Efficacious, Orally Bioavailable Thrombin Inhibitors Based on 3-Aminopyridinone or 3-Aminopyrazinone Acetamide Peptidomimetic Templates

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We have addressed the key deficiency of noncovalent pyridinone acetamide thrombin inhibitor L-374,087 (**1**), namely, its modest half-lives in animals, by making a chemically stable 3-alkylaminopyrazinone bioisostere for its 3-sulfonylaminopyridinone core. Compound **3** (L-375,378), the closest aminopyrazinone analogue of **1**, has comparable selectivity and slightly decreased efficacy but significantly improved pharmacokinetics in rats, dogs, and monkeys to **1**. We have developed an efficient and versatile synthesis of **3**, and this compound has been chosen for further preclinical and clinical development.

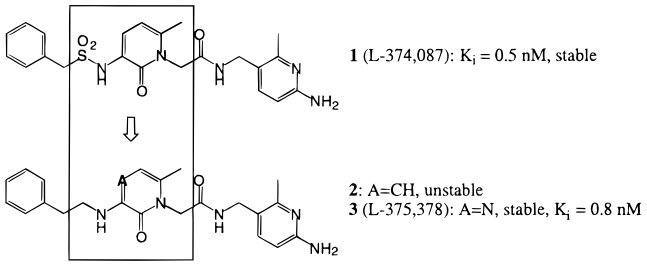
Introduction

The mechanistic limitations of the existing oral anticoagulant warfarin, as well as the intensive monitoring burden for the patient and health care provider required in its use, are driving the search for alternative antithrombotics. Intravenously administered direct inhibitors of thrombin have been shown to be clinically effective antithrombotics.[1] Consequently, a prominent medicinal chemistry goal is the development of an orally active, direct thrombin inhibitor which has predictable pharmacokinetics and which is suitable for once or twice a day dosing.[2,3]

There have been very few reports of orally active thrombin inhibitors which are efficacious in animal models of thrombosis.[4−6] Recently, in a preliminary communication we reported the development of L-374,087 (**1**), a highly selective and efficacious thrombin inhibitor which is orally bioavailable in dogs and monkeys (Chart 1).[7] The further development of **1** as a potential clinical candidate was precluded by its poor oral bioavailability in rats and its modest half-lives in dogs and monkeys. Since compound **1** is an excellent lead structure in all other respects, we have continued to refine its structure in order to improve its pharmacokinetics.

The design of **1** is based on the 3-amino-2-pyridinone acetamide peptidomimetic template[8] which mimics the hydrogen bond array of the backbone of peptide inhibitors of thrombin. The X-ray crystal structure of **1** bound to thrombin[7] shows that the three primary pockets in the active site of thrombin[9] are filled by groups appended to this pyridinone acetamide scaffold (Figure 1). First, a 2-amino-6-methylpyridine fills the specificity pocket (S1).[10] Second, a methyl substituent at the 6-position occupies the proximal hydrophobic pocket (S2) and acts as a conformational constraint. Third, the alkylsulfonyl link stabilizes the electron-rich pyridinone ring and is flexible enough to allow the phenyl group to fill the distal hydrophobic pocket.[11] The importance of this sulfonyl group is illustrated by compound **2**, the phenethyl analogue of **1**. Compound **2** is air-sensitive, slowly developing highly colored impurities on standing.[7] We reasoned that if we were to dispense with the sulfonyl group, an electron-withdrawing group at the 4-position of the pyridinone would have to be incorporated to stabilize the heterocycle. A number of lines of investigation can be conceived to achieve this end. In this paper we report the results of perhaps the simplest, the development of a stable 4-aza (pyrazinone) analogue of the pyridinone of **2** (Chart 1).[12] This change has resulted in the development of a compound with greatly improved pharmacokinetics over the parent sulfonylaminopyridinone.

Chart 1



Chemistry

The synthesis of **1** is shown in Scheme 1 and starts from commercially available 2-hydroxy-6-methylpyri-

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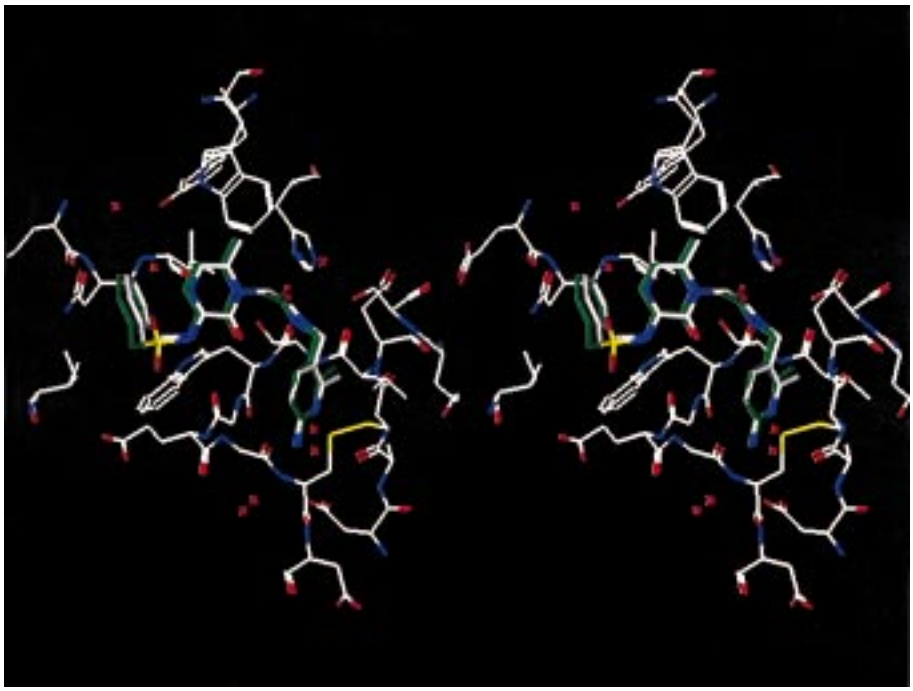
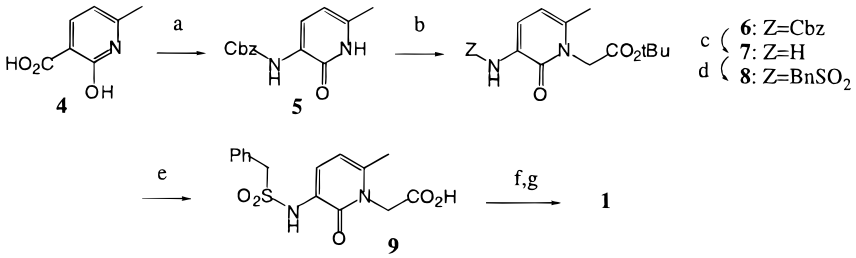


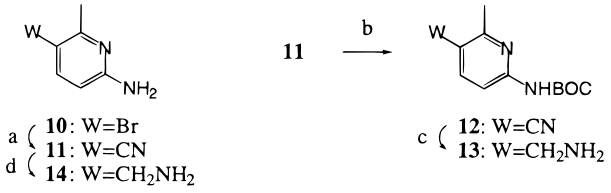
Figure 1. X-ray crystal structure of **1** (carbons in white) and **3** bound in the thrombin active site.

Scheme 1[a]



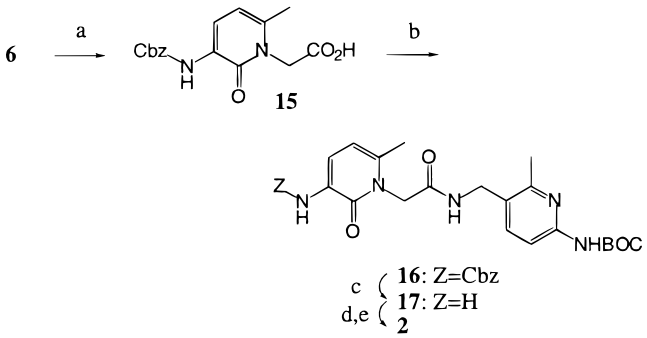
[a] (a) DPPA, Et_3N, dioxane, reflux 16 h, then BnOH, Et_3N, reflux 24 h, 59%; (b) NaH, $BrCH_2CO_2tBu$, THF, 2 h (97%); (c) H_2 (60 psi), $Pd(OH)_2$, $EtOH/H_2O$, 2 h (98%); (d) $BnSO_2Cl$, pyridine, 1 h (83%); (e) HCl, EtOAc, 1.25 h (99%); (f) DCC, **13**, CH_2Cl_2, 3 h; (g) HCl, EtOAc, 0 °C, 1.25 h (72% over two steps).

Scheme 2[a]



[a] (a) CuCN, DMF, reflux 4 h (85%); (b) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, 19 h (84%); (c) H_2 (60 psi), 10% Pd/C, AcOH, 60 h (69%); (d) H_2 (60 psi), 10% Pd/C, EtOH, MeOH, 6 N HCl, 25 h (94%).

Scheme 3[a]



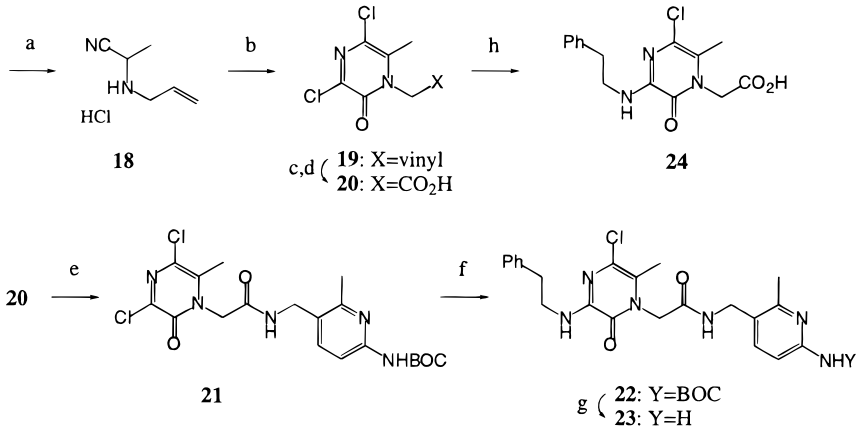
[a] (a) HCl, EtOAc, 1.25 h (77%); (b) EDC, HOBT, Et_3N, **13**, DMF, 64 h (84%); (c) H_2 (50 psi), $Pd(OH)_2$, $EtOH/H_2O$, 2 h (96%); (d) $PhCH_2CHO$, $NaBH(OAc)_3$, $(CH_2Cl)_2$, AcOH, 16 h; (e) HCl, EtOAc, 0 °C, 1.25 h (see Experimental Section).

dine-3-carboxylic acid (**4**). The differentially protected peptidomimetic scaffold **6** is constructed in two steps via the Cbz-protected 3-amino-2-hydroxypyridine. Intermediate **6** is hydrogenolyzed to the amine, sulfonylated, and deprotected to give acetic acid derivative **9**.[11,13]

The BOC-protected 2-amino-5-aminomethyl-6-methylpyridine P1 piece **13** is made in three steps from commercially available 6-amino-3-bromo-2-methylpyridine (**10**; Scheme 2). Reaction of **10** with copper (I) cyanide in refluxing DMF gives nitrile **11** which is first BOC-protected and then reduced to give the aminomethyl compound **13** as the free base. This is cleanly coupled to **9** using DCC in dichloromethane, and final BOC group deprotection using HCl in ethyl acetate gives **1**.

The synthesis of **2** is shown in Scheme 3 and proceeds from **6** by C-terminus deprotection, coupling to **13**, and N-terminus deprotection to give aminopyridinone **17**. Reductive amination with phenylacetaldehyde followed by BOC group removal gives **2**. Compound **2** was found to be air-sensitive, like a previous phenethylamino-

Scheme 4[a]



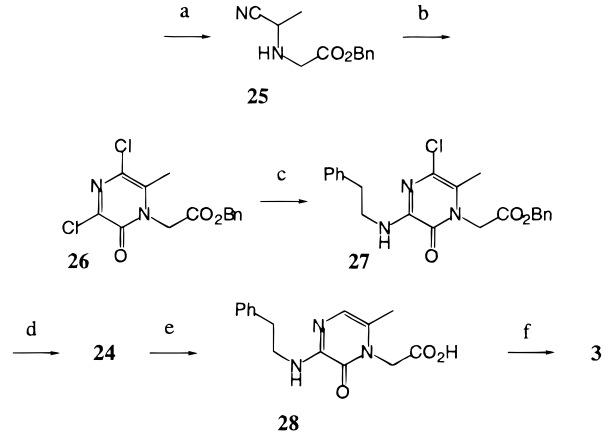
[a] (a) KCN, allylamine, CH_3CHO, EtOH/H_2O, HCl, reflux 15 h, then HCl (83%); (b) $(COCl)_2$, *o*-$C_6H_4Cl_2$, 100 °C, 15 h (54%); (c) $RuCl_3$, $NaIO_4$, $H_2O/CH_3CN/CCl_4$, 3 h; (d) Jones reagent (2.7 M), acetone (53% over two steps); (e) EDC, HOBT, NMM, **13**, DMF, 2 h (91%); (f) 2-phenethylamine, dioxane, 60 °C, 16 h (38%); (g) HCl, EtOAc, 1 h (81%); (h) 2-phenethylamine, dioxane, 65 °C, 16 h (68%).

pyridinone,[11] and could not be isolated absolutely pure using normal laboratory practices.

We are aware of only one published method for the synthesis of 3-aminopyrazinones, that of Hoornaert et al.[14] who showed that the HCl salt of an *N*-alkyl-α-aminonitrile reacts with oxalyl chloride in hot *o*-dichlorobenzene to give an intermediate 1-alkyl-3-hydroxy-5-chloropyrazinone. This reacts with a second equivalent of oxalyl chloride to give, in one operation, the 1-alkyl-3,5-dichloropyrazinone. It was then shown that the 3-chloro group is readily displaced by ammonia or diethylamine. Initially we chose an allyl group as a robust masked acetate equivalent for the 1-position, and condensation of allylamine with acetaldehyde and sodium cyanide gave α-aminonitrile **18** as our starting material (Scheme 4). Reaction with oxalyl chloride under Hoornaert's conditions gave the dichloropyrazinone **19**. Katsuki−Sharpless oxidation[15] gave a mixture of the aldehyde and the desired carboxylic acid. The transformation to the acid **20** was completed using Jones reagent. Coupling with **13** could then be performed under standard conditions to give amide **21** and the 3-chloro group displaced by phenethylamine in warm dioxane to give **22**, albeit in low yield. Deprotection gave the 5-chloro derivative **23**.

Attempts at the palladium-catalyzed hydrogenolysis of the 5-chlorine of **22** or **23** under a variety of conditions proved fruitless, resulting in either no reaction or overreduction. So, to gain access to the 5-deschloro derivatives, we needed to change the order of the synthesis removing the chlorine at an earlier stage. However, the displacement of the 3-chloro group of **20** with excess phenethylamine in warm dioxane to give **24** was not clean, presumably because of competitive reaction with the carboxylate. Consequently, we decided to rework the route to **24** in order to dispense with the allyl group oxidative cleavage and improve the displacement reaction. Thus, starting with the free base of glycine benzyl ester, the aminonitrile **25** was prepared using the procedure of Gibson[16] as an oil (Scheme 5). The crystalline HCl salt of **25** was isolated from ethyl acetate/ethanol. Subjection of this salt to the Hoornaert conditions gave, after evaporative workup and flash filtration through a silica plug, the crystalline dichloropyrazinone **26**. The displacement of the 3-chloro

Scheme 5[a]



[a] (a) TMSCN, CH_3CHO, GlyOBn, CH_2Cl_2, 4 h, then HCl, EtOAc (77%); (b) $COCl)_2$, *o*-$C_6H_4Cl_2$, 100 °C, 15 h (56%); (c) 2-phenethylamine, EtOAc, reflux 2 h; (d) LiOH, MeOH/THF/H_2O, 15 h (91% over two steps); (e) either Raney nickel alloy, MeOH/NaOH (1 M), 2 h (94%), or H_2, 10% Pd/C, KOH, H_2O (88%); (f) EDC, HOBT, NMM, **14**, DMF, 4 h then HCl, EtOH (88%).

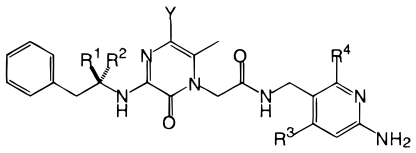
group by excess phenethylamine in refluxing ethyl acetate was very clean and gave crystalline, sparingly soluble aminopyrazinone **27**. Phentermine addition to **26** under these conditions (en route to **33**) requires longer reaction times. We intended to hydrogenolyze the benzyl group and the chlorine simultaneously, but the poor solubility of **27** precluded this. Instead the benzyl group was first hydrolyzed to give **24**. Dechlorination of **24** as a solution in aqueous hydroxide was then possible either by adding Raney Nickel or by palladium-catalyzed hydrogenolysis. In the latter case, filtration followed by acidification precipitated **28** cleanly.

Coupling of **28** to the unprotected 2-amino-5-aminomethyl-6-methylpyridine (**14**) (prepared by direct reduction of **11**, Scheme 2) under standard EDC conditions gives the free base of L-375,378 (**3**). Addition of 2 equiv of ethanolic HCl to a stirred fine suspension of the free base in ethanol first gives a solution. The bis-HCl salt of **3** then precipitates as a stable, uniform, microcrystalline solid.

Results and Discussion

The inhibition constants (K_i values) versus thrombin and trypsin for pyrazinones **3**, **23**, and **29**−**33** are given

Table 1. Inhibition Constants (K_i) versus Thrombin (IIa) and Trypsin (tryp), in Vitro Anticoagulant Potency (2×APTT), and in Vivo Antithrombotic Efficacy in the Rat $FeCl_3$ Arterial Thrombosis Model[a]



compd	R^1	R^2	R^3	R^4	Y	K_i (nM) IIa	K_i (nM) tryp	2×APTT (nM)[b]	rat $FeCl_3$[c]	final plasma concn (nM)
1						0.5	3200	210	0/9	586 ± 59
								(250)[d]	(1/6)[e]	(221 ± 15)[e]
3	H	H	H	CH_3	H	0.8	1800	410	0/6	445 ± 35
								(380)[d]	(4/6)[e]	(238 ± 8)[e]
23	H	H	H	CH_3	Cl	7	2100	5470		
29	H	H	CH_3	CH_3	H	0.35	1000	420	3/6	224 ± 29
30	H	H	H	H	H	8.3	1200	2100		
31	CH_3	H	H	CH_3	H	0.52	1500	350	0/6	554 ± 36
32	H	CH_3	H	CH_3	H	22	4800			
33	CH_3	CH_3	H	CH_3	H	24	2600			

[a] See refs 17 and 18. [b] Human plasma. [c] Occlusions after iv infusion at 10 μg/kg/min. [d] Rat plasma. [e] Infusion at 5 μg/kg/min.

in Table 1, with **1** included for comparison. The first point to note is that the phenethylaminopyrazinone of **3** is an excellent replacement for the benzylsulfonylaminopyridinone of **1**. The X-ray crystal structure of the ternary complex of **3**, thrombin, and hirugen shown in Figure 1 confirms that **3** binds to thrombin in a similar conformation as **1**.[7] The structure provides an explanation for the deleterious effect of the 5-chloro group in compound **23**. The distance from the 5-position carbon of **3** to the phenolic oxygen of the side chain of Tyr-60A is 3.6 Å, too close to accommodate a chlorine substituent without a reorganization of the structure.

Consistent with the crystal structure as well as with the previous experience in the sulfonylaminopyridinone series,[7] the unsubstituted aminopyridine **30** was less potent than **3** and the 2-amino-4,6-dimethylpyridine derivative **29** is somewhat more potent than **3**. The former result reflects the importance of the hydrophobic contact of the 6-methyl group with the side chain of Val-213. The latter result shows that the open nature of the 4-position permits the substitution of an entropically beneficial, conformationally restrictive group.

With a methylene in the place of the sulfonyl group, substitution α to the amine is now possible (compounds **31**−**33**). With a methyl group in the *pro-R* configuration a modest increase in potency is seen (**31**), whereas a methyl group in the *pro-S* position, with or without a methyl group in the *pro-R* position, is strongly deleterious (compounds **32** and **33**). If one makes the reasonable assumption that the entropies of the diastereomeric complexes of **31** and **32** are similar, then the difference in their K_i's must reflect the relative enthalpies of their complexes (given that the free energies of **31** and **32** in solution are the same). Consistent with this picture, molecular modeling indicates that a methyl group in the *pro-S* position unfavorably interacts with both the pyrazinone N-4 and the ortho-proton of the phenyl group. Substitution in the opposite configuration avoids these steric clashes by placing the methyl group out toward the solvent interface without making any contacts with the enzyme.

Table 1 also shows the results from the rat ferric chloride model of arterial thrombosis.[18] Compounds **1**, **3**, and **31** were fully efficacious, while **29** was only partially efficacious, when dosed by iv infusion at 10 μg/kg/min. A more detailed analysis of the results for **1** and **3** shows that they are consistent with the 2×APTT values in rat plasma when the final plasma levels achieved in each case are taken into consideration. This is clearly seen with the occlusion data at the 5 μg/kg/min infusion rate. The plasma concentrations of **1** and **3** are the same, within error, but the rate of occlusion is significantly greater for **3**, reflecting its higher 2×APTT value.

Table 2. Pharmacokinetic Parameters for Compounds **1**, **3**, and **31** in Dogs after Oral Administration

compd	dose (mg/kg)	*n*	C_{max} (μM)	t_{max} (min)	$t_{1/2}$ (min)	AUC (μM·h)
1	1	2	0.99	75	154	4.42
3	0.5	4	1.96 ± 0.51	52.5 ± 28.7	231 ± 45.4	11.2 ± 1.74
31	1	2	0.60	25	128	1.85

The pharmacokinetic parameters for compounds **1**, **3**, and **31** after oral administration in dogs are shown in Table 2. Compound **3** when dosed at 0.5 mg/kg was clearly superior (C_{max} = 1.96 μM; AUC = 11.2 μM·h; $t_{1/2}$ = 231 min) to **1** or **31** dosed at 1 mg/kg. After an iv crossover at 0.5 mg/kg, **3** was determined to be 91% orally bioavailable ($t_{1/2}$ = 185 ± 35 min). Compound **3** was well-absorbed after oral administration in rats (at 10 mg/kg, C_{max} = 1.48 ± 0.42 μM), and the $t_{1/2}$ after iv administration at 5 mg/kg was 29 min (F = 42%, n = 4). In rhesus monkeys, **3** was again orally bioavailable (at 5 mg/kg, C_{max} = 6.80 ± 2.38 μM), and the $t_{1/2}$ after iv administration at 2 mg/kg was 49 ± 14 min (F = 60%, n = 2).

Compound **3** has good selectivity versus trypsin (K_i = 1.8 μM), and it does not significantly inhibit t-PA, urokinase, plasmin, factor Xa, plasma kallikrein, activated protein C, chymotrypsin, and elastase (K_i > 10 μM).

In summary, we have circumvented a key deficiency of compound **1**, namely, its modestly short pharmacokinetic half-lives in animals, by substituting a chemically stable 3-alkylaminopyrazinone bioisostere for the 3-sulfonylaminopyridinone of **1**. Compound **3** (L-375,-378), the closest aminopyrazinone analogue of **1**, has comparable selectivity and slightly decreased efficacy but significantly improved pharmacokinetics in rats,

dogs, and monkeys. We have developed an efficient and versatile synthesis of **3**, and this compound has been chosen for further preclinical and clinical development.

Experimental Section

Melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on Varian Unity Plus 400, VXR 400, or VXR 300 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane. All reagents and solvents were of commercial synthetic grade unless otherwise specified. The reverse-phase preparative HPLC was performed using a Waters Delta Prep 3000 and a Waters C_{18} PrepPac column. The analytical HPLC was performed using either a Waters 3.9- × 300-mm C_{18} column with a 20-min linear gradient running from 95:5 to 5:95 H_2O/H_3PO_4 (0.1%):CH_3CN at a flow rate of 2.5 mL/min with UV detection at 215 nm (system A) or a Supelco 4.6- × 150-mm C_{16} column with a 30-min linear gradient running from 95:5 to 0:100 H_2O/H_3PO_4 (0.1% adjusted to pH 6.7 with triethylamine):CH_3CN at a flow rate of 1.0 mL/min with UV detection at 235 and 320 nm (system B).

3-Benzyloxycarbonylamino-6-methyl-2-pyridinone (5). DPPA (35.6 mL, 165 mmol) was added to a stirred solution of 2-hydroxy-6-methylpyridine-3-carboxylic acid (**4**; 22.97 g, 165 mmol) and triethylamine (23.0 mL, 165 mmol) in dry dioxane (300 mL), and the resulting solution was heated to reflux. After 16 h more triethylamine (23.0 mL, 165 mmol) and benzyl alcohol (17.1 mL, 150 mmol) were added, and the solution was refluxed for a further 24 h. The reaction was concentrated in vacuo to remove most of the volatiles. The residue was partitioned between methylene chloride (500 mL) and brine (500 mL) and acidified to pH 1 with 1 M HCl (165 mL). The aqueous layer was extracted with methylene chloride (2 times), and the combined organic layers were washed with sodium hydrogen carbonate solution and brine, dried (Na_2SO_4), and evaporated in vacuo to a brown solid. This was recrystallized from methanol, to give the title compound (22.70 g, 59%) as a tan solid: ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3 H, CH_3), 5.20 (s, 2 H, $PhCH_2$), 6.06 (d, J = 7.6 Hz, 1 H, pyridinone H-5), 7.32−7.43 (m, 5 H, Ph), 7.67 (br s, 1 H, CbzNH), 8.03 (br d, 1 H, pyridinone H-4).

3-Benzyloxycarbonylamino-6-methyl-1-*tert*-butylmethylenecarboxy-2-pyridinone (6). Sodium hydride (5.3 g, 0.22 mol) was added to a stirred slurry of **5** (53.2 g, 0.20 mol) at 0 °C. *tert*-Butyl bromoacetate (45 mL, 0.27 mol) was added to the resulting solution, and a precipitate rapidly formed. The reaction was warmed to room temperature over 1 h. After 2 h the solvent was evaporated in vacuo and the residue was partitioned between 1:1 water/brine (200 mL) and 6:1 THF/methylene chloride (700 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to a solid which was triturated with hexane to give the title compound (72.0 g, 97%) as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9 H, *t*-Bu), 2.25 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 5.19 (s, 2 H, CH_2), 6.09 (d, J = 7.8 Hz, 1 H, pyridinone H-5), 7.30−7.40 (m, 5 H, Ph), 7.75 (br s, 1 H, NH), 7.94 (br d, 1 H, pyridinone H-4).

3-Amino-6-methyl-1-*tert*-butylmethylenecarboxy-2-pyridinone (7). A mixture of **6** (16.18 g, 43.4 mmol) and Pearlman's catalyst (1.6 g) in 4:1 ethanol/water (200 mL) was shaken in a Parr apparatus under H_2 (60 psi) for 2 h. The reaction mixture was filtered through Celite and evaporated in vacuo, azeotroping with ethanol to give the title compound (10.15 g, 98%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H, *t*-Bu), 2.18 (s, 3 H, CH_3), 4.02 (br s, 2 H, NH_2), 4.74 (s, 2 H, CH_2), 5.90 (d, J = 7.3 Hz, 1 H, pyridinone H-5), 6.47 (d, J = 7.3 Hz, 1 H, pyridinone H-4).

3-Benzylsulfonylamino-6-methyl-1-*tert*-butylmethylenecarboxy-2-pyridinone (8). Benzylsulfonyl chloride (4.82 g, 25.3 mmol) was added to a solution of **7** (5.48 g, 23.0 mmol) in pyridine (50 mL) at 0 °C, and as the resulting solution was stirred a thick precipitate formed. After 1 h the reaction mixture was evaporated in vacuo to a thick paste. This was partitioned between methylene chloride and 10% potassium hydrogen sulfate solution. The organic layer was dried (Na_2SO_4) and evaporated in vacuo to an ochre solid. The crude product was heated to reflux as a suspension in EtOAc, then cooled, and collected by filtration to give the desired product (7.47 g, 83%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, *t*-Bu), 2.26 (s, 3 H, CH_3), 4.31 (s, 2 H, $PhCH_2$), 4.75 (s, 2 H, NCH_2), 6.01 (d, J = 7.7 Hz, 1 H, pyridinone H-5), 7.22−7.34 (m, 7 H, remaining H).

3-Benzylsulfonylamino-6-methyl-1-methylenecarboxy-2-pyridinone (9). HCl gas was bubbled through a stirred suspension of **8** (7.47 g, 19.05 mmol) in ethyl acetate (80 mL) at 0 °C until a solution had formed which was saturated with HCl. After 1 h at room temperature a thick suspension had formed. The mixture was degassed with nitrogen and filtered to give the title compound (6.37 g, 99%) as a pale-pink solid: ^{1}H NMR (CD_3OD) δ 2.32 (s, 3 H, CH_3), 4.43 (s, 2 H, $PhCH_2$), 4.89 (s, 2 H, NCH_2), 6.14 (d, J = 7.7 Hz, 1 H, pyridinone H-5), 7.28−7.33 (m, 6 H, remaining H).

2-Amino-5-cyano-6-methylpyridine (11). A mixture of 6-amino-3-bromo-2-methylpyridine (**10**; 20.0 g, 0.107 mol) and copper(I) cyanide (11.0 g, 0.123 mol) in DMF (25 mL) was heated to reflux for 4 h. The DMF was evaporated in vacuo, and the residue was partitioned between ethyl acetate and 10% sodium cyanide solution. The organic layer was washed with 10% sodium cyanide solution and brine, dried (Na_2SO_4), and evaporated in vacuo to a brown solid. This was dissolved in a minimum amount of ethyl acetate, and the product was precipitated by adding hexanes. The mixture was filtered to give the title compound (12.0 g, 85%) as a brown powder: ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3 H, Me), 4.97 (br s, 2 H, NH_2), 6.33 (d, J = 8.6 Hz, 1 H, pyridine H-3), 7.54 (d, J = 8.6 Hz, 1 H, pyridine H-4).

2-*tert*-Butoxycarbonylamino-5-cyano-6-methylpyridine (12). A mixture of **11** (10.0 g, 75.1 mmol), $(BOC)_2O$ (16.39 g, 75.1 mmol), triethylamine (11.5 mL, 82.6 mmol), and DMAP (92 mg, 7.5 mmol) in methylene chloride (200 mL) was stirred for 3 h. More triethylamine (4.22 mL) and $(BOC)_2O$ (1.64 g) were added, and after 16 h the reaction was diluted with ethyl acetate, washed with 1 M AcOH (3 times), dried (Na_2SO_4), and evaporated in vacuo to give a dark-brown solid. The crude product was purified by flash column chromatography (10% ethyl acetate/hexanes) to give the title compound (14.68 g, 84%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H, *t*-Bu), 2.62 (s, 3 H, CH_3), 7.46 (br s, 1 H, NH), 7.80 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H).

2-*tert*-Butoxycarbonylamino-5-methylamino-6-methylpyridine (13). A mixture of **12** (7.93 g, 34.0 mmol) and 10% Pd/C (0.79 g) in glacial acetic acid (200 mL) was shaken on a Parr apparatus at 60 psi for 60 h. The reaction was filtered through Celite, washing with ethanol, and was evaporated in vacuo. The residue was dissolved in water (200 mL), and the solution was washed with methylene chloride (two times), then was basified with sodium carbonate, and extracted with ethyl acetate (three times). The combined ethyl acetate layers were dried (Na_2SO_4) and evaporated in vacuo to give the title compound (5.53 g, 69%), as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H, *t*-Bu), 2.43 (s, 3 H, CH_3), 3.81 (s, 2 H, CH_2), 7.23 (br s, 1 H, NH), 7.57 (d, J = 8.3 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 1 H).

3-Benzylsulfonylamino-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (1). DCC (1.86 g, 9.00 mmol) was added to a stirred solution of **9** (3.03 g, 9.00 mmol) and **13** (2.14 g, 9.00 mmol) in methylene chloride (20 mL) at 0 °C. After 3 h the reaction was filtered through Celite and evaporated in vacuo to a pale-yellow foam. Ethyl acetate (80 mL) was added resulting in a thick precipitate. HCl gas was blown onto the stirred mixture at 0 °C causing the bulk of the material to dissolve. Undissolved material was broken up with a spatula, and after bubbling HCl through the mixture for 15 min dissolution was complete. After 1 h at room temperature some precipitate formed. The mixture was degassed with nitrogen and was evaporated in vacuo to a solid. Water (200 mL) was added, and the undissolved material was removed by filtration

through a frit. The filtrate was basified with saturated sodium hydrogen carbonate solution to give a thick precipitate which was collected by filtration, washing with water, methanol, and ether, and was dried at 50 °C, 0.5 mmHg, for 16 h to give the free base of the title compound (2.97 g, 72%) as a solid: ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 4.13 (d, J = 5.3 Hz, 2 H, NHCH_2), 4.50 (s, 2 H, CH_2), 4.72 (s, 2 H, CH_2), 5.73 (s, 2 H, NH_2), 6.08 (d, J = 8.1 Hz, 1 H), 6.22 (d, J = 8.3 Hz, 1 H), 7.11 (d, J = 7.3 Hz, 1 H), 7.22 (d, J = 8.3 Hz, 1 H), 7.31−7.35 (m, 5 H, Ph), 8.47 (t, J = 5.3 Hz, 1 H, N*H*CH$_2$), 8.58 (s, 1 H, SO_2NH).

3-Benzylsulfonylamino-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone Hydrochloride (1). The free base of **1** (2.97 g, 6.52 mmol) was dissolved in 0.5 M HCl (15 mL), and the solution was azeotroped dry with ethanol (3 × 100 mL). The resulting syrup crystallized from ethanol (50 mL), and after heating to reflux, cooling, and collecting the solids by filtration, the title compound (2.81 g, 82%) was obtained as a crystalline hydrated ethanolate. Anal. ($C_{22}H_{25}N_5O_4S$·1.0HCl·0.5 EtOH·0.6H_2O) C, H, N.

3-Benzyloxycarbonylamino-6-methyl-1-methylenecarboxy-2-pyridinone (15). The title compound was prepared from **6** by the procedure used to make **9** from **8**, as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H, CH_3), 4.73 (s, 2 H, CH_2), 5.11 (s, 2 H, CH_2), 6.08 (d, J = 7.7 Hz, 1 H, pyridinone H-5), 7.24−7.30 (m, 5 H, Ph), 7.72 (s, 1 H, NH), 7.88 (br d, pyridinone H-4).

3-Benzyloxycarbonylamino-6-methyl-1-(2-*tert*-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (16). EDC hydrochloride (2.46 g, 12.83 mmol) was added to a stirred mixture of **15** (3.12 g, 9.87 mmol), **13** (2.34 g, 9.87 mmol), HOBT (1.73 g, 12.83 mmol), and triethylamine (3.16 mL, 22.7 mmol) in dry DMF (20 mL). After 64 h the volatiles were evaporated in vacuo. The residue was partitioned between methylene chloride and water, and the organic layer was dried (Na_2SO_4) and evaporated in vacuo to a solid which was crystallized from refluxing ethyl acetate to give the title compound (4.43 g, 84%) as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, t-Bu), 2.35 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 4.33 (d, J = 5.7 Hz, 2 H, NHCH_2), 4.73 (s, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 6.16 (d, J = 7.5 Hz, 1 H, pyridinone H-5), 6.98 (br t, 1 H, CH_2N*H*), 7.13 (s, 1 H, NH), 7.32−7.41 (m, 6 H), 7.65 (d, J = 8.2 Hz, 1 H), 7.67 (s, 1 H, NH), 7.98 (br d, 1 H).

3-Amino-6-methyl-1-(2-*tert*-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (17). The title compound was prepared from **16** by the procedure used to make **7** from **6**, as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, t-Bu), 2.35 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 4.02 (br s, 2 H, NH_2), 4.33 (d, J = 5.7 Hz, 2 H, CH_2NH), 4.76 (s, 2 H, CH_2CO), 6.00 (d, J = 7.3 Hz, 1 H, pyridinone H-5), 6.52 (d, J = 7.3 Hz, 1 H, pyridinone H-4), 7.12 (s, 1 H, BOCNH), 7.22 (br t, 1 H, CH_2N*H*), 7.38 (d, J = 8.4 Hz, 1 H, pyridine H-3), 7.64 (d, J = 8.4 Hz, 1 H, pyridine H-4).

3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (2). A mixture of **17** (60 mg, 0.15 mmol), sodium triacetoxyborohydride (48 mg, 0.225 mmol), and phenylacetaldehyde (20 μL, 0.17 mmol) in 0.24 M acetic acid in 1,2-dichloroethane (0.75 mL) was stirred for 16 h. The mixture was partitioned between sodium hydrogen carbonate solution and ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo to a gum. The crude product was purified by flash column chromatography on silica (ethyl acetate/hexanes gradient, 70−100% ethyl acetate) to give 3-(2-phenethylamino)-6-methyl-1-(2-*tert*-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone which was carried through the next step: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H, BOC), 2.32 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.92 (t, J = 7.2 Hz, 2 H, PhCH_2), 3.30 (br q, J = 6.8 Hz, 2 H, PhCH_2CH_2NH), 4.30 (d, J = 5.9 Hz, 2 H, CONHCH_2), 4.72 (s, 2 H, CH_2CO), 4.77 (br t, J = 6.0 Hz, 1 H, CON*H*CH_2), 6.04 (d, J = 7.6 Hz, 1 H, pyridinone H-5), 6.19 (d, J = 7.6 Hz, 1 H, pyridinone H-4), 7.21−7.35 (m, 8 H), 7.62 (d, J = 8.3 Hz, 1 H, pyridine H-4).

The product from the previous reaction was dissolved in ethyl acetate (5 mL), and HCl gas was bubbled through the solution for 15 min at 0 °C. After an additional 1 h at room temperature, the solvent was evaporated in vacuo and the crude product was purified by preparative HPLC (C_{18}, 0.1% TFA, H_2O/CH_3CN gradient), to give the title compound as an air-sensitive TFA salt: ^{1}H NMR (CD_3OD) δ 2.34 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 2.97 (t, J = 7.7 Hz, 2 H, PhCH_2), 3.48 (t, J = 7.3 Hz, 2 H, PhCH_2CH_2NH), 4.31 (d, J = 5.5 Hz, 2 H, CH_2-NH), 4.83 (obscured s, 2 H, CH_2), 6.28 (d, J = 7.5 Hz, 1 H, pyridinone H-5), 6.81 (d, J = 9.0 Hz, 1 H, pyridinone H-4), 7.15−7.32 (m, 6 H), 7.86 (d, J = 9.0 Hz, 1 H, pyridine H-4), 8.77 (br t, 1 H, CH_2N*H*); HPLC retention time (system A) 8.18 min (94%); HRMS (FAB) $C_{23}H_{28}N_5O_2$ (M + 1) calcd 406.2248, found 406.2247.

α-Allylaminopropionitrile Hydrochloride (18). Concentrated HCl (80 mL, 0.96 mol) was added to a stirred solution of allylamine (144 mL, 1.92 mol) in water (400 mL) and ethanol (240 mL) at 0 °C. Potassium cyanide (60 g, 0.92 mol) and acetaldehyde (44.8 mL, 0.80 mol) were then added, and the mixture was heated to reflux. After 15 h the volatiles were removed in vacuo, and the residual solution was saturated with NaCl and was extracted with methylene chloride (three times). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to an oil which was dissolved in 2 M HCl (400 mL). The solution was evaporated in vacuo, azeotroping with 1:1 toluene/methanol, to give a solid which was heated to reflux in ethyl acetate (500 mL), cooled, filtered, and dried to give the title compound (97.7 g, 83%) as the HCl salt: ^{1}H NMR (CD_3OD) δ 1.72 (d, J = 7.0 Hz, 3 H, CH_3), 3.78−3.90 (m, 2 H, CH_2), 4.63 (q, J = 7.0 Hz, 1 H, α-CH), 5.56−5.66 (m, 2 H, CHCH_2), 5.91−6.02 (m, 1 H, C*H*CH_2).

1-Allyl-3,5-dichloro-6-methylpyrazinone (19). A stirred mixture of oxalyl chloride (105 mL, 1.20 mol) and **18** (44.0 g, 0.30 mol) in *o*-dichlorobenzene (350 mL) was heated to 100 °C for 15 h. The solvent was evaporated in vacuo, and the residual black oil was purified by flash column chromatography on silica (eluting with 30% ethyl acetate/hexanes) to give the title compound (35.5 g, 54%) as a tan crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3 H, CH_3), 4.75 (m, 2 H, NCH_2), 5.18 (m, 1 H, CHCH_aH$_b$), 5.33 (m, 1 H, CHCH_aH$_b$), 5.85−5.92 (m, 1 H, C*H*CH$_a$H$_b$).

3,5-Dichloro-6-methyl-1-methylenecarboxypyrazinone (20). Ruthenium trichloride hydrate (114 mg, 0.547 mmol) was added to a stirred mixture of **19** (5.45 g, 24.88 mmol) and sodium periodate (21.82 g, 0.102 mol) in water (75 mL), acetonitrile (50 mL), and carbon tetrachloride (50 mL). After 3 h the reaction mixture was extracted with methylene chloride (four times), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to a syrup. The ^{1}H NMR ($CDCl_3$) of this material showed it to be a 1:1 mixture of the acid and the aldehyde. The crude mixture was dissolved in acetone (50 mL), and Jones reagent (2.7 M) was added until the reaction remained orange. The reaction was then extracted into ethyl acetate, washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the title compound (3.12 g, 53%) as a tan solid: ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3 H, CH_3), 4.86 (s, 2 H, CH_2).

3,5-Dichloro-6-methyl-1-(2-*tert*-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)pyrazinone (21). EDC·HCl (249 mg, 1.3 mmol) was added to a stirred mixture of **20** (237 mg, 1.0 mmol), HOBT·H_2O (176 mg, 1.3 mmol), **13** (237 mg, 1.0 mmol), and *N*-methylmorpholine (0.25 mL, 2.3 mmol) in DMF (4 mL), and the mixture was stirred for 2 h. The reaction was diluted with ethyl acetate, washed with 10% citric acid solution, water, sodium hydrogen carbonate solution, and brine, dried (Na_2SO_4), and evaporated in vacuo to give the title compound (413 mg, 91%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, *t*-Bu), 2.39 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 4.37 (d, J = 5.5 Hz, 2 H, NHCH_2), 4.71 (s, 2 H, CH_2CO), 6.76 (br t, 1 H, N*H*CH_2), 7.14

(s, 1 H, NHBOC), 7.44 (d, J = 8.3 Hz, 1 H, pyridine H-3), 7.66 (d, J = 8.3 Hz, 1 H, pyridine H-3).

3-(2-Phenethylamino)-5-chloro-6-methyl-1-(2-*tert*-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)pyrazinone (22). Phenethylamine (0.10 mL, 0.80 mmol) was added to a stirred solution of **21** (182 mg, 0.40 mmol) in dioxane (0.8 mL), and the resulting solution was warmed to 60 °C under argon. After 16 h the reaction mixture was partitioned between water and chloroform. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by flash column chromatography on silica (ethyl acetate/hexanes gradient, 40−75% ethyl acetate) to give the title compound (83 mg, 38%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, *t*-Bu), 2.36 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 2.92 (t, J = 7.1 Hz, 2 H, PhCH_2), 3.66 (q, J = 7.1 Hz, 2 H, PhCH_2CH_2), 4.35 (d, J = 5.4 Hz, 2 H, CONHCH_2), 4.63 (s, 2 H, CH_2CO), 6.05 (br t, 1 H, NH), 6.54 (br t, 1 H, NH), 7.14 (s, 1 H, NHBOC), 7.21−7.31 (m, 5 H, Ph), 7.43 (d, J = 8.3 Hz, 1 H, pyridine H-3), 7.69 (d, J = 8.3 Hz, 1 H, pyridine H-4).

3-(2-Phenethylamino)-5-chloro-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyrazinone (23). HCl gas was bubbled through a solution of **22** (83 mg, 0.153 mmol) in ethyl acetate (10 mL) at 0 °C for 10 min. The reaction was warmed to room temperature, and after 1 h the solution was degassed with argon to give a white precipitate which was collected by filtration and dried to give the title compound (64 mg, 81%) as a solid: ^{1}H NMR (CD_3-OD) δ 2.26 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3), 2.91 (t, J = 7.0 Hz, 2 H, PhCH_2), 3.60 (t, J = 7.0 Hz, 2 H, PhCH_2CH_2), 4.29 (s, 2 H, CONHCH_2), 4.74 (s, 2 H, CH_2CO), 6.82 (d, J = 9.0 Hz, 1 H, pyridine H-3), 7.18−7.29 (m, 5 H, Ph), 7.83 (d, J = 9.0 Hz, 1 H, pyridine H-4); HPLC retention times 9.05 min (98%, system A) and 18.75 min (95% and 96% at 235 and 320 nm, respectively, system B); HRMS (FAB) $C_{22}H_{26}N_6O_2Cl$ calcd 441.1806 (M + 1), found 441.1807.

3-(2-Phenethylamino)-5-chloro-6-methyl-1-methylene carboxypyrazinone (24). Phenethylamine (39.7 mL, 0.316 mol) was added to a stirred solution of **20** (15.0 g, 63.28 mmol) in dioxane (200 mL), and the resulting solution was warmed to 65 °C under argon. After 16 h the reaction mixture was partitioned between methylene chloride and 1 N $KHSO_4$ solution. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to a thick brown oil which was purified by flash column chromatography (eluting with a methanol/chloroform/2% acetic acid gradient, 2−5% methanol) to give after azeotroping dry with toluene the title compound (13.9 g, 68%) as a tan solid: ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3 H, CH_3), 2.84 (t, J = 7.0 Hz, 2 H, PhCH_2), 3.45 (q, J = 7.0 Hz, 2 H, CH_2NH), 4.70 (s, 2 H, CH_2CO_2), 7.18−7.31 (m, 5 H, Ph), 7.46 (br t, 1 H, NH).

Benzyl *N*-(1-Cyanoethyl)glycine Hydrochloride (25). TMSCN (18.8 mL, 0.141 mol) was added cautiously (the reaction is exothermic) to a stirred solution of benzyl glycine free base (23.3 g, 0.141 mol, from the HCl salt by partition between EtOAc and $NaHCO_3$ solution) and acetaldehyde (7.9 mL, 0.141 mol) in methylene chloride (50 mL) at 0 °C. After 5 min more acetaldehyde (3.95 mL) was added, and the reaction was warmed to room temperature. After 4 h the volatiles were removed in vacuo, and the residue was taken up in EtOAc, washed with brine, dried (Na_2SO_4), and evaporated in vacuo to an oil. The oil was redissolved in EtOAc (300 mL), and 9.9 M HCl in EtOH (15.25 mL, 151 mmol) was added at 0 °C to give a heavy crystalline precipitate which was isolated by filtration, washing with EtOAc and ether, and dried to give the title compound (29.51 g, 77%): ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 7.1 Hz, 3 H, CH_3), 3.54 (d, J = 17.3 Hz, 1 H, CH_aH_b), 3.64 (d, J = 17.3 Hz, 1 H, CH_aH_b), 3.74 (q, J = 7.0 Hz, α-CH), 5.18 (s, 2 H, CH_2O), 7.36 (s, 5 H, Ph).

1-Benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone (26). A stirred mixture of oxalyl chloride (40.4 mL, 0.463 mol) and **25** (29.51 g, 0.116 mol) in *o*-dichlorobenzene (110 mL) was heated over 15 min to 100 °C. After 15 h, the excess reagent was evaporated in vacuo, and the dark-brown solution was purified by flash column chromatography on silica (eluting with hexanes to wash out the dichlorobenzene, followed by 30% ethyl acetate/hexanes) to give a tan solid. The crude product was heated to reflux as a suspension in 2:5 ethyl actetate/hexanes (140 mL), then cooled (finally to 0 °C), and filtered to give the title compound (21.38 g, 56%) as a pale-yellow/green crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3 H, CH_3), 4.88 (s, 2 H, CH_2), 5.24 (s, 2 H, CH_2), 7.38 (m, 5 H, Ph).

3-(2-Phenethylamino)-5-chloro-6-methyl-1-benzyloxycarbonylmethylpyrazinone (27). Phenethylamine (15.07 mL, 0.12 mol) was added to a stirred mixture of **26** (13.09 g, 40.0 mmol) in EtOAc (80 mL), and the resulting mixture was heated to reflux under argon. After 2 h the reaction mixture was cooled and partitioned between chloroform (500 mL) and 5% citric acid solution (200 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the title compound as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H, CH_3), 2.93 (t, J = 7.1 Hz, 2 H, PhCH_2-CH_2), 3.67 (q, J = 7.1 Hz, 2 H, CH_2NH), 4.79 (s, 2 H, CH_2-CO_2), 5.21 (s, 2 H, PhCH_2O), 6.10 (br t, 1 H, NH), 7.20−7.39 (m, 5 H, Ph).

3-(2-Phenethylamino)-5-chloro-6-methyl-1-methylenecarboxypyrazinone (24). $LiOH·H_2O$ (3.36 g, 80 mmol) was added to a stirred suspension of **27** (the total product from the previous reaction) in 3:3:1 THF/MeOH/H_2O (280 mL). The solids went into solution over 1 h. After 15 h, the reaction was diluted with water (500 mL) and was washed with EtOAc. The aqueous layer was acidified with 20% $KHSO_4$ solution (20 mL) to give a thick precipitate; 1:1 EtOAc/THF (400 mL) was added to dissolve the solids, and the mixture was saturated with NaCl and partitioned. The organic layer was dried (Na_2-SO_4) and evaporated in vacuo to a solid. The crude product was heated to reflux as a suspension in 1:1 EtOAc/hexanes, then cooled, and filtered give the title compound as a crystalline solid (11.66 g, 91% over two steps): ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3 H, CH_3), 2.84 (t, J = 7.0 Hz, 2 H, PhCH_2), 3.45 (q, J = 7.0 Hz, 2 H, CH_2NH), 4.70 (s, 2 H, CH_2CO_2), 7.18−7.31 (m, 5 H, Ph), 7.46 (br s, 1 H, NH).

3-(2-Phenethylamino)-6-methyl-1-methylenecarboxypyrazinone Trifluoroacetate Salt (28). Raney nickel alloy (1.0 g) was added to a stirred solution of **24** (158 mg, 0.49 mmol) in 1:1 methanol/1 M NaOH (24 mL). After 2 h the reaction mixture was filtered through Celite, washing with 1:1 methanol/water, and the filtrate was evaporated in vacuo to a white solid. This crude product, which was contaminated by inorganic salts, was purified by preparative HPLC (C_{18}, water/acetonitrile/0.1% TFA gradient) to give the title compound (185 mg, 94%) as a foam: ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3 H, CH_3), 2.87 (t, J = 7.6 Hz, 2 H, PhCH_2), 3.53 (br s, 2 H, CH_2NH), 4.68 (s, 2 H, CH_2CO_2), 6.68 (s, 1 H, pyrazinone H-5), 7.20−7.31 (m, 5 H, Ph), 8.16 (br s, 1 H, NH).

3-(2-Phenethylamino)-6-methyl-1-methylenecarboxypyrazinone (28). Potassium hydroxide (86% pellets, 6.10 g, 93.5 mmol) was added to a stirred suspension of compound **24** (11.66 g, 36.24 mmol) in water (400 mL) at 0 °C. The mixture was warmed to room temperature, and after the resulting solution was degassed with nitrogen, 10% Pd/C (3.48 g) was added and the mixture was stirred under a hydrogen-filled balloon. After 16 h, HPLC (C_{18}, water/0.1% H_3PO_4/acetonitrile) showed that 20% of the starting material remained (monitoring at 215 nm). The mixture was degassed with nitrogen, more 10% Pd/C (3.0 g) was added, and the mixture was stirred under a hydrogen-filled balloon for a further 7 h. The mixture was filtered through Celite, washing with water (200 mL), and the filtrate was acidified by the addition of a solution of $KHSO_4$ (7.8 g, 57.25 mmol) in water (35 mL) to give a heavy precipitate. The precipitate was collected by filtration, washing with water (200 mL), and was dried for 16 h at 50 °C, 0.5 mmHg, to give the title compound as a crystalline solid (9.14 g, 88%): ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3 H, CH_3), 2.87 (t, J = 7.6 Hz, 2 H, PhCH_2), 3.53 (br s, 2 H, CH_2NH), 4.68 (s, 2 H, CH_2CO_2), 6.68 (s, 1 H, pyrazinone H-5), 7.20−7.31 (m, 5 H, Ph), 8.16 (br s, 1 H, NH).

2-Amino-5-methylamino-6-methylpyridine Dihydro-

chloride (14). A mixture of **11** (4.0 g, 30.0 mmol) and 10% Pd/C (3.08 g) in ethanol (80 mL), methanol (30 mL), concentrated HCl (6 mL), and water (10 mL) was shaken on a Parr apparatus at 60 psi for 25 h. The reaction was filtered through Celite, rinsing with 1:1 ethanol/methanol, and was evaporated in vacuo to a solid, which was triturated with 5:1 ethyl acetate/ethanol to give the title compound (5.95 g, 94%): ^{1}H NMR (CD_3OD) δ 2.58 (s, 3 H), 4.12 (s, 2 H), 6.92 (d, J = 9.2 Hz, 1 H), 7.93 (d, J = 9.2 Hz, 1 H).

3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)pyrazinone Dihydrochloride (3). *N*-Methylmorpholine (15.08 mL, 0.137 mol) was added to a stirred mixture of **28** (8.33 g, 29.0 mmol), **14** (6.09 g, 29.0 mmol), HOBT·H_2O (5.09 g, 37.7 mmol), and EDC·HCl (7.23 g, 37.7 mmol) in dry DMF (100 mL) at 0 °C, and after 5 min the reaction mixture was warmed to room temperature. After 4 h, the volume of the reaction was reduced by one-half by evaporation in vacuo, and the residual slurry was partitioned between methylene chloride (100 mL) and 0.2 M HCl solution (500 mL). The aqueous layer was adjusted to pH 7−8 with saturated sodium hydrogen carbonate solution, and the voluminous precipitate was collected by filtration, washing with water and ethanol, and dried to give the title compound (11.0 g) as the free base. This was crushed to a fine powder and stirred as a suspension in ethanol (20 mL). Ethanolic HCl (9.9 M, 5.47 mL, 54.2 mmol) was added rapidly to give a solution. After 30 min the mixture was cooled to 0 °C, and after a further 30 min the bis-HCl salt was collected by filtration, washing with ethanol (100 mL). The product was resuspended in ethanol (100 mL), heated to reflux, cooled, collected by filtration washing with ethanol (50 mL), and dried for 16 h at 50 °C, 0.5 mmHg, to give the title compound (12.79 g, 88%): mp >200 °C;^{1}H NMR (DMSO-d_6) δ 2.10 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.91 (t, J = 7.6 Hz, 2 H, PhCH_2), 3.63 (br q, 2 H, PhCH_2CH_2), 4.16 (d, J = 5.5 Hz, 2 H, CONHCH_2), 4.62 (s, 2 H, CH_2CO), 6.68 (s, 1 H, pyrazinone H-5), 6.82 (d, J = 9.0 Hz, 1 H, pyridine H-3), 7.21−7.31 (m, 5 H, Ph), 7.76 (d, J = 9.0 Hz, 1 H, pyridine H-4), 7.77 (s, 1 H, NH), 8.81 (br t, 1 H, NH); HRMS (FAB) calcd $C_{22}H_{27}N_6O_2$ (M + 1) 407.2195, found 407.2189. Anal. ($C_{22}H_{26}N_6O_2$·2HCl·1.1H_2O) C, H, N.

By the same procedures, the following compounds were prepared.

3-(2-Phenethylamino)-6-methyl-1-(2-amino-4,6-dimethyl-5-methylcarboxamidomethylpyridinyl)pyrazinone (29). The title compound was prepared as the bis-HCl salt from **28** and 2-amino-5-aminomethyl-4,6-dimethylpyridine dihydrochloride:[10] mp >200 °C; ^{1}H NMR (CD_3OD) δ 2.19 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 3.01 (t, J = 7.5 Hz, 2 H, PhCH_2), 3.68 (t, J = 7.5 Hz, 2 H, PhCH_2CH_2), 4.38 (s, 2 H, CONHCH_2), 4.73 (s, 2 H, CH_2CO), 6.55 (s, 1 H, pyrazinone H-5), 6.71 (s, 1 H, pyridine H-3), 7.23−7.33 (m, 5 H, Ph); HPLC retention times 5.01 min (100%, system A) and 15.51 min (99% and 97% at 235 and 320 nm, respectively, system B); HRMS (FAB) $C_{23}H_{29}N_6O_2$ calcd 421.2352 (M + 1), found 421.2349.

3-(2-Phenethylamino)-6-methyl-1-(2-amino-5-methylcarboxamidomethylpyridinyl)pyrazinone (30). The title compound was prepared as the bis-HCl salt from **28** and 2-amino-5-aminomethylpyridine dihydrochloride:[10] mp >220 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3 H, CH_3), 2.92 (t, J = 7.6 Hz, 2 H, PhCH_2), 3.65 (br q, 2 H, PhCH_2CH_2), 4.19 (d, J = 5.7 Hz, 2 H, CONHCH_2), 4.65 (s, 2 H, CH_2CO), 6.69 (s, 1 H, pyrazinone H-5), 7.00 (d, J = 9.9 Hz, 1 H, pyridine H-3), 7.21−7.30 (m, 5 H, Ph), 7.82 (obscured d, 1 H, pyridine H-4), 7.83 (s, 1 H, pyridine H-6), 8.10 (br s, 2 H, NH_2), 8.86 (br t, 1 H, NH); HRMS (FAB) $C_{21}H_{25}N_6O_2$ calcd 393.2033 (M + 1), found 393.2024. Anal. ($C_{21}H_{24}N_6O_2$·2HCl·0.5H_2O) C, H, N.

(*R*)-3-(1-Phenyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone (31). The title compound was prepared as an amorphous bis-HCl salt starting from **26** and (*R*)-1-phenyl-2-propylamine: ^{1}H NMR (CD_3OD) δ 1.36 (d, J = 6.4 Hz, 3 H, CHCH_3), 2.15 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 3.00 (m, 2 H, PhCH_2), 4.11 (m, 1 H, CHCH$_3$), 4.33 (d, J = 5.5 Hz, 2 H, CONHCH_2), 4.71 (d, J = 16.5 Hz, 1 H, CH_aH$_b$CO), 4.76 (d, J = 16.5 Hz, 1 H, CH$_a$$H_b$CO), 6.45 (s, 1 H, pyrazinone H-5), 6.85 (d, J = 9.2 Hz, 1 H, pyridine H-3), 7.18−7.30 (m, 5 H, Ph), 7.86 (d, J = 9.2 Hz, 1 H, pyridine H-4), 8.87 (br t, 1 H, CONH); HRMS (FAB) calcd $C_{23}H_{29}N_6O_2$ (M + 1) 421.2352, found 421.2351. Anal. ($C_{28}H_{28}N_6O_2$·2HCl·1.2H_2O·0.3EtOAc) C, H, N.

(*S*)-3-(1-Phenyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone (32). The title compound was prepared as an amorphous bis-HCl salt starting from **26** and (*S*)-1-phenyl-2-propylamine: HPLC retention times 5.13 min (99%, system A) and 16.26 min (96% and 96% at 235 and 320 nm, respectively, system B); HRMS (FAB) calcd $C_{23}H_{29}N_6O_2$ (M + 1) 421.2352, found 421.2344.

3-(1-Phenyl-2-methyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone (33). The title compound was prepared as an amorphous bis-HCl salt from **26** and 1-phenyl-2-methyl-2-propylamine: ^{1}H NMR (CD_3OD) δ 1.53 (s, 6 H, C(CH_3)$_2$), 2.22 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 3.13 (s, 2 H, PhCH_2), 4.34 (d, J = 5.5 Hz, 2H, CONHCH_2), 4.78 (s, 2 H, CH_2CO), 6.62 (s, 1 H, pyrazinone H-5), 6.84 (d, J = 9.2 Hz, 1 H, pyridine H-3), 7.24−7.34 (m, 5 H, Ph), 7.86 (d, J = 9.2 Hz, 1 H, pyridine H-4), 8.89 (br t, 1 H, CONH); HPLC retention times 7.81 min (99%, system A) and 18.91 min (93% and 92% at 235 and 320 nm, respectively, system B); HRMS (FAB) calcd $C_{24}H_{31}N_6O_2$ (M + 1) 435.2506, found 435.2501.

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Supporting Information Available: Procedures for the K_i determinations, the APTT assay, the rat thrombosis model, the conscious dog and monkey bioavailability studies, and the X-ray crystallography (4 pages). Ordering information is given on any current masthead page.

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