Synthesis and Structure−Activity Relationships of the (Alkylamino)piperidine-Containing BHAP Class of Non-Nucleoside Reverse Transcriptase Inhibitors: Effect of 3-Alkylpyridine Ring Substitution

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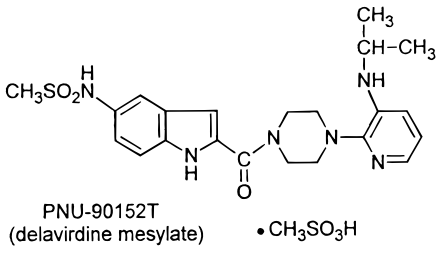
Development of resistance to currently approved HIV therapies has continued to fuel research efforts to improve the metabolic stability and spectrum of activity of the (alkylamino)piperidine-containing bis(heteroaryl)piperazine (AAP−BHAP) class of non-nucleoside reverse transcriptase inhibitors (NNRTIs). The synthesis of analogues in which the usual 3-alkylamino substituent on the pyridine ring is replaced by a 3-alkyl substituent led to compounds which retained activity against recombinant P236L and wild-type (WT) reverse transcriptase (RT), while inhibition of the Y181C mutant RT was reduced relative to the activity of the 3-alkylamino-substituted congeners. Testing of representative analogues in an in vitro liver microsome assay indicated that the alkyl substituent would not appreciably improve the metabolic stability of the AAP−BHAP template. In vivo pharmacokinetic evaluation of three compounds confirmed these results in that high systemic clearances were observed. Nevertheless, one compound (**13**), PNU-103657, possessed oral bioavailability in rats approaching that of the structurally related NNRTI drug delavirdine which is currently on the market for the treatment of HIV infection.

Introduction

A number of drugs which target either the viral protease[1] or reverse transcriptase (RT) enzymes[2] of human immunodeficiency virus (HIV) are now available for the treatment of acquired immune deficiency syndrome (AIDS). Due to the facility with which HIV can mutate, therapy with one of the approved drugs usually results in emergence of drug-resistant viral strains.[3] Thus, current best practice generally involves treatment with combinations of drugs in order to delay emergence of resistance.[4,5] Of the approved drugs, only three are reverse transcriptase inhibitors of the non-nucleoside (NNRTIs) class: Rescriptor (delavirdine mesylate, **1**),[6] Viramune (nevirapine),[7,8] and Sustiva (DMP-266).[9]



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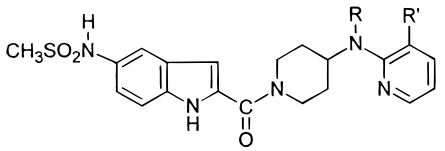
On the basis of the hypothesis that sequential treatment with delavirdine followed by a compound with enhanced activity against delavirdine-resistant virus might result in an effective anti-HIV therapy,[10,11] we had previously embarked upon a program to identify compounds complimentary to delavirdine.[12−14] In short, screening of formerly identified NNRTIs from our compound collection and structurally diverse delavirdine analogues was conducted against a panel of recombinant RTs to target compounds with enhanced activity against a mutant which contained a proline to leucine substitution at amino acid 236 (P236L RT) relative to wild-type (WT) RT. (The P236L mutant arises upon serial HIV-1 passage in vitro in the presence of increasing concentrations of delavirdine.[11]) These efforts resulted in the discovery that certain delavirdine analogues, namely those of the (alkylamino)piperidine (AAP−BHAP) variety (e.g., **2** and **3**), possessed better activity than delavirdine against the P236L mutant enzyme. In addition, 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).



2 R = Me R' = -NH-*i*-propyl
3 R = Et R' = -NH-*n*-propyl
4 R = Et R' = -NH-*t*-butyl
5 R = Me R' = OEt

Investigation of the pharmaceutical properties of the AAP−BHAPs revealed that this structural series suffered the same metabolic fate as the BHAPs: oxidative N-dealkylation of the 3-(alkylamino)pyridine substitu-

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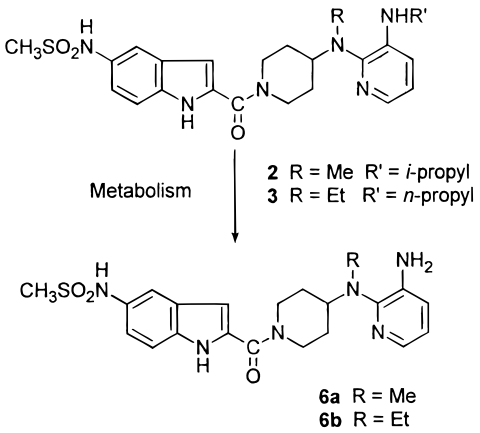
Chart 1



ent, albeit at a more rapid rate. A number of structural modifications were explored in attempts to enhance the metabolic stability of the AAP−BHAP template while maintaining the desired activity profile. These included replacing the usual 3-isopropylamino substituent on the pyridine ring with a *tert*-butylamino moiety (**4**)[12] or an alkoxy group (**5**).[15] Herein, we describe further investigation of the SAR of the 3-pyridyl substituent via the synthesis of AAP−BHAPs containing 3-alkyl or ether-containing 3-alkyl substituents which afforded another opportunity to circumvent metabolism at this site.

Synthesis

Synthesis of the desired 3-alkylpyridine analogues was straightforward and began with 2-bromo-3-formylpyridine (**7**) which was available according to literature precedent via deprotonation of 2-bromopyridine with lithium diisopropylamide and subsequent quenching of the resulting anion with dimethylformamide (Scheme 1).[16] Nucleophilic aromatic substitution of **7** with an (alkylamino)piperidine in the presence of *N*-ethyldiisopropylamine base at 100 °C in a sealed tube provided compounds **9a** and **9b**. Olefination and subsequent reduction served to introduce the desired 3-alkyl substituent while simultaneously deprotecting the piperidine. Coupling to 5-methanesulfonamidoindole-2-carboxylic acid afforded compounds **12**−**15**. Alternatively, a BOC group could be employed as a protecting group for the piperidine nitrogen (see Experimental Section for preparation of compound **13**).

In an effort to avoid the synthesis of the 2-bromo-3-formylpyridine and improve upon the previous route, we investigated an alternate route which employed the commercially available 2-bromo-3-cyanopyridine (**16**) as a partner in the nucleophilic aromatic substitution (Scheme 2). Reaction of the desired (alkylamino)piperidine spacer groups with the cyanopyridine was conducted neat at 115−120 °C and resulted in moderate yields of the desired products. Elaboration of the cyano group was accomplished by treatment with methyllithium to provide the methyl ketones **18a**−**c** which were reduced under Wolff−Kischner conditions to provide the 3-ethylpyridine intermediates **19a**−**c** in good yields. Deprotection and coupling with the desired substituted indole-2-carboxylic acid under previously described conditions provided analogues **20**−**22**.

In addition to the alkyl-substituted pyridine analogues described above, we also prepared some analogues containing ethers in the alkyl substituent to investigate the effect of the oxygen atom on the activity as well as the pharmacokinetics (Scheme 3). Nucleophilic aromatic substitution of commercially available methyl nicotinate with the 4-(alkylamino)piperidines **8a** and **8b** afforded the pyridinyl esters **24a** and **24b** in modest yield. LAH reduction of the ester afforded the hydroxymethyl-substituted intermediates, which could be methylated upon treatment with methyl iodide and potassium hydroxide in DMSO. Deprotection of the benzylamine and coupling with the indole-2-carboxylic acid proceeded uneventfully to afford **27** and **28**. An ester-substituted pyridine analogue was synthesized by deprotecting intermediate **24a** and coupling with the indole-2-carboxylic acid to afford **29** (Scheme 4). Similarly, hydroxymethyl-substituted derivative **30** was prepared from intermediate **25a**.

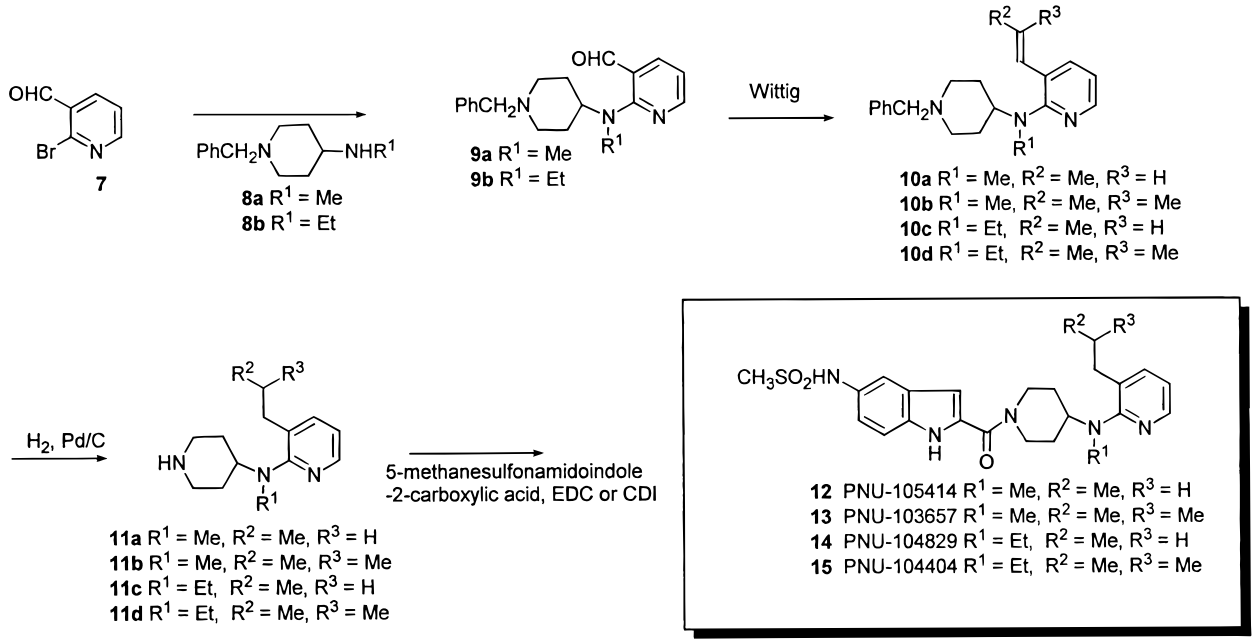
Biological Results and Discussion

Compounds were evaluated in an in vitro assay against a panel of recombinant RTs which included WT RT and the P236L and Y181C mutant RTs. Compounds were further tested in cell culture against resistant virus selected by serial passage in the presence of delavirdine or Merck's L-697,661. Table 1 presents the results of the in vitro RT assay against the panel of RTs for a variety of alkylpyridine analogues as well as for three parent (alkylamino)pyridine congeners (**2**, **31**, **32**). Several trends can be discerned from these results. For example, analogues containing the 3-alkyl substituent retain activity comparable to that of the parent in the assays against the P236L mutant or WT RT. However, potency against the Y181C mutant RT is less than that of the alkylamino counterparts (e.g., comparison of compound **2** to **13** and comparison of compound **15** to **32**). In addition, the (ethylamino)piperidine-linked analogues are more potent against P236L and Y181C mutant RTs than the corresponding (methylamino)-piperidine-linked compounds (**21** vs **20** and **15** vs **13**). This trend was observed previously in the 3-(alkylamino)pyridine series.[12] (Propylamino)piperidine-linked compound **22** was 2-fold less potent than the analogous (ethylamino)piperidine **21** against P236L and Y181 RTs.

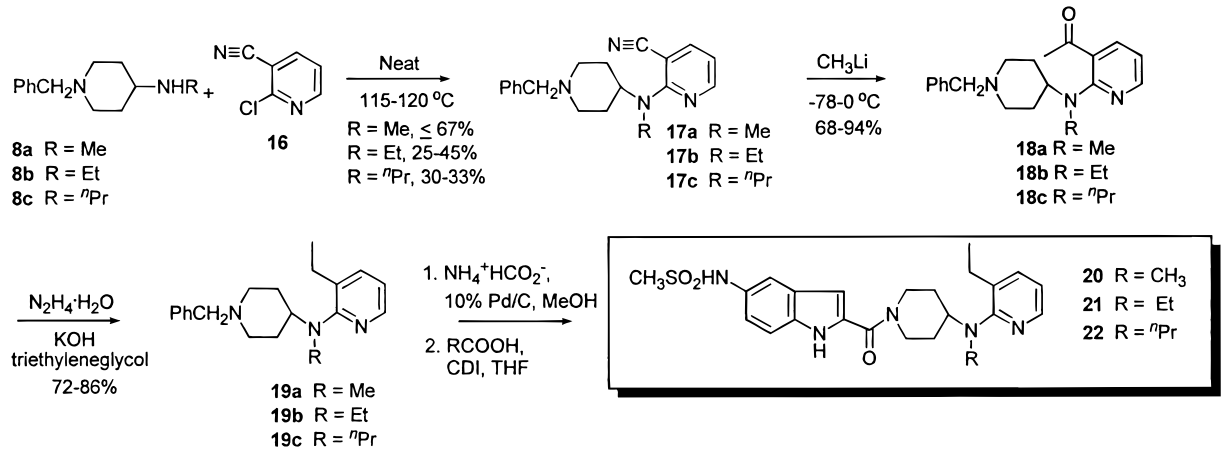
Table 2 shows the effect of placing oxygen atoms in the 3-alkylpyridine side chain. (Methylamino)piperidine **27** which contains a methyl ether in the 3-pyridine side chain lost considerable potency against P236L and Y181C RTs as compared to its WT potency. On the other hand, the analogous (ethylamino)pyridine compound **28** retained good potency against all three enzymes and compared favorably to the *n*-propyl compound **14**. The presence of an ester at the 3-position, as in compound **29**, was not well tolerated by the P236L and Y181C RT enzymes. Last, a 3-hydroxymethyl-substituted pyridine **30** exhibited decreased activity for all three enzymes as compared to the corresponding ethyl-substituted pyridine **21**.

Antiviral activities of selected 3-alkylpyridine AAP−BHAPs and comparator compounds (delavirdine (**1**), L-697,661, and **2**) against BHAP and L-drug-resistant viral strains are presented in Table 3.[12] Three of the five 3-alkylpyridine-substituted compounds tested possessed good activities against the delavirdine and L-drug-resistant viruses. Compounds **14** and **15**, contain-

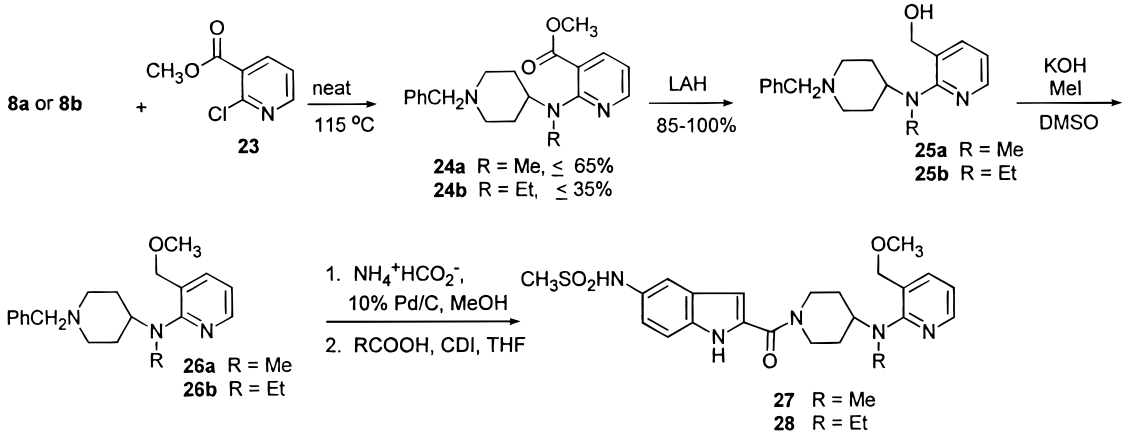
Scheme 1



Scheme 2



Scheme 3



ing the (ethylamino)piperidine, were the most potent against the viruses tested and confirmed the importance of this substituent in conferring enhanced potency over that observed for the (methylamino)piperidine homologues. The two compounds that demonstrated the weakest activities against the Y181C RT-containing virus each had a (methylamino)piperidine and either an 3-alkyl ether (**27**) or a 3-isobutyl (**13**) pyridine substituent.

Next, compounds of interest were evaluated for in vitro metabolic stability in the presence of hepatic cytochrome P450 (Table 4). Clinical candidates atevir-

Scheme 4

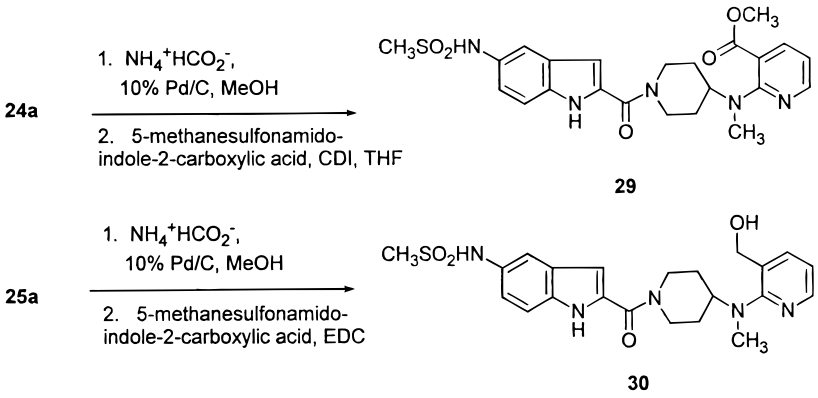
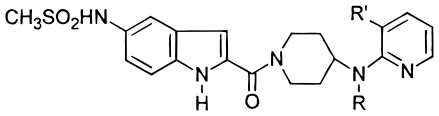


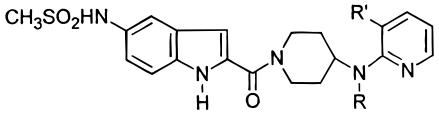
Table 1. RT Inhibitory Activities of AAP-BHAP Analogues Containing a 3-Alkylpyridine



no.	R	R′	IC (μM)[a] WT	P236L	Y181C
1 (delavirdine)			0.26	18.0	8.32
2	CH_3	NH-*i*Pr	0.50	1.5	1.1
31	Et	NHEt	0.43	0.36	0.39
32	Et	NH-*i*Pr	0.25	0.17	0.40
20	CH_3	Et	0.061	1.1	2.0
12	CH_3	*n*Pr	*b*	*b*	*b*
13	CH_3	*i*Bu	0.51	1.1	2.6
21	Et	Et	0.098	0.21	0.43
14	Et	*n*Pr	0.27	0.37	0.45
15	Et	*i*Bu	0.41	0.43	0.88
22	*n*Pr	Et	0.13	0.54	0.91

[a] RNA-dependent DNA polymerase activity of mutant RTs was assayed as described in the Experimental Section of ref 12 using poly(rA)$_{600}$:oligo(dT)$_{10}$ as template:primer. IC_{50} values were determined by nonlinear least-squares fit of data from duplicate points at 6 drug concentrations. [b] At 1 μM compound **12** exhibited the following percent inhibitions: WT = 84%; P236L = 40%; Y181C = 25%.

Table 2. RT Inhibitory Activities of Compounds Containing Oxygen in the 3-Alkylpyridine Side Chain



no.	R	R′	IC_{50} (μM)[a] WT	P236L	Y181C
27	CH_3	CH_2OCH_3	0.14	6.8	11
29	CH_3	$C(O)OCH_3$	0.25	13	21
28	CH_2CH_3	CH_2OCH_3	0.14	0.30	0.84
30	CH_3	CH_2OH	*b*	*b*	*b*

[a] RNA-dependent DNA polymerase activity of mutant RTs was assayed as described in the Experimental Section of ref 12. IC_{50} values were determined by nonlinear least-squares fit of data from duplicate points at 6 drug concentrations. [b] At 50 μM compound **30** exhibited the following percent inhibitions: WT = 50%; P236L = 7%; Y181C = 15%.

dine and delavirdine (**1**) were run as comparator compounds. The in vitro metabolism data indicates that, in general, the 3-alkylpyridine AAP−BHAPs possess half-lives substantially shorter than **1**. As in the 3-(alkylamino)pyridine AAP−BHAP series, 3-alkylpyridine-substituted compounds containing the (ethylamino)-piperidine linker were metabolized more quickly than those containing the (methylamino)piperidine linker (**15** vs **13**).[17] The analogue with a 3-propylpyridine substituent was metabolically less stable than the one which contained a 3-isobutylpyridine substituent (**14** vs **15**). The in vivo administration of **13** and **14** to rats allowed determination of the systemic clearances and oral bioavailabilities and confirmed the in vitro metabolic results (Table 5).

The systemic clearances of compounds **2** and **13** were the same (Table 5). However, oral bioavailability of **13**, the alkylpyridine AAP−BHAP, was better than that of **2**. Comparison of a 15 mg/kg oral dose of **13** to the 30 mg/kg oral dose indicated nonlinear pharmacokinetic behavior (data not shown). Since the volumes of distribution (V_{ss}) for **2** and **13** were also similar, it is likely that differences in the nonlinear pharmacokinetics are responsible for the differences in bioavailabilities ob-

Table 3. Antiviral Activities of Selected Compounds against Resistant Viruses

no.	EC_{90} (μM)[a] U-90152^R HIV-1$_{MF}$[b] (P236L)	U-90152^R HIV-1$_{IIIB}$[b] (L100I, M230L)	L-697,661^R HIV-1$_{IIIB}$[c] (Y181C)
1	>10	>10	5.2
L-697,661	0.43	4.0	>10
2	5.3	NT	1.0
13	1.8	NT[‘]	*d*
14	0.10	0.04	0.09
15	1.0	0.03−0.05	0.03−0.1
27	*e*	NT	*f*
28	0.77	NT	1.0

[a] EC_{90}, concentration of drug that inhibited p24 production in the antiviral assay by 90%. [b] Delaviridine was used for the selection of BHAP-resistant MF and IIIB HIV-1 variants as described in ref 12. [c] L-697,661 was used for the selection of the L-drug-resistant IIIB HIV-1 variant. [d] EC_{50} = >1 μM. [e] EC_{50} = 0.3−3 μM. [f] EC_{50} = >3 μM. NT, not tested.

Table 4. In Vitro $t_{1/2}$ of Selected Compounds

no.	$t_{1/2}$ (min)[a]
Atevirdine (PNU-87201)	14.7
1	10.8
2	1.40
13	5.90
14	1.68
15	2.29

[a] Half-life of parent compound upon microsomal incubation in the presence of hepatic microsomal cytochrome P450 (see Experimental Section of ref 12 for a description of the assay).

Table 5. Selected Pharmacokinetic Parameters of 3-Alkylpyridine AAP−BHAPs and Selected Comparator Compounds in Male Sprague−Dawley Rats[a]

no.	dose (mg/kg) iv	dose (mg/kg) po	V_{SS} (L/kg)	IV $t_{1/2}\beta$ (h)	IV clearance (mL/min/kg)	absolute oral bioavailability (%)
1	14	15	1.21 ± 0.11	1.00 ± 0.096	13.6 ± 0.3	64 ± 8
	14	28				169 ± 25[b]
2	15	30.2	2.5 ± 0.4	0.67 ± 0.026	44 ± 6	4.3 ± 4.2
13	15.2	30.3	2.73 ± 0.22	0.89 ± 0.04	45 ± 4	64 ± 7
14	15	30	3.2 ± 0.5	0.82 ± 0.12	67 ± 4	9.8

[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 **1** (PNU-90152) result in an apparent bioavailability >100%. V_{SS}, steady-state volume of distribution; IV $t_{1/2}\beta$, apparent terminal disposition half-life.

served for the 30 mg/kg oral dose. Such nonlinearity was also observed for delavirdine but to a much greater degree (Table 5). Compound **14** possessed increased clearance and decreased oral bioavailability relative to compound **13**. Thus the short half-lives (IV $t_{1/2}\beta$) observed for compounds **2**, **13**, and **14** in the in vitro liver microsome assay are correlated with the high IV clearances observed in vivo.

Conclusions

A variety of 3-alkylpyridine-substituted AAP−BHAPs were successfully synthesized. In general, compounds containing a 3-ethyl-, *n*-propyl-, or isobutylpyridine substituent were active against the P236L, Y181C, and WT RTs. However, relative to their 3-ethylamino or 3-isopropylamino counterparts, these compounds demonstrated a slight reduction in activities against the P236L and WT RTs, whereas the reduction in activity against the Y181C RT was more pronounced. Compounds containing an ether or ester in the 3-alkyl side chain were significantly less active against all three enzymes, except in the case of compound **28**, an (ethylamino)piperidine containing a 3-(methoxymethyl)pyridine. The antiviral activities observed in cell culture assays for selected compounds (**13**−**15**, **28**) were consistent with their relative potencies measured in the in vitro RT assays. Several compounds were selected for evaluation in an in vitro liver microsome assay. While one compound, **13**, possessed a half-life 4.2 times longer than that of **2** (PNU-92884), the AAP−BHAP containing a 3-(isopropylamino)pyridine, none of the compounds possessed half-lives as long as delavirdine. Administration (iv and po) of compounds **13** and **14** to rats indicated that these compounds both had high clearances relative to delavirdine. Only the 3-isobutylpyridine analogue **13** had an oral bioavailability which approached that of delavirdine.

Materials and Methods

Flash chromatography utilized E. Merck silica gel (230−400 mesh) unless otherwise indicated. 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 and Upjohn. 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.

1-Benzyl-4-(*N*-ethyl-*N*-(3-formyl-2-pyridinyl)amino)piperidine (9b). 2-Bromo-3-formylpyridine[16] (0.98 g, 5.3 mmol), 1-benzyl-4-(ethylamino)piperidine[12] (1.15 g, 5.3 mmol), and diisopropylethylamine (0.92 mL, 5.3 mmol) were heated in a sealed tube at 100 °C for 2 days. The reaction was cooled and partitioned between H_2O and $CHCl_3$. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on a 2- × 40-cm column with EtOAc/hexane (1:3 to 1:1). The product was isolated as an oil (0.44 g, 26%): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.55−1.64 (m, 2H), 1.68−1.83 (m, 4H), 2.69−2.75 (m, 2H), 3.15−3.25 (m, 1H), 3.29 (s, 2H), 3.33 (q, 2H), 6.68 (dd, 1H), 7.03−7.16 (m, 5H), 7.81 (dd, 1H), 8.20 (dd, 1H); MS (EI) *m*/*z* (rel intensity) 323 (M^+, 3), 294 (11), 173 (35), 172 (83), 152 (8), 151 (80), 146 (9), 92 (12), 91 (99), 82 (11), 41 (11). HRMS (EI) calcd for $C_{20}H_{25}N_3O$: 323.1997. Found: 323.1997.

1-Benzyl-4-(*N*-methyl-*N*-(3-formyl-2-pyridinyl)amino)piperidine (9a). Prepared as described above for **9b** using 2-bromo-3-formylpyridine (5.0 g, 26.9 mmol), 1-benzyl-4-(methylamino)piperidine[12] (5.49 g, 26.9 mmol), and diisopropylethylamine (4.7 mL, 26.9 mmol). The product was isolated as an oil (3.4 g, 41%): ^{1}H NMR ($CDCl_3$) δ 1.80−1.86 (m, 2H), 1.94−2.07 (m, 2H), 2.09−2.18 (m, 2H), 2.99 (s, 3H), 3.00−3.05 (m, 2H), 3.57 (s, 2H), 3.99−4.09 (m, 1H), 6.81 (dd, 1H), 7.27−7.40 (m, 5H), 7.99 (dd, 1H), 8.34 (dd, 1H); MS (EI) *m*/*z* (rel intensity) 309 (M^+, 3), 280 (9), 173 (32), 172 (97), 137 (60), 92 (12), 91 (99), 82 (13), 65 (8), 43 (8), 41 (12). HRMS (EI) calcd for $C_{19}H_{23}N_3O$: 309.1841. Found: 309.1845.

1-*tert*-Butoxycarbonyl-4-(*N*-methyl-*N*-(3-formyl-2-pyridinyl)amino)piperidine. Prepared as described above for **9b** using 2-bromo-3-formylpyridine (2.67 g, 14.4 mmol), 1-*tert*-butoxycarbonyl-4-(methylamino)piperidine (2.8 g, 13.1 mmol), and diisopropylethylamine (2.3 mL). The product was isolated as an oil which solidified on standing (2.0 g, 48%): mp 90−91 °C; MS (EI) *m*/*z* (rel intensity) 319 (M^+, 8), 290 (36), 246 (14), 234 (25), 161 (20), 137 (50), 108 (15), 82 (21), 57 (99), 41 (16), 40 (32). HRMS (EI) calcd for $C_{17}H_{25}N_3O_3$: 319.1896. Found: 319.1909.

1-Benzyl-4-(*N*-methyl-*N*-(3-(propen-1-yl)-2-pyridinyl)amino)piperidine (10a). *n*-BuLi (1.6 M, 1.51 mL, 2.42 mmol) was added to a suspension of ethyltriphenylphosphonium bromide (0.9 g, 2.42 mmol) in dry THF. The reaction was stirred for 45 min at room temperature under N_2 before a solution of **9a** (0.5 g, 1.62 mmol) in dry THF was added. The reaction was stirred an additional 30 min before being quenched with water and extracted with $CHCl_3$. The extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave a residue which was purified by flash chromatography eluting with EtOAc/hexane (1:3 to 1:1). The product was isolated as an oil which was a 2:3 ratio of geometrical isomers (0.47 g, 90%): ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, $J = 1.8$, 4.8 Hz, 1H), 7.49 (dd, $J = 1.8$, 7.5 Hz, 0.4H), 7.33 (dd, $J = 1.7$, 7.4 Hz, 0.6H), 7.23 (m, 5H), 6.71 (m, 1H), 3.32 (d, $J = 15.9$ Hz, 0.4H), 6.20 (d, $J = 11.3$ Hz, 0.6 H), 6.05 (dq, $J = 6.5$, 15.9 Hz, 0.4H), 5.70 (dq, $J = 7.0$, 11.3 Hz, 0.6H), 3.44 (m, 0.6H), 3.40 (s, 2H), 3.31 (m, 0.4H), 2.86 (m, 2H), 2.74 (s, 0.6H), 2.72 (s, 0.4H), 1.91−1.75 (m, 7H), 1.57(m, 2H); MS (EI) *m*/*z* (rel intensity) 321 (M^+, 28), 321 (28), 230 (27), 174 (25), 173 (99), 172 (45), 149 (25), 92 (11), 91 (99), 82 (18). HRMS (EI) calcd for $C_{21}H_{27}N_3$: 321.2205. Found: 321.2220.

1-Benzyl-4-(*N*-methyl-*N*-(3-(2-methylpropyl-1-ene)-2-pyridinyl)amino)piperidine (10b). Prepared in a manner

analogous to **10a** using *n*-BuLi (1.6 M, 8.1 mL, 12.93 mmol), isopropyltriphenylphosphonium iodide (5.6 g, 12.93 mmol), and **9a** (2.0 g, 6.5 mmol). The product was isolated as an oil (1.7 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.55−1.65 (m, 2H), 1.74 (s, 3H), 1.79−1.85 (m, 2H), 1.85 (s, 3H), 2.75 (s, 3H), 2.87−2.90 (m, 2H), 3.40−3.48 (m, 1H), 3.42 (s, 2H), 5.97 (s, 1H), 6.69 (dd, 1H), 7.16−7.28 (m, 6H), 8.04 (dd, 1H).

1-Benzyl-4-(*N*-ethyl-*N*-(3-(1-propylene)-2-pyridinyl)-amino)piperidine (10c). Prepared as above for **10a** making noncritical variations using *n*-BuLi (1.6 M, 1.16 mL, 1.86 mmol), ethyltriphenylphosphonium bromide (0.69 g, 1.86 mmol), and **9b** (0.40 g, 1.24 mmol). The product was isolated as an oil in a 2:3 ratio of geometrical isomers (0.40 g, 96%): ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, J = 2.0, 4.8 Hz, 1H), 7.60 (dd, J = 2.0, 7.5 Hz, 0.4H), 7.43 (dd, J = 1.7, 7.4 Hz, 0.6H), 7.30−7.20 (m, 5H), 6.83 (dd, J = 4.8, 7.5 Hz, 0.4H), 6.79 (dd, J = 4.8, 7.4 Hz, 0.6H), 6.50 (d, J = 15.8 Hz, 0.4H), 6.29 (d, J = 11.4 Hz, 0.6H), 6.11(dd, J = 6.6, 15.8 Hz, 0.4H), 5.76 (dq, J = 7.1, 11.4 Hz, 0.6H), 3.45 (s, 2H), 3.30 (m, 2H), 3.26 (m, 1H), 2.87 (m, 2H), 1.95−1.60 (m, 9H), 0.92 (m, 3H); MS (EI) *m*/*z* (rel intensity) 335 (M^+, 9), 244 (13), 217 (17), 178 (20), 174 (19), 173 (69), 172 (26), 146 (20), 135 (14), 92 (19), 91 (99). HRMS (EI) calcd for $C_{22}H_{29}N_3$: 335.2361. Found: 335.2368.

1-Benzyl-4-(*N*-ethyl-*N*-(3-(2-methylpropyl-1-ene)-2-pyridinyl)amino)piperidine (10d). Prepared in a manner analogous to **10a** using *n*-BuLi (1.6 M, 4.3 mL, 6.8 mmol), isopropyltriphenylphosphonium iodide (2.9 g, 6.8 mmol), and **9b** (1.1 g, 3.4 mmol). The product was isolated as an oil (0.67 g, 56%): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H), 1.71−1.80 (m, 2H), 1.90 (s, 3H), 1.90−2.00 (m, 2H), 2.01 (s, 3H), 2.98−3.03 (m, 2H), 3.30−3.45 (m, 1H), 3.43 (q, 2H), 3.57 (s, 2H), 6.18 (s, 1H), 6.89 (dd, 1H), 7.32−7.45 (m, 5H), 7.46 (dd, 1H), 8.24 (dd, 1H); MS (EI) *m*/*z* (rel intensity) 349 (M^+, 8), 278 (21), 277 (40), 263 (20), 262 (99), 184 (17), 183 (79), 173 (44), 108 (36), 107 (19), 91 (45). HRMS (EI) calcd for $C_{23}H_{31}N_3$: 349.2518. Found: 349.2516.

1-*tert*-Butoxycarbonyl-4-(*N*-methyl-*N*-(3-isobutylene-2-pyridinyl)amino)piperidine. Prepared in a manner analogous to **10b** using *n*-BuLi (1.6 M, 3.9 mL, 6.26 mmol), isopropyltriphenylphosphonium iodide (2.71 g, 6.26 mmol), and 1-*tert*-butoxycarbonyl-4-(*N*-methyl-*N*-(3-formyl-2-pyridinyl)-amimo)piperidine (1.0 g, 3.13 mmol). The product was isolated as an oil (1.05 g, 97%): ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.50−1.59 (m, 2H), 1.64 (s, 3H), 1.75 (s, 3H), 2.42−2.50 (m, 2H), 2.61 (s, 3H), 3.40−3.50 (m, 1H), 3.95−4.06 (m, 1H), 5.88 (s, 1H), 6.62 (dd, 1H), 7.18 (dd, 1H), 7.95 (dd, 1H).

1-[5-Methanesulfonamidoindol-2-ylcarbonyl]-4-(*N*-methyl-*N*-(3-propyl-2-pyridinyl)amino)piperidine (12). To a stirred solution of **10a** (0.35 g, 0.11 mmol) in MeOH (50 mL) was added 10% $Pd(OH)_2$−C (100 mg) and the resulting mixture was hydrogenated at 40 psi overnight. The resulting mixture was filtered through Celite and the solvent was evaporated to afford a brown oil (117 mg, 0.05 mmol) which was contaminated with unreacted *N*-benzylalkane-reduced material. The resulting oil was taken up in CH_2Cl_2/THF/DMF (10/5/2 v/v/v 17 mL), the temperature was reduced to 0 °C, and the resulting solution was treated with 5-methanesulfonamidoindole-2-carboxylic acid (0.13 g 0.05 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 0.097 g, 0.05 mmol). The mixture was stirred overnight allowing the solution to warm to ambient temperature. The resulting mixture was poured into H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography with EtOAc/hexane to yield pure product as a foam: ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.10 (dd, J = 1.8, 4.8 Hz, 1H), 7.73 (s, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.39 (dd, J = 1.8, 7.5 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.07 (dd, J = 2.0, 8.8 Hz, 1H), 6.83 (dd, J = 4.8, 7.5 Hz, 1H), 6.62 (d, J = 1.4 Hz, 1H), 4.60 (d, J = 12.8 Hz, 2H), 3.48 (m, 1H), 3.07 (br, 2H), 2.85 (s, 3H), 2.61 (s, 3H), 2.52 (m, 2H), 1.85 (m, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); MS (EI) *m*/*z* (rel intensity) 469 (M^+, 7), 190 (84), 189 (99), 175 (49), 158 (44), 157 (71), 151 (97), 149 (68), 130 (91), 96 (64), 82 (53). HRMS (EI) calcd for $C_{24}H_{31}N_5O_3S$: 469.2148. Found: 469.2138. Anal. ($C_{24}H_{31}N_5O_3S\cdot 1.5H_2O$) C, N; H: calcd, 6.90; found, 6.28.

1-*tert*-Butoxycarbonyl-4-(*N*-methyl-*N*-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine. 1-*tert*-Butoxycarbonyl-4-(*N*-methyl-*N*-(3-isobutylene-2-pyridinyl)amino)piperidine (1.07 g, 3.1 mmol) was hydrogenated on a Parr shaker at 20 psi of hydrogen overnight using 10% Pd/C (0.1 g) as catalyst. The reaction was filtered and the solvent was evaporated in vacuo to an oil which was used without further purification (1.08 g, 100%): ^{1}H NMR ($CDCl_3$) δ 0.66 (d, 6H), 1.25 (s, 9H), 1.34−1.42 (m, 2H), 1.50−1.56 (m, 2H), 1.72−1.81 (m, 1H), 2.28 (d, 2H), 2.46 (s, 3H), 2.50−2.56 (m, 2H), 3.50−3.13 (m, 1H), 3.88 (br, 2H), 6.70 (dd, 1H), 7.21 (dd, 1H), 7.98 (dd, 1H).

1-[5-Methanesulfonamidoindol-2-ylcarbonyl]-4-(*N*-methyl-*N*-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine (13). 1-*tert*-Butoxycarbonyl-4-(*N*-methyl-*N*-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine (1.08 g, 3.1 mmol) was deprotected in 4 N HCl/dioxane for 15 min. The solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 and stripped of solvent. The foam was dried under high vacuum for 1 h. In a separate flask a solution of 5-methanesulfonamidoindole-2-carboxylic acid (1.6 g, 6.2 mmol) and CDI (1.0 g, 6.2 mmol) were stirred for 1 h in dry THF. This was cooled to 0 °C and a solution of the above foam and NEt_3 (0.45 mL, 3.2 mmol) in dry THF was added. The reaction was stirred at room temperature overnight and partitioned between $CHCl_3$ and 1 N NaOH. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography with EtOAc afforded the product as a white solid (0.7 g, 67%): mp 200−201 °C; ^{1}H NMR ($CDCl_3$) δ 9.58 (s, 1H), 8.21 (dd, J = 1.9, 4.8 Hz, 1H), 7.57 (m, 1H), 7.55 (m, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 1.9, 7.5 Hz, 1H), 6.93 (dd, J = 4.8, 7.5 Hz, 1H), 6.74 (m, 2H), 4.67 (d, J = 13.3 Hz, 2H), 3.55 (m, 1H), 3.20 (br, 2H), 2.95 (s, 3H), 2.69 (s, 3H), 2.51 (d, J = 7.3 Hz, 2H), 1.97 (m, 3H), 1.69 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H). Anal. ($C_{25}H_{33}N_5O_3S\cdot 0.2H_2O$) C, H, N.

1-[5-Methanesulfonamidoindol-2-ylcarbonyl]-4-(*N*-ethyl-*N*-(3-propyl-2-pyridinyl)amino)piperidine (14). 10c (0.60 g, 1.8 mmol) was reduced and deprotected simultaneously on a Parr Shaker at 40 psi of H_2 in MeOH for 24 h using $Pd(OH)_2$−C (0.1 g). The reaction was filtered and concentrated in vacuo to afford an oil: ^{1}H NMR ($CDCl_3$) δ 8.01 (dd, J = 1.9, 4.7 Hz, 1H), 7.28 (dd, J = 1.9, 7.5 Hz, 1H), 6.74 (dd, J = 4.7, 7.5 Hz, 1H), 3.10−2.90 (m, 7H), 2.41 (m, 4H), 1.62 (m, 2H), 1.42 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H), 0.71 (t, J = 7.0 Hz, 3H). In a separate flask CDI (0.33 g, 2.04 mmol) and 5-methanesulfonamidoindole-2-carboxylic acid (0.52 g, 2.04 mmol) were stirred in dry THF at room temperature for 1 h. This solution was then cooled to 0 °C, a solution of the above oil (0.27 g, 1.03 mmol) in dry THF was added, and the reaction was stirred at room temperature overnight. The reaction was partitioned between 0.5 N NaOH and $CHCl_3$. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash column chromatography with EtOAc/hexane (50% to 100% EtOAc). The product was isolated as a foam (0.32 g, 65%): ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H), 8.16 (dd, J = 1.9, 4.7 Hz, 1H), 7.51 (m, 1H), 743 (dd, J = 1.9, 7.5 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 2.1, 8.7 Hz, 1H), 6.89 (dd, J = 4.7, 7.5 Hz, 1H), 6.76 (s, 1H), 6.65 (m, 1H), 4.58 (d, J = 13.5 Hz, 2H), 3.36 (m, 1H), 3.12 (q, J = 7.1 Hz, 2H), 2.88 (s, 3H), 2.56 (m, 2H), 1.88 (m, 2H), 1.72−1.50 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H); MS (EI) *m*/*z* (rel intensity) 483 (M^+, 8), 203 (39), 201 (26), 189 (26), 165 (27), 164 (22), 163 (99), 158 (26), 157 (41), 130 (58), 82 (27). HRMS (EI) calcd for $C_{25}H_{33}N_5O_3S$: 483.2304. Found: 483.2303. Anal. ($C_{25}H_{33}N_5O_3S\cdot 1.0H_2O$) C, H; N: calcd, 13.96; found, 13.51.

1-[5-Methanesulfonamidoindol-2-ylcarbonyl]-4-(*N*-ethyl-*N*-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine (15). Prepared in a manner analogous to **12** using **10d** (0.67 g, 1.92 mmol) and Pearlman's catalyst (0.1 g) to afford the amine: ^{1}H NMR ($CDCl_3$) δ 8.00 (dd, J = 1.9, 4.8 Hz, 1H), 7.24 (dd, J = 1.9, 7.4 Hz, 1H), 6.72 (dd, J = 4.8, 7.4 Hz, 1H), 5.31 (br, 1H),

3.02 (m, 4H), 2.80 (m, 1H), 2.50 (m, 2H), 2.29 (m, 2H), 1.85 (m, 1H), 1.75−1.50 (m, 4H), 0.68 (d, J = 6.5 Hz, 6H), 0.68 (t, 3H). The amine was coupled with 5-methanesulfonamidoindole-2-carboxylic acid (0.53 g, 2.06 mmol) using 1,1′-carbonyldiimidazole (CDI; 0.33 g, 2.06 mmol). The product was isolated as a foam (0.31 g, 60%): ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1H), 8.14 (dd, J = 1.8, 4.8 Hz, 1H), 7.47 (m, 1H), 7.38((m, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.05 (dd, J = 2.0, 8.7 Hz, 1H), 6.86 (dd, J = 4.8, 7.4 Hz, 1H), 6.60 (m, 1H), 4.58 (br d, 2H), 3.35 (br m, 1H), 3.11 (q, J = 7.0 Hz, 2H), 2.84 (s, 3H), 2.41 (d, J = 7.3 Hz, 2H), 1.93 (m, 1H), 1.84 (m, 2H), 1.61 (m, 2H), 0.83 (t, J = 7.0 Hz, 3H), 0.77 (d, J = 6.6 Hz, 6H); MS (EI) *m/z* (rel intensity) 497 (M^+, 27), 497 (27), 468 (26), 440 (24), 218 (27), 217 (44), 215 (31), 179 (27), 177 (99), 157 (25), 130 (29). HRMS calcd for $C_{26}H_{35}N_5O_3S$: 497.2460. Found: 497.2472. Anal. ($C_{26}H_{35}N_5O_3S\cdot0.5H_2O$) C, H, N.

1-Benzyl-4-(*N*-methyl-*N*-(3-cyano-2-pyridinyl)amino)-piperidine (17a). A mixture of **8a** (10.97 g, 53.7 mmol, 2 equiv) and 2-chloro-3-cyanopyridine (3.72 g, 26.8 mmol) were placed in two sealed tubes and maintained at 115−120 °C for 2 h. The residue was diluted with CH_2Cl_2 (125 mL), washed with H_2O (2 × 50 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting semisolid was then purified by flash column chromatography eluting with a gradient of EtOAc/hexane (25/75−50/50) to afford 5.38 g (65%) of the product as a pale yellow, low-melting solid: mp 58−60 °C; IR (mull, cm^{-1}) 2950 (s), 2209 (s), 1584 (s), 1549 (s), 1500 (s), 1458 (m), 1413 (s), 1241 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H), 7.72 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.33 (m, 4H), 7.28 (m, 1H), 6.61 (dd, J_1 = 7.6 Hz, J_2 = 4.7 Hz, 1H), 4.42 (tt, J_1 = 11.8 Hz, J_2 = 4.0 Hz, 1H), 3.54 (s, 2H), 3.13 (s, 3H), 2.99 (bd, J = 11.1 Hz, 2H), 2.16 (bt, J = 11.3 Hz, 2H), 1.93 (m, 2H), 1.77 (m, 2H); EI-MS (*m/z*, rel abundance) 306 (M^+, 15), 173 (98), 146 (51), 91 (100), 82 (30). Anal. ($C_{19}H_{22}N_4$) C, H, N.

1-Benzyl-4-(*N*-ethyl-*N*-(3-cyano-2-pyridinyl)amino)piperidine (17b). Prepared in a manner analogous to **17a** using **8b** (11.10 g, 50.8 mmol) and 2-chloro-3-cyanopyridine (3.52 g, 25.4 mmol) to afford 3.24 g (40%) of the product as a pale yellow, viscous oil: IR (neat, cm^{-1}) 2941 (m), 2802 (m), 2762 (m), 2208 (m), 1588 (s), 1547 (s), 1487 (s), 1445 (s), 1237 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (dd, J_1 = 4.7 Hz, J_2 = 2.0 Hz, 1H), 7.72 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.33 (m, 4H), 7.26 (m, 1H), 6.60 (dd, J_1 = 7.6 Hz, J_2 = 4.6 Hz, 1H), 4.47 (m, 1H), 3.66 (q, J = 7.0 Hz, 2H), 3.53 (s, 2H), 2.98 (m, 2H), 2.16 (m, 2H), 1.93 (m, 2H), 1.80 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H); EI-MS (*m/z*, rel abundance) 320 (M^+, 15), 305 (1), 229 (3), 174 (23), 173 (77), 172 (37), 146 (29), 91 (100). Anal. ($C_{20}H_{24}N_4$) C, H, N.

1-Benzyl-4-(*N*-propyl-*N*-(3-cyano-2-pyridinyl)amino)-piperidine (17c). Prepared in a manner analogous to **17a** using **8c** (4.00 g, 17.2 mmol) and 2-chloro-3-cyanopyridine (1.19 g, 8.61 mmol). The resulting semisolid was then purified by flash column chromatography eluting with a gradient of CH_3OH/CH_2Cl_2 (1/99−2/98) to afford 894 mg (31%) of the product as a pale yellow, viscous oil: IR (neat, cm^{-1}) 2962 (m), 2208 (m), 1589 (s), 1547 (s), 1485 (s), 1442 (s), 1367 (m), 1234 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (dd, J_1 = 4.6 Hz, J_2 = 2.0 Hz, 1H), 7.71 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.34 (m, 4H), 7.26 (m, 1H), 6.61 (dd, J_1 = 7.6 Hz, J_2 = 4.7 Hz, 1H), 4.42 (m, 1H), 3.54 (s, 2H), 3.50 (m, 2H), 2.99 (m, 2H), 2.15 (m, 2H), 1.89 (m, 2H), 1.81 (m, 2H), 1.60 (sext, J = 7.8 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 151.9, 144.6, 129.2, 128.2, 127.1, 119.2, 112.1, 92.0, 63.1, 57.2, 53.2, 45.7, 30.4, 22.6, 10.9; EI-MS (*m/z*, rel abundance) 334 (M^+, 4), 173 (43), 146 (13), 91 (100). HRMS (FAB) calcd for $C_{21}H_{26}N_4$ + H: 335.2236. Found: 335.2240.

1-Benzyl-4-(*N*-methyl-*N*-(3-acetyl-2-pyridinyl)amino)-piperidine (18a). To a flame-dried flask containing a mixture of CH_3Li (1.5 M in diethyl ether as complexed LiBr, 5.2 mL, 7.83 mmol, 2 equiv) in anhydrous Et_2O (5.2 mL) at −78 °C under N_2 was added a solution of **17a** (1.20 g, 3.92 mmol, 1 equiv) in anhydrous Et_2O (5.3 mL) over 5 min. The resulting mixture was allowed to warm to 0 °C over approximately 2.25 h, quenched with 2 N aqueous H_2SO_4 (3.9 mL), and stirred at room temperature for 2 h. The biphasic mixture was then adjusted to pH 10−11 with 5% aqueous NaOH and diluted with Et_2O (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous phase was extracted with additional Et_2O (30 mL), and the combined organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by flash column chromatography eluting with ethyl acetate/hexane (50/50) to afford 0.99 g (78%) of the product as a pale yellow solid: mp 93−94 °C; IR (mull, cm^{-1}) 2926 (s), 1674 (s), 1587 (s), 1541 (s), 1493 (s), 1410 (s), 1363 (s), 1239 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, J_1 = 4.6 Hz, J_2 = 2.0 Hz, 1H), 7.72 (dd, J_1 = 7.5 Hz, J_2 = 1.9 Hz, 1H), 7.33 (m, 4H), 7.26 (m, 1H), 6.67 (dd, J_1 = 7.6 Hz, J_2 = 4.7 Hz, 1H), 4.14 (m, 1H), 3.53 (s, 2H), 2.98 (bd, J = 11.4 Hz, 2H), 2.74 (s, 3H), 2.51 (s, 3H), 2.12 (bd, J = 11.1 Hz, 2H), 1.89 (m, 2H), 1.77 (m, 2H); EI-MS (*m/z*, rel abundance) 323 (M^+, 1), 308 (1), 280 (9), 173 (34), 172 (38), 151 (100), 91 (81). Anal. ($C_{20}H_{25}N_3O$) C, H, N.

1-Benzyl-4-(*N*-ethyl-*N*-(3-acetyl-2-pyridinyl)amino)piperidine (18b). Prepared in a manner analogous to **18a** with methyllithium (1.5 M in diethyl ether as complexed with lithium bromide, 2.66 mL, 3.99 mmol) and **17b** (640 mg, 2.00 mmol) to provide 634 mg (94%) of the product as a faint yellow, partially crystalline oil: IR (neat, cm^{-1}) 2961 (m), 2801 (m), 1682 (s), 1580 (s), 1427 (s), 1351 (m), 1285 (m), 1246 (m), 1093 (m), 1030 (m), 741 (m), 699 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (dd, J_1 = 4.8 Hz, J_2 = 1.9 Hz, 1H), 7.66 (dd, J_1 = 7.5 Hz, J_2 = 1.9 Hz, 1H), 7.30 (m, 4H), 7.27 (m, 1H), 6.81 (dd, J_1 = 7.5 Hz, J_2 = 4.7 Hz, 1H), 3.48 (s, 2H), 3.40 (m, 3H), 2.90 (m, 2H), 2.56 (s, 3H), 1.98 (m, 2H), 1.82 (m, 2H), 1.76 (m, 2H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5, 158.8, 149.5, 137.8, 129.1, 128.2, 127.1, 127.0, 115.2, 63.0, 61.2, 53.3, 39.4, 29.7, 28.2, 14.0; EI-MS (*m/z*, rel abundance) 337 (M^+, 2), 294 (11), 246 (1), 217 (2), 173 (34), 165 (100), 91 (80). HRMS calcd for $C_{21}H_{27}N_3O$: 337.2154. Found: 337.2133.

1-Benzyl-4-(*N*-propyl-*N*-(3-acetyl-2-pyridinyl)amino)-piperidine (18c). Prepared in a manner analogous to **18a** with methyllithium (1.5 M in diethyl ether as complexed with lithium bromide, 2.52 mL, 3.77 mmol) and **17c** (650 mg, 1.89 mmol) to afford 405 mg (61%) of the product as a faint yellow, oily film. An additional 46 mg (7%) of slightly impure product was also isolated: IR (neat, cm^{-1}) 2960 (m), 1682 (s), 1581 (s), 1554 (m), 1425 (s), 1367 (m), 1261 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (dd, J_1 = 4.7 Hz, J_2 = 1.9 Hz, 1H), 7.65 (d, J = 5.7 Hz, 1H), 7.31 (m, 4H), 7.27 (m, 1H), 6.80 (dd, J_1 = 7.4 Hz, J_2 = 4.7 Hz, 1H), 3.49 (s, 2H), 3.40 (m, 1H), 3.30 (m, 2H), 2.92 (m, 2H), 2.56 (s, 3H), 1.98 (m, 2H), 1.88 (m, 2H), 1.75 (m, 2H), 1.46 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.7, 159.3, 149.8, 138.2, 129.5, 128.6, 127.4, 127.1, 115.4, 63.3, 62.6, 53.6, 46.8, 30.1, 28.5, 22.1, 12.0; EI-MS (*m/z*, rel abundance) 351 (M^+, 2), 308 (12), 179 (100), 173 (37), 172 (29), 91 (77). HRMS (FAB) calcd for $C_{22}H_{29}N_3O$ + H: 352.2389. Found: 352.2397.

1-Benzyl-4-(*N*-methyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (19a). A mixture of **18a** (260 mg, 0.804 mmol, 1 equiv), hydrazine monohydrate (0.78 mL, 16.1 mmol, 20 equiv), and powdered KOH (0.90 g, 16.1 mmol, 20 equiv) in triethylene glycol (16 mL) was stirred at 120 °C for 2 h. The condenser was removed, the mixture was heated to approximately 185−190 °C, the condenser was reattached, and the mixture was stirred at 190 °C for 3 h. After cooling to room temperature, the mixture was added to water (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL), and the organic phase was washed with H_2O (20 mL) and brine (20 mL), dried Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography eluting with EtOAc/hexane (25/75−50/50) to afford 193 mg (78%) of the product as a colorless, viscous oil: IR (neat, cm^{-1}) 2942 (s), 2799 (m), 1584 (s), 1438 (s, br), 1410 (s), 1282 (m), 1083 (m), 791 (m), 737 (m), 698 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.31 (m, 4H), 7.26 (m, 1H), 6.88 (dd, J_1 = 7.4 Hz, J_2 = 4.8 Hz, 1H), 3.50 (bs, 2H), 3.15 (m, 1H), 2.92 (m, 2H), 2.73 (s, 3H), 2.63 (q, J = 7.5 Hz, 2H), 2.00 (m, 2H), 1.82 (m, 2H), 1.73 (m, 2H), 1.23 (t, J = 7.5

Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 145.3, 138.9, 137.4, 132.4, 129.5, 128.5, 127.3, 118.4, 63.5, 59.8, 53.7, 34.7, 29.6, 24.3, 14.5; EI-MS (*m*/*z*, rel abundance) 309 (M^+, 7), 280 (8), 173 (100), 91 (72). HRMS calcd for $C_{20}H_{27}N_3$: 309.2205. Found: 309.2222.

1-Benzyl-4-(*N*-ethyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (19b). Prepared in a manner analogous to **19a** with **18b** (300 mg, 0.889 mmol), hydrazine monohydrate (0.86 mL, 17.8 mmol), and powdered potassium hydroxide (1.00 g, 17.8 mmol) to afford 207 mg (72%) of the product as a colorless, viscous oil: IR (neat, cm^{-1}) 2964 (s), 1583 (m), 1428 (s), 1092 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (m, 1H), 7.47 (m, 1H), 7.30 (m, 5H), 6.92 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, 1H), 3.47 (s, 2H), 3.22 (q, $J = 7.0$ Hz, 2H), 3.05 (m, 1H), 2.90 (m, 2H), 2.65 (q, $J = 7.5$ Hz, 2H), 1.94 (m, 2H), 1.74 (m, 4H), 1.21 (t, $J = 7.5$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H). Anal. ($C_{21}H_{29}N_3$) C, H, N.

1-Benzyl-4-(*N*-propyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (19c). Prepared in a manner analogous to **19a** with **18c** (320 mg, 0.910 mmol), hydrazine monohydrate (0.88 mL, 18.2 mmol), and powdered KOH (1.02 g, 18.2 mmol) to afford 265 mg (86%) of the product as a colorless, viscous oil: IR (neat, cm^{-1}) 2961 (s), 1584 (m), 1455 (s), 1427 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (m, 1H), 7.48 (d, $J = 7.3$ Hz, 1H), 7.31 (m, 4H), 7.27 (m, 1H), 6.91 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 3.49 (s, 2H), 3.16 (m, 2H), 2.93 (m, 3H), 2.65 (q, $J = 7.5$ Hz, 2H), 1.95 (m, 2H), 1.82 (m, 2H), 1.59 (m, 2H), 1.29 (sext, $J = 7.2$ Hz, 2H), 1.22 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3, 144.9, 137.0, 134.2, 129.2, 128.2, 127.0, 118.5, 63.1, 60.4, 53.4, 47.2, 29.6, 23.5, 21.5, 14.1, 11.8; EI-MS (*m*/*z*, rel abundance) 337 (M^+, 5), 308 (7), 173 (100), 91 (47). HRMS (FAB) calcd for $C_{22}H_{31}N_3$ + H: 338.2596. Found: 338.2610.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-methyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (20). A mixture containing **19a** (160 mg, 0.517 mmol, 1 equiv), ammonium formate (98 mg, 1.55 mmol, 3 equiv), and 10% Pd/C (160 mg) in CH_3OH (10 mL) under N_2 was degassed, heated to reflux, and refluxed for 1 h. The catalyst was then removed by filtration through Celite and the filtrate was concentrated in vacuo to give 108 mg (96%) of the debenzylated intermediate 4-(*N*-methyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine as a colorless film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.7$ Hz, 1H), 7.45 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz, 1H), 6.88 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 3.24 (m, 1H), 3.13 (bd, $J = 12.4$ Hz, 2H), 2.72 (s, 3H), 2.62 (m, 4H), 2.26 (bs, 1H), 1.76 (m, 2H), 1.67 (m, 2H), 1.22 (t, $J = 7.6$ Hz, 3H). To a flame-dried flask under N_2 were added 5-(methanesulfonylamino)-indole-2-carboxylic acid (145 mg, 0.569 mmol, 1.15 equiv), CDI (88 mg, 0.543 mmol, 1.10 equiv), and dry THF (3 mL) and the mixture was stirred at room temperature for 1.5 h. Then a solution of the intermediate (108 mg, 0.492 mmol, 1 equiv) in dry THF (4 mL) was added and the resultant mixture was stirred at room temperature for 19 h and concentrated in vacuo to remove solvent. The residue was diluted CH_2Cl_2 (25 mL), washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and flushed through a pad of silica gel (10 g), eluting with CH_3OH/CH_2Cl_2 (5/95); concentration in vacuo gave the crude product which was purified by radial chromatography (4000-μm silica gel plate), eluting with CH_3OH/CH_2Cl_2 (5/95), to give 166 mg (74%, 71% overall) of the product as a faint yellow, amorphous solid. An additional 49 mg (22%) of slightly impure product was also isolated: IR (mull, cm^{-1}) 3253 (m), 2924 (s), 1598 (s), 1533 (s), 1447 (s), 1411 (s), 1325 (s), 1153 (s), 1012 (m), 975 (m), 806 (m), 760 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.38 (s, 1H), 8.20 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz, 1H), 7.72 (s, 1H), 7.59 (d, $J = 1.8$ Hz, 1H), 7.50 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 7.15 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz, 1H), 6.95 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 6.72 (d, $J = 1.5$ Hz, 1H), 4.67 (bd, $J = 12.7$ Hz, 2H), 3.57 (m, 1H), 3.17 (bm, 2H), 2.94 (s, 3H), 2.71 (s, 3H), 2.67 (q, $J = 7.5$ Hz, 2H), 1.95 (m, 2H), 1.75 (m, 2H), 1.24 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 162.1, 145.1, 137.5, 134.3, 132.6, 130.7, 129.6, 127.6, 120.7, 118.9, 115.9, 112.9, 105.0, 58.3, 45.0 (broad), 38.5, 35.8, 30.0, 23.9, 14.1; EI-MS (*m*/*z*, rel abundance) (M^+, 74), 440 (10), 426 (43), 240 (44), 189 (55), 176 (100), 175 (98), 157 (72), 130 (91). HRMS (FAB) calcd for $C_{23}H_{29}N_5O_3S$ + H: 456.2069. Found: 456.2073. Anal. ($C_{23}H_{29}N_5O_3S\cdot 2H_2O$) C, N; H: calcd, 6.77; found, 6.05.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-ethyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (21). Prepared in a manner analogous to **20** using **19b** (144 mg, 0.445 mmol), ammonium formate (84 mg, 1.34 mmol), and 10% Pd/C (140 mg) in CH_3OH (9 mL) afforded 98 mg (94%) of the debenzylated intermediate 4-(*N*-ethyl-*N*-(3-ethyl-2-pyridinyl)-amino)piperidine as a colorless film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz, 1H), 7.48 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 6.92 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, 1H), 3.21 (q, $J = 7.0$ Hz, 2H), 3.13 (m, 4H), 2.65 (q, $J = 7.5$ Hz, 2H), 2.58 (bt, $J = 12.1$ Hz, 2H), 1.80 (m, 2H), 1.64 (qd, $J_1 = 11.8$ Hz, $J_2 = 3.7$ Hz, 2H), 1.21 (t, $J = 7.5$ Hz, 3H), 0.89 (t, $J = 7.0$ Hz, 3H). Coupling to 5-(methanesulfonylamino)indole-2-carboxylic acid (125 mg, 0.490 mmol) as described for **20** with CDI (76 mg, 0.467 mmol) afforded 175 mg (89%, 83% overall) of the product as a faint yellow, amorphous solid: IR (mull, cm^{-1}) 3254 (m), 2923 (s), 1600 (s), 1533 (s), 1448 (s), 1428 (s), 1324 (s), 1152 (s), 972 (m), 805 (m), 760 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (s, 1H), 8.27 (d, $J = 3.4$ Hz, 1H), 7.59 (s, 1H), 7.55 (d, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 1H), 7.00 (dd, $J_1 = 7.2$ Hz, $J_2 = 4.9$ Hz, 1H), 6.85 (s, 1H), 6.73 (s, 1H), 4.65 (bd, $J = 13.1$ Hz, 2H), 3.47 (m, 1H), 3.22 (m, 2H), 3.15 (bm, 2H), 2.97 (s, 3H), 2.71 (q, $J = 7.5$ Hz, 2H), 1.96 (m, 2H), 1.72 (m, 2H), 1.24 (t, $J = 7.5$ Hz, 3H), 0.92 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 160.9, 145.6, 137.7, 135.6, 134.7, 131.1, 130.0, 128.1, 121.1, 119.9, 116.4, 113.3, 105.4, 58.7, 46.0 (broad), 41.8, 39.0, 30.6, 24.0, 14.5, 13.4; EI-MS (*m*/*z*, rel abundance) 469 (M^+, 33), 440 (52), 390 (s), 237 (22), 189 (56), 149 (100), 130 (35). HRMS (FAB) calcd for $C_{24}H_{31}N_5O_3S$ + H: 470.2226. Found: 470.2240. Anal. ($C_{24}H_{31}N_5O_3S\cdot 0.5H_2O$) C, H, N.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-propyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine (22). Prepared in a manner analogous to **20** using **19c** (210 mg, 0.622 mmol), ammonium formate (118 mg, 1.87 mmol), and 10% Pd/C (200 mg) provided 144 mg (93%) of the debenzylated intermediate 4-(*N*-propyl-*N*-(3-ethyl-2-pyridinyl)amino)piperidine as a colorless film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.9$ Hz, 1H), 7.51 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.9$ Hz, 1H), 6.94 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.7$ Hz, 1H), 3.23 (bd, $J = 12.5$ Hz, 2H), 3.15 (m, 3H), 2.66 (m, 4H), 1.80 (m, 4H), 1.29 (m, 2H), 1.23 (t, $J = 7.6$ Hz, 3H), 0.81 (t, $J = 7.4$ Hz, 3H). Coupling of the intermediate with 5-(methanesulfonylamino)-indole-2-carboxylic acid (178 mg, 0.698 mmol) as described for **20** afforded 264 mg (94%, 87% overall) of the product as a faint yellow, amorphous solid: IR (mull, cm^{-1}) 3255 (m), 2926 (s), 1601 (s), 1455 (s), 1533 (s), 1428 (s), 1324 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.54 (s, 1H), 8.25 (d, $J = 3.2$ Hz, 1H), 7.59 (s, 1H), 7.56 (d, $J = 7.1$ Hz, 1H), 7.41 (d, $J = 8.7$ Hz, 1H), 7.16 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.0$ Hz, 1H), 7.00 (m, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 4.69 (bd, $J = 13.1$ Hz, 2H), 3.39 (m, 1H), 3.10 (m, 4H), 2.97 (s, 3H), 2.71 (q, $J = 7.5$ Hz, 2H), 1.96 (m, 2H), 1.75 (m, 2H), 1.31 (sext, $J = 7.3$ Hz, 2H), 1.25 (t, $J = 7.5$ Hz, 3H), 0.82 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 161.1, 145.5, 137.7, 135.0, 134.7, 131.1, 130.0, 128.1, 121.1, 119.7, 116.4, 113.3, 105.4, 59.7, 48.7, 39.0, 30.5 (broad), 23.9, 21.5, 14.5, 12.1; EI-MS (*m*/*z*, rel abundance) 483 (M^+, 15), 454 (23), 440 (18), 318 (10), 237 (34), 203 (45), 163 (100), 130 (50). HRMS (FAB) calcd for $C_{25}H_{33}N_5O_3S$ + H: 484.2382. Found: 484.2394. Anal. ($C_{25}H_{33}N_5O_3S\cdot H_2O$) C, H, N.

1-Benzyl-4-(*N*-methyl-*N*-(3-methoxycarbonyl-2-pyridinyl)amino)piperidine (24a). A mixture of 1-benzyl-4-(methylamino)piperidine (8.00 g, 39.2 mmol) and methyl 2-chloro-3-nicotinate (3.36 g, 19.6 mmol) was placed in a sealed tube and maintained at 115−120 °C for 2 h. The residue was diluted with CH_2Cl_2 (125 mL), washed with H_2O (2 × 50 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting semisolid was then chromatographed on silica gel (230−400 mesh, 350 g), eluting with a gradient of EtOAc/

hexane (25/75−50/50) to afford 4.44 g (67%) of the product as a white solid: mp 109−110 °C; IR (mull, cm^{-1}) 2925 (s), 2872 (m), 1708 (s), 1588 (s), 1496 (s), 1462 (s), 1410 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (dd, $J_1 = 4.6$ Hz, $J_2 = 1.9$ Hz, 1H), 7.87 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.33 (m, 4H), 7.26 (m, 1H), 6.60 (dd, $J_1 = 7.6$ Hz, $J_2 = 4.6$ Hz, 1H), 4.15 (tt, $J_1 = 11.7$ Hz, $J_2 = 4.1$ Hz, 1H), 3.87 (s, 3H), 3.53 (s, 2H), 2.98 (bd, $J = 11.5$ Hz, 2H), 2.79 (s, 3H), 2.11 (bt, $J = 11.6$ Hz, 2H), 1.89 (qd, $J_1 = 12.0$ Hz, $J_2 = 3.5$ Hz, 2H), 1.79 (m, 2H); EI-MS (*m*/*z*, rel abundance) 339 (M^+, 1), 308 (1), 280 (7), 173 (100), 91 (61). Anal. ($C_{20}H_{25}N_3O_2$) C, H, N.

1-Benzyl-4-(*N*-ethyl-*N*-(3-methoxycarbonyl-2-pyridinyl)amino)piperidine (24b). Prepared in a manner analogous to **24a** using 1-benzyl-4-(ethylamino)piperidine (7.69 g, 35.2 mmol) and methyl 2-chloro-3-nicotinate (3.02 g, 17.6 mmol) afforded 2.05 g (33%) of the product as an amber oil: IR (neat, cm^{-1}) 2947 (m), 2800 (m), 2758 (m), 1720 (s), 1585 (s), 1553 (s), 1445 (s), 1475 (s), 1431 (s), 1287 (s), 1236 (s), 1119 (s), 1084 (s), 800 (m), 741 (m), 699 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (dd, $J_1 = 4.6$ Hz, $J_2 = 1.9$ Hz, 1H), 7.81 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.9$ Hz, 1H), 7.31 (m, 4H), 7.26 (m, 1H), 6.64 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.7$ Hz, 1H), 3.86 (s, 3H), 3.46 (m, 4H), 2.95 (bd, $J = 10.4$ Hz, 2H), 1.95 (m, 2H), 1.88 (m, 2H), 1.75 (m, 2H), 1.09 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 157.9, 149.9, 139.8, 138.5, 129.1, 128.2, 127.0, 114.5, 112.7, 63.7, 60.6, 53.6, 52.1, 38.1, 29.8, 14.5; EI-MS (*m*/*z*, rel abundance) 353 (M^+, 1), 322 (3), 294 (17), 173 (100), 91 (85). Anal. ($C_{21}H_{27}N_3O_2$) C, H, N.

1-Benzyl-4-(*N*-methyl-*N*-(3-hydroxymethyl-2-pyridinyl)amino)piperidine (25a). To a flame-dried flask containing **24a** (750 mg, 2.21 mmol, 1 equiv) in dry THF (22 mL) at 0 °C under N_2 was added LAH (84 mg, 1 mol-equiv) in two portions. The mixture was stirred at 0 °C for 1.5 h, quenched carefully with 5% aqueous NaOH (5 mL), diluted with H_2O (10 mL), and filtered through a pad of Celite. The filtrate was then extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to give 687 mg (100%) of the product as a colorless, viscous oil: IR (neat, cm^{-1}) 3287 (br, m), 2944 (s), 2806 (s), 1587 (s), 1568 (m), 1447 (s), 1412 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.7$ Hz, 1H), 7.53 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, 1H), 7.31 (m, 4H), 7.24 (m, 1H), 6.99 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 4.90 (bs, 1H), 4.71 (s, 2H), 3.48 (s, 2H), 3.16 (m, 1H), 2.91 (bd, $J = 11.9$ Hz, 2H), 2.74 (s, 3H), 1.99 (m, 2H), 1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4, 146.9, 138.3, 136.9, 129.7, 129.1, 128.2, 127.0, 119.3, 63.04, 63.00, 59.7, 52.9, 35.4, 29.5; EI-MS (*m*/*z*, rel abundance) 311 (M^+, 2), 280 (8), 191 (2), 173 (100), 91 (58).

1-Benzyl-4-(*N*-ethyl-*N*-(3-hydroxymethyl-2-pyridinyl)amino)piperidine (25b). Prepared in a manner analogous to **25a** with **24b** (600 mg, 1.70 mmol) and LAH (64 mg, 1 mol-equiv) in dry THF (17 mL) to afford 486 mg (88%) of the product as a colorless oil: IR (neat, cm^{-1}) 3306 (br, w), 2935 (m), 1585 (m), 1429 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (m, 1H), 7.48 (m, 1H), 7.27 (m, 5H), 7.03 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, 1H), 5.75 (bs, 1H), 4.75 (s, 2H), 3.47 (s, 2H), 3.26 (q, $J = 7.1$ Hz, 2H), 3.05 (m, 1H), 2.89 (bd, $J = 11.2$ Hz, 2H), 1.95 (m, 2H), 1.75 (m, 4H), 0.93 (t, $J = 7.0$ Hz, 3H); EI-MS (*m*/*z*, rel abundance) 325 (M^+, 2), 294 (6), 173 (100), 91 (65). HRMS calcd for $C_{20}H_{27}N_3O$: 325.2154. Found: 325.2149.

1-Benzyl-4-(*N*-methyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine (26a). To a mixture of powdered KOH (356 mg, 6.34 mmol, 4 equiv) in dry DMSO (2 mL) under N_2 was added a solution of **25a** (494 mg, 1.58 mmol, 1 equiv) in dry DMSO (1.2 mL) followed by CH_3I (118 μL, 1.90 mmol). The resulting mixture was stirred at room temperature for 30 min, then diluted with water (15 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was washed with H_2O (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to give an oil which was then purified by flash chromatography by eluting with a gradient of EtOAc/hexane (20/80−40/60) to afford 313 mg (61%) of the product as a colorless, viscous oil: IR (neat, cm^{-1}) 2940 (s), 2900 (s), 1587 (s), 1448 (s), 1412 (s), 1115 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz, 1H), 7.67 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.6$ Hz, 1H), 7.31 (m, 4H), 7.25 (m, 1H), 6.89 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 4.40 (s, 2H), 3.50 (s, 2H), 3.41 (s, 3H), 3.28 (m, 1H), 2.94 (bd, $J = 11.5$ Hz, 2H), 2.77 (s, 3H), 2.01 (bt, $J = 11.3$ Hz, 2H), 1.86 (bq, $J = 11.7$ Hz, 2H), 1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 146.6, 137.9, 129.2, 128.2, 127.0, 125.1, 117.2, 70.9, 63.1, 59.5, 58.5, 53.2, 33.7, 29.2; EI-MS (*m*/*z*, rel abundance) 325 (M^+, 2), 280 (5), 173 (96), 91 (100), 82 (20). HRMS calcd for $C_{20}H_{27}N_3O$: 325.2154. Found: 325.2155.

1-Benzyl-4-(*N*-ethyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine (26b). Prepared in a manner analogous to **26a** using KOH (276 mg, 4.92 mmol), **25b** (400 mg, 1.23 mmol), and CH_3I (92 μL, 1.48 mmol) afforded 240 mg (58%) of the product as an amber oil: IR (neat, cm^{-1}) 2935 (m), 2802 (m), 1585 (m), 1429 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (m, 1H), 7.73 (m, 1H), 7.31 (m, 4H), 7.27 (m, 1H), 6.97 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, 1H), 4.46 (s, 2H), 3.48 (s, 2H), 3.41 (s, 3H), 3.24 (q, $J = 7.0$ Hz, 2H), 3.05 (m, 1H), 2.90 (m, 2H), 1.95 (m, 2H), 1.73 (m, 4H), 0.90 (t, $J = 6.9$ Hz, 3H); EI-MS (*m*/*z*, rel abundance) 339 (M^+, 3), 294 (6), 173 (100), 91 (73). HRMS calcd for $C_{21}H_{29}N_3O$: 339.2310. Found: 339.2316.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-methyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine (27). Prepared in a manner analogous to **20** using **26a** (150 mg, 0.461 mmol), ammonium formate (87 mg, 1.38 mmol), and 10% Pd/C (150 mg) to give 102 mg (94%) of the debenzylated intermediate 4-(*N*-methyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine as a colorless film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.7$ Hz, 1H), 7.65 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz, 1H), 6.87 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 4.39 (s, 2H), 3.39 (s, 3H), 3.32 (m, 1H), 3.10 (bd, $J = 12.3$ Hz, 2H), 2.75 (s, 3H), 2.58 (td, $J_1 = 12.0$ Hz, $J_2 = 2.9$ Hz, 2H), 2.12 (bs, 1H), 1.68 (m, 4H). The intermediate amine was coupled to 5-(methanesulfonylamino)indole-2-carboxylic acid (116 mg, 0.456 mmol) using CDI (74 mg, 0.456 mmol) as described for **20** to give 159 mg (76%, 73% overall) of the product as a faint yellow, amorphous solid: IR (mull, cm^{-1}) 3251 (m), 2924 (s), 2855 (s), 1590 (s), 1533 (m), 1447 (s), 1413 (s), 1322 (s), 1152 (s), 804 (w), 761 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H), 8.27 (m, 1H), 7.72 (m, 1H), 7.60 (s, 1H), 7.41 (d, $J = 8.7$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 1H), 6.97 (m, 1H), 6.77 (s, 1H), 6.57 (s, 1H), 4.71 (bd, $J = 12.2$ Hz, 2H), 4.45 (s, 2H), 3.80 (m, 1H), 3.45 (s, 3H), 3.15 (bm, 2H), 2.97 (s, 3H), 2.78 (s, 3H), 1.97 (m, 2H), 1.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 161.8, 147.0, 138.3, 134.2, 130.8, 129.5, 127.9, 125.6, 120.9, 117.9, 116.3, 112.8, 105.0, 70.9, 58.6, 38.8, 34.8, 29.7; EI-MS (*m*/*z*, rel abundance) 471 (M^+, 37), 426 (21), 237 (37), 192 (50), 177 (36), 151 (100), 130 (76), 92 (41). HRMS calcd for $C_{23}H_{29}N_5O_4S$: 471.1940. Found: 471.1939. Anal. ($C_{23}H_{29}N_5O_4S \cdot 0.25H_2O$) C, H, N.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-ethyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine (28). Prepared in a manner analogous to **20** using **26b** (110 mg, 0.324 mmol), ammonium formate (61 mg, 0.972 mmol), and 10% Pd/C (110 mg) to give 66 mg (82%) of the debenzylated intermediate 4-(*N*-ethyl-*N*-(3-methoxymethyl-2-pyridinyl)amino)piperidine as a colorless film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.8$ Hz, 1H), 7.72 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 6.96 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, 1H), 4.45 (s, 2H), 3.39 (s, 3H), 3.22 (q, $J = 7.0$ Hz, 2H), 3.11 (m, 1H), 3.07 (bd, $J = 12.2$ Hz, 2H), 2.52 (td, $J_1 = 12.2$ Hz, $J_2 = 2.1$ Hz, 2H), 2.02 (bs, 1H), 1.75 (m, 2H), 1.57 (qd, $J_1 = 12.0$ Hz, $J_2 = 4.0$ Hz, 2H), 0.88 (t, $J = 7.0$ Hz, 3H). Coupling of the intermediate amine with 5-(methanesulfonylamino)-indole-2-carboxylic acid (71 mg, 0.279 mmol) using CDI (45 mg, 0.279 mmol) as described for **20** afforded 94 mg (73%, 60% overall) of the product as a faint yellow, amorphous solid: IR (mull, cm^{-1}) 3251 (m), 2925 (s), 2856 (s), 1600 (s), 1448 (s), 1430 (s), 1227 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H), 8.34 (m, 1H), 7.78 (m, 1H), 7.59 (s, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 6.65 (s, 1H), 4.67 (bd, $J = 12.9$ Hz, 2H), 4.50 (s, 2H), 3.55 (m, 1H), 3.45 (s, 3H), 3.23 (m, 2H), 3.15 (bm, 2H), 2.97 (s, 3H), 1.94 (m,

2H), 1.74 (m, 2H), 0.93 (t, J = 6.9 Hz, 3H); EI-MS (*m*/*z*, rel abundance) 485 (M^+, 44), 470 (6), 456 (10), 440 (27), 237 (31), 205 (35), 191 (23), 165 (100), 130 (39). Anal. ($C_{24}H_{31}N_5O_4S$) C, H, N.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-methyl-*N*-(3-methoxycarbonyl-2-pyridinyl)amino)piperidine (29). Prepared as described for **14** using **24a** (250 mg, 0.736 mmol) and 20% $Pd(OH)_2$ on carbon (45% moisture, 100 mg) in CH_3OH (14 mL) provided 112 mg (61%) of the debenzylated intermediate 4-(*N*-methyl-*N*-(3-methoxycarbonyl-2-pyridinyl)amino)piperidine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, J_1 = 4.6 Hz, J_2 = 1.9 Hz, 1H), 7.88 (dd, J_1 = 7.6 Hz, J_2 = 1.9 Hz, 1H), 6.61 (dd, J_1 = 7.6 Hz, J_2 = 4.6 Hz, 1H), 4.25 (m, 1H), 3.87 (s, 3H), 3.17 (bd, J = 12.2 Hz, 2H), 2.79 (s, 3H), 2.73 (bt, J = 12.0 Hz, 2H), 1.75 (m, 4H). Coupling of the intermediate amine with 5-(methanesulfonylamino)indole-2-carboxylic acid (135 mg, 0.529 mmol) using CDI (754 mg, 0.463 mmol) as described for **14** afforded 179 mg (84%, 51% overall) of the product as a white solid: mp 223−224 °C; IR (mull, cm^{-1}) 3291 (s), 2924 (s), 2855 (s), 1715 (s), 1595 (s), 1459 (m), 1413 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (s, 1H), 8.25 (m, 1H), 7.93 (d, J = 6.6 Hz, 1H), 7.61 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 6.68 (m, 1H), 4.84 (bd, J = 12.3 Hz, 2H), 4.63 (m, 1H), 3.89 (s, 3H), 3.15 (bm, 2H), 2.97 (s, 3H), 2.76 (s, 3H), 2.02 (m, 2H), 1.86 (m, 2H); EI-MS (*m*/*z*, rel abundance) 485 (M^+, 27), 470 (7), 426 (80), 319 (29), 240 (82), 237 (47), 219 (47), 206 (96), 205 (100), 191 (45), 157 (89), 130 (88). Anal. ($C_{23}H_{27}N_5O_5S$) C, H, N.

1-(5-(Methanesulfonylamino)indol-2-ylcarbonyl)-4-(*N*-methyl-*N*-(3-hydroxymethyl-2-pyridinyl)amino)piperidine (30). Prepared in a manner analogous to **20** with **25a** (50 mg, 0.160 mmol), ammonium formate (30 mg, 0.482 mmol), and 10% Pd/C (50 mg) afforded 35 mg (100%) of the debenzylated intermediate 4-(*N*-methyl-*N*-(3-hydroxymethyl-2-pyridinyl)amino)piperidine as an opaque film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (dd, J_1 = 4.8 Hz, J_2 = 1.8 Hz, 1H), 7.55 (dd, J_1 = 7.4 Hz, J_2 = 1.8 Hz, 1H), 7.00 (dd, J_1 = 7.4 Hz, J_2 = 4.8 Hz, 1H), 4.73 (s, 2H), 3.24 (m, 1H), 3.11 (bd, J = 12.4 Hz, 2H), 2.75 (s, 3H), 2.60 (td, J_1 = 12.3 Hz, J_2 = 2.3 Hz, 2H), 1.78 (m, 2H), 1.58 (qd, J_1 = 12.1 Hz, J_2 = 4.0 Hz, 2H). Coupling of the intermediate amine to 5-(methanesulfonylamino)indole-2-carboxylic acid (43 mg, 0.168 mmol) with EDC (32 mg, 0.168 mmol) as described for **12** afforded 40 mg (55%) of the product as a faint yellow, amorphous solid: IR (mull, cm^{-1}) 3253 (m, br), 2923 (s), 1589 (s), 1446 (s), 1323 (s); ^{1}H NMR (MeOH-d_4, 400 MHz) δ 8.19 (dd, J_1 = 4.7 Hz, J_2 = 1.7 Hz, 1H), 7.89 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.18 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1H), 7.08 (dd, J_1 = 7.4 Hz, J_2 = 4.9 Hz, 1H), 6.81 (s, 1H), 4.69 (s, 2H), 4.56 (bd, J = 12.3 Hz, 2H), 3.64 (m, 1H), 3.15 (bm, 2H), 2.91 (s, 3H), 2.78 (s, 3H), 1.82 (m, 4H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 163.7, 161.3, 146.0, 138.1, 134.9, 131.1, 130.7, 130.4, 127.9, 120.6, 118.6, 115.7, 112.5, 104.7, 60.1, 59.2, 37.5, 34.0, 29.7; FAB-MS (*m*/*z*, rel abundance) 458 ($[M + H]^+$, 100), 237 (25), 139 (25), 121 (39). HRMS calcd for $C_{22}H_{27}N_5O_4S$ + H: 458.1868. Found: 458.1862. Anal. ($C_{22}H_{27}N_5O_4S\cdot H_2O$) C, H, N.

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