3 mg, 32%). Through a solution of [2-(1*H*-pyrazol-3-yl)-benzyl]carbamic acid *tert*-butyl ester (60 mg, 0.22 mmol) in ethyl acetate (5 mL), cooled to 0 °C, was bubbled HCl(g) for 2 min. The reaction was stirred for 40 min. Concentration from ethyl acetate gave 2-(1*H*-pyrazol-3-yl)-benzylamine hydrochloride salt **50** (46 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 1H), 6.72 (d, J = 2.2 Hz, 1H), 4.20 (s, 2H).

2-Bromo-1-(2-bromophenyl)ethanone (51). To a solution of 2-bromoacetophenone (75 g, 0.37 mol) in methanol (220 mL) was added trimethyl borate (55 mL, 0.48 mol). After the mixture was stirred at room temperature for 45 min, bromine (20.4 mL, 0.39 mol) was added dropwise over 2 h. The reaction

was maintained between 23 and 27 °C for 1 h, water (220 mL) was added, and the reaction mixture was heated to reflux for 40 min. After the mixture cooled to room temperature, two layers separated. Concentration of the bottom layer gave 2-bromo-1-(2-bromophenyl)ethanone **51** (95.6 g, 91%).

4-(2-Bromophenyl)-1*H*-imidazole (52). A mixture of 2-bromo-1-(2-bromophenyl)ethanone **51** (95 g, 0.34 mol) and formamide (240 mL, 6.8 mol) was heated to 145 °C for 14 h. After cooling, the reaction mixture was diluted with ethyl acetate (500 mL), and potassium carbonate solution (15% in water, 440 mL) was added in portions. The reaction was extracted with ethyl acetate and washed with brine. The combined organic layer was then washed with brine. Drying and solvent evaporation gave 4-(2-bromophenyl)-1*H*-imidazole **52** (80 g).

2-(1-Trityl-1*H*-imidazol-4-yl)benzylamine Oxalate Salt (53). To a solution of 4-(2-bromophenyl)-1*H*-imidazole **52** (73.5 g, 0.33 mol) and triethylamine (45.8 mL, 0.33 mol) in DMF (750 mL), cooled to 0 °C, was added a solution of trityl chloride in DMF (850 mL) dropwise over 40 min. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with ice water (∼2 L). The resultant precipitate was stirred for 20 min, filtered, and dried to give 4-(2-bromophenyl)-1-trityl-1*H*-imidazole (136.7 g, 89%).

To a solution of 4-(2-bromophenyl)-1-trityl-1*H*-imidazole (73 g, 163.3 mmol) in DMF (500 mL) was added copper(I) cyanide (17.5 g, 195.9 mmol). The reaction mixture was heated to ∼80 °C for 14 h, cooled to ∼50 °C, and diluted with toluene (∼300 mL). The reaction was slowly poured into ammonium hydroxide solution (3 N, 1.5 L), stirred for 40 min, and filtered over Celite. The layers were separated, and the organic layer was washed with brine. Drying and solvent evaporation gave 2-(1-trityl-1*H*-imidazol-4-yl)benzonitrile (76.7 g).

To a solution of 2-(1-trityl-1*H*-imidazol-4-yl)benzonitrile (17.6 g, 42.7 mmol) in THF (320 mL) was added lithium aluminum hydride (1.0 M in THF, 45 mL, 45 mmol) dropwise. After being stirred for 45 min to 1.5 h, the reaction mixture was diluted with THF and quenched with water (1.7 mL), sodium hydroxide solution (15% in water, 1.7 mL), and water (5.1 mL). The reaction mixture was stirred at room temperature for 3 h, filtered, and concentrated to give 2-(1-trityl-1*H*-imidazol-4-yl)benzylamine (18.5 g).

To a solution of 2-(1-trityl-1*H*-imidazol-4-yl)benzylamine (66.1 g, 159 mmol) in THF (420 mL) was added oxalic acid (14.3 g, 159 mmol). After being stirred for 15 min, the mixture was added dropwise to hexane (2 L). The resultant solid was stirred for 20 min, filtered, and dried to give 2-(1-trityl-1*H*-imidazol-4-yl)benzylamine oxalate salt **53** (60.9 g, 76%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.47 (br s, 2H), 7.61 (m, 2H), 7.49−7.31 (m, 12H), 7.19 (m, 5H), 4.14 (s, 2H).

2-(1*H*-Imidazol-2-yl)benzonitrile (55). A suspension of phthalonitrile (70 g, 0.55 mol) in ethanol (100 mL) and chloroform (200 mL) was warmed and then cooled to 0 °C. The reaction mixture was saturated with hydrochloric acid (g) and kept at 0 °C for 2 weeks. The resultant precipitate was filtered and washed with chloroform. Dilution of the filtrate with ether produced additional 2-cyanobenzimidic acid ethyl ester hydrochloride salt **54** (58.8 g, 51%).

A solution of 2-cyanobenzimidic acid ethyl ester hydrochloride salt **54** (43 g, 0.20 mol) and 2,2-diethoxyethylamine (30 mL, 0.21 mol) in methanol (430 mL) stood at room temperature for 1 h. The reaction mixture was concentrated, and sulfuric acid (36 N, 110 mL) was added. After being heated on a steam bath for 1.5 h, the mixture was diluted with water (700 mL) and extracted with chloroform. The aqueous phase was made strongly basic with sodium hydroxide (12 N) and extracted with chloroform. Hydrochloric acid (12 N) was added to give pH 3−4, insoluble residue was filtered, and the filtrate was concentrated. The resultant brown solid was sublimed at 200−220 °C. The purified solid was dissolved in hydrochloric acid (6 N, 110 mL) and heated, byproducts were filtered (phthalimide), and the filtrate was concentrated. The residue was diluted with ethanol (∼120 mL) containing hydrochloric acid (12 N, 1 mL) and refluxed briefly, and the insoluble material was filtered. Further concentration to ∼80 mL and cooling of the filtrate to 0 °C gave 2-(1*H*-imidazol-2-yl)benzonitrile hydrochloride (1.5 g). The filtrate was concentrated further to ∼30 mL and diluted with acetone (∼150 mL). Filtration gave 2-(1*H*-imidazol-2-yl)benzoic acid hydrochloride (7.3 g). Further dilution of the filtrate with acetone and filtration of the resultant solid gave additional 2-(1*H*-imidazol-2-yl)benzonitrile hydrochloride (1.5 g); mp 200−204 °C. IR: 4.5 μm.

To a solution of 2-(1*H*-imidazol-2-yl)benzonitrile hydrochloride (3 g, 0.014 mol) in water (20 mL) was added sodium hydroxide (2.5 N, 5 mL). Filtration of the resultant precipitate and recrystallization from ethyl acetate gave 2-(1*H*-imidazol-2-yl)benzonitrile **55** (1.31 g). Elemental analysis for $C_{10}H_7N_3$: C (calcd 70.99, found 70.74); H (calcd 4.17, found 4.08); N (calcd 24.84, found 25.24). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.73 (br s, 1H), 7.91 (m, 2H), 7.78 (td, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.54 (td, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.38 (br s, 1H), 7.15 (br s, 1H).

2-(1*H*-Imidazol-2-yl)benzylamine (56). A solution of 2-(1*H*-imidazol-2-yl)benzonitrile **55** (50 mg, 0.30 mmol) in ethanol saturated with ammonia (5 mL) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 2 h. The reaction mixture was filtered over Celite and concentrated to give 2-(1*H*-imidazol-2-yl)benzylamine **56** (42 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, J = 7.5 Hz, 1H), 7.42 (m, 1H), 7.28 (m, 2H), 7.18 (br s, 2H), 3.96 (s, 2H).

2-Pyrazol-1-yl-benzylamine Trifluoroacetic Acid Salt (57). To a solution of 2-hydrazinobenzoic acid hydrochloride (50 g, 0.27 mol) and malonaldehyde bis(dimethylacetal) (43 mL, 0.27 mol) in water (630 mL) was added hydrochloric acid (12 M, 30 mL). The reaction mixture was heated to reflux for 2 h and concentrated to remove methanol. The aqueous residue was treated with charcoal and cooled for 2 h. The resultant solid was filtered, washed with cold water, and dried to give 2-pyrazol-1-yl-benzoic acid (30 g, 59%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.87 (br s, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.72−7.62 (m, 3H), 7.56 (m, 1H), 7.49 (td, J = 7.4 Hz, J = 1.2 Hz, 1H), 6.48 (m, 1H).

A solution of 2-pyrazol-1-yl-benzoic acid (50 mg, 0.26 mmol), ammonium chloride (28 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol), 1-hydroxy-7-azabenzotriazole (71 mg, 0.52 mmol), and diisopropylethylamine (0.17 mL, 1.0 mmol) in DMF (0.75 mL) was stirred at room temperature for 5 h. Water was added, and the reaction mixture was extracted with ethyl acetate. Drying and solvent evaporation gave 2-pyrazol-1-yl-benzamide (68 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.92 (d, J = 2.4 Hz, 1H), 7.70−7.48 (m, 5H), 6.49 (m, 1H).

A solution of 2-pyrazol-1-yl-benzamide (68 mg) and borane−tetrahydrofuran complex (1 M in THF, 1.4 mL, 1.4 mmol) in THF (2 mL) was heated at reflux temperature for 2 h. Hydrochloric acid solution (1 M in water, 2.8 mL) was added, and the reaction mixture was heated at reflux temperature for 30 min. The solution was neutralized with sodium hydroxide solution (1 N), concentrated to remove THF, and extracted with chloroform. Drying and solvent evaporation gave an oil; purification by reversed-phase preparative HPLC (5% to 95% CH_3CN in water containing 0.1% TFA, C18 PRO YMC 20 × 150 mm) gave 2-pyrazol-1-yl-benzylamine trifluoroacetic acid salt **57** (23 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.80 (br s, 2H), 7.80 (m, 2H), 7.62−7.37 (m, 4H), 6.56 (t, J = 2.2 Hz, 1H), 4.07 (s, 2H).

2-Imidazol-1-yl-benzylamine (58). To a solution of 1*H*-imidazole (0.61 g, 9.0 mmol) in DMF (8 mL) was added sodium hydride (60% in oil, 0.36 g, 9.0 mmol), and the reaction mixture was stirred at room temperature for 40 min. 2-Fluorobenzonitrile (0.9 mL, 8.2 mmol) was added, and the reaction was stirred at room temperature for 45 min, heated to 60 °C for 45 min, and then stirred at room temperature overnight. Ethyl acetate was added, and the mixture was washed with water and brine. Drying and solvent evaporation gave 2-imidazol-1-yl-benzonitrile (1.3 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (br s, 1H), 7.84 (m, 1H), 7.75 (m, 1H), 7.54 (m, 1H), 7.47 (dd, J = 8.1 Hz, J = 1 Hz, 1H), 7.36 (m, 1H), 7.27 (m, 1H).

A solution of 2-imidazol-1-yl-benzonitrile (200 mg, 1.2 mmol) in ethanol saturated with ammonia (20 mL) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 4 h. The reaction mixture was filtered over Celite and concentrated to give 2-imidazol-1-yl-benzylamine **58** (150 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (br s, 1H), 7.57 (m, 1H), 7.47 (m, 1H), 7.38 (m, 1H), 7.27 (m, 1H), 7.22 (br s, 1H), 7.16 (m, 1H), 3.73 (s, 2H).

2-[1,2,4]Triazol-1-yl-benzylamine (59) and 2-[1,2,4]-Triazol-4-yl-benzylamine (60). To a solution of 2-fluorocyanobenzene (5.0 g, 41 mmol) in DMF (75 mL) were added 1,2,4-triazole (3.0 g, 43 mmol) and cesium carbonate (14 g, 43 mmol). The reaction mixture was stirred at 50 °C for 18 h, diluted with ethyl acetate (75 mL), and filtered. The filtrate was concentrated and partitioned between ether and water. The undissolved solid was filtered and dried to give a 10:1 mixture of regioisomers (4.6 g). The mixture was separated by flash chromatography (silica gel, ethyl acetate−methanol, 100:0−95:5) to give 2-[1,2,4]triazol-1-yl-benzonitrile (4.0 g) [^{1}H NMR (DMSO-d_6): δ 9.19 (s, 1H), 8.37 (s, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.96−7.87 (m, 2H), 7.71 (t, J = 7.7 Hz, 1H)] and 2-[1,2,4]-triazol-4-yl-benzonitrile (0.38 g) [^{1}H NMR (DMSO-d_6): δ 9.03 (s, 2H), 8.13 (d, J = 7.6 Hz, 1H), 7.93 (t, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H)].

To a solution of 2-[1,2,4]triazol-1-yl-benzonitrile (508 mg, 2.99 mmol) in ethanol (75 mL) was added palladium-on-carbon (10%, 134 mg). The reaction was hydrogenated on a Parr apparatus at 55 psi overnight. Filtration through Celite and solvent evaporation gave 2-[1,2,4]triazol-1-yl-benzylamine **59** (501 mg, 96%). ^{1}H NMR (CD_3OD): δ 8.80 (s, 1H), 8.22 (s, 1H), 7.64−7.43 (m, 4H), 3.66 (s, 2H).

To a solution of 2-[1,2,4]triazol-4-yl-benzonitrile (0.3 g, 1.76 mmol) in ethanol (75 mL) was added palladium-on-carbon (10%, 100 mg). The reaction was hydrogenated on a Parr apparatus at 55 psi for 48 h. Filtration through Celite and solvent evaporation gave 2-[1,2,4]triazol-4-yl-benzylamine **60** (268 mg, 87%). ^{1}H NMR (CD_3OD): δ 8.77 (s, 2H), 7.69−7.59 (m, 4H), 3.61 (s, 2H).

5-Chloro-2-[1,2,4]triazol-1-yl-benzylamine (61). To a solution of 2,5-dichlorobenzonitrile (10 g, 58.1 mmol) in DMF (100 mL) were added cesium carbonate (22.7 g, 69.8 mmol) and 1,2,4-triazole (4.8 g, 69.8 mmol). The reaction mixture was stirred at 65 °C for 5.5 h, 75 °C for 16 h, and 85 °C for 7 h. Additional 1,2,4-triazole (5 g) was added, and the reaction mixture was stirred at 85 °C for 18 h and 100 °C for 4 h. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with aqueous lithium chloride, dried, and concentrated to give 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (11.9 g). A suspension of 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (11.9 g, 58 mmol) in ethanol saturated with ammonia (500 mL) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 26 h. The reaction mixture was filtered over Celite and concentrated. Purification by flash chromatography (silica gel, methylene chloride−10% ammonium hydroxide/methanol, 95:5−90:10) gave 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine **61** (9.3 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (s, 1H), 8.14 (s, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 7.9 Hz, J = 2.3 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 3.70 (s, 2H).

2-Tetrazol-1-yl-benzylamine (62). A suspension of 2-aminobenzoic acid (6.0 g, 0.044 mol), trimethyl orthoformate (14.2 mL, 0.13 mol), and sodium azide (8.4 g, 0.13 mol) in glacial acetic acid (150 mL) was stirred at room temperature for 2 h. Filtration and concentration from toluene gave 2-tetrazol-1-yl-benzoic acid (5.6 g, 67%). ^{1}H NMR (CD_3OD, 400 MHz): δ 9.47 (s, 1H), 8.19 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.79 (m, 2H), 7.61 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H).

A solution of 2-tetrazol-1-yl-benzoic acid (1.0 g, 5.2 mmol), ammonium chloride (0.56 g, 10.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.0 g, 10.4 mmol), 1-hydroxy-7-azabenzotriazole (1.4 g, 10.4 mmol), and diisopropylethylamine (3.6 mL, 20.8 mmol) in DMF (15 mL) was stirred at room temperature overnight. Water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave 2-tetrazol-1-yl-benzamide (0.68 g, 69%). ^{1}H NMR (CD_3OD, 400 MHz): δ 9.44 (s, 1H), 7.72 (m, 4H).

To a solution of 2-tetrazol-1-yl-benzamide (1.5 g, 7.9 mmol) in THF (50 mL) was added (methoxycarbonylsulfamoyl)-ammonium hydroxide, inner salt (2.8 g, 11.8 mmol), in three portions over 1.5 h. Water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave 2-tetrazol-1-yl-benzonitrile (1.3 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.27 (s, 1H), 7.90 (m, 3H), 7.72 (m, 1H).

A solution of 2-tetrazol-1-yl-benzonitrile (1.3 g, 7.6 mmol) in ethanol saturated with ammonia (125 mL) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere overnight. The reaction mixture was filtered over Celite and concentrated to give 2-tetrazol-1-yl-benzylamine **62** (750 mg, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.28 (s, 1H), 7.59 (m, 2H), 7.47 (m, 2H), 3.70 (s, 2H).

5-Chloro-2-tetrazol-1-yl-benzylamine (63). Compound **63** was prepared from 2-amino-5-chlorobenzoic acid using a procedure similar to that described for the preparation of **62**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.46 (m, 1H), 7.38 (m, 1H), 3.68 (s, 2H).

***C*-(3-[1,2,4]Triazol-1-yl-pyridin-2-yl)methylamine Hydrochloride Salt (64).** To a solution of 2-cyano-3-fluoropyridine[23] (2.99 g, 24.49 mmol) in DMF (30 mL) were added cesium carbonate (2.03 g, 29.39 mmol) and 1,2,4-triazole (2.03 g, 29.39 mmol). The reaction mixture was stirred at 65 °C for 4 h, diluted with water, and extracted with ethyl acetate. The aqueous layer was saturated with lithium chloride and further extracted with ethyl acetate. The combined organic layers were dried and concentrated. Purification by flash chromatography (silica gel, methylene chloride−10% ammonium hydroxide/methanol, 98:2−94:6) gave 3-[1,2,4]triazol-1-yl-pyridine-2-carbonitrile (3.85 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (s, 1H), 8.80 (d, J = 4 Hz, 1H), 8.24 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.75 (dd, J = 8.5 Hz, J = 4 Hz, 1H).

A suspension of 3-[1,2,4]triazol-1-yl-pyridine-2-carbonitrile (3.74 g, 21.88 mmol) in methanol saturated with ammonia (200 mL) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 18 h. Filtration over Celite and solvent evaporation gave *C*-(3-[1,2,4]triazol-1-yl-pyridin-2-yl)-methylamine. To a solution of this material in methylene chloride (100 mL) and methanol (10 mL) was added di-*tert*-butyl dicarbonate (6.2 g, 28.4 mmol), and the reaction mixture was stirred at room temperature for 30 min. Concentration and purification by flash chromatography (silica gel, methylene chloride−10% ammonium hydroxide/methanol, 98:2−94:6) gave (3-[1,2,4]triazol-1-yl-pyridin-2-ylmethyl)carbamic acid *tert*-butyl ester (4.1 g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (d, J = 4.8 Hz, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.40 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 5.85 (br s, 1H), 4.43 (d, J = 5.4 Hz, 2H), 1.45 (s, 9H).

Through a solution of (3-[1,2,4]triazol-1-yl-pyridin-2-ylmethyl)carbamic acid *tert*-butyl ester (4.08 g, 14.8 mmol) in methylene chloride (100 mL) and methanol (20 mL), cooled to 0 °C, was bubbled HCl(g) for 10 min. The reaction was stirred at room temperature for 18 h. Nitrogen was bubbled through the reaction mixture for 5 min. Concentration gave *C*-(3-[1,2,4]-triazol-1-yl-pyridin-2-yl)methylamine hydrochloride salt **64** (4.4 g). ^{1}H NMR (CD_3OD, 400 MHz): δ 9.67 (s, 1H), 8.85 (d, J = 5.3 Hz, 1H), 8.72 (s, 1H), 8.18 (d, J = 8 Hz, 1H), 7.70 (dd, J = 8 Hz, J = 5.3 Hz, 1H), 4.45 (s, 2H).

***C*-(3-Tetrazol-1-yl-pyridin-2-yl)methylamine (65).** To a solution of tetrazole (1.0 g, 14 mmol) in DMF (150 mL) was added tetrabutylammonium hydroxide solution (40% in water, 7.8 g, 12 mmol). The reaction mixture was concentrated from DMF three times to ensure the removal of all water. To a solution of the residue in DMF (60 mL) was added 2-cyano-

3-fluoropyridine[23] (1.5 g, 12 mmol). The reaction was stirred at room temperature for 4 days and concentrated. The mixture was partitioned between ethyl acetate and water, and the layers were separated. Drying, solvent evaporation, and purification by flash chromatography (silica gel, hexanes−ethyl acetate, 80:20−0:100) gave 3-tetrazol-1-yl-pyridine-2-carbonitrile (0.25 g, 12%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.42 (s, 1H), 8.94 (dd, J = 4.6 Hz, J = 1.3 Hz, 1H), 8.31 (dd, J = 8.4 Hz, J = 1.3 Hz, 1H), 7.87 (dd, J = 8.4 Hz, J = 4.6 Hz, 1H).

To a solution of 3-tetrazol-1-yl-pyridine-2-carbonitrile (250 mg, 1.45 mmol) in ethanol (75 mL) was added palladium-on-carbon (10%, 110 mg). The reaction was hydrogenated on a Parr apparatus at 55 psi overnight. Filtration and solvent evaporation gave *C*-(3-tetrazol-1-yl-pyridin-2-yl)methylamine **65** (247 mg, 97%). ^{1}H NMR (CD_3OD, 400 MHz): δ 9.60 (s, 1H), 8.83−8.81 (m, 1H), 7.99−7.97 (m, 1H), 7.59−7.56 (m, 1H), 3.77 (s, 2H).

[2-(1*H*-Tetrazol-5-yl)benzyl]carbamic Acid *tert*-Butyl Ester (66). A solution of 2-(bromomethyl)benzonitrile (1.0 g, 5.1 mmol) and sodium azide (0.40 g, 6.1 mmol) in DMF (10 mL) was stirred at room temperature for 2 h. Ethyl acetate was added, and the reaction mixture was washed with water and brine. Drying and solvent evaporation gave 2-(azidomethyl)benzonitrile (0.81 g, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, J = 7.7 Hz, 1H), 7.64 (m, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 4.62 (s, 2H).

A solution of 2-(azidomethyl)benzonitrile (0.59 g, 3.7 mmol), tin(II) chloride (1.0 g, 5.5 mmol), and di-*tert*-butyl dicarbonate (1.2 g, 5.5 mmol) in methanol (16 mL) and THF (8 mL) was stirred at room temperature for 1 h. Concentration and flash chromatography (silica gel, hexanes−ethyl acetate, 85:15) gave (2-cyanobenzyl)carbamic acid *tert*-butyl ester (0.12 g, 14%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 7.8 Hz, 1H), 7.58 (m, 1H), 7.52 (m, 1H), 7.37 (m, 1H), 5.12 (br s, 1H), 4.50 (d, J = 6 Hz, 2H), 1.45 (s, 9H).

A solution of (2-cyanobenzyl)carbamic acid *tert*-butyl ester (35 mg, 0.15 mmol), sodium azide (49 mg, 0.75 mmol), and ammonium chloride (40 mg, 0.75 mmol) in DMF (0.5 mL) was heated to 110 °C for 8 h. After the solution cooled to room temperature, ethyl acetate was added and the resultant solid filtered. Concentration of the filtrate gave [2-(1*H*-tetrazol-5-yl)benzyl]carbamic acid *tert*-butyl ester **66** (33 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.71(d, J = 7.5 Hz, 1H), 7.58 (m, 2H), 7.48 (m, 1H), 4.44 (s, 2H), 1.42 (s, 9H).

2-(1*H*-Tetrazol-5-yl)benzylamine Hydrochloride Salt (67). Through a solution of [2-(1*H*-tetrazol-5-yl)benzyl]carbamic acid *tert*-butyl ester **66** (33 mg) in ethyl acetate (15 mL), cooled to 0 °C, was bubbled HCl(g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture, and ether was added. Filtration gave 2-(1*H*-tetrazol-5-yl)benzylamine hydrochloride salt **67** (12.8 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.86 (d, J = 7.7 Hz, 1H), 7.79 (m, 1H), 7.69 (m, 1H), 7.63 (m, 1H), 4.36 (s, 2H).

2-(1-Methyl-1*H*-tetrazol-5-yl)benzylamine Hydrochloride Salt (68) and 2-(2-Methyl-2*H*-tetrazol-5-yl)benzylamine Hydrochloride Salt (69). A solution of [2-(1*H*-tetrazol-5-yl)benzyl]carbamic acid *tert*-butyl ester **66** (0.23 g, 0.84 mmol), crushed potassium carbonate (0.58 g, 4.2 mmol), and iodomethane (0.26 mL, 4.2 mmol) in DMF (4.7 mL) was stirred at room temperature for 1 h. Water was added, and the reaction mixture was extracted with chloroform. Drying and solvent evaporation gave a mixture of regioisomers; separation and purification by reversed-phase preparative HPLC (5% to 95% CH_3CN in water containing 0.1% TFA, C18 PRO YMC 20 × 150 mm) gave [2-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]carbamic acid *tert*-butyl ester (10 mg) [^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, J = 7.5 Hz, 1H), 7.58 (td, J = 7.5 Hz, J = 1.1 Hz, 1H), 7.46 (m, 1H), 7.33 (d, J = 7.5 Hz, 1H), 4.17 (d, J = 6.3 Hz, 2H), 4.05 (s, 3H), 1.41 (s, 9H)] and [2-(2-methyl-2*H*-tetrazol-5-yl)benzyl]carbamic acid *tert*-butyl ester (15 mg) [^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.44 (m, 2H), 5.82 (br s, 1H), 4.52 (d, J = 6.5 Hz, 2H), 4.44 (s, 3H), 1.43 (s, 9H)].

Through a solution of [2-(1-methyl-1*H*-tetrazol-5-yl)benzyl]-carbamic acid *tert*-butyl ester (10 mg) in ethyl acetate (5 mL), cooled to 0 °C, was bubbled HCl(g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture. Concentration from ethyl acetate gave 2-(1-methyl-1*H*-tetrazol-5-yl)benzylamine hydrochloride salt **68** (9 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.75 (m, 4H), 4.18 (s, 3H), 4.11 (m, 2H).

Through a solution of [2-(2-methyl-2*H*-tetrazol-5-yl)benzyl]-carbamic acid *tert*-butyl ester (15 mg) in ethyl acetate (5 mL), cooled to 0 °C, was bubbled HCl(g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture. Concentration from ethyl acetate gave 2-(2-methyl-2*H*-tetrazol-5-yl)benzylamine hydrochloride salt **69** (12 mg, 100%). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.24 (m, 1H), 7.63 (m, 3H) 4.48 (s, 3H), 4.47 (m, 2H).

Conscious Dog Bioavailability. Male beagle dogs weighing 10−12 kg were used for the absorption and kinetic studies. After an overnight fast, the dogs received oral doses of inhibitor at the appropriate milligrams-per-kilogram dosage, either as a solution or suspension in 0.5% methocel. Blood samples were collected via the jugular vein at 0, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 480 min after dosing. Plasma samples were kept frozen (−20 °C) until assayed by HPLC.

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Supporting Information Available: HPLC data obtained using two systems, X-ray crystallographic data, and combustion analysis figures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Thrombosis in Cardiovascular Disorders*; Fuster, V., Verstraete, M., Eds.; W. B. Saunders Co.: Philadelphia, 1992.
(2) *Pharmacology*; Brenner, G. M.; W. B. Saunders Co.: Philadelphia, 2000.
(3) Anand, S. Direct Thrombin Inhibitors. *Haemostasis* **1999**, *29* (Suppl. 1), 76−78.
(4) Sorbera, L. A.; Bayes, M.; Castaner, J.; Silvestre, J. Melagatran and Ximelagatran. *Drugs Future* **2001**, *26* (12), 1155−1170.
(5) Marder, V. J. Thrombolytic Therapy: 2001. *Blood Rev.* **2001**, *15*, 143−157.
(6) Bajusz, S.; Szell, E.; Bagdy, D.; Barabas, E.; Horvath, G.; Dioszegi, M.; Fittler, Z.; Szabo, G.; Juhasz, A.; Tomori, E.; Szilagyi, G. Highly Active and Selective Anticoagulants: D-Phe-Pro-Arg-H, a Free Tripeptide Aldehyde Prone to Spontaneous Inactivation, and Its Stable *N*-Methyl Derivative, D-MePhe-Pro-Arg-H. *J. Med. Chem.* **1990**, *33*, 1729−1735.
(7) Coburn, C. A. Small-molecule Direct Thrombin Inhibitors: 1997−2000. *Exp. Opin. Ther. Patents* **2001**, *11*, 1−18.
(8) For simplicity, we will refer to that portion of the inhibitor which binds to the proximal hydrophobic binding pocket as P_2 and the distal pocket as P_3.
(9) Lumma, W. C.; Witherup, K. M.; Tucker, T. J.; Brady, S. F.; Sisko, J. T.; Naylor-Olsen, A. M.; Lewis, S. D.; Lucas, B. J.; Vacca, J. P. Design of Novel, Potent, Noncovalent Inhibitors of Thrombin with Nonbasic P-1 Substructures: Rapid Structure−Activity Studies by Solid-Phase Synthesis. *J. Med. Chem.* **1998**, *41*, 1011−1013.
(10) Tucker, T. J.; Brady, S. F.; Lumma, W. C.; Lewis, S. D.; Gardell, S. J.; Naylor-Olsen, A. M.; Yan, Y.; Sisko, J. T.; Stauffer, K. J.; Lucas, B. J.; Lynch, J. J.; Cook, J. J.; Stranieri, M. T.; Holahan, M. A.; Lyle, E. A.; Baskin, E. P.; Chen, I.-W.; Dancheck, K. B.; Krueger, J. A.; Cooper, C. M.; Vacca, J. P. Design and Synthesis of a Series of Potent and Orally Bioavailable Noncovalent Thrombin Inhibitors That Utilize Nonbasic Groups in the P1 Position. *J. Med. Chem.* **1998**, *41*, 3210−3219.
(11) Sanderson, P. E. J.; Lyle, T. A.; Cutrona, K. J.; Dyer, D. L.; Dorsey, B. D.; McDonough, C. M.; Naylor-Olsen, A. M.; Chen, I.-W.; Chen, Z.; Cook, J. J.; Cooper, C. M.; Gardell, S. J.; Hare, T. R.; Krueger, J. A.; Lewis, S. D.; Lin, J. H.; Lucas, B. J.; Lyle, E. A.; Lynch, J. J.; Stranieri, M. T.; Vastag, K.; Yan, Y.; Shafer, J. A.; Vacca, J. P. Efficacious, Orally Bioavailable Thrombin Inhibitors Based on 3-Aminopyridinone or 3-Aminopyrazinone Acetamide Peptidomimetic Templates. *J. Med. Chem.* **1998**, *41*, 4466−4474.
(12) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Sanderson, P. E. J.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Lyle, E. A.; Stranieri, M. T.; Holahan, M. A.; Sitko, G. R.; Cook, J. J.; Wallace, A. A.; Clayton, F.; Bohn, D.; Leonard, Y.; Detwiler, T.; Lynch, J. J.;

Williams, P. D.; Coburn, C. A.; Dorsey, B. D.; McMasters, D. R.; McDonough, C. M.; Sanders, W. M.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. Metabolism Directed Optimization of 3-Aminopyrazinone Acetamide Thrombin Inhibitors. Development of an Orally Bioavailable Series Containing P1 and P3 Pyridines. *J. Med. Chem.* **2003**, *46*, 461−473.

(13) Lewis, S. D.; Ng, A. S.; Lyle, E. A.; Mellott, M. J.; Appleby, S. D.; Brady, S. F.; Stauffer, K. J.; Sisko, J. T.; Mao, S.-S.; Veber, D. F.; Nutt, R. F.; Lynch, J. J.; Cook, J. J.; Gardell, S. J.; Shafer, J. A. Inhibition of Thrombin by Peptides Containing Lysyl-α-Keto Carbonyl Derivatives. *Thromb. Haemost.* **1995**, *74*, 1107−1112.

(14) Breinlinger, E. C.; Keenan, C. J.; Rotello, V. M. Modulation of Flavin Recognition and Redox Properties Through Donor Atom−π Interactions. *J. Am. Chem. Soc.* **1998**, *120*, 8606−8609.

(15) Rotello, V. M. The Donor Atom−pi Interaction of Sulfur with Flavin. A Density Functional Investigation. *Heteroat. Chem.* **1998**, *9* (7), 605−606.

(16) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Nantermet, P. G.; Selnick, H. G.; Isaacs, R. C. A.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; Wong, B.; Lyle, E. A.; Stranieri, M. T.; Cook, J. J.; McMasters, D. R.; Pellicore, J. M.; Pal, S.; Wallace, A. A.; Clayton, F. C.; Bohn, D.; Welsh, D. C.; Lynch, J. J.; Yan, Y.; Chen, Z.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. Pharmacokinetic Optimization of 3-Amino-6-chloropyrazinone Acetamide Thrombin Inhibitors. Implementation of P3 Pyridine N-Oxides to Deliver an Orally Bioavailable Series Containing P1 N-Benzylamides. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1353−1357.

(17) Tucker, T. J.; Lumma, W. C.; Lewis, S. D.; Gardell, S. J.; Lucas, B. J.; Baskin, E. P.; Woltmann, R.; Lynch, J. J.; Lyle, E. A.; Appleby, S. D.; Chen, I.-W.; Dancheck, K. B.; Vacca, J. P. Potent Noncovalent Thrombin Inhibitors That Utilize the Unique Amino Acid D-Dicyclohexylalanine in the P3 Position. Implications on Oral Bioavailability and Antithrombotic Efficacy. *J. Med. Chem.* **1997**, *40*, 1565−1569.

(18) Sanderson, P. E. J.; Cutrona, K. J.; Dyer, D. L.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; Yan, Y. Small, Low Nanomolar, Noncovalent Thrombin Inhibitors Lacking a Group to Fill the 'Distal Binding Pocket'. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 161−164.

(19) Rittle, K. E.; Barrow, J. C.; Cutrona, K. J.; Dyer, D. L.; Glass, K. L.; Krueger, J. A.; Kuo, L.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Morrissette, M. M.; Nantermet, P. G.; Newton, C. L.; Sanders, W. M.; Yan, Y.; Vacca, J. P.; Selnick, H. G. Unexpected Enhancement of Thrombin Inhibitor Potency with *o*-Aminoalkylbenzylamides in the P1 position. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3477−3482.

(20) Sanderson, P. E. J. Chapter 8. Anticoagulants: Inhibitors of Thrombin and Factor Xa. *Annu. Rep. Med. Chem.* **2001**, *36*, 79−88.

(21) Burgey, C. S.; Isaacs, R. C.; Dorsey, B. D.; Robinson, K. A.; Staas, D. D.; Sanderson, P. E. J.; Barrow, J. C. Pyrazinone Thrombin Inhibitors. United States Patent US 6,387,911 B1, May 14, 2002.

(22) DeVita, R. J.; Bochis, R.; Frontier, A. J.; Kotliar, A.; Fisher, M. H.; Schoen, W. R.; Wyvratt, M. J.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Jacks, T. M.; Hickey, G. J.; Schleim, K. D.; Leung, K.; Chen, Z.; Chiu, S.-H. L.; Feeney, W. P.; Cunningham, P. K.; Smith, R. G. A Potent, Orally Bioavailable Benzazepinone Growth Hormone Secretagogue. *J. Med. Chem.* **1998**, *41*, 1716−1728.

(23) Sakamoto, T.; Kaneda, S.-I.; Nishimura, S.; Yamanaka, H. Site-Selectivity in the Cyanation of 3-Substituted Pyridine 1-Oxides with Trimethylsilanecarbonitrile. *Chem. Pharm. Bull.* **1985**, *33* (2), 565−571.

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