Novel Non-nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. 5. 4-Substituted and 2,4-Disubstituted Analogs of Nevirapine[1]

Terence A. Kelly,* John R. Proudfoot, Daniel W. McNeil, Usha R. Patel, Eva David,† Karl D. Hargrave, Peter M. Grob, Mario Cardozo, Atul Agarwal, and Julian Adams‡

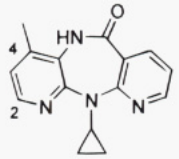
Research and Development Center, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877

Received June 26, 1995[⊗]

Molecular modeling analysis of the recently published X-ray crystal structure of nevirapine bound to wild type human immunodeficiency virus type 1 reverse transcriptase (WT-RT) indicated the presence of a lipophilic cavity proximal to the 4-position of the inhibitor. A series of 4-substituted derivatives of nevirapine were thus synthesized to assess structure–activity relationships (SARs) and to see if increased binding to this region might translate into greater activity against mutant RTs. The results show that compounds with an appropriately spaced aryl ring appended to the 4-position of the dipyridodiazepinone ring system show good activity against WT-RT. Furthermore certain derivatives appear to inhibit the Y181C mutant RT. Attempts to combine these results with the recent discovery that 2-substituents enhance activity against the Y181C mutant led to a few compounds with moderate activity against both enzymes. The SAR of these two positions, however, could not be combined in a simple fashion.

Introduction

Mutant viruses that are resistant to non-nucleoside inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (HIV-1-RT) such as nevirapine (**1**)[2] have emerged in both cell culture[3] and clinical settings.[4] As part of a program to develop compounds that possess broad spectrum activity against a variety of mutant RTs, we sought to modify the nevirapine structure in a manner to maximize binding to sites believed to be conserved throughout the RT family.



1

Analysis of a model derived from a 3.5 Å X-ray crystal structure of a complex between wild type HIV-1-RT and nevirapine[5] indicated that the inhibitor binds to a highly lipophilic cavity formed by β-strands 6, 9, 10, and 12–14 of the enzyme and their connecting loops (Figure 1). These antiparallel β-sheets contain the catalytic aspartic acid residues (110, 185, and 186) thought to be responsible for the polymerase activity of the enzyme.[6] Moreover, this region also houses several aromatic amino acids, proximal to the catalytic region, that appear to be conserved across the RT family.[5b,7] The distances between the 4-methyl carbon atom of nevirapine and the side chains of these aromatic residues (Tyr183, Trp229, Tyr232, and Trp239) range approximately from 5 to 9 Å. According to our model, appropriate substitution at the 4-position of nevirapine could provide additional aromatic–aromatic interactions with the enzyme. It was also believed that by targeting interactions with these conserved and catalytic residues, mutations which cause a decreased binding of the inhibitor will be less likely to generate viable enzyme. Figure 2 depicts a stereoview of the nevirapine-binding pocket. In yellow are shown the amino acids that make direct contact with nevirapine, in red are shown the targeted residues for interaction with the 4-position, and nevirapine is shown in pink.

Figure 1. Depiction of the nevirapine-binding pocket in the region of the 4-position of the dipyridodiazepinone ring system. The distances from the carbon atom of the 4-methyl group of nevirapine to the side chains of the aromatic residues of interest are as follows: Tyr183 (between 4 and 7 Å), Trp229 (between 8 and 9 Å), Tyr232 (between 8 and 9 Å), and Trp239 (between 8 and 9 Å). Tyr183 and Trp229 are in red. Tyr232 and Trp239 are in pink. Residues colored in brown interact directly with the nevirapine ring system.

† Deceased August 19, 1995.
‡ Current address: MyoGenics Inc., 38 Sidney St., Cambridge, MA 02139.
[⊗] Abstract published in *Advance ACS Abstracts*, October 15, 1995.

0022-2623/95/1838-4839$09.00/0

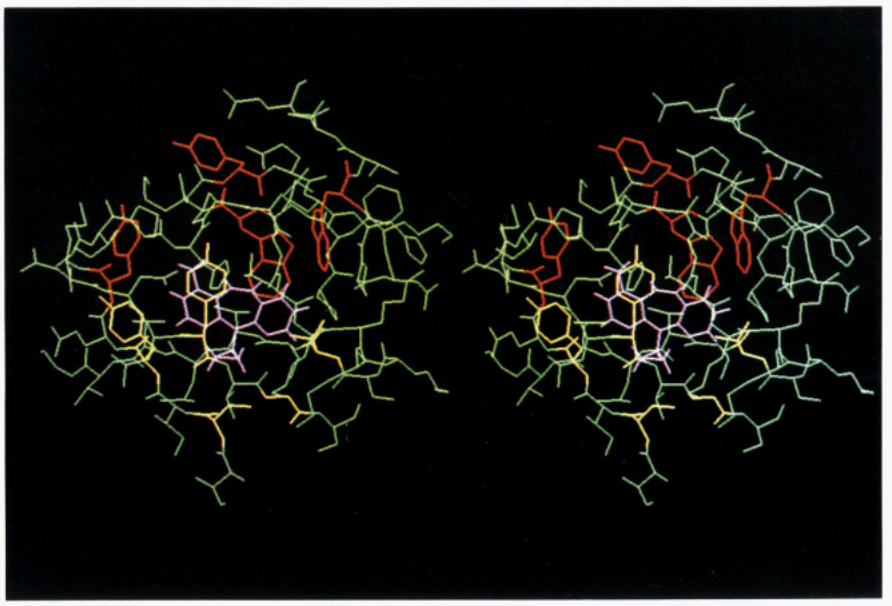
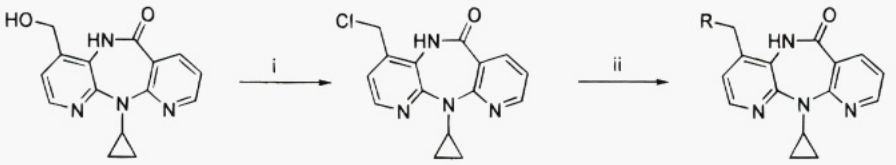


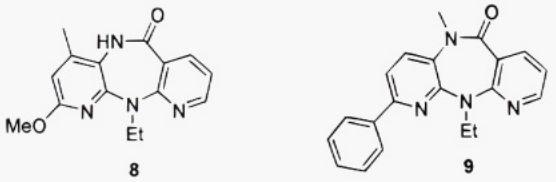
Figure 2. Stereoview of nevirapine-binding pocket. Yellow depicts the residues that make direct contact with nevirapine (shown in pink). Red indicates the residues targeted for interaction with substituents at the 4-position.

Scheme 1[a]



[a] Reagents: (i) $SOCl_2$, CH_2Cl_2; (ii) nucleophile, base (see the Experimental Section), THF.

Our approach, therefore, was to examine the structure–activity relationship (SAR) of analogs of nevirapine that had been modified in the 4-position against both wild type (WT) RT and the RT derived from a primary mutant derived from clinical isolates (Y181C).[4] Furthermore, with the discovery that 2-heteroatom-4-methyl (*e.g.*, **8**) and 2-aryl-5-methyl (*e.g.*, **9**) substitutions often provide enhanced activity against both WT and Y181C RTs,[1] we sought to synthesize a set of 2,4-disubstituted derivatives in order to gauge potential synergistic effects.



Chemistry

The 4-substituted derivatives described in Table 1 were obtained from compounds **2**[8] and **5**[8] as shown in Schemes 1 and 2. Treatment of the hydroxymethyl compound **2** with $SOCl_2$ produced the chloromethyl compound **3** which reacted readily with nucleophiles yielding compounds of structure **4**. Compounds **4aa**,**ab**,**ac** are side products resulting from C-alkylation of the phenoxy nucleophiles during the syntheses of **4c**,**w**,**q**. Compound **4z** was synthesized from its A-ring precursor (2-methoxy-4-(phenylmethyl)-3-pyridinecarbamic acid, 1,1-dimethyl ester)[9] in four steps in a manner analogous to that reported[9] for the synthesis of nevirapine (see also the syntheses of **11a–c** shown in Scheme 3).

Wittig or Horner–Emmons–Wittig procedures on aldehyde **5** produced olefins **6a–c**. Compound **6d** arose from saponification of **6c**. Hydrogenolysis of **6b–d** over Pd/C produced **7a–d**, respectively.

The 2,4-disubstituted derivatives (Table 2) were prepared as shown in Scheme 3. Compounds **10a–c** were converted into **11a–c**, respectively, by four-step procedures directly analogous to a method previously reported[9] for the synthesis of nevirapine. The acetal protecting group of **11c** was removed ($AcOH/H_2O$ at 100 °C)[10] to yield **11d**. The aldehyde **11d** was reduced to the alcohol **11e** with $NaBH_4$. Conversion of **11d** into **11f** proceeded with $SOCl_2$, and the phenyl ether **11g** was then generated by treatment with NaOPh.

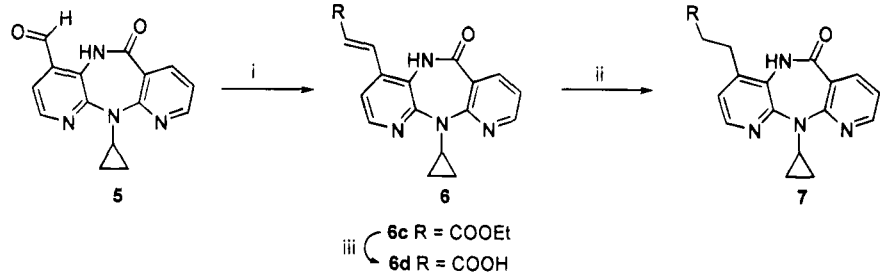
The 2-methoxy compounds **11a–c**,**g** were converted to their respective 2-hydroxy derivatives by treatment with LiI in collidine at 160 °C for 4–16 h.[11] Compound **12c** was converted to the aldehyde **12d** and then to the alcohol **12e** as described above.

Treatment of compounds **12a–c**,**g** with Tf_2O in CH_2Cl_2 containing *i*-Pr_2NEt produced the respective triflate which reacted with 3-(tri-*n*-butylstannyl)anisole (DMF, LiCl, $PdCl_2(Ph_3P)_2$, 110 °C)[12] producing the 2-aryl compounds **13a–c**,**g** in good yields. Compound **13c** was deprotected to the aldehyde **13c** which was then reduced to form the alcohol **13e**.

Results and Discussion

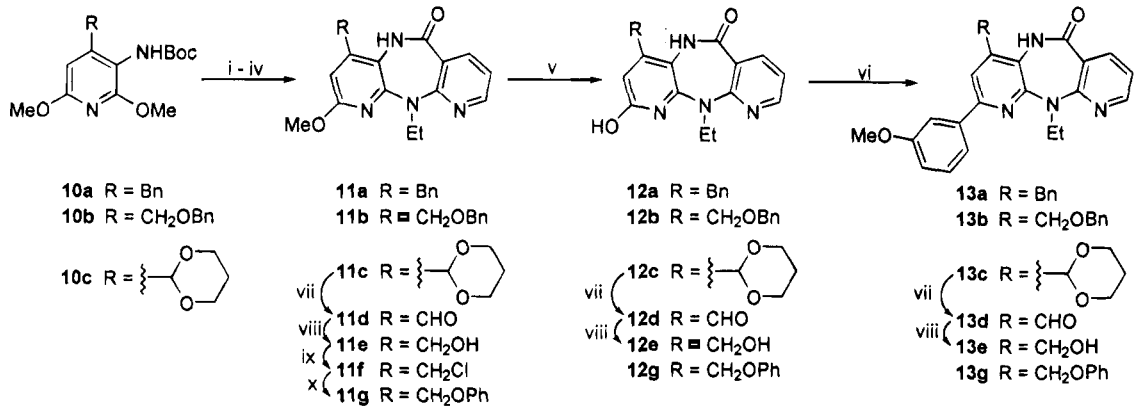
Previous SAR studies showed that the 4-hydroxymethyl derivative of nevirapine (**2**)[13] had greatly dimin-

Scheme 2[a]



[a] Reagents: (i) $RCH{=}P(Ph)_3{\cdot}HBr$, *n*-BuLi, THF or $RCH_2P(OEt)_2$, NaH, THF; (ii) H_2, Pd/C, EtOH; (iii) KOH, EtOH.

Scheme 3[a]



[a] Reagents: (i) HCl, EtOAc; (ii) 2-chloronicotinoyl chloride, EtOAc, *i*-$PrNEt_2$, 0 °C; (iii) $EtNH_2$, 110 °C; (iv) NaHMDS (2 equiv), pyridine, 90 °C; (v) LiI, 2,4,6-collidine, 160 °C; (vi) 1. TF_2O, *i*-$PrNEt_2$, CH_2Cl_2, 2. 3-(tributylstannyl)anisole, $PdCl_2(PPh_3)_2$, LiCl, DMF, 110 °C; (vii) AcOH, H_2O, 100 °C; (viii) $NaBH_4$, *i*-PA; (ix) $SOCl_2$, CH_2Cl_2; (x) PhONa, THF.

ished activity against WT-RT.[2b] Similarly, simple 4-alkoxymethyl-substituted compounds (**4a,b**) displayed only weak activity (Table 1). The phenoxymethyl compound **4c** regained activity against the WT virus (IC_{50} = 120 nM) and also showed slight activity against the Y181C RT (IC_{50} = 2.58 μM). This result supported the hypothesis derived from modeling and encouraged us to probe the size of the cavity. Extension of the side chain by one to three methylene groups produced compounds **4d–f**, which showed weaker inhibition of the WT-RT as the length of the linker increased. Replacement of the oxygen atom in the tether with nitrogen produced **4g** with improved potency against both enzymes (IC_{50} = 60 nM and 1.37 μM, respectively). A sulfur atom in the tether gave **4h,i** which were less potent than **4c**. Attempts to improve activity by substituting small heterocyclic rings (**4j–o**) for the phenyl moiety were unsuccessful.

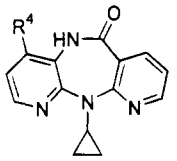
The SAR about the phenyl ring of **4c** was also explored. Incorporation of a methyl group at the *ortho*, *meta*, and *para* positions (**4p–r**) produced less potent compounds, indicating a steric limit, especially at the *meta* position. Compounds with substituents at the *ortho* position retained some activity against WT-RT but displayed no appreciable inhibition of Y181C RT. At the *para* position, methoxy, cyano, and nitro substituents (**4w–y**) were not particularly effective; however, the *p*-amino and *p*-ethylamino substituents improved activity against both enzymes (**4u,v**). Molecular modeling indicated that the substituents may be interacting with the Tyr232 or Tyr183 residue of the enzyme. Another possibility that cannot be ruled out is that aryl–aryl interactions are taking place between these compounds and Trp239.

The side product from the synthesis of compound **4c**, the C-alkylated phenol **4aa**, displayed surprising activity against WT-RT and was even weakly active against the Y181C RT. Analogs **4ab,ac**, however, showed no activity against the Y181C RT mutant. The unsubstituted compound **4z** displayed a similar spectrum of activity. The one-carbon atom homolog of this material (**7b**) was inactive against both WT-RT and the Y181C RT as were the other derivatives with alkyl or alkenyl linkers with the sole exception of olefin **6a** which is consistent with previously published data.[2b]

In the preceding paper[1] we demonstrated that the combination of a 2-substituent and a 4-methyl substituent can lead to enhanced activity against WT-RT. We were interested in combining some of these recently discovered 4-aryl substituents with 2-substituted substituents to examine whether a similar synergy is possible with these larger 4-substituents. Our initial target was the [2-(*m*-methoxyphenyl)-4-phenoxy]methyl derivative **13g**. Biological evaluation of a number of synthetic intermediates, however, produced some unexpected results. The data are reported in Table 2.

For the 2,4-disubstituted series, the SAR did not parallel that of the simple 4-substituted series. Firstly, in combination with the 2-OMe substituent, the 4-formyl and 4-hydroxymethyl substituents (compounds **11d,e**) produced highly active compounds against the WT-RT (IC_{50} = 240 and 50 nM, respectively). The analogous 4-substituted, 2-unsubstituted compounds were essentially inactive against this enzyme. Furthermore, the (2-methoxy-4-phenoxy)methyl (**11g**) and [(2-methoxy-4-benzyl)oxy]methyl (**11b**) compounds had greatly diminished activity against the WT enzyme *vis-à-vis*

Table 1. 4-Substituted Derivatives



compd	R^4	inhibition at 1 μM (%) WT	inhibition at 1 μM (%) Y181C	IC_{50} (μM) WT	IC_{50} (μM) Y181C
1	CH_3	85	59[a]	0.08	2.6
2	CH_2OH	34	4	3.0	
4a	CH_2OEt	41	29	1.30	
4b	$CH_2OCH_2CH{=}CH_2$	35	29	1.41	
4c	CH_2OPh	78	26	0.12	2.58
4d	CH_2OCH_2Ph	67	37	0.27	
4e	$CH_2O(CH_2)_2Ph$	55	28	0.42	
4f	$CH_2O(CH_2)_3Ph$	29	20		
4g	CH_2NHPh	87	41	0.06	1.37
4h	CH_2SPh	44	14	1.03	
4i	CH_2SCH_2Ph	33	28		
4j	CH_2(4-morpholinyl)	50	21	1.03	
4k	CH_2(1-pyrrolidinyl)	51	16	0.70	
4l	CH_2(1-piperidinyl)	29	20		
4m	CH_2(1-pyrazolyl)	36	5	2.20	
4n	CH_2(3-pyrrolinyl)	54	26	0.64	
4o	CH_2(1-imidazolyl)	13	20		
4p	CH_2O(Ph-*o*-Me)	65	28	0.29	
4q	CH_2O(Ph-*m*-Me)	38	9	2.43	
4r	CH_2O(Ph-*p*-Me)	55	33	0.58	
4s	CH_2O(Ph-*o*-OH)	59	42	0.46	
4t	CH_2O(Ph-*o*-Cl)	30	20	3.05	
4u	CH_2O(Ph-*p*-NH_2)	91	49	0.10	1.01
4v	CH_2O(Ph-*p*-NHEt)	88	58	0.08	0.43
4w	CH_2O(Ph-*p*-OMe)	47	41	1.04	
4x	CH_2O(Ph-*p*-CN)	57	11	0.41	
4y	CH_2O(Ph-*p*-NO_2)	43	12	1.13	
4z	CH_2Ph	73	8	0.14	
4aa	CH_2(Ph-*o*-OH)	75	50	0.19	1.12
4ab	CH_2(Ph-2-OH-5-OMe)	42	47	0.85	
4ac	CH_2(Ph-2-OH-4-Me)	76	29	0.20	
6a	$CH{=}CH_2$	83	16	0.11	
6b	$CH{=}CHPh$	23	25		
6c	$CH{=}CHCO_2Et$	27	22		
6d	$CH{=}CHCO_2H$	0	0		
7b	CH_2CH_2Ph	36	38		
7c	$CH_2CH_2CO_2Et$	13	11		
7d	CH_2CH_2COOH	2	8		

[a] Percent inhibition at 10 μM.

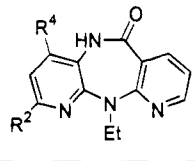
both the simple 4-substituted compounds (*e.g.*, **4c,d**) and the 2-methoxy-4-unsubstituted[2b] compounds.

Conversion of the 2-methoxy compounds to their 2-hydroxy derivatives also produced some unexpected results. Whereas the 2-hydroxy-4-hydroxymethyl compound **12e** and 2-hydroxy-4-carboxaldehyde **12d** lost significant activity compared with their 2-methoxy analogs, the 2-hydroxy-4-benzyl (**12a**) and (2-hydroxy-4-benzyl)oxy (**11b**) compounds showed good activity against WT-RT and fair activity against Y181C RT.

To analyze the ability to combine the 2-aryl substituents with the variou 4-substituents, the 2-*m*-methoxyphenyl derivative was used. The only compounds of this series that had significant activity against the WT enzyme were the [2-(*m*-methoxyphenyl)-4-phenoxy]-methyl **13g** and the 2-(*m*-methoxyphenyl)-4-carboxaldehyde **13d** (which also had good activity against the Y181C mutant).

We have rationalized the SAR derived from Tables 1 and 2 by making two assumptions about the binding site of these compounds. The first is that there exists a size-limited pocket in the WT enzyme in the area of the 4-position which may allow further binding interactions to occur. Since many of the active compounds containing an aryl ring in the 4-position lose activity against Y181C RT, it might be that these rings interact directly with the Tyr181 during binding to the WT enzyme.

Table 2. 2,4-Disubstituted Derivatives



compd	R^2	R^4	inhibition at 1 μM (%) WT	inhibition at 1 μM (%) Y181C	IC_{50} (μM) WT	IC_{50} (μM) Y181C
11a	OMe	CH_2Ph	0	0		
11b	OMe	CH_2OCH_2Ph	42	26	0.92	
11c	OMe	2-(1,3-dioxanyl)	52	22	0.80	
11d	OMe	CHO	78	38	0.24	
11e	OMe	CH_2OH	89	24	0.05	
11g	OMe	CH_2OPh	44	17	4.00	
12a	OH	CH_2Ph	67	42	0.34	1.30
12b	OH	CH_2OCH_2Ph	83	38	0.11	1.07
12c	OH	2-(1,3-dioxanyl)	0	0		
12d	OH	CHO	36	6		
12e	OH	CH_2OH	51	25	0.42	
12g	OH	CH_2OPh	33	20		
13a	Ph-*m*-OMe	CH_2Ph	20	15		
13b	Ph-*m*-OMe	CH_2OCH_2Ph	0	12		
13c	Ph-*m*-OMe	2-(1,3-dioxanyl)	40	7		
13d	Ph-*m*-OMe	CHO	71	63	0.33	0.42
13e	Ph-*m*-OMe	CH_2OH	16	0		
13g	Ph-*m*-OMe	CH_2OPh	69	37	0.49	

The second assumption is that compounds with a 2-substituent bind differently from compounds without a 2-substituent. It may be that the dipyridodiazepinone ring system is rotated to access the enzymatic residues near the 2-position substituent. This rotation would now be expected to change the binding environment of the 4-position and change the SAR for this position which is consistent with our observations.

Conclusions

We have synthesized and tested a number of 4-substituted and 2,4-disubstituted analogs of nevirapine. It appears clear that there exists a cavity in the area of the 4-position which allows for the placement of aryl groups in this area. Substitution of an amino group at the *para* position of this aryl ring (**4u,v**) can confer activity against the Y181C mutant enzyme.

It has also been noted that combining of 2- and 4-substituents does not lead to additive activity. This is possibly due to a different binding orientation of the core ring system mediated by the 2-position substituent which changes the environment about the 4-position.

Experimental Section[14]

4-(Chloromethyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*d*:2′,3′-*e*][1,4]diazepin-6-one (3). A solution of **2**[8] (1.00 g, 3.6 mmol) and *i*-Pr_2NEt (0.46 g, 3.6 mmol) in 50 mL of CH_2Cl_2 was treated at room temperature with thionyl chloride (15 mL). After 3 h, excess thionyl chloride was removed by careful rotary evaporation; the residue was extracted with EtOAc, washed with H_2O, and dried over Na_2SO_4. Removal of solvent gave **3** (0.95 g, 89%) which was used without further purification: ^{1}H-NMR ($CDCl_3$) δ 8.55 (dd, *J* = 5, 2 Hz, 1 H), 8.31 (d, *J* = 8 Hz, 1 H), 8.13 (dd, *J* = 8, 2 Hz,

1 H), 7.95 (br s, 1 H), 7.11 (dd, J = 8, 5 Hz, 1 H), 7.00 (d, J = 8, Hz, 1 H), 4.60 (dd, J = 38.0, 14 Hz, 2 H), 3.70−3.80 (m, 1 H), 1.08 (m, 2 H), 0.52 (m, 2 H).

General Method for the Syntheses of 4a−y. Unless otherwise stated, compounds **4a−y** were prepared by treating compound **3** with an excess of the appropriate nucleophile in THF at room temperature in the presence of a base. For the aliphatic amines, the need for an extra base was avoided by using the amine in excess or as solvent. For the reaction of alcohols, phenols, thiophenols, and aromatic amines, the reaction proceeded by first forming the sodium salt of the nucleophile and then adding it in THF to compound **3**. Workup consisted of partitioning between water and EtOAc followed by washing the organic layer with H_2O, drying, concentrating, and purifying via flash chromatography.

11-Cyclopropyl-5,11-dihydro-4-(ethoxymethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4a): 44%; mp 156−8 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 9.70 (br s, 1 H), 8.51 (dd, J = 5, 2 Hz, 1 H), 8.20 (d, J = 5 Hz, 1 H), 8.01 (dd, J = 8, 2 Hz, 1 H), 7.18−7.23 (m, 2 H), 4.64 (ABq, $\delta\nu$ = 35 Hz, J = 14 Hz, 2 H), 3.39−3.67 (m, 3 H), 1.17 (t, J = 7 Hz, 3 H), 0.87 (m, 2 H), 0.37 (m, 2 H); MS (CI) 311 (MH$^+$, 100). Anal. ($C_{17}H_{18}N_4O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[(2-propenyloxy)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4b): 75%; mp 160−2 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 9.76 (br s, 1 H), 8.52 (dd, J = 5, 2 Hz, 1 H), 8.21 (d, J = 5 Hz, 1 H), 8.01 (dd, J = 8, 2 Hz, 1 H), 7.21 (m, 2 H), 5.86−6.02 (m, 1 H), 5.16−5.35 (m, 2 H), 4.66 (ABq, $\delta\nu$ = 29 Hz, J = 15 Hz, 2H), 4.05 (m, 2 H), 3.64 (m, 1 H), 0.91 (m, 2 H), 0.35 (m, 2 H); MS (CI) 323 (MH$^+$, 100). Anal. ($C_{18}H_{18}N_4O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[(phenyloxy)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4c): 34%; mp 204−6 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 10.00 (br s, 1 H), 8.52 (dd, J = 5, 2 Hz, 1 H), 8.22 (d, J = 5 Hz, 1 H), 8.03 (dd, J = 8, 2 Hz, 1 H), 6.90−7.40 (m, 7 H), 5.32 (ABq, $\delta\nu$ = 20 Hz, J = 15 Hz, 2H), 3.66 (m, 1 H), 0.90 (m, 2 H), 0.44 (m, 2 H); MS (CI) 359 (MH$^+$, 100). Anal. ($C_{21}H_{18}N_4O_2$) C, H, N.

4-[(Benzyloxy)methyl]-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4d): 24%; mp 123−5 °C (EtOAc:*i*-Pr_2O); ^{1}H-NMR (DMSO-d_6) δ 9.79 (br s, 1 H), 8.52 (dd, J = 5, 2 Hz, 1 H), 8.22 (d, J = 5 Hz, 1 H), 8.00 (dd, J = 8, 2 Hz, 1 H), 7.18−7.37 (m, 7 H), 4.71 (ABq, $\delta\nu$ = 17 Hz, J = 14 Hz, 2H), 4.58 (ABq, $\delta\nu$ = 13 Hz, J = 12 Hz, 2H), 3.62 (m, 1 H), 0.88 (m, 2 H), 0.37 (m, 2 H); MS (CI) 373 (MH$^+$, 100). Anal. ($C_{22}H_{20}N_4O_2$·0.25H_2O) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(2-phenylethyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4e): 31%; mp 111−3 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.52 (dd, J = 5, 2 Hz, 1 H), 8.42 (br s, 1 H), 8.20 (d, J = 5 Hz, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 7.16−7.35 (m, 5 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.89 (d, J = 5 Hz, 1 H), 4.53 (ABq, $\delta\nu$ = 135 Hz, J = 12 Hz, 2H), 3.62−3.84 (m, 3 H), 2.96 (t, J = 7 Hz, 2 H), 0.96 (m, 2 H), 0.48 (m, 2 H); MS (CI) 387 (MH$^+$, 100). Anal. ($C_{23}H_{22}N_4O_2$·H_2O) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(3-phenylpropyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4f): 21%; mp 114−5 °C (*i*-Pr_2O:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.65 (br s, 1 H), 8.53 (dd, J = 5, 2 Hz, 1 H), 8.22 (d, J = 5 Hz, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 7.17−7.31 (m, 5 H), 7.06 (dd, J = 8, 5 Hz, 1 H), 6.88 (d, J = 5 Hz, 1 H), 4.52 (ABq, $\delta\nu$ = 133 Hz, J = 12 Hz, 2H), 3.51−3.79 (m, 3 H), 2.74 (t, J = 7 Hz, 2 H), 2 (m, 2 H), 0.98 (m, 2 H), 0.48 (m, 2 H); MS (CI) 401 (MH$^+$, 100). Anal. ($C_{24}H_{24}N_4O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[(phenylamino)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4g): 67%; mp 237−9 °C (EtOAc;hexanes); ^{1}H-NMR ($CDCl_3$) δ 9.00 (br s, 1 H), 8.53 (dd, J = 5, 2 Hz, 1 H), 8.25 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.04−7.27 (m, 5 H), 6.88 (t, J = 7 Hz, 1 H), 6.75 (d, J = 9, Hz, 1 H), 4.34 (ABq, $\delta\nu$ = 110 Hz, J = 14 Hz, 2 H), 3.75 (m, 1 H), 0.97 (m, 2 H), 0.48 (m, 2 H); MS (CI) 358 (MH$^+$, 100). Anal. ($C_{21}H_{19}N_5O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[(phenylthio)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4h): 77%; mp 178−80 °C (EtOAc;hexanes); ^{1}H-NMR (DMSO-d_6) δ 10.04 (br s, 1 H), 8.51 (dd, J = 5, 2 Hz, 1 H), 8.01−8.09 (m, 2 H), 7.11−7.25 (m, 7 H), 4.43 (ABq, $\delta\nu$ = 94 Hz, J = 14 Hz, 2 H), 3.62 (m, 1 H), 0.89 (m, 2 H), 0.41 (m, 2 H); MS (CI) 375 (MH$^+$, 15), 265 (100). Anal. ($C_{21}H_{18}N_4OS$) C, H, N.

4-[(Benzylthio)methyl]-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4i): 77%; mp 160−2 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 9.91 (br s, 1 H), 8.53 (dd, J = 5, 2 Hz, 1 H), 8.12 (d, J = 5 Hz, 1 H), 8.04 (dd, J = 8, 2 Hz, 1 H), 7.11−7.25 (m, 7 H), 4.13 (d, J = 15 Hz, 1 H), 3.53−3.68 (m, 4 H), 0.88 (m, 2 H), 0.41 (m, 2 H); MS (CI) 389 (MH$^+$, 20), 91 (100). Anal. ($C_{22}H_{20}N_4OS$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(4-morpholinylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4j): 100%; mp 215−7 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 10.23 (br s, 1 H), 8.53 (dd, J = 5, 2 Hz, 1 H), 8.16 (d, J = 5 Hz, 1 H), 8.04 (dd, J = 8, 2 Hz, 1 H), 7.20 (dd, J = 8, 5 Hz, 1 H), 7.14 (d, J = 5 Hz, 1 H), 3.66 (ABq, $\delta\nu$ = 111 Hz, J = 14 Hz, 2H), 3.59−3.65 (m, 5 H), 2.31−2.52 (m, 4 H), 0.87 (m, 2 H), 0.37 (m, 2 H); MS (CI) 352 (MH$^+$, 100). Anal. ($C_{19}H_{21}N_5O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(1-pyrrolidinylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4k): 90%; mp 208−10 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 10.44 (br s, 1 H), 8.53 (dd, J = 5, 2 Hz, 1 H), 8.15 (d, J = 5 Hz, 1 H), 8.03 (dd, J = 8, 2 Hz, 1 H), 7.20 (dd, J = 8, 5 Hz, 1 H), 7.13 (d, J = 5 Hz, 1 H), 4.16 (d, J = 14 Hz, 1 H), 3.59−3.65 (m, 1 H), 3.37 (d, J = 14 Hz, 1 H), 2.4−2.5 (m, 4 H), 1.75−1.99 (m, 4 H), 0.87 (m, 2 H), 0.36 (m, 2 H); MS (CI) 336 (MH$^+$, 100). Anal. ($C_{19}H_{21}N_5O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(1-piperidinylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4l): 100%; mp 212−4 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 10.73 (br s, 1 H), 8.50 (dd, J = 5, 2 Hz, 1 H), 8.10−8.16 (m, 2 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.81 (d, J = 5 Hz, 1 H), 3.73 (m, 1 H), 3.52 (ABq, $\delta\nu$ = 194 Hz, J = 13 Hz, 2 H), 2.2−2.4 (m, 4 H), 1.4−1.7 (m, 6 H), 0.98 (m, 2 H), 0.48 (m, 2 H); MS (CI) 350 (MH$^+$, 100). Anal. ($C_{20}H_{23}N_5O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(1-pyrazolylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4m): 45%; mp 240−2 °C (EtOAc); ^{1}H-NMR (DMSO-d_6) δ 10.35 (br s, 1 H), 8.54 (dd, J = 5, 2 Hz, 1 H), 8.18 (d, J = 5 Hz, 1 H), 8.05 (dd, J = 8, 2 Hz, 1 H), 7.88 (d, J = 2 Hz, 1 H), 7.55 (d, J = 1 Hz, 1 H), 7.21 (dd, J = 8, 5 Hz, 1 H), 6.55 (d, J = 5 Hz, 1 H), 6.35 (dd, J = 2, 1 Hz, 1 H), 5.59 (s, 2 H), 3.65 (m, 1 H), 0.88 (m, 2 H), 0.38 (m, 2 H); MS (CI) 333 (MH$^+$, 100). Anal. ($C_{18}H_{16}N_6O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(3-pyrrolinylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4n): 39%; mp 198−200 °C (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 10.54 (br s, 1 H), 8.52 (dd, J = 5, 2 Hz, 1 H), 8.18 (d, J = 5 Hz, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.88 (d, J = 5 Hz, 1 H), 5.78 (s, 2 H), 4.21 (br d, J = 13 Hz, 1 H), 3.75 (m, 1 H), 3.5 (m, 5 H), 0.98 (m, 2 H), d 0.48 (m, 2 H); MS (CI) 334 (MH$^+$, 100). Anal. ($C_{19}H_{19}N_5O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(1-imidazolylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4o): 72%; mp 196−8 °C (EtOAc); ^{1}H-NMR (DMSO-d_6) δ 10.22 (br s, 1 H), 8.52 (dd, J = 5, 2 Hz, 1 H), 8.15 (d, J = 5 Hz, 1 H), 7.99 (dd, J = 8, 2 Hz, 1 H), 7.71 (s, 1 H), 7.21 (dd, J = 8, 5 Hz, 1 H), 7.16 (s, 1 H), 6.95 (s, 1 H), 6.44 (d, J = 5 Hz, 1 H), 5.43 (ABq, $\delta\nu$ = 22 Hz, J = 17 Hz, 2 H), 3.63 (m, 1 H), 0.88 (m, 2 H), 0.42 (m, 2 H); MS (CI) 333 (MH$^+$, 100); HRMS calcd for $C_{18}H_{16}N_6O$ (MH$^+$) 333.1464, found 333.1446. Anal. ($C_{18}H_{16}N_6O$·0.75H_2O) C, H; N: calcd, 24.28; found, 21.74.

11-Cyclopropyl-5,11-dihydro-4-[[(2-methylphenyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4p): 20%; mp 235−7 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.55 (dd, J = 5, 2 Hz, 1 H), 8.38 (br s, 1 H), 8.29 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 6.90−7.25 (m, 6 H), 5.10 (ABq, $\delta\nu$ = 74 Hz, J = 12 Hz, 2 H), 3.77 (m, 1 H), 2.31 (s, 3 H), 1.05 (m, 2 H), 0.55 (m, 2 H); MS (CI) 373 (MH$^+$, 100); HRMS calcd for $C_{22}H_{20}N_4O_2$ 372.1586, found 372.1594.

11-Cyclopropyl-5,11-dihydro-4-[[(3-methylphenyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4q): 16%; mp 196−7 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.54 (dd, J = 5, 2 Hz, 1 H), 8.29 (m, 2 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.18−7.26 (m, 1 H), 7.04−7.09 (m, 2 H), 6.80−6.89 (m, 3 H), 5.07 (ABq, $\delta\nu$ = 78 Hz, J = 11 Hz, 2 H), 3.78 (m, 1 H),

2.35 (s, 3 H), 1.00 (m, 2 H), 0.51 (m, 2 H); MS (CI) 373 (MH^+, 100). Anal. ($C_{22}H_{20}N_4O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(4-methylphenyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4r): 29%; mp 168–70 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.55 (dd, J = 5, 2 Hz, 1 H), 8.30 (m, 2 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 6.89–7.26 (m, 6 H), 5.06 (ABq, $\delta\nu$ = 81 Hz, J = 11 Hz, 2 H), 3.77 (m, 1 H), 2.31 (s, 3 H), 1.00 (m, 2 H), 0.50 (m, 2 H); MS (CI) 373 (MH^+, 100); HRMS calcd for $C_{22}H_{20}N_4O_2$ 372.1586, found 372.1568.

11-Cyclopropyl-5,11-dihydro-4-[[(2-hydroxyphenyl)-oxy]methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4s): 32%; mp 250–2 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.62 (br s, 1 H), 8.55 (dd, J = 5, 2 Hz, 1 H), 8.31 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 6.72–7.26 (m, 6 H), 5.14 (ABq, $\delta\nu$ = 88 Hz, J = 12 Hz, 2 H), 3.76 (m, 1 H), 1.00 (m, 2 H), 0.52 (m, 2 H); MS (CI) 375 (MH^+, 100). Anal. ($C_{21}H_{18}N_4O_3$) C, H, N.

11-Cyclopropyl-4-[[(2-chlorophenyl)oxy]methyl]-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4t): 54%; mp 220–2 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.64 (br s, 1 H), 8.54 (dd, J = 5, 2 Hz, 1 H), 8.30 (d, J = 5 Hz, 1 H), 8.10 (dd, J = 8, 2 Hz, 1 H), 7.42 (dd, J = 8, 2 Hz, 1 H), 6.98–7.27 (m, 5 H), 5.16 (ABq, $\delta\nu$ = 57 Hz, J = 12 Hz, 2 H), 3.79 (m, 1 H), 1.02 (m, 2 H), 0.54 (m, 2 H); MS (CI) 393 (MH^+, 100). Anal. ($C_{21}H_{17}ClN_4O_2$) C, H, N.

4-[[(4-Aminophenyl)oxy]methyl]-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4u). To a solution of **4y** (100 mg, 0.25 mmol) in 2 mL of glacial acetic acid at room temperature was added a solution of 400 mg of $SnCl_2$ in 1 mL of concentrated HCl. After 6 h the mixture was diluted with H_2O and neutralized with 2 N NaOH. Extraction into CH_2Cl_2 followed by drying and concentration gave the crude product which was purified by flash chromatography (1:1 EtOAc:hexanes): 54%; mp 208–10 °C (CH_2Cl_2:*i*-Pr_2O); ^{1}H-NMR ($CDCl_3$) δ 8.54 (dd, J = 5, 2 Hz, 1 H), 8.41 (br s, 1 H), 8.26 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.03–7.20 (m, 2 H), 6.74 (ABq, $\delta\nu$ = 50 Hz, J = 9 Hz, 4 H), 5.00 (ABq, $\delta\nu$ = 90 Hz, J = 12 Hz, 2 H), 3.78 (m, 1 H), 3.52 (br s, 2 H), 0.99 (m, 2 H), 0.54 (m, 2 H); MS (CI) 374 (MH^+, 100); HRMS calcd for $C_{21}H_{19}N_5O_2$ (MH^+) 374.1617, found 374.1631. Anal. ($C_{21}H_{19}N_5O_2 \cdot 0.5H_2O$) C, H; N: calcd, 18.31; found, 17.47.

4-[[[4-(Aminoethyl)phenyl]oxy]methyl]-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4v): obtained as a side product from the catalytic hydrogenolysis of **4y** over Pd/C in EtOH; purified by flash chromatography (1:1 EtOAc:hexanes); 12%; mp 208–9 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.54 (dd, J = 5, 2 Hz, 1 H), 8.43 (br s, 1 H), 8.26 (d, J = 5 Hz, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 7.02–7.10 (m, 2 H), 6.73 (ABq, $\delta\nu$ = 81 Hz, J = 7 Hz, 4 H), 5.00 (ABq, $\delta\nu$ = 91 Hz, J = 11 Hz, 2 H), 3.77 (m, 1 H), 3.12 (q, J = 7 Hz, 2 H), 1.25 (t, J = 7 Hz, 2 H), 0.99 (m, 2 H), 0.53 (m, 2 H); MS (CI) 402 (MH^+, 100). Anal. ($C_{23}H_{23}N_5O_2 \cdot 0.25H_2O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(4-methoxyphenyl)-oxy]methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4w): 31%; mp 225–6 °C (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 8.54 (dd, J = 5, 2 Hz, 1 H), 8.35 (br s, 1 H), 8.28 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 6.84–7.09 (m, 6 H), 5.04 (ABq, $\delta\nu$ = 88 Hz, J = 12 Hz, 2 H), 3.77 (m, 4 H), 1.00 (m, 2 H), 0.53 (m, 2 H); MS (CI) 389 (MH^+, 100). Anal. ($C_{22}H_{20}N_4O_3$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(4-cyanophenyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4x): 55%; mp 173–5 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.56 (dd, J = 5, 2 Hz, 1 H), 8.31 (d, J = 5 Hz, 1 H), 8.21 (br s, 1 H), 8.08 (dd, J = 8, 2 Hz, 1 H), 7.63 (d, J = 9 Hz, 2 H), 7.06–7.12 (m, 4 H), 5.16 (ABq, $\delta\nu$ = 74 Hz, J = 12 Hz, 2 H), 3.77 (m, 1 H), 1.00 (m, 2 H), 0.52 (m, 2 H); MS (CI) 384 (MH^+, 85), 89 (100). Anal. ($C_{22}H_{17}N_5O_2 \cdot 0.5$EtOAc) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[[(4-nitrophenyl)oxy]-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4y): 60%; mp 225–6 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 8.57 (dd, J = 5, 2 Hz, 1 H), 8.33 (m, 2 H), 8.23 (d, J = 9 Hz, 2 H), 8.08 (dd, J = 8, 2 Hz, 1 H), 7.06–7.16 (m, 4 H), 5.22 (ABq, $\delta\nu$ = 72 Hz, J = 12 Hz, 2 H), 3.78 (m, 1 H), 1.02 (m, 2 H), 0.52 (m, 2 H); MS (CI) 404 (MH^+, 100). Anal. ($C_{21}H_{17}N_5O_4$) C, H, N.

Synthesis of Compound 4z. Compound **4z** was synthesized from 2-methoxy-4-(phenylmethyl)-3-pyridinecarbamic acid, 1,1-dimethyl ester[9] in a four-step procedure directly analogous to that which has been reported for the synthesis of nevirapine.[9]

3-Amino-2-methoxy-4-(phenylmethyl)pyridine: prepared from 2-methoxy-4-(phenylmethyl)-3-pyridinecarbamic acid, 1,1-dimethyl ester;[9] 99%; ^{1}H-NMR ($CDCl_3$) δ 7.55 (d, J = 5 Hz, 1 H), 7.16–7.33 (m, 5 H), 6.61 (d, J = 5 Hz, 1 H), 3.98 (s, 3 H), 3.87 (s, 2 H); MS (CI) 215 (MH^+, 100).

2-Chloro-*N*-[2-methoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide: prepared from 3-amino-2-methoxy-4-(phenylmethyl)pyridine; 77%; ^{1}H-NMR ($CDCl_3$) δ 8.50 (dd, J = 5, 2 Hz, 1 H), 8.08 (dd, J = 8, 2 Hz, 1 H), 7.99 (d, J = 5 Hz, 1 H), 7.79 (br s, 1 H), 7.36 (dd, J = 8, 5 Hz, 1 H), 7.13–7.31 (m, 5 H), 4.07 (s, 2 H), 3.98 (s, 3 H).

2-(Cyclopropylamino)-*N*-[2-methoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide: prepared from 2-chloro-*N*-[2,6-dimethoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide; 41%; ^{1}H-NMR ($CDCl_3$) δ 8.37 (dd, J = 5, 2 Hz, 1 H), 8.01 (br s, 1 H), 7.97 (d, J = 5 Hz, 1 H), 7.52 (dd, J = 8, 2 Hz, 1 H), 7.07–7.26 (m, 5 H), 6.74 (d, J = 5 Hz, 1 H), 6.55 (dd, J = 8, 5 Hz, 1 H), 3.95 (s, 2 H), 3.93 (s, 3 H), 2.88 (m, 1 H), 0.83 (m, 2 H), 0.55 (m, 2 H).

11-Cyclopropyl-5,11-dihydro-4-(phenylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4z): prepared from 2-(cyclopropylamino)-*N*-[2-methoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide; 63%; mp 188–9 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.52 (dd, J = 5, 2 Hz, 1 H), 8.22 (d, J = 5 Hz, 1 H), 8.04 (dd, J = 8, 2 Hz, 1 H), 6.91–7.64 (m, 8 H), 4.11 (m, 2 H), 3.75 (m, 1 H), 0.98 (m, 2 H), 0.46 (m, 2 H); MS (CI) 343 (MH^+, 100). Anal. ($C_{21}H_{18}N_4O$) C, H, N.

Syntheses of Compounds 4aa,ab,ac. Compounds **4ac**,**ab**,**ac** were obtained as side products in the syntheses of compounds **4c**,**w**,**q**, respectively.

11-Cyclopropyl-5,11-dihydro-4-[(2-hydroxyphenyl)-methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4aa): side product from the synthesis of **4c**; 47%; mp 243–5 °C (EtOAc:hexanes); ^{1}H-NMR (DMSO-d_6) δ 10.03 (br s, 1 H), 9.79 (br s, 1 H), 8.51 (dd, J = 5, 2 Hz, 1 H), 8.06 (d, J = 5 Hz, 1 H), 7.98 (dd, J = 8, 2 Hz, 1 H), 7.19 (dd, J = 8, 5 Hz, 1 H), 7.03–7.10 (m, 2 H), 6.87 (d, J = 5 Hz, 1 H), 6.72–6.81 (m, 2 H), 3.97 (s, 2 H), 3.62 (m, 1 H), 0.87 (m, 2 H), 0.36 (m, 2 H); MS (CI) 359 (MH^+, 100); HRMS calcd for $C_{21}H_{18}N4O_2$ (MH^+) 359.1508, found 359.1503. Anal. ($C_{21}H_{18}N_4O_2$) H; C: calcd, 70.38; found, 69.91. N: calcd, 15.63; found, 14.65.

11-Cyclopropyl-5,11-dihydro-4-[(2-hydroxy-5-methoxyphenyl)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4ab): side product from the synthesis of **4w**; 23%; mp 253–5 °C (EtOAc:hexanes); ^{1}H-NMR ($CDCl_3$) δ 9.74 (br s, 1 H), 8.54 (dd, J = 5, 2 Hz, 1 H), 8.11–8.18 (m, 2 H), 7.07–7.11 (m, 2 H), 6.90 (d, J = 9 Hz, 1 H), 6.81 (d, J = 3 Hz, 1 H), 6.68 (dd, J = 9, 3 Hz, 1 H), 4.22 (d, J = 14 Hz, 1 H), 3.63–3.75 (m, 5 H), 0.96 (m, 2 H), 0.47 (m, 2 H); MS (CI) 389 (MH^+, 100). Anal. ($C_{22}H_{20}N_4O_3$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-[(2-hydroxy-4-methylphenyl)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (4ac): side product from the synthesis of **4q**; 28%; mp 255–7 °C (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 9.92 (br s, 1 H), 8.67 (br s, 1 H), 8.54 (dd, J = 5, 2 Hz, 1 H), 8.15–8.18 (m, 2 H), 7.06–7.18 (m, 3 H), 6.81 (s, 1 H), 6.71 (d, J = 7 Hz, 1 H), 4.22 (d, J = 14 Hz, 1 H), 3.72 (m, 1 H), 3.63 (d, J = 14 Hz, 1 H), 2.25 (s, 3 H), 0.94 (m, 2 H), 0.45 (m, 2 H); MS (CI) 373 (MH^+, 100). Anal. ($C_{22}H_{20}N_4O_2$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-ethenyl-6*H*-dipyrido-[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (6a). Methyltriphenylphosphonium bromide (0.66 g, 1.84 mmol) was dissolved in 1 mL of THF and treated with 0.72 mL (1.80 mmol) of a 2.5 M solution of *n*-BuLi. After 15 min, a solution of **5**[8] (0.20 g, 0.71 mmol) in 4 mL of THF was added dropwise. The mixture was stirred an additional 15 min at which point the precipitate was collected by filtration, washed with THF, and purified by flash chromatography (1:1 EtOAc:hexanes): 0.08 g, 39%; mp

257–9 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.67 (dd, J = 5, 2 Hz, 1 H), 8.12 (d, J = 5 Hz, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 7.99 (br s, 1 H), 7.05–7.16 (m, 2 H), 6.91 (dd, J = 17, 11 Hz, 1 H), 5.90 (d, J = 17 Hz, 1 H), 5.75 (d, J = 11 Hz, 1 H), 3.77 (m, 1 H), 1.00 (m, 2 H), 0.50 (m, 2 H); MS (CI) 279 (MH^+, 100). Anal. ($C_{16}H_{14}N_4O$) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(2-phenylethenyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (6b): prepared from benzyltriphenylphosphonium chloride and **5**,[8] analogously to the procedure described for the preparation of **6a**; 79%; mp 263–5 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 9.36 (br s, 1 H), 8.51 (dd, J = 5, 2 Hz, 1 H), 8.26 (d, J = 5 Hz, 1 H), 7.88 (d, J = 8, 2 Hz, 1 H), 7.09–7.57 (m, 8 H), 6.94 (dd, J = 8, 5 Hz, 1 H), 3.77 (m, 1 H), 0.97 (m, 2 H), 0.49 (m, 2 H); MS (CI) 355 (MH^+, 100). Anal. ($C_{22}H_{18}N_4O$·0.25CH_3CN) C, H, N.

4-(2-Carbethoxyethenyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (6c). A solution of triethyl phosphonoacetate (0.33 g, 1.48 mmol) in 2 mL of THF was added dropwise to an ice-cooled suspension of NaH (0.45 g, 1.50 mmol) in 0.5 mL of THF. After 15 min, a solution of **5**[8] (0.20 g, 0.71 mmol) in 3 mL of THF was added, and the mixture was allowed to warm to room temperature over 2 h. The supernatant was poured into H_2O and then extracted into EtOAc. The organic extract was washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated. Further purification was achieved using flash chromatography (1:1 EtOAc:hexanes): 0.19 g, 76%; mp 224–6 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.85 (br s, 1 H), 8.55 (dd, J = 5, 2 Hz, 1 H), 8.29 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.95 (d, J = 16 Hz, 1 H), 7.20 (d, J = 5 Hz, 1 H), 7.08 (dd, J = 8, 5 Hz, 1 H), 6.55 (d, J = 16 Hz, 1 H), 4.20 (q, J = 6 Hz, 2 H), 3.70 (m, 1 H), 1.29 (t, J = 6 Hz, 3 H), 1.01 (m, 2 H), 0.55 (m, 2 H); MS (CI) 351 (MH^+, 100). Anal. ($C_{19}H_{18}N_4O_3$) C, H, N.

4-(2-Carboxyethenyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (6d). Compound **6d** (0.19 g, 0.5 mmol) was treated with KOH (0.21 g, 5 mmol) in 20 mL of EtOH overnight. Upon removal of solvent, the residue was dissolved in H_2O and washed with EtOAc. The aqueous layer was acidified with HCl and the resulting precipitate filtered off, washed, and dried: 0.16 g, 93%; mp 300 °C dec; ^{1}H-NMR (DMSO-d_6) δ 12.75 (br s, 1 H), 10.50 (br s, 1 H), 8.55 (dd, J = 5, 2 Hz, 1 H), 8.24 (d, J = 5 Hz, 1 H), 8.05 (dd, J = 8, 2 Hz, 1 H), 7.87 (d, J = 16 Hz, 1 H), 7.60 (d, J = 5 Hz, 1 H), 7.21 (dd, J = 8, 5 Hz, 1 H), 6.70 (d, J = 16 Hz, 1 H), 3.69 (m, 1 H), 0.98 (m, 2 H), 0.40 (m, 2 H); MS (CI) 323 (MH^+, 100). Anal. ($C_{17}H_{14}N_4O_3$·0.5H_2O) C, H, N.

11-Cyclopropyl-5,11-dihydro-4-(2-phenylethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7b). Compound **6b** (0.08 g, 0.2 mmol) was hydrogenated at 50 psi over 10% Pd/C in 50 mL of EtOH overnight. Removal of catalyst and solvent left a residue that was purified by flash chromatography (1:1 EtOAc:hexanes): 0.04 g, 72%; mp 204–5 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.55 (dd, J = 5, 2 Hz, 1 H), 8.21 (d, J = 5 Hz, 1 H), 8.00 (dd, J = 8, 2 Hz, 1 H), 7.72 (br s, 1 H), 6.90–7.21 (m, 7 H), 3.77 (m, 1 H), 2.85–3.15 (m, 4 H), 1.01 (m, 2 H), 0.49 (m, 2 H); MS (CI) 357 (MH^+, 100). Anal. ($C_{22}H_{20}N_4O$) C, H, N.

4-(2-Carbethoxyethyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7c): prepared from **6c** analogously to the procedure described for the conversion of **6b** to **7b**; 98%; mp 166–8 °C; ^{1}H-NMR ($CDCl_3$) δ 9.15 (br s, 1 H), 8.55 (dd, J = 5, 2 Hz, 1 H), 8.20 (d, J = 5 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.89 (d, J = 5 Hz, 1 H), 4.19 (m, 2 H), 3.75 (m, 1 H), 2.60–3.15 (m, 4 H), 1.25 (t, J = 6 Hz, 3 H), 1.05 (m, 2 H), 0.50 (m, 2 H); MS (CI) 353 (MH^+, 100). Anal. ($C_{19}H_{20}N_4O_3$) C, H, N.

4-(2-Carboxyethyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7d): prepared from **6d** analogously to the procedure described for the conversion of **6b** to **7b**; 42%; mp 267–9 °C; ^{1}H-NMR (DMSO-d_6) δ 12.35 (br s, 1 H), 10.02 (br s, 1 H), 8.50 (dd, J = 5, 2 Hz, 1 H), 8.15 (d, J = 5 Hz, 1 H), 8.05 (dd, J = 8, 2 Hz, 1 H), 7.21 (dd, J = 8, 5 Hz, 1 H), 7.10 (d, J = 5 Hz, 1 H), 3.65 (m, 1 H), 2.80–3.20 (m, 2 H), 2.51–2.69 (m, 2 H), 0.89 (m, 2 H), 0.42 (m, 2 H); MS (CI) 325 (MH^+, 100). Anal. ($C31_7H_{16}N_4O_3$·0.5H_2O) C, H, N.

Syntheses of 2-Methoxy-4-substituted-dipyridodiazepinones 11a–g. a. Preparation of 11a–c. Compounds **11a–c** were synthesized from **10a–c**, respectively, in four-step procedures directly analogous to that which has already been reported for the synthesis of nevirapine.[9]

3-Amino-2,6-dimethoxy-4-(phenylmethyl)pyridine: prepared from **10a**[9] in 100% yield; ^{1}H-NMR ($CDCl_3$) δ 7.16–7.32 (m, 5 H), 6.08 (s, 1 H), 3.95 (s, 3 H), 3.87 (s, 2 H), 3.83 (s, 3 H); MS (CI) 245 (MH^+, 100).

2-Chloro-*N*-[2,6-dimethoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide: prepared from 3-amino-2,6-dimethoxy-4-(phenylmethyl)pyridine; 72%; mp 182–3 °C; ^{1}H-NMR ($CDCl_3$) δ 8.51 (dd, J = 5, 2 Hz, 1 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.49 (br s, 1 H), 7.36 (dd, J = 8, 5 Hz, 1 H), 7.12–7.32 (m, 5 H), 6.15 (s, 1 H), 4.01 (s, 2 H), 3.98 (s, 3 H), 3.89 (s, 3 H); MS (CI) 384 (MH^+, 100).

2-(Ethylamino)-*N*-[2,6-dimethoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide: prepared from 2-chloro-*N*-[2,6-dimethoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide; 86%; mp 171–2 °C; ^{1}H-NMR ($CDCl_3$) δ 8.25 (d, J = 5 Hz, 1 H), 8.0 (br s, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.10–7.25 (m, 5 H), 6.95 (br s, 1 H), 6.61 (dd, J = 5, 8 Hz, 1 H), 6.20 (s, 1 H), 3.91 (s, 5 H), 3.89 (s, 3 H), 3.45–3.89 (m, 2 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI) 393 (MH^+, 100).

5,11-Dihydro-11-ethyl-2-methoxy-4-(phenylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11a): prepared from 2-(ethylamino)-*N*-[2,6-dimethoxy-4-(phenylmethyl)-3-pyridinyl]-3-pyridinecarboxamide; 89%; mp 197–8 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.42 (dd, J = 5, 2 Hz, 1 H), 8.09 (dd, J = 8, 2 Hz, 1 H), 7.58 (br s, 1 H), 7.10–7.40 (m, 5 H), 7.00 (dd, J = 8, 5 Hz, 1 H), 6.45 (s, 1 H), 4.17 (q, J = 7 Hz, 2 H), 3.99 (s, 2 H), 3.89 (s, 3 H), 1.28 (t, J = 7 Hz, 3 H); MS (CI) 361 (MH^+, 100). Anal. ($C_{21}H_{20}N_4O$) C, H, N.

3-Amino-4-[(benzyloxy)methyl]-2,6-dimethoxypyridine: prepared from **10b**;[9] 89%; mp (HCl salt) 182–3 °C; ^{1}H-NMR (HCl salt, $CDCl_3$) δ 7.29–7.30 (m, 5 H), 6.37 (s, 1 H), 4.95 (s, 2 H), 4.65 (s, 2 H), 3.99 (s, 3 H), 3.91 (s, 3 H); MS (CI) 275 (MH^+, 100).

2-Chloro-*N*-[4-[(benzyloxy)methyl]-2,6-dimethoxy-3-pyridinyl]-3-pyridinyl]-3-pyridinecarboxamide: prepared from 3-amino-4-[(benzylyoxy)methyl]-2,6-dimethoxypyridine; 47%; mp 114–6 °C; ^{1}H-NMR ($CDCl_3$) δ 8.51 (dd, J = 5, 2 Hz, 1 H), 8.10 (dd, J = 8, 2 Hz, 1 H), 7.66 (br s, 1 H), 7.26–7.39 (m, 6 H), 6.59 (s, 1 H), 4.58 (s, 2 H), 4.57 (s, 2 H), 3.97 (s, 3 H), 3.93 (s, 3 H); MS (CI) 414 (MH^+, 100).

2-(Ethylamino)-*N*-[4-[(benzyloxy)methyl]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide: prepared from 2-chloro-*N*-[4-[(benzyloxy)methyl]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide; 94%; mp 111–3 °C; ^{1}H-NMR ($CDCl_3$) δ 8.28 (dd, J = 5, 2 Hz, 1 H), 7.97 (br s, 1 H), 7.69 (dd, J = 8, 2 Hz, 1 H), 7.41 (br s, 1 H), 7.32–7.42 (m, 5 H), 6.48–6.54 (m, 2 H), 4.54 (s, 2 H), 4.51 (s, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.44–3.55 (m, 2 H), 1.25 (t, J = 7 Hz, 3 H), MS (CI) 423 (MH^+, 100).

4-[(Benzyloxy)methyl]-5,11-dihydro-2-methoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11b): prepared from 2-(ethylamino)-*N*-[4-[(benzyloxy)methyl]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide; 77%; mp 136–8 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.42 (m, 2 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 7.30–7.45 (m, 5 H), 6.99 (dd, J = 8, 5 Hz, 1 H), 6.35 (s, 1 H), 4.61 (s, 2 H), 4.50 (s, 2 H), 4.17 (q, J = 7 Hz, 2 H), 3.90 (s, 3 H), 1.27 (t, J = 7 Hz, 3 H); MS (CI) 391 (MH^+, 100). Anal. ($C_{22}H_{22}N_4O_3$·0.25H_2O) C, H, N.

4-[2-(1,3-Dioxanyl)]-2,6-dimethoxy-3-pyridinecarbamic Acid, 1,1-Dimethylethyl Ester (10c). A mixture of 2,6-dimethoxy-4-formyl-3-pyridinecarbamic acid, 1,1-dimethyl ester[9] (10.94 g, 282 mmol), 1,3-propanediol (8 g, 100 mmol), Amberlyst 15 ion exchange resin (5 g) and 4 Å molecular sieves (5 g) in 50 mL of THF was stirred at room temperature overnight. The solids were then removed by filtration, and the solution was concentrated on a rotary evaporator. The oily residue was diluted with 100 mL of Et_2O and washed sequentially with saturated solutions of $NaHCO_3$ and NaCl. Upon drying with $MgSO_4$ and concentration, 10.89 g (87%) of **10c** was obtained as a white solid which was used without further purification: mp 106–7 °C; ^{1}H-NMR ($CDCl_3$) δ 6.54 (s, 1 H),

5.88 (br s, 1 H), 5.57 (s, 1 H), 4.20–4.30 (m, 2 H), 3.80–4.05 (m, 8 H), 2.15–2.31 (m, 1 H), 1.40–1.50 (br s, 10 H); MS (CI) 341 (MH^+, 90), 79 (100).

3-Amino-4-(2-(1,3-dioxanyl))-2,6-dimethoxypyridine. Prepared from **10c**, 95%; mp (HCl Salt) 172–3 °C; ^{1}H-NMR (HCl Salt, DMSO-d_6) δ 6.49 (s, 1 H), 5.78 (s, 1 H), 3.90–4.30 (m, 7 H), 3.81 (s, 3 H), 1.99–2.20 (m, 1 H), 1.30–1.48 (m, 1 H); MS (CI) 241 (MH^+, 100).

2-Chloro-*N*-[4-[2-(1,3-dioxanyl)]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide: prepared from 3-amino-4-[2-(1,3-dioxanyl)]-2,6-dimethoxypyridine; 86%; mp 209–11 °C; ^{1}H-NMR ($CDCl_3$) δ 8.52 (dd, J = 5, 2 Hz, 1 H), 8.25 (dd, J = 8, 2 Hz, 1 H), 7.81 (br s, 1 H), 7.45 (dd, J = 5, 8 Hz, 1 H), 6.61 (s, 1 H), 5.62 (s, 1 H), 3.95–4.30 (m, 7 H), 3.90 (s, 3 H), 2.10–2.29 (m, 1 H), 1.40–1.51 (m, 1 H); MS (CI) 380 (MH^+, 100).

2-(Ethylamino)-*N*-[4-[2-(1,3-dioxanyl)]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide: prepared from 2-chloro-*N*-[4-[2-(1,3-dioxanyl)]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide; 77%; mp 173–5 °C; ^{1}H-NMR ($CDCl_3$) δ 8.28 (dd, J = 5, 2 Hz, 1 H), 8.04 (br s, 1 H), 7.74 (dd, J = 8, 2 Hz, 1 H), 7.48 (br s, 1 H), 6.60 (s, 1 H), 6.53 (dd, J = 8, 5 Hz, 1 H), 5.50 (s, 1 H), 3.80–4.40 (m, 10 H), 3.41–3.55 (m, 2 H), 2.05–2.20 (m, 1 H), 1.32–1.41 (m, 1 H), 1.26 (t, J = 7 Hz, 3 H); MS (CI) 389 (MH^+, 100).

5,11-Dihydro-4-[2-(1,3-dioxanyl)]-11-ethyl-2-methoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11c): prepared from 2-(ethylamino)-*N*-[4-[2-(1,3-dioxanyl)]-2,6-dimethoxy-3-pyridinyl]-3-pyridinecarboxamide; 66%; mp 139–40 °C (i-Pr_2O); ^{1}H-NMR ($CDCl_3$) δ 8.43 (dd, J = 5, 2 Hz, 1 H), 8.38 (br s, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 7.00 (dd, J = 8, 5 Hz, 1 H), 6.65 (s, 1 H), 5.50 (s, 1 H), 4.25–4.35 (m, 2 H), 4.17 (q, J = 7 Hz, 2 H), 3.95–4.08 (m, 2 H), 3.85 (s, 3 H), 2.20–2.45 (m, 1 H), 1.45–1.60 (m, 1 H), 1.23 (t, J = 7 Hz, 3 H); MS (CI) 357 (MH^+, 100). Anal. ($C_{18}H_{20}N_4O_4$) C, H, N.

b. Preparation of 11d–g. 5,11-Dihydro-11-ethyl-4-formyl-2-methoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11d). A solution of 0.724 g (2 mmol) of **11c** was dissolved in 10 mL of a 4:1 mixture of AcOH:H_2O and heated to 100 °C overnight.[10] The mixture was then cooled and poured into a solution of saturated $NaHCO_3$. The product was next extracted into EtOAc and isolated after drying with $MgSO_4$ and removal of solvent. Further purification by flash chromatography over silica gel (1:1 hexanes:EtOAc) produced **11d** in 69% yield: mp 178–80 °C (CH_3CN:H_2O); ^{1}H-NMR ($CDCl_3$) δ 9.91 (s, 1 H), 9.89 (br s, 1 H), 8.40 (dd, J = 5, 1 Hz, 1 H), 8.10 (dd, J = 8, 1 Hz, 1 H), 6.96 (dd, J = 8, 5 Hz, 1 H), 6.77 (s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 3.89 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H); MS (CI) 299 (MH^+, 100). Anal. ($C_{15}H_{14}N_4O_3$·0.5H_2O) C, H, N.

5,11-Dihydro-11-ethyl-4-(hydroxymethyl)-2-methoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11e). A solution of 0.12 g (0.37 mmol) of **11d** was dissolved in 1 mL of isopropyl alcohol and cooled to 0 °C. Sodium borohydride (0.04 g, 1.1 mmol) was added, and the reaction was monitored by TLC. After 2 h a second portion of $NaBH_4$ was added, and the reaction was quenched 1 h later by the addition of 2 mL of H_2O and 2 mL of saturated $NaHCO_3$. Partitioning between H_2O and EtOAc gave an organic layer that was dried over $MgSO_4$ and concentrated to produce the crude alcohol. Flash chromatography (1:1 EtOAc:hexanes) produced 90 mg (81%) of purified **11e**: mp 206–8 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.78 (br s, 1 H), 8.45 (dd, J = 5, 2 Hz, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 7.01 (dd, J = 8, 5 Hz, 1 H), 6.40 (s, 1 H), 4.71 (s, 2 H), 4.20 (q, J = 7 Hz, 2 H), 3.89 (s, 3 H), 2.80 (br s, 1 H), 1.28 (t, J = 7 Hz, 3 H); MS (CI) 301 (MH^+, 100). Anal. ($C_{15}H_{16}N_4O_3$·0.5H_2O) C, H, N.

5,11-Dihydro-4-(chloromethyl)-11-ethyl-2-methoxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (11f). A solution of **11e** (0.51 g, 1.31 mmol) and i-Pr_2NEt (0.17 g, 1 mmol) in CH_2Cl_2 at 0 °C was added to a solution of thionyl chloride (0.17 g, 1 mmol) in 1 mL of CH_2Cl_2. After 15 min the mixture was poured into 1 N HCl, and the CH_2Cl_2 layer was washed once with 1 N HCl, dried over $MgSO_4$, and concentrated to give an oil that was purified by flash chromatography (1:3 EtOAc:hexanes): 0.31 g, 75%; ^{1}H-NMR ($CDCl_3$) δ 8.45 (m, 1 H), 8.17 (dd, J = 8, 2 Hz, 1 H), 7.79 (br s, 1 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.49 (s, 1 H), 4.51 (s, 2 H), 4.19 (q, J = 7 Hz, 2 H), 3.89 (s, 3 H), 1.28 (t, J = 7 Hz, 3 H).

5,11-Dihydro-11-ethyl-2-methoxy-4-(phenoxymethyl)-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one (11g): prepared from **11f** in 66% yield by a method analogous to that shown above for the synthesis of **4a** from **3**; mp 164–6 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.43 (dd, J = 5, 2 Hz, 1 H), 8.20 (br s, 1 H), 8.10 (dd, J = 8, 2 Hz, 1 H), 7.10–7.40 (m, 3 H), 6.95–7.10 (m, 3 H), 6.54 (s, 1 H), 5.02 (s, 2 H), 4.21 (q, J = 7 Hz, 2 H), 3.90 (s, 3 H), 1.30 (t, J = 7 Hz, 3 H); MS (CI) 377 (MH^+, 100). Anal. ($C_{21}H_{20}N_4O_3$) C, H, N.

Syntheses of 2-Hydroxy-4-substituted-dipyridodiazepinones 12a–g. 5,11-Dihydro-11-ethyl-2-hydroxy-4-(phenylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12a). A mixture of **11a** (0.44 g, 1.2 mmol), LiI (0.5 g, 3.7 mmol), and 2,6-collidine (4 mL) was placed in a sealed tube and heated at 160 °C overnight.[11] The tube was carefully opened, and the hot solution was poured into a mixture of EtOAc and 0.1 N HCl. The EtOAc layer was washed with 0.1 N HCl three times, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (1:1 EtOAc:hexanes): 276 mg, 65%; mp 260–2 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.41 (dd, J = 5, 2 Hz, 1 H), 8.05 (dd, J = 8, 2 Hz, 1 H), 7.15–7.40 (m, 6 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.33 (s, 1 H), 4.17 (q, J = 7 Hz, 2 H), 3.95 (s, 2 H), 1.21 (t, J = 7 Hz, 3 H); MS (CI) 347 (MH^+, 100). Anal. ($C_{20}H_{18}N_4O_2$) C, H, N.

4-[(Benzyloxy)methyl]-5,11-dihydro-11-ethyl-2-hydroxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12b): prepared from **11b** in 37% yield by a method analogous to that shown for the conversion of **11a** to **12a** (note: only heated for 2 h); mp 205–7 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.55 (br s, 1 H), 8.39 (m, 1 H), 8.16 (m, 1 H), 7.30–7.45 (m, 5 H), 7.18 (dd, J = 8, 5 Hz, 1 H), 6.39 (s, 1 H), 4.61 (s, 2 H), 4.48 (s, 2 H), 4.12 (q, J = 7 Hz, 2 H), 1.27 (t, J = 7 Hz, 3 H); MS (CI) 377 (MH^+, 100). Anal. ($C_{21}H_{20}N_4O_3$) C, H, N.

5,11-Dihydro-4-[2-(1,3-dioxanyl)]-11-ethyl-2-hydroxy-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12c): prepared from **11c** in 79% yield by a method analogous to that shown for the conversion of **11a** to **12a**; mp 235–6 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.40 (dd, J = 5, 2 Hz, 1 H), 8.37 (br s, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 7.03 (dd, J = 8, 5 Hz, 1 H), 6.62 (s, 1 H), 5.50 (s, 1 H), 4.29–4.35 (m, 2 H), 3.97–4.11 (m, 4 H), 2.20–2.30 (m, 1 H), 1.45–1.60 (m, 1 H), 1.19 (t, J = 7 Hz, 3 H); MS (CI) 343 (MH^+, 100); HRMS calcd for $C_{17}H_{18}N_4O_4$ 342.1328, found 342.1336.

5,11-Dihydro-11-ethyl-4-formyl-2-hydroxy-6*H*-dipyrido-[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12d): prepared from **12c** in 63% yield by a method analogous to that shown for the conversion of **11c** to **11d**; mp 250 °C dec; ^{1}H-NMR ($CDCl_3$) δ 9.95 (s, 1 H), 9.75 (br s, 1 H), 8.40 (dd, J = 5, 1 Hz, 1 H), 8.21 (dd, J = 8, 1 Hz, 1 H), 7.10 (dd, J = 8, 5 Hz, 1 H), 6.85 (s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 1.20 (t, J = 7 Hz, 3 H); MS (CI) 285 (MH^+, 30), 75 (100); HRMS calcd for $C_{14}H_{12}N_4O_3$ 284.0909, found 284.0899.

5,11-Dihydro-11-ethyl-2-hydroxy-4-(hydroxymethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12e): prepared from **12d** in 62% yield by a method analogous to that shown for the conversion of **11d** to **11e**; mp 260–2 °C (MeOH); ^{1}H-NMR (DMSO-d_6) δ 9.95 (br s, 1 H), 8.44 (dd, J = 5, 2 Hz, 1 H), 8.00 (dd, J = 8, 2 Hz, 1 H), 7.15 (dd, J = 8, 5 Hz, 1 H), 6.50 (s, 1 H), 5.45 (t, J = 7 Hz, 1 H), 4.55 (d, J = 7 Hz, 2 H), 4.11 (q, J = 7 Hz, 2 H), 1.19 (t, J = 7 Hz, 3 H); MS (CI) 287 (MH^+, 100); HRMS calcd for $C_{14}H_{14}N_4O_3$ 286.1066, found 286.1059.

5,11-Dihydro-11-ethyl-2-hydroxy-4-(phenoxymethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (12g): prepared from **11g** in 40% yield by a method analogous to that shown above for the synthesis of **12a** from **11a** (note: only heated for 2 h); mp 237–9 °C (CH_3CN); ^{1}H-NMR (DMSO-d_6) δ 8.44 (dd, J = 5, 2 Hz, 1 H), 8.02 (dd, J = 8, 2 Hz, 1 H), 7.26–7.31 (m, 2 H), 7.19 (dd, J = 8, 5 Hz, 1 H), 6.95–7.10 (m, 3 H), 6.50 (s, 1 H), 5.22 (s, 2 H), 4.05 (q, J = 7 Hz, 2 H), 1.30 (t, J = 7 Hz, 3 H); MS (CI) 363 (MH^+, 100); HRMS calcd for $C_{20}H_{18}N_4O_3$ 362.1379, found 362.1385.

Syntheses of 2-(3-Methoxyphenyl)-4-substituted-dipyridodiazepinones 13a–g. 5,11-Dihydro-11-ethyl-2-(3-methoxyphenyl)-4-(phenylmethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13a). To a mixture of **12a** (0.16 g, 0.46 mmol) and diisopropylethylamine (0.06 g, 0.46 mmol) in 10 mL of CH_2Cl_2 cooled to 0 °C was added dropwise a solution of Tf_2O (0.13 g, 0.46 mmol) in 2 mL of CH_2Cl_2. After 15 min the solvent was removed by rotary evaporation to produce the crude triflate that was purified by flash chromatography (1:4 EtOAc:hexanes). Yield: 0.22 g, 100%. The purified triflate was mixed with 3-(tri-*n*-butylstannyl)anisole (0.60 g, 2 mmol), $Pd(Cl)_2(Ph_3P)_2$ (0.07 g, 0.1 mmol), and LiCl (0.17 g, 4.0 mmol) in 5 mL of DMF under an argon atmosphere, and the mixture was heated at 110 °C overnight.[12] Upon cooling, the solution was treated with 2 mL of 1 M Bu_4NF in THF and then partitioned between EtOAc and H_2O. After drying ($MgSO_4$) and concentration of the EtOAc layer, the residue was chromatographed (1:1 EtOAc:hexanes) to yield 0.12 g (76%) of the desired product **13a**: mp 177–9 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.45 (dd, J = 5, 2 Hz, 1 H), 8.09 (dd, J = 8, 2 Hz, 1 H), 7.65 (s, 1 H), 7.15–7.59 (m, 9 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.99 (m, 1 H), 4.25 (m, 4 H), 3.89 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H); MS (CI) 437 (MH^+, 100). Anal. ($C_{27}H_{24}N_4O_2$) C, H, N.

4-[(Benzyloxy)methyl]-5,11-dihydro-11-ethyl-2-(3-methoxyphenyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13b): prepared from **12b** in 54% overall yield (Tf_2O reaction, 72%; X-coupling, 75%) by a method analogous to that shown for the conversion of **12a** to **13a**; mp 112–3 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.66 (br s, 1 H), 8.44 (dd, J = 5, 3 Hz, 1 H), 8.14 (dd, J = 8, 3 Hz, 1 H), 7.59 (s, 1 H), 7.19–7.54 (m, 8 H), 7.00 (dd, J = 8, 5 Hz, 1 H), 6.93 (m, 1 H), 4.67 (s, 2 H), 4.63 (s, 2 H), 4.33 (q, J = 7 Hz, 2 H), 3.88 (s, 3 H), 1.27 (t, J = 7 Hz, 3 H); MS (CI) 437 (MH^+, 100). Anal. ($C_{27}H_{24}N_4O_2$) C, H, N.

5,11-Dihydro-4-[2-(1,3-dioxanyl)]-11-ethyl-2-(3-methoxyphenyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13c): prepared from **12c** in 73% overall yield (Tf_2O reaction, 73%; X-coupling, 100%) by a method analogous to that shown for the conversion of **12a** to **13a**; mp 141–3 °C (heptane); ^{1}H-NMR ($CDCl_3$) δ 8.62 (br s, 1 H), 8.48 (dd, J = 5, 2 Hz, 1 H), 8.15 (dd, J = 8, 2 Hz, 1 H), 7.65 (m, 2 H), 7.54 (d, J = 8 Hz, 1 H), 7.43 (t, 8 Hz, 1 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.91 (dd, J = 8, 2 Hz, 1 H), 5.55 (s, 1 H), 4.01–4.45 (m, 6 H), 3.88 (s, 3 H), 2.20–2.30 (m, 1 H), 1.45–1.60 (m, 1 H), 1.19 (t, J = 7 Hz, 3 H); MS (CI) 433 (MH^+, 100); HRMS calcd for $C_{24}H_{14}N_4O_4$ 432.1797, found 432.1801.

5,11-Dihydro-11-ethyl-4-formyl-2-(3-methoxyphenyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13d): prepared from **13c** in 68% yield by a method analogous to that shown for the conversion of **11c** to **11d**; mp 188–9 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 10.25 (br s, 1 H), 10.02 (s, 1 H), 8.50 (dd, J = 5, 2 Hz, 1 H), 8.19 (dd, J = 8, 2 Hz, 1 H), 7.75 (s, 1 H), 7.58–7.64 (m, 2 H), 7.40 (t, J = 8 Hz, 1 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 6.98 (dd, J = 8, 3 Hz, 1 H), 4.15 (q, J = 6 Hz, 2 H), 3.88 (s, 3 H), 1.20 (t, J = 6 Hz, 3 H); MS (CI) 375 (MH^+, 100). Anal. ($C_{21}H_{18}N_4O_3$) C, H, N.

5,11-Dihydro-11-ethyl-2-(3-methoxyphenyl)-4-(hydroxymethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13e): prepared from **13d** in 32% yield by a method analogous to that shown for the conversion of **11d** to **11e**; mp 222–3 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.85 (br s, 1 H), 8.46 (dd, J = 5, 2 Hz, 1 H), 8.15 (dd, J = 8, 2 Hz, 1 H), 7.54–7.72 (m, 2 H), 6.93–7.35 (m, 4 H), 4.86 (s, 2 H), 4.33 (q, J = 2 Hz, 2 H), 3.88 (s, 3 H), 1.28 (t, J = 6 Hz, 3 H); MS (CI) 377 (MH^+, 100). Anal. ($C_{21}H_{20}N_4O_3$) C, H, N.

5,11-Dihydro-11-ethyl-2-(3-methoxyphenyl)-4-(phenoxymethyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (13g): prepared from **12g** in 30% overall yield (Tf_2O reaction, 33%; X-coupling, 91%) by a method analogous to that shown above for the synthesis of **13a** from **12a**; mp 204–6 °C (CH_3CN); ^{1}H-NMR ($CDCl_3$) δ 8.48 (br s, 1 H), 8.32 (dd, J = 5, 2 Hz, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 6.9–7.6 (m, 11 H), 5.12 (s, 2 H), 4.35 (q, J = 2 Hz, 2 H), 3.88 (s, 3 H), 1.29 (t, J = 6 Hz, 3 H); MS (CI) 453 (MH^+, 65), 95 (100). Anal. ($C_{27}H_{24}N_4O_3 \cdot 0.3H_2O$) C, H, N.

Supporting Information Available: Copies of ^{1}H-NMR spectra of **4o,p,r,u,aa**, **12c–g**, and **13c** (10 pages). Ordering information is given on any current masthead page.

References

(1) Proudfoot, J. R.; Hargrave, K. D.; Kapadia, S. R.; Patel, U. R.; Grozinger, K. G.; McNeil, D. W.; Cullen, E.; Cardozo, M.; Tong, L.; Kelly, T. A.; Mauldin, S. C.; Fuchs, V. U.; Vituous, J.; West, M.; Klunder, J.; Raghavan, P.; Skiles, J. W.; Mui, P.; Rose, J.; David, E.; Richmond, D.; Sullivan, J. L.; Farina, V.; Shih, C.-K.; Grob, P.; Adams, J. Novel Non-Nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 (HIV-1) Reverse Transcriptase. 4. 2-Substituted Dipyridodiazepinones as Potent Inhibitors of Both Wild-Type and Cysteine-181 HIV-1 Reverse Transcriptase Enzymes. *J. Med. Chem.* **1995**, *38*, 4830–4838.

(2) (a) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. Inhibition of HIV-1 Replication by a Non-Nucleoside Reverse Transcriptase Inhibitor. *Science* **1990**, *250*, 1411–3. (b) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones. *J. Med. Chem.* **1991**, *34*, 2231–41.

(3) Richmond, D.; Shih, C.-K.; Lowry, I.; Rose, J.; Prodanovich, P.; Griffin, J. Human Immunodeficiency Virus Type 1 Mutants Resistant to Nonnucleoside Inhibitors of Reverse Transcriptase Arise in Tissue Culture. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 11241–5.

(4) Richman, D.; Havlir, D.; Corbeil, J.; Looney, D.; Ignacio, C.; Spector, S. A.; Sullivan, J.; Cheeseman, S.; Barringer, K.; Pauletti, D.; Shih, C.-K.; Myers, M.; Griffin, J. Nevirapine Resistance Mutations of Human Immunodeficiency Virus Type 1 Selected During Therapy. *J. Virol.* **1994**, *68*, 1660–6.

(5) (a) Kohlstaedt, L. A.; Wang, J.; Friedman, J. M.; Rice, P. A.; Steitz, T. A. Crystal Structure at 3.5A Resolution of HIV-1 Reverse Transcriptase Complexed with an Inhibitor. *Science* **1992**, *256*, 1783–90. (b) Smerdon, S. J.; Jager, J.; Wang, J.; Kohlstaedt, L. A.; Friedman, J. M.; Rice, P. A.; Steitz, T. A. Structure of the Binding Site for Nonnucleoside Inhibitors of the Reverse Transcriptase of Human Immunodeficiency Virus Type 1. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3911–5.

(6) Larder, B. A.; Purifoy, D. J. M.; Powell, K. L.; Darby, G. Site-Specific Mutagenesis of AIDS Virus Reverse Transcriptase. *Nature* **1987**, *327*, 716–7.

(7) Tong, L.; Cardozo, M.; Jones, P.-J.; Adams, J. Preliminary Structural Analysis of the Mutations Selected By Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 721–6.

(8) Grozinger, K. G.; Fuchs, V.; Hargrave, K. D.; Mauldin, S.; Vitous, J.; Campbell, S.; Adams, J. Synthesis of Nevirapine and its Major Metabolite. *J. Heterocycl. Chem.* **1995**, *32*, 259–63.

(9) Kelly, T. A.; Patel, U. R. Directed Lithiation of (3-tert-Butoxycarbonylamino)-2-Methoxypyridines: Synthetic Route to Nevirapine and its 4-Substituted Derivatives. *J. Org. Chem.* **1995**, *60*, 1875–7.

(10) Babler, J. H.; Malek, N. C.; Coghlan, M. J. Selective Hydrolysis of α,β- and β,γ-Unsaturated Ketals: a Method for Deconjugation of β,β-Disubstituted α,β-Unsaturated Ketones. *J. Org. Chem.* **1978**, *43*, 1821–3.

(11) Harrison, I. T. Cleavage of Alkyl Aryl Ethers with Lithium Iodide. *J. Chem. Soc., Chem. Commun.* **1969**, 616.

(12) Echavarren, A. M.; Stille, J. K. Palladium Catalyzed Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109*, 5478–86.

(13) Patel, U. R.; Proudfoot, J. R. The Synthesis of 11-Cyclopropyl-5,11-dihydro-4-(hydroxymethyl)-6H-dipyrido[3,2-b:2′,3′-e][1,4]-diazepin-6-one, a Putative Metabolite of the HIV-1 Reverse Transcriptase Inhibitor Nevirapine. *J. Org. Chem.* **1992**, *14*, 4023–5.

(14) For general experimental information, see ref 2b. For construction of the mutant enzyme, see ref 1.

JM950469I