# Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones

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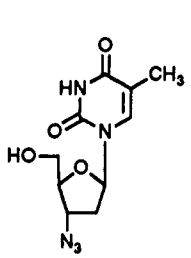
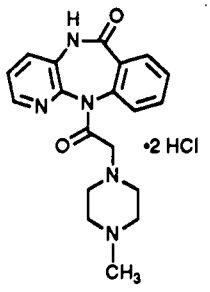
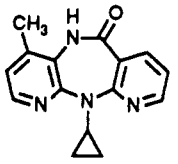
Novel pyrido[2,3-*b*][1,4]benzodiazepinones (I), pyrido[2,3-*b*][1,5]benzodiazepinones (II), and dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinones (III) were found to inhibit human immunodeficiency virus type 1 (HIV-1) reverse transcriptase in vitro at concentrations as low as 35 nM. In all three series, small substituents (e.g., methyl, ethyl, acetyl) are preferred at the lactam nitrogen, whereas slightly larger alkyl moieties (e.g., ethyl, cyclopropyl) are favored at the other (N-11) diazepinone nitrogen. In general, lipophilic substituents are preferred on the A ring, whereas substitution on the C ring generally reduces potency relative to the corresponding compounds with no substituents on the aromatic rings. Maximum potency is achieved with methyl substitution at the position ortho to the lactam nitrogen atom; however, in this case an unsubstituted lactam nitrogen is preferred. Additional substituents on the A ring can be readily tolerated. The dipyridodiazepinone derivative 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (**96**, nevirapine) is a potent ($IC_{50}$ = 84 nM) and selective non-nucleoside inhibitor of HIV-1 reverse transcriptase, and has been chosen for clinical evaluation.

It is widely accepted that the primary etiological agent for the acquired immunodeficiency syndrome (AIDS) is the human immunodeficiency virus type 1 (HIV-1). An essential component of the life cycle of this retrovirus is the transcription of single-stranded viral genomic RNA into double-stranded DNA by the enzyme reverse transcriptase (RT). Inhibition of this viral enzyme should therefore provide an effective means of blocking the spread of HIV-1 infection. In fact, the clinical potential of compounds that interfere with the function of the RT enzyme has already been demonstrated by zidovudine (AZT), the


zidovudine (AZT)


pirenzepine


nevirapine (**96**)

only drug thus far approved for use in the treatment of AIDS and AIDS-related complex (ARC).[1] It has been shown that AZT is phosphorylated by kinases within the cell (a process known as anabolic phosphorylation) to form AZT-5′-triphosphate.[2] It appears that this substance effectively competes with the natural substrate thymidine triphosphate and acts as a chain terminator in the synthesis of DNA since it lacks the 3′-hydroxyl group necessary for the formation of phosphodiester linkages.[2b,3] Structurally similar to the natural nucleotide substrates, AZT and other nucleoside analogues that are in clinical trials have been claimed to be selective for RT, but also inhibit other enzymes involved in DNA synthesis, such as mammalian DNA polymerases $\alpha$, $\beta$, $\gamma$, and $\delta$.[2b,4] These dideoxynucleoside analogues often exhibit dose limiting side effects such as bone marrow suppression, anemia, neutropenia,[5] mitochondrial myopathy,[6] peripheral neuropathy, and pancreatitis.[7] Less severe side effects such

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§ Deceased.

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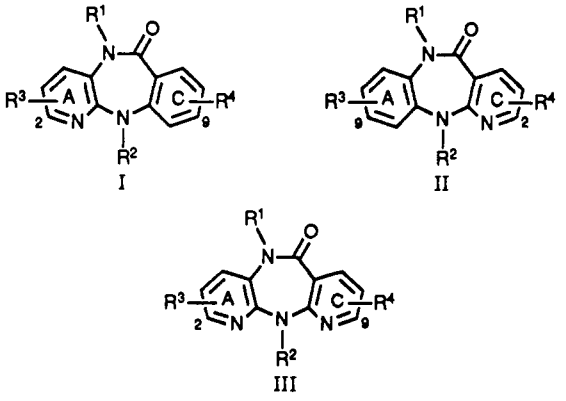
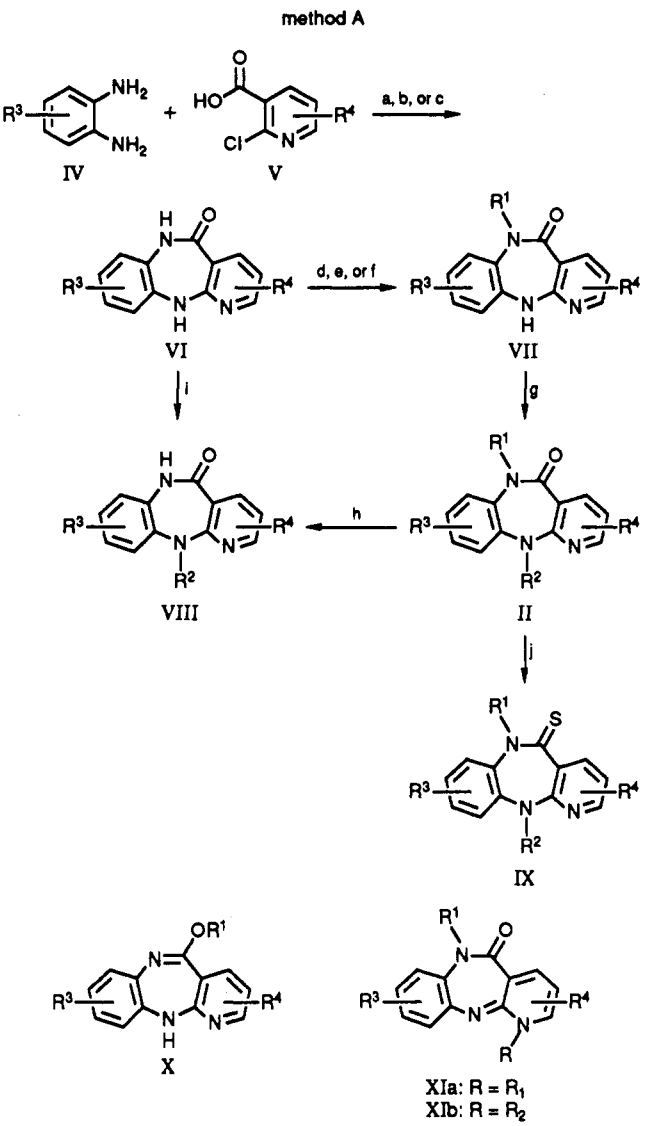
as nausea, headaches, and cutaneous eruptions have also been observed.[5a,7a] Moreover, AZT-resistant strains of HIV-1 have emerged.[8]

Wishing to avoid the toxicological disadvantages inherent in many nucleoside inhibitors, we initiated a search for non-nucleoside inhibitors of HIV-1 RT. Lacking suitable structural leads on which to base a program of rational drug design, we screened a structurally diverse group of compounds on a random basis and found a pyrido[2,3-*b*][1,4]benzodiazepinone (I) to be weakly active. Since this compound is structurally related to the $M_1$-selective antimuscarinic compound pirenzepine,[9] a large number of pyrido[2,3-*b*][1,4]benzodiazepinones (I) and pyrido[2,3-*b*][1,5]benzodiazepinones (II) and a few dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinone (III) analogues were available for testing. Screening of these three series led to the selection of 6,11-dihydro-11-ethyl-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (**11**) as a lead compound ($IC_{50}$ = 350 nM). The preliminary structure–activity relationship (SAR) derived from all of these compounds thus formed a basis from which to explore the therapeutic potential of the series, the synthesis and SAR of which are herein described. On the basis of this information, we focused our synthetic efforts on the pyrido[2,3-*b*][1,5]benzodiazepinones (II) and dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinones (III).




The criteria set for the selection of a preclinical candidate was that the compound have an $IC_{50}$ of less than 100 nM in both the enzyme and cellular (vide infra) assays, that it be nontoxic and specific for RT, that it exhibit suitable solubility and bioavailability, and that it be relatively stable to metabolic degradation. Furthermore, it was deemed necessary that the selected preclinical candidate distribute between the brain and plasma since the virus infects the CNS, resulting in AIDS dementia complex, an often fatal consequence of viral infection.[10] Preliminary measurements of solubility in aqueous solutions at various pH's and, more importantly, bioavailability and metabolism of selected compounds in rats provided important information which influenced the selection of synthetic targets. On the basis of our SAR studies and the above criteria, 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (**96**, nevirapine) was selected for clinical evaluation.

**Scheme I**[a]




[a] (a) ~150 °C, neat; (b) ~150 °C, butyl glycol; (c) ~150 °C, sulfolane; (d) 30% aq NaOH, DMSO, $R^1X$; (e) KO-*t*-Bu, 1,4-dioxane, $R^1X$; (f) NaH, DMF, DMSO, $R^1X$; (g) NaH, DMF or DMSO, $R^2X$; (h) 5% concentrated $H_2SO_4$ in $CF_3COOH$, anisole, reflux; (i) 2 equiv of NaH, DMF, 1 equiv of $R^2X$; (j) Lawesson's reagent, toluene, reflux.

## Chemistry

The pyrido[2,3-*b*][1,5]benzodiazepinones (II)[11] were prepared as outlined in Scheme I (method A). Condensation of *o*-phenylenediamines IV with 2-halonicotinic acids V in an inert solvent at ~150 °C gave the diazepinones VI in one step and not, as might have been expected, the corresponding 2-(2-chloro-3-pyridinyl)-1*H*-benzimidazoles. Mixtures of isomers (ring A) often resulted when the reaction was carried out with substituted *o*-

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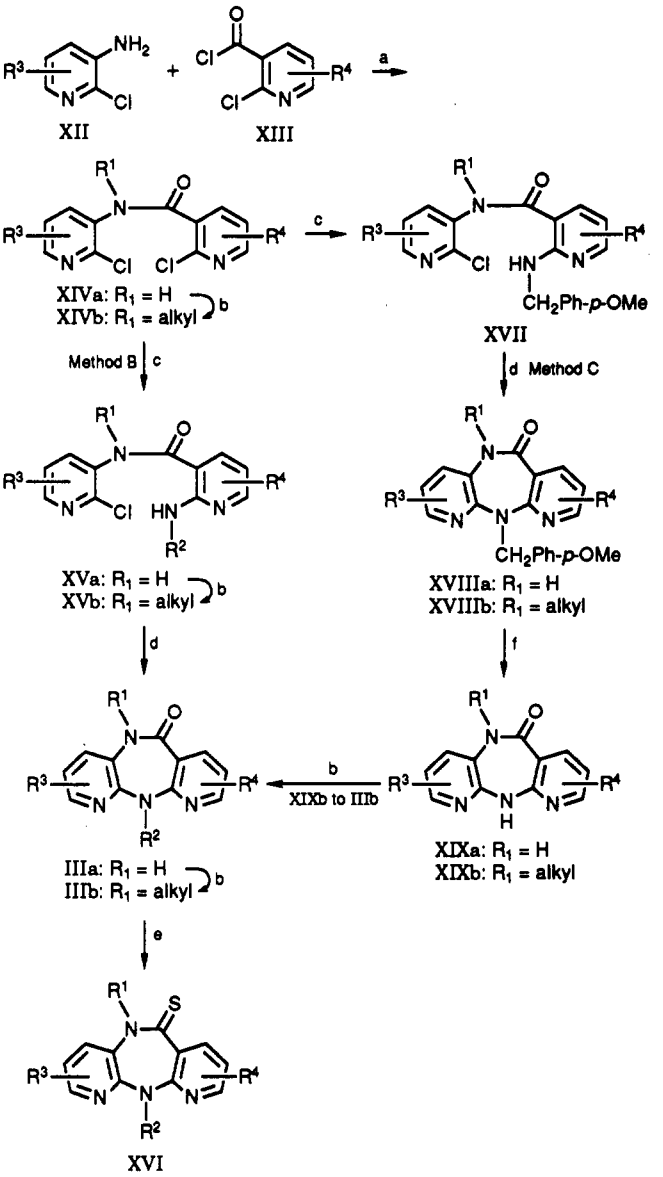
phenylenediamines. In many cases, the major isomer could be isolated by fractional recrystallization, either at this stage or following alkylation at N-6 and/or N-11. Occasionally, however, separation of the isomers was not practically achieved at any stage. Monoalkylation of the tricyclic ring system occurred at the lactam nitrogen (N-6) with 1 equiv each of a suitable base and alkylating agent, and subsequent alkylation provided the desired N,N′-disubstituted diazepinones (II, $R^1 \neq R^2$). Monoalkylation at N-11 required protection (e.g., benzyl, benzoyl) of the lactam nitrogen, though it could be achieved in low yields by the use of two equivalents of a suitable base and 1 equiv of alkylating agent. In those cases wherein $R^1 = R^2$, dialkylation was achieved in one step using 2 equiv each of base and alkylating agent. The choice of base used in the alkylation of N-6 was often critical in order to minimize the formation of side products such as X and XI. In some cases, 30% aqueous sodium hydroxide in DMSO or potassium *tert*-butoxide in 1,4-dioxane proved more convenient than sodium hydride in DMF, which was generally preferred for alkylation at N-11. Occasionally, the formation of some N-1 alkylated product (XIa or XIb) was observed following the alkylation of VI or VII, respectively. Conversion of II to the corresponding thiolactams (IX) was effected by treatment with Lawesson's reagent[12] in toluene at reflux.

In addition to the synthetic sequence depicted in Scheme I, further functional group manipulation was required for the preparation of several of the compounds listed in Table I. Thus, carboxylic acid **47** was obtained by hydrolysis of the corresponding ester **46**, and carboxamides **48** and **49** were prepared by the mixed anhydride method from **47** and the appropriate amines. Treatment of the 8-methoxy derivative **36** with boron tribromide in methylene chloride gave the corresponding phenol **37**. Reduction of the nitro compound **42** with stannous chloride in concentrated HCl afforded the amine **43**, which was treated with acetic anhydride to provide the acetamide **44** or diazotized and reacted with sodium azide to give the azido compound **45**. Treatment of **11** with chlorine in trimethyl phosphate[13] unexpectedly provided the 3-chloro derivative **38** (see Experimental Section). Although we have no explanation for the regioselectivity of this reaction, it should be noted that electrophilic aromatic substitution would be expected to occur preferentially on the phenyl (A) ring. Indeed, Tscherniac–Einhorn reaction[14] of **11** provided the expected regioisomeric phthalamidomethyl intermediate, which was deprotected to give the desired 8-aminomethyl derivative **50**. The hydroxymethyl analogue **52** was subsequently prepared by diazotization of **50** followed by treatment with water.

The dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinones (III) were synthesized as shown in Scheme II.[15] In method B, condensation of 3-amino-2-chloropyridines (XII; X = Cl) with 2-chloronicotinoyl chlorides XIII provided the 2,2′-dihalo amides XIV. These were converted to the 2′-alkylamino compounds XV by treatment with the appropriate amine, usually at >100 °C in a sealed tube. In general, activation by the adjacent carbonyl group was sufficient to ensure

**Scheme II**[a]




[a] (a) Inert solvent; (b) NaH, DMSO, $R^1X$; (c) $R^2NH_2$, 1,4-dioxane or xylene or neat; (d) NaH, pyridine or bis(2-methoxyethyl)ether or xylene; (e) Lawesson's reagent, toluene; (f) trifluoroacetic acid.

that only the 2′-chlorine atom was displaced, and excellent yields of the desired amines XV were obtained. If, however, electron-withdrawing groups (e.g., Cl or $CF_3$) were present on the other pyridine ring, then competing substitution of the 2-chloro substituent was observed and the yield of the desired XV was decreased. Ring closure to the dipyridodiazepinones IIIa was effected by heating the dianion of XVa, generated with 2 equiv of sodium hydride, under reflux in either pyridine or bis(2-methoxyethyl) ether. Dimethylformamide could also be used as a solvent for this reaction, but led to lower yields of less pure product. Alkylation of the lactam nitrogen, if desired, was achieved by procedures described above. The dipyridodiazepinones IIIb could also be obtained by a variation of this sequence involving alkylation of the amides XIVa to give XIVb, which were often observed by NMR as a mixture of conformers (see Experimental Section). Subsequent conversion of XIVb to XVb with the appropriate alkylamine as described above, and cyclization of the monoanion of XVb in xylene at reflux provided IIIb. In some cases, the desired diazepinones were synthesized by reaction of the anion of XIXb with the appropriate elec-

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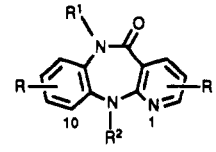
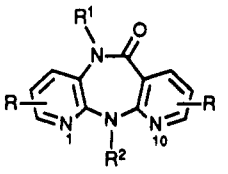
**Table I.** 6,11-Dihydro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-ones[a]



| no. | $R^1$ | $R^2$ | R | recryst solvent | mp, °C | formula | % inh @ 10 μg mL[b] | $IC_{50}$,[b] μM |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | 5% DMF/dioxane | 283–287 | $C_{12}H_9N_3O$ | 22 | ≫1 |
| 2 | H | $CH_3$ | H | 1-propanol | 235–237 | $C_{13}H_{11}N_3O$ | 75 | >1 |
| 3 | H | $CH_2CH_3$ | H | EtOAc | 210–220 | $C_{14}H_{13}N_3O$ | 99 | 0.38 |
| 4 | $CH_3$ | $CH_2C_6H_5$ | H | $CH_2Cl_2$/pet. ether | 168–170 | $C_{20}H_{17}N_3O$ | 93 | 9 |
| 5 | $CH_3$ | H | H | EtOH | 171 | $C_{13}H_{11}N_3O$ | 43 | ≫1 |
| 6 | $CH_2CH_3$ | H | H | MeOH | 149–151 | $C_{14}H_{13}N_3O$ | 87 | >1 |
| 7 | $CH_2COO$-*t*-Bu | H | H | EtOAc/hexane | 200–202 | $C_{18}H_{19}N_3O_3$ | 39 | ≫1 |
| 8 | $CH_2CH{=}CH_2$ | H | H | EtOH | 105–107 | $C_{15}H_{13}N_3O$ | 96 | 1.4 |
| 9 | $CH_2CH_2OH$ | H | H | EtOH | 190–192 dec | $C_{14}H_{13}N_3O_2{\cdot}CHl$ | 46 | ≫1 |
| 10 | $CH_2CH_2OCH_3$ | H | H | 70% aq EtOH | 125–126 | $C_{15}H_{15}N_3O_2$ | 36 | ≫1 |
| 11 | $CH_3$ | $CH_2CH_3$ | H | cyclohexane | 106–111 | $C_{15}H_{15}N_3O$ | 100 | 0.35 |
| 12 | $CH_3$ | $CH_3$ | H | cyclohexane | 126–128 | $C_{14}H_{13}N_3O$ | 85 | >1 |
| 13 | $CH_2CH_3$ | $CH_3$ | H | cyclohexane | 118–119 | $C_{15}H_{15}N_3O$ | 84 | >1 |
| 14 | $CH_2CH_3$ | $CH_2CH_3$ | H | heptane | 108–110 | $C_{16}H_{17}N_3O$ | 99 | 0.38 |
| 15 | $CH_3$ | $CH_2CH_2CH_3$ | H | pet. ether | 96–98 | $C_{16}H_{17}N_3O$ | 99 | 0.23 |
| 16 | $CH_3$ | $CH(CH_3)_2$ | H | cyclohexane | 144–147 | $C_{16}H_{17}N_3O$ | 98 | 0.20 |
| 17 | $CH_3$ | $CH_2CH_2CH_2CH_3$ | H | pet. ether | 56–58 | $C_{17}H_{19}N_3O$ | 81 | 1 |
| 18 | $CH_3$ | $CH_2SCH_3$ | H | ether/pet. ether | 127–129 | $C_{15}H_{15}N_3OS$ | 84 | 6.6 |
| 19 | $CH_3$ | $CH_2COO$-*t*-Bu | H | $CH_2Cl_2$/EtOAc | 64–65 | $C_{19}H_{21}N_3O_3$ | 87 | >1 |
| 20 | $CH_3$ | $CH_2COOC_2H_5$ | H | EtOAc/hexane | 99–100 | $C_{17}H_{17}N_3O_3$ | 56 | 16 |
| 21 | $CH_3$ | $CH_2CH_2OH$ | H | xylene | 133–134 | $C_{15}H_{15}N_3O_2$ | 58 | >1 |
| 22 | $CH_3$ | $COCH_3$ | H | cyclohexane | 140–142 | $C_{15}H_{13}N_3O_2$ | 72 | >1 |
| 23 | $CH_3$ | $CH_2CH_2F$ | H | EtOAc/pet. ether | 118–120 | $C_{15}H_{14}FN_3O$ | 97 | 1 |
| 24 | $CH_2F$ | $CH_2CH_3$ | H | $CH_2Cl_2$/pet. ether | 113–116 | $C_{15}H_{14}FN_3O$ | 85 | >1 |
| 25 | $CH_3$ | $COOC_2H_5$ | H | $CH_2Cl_2$/ether | 123–125 | $C_{16}H_{15}N_3O_3$ | 13 | ≫1 |
| 26 | $CH_2CON(CH_3)_2$ | H | H | $CH_3CN$ | 199–201 | $C_{16}H_{16}N_4O_2$ | 24 | ≫1 |
| 27 | $CH_3$ | $CH_2CO_2H$ | H | *c* | 189–192 | $C_{15}H_{13}N_3O_3$ | 60 | >1 |
| 28 | $CH_3$ | C≡CH | H | *c* | 142–143 | $C_{15}H_{11}N_3O$ | 97 | 0.65 |
| 29 | $CH_2CH_3$ | $CH_2CH_3$ | 7-$CH_3$ | pet. ether | 120–122 | $C_{17}H_{19}N_3O$ | 90 | 8 |
| 30 | H | H | 7-$CH_3$ | 1,4-dioxane/$H_2O$ | 233–234 | $C_{13}H_{11}N_3O{\cdot}0.1H_2O$ | 77 | >1 |
| 31 | $CH_3$ | $CH_2CH_3$ | 7-$CH_3$ | $CH_3CN$ | 132–134 | $C_{16}H_{17}N_3O$ | 100 | 0.24 |
| 32 | $CH_2C_6H_5$ | $CH_2CH_3$ | 7-$CH_3$ | EtOH | 145–147 | $C_{22}H_{21}N_3O$ | 40 | ≫1 |
| 33 | H | $CH_2CH_3$ | 7-$CH_3$ | EtOAc | 225–227 | $C_{15}H_{15}N_3O$ | 100 | 0.038 |
| 34 | $CH_3$ | $CH_2CH_3$ | 8-$CH_3$ | *c* | oil | $C_{16}H_{17}N_3O{\cdot}0.2H_2O$ | 100 | 0.19 |
| 35 | $CH_3$ | $CH_2CH_2N(CH_3)_2$ | 8,9-$(CH_3)_2$ | EtOAc | 185–188 | $C_{19}H_{24}N_4O$ | 0 | ≫1 |
| 36 | $CH_3$ | $CH_2CH_3$ | 8-$OCH_3$ | *c* | oil | $C_{16}H_{17}N_3O_2$ | 95 | 2.1 |
| 37 | $CH_3$ | $CH_2CH_3$ | 8-OH | *c* | 207–209 | $C_{15}H_{15}N_3O_2$ | 47 | ≫1 |
| 38 | $CH_3$ | $CH_2CH_3$ | 3-Cl | pet. ether | 131–132 | $C_{15}H_{14}ClN_3O$ | 91 | 7.6 |
| 39 | $CH_3$ | $CH_2CH_3$ | 9-$CF_3$ | *c* | 104–106 | $C_{16}H_{14}F_3N_3O$ | 97 | 0.23 |
| 40 | $CH_3$ | $CH_2CH_3$ | 2-F | EtOAc/hexane | 100–101 | $C_{15}H_{14}FN_3O$ | 84 | 2.9 |
| 41 | $CH_3$ | $CH_2CH_3$ | 8-$NO_2$ | EtOAc/hexane | 173–176 | $C_{15}H_{14}N_4O_3$ | 56 | >1 |
| 42 | $CH_3$ | $CH_2CH_3$ | 9-$NO_2$ | EtOAc/hexane | 179.5–180.5 | $C_{15}H_{14}N_4O_3$ | 99 | 0.4 |
| 43 | $CH_3$ | $CH_2CH_3$ | 9-$NH_2$ | EtOAc | 193–195 | $C_{15}H_{16}N_4O$ | 89 | 4.5 |
| 44 | $CH_3$ | $CH_2CH_3$ | 9-NHAc | toluene/EtOAc/$CH_2Cl_2$ | 105–107 | $C_{17}H_{18}N_4O_2$ | 49 | ≫1 |
| 45 | $CH_3$ | $CH_2CH_3$ | 9-$N_3$ | ether | 115–118 | $C_{15}H_{14}N_6O$ | 100 | 0.14 |
| 46 | $CH_3$ | $CH_2CH_3$ | 8-$COOCH_3$ | *c* | 132–136 | $C_{17}H_{17}N_3O_3$ | 94 | 1.1 |
| 47 | $CH_3$ | $CH_2CH_3$ | 8-COOH | EtOH | 290–291 | $C_{16}H_{15}N_3O_3$ | 18 | ≫1 |
| 48 | $CH_3$ | $CH_2CH_3$ | 8-$CONH_2$ | *c* | 104–105 | $C_{16}H_{16}N_4O_2{\cdot}H_2O$[d] | 66 | 27 |
| 49 | $CH_3$ | $CH_2CH_3$ | 8-$CONEt_2$ | *c* | oil | $C_{10}H_{24}N_4O_2{\cdot}H_2O$[e] | 11 | ≫1 |
| 50 | $CH_3$ | $CH_2CH_3$ | 8-$CH_2NH_2$ | *c* | oil | $C_{16}H_{18}N_4O{\cdot}0.5H_2O$ | 84 | >1 |
| 51 | $CH_3$ | $CH_2CH_3$ | 8-$CH_2NHCO$-*t*-Bu | ether/hexane | 118–120 | $C_{21}H_{28}N_4O_2$ | 15 | ≫1 |
| 52 | $CH_3$ | $CH_2CH_3$ | 8-$CH_2OH$ | *c* | oil | $C_{16}H_{17}N_3O_2$ | 78 | >1 |
| 53 | $CH_3$ | $CH_2CH_3$ | 8,9-$(CH_3)_2$ | pet. ether | 140–144 | $C_{17}H_{19}N_3O$ | 100 | 0.04 |
| 54 | $CH_3$ | $COCH_3$ | 8,9-$(CH_3)_2$ | cyclohexane | 168–170 | $C_{17}H_{17}N_3O_2$ | 96 | 0.42 |
| 55 | $CH_3$ | $CH_2CH_3$ | 7,8-$(CH_3)_2$ | *c* | 140–144 | $C_{17}H_{19}N_3O$ | 99 | 0.036 |
| 56 | $CH_3$ | $CH_2CH_3$ | 8,9-$Cl_2$ | *c* | 146–147 | $C_{15}H_{13}Cl_2N_3O$ | 100 | 0.062 |
| 57 | $CH_3$ | $CH_2CH_3$ | 7-Cl, 9-$CF_3$ | *c* | 109–111 | $C_{16}H_{13}ClF_3N_3O$ | 96 | 0.29 |
| 58 | $CH_3$ | $CH_2CH_3$ | 7-Br, 9-$CF_3$ | *c* | oil | $C_{16}H_{13}BrF_3N_3O{\cdot}0.2H_2O$ | 71 | >1 |
| 59 | $CH_3$ | $CH_3$ | 2,4,8-$(CH_3)_3$ | pet. ether (100–140 °C) | 174–176 | $C_{17}H_{19}N_3O$ | 49 | ≫1 |
| 60 | $CH_2CH{=}CH_2$ | $COCH_3$ | H | cyclohexane | 152–154 | $C_{17}H_{15}N_3O_2$ | 83 | >1 |
| 61 | $CH_2CH{=}CH_2$ | $COCH_2CH_3$ | H | cyclohexane | 118–120 | $C_{18}H_{17}N_3O_2$ | 72 | >1 |
| 62 | $CH_3$ | $CH_2CH_3$ | 3-$CF_2CF_3$ | *c* | oil | $C_{17}H_{14}F_5N_3O$ | 5 | ≫1 |
| 63 | $CH_3$ | $CH_2CH_3$ | 3-Br, 9-$NO_2$ | *c* | 156–158 | $C_{15}H_{13}BrN_4O_3$ | 95 | 0.89 |
| 64 | $CH_3$ | $CH_2CH_3$ | 3-Br, 8-$NO_2$ | *c* | 171–173 | $C_{15}H_{13}BrN_4O_3$ | 64 | >1 |
| 65 | $CH_3$ | $CH_2CH_3$ | 8-Cl | cyclohexane/pet. ether | 158–159 | $C_{15}H_{14}ClN_3O$[f] | 99 | 0.17 |
| 66 | $CH_2CH{=}CH_2$ | H | 8-Cl | EtOH | 167–169 | $C_{15}H_{12}ClN_3O$ | 79 | >1 |
| 67 | $CH_3$ | $CH_2CH_3$ | 9-$COC_6H_5$ | *c* | 67–72 | $C_{22}H_{19}N_3O_2$ | 73 | >1 |
| 68 | $CH_3$ | $CH_2CH_3$ | 9-Cl | pet. ether | 169–171 | $C_{15}H_{14}ClN_3O$ | 100 | 0.17 |

[a] All compounds were prepared by method A. [b] Inhibition of HIV-1 RT. See Experimental Section. [c] Sample purified by column chromatography and not requiring recrystallization. [d] N: calcd, 17.82; found, 17.32. [e] N: calcd, 15.12; found, 14.38. [f] H: calcd, 4.90; found, 5.41.

**Table II.** 5,11-Dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one



| no. | $R^1$ | $R^2$ | R | method | recryst solvent | mp, °C | formula | % inh @ 10 μg/mL[a] | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|---|---|---|
| **69** | $CH_3$ | $C_2H_5$ | H | B | EtOAc/hexane | 130–132 | $C_{14}H_{14}N_4O$ | 100 | 0.125 |
| **70** | H | $C_2H_5$ | H | B | EtOAc/EtOH | 211–212 | $C_{13}H_{12}N_4O$ | 99 | 0.44 |
| **71** | H | c-$C_3H_5$ | H | B | EtOAc | 240–250 | $C_{14}H_{12}N_4O$ | 99 | 0.45 |
| **72** | H | c-$C_4H_7$ | H | B | EtOAc | 241–243 | $C_{15}H_{14}N_4O$ | 99 | 0.43 |
| **73** | H | c-$C_5H_9$ | H | B | EtOAc/ether | 225–228 | $C_{16}H_{16}N_4O$ | 94 | >1 |
| **74** | $CH_3$ | *n*-$C_3H_7$ | H | B | *b* | oil | $C_{15}H_{16}N_4O$ | 100 | 0.45 |
| **75** | H | *i*-$C_3H_7$ | H | B | EtOAc/hexane | 204–206 | $C_{14}H_{14}N_4O$ | 99 | 0.59 |
| **76** | $CH_3$ | *t*-$C_4H_9$ | H | B | hexane | 192–194 | $C_{16}H_{18}N_4O$ | 87 | 11 |
| **77** | $CH_3$ | c-$C_6H_{11}$ | H | B | ether/pet. ether | 145–146 | $C_{18}H_{20}N_4O \cdot {}^1/_4H_2O$ | 73 | >1 |
| **78** | $CH_3$ | $CH_2CH{=}CH_2$ | H | C | EtOAc/hexane | 93–95 | $C_{15}H_{14}N_4O$ | 99 | 0.85 |
| **79** | $CH_3$ | $CH_2C{\equiv}CH$ | H | B | EtOAc | 169–170 | $C_{15}H_{12}N_4O$[c] | 94 | >1 |
| **80** | H | (*R*)-$C_4H_9$ | H | B | EtOAc/hexane | 172–174 | $C_{15}H_{16}N_4O$ | 85 | >1 |
| **81** | H | (*S*)-$C_4H_9$ | H | B | EtOAc/hexane | 173–175 | $C_{15}H_{16}N_4O$ | 88 | >1 |
| **82** | H | $C_6H_5$ | H | B | EtOAc/hexane | 220–222 | $C_{17}H_{12}N_4O$ | 71 | >1 |
| **83** | $COCH_3$ | $C_2H_5$ | H | B | EtOAc/hexane | 123–124.5 | $C_{15}H_{14}N_4O_2$ | 99 | 0.36 |
| **84** | $CH_3$ | $COCH_3$ | H | C | EtOAc/hexane | 138–143 | $C_{14}H_{12}N_4O_2$ | 73 | 15.3 |
| **85** | $CH_3$ | $CH_2CH_2F$ | H | C | pet. ether/ether | 117–118 | $C_{14}H_{13}FN_4O$ | 96 | 2.9 |
| **86** | $CH_3$ | $SO_2CH_3$ | H | C | EtOAc/hexane | 239–241 | $C_{13}H_{12}N_4O_3S$ | 77 | >1 |
| **87** | $CH_3$ | $CH_2SCH_3$ | H | C | ether/pet. ether | 109–110 | $C_{14}H_{14}N_4OS$ | 99 | 0.85 |
| **88** | $CH_3$ | $C_2H_5$ | 2-$CH_3$ | B | hexane | 124–126 | $C_{15}H_{16}N_4O$ | 100 | 0.17 |
| **89** | $CH_3$ | $C_2H_5$ | 2-Cl | B | heptane | 125–126 | $C_{14}H_{13}ClN_4O$ | 100 | 0.15 |
| **90** | $CH_3$ | $C_2H_5$ | 3-$CH_3$ | B | hexane | 94–96 | $C_{15}N_{16}N_4O$ | 100 | 0.76 |
| **91** | $CH_3$ | $C_2H_5$ | 3-Cl | B | heptane | 124–125 | $C_{14}H_{13}ClN_4O$ | 99 | >1 |
| **92** | $CH_3$ | $C_2H_5$ | 3-$NO_2$ | B | EtOAc/hexane | 154–156 | $C_{14}H_{13}N_5O_3$ | 64 | >1 |
| **93** | $CH_3$ | $C_2H_5$ | 3-$NH_2$ | B | EtOAc/MeOH | 235–240 | $C_{14}H_{15}N_5O$ | 92 | >1 |
| **94** | H | $C_2H_5$ | 4-$CH_3$ | B | $CH_2ClCH_2Cl$ | 212–214 | $C_{14}H_{14}N_4O$ | 100 | 0.035 |
| **95** | $CH_3$ | $C_2H_5$ | 4-$CH_3$ | B | EtOAc/hexane | 157–159 | $C_{15}H_{16}N_4O$ | 98 | 1.9 |
| **96** | H | c-$C_3H_5$ | 4-$CH_3$ | B | EtOAc | 247–249 | $C_{15}H_{14}N_4O$ | 100 | 0.084 |
| **97** | $CH_3$ | c-$C_3H_5$ | 4-$CH_3$ | B | EtOAc/ether | 244–245 | $C_{16}H_{16}N_4O$ | 96 | >1 |
| **98** | H | $C_2H_5$ | 4-Cl | B | $CH_3CN$ | 184–186 | $C_{13}H_{11}ClN_4O$ | 100 | 0.095 |
| **99** | H | $C_2H_5$ | 4-$C_2H_5$ | B | EtOAc | 218–219 | $C_{15}H_{16}N_4O$ | 100 | 0.11 |
| **100** | H | $C_2H_5$ | 4-$OCH_3$ | B | EtOAc/hexane | 156–157 | $C_{14}H_{14}N_4O_2$ | 96 | >1 |
| **101** | H | $C_2H_5$ | 4-OH | B | HOAc | 295–296 | $C_{13}H_{12}N_4O_2 \cdot 2HBr \cdot H_2O$ | 94 | >1 |
| **102** | H | c-$C_3H_5$ | 4-$CH_2OH$ | B[d] | EtOAc/hexane | 243–245 | $C_{15}H_{14}N_4O_2$ | 94 | 3.0 |
| **103** | H | c-$C_3H_5$ | 4-CN | B[d] | EtOAc/hexane | 243–245 | $C_{15}H_{11}N_5O$[e] | 96 | 1.25 |
| **104** | H | $C_2H_5$ | 2,3-$(CH_3)_2$ | B | EtOAc/hexane | 212–214 | $C_{15}H_{16}N_4O$ | 100 | 0.41 |
| **105** | $CH_3$ | $C_2H_5$ | 2,3-$(CH_3)_2$ | B | hexane | 143–145 | $C_{16}H_{18}N_4O$ | 100 | 0.24 |
| **106** | $CH_3$ | $C_2H_5$ | 2-$NO_2$, 3-Cl | B | EtOAc/hexane | 153–157 | $C_{14}H_{12}ClN_5O_3$ | 98 | >1 |
| **107** | $CH_3$ | $C_2H_5$ | 2-$NH_2$, 3-Cl | B | EtOAc/hexane | 160–162 | $C_{14}H_{14}ClN_5O$ | 98 | 0.85 |
| **108** | H | $C_2H_5$ | 7-$CH_3$ | B | EtOAc/hexane | 193–194 | $C_{14}H_{14}N_4O \cdot H_2O$[g] | 80 | >1 |
| **109** | H | $C_2H_5$ | 8-$CH_3$ | B | EtOAc/hexane | 182–183 | $C_{14}H_{14}N_4O \cdot 0.1H_2O$ | 89 | >1 |
| **110** | $CH_3$ | $C_2H_5$ | 8-Cl | B | hexane | 105–106 | $C_{14}H_{13}ClN_4O$ | 87 | 3.5 |
| **111** | H | c-$C_3H_7$ | 4-$CH_3$, 7-OH | B[d] | EtOAc/hexane | 225–227 | $C_{15}H_{14}N_4O_2 \cdot {}^3/_4H_2O$[h] | 96 | >1 |
| **112** | $CH_3$ | $C_2H_5$ | 9-$CH_3$ | B | hexane | 79–93 | $C_{15}H_{16}N_4O$ | 65 | >1 |
| **113** | $CH_2CH_2N(CH_3)_2$ | c-$C_3H_7$ | H | B | $CH_2Cl_2$/MeOH | 88–89 | $C_{18}H_{21}N_5O$ | 34 | ≫1 |

[a] Inhibition of HIV-1 RT. See Experimental Section. [b] Sample purified by column chromatography and not requiring recrystallization. [c] N: calcd, 21.20; found, 20.61. [d] Derived from compound 90. [e] No elemental analysis available; characterized by NMR and MS. [f] C: calcd, 67.15; found, 66.54. [g] N: calcd, 21.65; found, 20.74. [h] N: calcd, 18.94; found, 18.31.

trophile (method C). Sulfurization to provide the thiolactam (XVI) from III was achieved with Lawesson's reagent,[12] as described earlier.

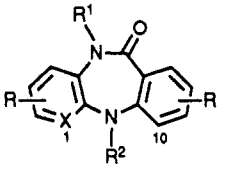
The chemistry of the diypridodiazepinones III is currently being explored further, and we have found, for example, that nitration of the pyridine rings can be achieved using nitronium tetrafluoroborate in acetonitrile. Thus, **69** gives the 3-nitro and 3,8-dinitro derivatives upon treatment with 1 equiv of the nitrating agent. Interestingly, the 3-chloro analogue of **69** (**91**) gives the 2-nitro and 2,8-dinitro derivatives under the same conditions, with the initial nitration occurring on ring A.

## Results and Discussion

The in vitro HIV-1 RT enzyme assay was the primary screen used to evaluate these compounds for their potential as anti-AIDS drugs; the test results are presented in Tables I–III. Selected compounds were further tested for their ability to block the proliferation of HIV-1 infection in vitro. This was demonstrated by their inhibition of the formation of syncytia and p24 antigen in cultures of $CD4^+$ human T-cells (c8166) infected with HIV-1. A direct correlation between the enzymatic and cellular potencies of representatives of II and III is observed. These and other data support the hypothesis that the compounds reported here inhibit the spread of HIV-1 infection in vitro as a result of their ability to inhibit RT.[16] Utilizing cells from the same c8166 cell line, these compounds were also tested in an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-

(16) Hargrave, K. D.; Sullivan, J. L.; Eckner, R. J.; Merluzzi, V. J.; Koup, R. A. Unpublished results.

**Table III.** 5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones and 5,10-Dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-ones



| no. | $R^1$ | $R^2$ | R | X | recryst solvent | mp, °C | formula | % inh @ 10 μg/mL[a] | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|---|---|---|
| 114 | H | H | H | N | DMF | 282.6–282.9 | $C_{12}H_9N_3O$ | 23 | ≫1 |
| 115 | $CH_3$ | $CH_3$ | H | N | EtOH | 113.5–114.5 | $C_{14}H_{13}N_3O$ | 74 | >1 |
| 116 | $CH_3$ | $CH_2CH_3$ | H | N | EtOAc | 127–128 | $C_{15}H_{15}N_3O$ | 99 | 0.50 |
| 117 | $CH_2CH_3$ | $CH_2CH_3$ | H | N | cyclohexane | 95–97 | $C_{16}H_{17}N_3O$ | 96 | 0.69 |
| 118 | $CH_3$ | $CH_2CH_3$ | 8-$CH_3$ | N | EtOH | 137–138 | $C_{16}H_{17}N_3O$ | 99 | 0.58 |
| 119 | $CH_2CH_3$ | $CH_2CH_3$ | 10-$CH_3$ | N | pet. ether (100–140 °C) | 143–144 | $C_{17}H_{19}N_3O$ | 99 | 0.65 |
| 120 | $CH_2CH_3$ | $CH_3$ | 2-Cl | N | cyclohexane | 162–164 | $C_{15}H_{14}ClN_3O$ | 76 | 3.3 |
| 121 | H | H | 2-$CH_3$ | N | 80% aq. HOAc | 260–262 | $C_{13}H_{11}N_3O$ | 46 | >1 |
| 122 | H | H | 2,4-$(CH_3)_2$ | N | dimethylacetamide | 281–283 | $C_{14}H_{13}N_3O$ | 51 | >1 |
| 123 | $CH_3$ | $CH_3$ | H | CH | EtOH | 137.5–139 | $C_{15}H_{14}N_2O$ | 52 | >1 |
| 124 | $CH_3$ | $CH_2CH_3$ | H | CH | heptane | 189.5–190.5 | $C_{16}H_{16}N_2O$ | 80 | >1 |

[a] Inhibition of HIV-1 RT. See Experimental Section.

tetrazolium bromide] cytotoxicity assay[17] and were found to be nontoxic at the doses required for activity (therapeutic index >1000). Specificity was established by the inactivity of selected compounds at relatively high doses in an HIV-2 cell culture assay, and by their lack of inhibition of HIV-2 RT and various non-HIV RT enzymes, including those of the simian immunodeficiency virus, feline leukemia virus, Moloney murine leukemia virus, and avian myeloblastosis virus. In addition, nevirapine does not inhibit other mammalian DNA polymerases (vide infra).

Evaluation of representative examples from the two monopyridodiazepinone series (I and II) and the dipyridodiazepinone series (III) suggests that, in general, the dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinones (III) inhibit RT with equivalent or slightly enhanced potency relative to the corresponding pyrido[2,3-*b*][1,5]benzodiazepinones (II), which are, in turn, slightly more potent than the corresponding pyrido[2,3-*b*][1,4]benzodiazepinones (I). Moreover, the corresponding dibenzo[*b*,*e*][1,4]diazepinones are less active relative to the mono- or dipyrido analogues. The pyrido[2,3-*b*][1,4]benzodiazepinones[18] (I) and dibenzo[*b*,*e*][1,4]diazepinones[19] were synthesized as previously described. The test results (Table III) suggest that compounds with a methyl group in the 2-, 4-, 8-, or 10-positions or a chloro group in the 2-position generally exhibit potencies similar to or greater than those of the corresponding unsubstituted analogues. In addition to the finding that at least one of the aromatic rings in this series must be a pyridine ring for potent activity, the position of the pyridine nitrogen is also critical. For example, isomers of III in which the A-ring nitrogen is at position 3 are very weakly active. As a result, our synthetic efforts focused primarily on the pyrido[2,3-*b*][1,5]benzodiazepinones (II) and dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepinones (III).

**6,11-Dihydro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-ones (Table I).** In the following evaluation of the pyrido[2,3-*b*][1,5]benzodiazepinone (II) series, compound **11**, which is unsubstituted on the aromatic rings, is used as the reference standard. Derivatives with substituents present on the C ring all exhibit less activity than the corresponding unsubstituted analogues. For example, the 2-fluoro (**40**) and 3-chloro (**38**) analogues are less potent than the corresponding unsubstituted compound (**11**). A methyl group at position 7 enhances potency if the lactam nitrogen (N-6) is unsubstituted (compound **33**). In the 8-position, potency of 6-methylated compounds is enhanced by methyl (**34**) and chloro (**65**) substitution. In contrast, 8-substituted compounds with electronegative groups such as nitro, methoxycarbonyl, carboxy, aminocarbonyl, and (*N*,*N*-diethylamino)carbonyl are significantly less potent (compare compounds **41**, **46**, **47**, **48**, and **49** to **11**). Also, nonlipophilic substituents in the 8-position, such as methoxy, hydroxy, hydroxymethyl, and aminomethyl, all lower activity (compare compounds **36**, **37**, **52**, and **50** to **11**). At the 9-position, chloro, trifluoromethyl, and azido[20] groups enhance potency, whereas amino and acetamido groups reduce activity, and nitro substitution is relatively neutral (compare compounds **68**, **39**, **45**, **43**, **44**, **42**, and **11**). The most potent compounds, with $IC_{50}$'s in the 35–65 nM range, are derivatives disubstituted with the lipophilic methyl (**53** and **55**) or chloro (**56**) groups at positions 7 and 8 or 8 and 9, or the analogue monomethylated at position 7 (**33**).

**5,11-Dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-ones (Table II).** Synthetic efforts in the dipyridodiazepinone (III) series focused on substitutions at the six available positions of the aromatic rings. Substituents at the 2-position generally appear to have no dramatic effect on activity, with methyl, chloro, nitro, and amino derivatives exhibiting potencies similar to those of the corresponding 2-unsubstituted analogues. On the other hand, the same groups placed at the 3-position have a detrimental effect on potency relative to the corresponding unsubstituted compound **69**. In the 4-position, methyl substitution produces the best activity, provided the lactam nitrogen (N-5) is unsubstituted. If the lactam nitrogen is substituted, then a 4-methyl group is detrimental. This

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combination of a 4-methyl group and an unsubstituted lactam is present in all of the most active compounds, although 4-chloro and -ethyl compounds are also highly active. In contrast, potency is reduced by the presence in the 4-position of electron-donating, electron-withdrawing, and/or hydrophilic groups such as methoxy, hydroxy, cyano, or hydroxymethyl. Methyl substitution at positions 7, 8, or 9 has a detrimental effect on potency; and similar results were obtained with 7-hydroxy or with 8-chloro derivatives.

Summarizing the SAR of the dipyridodiazepinones based on available data, maximum enzyme inhibition is obtained with compounds containing a 4-methyl substituent in the absence of substitution at the lactam nitrogen (N-5); however, 5-methyl substitution is preferred if the 4-position is not substituted. Substitution at positions 2, 3, 7, 8, and 9 appears to have little effect or to reduce activity of the analogues evaluated thus far. At N-11, small alkyl groups such as ethyl and cyclopropyl are preferred.

Although there are some differences between series in the SAR involving substitution of the aromatic rings, a similar SAR is operative for the two diazepinone nitrogen substituents. Specifically, small substituents such as methyl, ethyl, or acetyl at the lactam nitrogen atom are generally preferred. Larger substituents such as allyl, methoxyethyl, or (*N*,*N*-dimethylamino)ethyl, which is present on some tricyclic antidepressants, reduce activity. In contrast, an unsubstituted lactam nitrogen ($R^1$ = H) is much preferred when the position ortho to the lactam nitrogen in II or III is occupied by a methyl or chloro substituent. In general, thiolactams are more potent than the corresponding lactams. However, due to poor solubility and rapid metabolism, the thiolactams were not considered for further development. At the N-11 position, relatively small lipophilic groups are required for optimum activity ($R^2$ = Et, *c*-Pr); analogues with smaller ($R^2$ = H, Me) or larger ($R^2$ = Bu, Ph) groups are less potent. Furthermore, basic aminoalkyl substituents at N-11, which are necessary for antimuscarinic activity,[21] result in very weak or inactive compounds in the RT assay. Also, hydrophilic or electron-withdrawing substituents reduce potency relative to that of the *N*-ethyl derivative.

Studies with representatives of the three series suggest that, as a class, the dipyridodiazepinones (III) are not only more potent, but are also more water-soluble, less cytotoxic, and more resistant to metabolic N-dealkylation than either of the monopyridodiazepinone series (I or II). The most active compounds of series I and II are poorly soluble in aqueous solution. When the more soluble unsubstituted compound **11** was evaluated in rats following oral administration, it was found to be dealkylated quite rapidly at both diazepinone nitrogen atoms. Metabolism studies with **69**, the dipyrido analogue of **11**, suggested that N-dealkylation would also be a potential problem in series III, although the degradation was not as rapid. However, the finding that the combination of a 4-methyl substituent and an unsubstituted lactam results in maximal activity eliminated the dealkylation problem at N-5. In fact, metabolism studies in the rat and monkey with **94** and **96** indicated that the presence of a 4-methyl substituent also significantly reduces dealkylation at N-11.[22]

Nevirapine has been found to be a potent ($IC_{50}$ = 84 nM) and specific noncompetitive ($K_i$ = 200 nM) inhibitor of HIV-1 RT which acts at an allosteric site of the enzyme.[20,23] It blocks HIV-1 replication in vitro ($IC_{50}$ = 40 nM) in $CD4^+$ human T-cells (c8166), but is noncytotoxic except at significantly higher doses ($CC_{50}$ = 321 000 nM).[23a] In comparison, AZT is a more potent inhibitor of HIV-1 replication in vitro ($IC_{50}$ = 6 nM), but is more cytotoxic ($CC_{50}$ = 66 000 nM) than nevirapine in the same assays.[16] Furthermore, nevirapine has been found to be effective against all clinical isolates of HIV-1 which have been tested, including those which were AZT-sensitive or AZT-resistant. Nevirapine is specific for HIV-1; it is ineffective against HIV-2 and is inactive against simian and feline RT. Moreover, it does not inhibit human DNA polymerases $\alpha$, $\beta$, $\gamma$, and $\delta$, and calf thymus DNA polymerase $\alpha$.[23] Similar results in many of these tests were obtained for **94**; however, the 11-cyclopropyl compound (**96**) exhibited greater bioavailability in the rat and monkey compared to the corresponding 11-ethyl analogue (**94**).[22] Thus, on the basis of these and other results, and on the basis of its favorable levels of specificity, bioavailability, and metabolic stability, nevirapine was selected for clinical evaluation. Details of pharmacology,[24] toxicology,[25] kinetics,[26] metabolism,[22] and pharmacokinetics[27] studies, and the proposed mechanism of action of this compound will be reported elsewhere.

Tetrahydroimidazobenzodiazepinone (TIBO) compounds were recently reported[28] to block in vitro replication of HIV-1. These substances, which were discovered by random screening, also act by inhibiting the HIV-1 RT enzyme, and are ineffective against HIV-2 replication. Although structurally distinct from the compounds reported here, a representative of these TIBO analogues acts on the enzyme at the same allosteric site as the tricyclic diazepinones.[20]

## Experimental Section

**General.** Compounds were purified by gravity chromatography over silica gel. 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 and $^{13}$C NMR spectra were recorded on a Bruker AC-270 (69.2 MHz) spectrometer with $Me_4Si$ as the internal standard. NOE enhancements were measured by saturating the resonance of interest for one second prior to the observation pulse. All NOE enhancements reported were greater than 5%. 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.

**Method A. 6,11-Dihydro-7-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (30).** A well-stirred mixture of 3-methyl-*o*-phenylenediamine (15 g, 0.123 mol) and 2-chloronicotinic

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acid (23.2 g, 0.147 mol) in 2-butoxyethanol (200 mL) was heated at 140–150 °C for 6 h. The dark solution was then poured over crushed ice, and the resulting dark brown solid was collected, washed with water, and dried. Recrystallization from 50% 1,4-dioxane/water with charcoal treatment afforded **30** (13.7 g, 50%) as a light yellow crystalline solid: mp 231–232 °C; $^1$H NMR ($d_6$-DMSO) δ 9.35 (s, 1 H, NH), 8.6 (s, 1 H, NH), 8.26 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.0 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.05 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 6.96 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 6.92 (apparent t, $J$ = 7.7 Hz, 1 H), 6.84 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 2.3 (s, 3 H). The position of the methyl group was assigned on the basis of the observed NOE between δ 9.3 (–NHCO–) and δ 2.3 ($CH_3$). Anal. ($C_{13}H_{11}N_3O$·0.1$H_2O$) C, H, N.

**8,9-Dichloro-6,11-dihydro-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (VII; R$^1$ = Me, R$^3$ = 8,9-Cl$_2$, R$^4$ = H).** A 30% aqueous NaOH solution (2.9 mL, 22 mmol) was added to a suspension of 6,11-dihydro-8,9-dichloro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (5.6 g, 20 mmol), obtained in 83% yield from 3,4-dichloro-*o*-phenylenediamine and 2-chloronicotinic acid according to the above procedure, in DMSO (40 mL). After 2 h, methyl iodide (5.0 mL, 80 mmol) was added and stirring was continued for 3 days at ambient temperature. The reaction mixture was then diluted with water, and the resulting solid was collected, washed with water, and air-dried. Trituration with EtOH afforded the title compound (5.3 g, 91%) as a light yellow solid: mp 294–297 °C; $^1$H NMR ($d_6$-DMSO) δ 8.97 (s, 1 H, N*H*), 8.32 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 8.08 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.61 (s, 1 H), 7.49 (s, 1 H), 7.07 (dd, $J$ = 7.7, 4.8 Hz, 1 H), 3.38 (s, 3 H, C*H*$_3$). Anal. ($C_{13}H_9Cl_2N_3O$·0.2$H_2O$) C, H, N.

**6,11-Dihydro-6-ethyl-7-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (VII; R$^1$ = Et, R$^3$ = 7-Me, R$^4$ = H) and 5-Ethoxy-7-methyl-11*H*-pyrido[2,3-*b*][1,5]benzodiazepine (X; R$^1$ = Et, R$^3$ = 7-Me, R$^4$ = H).** Sodium hydride (0.13 g, 5.5 mmol) was added at room temperature to a suspension of **30** (1.12 g, 5.0 mmol) in DMF (20 mL) under argon. The reaction mixture was heated at 60 °C for 1 h and then was cooled in an ice bath before the addition of ethyl iodide (0.86 g, 5.5 mmol). Stirring was continued at room temperature overnight, followed by warming to 60 °C for 1 h. The solution was concentrated in vacuo to near dryness, the residue was poured over ice–water, and the resulting solid was collected, washed with water, and dried. Purification by chromatography (elution with 1% MeOH/$CH_2Cl_2$) afforded, in order of elution, X (R$^1$ = Et, R$^3$ = 7-Me, R$^4$ = H) (0.23 g, 18%) and VII (R$^1$ = Et, R$^3$ = 7-Me, R$^4$ = H) (0.61 g, 49%). The *O*-alkylated product, X, crystallized as yellow needles from petroleum ether (30–60 °C): mp 135–136 °C; $^1$H NMR ($d_6$-DMSO) δ 8.18 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.94 (s, 1 H, N*H*), 7.72 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 6.91 (dd, $J$ = 7.7, 4.8 Hz, 1 H), 6.82 (m, 3 H), 4.34 (q, $J$ = 7.0 Hz, 2 H), 2.21 (s, 3 H), 1.36 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR ($d_6$-DMSO) δ 163.06, 155.97 (N=CO), 151.13, 137.38, 138.32, 134.70, 134.55, 125.13, 124.57, 61.83 ($OCH_2$), 18.33, 14.02; MS (EI) $m/z$ 253 ($M^+$), 238 ([M – $CH_3$]$^+$), 225 ([M – $C_2H_4$]$^+$), 208 ([M – $OC_2H_5$]$^+$), 196 ([M – $COC_2H_5$]$^+$). Anal. ($C_{15}H_{15}N_3O$·0.1$H_2O$) C, H, N.

The N-alkylated product VII (R$^1$ = Et, R$^3$ = 7-Me, R$^4$ = H) crystallized from 1,4-dioxane/water: mp 186–188 °C; $^1$H NMR ($d_6$-DMSO) δ 8.59 (s, 1 H, N*H*), 8.25 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 8.01 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.08 (m, 4 H), 4.38 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 3.09 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 2.25 (s, 3 H), 0.97 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR ($d_6$-DMSO) δ 167.50, 161.09 (C=O), 150.44, 145.26, 140.86, 134.44, 132.00, 126.45, 118.62, 117.79, 44.53 ($NCH_2$), 18.55, 13.11; MS (CI) 254 ($MH^+$). Anal. ($C_{15}H_{15}N_3O$) C, H, N.

**6,11-Dihydro-11-ethyl-6,7-dimethyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (31).** Sodium hydride (80% oil dispersion, 0.165 g, 5.5 mmol) was added in several portions to a stirred suspension of 5,6-dihydro-6,7-dimethyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (VII; R$^1$ = Me, R$^3$ = 7-Me, R$^4$ = H) (1.2 g, 5.0 mmol) in DMF (10 mL) under argon. The resulting mixture was stirred at room temperature for 3 h and at 60 °C for 1 h, and then was cooled to room temperature prior to the addition of ethyl iodide (0.86 g, 5.5 mmol). After 2 days, the reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc, washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Purification by chromatography (elution with 10→30% EtOAc/hexane) and recrystallization from $CH_3CN$ afforded **31** (1.0 g, 78%): mp 132–134 °C; $^1$H NMR ($d_6$-DMSO) δ 8.34 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.95 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.10 (m, 4 H), 4.10 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 3.64 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 3.28 (s, 3 H), 2.28 (s, 3 H), 1.16 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

**6-Benzyl-6,11-dihydro-7-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (VII; R$^1$ = CH$_2$C$_6$H$_5$, R$^3$ = 7-Me, R$^4$ = H).** Potassium (0.215 g, 5.5 mmol) was dissolved in *t*-BuOH (8 mL) and the resulting solution was added in portions to a stirred solution of **30** (1.18 g, 5.0 mmol) in dry dioxane (10 mL) under argon. The mixture was heated at 60 °C for 3 h, and then cooled to room temperature. Benzyl bromide (0.94 g, 5.5 mmol) was added and the reaction mixture was stirred overnight at room temperature. Dilution with ice–water produced an oil, which solidified upon standing. The solid was collected, air-dried, and recrystallized from EtOH/water to give VII (R$^1$ = $CH_2C_6H_5$, R$^3$ = 7-Me, R$^4$ = H) (1.11 g, 69%): mp 174–175 °C; $^1$H NMR ($d_6$-DMSO) δ 8.72 (s, 1 H, N*H*), 8.26 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 8.12 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.18 (m, 9 H), 5.52 (d, $J$ = –15.1 Hz, 1 H), 4.34 (d, $J$ = –15.1 Hz, 1 H), 2.37 (s, 3 H). Anal. ($C_{20}H_{17}N_3O$) C, H, N.

**6-Benzyl-6,11-dihydro-11-ethyl-7-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (32).** This product was prepared in 80% yield as described above for **31**. It was crystallized from EtOH: mp 145.5–147 °C; $^1$H NMR ($d_6$-DMSO) δ 8.34 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.97 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.20 (m, 9 H), 5.61 (d, $J$ = –15.1 Hz, 1 H), 4.39 (d, $J$ = –15.1 Hz, 1 H), 4.14 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 3.54 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 2.39 (s, 3 H), 1.08 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{22}H_{21}N_3O$) C, H, N.

**6,11-Dihydro-11-ethyl-7-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (33).** A stirred mixture of **32** (79 mg, 0.2 mmol) and anisole (0.05 mL, 0.02 mmol) in trifluoroacetic acid (5 mL) containing concentrated $H_2SO_4$ (0.25 mL) was heated at 110 °C for 8 h. The resulting dark solution was poured into ice-water (100 mL), and the milky suspension was extracted with EtOAc (3 × 50 mL). The combined extract was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (elution with 10→20% EtOAc/hexane) to give **33** (30 mg, 52%): mp 225–227 °C; $^1$H NMR ($d_6$-DMSO) δ 9.81 (s, 1 H, N*H*), 8.41 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.97 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.12 (dd, $J$ = 7.7, 4.8 Hz, 1 H), 7.04 (m, 3 H), 4.08 (br, 1 H), 3.69 (br, 1 H), 2.31 (s, 3 H), 1.13 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{15}H_{15}N_3O$) C, H, N.

**6,11-Dihydro-11-ethyl-6,7-dimethyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepine-5-thione (IX; R$^1$ = Me, R$^2$ = Et, R$^3$ = 7-Me, R$^4$ = H).** Lawesson's reagent[12] (0.25 g, 0.625 mmol) was added to a solution of **31** (0.32 g, 1.25 mmol) in toluene (10 mL), and the reaction mixture was stirred at reflux for 3 h. Concentration in vacuo followed by chromatography (elution with $CH_2Cl_2$) of the residue and recrystallization from $CH_3CN$ afforded the title compound (0.3 g, 86%): mp 196–199 °C; $^1$H NMR ($d_6$-DMSO) δ 8.28 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 8.16 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.15 (m, 4 H), 4.02 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 3.71 (s, 3 H), 3.61 (dq, $J$ = –14.0, 7.0 Hz, 1 H), 2.28 (s, 3 H), 1.16 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{16}H_{17}N_3S$) C, H, N, S.

**6,11-Dihydro-3-chloro-11-ethyl-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (38).** Chlorine gas (0.15 g, 2.2 mmol) was absorbed in trimethyl phosphate (TMP) (1.5 mL) and added to an ice-cold, stirred solution of **11** (0.50 g, 1.97 mmol) in TMP (5.0 mL). The resulting mixture was allowed to warm to room temperature overnight. An additional equivalent of the TMP-$Cl_2$ solution was added at 24 h, and then a third equivalent at 48 h. On the 4th day, excess chlorine was removed in vacuo and the reaction mixture was then poured into ice–water. The resulting white solid was collected, washed, dried, and purified by chromatography (elution with 0→30% EtOAc/hexane). The product crystallized from petroleum ether (30–60 °C) in white needles (130 mg, 23%): mp 131–132 °C; $^1$H NMR ($d_6$-DMSO) δ 8.45 (d, $J$ = 2.6 Hz, 1 H), 8.00 (d, $J$ = 2.6 Hz, 1 H), 7.41–7.44 (m, 1 H), 7.21–7.31 (m, 3 H), 4.15 (dq, $J$ = –14, 7.0 Hz, 1 H), 3.60 (dq, $J$ = 14, 7.0 Hz, 1 H), 3.45 (s, 3 H), 1.15 (t, $J$ = 7.0 Hz, 3 H). Anal. ($C_{15}H_{14}ClN_3O$) C, H, N.

**Synthesis of the Photoaffinity Probe (45). 6,11-Dihydro-6-methyl-9-nitro-5*H*-pyrido[2,3-*b*][1,5]benzo-**

**diazepin-5-one (VII; $R^1$ = $CH_3$, $R^3$ = 9-$NO_2$, $R^4$ = H) and 6,11-Dihydro-6-methyl-8-nitro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (VII; $R^1$ = $CH_3$, $R^3$ = 8-$NO_2$, $R^4$ = H).** A mixture of 2-chloronicotinic acid (15.7 g, 0.1 mol) and 4-nitro-*o*-phenylenediamine (15.3 g, 0.1 mol) was heated in sulfolane (100 mL) at 170 °C for 5 h. After cooling to room temperature, the solid material was removed by filtration, washed with hot EtOH, and air-dried to give a mixture of the 8- and 9-nitro isomers (21 g, 0.079 mol, 79%). This mixture was added, as a solution in DMSO (100 mL), to a solution of dimsyl sodium (200 mL, 0.42 M). After the reaction mixture had stirred for 1 h, methyl iodide (12 g, 0.08 mol) was added and stirring was continued for an additional 12 h. Water (200 mL) was added and the precipitate was removed by filtration. Fractional recrystallization from EtOH afforded VII ($R^1$ = $CH_3$, $R^3$ = 9-$NO_2$, $R^4$ = H) (6.8 g, 0.025 mol, 31%): mp 278–280 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 9.20 (br s, 1 H, NH), 8.34 (dd, $J$ = 2.0, 4.7 Hz, 1 H), 8.18 (d, $J$ = 3.0 Hz, 1 H), 8.10 (dd, $J$ = 2.0, 7.7 Hz, 1 H), 7.96 (dd, $J$ = 3.0, 9.0 Hz, 1 H), 7.53 (d, $J$ = 9.0 Hz, 1 H), 7.08 (dd, $J$ = 4.7, 7.7 Hz, 1 H), 3.42 (s, 3 H). An NOE was observed between the resonances at $\delta$ 3.42 and 7.53, and between the resonances at $\delta$ 9.2 and 8.18; MS (CI) $m/z$ 271 ($MH^+$). Anal. ($C_{13}H_{10}N_4O_3$) C, H, N. The combined supernatants were concentrated in vacuo, and the residue was purified by chromatography (elution with 0.5% $CH_2Cl_2$/hexane). A second chromatographic purification (elution with 30→50% EtOAc/hexane) gave VII ($R^1$ = $CH_3$, $R^3$ = 8-$NO_2$, $R^4$ = H) (0.3 g, 1.4%): mp 245–247 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 9.54 (br s, 1 H, NH), 8.35 (dd, $J$ = 1.9, 4.7 Hz, 1 H), 8.11–8.14 (m, 2 H), 8.03 (dd, $J$ = 2.5, 9 Hz, 1 H), 7.43 (d, $J$ = 9 Hz, 1 H), 7.10 (dd, $J$ = 4.7, 7.7 Hz, 1 H), 3.44 (s, 3 H). An NOE was observed between the resonances at $\delta$ 3.44 and 8.11–8.14, and between the resonances at $\delta$ 9.54 and 7.43; MS (CI) $m/z$ 271 ($MH^+$). Anal. ($C_{13}H_{10}N_4O_3$) C, H, N.

**6,11-Dihydro-11-ethyl-6-methyl-9-nitro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (42).** A solution of VII ($R^1$ = $CH_3$, $R^3$ = 9-$NO_2$, $R^4$ = H) (1.5 g, 5.3 mmol) in DMSO (5 mL) was added to a solution of dimsyl sodium (5 mL, 1.1 M), and the resulting mixture was stirred for 20 min. Ethyl iodide (0.98 g, 6.3 mmol) was added and stirring was continued for an additional 20 min. Water (100 mL) was then added, and the mixture was extracted with $CH_2Cl_2$. The organic phase was washed with water, dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by chromatography (elution with $CH_2Cl_2$/EtOH) to give **42**, which crystallized from diisopropyl ether (0.5 g, 31%): mp 175–178 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 8.47 (dd, $J$ = 1.9, 4.8 Hz, 1 H), 7.99–8.09 (m, 3 H), 7.66 (d, $J$ = 8.9 Hz, 1 H), 7.20 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 4.30 (m, 1 H), 3.67 (m, 1 H), 3.50 (s, 3 H), 1.18 (t, $J$ = 7.0 Hz, 3 H); MS (EI) $m/z$ 298 ($M^+$). Anal. ($C_{15}H_{14}N_4O_3$) C, H, N. The supernatant was concentrated and the residue was purified by chromatography (elution with 30% EtOAc/hexane) to give the 1-ethylated product (XIb; R = Et, $R^1$ = Me, $R^3$ = 9-$NO_2$, $R^4$ = H), which crystallized from EtOAc/hexane (0.09 g, 6%): mp 179–180.5 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 7.92 (dd, $J$ = 1.9, 7.2 Hz, 1 H), 7.88 (dd, $J$ = 1.9, 6.5 Hz, 1 H), 7.80 (dd, $J$ = 2.8, 9.0 Hz, 1 H), 7.59 (d, $J$ = 2.8 Hz, 1 H), 7.24 (d, $J$ = 9.0 Hz, 1 H), 6.16 (dd, $J$ = 6.5, 7.2 Hz, 1 H), 4.15 (q, $J$ = 7.0 Hz, 2 H), 3.25 (s, 3 H), 1.35 (t, $J$ = 7.0 Hz, 3 H); MS (CI) $m/z$ 299 ($MH^+$). Anal. ($C_{15}H_{14}N_4O_3$) C, H, N.

**9-Amino-6,11-dihydro-11-ethyl-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (43).** To a solution of **42** (0.3 g, 1.0 mmol) in HOAc (5 mL) was added a solution of $SnCl_2 \cdot 2H_2O$ (1.7 g, 7.5 mmol) in concentrated HCl (2.2 mL). The mixture was stirred at room temperature for 6 h and then basified with saturated aqueous $NaHCO_3$. Extraction with EtOAc and concentration in vacuo afforded a solid residue, which recrystallized from EtOAc to give **43** (0.12 g, 45%): mp 193–195 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 8.35 (dd, $J$ = 2.0, 4.8 Hz, 1 H), 7.94 (dd, $J$ = 2.0, 7.5 Hz, 1 H), 7.09 (dd, $J$ = 4.8, 7.5 Hz, 1 H), 7.02 (d, $J$ = 8.5 Hz, 1 H), 6.35–6.41 (m, 2 H), 5.17 (br s, 2 H, $NH_2$), 4.08 (m, 1 H), 3.48 (m, 1 H), 3.35 (s, 3 H), 1.15 (t, $J$ = 7.0 Hz, 3 H); MS (CI), $m/z$ 269 ($MH^+$). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

**9-Azido-6,11-dihydro-11-ethyl-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (45).** To a solution of **43** (0.21 g, 0.78 mmol) in water (3.5 mL) and concentrated HCl (0.5 mL) was added over 40 min (at such a rate that the internal temperature remained below 5 °C) a solution of $NaNO_2$ (0.24 g, 2.4 mmol) in water (10 mL). The mixture was stirred at 5 °C for an additional 20 min. A solution of $NaN_3$ (0.41 g, 6.3 mmol) in water (3 mL) was then added all at once, and stirring was continued for 15 min. The reaction mixture was extracted with $CH_2Cl_2$, and the organic phase was dried ($Na_2SO_4$) and concentrated. The residue was recrystallized from $Et_2O$ to give **45** (0.13 g, 56%): mp 115–118 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 8.41 (dd, $J$ = 2.0, 4.8 Hz, 1 H), 7.99 (dd, $J$ = 2.0, 7.7 Hz, 1 H), 7.43 (d, $J$ = 8.6 Hz, 1 H), 7.15 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 6.98 (dd, $J$ = 2.4, 8.6 Hz, 1 H), 6.91 (d, $J$ = 2.4 Hz, 1 H), 4.19 (m, 1 H), 3.60 (m, 1 H), 3.42 (s, 3 H), 1.15 (t, $J$ = 7.0 Hz, 3 H); MS (CI) $m/z$ 295 ($MH^+$). Anal. ($C_{15}H_{14}N_6O$) C, H, N.

**6,11-Dihydro-11-ethyl-6-methyl-8-(phthalimidomethyl)-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (II; $R^1$ = Me, $R^2$ = Et, $R^3$ = 8-phthalimidomethyl, $R^4$ = H).** Into a stirred solution of *N*-(hydroxymethyl)phthalimide (26.57 g, 0.15 mol) in $H_2SO_4$ (200 mL) at 5 °C was added a solution of **11** (38 g, 0.15 mol) in $H_2SO_4$ (300 mL), and the resulting mixture was stirred at room temperature for 5 days. The reaction mixture was then poured onto ice, neutralized to pH 8 with $NH_4OH$, and extracted with $CH_2Cl_2$. The organic layer was concentrated in vacuo and the residue was purified by chromatography (elution with 2% MeOH/$CH_2Cl_2$). Recrystallization from $CH_2Cl_2$/$Et_2O$ afforded the title compound (42 g, 68%): mp 190–192 °C; $^1$H NMR ($d_6$-DMSO) 8.38 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.96 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.86 (m, 4 H), 7.39 (d, $J$ = 1.5 Hz, 1 H), 7.22 (d, $J$ = 8.1 Hz, 1 H), 7.11 (m, 2 H), 4.75 (s, 2 H), 4.16 (dq, $J$ = −14.0, 7.0 Hz, 1 H), 3.57 (dq, $J$ = −14.0, 7.0 Hz, 1 H), 3.43 (s, 3 H), 1.13 (t, $J$ = 7.0 Hz, 3 H); MS (CI) $m/z$ 413 ($MH^+$). Anal. ($C_{24}H_{20}N_4O_3$) C, H, N.

**8-(Aminomethyl)-6,11-dihydro-11-ethyl-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (50).** A suspension of II ($R^1$ = Me, $R^2$ = Et, $R^3$ = 8-phthalimidomethyl, $R^4$ = H) (38 g, 0.09 mol) and hydrazine hydrate (23 g, 0.46 mol) in EtOH (900 mL) was stirred at reflux for 1 h. The mixture was then filtered and the filtrate was concentrated to 150 mL. Water (500 mL) was added and the solution was basified with 2 N NaOH. Following extraction into $CH_2Cl_2$ and concentration in vacuo, the crude product was purified by chromatography (elution with 10% MeOH/$CH_2Cl_2$) to give **50** (25 g, 96%) as a colorless, hygroscopic resin: $^1$H NMR ($d_6$-DMSO) $\delta$ 8.38 (m, 1 H), 7.9 (m, 1 H), 7.2–7.3 (m, 4 H), 4.2 (m, 1 H), 3.5–3.6 (m, 1 H), 3.7 (s, 2 H), 3.4 (s, 3 H), 1.1 (m, 3 H); MS (CI) $m/z$ 283 ($MH^+$). Anal. ($C_{16}H_{18}N_4O \cdot 0.5H_2O$) C, H, N.

**6,11-Dihydro-11-ethyl-8-(hydroxymethyl)-6-methyl-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5-one (52).** A solution of **50** (1.9 g, 7 mmol) in 50% HOAc (50 mL) was treated with $NaNO_2$ (5.7 g, 80 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then basified with 40% aqueous NaOH and extracted with $Et_2O$. The organic extract was treated with a solution of 5% KOH/MeOH (50 mL) for 2 h in order to effect hydrolysis. The reaction mixture was washed with water and the organic layer was concentrated in vacuo. Chromatographic purification (elution with 1.5% MeOH/$CH_2Cl_2$) of the residue afforded **52** (1.75 g, 92%) as a colorless oil: $^1$H NMR ($d_6$-DMSO) $\delta$ 8.38 (dd, $J$ = 4.8, 1.8 Hz, 1 H), 7.98 (dd, $J$ = 7.7, 1.8 Hz, 1 H), 7.1–7.2 (m, 4 H), 5.20 (t, $J$ = 5.5 Hz, 1 H), 4.46 (d, $J$ = 5.5 Hz, 1 H), 4.17 (dq, $J$ = −14.0, 7.0 Hz, 1 H), 3.60 (dq, $J$ = −14.0, 7.0 Hz, 1 H), 3.45 (s, 3 H), 1.15 (t, $J$ = 7.0 Hz, 3 H); MS (CI) $m/z$ 284 ($MH^+$). Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

**Method B. 2-Chloro-*N*-(2-chloro-3-pyridinyl)-3-pyridinecarboxamide (XIVa; $R^3$ = $R^4$ = H).** To a solution of 3-amino-2-chloropyridine (215 g, 1.672 mol) in a mixed solvent system of 1,4-dioxane (400 mL), cyclohexane (500 mL), and pyridine (130 mL) was added over 30 min a solution of 2-chloronicotinoyl chloride (292.2 g, 1.7 mol) in 1,4-dioxane (200 mL). The reaction mixture was stirred overnight at ambient temperature under $N_2$ atmosphere. The solid product was removed by filtration, dissolved in $CH_2Cl_2$, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The resultant solid was washed with EtOAc, filtered, and dried in vacuo to give the desired product (386 g, 84%): mp 156–159 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 10.61 (br s, 1 H), 8.56 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.32 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.23 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 8.1 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.59 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 7.53 (dd, $J$ = 4.8,

7.7 Hz, 1 H); MS (CI) $m/z$ 268 ($MH^+$). Anal. ($C_{11}H_7Cl_2N_3O$) C, H, Cl, N.

**2-Chloro-*N*-methyl-*N*-(2-chloro-3-pyridinyl)-3-pyridinecarboxamide (XIVb; $R^1$ = Me, $R^3$ = $R^4$ = H).** Sodium hydride (60% dispersion in oil, 5.0 g, 0.125 mol) was added in several portions over 30 min to a solution of 2-chloro-*N*-(2-chloro-3-pyridinyl)-3-pyridinecarboxamide (27 g, 0.1 mol) in DMSO (100 mL) under nitrogen, and the mixture was heated at 60 °C for 1 h. The solution was then cooled to room temperature, methyl iodide (8.0 mL, 0.125 mol) was added, and the reaction mixture was stirred overnight at room temperature. Excess base was destroyed by the addition of ice, and the mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and the combined organic extract was concentrated in vacuo. The residue was taken up in $Et_2O$, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give an oil. Trituration with $Et_2O$/petroleum ether (30–60 °C) afforded the title compound (22.0 g, 77%): $^1H$ NMR ($CDCl_3$) (2:1 mixture of conformers) $\delta$ 8.58 (dd, $J$ = 1.8, 4.8 Hz, $^1/_3$ H), 8.48 (dd, $J$ = 1.8, 4.7 Hz, $^1/_3$ H), 8.28–8.32 (m, 2 × $^2/_3$ H), 8.05–8.11 (m, 2 × $^1/_3$ H), 7.89 (dd, 1.9, 7.6 Hz, $^2/_3$ H), 7.59–7.65 (m, 2 × $^1/_3$ H), 7.42 (dd, $J$ = 4.7, 7.9 Hz, $^2/_3$ H), 7.35 (dd, $J$ = 4.8, 7.6 Hz, $^2/_3$ H), 3.34 (s, 3 × $^2/_3$ H), 3.12 (s, 3 × $^1/_3$ H).

**Synthesis of 11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (96). 3-Amino-2-chloro-4-methylpyridine.** 2-Chloro-4-methyl-3-nitropyridine (21.4 g, 0.124 mol) in EtOH (100 mL) was hydrogenated under pressure (50 psi) in the presence of 5% Rh/C (1.3 g) for 3 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was treated with hot EtOAc (100 mL) and the resultant solution was filtered through Celite. Concentration of the clear filtrate afforded the title compound (13.3 g, 75%): mp 65–66 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 7.51 (d, $J$ = 4.6 Hz, 1 H), 7.00 (d, $J$ = 7.6 Hz, 1 H), 5.23 (br s, 2 H), 2.16 (s, 3 H); MS (CI) $m/z$ 143 ($MH^+$). Anal. ($C_6H_7ClN_2$) C, H, Cl, N.

**2-Chloro-*N*-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide (XIVa; $R^3$ = Me, $R^4$ = H).** To a solution of 3-amino-2-chloro-4-methylpyridine (260 g, 1.82 mol) in a mixture of cyclohexane (600 mL), 1,4-dioxane (100 mL), and pyridine (575 mL) was added in portions over 30 min a solution of 2-chloronicotinoyl chloride (321 g, 1.28 mol) in 1,4-dioxane (500 mL). The resulting mixture was stirred at ambient temperature for 48 h to produce a crystalline precipitate, which was removed by filtration and washed with water. The wet filter cake was added to a mixture of EtOH (1.75 L) and aqueous NaOH (0.1 N, 360 mL), heated under reflux for 2 h, and then stirred overnight at ambient temperature. The solvent was evaporated in vacuo and water (1 L) was added, with stirring, to the residue. The mixture was cooled to 10 °C and the crystalline product was collected by filtration, washed with cold water and dried under vacuum to give the title compound (337 g, 65.5%): mp 189–191 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 10.60 (br s, 1 H), 8.58 (dd, $J$ = 1.9, 5.0 Hz, 1 H), 8.27 (d, $J$ = 5.0 Hz, 1 H), 8.09 (dd, $J$ = 1.9, 7.6 Hz, 1 H), 7.61 (dd, $J$ = 5.0, 7.6 Hz, 1 H), 7.43 (d, $J$ = 5.0 Hz, 1 H), 2.38 (s, 3 H); MS (CI) $m/z$ 282 ($MH^+$). Anal. ($C_{12}H_9Cl_2N_3O$) C, H, Cl, N.

***N*-(2-Chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (XVa; $R^2$ = c-Pr, $R^3$ = Me, $R^4$ = H).** A mixture of 2-chloro-*N*-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide (167 g, 0.59 mol) and cyclopropylamine (135 g, 2.35 mol) in xylene (1 L) was heated with stirring at 110 °C in a 2-L autoclave for 18 h. After cooling to room temperature, the mixture was diluted with $CH_2Cl_2$ (2 L), washed with water, dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residual oil was triturated with $CH_2Cl_2$ and $Et_2O$ to give the title compound (147 g, 83%): mp 127–129 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 10.2 (br s, 1 H), 8.33 (dd, $J$ = 1.7, 4.8 Hz, 1 H), 8.19–8.25 (m, 3 H), 7.41 (d, $J$ = 5.2 Hz, 1 H), 6.75 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 2.84 (m, 1 H), 2.25 (s, 3 H), 0.72 (m, 2 H), 0.43 (m, 2 H); MS (CI) $m/z$ 303 ($MH^+$). Anal. ($C_{15}H_{15}ClN_4O$) C, H, Cl, N.

**11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (96).** To a solution of *N*-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (145 g, 0.48 mol) in bis(2-methoxyethyl) ether (870 mL) under nitrogen was added, in portions, NaH (50% dispersion in oil, 46 g, 0.96 mol). The mixture was heated slowly to 160 °C (**Caution**! Potential exotherm with vigorous $H_2$ evolution at 150 °C) and then heated under gentle reflux for 1.5 h. The mixture was cooled to 65 °C, poured onto ice (2 kg) and water (1 L), and left stirring overnight. The precipitate was removed by filtration and dissolved in hot pyridine (1 L). The product was precipitated by the slow addition of water (10 L), collected by suction filtration, and stirred in MeOH (1 L) at reflux. Filtration, followed by recrystallization of the collected solid from pyridine/water, gave **96** (85.6 g, 67%): mp 247–249 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 9.90 (br s, 1 H), 8.51 (dd, $J$ = 1.9, 4.7 Hz, 1 H), 8.08 (d, $J$ = 5.0 Hz, 1 H), 8.02 (dd, $J$ = 1.9, 8.0 Hz, 1 H), 7.20 (dd, $J$ = 4.7, 8.0 Hz, 1 H), 7.07 (d, $J$ = 5.0 Hz, 1 H), 3.62 (m, 1 H), 2.34 (s, 3 H), 0.88 (m, 2 H), 0.35 (m, 2 H); MS (CI) $m/z$ 267 ($MH^+$). Anal. ($C_{15}H_{14}N_4O$) C, H, N.

**Method C. *N*-(2-Chloro-3-pyridinyl)-2-[[(4-methoxyphenyl)methyl]amino]-3-pyridinecarboxamide (XVII; $R^1$ = $R^3$ = $R^4$ = H).** A mixture of 2-chloro-*N*-(2-chloro-3-pyridinyl)-3-pyridinecarboxamide (67.4 g, 0.251 mol) and 4-methoxybenzylamine (34.5 g, 0.251 mol) in xylene (400 mL) was heated under reflux for 2 h. The solvent was evaporated, and the residue was diluted with water and extracted with $CH_2Cl_2$. The organic phase was dried ($Na_2SO_4$), filtered, and concentrated in vacuo to give a brown oil. This crystallized upon addition of $Et_2O$ to provide XVII ($R^1$ = $R^3$ = $R^4$ = H) (78.0 g, 91%) as a beige powder: mp 121–122 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 10.2 (br s, 1 H, NH), 8.44 (br t, $J$ = 5.5 Hz, 1 H, NH), 8.32 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.27 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.19 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 8.01 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.49 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 7.24–7.29 (m, 2 H), 6.85–6.90 (m, 2 H), 6.70 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 4.56 (d, $J$ = 5.5 Hz, 1 H), 3.72 (s, 3 H); MS (CI) $m/z$ 369 ($MH^+$).

**5,11-Dihydro-11-[(4-methoxyphenyl)methyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XVIIIa; $R^3$ = $R^4$ = H).** Sodium hydride (50% dispersion in oil, 13.3 g, 270 mmol) was added to a solution of *N*-(2-chloro-3-pyridinyl)-2-[[(4-methoxyphenyl)methyl]amino]-3-pyridinecarboxamide (34.03 g, 90 mmol) in DMF (500 mL). When hydrogen evolution had ceased, the reaction mixture was heated to 140 °C and left stirring overnight. The reaction mixture was quenched with ice, diluted with water, and extracted with $Et_2O$ and $CH_2Cl_2$. The combined organic extract was concentrated in vacuo, redissolved in water, and extracted with $Et_2O$. The product crystallized from the $Et_2O$ layer and was collected by filtration to give XVIIIa ($R^3$ = $R^4$ = H) (12.63 g, 42%): mp 209–210 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 10.50 (s, 1 H, NH), 8.44 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.11 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.07 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.47 (dd, $J$ = 1.8, 5.9 Hz, 1 H), 7.28 (d, $J$ = 8.8 Hz, 2 H), 7.14 (m, 2 H), 6.79 (d, $J$ = 8.8 Hz, 2 H), 5.23 (s, 2 H), 3.67 (s, 3 H). Anal. ($C_{19}H_{16}N_4O_2$) C, H, N.

**5,11-Dihydro-11-[(4-methoxyphenyl)methyl]-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XVIIIb; $R^1$ = Me, $R^3$ = $R^4$ = H).** To a stirred slurry of XVIIIa ($R^3$ = $R^4$ = H) (2.92 g, 8.79 mmol) in DMF (20 mL) was added NaH (50% dispersion in oil, 0.464 g, 9.66 mmol) in one portion. After 2 h, methyl iodide (2.49 g, 17.6 mmol) was added and the reaction mixture was stirred for an additional 2 h. Diethyl ether (200 mL) was added, and the organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. Purification by chromatography (elution with $CH_2Cl_2$) afforded XVIIIb ($R^1$ = Me, $R^3$ = $R^4$ = H) (0.85 g, 28%): mp 120–121.5 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.36 (dd, $J$ = 4.8, 1.9 Hz, 1 H), 8.16 (dd, $J$ = 4.6, 1.6 Hz, 1 H), 8.11 (dd, $J$ = 7.7, 1.9 Hz, 1 H), 7.48 (dd, $J$ = 7.9, 1.6 Hz, 1 H), 7.34 (d, $J$ = 8.7 Hz, 2 H), 7.05 (dd, $J$ = 7.9, 4.7 Hz, 1 H), 7.00 (dd, $J$ = 7.7, 4.8 Hz, 1 H), 6.76 (d, $J$ = 8.7 Hz, 2 H), 3.73 (s, 3 H), 3.53 (s, 3 H); MS (CI) $m/z$ 347 ($MH^+$). Anal. ($C_{20}H_{18}N_4O_2$) C, H, N.

**5,11-Dihydro-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (XIXb, $R^1$ = Me, $R^3$ = $R^4$ = H).** A solution of XVIIIb ($R^1$ = Me, $R^3$ = $R^4$ = H) (2.6 g, 7.5 mmol) in trifluoroacetic acid (15 mL) was stirred at room temperature for 1.5 h. After removal of the solvent, the residue was stirred with 0.5% $NH_4OH$ for 2 h. The precipitated solid was removed by filtration, washed with water, air-dried, and recrystallized from EtOH to give XIXb ($R^1$ = Me, $R^3$ = $R^4$ = H) (1.51 g, 89%): mp 227–229 °C; $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.83 (br s, 1 H, NH), 8.35 (dd, $J$ = 1.8, 4.8 Hz, 1

H), 8.10 (dd, $J$ = 1.0, 4.8 Hz, 1 H), 8.11 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.78 (dd, $J$ = 1.0, 7.7 Hz, 1 H), 7.21 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 7.09 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 3.38 (s, 3 H); MS (CI) $m/z$ 227 ($MH^+$). Anal. ($C_{12}H_{10}N_4O$) C, H, N.

**11-Allyl-5,11-dihydro-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (78).** To a suspension of XIXb ($R^1$ = Me, $R^3$ = $R^4$ = H) (0.5 g, 2.2 mmol) in DMF (20 mL) at 60 °C was added NaH (50% dispersion in oil, 0.2 g, 4.2 mmol), and the resultant mixture was stirred at 50 °C for 1 h. Allyl bromide (0.35 mL, 4.0 mmol) was added and stirring was continued at 50 °C for an additional 2 h and at room temperature overnight. The reaction was quenched with alcohol and the solvent was removed in vacuo. The residue was dissolved in $CH_2Cl_2$, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give the crude product. Chromatography (elution with 50% EtOAc/hexane) and recrystallization from EtOAc/hexane afforded **78** (0.42 g, 72%): mp 93–95 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 8.43 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.20 (dd, $J$ = 1.8, 4.8 Hz, 1 H), 8.06 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 7.87 (dd, $J$ = 1.8, 8.1 Hz, 1 H), 7.29 (dd, $J$ = 4.8, 8.1 Hz, 1 H), 7.18 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 5.92 (m, 1 H), 5.19 (m, 1 H), 5.02 (m, 1 H), 4.76 (br m, 1 H), 3.44 (s, 3 H); MS (CI) $m/z$ 267 ($MH^+$). Anal. ($C_{15}H_{14}N_4O$) C, H, N.

**HIV-1 Reverse Transcriptase Enzyme Assay.** Recombinant HIV-1 reverse transcriptase was obtained from T. Steitz (Yale University). This enzyme was homogeneous (>95%) p66/p51 heterodimer. Reverse transcriptase was assayed by a modification of the previously described procedure.[23a] The reaction mixture consisted of 50 mM Tris (pH 7.8), 50 mM glutamic acid, 1 mM DTT, 2 mM $MgCl_2$, 0.02% CHAPS, 0.8 μg/mL poly(rC):oligo(dG) (Pharmacia), and 500 nM [$^3$H]dGTP (NEN Du Pont), adjusted to a final volume of 60 μL. Inhibitors were assayed at a concentration of 10 μg/mL in the presence of RT (0.5 nM). The inhibitors, which were dissolved in DMSO and diluted many-fold with buffer, were added as solutions, and reaction was initiated by the addition of enzyme. After 1 h at room temperature, 50 μL each of ice-cold 10% aqueous trichloroacetic acid and 2% aqueous sodium pyrophosphate was added and the mixture was cooled at 4 °C for 15 min. Acid insoluble products were harvested onto #30 glass fiber filters (Schleicher and Schuell) using a Skatron cell harvester. Dried filters were counted in an LKB 1205 Betaplate liquid scintillation counter. Inhibition was determined by comparison of the amount of product in reactions run with and without test compound. $IC_{50}$s were determined by comparison of the amounts of product produced in the presence and absence of test compound. Plots of per cent inhibition versus log ([compound]) yielded the concentration at which half maximal inhibition was observed.

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