Targeting Delavirdine/Atevirdine Resistant HIV-1: Identification of (Alkylamino)piperidine-Containing Bis(heteroaryl)piperazines as Broad Spectrum HIV-1 Reverse Transcriptase Inhibitors

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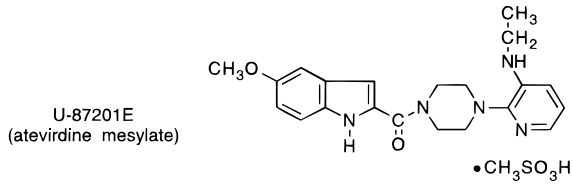
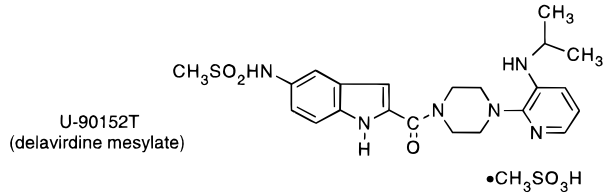
A novel class of bis(heteroaryl)piperazine (BHAP) analogs which possesses the ability to inhibit NNRTI (non-nucleoside reverse transcriptase inhibitor) resistant recombinant HIV-1 reverse transcriptase (RT) and NNRTI resistant variants of HIV-1 has been identified via targeted screening. Further investigation of the structure−activity relationships of close congeners of these novel (alkylamino)piperidine BHAPs (AAP-BHAPs) led to the synthesis of several compounds possessing the desired phenotype (e.g., activity against recombinant RTs carrying the Y181C and P236L substitutions). Further structural modifications were required to inhibit metabolism and modulate solubility in order to obtain compounds with the desired biological profile as well as appropriate pharmaceutical properties. The AAP-BHAPs with the most suitable characteristics were compounds **7**, **15**, and **36**.

Introduction

Nucleoside HIV-1 reverse transcriptase inhibitors (RTIs) such as AZT, ddI, and 3TC[1] benefit HIV-1-infected patients and have been approved by the FDA for the treatment of acquired immune deficiency syndrome (AIDS). A major limitation of such treatment is the emergence of resistant virus with specific mutations in the RT gene.[2,5] A major thrust of more recent research targets non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) because theory held that a viable treatment of AIDs would involve coadministration of drugs which inhibit RT via disparate mechanisms. Our efforts along these lines led to the identification of two clinical candidates of the bis(heteroaryl)piperazine (BHAP) class of NNRTIs, atevirdine mesylate (**1**, U-87201E)[6] and delavirdine mesylate (**2**, U-90152T).[7] Thus far, clinical trials of several NNRTIs as monotherapies have also demonstrated rapid emergence of resistant virus.[8−12]

Early experiments indicated that several structurally diverse NNRTIs interact at a common site on RT, giving rise to the thought that resistance against one type of NNRTI would engender cross-resistance to all others. This was supported by the observation that HIV-1 variants generated via serial passage in the presence of one NNRTI exhibited substantial cross-resistance to all other NNRTIs. In addition, the construction of recombinant RTs, which contained the mutations at amino acids 103, 181, or 188 responsible for resistance, showed that cross-resistance was engendered to the other NNRTIs.[13] More recently, it was demonstrated that in some cases HIV-1 variants resistant to one





NNRTI are not resistant to all other NNRTIs but, in fact, can exhibit increased sensitivity.[14] For example, serial HIV-1 passage *in vitro* in the presence of increasing concentrations of the BHAP NNRTIs U-87201E or U-90152S[15] causes a proline to leucine substitution at amino acid 236 of RT (P236L). Mutations which arise upon serial passage in the presence of NNRTIs in cell culture are usually, but not always, found in human patients receiving that particular NNRTI.[16] The P236L substitution conferred resistance against atevirdine and delavirdine as expected but caused sensitization to other NNRTIs (e.g., TIBO R82913 and L-697,661). This intriguing property of the BHAPs indicates that HIV-1 resistant to one NNRTI will not necessarily be cross-resistant to other NNRTIs and, furthermore, emphasizes the need to investigate combinations (sequentially and simultaneously) of various RTIs in HIV-1-infected patients.[17] In particular, could sequential treatment with delavirdine followed by another drug with enhanced activity against delavirdine resistant virus result in effective anti-HIV therapy? To answer this question, we undertook a project to determine whether a BHAP of a different structural type might be a

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Table 1. *In Vitro* Inhibition of Recombinant HIV-1_{IIIB} RT Mutants

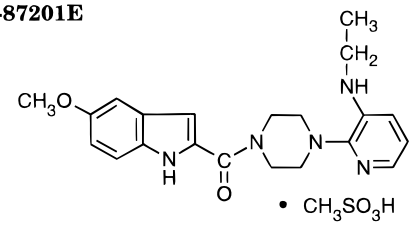
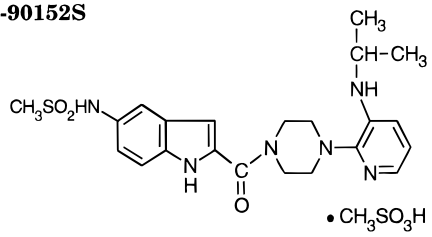
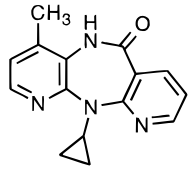
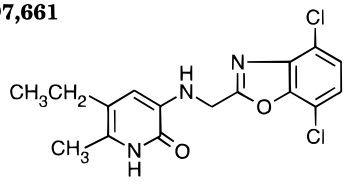
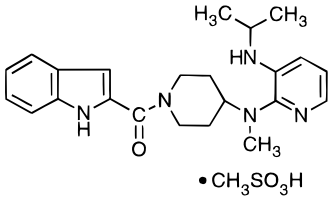
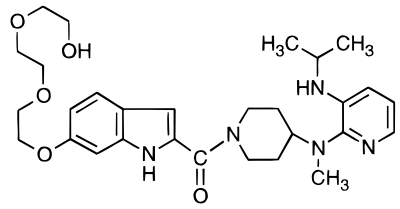
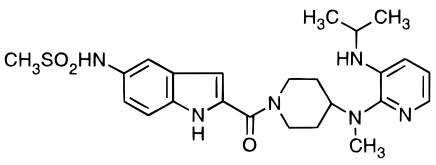
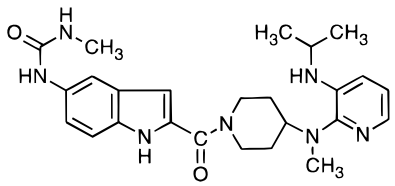
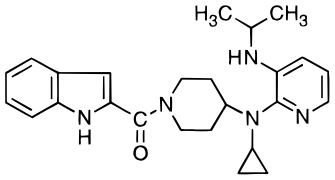
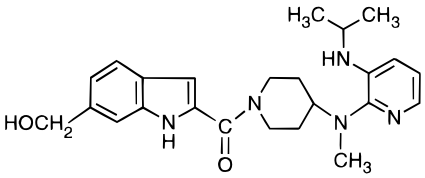
Compound	IC_{50} (μM)[a]			mp (°C)	Formula[b]
	WT	P236L	Y181C		
U-87201E 	2.3	>60[c]	>60[c]	215-216	$C_{21}H_{25}N_5O_2$ •CH_3SO_3H
U-90152S 	0.26	18.0	8.32	220-222	$C_{22}H_{28}N_6O_3S$ •CH_3SO_3H
Nevirapine 	3.1	0.32	>60[c]	--	--
L-697,661 	0.80	0.11	>60[c]	--	--
1 	0.23	0.74	0.80	136-138	$C_{23}H_{29}N_5O$ •CH_3SO_3H
2 	0.3	0.41	0.77	217-220 **dec**	$C_{29}H_{41}N_5O_5$[d]
3 	0.50	1.5	1.1	217-220 **dec**	$C_{24}H_{32}N_6O_3S_1$

Table 1. (Continued)

	Compound	IC_{50} (μM)[a]			mp (°C)	Formula[b]
		WT	P236L	Y181C		
4		0.18	NT	1.6	--	$C_{25}H_{33}N_7O_2 \cdot 0.4H_2O$
5		0.70	0.59	2.31	--	$C_{25}H_{31}N_5O_1$[d]
6		0.17	0.37	0.49	79-81	$C_{24}H_{31}N_5O_2$[d]

[a] RNA-dependent DNA polymerase activity of mutant RTs was assayed as described in the Experimental Section. IC_{50} values were determined by nonlinear least-squares fit of data from duplicate points at six drug concentrations. [b] Analyses for C, H, and N are within ±0.4% of theoretical values unless otherwise indicated. [c] Highest concentration tested. [d] Satisfactory HRMS data were obtained.

suitable partner for use in just such a combination with delavirdine.

Biological Results and Discussion

Since we had already synthesized a diverse set of analogs related to atevirdine and delavirdine, we screened a subset of these analogs versus a panel of recombinant RTs to identify compounds that retained activity against the P236L RT. Although none of the screened compounds possessed the sensitization phenotype, we were successful in identifying a subclass of analogs, the (methylamino)piperidines, which were more active than either atevirdine or delavirdine against the P236L mutant enzyme (Table 1). We were pleased to find that these compounds were also more active against other recombinant RTs containing known NNRTI resistance mutations, such as the mutant RT enzyme containing a tyrosine to cysteine substitution at amino acid 181 (Y181C), a substitution known to confer broad cross-resistance to most NNRTIs currently in development.[16] Confirmation of these results in cell culture assays employed resistant virus generated by serial passage in the presence of either delavirdine or Merck's L-697,661. Compound **3** demonstrated enhanced antiviral activity against both resistant viruses as compared to delavirdine (Table 2).

Since the (alkylamino)piperidines had previously demonstrated excellent activity against the WT virus, we had already evaluated the pharmacokinetic parameters of several such compounds as part of our original structure−activity relationship (SAR) program. However, neither **3** nor **4** possessed the desired pharmacokinetic profile when administered orally to rats. Both compounds exhibited low oral bioavailabilities primarily due to high clearance rates (Table 9). Therefore we began a program to expand upon the scope of our initial SAR effort by focusing on the synthesis of a variety of (alkylamino)piperidines. We sought to design compounds with increased inhibitory activity against mutant RTs (P236L and Y181C), with the appropriate pharmaceutical properties required for an anti-HIV-1 drug.

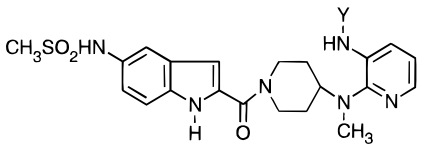
Table 2. Comparison of the Antiviral Activities of U-90152 vs the Lead (Alkylamino)piperidine BHAP Analog

	IC_{90} (μM)[c]		
no.	U-90152[R] HIV-1_{MF}[a]	L-697,661[R] HIV-1_{IIIB}[b]	WT HIV-1_{IIIB}
U-90152	>10	5.2	0.05
3	5.3	1.0	0.02

[a] Delavirdine was used for the selection of the BHAP resistant MF HIV-1 variant. [b] L-697,661 was used for the selection of the L-drug resistant IIIB HIV-1 variant. [c] IC_{90} = concentration of drug that inhibited p24 production in the antiviral assay by 90%.

Analysis of HPLC traces obtained from plasma of rats dosed with **3** revealed the presence of one major more polar metabolite which was subsequently shown to be the *N*-desisopropyl metabolite.[18] N-Dealkylation of the pyridine 3-alkylamino substituent is a predominant pathway for metabolism of the BHAPs.[19−21] Unfortunately, it appeared that the novel (methylamino)-piperidine spacer which linked the two heterocyclic portions of the template facilitated metabolic N-dealkylation of the 3-(isopropylamino)pyridine substituent, relative to the corresponding piperazine analog (i.e., U-90152). Consequently, the analogs in Table 3 were synthesized in hopes of boosting metabolic stability. For example, the isopropylamino substituent of **3** was replaced with a *tert*-butylamino substituent in com-

Table 3. Alterations in the 3-Pyridine Substituent for the Purpose of Gaining Metabolic Stability



		IC$_{50}$(μM)				
no.	Y	WT	P236L	Y181C	mp (°C)	formula[a]
3	*i*-Pr	0.5	1.5	1.1	217−220 dec	$C_{24}H_{32}N_6O_3S$[b]
7	*t*-Bu	0.39	1.46	0.51	130−132	$C_{25}H_{34}N_6O_3S$
8	*t*-amyl	0.35	3.33	0.53	−	$C_{26}H_{36}N_6S_1O_3$[b]
9	CH_2-*c*-Pr	0.52	14.6	2.91	187−189	$C_{25}H_{32}N_6O_3S\cdot0.625H_2O$
10	*c*-Pr	0.09	0.21	0.28	175 dec	$C_{24}H_{30}N_6O_3S\cdot0.6H_2O$
11	1-Me-*c*-Pr	0.16	1.45	0.37	201−204	$C_{25}H_{32}N_6O_3S\cdot0.1H_2O$

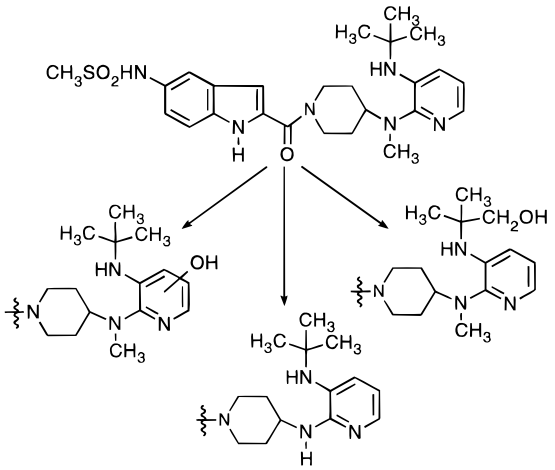
[a] Analyses for C, H, and N are within ±0.4% of theoretical values unless otherwise indicated. [b] Satisfactory HRMS data were obtained.

pound **7** or a *tert*-amylamino substituent in compound **8** because the lack of an abstractable hydrogen atom α to nitrogen should alter the mechanism of dealkylative metabolism, possibly decreasing the rate.[22−24] Cyclopropylmethyl-substituted amines (e.g., **9**) are reportedly more resistant to oxidative N-dealkylation.[25] Experience with nevirapine suggested that a cyclopropylamine[26,27] (**10**) might also be advantageous in terms of reducing the rate of metabolic N-dealkylation. Furthermore, compound **11** was designed to take advantage of both of these structural features. Thus, it contains a cyclopropyl group in which the postion α to nitrogen is blocked by a methyl substitutuent on the ring. In terms of the effect of the 3-pyridine substituent on activity, the bulky *tert*-butyl analog **7** demonstrated inhibitory activity superior to the isopropyl parent **3**, particularly with respect to activity against the Y181C mutant enzyme. Further increases in steric bulkiness as in the *tert*-amyl case (**8**) were detrimental to activity against the P236L RT mutant. The enzyme inhibitory activity of the cyclopropyl compound **10** was better than that of **3**, but it possessed very poor antiviral activity in cell culture (Table 8). Moreover, the cyclopropyl group did not appear to enhance the metabolic stability in an *in vitro* metabolism study in rat liver microsomes where it was determined that its half-life was 16% of that of U-90152. Likewise, the 1-methylcyclopropyl analog **11** exhibited slightly enhanced potency compared to **3** but was much less inhibitory of the BHAP resistant mutant enzyme (P236L) relative to WT. It also possessed poor antiviral activity (Table 7). Accordingly, **7** was the only compound of this group selected to undergo further evaluation.

Pharmacokinetic evaluation of **7** in rats (iv) demonstrated that it too possessed a high clearance rate but possessed a slightly increased po bioavailability (10 times) relative to **3**. LC/MS examination of the metabolites formed indicated the desired absence of the *N*-(desalkylamino)pyridine metabolite. However, substantial pyridine ring hydroxylation as well as small amounts of N-dealkylation of the linker and hydroxylation of the *tert*-butyl group occurred (Scheme 1). Nonlinear pharmacokinetics, similar to those observed for the piperazine U-90152, suggested that the increase in oral bioavailability observed with **7** at the higher dose was likely due to inhibition of a capacity-limited clearance process rather than increased absorption efficiency.

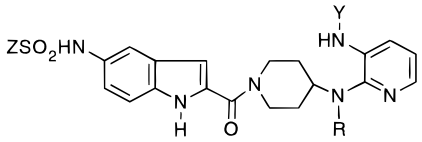
Meanwhile, efforts aimed at improving both the pharmacokinetic profile and spectrum of activity con-

Scheme 1. Metabolic Fate of Compound **7**



tinued. Fortunately, incorporation of the *tert*-butylamino group on the pyridine ring increased the inhibition of the mutant RT containing the Y181C substitution, although as demonstrated above it was clear that further increases in the steric bulk of the 3-pyridine substituent were not leading to the desired enhancements in activity. In order to determine whether further enhancement of inhibitory activity could be garnered by increasing the lipophilicity in the vicinity of this region of the molecule, the effect of shifting lipophilicity to the alkyl substituent on the aminopiperidine linker was explored in both the 3-(isopropylamino)- and 3-(*tert*-butylamino)pyridine series (Table 4). It was gratifying to find that progressing from a (methylamino)piperidine linker to an (ethylamino)- or (*n*-propylamino)piperidine linker in the 3-(isopropylamino)pyridine series (**3** vs **12**, **13**) improved the enzyme inhibitory activity against all three enzymes. (Cyclopropylamino)piperidine **14** offered no advantages in terms of activity. The results in the 3-(*tert*-butylamino)-pyridine series were comparable, in that the (ethylamino)- and (*n*-propylamino)piperidines **15** and **16** were more active than the (methylamino)piperidine compound **7**. However, in the *tert*-butyl series (ethylamino)-piperidine **15** appeared more inhibitory than the (*n*-propylamino)piperidine **16** in both the P236L and Y181C mutant enzymes, perhaps indicative of an upper limit on lipophilicity. Nevertheless, antiviral activities appeared virtually identical for these two compounds, and both proved advantageous over **7** in cell culture (Table 8).

Table 4. Effect of Varying the Lipophilicity of (Alkylamino)piperidine BHAPs



				IC$_{50}$ (μM)				
no.	R	Y	Z	WT	P236L	Y181C	mp (°C)	formula[a]
3	CH_3	*i*-Pr	CH_3	0.5	1.5	1.1	217−220 dec	$C_{24}H_{32}N_6O_3S$[b]
12	Et	*i*-Pr	CH_3	0.25	0.2	0.40	215−216	$C_{25}H_{34}N_6O_3S$
13	*n*-Pr	*i*-Pr	CH_3	0.24	0.24	0.61	177−179 dec	$C_{26}H_{36}N_6O_3S$
14	*c*-Pr	*i*-Pr	CH_3	0.23	0.7	0.94	138−140 dec	$C_{26}H_{34}N_6O_3S$
7	CH_3	*t*-Bu	CH_3	0.39	1.46	0.51	130−132	$C_{25}H_{34}N_6O_3S$
15	Et	*t*-Bu	CH_3	0.32	0.46	0.66	193−194	$C_{26}H_{36}N_6O_3S$
16	*n*-Pr	*t*-Bu	CH_3	0.48	1.45	2.48	195−197 dec	$C_{27}H_{38}N_6O_3S$
17	Et	Et	CH_3	0.46	0.54	0.88	204−205	$C_{24}H_{32}N_6O_3S{\cdot}0.33H_2O$
18	Et	Et	Et	0.40	0.26	0.48	211−213	$C_{25}H_{34}N_6O_3S{\cdot}0.33H_2O$
19	Et	Et	*i*-Pr	0.45	0.33	0.66	206−207	$C_{26}H_{36}N_6O_3S{\cdot}0.25H_2O$
20	*n*-Pr	Et	CH_3	0.15	0.52	0.95	133−135 dec	$C_{25}H_{34}N_6O_3S$
21	*i*-Pr	Et	CH_3	0.38	2.6	3.6	115−117	$C_{25}H_{34}N_6O_3S$
22	Et	Pr	CH_3	0.13	0.28	0.45	209−210	$C_{25}H_{34}N_6O_3S$

[a] Analyses for C, H, and N are within ±0.4% of theoretical values unless otherwise indicated. [b] Satisfactory HRMS data were obtained.

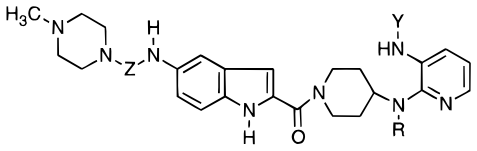
Selection of **14** and **15** for pharmacokinetic evaluation in rats followed (Table 9). Replacing ethyl for methyl on the aminopiperidine linker slightly worsened the pharmacokinetic parameters (i.e., **15** vs **7**). As in the case of U-90152 and compound **7**, nonlinear pharmacokinetics were observed. However, higher doses of **15**, relative to **7**, were required to cause the same degree of saturation of systemic clearance. The cyclopropyl substituent on the 4-aminopiperidine, as in compound **14**, only resulted in lowering the oral bioavailability. Thus, the trend appeared to be that increasing the number of carbons on the 4-aminopiperidine substituent led to compounds with poorer pharmacokinetic profiles.

Since previous experience with atevirdine analogs had shown that a 3-(ethylamino)pyridine substituent was more metabolically stable than a 3-isopropylamino substituent,[28] a series of analogs in which the 3-(ethylamino)pyridine substituent was held constant while the lipophilicity was shifted to other parts of the template were synthesized (compounds **17**−**21**). As anticipated from the studies previously detailed, it was demonstrated that the 3-ethylamino substituent (**17**) slightly diminished the RT enzyme inhibitory activities relative to the 3-isopropyl- and 3-*tert*-butylamino-substituted compounds **12** and **15**. Shifting lipophilicity to the left-hand side in the form of a 5-isopropyl- or 5-ethylsulfonamide-substituted indole did not appreciably alter the activity. Although shifting lipophilicity to the linker may have offered a slight advantage in the case of **20** which contained an (*n*-propylamino)piperidine, this approach was definitely detrimental in the case of **21** which contained an (isopropylamino)piperidine. One last attempt involved synthesis of a compound with a 3-(*n*-propylamino)pyridine substituent (**22**), which surprisingly, in light of past experience in the piperazine-linked series,[19] exhibited enzyme inhibitory activity comparable to the 3-isopropyl- and 3-*tert*-butyl-substituted parents **12** and **15**. In contrast to the pharmacokinetic results obtained in the [3-(ethylamino)pyridyl]-piperazine series, the presence of the *N*-ethyl moiety did not result in enhanced metabolic stabilities in the (alkylamino)piperidine series. The *in vitro* half-life of **17** in the presence of liver microsomes was one-fourth that of **7**. Poor *in vivo* clearances and oral bioavailabilities were also observed in rats (compound **17** vs **7**, Table 9).

Next we investigated the effect of decreasing the lipophilicity of these molecules, in order to probe whether a corresponding decrease in the rate of metabolism would result. It was thought that decreasing the lipophilicity of these compounds would diminish their interactions with the lipophilic active sites of the enzymes responsible for their metabolism. Thus polar water-solubilizing groups were introduced as substituents on the indole ring (Table 5). We had successfully utilized this approach previously to solubilize BHAPs while retaining activity.[29] In all cases, the compounds containing the water-solubilizing urea substituents were more inhibitory than those containing the sulfamoyl substituents against the panel of RTs. In general, the compounds appeared to be less inhibitory of the Y181C mutant RT than their methylsulfonamide parents. Evaluation in the antiviral assays revealed that compounds **25**−**28** possessed comparable activities. Thus, they were submitted to the *in vitro* metabolism assay to compare metabolic stabilities. These results indicated that **26** was by far the most stable with a half-life 6.7 times longer than that of **15**. Compounds **25**−**28** were selected for pharmacokinetic evaluation in rats. In spite of their enhanced *in vitro* metabolic stability, the systemic clearances of compounds **26**−**28** were increased relative to their parent **15**, which lacked the water-solubilizing substituent, possibly due to their enhanced aqueous solubility (Table 9).

The next approach to improve pharmacokinetic performance was an attempt to suppress the pyridine ring hydroxylation which occurred when N-dealkylation was hindered by the presence of the *tert*-butylamino moiety. Since it had been conclusively demonstrated that delavirdine underwent hydroxylation at C-6,[30] that position of the AAP-BHAPs was targeted for blocking. Therefore, a compound (**30**) containing a pyridazine ring wherein a nitrogen atom replaced C-6 was synthesized, in addition to several compounds containing a halogen

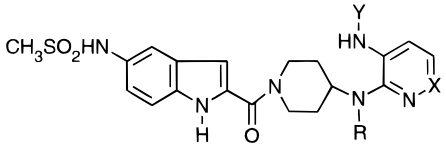
Table 5. Effect of Adding Water-Solubilizing Substituents on the Indole Ring



				IC$_{50}$ (μM)			
no.	Y	R	Z	WT	P236L	Y181C	formula[a]
23	Et	Et	−CO−	0.14	0.24	1.23	$C_{25}H_{34}N_6O_3S$[b]
24	Et	Et	−SO$_2$−	0.24	0.44	1.11	$C_{25}H_{34}N_6O_3S$[b]
25	*i*-Pr	Et	−CO−	0.14	0.18	0.41	$C_{30}H_{42}N_8O_2\cdot0.4H_2O$
26	*i*-Pr	Et	−SO$_2$−	0.38	0.57	0.77	$C_{29}H_{42}N_8O_3S$
27	*t*-Bu	Et	−CO−	0.22	0.37	0.61	$C_{31}H_{44}N_8O_2\cdot0.5H_2O$
28	*t*-Bu	Et	−SO$_2$−	0.79	1.25	1.83	$C_{30}H_{44}N_8O_3S\cdot0.3H_2O$
29	*i*-Pr	*n*-Pr	−CO−	0.19	0.40	0.86	$C_{31}H_{44}N_8O_2\cdot0.8H_2O$

[a] All compounds were amorphous. Analyses for C, H, and N are within ±0.4% of theoretical values unless otherwise indicated. [b] Satisfactory HRMS data were obtained.

Table 6. Effect of C-6-Modified Pyridines on HIV-1 WT and Mutant RT Enzyme Inhibitory Activities



				IC$_{50}$ (μM)				
no.	X	R	Y	WT	P236L	Y181C	mp (°C)	formula[a]
30	N	CH_3	*i*-Pr	0.74	4.56	1.31	193−194	$C_{23}H_{31}N_7O_3S\cdot0.7H_2O$
31	C-Cl	CH_3	*i*-Pr	0.36	1.7	2.13	101−102	$C_{24}H_{31}N_6O_3ClS$
32	C-F	CH_3	*t*-Bu	0.53	1.9	0.72	203−204	$C_{25}H_{33}N_6O_3FS$
33	C-F	Et	*i*-Pr	0.46	0.54	0.88	166−168	$C_{25}H_{33}N_6O_3FS$
34	C-Cl	Et	*t*-Bu	1.02	1.52	3.0	206−207	$C_{26}H_{35}N_6O_3ClS$
35	C-F	Et	*t*-Bu	0.73	1.05	1.06	221−223	$C_{26}H_{35}N_6O_3FS$

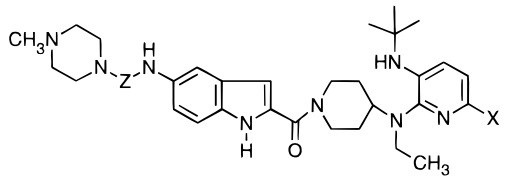
[a] Analyses for C, H, and N are within ±0.4% of theoretical values.

atom substituent (fluorine or chlorine) at the C-6 position of the pyridine ring (compounds **31**−**35**, Table 6).

In all cases introduction of the halogen atom caused slight to moderate increases in the IC$_{50}$s against the three RT enzymes tested. The presence of the pyridazine ring (**30**) also decreased inhibitory activities relative to **3**, especially against the P236L recombinant RT. All of these results were not necessarily paralleled in the antiviral assays. For example, **32** and **35** possessed antiviral activities comparable to their deshalo parents **7** and **15**, respectively. *In vitro* metabolism studies of the 3-(*tert*-butylamino)-6-fluoropyridines **32** and **35** and the pyridazine **30** demonstrated substantial improvements in metabolic stability. For example, **32** which contains the (methylamino)piperidine linker had a half-life 2.8 times greater than that of the nonfluorinated parent **7**. Furthermore, **35**, which contains the (ethylamino)piperidine linker, had a half-life 5.2 times that of the nonfluorinated parent **15** and 0.78 times that of U-90152. The pyridazine analog contained the (methylamino)piperidine linker and a 3-isopropylamino substituent on the pyridine ring. Even with the presence of the more metabolically labile 3-isopropylamino moiety, **30** possessed an *in vitro* half-life 3 times longer than that of the analogous compound **3**, which lacks the additional nitrogen in the ring. According to calculated log *P* values, incorporation of the pyridazine ring should decrease the lipophilicity of **30** relative to the analogous pyridine **3**. Apparently, this alteration was not well tolerated as indicated by pharmacokinetic studies which demonstrated that **30** was not absorbed. The *in vitro* results with the fluorinated compounds were confirmed upon pharmacokinetic evaluation of **35**, which was selected because of its superior antiviral activity. The iv clearance of **35** in rats was approximately one-half that of **15**; nevertheless, the oral bioavailability was lower than anticipated and was ascribed to malabsorption due to extremely poor solubility (Table 9).[31] In general, there was a reasonably good inverse correlation between systemic (iv) clearance and absolute oral bioavailability for this class of AAP-BHAP analogs. Exceptions, as in the case of compound **35**, arose when aqueous solubility was low and absorption efficiency was poor. Apparently, the addition of the fluorine atom in compound **35** dramatically decreased the aqueous solubility due to either the increase in lipophilicity and/or the anticipated decreased basicity of the 3-(*tert*-butylamino)pyridine substituent.[32] In order to counteract this effect, we attempted to increase the solubility of these compounds in the manner described above (Table 7).

Comparison of the fluoro-containing analogs **36** and **37** in the enzyme assay confirmed the trend observed previously, in that the urea-containing compound **36** was more effective at inhibiting the RT enzymes. In fact in this fluorinated series, the urea-based water-solubilizing indole substituent does not adversely effect the RT enzyme activities compared to the methanesulfonamido-substituted indole. Regardless, both compounds possessed very comparable antiviral activities (Table 8). The sulfamide-linked methylpiperazine **37** was cleared rapidly upon iv administration to rats, although it demonstrated relatively good oral bioavail-

Table 7. Enzyme Inhibitory Activities of Fluorinated Pyridine AAP-BHAPs Containing a Water-Solubilizing Substituent on the 5-Indole Position



			IC_{50} (μM)				
no.	Z	X	WT	P236L	Y181C	mp (°C)	formula[a]
36	−CO−	F	0.21	0.43	0.79	203−204	$C_{29}H_{38}N_8O_2F$
37	$-SO_2-$	F	0.83	1.09	2.07	181−183	$C_{30}H_{43}N_8O_3FS$

[a] Analyses for C, H, and N are within ±0.4% of theoretical values.

Table 8. Antiviral Activities of Selected Compounds Against Resistant Viruses

	IC_{90} (μM)[a]		
no.	U-90152^R HIV-1_{MF}[b] (P236L)	U-90152^R HIV-1_{IIIB}[c] (L100I, M230L)	L-697,661^R HIV-1_{IIIB}[c] (Y181C)
90152T	>10	>10	5.2
L-697,661	0.43	4.0	>10
3	5.3	NT	1.0
7	5.4	0.83	0.22
10	>10	NT	4.4
11	>0.3	NT	2.3
13	0.22	NT	0.06
15	0.19	0.08	0.03
16	0.32	0.11	0.03
17	0.31	0.08	0.18
22	0.4	NT	0.14
25	0.24	0.11	0.05−0.1
26	0.3	NT	0.17
27	0.16	0.16	∼0.05−0.10
28	0.34	0.14	<0.03
32	2.6	1.6	0.44
33	0.3−1.0	0.11	0.14
34	0.24	NT	>0.3
35	0.22	0.12	≤ 0.03
36	0.16	0.14	0.13
37	0.29	0.29	0.15

[a] IC_{90} = concentration of drug that inhibited p24 production in the antiviral assay by 90%. [b] Delavirdine was used for the selection of BHAP resistant MF and IIIB HIV-1 variants. [c] L-697,661 was used for the selection of the L-drug resistant IIIB HIV-1 variant.

ability (Table 9). The urea-linked methylpiperazine **36** possessed a greatly diminished iv clearance relative to **7** and the nonfluorinated **27**, and it possessed an oral bioavailability similar to that of **7**. Thus it appears that incorporation of the 6-fluorine to inhibit pyridine ring hydroxylation and incorporation of the 5-methylpiperazine urea indole substituent to counteract the effect of the fluorine on solubility enhanced the pharmacokinetic properties of the (ethylamino)piperidine template without negatively effecting the activity.

Experiments designed to determine the kinetics of inhibition of HIV-1 WT, P236L, and Y181C RTs were conducted with compounds **7**, **15**, and **36**. All three compounds are noncompetitive inhibitors with respect to dGTP, dTTP, and poly(rA):$(dT)_{10}$. Previous experiments with the BHAP atevirdine mesylate[33] revealed that it acts as a noncompetitive inhibitor with respect to deoxyribonucleotide triphosphate (dNTP) irrespective of the template:primer [poly(rA):$(dT)_{10}$ or poly(rC):$(dG)_{10}$] used. The BHAP U-88204E[34] acts as a mixed inhibitor with respect to poly(rC):$(dG)_{10}$ and as a noncompetitive inhibitor with respect to poly(rA):$(dT)_{10}$ and dTTP. Delavirdine mesylate,[35] on the other hand, acts as a mixed inhibitor regardless of template:primer in that it binds more tightly to the enzyme−substrate complexes than to the free enzyme. The K_i values for all three (alkylamino)piperidines were quite similar for all three enzymes (Table 10). Interestingly, the relative ordering of K_i values was not consistent between enzymes.

Table 9. Selected Pharmacokinetic Parameters of Some Indole-Substituted (Alkylamino)piperidine HIV-1 RT Inhibitors in Male Sprague−Dawley Rats[a]

	dose (mg/kg)		iv clearance	absolute oral
compd	iv	po	(mL/min/kg)	bioavailability (%)
U-87201	12	23	13.0 ± 1.3	75 ± 14
U-90152	14	15	13.6 ± 0.3	64 ± 8
	14	28	13.6 ± 0.3	169 ± 25[b]
3	15	30.2	44 ± 6	4.3 ± 4.2
4	16	35	42 ± 4	12.3 ± 1.8
7	15	29.1	46.0 ± 1.9	44 ± 3
14	15.7	31.4	22.6±1.3	1.6 ± 0.4
15	15	30	50 ± 10	14 ± 10
	15	60	50 ± 10	42 ± 17
	15	120	50 ± 10	124 ± 35
	15	240	50 ± 10	240 ± 90
17	15	30	66.6 ± 1.7	2.8 ± 0.7
25	15	30	50 ± 7	21.3 ± 1.2
26	15	30	89 ± 3	8 ± 3
27	15	30	61 ± 7	35.1 ± 2.9
28	15	30	73.7 ± 2.1	32 ± 24
30	15.6	31.2	40 ± 7	0
35	15	30	27 ± 3	17.1 ± 1.6
36	15	30	16 ± 4	42 ± 16
37	15	30	61 ± 12	54 ± 29

[a] Compounds were administered as solutions in propylene glycol/water (80/20, v/v) acidified with a molar excess of methanesulfonic acid. Doses were administered to fasted animals in a crossover design with a 1 week washout period between treatments (N = 3). [b] The nonlinear pharmacokinetics of U-90152 result in an apparent bioavailability >100%.

Resistance selection studies were conducted with compounds **7** and **15**.[36] Selection of HIV-1 variants resistant to these compounds was prolonged relative to other NNRTIs. The derived virus stocks were of lower infectious titer and grew more slowly than wild type virus in cell culture. Analysis of the DNA sequence of the RT gene indicated that high-level resistance to **7** required simultaneous multiple amino acid substitutions, including a glycine to glutamate substitution at amino acid 190 (G190E). Furthermore, genotypic analysis of the HIV-1 variant resistant to **15** revealed one other substitution (Leu214 → Phe) in addition to G190E. The G190E mutation has been reported to drastically reduce the enzyme activity, and preliminary data suggested that the corresponding HIV-1 variant exhibited impeded growth in tissue culture.[37] Analogous results were obtained in our labs when the G190E substitution was incorporated into recombinant HIV-1_{IIIB} RT. The reduced replicative capacity of the HIV-1_{IIIB} variants resistant to **7** and **15** also supports the notion that the G190E mutation compromises virus growth. Generation of such a mutation in patients treated with these types of (alkylamino)piperidines could be beneficial, since selection of a virus population with diminished replication might lead to a decrease in the steady-state level of virus.

Chemistry

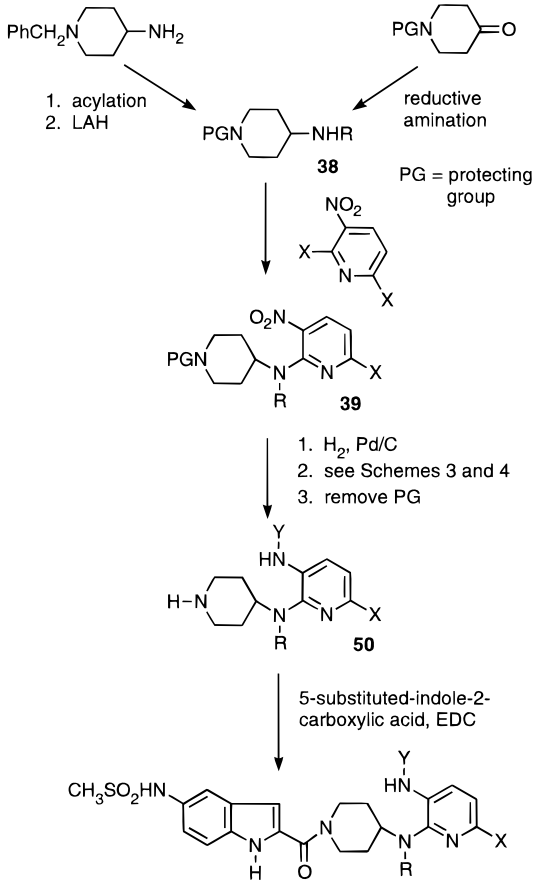
The (alkylamino)piperidine-linked template could be easily prepared starting with 4-amino-1-benzylpiperi-

Table 10. K_i Values for Compounds **7**, **15**, and **36** Against HIV-1 WT, P236L, and Y181C RTs

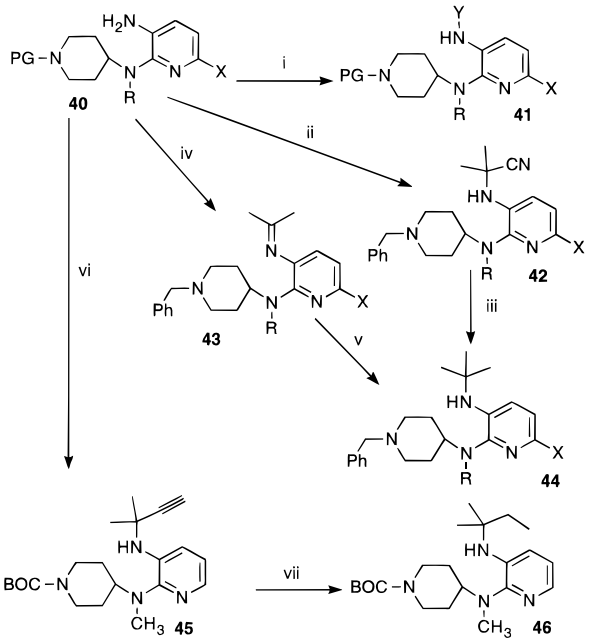
	K_i (μM) versus dTTP[a]			K_i (μM) versus poly(rA)$_{300}$:oligo(dT)$_{10}$		
no.	WT	P236L	Y181C	WT	P236L	Y181C
7	0.714 (0.046)	2.759 (0.213)	1.046 (0.086)	0.853 (0.052)	2.515 (0.119)	1.790 (0.088)
15	1.033 (0.113)	1.114 (0.046)	1.922 (0.171)	1.380 (0.039)	1.603 (0.077)	3.089 (0.295)
36	1.262 (0.061)	2.022 (0.105)	2.547 (0.194)	1.640 (0.144)	1.739 (0.148)	3.025 (0.195)

[a] Data shown were generated in a single experiment which involved two determinations at a total of four substrate and four inhibitor concentrations (16 data points). The experiments were repeated at least three times with consistent results.

Scheme 2



Scheme 3[a]

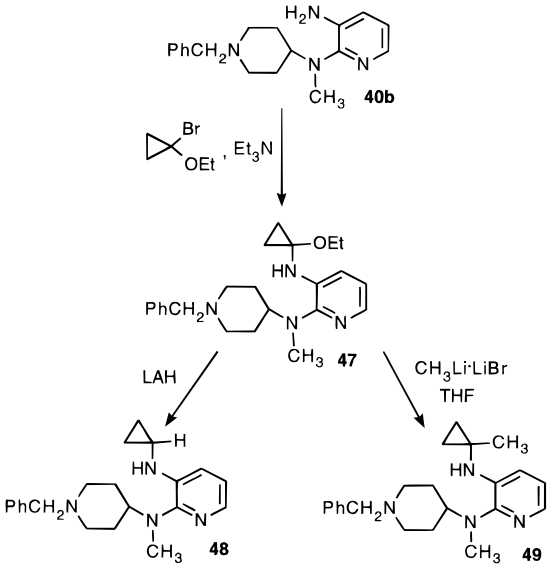


[a](i) Acetone, $NaCNBH_3$, AcOH, methanol; (ii) acetone, TMSCN, $ZnCl_2$; (iii) CH_3Li, toluene; (iv) 2-methoxypropene, PPTS; (v) CH_3Li·LiBr, toluene; (vi) 3-chloro-3-methyl-1-butyne, Cu, CuCl; (vii) Raney Ni, H_2.

dine or 1-(*tert*-butoxycarbonyl)-4-piperidone (Scheme 2). Formylation or acylation of the primary amine of 4-amino-1-benzylpiperidine followed by reduction with lithium aluminum hydride provided 4-(alkylamino)-1-benzylpiperidines **38** (PG = benzyl). A more expedient route to **38** involved reductive amination of amino-protected 4-piperidones (PG = benzyl or BOC) which occurred upon treatment with alkylamines and sodium cyanoborohydride. Even more conveniently, hydrogenation of a solution of aqueous methyl- or ethylamine and *N*-benzyl-4-piperidone over palladium on carbon in THF provided the desired intermediates **38** (PG = benzyl, R = methyl or ethyl) in excellent yields.[38] The secondary amines produced via these methods were used as nucleophiles in a nucleophilic aromatic substitution of 2-chloro-3-nitropyridines or 2,6-dichloro- or 2,6-difluoro-3-nitropyridines.[39,40] In the case of (methylamino)- or (ethylamino)piperidines, these reactions were typically conducted in refluxing acetonitrile with 1 equiv of potassium carbonate to scavage the acid byproduct. When more hindered (alkylamino)piperidines were employed, such as isopropyl or *n*-propyl, the reactions were very sluggish, and thus they were conducted using Hunig's base as solvent or neat in a sealed tube at high temperature. Reduction of the resultant nitropyridines **39** via hydrogenation over palladium or platinum oxide was uneventful and provided the desired 3-aminopyridines **40**. Functionalization of the 3-amino moiety of these pyridines is outlined in Schemes 3 and 4. Removal of the piperidine-protecting group (generally hydrogenation over palladium on carbon in the case of the benzyl protecting group[41] or treatment with TFA in methylene chloride in the case of the BOC protecting group) provided the 4-functionalized piperidines **50** suitable for coupling with the desired 5-substituted-indole-2-carboxylic acid (usually 5-methanesulfonamido) utilizing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) or 1,1′-carbonyldiimidazole (CDI) as coupling agents.

Scheme 3 describes the sequence of reactions utilized to generate the isopropylamino, *tert*-butylamino, and *tert*-amylamino groups at the 3-position of the pyridine ring. (Isopropylamino)pyridines **41** were synthesized by treating the 3-aminopyridine **40** with acetone and sodium cyanoborohydride in acetic acid/methanol solvent. The 3-(ethylamino)- and 3-(propylamino)pyridines were synthesized similarly. The *tert*-butylamine congeners were synthesized as previously described.[42] In short, treatment of the 3-aminopyridine **40** with acetone and trimethylsilyl cyanide in the presence of catalytic zinc chloride afforded the α-aminonitrile **42**, which upon treatment with excess methyllithium in toluene afforded the desired *tert*-butylamine intermediate **44**. An alternate route involves formation of the acetonylimine **43**

Scheme 4



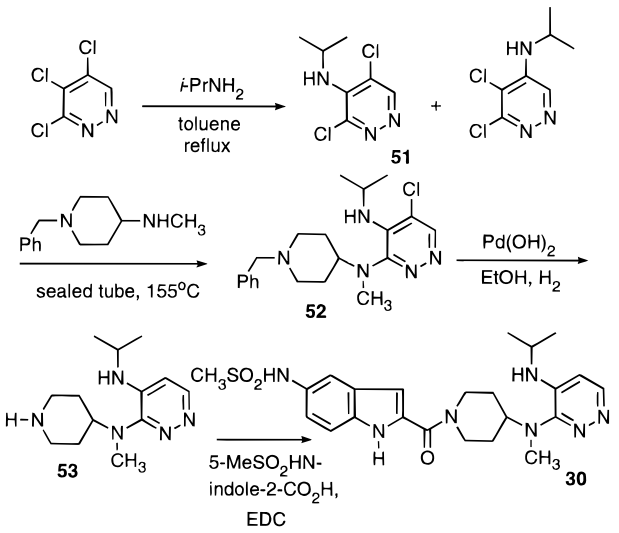
by treating the 3-aminopyridine with 2-methoxypropene and 10 mol % of pyridinium *p*-toluenesulfonic acid.[43] Subsequent addition of methyllithium−lithium bromide complex to the imine also affords the desired *tert*-butylamine analogs. The *tert*-amyl analogs were prepared in a manner similar to literature precedent.[44] 3-Chloro-3-methyl-1-butyne[45] could be coupled with the 3-aminopyridine moiety (**40**) upon treatment with approximately stoichiometric quantities of copper powder and cuprous chloride in DMF, providing intermediate **45**. The alkyne product was reduced with hydrogen over Raney nickel to provide the desired (*tert*-amylamino)pyridine intermediate **46**.

Cyclopropylamines were prepared by treating 3-aminopyridine **40** with 1-bromo-1-ethoxycyclopropane and triethylamine in THF at reflux to afford the intermediate (ethoxyamino)cyclopropane **47** (Scheme 4).[46] Reduction with lithium aluminum hydride was capricious but afforded the desired aminocyclopropane product **48**. Reaction of the 1-amino-1-ethoxycyclopropane with methyllithium in toluene afforded the desired 1-amino-1-methylcyclopropane **49**.

Nucleophilic aromatic substitution of 3,4,5-trichloropyridazine with isopropylamine in refluxing toluene provided two regioisomeric products in an approximately 1:1 ratio (Scheme 5).[47] Chromatography afforded the desired isomer **51** which was treated with 1-benzyl-4-(methylamino)piperidine and heated (neat) to 155 °C in a sealed tube. The coupled product **52** was hydrogenated over palladium hydroxide on carbon to dechlorinate the pyridazine and remove the benzyl protecting group providing **53**. Standard coupling to the indole-2-carboxylic acid afforded **30**.

Introduction of the water-solubilizing substituents was accomplished by treating the 5-aminoindole intermediate **55**, available via reduction of nitroindoles **54**, with 4-methyl-1-piperazinylcarbamoyl chloride hydrochloride or 4-methyl-1-piperazinylsulfamoyl chloride hydrochloride and pyridine (Scheme 6). These reagents were prepared by treating excess phosgene or excess sulfuryl chloride with *N*-methylpiperazine in methylene chloride at 0 °C, and concentrating *in vacuo* after strirring for 3 h at room temperature. The ethyl- and isopropylsulfonamide-containing compounds **18** and **19**

Scheme 5



were prepared similarly, but ethyl- or isopropylsulfonyl chloride was employed.

Conclusion

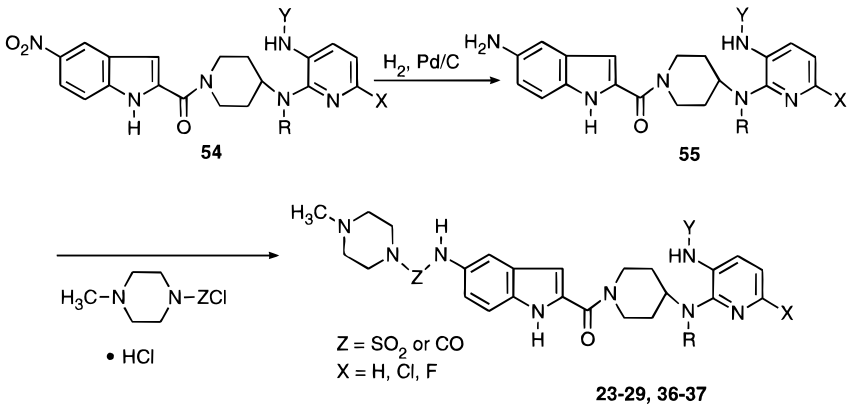
In summary, investigation of the SAR surrounding the bis(heteroaryl)(alkylamino)piperidine template resulted in the synthesis of a number of compounds with the desired phenotypes. In particular, substituting an ethyl for a methyl group on the aminopiperidine spacer enhanced the desired activities against both Y181C and P236L mutant RTs. Several of the (alkylamino)piperidine analogs described herein demonstrate excellent activities against both mutant RT enzymes and viruses. Once the activity barrier was hurdled, the primary strategy became synthetic manipulation of the chemical structure with the object of obtaining a suitable pharmacokinetic profile in the rat. The strategies pursued involved substituting the more stable *tert*-butylamino group (**15**) for a metabolically labile isopropylamino group, introduction of a heteroaromatic fluorine substituent to thwart ring hydroxylation (**35**), and introduction of water-solubilizing substituents to counteract the decreased solubility attributed to the fluorine atom (**36**). Investigations which define the pharmacokinetic parameters and safety profiles of three of these analogs, **7**, **15**, and **36**, in laboratory animals will be detailed elsewhere.

Experimental Section

Flash chromatography utilized E. Merck silica gel (230−400 mesh). Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra, infrared spectra, and combustion analyses were obtained by the Structural, Analytical and Medicinal Chemistry Department of Pharmacia & Upjohn, Inc. Unless otherwise indicated, proton NMR spectra were recorded with a Brucker Aspect 3000 300 MHz spectrometer. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All other solvents were Burdick and Jackson or Fisher reagent grade.

In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction with water, dilute the mixture with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator at reduced pressure. When "basic workup (organic solvent, aqueous base, drying agent)" is indicated, the proce-

Scheme 6



dure was similar to the aqueous workup, except the indicated aqueous base was used instead of water.

General Procedure for the Acylation and Subsequent Reduction of 4-Amino-1-benzylpiperidine. 1-Benzyl-4-acetamidopiperidine. 4-Amino-1-benzylpiperidine (20.0 g, 105.1 mmol) was dissolved in 210 mL of CH_2Cl_2 and cooled to 0 °C. Then pyridine (10.29 mL, 127.2 mmol) was added followed by the dropwise addition of acetyl chloride (9.06 mL, 127.4 mmol). The reaction mixture was stirred for 30 min at 0 °C and slowly warmed to room temperature. When complete by TLC, basic workup ($CHCl_3$, 1 N aqueous NaOH, Na_2SO_4) and recrystallization from EtOAc afforded 19.09 g (78%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.29−7.36 (m, 5H), 5.57 (br s, 1H), 3.75−3.90 (m, 1H), 3.59 (s, 2H), 2.89−2.93 (br m, 2H), 2.21 (t, J = 9.5 Hz, 2H), 1.98 (s, 3H), 1.93−1.98 (m, 2H), 1.51−1.63 (m, 2H).

1-Benzyl-4-(ethylamino)piperidine, 38a (PG = benzyl, R = Et). 1-Benzyl-4-acetamidopiperidine (19.09 g, 82.17 mmol) was dissolved in 164.3 mL of anhydrous THF and cooled to 0 °C. Then LAH in THF (1 M, 82.17 mL, 82.17 mmol) was added dropwise via an addition funnel. When the addition was complete, the reaction mixture was warmed to room temperature and heated to reflux for 16 h. TLC of an aliquot quenched with 1 N NaOH and partitioned in $CHCl_3$ showed complete reduction. The reaction was cooled to 0 °C and quenched by the dropwise addition of 3.12 mL of water, 3.12 mL of 15% aqueous NaOH, and 9.36 mL of water. The reaction mixture was filtered through a pad of Celite/sodium sulfate and concentrated *in vacuo* to afford 14.98 g (84%) of the title compound which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.06−7.14 (m, 5H), 3.33 (s, 2H), 2.65−2.71 (m, 2H), 2.52 (q, J = 7.2 Hz, 2H), 2.27−2.37 (m, 1H), 1.80−1.88 (m, 3H), 1.68−1.72 (m, 2H), 1.18−1.31 (m, 2H), 0.96 (t, J = 7.1 Hz, 3H).

General Procedures for the Reductive Amination of N-Protected-piperidones. 1-Benzyl-4-(methylamino)piperidine, 38b (PG = benzyl, R = Me). 1-Benzyl-4-piperidone (10.0 g, 52.8 mmol) was dissolved in 200 mL of methanol and cooled to 0 °C. Then methylamine hydrochloride (3.57 g, 52.8 mmol) and 4 Å molecular sieves were added followed by 3.32 g of $NaCNBH_3$ (52.8 mmol). The reaction mixture was warmed to room temperature and stirred for 24 h. Basic workup ($CHCl_3$, $NaHCO_3$, Na_2SO_4) afforded a residue which was dissolved in $CHCl_3$, washed with 1 N HCl, basified with 1 N NaOH, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo* to provide 8.1 g of the title amine (76%): ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 5H), 3.49 (s, 2H), 2.83 (m, 2H), 2.41 (s, 3H), 2.33 (m, 1H), 2.01 (m, 2H), 1.83 (m, 2H), 1.31 (m, 2H).

1-Benzyl-4-(propylamino)piperidine, 38c (PG = benzyl, R = propyl). A solution of 1-benzyl-4-piperidone (20.0 g, 106 mmol) in CH_3OH (200 mL) maintained at 0 °C was treated with *n*-propylamine (12.2 mL, 148 mmol) and $NaCNBH_3$ (3.33 g, 53 mmol), adjusted to pH 7 with glacial acetic acid as determined on moistened pH test paper, warmed to room temperature, and stirred at room temperature for 20 h. The mixture was then adjusted to pH 3 using 3 M HCl and concentrated *in vacuo*. Basic workup (CH_2Cl_2, aqueous KOH to pH 12, Na_2SO_4) and chromatography (ammonium hydroxide/CH_3OH/CH_2Cl_2, 0.5/4.5/95−0.5/14.5/85) afforded a residue which was dissolved in CH_2Cl_2 (100 mL), washed with 5% aqueous NaOH (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide 23.7 g (96%) of the product as a pale amber oil: ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 4H), 7.24 (m, 1H), 3.50 (s, 2H), 2.85 (br d, J = 11.7 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H), 2.46 (m, 1H), 2.02 (br t, J = 11.5 Hz, 2H), 1.85 (br d, J = 12.6 Hz, 2H), 1.50 (sext, J = 7.4 Hz, 2H), 1.39 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 129.4, 128.5, 127.2, 63.5, 55.4, 52.9, 49.2, 33.3, 23.9, 12.2.

1-Benzyl-4-[(1-methylethyl)amino]piperidine, 38d (PG = benzyl, R = isopropyl): prepared in a manner analogous to **38c** to afford 45% of the title amine; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H) 3.40 (s, 2H), 2.99 (m, 1H), 2.78 (br d, J = 12.1 Hz, 2H), 2.58 (m, 1H), 1.92 (t, J = 11.8 Hz, 2H), 1.79 (m, 2H), 1.35 (m, 2H), 1.04 (d, J = 4.2 Hz, 6H); MS-EI *m/e* (rel intensity) 232 (4), 189 (4), 173 (60), 146 (11), 91 (100).

1-[(1,1-Dimethylethoxy)carbonyl]-4-(cyclopropylamino)piperidine, 38e (PG = BOC, R = cyclopropyl): prepared in a manner analogous to **38c** to afford 84% of the title amine as a colorless oil; IR (atr) 3316 (w), 3087 (w), 2976 (m), 2933 (m), 2855 (m), 1685 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.02 (br m, 2H), 2.75 (m, 3H), 2.13 (m, 1H), 1.90 (br d, J = 10.9 Hz, 2H), 1.59 (s, 1H), 1.45 (s, 9H), 1.25 (m, 2H), 0.45 (m, 2H), 0.32 (m, 2H); MS-EI *m/e* 240 (M^+), 184, 169, 155, 110, 84, 82, 57, 40. Anal. ($C_{13}H_{24}N_2O_2$) C, H, N.

General Procedure for the Nucleophilic Substitution of Nitropyridines with 1-Protected-4-(alkylamino)piperidines. 1-Benzyl-4-[*N*-ethyl-(*N*-3-nitro-2-pyridinyl)amino]piperidine, 39a (PG = benzyl, R = Et, X = H). 38a (12.91 g, 59.1 mmol), 2-chloro-3-nitropyridine (9.37 g, 59.1 mmol), and K_2CO_3 (8.17 g, 59.1 mmol) were placed in 118 mL of CH_3CN and heated to reflux for 72 h. Then the reaction mixture was cooled to room temperature. Aqueous workup ($CHCl_3$, Na_2SO_4) and purification by flash column chromatography (10% EtOAc/hexane) afforded 13.7 g (69%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, J = 4.5, 1.6 Hz, 1H), 7.92 (dd, J = 8.1, 1.8 Hz, 1H), 7.12−7.24 (m, 5H), 6.58 (dd, J = 7.7, 4.5 Hz, 1H), 3.55−3.70 (m, 1H), 3.47 (s, 2H), 3.35 (q, J = 7.1 Hz, 2H), 2.89−2.93 (br m, 2H), 1.80−2.10 (m, 4H), 1.65−1.73 (br m, 2H), 0.93 (t, J = 7.1 Hz, 3H).

1-Benzyl-4-[*N*-methyl-*N*-(3-nitro-2-pyridinyl)amino]piperidine, 39b (PG = benzyl, R = methyl, X = H). A mixture of **38b** (10.80 g, 52.8 mmol), 2-chloro-3-nitropyridine (6.70 g, 42.2 mmol, 0.8 equiv), and anhydrous K_2CO_3 (14.6 g, 106 mmol, 2 equiv) in dry CH_3CN (211 mL) was stirred at room temperature for 5 days and then concentrated to remove solvent. Aqueous workup (CH_2Cl_2, Na_2SO_4), concentration *in vacuo*, and chromatography (50% EtOAc/hexane) afforded 13.10 g (95%) of the product as a yellow solid: mp 92−95 °C; IR (mull) 2926 (s), 1597 (s), 1556 (s), 1501 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, J = 1.7, 4.4 Hz, 1H), 8.09 (dd, J = 1.7, 8.0 Hz, 1H), 7.29 (m, 5H), 6.63 (dd, J = 4.4, 8.0 Hz, 1H), 4.45 (m, 1H), 3.54 (s, 2H), 2.99 (br d, J = 11.6 Hz, 2H), 2.69 (s, 3H),

2.15 (td, J = 2.7, 11.6 Hz, 2H), 1.90 (m, 2H), 1.81 (m, 2H). EI-MS m/z (rel intensity) 326 (M^+, 1), 280 (6), 172 (100), 91 (100). Anal. ($C_{18}H_{22}N_4O_2$) C, H, N.

1-[(1,1-Dimethylethoxy)carbonyl]-4-[*N*-cyclopropyl-*N*-(3-nitro-2-pyridinyl)amino]piperidine, 39c (PG = BOC, R = cyclopropyl, X = H). A mixture of **38e** (100 mg, 0.42 mmol), 2-chloro-3-nitropyridine (53 mg, 0.33 mmol), and 145 μL of diisopropylethylamine (0.83 mmol) in 1.5 mL of *N*-methyl-2-pyrrolidinone was stirred at room temperature for 1 day, at 90 °C for 4 days, and again at room temperature for 1 day. Aqueous workup (CH_2Cl_2, Na_2SO_4), concentration, and chromatography (10−20% EtOAc/hexane) afforded 54 mg of a yellow film which was chromatographed on one 2000 μm preparative silica gel plate, eluting with 10% and 25% EtOAc/hexane. The band with R_f = 0.38−0.50 was extracted with 5% MeOH/$CHCl_3$ and concentrated to give 48 mg (40%) of the title compound as a yellow film: IR (atr) 2974 (m), 2934 (m), 2863 (m), 1689 (s), 1594 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28 (dd, J = 1.7, 4.5 Hz, 1H), 8.05 (dd, J = 1.7, 8.0 Hz, 1H), 6.72 (dd, J = 4.5, 8.0 Hz, 1H), 4.50 (m, 1H), 4.23 (br m, 2H), 2.83 (br t, J = 10.8 Hz, 2H), 2.57 (m, 1H), 2.06 (m, 4H), 1.49 (s, 9H), 0.70 (m, 2H), 0.45 (m, 2H); MS-EI m/e 289, 178, 164, 126, 82, 57; HRMS (FAB) calcd for $C_{18}H_{26}N_4O_4 + H_1$ 363.2032, found 363.2037.

1-Benzyl-4-[*N*-ethyl-*N*-(6-chloro-3-nitro-2-pyridinyl)amino]piperidine, 39d (PG = benzyl, R = ethyl, X = Cl): prepared in a manner analogous to **39b** but employing **28a** and 2,6-dichloro-3-nitropyridine in place of 2-chloro-3-nitropyridine afforded 74% of the title compound; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 1H), 7.11 (m, 5H), 6.45 (d, J = 8.4 Hz, 1H), 3.44 (m, 1H), 3.33 (s, 2H), 3.31 (m, 2H), 2.79 (m, 2H), 1.86 (m, 2H), 1.72 (m, 2H), 1.65 (m, 2H), 0.90 (t, J = 7.0 Hz, 3H).

1-Benzyl-4-[*N*-methyl-*N*-(3-nitro-6-fluoro-2-pyridinyl)amino]piperidine, 39e (PG = benzyl, R = methyl, X = F): prepared in a manner analogous to **39b** but employing 2,6-difluoro-3-nitropyridine[39,40] instead of 2-chloro-3-nitropyridine to afford 55% of the title compound; ^1H NMR (CD_3OD) δ 8.47 (dd, J = 7.2, 8.6 Hz, 1H), 7.43−7.51 (m, 5H), 6.49 (dd, J = 3.5, 8.6 Hz, 1H), 4.42−4.51 (m, 1H), 3.72 (s, 2H), 3.19 (br d, J = 11.8 Hz, 2H), 2.86 (s, 3H), 2.30−2.37 (m, 2H), 2.04−2.12 (m, 2H), 1.95 (m, 2H).

1-Benzyl-4-[*N*-ethyl-*N*-(3-nitro-6-fluoro-2-pyridinyl)amino]piperidine, 39f (PG = benzyl, R = ethyl, X = F): prepared in a manner similar to **39b** but employing **38a** and 2,6-difluoro-3-nitropyridine instead of **38b** and 2-chloro-3-nitropyridine; reaction was run at 0 °C to room temperature for 6 h to afford 54% of the title compound; ^1H NMR ($CDCl_3$) δ 8.01 (dd, J = 7.4, 8.6 Hz, 1H), 7.11 (m, 5H), 6.04 (dd, J = 3.9, 8.6 Hz, 1H), 3.43 (m, 1H), 3.31 (q, J = 7.0 Hz, 2H), 3.32 (s, 2H), 1.78 (m, 2H), 1.85 (m, 2H), 1.72 (m, 2H), 1.66 (m, 2H), 0.88 (t, J = 7.0 Hz, 3H).

1-Benzyl-4-[*N*-propyl-*N*-(3-nitro-2-pyridinyl)amino]piperidine, 39g (PG = benzyl, R = propyl, X = H). A mixture of **38c** (4.00 g, 17.2 mmol) and 2-chloro-3-nitropyridine (1.36 g, 8.61 mmol) was stirred at 110 °C in a sealed tube for 5 min, diluted with CH_2Cl_2 (40 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed (25−50% EtOAc/CH_2Cl_2) to afford 2.77 g (91%) of the product as a deep yellow oil: IR (neat) 2963 (m), 1595 (s), 1553 (s), 1512 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (dd, J = 1.8, 4.5 Hz, 1H), 8.02 (dd, J = 1.8, 8.0 Hz, 1H), 7.32 (m, 4H), 7.26 (m, 1H), 6.68 (dd, J = 4.5, 7.9 Hz, 1H), 3.61 (m, 1H), 3.50 (s, 2H), 3.34 (m, 2H), 2.95 (br d, J = 11.4 Hz, 2H), 2.02 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H), 1.44 (sext, J = 7.4 Hz, 2H), 0.83 (t, J = 7.3 Hz, 3H); EI-MS m/z (rel intensity) 308 (3), 172 (73), 90 (100). Anal. ($C_{20}H_{26}N_4O_2$) C, H, N.

1-Benzyl-4-[*N*-(1-methylethyl)-*N*-(3-nitro-2-pyridinyl)amino]piperidine, 39h (PG = benzyl, R = isopropyl, X = H). 38d (7.55 g, 32.49 mmol) and 2-chloro-3-nitropyridine (5.15 g, 32.49 mmol) were heated in a sealed tube under nitrogen to 160 °C for 3 h. The mixture was then applied to the top of a 400 g silica gel column in a few milliliters of chloroform and eluted with 15% EtOAc in hexane to yield 1.66 g (14%) of product as an oil: ^1H NMR ($CDCl_3$) δ 8.51 (dd, J = 1.7, 4.7 Hz, 1H), 8.10 (dd, J = 1.7, 8.1 Hz, 1H), 7.34 (dd, J = 4.7, 8.1 Hz, 1H), 7.18 (m, 5H), 3.48 (m, 1H), 3.39 (m, 2H), 2.85 (m, 3H), 2.15 (m, 2H), 1.85 (m, 2H), 1.67 (m, 2H), 1.25 (d, J = 6.6 Hz, 6H); MS-EI m/e (rel intensity) 354 (1), 337 (2), 308 (8), 172 (100), 146 (15), 91 (99).

1-Benzyl-4-[*N*-methyl-*N*-(6-chloro-3-nitro-2-pyridinyl)amino]piperidine, 39i (PG = benzyl, R = methyl, X = Cl): prepared in a manner analogous to **39b** but employing 2,6-dichloro-3-nitropyridine and **38b** to afford 69% of the title compound; ^1H NMR ($CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 1H), 7.14 (m, 5H), 6.47 (d, J = 8.3 Hz, 1H), 4.23 (sept J = 6.2 Hz, 1H), 3.40 (s, 2H), 2.85 (m, 2H), 2.57 (s, 3H), 2.02 (m, 2H), 1.72 (m, 2H); HRMS (EI) calcd for $C_{18}H_{21}N_4O_2Cl$ + H 361.1431, found 361.1447.

Nucleophilic Aromatic Substitution of Pyridazines. 4-(Isopropylamino)-3,5-dichloropyridazine, 51. 3,4,5-Trichloropyridazine (9.2 g 0.05 mol) was dissolved in 24 mL of toluene. Isopropylamine (16.5 g 0.28 mol) was added and the solution refluxed for 3 hours. Basic workup ($CHCl_3$, 1 N NaOH, Na_2SO_4) and chromatography (30% EtOAc/hexane) yielded 4.33 g of 4-(isopropylamino)-3,5-dichloropyridazine (the desired product) plus 4.73 g of 5-(isopropylamino)-3,4-dichloropyridazine: ^1H NMR ($CDCl_3$) δ 8.50 (s, 1H), 4.74 (br s, 1H), 4.47 (m, 1H), 1.20 (d, J = 6.4 Hz, 6H).

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-methylethyl)amino]-4-chloro-2-pyridazinyl]amino]piperazine, 52. 38b (2.30 g, 11.4 mmol) and **51** (1.0 g, 4.8 mmol) were heated in a sealed tube under a nitrogen atmosphere to 155 °C for 3 h. The mixture was chromatographed (50−100% EtOAc/hexane) to yield 320 mg (18%) of the title compound as an oil: ^1H NMR (CD_3OD) δ 8.43 (s, 1H), 7.30 (m, 5H), 4.5 (m, 1H), 3.51 (s, 2H), 2.90 (br d, 2H), 2.72 (s, 3H), 2.05 (m, 2H), 1.75 (m, 4H), 1.21 (d, J = 6.3 Hz, 6H).

General Procedures for Reduction of 3-Nitropyridines. 1-Benzyl-4-[*N*-ethyl-*N*-(3-amino-6-chloro-2-pyridinyl)amino]piperidine, 40a (PG = benzyl, R = Et, X = Cl). 39d (14.7 g, 39.21 mmol) and platinum oxide (6.0 g) in 130 mL of THF was hydrogenated on a Parr apparatus under 10 psi of hydrogen for 1 h. Filtration and evaporation of the solvent gave 14.4 g of the title compound as an oil: ^1H NMR (CD_3OD) δ 7.38 (m, 5H), 7.12 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 3.60 (s, 2H), 3.41 (s, 2H), 3.21 (q, J = 7.1 Hz, 2H), 3.17 (m, 1H), 2.98 (d, J = 12.1 Hz, 2H), 2.15 (t, J = 8.7 Hz, 2H), 1.78 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H).

1-Benzyl-4-[*N*-methyl-*N*-(3-amino-2-pyridinyl)amino]-piperidine, 40b (PG = benzyl, R = Me, X = H, Y = isopropyl). A mixture of **39b** (4.50 g, 13.8 mmol, 1 equiv) and aqueous titanium(III) chloride (19 wt % in 20 wt % aqueous hydrochloric acid, 56 mL, 82.7 mmol, 6 equiv) was stirred for 21 h at room temperature under reduced pressure and then added to concentrated aqueous ammonium hydroxide (500 mL) with cooling. The resulting mixture was extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic phase was washed with brine (50 mL), dried over sodium sulfate, and concentrated *in vacuo* to give 4.14 g (100%) of the product as a dark green, viscous oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.80 (dd, J = 1.7, 4.7 Hz, 1H), 7.25 (m, 5H), 6.93 (dd, J = 1.7, 7.7 Hz, 1H), 6.82 (dd, J = 4.7, 7.7 Hz, 1H), 3.85 (br s, 2H), 3.48 (s, 2H), 3.14 (m, 1H), 2.88 (br d, J = 11.8 Hz, 2H), 2.68 (s, 3H), 2.00 (td, J = 3.1, 11.3 Hz, 2H), 1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.0, 138.4, 137.5, 137.0, 129.2, 128.1, 126.9, 121.6, 119.7, 63.1, 57.3, 52.9, 34.4, 29.5.

General Procedure for Reduction and Alkylation of 3-Nitropyridines. 1-[(1,1-Dimethylethoxy)carbonyl]-4-[*N*-cyclopropyl-*N*-[3-((1-methylethyl)amino]-2-pyridinyl]-amino]piperidine, 41a (PG = BOC, R = cyclopropyl, X = H, Y = isopropyl). To a solution of **39c** (965 mg, 2.66

mmol) in CH_3OH (20 mL) under N_2 was added 10% Pd/C (567 mg), and the mixture was stirred under a hydrogen atmosphere (balloon) for 2 h. The mixture was then filtered through Celite and concentrated *in vacuo* to give 828 mg (94%) of the crude aminopyridine intermediate (R_f = 0.14 by TLC, EtOAc/hexane, 25/75). This intermediate was dissolved in absolute ethanol (10 mL) and treated with acetone (2.74 mL, 37.4 mmol) and $NaCNBH_3$ (78 mg, 1.24 mmol). The pH was adjusted to 5 with glacial CH_3COOH as measured on moistened pH test paper, and the mixture was stirred at room temperature for 6 days, during which additional $NaCNBH_3$ (312 mg) and acetone (5.48 mL) were added, the pH being adjusted after each addition. The mixture was then adjusted to pH 3 with 10% hydrochloric acid (aqueous), neutralized with 5% NaOH (aqueous), and concentrated to remove EtOH. The residue was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, concentrated, and chromatographed (5−15% EtOAc/hexane) to afford 497 mg (53%, 50% overall) of the product as an oil: ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, J = 1.7, 4.7 Hz, 1H), 6.95 (dd, J = 4.7, 8.0 Hz, 1H), 6.80 (dd, J = 1.7, 8.0 Hz, 1H), 4.48 (d, J = 8.4 Hz, 1H), 4.05 (br m, 2H), 3.51 (m, 1H), 3.20 (tt, J = 3.6, 11.2 Hz, 1H), 2.68 (br t, J = 12.2 Hz, 2H), 2.57 (m, 1H), 1.85 (m, 2H), 1.54 (m, 2H), 1.45 (s, 9H), 1.17 (d, J = 6.3 Hz, 6H), 0.51 (m, 2H), 0.34 (m, 2H); IR (neat) 3370 (w), 2969 (m), 1694 (s), 1577 (m), 1481 (s) cm^{-1}; EI-MS m/z (rel intensity) 374 (M^+, 24), 318 (4), 301 (8), 190 (60), 176 (26), 162 (18), 148 (100). Anal. ($C_{21}H_{34}N_4O_2$) C, H, N.

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 41b (PG = benzyl, R = Et, X = H, Y = *i*-Pr): prepared in a manner analogous to **41a** but reducing with platinum oxide for 50 min instead of Pd/C (see compound **40a**) to afford 63% of the title compound; ^{1}H NMR (CD_3OD) δ 7.41 (m, 5H), 7.07 (m, 2H), 3.71 (sept, J = 6.3 Hz, 1H), 3.63 (s, 2H), 3.24 (m, 1H), 3.02 (m, 2H), 2.72 (s, 3H), 2.17 (m, 2H), 1.90−1.72 (m, 4H), 1.33 (d, J = 6.3 Hz, 6H); HRMS calcd for $C_{21}H_{29}N_4Cl$ 372.2081, found 372.2079.

1-Benzyl-4-[*N*-ethyl-*N*-[3-(propylamino)-2-pyridinyl]-amino]piperidine, 41c (PG = benzyl, R = methyl, Y = propyl, X = H): prepared in a manner analogous to **41a** but the reduction of the nitro intermediate was conducted with platinum oxide to afford 90% of the title compound; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 1.4, 4.7 Hz, 1H), 7.27 (m, 5H), 6.91 (dd, J = 4.7, 7.9 Hz, 1H), 6.78 (dd, J = 1.4, 7.9 Hz, 1H), 4.79 (m, 1H), 3.48 (br s, 2H), 3.14 (q, J = 7.3 Hz, 2H), 3.04 (q, J = 7.0 Hz, 2H), 3.02 (m, 1H), 2.86 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.68 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H).

1-[(1,1-Dimethylethoxy)carbonyl]-4-[*N*-methyl-*N*-[3-[(cyclopropylmethyl)amino]-2-pyridinyl]amino]piperidine, 41d (PG = BOC, R = Me, X = H, Y = CH_2-*c*-Pr): prepared in a manner analogous to **41a** to afford 75% of the title compound; ^{1}H NMR (CD_3OD) δ 7.39 (dd, J = 2.8, 3.7 Hz, 1H), 6.79 (m, 2H), 3.79 (br d, J = 13.1 Hz, 2H), 3.07 (m, 1H), 2.80 (d, J = 6.7 Hz, 2H), 2.63 (m, 2H), 2.44 (s, 3H), 1.52 (m, 2H), 1.33 (m, 2H), 1.27 (s, 9H), 0.93 (m, 1H), 0.35 (m, 2H), 0.05 (m, 2H).

1-Benzyl-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 41e (PG = benzyl, R = Et, X = H, Y = *i*-Pr): prepared in a manner analogous to **41a** to afford 73% of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.49 (dd, J = 4.7, 1.6 Hz, 1H), 7.03−7.10 (m, 5H), 6.68 (dd, J = 7.9, 4.7 Hz, 1H), 6.58 (dd, J = 8.0, 1.7 Hz, 1H), 4.49 (d, J = 8.4 Hz, 1H), 3.30−3.38 (m, 3H), 2.89 (q, J = 7.1 Hz, 2H), 2.75−2.86 (m, 1H), 2.67−2.70 (br m, 2H), 1.77−1.84 (br m, 2H), 1.40−1.53 (br m, 4H), 0.97 (d, J = 6.3 Hz, 6H), 0.64 (t, J = 7.1 Hz, 3H).

1-Benzyl-4-[*N*-ethyl-*N*-[6-fluoro-3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 41f (PG = benzyl, R = Et, X = F, Y = *i*-Pr): prepared in a manner analogous to **41a** but the reduction of the nitro intermediate was carried out using palladium hydroxide to afford 93% of the title compound; ^{1}H NMR ($CDCl_3$) δ 6.93 (dd, J = 7.7, 8.5 Hz, 1H), 6.55 (dd, J = 3.5, 8.5 Hz, 1H), 4.30 (m, 1H), 3.51 (m, 1H), 3.09 (q, J = 7.0 Hz, 2H), 3.14−2.85 (m, 3H), 2.59 (m, 2H), 1.76 (m, 2H), 1.58 (m, 2H), 1.18 (d, J = 6.3 Hz, 6H), 0.85 (t, J = 7.0 Hz, 3H).

1-Benzyl-4-[*N*-(1-methylethyl)-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 41g (PG = benzyl, R = *i*-Pr, X = H, Y = Et). 39h (2.1 g, 5.9 mmol) and platinum oxide (1.0 g) in 50 mL of THF were hydrogenated on a Parr apparatus at 10 psi for 1 h. Filtration and evaporation of the solvent gave 1.95 g of oil. The oil was dissolved in methanol (0.4 M) and chilled to 0 °C. Acetaldehyde (0.5 mL, 8.9 mmol) and then sodium cyanoborohydride (558 mg, 8.9 mmol) were added, and the reaction mixture was stirred at room temperature overnight. It was then poured into 1 N NaOH solution and extracted with chloroform and the extract dried over sodium sulfate, filtered, and evaporated to an oil. Chromatography (20% EtOAc/hexane) yielded 900 mg (43%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 1H), 7.19 (m, 5H), 6.84 (dd, J = 4.7, 7.9 Hz, 1H), 6.67 (dd, J = 7.9 Hz, 1H), 4.98 (m, 1H), 3.46 (m, 3H), 3.15 (m, 1H), 2.96 (q, J = 7.1 Hz, 2H), 2.75 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H), 1.40 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 0.90 (d, J = 6.4 Hz, 6H); MS-EI m/e (rel intensity) 352 (7), 293 (10), 219 (24), 203 (14), 190 (24), 173 (45), 172 (44), 91 (100).

1-Benzyl-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 41h (PG = benzyl, R = Et, X = H, Y = Et): prepared in a manner analogous to **41g** to afford 83% of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, J = 1.5, 4.7 Hz, 1H), 7.33 (m, 5H), 6.95 (dd, J = 4.7, 7.9 Hz, 1H), 6.82 (dd, J = 1.5, 7.9 Hz, 1H), 4.75 (br t, 1H), 3.55 (s, 2H), 3.16 (m, 4H), 3.05 (m, 1H), 2.92 (m, 2H), 2.05 (m, 2H), 1.86−1.68 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H).

1-Benzyl-4-[*N*-propyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 41i (PG = benzyl, R = Pr, X = H, Y = *i*-Pr). A mixture of **39g** (2.61 g, 7.36 mmol, 1 equiv) in aqueous $TiCl_3$ (30.0 mL, 19 wt % in 20% aqueous HCl, 44.2 mmol, 6 equiv) was stirred under reduced pressure for 20 h and then added carefully to concentrated aqueous ammonium hydroxide (250 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product which was then chromatographed, eluting with a gradient of CH_3OH/CH_2Cl_2 (2.5/97.5−5/95). Fractions with an R_f = 0.17 by TLC (methanol/chloroform, 5/95) were pooled and concentrated *in vacuo* to give 1.51 g (63%) of the product as a faint green solid: mp 73−74 °C; IR (mull) 3400 (m), 3174 (m), 3073 (m), 2926 (s), 1621 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, J = 1.6, 4.8 Hz, 1H), 7.30 (m, 4H), 7.25 (m, 1H), 6.95 (dd, J = 1.6, 7.8 Hz, 1H), 6.84 (dd, J = 4.8, 7.8 Hz, 1H), 3.94 (s, 2H), 3.50 (s, 2H), 3.12 (m, 2H), 3.00 (m, 1H), 2.90 (br d, J = 11.3 Hz, 2H), 1.98 (m, 2H), 1.75 (m, 4H), 1.29 (sext, J = 7.3 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H); EI-MS m/z (rel intensity) 324 (M^+, 6), 265 (8), 191 (21), 173 (63), 91 (100). Anal. ($C_{20}H_{28}N_4$) C, H, N.

A solution of 1-benzyl-4-[*N*-propyl-*N*-(3-amino-2-pyridinyl)-amino]piperidine (0.35 g, 1.08 mmol, 1 equiv) in absolute ethanol (4.3 mL) under N_2 was treated with acetone (1.19 mL, 16.2 mmol, 15 equiv) and $NaCNBH_3$ (135 mg, 2.16 mmol, 2 mol equiv), and the pH was adjusted to 5 with glacial acetic acid as measured on moistened pH test paper. The resulting mixture was stirred at room temperature for 65 h, during which additional acetone (2.38 mL, 32.4 mmol) and $NaCNBH_3$ (152 mg, 2.42 mmol) were added. Then the reaction mixture was adjusted to pH 3 with 3 N HCl (aqueous), neutralized with 5% aqueous NaOH, and concentrated *in vacuo*. The residue was chromatographed eluting with a gradient of CH_3OH/CH_2Cl_2 (1/99−2/98), and those fractions with an R_f = 0.13 by TLC (5% $CH_3OH/CHCl_3$) were pooled and concentrated *in vacuo* to give 298 mg (75%) of the product as a faint green, viscous oil: IR (neat) 3361 (w), 2961 (s), 1577 (s), 1481 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, J = 1.5, 4.7 Hz, 1H), 7.31−7.24 (m, 5H), 6.90 (dd, J = 4.7, 7.9 Hz, 1H), 6.79 (m, 1H), 4.66 (br d, J = 8.3 Hz, 1H), 3.53 (m, 3H), 3.06 (m, 2H), 2.91 (br m, 3H), 1.98 (br m, 2H), 1.73 (br m, 4H), 1.26 (sext, J = 7.3 Hz, 2H), 1.20 (d, J = 6.3 Hz, 6H), 0.80 (t, J = 7.3 Hz, 3H); EI-MS

m/z (rel intensity) 366 (M^+, 34), 307 (27), 233 (55), 216 (15), 173 (90), 172 (82), 91 (100). Anal. ($C_{23}H_{34}N_4$) C, H, N.

1-Benzyl-4-[*N*-methyl-*N*-[6-chloro-3-[(1-methylethyl)-amino]pyridinyl]amino]piperidine, 41j (PG = benzyl, R = Me, X = Cl, Y = *i*-Pr). The reductive alkylation was conducted in a manner similar to that described for **41a**, starting with **40a** to afford 63% of the title compound: ^{1}H NMR (CD_3OD) δ 7.44 (m, 5H), 7.07 (m, 2H), 3.71 (sept, J = 6.3 Hz, 1H), 3.63 (s, 2H), 3.24 (sept, 1H), 3.02 (m, 2H), 2.72 (s, 3H), 2.18 (m, 2H), 1.85 (m, 4H), 1.33 (d, J = 6.3 Hz, 6H); HRMS calcd for $C_{21}H_{29}N_4Cl$ 372.2081, found 372.2079.

General Procedures for the Synthesis of 3-(*tert*-Butylamino)pyridines. 1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-cyano-1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 42a (R = Me, X = H): prepared according to literature ref 42 but starting with compound **40b** to afford 85% of the title compound; ^{1}H NMR (CD_3OD) δ 7.76 (dd, J = 1.5, 4.8 Hz, 1H), 7.41 (dd, J = 1.5, 8.1 Hz, 1H), 7.29 (m, 5H), 7.08 (dd, J = 4.8, 8.1 Hz, 1H), 3.49 (s, 2H), 3.07 (m, 1H), 2.85 (m, 2H), 2.51 (s, 3H), 2.03 (m, 2H), 1.74 (s, 6H), 1.74−1.55 (m, 4H); HRMS (EI) calcd for $C_{23}H_{31}N_4$ 377.2579, found 377.2581.

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 44a (R = Me, X = H). 42a (1.94 g, 5.35 mmol) was dissolved in 10 mL of toluene and cooled to −78 °C. In a separate flask, 38 mL of CH_3Li (53.5 mmol, 1.4 M in ether) was dissolved in 10 mL of toluene and cooled to −78 °C. Then the toluene solution of the cyanoamine **42a** was cannulated to the CH_3Li solution, and the reaction mixture was allowed to warm gradually to 0 °C. The reaction was quenched by the dropwise addition of water and the mixture extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (40% EtOAc/hexane) provided 1.45 g of the *tert*-butylamine (84%): ^{1}H NMR (CD_3OD) δ 7.64 (dd, J = 1.5, 4.8 Hz, 1H), 7.37 (m, 5H), 7.29 (dd, J = 1.5, 8.1 Hz, 1H), 7.03 (dd, J = 4.8, 8.1 Hz, 1H), 3.57 (s, 2H), 3.09 (s, 1H), 2.93 (m, 2H), 2.64 (s, 3H), 2.12 (m, 2H), 1.80−1.62 (m, 4H), 1.44 (s, 9H); HRMS (EI) calcd for $C_{23}H_{34}N_4$ 366.2783, found 366.2779.

1-Benzyl-4-[*N*-ethyl-*N*-[3-[(1-cyano-1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 42b (R = Et, X = H): prepared according to literature ref 42, starting with compound **40**, to afford 85% of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J = 1.7, 4.8 Hz, 1H), 7.32 (m, 6H), 7.03 (dd, J = 4.8, 8.0 Hz, 1H), 5.39 (s, 1H), 3.51 (s, 2H), 3.14 (q, J = 7.1 Hz, 2H), 2.98 (m, 1H), 2.88 (m, 2H), 1.99 (m, 2H), 1.75 (s, 6H), 1.75 (m, 2H), 1.65 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H).

[2-[*N*-Ethyl-*N*-[1-(phenylmethyl)piperidin-4-yl]amino]-pyridin-3-yl](1-methylethylidene)amine, 43b (R = Et, X = H): prepared according to literature ref 43, starting with compound **40**, to afford 100% of the title compound; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 6.9 Hz, 3H), 1.49−1.52 (m, 2H), 1.69 (s, 3H), 1.77−2.02 (m, 4H), 2.16 (s, 3H), 2.88−2.92 (m, 2H), 3.02 (q, J = 6.9, 13.9 Hz, 2H), 3.45−3.59 (m, 3H), 6.71−6.83 (m, 2H), 7.22 −7.31 (m, 5H), 7.97−7.99 (m, 1H); HRMS calcd for $C_{22}H_{30}N_4 + H_1$ 351.2549, found 351.2558.

1-Benzyl-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 44b (R = Et, X = H): prepared according to literature ref 42 from **42b** (see also preparation of **44a**) or according to literature ref 43 from **43b** to afford 69% or 61%, respectively, of the title *tert*-butylamine; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, J = 1.5, 4.7 Hz, 1H), 7.30 (m, 5H), 7.09 (dd, J = 1.5, 8.1 Hz, 1H), 6.89 (dd, J = 4.7, 8.1 Hz, 1H), 5.21 (s, 1H), 3.52 (s, 2H), 3.14 (q, J = 7.1 Hz, 1H), 2.97 (m, 1H), 2.90 (m, 2H), 2.01 (m, 2H), 1.80−1.65 (m, 4H), 1.39 (s, 9H), 0.89 (t, J = 7.1 Hz, 3H). Anal. ($C_{23}H_{34}N_4$) C, H, N.

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-cyano-1-methylethyl)-amino]-6-fluoro-2-pyridinyl]amino]piperidine, 42c (R = Me, X = F): prepared according to literature ref 42 from 1-benzyl-4-[*N*-methyl-*N*-(3-amino-6-fluoro-2-pyridinyl)amino]-piperidine (prepared from **39e** via hydrogenation over Pd/C, see beginning portion of preparation of compound **41a**) to afford 43% of the title cyanoamine; ^{1}H NMR (CD_3OD) δ 7.64 (dd, J = 7.3, 8.4 Hz, 1H), 7.36−7.41 (m, 5H), 6.73 (dd, J = 3.3, 8.4 Hz, 1H), 3.60 (s, 2H), 3.35 (m, 1H), 3.00 (br d, J = 12.5 Hz, 2H), 2.74 (s, 3H), 2.10−2.20 (m, 2H), 1.81 (m, 4H), 1.77 (s, 6H).

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 44c (R = Me, X = F): prepared according to literature ref 42 from **42c** to afford 33% of the title *tert*-butylamine; ^{1}H NMR (CD_3OD) δ 7.55 (m, 1H), 7.48 (m, 5H), 6.78 (m, 1H), 3.68 (s, 2H), 3.25 (m, 1H), 3.10 (br d, 2H), 2.74 (s, 3H), 2.20−2.30 (m, 2H), 1.75−1.90 (m, 4H), 1.52 (s, 9H).

[2-[*N*-Ethyl-*N*-[1-(phenylmethyl)piperidin-4-yl]amino]-6-fluoro-pyridin-3-yl](1-methylethylidene)amine, 43d (R = Et, X = F): prepared according to literature ref 43 to afford 99% of the title compound; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7 Hz, 3H), 1.51 (m, 2H), 1.72 (s, 3H), 1.77−1.85 (m, 2H), 1.96−2.08 (m, 2H), 2.16 (s, 3H), 2.90 (m, 2H), 3.30 (q, J = 7, 13.9 Hz, 2H), 3.48 (s, 2H), 3.62−3.70 (m, 1H), 6.26 (dd, J = 3.7, 8.0 Hz, 1H), 6.82 (t, J = 7.9 Hz, 1H), 7.22−7.31 (m, 5H). Anal. ($C_{22}H_{29}FN_4$) C, H, N.

1-Benzyl-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 44d (R = Et, X = F): prepared according to literature ref 43 from **43d** to afford 72% of the title *tert*-butylamine; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 5H), 7.21 (dd, J = 7.8, 8.6 Hz, 1H), 6.52 (dd, J = 3.5, 8.6 Hz, 1H), 4.77 (s, 1H), 3.47 (s, 2H), 3.09 (q, J = 7.1 Hz, 2H), 2.92 (m, 1H), 2.87 (m, 2H), 1.95 (m, 2H), 1.71 (m, 2H), 1.65 (m, 2H), 1.33 (s, 9H), 0.87 (t, J = 7.1 Hz, 3H); HRMS calcd for $C_{23}H_{33}N_4F$ 385.2767, found 385.2777. Anal. ($C_{23}H_{33}FN_4$) C, H, N.

1-Benzyl-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-chloro-2-pyridinyl]amino]piperidine, 44e (R = Et, X = Cl): prepared according to literature ref 43 from **40a** to afford 31% of the title compound as an oil; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 7.01 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.01 (s, 1H), 3.47 (s, 2H), 3.07 (q, J = 7.1 Hz, 2H), 2.87 (m, 3H), 1.96 (m, 2H), 1.69 (m, 4H), 1.32 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H).

1-Benzyl-4-[*N*-propyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 44f (R = Pr, X = H): prepared according to literature ref 42 from 1-benzyl-4-[*N*-propyl-*N*-(3-amino-2-pyridinyl)amino]piperidine (prepared from **39g** via hydrogenation over Pd/C, see beginning portion of preparation of compound **41a**) to afford 63% of the title compound as a pale green, viscous oil; IR (neat) 3338 (w), 2960 (s), 1575 (s), 1488 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, J = 1.6, 4.8 Hz, 1H), 7.31 (m, 4H), 7.25 (m, 1H), 7.05 (dd, J = 1.6, 8.0 Hz, 1H), 6.85 (dd, J = 4.8, 8.0 Hz, 1H), 5.13 (s, 1H), 3.49 (br s, 2H), 3.05 (m, 2H), 2.89 (m, 3H), 1.97 (br m, 2H), 1.73 (br m, 4H), 1.36 (s, 9H), 1.25 (sext, J = 7.3 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H); EI-MS *m/z* (rel intensity) 380 (M^+, 31), 321 (24), 289 (10), 247 (46), 203 (29), 173 (100), 172 (80), 91 (94); HRMS (FAB) calcd for $C_{24}H_{36}N_4$ + H 381.3018, found 381.3021.

Synthesis of *tert*-Amyl-Substituted Compounds. 1-[(1,1-Dimethylethoxy)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylprop-2-ynyl)amino]-2-pyridinyl]amino]piperidine, 45. To a solution of 1-[(1,1-dimethylethoxy)carbonyl]-4-[*N*-methyl-*N*-(3-nitro-2-pyridinyl)amino]piperidine (5.00 g, 14.9 mmol) in 85 mL of MeOH was added 800 mg of 10% Pd/C. The mixture was hydrogenated at 40 psi (Parr) for 5.5 h, filtered through Celite, and concentrated *in vacuo* to give 4.50 g (99%) of the amine intermediate as an off-white solid (R_f = 0.23, 50% EtOAc/hexane). This intermediate was then dissolved in 20 mL of dry DMF under N_2 at 0 °C, and 750 mg (11.8 mmol) of copper powder and 750 mg (7.58 mmol) of cuprous chloride were added. To this was added a solution of 1.51 g (14.7 mmol) of 3-chloro-3-methyl-1-butyne in 4 mL of dry DMF in 5 portions over 15 min. The resulting mixture was stirred at room temperature for 2 h and concentrated to remove DMF. Aqueous workup (CH_2Cl_2, Na_2SO_4) and chromatography (10−40% EtOAc/hexane) provided 2.42 g (44%) of the title compound as an orange oil: IR (atr) 3300 (w), 2976 (m), 1692 (s), 1577 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, 1H, J = 1.5, 4.8 Hz, 1H), 7.51 (d, J = 6.8 Hz, 1H), 6.95 (dd, J = 4.8, 8.0 Hz, 1H), 4.92 (br s, 1H), 4.05 (br m, 2H), 3.19 (m, 1H), 2.75 (br t, J = 12.6 Hz, 2H), 2.61 (s, 3H), 2.38 (s, 1H), 1.75 (m, 2H), 1.62 (s, 6H), 1.49 (m, 2H), 1.45 (s, 9H); MS-EI *m/e* 372 (M^+), 299, 271, 214, 188, 174, 57; HRMS calcd for $C_{21}H_{32}N_4O_2$ 372.2525, found 372.2525.

1-[1,1-Dimethylethoxy)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylpropyl)amino]-2-pyridinyl]amino]piperidine, 46. To a solution of 2.41 g (6.48 mmol) of **45** in 40 mL of absolute EtOH under N_2 was added 620 mg of wet Raney nickel. The mixture was hydrogenated at 40 psi (Parr) for 21 h, filtered through Celite, and concentrated to give 2.52 g of a yellow viscous oil which was chromatographed, eluting with a gradient of 10−35% EtOAc/hexane. Pooling of fractions giving an $R_f = 0.31$ by TLC (25% EtOAc/hexane) and removal of solvent *in vacuo* gave 2.43 g (99%) of the title compound as a pale green viscous oil: IR (atr) 3357 (w), 2971 (s), 1695 (s), 1576 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (dd, $J = 1.5$, 4.8 Hz, 1H), 7.04 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.87 (dd, $J = 4.8$, 8.0 Hz, 1H), 4.87 (s, 1H), 4.04 (br m, 2H), 3.20 (m, 1H), 2.76 (br t, $J = 11.9$ Hz, 2H), 2.61 (s, 3H), 1.71 (m, 4H), 1.50 (m, 2H), 1.45 (s, 9H), 1.31 (s, 6H), 0.86 (t, $J = 7.4$ Hz, 3H); MS (EI) *m/e* 376 (M^+), 347, 305, 303, 275, 249, 233, 191, 164, 148, 122, 57; HRMS calcd for $C_{21}H_{36}N_4O_2$ 376.2838, found 376.2838.

Synthesis of 3-(Cyclopropylamino)pyridines. 1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-ethoxycyclopropyl)amino]-2-pyridinyl]amino]piperidine, 47. A mixture of **40b** (825 mg, 2.78 mmol), 1-bromo-1-ethoxycyclopropane (919 mg, 5.57 mmol), and triethylamine (0.78 mL, 5.57 mmol) in dry tetrahydrofuran (1.4 mL) under N_2 was refluxed for 48 h and cooled to room temperature. Aqueous workup (CH_2Cl_2, Na_2SO_4) and chromatography (1−5% methanol/CH_2Cl_2) afforded 185 mg (17%) of the product as a pale yellow oil. An additional 279 mg (26%) of slightly impure product was also isolated: ^1H NMR ($CDCl_3$) δ 7.80 (dd, $J = 1.7$, 4.7 Hz, 1H), 7.41 (dd, $J = 1.7$, 8.0 Hz, 1H), 7.25 (m, 5H), 6.93 (dd, $J = 4.8$, 7.9 Hz, 1H), 5.62 (s, 1H), 3.51 (q, $J = 7.0$ Hz, 2H), 3.48 (s, 2H), 3.03 (m, 1H), 2.87 (br d, $J = 11.8$ Hz, 2H), 2.60 (s, 3H), 1.98 (br t, $J = 11.5$ Hz, 2H), 1.71 (m, 2H), 1.64 (m, 2H), 1.13 (m, 5H), 0.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.2, 138.2, 136.8, 129.2, 128.2, 127.0, 120.5, 120.0, 68.2, 63.1, 61.0, 58.2, 52.8, 36.1, 30.0, 15.3, 14.6.

1-Benzyl-4-[*N*-methyl-*N*-[3-(cyclopropylamino)-2-pyridinyl]amino]piperidine, 48. A solution of **47** (178 mg, 0.468 mmol) in dry THF (4.7 mL) under N_2 was treated with LAH (18 mg), and the resulting mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous ammonium chloride (5 mL), and the mixture was diluted with water (30 mL) and CH_2Cl_2 (20 mL) and filtered through Celite. The layers of the filtrate were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phase was washed with saline (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was then chromatographed (2.5−5% MeOH/$CHCl_3$) to give 93 mg (59%) of the product as an amber film: IR (neat) 3363 (w), 2946 (m), 2926 (m), 1578 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (dd, $J = 1.6$, 4.8 Hz, 1H), 7.31 (m, 4H), 7.24 (m, 1H), 7.21 (dd, $J = 1.6$, 7.9 Hz, 1H), 6.92 (dd, $J = 4.8$, 7.9 Hz, 1H), 4.92 (s, 1H), 3.50 (s, 2H), 3.04 (m, 1H), 2.89 (br d, $J = 11.2$ Hz, 2H), 2.62 (s, 3H), 2.35 (m, 1H), 1.99 (m, 2H), 1.70 (m, 4H), 0.75 (m, 2H), 0.51 (m, 2H); EI-MS *m/z* (rel intensity) 336 (M^+, 6), 280 (3), 173 (73), 91 (100); HRMS calcd for $C_{21}H_{28}N_4$ 336.2314, found 336.2329.

1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-methylcyclopropyl)amino]-2-pyridinyl]amino]piperidine, 49. To a solution of CH_3Li·LiBr (1.5 M in diethyl ether, 2.28 mL, 3.42 mmol) in dry toluene (6.3 mL) at −78 °C under N_2 in a flame-dried flask was added a solution of **47** (325 mg, 0.854 mmol) in dry toluene (8.5 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, the reaction was quenched carefully with saturated aqueous ammonium chloride (10 mL), and water (10 mL), and the mixture as warmed to room temperature. Aqueous workup (EtOAc, $MgSO_4$) and chromatography (1−4% MeOH/$CHCl_3$) gave 232 mg (78%) of the product as a faint green, oily film: IR (neat) 3366 (w), 2949 (m), 1577 (s), 1476 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, $J = 1.6$, 4.8 Hz, 1H), 7.31 (m, 5H), 7.17 (dd, $J = 1.6$, 7.9 Hz, 1H), 6.91 (dd, $J = 4.8$, 7.9 Hz, 1H), 5.02 (s, 1H), 3.50 (br s, 2H), 3.05 (br m, 1H), 2.88 (br m, 2H), 2.59 (s, 3H), 2.01 (br m, 2H), 1.71 (br m, 4H), 1.32 (s, 3H), 0.76 (m, 2H), 0.65 (m, 2H); EI-MS *m/z* (rel intensity) 350 (M^+, 9), 335 (3), 280 (4), 174 (46), 173 (100), 172 (35), 91 (84); HRMS (FAB) calcd for $C_{22}H_{30}N_4$ + H 351.2549, found 351.2542.

General Procedures for the Deprotection of Benzylpiperidines. 4-[*N*-Methyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 50a (Y = *tert*-butyl, R = Me, X = H). 44a (1.84 g, 5.2 mmol) was dissolved in 60 mL of EtOH. Then 800 mg of 10% Pd/C was added, and the reaction mixture was placed on a Parr hydrogenator for 7 h at 40 psi. Filtration and concentration *in vacuo* afforded 1.3 g of the desired product (96%) which was used without further purification: ^1H NMR (CD_3OD) δ 7.47 (dd, $J = 1.5$, 4.8 Hz, 1H), 7.13 (dd, $J = 1.5$, 8.1 Hz, 1H), 6.86 (dd, $J = 4.8$, 8.1 Hz, 1H), 2.99 (m, 1H), 2.93 (m, 2H), 2.50 (s, 3H), 2.42 (m, 2H), 1.61 (m, 2H), 1.42 (m, 2H), 1.29 (s, 9H).

4-[*N*-Ethyl-*N*-[(3-(ethylamino)-2-pyridinyl]amino]piperidine, 50b (R = Et, Y = Et, X = H): prepared in a manner analogous to **50a** using **41h** but employing $Pd(OH)_2$/C to afford 84% of the title amine; ^1H NMR ($CDCl_3$) δ 7.60 (dd, $J = 1.5$, 4.7 Hz, 1H), 6.81 (dd, $J = 4.7$, 7.9 Hz, 1H), 6.69 (dd, $J = 1.5$, 7.9 Hz, 1H), 4.52 (m, 1H), 3.27 (m, 2H), 3.01 (m, 4H), 2.88 (m, 1H), 2.64 (m, 2H), 1.81 (m, 2H), 1.68 (m, 2H), 1.14 (t, $J = 7.1$ Hz, 1H), 0.75 (t, $J = 7.0$ Hz, 3H).

4-[*N*-Ethyl-*N*-[(3-(propylamino)-2-pyridinyl]amino]piperidine, 50c (R = Et, Y = propyl, X = H): prepared in a manner analogous to **50a** but employing $Pd(OH)_2$/C to afford 99% of the title amine; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, $J = 1.5$, 4.7 Hz, 1H), 6.94 (dd, $J = 4.7$, 7.9 Hz, 1H), 6.82 (dd, $J = 1.5$, 7.9 Hz, 1H), 4.65 (br, 1H), 3.43 (m, 3H), 3.09 (m, 4H), 2.88 (m, 2H), 2.05−1.85 (m, 2H), 1.66 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 7.01$ Hz, 3H).

4-[*N*-Ethyl-*N*-[6-fluoro-3-[(1-methylethyl)amino]-2--pyridinyl]amino]piperidine, 50d (R = Et, Y = propyl, X = F): prepared in a manner analogous to **50a** but employing $Pd(OH)_2$/C to afford 93% of the title amine; ^1H NMR ($CDCl_3$) δ 6.93 (dd, $J = 8.1$, 8.5 Hz, 1H), 6.54 (dd, $J = 3.5$, 8.5 Hz, 1H), 4.30 (br d, 1H), 3.50 (m, 1H), 3.09 (m, 4H), 3.00 (br, 1H), 2.59 (m, 2H), 1.80 (m, 2H), 1.55 (m, 2H), 1.18 (d, $J = 6.3$ Hz, 1H), 0.86 (t, $J = 7.0$ Hz, 3H).

4-[*N*-Methyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 50e (R = Me, Y = *tert*-butyl, X = F): prepared in a manner analogous to **50a** to afford 99% of the title compound; ^1H NMR (CD_3OD) δ 7.38 (dd, $J = 7.4$, 8.5 Hz, 1H), 6.61 (dd, J =3.3, 8.7 Hz, 1H), 3.16−3.27 (m, 3H), 2.71−2.79 (m, 2H), 2.56 (s, 3H), 1.84 (d, $J = 12.0$ Hz, 2H), 1.61−1.66 (m, 2H), 1.33 (s, 9H).

4-[*N*-Ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 50f (R = Et, Y = *tert*-Bu, X = F): prepared in a manner analogous to **50a** but employing $Pd(OH)_2$/C to afford 99% of the title compound; ^1H NMR ($CDCl_3$) δ 7.19 (dd, $J = 8.1$, 8.6 Hz, 1H), 6.51 (dd, $J = 3.5$, 8.6 Hz, 1H), 4.24 (br s, 1H), 3.08 (m, 4H), 2.95 (m, 1H), 2.52 (m, 2H), 1.72 (m, 2H), 1.50 (m, 2H), 1.32 (s, 9H), 0.85 (t, $J = 7.1$ Hz, 3H).

4-[*N*-Ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]-amino]piperidine, 50g (Y = isopropyl, R = Et, X = H): prepared in a manner analogous to **50a** but employing Pd-$(OH)_2$/C to afford 93% of the title compound as a green oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, $J = 1.5$, 4.7 Hz, 1H), 6.91 (m, 1H), 6.80 (m, 1H), 4.70 (m, 1H), 3.56 (m, 1H), 3.10 (m, 5H), 2.61 (m, 2H), 1.83 (m, 2H), 1.55 (m, 2H), 1.20 (d, $J = 6.2$ Hz, 6H), 0.86 (t, $J = 7.0$ Hz, 3H).

4-[*N*-Ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]-amino]piperidine, 50h (R = Et, Y = *tert*-butyl, X = H): prepared in a manner analogous to **50a** to afford 93% of the amine as an amber oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (m, 1H), 7.06 (d, $J = 8.1$ Hz, 1H), 6.87 (dd, $J = 4.7$, 8.0 Hz, 1H), 5.18 (s, 1H), 3.11 (m, 4H), 3.00 (m, 1H), 2.57 (m, 2H), 1.80 (m, 2H), 1.52 (m, 2H), 1.36 (s, 9H), 0.87 (t, $J = 7.0$ Hz, 3H).

4-[*N*-Methyl-*N*-[3-[(1-methylcyclopropyl)amino]-2-pyridinyl]amino]piperidine, 50i (R = Me, Y = CH_2-*c*-Pr, X = H): prepared in a manner analogous to **50a** but starting with compound **49** and employing $Pd(OH)_2$/C to afford 100% of the amine; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, $J = 1.5$, 4.8 Hz, 1H), 7.20 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.94 (dd, $J = 4.8$, 8.0 Hz, 1H), 5.20 (br s, 1H), 3.30 (m, 3H), 2.80 (br t, $J = 11.4$ Hz, 2H), 2.56 (s, 3H), 1.93 (m, 2H), 1.77 (m, 2H), 1.32 (s, 3H), 0.77 (m, 2H), 0.67 (m, 2H).

4-[*N*-Methyl-*N*-[6-chloro-3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 50j (R = Me Y = isopropyl, X = Cl). 1-Benzyl-4-[*N*-methyl-*N*-[3-[(1-methylethyl)amino]-6-chloro-2-pyridinyl]amino]piperidine (**41j**) (1.60 g, 4.84 mmol) was dissolved in CH_2Cl_2 (0.2 M) and cooled to 0 °C. 1-Chloroethyl chloroformate (0.57 mL, 5.32 mmol) was added dropwise. The solution was allowed to warm to room temperature and then refluxed for 0.5 h. The solvent was evaporated to one-third volume, 15 mL CH_3OH was added, and the solution was refluxed for 2 h. Aqueous workup ($CHCl_3$, Na_2SO_4) and evaporation of the solvent gave 1.5 g of an oil. Chromatography (10% MeOH/$CHCl_3$) yielded 432 mg (31%) of the title compound: ^{1}H NMR (CD_3OD) δ 6.88 (d, J = 2.3 Hz, 2H), 3.49 (m, 1H), 3.23 (m, 2H), 2.87 (m, 2H), 2.50 (s, 3H), 1.95 (br d, 2H), 1.70 (m, 2H), 1.12 (d, J = 6.3 Hz, 6H).

4-[*N*-Ethyl-*N*-[6-chloro-3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 50k (Y = *tert*-butyl, R = Et, X = Cl): prepared analogous to **50j** to afford 31% of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 4.91 (s, 1H), 3.35 (m, 2H), 3.20 (m, 1H), 3.03 (q, J = 7.0 Hz, 2H), 2.81 (m, 2H), 1.92 (m, 4H), 1.32 (s, 9H), 0.85 (t, J = 7.0 Hz, 3H).

4-[*N*-Methyl-*N*-[3-[(1-methylethyl)amino]-2-pyridazinyl]-amino]piperidine, 53: prepared in a manner analogous to **50a** but starting with compound **52** and employing $Pd(OH)_2$ to afford 63% of the title compound; ^{1}H NMR (CD_3OD) δ 8.54 (d, J = 5.9 Hz, 1H), 6.84 (d, J = 5.9 Hz, 1H), 3.89 (m, 1H), 3.67 (m, 1H), 3.54 (m, 2H), 3.15 (m, 2H), 2.86 (s, 3H), 2.26 (m, 2H), 2.05 (m, 2H), 1.42 (d, J = 6.3 Hz, 6H).

Reduction Employing Ammonium Formate as Reducing Agent. 4-[*N*-Methyl-*N*-[3-(cyclopropylamino)-2-pyridinyl]amino]piperidine, 50l (Y = cyclopropyl, R= Me, X = H). A mixture of **48** (135 mg, 0.401 mmol), ammonium formate (76 mg, 1.20 mmol, 3 equiv), and 10% Pd/C (135 mg) in methanol (8 mL) under N_2 was degassed and placed in an oil bath maintained at 60−65 °C. The mixture was refluxed for 45 min, cooled to room temperature, filtered through Celite, and concentrated *in vacuo* to provide 120 mg (100%) of the title amine: ^{1}H NMR (MeOD, 400 MHz) δ 7.66 (m, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.06 (dd, J = 4.8, 7.9 Hz, 1H), 3.43 (m, 3H), 3.01 (br t, J = 11.8 Hz, 2H), 2.62 (s, 3H), 2.38 (m, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 0.80 (m, 2H), 0.54 (m, 2H).

4-[*N*-Propyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]-amino]piperidine, 50m (Y = isopropyl, R = propyl, X = H): prepared in a manner analogous to **50l** to afford 81% of the title amine; ^{1}H NMR ($CDCl_3$) δ 7.70 (dd, J = 1.6, 4.7 Hz, 1H), 6.91 (dd, J = 4.7, 7.9 Hz, 1H), 6.80 (m, 1H), 5.24 (br s, 1H), 4.63 (d, J = 8.4 Hz, 1H), 3.53 (m, 1H), 3.21 (br d, J = 12.6 Hz, 2H), 3.04 (m, 3H), 2.66 (br t, J = 12.1 Hz, 2H), 1.84 (m, 2H), 1.70 (m, 2H), 1.25 (m, 2H), 1.20 (d, J = 6.3 Hz, 6H), 0.80 (t, J = 7.4 Hz, 3H).

4-[*N*-Propyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 50n (Y = *tert*-butyl, R = propyl, X = H): prepared in a manner analogous to **50l** to afford 94% of the title amine; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, J = 1.5, 4.7 Hz, 1H), 7.05 (dd, J = 1.5, 8.0 Hz, 1H), 6.85 (dd, J = 4.7, 8.0 Hz, 1H), 5.14 (s, 1H), 3.05 (m, 4H), 2.90 (m, 1H), 2.54 (br t, J = 12.2 Hz, 2H), 1.75 (m, 2H), 1.52 (m, 2H), 1.35 (s, 9H), 1.25 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H).

General Procedures for Deprotection of 1-BOC-4-[*N*-alkyl-*N*-[3-(alkylamino)pyridinyl]amino]piperidines. 4-[*N*-Cyclopropyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]-amino]piperidine, 50o (R = cyclopropyl, Y = isopropyl, X = H). A solution of **41a** (430 mg, 1.15 mmol, 1 equiv) in dry CH_2Cl_2 (5.7 mL) under N_2 was treated with TFA (1.15 mL, 14.9 mmol, 13 equiv). The mixture was stirred at room temperature. Basic workup (CH_2Cl_2, NaOH, Na_2SO_4) afforded 290 mg (92%) of the deprotected piperidine: ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, J = 1.6, 4.7 Hz, 1H), 6.93 (dd, J = 4.7, 8.0 Hz, 1H), 6.79 (dd, J = 1.5, 8.0 Hz, 1H), 4.51 (d, J = 8.6 Hz, 1H), 3.51 (m, 1H), 3.13 (m, 1H), 3.07 (br d, J = 11.0 Hz, 2H), 2.62−2.52 (m, 3H), 1.95−1.80 (m, 3H), 1.61 (qd, J = 3.9, 11.9 Hz, 2H), 1.17 (d, J = 6.3 Hz, 6H).

4-[*N*-Methyl-*N*-[3-[(1,1-dimethylpropyl)amino]-2-pyridinyl]amino]piperidine, 50p (R = Me, Y = *tert*-amyl, X = H): prepared in a manner analogous to **50o** from compound **46** to afford 94% of the title amine as a yellow oil; IR (atr) 3349 (w), 2966 (s), 1574 (s), 1489 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 1.6, 4.7 Hz, 1H), 7.02 (dd, J = 1.6, 8.0 Hz, 1H), 6.84 (dd, J = 4.7, 8.0 Hz, 1H), 4.86 (s, 1H), 3.39 (br s, 1H), 3.13 (m, 3H), 2.63 (m, 5H), 1.81−1.52 (m, 6H), 1.31 (s, 6H), 0.87 (t, J = 7.4 Hz, 3H); MS-EI m/e 276 (M^+), 205, 191, 164, 150, 124; HRMS calcd for $C_{16}H_{28}N_4$ 276.2314, found 276.2314.

4-[*N*-Methyl-*N*-[3-[(cyclopropylmethyl)amino]-2-pyridinyl]amino]piperidine, 50q (R = Me, Y = CH_2-*c*-Pr, X = H). **41d** (1.46 g, 4.05 mmol) was dissolved in 10 mL of dioxane, and 30 mL of hydrochloric acid (4.0 M in dioxane) was added. The solvent was removed by evaporation, and the residue was suspended in water. The water was adjusted to pH 12 with 1 N NaOH and extracted with chloroform/methanol. The organic phase was dried over Na_2SO_4 and the solvent evaporated to yield 1.22 g (100%) of the title compound: ^{1}H NMR (CD_3OD) δ 7.37 (dd, J = 2.7, 6.4 Hz, 1H), 6.77 (dd, J = 1.0, 3.7 Hz, 2H), 3.3−3.5 (m, 1H), 2.85 (br d, J = 12.8 Hz, 2H), 2.79 (d, J = 6.7 Hz, 2H), 2.45 (s, 3H), 2.36 (m, 2H), 1.53 (m, 2H), 1.40 (m, 2H), 0.92 (m, 1H), 0.33 (m, 2H), 0.56 (m, 2H).

General Method for Coupling to Indole-2-carboxylic Acids Using 1,1′-Carbonyldiimidazole (CDI). 1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 15. 5-Methanesulfonamidoindole-2-carboxylic acid (1.66 g, 6.52 mmol) and CDI (1.06 g, 6.52 mmol) were stirred together for 1 h at room temperature in 6.5 mL of THF. Then the reaction mixture was cooled to 0 °C, and **50h** (0.90 g, 3.26 mmol) dissolved in 6.52 mL of THF was added. The reaction mixture was warmed to room temperature and stirred overnight. Standard workup, chromatography (2.5% $CH_3OH/CHCl_3$), and crystallization afforded 1.33 g (80%) of the title piperidine: mp 193−194 °C; ^{1}H NMR (CD_3OD) δ 7.76 (dd, J = 1.5, 4.8 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.38 (dd, J = 1.5, 8.2 Hz, 1H), 7.28 (dd, J = 2.0, 0.7 Hz, 2H), 3.25−3.20 (br, 2H), 3.01 (s, 3H), 2.01 (br, 2H), 1.72 (m, 2H), 1.51 (s, 9H), 1.00 (t, J = 7.0 Hz, 3H); HRMS calcd for $C_{26}H_{36}N_6O_3S$ 512.2569, found 512.2569. Anal. calcd for $C_{26}H_{36}N_6O_3S$: C, 60.91; H, 7.08; N, 16.39; S, 6.25. Found C, 60.64; H, 7.10; N, 16.16; S, 6.12.

1-[(5-Nitroindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylpropyl)amino]-2-pyridinyl]amino]piperidine, 54a (Y = *tert*-amyl, R = Me, X = H): prepared in a manner analogous to **15** to afford 72% of the title compound as a pale yellow solid; mp 205.5−207.5 °C; IR (atr) 3240 (m), 2967 (m), 1603 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.12 (s, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 2.2, 9.1 Hz, 1H), 7.70 (dd, J = 1.4, 4.7 Hz, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.09 (m, 1H), 6.91 (m, 2H), 4.93 (s, 1H), 4.66 (br m, 2H), 3.50 (m, 1H), 3.48−3.05 (m, 2H), 2.65 (s, 3H), 2.03 (m, 2H), 1.70 (m, 4H), 1.33 (s, 6H), 0.87 (t, J = 7.3Hz, 3H); MS-EI m/e 464 (M^+), 449, 435, 393, 189, 164, 143, 122. Anal. ($C_{25}H_{32}N_6O_3$) C, H, N.

1-[(5-Nitroindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 54b (Y = isopropyl, R = Et, X = H): prepared in a manner analogous to **15** to afford 67% of the title compound as a yellow solid; mp 198−200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.25 (s, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 2.2, 9.0 Hz, 1H), 7.76 (dd, J = 1.5, 4.7 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 6.99 (m, 1H), 6.91 (d, J = 1.4 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 4.74 (m, 1H), 4.64 (m, 2H), 3.56 (m, 1H), 3.44 (m, 1H), 3.30−2.90 (m, 2H), 3.16 (m, 2H), 2.01 (m, 2H), 1.64 (m, 2H), 1.22 (d, J = 6.2 Hz, 6H), 0.92 (t, J = 7.0 Hz, 3H); EI-MS m/z (rel intensity) 450 (M^+, 55), 435 (6), 421 (22), 407 (8), 216 (37), 189 (33), 178 (100). Anal. ($C_{24}H_{30}N_6O_3$) C, H, N.

1-[(5-Nitroindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 54c (Y = *tert*-butyl, R = Et, X = H): prepared in a manner analogous to **15** to provide 30% yield of an an off-white solid; mp 182−184 °C; IR (mull) 1605 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.18 (s, 1H), 8.62 (s, 1H), 8.16 (dd, J = 2.2, 9.1 Hz, 1H), 7.75 (m, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.95 (m, 1H), 6.92 (s, 1H), 5.18 (s, 1H), 4.64 (m, 2H),

3.39 (m, 1H), 3.30−2.95 (m, 2H), 3.14 (m, 2H), 2.01 (m, 2H), 1.64 (m, 2H), 1.38 (s, 9H), 0.92 (t, J = 7.0 Hz, 3H); EI-MS m/z (rel intensity) 464 (M^+, 82), 449 (16), 435 (22), 407 (43), 189 (50), 178 (49), 174 (50), 136 (100); HRMS (FAB) calcd for $C_{25}H_{32}N_6O_3$ + H 465.2614, found 465.2634.

1-[(5-Nitroindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 54d (Y = *tert*-butyl, R = Et, X = F): prepared in a manner analogous to **15** to provide 63% of the title compound; IR (mull) 3292 (s), 1602 (s), 1584 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.54 (d, J = 2.1 Hz, 1H), 8.07 (dd, J = 2.3, 9.1 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 7.19 (dd, J = 7.6, 8.6 Hz, 1H), 6.84 (m, 1H), 6.52 (dd, J = 3.4, 8.6 Hz, 1H), 4.73 (s, 1H), 4.60 (m, 2H), 3.27 (m, 1H), 3.04 (q, J = 7.1 Hz, 2H), 3.05−2.80 (br, 2H), 1.93 (m, 2H), 1.59 (m, 2H), 1.27 (s, 9H), 0.84 (t, J = 7.1 Hz, 3H); MS-EI m/z (rel intensity) 482 (M^+, 93), 482 (93), 211 (30), 194 (40), 192 (32), 189 (56), 155 (28), 154 (99); HRMS (FAB) calcd for $C_{25}H_{31}N_6O_3F$ + H 483.2520, found 483.2522. Anal. ($C_{25}H_{31}FN_6O_3$) C, H, N.

1-[(5-Nitroindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 54e (Y = Et, R = Et, X = H): prepared in a manner analogous to **15** to provide 65% of the title compound; ^1H NMR (CD_3OD) δ 8.71 (s, 1H), 8.19 (dd, J = 1.5, 9.0 Hz, 1H), 7.73 (m, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.12 (m, 3H), 4.55 (m, 2H), 3.48 (m, 1H), 2.27 (m, 4H), 3.25−2.95 (br, 2H), 2.01 (m, 2H), 1.72 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.0 Hz, 3H).

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 7: prepared in a manner analogous to **15** to provide 34% yield of the title compound; mp 192−193 °C; ^1H NMR (CD_3OD) δ 7.48 (dd, J = 1.5, 4.8 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.12 (dd, J = 1.5, 8.2 Hz, 1H), 7.02 (dd, J = 2.1, 8.8 Hz, 1H), 6.87 (dd, J = 4.8, 8.2 Hz, 1H), 6.66 (s, 1H), 4.33 (br d, 2H), 3.2−2.9 (br m, 2H), 2.76 (s, 3H), 2.50 (s, 3H), 1.74 (br d, 2H), 1.47 (m, 2H), 1.26 (s, 9H). Anal. ($C_{25}H_{34}N_6O_3S$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(cyclopropylmethyl)amino]-2-pyridinyl]amino]piperidine, 9: prepared in a manner analogous to **15** to provide 53% yield of the title compound; mp 187−189 °C; ^1H NMR (CD_3OD) δ 7.59 (m, 1H), 7.53 (m, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.14 (d, 1H, J = 8.8 Hz), 7.00 (d, J = 3.4 Hz, 2H), 6.78 (s, 1H), 4.45 (br d, 2H), 3.45 (m, 1H), 3.00 (d, 2H, J = 6.7 Hz), 2.88 (s, 3H), 2.66 (s, 3H), 1.85 (br d, 2H), 1.70 (m, 2H), 1.10 (m, 1H), 0.55 (m, 2H), 0.25 (m, 2H); EI-MS m/z (rel intensity) 496 (84), 259 (17), 237 (47), 228 (36), 217 (27), 204 (21), 176 (100). Anal. ($C_{25}H_{32}N_6SO_3 \cdot 0.625H_2O$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-(cyclopropylamino)-2-pyridinyl]amino]piperidine, 10: prepared in a manner analogous to **15** to provide 57% yield of the product as a faint yellow solid; mp 175 °C dec; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.02 (s, 1H), 7.78 (dd, J = 1.6, 4.8 Hz, 1H), 7.58 (d, J = 1.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.25 (m, 1H), 7.15 (dd, J = 2.9, 8.7 Hz, 1H), 6.98 (dd, J = 4.8, 7.9 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 4.95 (s, 1H), 4.62 (br d, J = 13.0 Hz, 2H), 3.45 (m, 1H), 3.15 (br m, 2H), 2.95 (s, 3H), 2.61 (s, 3H), 2.36 (m, 1H), 1.93 (m, 2H), 1.63 (bq, J = 11.3 Hz, 2H), 0.77 (m, 2H), 0.53 (m, 2H); EI-MS m/z (rel intensity) 482 (M^+, 13), 440 (3), 426 (5), 237 (68), 162 (100), 130 (90); HRMS calcd for $C_{24}H_{30}N_6O_3S$ 482.2100, found 482.2086. Anal. ($C_{24}H_{30}N_6S_1O_3 \cdot 0.6H_2O$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(1-methylcyclopropyl)amino]-2-pyridinyl]-amino]piperidine, 11: prepared in a manner analogous to **15** to provide 62% yield of the title compound; mp 201−204 °C dec; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 7.76 (m, 1H), 7.59 (s, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.25 (m, 1H), 7.15 (br d, J = 8.7 Hz, 1H), 6.90 (m, 1H), 6.74 (s, 1H), 6.50 (s, 1H), 5.04 (s, 1H), 4.60 (br d, J = 13.0 Hz, 2H), 3.47 (m, 1H), 3.30−3.00 (br m, 2H), 2.97 (s, 3H), 2.62 (s, 3H), 1.94 (m, 2H), 1.60 (m, 2H), 1.34 (s, 3H), 0.78 (m, 2H), 0.69 (m, 2H); EI-MS m/z (rel intensity) 496 (M^+, 22), 237 (43), 176 (100), 158 (35), 148 (32), 130 (62); HRMS calcd for $C_{25}H_{32}N_6O_3S$ 496.2256, found 496.2258. Anal. ($C_{25}H_{32}N_6O_3S \cdot 0.1H_2O$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 12: prepared in a manner analogous to **15** to provide 77% of the title piperidine; mp 215−216 °C; ^1H NMR ($CDCl_3$) δ 9.51 (s, 1H), 7.68 (dd, J = 1.3, 4.8 Hz, 1H), 7.37 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.09 (dd, J = 1.9, 8.7 Hz, 1H), 6.90 (dd, J = 4.8, 7.9 Hz, 1H), 6.77 (d, J = 7.4 Hz, 1H), 6.61 (s, 1H), 4.60 (br m, 3H), 3.33 (br, 1H), 3.16 (m, 2H), 3.07 (m, 5H), 1.87 (m, 2H), 1.53 (m, 2H), 1.29 (d, J = 6.9 Hz, 6H), 1.18 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 6.8 Hz, 3H); HRMS calcd for $C_{25}H_{34}N_6O_3S$ 498.2413, found 498.2427. Anal. ($C_{25}H_{34}N_6O_3S$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-cyclopropyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 13: prepared in a manner analogous to **15** to provide 68% yield of the title compound as an off-white powder; mp 138−140 °C dec; ^1H NMR ($CDCl_3$) δ 10.11 (s, 1H), 7.77 (m, 1H), 7.58 (s, 1H), 7.40 (m, 2H), 7.15 (d, J = 8.7 Hz, 1H), 6.99 (dd, J = 4.8, 8.0 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 4.68 (br d, J = 12.9 Hz, 2H), 4.49 (d, J = 8.4 Hz, 1H), 3.58−3.40 (m, 2H), 3.40−2.80 (br m, 2H), 2.95 (s, 3H), 2.60 (m, 1H), 2.01 (m, 2H), 1.68 (m, 2H), 1.17 (d, J = 6.3 Hz, 6H), 0.52 (m, 2H), 0.37 (m, 2H); EI-MS m/z (rel intensity) 510 (M^+, 74), 495 (5), 481 (23), 237 (33), 190 (100), 148 (97). Anal. ($C_{26}H_{34}N_6O_3S$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-propyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]-piperidine, 14: prepared in a manner analogous to **15** to provide 69% yield of an off-white solid; mp 177−179 °C dec; IR (mull) 1578 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.10 (s, 1H), 7.73 (dd, J = 1.4, 4.7 Hz, 1H), 7.58 (s, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.35 (s, 1H), 7.15 (dd, J = 1.9, 8.7 Hz, 1H), 6.95 (dd, J = 4.7, 8.0 Hz, 1H), 6.84 (m, 1H), 6.71 (s, 1H), 4.67 (m, 3H), 3.55 (m, 1H), 3.28 (m, 1H), 3.20−2.80 (br m, 2H), 3.05 (m, 2H), 2.95 (s, 3H), 1.94 (m, 2H), 1.65 (m, 2H), 1.28 (m, 2H), 1.21 (d, J = 6.3 Hz, 6H), 0.81 (t, J = 7.3 Hz, 3H); EI-MS m/z (rel intensity) 512 (M^+, 65), 483 (34), 275 (7), 237 (41), 216 (44), 192 (100), 178 (47), 163 (37). Anal. ($C_{26}H_{36}N_6O_3S$) C, H, N, S.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-propyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 16: prepared in a manner analogous to **15** to provide 74% of a white solid; mp 195−197 °C dec; IR (mull) 1580 (s), 1456 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.15 (s, 1H), 7.72 (dd, J = 1.4, 4.7 Hz, 1H), 7.58 (s, 1H), 7.48 (s, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.15 (dd, J = 2.0, 8.7 Hz, 1H), 7.09 (dd, J = 1.4, 8.0 Hz, 1H), 6.91 (dd, J = 4.7, 8.0 Hz, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 4.68 (br d, J = 12.4 Hz, 2H), 3.23 (m, 1H), 3.20−2.80 (br m, 2H), 3.04 (m, 2H), 2.95 (s, 3H), 1.94 (m, 2H), 1.65 (m, 2H), 1.37 (s, 9H), 1.29 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); EI-MS m/z (rel intensity) 526 (M^+, 83), 511 (12), 497 (27), 483 (16), 469 (38), 441 (11), 237 (67), 206 (60), 192 (61), 174 (56), 150 (100), 130 (52). Anal. ($C_{27}H_{38}N_6O_3S$) C, H, N, S.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 17: prepared in a manner analogous to **15** to provide 59% of the title piperidine; mp 204−205 °C; ^1H NMR ($CDCl_3$) δ 9.38 (s, 1H), 7.57 (d, J = 3.3 Hz, 1H), 7.37 (m, 1H), 7.18 (m, 1H), 6.95 (dd, J = 2.1, 8.7 Hz, 1H), 6.81 (m, 1H), 6.65 (m, 2H), 6.50 (s, 1H), 4.52 (m, 1H), 4.42 (br d, 2H), 3.25 (br, 1H), 2.95 (br m, 6H), 2.76 (s, 3H), 1.75 (m, 2H), 1.42 (m, 2H), 1.07 (t, J = 7.0 Hz, 3H), 0.71 (t, J = 6.9 Hz, 3H); HRMS calcd for $C_{24}H_{32}N_6O_3S$ 484.2252, found 484.2256. Anal. ($C_{24}H_{32}N_6O_3S \cdot 0.33H_2O$) C, H, N.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-(propylamino)-2-pyridinyl]amino]piperidine, 22: prepared in a manner analogous to **15** to provide 37% yield of the title compound; mp 208−209 °C; ^1H NMR (DMSO-d_6) δ 11.42 (s, 1H), 9.19 (s, 1H), 7.45 (d, J = 2.9 Hz, 1H), 7.30 (s, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 6.77 (m, 1H), 6.73 (m, 1H), 6.59 (s, 1H), 4.86 (m, 1H), 4.20 (br d, 2H), 2.91 (m, 4H), 271 (s, 2H), 1.64 (m, 2H), 1.37 (m, 4H), 0.76 (t, J = 7.3 Hz, 3H), 0.64 (t, J = 6.9 Hz, 3H); EI-MS m/z (rel intensity) 498 (39), 469 (10), 261 (8), 237 (27), 216 (47), 178 (100). Anal. ($C_{25}H_{34}N_6O_3S$) C, H, N, S.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-(isopropylamino)-2-pyridazinyl]amino]piperidine, 30: prepared in a manner analogous to **15** to provide 39% yield of the title compound; mp 193−194 °C; IR (mull) 3253, 1600, 1579, 1560, 1532, 1495, 1448 cm^{-1}; ^1H NMR (CD_3OD) δ 8.17 (d, J = 5.8 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H) 7.21 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 2.0, 8.7 Hz, 1H), 6.59 (s, 1H), 6.47 (d, J = 5.9 Hz, 1H), 4.35 (br d, 2H), 3.53 (m, 1H), 3.32 (m, 1H), 2.68 (s, 3H), 2.53 (s, 3H), 1.75 (br d, 2H), 1.55 (m, 2H), 1.07 (d, J = 6.3 Hz, 6H); EI-MS *m/z* (rel intensity) 485 (100), 470 (27), 442 (21), 406 (26), 237 (30), 167 (77). Anal. ($C_{23}H_{31}N_7O_3S \cdot 0.7H_2O$) C, H, N, S.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[6-chloro-3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 31: prepared in a manner analogous to **15** to provide 54% yield of the title compound; mp 101−102 °C; ^1H NMR (CD_3OD) δ 7.37 (d, J = 2.1 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.00 (dd, J = 2.1, 8.7 Hz, 1H), 6.80 (d, J = 2.2 Hz, 2H), 6.62 (s, 1H), 4.30 (br d, 2H), 3.43 (m, 1H), 3.30 (m, 1H), 2.8−3.0 (m, 2H), 2.72 (s, 3H), 2.46 (s, 3H), 1.73 (br d, 2H), 1.50 (m, 2H), 1.05 (d, 6H, J = 6.3 Hz, 6H); EI-MS *m/z* (rel intensity) 518 (100), 281 (14), 250 (12), 237 (28), 198 (32). Anal. ($C_{24}H_{31}N_6O_3ClS$) C, H, N, Cl, S.

1-[(5-Methanesulfonamidoindo-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 32: prepared in a manner analogous to **15** to provide 67% yield of the title compound; mp 203−204 °C; IR (mull) 3301, 1600, 1531, 1492, 1461, 1447 cm^{-1}; ^1H NMR (CD_3OD) δ 7.57 (d, J = 1.6 Hz, 1H), 7.43 (m, 2H), 7.19 (m, 1H), 6.82 (s, 1H), 6.65 (dd, J = 3.3, 8.5 Hz, 1H), 4.55 (br d, 2H), 3.2−3.4 (br m, 2H), 2.92 (s, 3H), 2.65 (s, 3H), 1.90 (br d, 2H), 1.70 (m, 2H), 1.39 (s, 9H); EI-MS *m/e* (rel intensity) 516 (73), 501 (4), 459 (5), 237 (86), 223 (18), 197 (41), 180 (52), 158 (61). Anal. ($C_{25}H_{33}N_6O_3SF$) C, H, N, S, F.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[6-fluoro-3-[(1-methylethyl)amino]-2-pyridinyl]-amino]piperidine, 33: prepared in a manner analogous to **15** to provide 85% of the title piperidine; mp 166−168 °C; ^1H NMR (CD_3OD) δ 7.35 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.97 (m, 2H), 6.59 (s, 1H), 6.48 (dd, J = 3.2, 8.5 Hz, 1H), 4.32 (m, 2H), 3.41 (sept, J = 6.3 Hz, 1H), 3.16 (m, 1H), 2.95 (q, J = 7.0 Hz, 2H), 2.95−2.72 (br, 2H), 2.70 (s, 3H), 1.70 (m, 2H), 1.43 (m, 2H), 1.01 (d, J = 6.3 Hz, 6H), 0.70 (t, J = 7.0 Hz, 3H); HRMS calcd for $C_{25}H_{33}N_6O_3SF$ 516.2319, found 516.2320. Anal. ($C_{25}H_{33}N_6O_3SF$) C, H, N, S, F.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[6-chloro-3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 34: prepared in a manner analogous to **15** to provide 70% yield of the title compound; mp 206−207 °C; IR (mull) 1608, 1531 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.44 (s, 1H), 9.21 (s, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 4.78 (s, 1H), 4.27 (br d, 2H), 2.92 (q, J = 7.0 Hz, 2H), 2.73 (s, 3H), 1.64 (br d, 2H), 1.40 (m, 2H), 1.18 (s, 9H), 0.68 (t, J = 7.0 Hz, 3H); MS-EI *m/z* (rel intensity) 546 (61), 489 (20), 309 (16), 264 (25), 237 (100), 226 (44), 210 (59). Anal. ($C_{26}H_{35}N_6O_3SCl$) C, H, N, S, Cl.

1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 35: prepared in a manner analogous to **15** to provide 72% of the title piperidine; mp 221−223 °C; ^1H NMR (DMSO-d_6) δ 7.47 (m, 1H), 7.37 (m, 2H), 7.09 (dd, J = 1.9, 8.7 Hz, 1H), 6.77 (m, 1H), 6.70 (dd, J = 3.5, 8.6 Hz, 1H), 4.67 (s, 1H), 4.42 (br d, J = 12.8, 2H), 3.20 (m, 1H), 3.05 (q, J = 6.9 Hz, 2H), 3.05−2.92 (br, 2H), 2.87 (s, 3H), 1.78 (m, 2H), 1.54 (m, 2H), 1.31 (s, 9H), 0.82 (t, J = 6.9 Hz, 3H); HRMS calcd for $C_{26}H_{35}FN_6O_3S$ 531.2553, found 531.2550. Anal. ($C_{26}H_{35}FN_6O_3S$) C, H, N, S.

General Procedure for Coupling with EDC. 1-[(5-Methanesulfonamidoindol-2-yl)carbonyl]-4-[*N*-(1-methylethyl)-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 21. 41g (900 mg, 2.55 mmol) and palladium hydroxide on carbon (500 mg) in 50 mL of ethanol were hydrogenated on a Parr apparatus under 40 psi hydrogen for 48 h. Filtration and evaporation of solvent yielded 700 mg of oil. Without purification this oil was dissolved in a mixture of 12 mL of THF and 2.5 mL of DMF. 5-Methanesulfonamidoindole-2-carboxylic acid (77 mg, 3.0 mmol) was added, and the solution was chilled to 0 °C. EDC (582 mg, 3.0 mmol) was added, and the reaction mixture was stirred overnight at room temperature. It was then poured into 1 N NaOH solution and extracted with $CHCl_3/CH_3OH$, breaking emulsions with the addition of brine. The extract was dried over Na_2SO_4, filtered, and evaporated to an oil. Chromatography on a silica gel column with 5% $CH_3OH/CHCl_3$ followed by chromatography with 75−100% EtOAc in hexane yielded 585 mg (47%) of the title compound as an amorphous solid: IR (mull) 3255, 1600, 1578, 1533, 1478, cm^{-1}; ^1H NMR (CD_3OD) 7.69 (dd, J = 1.6, 4.7 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.17 (dd, J = 2.0, 8.7 Hz, 1H), 7.11 (dd, J = 4.7, 8.0 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.76 (s, 1H), 4.53 (br d, 2H), 3.66 (m, 2H), 3.19 (q, J = 7.1 Hz, 2H), 2.92 (s, 3H), 2.00 (br d, 2H), 1.46 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.4 Hz, 6H); MS-EI *m/e* (rel intensity) 498 (11), 483 (13), 455 (33), 237 (39), 202 (83), 178 (100). Anal. ($C_{25}H_{34}N_6O_3S$) C, H, N, S.

General Procedure for Reduction of 5-Nitroindoles. 1-[(5-Aminoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 55a (Y = *tert*-butyl, R = Et, X = H). To a solution of **54c** (1.24 g, 2.67 mmol) in DMF/MeOH (25/75, 80 mL) under N_2 was added 10% Pd/C (0.570 g). The mixture was put under a hydrogen atmosphere (balloon) for 2 h and N_2 for 16 h, filtered through Celite, and concentrated *in vacuo* to give the crude product which was then triturated with diethyl ether (50 mL) and filtered to give 0.88 g (76%) of the product (R_f = 0.22 by TLC, methanol/chloroform, 5/95) as a pale yellow solid: mp 104 °C dec; IR (mull) 3286 (m), 2924 (s), 1580 (s), 1530 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.98 (s, 1H), 7.74 (dd, J = 1.6, 4.8 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.10 (dd, J = 1.6, 8.1 Hz, 1H), 6.92 (dd, J = 4.8, 8.1 Hz, 1H), 6.89 (d, J = 1.9 Hz, 1H), 6.75 (dd, J = 2.1, 8.6 Hz, 1H), 6.57 (d, J = 1.6 Hz, 1H), 5.18 (s, 1H), 4.63 (br d, J = 13.2 Hz, 2H), 3.65 (m, 2H), 3.31 (m, 1H), 3.13 (q, J = 7.1 Hz, 2H), 3.20−3.00 (m, 2H), 1.93 (m, 2H), 1.61 (m, 2H), 1.37 (s, 9H), 0.90 (t, J = 7.1 Hz, 3H); EI-MS *m/z* (rel intensity) 434 (M^+, 94), 419 (7), 377 (18), 230 (51), 192 (46), 174 (36), 159 (100); HRMS (FAB) calcd for $C_{25}H_{34}N_6O$ + H 435.2872, found 435.2883.

1-[(5-Aminoindol-2-yl)carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylpropyl)amino]-2-pyridinyl]amino]piperidine, 55b (Y = *tert*-butyl, R = Me, X = H): prepared in a manner similar to **55a**, starting with **54a,** to afford 57% of the title amine as a pale yellow film; IR (atr) 3269 (m), 2967 (m), 1597 (s), 1577 (s), 1451 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.95 (s, 1H), 7.69 (dd, J = 1.5, 4.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.05 (dd, J = 1.5, 8.1 Hz, 1H), 6.88 (m, 2H), 6.71 (dd, J = 2.1, 8.7 Hz, 1H), 6.55 (d, J = 1.2 Hz, 1H), 4.91 (s, 1H), 4.64 (d, J = 13.2 Hz, 2H), 3.86 (br s, 2H), 3.40 (m, 1H), 3.11 (br s, 2H), 2.62 (s, 3H), 1.91 (m, 2H), 1.63 (m, 4H), 1.31 (s, 6H), 0.86 (t, J = 7.3 Hz, 3H); MS-EI *m/e* 434 (M^+), 419, 405, 363, 275, 244, 191, 159, 131; HRMS calcd for $C_{25}H_{34}N_6O_1$ 434.2794, found 434.2796.

1-[(5-Aminoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 55c (Y = isopropyl, R = Et, X = H): prepared in a manner similar to **55a**, starting with **54b**, to afford 89% of the product (R_f = 0.22 by TLC, MeOH/$CHCl_3$, 5/95) as a pale yellow solid; mp 159−162 °C dec; IR (mull) 3431 (w), 3263 (m), 2924 (s), 1586 (s), 1530 (s), 1445 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.92 (s, 1H), 7.75 (dd, J = 1.5, 4.7 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.96 (m, 1H), 6.88 (s, 1H), 6.85 (m, 1H), 6.75 (dd, J = 2.1, 8.6 Hz, 1H), 6.57 (d, J = 1.3 Hz, 1H), 4.70 (m, 1H), 4.64 (br d, J = 13.2 Hz, 2H), 3.70 (br m, 2H), 3.57 (m, 1H), 3.36 (m, 1H), 3.14 (m, 2H), 3.10 (br m, 2H), 1.94 (m, 2H), 1.62 (m, 2H), 1.22 (d, J = 6.2 Hz, 6H), 0.90 (t, J = 7.0 Hz, 3H); EI-MS *m/z* (rel intensity) 420 (M^+, 85), 405 (4), 377 (5), 261 (18), 216 (50), 178 (100); HRMS (FAB) calcd for $C_{24}H_{32}N_6O$ + H 421.2716, found 421.2707.

1-[(5-Aminoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 55d (Y = *tert*-butyl, R = Et, X = F): prepared in a manner similar to **55a**, starting with **54d** and using THF as solvent, to afford 54% of the title compound; ^1H NMR ($CDCl_3$)

δ 7.42 (m, 2H), 7.06 (d, J = 2.1 Hz, 1H), 6.92 (dd, J = 2.1, 8.7 Hz, 1H), 6.75 (m, 2H), 4.96 (s, 1H), 4.83 (m, 2H), 3.73 (br, 1H), 3.46 (m, 1H), 3.27 (t, J = 7.1 Hz, 2H), 3.28−3.12 (m, 2H), 2.09 (m, 2H), 1.79 (m, 2H), 1.52 (s, 9H), 1.07 (t, J = 7.1 Hz, 3H).

1-[(5-Aminoindol-2-yl)carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 55e (Y = ethyl, R = Et, X = H): prepared in a manner similar to **55a**, starting with **54e** and using ethanol/ethyl acetate as solvent, to afford 93% of the title amine; ^{1}H NMR ($CDCl_3$) δ 7.56 (dd, J = 1.6, 4.8 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 4.8, 7.9 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 6.93 (dd, J = 1.6, 7.9 Hz, 1H), 6.84 (dd, J = 2.1, 8.6 Hz, 1H), 6.65 (d, J = 1.6 Hz, 1H), 4.73 (m, 2H), 3.49 (m, 1H), 3.24 (m, 4H), 2.7 (br, 2H), 2.03 (m, 2H), 1.71 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.0 Hz, 3H).

General Procedure for Sulfonylating Aminoindoles. 1-[[5-[(Methylsulfonyl)amino]indol-2-yl]carbonyl]-4-[*N*-methyl-*N*-[3-[(1,1-dimethylpropyl)amino]-2-pyridinyl]-amino]piperidine, 8. A mixture of 508 mg (1.17 mmol) of **55b**, 189 μL (2.34 mmol) of pyridine, 91 μL (1.17 mmol) of methanesulfonyl chloride, and 5 mL of CH_2Cl_2 was prepared and stirred at room temperature for 20 h. The mixture was diluted with 25 mL of CH_2Cl_2 and 10 mL of water, the layers were separated, and the organic layer was washed with 10 mL of brine, dried over Na_2SO_4, and concentrated *in vacuo* to give 532 mg of an orange residue which was then chromatographed on 70 g of 230−400 mesh silica gel, eluting with 3% MeOH/$CHCl_3$. Pooling of fractions giving an R_f = 0.25 by TLC (3 × 5% MeOH/$CHCl_3$) and removal of solvent *in vacuo* gave 345 mg (58%) of the title compound as an amorphous solid: IR (atr) 3262 (m), 2966 (m), 1602 (s), 1450 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 7.70 (dd, J = 1.4, 4.8 Hz, 1H), 7.58 (s, 1H), 7.39 (m, 2H), 7.16 (dd, J = 2.0, 8.7 Hz, 1H), 7.08 (m, 1H), 6.91 (dd, J = 4.8, 8.1 Hz, 1H), 6.71 (s, 1H), 4.90 (s, 1H), 4.63 (d, J = 13.1 Hz, 2H), 3.45 (m, 1H), 3.20 (br m, 2H), 2.95 (s, 3H), 2.64 (s, 3H), 1.94 (m, 2H), 1.68 (m, 4H), 1.32 (s, 6H), 0.87 (t, J = 7.3 Hz, 3H); MS-EI m/e 512 (M$^+$), 497, 483, 441, 237, 158, 157, 130, 43; HRMS calcd for $C_{26}H_{36}N_6S_1O_3$ 512.2569, found 512.2584.

1-[[5-[(Ethylsulfonyl)amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 18: prepared in a manner analogous to **8** but starting with **55e** and employing ethanesulfonyl chloride in place of methanesulfonyl choride to provided 42% of the title compound; mp 211−213 °C; IR (mull) 3256 (s), 1606 (s), 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.46 (m, 1H), 7.29 (m, 1H), 7.18 (d, J = 8.7 Hz, 1H), 6.92 (m, 1H), 6.78 (m, 1H), 6.73 (m, 1H), 6.57 (br s, 1H), 4.21 (br, 2H), 3.21 (br, 2H), 2.92 (m, 4H), 2.79 (q, J = 7.3 Hz, 2H), 1.65 (m, 2H), 1.37 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 6.9 Hz, 3H), 0.63 (t, J = 6.9 Hz, 3H); MS-EI m/z (rel intensity) 498 (M$^+$, 64), 202 (47), 165 (22), 164 (99), 157 (25), 150 (36); HRMS (EI) calcd for $C_{25}H_{34}N_6O_3S$ 498.2413, found 498.2419. Anal. ($C_{25}H_{34}N_6O_3S\cdot0.33H_2O$) C, H, N.

1-[[5-[(Isopropylsulfonyl)amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]amino]piperidine, 19: prepared in a manner analogous to **8**, starting with **55e** and employing 2-propanesulfonyl chloride in place of methanesulfonyl choride, to provided 20% of the title compound; mp 206−207 °C; ^{1}H NMR (CD_3OD) δ 7.70 (m, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.52−7.48 (m, 4H), 7.19 (m, 1H), 6.80 (s, 1H), 4.61 (br d, 2H), 4.03 (dq, J = 7.2 Hz, 1H), 3.62 (m, 1H), 3.35 (m, 4H), 3.21 (m, 2H), 2.00 (br d, 2H), 1.75 (m, 2H), 1.35 (d, J = 6.9 Hz, 6H), 1.30 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H); MS-EI m/z (rel %) 512 (M$^+$, 46), 512 (46), 202 (55), 165 (22), 164 (99), 158 (30), 157 (37), 150 (37); HRMS (EI) calcd for $C_{26}H_{36}N_6O_3S$ 512.2569, found 512.2576. Anal. ($C_{26}H_{36}N_6O_3S_1\cdot0.25H_2O$) C, H, N.

Water-Solubilizing Substituents. 1-[[5-[[(4-Methyl-1-piperazinyl)carbonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]-amino]piperidine, 36. 55d (0.30 g, 0.663 mmol) was dissolved in 2.2 mL of CH_2Cl_2 and cooled to 0 °C. Then pyridine (0.11 mL, 1.4 mmol) was added followed by 0.19 g of 4-methyl-1-piperazinylcarbonyl chloride (0.95 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 4 days. Then a further 0.094 g of 4-methyl-1-piperazinylcarbonyl chloride and 0.056 mL of pyridine were added, and the reaction mixture was stirred for a further 6 h. Then it was poured into H_2O, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (5% $CH_3OH/CHCl_3$) and crystallization from EtOAc/hexane afforded 0.28 g of the title piperidine (75%): mp 203−204 °C; ^{1}H NMR (CD_3OD) δ 7.35 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 7.5, 8.6 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.97 (dd, J = 3.0, 8.6 Hz, 1H), 6.54 (s, 1H), 6.45 (dd, J = 2.0, 8.7 Hz, 1H), 4.34 (br d, 2H), 3.37 (m, 4H), 3.07 (m, 1H), 2.93 (q, J = 7.0 Hz, 2H), 2.95 (br, 2H), 2.30 (m, 4H), 2.14 (s, 3H), 1.72 (m, 2H), 1.41 (m, 2H), 1.16 (s, 9H), 0.69 (t, J = 7.0 Hz, 3H); HRMS calcd for $C_{29}H_{38}N_8O_2F$ 578.3493, found 578.3503. Anal. ($C_{29}H_{38}N_8O_2F$) C, H, N.

1-[[5-[[(4-Methyl-1-piperazinyl)sulfonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-6-fluoro-2-pyridinyl]amino]piperidine, 37. 55d (0.30 g, 0.663 mmol) was dissolved in 2.2 mL of CH_2Cl_2 and cooled to 0 °C. Then pyridine (0.11 mL, 1.4 mmol) was added followed by 0.19 g of 4-methyl-1-piperazinylsulfamoyl chloride (0.80 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 4 days. Then a further 0.094 g of 4-methyl-1-piperazinylsulfamoyl chloride and 0.056 mL of pyridine were added, and the reaction mixture was stirred for a further 6 h. Then it was poured into H_2O, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (5% $CH_3OH/CHCl_3$), a second chromatography (5% CH_3OH/EtOAc), and crystallization from EtOAc/hexane afforded 0.20 g of the title piperidine (50%): mp 181−183 °C; ^{1}H NMR (CD_3OD) δ 7.43 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.07 (dd, J = 2.1, 8.7 Hz, 1H), 6.65 (s, 1H), 6.55 (dd, J = 3.3, 8.7 Hz, 1H), 4.42 (br d, 2H), 3.19 (m, 1H), 3.11 (m, 4H), 3.02 (q, J = 7.0 Hz, 2H), 3.02−2.95 (br m, 2H), 2.26 (m, 4H), 2.10 (s, 3H), 1.80 (m, 2H), 1.55 (m, 2H), 1.26 (s, 9H), 0.79 (t, J = 7.0 Hz, 3H); HRMS calcd for $C_{30}H_{43}N_8O_3F$ 615.3248, found 615.3241. Anal. ($C_{30}H_{43}N_8O_3F$) C, H, N.

1-[[5-[[(4-Methyl-1-piperazinyl)carbonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]-amino]piperidine, 23: prepared in a manner analogous to **36,** starting with **55e**, to provide 63% of a hygroscopic foam; ^{1}H NMR ($CDCl_3$) δ 9.41 (br s, 1H), 7.68 (m, 1H), 7.57 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.03 (br d, J = 8.7 Hz, 1H), 6.85 (dd, J = 4.7, 7.8 Hz, 1H), 6.76 (br d, J = 7.8 Hz, 1H), 6.56 (br s, 1H), 6.52 (br s, 1H), 4.63 (m, 1H), 4.52 (br d, 2H), 3.45 (m, 4H), 3.29 (m, 1H), 3.12−2.70 (m, 6H), 2.37 (m, 4H), 2.24 (s, 3H), 1.83 (m, 2H), 1.53 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 6.9 Hz, 3H); MS-EI m/z (rel %) 532 (M$^+$, 0), 432 (40), 406 (31), 202 (39), 185 (39), 164 (99), 159 (28), 150 (35); HRMS (FAB) calcd for $C_{29}H_{40}N_8O_2$ + H_1 533.3352, found 533.3338.

1-[[5-[[(4-Methyl-1-piperazinyl)sulfonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-(ethylamino)-2-pyridinyl]-amino]piperidine, 24: prepared in a manner analogous to **37**, starting with **55e**, to provide 17% of a hygroscopic foam; ^{1}H NMR ($CDCl_3$) δ 10.1 (s, 1H), 7.65 (dd, J = 1.5, 4.7 Hz, 1H), 7.56 (br, 1H), 7.41 (d, J = 1.5 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.00 (dd, J = 1.9, 8.7 Hz, 1H), 6.85 (dd, J = 4.7, 7.9 Hz, 1H), 6.72 (dd, J = 1.5, 7.9 Hz, 1H), 6.55 (br s, 1H), 4.59 (t, J = 4.3 Hz, 1H), 4.52 (br d, J = 12.6 Hz, 2H), 3.27 (m, 1H), 3.13 (m, 4H), 3.00 (m, 6H), 2.23 (m, 4H), 2.10 (s, 3H), 1.82 (br d, J = 10.7 Hz, 2H), 1.49 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.0 Hz, 3H); MS-EI m/z (rel intensity) 568 (M$^+$, 7), 406 (54), 202 (54), 164 (99), 159 (58), 158 (49), 150 (35); HRMS (FAB) calcd for $C_{28}H_{40}N_8O_3S$ + H_1 569.3022, found 569.3010.

1-[[5-[[(4-Methyl-1-piperazinyl)carbonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 25: prepared in a manner analogous to **36**, starting with **55c**, to afford 49% of the title compound as a green solid; IR (mull) 3288 (m), 2924 (s), 1633 (s), 1600 (s), 1530 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.25 (s, 1H), 7.75 (m, 1H), 7.66 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 6.95 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.44 (s, 1H), 4.71 (d, J = 8.3 Hz, 1H), 4.62 (d, J = 13.1 Hz, 2H), 3.54 (m, 5H), 3.35 (m, 1H), 3.13 (m, 2H), 3.20−2.90 (br m, 2H), 2.46 (m, 4H), 2.33 (s, 3H), 1.92 (m, 2H), 1.61 (m, 2H), 1.21 (d, J = 6.2 Hz, 6H), 0.89 (t, J = 7.0 Hz,

3H); FAB-MS *m/z* (rel intensity) 1094 ([2M + 2H]$^+$, 8), 547 ([M + H]$^+$, 100), 447 (6), 285 (17), 185 (24), 101 (92); HRMS calcd for $C_{30}H_{42}N_8O_2$ + H 547.3509, found 547.3501. Anal. ($C_{30}H_{42}N_8O_2 \cdot 0.4H_2O$). C, H, N.

1-[[5-[[(4-Methyl-1-piperazinyl)sulfonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1-methylethyl)amino]-2-pyridinyl]amino]piperidine, 26: prepared in a manner analogous to **37**, starting with **55c**, to provide 56% of an off-white solid, amorphous solid; IR (mull) 1607 (s), 1455 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H), 7.75 (dd, J = 1.5, 4.7 Hz, 1H), 7.54 (s, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 2.0, 8.7 Hz, 1H), 6.96 (dd, J = 4.7, 7.9 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.70 (m, 2H), 4.70 (m, 1H), 4.63 (br d, J = 13.2 Hz, 2H), 3.55 (m, 1H), 3.37 (m, 1H), 3.28 (m, 4H), 3.13 (q, J = 7.0 Hz, 2H), 3.10 (br m, 2H), 2.40 (m, 4H), 2.26 (s, 3H), 1.96 (m, 2H), 1.62 (m, 2H), 1.22 (d, J = 6.3 Hz, 6H), 0.90 (t, J = 7.0 Hz, 3H); EI-MS *m/z* (rel intensity) 582 (M$^+$, 19), 420 (64), 261 (12), 216 (43), 178 (100), 159 (56), 100 (36), 58 (88). Anal. ($C_{29}H_{42}N_8O_3S$) C, H, N.

1-[[5-[[(4-Methyl-1-piperazinyl)carbonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 27: prepared in a manner analogous to **36**, starting with **55a**, to provide 41% of the product as a faint green, amorphous solid; additional 216 mg (48%) of slightly impure product also isolated; IR (mull) 1628 (s), 1530 (s), 1455 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 7.74 (d, J = 4.6 Hz, 1H), 7.67 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.91 (dd, J = 4.7, 8.1 Hz, 1H), 6.66 (s, 1H), 6.42 (s, 1H), 5.18 (s, 1H), 4.62 (d, J = 13.1 Hz, 2H), 3.55 (m, 4H), 3.30 (m, 1H), 3.11 (q, J = 7.0 Hz, 2H), 3.20−2.95 (m, 2H), 2.47 (m, 4H), 2.34 (s, 3H), 1.92 (m, 2H), 1.62 (m, 2H), 1.37 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); EI-MS *m/z* (rel intensity) 460 (31), 230 (25), 185 (52), 174 (46), 136 (74), 58 (100); HRMS (FAB) calcd for $C_{31}H_{44}N_8O_2$ + H 561.3665, found 561.3663. Anal. ($C_{31}H_{14}N_8O_2 \cdot 0.5H_2O$).

1-[[5-[[(4-Methyl-1-piperazinyl)sulfonyl]amino]indol-2-yl]carbonyl]-4-[*N*-ethyl-*N*-[3-[(1,1-dimethylethyl)amino]-2-pyridinyl]amino]piperidine, 28: prepared in a manner analogous to **37**, starting with **55a**, to provide 56% of an off-white, amorphous solid: IR (mull) 1612 (s), 1455 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (s, 1H), 7.74 (dd, J = 1.5, 4.8 Hz, 1H), 7.54 (s, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 2.0, 8.7 Hz, 1H), 7.10 (dd, J = 1.5, 8.1 Hz, 1H), 6.92 (dd, J = 4.8, 8.1 Hz, 1H), 6.85 (br s, 1H), 6.70 (s, 1H), 5.18 (s, 1H), 4.62 (br d, J = 13.1 Hz, 2H), 3.32 (m, 1H), 3.27 (m, 4H), 3.12 (q, J = 7.0 Hz, 2H), 3.20−3.00 (m, 2H), 2.38 (m, 4H), 2.25 (s, 3H), 1.95 (m, 2H), 1.61 (m, 2H), 1.37 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); FAB-MS *m/z* (rel intensity) 1194 ([2M + 2H]$^+$, 4), 597 ([M + H]$^+$, 100), 433 (7), 101 (24), 99 (34), 97 (38), 57 (25); HRMS calcd for $C_{30}H_{44}N_8O_3S$ + H 597.3335, found 597.3332. Anal ($C_{30}H_{44}N_8O_3S \cdot 0.3H_2O$) C, H, N.

HIV RT Assay Protocol. The RT assays were carried out at 28 °C for 10 min in a 100 μL reaction mixture consisting of 2 mM dithiothreitol, 60 mM NaCl, 10 mM $MgCl_2$, 50 mM Tris-HCl (pH 8.3), 0.05% Nonidet P-40, 50 μM thymidine triphosphate with 12 μCi/mL [*methyl*-^{3}H]thymidine 5′-triphosphate (Amersham), 200 nM template:primer (poly(rA)$_{600}$:oligo(dT)$_{10}$ from Pharmacia), and 4 μg/mL purified HIV RT. The RT enzymes (WT, P236L, and Y181C) were used as the homodimers and obtained as previously described.[14,48,49] The reaction was stopped with 100 μL of 10% (v/v) trichloroacetic acid. The acid-precipitated materials, recovered on glass fiber filters, were analyzed for radioactivity. Non-nucleoside drugs were added from DMSO stocks. In all cases the final DMSO concentration was 1% (v/v).

Antiviral Assay.[50] Assessment of the antiviral activities of the NNRTIs versus the panel of viruses used in these studies was carried out mainly in MT4 cells. Cells were batch-infected with the appropriate virus stock at a multiplicity of infection of 0.001−0.005 $TCID_{50}$ per cell for 2 h at 37 °C. The cells were washed, resuspended in RPMI/FBS, and plated in 24-well dishes at a final concentration of 1.5×10^5 cells/mL to which were added 2× drug treatments prepared in RPMI/FBS. All treatment concentrations were tested in duplicate. The final DMSO concentration for all treatments or vehicle control cultures was 0.1%. At 4 days postinfection culture fluid samples were collected for HIV-1 p24 core antigen quantitation to determine antiviral effects. Linear regression analysis was used to calculate the drug concentration necessary to inhibit 90% of nondrug p24 antigen production.

Selection of Drug Resistant Variants. MT4 cells were infected with HIV-1_{IIIB} or HIV-1_{MF} as described for the antiviral assay and initially treated with a concentration of NNRTI approximating its IC_{50}. Infected cells were serially passaged (1:4) typically every 3−4 days. Each passage was initiated by pelleting one-quarter of the cells, resuspending in fresh medium with drug, and supplementing with uninfected cells to yield a cell density of ∼3−5 × 10^5/mL. The infections were monitored by the progression of the cytopathic effect (i.e., syncytium formation) as well as p24 productions. Inhibitor concentrations were increased by 0.5 log 10 increments during the passage series when p24 antigen levels approached 1 × 10^6 pg/mL. Resistant virus stocks were harvested once growth was sustained in 10 μM of the respective NNRTI.

Assay for Metabolic Stability. Analogs were screened for metabolic stability in the presence of hepatic microsomal cytochrome P450 by measuring loss of the parent drug in the following manner. Hepatic microsomes (0.4 mg), obtained from untreated rats, were diluted into 1 mL (final volume) of 50 mM potassium phosphate buffer, pH 7.4, 0.1 mM EDTA. Drug was added from 1 mM stock in MeOH to a final concentration of 5 μM. Following a preincubation at 37 °C, reaction was started by addition of an NADPH-generating system consisting of (final concentration) 0.5 mM NADPH, 5 mM isocitrate, 5 mM $MgCl_2$, and 0.4 U of isocitrate dehydrogenase. At 2 min intervals between 0 and 12 min from start of reaction, 100 μL aliquots of incubation were removed and quenched with 100 μL of acetonitrile followed by addition of an appropriate internal standard contained in 10 μL of acetonitrile. Samples were vortex, mixed, and centrifuged to pellet protein. The supernatant was diluted 1:1 with HPLC buffer, and a 100 μL sample was assayed by reverse phase HPLC using a Zorbax Rx-C8 column (15 × 0.49 cm). The mobile phase consisted of a 12 min gradient of 20−60% acetonitrile balanced by 100 mM ammonium acetate, pH 4.0, flowing at 1 mL/min. Detection was by UV absorbance at 295 nM. Drug concentration was estimated by peak height ratio to the internal standard. Concentration data were fitted to a monoexponential equation, yielding the rate constant (k) for loss of drug, which was converted to half-life by $t_{1/2} = \ln 2/k$. Delavirdine and/or atevirdine were run as controls in each assay.

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(50) In the *in vitro* enzyme assay, the inhibition of RT activity is measured directly by the reduction in radiolabel incorporation into DNA, whereas in cell culture the inhibition is measured indirectly by assay of viral p24 production. Differences in the IC values between the two systems can be explained by the fact that reverse transcription of the RNA genome into full length proviral DNA is a vital stage in the viral replication cycle. If the intracellular viral RT activity were inhibited by just 5−10%, that low level of inhibition could conceivably have a profound effect on the full length proviral DNA synthesis that is necessary for productive infection and replication over the 4 day assay period. However, a 5−10% reduction in radiolabel incorporation in the enzyme assay would not be meaningful. In addition, the outcome of the cell-based assays can be dependent upon factors such as cell type, amount of infectious innocula, method of end point determination, strain of virus, and time line of the assay. These explanations most likely account for the lower IC_{90} values observed in the viral spread assay as compared to IC_{50} values obtained in the enzyme assays.

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