Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 7. 8-Arylethyldipyridodiazepinones as Potent Broad-Spectrum Inhibitors of Wild-Type and Mutant Enzymes

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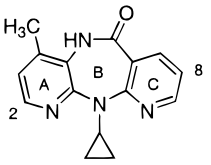
Like other nonnucleoside inhibitors of HIV-1 reverse transcriptase, the dipyridodiazepinone nevirapine (Viramune, **1**) selects for drug resistant variants of HIV-1, both in cell culture and in patients. In particular, the mutation of residue 181 from tyrosine to cysteine (Y181C) is associated with resistance to most reported nonnucleoside inhibitors. Introduction of an arylethyl substituent at the 8-position of the tricyclic dipyridodiazepinone skeleton confers enhanced potency against Y181C RT. Several analogues of this series display good broad spectrum potency against a panel of mutant enzymes.

Introduction

In the quest for effective therapies for treatment of human immunodeficiency virus (HIV) infection, demonstrated clinical benefit has now been achieved with drugs that target the viral protease[1] or reverse transcriptase[2] enzymes. As monotherapies, however, currently available agents provide only transient benefit, due to the rapid emergence of drug-resistant viral strains.[3] Combinations of drugs have been tried in an attempt to avoid the problem of resistance, with some promising results,[4,5] and combination therapy now represents the standard of care. However, there is a continuing need to identify improved agents within each class in order to provide the optimum clinical benefit.

Among reverse transcriptase inhibitors that have undergone clinical development, the majority are nucleoside analogues. However, a number of structurally diverse nonnucleoside reverse transcriptase (RT) inhibitors have also been reported, all of which are characterized by specificity for HIV-1. The dipyridodiazepinone nevirapine[6] (Viramune, **1**) is the first such nonnucleoside RT inhibitor to achieve regulatory approval. Like the other nonnucleoside RT inhibitors, nevirapine selects for drug resistant variants of HIV-1, both in cell culture and in patients. In particular, the mutation of residue 181 from tyrosine to cysteine (Y181C) is associated with resistance to nevirapine[7] and to most reported nonnucleoside inhibitors.[8] Other mutations associated with resistance to nevirapine include K103N, V106A, G190A, and Y188L.

Our primary goal in the design of second generation RT inhibitors, therefore, was to achieve broad-spectrum inhibitory activity against a variety of mutated, yet enzymatically competent, viruses. As revealed by crystallographic studies,[9] the nonnucleoside RT inhibitors bind at an allosteric site adjacent to the active site of the enzyme. Many of the residues surrounding this binding pocket are highly variable, including many of those identified in connection with nonnucleoside drug resistance. However, also located in this same region are a number of other residues that are more highly conserved, including in particular the catalytic aspartic acid residues (Asp110, Asp185, Asp186). Mutation of these residues results in inactive RT enzymes.[10] The side chains of several of these conserved residues face nevirapine, suggesting that binding interactions with these residues might be possible, given appropriate substitution on the tricyclic skeleton. In addition, by achieving multiple interactions with the enzyme, we hoped both to enhance potency and to lessen the impact of mutation at any given residue.



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Successful application of this approach has already been reported for compounds in the 2-aryldipyridodiazepinone series.[11] We now report that dipyridodiazepinone analogues bearing arylalkyl substituents at the 8-position of the tricyclic nucleus exhibit good potency against both wild-type and mutant HIV-1 reverse transcriptase enzymes. In the following paper,[12] we report that 8-aryloxymethyl and 8-arylthiomethyl dipyridodiazepinones are also potent broad spectrum inhibitors of wild-type and mutant enzymes.

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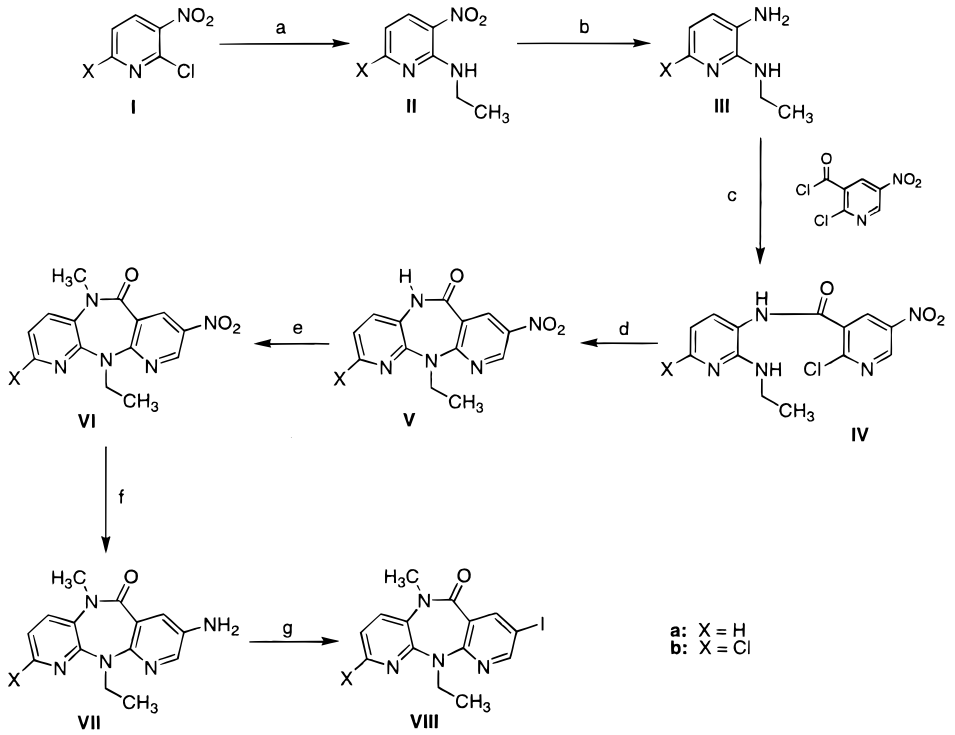
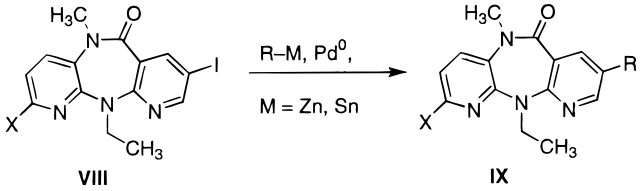
Scheme 1[a]



[a] (a) Et_2NH, xylenes, 105 °C; (b) $SnCl_2 \cdot 2H_2O$, HOAc, HCl; (c) DIEA, THF; (d) xylenes, 140 °C; (e) NaH, MeI, DMF; (f) $SnCl_2 \cdot 2H_2O$, HOAc, HCl; (g) $NaNO_2$, NaI.

Scheme 2



Chemistry

The synthesis of 8-iodo dipyridodiazepinones **VIIIa** and **VIIIb** is illustrated in Scheme 1. These compounds served as precursors for the majority of compounds reported here, with the 8-iodo substituent offering a versatile handle for introduction of a variety of groups at this position. In some of the chemistry that follows, the 8-bromo derivative corresponding to **VIIIb** was used in its place, with similar results. The synthesis of this compound is reported in the following paper.

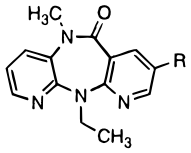
Stille[13] methodology was first explored (Scheme 2, method A); in the presence of Pd^0, **VIIIa** coupled efficiently both with allyltributylstannane and with vinyltributylstannane. Subsequent functional group transformations then provided analogues **7**−**10** (Table 1). The 8-benzyl analogue **15** and 8-anisyl derivative **16** were also prepared by Stille coupling, but in those cases, dimerization of the dipyridodiazepinone represented the predominant reaction pathway. Coupling reactions of **VIIIa** with organozinc reagents[14] were also briefly explored, with the phenylpropyl analogue **18** being synthesized by this method.

Despite its successful application in the synthesis of 8-allyl and 8-vinyl analogues, the Stille approach suffers the limitation that all but the simplest stannanes must be prepared in a separate step. With the discovery that 8-substituents attached to the tricyclic nucleus by means of a two-carbon tether provided good activity (vide infra), the Heck reaction[15] appeared to offer an especially convenient alternative (Scheme 3, method B). Indeed, coupling of methyl acrylate or acrylamide with compound **VIIIa** ($Cl_2Pd(PPh_3)_4$, Et_3N, DMF, 100 °C) proceeded smoothly to afford the corresponding 8-substituted dipyridodiazepinones in 70% and 90% yields, respectively. A variety of vinylaromatic compounds also served as suitable coupling partners. Although dimerization was in some cases a troubling side reaction, the *trans*-olefin **XI** was the only geometrical isomer or regioisomer observed in any of these reactions. Hydrogenation then afforded the saturated analogues **XII**.

Surprisingly, many of the olefinic compounds **XI** proved remarkably resistant to standard hydrogenation conditions. For example, elevated temperatures and pressures and extended reaction times (150 psi, 60 °C, 48 h) were required in order to achieve reduction of the (4-pyridyl)ethenyl side chain. Such forcing conditions were obviously unsuitable for the synthesis of 8-arylethyldipyridodiazepinones bearing a 2-chloro substituent. The use of platinum catalysts in an attempt to minimize hydrogenolysis of the 2-chloro substituent served instead to retard hydrogenation of the side chain.

Ultimately, transfer hydrogenation[16] provided a solution to this problem and significantly simplified isolation and purification of the product. Sodium hypophosphite was employed as hydrogen donor, on the basis of literature reports that its use minimizes hydrogenolysis of aryl chlorides.[17] In fact, at reaction temperatures of 70−80 °C, selective reduction of the olefin was achieved, and **37** was isolated in 75% yield. However, rapid

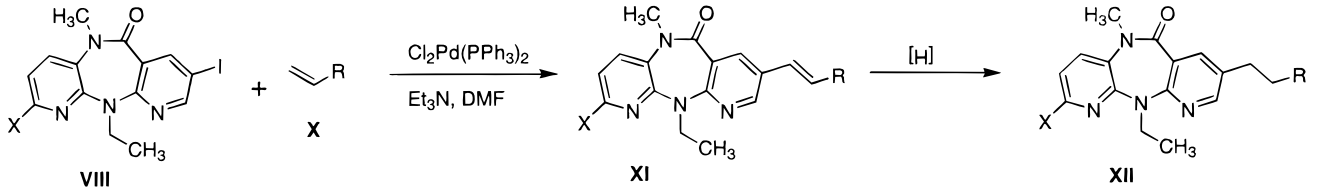
Table 1. Inhibition of HIV-1 Wild-Type RT and HIV-1 Y181C RT by 8-Substituted Dipyridodiazepinones



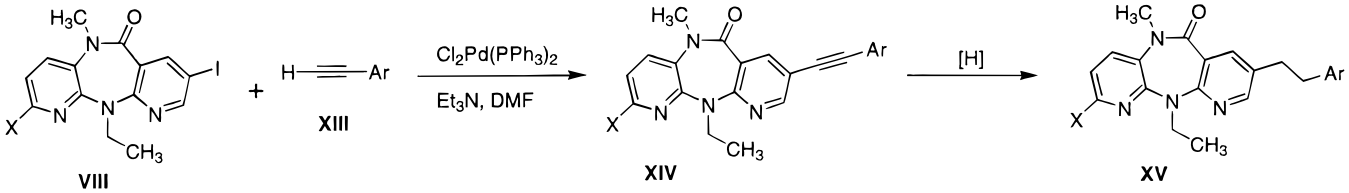
						IC$_{50}$ (μM)	
no.	R	method	mp (°C)	recryst solvent	formula	WT RT	Y181C RT
2	H	ref 6b	130−132	EtOAc/hexanes	$C_{14}H_{14}N_4O$	0.09	NT
3	CH_3	NA[a]	95−95.5	triturated with petroleum ether	$C_{15}H_{16}N_4O$	0.75	>>1
4	Cl	ref 6b	105−106	hexanes	$C_{14}H_{13}ClN_4O$	0.54	>>1
5	NH_2	NA[a]	193−194	1,2-dichloroethane/hexanes	$C_{14}H_{15}N_5O{\cdot}0.4H_2O$	0.10	NT
6	$NHC(O)NH_2$	NA[b]	235−237	MeOH/ether	$C_{15}H_{16}N_6O_2$	1.1	NT
7	CO_2H	A[c]	148−250	EtOH/ether	$C_{15}H_{14}N_4O_3$	>>1	NT
8	CH_2OH	A[d]	129−131	ether/petroleum ether	$C_{15}H_{16}N_4O_2$	0.05	0.74
9	$(CH_2)_2OH$	A[e]	114−115	ether/petroleum ether	$C_{16}H_{18}N_4O_2$	0.43	2.50
10	$(CH_2)_3OH$	A[f]	109−111	ether	$C_{17}H_{20}N_4O_2$	0.30	2.90
11	$(CH_2)_2CN$	B	157	EtOAc/hexanes	$C_{17}H_{17}N_5O$	0.21	2.16
12	$(CH_2)_2CONH_2$	B	177−179	EtOAc/hexanes	$C_{17}H_{19}N_5O_2$	0.62	6.1
13	$(CH_2)_2CO_2Me$	B	98−99	EtOAc/hexanes	$C_{18}H_{20}N_4O_3$	0.09	0.14
14	*trans*-CH=CHCO$_2$Me	B	183−185	EtOAc/hexanes	$C_{18}H_{18}N_4O_3$	>>1	NT
15	CH_2Ph	A	oil	ether/petroleum ether	$C_{21}H_{21}N_4O$	0.12	1.20
16	(3-OMe)Ph	A	127−129	ether/petroleum ether	$C_{21}H_{20}N_4O_2$	>>1	>>1
17	$(CH_2)_2Ph$	B	129−131	EtOAc/hexanes	$C_{22}H_{22}N_4O$	0.05	0.13
18	$(CH_2)_3Ph$	A	100−102	EtOAc/hexanes	$C_{23}H_{24}N_4O$	0.12	1.17
19	*cis*-CH=CHPh	C	oil	ether/petroleum ether	$C_{22}H_{20}N_4O$	0.25	0.58
20	*trans*-CH=CH(4-pyr)	B	151−153	EtOAc/hexanes	$C_{21}H_{19}N_5O{\cdot}0.5H_2O$	3.0	>1

[a] Prepared by methods analogous to those described in ref 6b. [b] Prepared from **5** (KCNO, HOAc/H_2O). [c] prepared by coupling **VIIIa** with (*n*-Bu)$_3$Sn(CH=CH$_2$) to produce the 8-vinyl derivative followed by oxidative cleavage ($RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O). [d] Prepared from **7** [(i) $ClCO_2Et$, TEA, THF; (ii) $NaBH_4$, H_2O]. [e] Prepared by hydroboration/oxidation of the 8-vinyl derivative. [f] Prepared by coupling **VIIIa** with (*n*-Bu)$_3$Sn($CH_2CH=CH_2$) to produce the 8-allyl derivative followed by hydroboration/oxidation.

Scheme 3



Scheme 4



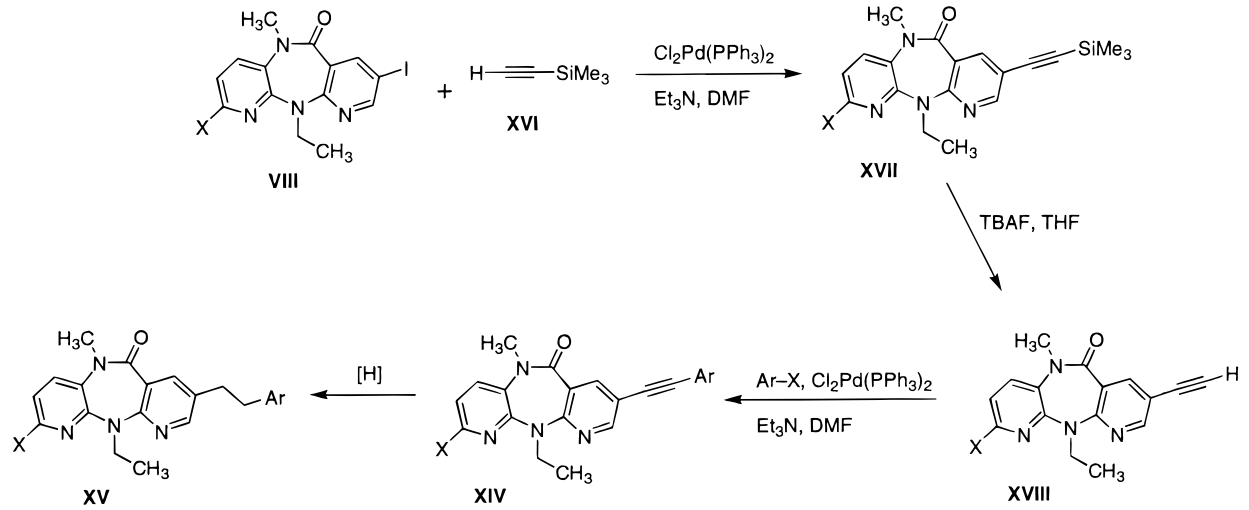
hydrogenolysis of the 2-chloro substituent was observed when the temperature was allowed to climb above 85−90 °C.

The 2-fluoro analogues **39** and **42** were prepared analogously to method B, by Heck reaction of the 2-fluoro-8-bromo precursor[12] with the corresponding vinylaromatics. Other compounds with varied substituents at the 2-position were prepared from the corresponding 2-chloro analogues. Compound **37** was converted to the 2-iodo derivative **40**, via the 2-trimethylstannane intermediate, by reaction with hexamethylditin under palladium catalysis, followed by treatment with iodine. The preparation of 2-cyano derivative **38** was accomplished by treatment of **37** with sodium cyanide impregnated silica gel under palladium catalysis.[18] Coupling of **36** with *N*-Boc-pyrrole ($(Ph_3P)_4Pd$, KOAc, DMF),[19] afforded 2-pyrrolyl analogue **35**.

Arylacetylenes were also employed as coupling partners in reactions with **VIII** (Scheme 4, method C). The reaction conditions ($Cl_2Pd(PPh_3)_2$, Et_3N, DMF, 100 °C) used for reactions of vinylaromatics were suitable also for arylacetylenes, and yields were generally high. This route offered the advantage that hydrogenation of the acetylenes **XIV** appeared to proceed more smoothly than did hydrogenation of the corresponding olefins **XI**. Preparation of *cis*-olefin **19** was achieved by Lindlar reduction of the corresponding acetylene, itself prepared in 80% yield according to method C (Ar = phenyl).

As an alternative to methods B and C, the nature of the coupling reaction was reversed, with the dipyridodiazepinone serving as the acetylene partner (Scheme 5, method D). Synthesis of the requisite 8-ethynyldipyridodiazepinones **XVIII** was accomplished in two steps by coupling 8-iodo derivatives **VIII** with trimethylsilylacetylene, followed by fluoride-induced cleavage of the silyl group. With compounds **XVIII** in hand, the scope

Scheme 5



of compounds **XV** accessible by this methodology was greatly expanded, due to the wide variety of commercially available aryl halides. Coupling reactions and hydrogenation proceeded analogously to methods B and C.

According to method D, compound **XVIII** was coupled with 4-bromo-2-picoline *N*-oxide to produce the acetylene in 95% yield. *N*-Oxide rearrangement (Ac_2O, 105 °C),[20] followed by hydrogenation (Pd, NaH_2PO_2, 1,4-dioxane, 80−90 °C), then afforded compound **53**. In a similar fashion, coupling of **XVIII** with 4-bromo-2-picolinic acid[21] and hydrogenation of the resultant acetylene afforded the acid **57**. Curtius rearrangement ($(PhO)_2P(O)N_3$, Et_3N, *t*-BuOH) of **57** produced **56**, while esterification and aminolysis provided compounds **54**−**55**.

Biological Results

At the outset of the project, available SAR at the 8-position was not promising, with most simple substituents at this position leading to a decrease in potency (Table 1, **3**−**5**). Compounds bearing an 8-amino substituent (e.g., **5**) provided a notable exception to this trend, being roughly equipotent to the corresponding unsubstituted compounds. Interestingly, comparably positioned amino substituents were found to enhance potency in related series of tricyclic oxazepinones.[22] These data offered some hope that polar functionalities, such as those intended to interact with the conserved aspartate residues, might be tolerated at this position. In fact, the 8-hydroxymethyl analogue **8** was found to exhibit enhanced activity against the wild-type enzyme, as well as submicromolar potency against the Y181C mutant enzyme.

Esters, amides, nitriles and alcohols were all examined in the attempt to achieve electrostatic or hydrogen bonding interactions with D185 or D186. Ester **13** represented a significant breakthrough, exhibiting good potency against both wild-type and Y181C mutant enzymes. By contrast, compound **14**, in which the ester is connected to the tricyclic core by means of a *trans*-olefin linker, is almost completely inactive. Concerned that the ester moiety in **13** might prove metabolically unstable, we replaced it with a phenyl substituent. The resultant analogue, **17**, displayed an inhibitory profile virtually identical to that of the ester **13**, and further efforts focused exclusively on the 8-arylalkyl series.

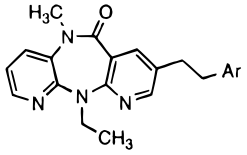
Variations in the connecting chain (**15**−**18**) revealed that a two-carbon linker is optimum for 8-arylalkyl substituents, although a one-carbon linker is preferred in the 8-hydroxyalkyl series. As noted above, *trans*-unsaturation in the linking chain virtually abolishes activity (e.g., **20**). However, significant potency is retained by compounds with *cis*-olefinic linkers (e.g., **19**), and *cis*-epoxides are also active (data not shown). This suggests that the 8-arylalkyl side chain is bent in the bioactive conformation of the inhibitor. A variety of aromatic substituents were examined in place of the phenyl group, with largely consistent results (Table 2). However, ortho substitution on the aromatic ring is not well tolerated by the Y181C mutant enzyme (e.g., **28**, **33**).

Substitution at the 2-position of the dipyridodiazepinone nucleus was previously shown to confer potency against the Y181C mutant enzyme.[11] It was therefore of some interest to determine if the effects of 2- and 8-substitution might be additive. In the event, the 2-pyrrolyl-8-phenethyl derivative **35** was found to suffer a 10-fold reduction in potency as compared to the corresponding compounds bearing either substituent alone. Surprisingly, however, this compound exhibited measurable activity against the highly refractory Y188L mutant enzyme. Encouragingly, 2-chloro-8-phenethyl disubstitution (**36**) also afforded inhibition of the Y188L mutant enzyme, while at the same time retaining potency against both the wild-type and the Y181C mutant enzymes.

Compounds bearing 2-fluoro or 2-iodo substituents, as exemplified by compounds **39** and **40**, also exhibited good potencies against wild-type and mutant enzymes. However, the 2-cyano derivative **38** displayed a marked decrease in potency against all three enzymes. Hydroxy and amino substituents at the 2-position also led to decreased activity (data not shown).

In general, 2-chloro derivatives and the corresponding 2-unsubstituted analogues are roughly equipotent against wild-type enzyme (compare, for example, compounds **17** and **36** or **21** and **37**). A notable exception to this trend is compound **41**, which is 10-fold less active than **30**. Apparently, in this case, the steric requirements of the

Table 2. Inhibition of HIV-1 Wild-Type RT, HIV-1 Y181C RT, and HIV-1 Y188L RT by 8-Arylethyl Dipyridodiazepinones



						IC_{50} (μM)		
no.	Ar	method	mp (°C)	recryst solvent	formula	WT RT	Y181C RT	Y188L
17	phenyl	C	129−131	EtOAc/hexanes	$C_{22}H_{22}N_4O$	0.05	0.13	>>1
21	4-pyridyl	B	109−110	EtOAc/hexanes	$C_{21}H_{21}N_5O$	0.03	0.11	>>1
22	3-pyridyl	D	79−80	ether/petroleum ether	$C_{21}H_{21}N_5O$	0.13	0.32	>>1
23	2-pyridyl	C	68−72	EtOAc/hexanes	$C_{21}H_{21}N_5O{\cdot}0.25H_2O$	0.19	>1	>>1
24	5-pyrimidyl	D	142−143	EtOAc/hexanes	$C_{20}H_{20}N_6O$	0.54	>1	>>1
25	2-thiazolyl	D	oil		$C_{19}H_{19}N_5OS$[a,b]	0.04	0.44	>>1
26	4-tolyl	C	120−122	EtOAc/petroleum ether	$C_{23}H_{23}N_4O$	0.10	0.25	>1
27	3-tolyl	B	103−104	EtOAc/ether/petroleum ether	$C_{23}H_{24}N_4O$	0.11	0.28	>>1
28	2-tolyl	D	151−152	EtOAc/hexanes	$C_{23}H_{24}N_4O$	0.20	1.6	>1
29	4-(2-picolyl)	D	128−129	ether/petroleum ether	$C_{22}H_{23}N_5O{\cdot}0.25H_2O$	0.03	0.09	>>1
30	2-naphthyl	B	136−137	EtOAc/hexanes	$C_{26}H_{24}N_4O$	0.08	0.15	>>1
31	4-anilinyl	B	157−158	EtOH/hexanes	$C_{22}H_{23}N_5O$	0.06	0.20	>>1
32	3-anilinyl	B	129−130	EtOAc/hexanes	$C_{22}H_{23}N_5O$	0.04	0.07	>1
33	2-anilinyl	D	157−158	EtOH/hexanes	$C_{22}H_{23}N_5O$	0.08	1.7	>1
34	3-fluorophenyl	B	130−131	EtOAc/hexanes	$C_{22}H_{21}N_4F$	0.12	0.37	>>1

[a] C: calcd, 62.45; found 63.07. [b] N: calcd, 19.16; found, 16.69.

naphthylethyl side chain are such that the 2-chloro substituent cannot be simultaneously accommodated by the enzyme. Replacement of the 2-chloro group with a smaller fluoro substituent (**42**) achieves the desired increase in potency against mutant enzymes while at the same time also maintaining potency against the wild-type enzyme.

Limited exploration was made of SAR in the side chain aromatic group. As already noted, ortho substitution is not well tolerated by the Y181C mutant, and in combination with a 2-chloro substituent the 8-(2-tolyl)-ethyl substituent (e.g., **45**) abolishes activity against wild-type enzyme as well. By contrast, substitution at the position meta to the point of attachment is well tolerated. An amino group at this position is particularly favorable, especially for activity against the Y188L mutant enzyme. Indeed, compounds **47** and **56** are among the most potent analogues reported here against all three enzymes of our primary assay.

Secondary Assays

Selected compounds active in the primary assay were tested for their ability to inhibit syncytia formation in cell cultures infected with wild-type HIV-1_{IIIB} virus (Table 4). Consistent with the enzyme inhibitory potency of this series of compounds, all compounds tested were also effective antiviral agents in culture. An MTT assay was conducted as a measure of the cytotoxic effects of the compounds. In general, the 8-substituted dipyridodiazepinone series is characterized by relatively low cytotoxicity, and most compounds reported here displayed CC_{30} values above 60 μM (data not shown).

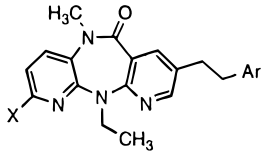
Ironically, although the Y181C mutation confers cross-resistance to many nonnucleoside inhibitors of varied chemical structure, it has proven relatively easy to identify dipyridodiazepinone analogues, including the 8-arylethyl derivatives reported here, with good potency against Y181C RT. By contrast, as is evident from the results presented in Table 1, the Y188L mutation represents a significantly greater challenge. This mutation is not typically observed in cell culture or in patients undergoing monotherapy with nevirapine, but it does appear in patients being treated with both nevirapine and AZT. The good activity exhibited by compounds such as **39**, **47**, and **56** against this mutant was therefore very encouraging.

Having optimized the 8-arylethyldipyridodiazepinones for potency against wild-type, Y181C, and Y188L RT enzymes, however, we fully appreciated that alternative mutations might arise equally readily and result in resistance to these new agents. Selected compounds were therefore tested against an expanded panel of mutant RT enzymes (Table 5). Represented in this panel were mutations associated with resistance to BHAP derivatives including delavirdine (P236L)[23] and to the pyridinones (K103N),[24] as well as additional mutations associated with resistance to nevirapine (V106A, G190A). The enzymes of this panel were also selected to be representative of possible mutations in various regions of the nonnucleoside binding pocket.

All compounds tested potently inhibited the K103N and G190A mutant enzymes. Structural analysis of binding interactions between nevirapine and HIV-1 RT[25] suggested that mutations at Gly 190 confer resistance to the inhibitor due to repulsive steric interaction between the amino acid side chain and the cyclopropyl ring of nevirapine. This negative interaction and therefore resistance are less profound for compounds, such as those reported here, with an *N*-ethyl substituent in place of the cyclopropyl ring. Interactions of the dipyridodiazepinones with Lys 103, which points toward the C-ring nitrogen atom, are more complex. Although conferring modest resistance to nevirapine, mutation of this residue has little impact on sensitivity to many dipyridodiazepinones.

The 8-phenethyl analogue **36** exhibits a 10-fold reduction in potency against the P236L mutant enzyme as compared to wild-type enzyme. This finding is noteworthy, since the P236L mutation, although conferring resistance to BHAP derivatives, generally has no effect on enzyme sensitivity to inhibition by dipyridodiazepinones. The data are consistent with crystallographic

Table 3. Inhibition of HIV-1 Wild-Type RT, HIV-1 Y181C RT, and HIV-1 Y188L RT by 2,8-Disubstituted Dipyridodiazepinones



							IC_{50} (μM)		
no.	X	Ar	method	mp (°C)	recryst solvent	formula	WT RT	Y181C RT	Y188L RT
17	H	phenyl	C	129−131	EtOAc/hexanes	$C_{22}H_{22}N_4O$	0.05	0.13	>>1
35	2-pyrrolyl	phenyl	C[a]	82−84	ether	$C_{26}H_{25}N_5O$	0.59	0.52	1.28
36	Cl	phenyl	C	128−129.5	EtOAc/hexanes	$C_{22}H_{21}ClN_4O$	0.05	0.15	0.96
37	Cl	4-pyridyl	B	152−153	EtOAc/hexanes	$C_{21}H_{20}ClN_5O$	0.08	0.12	1.85
38	CN	4-pyridyl	B[b]	149−150	EtOAc/hexanes	$C_{22}H_{20}N_6O$	0.46	0.29	>>1
39	F	4-pyridyl	B	109−111	ether/petroleum ether	$C_{21}H_{20}FN_5O$	0.05	0.08	0.25
40	I	4-pyridyl	B[b]	174	EtOAc/hexanes	$C_{21}H_{20}IN_5O{\cdot}0.25H_2O$	0.09	0.18	0.43
41	Cl	2-naphthyl	B	115−117	ether/hexanes	$C_{26}H_{23}ClN_4O$	1.02	2.88	>>1
42	F	2-naphthyl	B	112−114	EtOAc/hexanes	$C_{26}H_{23}FN_4O$	0.02	0.03	>1
43	Cl	4-tolyl	D	120−122	EtOAc/hexanes	$C_{23}H_{23}ClN_4O{\cdot}0.25H_2O$	0.23	1.18	>>1
44	Cl	3-tolyl	D	100−102	ether/petroleum ether	$C_{23}H_{23}ClN_4O$	0.11	0.46	>1
45	Cl	2-tolyl	D	180−182	EtOAc/hexanes	$C_{23}H_{23}ClN_4O$	>>1	>>1	>>1
46	Cl	4-anilinyl	B	191−192	EtOH/hexanes	$C_{22}H_{22}ClN_5O$	0.16	0.36	>>1
47	Cl	3-anilinyl	B	121−123	EtOH/petroleum ether	$C_{22}H_{22}ClN_5O$	0.12	0.23	0.25
48	Cl	3-ureidophenyl	B[c]	121−123	EtOAc/petroleum ether	$C_{23}H_{23}ClN_6O_2{\cdot}0.2H_2O$	0.06	0.08	0.23
49	Cl	4-(methylsulfonamido)phenyl	B[d]	199−204	EtOH/hexanes	$C_{23}H_{24}ClN_5O_3S{\cdot}0.25H_2O$	0.33	0.56	>1
50	Cl	3-(methylsulfonamido)phenyl	B[e]	131−132	EtOAc/hexanes	$C_{23}H_{24}ClN_5O_3S$	0.14	0.14	>1
51	Cl	3-azidophenyl	B[f]	104−105	ether/petroleum ether	$C_{22}H_{20}ClN_7O$	0.08	0.16	>1
52	Cl	4-(2-picolyl)	D	94−96	ether/petroleum ether	$C_{22}H_{22}N_5OCl{\cdot}0.5H_2O$	0.06	0.14	>>1
53	Cl	4-(2-hydroxymethylpyridyl)	D	133−134.5	ether/petroleum ether	$C_{22}H_{22}N_5O_2Cl$	0.16	0.28	>>1
54	Cl	4-(2-carbomethoxypyridyl)	D	149	EtOAC/ether	$C_{23}H_{22}N_5O_3Cl{\cdot}0.25H_2O$	0.15	0.48	6.0
55	Cl	4-(2-amidopyridyl)	D	145−147	EtOAc/hexanes	$C_{22}H_{21}N_6O_2Cl{\cdot}0.25EtOAc$	0.05	0.25	4.0
56	Cl	4-(2-aminopyridyl)	D	95 dec	ether/petroleum ether	$C_{21}H_{21}N_6OCl$	0.02	0.07	0.16
57	Cl	4-(2-carboxypyridyl)	D	244−246	CH_2Cl_2/hexanes	$C_{22}H_{20}N_5O_3Cl$[g]	1.5	3.8	>>1

[a] Prepared from **36**; see Experimental Section. [b] Prepared from **37**; see Experimental Section. [c] Prepared from **47** (KCNO, HOAc/H_2O). [d] Prepared from **46** (MsCl, pyr, CH_2Cl_2). [e] Prepared from **47** (MsCl, pyr, CH_2Cl_2). [f] Prepared from **47** ($NaNO_2$, NaN_3). [g] C: calcd, 60.34; found, 59.66. N: calcd, 16.00; found, 14.79.

Table 4. Inhibition of HIV-1_{IIIB} Replication in C8166 Cells

no.	IC_{50} (nM)[a]
21	25
36	12
37	9
48	39

[a] Inhibitory concentration of compound producing a 50% reductions in the centers of syncytia. See ref 6a.

Table 5. Inhibition of HIV-1 Mutant RT Enzymes

	IC_{50} (μM)			
no.	K103N	V106A	G190A	P236L
1	1.9			0.08
36	0.05	0.84	0.12	0.71
37	0.12	0.55	0.03	0.11
39	0.02	0.25	0.06	0.05
47	0.01	0.09	0.01	0.04
56	0.01	0.19	0.03	0.10

information showing the 8-position of nevirapine to be pointed toward Pro 236 and provide additional confirmation that nonnucleoside inhibitors of diverse chemical structures occupy overlapping regions of the same binding pocket. Note, however, that the 8-pyridylethyl analogue **37** shows little loss in potency against P236L RT. The reasons for the different resistance profiles of **36** and **37** are not clear.

Consistent with their potency against enzymes of the primary assay, compounds **39**, **47**, and **56** exhibit good potency against the entire panel of mutant enzymes. For all three compounds, as well as for compounds **36** and **37**, inhibitory potency is weakest against the V106A mutant. After the Y181C mutation, a valine to alanine mutation at codon 106 is the most commonly identified mutation in viral strains resistant to dipyridodiazepinone inhibitors. Indeed, viral selection in the presence of **37** resulted in emergence of the V106A mutant.[26]

Compounds **36, 37, 39,** and **47** were additionally evaluated for in vitro metabolic stability in human liver microsomes.[27] In comparison to nevirapine (**1**), which exhibits a very slow rate of metabolism (2 (pmol/min)/mg of microsomal protein) in this assay, compound **36** was rapidly metabolized (266 (pmol/min)/mg). Compounds **37, 39**, and **47** were all metabolized at a rate of approximately 145 (pmol/min)/mg. Metabolites of these compounds were found to be oxidized at both ring and benzylic positions of the 8-arylethyl substituent (data not shown).

Conclusions

Introduction of an arylethyl substituent at the 8-position of the tricyclic dipyridodiazepinone skeleton confers enhanced potency against Y181C RT, and several analogues of this series with good broad spectrum potency against a panel of mutant enzymes were identified. The factors responsible for the improved inhibitory profile of these compounds remain to be elucidated. The fact that dramatic enhancements in potency against wild-type enzyme were not observed suggests that one set of binding interactions has been substituted for another. Inspection of the crystal structure of HIV-1 RT reveals the presence of a number of aromatic amino acid residues in the nonnucleoside binding pocket that appear to be within reach of the 8-arylethyl substituent, including Phe 227, Trp 229, and Tyr 232. Favorable

interactions between the side chain aryl substituent of the inhibitor with these aromatic residues may contribute to binding affinity and diminish the importance of interactions with residues such as Tyr 181. It should be noted that Trp 229 in particular is highly conserved, and mutation of this residue to alanine results in a substantial decrease in RT activity.[28] The analogues reported here may therefore accomplish our goal of achieving binding interactions with conserved residues at the expense of interactions with more variable residues. Whether this will result in prolonged efficacy remains to be determined. Unfortunately, in vivo studies with the compounds reported here are likely to be hindered by their rapid metabolism and poor bioavailability. The design of broad-spectrum inhibitors with improved metabolic stability is described in the following paper.

Experimental Section

General. The procedures for the reverse transcriptase wild-type and mutant enzyme, inhibition of HIV-1_{IIIB} replication in C8166 cells, the in vitro metabolism, and MTT toxicity assays have appeared elsewhere.[6a,11b,12] Short-path chromatography was performed with EM-Science silica gel 60 (finer than 230 mesh). Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) spectrometer with Me_4Si as the internal standard. Mass spectra were recorded on a Finnegan 4023 GC/MS/DS spectrometer. Elemental analyses were determined by Midwest Laboratories, Indianapolis, IN, and are within 0.4% of theoretical values unless otherwise noted.

5,11-Dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (VIIIa). (a) 2-Ethylamino-3-nitropyridine. A stirred mixture of 2-chloro-3-nitropyridine (50.0 g, 0.32 mol), ethylamine (33.5 g, 0.74 mol), and xylenes (85 mL) was heated at 105 °C in a sealed vessel for 3 h. After cooling, the solvent was removed in vacuo, and water was added to the residue. The product was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo to give 56.8 g of the title compound as a brown oil, suitable for use in the next reaction: ^{1}H NMR (DMSO-d_6) δ 8.46 (m, 2 H), 8.38 (dd, J = 1, 8 Hz, 1 H), 8.72 (dd, J = 4, 8 Hz, 1 H), 3.58 (dq, J = 7, 7 Hz, 2 H), 8.18 (t, J = 7 Hz, 3 H); MS (CI) m/z 168 (MH^+).

(b) 3-Amino-2-ethylaminopyridine. A solution of 160 g (1.05 mol) of $SnCl_2 \cdot H_2O$ in 200 mL of concentrated HCl was added to 2-ethylamino-3-nitropyridine (52.7 g, 0.32 mol) in 650 mL of AcOH, and the resultant mixture was stirred overnight at room temperature. The white precipitate was collected and washed with AcOH. The collected solid was dissolved in 300 mL of water, and the mixture was basified with 12 N NaOH. The product was extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to give 34 g of solid. Recrystallization (EtOAc) afforded 28 g of 3-amino-2-ethylaminopyridine: mp 106 °C; ^{1}H NMR (DMSO-d_6) δ 7.35 (dd, J = 1.5, 5 Hz, 1 H), 6.65 (dd, J = 1.5, 7 Hz, 1 H), 6.31 (dd, J = 5, 7 Hz, 1 H), 5.45 (t, J = 5 Hz, 1 H), 4.65 (br s, 2 H), 3.34 (m, 2 H), 1.15 (t, J = 7 Hz, 3 H); MS (CI) m/z 137 (MH^+).

(c) 2-Chloro-*N*-(2-ethylamino-3-pyridinyl)-5-nitro-3-pyridinecarboxamide. A solution of 2.21 g of 2-chloro-5-nitronicotinoyl chloride[22] (obtained by nitration of 2-hydroxynicotinic acid, followed by conversion to 2-chloro-5-nitronicotinic acid, which was then treated with thionyl chloride) in 10 mL of THF was slowly added over 15 min to a cooled, stirred mixture of 1.34 g of 3-amino-2-ethylaminopyridine, 1.29 g of diisopropylethylamine, and 40 mL of THF. The resulting mixture was allowed to stir overnight at room temperature and then was concentrated in vacuo. The title compound (2.30 g), which precipitated out when the residue was treated with CH_2Cl_2, was suitable for use in the next reaction: mp 185−186 °C; ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1 H), 9.36 (d, J = 2.8 Hz, 1 H), 9.13 (d J = 2.8 Hz, 1 H), 7.97 (dd, J = 2, 4.9 Hz, 1 H), 7.59 (dd, J = 2, 8 Hz, 1 H), 6.60 (dd, J = 4.9, 8 Hz, 1 H), 6.09 (t, J = 5 Hz, 1 H), 3.39 (dq, J = 7, 5 Hz, 2 H), 1.16 (t, J = 7 Hz, 3 H); MS (CI) m/z 321 (MH^+).

(d) 5,11-Dihydro-11-ethyl-8-nitro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. A solution of 1.80 g of 2-chloro-*N*-(2-ethylamino-3-pyridinyl)-5-nitro-3-pyridinecarboxamide in 25 mL of xylenes was heated at reflux for 4 h. After concentration in vacuo, the residue was purified on a silica gel column, eluting with 50% EtOAc/hexane, to give 0.93 g of the title compound: mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 10.73 (br s, 1 H), 9.24 (d, J = 2.8 Hz, 1 H), 8.68 (d, J = 2.8 Hz, 1 H), 8.23 (dd, J = 2.5 Hz, 1 H), 7.55 (dd, J = 2, 8 Hz, 1 H), 7.27 (dd, J = 5, 8 Hz, 1 H), 4.25 (q, J = 7 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H); MS (CI) m/z 285 (MH^+).

(e) 5,11-Dihydro-11-ethyl-5-methyl-8-nitro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. Sodium hydride (60% oil dispersion, 1.0 g, 0.025 mol) was added to a solution of 5,11-dihydro-11-ethyl-8-nitro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7.0 g, 0.025 mol) in 120 mL of DMF. After 1 h, iodomethane (1.6 mL, 0.026 mol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The crude product was purified by flash chromatography, eluting with EtOAc/CH_2Cl_2, to give 6.4 g of the title compound: ^{1}H NMR (DMSO-d_6) δ 9.23 (d, J = 2.8 Hz, 1 H), 8.66 (d, J = 2.8 Hz, 1 H), 8.29 (dd, J = 4.6, 2 Hz, 1 H), 7.94 (dd, J = 2, 8 Hz, 1 H), 7.39 (dd, J = 4.6, 8 Hz, 1 H), 4.23 (q, J = 7 Hz, 2 H), 3.45 (s, 3 H), 1.24 (t, J = 7 Hz, 3 H).

(f) 8-Amino-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (5). Following a procedure analogous to that described in (b) above, 6.2 g of 5,11-dihydro-11-ethyl-5-methyl-8-nitro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one was reduced to give, after recrystallization, 4.4 g of the title compound as a yellow powder: ^{1}H NMR (DMSO-d_6) δ 8.19 (dd, J = 2, 5 Hz, 1 H), 7.83 (d, J = 3 Hz, 1 H), 7.82 (dd, J = 2, 8 Hz, 1 H), 7.30 (d, J = 3 Hz, 1 H), 7.23 (dd, J = 5, 8 Hz, 1 H), 5.27 (s, 2 H), 3.97 (br q, J = 7 Hz, 2 H), 3.43 (s, 3 H), 1.15 (t, J = 7 Hz, 3 H); MS (CI) m/z 270 (MH^+). Anal. ($C_{14}H_{15}N_5O \cdot 0.4H_2O$) C, H, N.

(g) 5,11-Dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (VIIIa). A solution of $NaNO_2$ (0.14 g, 2.0 mmol) was added at 0 °C to 0.5 g (1.9 mmol) of 8-amino-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one in 4 mL of 10% H_2SO_4. After 20 min, NaI (0.39 g, 2.6 mmol) was added and the mixture was warmed to room temperature. Extraction with CH_2Cl_2 and purification of the crude product by flash chromatography, eluting with EtOAc/CH_2Cl_2, afforded 0.45 g of the title compound: mp 167−169 °C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, J = 2.3 Hz, 1 H), 8.25 (d, J = 2.3 Hz, 1 H), 8.23 (dd, J = 2, 5 Hz, 1 H), 7.86 (dd, J = 2, 8 Hz, 1 H), 7.30 (dd, J = 5, 8 Hz, 1 H), 4.05 (q, J = 7 Hz, 2 H), 3.42 (s, 3 H), 1.17 (t, J = 7 Hz, 3 H); MS (CI) m/z 381 (MH^+). Anal. ($C_{14}H_{13}IN_4O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (VIIIb). By procedures analogous to those described in a−g above, the title compound was prepared: mp 220−222 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, J = 2 Hz, 1 H), 8.33 (d, J = 2 Hz, 1 H), 7.43 (d, J = 3 Hz, 1 H) 7.11 (d, J = 8.3 Hz, 1 H), 4.13 (q, J = 7 Hz, 2 H), 3.46 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) m/z 415 (MH^+). Anal. ($C_{14}H_{12}ClIN_4O$) C, H, N.

Method A. 8-Benzyl-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (15). (a) Benzyltributyltin. To a solution of benzylmagnesium chloride (2.0 M in THF, 1.32 mmol) in 5 mL of THF at −78 °C under argon was added tributyltin chloride (0.36, 1.27 mmol). After 15 min, the reaction mixture was allowed to warm to room temperature. After 3 h, solvent was removed, and the residue was purified by flash chromatography, eluting with CH_2Cl_2/hexanes, to give 0.45 g of a clear, colorless oil, which was used directly in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 2

H), 6.98 (m, 3 H), 2.30 (s, 2 H), 1.43 (m, 6 H), 1.31 (m, 6 H), 0.83 (m, 15 H); MS (CI) *m*/*z* 325 (MH^+).

(b) 8-Benzyl-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (15). To a solution of 5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.3 g, 0.79 mmol), $(Ph_3P)_2PdCl_2$ (18 mg, 0.03 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (1 crystal) in 5 mL of DMF was added benzyltributylstannane (0.36 g, 0.94 mmol). The resultant reaction mixture was heated at 100 °C under argon for 5 h. An aqueous solution of potassium fluoride was added, and the mixture was stirred for 5 h. The product was extracted with CH_2Cl_2 and purified by flash chromatography, eluting with EtOAc/CH_2Cl_2, to give 20 mg of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 2.5 Hz, 1 H), 8.19 (dd, J = 2, 5 Hz, 1 H), 7.90 (d, J = 2.5 Hz, 1 H), 7.45 (dd, J = 2, 8 Hz, 1 H), 7.20 (m, 5 H), 7.07 (dd, J = 5, 8 Hz, 1 H), 4.17 (q, J = 7 Hz, 2 H), 3.92 (s, 2 H), 3.49 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 345 (MH^+); HRMS (MH^+, $C_{21}H_{22}N_4O$) calcd 345.1715, found 345.1726.

5,11-Dihydro-11-ethyl-5-methyl-8-(3-phenylpropyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (18). A solution of naphthalene (0.65 g, 5.07 mmol) in 2 mL of THF was added to lithium wire (35 mg, 5.04 mmol), and the mixture was stirred overnight at room temperature under argon. A solution of zinc chloride in THF (0.5 M, 5.25 mL, 2.63 mmol) was then added. After 20 min, 1-bromo-3-phenylpropane (0.18 mL, 1.15 mmol) was added, and the reaction mixture was stirred at room temperature for 4.5 h. Unreacted zinc was allowed to settle, and the supernatant was added by cannula to a solution of 5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.22 g, 0.58 mmol) and $(Ph_3)_4Pd$ (70 mg, 0.06 mmol) in 3 mL of THF. The reaction mixture was allowed to stir overnight at room temperature under argon. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the product was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. Purification by flash chromatography, eluting with EtOAc/CH_2Cl_2, and recrystallization afforded 16 mg of the title compound as off-white crystals: ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 2 Hz, 1 H), 8.20 (dd, J = 2, 5 Hz, 1 H), 7.92 (d, J = 2 Hz, 1 H), 7.48 (dd, J = 2, 8 Hz, 1 H), 7.20 (m, 5 H), 7.09 (dd, J = 5, 8 Hz, 1 H), 4.17 (q, J = 6 Hz, 2 H), 3.52 (s, 3 H), 2.63 (t, J = 8 Hz, 2 H), 2.60 (t, J = 8 Hz, 2 H), 1.92 (m, 2 H), 1.26 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 373 (MH^+). Anal. ($C_{23}H_{24}N_4O$) C, H, N.

Method B. 5,11-Dihydro-11-ethyl-5-methyl-8-[2-(pyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (21). (a) 5,11-Dihydro-11-ethyl-5-methyl-8-[*trans*-2-(4-pyridyl)ethen-1-yl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (20). A mixture containing 5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.7 g, 1.9 mmol), 4-vinylpyridine (0.3 mL, 2.9 mmol), $(Ph_3P)_2PdCl_2$ (60 mg, 0.09 mmol), Et_3N (1.8 mL, 12.8 mmol), and 1 crystal of BHT in 4 mL of DMF was heated at 125 °C under argon for 3 h. The reaction mixture was then cooled to room temperature, diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give a yellow oil. Purification by flash chromatography, eluting with EtOAc/hexanes, and recrystallization provided the 0.5 g of the title compound as yellow crystals: ^{1}H NMR ($CDCl_3$) δ 8.59 (br d, J = 5.5 Hz, 2 H), 8.50 (d, J = 2.4 Hz, 1 H), 8.32 (d, J = 2.4 Hz, 1 H), 8.23 (dd, J = 1.5, 4.6 Hz, 1 H), 7.52 (dd, J = 1.5, 8 Hz, 1 H), 7.40 (br d, J = 5.5 Hz, 2 H), 7.26 (d, J = 16 Hz, 1 H), 7.14 (dd, J = 4.6, 8 Hz, 1 H), 7.00 (d, J = 16 Hz, 1 H), 4.24 (q, J = 7 Hz, 2 H), 3.54 (s, 3 H), 1.30 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 358 (MH^+). Anal. ($C_{21}H_{19}N_5O\cdot 0.5H_2O$) C, H, N.

(b) 5,11-Dihydro-11-ethyl-5-methyl-8-[2-(pyrid-4-yl)-ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (21). The title compound was prepared from 5,11-dihydro-11-ethyl-5-methyl-8-[*trans*-2-(4-pyridyl)ethen-1-yl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.38 g, 1.0 mmol) by catalytic hydrogenation over PtO_2 in EtOAc at 150 psi and 60 °C. Recrystallization afforded 0.18 g of the product as off-white crystals: ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5 Hz, 2 H), 8.21 (dd, J = 2, 5 Hz, 1 H), 8.18 (d, J = 3 Hz, 1 H), 7.93 (d, J = 3 Hz, 1 H), 7.49 (dd, J = 2, 8 Hz, 1 H), 7.12 (d, 2 H), 7.10 (dd, J = 5, 8 Hz, 1 H), 4.17 (q, J = 7 Haz, 2 H), 3.52 (s, 3 H), 2.90 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 360 (MH^+). Anal. ($C_{21}H_{21}N_5O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(pyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (37). (a) 2-Chloro-5,11-dihydro-11-ethyl-8-[*trans*-2-(4-pyridyl)-ethen-1-yl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. 2-Chloro-5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.5 g, 1.2 mmol) was coupled with 4-vinylpyridine in the presence of $(Ph_3P)_2PdCl_2$ and Et_3N as described above to give 0.28 g of the title compound as brown crystals, which was used directly in the next reaction: mp 150−152 °C.

(b) 2-Chloro-5,11-dihydro-11-ethyl-8-[2-(4-pyridyl)ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (37). To a mixture of 2-chloro-5,11-dihydro-11-ethyl-8-[*trans*-2-(4-pyridyl)ethen-1-yl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (2.3 g, 5.9 mmol) and palladium black (0.25 g) in 30 mL of 1,4-dioxane was added a solution of NaH_2PO_2 (0.82 g, 7.7 mmol) in 15 mL of water. The reaction mixture was heated at 80−90 °C for 3 h. The reaction mixture was then filtered through Celite and extracted with EtOAc. The product was purified by chromatography over silica gel, eluting with MeOH/CH_2Cl_2, and recrystallized to give 1.75 g of the title compound as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 6 Hz, 2 H), 8.19 (d, J = 2.5 Hz, 1 H), 7.91 (d, J = 2.5 Hz, 1 H), 7.43 (d, J = 8.3 Hz, 1 H), 7.15 (d, J = 6 Hz, 2 H), 7.10 (d, J = 8.3 Hz, 1 H), 4.15 (q, J = 7 Hz, 2 H), 3.48 (s, 3 H), 2.93 (s, 4 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 394 (MH^+). Anal. ($C_{21}H_{20}N_5OCl$) C, H, N.

2-Cyano-5,11-dihydro-11-ethyl-8-[2-(4-pyridyl)ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (38). A solution of 2-chloro-5,11-dihydro-11-ethyl-8-[2-(4-pyridyl)-ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (**37**) (78 mg, 0.2 mmol), sodium cyanide impregnated alumina (2 g/4 g, 0.44 g, 4.5 mmol),[29] and $(Ph_3)_4Pd$ (45 mg, 0.04 mmol) in 5 mL of toluene was heated at 100 °C under argon for 8 h. The reaction mixture was filtered, and the collected solid was washed with EtOAc. The filtrate was concentrated to give a yellow oil, which was purified by flash chromatography (elution with 2-propanol/hexanes) and recrystallization to afford 11.5 mg (15%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.49 (v br s, 2 H), 8.23 (d, J = 2.5 Hz, 1 H), 7.92 (d, J = 2.5 Hz, 1 H), 7.54 (d, J = 8.1 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.08 (br d, J = 6 Hz, 2 H), 4.18 (q, J = 7 Hz, 2 H), 3.52 (s, 3 H), 2.91 (s, 4 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) *m*/*z* 385 (MH^+). Anal. ($C_{22}H_{20}N_6O$) C, H, N.

5,11-Dihydro-11-ethyl-2-iodo-8-[2-(4-pyridyl)ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (40). (a) 5,11-Dihydro-11-ethyl-8-[2-(4-pyridyl)ethyl]-2-trimethylstannyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. To a solution of 2-chloro-5,11-dihydro-11-ethyl-8-[2-(4-pyridyl)ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (**37**) (60 mg, 0.15 mmol) in 3.5 mL of THF under argon were added hexamethylditin (45μL, 0.15 mmol) and $(Ph_3)_4Pd$ (10 mg, 0.0085 mmol), and the resultant mixture was heated at 85 °C in a sealed tube. After 22 h, additional catalyst (10 mg) was added. $(Ph_3P)_2PdCl_2$ (10 mg) was added after an additional 7 h, and the temperature was increased to 100 °C. After 40 h total reaction time, the reaction mixture was diluted with water and extracted with EtOAc. Purification by flash chromatography (elution with MeOH/CH_2Cl_2) afforded 47 mg of the title compound, which was used directly in the next reaction: ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 6 Hz, 2 H), 8.18 (d, J = 2.5 Hz, 1 H), 7.93 (d, J = 2.5 Hz, 1 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.23 (d, J = 7.7 Hz, 1 H), 7.11 (d, J = 6 Hz, 2 H), 4.21 (q, J = 7 Hz, 2 H), 3.49 (s, 3 H), 2.89 (s, 4 H), 1.25 (t, J = 7 Hz, 3 H), 0.31 (s, 9 H); MS (CI) *m*/*z* 522 (MH^+).

(b) 5,11-Dihydro-11-ethyl-2-iodo-8-[2-(4-pyridyl)ethyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (40). To a solution of 5,11-dihydro-11-ethyl-8-[2-(4-pyridyl)ethyl]-

2-trimethylstannyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (47 mg, 0.09 mmol) in chloroform was added a solution of iodine in chloroform (0.1 M, 4 mL, 0.4 mmol). After 24 h, the reaction mixture was washed with saturated aqueous KF, 5% $NaHSO_3$, and saturated aqueous NaCl. Purification by flash chromatography (elution with $MeOH/CH_2Cl_2$) and recrystallization afforded 15 mg of the title compound: ^1H NMR ($CDCl_3$) δ 8.5 (br s, 2 H), 8.18 (d, $J = 2.5$ Hz, 1 H), 7.89 9d, $J = 2.5$ Hz, 1 H), 7.48 (d, $J = 8$ Hz, 1 H); 7.26 (br s, 2 H), 7.09 (d, $J = 8$ Hz, 1 H), 4.13 (q, $J = 7$ Hz, 2 H), 3.46 (s, 3 H), 2.95 (s, 4 H), 1.24 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 486 (MH^+). Anal. ($C_{21}H_{20}IN_5O \cdot {}^1/_4H_2O$) C, H, N.

Method C. 5,11-Dihydro-11-ethyl-5-methyl-8-(2-phenylethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (17). (a) 5,11-Dihydro-11-ethyl-5-methyl-8-phenylethynyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. A mixture of 5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.20 g, 0.53 mmol), phenylacetylene (0.06 mL, 0.55 mmol), $(Ph_3P)_2PdCl_2$ (25 mg, 0.04 mmol), and Et_3N (0.16 mL, 1.14 mmol) in 3 mL of DMF was heated at 95 °C under argon for 19 h. The reaction mixture was then cooled to room temperature, diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. Purification by flash chromatography, eluting with $EtOAc/CH_2Cl_2$, afforded 0.1 g of the title compound, which was used directly in the next reaction: ^1H NMR ($CDCl_3$) δ 8.5 (d, $J = 2$ Hz, 1 H), 8.25 (d, $J = 2$ Hz, 1 H), 8.25 (dd, $J = 1$, 4 Hz, 1 H), 7.55 (dd, $J = 1$, 8 Hz, 1 H), 7.5 (m, 2 H), 7.35 (m, 3 H), 7.15 (dd, $J = 4$, 8 Hz, 1 H), 4.25 (q, $J = 7$ Hz, 2 H), 3.55 (s, 3 H), 1.25 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 355 (MH^+).

(b) 5,11-Dihydro-11-ethyl-5-methyl-8-(2-phenethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. 5,11-Dihydro-11-ethyl-5-methyl-8-(2-phenylethynyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (70 mg, 0.2 mmol) was hydrogenated over PtO_2 in EtOAc under 50 psi of hydrogen. The reaction mixture was filtered through Celite and concentrated. Purification by flash chromatography and preparative TLC, eluting with $EtOAc/CH_2Cl_2$, afforded 31 mg of the title compound as yellow crystals: ^1H NMR ($CDCl_3$) δ 8.21 (dd, $J = 2$, 5 Hz, 1 H), 8.19 (d, $J = 3$ Hz, 1 H), 7.95 (d, $J = 3$ Hz, 1 H), 7.49 (dd, $J = 2$, 8 Hz, 1 H), 7.22 (m, 5 H), 7.09 (dd, $J = 5$, 8 Hz, 1 H), 4.17 (q, $J = 7$ Hz, 2 H), 3.52 (s, 3 H), 2.88 (s, 4 H), 1.26 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 359 (MH^+). Anal. ($C_{22}H_{22}N_4O$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-8-(*cis*-2-phenylethen-1-yl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (19). 5,-11-Dihydro-11-ethyl-5-methyl-8-phenylethynyl-6*H*-dipyrido-[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.12 g, 0.34 mmol) was hydrogenated over Lindlar catalyst in ethanol under 50 psi of hydrogen. The reaction mixture was filtered through Celite and concentrated. Purification by flash chromatography and preparative TLC, eluting with $EtOAc/CH_2Cl_2$, afforded 20 mg of the title compound as a yellow-orange oil: ^1H NMR ($CDCl_3$) δ 8.25 (d, $J = 2$ Hz, 1 H), 8.22 (dd, $J = 2$, 8 Hz, 1 H), 7.97 (d, $J = 2$ Hz, 1 H), 7.48 (dd, $J = 2$, 8 Hz, 1 H), 7.20 (m, 5 H), 6.68 (d, $J = 12.2$ Hz, 1 H), 6.44 (d, $J = 12.2$ Hz, 1 H), 4.16 (q, $J = 7$ Hz, 2 H), 3.48 (s, 3 H), 1.24 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 357 (MH^+); HRMS (MH^+, $C_{22}H_{21}N_4O$) calcd 357.171 54; found 357.172 05.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-phenylethyl)-6H-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one (36). From 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-phenylethynyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.33 g) (prepared from 2-chloro-5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one and phenylacetylene) by procedures analogous to those described for the preparation of **17**. The title compound was obtained as white needles: ^1H NMR ($CDCl_3$) δ 8.18 (d, $J = 2$ Hz, 1 H), 7.94 (d, $J = 2$ Hz, 1 H), 7.42 (d, $J = 8$ Hz, 1 H), 7.15−7.35 (m, 5 H), 7.09 (d, $J = 8$ Hz, 1 H), 4.15 (q, $J = 7$ Hz, 2 H), 3.48 (s, 3 H), 2.88 (s, 4 H), 1.25 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 393 (MH^+). Anal. ($C_{22}H_{21}ClN_4O$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-8-(2-phenylethyl)-2-(2-pyrrolyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (35). A mixture containing 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-phenylethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.10 g, 0.26 mmol), potassium acetate (0.05 g, 0.51 mmol), *N*-(*tert*-butyloxycarbonyl)pyrrole (0.078 g, 0.47 mmol), and $(Ph_3)_4Pd$ (20 mg, 0.02 mmol) in 2 mL of DMF was heated in a sealed tube at 125 °C for 10 h. Additional potassium acetate (50 mg), *N*-(*tert*-butyloxycarbonyl)pyrrole (0.08 g), and $(Ph_3)_4$-Pd (15 mg) were added, and the reaction mixture was heated at 140 °C for an additional 8 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. Purification by flash chromatography, eluting with EtOAc/hexanes, provided 20 mg of the title compound, as a foam: ^1H NMR ($CDCl_3$) δ 9.39 (b s, 1 H), 8.17 (d, $J = 2.4$ Hz, 1 H), 7.96 (d, $J = 2.4$ Hz, 1 H), 7.43 (d, $J = 8.4$ Hz, 1 H), 7.30 (d, $J = 8.4$ Hz, 1 H), 7.22 (m, 5 H), 6.91 (m, 1 H), 6.66 (m, 1 H), 6.28 (m, 1 H), 4.21 (q, $J = 7$ Hz, 2 H), 3.51 (s, 3 H), 2.88 (s, 4 H), 1.28 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 424 (MH^+). Anal. ($C_{26}H_{25}N_5O \cdot 0.25H_2O$) C, H, N.

Method D. 2-Chloro-5,11-dihydro-11-ethyl-8-ethynyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. A mixture containing 2-chloro-5,11-dihydro-11-ethyl-8-iodo-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (1.37 g, 0.37 mmol), trimethylsilylacetylene (0.59 mL, 4.2 mmol), $(Ph_3P)_2PdCl_2$ (0.53 g, 0.76 mmol), Et_3N (1.1 mL, 7.8 mmol), CuI (0.1 g, 0.53 mmol), and 1−2 crystals of BHT in 40 mL of THF was heated at 80 °C under argon in a sealed tube for 2 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. Purification by flash chromatography, eluting with EtOAc/hexanes, provided 0.92 g of the coupled product, which was then dissolved in THF (10 mL) and treated at room temperature with a 1.1 M solution of Bu_4NF in THF (2.2 mL, 2.39 mmol). After 30 min, solvent was removed at reduced pressure and the residue was purified by flash chromatography, eluting with EtOAc/hexanes, to give 0.64 g of the title compound as a beige solid: mp 157−159 °C; ^1H NMR ($CDCl_3$) δ 8.47 (d, $J = 2$ Hz, 1 H), 8.18, d, $J = 2$ Hz, 1 H), 7.44 (d, $J = 8$ Hz, 1 H), 7.12 (d, $J = 8$ Hz, 1 H), 4.18 (q, $J = 7$ Hz, 2 H), 3.47 (s, 3 H), 3.15 (s, 1 H), 1.26 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 313 (MH^+). Anal. ($C_{16}H_{13}N_4OCl$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-8-[2-(2-methylpyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (52). (a) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-methylpyrid-4-yl)ethynyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. A mixture containing 48 mg (0.15 mmol) of 2-chloro-5,11-dihydro-11-ethyl-8-ethynyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one, 4-bromo-2-picoline[21] (31 mg, 0.15 mmol), $(Ph_3)_4Pd$ (9.7 mg, 0.008 mmol), Et_3N (0.2 mL), and 1 crystal of BHT in 1.0 mL of DMF was heated at 105 °C in a sealed tube for 3 h. The reaction mixture was cooled to room temperature and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography, eluting with EtOAc/hexanes, to give 0.051 g of the title compound as a yellow foam: ^1H NMR ($CDCl_3$) δ 8.53 (d, $J = 2$ Hz, 1 H), 8.50 (d, $J = 6$ Hz, 1 H), 8.24 (d, $J = 2$ Hz, 1 H), 7.46 (d, $J = 8$ Hz, 1 H), 7.26 (s, 1 H), 7.18 (d, $J = 6$ Hz, 1 H), 7.14 (d, $J = 8$ Hz, 1 H), 4.23 (q, $J = 7$ Hz, 2 H), 3.49 (s, 3 H), 2.57 (s, 3 H), 1.29 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 404 (MH^+).

(b) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-methylpyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (52). 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[*trans*-2-(2-methylpyrid-4-yl)ethynyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (50 mg, 0.12 mmol) was hydrogenated over PtO_2, as described for the synthesis of **17**, to afford 18 mg (37%) of the title compound: ^1H NMR ($CDCl_3$) δ 8.37 (d, $J = 5$ Hz, 1 H), 8.18 (d, $J = 2.5$ Hz, 1 H), 7.90 (d, $J = 2.5$ Hz, 1 H), 7.42 (d, $J = 8$ Hz, 1 H), 7.09 (d, $J = 8$ Hz, 1 H), 6.95 (s, 1 H), 6.90 (d, $J = 5$ Hz, 1 H), 4.14 (q, $J = 7$ Hz, 2 H), 3.47 (s, 3 H), 2.86 (m, 4 H), 2.50 (s, 3 H), 1.24 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 408 (MH^+). Anal. ($C_{22}H_{22}ClN_5O \cdot {}^1/_2H_2O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-hy-

droxymethyl-4-pyridyl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (53). (a) 4-Bromo-2-picoline *N*-Oxide. A mixture of 4-nitro-2-picoline *N*-oxide (1.0 g, 6.5 mmol) and AcBr (3.5 mL, 47 mmol) was heated at reflux under argon for 8 h. The reaction mixture was poured onto ice, neutralized with $NaHCO_3$, and extracted with EtOAc and CH_2Cl_2. The organic layer was washed with 5% aqueous $NaHSO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography, eluting with $MeOH/CH_2Cl_2$, EtOAc/hexanes, EtOAc, and $MeOH/CH_2Cl_2$ to afford the title compound (0.38 g, 31%) as an orange-brown oil: ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, J = 4, 8 Hz, 1 H), 7.40 (d, J = 2 Hz, 1 H), 7.26 (dd, J = 2, 4 Hz, 1 H), 2.49 (s, 3 H); MS (CI) m/z 188 (MH^+).

(b) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-oxo-2-methylpyrid-4-yl)ethynyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one. 2-Chloro-5,11-dihydro-11-ethyl-8-ethynyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.2 g, 0.64 mmol) was coupled with 4-bromo-2-picoline *N*-oxide (0.12 g, 0.64 mmol) by a procedure analogous to that described for the synthesis of **52** to provide the title compound (0.26 g, 95%), which was used directly in the next reaction: ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 2.3 Hz, 1 H), 8.21 (d, J = 2.3 Hz, 1 H), 8.19 (d, J = 6 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 7.37 (d, J = 2 Hz, 1 H), 7.22 (dd, J = 2, 6 Hz, 1 H), 7.14 (d, J = 8 Hz, 1 H), 4.21 (q, J = 7 Hz, 2 H), 3.84 (s, 3 H), 2.50 (s, 3 H), 1.28 (t, J = 7 Hz, 3 H).

(c) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-hydroxymethylpyrid-4-yl)ethynyl-6*H*-dipyrido [3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-oxo-2-methylpyrid-4-yl)ethynyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.26 g, 0.61 mmol) was dissolved in Ac_2O (5 mL) and heated at 105 °C in a sealed tube. After 3.5 h, excess Ac_2O was removed by rotary evaporation, the residue was neutralized with aqueous $NaHCO_3$, and the product was extracted with EtOAc. The organic layer was concentrated, the residue was dissolved in 12 mL of MeOH, and a solution of K_2CO_3 (0.18 g, 1.3 mmol) in 1 mL of water was added. After 30 min, the reaction mixture was concentrated, and the residue was diluted with CH_2Cl_2, filtered, and concentrated. Purification by flash chromatography (elution with $MeOH/CH_2Cl_2$) afforded the title compound (0.07 g, 27%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 1 H), 8.53 (d, J = 2.3 Hz, 1 H), 8.24 (d, J = 2.3 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 7.37 (br s, 1 H), 7.27 (br s, 1 H), 7.15 (d, J = 8 Hz, 1 H), 4.79 (br s, 2 H), 4.22 (q, J = 7 Hz, 2 H), 3.50 (s, 3 H), 1.29 (t, J = 7 Hz, 3 H); MS (CI) m/z 420 (MH^+).

(d) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-hydroxymethylpyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (53). 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-hydroxymethylpyrid-4-yl)ethynyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (66 mg, 0.16 mmol) was hydrogenated, according to the procedure described for the synthesis of **37**, to provide the title compound (34 mg, 50%): ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 5 Hz, 1 H), 8.19 (d, J = 2.5 Hz, 1 H), 7.85 (d, J = 2.5 Hz, 1 H), 7.43 (d, J = 8.2 Hz, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 7.03 (s, 1 H), 7.01 (d, J = 5 Hz, 1 H), 4.71 (s, 2 H), 4.15 (q, J = 7 Hz, 2H), 3.71 (br s, 1 H), 3.48 (s, 3 H), 2.90 (s, 4 H), 1.26 (t, J = 7 Hz, 3 H); MS (CI) m/z 424 (MH^+). Anal. ($C_{22}H_{22}ClN_5O_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carbomethoxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (54). (a) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carboxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one. By procedures analogous to those described for the synthesis of **52**, 2-chloro-5,11-dihydro-11-ethyl-8-ethynyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.83 g, 2.64 mmol) was coupled with 4-bromopicolinic acid[21] (0.53 g, 2.62 mmol) and hydrogenated to provide 0.4 g of the title compound, as a mixture containing the corresponding des-chloro analogue. The mixture was used directly in the next reaction. Data for 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carboxypyrid-4-yl)ethynyl]6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 8.73 (apparent s, 1 H), 8.28 (d, J = 2 Hz, 1 H), 8.21 (apparent s, 1 H), 8.12 (s, 1 H), 7.95 (d, J = 8.4 Hz, 1 H), 7.66 (br s, 1 H), 7.44 (d, J = 8.4 Hz, 1 H), 4.09 (apparent d, J = 7 Hz, 2 H), 3.43 (s, 3 H), 1.22 (t, J = 7 Hz, 3 H).

(b) 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carbomethoxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (54). The mixture obtained above was dissolved in 50 mL of MeOH containing a few drops of concentrated H_2SO_4, and the resultant solution was heated at reflux under argon for 15 h. The reaction mixture was diluted with water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 and EtOAc. Purification by flash chromatography, radial chromatography, and preparative TLC (elution with $MeOH/CH_2Cl_2$) afforded the title compound (0.20 g, 46%). A portion of this material was recrystallized to afford the pure product as off-white crystals: ^{1}H NMR ($CDCl_3$) δ 8.62 (d, J = 5 Hz, 1 H), 8.19 (d, J = 2 Hz, 1 H), 7.97 (s, 1 H), 7.92 (d, J = 2 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H), 7.24 (m, 1 H), 7.10 (d, J = 8 Hz, 1 H), 4.15 (q, J = 7 Hz, 2 H), 4.00 (s, 3 H), 3.48 (s, 3 H), 2.96 (s, 4 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) m/z 452 (MH^+). Anal. ($C_{23}H_{22}ClN_5O_3 \cdot {}^1/_4H_2O$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carboxamidopyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]-diazepin-6-one (55). 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carbomethoxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (32 mg, 0.07 mmol) was dissolved in 5 mL of MeOH, and the solution was saturated with NH_3. After 6 h, solvents were removed and the residue was purified by flash chromatography (elution with $MeOH/CH_2Cl_2$). Recrystallization afforded the title compound (25 mg, 82%) as white crystals: ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 5 Hz, 1 H), 8.17 (d, J = 2.5 Hz, 1 H), 8.07 (s, 1 H), 7.93 (d, J = 2.5 Hz, 1 H), 7.85 (br s, 1 H), 7.43 (d, J = 8.2 Hz, 1 H), 7.21 (dd, J = 2, 5 Hz, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 5.54 (br s, 1 H), 4.12 (q, J = 7 Hz, 2 H), 3.49 (s, 3 H), 2.96 (s, 4 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) m/z 437 (MH^+). Anal. ($C_{22}H_{21}ClN_6O_2 \cdot {}^1/_4$EtOAc) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carboxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]di-azepin-6-one (57). 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carbomethoxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.15 g, 0.33 mmol) was dissolved in 30 mL of THF, aqueous LiOH (1.0 *M*, 1.0 mL, 1.0 mmol) was added, and the reaction mixture was heated at reflux under argon. After 1 h, additional LiOH (0.5 mL) was added, and heating was continued for an additional 3 h. The reaction mixture was concentrated, acidified with 2 N HCl, saturated with NaCl, and extracted with chloroform/ethanol (3:1). Concentration afforded a yellow foam, which was recrystallized to provide the title compound (58 mg, 40%) as a pale yellow solid: ^{1}H NMR (DMSO-d_6) δ 8.57 (d, J = 5 Hz, 1 H), 8.36 (d, J = 2 Hz, 1 H), 8.00 (d, J = 2 Hz, 1 H), 7.97 (s, 1 H), 7.90 (d, J = 8.4 Hz, 1 H), 7.52 (dd, J = 2, 5 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 1 H), 4.01 (app. br s, 2 H), 3.41 (s, 3 H), 2.94 (s, 4 H), 1.17 (t, J = 7 Hz, 3 H); MS (CI) m/z (MH^+)438; HRMS (MH^+, $C_{22}H_{21}ClN_5O_3$) calcd 438.133 29, found 438.131 57.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-aminopyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (56). To a solution of 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-[2-(2-carboxypyrid-4-yl)ethyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (92 mg, 0.21 mmol) and Et_3N (0.03 mL, 0.22 mmol) in *tert*-butyl alcohol (20 mL) was added diphenylphosphoryl azide (0.046 g, 0.21 mmol). The reaction mixture was heated at reflux under argon for 16 h. Solvents were removed by rotary evaporation, and the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was treated with 2 N HCl in ethanol at 25−50 °C for 30 h. The reaction mixture was concentrated, basified with 6 N NaOH, and extracted with EtOAc. Purification by flash chromatography (elution with $MeOH/CH_2Cl_2$) and recrystallization afforded 14 mg (16%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 2 Hz, 1 H), 7.95 (d, J = 5.1 Hz, 1 H), 7.92 (d, J = 2 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H); 7.09 (d, J = 8 Hz, 1 H); 6.48 (d, J =

5.1 Hz, 1 H), 6.28 (s, 1 H), 4.37 (br s, 2 H), 4.15 (q, $J = 7$ Hz, 2 H), 3.48 (s, 3 H), 2.81 (m, 4 H), 1.25 (t, $J = 7$ Hz, 3 H); MS (CI) *m*/*z* 409 (MH^+); HRMS (MH^+, $C_{21}H_{22}ClN_6O$) calcd 409.154 36, found 409.154 69.

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