Discovery, Synthesis, and Bioactivity of Bis(heteroaryl)piperazines. 1. A Novel Class of Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors

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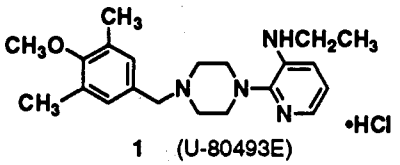
A variety of analogues of 1-[4-methoxy-3,5-dimethylbenzyl]-4-[3-(ethylamino)-2-pyridyl]piperazine hydrochloride (U-80493E) were synthesized and evaluated for their inhibition of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT). Replacement of the substituted aryl moiety with various substituted indoles provided bis(heteroaryl)piperazines (BHAPs) that were 10–100-fold more potent than U-80493E. The pyridyl portion of the lead molecule was found to be very sensitive to modifications. Extensive preclinical evaluations of several of these compounds led to the selection of 1-[(5-methoxyindol-2-yl)carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine methanesulfonate (U-87201E, atevirdine mesylate) for clinical evaluation.

The human immunodeficiency virus type-1 (HIV-1) is a member of a class of viruses known as retroviruses, wherein the normal flow of genetic information is reversed during viral replication. This process is accomplished by a unique enzyme responsible for converting the information encoded in viral genomic RNA into double-stranded DNA. This enzyme, reverse transcriptase (RT), possesses an RNA-dependent DNA polymerase, a DNA-dependent DNA polymerase, and a ribonuclease H function. These functions are essential for retroviral replication.[2] The uniqueness of RT causes it to be an especially advantageous target for therapeutic intervention. Since no closely related cellular homologues have been identified, the possibility of developing drugs selective for HIV-1 RT exists.

Since the elucidation of the viral life cycle of HIV-1, only three therapeutics have been licensed by the FDA for the treatment of AIDS, AZT, ddI, and ddC.[3,4] All three drugs are inhibitors of the enzyme reverse transcriptase and function by mimicking the normal deoxynucleoside triphosphate substrates of the enzyme eventually resulting in chain termination. Such nucleoside drugs require phosphorylation by cellular enzymes in order to function as inhibitors. Although these drugs appear to provide some clinical benefit for AIDS victims, their utility is limited by serious side effects[5] and the emergence of resistant viral strains.[6,7] More efficacious drugs and/or combinations of drugs are clearly needed for an effective long-term treatment of HIV-1 infection. In order to discover drugs which inhibit RT in a manner distinct from the nucleoside drugs, we focused our efforts on the identification of suitable non-nucleoside lead compounds. Indeed, our laboratories previously reported the discovery and biological activity of the bis(heteroaryl)piperazine (BHAP) class.[8] In addition, several unique classes of non-nucleoside RT inhibitors (NNRTIs) have also been identified such as the TIBO,[9] HEPT,[10] pyridinone,[11] TSAO,[12] and dipyridodiazepinone[13] classes.[14] Herein we present a more detailed description of the chemistry and structure–activity relationships (SAR) which led to the optimization of HIV-1 RT inhibitory activity and ultimately to the selection of a first-generation clinical candidate.

In order to efficiently evaluate the Upjohn chemical inventory, a computational dissimilarity analysis[15] was conducted on the entire sample collection to select compounds from diverse structural classes for initial screening. Using this approach, approximately 1500 compounds were evaluated for their inhibition of a purified[16] recombinant HIV-1 RT in vitro.[17] From this group of compounds, approximately 100 inhibitors were identified and subsequently evaluated for antiviral activity and selectivity by assaying for inhibition of syncytia formation in HIV-1-infected MT-2 cells, inhibition of cellular DNA polymerases α and δ,[18] and cytotoxicity. Compounds which exhibited a 50% reduction in syncytia formation (ED_{50}) at noncytotoxic concentrations were further evaluated for anti-HIV activity in other human cells [peripheral blood mononuclear cells (PBMC), H9] using diverse viral isolates (D34, JR-CSF).

As a result of this strategy, arylpiperazine 1 (Table I, U-80493E), was selected as a lead template. It demonstrated modest activity as compared to AZT in 3–4 day HIV-1 replication assays or longer assays with more rounds of viral infection. Compound 1 had a cytotherapeutic ratio (CC_{50}/ED_{50}) of approximately 10-fold. In addition, it was a selective inhibitor of RT compared to the cellular DNA polymerases α and δ and did not exhibit other significant pharmacological activities. These preliminary results led to the initiation of a chemistry program aimed at designing more potent compounds.



1 (U-80493E)

Chemistry

The majority of the desired analogues (including initial lead U-80493E, 1) were easily prepared via the reaction

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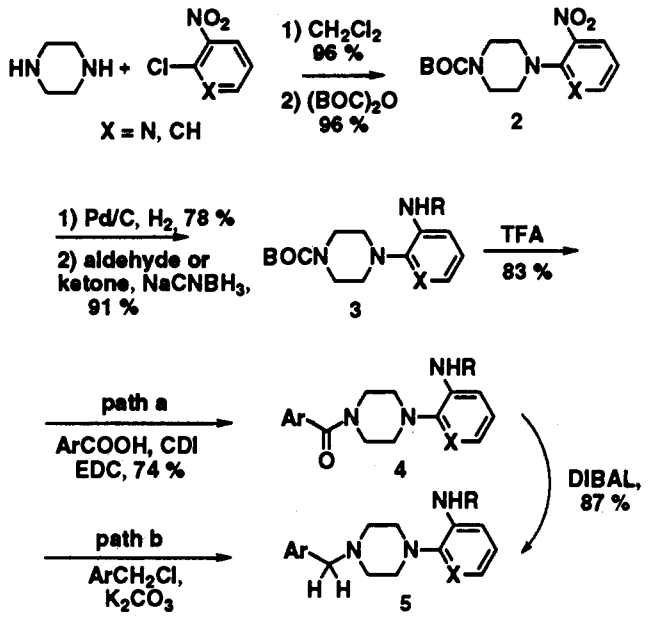
Scheme 1[a]



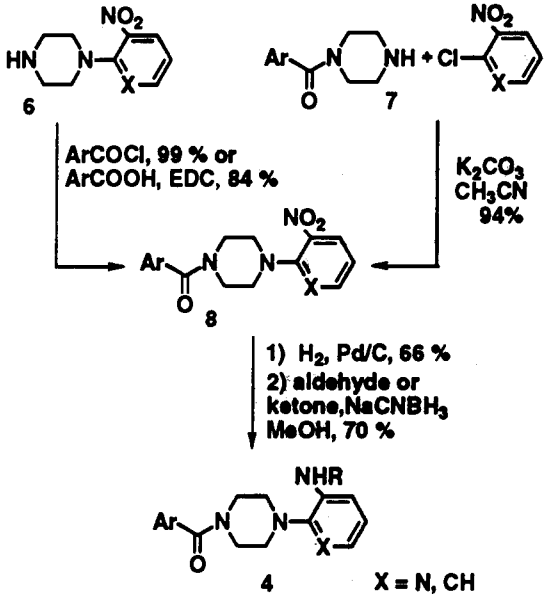
[a] Yields quoted for Ar = 2-indole, R = isopropyl, X = N.

sequences outlined in Schemes 1–4. Variation of the left-hand portion of the molecule was most easily accomplished utilizing the approach illustrated in Scheme 1. Nucleophilic aromatic substitution of 2-chloro-3-nitropyridine or 1-chloro-2-nitrobenzene with excess piperazine afforded substituted pyridylpiperazines or phenylpiperazines. Protection of the remaining free nitrogen of the piperazine ring as *tert*-butyl carbamate 2 and subsequent manipulation of the 3-nitro group (hydrogenation and reductive alkylation) afforded 3 with the desired alkylamino substituent in place. Removal of the BOC protecting group with concentrated hydrochloric acid or trifluoroacetic acid afforded the desired [3-(alkylamino)pyridyl]- or [2-(alkylamino)phenyl]piperazine. A simple appendage of an appropriate left-hand piece allowed efficient variation of the structure. Coupling of these piperazine derivatives or commercially available substituted phenylpiperazines with the desired carboxylic acids (path a) was accomplished utilizing 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) or 1,1′-carbonyldiimidazole (CDI) to afford amide analogues 4. Alkylation of the piperazine with the corresponding alkyl halide (path b) afforded the methylene-linked analogues 5. Alternatively, reduction of the amides 4 with DIBAL afforded the methylene linked congeners 5.

Scheme 2 illustrates two methods of preparing key intermediate 8 which allowed the right-hand amine substituent to be varied more efficiently. In other words, simply changing the order of the reactions depicted in Scheme 1 allowed modification of the 3-alkylamino substituent at the final stage of the synthetic sequence. Thus, piperazine 6 can be coupled with the desired aromatic acid or aromatic acid chloride to provide 8. Alternatively, the aromatic acid or acid chloride can be coupled with excess piperazine to afford substituted piperazine 7. Subsequent nucleophilic aromatic substitution of 7 with either 2-chloro-3-nitropyridine or 1-chloro-2-nitrobenzene provides 8. Finally, reduction of the nitro group and reductive alkylation provide the required analogues 4 from intermediate 8.

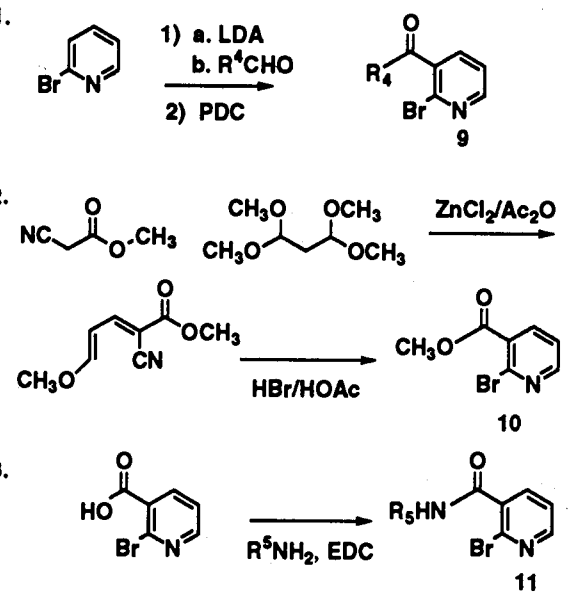
Synthesis of other 3-substituted pyridine congeners began with the literature syntheses of the 3-substituted

Scheme 2[a]



[a] Yields quoted for Ar = 2-indole, R = isopropyl, X = N.

Scheme 3



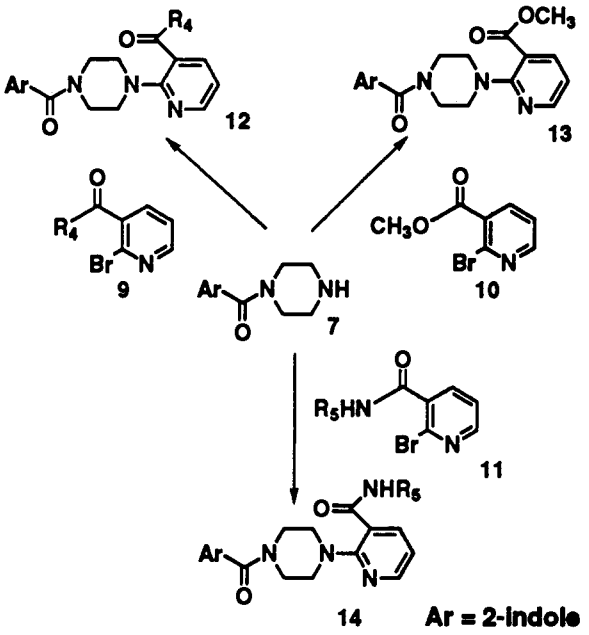
2-bromopyridine precursors (Scheme 3).[19,20] Nucleophilic aromatic substitution of 3-substituted 2-bromopyridines with these 1-aroylpiperazines as depicted in Scheme 4 afforded analogues of type 12–14.

Biological Results and Discussion

Preliminary evaluation of the compounds described herein was performed utilizing an in vitro recombinant HIV-1 RT enzyme assay with poly(rA):$(dT)_{10}$ as template: primer (results in Tables 1–5).[8] Compounds with activities inhibitory to the HIV-1 RT were subsequently assessed to determine their ability to block the spread of HIV-1 infection in human lymphocytes, such as PBMC by measuring levels of supernatant p24, and/or MT-2 cells by monitoring the formation of syncytia. A reasonably good correlation between the inhibition of RT in vitro and antiviral potencies was observed in this series of compounds.

For the purposes of discussion, the target structures can be divided into three portions: the left and right aryl

Scheme 4



groups and the central piperazine linking region. Several modifications of the U-80493E (1) template are presented in Table 1. Eliminating the 3-ethylamino substituent present on the right-hand pyridine nucleus, as in compound 17, resulted in a complete loss of RT activity. Likewise, no activity was observed when a 1,3-pyrimidine (18) was substituted for the pyridine. Other 3-amino substituents such as isopropyl (20) and propyl (21) resulted in analogues with good RT inhibitory activities. In cell culture, the isopropylamino-substituted analogue 20 was approximately 10-fold better than the lead compound 1, which contains the ethylamino substituent. The methylene linker between the left-hand aryl group and the piperazine could be replaced by a carbonyl group, providing amide analogues with potencies similar to that of the parent (1 versus 22 and 20 versus 23). Varying the length of the alkyl spacer between the piperazine and the aryl ring to ethylene [15, Y = $-(CH_2)_2-$, X = N, Z = $C(NHCH_2CH_3)$; for structure, see heading Table 1] and propylene [16, Y = $-(CH_2)_3-$, X = N, Z = $C(NHCH_2CH_3)$; for structure, see heading Table 1] spacer groups significantly decreased inhibition of RT (~30% at 100 μM) compared to the original lead (1, Y = $-CH_2-$).

The trends observed for the RT inhibitory activities in the amide series of analogues (Y = –CO–, Table 1) paralleled those in the methylene (Y = $-CH_2-$) series. For example, elimination of the 3-(alkylamino)pyridine substituent (26) obliterated RT inhibition, as it did in the methylene series. Also, the more sterically demanding isopropylamino substituent (23) still proved more beneficial to anti-RT activity than the ethylamino substituent (22) in cell culture. Replacing the 3-(ethylamino)pyridine with a 2-(ethylamino)phenyl moiety as in 24 resulted in a drastic loss of potency. A 2-ethoxyphenyl moiety (25) was completely inactive, as in the methylene series (19). It appeared that the pyridine nitrogen (X = N) played an important role in maintaining high potency (e.g. 22 versus 24).

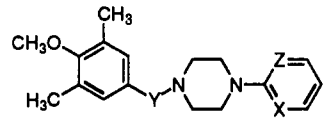
As a consequence of a substructure search of Upjohn's collection of compounds at the start of this program, the highly substituted indole 27 (Table 2) was selected for testing in the RT assay. Assay results indicated that 27 was comparable in potency to the lead arylpiperazine 1, opening up a new avenue for structural variation. Thus a systematic investigation in which an assortment of heteroaromatic groups were interchanged for the left-hand phenyl ring of 1 was undertaken. These substitutions resulted in the preparation of a series of analogues in which dramatic variations in potency were observed and also led to the discovery of significantly more potent compounds (Table 2). Since it was apparent from the arylpiperazine series (Table 1) that a carbonyl spacer was equipotent to a methylene spacer (1 versus 22, 20 versus 23), carbonyl spacers were employed for this study due to the relative ease of synthesis. As a consequence of this work, it was determined that many heterocycles such as those incorporated into compounds 29–31, 34–36, and 38–44 were not suitable replacements for the 3,5-dimethyl-4-methoxybenzoyl moiety. Nevertheless, some heterocyclic replacements (e.g. 32, 33, 37) as well as the 2-napthyl derivative (45) provided analogues with RT inhibition similar to trisubstituted benzoyl derivative 22. Most noteworthy, removal of the substituents from the highly substituted indole 27 afforded indole congener 28, which exhibited a marked increase in inhibition of RT compared to either 22 or 27. Other indole isomers wherein connection to the piperazine is via a carbonyl spacer in the 3-, 4-, or 5-positions (29, 30, 31) of the indole moiety were not as effective at inhibiting RT. Connection via the 7-position provided a compound (32) possessing a potency somewhat less than the 2-indole isomer (28). The increase in enzyme inhibition observed with the indole linked through the 2-position was corroborated by the antiviral assay results, which indicated that 28 was 10–100-fold more potent than the original lead arylpiperazine 1.

Unlike the arylpiperazine series (Table 1), where a methylene spacer is approximately equipotent to a carbonyl spacer (20 versus 23, 1 versus 22), it is interesting to note that in the indole series a methylene spacer was much less potent. For example, the methylene-linked congener of compound 28 exhibited 64% inhibition of RT at 100 μM and had an ED_{50} of 1 μM in the PBMC cell culture assay. Thus the indole analogue 28 became the chemical template of choice for optimizing anti-HIV activity.

Next, the effect of the right-hand aryl ring as well as its substitution pattern on anti-RT activity was investigated by utilizing the indole template 28. An exploration of the consequences of substitution on the right-hand phenyl ring are presented in Table 3, and the effects of substitution on a right-hand pyridyl ring are presented in Table 4. In the phenyl series, replacing the 2-ethylamino substituent (50) with 2-ethyl (46) or 2-cyano (47) caused all activity to be lost. However the RT assay indicated that both the 2-ethoxy (49) and the 2-isopropylamino (51) were adequate replacements, but a 2-methoxy group (48) was not. Disubstitution of the phenyl ring with two *ortho* substituents such as 2,6-dimethyl or 2,6-bis(ethylamino) resulted in a loss of RT inhibitory activity. Other disubstituted analogues such as 2,4-dimethoxy (7% inhibition at 100 μM) or 2-(isopropylamino)-4-(trifluoromethyl) (52) were much less inhibitory of RT. In contrast, the smaller fluorine atom was tolerated in either position 4 or 5 (53, 54).

In the pyridine series we replaced the 3-alkylamino substituent with a variety of other functional groups (Table 4). Nitrogen-based substituents other than 3-alkylamino

Table 1. Arylpiperazines Inhibit HIV-1 Reverse Transcriptase

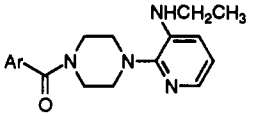


15: Y = $-(CH_2)_2-$; X = N; Z = C(NHEt)
16: Y = $-(CH_2)_3-$; X = N; Z = C(NHEt)

no.[a]	Y	Z	X	% inhibn[b] of RT	PBMC/D34[c] ED_{50} (μM)	PBMC/D34[c] CC_{50} (μM)	mp (°C)	formula[d]
1	$-CH_2-$	C(NHEt)	N	73	1–10	>10	214–216	$C_{21}H_{30}N_4O\cdot 2HCl\cdot {}^1/_2H_2O$
17	$-CH_2-$	C(H)	N	0	>10	>100	249–250	$C_{19}H_{25}N_3O\cdot 2HCl$
18	$-CH_2-$	N	N	0	NT	NT	238–239	$C_{18}H_{24}N_4O\cdot HCl$
19	$-CH_2-$	C(OEt)	C(H)	0	NT	NT	204–205	$C_{22}H_{30}N_2O_2\cdot HCl$[e]
20	$-CH_2-$	C(NH*i*-Pr)	N	84	0.1–1	~10	198–200	$C_{22}H_{32}N_4O\cdot HCl\cdot {}^1/_2H_2O$[f]
21	$-CH_2-$	C(NHPr)	N	60	NT	NT	223–225	$C_{22}H_{32}N_4O\cdot 1.8HCl\cdot {}^1/_2H_2O$
22	-(CO)-	C(NHEt)	N	69	1	>100	183–189	$C_{21}H_{28}N_4O_2\cdot 0.6HCl$
23	-(CO)-	C(NH*i*-Pr)	N	78	0.1–1	>10	99–101	$C_{22}H_{30}N_4O_2$[g]
24	-(CO)-	C(NHEt)	C(H)	21	>1	~10	75–77	$C_{22}H_{29}N_3O_2$[g]
25	-(CO)-	C(OEt)	C(H)	0	>1	<10	200–201	$C_{22}H_{28}N_2O_3\cdot {}^1/_3HCl\cdot {}^1/_5H_2O$
26	-(CO)-	C(H)	N	5	>10	>100	130–131	$C_{19}H_{23}N_3O_2$
AZT	NA	NA	NA	NT	0.001	10		

[a] All compounds tested as hydrochloride salts except 23, 24, and 26, which were tested as their free bases. [b] The HIV-1 RT in vitro assay was carried out with recombinant enzyme using the template:primer poly(rA):$(dT)_{10}$ and dTTP as the mononucleotide substrate as described in the Experimental Section. Reported for drug concentrations of 100 μM as the average of at least two determinations. [c] See Experimental Section for a description of the assay. ED_{50} = 50% effective antiviral dose. In some cases the ED_{50} was estimated, since appropriate concentrations were not employed due to a lack of cell viability or activity at the highest concentration tested. The > symbol indicates that the ED_{50} was not reached at the highest concentration tested. CC_{50} = the drug concentration required to decrease cell viability compared to uninfected controls; in most cases CC_{50} is estimated since cell viability was >50% at the highest concentrations tested. [d] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained except where noted, in which case a satisfactory HRMS was obtained. [e] H: calcd, 7.22; found, H, 7.65. [f] H: calcd, 8.28; found, 7.77. [g] Satisfactory HRMS were obtained. NT = not tested. NA = not applicable.

Table 2. Bioactivity of Selected Analogues with Heterocycles Replacing the Benzoyl Ring of 1

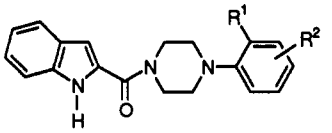


no.	Ar	% inhibn[a] of RT	PBMC/D34[b] ED_{50} (μM)	PBMC/D34[b] CC_{50} (μM)	mp (°C)	formula[c]
27[d]	5-methoxy-4,6,7-trimethyl-2-indolyl	63	>10	>10	166–168	$C_{24}H_{31}N_5O_2$
28	2-indolyl	96	0.01	>10	138–139	$C_{20}H_{23}N_5O$
29	3-indolyl	22	NT	NT	179–180	$C_{20}H_{23}N_5O$
30	4-indolyl	28	NT	NT	210–211	$C_{21}H_{23}N_5O$
31	5-indolyl	45	~10	>100	170–172	$C_{20}H_{23}N_5O$
32	7-indolyl	87	0.1–1	>100	126–128	$C_{20}H_{23}N_3O\cdot H_2O$
33	2-pyrryl	87	>1	>100	61–62	$C_{18}H_{21}N_5O$
34	2-thienyl	60	~10	>100	oil	$C_{16}H_{20}N_4OS$
35	2-furyl	39	>10	>100	oil	$C_{16}H_{20}N_4O_2$[e]
36	2-benzofuryl	37–57	10	>10	foam	$C_{20}H_{22}N_4O_2$[e]
37	2-benzimidazolyl	69	1–10	>10	161–163	$C_{18}H_{22}N_6O$
38	2-benzothienyl	50	10	~100	110–112	$C_{20}H_{21}N_4OS$
39	2-benzothiazolyl	0	NT	NT	oil	$C_{18}H_{21}N_5OS$[e]
40	2-benzoxazolyl	0	NT	NT	oil	$C_{19}H_{21}N_5O_2$[e]
41	2-quinolyl	0	NT	NT	121–122	$C_{21}H_{23}N_5O$
42	3-quinolyl	14	NT	NT	140–143	$C_{21}H_{23}N_5O$
43	2-pyrazinyl	0	NT	NT	72–74	$C_{18}H_{20}N_6O$
44	3-(1,2-benzopyronyl)	16	NT	NT	200–202	$C_{21}H_{22}N_4O_3$
45	2-naphthyl	74	1–10	>10	146–148	$C_{22}H_{24}N_4O$

[a] See footnote *b*, Table 1. [b] See footnote c, Table 1. [c] Satisfactory C, H, and N (±0.4%) were obtained except where noted, in which case a satisfactory HRMS was obtained. [d] Sample obtained from the Upjohn collection. [e] Satisfactory HRMS were obtained.

such as 3-nitro (**55**), 3-amino (**56**), 3-acetamido (**58**), and 3-(*N*-ethylacetamido) (**59**) were not very well tolerated by the enzyme. Likewise, incorporation of carbon-based substituents such as 3-cyano (**57**) and 3-(*N*-methylcarbamoyl) (**67**) provided essentially inactive compounds. 3-Acetyl-, 3-propionyl-, 3-isopropionyl-, 3-*tert*-butyryl (**69–72**), 3-(*N*-*tert*-butylcarbamoyl) (**68**), and 3-[(isopropylamino)-methyl] (**75**) substituents provided analogues which were less potent than those containing the 3-(isopropylamino) (**63**, U-88204) or 3-(ethylamino) (**28**) substituent. Interestingly, compounds **73** and **74**, which contain a 3-(methoxycarbonyl) or 3-(ethoxycarbonyl) substituent, possess moderate activity in the RT enzyme assay. Unfortunately, **73** did not demonstrate inhibition of HIV-1 in a cell culture assay (ED_{50} > 2.7 μM, MT-2 cells), possibly due to hydrolysis of the ester under the assay conditions. Within a series wherein the substitution pattern on the right-hand ring is consistent, it is evident that the pyridine ring is favored over the phenyl ring (**50** vs **28** or **51** vs **63**). Of the substituents shown, a 3-(alkylamino)-substituted

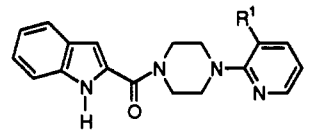
Table 3. Bioactivity of Selected Analogues with Alterations in the Right-Hand Phenyl Ring



no.	R^1	R^2	% inhibn[a] of RT	PBMC/D34[b] $ED_{50}(\mu M)$	PBMC/D34[b] $CC_{50}(\mu M)$	mp (°C)	formula[c]
46	CH_2CH_3	H	0	NT	NT	202–203	$C_{21}H_{23}N_3O$
47	CN	H	0	NT	NT	191–192	$C_{20}H_{18}N_4O$
48	OCH_3	H	33	NT	NT	195–196	$C_{20}H_{21}N_3O_2$
49	OCH_2CH_3	H	76	>1	<10	205–210	$C_{21}H_{24}N_3O$
50	NHEt	H	78	0.1–1	>100	184–185	$C_{21}H_{24}N_4O$
51	NH-*i*-Pr	H	87	NT	NT	185–187	$C_{22}H_{26}N_4O$
52	NH-*i*-Pr	4-CF_3	22	~1	>10	179–180	$C_{22}H_{23}N_4OF_3$
53	NH-*i*-Pr	4-F	83	0.1	>10	154–155	$C_{22}H_{25}N_4OF$
54	NH-*i*-Pr	5-F	77	0.1	>100	193–194	$C_{22}H_{25}N_4OF$

[a] See footnote *b*, Table 1. [b] See footnote *c*, Table 1. [c] Satisfactory C, H, and N analyses (±0.4%) were obtained.

Table 4. Effect of 3-Pyridyl Substituent



no.	R^1	% RT inhibn[a] (100 μM)	PBMC/D34[b] ED_{50} (μM)	PBMC/D34[b] CC_{50} (μM)	formula	mp (°C)
55	NO_2	5	NT	NT	$C_{18}H_{17}N_5O_3$	206–207
56	NH_2	20	>10	>100	$C_{18}H_{18}N_5O \cdot {}^1/_4H_2O$	191–192
57	CN	5	NT	NT	$C_{19}H_{17}N_5O$	194–195
58	$NH(CO)CH_3$	0	>10	>100	$C_{20}H_{21}N_5O_2$[d]	242–243
59	N(Et)(Ac)	8	NT	NT	$C_{22}H_{25}N_5O_2$	173–176
28	NHEt	96	0.01	>10	$C_{20}H_{23}N_5O$	138–139
60	$N(Et)_2$	69	0.1–1	>10	$C_{22}H_{27}N_5O$[d]	173–174
61	$NHCH_3$	85	~1	>10	$C_{18}H_{21}N_5O$	153–154
62	NHPr	64	0.01–0.1	>100	$C_{21}H_{25}N_5O \cdot {}^1/_4H_2O$	153–155
63[e]	NH-*i*-Pr	96	0.001	>10	$C_{21}H_{25}N_5O \cdot CH_4SO_3$	169–170
64	$NHCH_2Ph$	14	NT	NT	$C_{25}H_{25}N_5O \cdot {}^1/_2H_2O$	229–231
65	NH-*s*-Bu	95	0.01	>10	$C_{22}H_{27}N_5O$	165–166
66	$NHCH(CH_2CH_3)_2$	82	0.01–0.1	>10	$C_{23}H_{29}N_5O$	190–192
67	$CONHCH_3$	0	NT	NT	$C_{20}H_{21}N_5O_2$	191–192
68	CONH-*t*-Bu	50	NT	NT	$C_{23}H_{27}N_5O_2$[d]	
69	$COCH_3$	30	NT	NT	$C_{20}H_{20}N_4O_2$	198–199
70	$COCH_2CH_3$	40	NT	NT	$C_{21}H_{22}N_4O_2 \cdot {}^1/_2H_2O$	163–164
71	CO-*i*-Pr	26	NT	NT	$C_{22}H_{24}N_4O_2 \cdot {}^1/_4H_2O$	193–194
72	CO-*t*-Bu	58	NT	NT	$C_{23}H_{26}N_4O_2 \cdot {}^1/_4H_2O$	178–179
73	$COOCH_3$	82	NT	NT	$C_{20}H_{20}N_4O_3 \cdot {}^1/_4H_2O$	171–173
74	$COOCH_2CH_3$	68	NT	NT	$C_{21}H_{22}N_4O_3$	149–150
75	CH_2NH-*i*-Pr	0	NT	NT	$C_{22}H_{27}N_5O$	138–140
76	$NHCH_2$-*c*-Pr	71	0.01	>100	$C_{22}H_{25}N_5O$[d]	157–158
77	NH-*t*-Bu	89	0.001–0.01	10	$C_{22}H_{27}N_5O$[d]	188–189
78	$NHCH_2CF_3$	40	1	>10	$C_{20}H_{20}N_5F_3O$	172–175

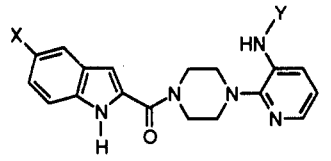
[a] See footnote *b*, Table 1. [b] See footnote *c*, Table 1. [c] Satisfactory C, H, and N analyses (±0.4%) were obtained except where noted, in which case a satisfactory HRMS was obtained. [d] Satisfactory HRMS were obtained. [e] Tested as the mesylate salt.

pyridine is the optimum right-hand piece. Moving the alkylamino substituent around the pyridine ring [e.g. 5-(isopropylamino)-3-pyridazinyl,[21] 5-(isopropylamino)-pyridyl, 6-(ethylamino)pyridyl (39%, 0%, 0% inhibition at 100 μM, respectively)] substantially decreased the RT inhibitory activity.

Consideration of the results presented in Table 4 and previously in Table 1, for both the pyridine and phenyl series of congeners, suggests that the enzyme requires a particular type of suitably placed substituent adjacent to the point of attachment of the piperazine ring. Moveover, the following results suggest that there is also an optimum steric and/or lipophilic requirement for this adjacent substituent. A 3-(diethylamino) (**60**) substituent is less preferred than a 3-(monoethylamino) (**28**) substituent. Large substituents such as 3-(benzylamino) (**64**) and 3-(1-ethylpropyl)amino (**66**) and small substituents such as 3-(methylamino) (**61**) are not as favorable as 3-(ethylamino) (**28**) and 3-(isopropylamino) (**63**) and *sec*-butylamino (**65**) substituents. In the indole series of analogues a direct comparison of analogs in which the only difference is between the ethylamino and isopropylamino substituents indicates that isopropylamino substitution confers greater HIV inhibitory activity (**63** versus **28**; also see ref 9c).

As an ongoing part of the program to identify suitable compounds for clinical evaluation, metabolic stability of the indole analogue **28** was studied. From such experiments, it was shown that N-dealkylation was the primary route of phase I metabolism in rats. This was also shown to be the case with the isopropylamino derivative **63**. In efforts to prohibit this route of metabolism, we attempted to inhibit oxidation of the α-carbon and thus prepared the

Table 5. Bioactivities of Selected Indole-Containing BHAPs



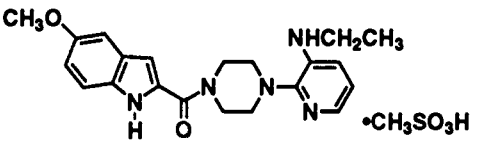
no.	X	Y	% RT inhibn[a] (100 μM)	PBMC/D34[b] ED_{50} (μM)	MT-2/IIIb[c] ED_{50} (μM)	MT-2/IIIb[c] CC_{50} (μM)	selectivity index[d] pol α/RT	selectivity index[d] pol δ/RT	mp (°C)	formula
1[e]	NA	NA	73	1–10	2	15	30	>60	214–216	$C_{21}H_{30}N_4O{\cdot}2HCl{\cdot}^1/_2H_2O$
28	H	Et	96	0.01	0.3	>30	1500	2800	138–139	$C_{20}H_{28}N_5O$
79[f]	F	Et	93	0.001	<0.3	>27	220	1670	222–223	$C_{20}H_{22}N_5OF{\cdot}CH_3SO_3H$
80[f]	OCH_3	Et	92	0.001	<0.2	>20	200	1500	215–216	$C_{21}H_{25}N_5O_2{\cdot}CH_3SO_3H$
63[f]	H	*i*-Pr	96	0.001	0.3	>27	1100	10,000	169–170	$C_{21}H_{25}N_5O{\cdot}CH_3SO_3H$
81[f]	F	*i*-Pr	96	0.003	0.3	>26	810	10,000	174–175	$C_{21}H_{24}N_5OF{\cdot}CH_3SO_3H$
82[f]	OCH_3	*i*-Pr	97	0.001	0.3	>25	1500	8,000	169–171	$C_{22}H_{27}N_5O_2{\cdot}CH_3SO_3H{\cdot}^1/_2H_2O$
77[e]	H	*t*-Bu	89	0.01–0.001	~0.2	>2.4	225	2500	188–189	$C_{22}H_{27}N_5O$[g]
83[e]	F	*t*-Bu	89	0.01–0.001	0.23–2.3	>23	233	1666	220–221	$C_{22}H_{26}N_5OF$
84[e]	OCH_3	*t*-Bu	86	0.01	0.22–2.2	>22	>83	>83[h]	200–202	$C_{23}H_{29}N_5O_2{\cdot}^1/_4H_2O$
AZT[i]	NA	NA	NA	0.001	0.07	123	400	930		

[a] See footnote *b*, Table 1. [b] See footnote, *c*, Table 1. [c] Compounds were evaluated in an assay based on the formation of HIV-1 (IIIb isolate) induced syncytia in MT-2 cells; see the Experimental Section. [d] The selectivity index = IC_{50} (cellular DNA polymerase)/IC_{50}(HIV-1 RT). The RT IC_{50} values were determined using recombinant HIV-1 RT and synthetic poly(rA):olido(dT)$_{10}$ template:primer as described. DNA polymerases α and δ were assayed as described.[18,19] The IC_{50} values used in the selectivity index were derived from at least two independent determinations. [e] Compounds 1, 77, 83, and 84 were tested as their hydrochloride salts. [f] Compounds were tested as mesylate salts in the PBMC assay. [g] Satisfactory HRMS was obtained. [h] Value could not be accurately determined due to insolubility of 84 at high concentrations. [i] AZT triphosphate was used in the RT and polymerase determinations. NA = not applicable.

cyclopropylmethyl analogue **76** and the *tert*-butyl analogue **77**. For the same reason we also synthesized compound **78**, anticipating that the presence of electronegative fluorine atoms adjacent to the α-carbon would inhibit the N-dealkylative route of metabolism. Unfortunately both the (cyclopropylmethyl)amino and (trifluoroethyl)amino derivatives proved to be significantly less active than **28** or **63**; therefore, experiments to determine their metabolic stabilities were not pursued. Studies of the metabolic stabilities of the compounds retaining anti-RT activities were conducted in an in vitro rat liver microsomal assay.[22] These preliminary results indicated that the *tert*-butylamine **77** reduced the amount of N-desalkyl metabolite formed relative to the isopropylamine. Thus, the metabolic stability of the BHAPs can be manipulated by alterations in the 3-pyridine substituent.

To investigate the effects of indole substitution on activity and to block other potential sites of metabolism, such as 5-hydroxylation of the indole,[23] analogues which incorporated a 5-substituted-indole nucleus were prepared (Table 5). The 3-(ethylamino)-, 3-(isopropylamino)-, and 3-(*tert*-butylamino)pyridine congeners were synthesized in order to investigate the effect of the combination of two modifications: those in the indole portion and those in the 3-amino substituent. All of the indole analogues presented in Table 5 effectively inhibited the spread of HIV-1 infection in PBMCs (ED_{50}s of about 1–10 nM) and in MT-2 cells (ED_{50}s of about 0.2–2.3 μM). In both assay systems the cytotoxic concentrations of the compounds were at least 10^2–10^3 times higher than their effective antiviral doses. The indole congeners were also more selective for RT than the original lead arylpiperazine **1**, in other words, they were much less inhibitory of pol α and pol δ than of HIV-1 RT.

Several pharmaceutical properties of the indole congeners (Table 5, **28**, **63**, **79–84**) were evaluated in order to determine which compound was most suitable for clinical evaluation. Formulation considerations favored the analogues containing the (*N*-ethylamino)- or (*N*-isopropylamino)pyridyl substituents, due to the greater insolubility of the *tert*-butyl analogues in aqueous media. The 5-fluoro-substituted indole analogues were less attractive due to concerns regarding the cost and availability of the 5-fluoroindole required for their synthesis. Through preliminary pharmacokinetic and safety evaluations of the remaining compounds, it was evident that **80** possessed



80 (U-87201E, atevirdine mesylate)

the most desirable overall properties. For example, comparison of the total plasma clearances obtained by iv infusion in rats (16 mg/kg in 80% ethanol) indicated that **80** was cleared approximately 2 times more slowly than its unsubstituted indole analogues **28** and **63**.[24,25] In addition, **80** demonstrated good oral bioavailability in animals (50 ± 20% in female beagle dogs; 62 ± 20% in male rats) and drug concentrations in serum greatly exceeded those required for in vitro antiviral activity (C_{max} = 16–33 μM, T_{max} = 1 h, in female beagle dogs; C_{max} = 4.6–17.4 μM, T_{max} = 0.5–1 h, in male rats).[25] Moreover, in preclinical studies **80** (atevirdine mesylate, U-87201E) proved to have a good margin of safety upon multiple dosing.[26] Clinical trials designed to evaluate the safety and efficacy of atevirdine mesylate in HIV-1 infected patients are underway.[25,27]

Several reports detailing the emergence of resistance to potent NNRTIs such as nevirapine, TIBO, and pyridinone compounds have appeared.[28] The speed in which HIV-1 acquires resistance to atevirdine mesylate will impact its clinical usefulness. Serial HIV-1 passage in vitro with increasing concentrations of **80** yielded highly resistant HIV-1 variants. DNA-sequence analysis indicated that BHAP resistance was caused by a proline to leucine

substitution at amino acid 236 (P236L) of RT.[29] Surprisingly, this mutated RT (P236L) was more sensitive to other NNRTIs like nevirapine, L-697,661, and TIBO-R82913.[29] The rate of resistance development and type of mutations that develop when HIV-1-infected patients are dosed with atevirdine mesylate (80) remains to be fully characterized. However, if treatment with a BHAP results in the P236L RT mutation in vivo, this may lead to a virus population more susceptible to other nonnucleosides. In any case, it is likely that treatment strategies which employ combination drug therapies will delay the onset of resistance.[30,31]

Conclusion

A computational dissimilarity analysis of the Upjohn compound collection directed a broad screening effort which identified 1 as a potent and specific RT inhibitor. Extensive probing of the SAR resulted in the synthesis of the indole congener 28 which became the template for subsequent chemical modifications. Important structural features necessary for obtaining good biological activity are the 2-(indolylcarbonyl) moiety, a 3-(ethylamino)- or 3-(isopropylamino)pyridine substituent, and the 2-pyridine moiety itself. Preclinical evaluations of several of these compounds led to the selection of atevirdine mesylate (80) as the candidate with the best overall properties. Clinical studies designed to evaluate the safety and efficacy of atevirdine mesylate are in progress.

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 Physical and Analytical Chemistry Department of the Upjohn Company. 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 mixture with water, dilute 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 procedure was similar to the aqueous work-up, except that the indicated aqueous base was used instead of water.

1-[(1,1-Dimethylethoxy)carbonyl]-4-(3-amino-2-pyridyl)-piperazine. Compound 2 (X = N)[32] (10.0 g, 34.0 mmol) was dissolved in 150 mL of absolute ethanol and 0.75 g of 10% palladium on carbon was added. The reaction was hydrogenated on a Parr shaker at 49 psi for 6 h. Then the reaction was filtered through Celite and concentrated in vacuo to afford 7.41 g (78%) of the title amine as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 1.7, 4.8 Hz, 1H), 6.96 (dd, J = 1.7, 7.7 Hz, 1H), 6.85 (dd, J = 4.8, 7.7 Hz, 1H), 3.79 (br, 2H), 3.57 (m, 4H), 3.06 (m, 4H), 1.47 (s, 9H).

1-[(1,1-Dimethylethoxy)carbonyl]-4-[3-[(1-methylethyl)-amino]-2-pyridyl]piperazine (3, R = *i*-Pr, X = N). Compound 2 (X = N) (7.51 mmol, 2.0 g) was dissolved in 35 mL of CH_3OH, and acetone (8.26 mmol, 0.48 g) was added. After cooling to 0 °C, acetic acid (to pH 4.0) was added and the reaction was stirred 15 min at 0 °C. Then $NaCNBH_3$ (7.96 mmol, 0.50 g) was added and the reaction was allowed to warm slowly to room temperature and followed by TLC until completion. Basic workup ($CHCl_3$, saturated $NaHCO_3$, Na_2SO_4) and purification by flash column chromatography (75 g of silica gel, 4:1 hexane/EtOAc) provided 2.20 g (91%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, J = 1.5, 4.8, Hz, 1H), 6.91 (dd, J = 4.8, 7.8 Hz, 1H), 4.15 (m, 1H), 3.57 (m, 5H), 3.00 (m, 4H), 1.48 (s, 9H), 1.23 (d, J = 6.3 Hz, 6H).

1-[3-[(1-Methylethyl)amino]-2-pyridyl]piperazine. Compound 3 (R = *i*-Pr, X = N) (27.9 mmol, 8.95 g) was dissolved in CH_2Cl_2 (56 mL) and cooled to 0 °C. Then trifluoroacetic acid (373 mmol, 42.5 g) was added dropwise. Since TLC indicated incomplete reaction, 8 mL of additional TFA was added after 10 min, 6 mL after another 1.25 h, and 4 mL after another 45 min. Then the reaction was poured onto 200 mL of water and ice, adjusted to pH 12 with 2 N aqueous NaOH, and extracted with 10% THF/$CHCl_3$ (2 L) followed by 10% CH_3OH/$CHCl_3$ (1 L). The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide 5.08 g (23.1 mmol, 83%) of the crude product which was used without further purification: ^{1}H NMR($CDCl_3$) δ 7.65 (dd, J = 1.6, 4.8 Hz, 1H), 6.85 (dd, J = 4.8, 7.9 Hz, 1H), 6.76 (dd, J = 1.6, 7.9 Hz, 1H), 4.16 (br d, J = 7.2 Hz, 1H), 3.50 (septet, J = 6.4 Hz, 1H), 2.98 (br s, 8H), 1.20 (d, J = 6.4 Hz, 6H); ^{13}C NMR (CD_3OD) δ 149.5, 138.9, 134.0, 122.6, 120.6, 47.1, 44.9, 44.8, 22.6; MS m/z 220 (54), 164 (100), 162 (43), 151 (38), 150 (52), 148 (35), 136 (45), 134 (53), 69 (37); HRMS calcd for $C_{12}H_{20}N_4$ 220.1688, found 220.1688.

1-(Indolyl-2-carbonyl)-4-(3-nitro-2-pyridyl)piperazine (8). 1-(Indolyl-2-carbonyl)piperazine (0.10 g, 0.44 mmol) was dissolved in 1.45 mL of acetonitrile, and solid K_2CO_3 (0.051 g, 0.52 mmol) was added. The reaction was cooled to 0 °C and 2-chloro-3-nitropyridine (0.069 g, 0.44 mmol) was added. The reaction was slowly warmed to room temperature and stirred for 48 h. Basic workup ($CHCl_3$, saturated aqueous $NaHCO_3$, Na_2SO_4) and concentration in vacuo afforded 0.15 g (0.41 mmol, 94%) of the title compound: mp 206–207 °C; IR (Nujol) 3289, 3075–3026, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (dd, J = 1.8, 4.5 Hz, 1H), 8.20 (dd, J = 1.8, 8.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 6.87–6.83 (m, 2H), 4.11 (m, 4H), 3.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.3, 152.3, 151.6, 135.4, 132.9, 128.6, 127.2, 124.4, 121.7, 120.4, 113.9, 111.5, 105.4, 47.5; MS m/z 351 (20), 173 (14), 161 (12), 144 (100), 143 (14), 136 (15), 120 (13), 116 (15), 56 (15); HRMS calcd for $C_{18}H_{17}N_5O_3$ 351.1331, found 351.1338. Anal. ($C_{18}H_{17}N_5O_3$) C, H, N.

General Procedure I: Alkylation of Monosubstituted Piperazines with Benzyl Chlorides. 1-(4-Methoxy-3,5-dimethylbenzyl)-4-[3-(ethylamino)-2-pyridyl]piperazine Dihydrochloride (U-80493E) (1). A mixture of 3,5-dimethyl-4-methoxybenzyl chloride (3.70 g, 20.0 mmol), 1-[3-(ethylamino)-2-pyridyl]piperazine[33] (4.18 g, 20.0 mmol), and powdered K_2CO_3 in 15 mL of acetonitrile were combined and refluxed for 18 h. The mixture was cooled to room temperature, basic workup (CH_2Cl_2, 10% aqueous $NaHCO_3$, Na_2SO_4), concentration in vacuo, purification by flash column chromatography, and conversion to the dihydrochloride salt with ethereal HCl followed by recrystallization from CH_3OH/ether provided 4.7 g (59%) of the salt: mp 214–216 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H), 6.99 (s, 2H), 6.90–6.71 (m, 2H), 4.15 (br t, 1H), 3.71 (s, 3H), 3.48 (s, 2H), 3.10 (m, 4H), 2.59 (br m, 4H), 2.28 (s, 6H), 1.28 (t, 3H); MS m/z 354 (40), 149 (100), 137 (88), 150 (76), 148 (34). Anal. ($C_{21}H_{30}N_4O_1 \cdot 2HCl \cdot 0.5H_2O$) C, H, N; Cl: calcd, 16.25; found, 15.71.

1-(3,5-Dimethyl-4-methoxybenzyl)-4-(2-pyridyl)piperazine dihydrochloride (17): general procedure I, yield 41%; mp 249–250 °C; MS m/z 311 (M^+, 28), 149 (100), 107 (57), 56 (22), 79 (16); ^{1}H NMR ($CDCl_3$, free base) δ 2.28 (6H, s), 2.54 (4H, m), 3.43 (2H, s), 3.54 (4H, m), 3.72 (3H, s), 6.61 (2H, m), 6.98 (2H, s), 7.45 (1H, t), 8.18 (1H, d). Anal. ($C_{19}H_{25}N_3O \cdot 2HCl$) C, H, N; Cl: calcd, 18.45; found, 17.44.

1-(3,5-Dimethyl-4-methoxybenzyl)-4-(2-pyrimidinyl)piperazine hydrochloride (18): general procedure I; yield 78%; mp 238–239 °C; MS m/z 312 (M^+, 10), 149 (100), 56 (48), 108 (18), 91 (15), 80 (12); ^{1}H NMR ($CDCl_3$, free base) δ 2.28 (6H, s), 2.47 (4H, m), 3.45 (2H, s), 3.72 (3H, s), 3.83 (4H, m), 6.46 (1H, t), 6.98 (2H, s), 8.29 (2H, d). Anal. Calcd ($C_{18}H_{24}N_4O \cdot HCl$) C, N, Cl; H: calcd, 7.22; found, 7.65.

1-(3,5-Dimethyl-4-methoxybenzyl)-4-(2-ethoxyphenyl)-piperazine hydrochloride (19): general procedure I; yield 90%; mp 204–205 °C; MS m/z 354 (M^+, 56), 149 (100), 150 (86), 177 (65), 134 (31); ^{1}H NMR ($CDCl_3$, free base) δ 1.46 (3H, t), 2.29 (6H, s), 2.65 (4H, br s), 3.13 (4H, br s), 3.46 (2H, s), 3.72 (3H, s), 4.08 (2H, q) 6.83–7.03 (6H, m). Anal. ($C_{22}H_{30}N_2O_2 \cdot HCl$) C, H, N.

1-(3,5-Dimethyl-4-methoxybenzyl)-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine hydrochloride (20): general procedure I; yield 82%; mp 198–200 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.67 (d, 1H), 7.00 (s, 2H), 6.87 (dd, 1 H), 6.79 (d, 1H), 4.13 (br t, 1H), 3.72 (s, 3H), 3.53 (m, 1H), 3.47 (s, 2H), 3.09 (m, 4H), 2.59 (br, 4H), 2.28 (s, 6H), 1.23 (d, 6H); MS *m/z* 326 (14), 149 (100), 134 (21), 58 (20), 158 (18), 164 (14). Anal. ($C_{22}H_{32}N_4O$·HCl·0.5H_2O) C, H: calcd, 8.28; found, 7.77. Cl: calcd, 8.56; found, 8.99.

General Procedure II: Reductive Amination. 1-[(1,1-Dimethylethoxy)carbonyl]-4-[3-(propylamino)-2-pyridyl]piperazine (3, R = Pr, X = N). $NaCNBH_3$ (0.31 g, 5.0 mmol) was added to **2**, (X = N) (2.8 g, 5.0 mmol) and propionaldehyde (0.87 g, 15.0 mmol) dissolved in 15 mL of CH_3OH at 0 °C. The reaction was stirred at room temperature overnight. Then it was acidified to pH 2 with aqueous HCl and extracted with CH_2Cl_2. The aqueous layers were basified with aqueous ammonium hydroxide to pH 8 and extracted with $CHCl_3$. The organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to provide an oil (1.2 g, 75%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 1H), 6.88 (dd, 1H), 6.78 (d, 1H), 4.24 (br t, 1H), 3.54 (m, 4H), 3.01 (m, 8H), 1.65 (m, 2H), 1.45 (s, 9H), 0.97 (t, 3H).

1-(3,5-Dimethyl-4-methoxybenzyl)-4-[3-(propylamino)-2-pyridyl]piperazine Dihydrochloride (21). TFA (4 mL) was added to a solution of crude **3** (R = Pr, X = N) (1.2 g) in CH_2Cl_2 (15 mL) chilled to −78 °C. The reaction was warmed to room temperature and stirred for 3 h. The solvent was removed in vacuo; basic workup (CH_2Cl_2, K_2CO_3, Na_2SO_4) and concentration in vacuo provided 1-[3-(propylamino)-2-pyridyl]piperazine.

General alkylation procedure I yielded 51% of pale yellow crystals: mp 223–225 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.68 (d, 1H), 6.90 (s, 2H), 6.87 (dd, 1H), 6.77 (d, 1H), 4.23 (br s, 1H), 3.71 (s, 3H), 3.47 (s, 2H), 3.11 (m, 4H), 3.02 (q, 2H), 2.60 (br s, 4H), 2.27 (s, 6H), 1.67 (m, 2H), 1.01 (t, 3H); MS *m/z* 368 (31), 149 (100), 164 (61), 151 (48), 122 (36). Anal. ($C_{22}H_{32}N_4O$·1.8HCl·0.5H_2O) C, H, N, Cl.

General Procedure III: Coupling of Monosubstituted Piperazines with Carboxylic Acids Utilizing CDI. 1-(4-Methoxy-3,5-dimethylbenzoyl)-4-[3-(ethylamino)-2-pyridyl]piperazine Hydrochloride (22). 3,5-Dimethyl-4-methoxybenzoic acid (0.36 g, 2.14 mmol) was added to a solution of 1,1′-carbonyldiimidazole (CDI, 0.35 g, 2.14 mmol) in 4 mL of THF at room temperature. After 1 h of stirring the reaction was cooled to 0 °C and 1-[3-(ethylamino)-2-pyridyl]piperazine (0.42 g, 2.0 mmol) dissolved in 6 mL of THF was added via cannula. Then the reaction was slowly warmed to room temperature and stirred a further 18 h. Basic workup (CH_2Cl_2, $NaHCO_3$, Na_2SO_4), concentration in vacuo, and purification by flash column chromatography ($CHCl_3$) afforded 0.65 g (82%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.08 (s, 2H), 6.93 (dd, 1H), 6.83 (d, 1H), 4.20 (br s, 1H), 3.71 (s, 3H), 3.95–3.50 (br m, 2H), 3.10 (m, 8H), 2.28 (s, 6 H), 1.29 (t, 3H). The free base (0.64 g) was treated with ethereal HCl and the resulting oil was crystallized by dissolving in acetone (6 mL) and adding to ether dropwise (500 mL). The salt was collected and dried at 70 °C in vacuo to provide the title compound (0.56 g, 1.52 mmol, 87%) as the hydrochloride salt: mp 183–189 °C; IR (Nujol) 1632 cm^{-1}, MS *m/z* 368 (84), 163 (100), 150 (87), 148 (61), 176 (33). Anal. ($C_{21}H_{28}N_4O_2$·0.6HCl) C, H, N, Cl.

General Procedure IV: Coupling of Monosubstituted Piperazines with Carboxylic Acids Utilizing EDC. 1-(3,5-Dimethyl-4-methoxybenzoyl)-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine (23). 3,5-Dimethyl-4-methoxybenzoic acid (0.075 g, 0.42 mmol) and 1-(3-[(1-methylethyl)amino]-2-pyridyl]piperazine (0.101 g, 0.46 mmol) were dissolved in 0.8 mL of THF at room temperature. The 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide (EDC, 0.096 g, 0.50 mmol) was added and the reaction was stirred at room temperature for 4 h. Aqueous workup ($CHCl_3$, $NaHCO_3$, Na_2SO_4), filtration through a pad of silica gel, and recrystallization from ether/hexane provided the title compound (0.054 g, 34%): mp 89–93 °C; IR (Nujol) 3276, 1627, 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 1H), 7.14 (m, 2H), 7.01 (m, 2H), 3.98–3.70 (br, 2H), 3.77 (s, 3H), 3.65 (m, 3H), 3.05 (br, 4H), 2.33 (s, 6H), 1.25 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 157.9, 136.4, 134.3, 131.0, 127.5, 120.3, 116.7, 50.5, 49.0, 43.6, 22.7, 15.9; MS *m/z* 383 (20), 382 (79), 190 (26), 176 (22), 164 (88), 163 (100), 162 (51); HRMS calcd for $C_{22}H_{30}N_4O_2$ 382.2369, found 382.2379.

1-(3,5-Dimethyl-4-methoxybenzoyl)-4-[3-(ethylamino)-2-phenyl]piperazine (24): general procedure IV; yield 39%; mp 75–77 °C; ^{1}H NMR (CD_3OD) δ 7.80 (m, 1H), 7.03 (m, 3H), 6.70 (m, 2H), 3.8–3.9 (m, 1H), 3.64 (s, 3H), 3.60–3.50 (m, 3H), 3.12 (q, *J* = 7.16 Hz, 2H), 2.74 (br, 4H), 2.21 (s, 6H), 1.17 (t, *J* = 7.16 Hz, 3H); MS *m/z* 368 (25), 367 (100), 206 (31), 175 (90), 173 (41), 147 (70), 146 (31), 133 (25), 105 (25); HRMS calcd for $C_{22}H_{29}N_3O_2$ 367.2260, found 367.2263.

1-(3,5-Dimethyl-4-methoxybenzoyl)-4-(2-ethoxyphenyl)piperazine (25): general procedure III; yield 84%; mp 200–201 °C; MS *m/z* 368 (M$^+$, 56), 176 (99), 163 (83), 134 (39), 164 (36); ^{1}H NMR ($CDCl_3$, free base) δ 1.44 (3H, t), 2.29 (6H, s), 3.02–3.12 (4H, br d), 3.63–4.00 (4H, br m), 3.71 (3H, s), 4.06 (4H, q), 7.02 (2H, s). Anal. ($C_{22}H_{28}N_2O_3$·$^1/_3$HCl·$^1/_5H_2O$) C, H, N, Cl.

1-(3,5-Dimethyl-4-methoxybenzoyl)-4-(2-pyridyl)piperazine (26): general procedure III; yield 75%; mp 130–131 °C; IR (mineral oil) 1628 cm^{-1}; MS *m/z* 325 (M$^+$, 46), 107 (99), 163 (96), 133 (87), 56 (53); ^{1}H NMR ($CDCl_3$, free base) δ 2.30 (6H, s), 3.58–3.95 (8H, br), 3.74 (3H, s), 6.66 (1H, s), 6.69 (1H, t), 7.10 (2H, s), 7.52 (1H, t), 8.21 (1H, d). Anal. ($C_{18}H_{23}N_3O_2$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (28): general procedure III; yield 76%; mp 138–139 °C; IR (Nujol) 3360, 3261, 3000–2950, 1603, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.80 (br, 1H), 7.72 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 4.8, 7.9 Hz, 1H), 6.94–6.82 (m, 2H), 4.23 (m, 1H), 4.10 (m, 4H), 3.22–3.11 (m, 6H), 1.32 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 163.0, 149.8, 137.3, 135.9, 135.2, 129.1, 127.3, 124.2, 121.7, 120.4, 116.3, 111.7, 105.2, 49.0, 45.5, 37.9, 14.7; MS *m/z* 350 (18), 349 (75), 176 (28), 162 (28), 150 (100), 148 (60), 144 (35), 134 (17), 120 (17). Anal. ($C_{20}H_{23}N_4O$) C, H, N.

1-(Indolyl-3-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (29): general procedure IV; yield 19%; mp 179–180 °C; IR (Nujol): 3115, 1582, 1567, 1528 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.54 (m, 1H), 7.48 (s, 1H), 7.40 (m, 1H), 7.28 (m, 1H), 7.06–6.97 (m, 2H), 6.80 (m, 2H), 3.76 (m, 4H), 3.01 (q, *J* = 7.1 Hz, 2H), 2.92 (m, 4H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 169.3, 151.2, 139.4, 137.4, 135.1, 128.9, 126.8, 123.4, 121.7, 120.8, 117.8, 112.8, 110.9, 50.4, 38.6, 14.6; MS *m/z* 349 (75), 176 (35), 162 (41), 150 (100), 148 (89), 144 (88); HRMS calcd for $C_{20}H_{23}N_5O$ 349.1902, found 349.1898. Anal. ($C_{20}H_{23}N_5O$) C, H, N.

1-(Indolyl-4-carbonyl)-4-[3-(1-methylethyl)amino]-2-pyridyl)piperazine (30): general procedure IV; yield 66%; mp 210–211 °C; IR (Nujol) 3191, 3165, 3115, 3103, 3034, 1618, 1601, 1578 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.46 (t, *J* = 3.2 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.98 (dd, *J* = 1.0, 7.3 Hz, 1H), 6.88 (m, 2H), 6.40 (dd, *J* = 1.0, 3.3 Hz, 1H), 3.92 (br, 2H), 3.51 (m, 1H), 3.40 (br, 2H), 3.04 (br, 2H), 2.83 (br s, 2H), 1.12 (d, *J* = 6.3 Hz, 6H); MS *m/z* 363 (76), 190 (23), 176 (23), 164 (77), 144 (100), 116 (50). Anal. ($C_{21}H_{25}N_5O$) C, H, N.

1-(Indolyl-5-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (31): general procedure III; yield 86%; mp 170–172 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (br, 1H), 7.57 (m, 1H), 7.52 (dd, *J* = 1.9, 4.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.10–7.03 (m, 2H), 6.75 (dd, *J* = 4,8, 7.9 Hz, 1H), 6.64 (dd, *J* = 1.9, 4.8 Hz, 1H), 6.38 (m, 1H), 4.05 (br, 1H), 3.61 (br, 4H), 2.95 (m, 6H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 149.9, 137.4, 136.4, 135.0, 127.2, 126.8, 125.5, 121.1, 120.3, 120.0, 116.3, 111.1, 102.8, 49.2, 37.9, 14.6; HRMS calcd for $C_{20}H_{23}N_5O$ 349.1902, found 349.1904. Anal. ($C_{20}H_{23}N_5O$·$^1/_5H_2O$) C, H, N.

1-(Indolyl-7-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (32): general procedure II; indole-7-carboxylic acid[34] and 1-[3-ethylamino-2-pyridyl]piperazine were coupled; yield 97%; mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H), 3.16 (m, 6H), 3.89 (m, 4H), 6.58 (m, 1H), 6.86 (m, 1H), 6.95 (m, 1H), 7.07 (t, 1H), 7.24 (m, 2H), 7.72 (m, 2H); MS *m/z* 349 (M$^+$). Anal. ($C_{20}H_{23}N_5O$·H_2O) C, H, N.

1-[Pyrryl-2-carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine (33): general procedure III; yield 85%; mp 61–62 °C; IR (Nujol) 3257, 1589, 1579, 1486 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.46 (br, 1H), 7.70 (dd, *J* = 1.6, 4.8 Hz, 1H), 6.96–6.90 (m, 2H), 6.84

(d, J = 7.9 Hz, 1H), 6.56 (m, 1H), 6.25 (m, 1H), 4.20 (m, 1H), 3.98 (m, 4H), 3.14 (m, 6H), 1.31 (t, J = 7.2 Hz, 3H); MS m/z 299 (70), 176 (27), 162 (34), 150 (100), 148 (82), 137 (25), 134 (27), 94 (69), 66 (32); HRMS calcd for $C_{16}H_{21}N_5O$ 299.1746, found 299.1753. Anal. ($C_{16}H_{21}N_5O$) C, H, N.

1-(Thienyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (34): general procedure III; yield 95%; oil, IR (Nujol) 3356, 3070, 2968, 2921, 2894, 2843, 1621, 1579 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 3.05–3.25 (m, 6H), 3.83–3.95 (m, 4H), 4.22 (m, 1H), 6.84 (dd, 1H, J = 7.9, 1.5 Hz), 6.94 (dd, 1H, J = 7.9, 4.8 Hz), 7.05 (dd, 1H, J = 5.0, 3.7 Hz), 7.32 (dd, 1H, J = 3.7, 1.1 Hz), 7.45 (dd, 1H, J = 5.0, 1.1 Hz), 7.71 (dd, 1H, J = 4.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.66, 37.94, 49.00, 116.25, 120.34, 126.56, 128.44, 128.65, 135.15, 136.90, 137.31, 149.79, 163.65; HRMS calcd for $C_{16}H_{20}N_4OS$ 316.1358, found 316.1361. Anal. ($C_{16}H_{20}N_4OS$) C, H, N.

1-(Furyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (35): general procedure III; yield 90% yield; oil; IR (neat) 3356, 2969, 2920, 2896, 2845, 1627, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.0 Hz), 3.05–3.25 (m, 6H), 3.95 (bs, 4H), 4.22 (bs, 1H), 6.49 (dd, 1H, J = 3.4, 1.7 Hz), 6.85 (dd, 1H, J = 7.9, 1.5 Hz), 6.95 (dd, 1H, J = 7.9, 4.8 Hz), 7.01 (dd, 1H, J = 3.4, 0.7 Hz), 7.50 (t, 1H, J = 0.8 Hz), 7.72 (dd, 1H, J = 4.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.80, 38.12, 49.19, 111.27, 116.32, 116.45, 120.40, 135.19, 137.46, 143.72, 147.93, 149.92, 159.37 (one sp^3 signal overlapping); HRMS calcd for $C_{16}H_{20}N_4O_2$ 300.1586, found 300.1599.

1-(Benzofuryl-2-carbonyl)-4-[(3-ethylamino)-2-pyridyl]piperazine (36): general procedure III; yield 58%; oil; IR (neat) 3355, 3149, 3063–2845, 1635, 1578, 1479 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (dd, J = 1.6, 4.8 Hz, 1H), 7.65 (dd, J = 1.3, 7.0 Hz, 1H), 7.53 (dd, J = 1.3, 7.0 Hz, 1H), 7.40 (td, 1.3, 7.0 Hz, 1H), 7.32 (d, J = 0.8 Hz, 1H), 7.32–7.26 (m, 1H), 6.95 (dd, J = 4.8, 7.9 Hz, 1H), 6.87 (dd, J = 1.6, 7.9 Hz, 1H), 4.22 (m, 1H), 4.00 (m, 4H), 3.25–3.10 (m, 6H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 157.7, 152.3, 147.5, 146.6, 135.1, 132.9, 124.6, 124.1, 121.2, 119.9, 118.1, 114.1, 109.6, 109.5, 46.8, 35.7, 12.4 (2 small br humps at 41.5 and 44 ppm); MS m/z 351 (22), 350 (95), 176 (30), 162 (30), 150 (100), 148 (33), 145 (33), 134 (16), 120 (17); HRMS calcd for $C_{20}H_{22}N_4O_2$ 350.1743, found 350.1747.

1-(Benzimidazolyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (37): general procedure III; yield 23%; mp 161–163 °C; IR (Nujol) 3342, 3232, 2925, 2854, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 7.0 Hz), 3.06–3.22 (m, 2H), 3.22–3.39 (m, 4H), 4.11 (m, 2H), 4.23 (m, 1H), 4.93 (bs, 2H), 6.85 (dd, 1H, J = 8.0, 1.5 Hz), 6.94 (dd, 1H, J = 8.0, 4.8 Hz), 7.32 (m, 2H), 7.53 (d, 1H, J = 7.7 Hz), 7.72 (dd, 1H, J = 4.8, 1.5 Hz), 7.82 (d, 1H, J = 7.6 Hz), 12.01 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.71, 38.00, 43.44, 47.17, 48.78, 49.49, 111.83, 116.27, 120.26, 120.79, 122.88, 124.82, 132.95, 135.17, 137.31, 143.04, 145.18, 149.84, 158.75; HRMS calcd for $C_{19}H_{22}N_6O$ 350.1855, found 350.1856. Anal. ($C_{19}H_{22}N_6O$) C, H, N.

1-(Benzothienyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (38): general provedure III; yield 91%; mp 110–112 °C; IR (Nujol) 3362, 1629, 1579, 1526, 1482, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz), 3.05 (m, 6H), 3.83–4.00 (m, 4H), 4.22 (t, 1H, J = 5.5 Hz), 6.84 (dd, 1H, J = 7.9, 1.5 Hz), 6.95 (dd, 1H, J = 7.9, 4.8 Hz), 7.33–7.45 (m, 2H), 7.5 (d, 1H, J = 0.6 Hz), 7.72 (dd, 1H, J = 4.8, 1.5 Hz), 7.77–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.68, 37.94, 49.07, 116.31, 120.41, 122.27, 124.46, 124.69, 125.04, 125.63, 135.20, 136.52, 137.32, 138.52, 140.06, 149.75, 163.89; HRMS calcd for $C_{20}H_{22}N_4OS$: 366.1514, found 366.1513. Anal. ($C_{20}H_{22}N_4OS$) C, H, N.

1-(Benzothiazolyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (39). Ethyl benzothiazole-2-carboxylate (414.5 mg, 2 mmol) was treated with 8 mL of MeOH and 1.1 mL (2.2 mmol) of 2 N NaOH. A precipitate quickly formed. After stirring at room temperature for 2 h the reaction mixture was concentrated in vacuo and lyophilized overnight. The resulting sodium salt (ca. 2 mmol) was suspended in 6 mL of CH_2Cl_2 and 0.2 mL (2.2 mmol) of oxalyl chloride was added. After stirring at room temperature for 3 **h**, it was treated with 0.16 mL (2.0 mmol) of dry pyridine (distilled from barium oxide) followed by the addition of 1-[3-(ethylamino)-2-pyridyl]piperazine (454 mg, 2.0 mmol). The reaction mixture was then allowed to stir at room temperature for 3 h, basic workup (EtOAc, $NaHCO_3$, $MgSO_4$), concentration, and purification via flash column chromatography (1:4 hexane/EtOAc) afforded 398 mg (54%) of a light yellow oil. Further purification via a second flash chromatography (3:1 hexane/EtOAc) procedure afforded the desired product (194 mg, 26%): IR (neat) 3362, 2972, 2920, 2895, 2841, 1625, 1579 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.0 Hz), 3.05–3.35 (m, 6H), 4.01 (bs, 2H), 4.22 (bs, 1H), 4.59 (bs, 2H), 6.84 (dd, 1H, J = 7.9, 1.5 Hz), 6.94 (dd, 1H, J = 7.9, 4.8 Hz), 7.40–7.60 (m, 2H), 7.72 (dd, 1H, J = 4.8, 1.5 Hz), 7.95 (dd, 1H, J = 8.8, 1.4 Hz), 8.08 (dd, 1H, J = 8.0, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.70, 37.98, 43.73, 46.78, 48.77, 49.40, 116.23, 120.25, 121.70, 124.49, 126.40, 126.53, 135.20, 136.04, 137.26, 149.82, 152.94, 159.80, 164.53; HRMS calcd for $C_{19}H_{21}N_5OS$ 367.1467, found 367.1467.

1-(Benzoxazolyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (40). By starting with ethyl benzoxazole-2-carboxylate and following the procedure described for compound **39**, the title compound was produced as an oil (7% overall): ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.0 Hz), 3.05–3.19 (m, 2H), 3.19–3.30 (m, 4H), 4.02 (t, 2H, J = 5.0 Hz), 4.21 (bs, 1H), 4.34 (t, 2H, J = 5.0 Hz), 6.85 (dd, 1H, J = 7.9, 1.6 Hz), 6.94 (dd, 1H, J = 7.9, 4.8 Hz), 7.41 (ddd, 1H, J = 7.5, 7.5, 1.3 Hz), 7.47 (ddd, 1H, J = 7.4, 7.4, 1.4 Hz), 7.65 (dd, 1H, J = 7.5, 1.3 Hz), 7.72 (dd, 1H, J = 4.8, 1.6 Hz), 7.83 (dd, 1H, J = 7.6, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.66, 37.95, 43.06, 47.17, 48.62, 49.25, 111.41, 116.30, 120.32, 121.16, 125.13, 127.00, 135.21, 137.23, 140.03, 149.65, 149.80, 154.78, 156.15; IR (Nujol) 3032, 2969, 2924, 2844, 1655, 1608, 1580 cm^{-1}; MS m/z 352 (20), 351 (79), 176 (44), 162 (40), 150 (100), 148 (71), 147 (16), 146 (18); HRMS calcd for $C_{19}H_{21}N_5O_2$ 351.1708, found 351.1695.

1-(Quinolyl-2-carbonyl)-4-[3-(ethylamino)pyridyl]piperazine (41): general procedure III; yield 100%; mp 121–122 °C; IR (Nujol) 3360, 2955, 2925, 2853, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz), 3.03–3.20 (m, 4H), 3.20–3.30 (m, 2H), 3.84 (m, 2H), 4.04 (m, 2H), 4.23 (m, 1H), 6.83 (d, 1H, J = 7.8 Hz), 6.93 (dd, 1H, J = 7.9, 4.8 Hz), 7.60 (dd, 1H, J = 7.8, 7.8 Hz), 7.68–7.81 (m, 3H), 7.85 (d, 1H, J = 8.0 Hz), 8.12 (d, 1H, J = 8.4 Hz), 8.26 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.65, 37.94, 42.54, 47.52, 48.79, 49.24, 116.19, 120.25, 120.58, 127.43, 127.53, 127.89, 129.61, 129.94, 135.14, 137.06, 137.30, 146.52, 149.91, 153.63, 167.65; HRMS calcd for $C_{21}H_{23}N_5O$ 361.1902, found 361.1907. Anal. ($C_{21}H_{23}N_5O$) C, H, N.

1-(Quinolyl-3-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (42): general procedure III; yield 99%; mp 140–143 °C; IR (Nujol) 3303, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz), 3.05–3.30 (m, 6H), 3.68 (bs, 2H), 4.00 (bs, 2H), 4.24 (t, 1H, J = 5.0 Hz), 6.84 (dd, 1H, J = 7.9, 1.3 Hz), 6.94 (dd, 1H, J = 7.9, 4.8 Hz), 7.60 (dd, 1H, J = 7.9, 7.9 Hz), 7.72 (dd, 1H, J = 4.8, 1.4 Hz), 7.77 (ddd, 1H, J = 8.4, 7.9, 1.3 Hz), 7.86 (d, 1H, J = 7.7 Hz), 8.21 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, J = 1.9 Hz), 9.01 (d, 1H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.60, 37.83, 42.46, 48.00, 48.97, 116.31, 120.46, 126.78, 127.34, 128.12, 128.49, 129.19, 130.57, 134.91, 135.06, 137.28, 148.10, 148.30, 149.54, 167.81 (one sp^3 signal overlapping); HRMS calcd for $C_{21}H_{23}N_5O$ 361.1902, found 361.1908. Anal. ($C_{21}H_{23}N_5O$) C, H, N.

1-(Pyrazinyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (43): general procedure III; yield 63%; mp 72–74 °C; IR (Nujol) 3351, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz), 3.05–3.30 (m, 6H), 3.78 (m, 2H), 4.0 (m, 2H), 4.20 (m, 1H), 6.85 (dd, 1H, J = 7.9, 1.5 Hz), 6.94 (dd, 1H, J = 7.9, 4.8 Hz), 7.71 (dd, 1H, J = 4.8, 1.5 Hz), 8.56 (dd, 1H, J = 2.5, 1.5 Hz), 8.64 (d, 1H, J = 2.5 Hz), 8,97 (d, 1H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.65, 37.94, 42.64, 47.42, 48.69, 49.16, 116.26, 120.31, 135.20, 137.24, 142.48, 145.16, 145.47, 149.29, 149.72, 165.13; HRMS calcd for $C_{16}H_{20}N_6O$ 312.1698, found 312.1715. Anal. ($C_{16}H_{20}N_6O$) C, H, N.

1-(1,2-Benzopyronyl-3-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (44): general procedure III; yield 87%; mp 200–202 °C; IR (Nujol): 3322, 1714, 1627, 1614, 1572 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.68 (dd, J = 1.6, 4.8 Hz, 1H), 7.62–7.52 (m, 2H), 7.38–7.29 (m, 2H), 6.92 (dd, J = 4.8, 7.9 Hz, 1H), 6.82 (dd, J = 1.6, 7.9 Hz, 1H), 4.17 (br t, 1H), 3.94 (br, 2H), 3.57 (m, 2H), 3.12 (m, 6H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.5, 157.8, 154.0, 149.7, 143.0, 137.3, 135.1, 132.7, 128.5, 125.1, 124.8, 120.4, 118.2, 116.7, 116.3, 49.0, 48.6, 42.2, 38.0, 14.7; MS m/z 380 (3), 379 (21), 378 (84), 205 (22), 176 (20), 150 (100). Anal. ($C_{21}H_{22}N_4O_3$) C, H, N.

1-(Napthyl-2-carbonyl)-4-[3-(ethylamino)-2-pyridyl]piperazine (45): general procedure III; yield 97%; mp 146–148 °C; IR (Nujol) 3290, 1628, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz), 3.00–3.30 (m, 6H), 3.63 (bs, 2H), 3.98 (bs, 2H), 4.23 (t, 1H, J = 5.3 Hz), 6.82 (dd, 1H, J = 7.9, 1.4 Hz), 6.93 (dd, 1H, J = 7.9, 4.8 Hz), 7.72 (dd, 1H, J = 4.8, 1.4 Hz), 7.45–7.60 (m, 3H, Ar), 7.80–7.90 (m, 3H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.66, 37.91, 42.46, 45.23, 49.10, 116.28, 120.43, 124.22, 126.62, 126.74, 126.96, 127.69, 128.28, 132.58, 132.99, 133.53, 135.12, 137.37, 149.82, 170.44 (two carbon signals are overlapping); HRMS calcd for $C_{22}H_{24}N_4O$ 360.1950, found 360.1957. Anal. ($C_{22}H_{24}N_4O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(2-ethylphenyl)piperazine (46): general procedure III; yield 83%; mp 202–203 °C; ^1H NMR ($CDCl_3$) δ 9.15 (br, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.29 (m, 2H), 7.20–7.06 (m, 4H), 6.82 (d, J = 0.5 Hz, 1H), 4.09 (m, 4H), 2.99 (t, J = 5.0 Hz, 4H), 2.77 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H). Anal. ($C_{21}H_{23}N_3O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(2-cyanophenyl)piperazine (47): general procedure II; yield 85%; mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 10.01 (br, 1H), 7.67–7.54 (m, 2H), 7.54–7.43 (m, 2H), 7.28 (td, J = 0.99, 7.0 Hz, 1H), 7.16–6.99 (m, 3H), 6.82 (d, J = 1.9 Hz, 1H), 4.19 (br, 4H), 3.28 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.8, 155.1, 135.9, 134.4, 133.9, 128.9, 127.4, 124.5, 122.6, 121.9, 120.6, 118.9, 118.2, 111.9, 106.6, 105.5, 51.7, 45.9 (br). Anal. ($C_{20}H_{18}N_4O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(2-methoxyphenyl)piperazine (48): general procedure III; yield 87%; mp 195–196 °C; ^1H NMR (d_6-DMSO) δ 11.59 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.17 (t, J = 7.0 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.97–6.86 (m, 4H), 6.82 (s, 1H), 3.89 (br, 4H), 3.79 (s, 3H), 3.00 (br, 4H). Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[2-(ethylamino)phenyl]piperazine (50): general procedure III; yield 91%; mp 184–185 °C; ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.39 (m, 1H), 7.15 (m, 1H), 7.05 (m, 1H), 7.01 (dd, J = 1.4, 7.6 Hz, 1H), 6.82 (m, 1H), 6.68 (m, 2H), 4.65 (br, 1H), 4.50–3.60 (br, 4H), 3.19 (q, J = 7.1 Hz, 2H), 2.98 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.5, 143.1, 137.7, 135.6, 129.1, 127.3, 125.6, 124.3, 121.7, 120.5, 119.5, 116.5, 111.7, 110.2, 105.3, 51.4, 38.2, 14.9; MS calcd for $C_{21}H_{24}NO$: 348.1950. Found: 348.1948. Anal. ($C_{21}H_{24}NO$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[2-[(1-methylethyl)amino]-4-(trifluoromethyl)phenyl]piperazine (52). 4-Chloro-3-nitrobenzotrifluoride (0.91 g, 4.36 mmol), 7 (1.0 g, 4.36 mmol), and K_2CO_3 (0.72 g, 5.33 mmol) were dissolved in 14.5 mL of acetonitrile and stirred at room temperature for 4 h. Aqueous workup ($CHCl_3$, Na_2SO_4) and purification by flash column chromatography (30% EtOAc/hexane) afforded 1.77 g (97%) of 1-(indolyl-2-carbonyl)-4-[2-nitro-4-(trifluoromethyl)phenyl]piperazine. ^1H NMR ($CDCl_3$) δ 9.17 (br, 1H), 8.12 (m, 1H), 7.72 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.46 (m, 1H), 7.32 (m, 1H), 7.19 (m, 1H), 7.15 (m, 1H), 6.82 (m, 1H), 4.15 (br, 4H), 3.30 (br, 4H).

The above product was reduced via catalytic hydrogenation over palladium on carbon (40 psi, 18 h) to afford 1-(indolyl-2-carbonyl)-4-[3-amino-4-(trifluoromethyl)phenyl]-piperazine: yield 87%; ^1H NMR (CD_3OD) δ 7.61 (d, J = 8.0 Hz, 1H), 7,43 (d, J = 7.4 Hz, 1H), 7.22 (m, 1H), 7.10–7.00 (m, 3H), 6.89 (m, 1H), 6.86 (s, 1H), 4.05 (br, 4H), 3.01 (m, 4H).

General procedure II (reductive alkylation of the crude amine), except with additional amounts of $NaCNBH_3$ and acetone, afforded the title compound: yield 77%; mp 179–180 °C; ^1H NMR ($CDCl_3$) δ 9.46 (br, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.30 (td, J = 1.1, 7.0 Hz, 1H), 7.15 (td, J = 1.0, 8.0 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J = 2.1 Hz, 1H), 4.13 (br, 4H), 3.67 (septet, J = 6.3 Hz, 1H), 2.99 (br, 4H), 1.29 (d, J = 6.3 Hz, 6H); HRMS calcd for $C_{23}H_{25}N_4OF_3$ 430.1980, found 430.1987. Anal. ($C_{23}H_{25}N_4OF_3$) C, H, N, F.

1-(Indolyl-2-carbonyl)-4-[2-[(1-methylethyl)amino]-4-fluorophenyl]piperazine (53). Compound 7 (1.0 g, 4.37 mmol) and 2,5-difluoronitrobenzene (0.68 g, 4.37 mmol) were mixed together in 10 mL of acetonitrile, and 0.72 g of K_2CO_3 was added. The reaction was stirred for 24 h at room temperature and then heated to 50 °C for 8 h. Aqueous workup ($CHCl_3$, Na_2SO_4), concentration in vacuo, and purification by flash column chromatography (50% EtOAc/hexane to 1:1 THF/EtOAc) afforded 1.4 g of 1-(indolyl-2-carbonyl)-4-(4-fluoro-2-nitrophenyl)piperazine. ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.57 (dd, J = 2.3, 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.37–7.10 (m, 3H), 6.82 (m, 1H), 4.10 (m, 4H), 3.10 (m, 4H); MS m/z 368 (11), 195 (11), 190 (27), 161 (11), 153 (11), 144 (100), 143 (16).

The above nitro compound (1.4 g, 3.8 mmol) was dissolved in 90 mL of ethanol and 25 mL of THF. Then 0.27 g of 10% palladium on carbon was added and the reaction was hydrogenated at 40 psi for 18 h. Then it was filtered through a plug of Celite and concentrated in vacuo to afford 1.4 g of prdouct which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.88 (dd, J = 5.7, 8.6 Hz, 1H), 6.81 (s, 1H), 6.48–6.37 (m, 2H), 4.50–3.80 (m, 4H), 3.10–2.75 (m, 4H).

1-(Indolyl-2-carbonyl)-4-(4-fluoro-2-aminophenyl)piperazine (0.74 g, 2.19 mmol) was dissolved in 4.5 mL of CH_3OH and 3.13 mL of glacial acetic acid, and 0.24 mL of acetone (3.28 mmol) was added. After 10 min of stirring, $NaCNBH_3$ (0.21 g, 3.28 mmol) was added and the reaction was stirred for 24 h. Basic workup ($CHCl_3$, 1 N NaOH, Na_2SO_4), filteration through a plug (20 g) of silica gel, and concentration in vacuo afforded 0.55 g (66%) of the title compound: mp 154–155 °C; IR (Nujol) 3272, 1601, 1505 cm^{-1}; ^1H NMR (CD_3OD) δ 7.61 (d, J = 8.03 Hz, 1H), 7.43 (dd, J = 0.8, 8.3 Hz, 1H), 7.21 (td, J = 1.1, 7.0 Hz, 1H), 7.04 (m, 1H), 6.98 (dd, J = 6.0, 8.6 Hz, 1H), 6.85 (s, 1H), 6.35 (dd, J = 2.8, 11.6 Hz, 1H), 6.25 (td, J = 2.8, 8.6 Hz, 1H), 4.6 (br), 3.58 (septet, J = 6.3 Hz, 1H), 2.88 (br, 4H), 1.23 (d, J = 6.3 Hz, 6H); MS m/z (rel %): 381 (25), 380 (100), 365 (14), 207 (45), 144 (39). Anal. ($C_{22}H_{25}N_4FO$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[2-[(1-methylethyl)amino]-5-fluorophenyl]piperazine (54). Compound 7 (0.70 g, 3.06 mmol) and 2,4-difluoronitrobenzene (0.33 mL, 3.06 mmol) were mixed together in 7 mL of acetonitrile, and 0.42 g of K_2CO_3 was added. The reaction was stirred 24 h at room temperature and then heated to reflux for 12 h. Aqueous workup ($CHCl_3$, Na_2SO_4), and concentration in vacuo afforded 0.84 g of 1-(indolyl-2-carbonyl)-4-(5-fluoro-2-nitrophenyl)piperazine. ^1H NMR ($CDCl_3$) δ 9.39 (br, 1H), 7.96 (dd, J = 5.7, 8.8 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.32–7.25 (m, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.81–6.72 (m, 3H), 4.13 (m, 4H), 3.18 (m, 4H); MS m/z 368 (7), 190 (21), 153 (11), 144 (100), 143 (13).

The above nitro compound (0.84 g, 2.28 mmol) was dissolved in 54 mL of ethanol and 15 mL of THF. Then 0.16 g of 10% palladium on carbon was added and the reaction was hydrogenated at 40 psi for 18 h. Then it was filtered through a plug of Celite and concentrated in vacuo to afford 0.80 g of product which was used without further purification.

1-(Indolyl-2-carbonyl)-4-(5-fluoro-2-aminophenyl)piperazine (0.42 g, 1.24 mmol) was dissolved in 2.5 mL of CH_3OH and 1.77 mL of glacial acetic acid, and 0.14 mL of acetone (1.86 mmol) was added. After 10 min of stirring, $NaCNBH_3$ (0.12 g, 1.86 mmol) was added and the reaction was stirred 24 h. Then it was poured into 10% aqueous NaOH (30 mL), extracted with $CHCl_3$ (2 × 50 mL), dried over anhydrous Na_2SO_4, and filtered through a plug (10 g) of silica gel. The silica was washed with 5% $CH_3OH/CHCl_3$ (100 mL). The organics were combined and concentrated in vacuo to afford 0.27 g of the title compound: mp 193–194 °C; ^1H NMR (CD_3OD) δ 7.62 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 8.2 Hz, 1H), 7.06 (t, J = 8.2 Hz, 1H), 6.88–6.80 (m, 2H), 6.74 (dt, J = 2.3, 7.8 Hz, 1H), 6.53 (dd, J = 6.1, 7.8 Hz, 1H), 4.02 (m, 4H), 3.60 (septet, J = 6.3 Hz, 1H), 2.92 (m, 4H), 1.22 (d, J = 6.3 Hz, 1H). Anal. ($C_{22}H_{25}N_4OF$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(3-nitro-2-pyridyl)piperazine (55). Indole-2-carboxylic acid (2.00 g, 12.41 mmol) was dissolved in 62 mL of oxalyl chloride, and the reaction was stirred overnight at room temperature in the dark. The reaction was concentrated in vacuo and placed under vacuum to get rid of any residual oxalyl chloride. The product was used without any further purification.

1-(3-Nitro-2-pyridyl)piperazine (12.41 mmol, 2.58 g) was dissolved in 25 mL of CH_2Cl_2, and pyridine (13.03 mmol, 1.054 mL) was added. The reaction was cooled to 0 °C and indole-2-carbonyl chloride (12.41 mmol, 2.29 g) in 6 mL of CH_2Cl_2 was added dropwise. The reaction was stirred 30 min at 0 °C and

subjected to a basic workup (CH_2Cl_2, $NaHCO_3$, Na_2SO_4). The crude solid obtained was recrystallized from 10% CH_3OH/toluene to afford 3.98 g (11.3 mmol, 91%) of the title compound: mp 206–207 °C; IR (nujol) 3360, 3000–2950, 1597, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (dd, J = 1.8, 4.5 Hz, 1H), 8.20 (dd, J = 1.8, 8.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 6.87–6.83 (m, 2H), 4.11 (m, 4H), 3.61 (m, 4H); MS m/z 531 (20), 173 (14), 144 (100), 143 (14), 136 (15), 116 (15), 89 (27); HRMS calcd for $C_{18}H_{17}N_5O_3$ 351.1331, found 351.1338. Anal. ($C_{18}H_{17}N_5O_3$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(3-amino-2-pyridyl)piperazine (56). Compound **55** (3.67 g, 10.4 mmol) was suspended in dioxane (80 mL), and aqueous titanium trichloride (20%, 48.3 mL, 62.4 mmol) was added in one portion. The reaction was stirred for 30 min at room temperature, diluted with aqueous NaOH (2 N, 100 mL), extracted with CH_2Cl_2 (3 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (100 g silica gel) eluting with 3% CH_3OH/chloroform afforded 3.35 g (39%, 10.4 mmol) of the title compound: mp 191–192 °C; IR (Nujol) 3394, 3251, 1614, 1531 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (dd, J = 1.6, 4.8 Hz, 1H), 7.66 (dd, J = 0.5, 8.5 Hz, 1H), 7.43 (dd, J = 0.5, 8.5 Hz, 1H), 7.29 (td, J = 0.5, 7.0 Hz, 1H), 7.15 (td, J = 0.5, 7.0 Hz, 1H), 7.02 (dd, J = 1.6, 7.8 Hz, 1H), 6.91 (dd, J = 4.8, 7.8 Hz, 1H), 6.83 (m, 1H), 4.09 (br, 4H), 3.90 (br, 1H), 3.27 (m, 4H), 1.92 (br, 1H); MS m/z 322 (16), 321 (75), 148 (34), 135 (30), 134 (35), 122 (100), 109 (25), 90 (23); HRMS calcd for $C_{18}H_{19}N_5O$ 321.1590, found 321.1593. Anal. ($C_{18}H_{19}N_5O \cdot 0.25H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(3-cyano-2-pyridyl)piperazine (57). Following general procedure IV, the product was isolated as a white solid in a quantitative yield after workup. Recrystallization from EtOAc afforded a white flaky solid in 77% yield: mp 194–195 °C; IR (Nujol) 3305, 3259, 2217, 1614, 1584, 1555, 1528 cm^{-1}; ^1H NMR ($CDCl_3$/d_6-DMSO) δ 3.26 (s, 4H), 3.50 (s, 4H), 6.24 (s, 1H), 6.33 (dd, 1H, J = 7.6, 4.8 Hz), 6.52 (t, 1H, J = 7.4 Hz), 6.66 (t, 1H, J = 7.5 Hz), 6.94 (d, 1H, J = 8.2 Hz), 7.07 (d, 1H, J = 7.9 Hz), 7.33 (dd, 1H, J = 7.6, 1.8 Hz), 7.84 (dd, 1H, J = 4.8, 1.8 Hz), 10.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$/d_6-DMSO) δ 47.44, 94.66, 104.13, 111.71, 114.37, 117.16, 119.47, 120.94, 123.08, 126.52, 128.99, 135.72, 143.29, 151.31, 159.85, 162.28; Anal. ($C_{19}H_{17}N_5O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-(3-acetamido-2-pyridyl)piperazine (58). Compound **56** (0.10 g, 0.31 mmol) and pyridine (0.026 mL, 0.33 mmol) were dissolved in 0.6 mL of CH_2Cl_2 and cooled to 0 °C. Then acetyl chloride (0.022 mL, 0.33 mmol) was added and the reaction was stirred for 10 min and then removed from the cooling bath. After stirring for 50 min at room temperature, the reaction was diluted with CH_2Cl_2/$CHCl_3$ (1:1), washed with saturated aqueous $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The white solid obtained was recrystallized from CH_3OH/toluene (1:1) to afford 0.091 g (81%) of the title compound: mp 242–243 °C; ^1H NMR (300 MHz, d_6-DMSO) δ 11.60 (br, 1H), 9.20 (br, 1H), 8.20–8.00 (m, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.19 (m, 1H), 7.10–7.00 (m, 2H), 6.86 (m, 1H), 3.97 (br, 4H), 3.18 (br, 4H), 2.14 (s, 3H); MS m/z 363 (62), 190 (28), 177 (100), 176 (62), 164 (75), 148 (63), 122 (72); HRMS calcd for $C_{20}H_{21}N_5O_2$ 363.1695, found 363.1692.

1-(Indolyl-2-carbonyl)-4-[3-(*N*-ethylacetamido)-2-pyridyl]piperazine (59). Compound **80**·HCl (U-87201) (0.25 g, 0.65 mmol) and pyridine (0.11 mL, 1.3 mmol) were dissolved in 1.5 mL of CH_2Cl_2 and cooled to 0 °C. Then acetyl chloride (0.051 mL, 0.72 mmol) and 4-(dimethylamino)pyridine (DMAP, 4 mg, 0.58 mmol) were added. Then the reaction was allowed to warm to room temperature. Basic workup (CH_2Cl_2, saturated $NaHCO_3$, brine, Na_2SO_4) and purification by flash column chromatography (EtOAc) afforded 0.18 g (70%) of the title compound: mp 173–176 °C; ^1H NMR ($CDCl_3$) δ 8.26 (dd, J = 1.7, 4.8 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.29 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.93 (dd, J = 4.8, 7.6 Hz, 1H), 6.80 (d, J = 1.4 Hz, 1H), 4.29 (dq, J = 7.0, 13.4 Hz, 1H), 4.10 (br, 4H), 3.51 (m, 2H), 3.40 (m, 2H), 3.21 (dq, J = 7.0, 13.4 Hz, 1H), 1.96 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H); HRMS calcd for $C_{22}H_{25}N_5O_2$ 391.2008, found 391.2012. Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(diethylamino)-2-pyridyl]piperazine (60). Compound **80** (0.10 g, 31 mmol) was dissolved in 2.5 mL of CH_3OH and cooled to 0 °C. Then acetaldehyde (0.052 mL, 0.93 mmol) and 5 drops of acetic acid (to pH 5) were added. The reaction was stirred for 15 min, and then $NaCNBH_3$ (0.04 g, 0.65 mmol) was added. Additional acetaldehyde (5 × 0.052 mL) was added at 1-h intervals. Then the reaction was stirred for 18 h at room temperature, poured into aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (CH_2Cl_2) provided 0.10 g (88%) of the title product: mp 173–174 °C; ^1H NMR ($CDCl_3$) δ 9.56 (br, 1H), 7.93 (dd, J = 1.5, 4.7 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.19–7.10 (m, 2H), 6.86–6.82 (m, 2H), 4.06 (br, 4H), 3.60 (m, 4H), 3.22 (q, J = 7.0 Hz, 4H), 1.00 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 154.6, 140.3, 136.2, 135.7, 129.3, 128.5, 127.4, 124.1, 121.7, 120.4, 116.9, 111.7, 105.2, 47.2, 43.1, 11.4; MS m/z 378 (26), 377 (100), 205 (34), 204 (38), 178 (34), 176 (16), 162 (32), 144 (30); HRMS calcd for $C_{22}H_{27}N_5O$ 377.2217, found 377.2215.

1-(Indolyl-2-carbonyl)-4-[3-(methylamino)-2-pyridyl]piperazine (61). Formic acid (95–97%, 3.15 g, 65 mmol) was added to acetic anhydride (5.31 g, 52 mmol) at 0 °C. After addition, the mixture was heated to 50–60 °C for 2 h. Then it was cooled to room temperature and **2** (X = N) (5.57 g, 20 mmol), dissolved in 15 mL of THF, was added and the reaction was stirred at ambient temperature for 18 h. Basic workup ($CHCl_3$, $NaHCO_3$, Na_2SO_4) afforded 6.14 g (quant) of a colorless solid (**3**, R = CHO, X = N): mp 49–53 °C; IR (Nujol) 3301, 1695, 1589, 1578, 1502, 1458, 1417 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.00 (t, J = 5.0 Hz, 4H), 3.62 (t, J = 5.0 Hz, 4H), 7.09 (dd, J = 8.0, 4.8 Hz, 1H), 8.05 (brs, 1H), 8.13 (dd, J = 4.8, 1.6 Hz, 1H), 8.55 (s, 1H), 8.62 (dd, J = 8.0, 1.6 Hz, 1H).

3 (R = CHO, X = N) (5.92 g, 19.3 mmol) was dissolved in 15 mL of THF and cooled to 0 °C. Then 21 mL of borane–dimethyl sulfide complex (48.3 mmol) was added and the mixture was brought to a gentle reflux and maintained at reflux for 18 h. Then the reaction was cooled to 0 °C and 15 mL of anhydrous CH_3OH was added. Dry HCl was bubbled through the reaction until a pH of 2 was obtained and the resulting mixture was refluxed for 1.5 h. After cooling, a further 50 mL of CH_3OH was added and the excess solvent was removed in vacuo. Basic workup (ether, 2 N NaOH, $MgSO_4$) and concentrated in vacuo afforded 2.4 g (65%) of a white solid (**3**, R = CH_3, X = N): mp 100 °C; IR (Nujol) 3331, 1578, 1487, 1449, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84 (d, J = 5.5 Hz, 3H), 3.03 (s, 8H), 4.34 (m, 1H), 6.80 (dd, J = 7.9, 1.5 Hz, 1H), 6.93 (dd, J = 7.9, 4.8 Hz, 1H), 7.73 (dd, J = 4.8, 1.5 Hz, 1H).

General procedure III; yield 94%; mp 153–154 °C; IR (Nujol) 3344, 3300, 1614, 1587, 1571 cm^{-1}; ^1H NMR ($CDCl_5$) δ 2.86 (d, 3H, J = 5.2 Hz), 3.21 (t, 4H, J = 5.0 Hz), 4.09 (bs, 4H), 4.37 (m, 1H), 6.82 (d, 1H, J = 1.5 Hz), 6.85 (dd, 1H, J = 7.9, 1.3 Hz), 6.97 (dd, 1H, J = 7.9, 4.8 Hz), 7.12 (dd, 1H, J = 7.3, 7.3 Hz), 7.26 (dd, 1H, J = 7.3, 7.3 Hz), 7.43 (d, 1H, J = 8.1 Hz), 7.65 (d, 1H, J = 8.0 Hz), 7.74 (dd, 1H, J = 4.8, 1.4 Hz), 9.99 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 30.31, 49.04, 105.22, 111.78, 115.95, 120.35, 120.41, 121.68, 124.17, 127.28, 129.17, 135.30, 135.79, 138.34, 149.98, 162.68 (one sp^3 signal overlapping). Anal. ($C_{19}H_{21}N_5O \cdot 0.1H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(propylamino)-2-pyridyl]piperazine (62). Following general procedure II, **56** (0.20 g, 0.62 mmol) was treated with propionaldehyde (0.05 mL × 10, 0.68 mmol) and $NaCNBH_3$ (0.04 g × 10, 0.66 mmol). Recrystallization from ether afforded 0.27 g (69%) of the title compound: mp 153–155 °C; ^1H NMR ($CDCl_3$) δ 9.82 (br, 1H), 7.72 (dd, J = 1.5, 4.8 Hz, 1H), 7.35 (dd, J = 4.4, 8.9 Hz, 1H), 7.27 (dd, J = 2.4, 9.2 Hz, 1H), 7.03 (td, J = 2.4, 9.2 Hz, 1H), 6.95 (dd, J = 4.8, 7.9 Hz, 1H), 6.86 (dd, J = 1.5, 7.9 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 4.32 (br, 1H), 4.09 (m, 4H), 3.21 (m, 4H), 3.08 (q, J = 7.2 Hz, 2H), 1.71 (s, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); MS m/z 382 (17), 381 (69), 190 (25), 176 (24), 164 (100), 162 (71), 134 (30), 120 (18); HRMS calcd for $C_{21}H_{25}N_5O$ 363.2059, found 363.2053. Anal. ($C_{21}H_{25}N_5O \cdot 0.25H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-[(1-methylethyl)amino]pyridyl]piperazine (63): general procedure III; yield 74%, mp 155–156 °C; IR (Nujol) 3288, 1624, 1588, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.49 (br s, 1H), 7.70 (dd, J = 1.6, 4.8 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.94 (dd, J = 4.8, 7.9 Hz, 1H), 6.85 (dd, J = 1.6,

7.9 Hz, 1H), 6.83 (m, 1H), 4.08 (m, 4H), 3.58 (s, J = 6.26 Hz, 1H), 3.19 (m, 4H), 1.27 (d, J = 6.26 Hz, 6H); MS m/z 363 (77), 362 (22), 190 (26), 176 (25), 164 (99), 162 (54). Anal. ($C_{21}H_{25}N_5O$) C, H, N.

Methanesulfonate Salt: mp 169–170 °C; IR (Nujol) 3265, 3115–3010, 1602, 1555, 1526 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.69 (m, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.54–7.44 (m, 2H), 7.29 (td, J = 1.1, 6.8 Hz, 1H), 7.14 (td, J = 1.0, 8.0 Hz, 1H), 6.98 (d, J = 1.1 Hz, 1H), 4.21 (br m, 4H), 3.83 (septet, J = 6.0 Hz, 1H), 3.45 (br t, J = 5.1 Hz, 4H), 2.77 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (CD_3OD) δ 165.3, 146.4, 140.9, 138.0, 130.2, 128.7, 125.8, 125.3, 124.4, 122.8, 122.5, 121.4, 113.1, 106.7, 45.7, 39.7, 22.2; MS m/z 364 (20), 363 (81), 190 (26), 176 (25), 164 (100), 165 (51), 144 (39), 134 (32), 120 (22), 89 (31). Anal. ($C_{21}H_{25}N_5O\cdot CH_3SO_3H$) C, H, N, S.

1-(Indolyl-2-carbonyl)-4-[(3-benzylamino)-2-pyridyl]piperazine (64). Following general procedure II, **56** (0.31 mmol, 0.10 g) was treated with benzaldehyde (0.34 mmol, 0.036 g) and $NaCNBH_3$ (0.33 mmol, 0.021 g) in CH_3OH acidified with acetic acid. After warming to room temperature and stirring for 5 h, TLC indicated the presence of starting material, so 0.015 mL of additional benzaldehyde was added and the reaction was stirred a further 15 h. Purification by flash column chromatography (8 g silica gel, 2:1 hexane/EtOAc) afforded 0.084 g (0.20 mmol, 65%) of the title compound: mp 229–231 °C; ^{1}H NMR ($CDCl_3$) δ 9.47 (br, 1H), 7.75 (dd, J = 1.5, 4.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.38–7.26 (m, 10H), 7.14 (t, J = 7.3 Hz, 1H), 6.92 (dd, J = 4.8, 7.9 Hz, 1H), 6.85–6.81 (m, 2H), 4.79 (br, 1H), 4.36 (d, J = 5.1 Hz, 2H), 4.36 (br, 4H), 3.26 (br, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 150.0, 138.7, 137.1, 135.8, 135.6, 129.1, 128.7, 127.3, 126.9, 124.3, 121.7, 120.4, 120.3, 116.9, 111.6, 105.2, 49.1, 47.9, 45 (br); MS m/z 411 (80), 238 (29), 224 (26), 212 (76), 210 (39), 91 (100); HRMS calcd for $C_{25}H_{25}N_5O$ 411.2059, found 411.2058. Anal. ($C_{25}H_{25}N_5O\cdot 0.5H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-[(1-methylpropyl)amino]-2-pyridyl]piperazine (65): general procedure IV; quantitative yield; mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 9.40 (br, 1H), 7.70 (dd, J = 1.5, 4.8 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.29 (m, 1H), 7.14 (m, 1H), 6.97 (dd, J = 4.8, 8.0 Hz, 1H), 6.88 (dd, J = 1.5, 8.0 Hz, 1H), 6.83 (m, 1H), 4.21 (br, 1H), 4.10 (m, 4H), 3.37 (m, 1H), 3.29–3.16 (m, 4H), 1.60 (m, 2H), 1.22 (d, J = 6.3 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H); HRMS calcd for $C_{22}H_{27}N_5O$ 377.2215, found 377.2208. Anal. ($C_{22}H_{27}N_5O\cdot{}^1/_5H_2O$) C, H, N.

1-(2-Indolylcarbonyl]-4-[3-[(1-ethylpropyl)amino]-2-pyridyl]piperazine (66). Following general procedure II, 1-[(benzyloxy)carbonyl]-4-(3-amino-2-pyridyl)piperazine (0.5 g) was treated with 3-pentanone (0.15 g), $NaCNBH_3$ (0.11 g), and acetic acid (2.3 mL) in CH_3OH (3.2 mL). The crude 1-[(benzyloxy)carbonyl]-4-[3-[(1-ethylpropyl)amino]-2-pyridyl)piperazine was obtained (0.30 g, 48%) and used without further purification; ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 1.5, 4.8 Hz, 1H), 7.38–7.33 (m, 5H), 6.90 (dd, J = 4.8, 8.0 Hz, 1H), 6.79 (dd, J = 1.5, 8.0 Hz, 1H), 5.17 (s, 2H), 4.21 (br, 1H), 3.65 (m, 4H), 3.15 (m, 1H), 3.04 (m, 4H), 1.66–1.46 (m, 4H), 0.93 (t, 6H).

The above material (0.30 g, 0.78 mmol) was hydrogenated at 40 psi with 10% palladium on carbon (30 mg) in 10 mL of EtOAc for 24 h. Filtration through celite and concentration in vacuo afforded 0.15 g (78%) of the deprotected piperazine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 1.6, 4.8 Hz, 1H), 6.87 (dd, J = 4.8, 7.9 Hz, 1H), 6.78 (dd, J = 1.6, 7.9 Hz, 1H), 4.19 (m, 1H), 3.40–3.10 (m, 10H), 3.00–2.75 (m, 2H), 1.64–1.49 (m, 4H), 0.93 (t, J = 7.5 Hz, 6H).

Following general procedure IV indole-2-carboxylic acid (0.095 g, 5.93 mmol) and 1-[3-[(1-ethylpropyl)amino]-2-pyridyl]-piperazine (0.15 g, 5.93 mmol) were coupled, and the title compound was obtained (0.21 g, 89%): mp 190–192 °C; ^{1}H NMR ($CDCl_3$) δ 9.31 (br, 1H), 7.70 (dd, J = 1.5, 4.9 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.99 (dd, J = 4.9, 8.0 Hz, 1H), 6.88 (dd, J = 1.5, 8.0 Hz, 1H), 6.84 (m, 1H), 4.30 (br, 1H), 4.30–4.15 (m, 4H), 3.30–3.15 (m, 4H), 1.68–1.54 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H); HRMS calcd for $C_{23}H_{29}N_5O$ 391.2372, found 391.2383. Anal. ($C_{23}H_{29}N_5O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(*N*-methylcarbamoyl)-2-pyridyl]piperazine (67). 2-Chloro-3-nicotinic acid (1.0 g, 6.34 mmol) was dissolved in 3 mL of thionyl chloride and heated to reflux for 3 h. After concentration in vacuo, the remaining solid was dissolved in 6 mL of $CHCl_3$, and 1.6 mL of pyridine was added. The reaction was cooled to 0 °C and 0.43 g of methylamine hydrochloride (6.34 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. Since the reaction was incomplete by TLC a further 2 mL of pyridine and 230 mg of methylamine hydrochloride was added and the reaction was warmed to 50 °C for 2 h. Aqueous workup afforded 310 mg of 2-chloro-3-(*N*-methylcarbamoyl)pyridine (29%): ^{1}H NMR (CD_3OD) δ 8.42 (dd, J = 1.9, 5.0 Hz, 1H), 7.88 (dd, J = 1.9, 7.4 Hz, 1H), 7.45 (dd, J = 5.0, 7.5 Hz, 1H), 2.91 (s, 3H).

2-Chloro-3-(*N*-methylcarbamoyl)pyridine (0.31 g, 1.8 mmol) and 7 (0.41 g, 1.80 mmol) were dissolved in 5 mL of DMF. Then K_2CO_3 (0.30 g, 2.16 mmol) was added and the reaction was heated to 110 °C for 14 h. Basic workup ($CHCl_3$, $NaHCO_3$, Na_2SO_4) and concentration in vacuo afforded the crude product, which was dissolved in EtOAc and filtrated through a plug of silica gel. Recrystallization from CH_3OH afforded 0.28 g (42%) of the title compound: mp 191–192 °C; IR (Nujol) 3296, 1604, 1587, 1558, 1522 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 8.18 (dd, J = 1.9, 5.0 Hz, 1H), 7.76 (dd, J = 1.9, 7.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 1.0, 8.1 Hz, 1H), 7.12 (m, 1H), 6.97 (td, J = 1.0, 8.0 Hz, 1H), 6.89 (dd, J = 5.0, 7.5 Hz, 1H), 6.76 (d, J = 0.7 Hz, 1H), 3.91 (br, 4H), 3.31 (m, 4H), 2.85 (s, 3H); MS m/z 363 (53), 348 (17), 203 (29), 190 (72), 176 (100), 164 (56), 144 (63), 133 (51). Anal. ($C_{20}H_{21}N_5O_2$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(*N*-*tert*-butylcarbamoyl)-2-pyridyl]piperazine (68). 2-Chloro-3-nicotinic acid (1.6 g, 10.0 mmol) was dissolved in 4 mL of thionyl chloride and heated to reflux for 3 h. After concentration in vacuo, the remaining solid was dissolved in 16 mL of $CHCl_3$, and 2 mL of pyridine was added. The reaction was cooled to 0 °C and the 1.16 mL of *tert*-butylamine was added. The reaction was allowed to warm to room temperature and aqueous workup afforded 1.42 g (67%) of 2-chloro-3-(*N*-*tert*-butylcarbamoyl)pyridine: mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, J = 2.0, 4.8 Hz, 1H), 8.02 (dd, J = 2.0, 7.6 Hz, 1H), 7.32 (dd, J = 4.8, 7.6 Hz, 1H), 6.19 (bs, 1H), 1.49 (s, 9H).

The above 2-chloropyridine (0.58 g, 2.73 mmol) was dissolved in 1.8 mL of acetonitrile and added to a slurry of piperazine (1.18 g, 13.7 mmol) and K_2CO_3 (0.46 g, 3.3 mmol) in 9.8 mL of acetonitrile. The reaction was heated to reflux for 24 h, aqueous workup (CH_2Cl_2) provided 0.65 g of 1-[3-(*N*-*tert*-butylcarbamoyl)-2-pyridyl]piperazine as an oil (91%); ^{1}H NMR ($CDCl_3$) δ 8.64 (bs, 1H), 8.36 (dd, J = 1.9, 4.8 Hz, 1H), 8.26 (dd, J = 1.9, 7.7 Hz, 1H), 7.08 (dd, J = 4.8, 7.7 Hz, 1H), 3.16 (m, 4H), 3.07 (m, 4H), 1.66 (bs, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.6, 160.3, 149.2, 139.7, 122.8, 119.0, 52.5, 51.0, 46.0, 28.7.

68: General procedure III; yield 72%; ^{1}H NMR ($CDCl_3$) δ 9.98 (br s, 1H), 8.35 (dd, J = 4.8, 1.9 Hz, 1H), 8.24 (dd, J = 7.6, 1.9 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.10 (dd, J = 7.7, 4.8 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 4.13 (m, 4H), 3.37 (m, 4H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.7, 162.7, 158.9, 149.2, 139.8, 135.8, 128.7, 127.1, 124.3, 122.7, 121.7, 120.4, 119.2, 111.7, 105.3, 60.2, 51.2, 50.9, 28.9; MS m/z 405 (35), 219 (22), 218 (21), 176 (100); HRMS calcd $C_{23}H_{27}N_5O_2$ 405.2165, found 405.2174.

General Procedure IV. Deprotonation and Quenching of 2-Bromopyridine. LDA (12.6 mmol) was added to a solution of 2-bromopyridine (2.0 g; 12.6 mmol) in THF (10 mL) at −78 °C. The resulting red-brown solution was stirred at −78 °C for 2 hours followed by addition of the aldehyde (12.6 mmol) in 5 mL of THF at −78 °C. The mixture was allowed to warm to ambient temperature overnight, poured into a saturated aqueous ammonium chloride, extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified via flash chromatography (hexane/EtOAc).

General Procedure V. PDC Oxidation to Pyridines 9. The appropriate hydroxypyridine dissolved in DMF (5 mL) was added to pyridinium dichromate (1.5 equiv) in dimethylformamide (DMF, 5 mL) at ambient temperature. The resulting dark mixture was stirred overnight, diluted with ether (150 mL), and filtred through Celite. The filtrates were evaporated to dryness under reduced pressure and the resulting residues purified via flash chromatography (4:1 hexane/EtOAc) to afford analytically pure materials.

1-(2-Bromopyridin-3-yl)ethan-1-ol. Following general procedure IV and quenching with acetaldehyde, 55% of the title compound was obtained: ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H), 2.51 (bs, 1H), 5.18 (q, 1H), 7.30 (m, 1H), 7.92 (m, 1H), 8.25 (m, 1H); MS *m/z* 340 (M^+). Anal. (C_7H_8BrNO) C, H, N.

1-(2-Bromopyridin-3-yl)ethan-1-one. Following general procedure V, 1-(2-bromopyridin-3-yl)ethan-1-ol was oxidized to yield 71%: ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 7.37 (dd, 1H), 7.76 (dd, 1H), 8.4 (m, 1H); MS *m/z* 199 (M^+). Anal. ($C_7H_6BrNO \cdot 0.25H_2O$) C, H, N.

2-Methyl-1-(2-bromopyridin-3-yl)propan-1-ol. Following the general procedure IV and quenching with isobutyraldehyde, a 44% yield of the title compound was obtained: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3H), 1.01 (d, 3H), 2.10 (m, 1H), 2.18 (d, 1H), 4.85 (m, 1H), 7.29 (m, 1H), 7.82 (dd, 1H), 8.25 (m, 1H); MS *m/z* 229 (M^+). Anal. ($C_9H_{12}BrNO$) C, H, N.

2-Methyl-1-(2-bromopyridin-3-yl)propan-1-one. Following general procedure V, 2-methyl-1-(2-bromopyridine-3-yl)-propan-1-ol was oxidized at a yield of 72%: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H), 3.37 (septet, 1H), 7.35 (dd, 1H), 7.58 (dd, 1H), 8.44 (m, 1H); MS *m/z* 227 (M^+). Anal. ($C_9H_{10}BrNO$) C, H, N.

2,2-Dimethyl-1-(2-bromopyridin-3-yl)propan-1-ol. Following general procedure IV and quenching with pivaldehyde afford a 41% yield of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.20 (d, 1H), 4.95 (d, 1H), 7.28 (m, 1H), 7.86 (m, 1H), 8.27 (m, 1H); MS *m/z* 243 (M^+). Anal. ($C_{10}H_{14}BrNO$) C, H, N.

2,2-Dimethyl-1-(2-bromopyridin-3-yl)propan-1-one. Following general procedure V, 2,2-dimethyl-1-(2-bromopyridin-3-yl)propan-1-ol was oxidized in 52% yield: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 7.31 (m, 1H), 7.44 (m, 1H), 8.41 (m, 1H); MS (FAB$^+$) *m/z* 242 (M + H). Anal. ($C_{10}H_{12}BrNO$) H; C: calcd, 49.79; found, 50.20; N: calcd, 5.08; found, 5.59.

1-(2-Bromopyridin-3-yl)propan-1-ol. Following general procedure IV and quenching with propionaldehyde afford 42% of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.70 (m, 1H), 1.83 (m, 1H), 3.87 (bs, 1H), 4.94 (bs, 1H), 7.27 (m, 1H), 7.88 (m, 1H), 8.15 (m, 1H); MS *m/z* 215 (M^+). Anal. ($C_8H_{10}BrNO$) C, H, N.

1-(2-Bromopyridin-3-yl)propan-1-one. Following general procedure V, 1-(2-bromopyridin-3-yl)propan-1-ol was oxidized: yield 66%; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H), 2.98 (q, 2H), 7.36 (m, 1H), 7.66 (m, 1H), 8.44 (m, 1H); MS *m/z* 213 (M^+). Anal. (C_8H_8BrNO) C, H, N.

General Procedure VI. Coupling of Pyridines 9 with 1-(Indolyl-2-carbonyl)piperazine. Compound **7** (1 equiv), diisopropylethylamine (1 equiv), and the appropriate bromopyridine (1 equiv) were heated in a pressure bottle at 100 °C for 16 h in THF (10 mL). The reaction was cooled to ambient temperature and partitioned between water and EtOAc (100 mL of each). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography afforded the title compounds.

1-(Indolyl-2-carbonyl)-4-(3-acetyl-2-pyridyl)piperazine (69): general procedure VI; yield 51%; mp 198–199 °C; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 3.50 (m, 4H), 4.11 (bs, 4H), 6.81 (s, 1H), 6.89 (dd, 1H), 7.14 (t, 1H), 7.29 (t, 1H), 7.43 (d, 1H), 7.67 (d, 1H), 7.83 (m, 1H), 8.33 (m, 1H), 9.49 (bs, 1H); MS *m/z* 348 (M^+). Anal. ($C_{20}H_{20}N_4O_2$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(1-oxopropyl)-2-pyridyl]piperazine (70): general procedure VI; yield 32%; mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H), 3.00 (q, 2H), 3.47 (m, 4H), 4.06 (bs, 4H), 6.81 (s, 1H), 6.89 (dd, 1H), 7.14 (t, 1H), 7.29 (t, 1H), 7.44 (d, 1H), 7.66 (d, 1H), 7.75 (m, 1H), 8.32 (m, 1H), 9.24 (bs, 1H); MS *m/z* 362 (M^+). Anal. ($C_{21}H_{22}N_4O_2 \cdot {}^1/_3H_2O$) C, H, N: calcd, 15.21; found, 14.62.

1-(Indolyl-2-carbonyl)-4-[3-(2-methyl-1-oxopropyl)-2-pyridyl]piperazine (71): general procedure VI; yield 17%; mp 193–193.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 3.46 (m, 4H), 3.64 (septet, 1H), 4.10 (br s, 4H), 6.81 (m, 1H), 6.90 (dd, 1H), 7.14 (t, 1H), 7.31 (t, 1H), 7.44 (d, 2H), 7.69 (m, 1H), 8.32 (m, 1H), 9.49 (bs, 1H); MS *m/z* 376 (M^+). Anal. Calcd ($C_{22}H_{24}N_4O_2 \cdot 0.25H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(2,2-dimethyl-1-oxopropyl)-2-pyridyl]piperazine (72): general procedure VI; yield 31%, mp 178–179 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 3.32 (m, 4H), 4.00 (bs, 4H), 6.80 (s, 1H), 6.99 (dd, 1H), 7.14 (t, 1H), 7.29 (t, 2H), 7.43 (d, 1H), 7.65 (d, 1H), 8.34 (m, 1H), 9.17 (br s, 1H); MS *m/z* 390 (M^+). Anal. ($C_{23}H_{26}N_4O_2 \cdot 0.25H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(methoxycarbonyl)-2-pyridyl]piperazine (73). The reactants were heated in a pressure tube at 120 °C overnight to afford a 47% yield of the title compound as a white solid: mp 171–172.5 °C; ^{1}H NMR ($CDCl_2$) δ 3.56 (m, 4H), 3.91 (s, 3H), 4.11 (bs, 4H), 6.82 (m, 2H), 7.16 (t, 1H), 7.29 (t, 1H), 7.44 (d, 1H), 7.66 (d, 1H), 8.07 (dd, 1H), 8.33 (dd, 1H), 9.39 (bs, 1H); MS *m/z* 364 (M^+). Anal. ($C_{20}H_{20}N_4O_3$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-(ethoxycarbonyl)-2-pyridyl]piperazine (74). To a stirred suspension of **65** (0.20 g, 0.50 mmol) in absolute ethanol (30 mL) was added solid sodium ethoxide (0.015 g). The resulting mixture was refluxed overnight, in which time it became homogeneous. The solution was cooled, the solvent removed under reduced pressure, and the residue partitioned between CH_2Cl_2 and aqueous NH_4Cl (50 mL of each). The organic layers were dried over $MgSO_4$ and concentrated in vacuo. Recrystallization from EtOAc/hexane afforded 0.11 g of the title compound as a white solid: mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H), 3.56 (m, 4H), 4.09 (bs, 4H), 4.38 (q, 2H), 6.82 (m, 2H), 7.14 (t, 1H), 7.29 (t, 1H), 7.43 (d, 1H), 7.66 (d, 1H), 8.07 (dd, 1H), 8.32 (m, 1H), 9.34 (bs, 1H); MS *m/z* 378 (M^+). Anal. ($C_{21}H_{22}N_4O_3 \cdot {}^1/_4H_2O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-[[(1-methylethyl)amino]methyl]-2-pyridyl]piperazine (75). A suspension of **57** (0.50, 1.51 mmol) in 3% methanolic ammonia (100 mL) was diluted with THF (100 mL) and the solution was treated with a methanolic suspension of Raney nickel (ca. 0.3 g) and reduced at 40 psi of hydrogen pressure for 5 h. The suspension was diluted with ethanol (100 mL) and filtered free of catalyst, and the filtrate was evaporated to a solid residue. The residue was triturated with acetonitrile and filtered to yield 310 mg of the crude amine.

The amine (280 mg, 0.84 mmol) in CH_3OH (10 mL) and acetic acid (1.43 mL) was treated with acetone (1.6 mL) cooled to 0 °C during 1 h, and treated in portions with $NaCNBH_3$ (0.14 g, 22 mmol) during 1 h. The solution was treated with cold 2 N NaOH (13 mL) and then diluted to 50 mL with water. The precipitate was filtered, washed with water, and recrystallized from acetonitrile to provide 0.28 g of the title compound: mp 138–140°; ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 6H), 2.91 (m, 1H), 3.32 (m, 4H), 3.92 (s, 2H), 3.91 (m, 4H), 6.82 (m, 1H), 7.01 (m, 1H), 7.14 (m, 1H), 7.28 (m, 1H), 7.31 (m, 1H), 7.65 (d, 1H), 7.81 (b, 1H), 8.26 (m, 1H); MS *m/z* 377 (M^+). Anal. ($C_{22}H_{27}N_5O$) C, H, N.

1-(Indolyl-2-carbonyl)-4-[3-[(cyclopropylmethyl)amino]-2-pyridyl]piperazine (76). Following general procedure II, **56** (0.12 g, 0.38 mmol) was treated with cyclopropylcarboxaldehyde (0.028 mL, 0.38 mmol) and $NaCNBH_3$ (0.026 g, 0.38 mmol), and acetic acid (5 drops, pH 5) in CH_3OH: yield 64%; mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 9.40 (br, 1H), 7.72 (dd, J = 1.5, 4.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.30–7.23 (m, 1H), 7.18–7.11 (m, 2H), 6.95 (dd, J = 4.8, 7.9 Hz, 1H), 6.86–6.82 (m, 2H), 4.40 (br, 1H), 4.10 (br, 4H), 3.23 (m, 4H), 2.97 (m, 2H), 1.16 (m, 1H), 0.60 (m, 2H), 0.29 (m, 2H); MS *m/z* 375 (90), 188 (32), 176 (100), 174 (58), 144 (59), 134 (45), 120 (38), 55 (64), 43 (73); HRMS calcd for $C_{22}H_{25}N_5O$ 375.2059, found 375.2059.

1-(Indolyl-2-carbonyl)-4-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine (77). Following general procedure IV, indole-2-carboxylic acid and 1-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine[35] were coupled: yield 90%; mp 188–189 °C; IR (mull) 3270, 1610, 1495, 1465, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.35 (bs, 1H), 6.8–7.8 (m, 7H), 6.81 (d, 1H), 4.61 (bs, 1H), 4.2 (m, 4H), 3.16 (m, 4H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.9, 150.6, 135.9, 134.6, 129.2, 127.3, 124.1, 121.6, 120.3, 120.1, 118.4, 111.9, 105.2, 50.4, 49.3, 29.5; MS *m/z* 377 (100), 362 (15), 320 (12), 219 (16), 178 (42), 144 (39), 134 (48), 122 (71); HRMS calcd for $C_{22}H_{27}N_5O$ 377.2215, found 377.2205.

1-(Indolyl-2-carbonyl)-4-[3-[(2,2,2-trifluoroethyl)amino]-2-pyridyl]piperazine (78). 1-[(Benzyloxy)carbonyl]-4-[3-(2,2,2-trifluoroacetamido)-2-pyridyl]piperazine (2.14 g, 5.24 mmol) was dissolved in 70 mL of ethanol, and 0.25 g of 10% palladium on carbon was added. The reaction was hydrogenated at 40 psi for 20 h. Then it was filtered through a pad of Celite and concentrated in vacuo to afford 1.33 g (93%) of 1-[3-(2,2,2-trifluoroacetamido)-2-pyridyl]piperazine, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.51 (dd, J = 1.6, 8.1 Hz, 1H), 8.21 (dd, J = 1.6, 4.8 Hz, 1H), 7.19 (dd, J = 4.8, 8.1 Hz,

1H), 3.45–3.47 (m, 8H); MS *m/z* 274 (3), 232 (36), 218 (38), 206 (100), 134 (20), 122 (23), 120 (32), 69 (55), 56 (47); HRMS calcd for $C_{11}H_{13}N_4F_3O$ 274.1041, found 274.1030.

The above amide (0.66 g, 2.42 mmol) was dissolved in 5 mL of THF and cooled to 0 °C. Then 4.84 mL of LAH in THF (1.0 M, 4.84 mmol) was added dropwise. After 10 min of stirring at 0 °C, the reaction was warmed to room temperature and stirred for 45 min. The reaction was quenched at 0 °C with the dropwise addition of 0.4 mL of water, 0.6 mL of 10% aqueous NaOH, and 1 mL of water. The slurry was filtered through Celite, washed with 20% $CH_3OH/CHCl_3$, and concentrated in vacuo to afford 0.45 g (72%) of the amine, which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.82 (dd, J = 1.8, 8.9 Hz, 1H), 6.97–6.92 (m, 2H), 4.86 (br, 1H), 3.75 (m, 2H), 3.06–3.01 (m, 8H).

Following general procedure IV, 1-[3-[(2,2,2-trifluoroethyl)-amino]-2-pyridyl]piperazine (0.25 g, 0.99 mmol) and indole-2-carboxylic acid (0.15 g, 0.9 mmol) were coupled with EDC (0.23 g, 1.2 mmol), in 2 mL of THF and 0.5 mL of DMF: yield 55%; mp 172–175 °C; ^1H NMR ($CDCl_3$) δ 9.91 (br, 1H), 7.77 (dd, J = 2.4, 4.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.24–7.17 (m, 1H), 7.09–7.03 (m, 1H), 6.96–6.76 (m, 2H), 6.76 (m, 1H), 4.83 (t, J = 6.8 Hz, 1H), 4.04 (br, 4H), 3.72 (m, 2H), 3.13 (m, 4H); HRMS calcd for $C_{20}H_{20}N_5F_3O$ 403.1620, found 403.1623. Anal. ($C_{20}H_{20}N_5F_3O$) C, H, N, F.

1-[(5-Fluoroindol-2-yl)carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine (79). Following general procedure III, 5-fluoroindole-2-carboxylic acid (0.55 g, 3.08 mmol) and (3-ethylamino-2-pyridyl)piperazine (0.70 g, 3.39 mmol) were coupled with CDI (0.55 g, 5.39 mmol). Purification by flash column chromatography (4 cm column, 5% $CH_3OH/CHCl_3$) provided 0.85 g (2.3 mmol, 75%) of the title compound: mp 187–188 °C; IR (Nujol) 3250, 2950, 1595, 1540, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.33 (br, 1H), 7.64 (dd, J = 1.6, 4.8 Hz, 1H), 7.27 (dd, J = 4.4, 9.0 Hz, 1H), 7.17 (dd, J = 2.5, 9.4 Hz, 1H), 6.92 (td, J = 2.5, 9.0 Hz, 1H), 6.86 (dd, J = 4.8, 7.9 Hz, 1H), 6.77 (dd, J = 1.5, 7.9 Hz, 1H), 6.68 (d, 1.6 Hz, 1H), 4.15 (t, J = 5.4 Hz, 1H), 4.02 (br, 4H), 3.13 (m, 4H), 3.06 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); MS *m/z* 368 (22), 367 (94), 176 (26), 163 (14), 162 (44), 148 (55), 134 (21), 120 (13); HRMS calcd for $C_{20}H_{22}FN_5O$ 367.1808, found 367.1813. Anal. ($C_{20}H_{22}FN_5O$) C, H, N; F: calcd, 5.17; found, 4.64.

1-[[2-(5-Fluoroindolyl)]carbonyl]-4-(3-(ethylamino)-2-pyridyl)-piperazine (5.09 g, 13.85 mmol) was dissolved in CH_3OH and methanesulfonic acid (0.90 mL, 13.87 mmol) was added. The addition of diethyl ether resulted in crystallization of 5.92 g (92%) of the methanesulfonate salt mp: 222–223 °C; IR (Nujol) 3276, 1628, 1611, 1602, 1551, 1528 cm^{-1}. Anal. ($C_{20}H_{22}FN_5O \cdot CH_4SO_3$) C, H, N, S.

1-[(5-Methoxyindol-2-yl)carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine Methanesulfonate (80). Following general procedure IV, 5-methoxyindole-2-carboxylic acid (1.04 g, 5.45 mmol) and 1-(3-ethyl-2-pyridyl)piperazine (5.45 mmol, 1.12 g) were coupled; yield 82%; mp 153–154 °C. Free base: IR (Nujol) 3376, 3275, 3000–2950, 1603, 1535, 1230 cm^{-1}; MS *m/z* 380 (20), 379 (80), 176 (28), 174 (30), 162 (28), 150 (100), 148 (62), 137 (20). Anal. ($C_{21}H_{25}N_5O_2$) C, H, N.

Methanesulfonate salt: mp 215–216 °C; IR (Nujol) 3283, 3194–3041, 1634, 1612, 1564, 1526 cm^{-1}; ^1H NMR (CD_3OD) δ 7.41 (dd, J = 1.4, 5.7 Hz, 1H), 7.33 (dd, J = 1.4, 8.3 Hz, 1H), 7.22 (dd, J = 5.7, 8.3 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 2.4, 8.9 Hz, 1H), 6.62 (s, 1H), 3.94 (m, 4H), 3.6 (s, 3H), 3.22 (br t, 4H), 3.12 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 165.1, 155.9, 146.1, 141.6, 133.2, 130.3, 128.8, 125.5, 123.3, 122.3, 116.5, 113.7, 106.2, 102.9, 55.9, 45.6 (br), 39.4, 38.8, 13.9. Anal. ($C_{21}H_{25}N_5O_2 \cdot CH_4SO_3$) C, H, N, S.

1-[(5-Fluoroindol-2-yl)carbonyl]-4-[3-[(1-methylethyl)-amino]-2-pyridyl]piperazine methanesulfonate (81): general procedure III; yield 86%; mp 201–203 °C; IR (Nujol) 3382, 3228, 3180, 3075–3000, 1630, 1584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.37 (br, 1H), 7.70 (dd, J = 1.6, 4.8 Hz, 1H), 7.36 (dd, J = 4.4, 9.0 Hz, 1H), 7.28 (dd, J = 2.5, 8.6 Hz, 1H), 7.05 (td, J = 2.5, 9.0 Hz, 1H), 6.95 (dd, J = 4.8, 8.0 Hz, 1H), 6.87 (dd, J = 1.6, 8.0 Hz, 1H), 6.74 (m, 1H), 4.20 (m, 1H), 4.07 (m, 4H), 3.57 (m, 1H), 3.19 (m, 4H), 1.27 (d, J = 6.3, 6H); ^{13}C NMR ($CDCl_3$) δ 162.3, 159.5, 156.4, 149.8, 136.3, 134.9, 132.3, 127.5, 127.4, 120.4, 116.6, 113.4, 113.0, 112.7, 112.6, 106.1, 105.8, 105.1, 105.1, 102.6, 49.1, 43.7, 22.9; MS *m/z* 382 (18), 381 (72), 190 (23), 176 (23), 164 (100), 162 (73), 120 (20), 107 (23); HRMS calcd for $C_{21}H_{24}N_5FO$ 381.1965, found 381.1960. Anal. ($C_{21}H_{24}N_5OF \cdot {}^1/_3H_2O$) C, H, F; N: calcd, 18.08; found, 18.36.

1-[[2-(5-Fluoroindolyl)]carbonyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine (1.5 g, 3.93 mmol) was dissolved in 300 mL of CH_3OH and cooled to room temperature. Then methanesulfonic acid (0.26 mL, 3.93 mmol) was added and the reaction was diluted with ether to 2 L and chilled. The crystalline solids were collected to afford 1.41 g (75%), mp 174–175 °C. Anal. ($C_{21}H_{24}N_5OF \cdot CH_4SO_3$) C, H, N, F.

1-[(5-Methoxyindol-2-yl)carbonyl]-4-[3-[(1-methylethyl)-amino]-2-pyridyl]piperazine Methanesulfonate (82). Following general procedure III, 5-methoxyindole-2-carboxylic acid (0.174 g, 0.91 mmol) and 1-(3-[(1-methylethyl)amino]-2-pyridyl)-piperazine (0.20 g, 0.91 mmol) were coupled with CDI (0.147 g, 0.91 mmol). Purification by flash column chromatography (8 g of silica gel, 30% EtOAc/hexane) afforded 0.3 g (0.76 mmol, 85%) of the title compound (mp 167–168 °C): IR (Nujol) 3324, 3023, 1614, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.39 (br, 1H), 7.70 (dd, J = 1.5, 4.8 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.98–6.94 (m, 2H), 6.85 (dd, J = 1.5, 8 Hz, 1H), 6.76 (m, 1H), 4.18 (br d, 1H), 4.08 (m, 4H), 3.85 (s, 3H), 3.57 (septet, J = 6.5 Hz, 1H), 3.18 (m, 4H), 1.27 (d, J = 6.3 Hz, 6H); MS *m/z* 393 (70), 190 (26), 176 (24), 174 (33), 164 (100), 162 (52), 146 (21), 134 (30); HRMS calcd for $C_{22}H_{27}N_5O_2$ 393.2165, found 393.2162.

Methanesulfonate salt: mp 169–171 °C; ^1H NMR (CD_3OD) δ 7.50 (d, J = 5.8 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.28 (dd, J = 5.7, 8.3 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 6.96 (m, 1H), 6.77 (dd, J = 2.5, 8.9 Hz, 1H), 6.71 (s, 1H), 4.03 (m, 4H), 3.69 (s, 3H), 3.66 (septet, J = 6.3 Hz, 1H), 3.30 (m, 4H), 2.57 (s, 3H), 1.20 (d, J = 6.3 Hz, 6H); ^{13}C NMR (CD_3OD) δ 165.1, 156.0, 146.0, 140.6, 133.0, 130.5, 128.5, 126.0, 124.3, 122.5, 116.6, 113.8, 106.4, 103.1, 56.1, 45.5, 39.5 22.0. Anal. ($C_{22}H_{27}N_5O_2 \cdot CH_4SO \cdot {}^1/_3H_2O$) C, H, N, S.

1-[(5-Fluoroindol-2-yl)carbonyl]-4-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine (83). Following general procedure IV, 5-fluoroindole-2-carboxylic acid (0.088 g, 0.49 mmol) and 1-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine[35] (0.10 g, 0.52 mmol) were coupled with the aid of 5 mg of DMAP. Purification via flash column chromatography (4% CH_3OH/CH_2Cl_2) afforded 0.19 g of the title compound (90 %): mp 220–221 °C; ^1H NMR ($CDCl_3$) δ 10.50 (bs, 1H), 7.68 (dd, 1H), 7.36 (dd, 1H), 6.8–7.3 (m, 4H), 6.76 (d, 1H), 4.6 (br s, 1H), 4.1 (m, 4H), 3.16 (m, 4H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.5, 159.5, 156.4, 150.5, 135.9, 134.6, 132.6, 130.7, 127.4, 127.2, 120.2, 118.4, 113.2, 112.8, 112.7, 105.9, 105.6, 105.1, 105.0, 50.4, 49.3, 29.5; HRMS calcd for $C_{22}H_{28}FN_5O$ 395.2121, found 395.2115.

1-[(5-Methoxyindol-2-yl)carbonyl]-4-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine (84). Following general procedure IV, 5-methoxyindole-2-carboxylic acid (0.11 g, 0.49 mmol) and 1-[3-[(1,1-dimethylethyl)amino]-2-pyridyl]piperazine[35] (0.10 g, 0.52 mmol) were coupled with the aid of 5 mg of DMAP. Purification via flash column chromatography (4% CH_3OH/CH_2Cl_2) afforded 0.196 g of the title compound (98%): mp 200–202 °C; ^1H NMR ($CDCl_3$) δ 10.5 (bs, 1H), 7.68 (dd, 1H), 7.33 (d, 1H), 6.8–7.1 (m, 4H), 6.75 (dd, 1H), 4.60 (bs, 1H), 4.08 (bs, 4H), 3.84 (s, 3H), 3.15 (m, 4H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.7, 154.4, 150.6, 135.9, 134.6, 131.1, 129.6, 127.6, 120.1, 118.4, 115.5, 112.7, 104.9, 102.1, 55.6, 50.4, 49.3, 45.7, 29.5; HRMS calcd for $C_{23}H_{29}N_5O_2$ 407.2321, found 407.2324. Anal. ($C_{23}H_{29}N_5O_2 \cdot 0.25H_2O$) C, H, N.

HIV-1 Reverse Transcriptase Enzyme Assay. The expression of HIV-1 RT and its purification have been described.[17] For the polymerase assays, a partially purified RT preparation was used that was judged as 90–95% pure on the basis of SDS polyacrylamide gel electrophoresis. This preparation was devoid of *Escherichia coli* RNase H activity and consisted of p51/p66 heterodimers of RT, with no evidence of monomeric RT in the form of p66 or p51 alone. Poly(rA) and oligo(dT)$_{10}$, were purchased from Pharmacia. The standard reaction mixtures for the RNA-directed DNA polymerase assay contained 20 mM dithiothreitol, 60 mM NaCl, 0.05% Nonidet P-40 (Sigma), 10 mM $MgCl_2$, 50 mM Tris·HCl, pH 8.3, 8 μM of the cognate α-^{35}S-labeled deoxyribonucleotide 5′-triphosphate (final specific activity 1 Ci/mmol), 10 μg/mL of RNA template ((poly(rA) or poly(rC)), 5 μg/mL of the appropriate primer (dT)$_{10}$, and 0.0274 μM purified

HIV-1 RT. The total volume of the reaction mixtures was 50 μL. The samples were incubated at 37 °C for 15 min. The reactions were terminated by the addition of equal volumes of 10% trichloroacetic acid. Incorporation of radiolabeled precursor was determined by collecting the precipitates on glass-fiber filters, drying, and counting the samples.

HIV-1 Cell Culture Growth and Testing of Antiviral Compounds. In brief, the cell cultures were maintained at 37 °C in 5% CO_2/95% air. In PBMC, 1×10^6 cells were infected with an inoculum containing 1 ng of p24 of the HIV-1 D34 isolate. The level of HIV-1 replication was determined 4 days after infection by measuring the levels of supernatant p24. Cell viability was determined by measuring the levels of mitogen-stimulated cell proliferation.

MT-2 cells were infected with HIV-1 (IIIb isolate) at a multiplicity of infection of 0.001. Syncytium formation was determined 4 days after infection at the peak of viral cytopathic effect. Cell viability was determined by trypan blue exclusion.

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