Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 8. 8-Aryloxymethyl- and 8-Arylthiomethyldipyridodiazepinones[1]

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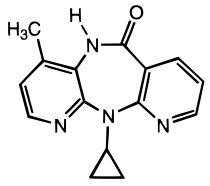
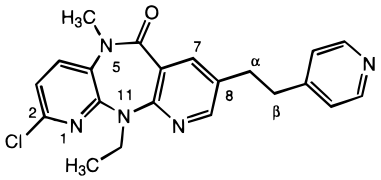
Nevirapine (**I**) is the first human immunodeficiency virus type 1 (HIV-1) nonnucleoside reverse transcriptase (RT) inhibitor to reach regulatory approval. As a result of a second generation program around the tricyclic core system of nevirapine, 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-(pyridin-4-yl)ethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (**II**)[1a] and 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-phenylethyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (**III**)[1a] were identified as broad spectrum HIV-1 RT inhibitors. A detailed examination of replacing either of the methylenes of the 8-ethyl linker of **II** or **III** is presented. It was found that 8-aryloxymethyl and 8-arylthiomethyl are the preferred pattern of substitution for potency against RT. The most potent compounds were further evaluated against a panel of clinically significant mutant RT enzymes (K103N, V106A, G190A, *P*236L) and in cytotoxicity and in vitro metabolism assays. The most potent compound was 2-chloro-8-phenylthiomethyl analogue **37** which displayed sub-100 nM activity against all HIV-1 RT enzymes tested.

Introduction

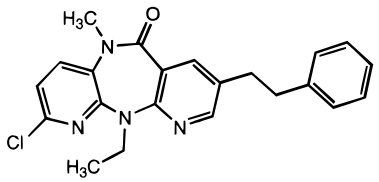
Nevirapine[4] (Viramune, **I**) was the first nonnucleoside reverse transcriptase inhibitor (NNRTI) to receive regulatory approval for the treatment of HIV-1 infection and is currently used in combination with nucleoside RT inhibitors such as AZT, 3TC, D4T, and DDI.[5] It has also been shown to have synergistic effects with the protease inhibitor saquinavir in vitro.[6] Clinical trials examining combinations of nevirapine and other HIV-protease inhibitors also show great promise.[7] Although combination therapy has become the standard of care, no single combination has proven completely effective in all patients and there is a need to develop new therapeutics with improved profiles.[8]



I



II



III

Nevirapine binds to an allosteric site on RT close to the polymerase active site inducing conformational changes and rendering the enzyme incompetent.[9] In the clinic, nevirapine monotherapy results in relatively rapid drug resistance due to mutation of the RT enzyme. Especially significant is the Y181C mutation which is the primary strain of resistant HIV-1 RT found in clinical isolates of patients on nevirapine monotherapy.[10] Here and in the preceding paper[1a] we present our successful design of a second generation inhibitor which retains nevirapine's favorable properties of wild-type RT potency, metabolic stability, good bioavailability and relatively low toxicity while adding broad spectrum activity against a variety of clinically relevant mutant RT enzymes. We found empirically that activity against wild-type (WT), Y181C, and Y188L enzymes provided good indication of potential potency against a larger number of mutants including those which have been identified in the clinical isolates of patients undergoing NNRTI monotherapy. As reported in the preceding paper, 8-arylalkyl substituents improve potency against several of these clinically significant mutants. The combination of the 8-substituent with a 2-halo substituent such as chlorine or fluorine as exemplified in compounds **II** and **III** was particularly effective. Modifications of the 8-ethyl linker of either of these compounds were not, however, fully explored and it was shown that this linker was a major site of metabolism.[1a] The major focuses of this report are the modifications of this linker in order to improve potency and determining their effect on metabolic stability. We have found that replacing one of the carbon atoms of the linker with a heteroatom, such as N, O, or S, in combination with changes in the aryl component has a significant impact on the potency of inhibitors and metabolic stability. We have identified several compounds with good activity

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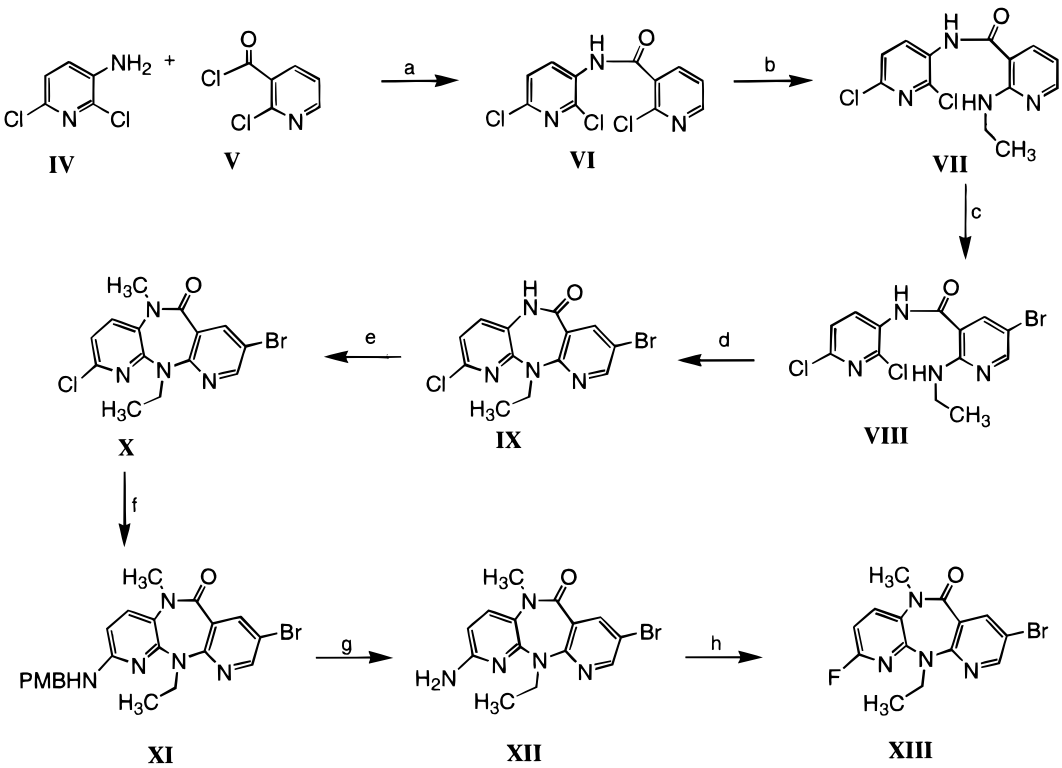
Scheme 1. Synthesis of 8-Bromo-2-halo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one Starting Materials[a]



[a] (a) Pyridine, 1,4-dioxane, cyclohexane, 80%; (b) $EtNH_2$, xylenes, 165 °C, 60%; (c) Br_2, AcOK, AcOH, 88%; (d) NaHMDS, pyridine, 50 °C, 92%; (e) NaH, MeI, DMF, 50 °C, 88%; (f) *p*-methoxybenzylamine, 1,4-dioxane, 170 °C, 4 days, 47%; (g) TFA, 58%; (h) HF·pyridine, $NaNO_2$, 87%.

against a panel of competent mutant RT enzymes and improved metabolic stability relative to **II** or **III**.

Chemistry

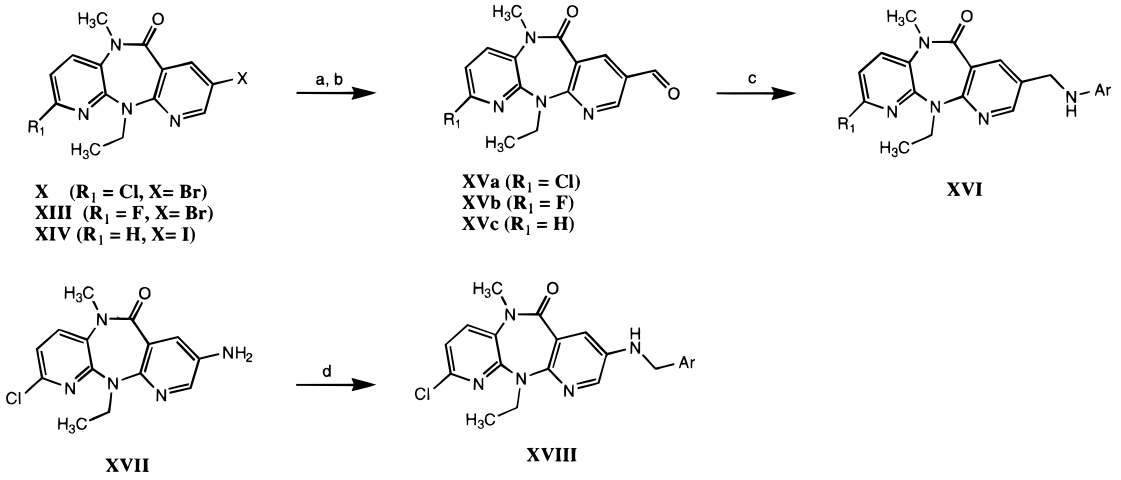
The synthesis of **X**, which was used as the starting material for most analogues reported herein, was accomplished from known 3-amino-2,6-dichloropyridine[11] (**IV**) and commercially available 2-chloronicotinyl chloride[12] (**V**) as outlined in Scheme 1. Condensation of **IV** and **V** in the presence of pyridine afforded **VI** in good yield. The selective displacement of the 2′-chloro substituent of the pyridinecarboxamide ring with ethylamine produced **VII** which was regioselectively brominated, a result of the newly incorporated amine functionality, to give **VIII**.[4b,13] This was a significant improvement over the synthesis of the 8-iodo compounds reported in the preceding paper which required the addition of several steps in order to manipulate a 8-nitro group, via diazonium chemistry, to desired iodo species.[1a] Formation of the diazepinone ring in the presence of sodium hexamethyldisilazane produced **IX**. Use of sodium hydride in this reaction led to debromination as a significant side reaction.[14] Compound **IX** was methylated under standard conditions to give the key 8-bromo intermediate **X**. The 2-fluoro analogue **XIII** was synthesized from **X** by displacement of the chloride with *p*-methoxybenzylamine followed by removal of the amine protecting group to give **XII**. Diazotization of **XII** followed by in situ conversion to the fluoride gave **XIII**.[15] With these intermediates in hand, we turned our attention to the synthesis of our target compounds. All of the modifications of the linker reported herein were synthetically accessible from the 8-halo compounds **X**, **XIII**, **XIV**,[1a] or the 8-amino compound **XVII**[1a] utilizing the methods outlined in Schemes 2−5.

The synthesis of analogues containing the amino linker is shown in Scheme 2. Palladium-mediated cross coupling of **X**, **XIII**, or **XIV** with vinyltributyltin yielded the unstable 8-vinyl compounds, which were immediately subjected to ozonolysis to afford the corresponding aldehyde **XV** in good yields (57−81%). Reductive amination of aldehydes **XV** in methanol with $NaCNBH_3$ and acetic acid produced the β-nitrogen linked analogues **XVI**.[16] A directly analogous procedure was used to produce the α-nitrogen linked analogues by reacting 8-amino analogue **XVII** with various benzaldehydes to yield compounds **XVIII**.

The oxygen and sulfur linked analogues were synthesized via complementary routes as shown in Scheme 3. Reduction of **XV** with $NaBH_4$ afforded **XIX**, which was converted to the corresponding chloride **XX** with $SOCl_2$ in $CHCl_3$. Reaction of **XX** with various phenolates or thiophenolates in a nonprotic solvent, such as THF or DMSO, gave the β-oxygen or sulfur compounds **XXI**. Compound **XXII** was produced by Baeyer−Villiger oxidation of **XVa** followed by in situ hydrolysis. The α-oxygen linked compounds **XXIII** were synthesized from pyridinol **XXII** via alkylation with benzyl halides.

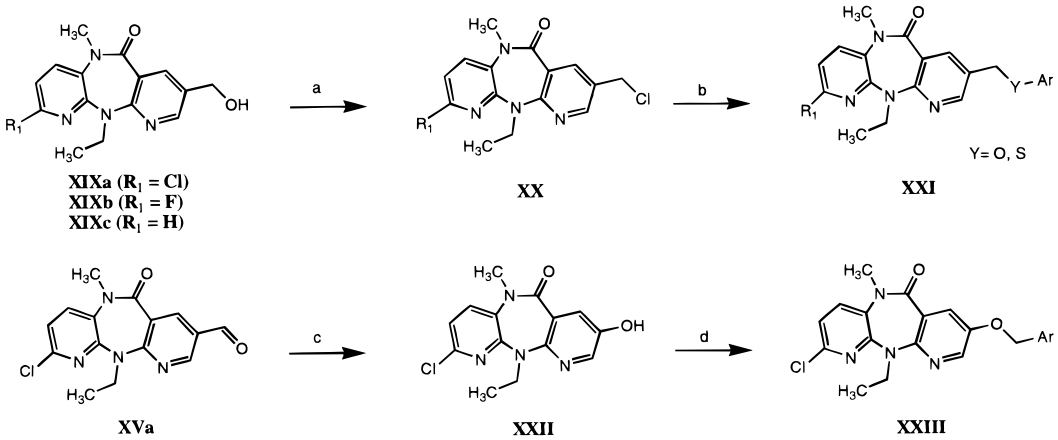
There were difficulties with these methods in certain cases. For instance the key pyridyl analogues **XXV** could not be efficiently produced via alkylation chemistry. The alkylation of **XX** with 4-hydroxypyridine leads predominately to N-substitution, with only trace amounts of the desired O-alkylated product **XXV**. Nu-

Scheme 2. Method A: Reductive Amination[a]



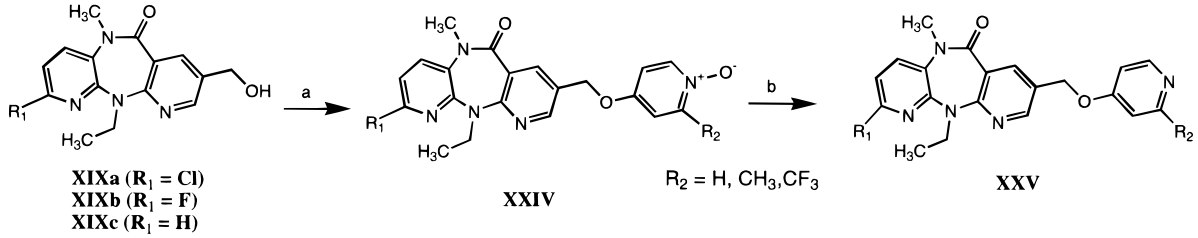
[a] (a) $CH_2CHSnBu_3$, $(Ph_3P)_4Pd$, DMF; (b) O_3, CH_2Cl_2/MeOH followed by DMS; (c) $ArNH_2$, AcOH, then $NaCNBH_3$, AcOH; (d) ArCHO, AcOH, $NaCNBH_3$, AcOH.

Scheme 3. Method B: Alkylation[a]



[a] (a) $SOCl_2$, $CHCl_3$; (b) ArYH, base (NaH, NaHMDS, *t*-BuOK, etc.), DMSO or THF; (c) MCPBA, CH_2Cl_2 then MeOH; (d) NaH, $ArCH_2Br$, THF.

Scheme 4. Method C: Nucleophilic Aromatic Substitution[a]



[a] (a) KH, THF, then substituted 4-nitropyridine *N*-oxides; (b) PCl_3, $CHCl_3$.

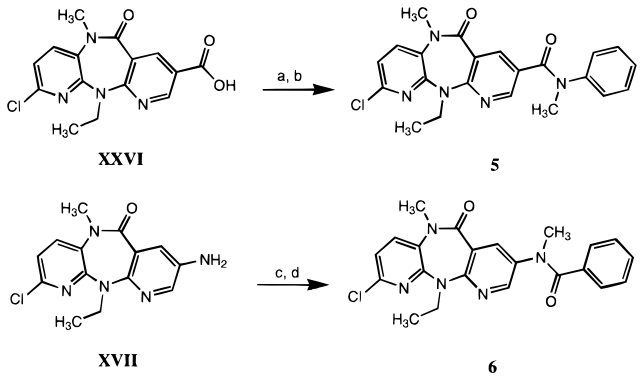
cleophilic aromatic substitution (Scheme 4) provided a successful alternative approach to these important compounds. Thus, reaction of the anion of **XIX** with 4-nitropyridine *N*-oxides provided **XXIV** in good yields. The parent pyridyl analogues **XXV** were produced via reduction with PCl_3 in $CHCl_3$ of **XXIV** followed by basic workup.

The amide linked analogues were synthesized as described in Scheme 5. Oxidation of **XIXa** with Jones reagent gave the starting acid **XXVI**. Amide **5** was synthesized in two steps from **XXVI** by treatment with oxalyl chloride followed by addition of *N*-methylaniline in 65% overall yield. Amide **6** was produced from **XVII** via acylation with benzoyl chloride followed by alkylation with MeI.

Biological Results

The results obtained from testing the analogues against wild-type (WT) RT along with Y181C and Y188L mutant RT in a purified enzyme assay are presented in Table 1. Early on it was decided to focus on compounds with the 2-chloro substituent which improved mutant RT enzyme potency profiles in the alkyl linked series. The first question addressed was whether a heteroatom would be tolerated in the linker at the 8-position. It was found that the β-position is the

Scheme 5. Method D: Acylation[a]



[a] (a) $(COCl)_2$, $CHCl_3$; (b) *N*-methylaniline, CH_2Cl_2; (c) PhCOCl, DIPEA, CH_2Cl_2; (d) NaH, MeI, DMF.

preferred site for substitution with heteroatoms on the linker as demonstrated by compounds **1**−**4** (Table 1). The α-amino compound **1** showed no inhibition of Y188L, and the α-oxygen analogue **3** was a completely ineffective inhibitor at 1 μM against either of the two mutants tested. The β-oxygen linked analogue **4** showed better potency vs Y188L mutant RT than the β-amino analogue **3**. The next question addressed was whether there could be an improvement in the potency of the analogues with nitrogen containing linkers by introducing rigidity either by substitution or by adding oxidation on the linker. Compounds **5**−**7** were synthesized to answer this question. The *N*-methyl analogue **7** did not show improvement against Y188L RT and was significantly weaker against Y181C. In the preceding paper it was reported that the *cis*-olefin geometry of the two carbon linker was preferred. It was found that secondary amides in the 8-position are very weak inhibitors (<40% inhibition at 1 μM against all three enzymes of the primary screen).[17] The lack of activity was attributed to these amides adopting a transoid geometry of the aromatic ring at the 8-position relative to the tricyclic nucleus. The tertiary amides **5** and **6** were synthesized in order to bias the amide geometry to mimic the *cis*-olefin linker. Although these compounds were an improvement relative to the secondary amides, none of these amide analogues improved potency against the Y188L mutant relative the β-oxygen analogue **4**.

It was clear that β-oxygen analogue **4** was the best of the first group of compounds tested with submicromolar activity against all three enzymes. In fact **4** proved to be slightly more potent against the Y188L mutant (0.64 vs 0.96 μM) than the analogous phenethyl derivative **III**.[1a] We examined the SAR of the phenyl ring of **4**. Compounds **10**−**25** showed trends very similar to those reported for the alkyl linked counterparts. The trend of substitution at the meta position being preferred continued in this series with compounds **10** and **20** having potencies very comparable to that of **4**. One notable exception was the *m*-dimethylamino analogue **22**. There was a trend in WT-RT activity displayed by substituted phenyloxymethyl groups at the 8-position that suggested an electronic component to the phenyl ring in the pharmacophore of the inhibitor. It was noticed that with electron donating substituents, such as hydroxyl, the preferred position is meta while with electron withdrawing groups such as fluoro ortho or para substitution is preferred (see compounds **9**−**14**). Inhibitors with a meta hydrogen bond donor, especially nitrogen, display improved potency against Y188L mutant (see compounds **18**−**20**, **24**). In the preceding paper the mutant RT activity profile of the phenyl series was paralleled in the pyridyl series. However when pyridyl compound **29** was tested against the Y188L mutant it showed diminished activity relative to that of **II**. In the previously described alkyl linked series the 2-fluoro substituent improved potency vs the Y188L mutant.[1a] The 2-fluoro compound **28**, however, showed only marginally improved activity against the Y188L mutant. This information clearly showed a divergent SAR of the alkyl linked analogues compared to those reported here. We further investigated the pyridyl series with an emphasis on improving the Y188L activity while maintaining potency against the other RT enzymes. In the alkyl linked series there was a preference for the pyrid-4-yl compound **II** which was the most potent of the pyridine isomers. The 3-pyridyl analogue **26**, however, showed virtually identical activity against the Y181C and Y188L mutants. We were able to improve Y188L mutant RT potency by incorporating electron donating meta substitution as shown with 2-methylpyridyl compound **30**. The trifluoromethyl analogue **31** and the *N*-oxides **32**−**36** displayed reduced potency against Y188L relative to **30**, consistent with a preference for an electron rich aromatic ring at the 8-position.

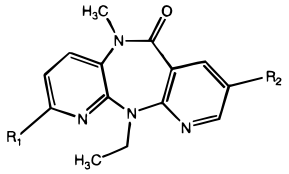
Since there was divergent SAR in the β-oxygen linked series we decided to examine the effect of β-sulfur substitution on the linker of **II**. Interestingly, the phenylthiomethyl compound **37** proved to be among the most potent nonnucleoside RT inhibitors reported. It displayed IC_{50}'s of ∼100 nM or less against all mutants tested. Sulfur oxidation products **38** and **39** showed reduced activity especially against the Y188L mutant. The trend of the phenyl moiety being preferred over the pyridyl ring continued in this series as well with **41** showing weaker activity against the Y188L mutant. Compounds **42** and **43**, however, were quite potent against Y188L RT. Both compounds have a nitrogen in the equivalent of the meta position which is consistent with trends of the other series.

Secondary Tests

Compounds with good profiles in the primary screening against the WT, Y181C, and Y188L enzymes were further evaluated for in vitro metabolic stability in human liver microsomes,[18] cytotoxicity,[19] and activity against a panel of mutant RT enzymes.[19] Nevirapine (**I**) itself has a very slow rate of metabolism in human liver microsomes (2 (pmol/min)/mg of microsomal protein) and low cytotoxicity (>500 μM).

The in vitro metabolism data for some representative examples are shown in Table 2. Compound **II**, which served as the benchmark for this work, was metabolized at a rate of 145 (pmol/min)/mg of microsomal protein. It should be noted that **II** was metabolized significantly faster than nevirapine (**I**) in this in vitro microsomal assay. However, the rate in this assay was virtually identical to delavirdine (U-90152), the only other approved NNRTI.[20] The β-oxygen linked analogues all

Table 1. Inhibition of HIV-1 RT



				IC$_{50}$ (μM) or % inhibition at 1 μM		
no.	R_1	R_2	method	WT RT	Y181C RT	Y188L RT
II	Cl	CH_2CH_2(pyrid-4-yl)		0.08	0.12	1.85
III	Cl	CH_2CH_2Ph		0.05	0.15	0.96
1	Cl	$NHCH_2Ph$	A	0.26	0.39	0%
2	Cl	CH_2NHPh	A	0.08	0.37	28%
3	Cl	OCH_2Ph	B	20%	0%	0%
4	Cl	CH_2OPh	B	0.11	0.06	0.64
5	Cl	$C(O)N(CH_3)Ph$	D	15%	20%	46%
6	Cl	$N(CH_3)C(O)Ph$	D	0.21	22%	13%
7	Cl	$CH_2N(CH_3)Ph$	B	0.59	18%	17%
8	Cl	CH_2NH(Ph-*m*-NH_2)	A	0.06	0.100	19%
9	Cl	CH_2O(Ph-*o*-OH)	B	0.10	0.35	15%
10	Cl	CH_2O(Ph-*m*-OH)	B	0.13	0.25	0.78
11	Cl	CH_2O(Ph-*p*-OH)	B	0.21	27%	21%
12	Cl	CH_2O(Ph-*o*-F)	B	0.17	0.57	13%
13	Cl	CH_2O(Ph-*m*-F)	B	24%	11%	16%
14	Cl	CH_2O(Ph-*p*-F)	B	0.28	1.66	16%
15	Cl	CH_2O(Ph-*o*-CO_2Me)	B	25%	2%	2%
16	Cl	CH_2O(Ph-*m*-CO_2Me)	B	0.70	23%	11%
17	Cl	CH_2O(Ph-*p*-CO_2Me)	B	0.80	33%	0%
18	Cl	CH_2O(Ph-*m*-CO_2H)	B[a]	0.09	0.55	20%
19	Cl	CH_2O(Ph-*m*-$CONH_2$)	B[b]	0.13	0.28	0.34
20	Cl	CH_2O(Ph-*m*-NH_2)	B[c]	0.05	0.10	0.37
21	Cl	CH_2O(Ph-*m*-NO_2)	B	0.17	0.35	0%
22	Cl	CH_2O(Ph-*m*-NMe_2)	B	0%	0%	7%
23	Cl	CH_2O(Ph-*m*-OMe)	B	0.10	0.28	34%
24	Cl	CH_2O(indol-4-yl)	B	0.33	0.71	1.36
25	Cl	CH_2O(indol-5-yl)	B	0.31	0.09	28%
26	Cl	CH_2O(pyrid-3-yl)	B	0.19	0.26	16%
27	H	CH_2O(pyrid-4-yl)	C	0.02	0.14	5.52
28	F	CH_2O(pyrid-4-yl)	C	0.05	0.19	30%
29	Cl	CH_2O(pyrid-4-yl)	C	0.07	0.26	17%
30	Cl	CH_2O(2-methylpyrid-4-yl)	C	0.03	0.03	0.23
31	Cl	CH_2O(2-trifluoromethylpyrid-4-yl)	C	0.04	0.07	45%
32	H	CH_2O(pyrid-4-yl *N*-oxide)	C	0.21	1.34	0%
33	F	CH_2O(pyrid-4-yl *N*-oxide)	C	0.03	0.30	31%
34	Cl	CH_2O(pyrid-4-yl *N*-oxide)	C	0.23	39%	0%
35	Cl	CH_2O(2-methylpyrid-4-yl *N*-oxide)	C	0.10	0.21	4.31
36	Cl	CH_2O(2-trifluoromethylpyrid-4-yl *N*-oxide)	C	0.12	0.27	34%
37	Cl	CH_2SPh	B	0.02	0.01	0.03
38	Cl	$CH_2S(O)Ph$	B[d]	0.07	0.14	2.42
39	Cl	CH_2SO_2Ph	B[d]	0.10	0.06	11.0
40	Cl	CH_2S(pyrimidin-2-yl)	B	0.03	0.06	30%
41	Cl	CH_2S(pyrid-4-yl)	B	0.02	0.05	42%
42	Cl	CH_2S(purin-6-yl)	B	0.07	0.09	0.13
43	Cl	CH_2S(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)	B	0.05	0.07	0.12

[a] From **16** by treatment with LiOH. [b] From **18** by treatment with $(COCl)_2$ followed by NH_3. [c] From **21** by treatment with $SnCl_2$/HCl. [d] From **37** by treatment with MCPBA.

showed a reduced rate of metabolism relative to the analogous previously reported ethyl linked analogues supporting the initial hypothesis leading to the design of these compounds. The phenoxymethyl compound **4** showed a rate similar to **II** and half that of the phenethyl analogue **III**,[1a] while displaying a marginal improvement in the enzymatic profile. Major metabolites of **4** were identified as phenyl ring hydroxylated derivatives. The potent *m*-hydroxyphenyl analogue **10** was unfortunately metabolized nearly twice as fast as **4**. The pyridyloxymethyl series, represented by compounds **28** and **29**, showed a marked improvement in their rate of in vitro metabolism. The primary metabolites of **28** and **29** were identified as the *N*-oxides by LC−MS and comparison to authentic samples. The *N*-oxide **33** was metabolized at a rate approximately 5 times slower than **28**. In contrast to the β-oxygen substitution, the β-sulfur substitution increased the rate of in vitro metabolism relative to **II**. Compound **37** was consumed at rate approximately 3 times faster than **4**. The sulfone **39**, which was identified as a metabolite of **37**, was metabolized at nearly twice the rate relative to **4**. Replacement of the phenyl ring of **37** with heterocycles did not result in a significant improvement in rates of metabolism (compounds **41**−**43** vs compound **37**).

A few compounds were tested for in vivo metabolism in rat. The pyridyloxymethyl compounds **28** and **29**

Table 2. In Vitro Metabolism in Human Liver Microsomes

no.	[(pmol/min)/mg of microsomal protein]	no.	[(pmol/min)/mg of microsomal protein]
I	2	**29**	53
II	145	**30**	371
III	288	**31**	206
4	171	**33**	9
10	318	**37**	554
12	264	**39**	322
19	292	**41**	372
20	95[a]	**42**	591
24	208	**43**	336
25	177	U-90152	144
28	41		

[a] Nonlinear rate.

Table 3. MTT Toxicity Assay

no.	CC_{30} (μM)	no.	CC_{30} (μM)
2	>60	**27**	>256
4	>60	**28**	160
8	60	**29**	>120
10	~50	**30**	>256
18	250	**37**	>60
19	130	**38**	45
20	60	**42**	25
24	>30	**43**	40

showed a metabolic profile similar to that observed in the in vitro studies with the *N*-oxides of the 8-pyridyl moiety being the predominant metabolite. The bioavailabilities of **28** and **29** were found to be 69 ± 9% and 57 ± 6%, respectively, in this system. The bioavailability of the phenylthiomethyl derivative **37** was below quantitation limits in this assay. The observed drop in bioavailability for **37** could be suggested by rate of in vitro metabolism in rat which was 2831 (pmol/min)/mg of rat microsomal protein which was approximately 10 times faster than either **28** or **29** (224 and 296 (pmol/min)/mg for **28** and **29** respectively).

Due to some observations of toxicity associated with 2-substituted analogues all compounds were screened in an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] cellular assay.[1b,19] The cytotoxicity of the 8-substituted series in general is relatively low with most displaying CC_{30}'s above 60 μM. Compounds with a *m*-amino or *m*-hydroxy aromatic substituent did exhibit a trend toward increased toxicity (Table 3, compounds **8**, **10**, and **20**), as did the arylthiomethyl series. Compounds **42** and **43** which are two of the more potent compounds were among the most toxic of those reported here. The purinylthiomethyl analogue **42** was the most toxic of the compounds reported herein but still is relatively less toxic than the highly potent but toxic 2-azaindole series reported previously which were approximately 6 μM in the MTT assay.[1b]

With a goal to develop a broad spectrum RT inhibitor, we further evaluated many compounds against a panel of mutant RT enzymes. Although, in general, the Y188L was the most resistant of the mutant RT enzymes tested, some compounds with relatively weak Y188L activity still displayed good activity against several other clinically significant mutants (see Table 4). Compounds **4** and **37** showed excellent activity against all mutants tested and showed no activity against calf thymus DNA polymerase-α at 50 μg/mL.[4a,17] The phenylthiomethyl analogue **37** was the most potent compound and showed excellent broad spectrum activity. The compound was further investigated in the Chow and Hirsch protocol which tests the ability of compounds or mixtures of compounds to eradicate HIV-1 virus from chronically infected peripheral blood mononuclear cell (PBMC) cultures.[21] Compound **37** alone, at 5 μM, effectively suppressed viral replication and p24 levels from the cell cultures fell to or below background level by the fourth week of treatment. No virus breakthrough was observed during the 6 weeks following drug removal at week 7. Qualitative PCR, which was able to detect 1 copy of HIV gene per approximately 7600 noninfected cells, showed no HIV-1 specific DNA's from these cultures.[22]

Table 4. Mutant HIV-1 RT Panel Data

no.	K103N (μM)	V106A (μM)	G190A (μM)	P236L (μM)
I	1.85	1.48	3.93	0.08
II	0.12	0.55	0.03	0.11
III	0.05	0.84	0.12	0.71
2	0.05	0.51	0.80	0.23
4	0.02	0.21	0.01	0.08
18	0.19	0.16	0.04	0.14
23	0.13	0.22	NT[a]	0.29
27	0.05	0.30	0.01	0.08
28	0.04	0.13	0.05	0.11
29	0.07	0.18	0.12	0.22
37	0.03	0.06	0.04	0.05

[a] NT= not tested.

Table 5. Inhibition of HIV-1_{IIIB} Replication in C8166 Cells

no.	IC_{50} (nM)[a]	IC_{90} (nM)[b]
4	50	113
20	19	36
29	6	24
37	5	13

[a] Inhibitory concentration of compound producing a 50% reductions in the centers of syncytia. [b] Inhibitory concentration of compound producing a 90% reductions in the centers of syncytia. See ref 4a.

A select few compounds including **37** were tested for their ability to inhibit syncytia formation in cell cultures infected with wild-type HIV-1_{IIIB} virus (Table 5).[4a] Activity in cell culture correlated well with the enzyme data, and all compounds tested showed activity in cell culture. Compound **37** was again the most potent among those tested with an IC_{90} of 13 nM but the 4-pyridyloxymethyl analogue **29** also was quite potent in this assay with an IC_{90} of 24 nM.

Conclusion

The multidrug or cocktail approach for the treatment of HIV-1 infection has shown great promise.[4,5] However with the emergence of resistance there will be a continued need for pharmaceuticals with improved profiles for use in the cocktails of the future. We have shown that the 2-halo-8-aryloxymethyl- and the 2-halo-8-arylthiomethyl-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-ones are effective inhibitors of wild-type and clinically relevant mutant RT enzymes. The 8-aryloxymethyl compounds possess improved activity and metabolic stability relative to the ethyl linked analogues while maintaining low cytotoxicity. These attributes are prerequisites to the development of new therapeutics and progress in this regard will be the subject of future reports.

Experimental Section

General Chemical Methods. Chromatography was performed on silica gel. Melting points were determined on a Fisher-Johns melting point apparatus in celsius (°C) and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 270 MHz on a Bruker AC-270 referencing to solvent unless otherwise noted with *J* values reported in hertz. Mass spectra were performed by Oneida Laboratories, Oneida, NY. High-resolution mass spectra were performed by the Department of Analytical Sciences of Boehringer Ingelheim Pharmaceuticals. Elemental analyses were performed by either Midwest Microanalytical Laboratories, Indianapolis, IN, or Quantitative Technologies, Inc., Whitehouse, NJ.

Preparation of 2-Halo-8-bromo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one Derivatives X and XIII. (a) *N*-(2,6-Dichloro-3-pyridinyl)-2-chloro-3-pyridinecarboxamide (VI). 3-Amino-2,6-dichloropyridine[11] (**IV**) (48.9 g, 0.30 mol) was dissolved in 1,4-dioxane (170 mL), and cyclohexane (110 mL) and pyridine (24.3 mL, 0.30 mol) were added. The 2-chloronicotinoyl chloride[12] (**V**) (52.8 g, 0.3 mol) in 1,4-dioxane (85 mL) was then added dropwise over a 1 h period. The resultant white suspension was stirred for 16 h and filtered. The solid was washed with H_2O, 1:1 hexanes/EtOAc (200 mL each), suspended in 1:1 CH_2Cl_2/H_2O (2 L), stirred for 1 h and refiltered. The CH_2Cl_2 layer was separated and concentrated, and the combined solid was washed with H_2O, EtOAc, and hexanes (150 mL each) and dried in vacuo at 60 °C to afford **VI** (72.7 g, 80%): mp 197−198; ^{1}H NMR 8.98 (br s, 1H), 8.90 (d, J = 8.5, 1H), 8.58 (dd, J = 4.8, 1.9, 1H), 8.31 (dd, J = 7.7, 1.9, 1H), 7.46 (dd, J = 7.7, 4.8, 1H), 7.36 (d, J = 8.5, 1H); CIMS (CH_4) 302 (MH^+). Anal. ($C_{11}H_6Cl_3N_3O$) C, H, N.

(b) *N*-(2,6-Dichloro-3-pyridinyl)-2-ethylamino-3-pyridinecarboxamide (VII). A mixture of **VI** (12.0 g, 39.8 mmol), ethylamine (3.6 g, 80.7 mmol), and 30 mL of xylenes in a sealed vessel was heated at 165 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with H_2O, and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated, and the resulting solid was washed with EtOAc and hexanes to give **VII** (7.4 g, 60%), suitable for use in the next reaction: mp 110−112; ^{1}H NMR 8.76 (d, J = 8.0, 1H), 8.33 (dd, J = 4.8, 1.7, 1H), 8.19 (s, 1H), 7.96 (br s, 1H), 7.74 (dd, J = 7.8, 1.7, 1H), 7.33 (d, J = 8.0, 1H), 6.58 (dd, J = 7.8, 4.83, 1H), 3.54 (m, 2H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 311 (MH^+). Anal. ($C_{13}H_{12}Cl_2N_4O$) C, H, N.

(c) *N*-(2,6-Dichloro-3-pyridinyl)-5-bromo-2-ethylamino-3-pyridinecarboxamide (VIII). To a solution of **VII** (7.4 g, 24 mmol) and KOAc (2.8 g, 28 mmol) in 90 mL of AcOH was added Br_2 (1.2 mL, 23 mmol). After 15 min, the reaction mixture was diluted with H_2O, and the precipitate was collected by suction filtration to give **VIII** (8.2 g, 88%), suitable for use in the next reaction: mp 195−196; ^{1}H NMR 8.69 (d, J = 8.5, 1H), 8.33 (d, J = 2.3, 1H), 8.09 (br s, 1H), 7.89 (br s, 1H), 7.79 (d, J = 2.3, 1H), 7.34 (d, J = 8.5, 1H), 3.51 (m, 2H), 1.27 (t, J = 7.2, 3H); CIMS (CH_4) 389 (MH^+). Anal. ($C_{13}H_{11}BrCl_2N_4O$) C, H, N.

(d) 8-Bromo-2-chloro-5,11-dihydro-11-ethyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (IX). To a solution of **VIII** (5.9 g, 15 mmol) in 30 mL of pyridine at 50 °C under argon was added by syringe a 1.0 M solution of sodium hexamethyldisilazide in THF (31.5 mL, 31.5 mmol). After 10 min, the reaction mixture was diluted with ice water and allowed to stir for 2 h. The resultant orange-yellow precipitate was collected by suction filtration and air-dried to give **IX** (4.9 g, 92%): mp 262−263; ^{1}H NMR 8.48 (d, J = 2.5, 1H), 8.25 (d, J = 2.5, 1H), 8.04 (br s, 1H), 7.25 (d, J = 8.1, 1H), 7.05 (d, J = 8.1, 1H), 4.18 (q, J = 7.0, 2H), 1.24 (t, J = 7.0, 3H); CIMS (CH_4) 353 (MH^+). Anal. ($C_{13}H_{10}BrClN_4O$) C, H, N.

(e) 8-Bromo-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (X). To a solution of **IX** (4.9 g, 14 mmol) in DMF (140 mL) was added NaH (0.86 g, 18 mmol), and the mixture was heated to 50 °C for 30 min. The mixture was cooled to room temperature and treated with MeI (0.90 mL, 15 mmol). After 1.5 h, the mixture was carefully diluted with H_2O and filtered, and the solid was washed with petroleum ether and dried to give **X** (4.45 g, 88%): mp 190−192; ^{1}H NMR 8.42 (d, J = 2.5, 1H), 8.19 (d, J = 2.5, 1H), 7.44 (d, J = 8.2, 1H), 7.12 (d, J = 8.2, 1H), 4.13 (q, J = 7.0, 2H), 3.48 (s, 3H), 1.24 (t, J = 7.0, 3H); CIMS (CH_4) 367 (MH^+). Anal. ($C_{14}H_{12}BrClN_4O$) C, H, N.

(f) 8-Bromo-5,11-dihydro-11-ethyl-2-(((4-methoxyphenyl)methyl)amino)-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (XI). A pressure tube was charged with **X** (3.7 g, 10 mmol), *p*-methoxybenzylamine (3 mL, 23 mmol), and 1,4-dioxane (15 mL), sealed, and heated to 170 °C in a sand bath. An additional 1 mL of the amine was added each day. After 4 days the mixture was cooled, diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organics were washed with H_2O, saturated aqueous NH_4Cl and brine, then dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes) followed by recrystallization from EtOAc/hexanes to give **XI** (2.2 g, 47%): mp 151−154; ^{1}H NMR 8.36 (d, J = 2.3, 1H), 8.15 (d, J = 2.3, 1H), 7.26 (d, J = 8.6, 2H), 7.24 (d, J = 8.7, 1H), 6.87 (d, J = 8.6, 2H), 6.17 (d, J = 8.7, 1H), 4.78 (t, J = 5.5, 1H), 4.41 (d, J = 5.5, 1H), 4.04 (q, J = 7.0, 1H), 3.80 (s, 3H), 3.41 (s, 3H), 1.20 (t, J = 7.0, 3H); CIMS (CH_4) 468 (MH^+). Anal. ($C_{22}H_{22}BrN_5O_2$) C, H, N.

(g) 2-Amino-8-bromo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XII). Compound **XI** (2.2 g, 4.7 mmol) was dissolved in TFA (25 mL). The mixture turned gradually orange and then red. The excess TFA was removed by rotary evaporation. To the yellow-orange residue was added 3% aqueous NH_4OH, and after 3 h the mixture was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The resulting solid was recrystallized (EtOAc/hexanes) to afford **XII** (0.949 g, 58%): mp 204−208; ^{1}H NMR 8.36 (d, J = 2.6, 1H), 8.16 (d, J = 2.6, 1H), 7.27 (d, J = 8.5, 1H), 6.29 (d, J = 8.7, 1H), 4.39 (br s, 2H), 4.04 (q, J = 7.0, 1H), 3.43 (s, 3H), 1.22 (t, J = 7.0, 3H); CIMS (CH_4) 348 (MH^+). Anal. ($C_{14}H_{14}BrN_5O$) C, H, N.

(h) 5,11-Dihydro-11-ethyl-2-fluoro-8-bromo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XIII). A plastic centrifuge tube was charged with **XII** (0.50 g, 1.4 mmol). HF·pyridine (10 mL) was added, and the resulting suspension was cooled to 0 °C. $NaNO_2$ was added in several portions over 10 min to produce a purple solution. The mixture was then capped and stirred for 16 h. The reaction mixture was poured onto ice and 6 N NaOH. EtOAc was added, and the mixture was filtered. The filtrate was separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (EtOAc/hexanes) and recrystallization (EtOAc/hexanes) afforded **XIII** (0.44 g, 87%): mp 154−156; ^{1}H NMR 8.41 (d, J = 2.3, 1H), 8.20 (d, J = 2.3, 1H), 7.58 (app. t, J = 8, 1H), 6.74 (dd, J = 8.5, 3.8, 1H), 4.11 (q, J = 7.0, 1H), 3.49 (s, 3H), 1.262 (t, J = 7.0, 3H); CIMS (CH_4) 351 (MH^+). Anal. ($C_{14}H_{12}BrFN_4O$) C, H, N.

Method A. Preparation of 2-Chloro-5,11-dihydro-11-ethyl-8-formyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (XVa, R1 = Cl). A solution of **X** (R1 = Cl, X = Br) (4.50 g, 12.2 mmol) in DMF (50 mL) was treated with $Pd(PPh_3)_4$ (0.28 g, 24 mmol) followed by vinyltributyltin (3.8 mL, 12.9 mmol) and heated to 90 °C with stirring. After 2.5 h the mixture was poured into H_2O and extracted with CH_2Cl_2 (4 × 100 mL) and EtOAc (2 × 100 mL). The combined organics were washed with 15% aqueous NH_4OH (2 × 100 mL) and brine (2 × 100 mL), then dried over Na_2SO_4, and concentrated, and the gross impurities were removed by rapid flash chromatography (gradient hexanes to EtOAc) to give the unstable 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-vinyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (100%) which was dissolved in 1:1 CH_2Cl_2/MeOH (40 mL) and cooled to −78 °C. This solution was then saturated with ozone, and a stream of ozone was bubbled through for 10 min more while stirring. The mixture was warmed to ambient temperatures and quenched with excess dimethyl sulfide. The mixture was then concentrated, and the residue was purified by flash chroma-

tography (gradient of hexanes to 1:1 hexanes/EtOAc) to give **XVa** (1.9 g, 81%): mp 199−201; ^{1}H NMR 10.00 (s, 1H), 8.84 (d, J = 2.3, 1H), 8.56 (d, J = 2.3, 1H), 7.48 (d, J = 8.3, 1H), 7.18 (d, J = 8.3, 1H), 4.29 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.31 (t, J = 7.0, 3H); CIMS (CH_4) 317 (MH^+). Anal.($C_{15}H_{13}ClN_4O_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-8-formyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (XVb, R1 = F). Starting from **XIII** by a procedure analogous to that used for preparation of **XVa**: 72%; mp 133−134; ^{1}H NMR 10.00 (s, 1H), 8.84 (d, J = 2.3, 1H), 8.57 (d, J = 2.3, 1H), 7.63 (dd, J = 8.5, 7.0, 1H), 6.80 (dd, J = 8.5, 3.9, 1H), 4.26 (q, J = 7.0, 2H), 3.50 (s, 3H), 1.32 (t, J = 7.0, 3H); CIMS (CH_4) 301 (MH^+). Anal. ($C_{15}H_{13}FN_4O_2$) C, H, N.

Preparation of Compounds XVI. 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylamino)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (2) (R1 = Cl, Ar = Ph). Compound **XVa** (50 mg, 0.16 mmol) was dissolved/suspended in MeOH (2 mL) and treated with $NaBH_3CN$ (30 mg, 0.47 mmol) followed by aniline (43 μL, 4.7 mmol). The mixture was stirred for 5 min, and then AcOH (20 μL, 0.35 mmol) was added. After an additional 3 h at room temperature the mixture was made alkaline with 15% aqueous NaOH, and the white suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient) to give **2** (31 mg, 50%): mp 79−80; ^{1}H NMR 8.40 (d, J = 2.4, 1H), 8.09 (d, J = 2.4, 1H), 7.41 (d, J = 8.3, 1H), 7.15 (dd, J = 7.7, 7.5, 2H), 7.08 (d, J = 8.3, 1H), 6.72 (t, J = 7.5, 1H), 6.59 (d, J = 7.7, 2H), 4.31 (s, 2H), 4.16 (q, J = 7.0, 2H), 3.47 (s, 3H), 1.57 (br s, 1H), 1.26 (t, J = 7.0, 3H); CIMS (CH_4) 394 (MH^+). Anal. ($C_{21}H_{20}ClN_5O$) C, H, N.

8-(3-Aminophenylamino)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (8). Compound **XVa** (50 mg, 0.16 mmol) was suspended in MeOH (3 mL) and treated with *m*-phenylenediamine (170 mg, 1.6 mmol). The resulting solution was stirred and treated with $NaBH_3CN$ (50 mg 0.79 mmol) followed by the dropwise addition of AcOH (20 μL, 0.35 mmol). After an additional 2.5 h at room temperature the mixture was made alkaline with 15% aqueous NaOH and extracted with CH_2Cl_2 (4 × 25 mL). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient), then chromatotron (10 to 50% 2-propanol/hexanes gradient), and finally recrystallization from CH_2Cl_2/petroleum ether to give **8** (20 mg, 31%): mp 88−90; ^{1}H NMR 8.39 (d, J = 2.4, 1H), 8.08 (d, J = 2.4, 1H), 7.41 (d, J = 8.2, 1H), 7.09 (d, J = 8.2, 1H), 6.93 (t, J = 8.0, 1H), 6.09−6.02 (m, 2H), 5.91 (t, J = 1.6, 1H), 4.27 (s, 2H), 4.16 (q, J = 7.1, 2H), 3.47 (s, 3H), 1.25 (t, J = 7.1, 3H); CIMS (CH_4) 409 (MH^+); HRMS (MH^+, $C_{21}H_{22}ClN_6O$) calcd 409.1544, found 438.1564. Anal. ($C_{21}H_{21}ClN_6O$) C, H; N: calcd, 20.55; found 19.44.

Preparation of Compound XVIII. 8-((Phenylmethyl)-amino)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (1). Compound **XVII**[1a] (27 mg, 0.09 mmol) was suspended in MeOH (2 mL) and AcOH (10 μL, 0.18 mmol), and benzaldehyde (9 μL, 0.09 mmol) was added. The resulting solution was stirred and treated with $NaBH_3CN$ (50 mg, 0.79 mmol) followed by the dropwise addition of AcOH (20 μL, 0.35 mmol). The mixture was stirred and extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient) and recrystallization from Et_2O/petroleum ether to give **1** (18 mg, 51%): mp 141; ^{1}H NMR 7.85 (d, J = 3.1, 1H), 7.39−7.26 (m, 2H), 7.03 (d, J = 8.2, 1H), 4.32 (d, J = 5.5, 2H), 4.10−4.03 (m, 3H), 3.46 (s, 3H), 1.22 (t, J = 7.0, 3H); CIMS (CH_4) 394 (MH^+). Anal. ($C_{21}H_{20}ClN_5O$) C, H, N.

General Method B. Synthesis of 2-chloro-5,11-dihydro-11-ethyl-8-hydroxy-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XXII). Compound **XVa** (1.02 g, 3.22 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with MCPBA (80 wt %, 1.04 g, 4.83 mmol). The mixture was stirred for 16 h, then treated with MeOH, and stirred for 8 h more. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) to give **XXII** (0.37 g, 38%). The product was recrystallized from hexanes/EtOAc: mp 236−237; ^{1}H NMR 8.09 (d, J = 3.1, 1H), 7.73 (d, J = 3.1, 1H), 7.42 (d, J = 8.3, 1H), 7.08 (d, J = 8.3, 1H), 6.22 (br s, 1H), 4.10 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.23 (t, J = 7.0, 3H); CIMS (CH_4) 305 (MH^+). Anal. ($C_{14}H_{13}ClN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-phenylmethoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (3). Compound **XXII** (52 mg, 0.17 mmol) was dissolved in THF and treated with excess NaH (60 wt %) followed by benzyl bromide (40 μL, 0.34 mmol). After 24 h of stirring, the mixture was cooled to 0 °C, and the excess NaH was quenched by the dropwise addition of H_2O, and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL) The combined organics were dried over $MgSO_4$ and concentrated, and the residue was purified by chromatography (hexanes to 1:1 hexanes/EtOAc gradient) followed by crystallization from hexanes to give **3** (35 mg, 52%): mp 159−160; ^{1}H NMR 8.17 (d, J = 3.1, 1H), 7.70 (d, J = 3.1, 1H), 7.42−7.32 (m, 6H), 7.07 (d, J = 8.2, 1H), 5.07 (s, 2H), 4.10 (q, J = 7.1, 2H), 3.48 (s, 3H), 1.23 (t, J = 7.1, 3H); CIMS (CH_4) 395 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-hydroxymethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one XIXa (R1 = Cl). To a solution of **XVa** (582 mg, 1.84 mmol) in THF (20 mL) was added H_2O (0.1 mL) followed by $NaBH_4$ (70 mg, 1.84 mmol). The mixture was stirred for 0.5 h, then diluted with brine (20 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were dried and concentrated, and the residue was purified by flash chromatography (gradient hexanes to EtOAc) to yield **XIXa (R1 = Cl)** (520 mg, 89%): mp 166−168; ^{1}H NMR 8.40 (d, J = 2.1, 1H), 8.10 (d, J = 2.1, 1H), 7.43 (d, J = 8.2, 1H), 7.11 (d, J = 8.2, 1H), 4.68 (d, J = 5.8, 2H), 4.17 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.78 (t, J = 5.8, 1H), 1.26 (t, J = 7.0, 3H); CIMS (CH_4) 319 (MH^+). Anal. ($C_{15}H_{15}ClN_4O_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-8-hydroxymethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XIXb, R1 = F). By a procedure analogous to that reported for **XIXa** from **XVb**: 100%; mp 77−80; ^{1}H NMR 8.39 (d, J = 2.4, 1H), 8.11 (d, J = 2.4, 1H), 7.57 (dd, J = 8.5, 7.2, 1H), 6.71 (dd, J = 8.5, 3.9, 1H), 4.68 (br s, 2H), 4.14 (q, J = 7.1, 2H), 3.49 (s, 3H), 1.84 (br s, 1H), 1.27 (t, J = 7.0, 3H); CIMS (CH_4) 302 (M^+). Anal. ($C_{15}H_{15}FN_4O_2$) C, H, N.

5,11-Dihydro-11-ethyl-8-hydroxymethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XIXc, R1 = H). By a procedure analogous to that reported for **XIXa** from **XVc**: 100%; mp 129−131; ^{1}H NMR (250 MHz, DMSO) 8.36 (d, J = 2.0, 1H), 8.21 (dd, J = 5.0, 1.5, 1H), 7.98 (d, J = 2.0, 1H), 7.84 (dd, J = 8.0, 1.5, 1H), 7.26 (dd, J = 8.0, 5.0, 1H), 5.29 (t, J = 5.7, 1H), 4.47 (d, J = 5.7, 2H), 4.07 (q, J = 7.0, 1H), 3.43 (s, 3H), 1.17 (t, J = 7.0, 3H); CIMS (CH_4) 285 (MH^+). Anal. ($C_{15}H_{16}N_4O_2$) C, H, N.

2-Chloro-8-chloromethyl-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one XXa (R1 = Cl). Compound **XIXa (R1 = Cl)** (0.52 g, 1.6 mmol) was dissolved in $CHCl_3$ (10 mL) and treated with $SOCl_2$ (0.12 mL, 1.6 mmol) followed by Et_3N (0.23 mL, 1.6 mmol). After 0.5 h of stirring, the mixture was made alkaline with 15% aqueous NaOH and diluted with brine (10 mL), and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by flash chromatography (gradient hexanes to 1:1 hexanes/EtOAc) to give **XXa** (0.51 g, 93%): mp 133−134; ^{1}H NMR 8.40 (d, J = 2.5, 1H), 8.13 (d, J = 2.5, 1H), 7.44 (d, J = 8.3, 1H), 7.12 (d, J = 8.3, 1H), 4.56 (s, 2H), 4.18 (q, J = 7.0,

2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 337 (MH^+). Anal. ($C_{15}H_{14}Cl_2N_4O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenyloxy)-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4). Phenol (18 mg, 0.19 mmol) in DMSO (4 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.19 mL, 0.19 mmol). After 10 min of stirring at ambient temperature, compound **XXa** (60 mg, 0.18 mmol) was added and the mixture was stirred for an additional hour. The mixture was quenched with brine (5 mL) and made alkaline with 15% aqueous NaOH. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the organics were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) to give **4** (55 mg, 78%): mp 140−141; ^{1}H NMR 8.46 (d, $J = 2.4$, 1H), 8.19 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.2$, 1H), 7.32−7.26 (m, 2H), 7.10 (d, $J = 8.2$, 1H), 6.99−6.92 (m, 3H), 5.02 (s, 2H), 4.19 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 395 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-methyl phenylamino)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (7). Compound **XXa** (50 mg, 0.15 mmol) was dissolved in *N*-methylaniline (1 mL) and stirred for 3 days. The mixture was purified by column chromatography (hexanes to EtOAc gradient) to give **7** (25 mg, 41%): mp foam, 55−57; ^{1}H NMR 8.28 (d, $J = 2.4$, 1H), 7.97 (d, $J = 2.4$, 1H), 7.40 (d, $J = 8.3$, 1H), 7.20 (br t, $J = 8.0$, 2H), 7.08 (d, $J = 8.3$, 1H), 6.74−6.70 (m, 3H), 4.47 (s, 2H), 4.14 (q, $J = 7.0$, 2H), 3.46 (s, 3H), 2.99 (s, 3H), 1.25 (t, $J = 7.0$ 3H); CIMS (CH_4) 408 (MH^+). Anal. ($C_{22}H_{22}ClN_5O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-hydroxyphenyloxy)-methyl-5-methyl-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one (9). Catechol (82 mg, 0.74 mmol) in DMSO (1 mL) was treated with *t*-BuOK (1.0 M in THF, 0.16 mL, 0.16 mmol). The resulting stirred solution was treated with **XXa** (50 mg, 0.14 mmol), and the mixture was stirred an additional 24 h. The mixture was diluted with EtOAc (20 mL) and washed with brine (3 × 10 mL). The organics were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) followed crystallization from hexanes/EtOAc to give **9** (35 mg, 58%): mp 172−173; ^{1}H NMR 8.46 (d, $J = 2.3$, 1H), 8.18 (d, $J = 2.3$, 1H), 7.45 (d, $J = 8.3$, 1H), 7.12 (d, $J = 8.3$, 1H), 6.95−6.80 (m, 4H), 5.07 (s, 2H), 4.20 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_3$) C, H, N.

Compounds 10−17, 21−26, 40, 42, and 43 were prepared in an analogous fashion from the indicated starting material and XXa.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-hydroxyphenyl)-methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (10): resorcinol; 51%; mp 219−220; ^{1}H NMR 8.45 (d, $J = 2.3$, 1H), 8.16 (d, $J = 2.3$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.15−7.09 (m, 1H), 7.11 (d, $J = 8.3$, 1H), 6.53−6.43 (m, 3H), 5.21 (s, 1H), 4.97 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49(s, 3H), 1.26 (t, $J = 7.0$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-hydroxyphenyloxy)-methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11): hydroquinone; 67%; mp 199−200; ^{1}H NMR 8.44 (d, $J = 2.4$, 1H), 8.16 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.78 (ab, $\Delta v = 13.2$, $J = 9.2$, 4H), 6.71 (s, 1H), 4.93 (s, 2H), 4.18 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-fluorophenyloxy)-methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12): 2-fluorophenol; 52%; mp 109−110; ^{1}H NMR 8.47 (d, $J = 2.2$, 1H), 8.19 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.4$, 1H), 7.11 (d, $J = 8.4$, 1H), 7.07−6.89 (m, 4H), 5.08 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($C_{21}H_{18}ClFN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-fluorophenyl)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13): 3-fluorophenol; 70%; mp 104−105; ^{1}H NMR 8.45 (d, $J = 2.2$, 1H), 8.17 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.26−7.18 (m, 1H), 7.11 (d, $J = 8.3$, 1H), 6.73−6.63 (m, 3H), 5.00 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($C_{21}H_{18}ClFN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-fluorophenyloxy)-methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (14): 4-fluorophenol; 57%, mp 143−144; ^{1}H NMR 8.44 (d, $J = 2.2$, 1H), 8.17 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.10 (d, $J = 8.3$, 1H), 7.00−6.84 (m, 4H), 4.97 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($C_{21}H_{18}ClFN_4O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-(methoxycarbonyl)phenyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (15): methyl salicylate; 57%; mp 196−197; ^{1}H NMR 8.53 (d, $J = 2.4$, 1H), 8.25 (d, $J = 2.4$, 1H), 7.83 (dd, $J = 7.7$, 1.7, 1H), 7.49−7.42 (m, 1H), 7.43 (d, $J = 8.3$, 1H), 7.11 (d, $J = 8.3$, 1H), 7.05−6.99 (m, 2H), 5.12 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.91 (s, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($C_{23}H_{21}ClN_4O_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-((3-(methoxycarbonyl)phenyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (16): methyl 3-hydroxybenzoate; 90%; mp 163−164; ^{1}H NMR 8.47 (d, $J = 2.4$, 1H), 8.20 (d, $J = 2.4$, 1H), 7.68−7.61 (m, 2H), 7.44 (d, $J = 8.2$, 1H), 7.35 (t, $J = 7.9$, 1H), 7.15−7.09 (m, 1H), 7.11 (d, $J = 8.2$, 1H), 5.06 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.91 (s, 3H), 3.49 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($C_{23}H_{21}ClN_4O_4$) C, H, N.

2-chloro-5,11-dihydro-11-ethyl-8-(4-(methoxycarbonyl)-phenyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (17): methyl 4-hydroxybenzoate; 45%; mp 196−197; ^{1}H NMR 8.46 (d, $J = 2.4$, 1H), 8.18 (d, $J = 2.4$, 1H), 7.99 (d, $J = 8.9$, 2H), 7.43 (d, $J = 8.3$, 1H), 7.11 (d, $J = 8.3$, 1H), 6.95 (d, $J = 8.9$, 2H), 5.07 (s, 2H), 4.19 (q, $J = 7.1$, 2H), 3.88 (s, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($C_{23}H_{21}ClN_4O_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(3-nitrophenylamino)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (21): 3-nitrophenol; 95%; mp 171−172; ^{1}H NMR 8.47 (d, $J = 2.4$, 1H), 8.20 (d, $J = 2.4$, 1H), 7.86 (ddd, $J = 8.1$, 1.9, 0.8, 1H), 7.79 (app t, $J = 2.3$, 1H), 7.45 (t, $J = 8.1$, 1H), 7.45 (d, $J = 8.3$, 1H), 7.26 (ddd, $J = 8.1$, 2.6, 0.8, 1H), 7.12 (d, $J = 8.3$, 1H), 5.09 (s, 2H), 4.20 (q, $J = 7.1$, 2H), 3.50 (s, 3H), 1.28 (t, $J = 7.1$, 3H); CIMS (CH_4) 440 (MH^+). Anal. ($C_{21}H_{18}ClN_5O_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-(*N*,*N*-dimethylamino)phenyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (22): 3-dimethylaminophenol; 65%; mp 132−133; ^{1}H NMR 8.46 (d, $J = 2.4$, 1H), 8.19 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.13 (t, $J = 8.4$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.39−6.30 (m, 3H), 5.01 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 2.92 (s, 6H), 1.27 (t, $J = 7.0$ 3H); CIMS (CH_4) 438 (MH^+). Anal. ($C_{23}H_{24}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-methoxyphenyloxy)-methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (23): 3-methoxyphenol; 54%; mp 95−97; ^{1}H NMR 8.46 (d, $J = 2.4$, 1H), 8.18 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.18 (t, $J = 8.1$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.55−6.48 (m, 3H), 5.00 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.78 (m, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 425 (MH^+). Anal. ($C_{22}H_{21}ClN_4O_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-indolyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (24): 4-hydroxyindole; 14%; mp 183−185; ^{1}H NMR 8.55 (d, $J = 2.4$, 1H), 8.24 (d, $J = 2.4$, 1H), 8.19 (br s, 1H), 7.43 (d, $J = 8.3$, 1H), 7.12−7.02 (m, 3H), 7.10 (d, $J = 8.3$, 1H), 6.65 (t, $J = 2.6$, 1H), 6.56 (dd, $J = 7.1$, 1.2, 1H), 5.18 (s, 2H), 4.17 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.28 (t, $J = 7.1$, 3H); CIMS (CH_4) 434 (MH^+). Anal. ($C_{23}H_{20}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(5-indolyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (25): 5-hydroxyindole; 22%; mp 176−178; ^{1}H NMR 8.49 (d, $J = 2.3$, 1H), 8.21 (d, $J = 2.3$, 1H), 7.42 (d, $J = 8.3$, 1H), 7.28 (d, $J = 8.8$, 1H), 7.18 (t, $J = 2.7$, 1H), 7.14 (d, $J = 2.3$, 1H), 7.09 (d, $J = 8.3$, 1H), 6.88 (dd, $J = 8.8$, 2.3, 1H), 6.47 (d, $J = 2.7$,

1H), 5.06 (s, 2H), 4.18 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.27 (t, J = 7.0 3H); CIMS (CH_4) 434 (MH^+). Anal. ($C_{23}H_{20}ClN_5O_2$·0.25 EtOAc) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(3-pyridyloxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (26): 3-hydroxypyridine; 72%; mp 183−184; ^{1}H NMR 8.46 (d, J = 2.3, 1H), 8.37 (br s, 1H), 8.27 (br s, 1H), 8.19 (d, J = 2.3, 1H), 7.44 (d, J = 8.3, 1H), 7.35 (br s, 1H), 7.12 (d, J = 8.3, 1H), 5.09 (s, 2H), 4.19 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 396 (MH^+). Anal. ($C_{20}H_{18}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-pyrimidinylthio)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (40): 6-mercaptopyrimidine; 69%; mp 163−164; ^{1}H NMR 8.51 (d, J = 4.8, 2H), 8.48 (d, J = 2.5, 1H), 8.16 (d, J = 2.5, 1H), 7.40 (d, J = 8.3, 1H), 7.07 (d, J = 8.3, 1H), 6.96 (t, J = 4.8, 1H), 4.32 (s, 2H), 4.13 (q, J = 7.0, 2H), 3.46 (s, 3H), 1.24 (t, J = 7.0, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($C_{19}H_{17}ClN_6OS$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(purin-6-ylthio)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (42): 6-mercaptopurine; 67%; mp 148−151; ^{1}H NMR 8.74 (s, 1H), 8.52 (d, J = 2.5, 1H), 8.21 (d, J = 2.5, 1H), 8.08 (s, 1H), 7.39 (d, J = 8.2, 1H), 7.06 (d, J = 8.2, 1H), 4.59 (s, 2H), 4.13 (q, J = 7.1, 2H), 3.45 (s, 3H), 1.23 (t, J = 7.0, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($C_{20}H_{17}ClN_8OS$·0.25 EtOAc) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylthio)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (43): 3-mercapto-1*H*-pyrazolo[3,4-*d*]-pyrimidine; 75%; mp 128−130; ^{1}H NMR 8.80 (s, 1H), 8.52 (d, J = 2.5, 1H), 8.22 (d, J = 2.5, 1H), 8.06 (s, 1H), 7.40 (d, J = 8.3, 1H), 7.07 (d, J = 8.3, 1H), 4.59 (s, 2H), 4.15 (q, J = 7.0, 2H), 3.47 (s, 3H), 1.24 (t, J = 7.0, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($C_{20}H_{17}ClN_8OS$·0.125DMSO) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylthio)-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (37). A solution of thiophenol (0.16 mL, 1.6 mmol) in DMF (15 mL) was treated with NaH (60 wt %, 62 mg, 1.6 mmol). After 15 min of stirring, compound **XXa** (0.50 g, 1.5 mmol) was added, and the mixture was stirred for an additional 18 h. The excess thiolate was quenched with MeOH, and the mixture was diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organics were dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate) and recrystallization from hexanes/EtOAc to give **37** (0.378 g, 62%): mp 92−93; ^{1}H NMR 8.23 (d, J = 2.4, 1H), 8.04 (d, J = 2.4, 1H), 7.41 (d, J = 8.3, 1H), 7.30−7.18 (m, 5H), 7.08 (d, J = 8.3, 1H), 4.14 (q, J = 7.0, 2H), 4.04 (s, 2H), 3.46 (s, 3H), 1.23 (t, J = 7.0, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($C_{21}H_{19}ClN_4OS$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(pyridinylthio)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (41). By a procedure analogous to that used for the preparation of **37**, and starting from **XXa** and 4-mercaptopyridin, compound **41** was produced in 79% yield: mp 140−142; ^{1}H NMR 8.40 (d, J = 2.5, 1H), 8.38 (d, J = 6.2, 2H), 8.13 (d, J = 2.5, 1H), 7.43 (d, J = 8.2, 1H), 7.11 (d, J = 8.2, 1H), 7.09 (d, J = 6.2, 2H), 4.16 (q, J = 7.0, 2H), 4.16 (s, 2H), 3.48 (s, 3H), 1.26 (t, J = 7.0, 3H); CIMS (CH_4) 412 (MH^+). Anal. ($C_{20}H_{18}ClN_5OS$·0.50H_2O) C, H, N.

Modifications to compounds synthesized by method B: 2-Chloro-5,11-dihydro-11-ethyl-8-(3-(carboxy)phenyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (18). Compound **16** 23 mg, 0.051 mmol) was dissolved in THF (1 mL) and treated with aqueous LiOH (1M, 2 mL, 2 mmol). The reaction was stirred until no starting material was detected by TLC. The mixture was then acidified to pH = 6 with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over Na_2SO_4 and concentrated, and the residue was recrystallized from hexanes/EtOAc to give **18** (15 mg, 67%): mp 181−182; ^{1}H NMR 8.48 (d, J = 2.4, 1H), 8.21 (d, J = 2.4, 1H), 7.72 (br d, J = 7.7, 1H), 7.66 (d, J = 2.5, 1H), 7.44 (d, J = 8.3, 1H), 7.39 (t, J = 7.7, 1H), 7.18 (dd, J = 7.7, 2.5, 1H), 7.11 (d, J = 8.3, 1H), 5.07 (s, 2H), 4.19 (q, J = 7.0, 2H), 3.50 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 439 (MH^+). Anal. ($C_{22}H_{19}ClN_4O_4$) C, H, N.

8-(3-(Aminocarbonyl)phenyloxy)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (19). Compound **16** (33 mg, 0.073 mmol) was dissolved in THF (5 mL) and treated with aqueous LiOH (1.0M, 73 μL, 0.073 mmol). After 16 h the mixture was diluted with saturated aqueous NH_4Cl (15 mL), extracted with EtOAc (2 × 20 mL), dried over Na_2SO_4, and concentrated. The residue was azeotropically dried with benzene (50 mL) and used directly. The residue was dissolved in CH_2Cl_2 (10 mL) and treated with oxalyl chloride (0.063 mL, 0.72 mmol) followed by a catalytic amount of DMF (4 μL). The mixture was stirred for 0.5 h and then concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL), treated with NH_3-(g), and stirred for 5 min more. The mixture was then diluted with EtOAc (15 mL), washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated, and the residue was purified by chromatography (hexanes to EtOAc gradient) to give **19** (25 mg, 79%): mp 96−98; ^{1}H NMR 8.46 (d, J = 2.3, 1H), 8.19 (d, J = 2.3, 1H), 7.45−7.34 (m, 3H), 7.43 (d, J = 8.3, 1H), 7.12−7.09 (m, 1H), 7.11 (d, J = 8.3, 1H), 5.07 (s, 2H), 4.19 (q, J = 6.9, 2H), 3.49 (s, 3H), 1.27 (t, J = 6.9, 3H); CIMS (CH_4) 438 (MH^+). Anal. ($C_{22}H_{20}ClN_5O_3$) C, H, N.

8-(3-Aminophenyloxy)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (20). Compound **21** (80 mg, 0.18 mmol) was dissolved in AcOH (5 mL) and treated with a solution of $SnCl_2$·$2H_2O$ (154 mg, 0.68 mmol) in concentrated HCl (2 mL). After 17 h of stirring, for the resulting mixture was made alkaline with 50% aqueous NaOH and extracted with CH_2Cl_2 (8 × 20 mL). The combined organics were dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography (hexanes to 1:1 hexanes/EtOAc gradient) to give **20** (46 mg, 62%): mp 148−149; ^{1}H NMR 8.44 (d, J = 2.3, 1H), 8.16 (d, J = 2.3, 1H), 7.43 (d, J = 8.3, 1H), 7.10 (d, J = 8.3, 1H), 7.04 (t, J = 8.0, 1H), 6.36−6.25 (d, J = 8.3, 3H), 4.97 (s, 2H), 4.18 (q, J = 7.0, 2H), 3.65 (br s, 2H), 3.48 (s, 3H), 1.27 (t, J = 7.0, 3H); CIMS (CH_4) 410 (MH^+). Anal. ($C_{21}H_{20}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylsulfinyl)-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (38) and 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylsulfonyl)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (39). Compound **37** (70 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (2.5 mL), cooled to 0 °C, and treated with MCPBA (60 wt %, 59 mg, 0.21 mmol). After 1 h the mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$. The organic phase was dried and concentrated, and the resulting residue was purified by preparative TLC to give **38** (8 mg, 11%) and **39** (29 mg, 39%). Data for **38**: mp 96−98; ^{1}H NMR 7.89 (br s, 1H), 7.79 (br s, 1H), 7.48−7.38 (m, 6H), 7.13 (d, J = 8.3, 1H), 4.14 (q, J = 7.0, 2H), 4.26 (ab, $\Delta\upsilon$ = 45, J = 13, 2H), 3.46 (s, 3H), 1.24 (t, J = 7.1, 3H); CIMS (CH_4) 427 (MH^+); HRMS (MH^+, $C_{21}H_{20}ClN_4O_2S$) calcd 427.0995, found 427.1007. Anal. ($C_{21}H_{19}ClN_4O_2S$) C, H; N: calcd, 13.12; found, 12.58. Data for **39**: mp 98−100; ^{1}H NMR 8.05 (d, J = 2.4, 1H), 7.95 (d, J = 2.4, 1H), 7.72−7.63 (m, 2H), 7.53−7.35 (m, 3H), 7.44 (d, J = 8.3, 1H), 7.14 (d, J = 8.3, 1H), 4.26 (s, 2H), 4.16 (q, J = 7.1, 2H), 3.46 (s, 3H), 1.24 (t, J = 7.1, 3H); CIMS (CH_4) 443 (MH^+). Anal. ($C_{21}H_{19}ClN_4O_3S$) C, H, N.

Method C. Synthesis of Compounds XXIV. 5,11-Dihydro-11-ethyl-5-methyl-8-((1-oxo-pyridin-4-yl)oxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (32). Compound **XIXc** (142 mg, 0.499 mmol) was dissolved in THF (5 mL) and was treated with excess KH followed by 4-nitropyridine *N*-oxide (0.105 g, 0.749 mmol). The reaction mixture was stirred for 18 h, then diluted with CH_2Cl_2 (20 mL), and quenched with brine (dropwise). The organic layer was separated, and the aqueous was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by

preparative TLC (10% MeOH/CH_2Cl_2), the resulting white foam was stirred vigorously with petroleum ether for 24 h, and the resulting white solid was collected by filtration to give **32** (115 mg, 61%): mp 218−219; ^{1}H NMR 8.43 (d, J = 2.4, 1H), 8.22 (dd, J = 4.7, 1.6, 1H), 8.16 (d, J = 2.4, 1H), 8.15 (d, J = 7.6, 2H), 7.51 (dd, J = 8.0, 1.6, 1H), 7.13 (dd, J = 8.0, 4.7, 1H), 6.85 (d, J = 7.6, 2H), 5.05 (s, 2H), 4.22 (q, J = 7.1, 2H), 3.52 (s, 3H), 1.28 (t, J = 7.1, 3H); CIMS (CH_4) 378 (MH^+). Anal. ($C_{20}H_{19}N_5O_3$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-5-methyl-8-((1-oxo-4-pyridinyl)oxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (33). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXb** and 4-nitropyridine *N*-oxide, compound **33** was produced in 69% yield: mp 194−196; ^{1}H NMR 8.43 (d, J = 2.4, 1H), 8.16 (d, J = 2.4, 1H), 8.12 (br d, J = 6.9, 2H), 7.59 (dd, J = 8.4, 7.1, 1H), 6.84 (br d, J = 6.9, 2H), 6.74 (dd, J = 8.4, 3.9, 1H), 5.05 (s, 2H), 4.16 (q, J = 7.0, 2H), 3.50 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 380 (MH^+ − O). Anal. ($C_{20}H_{18}FN_5O_3$·0.25H_2O) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((1-oxo-4-pyridinyl)oxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (34). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitropyridine *N*-oxide, compound **34** was produced in 86% yield: mp 208−210; ^{1}H NMR 8.44 (d, J = 2.3, 1H), 8.16 (d, J = 2.3, 1H), 8.15 (d, J = 7.3, 2H), 7.45 (d, J = 8.3, 1H), 7.13 (d, J = 8.3, 1H), 6.85 (d, J = 7.3, 2H), 5.05 (s, 2H), 4.20 (q, J = 7.1, 2H), 3.49 (s, 3H), 1.28 (t, J = 7.1 3H); CIMS (CH_4) 412 (MH^+), 396 (MH^+ − O). Anal. ($C_{20}H_{18}ClN_5O_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((4-(2-methyl-1-oxo-pyridinyl))oxy)methyl-6*H*-dipyrido[3,2-b:2′,3′-*e*]-[1,4]diazepin-6-one (35). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-picoline *N*-oxide, compound **35** was produced in 41% yield: mp 190−192; ^{1}H NMR 8.43 (d, J = 2.4, 1H), 8.16 (br s, 1H), 8.15 (d, J = 2.4, 1H), 7.45 (d, J = 8.3, 1H), 7.13 (d, J = 8.3, 1H), 6.84 (br s, 1H), 6.74 (br s, 1H), 5.03 (s, 2H), 4.20 (q, J = 7.0, 2H), 3.49 (s, 3H), 2.54 (br s, 3H), 1.26 (t, J = 7.0, 3H); CIMS (CH_4) 426 (MH^+); HRMS (MH^+, $C_{21}H_{21}ClN_5O_3$) calcd 426.1328, found 438.1330. Anal. ($C_{21}H_{20}ClN_5O_3$·0.5H_2O) C, H; N: calcd, 16.10; found, 15.21.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((2-trifluoromethyl-1-oxo-pyridin-4-yl)oxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (36). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-trifluoromethylpyridine *N*-oxide, compound **36** was produced in 36% yield: mp 105−108; ^{1}H NMR 8.43 (d, J = 2.4, 1H), 8.20 (d, J = 7.3, 1H), 8.15 (d, J = 2.4, 1H), 7.44 (d, J = 8.3, 1H), 7.25 (d, J = 3.4, 1H), 7.12 (d, J = 8.3, 1H), 7.00 (dd, J = 7.3, 3.4, 1H), 5.08 (s, 2H), 4.19 (q, J = 7.0, 2H), 3.48 (s, 3H), 1.27 (t, J = 7.0, 3H); CIMS (CH_4) 480 (MH^+). Anal. ($C_{21}H_{17}ClF_3N_5O_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-methyl-4-pyridinyloxy)methyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (30). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-picoline, compound **30** was produced in 69% yield: mp 163−164; ^{1}H NMR 8.44 (d, J = 2.4, 1H), 8.32 (d, J = 5.8, 1H), 8.17 (d, J = 2.4, 1H), 7.44 (d, J = 8.3, 2H), 7.12 (d, J = 8.3, 1H), 6.71 (d, J = 2.3, 1H), 6.68 (dd, J = 5.8, 2.3, 1H), 5.05 (s, 2H), 4.19 (q, J = 7.0, 2H), 3.49 (s, 3H), 2.52 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 410 (MH^+). Anal. ($C_{21}H_{20}ClN_5O_2$·0.25H_2O) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-8-(4-pyridinyloxy)ethyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (27). A solution of **32** (72 mg, 0.190 mmol) in $CHCl_3$ (5 mL) was treated with PCl_3 (24 μL, 0.28 mmol). After 3 h of stirring at ambient temperature, the mixture was made alkaline with 15% aqueous NaOH and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by preparative TLC (10% MeOH/CH_2Cl_2) and further purified by precipitation from EtOAc solution with hexanes to give **27** (57 mg, 83%): mp 164−165; ^{1}H NMR 8.44 (br d, J = 2.4, 3H overlaps broad s), 8.21 (dd, J = 4.7, 1.6, 1H), 8.17 (d, J = 2.4, 1H), 7.50 (dd, J = 8.0, 1.6, 1H), 7.12 (dd, J = 7.9, 4.7, 1H), 6.85 (d, J = 6.3, 2H), 5.06 (s, 2H), 4.21 (q, J = 7.0, 2H), 3.52 (s, 3H), 1.27 (t, J = 7.0, 3H); CIMS (CH_4) 362 (MH^+). Anal. ($C_{20}H_{19}N_5O_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-5-methyl-8-(4-pyridinyloxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (28). By a procedure analogous to that used for the preparation of **27**, and starting from **33**, compound **28** was produced in 81% yield: mp 146−148; ^{1}H NMR 8.45−8.44 (m, 3H), 8.18 (d, J = 2.3, 1H), 7.58 (dd, J = 8.5, 7.1, 1H), 6.85 (br d, J = 5.0, 2H), 6.73 (dd, J = 8.5, 3.9, 1H), 5.07 (s, 2H), 4.16 (q, J = 7.0, 2H), 3.50 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 380 (MH^+). Anal. ($C_{20}H_{18}FN_5O_2$·0.25H_2O) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(4-pyridyloxy)methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (29). By a procedure analogous to that used for the preparation of **27**, and starting from **34**, compound **29** was produced in 100% yield: mp 169−170; ^{1}H NMR 8.45 (d, J = 2.5, 1H), 8.45 (br s, 1H), 8.18 (d, J = 2.5, 1H), 7.44 (d, J = 8.3, 1H), 7.12 (d, J = 8.3, 1H), 6.85 (d, J = 6.2, 2H), 5.06 (s, 2H), 4.19 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.27 (t, J = 7.0, 3H); CIMS (CH_4) 396 (MH^+). Anal. ($C_{20}H_{18}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((2-trifluoromethylpyridin-4-yl)oxy)methyl-6*H*-dipyrido-[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (31). By a procedure analogous to that used for the preparation of **27**, and starting from **36**, compound **31** was produced in 67% yield: mp 170−171; ^{1}H NMR 8.55 (d, J = 5.6, 1H), 8.46 (d, J = 2.5, 1H), 8.18 (d, J = 2.5, 1H), 7.45 (d, J = 8.3, 1H), 7.24 (d, J = 2.4, 1H), 7.12 (d, J = 8.3, 1H), 6.99 (dd, J = 5.6, 2.4, 1H), 5.11 (s, 2H), 4.20 (q, J = 7.0, 2H), 3.49 (s, 3H), 1.28 (t, J = 7.0, 3H); CIMS (CH_4) 464 (MH^+). Anal. ($C_{21}H_{17}ClF_3N_5O_2$) C, H, N.

Method D. 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-methyl-*N*-phenyl)carboxamido-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (5). Compound **XIXa** (68 mg, 0.22 mmol) was dissolved in acetone (2.5 mL) and was treated with Jones reagent (2.5M, 174 μL, 0.435 mmol). The reaction mixture was stirred for 10 min. Then, 50% aqueous NaOH (2 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The aqueous phase was then acidified to pH = 5 (1.2 M aqueous HCl), extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4, and concentrated to give crude **XXVI**. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and treated with oxalyl chloride (112 μL, 1.28 mmol) followed by a catalytic amount of DMF (5 μL). After 15 min the solvent and excess oxalyl chloride were removed in vacuo. The acid chloride was redissolved in CH_2Cl_2 (9 mL) and treated with *N*-methylaniline (47 μL, 0.43 mmol). After 15 min of stirring, the reaction mixture was quenched with aqueous NaOH and extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography (1:1 hexanes/EtOAc to EtOAc gradient) followed by recrystallization from hexanes to give **5** (59 mg, 65%): mp 165−167; ^{1}H NMR 8.29 (d, J = 2.1, 1H), 8.05 (d, J = 2.1, 1H), 7.39 (d, J = 8.3, 1H), 7.30−7.06 (m, 6H), 4.11 (q, J = 7.0, 2H), 3.48 (s, 3H), 3.41 (s, 3H), 1.18 (t, J = 7.1, 3H); CIMS (CH_4) 422 (MH^+). Anal. ($C_{22}H_{20}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-benzenecarbonyl-*N*-methylamino-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (6). To a cooled solution of **XVII**[1a] (41 mg, 0.13 mmol) in CH_2Cl_2 and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) was added benzoyl chloride (16 μL, 0.14 mmol). After being warmed to ambient temperature, the mixture was diluted with EtOAc and washed with H_2O. The organics were dried over $MgSO_4$ and concentrated. The residue was dissolved in DMF (2 mL) and treated with NaH (8 mg, 0.17 mmol). After 15 min, MeI (12 μL, 0.19 mmol) was added. The mixture was worked up by quenching with ice and extracting with EtOAc. The organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (EtOAc/Hex) and recrystallization (EtOAc/Hex) to afford **6** (24 mg, 43%): mp 166−169; ^{1}H NMR 8.03 (d,

J = 2.7, 1H), 7.92 (d, J = 2.7, 1H), 7.42 (d, J = 8.2, 1H), 7.33−7.19 (m, 5H), 7.12 (d, J = 8.2, 1H), 4.09 (q, J = 7.0, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 1.19 (t, J = 7.0, 3H); CIMS (CH_4) 422 (MH^+). Anal. ($C_{22}H_{20}ClN_5O_2$) C, H, N.

General Biological Methods. The procedures for the reverse transcriptase wild-type and mutant enzyme, inhibition of HIV-1_{IIIB} replication in C8166 cells, and MTT toxicity assays have appeared elsewhere.[1b,4]

In Vitro Metabolism Assay. Male Sprague−Dawley rats were obtained from either Taconic Farms (Germantown, NY, strain Tac:N(SD)fBR). Human liver was received frozen (−80 °C) from the Department of Pharmacology and Toxicology of the Medical College of Wisconsin (Milwaukee, WI) and was collected according to their protocol from organ donors. The tissue was stored frozen at −80 °C until the microsomes were prepared.

Preparation of Microsomes. Animal and liver weights were recorded. Subsequently, the livers were processed into microsomes using a modification of the method of Guengerich.[18b] Modifications included centrifugation at 145 000*g* at 4 °C for 60 min, rather than 100 000*g* and suspension of the microsomes for storage in 66 mM Tris buffer (pH 7.4, containing 250 mM sucrose and 5.4 mM EDTA). The microsomal suspensions were stored in liquid nitrogen as 1 mL aliquots. Microsomal total protein concentration was determined by the method of Lowry et al.,[18c] using bovine serum albumin as a standard.

Determination of Rates of Metabolism. Metabolism of test compounds was determined by incubating 30 μM of test compound, 1 or 2 mg of microsomal protein (rat and human, respectively), and 2.5 mM NADPH at 37 °C in 66 mM Tris (pH 7.4) for 30 min (1 mL total assay volume). Test compound was added to the incubation mixtures as a methanol solution. Metabolism was initiated by addition of NADPH and terminated by addition of 100 μL of 1 N aqueous NaOH. Test compound and its metabolites were extracted into 5 mL of EtOAc that was subsequently evaporated under a stream of nitrogen at 40 °C. The dried residue was taken up into 200 μL of HPLC mobile phase, 100 μL of which was injected onto the HPLC. The HPLC system consisted of a Hewlett-Packard (Wilmington, DE) 1050 pump, 1050 autoinjector, and 1040A diode-array detector set to monitor UV absorbance between 200 and 400 nm and record a chromatogram at 240 nm. The HPLC column was a Waters (Milford, MA) NovaPac C18 (300 × 3.9 mm) that was maintained at 40 °C in a column oven. The flow rate was 1.0 mL/min with an isocratic mobile phase of 17/83 acetonitrile/0.05 M phosphate buffer (pH 4.6) containing 0.1% triethylamine (v/v). Test compounds and their metabolites were quantitated with calibration curves that were constructed using authentic standards.

In Vivo Rat Metabolism. Five male rats were fasted for 12−16 h prior to oral or intravenous administrations of test compounds. Two animals received test compound via intavenous injection in a 1.0 mg/mL solution (30% DMA, 0.9% NaCl in H_2O) at 1.0 mg/kg. Three animals received test compounds by gavage as 0.5 mg/mL suspensions (0.5% Methocel, 0.3% Tween 80) at 5 mg/kg. Blood samples were obtained from interdwelling jugular cannulas at 0.08 (iv treatment only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 h after dosing. Plasma was recovered and frozen (−20 °C) until analysis.

Assay Procedure. Plasma samples (400 μL) were alkalinized with 50 μL of 3.3 N NaOH and were shaken for 20 min with 5 mL of EtOAc. The EtOAc extracts were transferred to 16 × 100 mm glass tubes and evaporated to dryness under N_2 at 45 °C. The residues were dissolved in 200 μL of 40 mM KH_2PO_4, pH 4.5:AcCN (68:32) and centrifuged at 14 000*g*. Aliquots (100 μL) of the supernatants were injected onto the following HPLC system: column, C_{18} MetaChem Intersil 5 μ cm, 4.6 × 150 mm; mobile phase, 40 mM KH_2PO_4, pH 4.5: AcCN (68:32); flow rate, 1.2 mL/min; column temp, 40 °C; detector, UV set to monitor 236 nm. Test compounds and their metabolites were quantitated with calibration curves that were constructed using authentic standards.

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