Novel Non-nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 (HIV-1) Reverse Transcriptase. 4.[1] 2-Substituted Dipyridodiazepinones as Potent Inhibitors of Both Wild-Type and Cysteine-181 HIV-1 Reverse Transcriptase Enzymes

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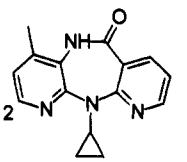
The major cause of viral resistance to the potent human immunodeficiency virus type 1 reverse transcriptase (RT) inhibitor nevirapine is the mutation substituting cysteine for tyrosine-181 in RT (Y181C RT). An evaluation, against Y181C RT, of previously described analogs of nevirapine revealed that the 2-chlorodipyridodiazepinone **16** is an effective inhibitor of this mutant enzyme. The detailed examination of the structure–activity relationship of 2-substituted dipyridodiazepinones presented below shows that combined activity against the wild-type and Y181C enzymes is achieved with aryl substituents at the 2-position of the tricyclic ring system. In addition, the substitution pattern at C-4, N-5, and N-11 of the dipyridodiazepinone ring system optimum for inhibition of both wild-type and Y181C RT is no longer the 4-methyl-11-cyclopropyl substitution preferred against the wild-type enzyme but rather the 5-methyl-11-ethyl (or 11-cyclopropyl) pattern. The more potent 2-substituted dipyridodiazepinones were evaluated against mutant RT enzymes (L100I RT, K103N RT, P236L RT, and E138K RT) that confer resistance to other non-nucleoside RT inhibitors, and compounds **42**, **62**, and **67**, with pyrrolyl, aminophenyl, and aminopyridyl substituents, respectively, at the 2-position, were found to be effective inhibitors of these mutant enzymes also.

Introduction

The only agents currently approved for the treatment of the acquired immune deficiency syndrome (AIDS) exert their therapeutic effect at the level of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) enzyme. These therapeutics, the nucleoside analogs AZT,[2] DDI,[3] DDC,[4] and D4T,[5] after intracellular transformation to the triphosphates, are incorporated by RT into the nascent proviral DNA and thereby terminate its synthesis.

In addition to the nucleoside analogs, there is a second class of RT inhibitors, the non-nucleosides, exemplified by the dipyridodiazepinone nevirapine (**1**).[6] The non-nucleoside RT inhibitors[7-11] bind close to the active site[12-15] inducing conformational changes that affect the catalytic efficiency of the enzyme.[16,17] Notwithstanding the differing mechanisms of action, the emergence of resistant virus is a major limitation associated with the use of either nucleoside or non-nucleoside inhibitors of RT.[18-20]

The primary cause of viral resistance to nevirapine is the mutation which substitutes cysteine for tyrosine-181 in RT (Y181C RT).[19] This Y181C RT is less sensitive to nevirapine than the wild-type enzyme (Table 1) and also less sensitive to other non-nucleoside inhibitors.[20] Besides improving potency against the wild-type enzyme, a major focus of the study presented below was to achieve significant activity against the Y181C RT. Of the previously reported dipyridodiazepinones,[21] only the 2-chloro derivative **16** displayed significant inhibition of the Y181C RT (IC_{50} = 0.21 μM, Table 1). This unique activity of the 2-chlorodipyridodiazepinone prompted us to extend the original structure–activity relationship (SAR) study and examine in detail the effect of 2-substitution on the inhibition of wild-type and Y181C RT enzymes.



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Chemistry

The optimal dipyridodiazepinone substituents at N-11 (ethyl or cyclopropyl), C-4 (methyl or hydrogen), and N-5 (hydrogen or methyl) have been previously determined,[21] and the effect of 2-substitution was evaluated in the context of the tricyclic nucleus A (4-methyl-11-cyclopropyl), B (4-methyl-11-ethyl), C (5-methyl-11-ethyl), or D (5-methyl-11-cyclopropyl) below. The general synthesis of 2-substituted-4-methyldipyridodiazepinones (derivatives of nuclei A and B) is outlined in Scheme 1. The reaction with $POCl_3$ of pyridones **I**[22] gave the 3-cyano-2-chloropyridines **II**. Conversion of the

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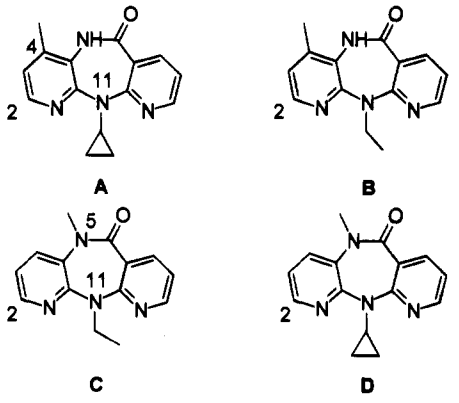
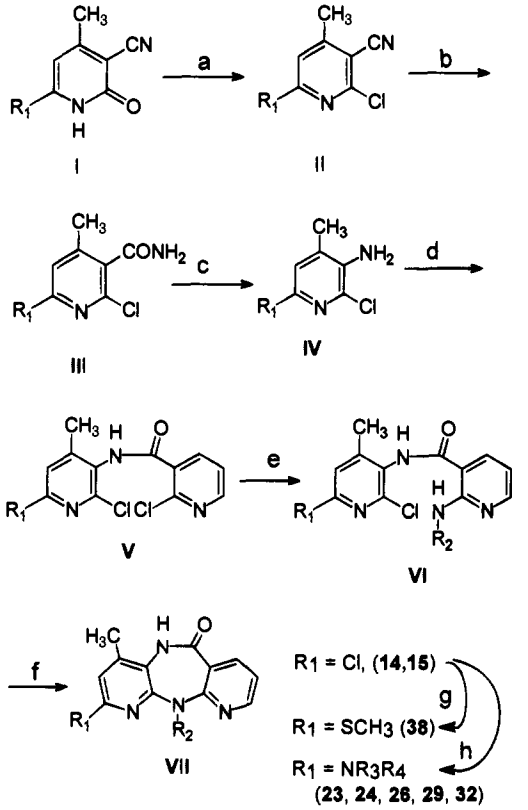


nitrile to the amide with hot concentrated sulfuric acid[23] was followed by Hofmann rearrangement which gave the 3-amino-2-chloropyridines **IV**. Derivatives of nucleus A were obtained by reaction of amides **V** with cyclopropylamine followed by cyclization as previously described.[21,24] Derivatives of nucleus B were obtained by an analogous sequence employing ethylamine in the conversion of **V** to **VI**. The 2-alkyl and 2-halo derivatives of A and B were obtained in this way.

Several of the dipyridodiazepinones were derived by further transformation of the tricyclics **VII**. Displacement of the 2-chloro substituent of **15** gave the 2-amino and 2-mercapto derivatives of B. The 2-fluorodipyridodiazepinone **13** was derived from the corresponding 2-amino compound by diazotization in the presence of HF/pyridine.[25]

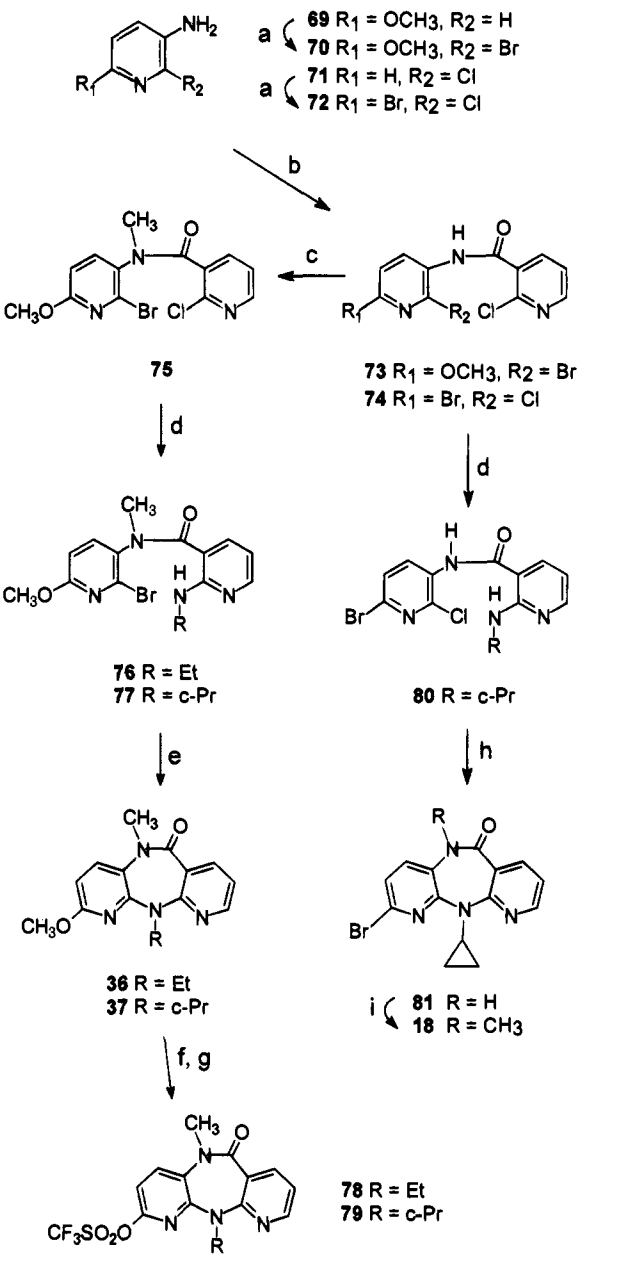
The 2-triflate derivatives **78** and **79** (Scheme 2) proved to be versatile intermediates for accessing derivatives

Scheme 1[a]



[a] (a) $POCl_3$, 120 °C; (b) concentrated H_2SO_4, heat; (c) NaOH, Br_2, heat; (d) 2-chloronicotinoyl chloride, inert solvent; (e) RNH_2, inert solvent, sealed tube, heat; (f) NaH, inert solvent, heat; (g) MeSNa, sulfolane, heat; (h) amine, sealed tube, heat.

Scheme 2[a]



[a] (a) Br_2, AcOH, NaOAc; (b) 2-chloronicotinoyl chloride, CH_2Cl_2, pyridine; (c) NaH, DMSO, MeI; (d) $EtNH_2$ or cyclopropylamine, inert solvent, sealed tube, 150 °C; (e) NaH, xylene, 150 °C; (f) HBr/AcOH, reflux; (g) Tf_2O, $^iPr_2NEt_2$, CH_2Cl_2; (h) NaHMDS, pyridine, 95 °C; (i) KO^{t}Bu, DMSO, MeI.

of nuclei C and D. Bromination of 3-amino-6-methoxypyridine (**69**) occurred selectively at the 2-position giving 3-amino-2-bromo-6-methoxypyridine (**70**) which was reacted with 2-chloronicotinoyl chloride to give the amide **73**. N-Methylation was followed by reaction with ethylamine or cyclopropylamine, and subsequent cyclization gave the 2-methoxydipyridodiazepinone **36** or **37**. Cleavage of the methyl ether and reaction of the 2-hydroxypyridine with triflic anhydride gave the 2-triflate **78** or **79**. The triflate group was readily displaced by amines giving the 2-amino derivatives of C and D. The 2-*N*-pyrrolyl derivative **33** and the 2-*N*-pyrazolyl derivative **34** were derived from the corresponding 2-amino and 2-hydrazino compounds by standard transformations.[26,27]

In addition, the triflates were precursors of the 2-alkenyl-, 2-alkynyl-, 2-aryl-, and 2-heteroaryl-substi-

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

no.	R	nucleus	mp (°C)	recryst solvent	formula[a]	IC_{50} (μM)[b] WT RT	IC_{50} (μM)[b] Y181C RT
1	H	A	247–249	EtOAc	$C_{15}H_{14}N_4O$[c]	0.08	2.6
2	H	B	212–214	CH_2ClCH_2Cl	$C_{14}H_{14}N_4O$[c]	0.04	1.8
3	H	C	130–132	EtOAc/hexane	$C_{14}H_{14}N_4O$[c]	0.13	2.2
4	CH_3	A	>300	EtOAc/hexane	$C_{16}H_{16}N_4O$[d]	0.07	1.2
5	CH_3	B	210–211	EtOAc/hexane	$C_{15}H_{16}N_4O$	0.02	>1
6	CH_3	C	124–126	hexane	$C_{15}H_{16}N_4O$	0.12	1.2
7	CH_2CH_3	B	188–190	e	$C_{16}H_{18}N_4O$	0.09	1.7
8	$CH(CH_3)_2$	B	212–214	EtOAc/hexane	$C_{17}H_{20}N_4O$	1	>1
9	$C(CH_3)_3$	B	248–250	EtOAc/hexane	$C_{18}H_{22}N_4O$	>1	>1
10	$C{=}CHCOOCH_3$	C	138–139	EtOAc/hexane	$C_{18}H_{18}N_4O_3$	0.18	0.67
11	$C{=}CHCONH_2$	C	122–125	EtOAc/hexane	$C_{17}H_{17}N_5O_2$	0.25	2.4
12	$C{\equiv}CH$	C	144–147	EtOAc/hexane	$C_{16}H_{14}N_4O{\cdot}0.25H_2O$[f]	0.14	0.42
13	F	B	215–216	CH_3CN	$C_{14}H_{13}FN_4O$	0.02	0.85
14	Cl	A	295–300	$AcOH/H_2O$	$C_{15}H_{13}ClN_4O$	0.02	0.78
15	Cl	B	224–228	CH_2Cl_2/hexane	$C_{14}H_{13}ClN_4O$	0.01	0.80
16	Cl	C	125–126	heptane	$C_{14}H_{13}ClN_4O$[c]	0.08	0.21
17	Cl	D	220–221	EtOAc/hexane	$C_{15}H_{13}ClN_4O$	0.09	0.92
18	Br	D	232–233	EtOAc/CH_2Cl_2	$C_{15}H_{13}BrN_4O$	0.03	2.1
19	NH_2	C	197–199	EtOAc/$^iPr_2O$	$C_{14}H_{15}N_5O$[g]	>1	>1
20	$NHCH_3$	C	186–189	EtOAc/$^iPr_2O$	$C_{15}H_{17}N_5O{\cdot}0.1H_2O$	0.19	0.71
21	NHC_2H_5	C	154–157	$^iPr_2O$/hexane	$C_{16}H_{19}N_5O$	0.23	1.3
22	$NHCH{=}CH_2CH_2$	C	167–170	EtOAc/hexane	$C_{17}H_{19}N_5O$	0.39	>1
23	$NHCH_2CH_2OH$	B	241–244	$CHCl_3$/EtOH	$C_{16}H_{19}N_5O_2{\cdot}0.25H_2O$	0.09	>1
24	$NHCH_2CH_2CH_2OH$	B	185–186	EtOAc/EtOH	$C_{17}H_{21}N_5O_2{\cdot}0.25H_2O$	0.09	>1
25	$N(CH_3)_2$	C	118–120	EtOAc/EtOH	$C_{16}H_{19}N_5O$	0.07	0.77
26	$N(CH_3)CH_2CH_2OH$	B	139–142	EtOAc/$^iPr_2O$	$C_{17}H_{21}N_5O_2$	0.01	>1
27	*N*-pyrrolidinyl	C	185–188	EtOH/DMF	$C_{18}H_{21}N_5O{\cdot}0.5H_2O$	0.02	3.8
28	*N*-3,4-didehydropyrrolidinyl	C	153–156	$CHCl_3/^iPr_2O$	$C_{18}H_{19}N_5O$	0.03	0.64
29	*N*-(3(*R*,*S*)-hydroxypyrrolidinyl)	B	131–134	$CHCl_3$/hexane	$C_{18}H_{21}N_5O_2$	0.04	>1
30	*N*-piperidinyl	C	164–166	EtOAc	$C_{19}H_{23}N_5O$	0.30	>1
31	*N*-morpholinyl	C	157–160	$^iPr_2O$/hexane	$C_{18}H_{21}N_5O_2$	0.40	>1
32	*N*-(thiomorpholinyl)	B	221–223	$^iPr_2O$/hexane	$C_{18}H_{21}N_5OS$	0.15	>1
33	*N*-pyrrolyl	C	180–182	EtOAc/hexane	$C_{18}H_{17}N_5O$	0.09	0.21
34	*N*-pyrazolyl	C	145–147	$^iPr_2O$	$C_{17}H_{16}N_6O$	0.31	0.56
35	OH	C	215–218	EtOAc	$C_{14}H_{14}N_4O_2$	0.47	>1
36	OCH_3	C	116–118	EtOAc/hexane	$C_{15}H_{16}N_4O_2$	0.04	0.60
37	OCH_3	D	161–164	heptane	$C_{16}H_{16}N_4O_2$	0.12	1.1
38	SCH_3	B	235–236	EtOH	$C_{15}H_{16}N_4OS$	0.02	>1
39	2-furanyl	C	foam	e	$C_{18}H_{16}N_4O_2$	0.11	0.16
40	3-furanyl	C	foam	e	$C_{18}H_{16}N_4O_2$[h]	0.04	0.11
41	2-pyrrolyl	C	foam	e	$C_{18}H_{17}N_5O{\cdot}0.5H_2O$[i]	0.07	0.07
42	3-pyrrolyl	C	173–174	CH_2Cl_2/hexane	$C_{18}H_{17}N_5O{\cdot}0.5H_2O$	0.03	0.04
43	3-pyrrolyl	D	254–255	EtOAc	$C_{19}H_{17}N_5O$[h]	0.05	0.06
44	2-thienyl	C	112–114	$EtOH/H_2O$	$C_{18}H_{16}N_4OS$	0.14	0.42
45	3-thienyl	C	160–162	EtOAc/hexane	$C_{18}H_{16}N_4OS$	0.10	0.30
46	2-thiazolyl	C	114–115	e	$C_{17}H_{15}N_5OS$	0.38	1.1
47	5-thiazolyl	C	foam	e	$C_{17}H_{15}N_5OS{\cdot}0.5EtOAc$	0.10	0.24
48	2-oxazolyl	C	160–162	EtOAc/hexane	$C_{17}H_{15}N_5O_2$	0.11	0.56
49	5-oxazolyl	C	158–159	EtOAc/hexane	$C_{17}H_{15}N_5O_2$	0.22	0.82
50	2-imidazolyl	C	270–274	EtOAc	$C_{17}H_{16}N_6O$	3.7	0.74
51	5-imidazolyl	C	177–180	EtOAc	$C_{17}H_{16}N_6O{\cdot}0.5H_2O$	0.13	0.19
52	3-pyrazolyl	C	foam	e	$C_{17}H_{16}N_6O{\cdot}0.5H_2O$[j]	0.39	0.29
53	4-pyrazolyl	C	194–196	EtOAc/$^iPr_2O$	$C_{17}H_{16}N_6O$	0.02	0.06
54	4-pyrazolyl	D	233–235	CH_3CN	$C_{18}H_{16}N_6O{\cdot}0.5H_2O$	0.06	0.05
55	phenyl	C	oil	e	$C_{20}H_{18}N_4O$	0.23	1.4
56	2-OCH_3-phenyl	C	125–127	$^iPr_2O$	$C_{21}H_{20}N_4O_2$[h]	0.82	2.5
57	3-OCH_3-phenyl	C	113–114	EtOAc/$^iPr_2O$	$C_{21}H_{20}N_4O_2$	0.15	0.21
58	3-OH-phenyl	C	205–206	EtOAc/$^iPr_2O$	$C_{20}H_{18}N_4O_2$	0.10	0.18
59	3-NH_2-phenyl	C	155–157	EtOAc/$^iPr_2O$	$C_{20}H_{19}N_5O$	0.07	0.56
60	4-OCH_3-phenyl	C	126–128	$^iPr_2O$	$C_{21}H_{20}N_4O_2$[h]	1.4	3.2
61	4-OH-phenyl	C	215–216	EtOH/hexane	$C_{20}H_{18}N_4O_2$	0.07	0.27
62	4-NH_2-phenyl	C	192–194	CH_3CN/H_2O	$C_{20}H_{19}N_5O$	0.04	0.12
63	2-pyridyl	C	168–169	EtOAc/hexane	$C_{19}H_{17}N_5O{\cdot}0.1H_2O$	0.18	1.6
64	3-pyridyl	D	196–198	EtOAc/hexane	$C_{20}H_{17}N_5O$	0.18	0.44
65	3-(6-OCH_3-pyridyl)	C	128–130	EtOAc/$^iPr_2O$	$C_{20}H_{19}N_5O_2$	1.2	3
66	3-(6-OH-pyridyl)	C	154–172	EtOAc/hexane	$C_{19}H_{17}N_5O_2{\cdot}1.5H_2O$[l]	1.1	>1
67	3-(6-NH_2-pyridyl)	C	213–216	EtOAc/$^iPr_2O$	$C_{19}H_{18}N_6O$[k]	0.05	0.26
68	4-pyridyl	D	176–178	EtOAc/hexane	$C_{20}H_{17}N_5O{\cdot}0.75H_2O$[m]	0.15	0.32

[a] Analyses for C, H, and N are within ±0.4% of theoretical values unless otherwise indicated. [b] For details, see ref 21. [c] Characterization of these compounds was previously described in ref 21. [d] N: calcd, 19.99; found, 19.49. [e] Purified by chromatography; no recrystallization necessary. [f] N: calcd, 19.81; found, 19.27. [g] N: calcd, 26.00; found, 25.13. [h] No elemental analysis available; characterized by NMR and mass spectroscopy. [i] N: calcd, 21.32; found, 19.26. [j] N: calcd, 25.52; found, 24.41. [k] N: calcd, 24.26; found, 23.19. [l] H: calcd, 5.38; found, 4.83. [m] N: calcd, 19.63; found, 18.93.

tuted tricyclics in Table 1 via Pd-catalyzed cross-coupling reactions.[28] The 2-bromo tricyclic **18** was also employed as a component in some cross-coupling reactions, and its synthesis is outlined in Scheme 2.

Table 2. Reaction Conditions for the Synthesis of 2-Alkenyl-, 2-Alkynyl-, and 2-Aryldipyridodiazepinones

product	starter	coupling partner	reaction conditions	yield (%)
10	**78**	methyl acrylate	Et_3N, $Pd(Ph_3P)_2Cl_2$, 110 °C, 2 h	57
11	**78**	acrylamide	Et_3N, $Pd(Ph_3P)_2Cl_2$, 120 °C, 4 h	44
12	**78**	TMS acetylene	1. Et_3N, $Pd(Ph_3P)_2Cl_2$, 90 °C, 2 h (86%), 2. TBAF, THF	80[a]
39	**78**	2-(tributylstannyl)furan	DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 90 °C, 10 min	56
40	**78**	3-(tributylstannyl)furan	dioxane, $Pd(Ph_3P)_4$, LiCl, reflux, 30 min	50
41	**78**	*N*-Boc-2-(tributylstannyl)pyrrole	dioxane, $Pd(Ph_3P)_4$, LiCl, reflux, 4 h	23
42	**78**	*N*-^{i}Pr$_3$Si-3-(tributylstannyl)pyrrole	1. dioxane, $Pd(Ph_3P)_4$, LiCl, reflux, 3 h (71%), 2. TBAF, THF	51[a]
43	**79**	*N*-^{i}Pr$_3$Si-3-(tributylstannyl)pyrrole	1. dioxane, $Pd(Ph_3P)_4$, LiCl, reflux, 3 h, 2. TBAF, THF	78[a]
44	**78**	2-(tributylstannyl)thiophene	DMF, $Pd(Ph_3P)_4$, LiCl, 90 °C, 1 h	51
45	**78**	3-(tributylstannyl)thiophene	NMP, $Pd(Ph_3P)_2Cl_2$, LiCl, 90 °C, 4 h	35
46	**78**	2-thiazolylzinc chloride	THF, $Pd(Ph_3P)_4$, 80 °C, 3 h	64
47	**78**	5-thiazolylzinc chloride	DMF, $Pd(Ph_3P)_2Cl_2$, 130 °C, 1.5 h	28
48	**78**	2-oxazolylzinc chloride	THF, $Pd(Ph_3P)_4$, reflux, 5 h	56
49	**78**	oxazole	DMA, $Pd(Ph_3P)_4$, 120 °C, 30 min	34
50	**78**	[*N*-(*N*,*N*-dimethylsulfonamido)-2-imidazolyl]zinc chloride	1. THF, $Pd(Ph_3P)_4$, reflux, 1.5 h (70%), 2. KOH, EtOH, reflux, 1.5 h	22[a]
51	**78**	[*N*-(*N*,*N*-dimethylsulfonamido)-5-imidazolyl]zinc chloride	1. THF, $Pd(Ph_3P)_4$, reflux, 1.5 h (22%), 2. KOH, EtOH, reflux, 2 h	12[a]
52	**78**	[1-(*N*,*N*-dimethylsulfonamido)-5-pyrazolyl]zinc chloride	1. THF, $Pd(Ph_3P)_4$, reflux, 5.5 h (22%), 2. $NH_2NH_2{\cdot}H_2O$, 100 °C, 72 h	11[a]
53	**78**	4-(tributylstannyl)pyrazole	DMF, $Pd(Ph_3P)_2Cl_2$, 110 °C, 4 h	39
54	**78**	4-(tributylstannyl)pyrazole	DMF, $Pd(Ph_3P)_2Cl_2$, 110 °C, 16 h	28
55	**78**	phenyltributylstannane	DMF, $Pd(Ph_3P)_2Cl_2$, 90 °C, 1 h	42
56	**78**	2-(tributylstannyl)anisole	DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 120 °C, 9 h	27
57	**78**	3-(tributylstannyl)anisole	DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 120 °C, 1.5 h	80
58	**57**	*b*	HBr/AcOH, 130 °C, 2 h	23
59	**78**	3-(tributylstannyl)aniline	DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 120 °C, 4 h	65
60	**78**	4-(tributylstannyl)anisole	DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 110 °C, 4 h	20
61	**78**	4-(tributylstannyl)phenol *O*-TBDMS ether	1. dioxane, $Pd(Ph_3P)_4$, LiCl, reflux, 1.5 h (69%), 2. TBAF, THF, room temperature, 1 h	51[a]
62	**78**	4-(tributylstannyl)-*N*-Boc-aniline	1. DMF, $Pd(Ph_3P)_2Cl_2$, LiCl, 115 °C, 4 h (84%), 2. HCl/EtOAc, 12 h	63[a]
63	**78**	2-(tributylstannyl)pyridine	dioxane, $Pd(Ph_3P)_4$, reflux, 10 min	66
64	**18**	3-(tributylstannyl)pyridine	NMP, $Pd(Ph_3P)_2Cl_2$, 100 °C, 3 h	23
65	**78**	6-methoxy-3-(tributylstannyl)pyridine	NMP, $Pd(Ph_3P)_2Cl_2$, LiCl, 100 °C, 24 h	74
66	**65**	*b*	HBr/AcOH, 120 °C, 20 min	84
67	**66**	*b*	1. Tf_2O, CH_2Cl_2, ^{i}Pr$_2$NEt, 2. benzylamine, 120 °C, 4 h, 3. TFA, room temperature, 12 h	57[a]
68	**18**	4-(tributylstannyl)pyridine	NMP, $Pd(Ph_3P)_2Cl_2$, 100 °C, 3 h	17

[a] Overall yield for the two or three steps. [b] Not applicable.

The cross-coupling reactions and results, and subsequent deprotections or functional group modifications, are summarized in Table 2. Standard literature procedures were employed, and the yields ranged from poor to excellent. Derivatives **10**–**12** were obtained by reaction with the appropriate acrylate or alkyne.[29] The pyridyl and phenyl derivatives were obtained by reaction with the appropriate aryltributylstannane[30] under standard Stille reaction conditions[31] or by modification of these primary products as shown in Table 2. The Stille reaction also proved useful for the synthesis of the 5-membered heterocycles **39**–**45**, **53**, and **54**.[32] Cross-coupling of the organozinc derivatives[33] (generated in situ from the corresponding organolithium[34] species) was used for the preparation of the imidazoles **50** and **51** and the 2-thiazole **46**. A direct coupling[35] of oxazole with the triflate **78** gave the 5-oxazolyl derivative **49**.

Biological Results

The results obtained on testing the 2-substituted dipyridodiazepinones against both wild-type RT and Y181C RT are presented in Table 1. In the initial phase of the SAR studies, exemplified by compounds **4**–**38**, we found that 2-substitution on the tricyclic ring system leads to good inhibition of the wild-type enzyme but does not consistently confer activity against the Y181C RT. Our lead structure, the 2-chlorodipyridodiazepinone **16**, still proved to be one of the most effective inhibitors of both enzymes.

Against wild-type RT, potency is enhanced by lipophilic substitution at the 2-position and no preference for electron-donating or electron-withdrawing substituents is apparent. Substitution on nucleus A or B rather than on nucleus C or D gives more potent inhibitors, i.e., in combination with a 2-substituent, a methyl group is preferred at the 4-rather than the 5-position, analogous to our earlier finding.[21] For example, the derivatives in which a 2-CH_3 or 2-Cl substituent is combined with a 4-methyl group (compounds **5** and **15**) display enhanced potency relative to the derivatives in which these substituents are combined with the N-5-methyl group (compounds **6** and **16**). The most potent dipyridodiazepinone inhibitors of wild-type RT are of this 2,4-disubstituted type. However, it should be noted that compound **16** with the N-5-methyl substitution is more effective than **15** against the Y181C enzyme.

The gradation in activity of the 2-alkyl derivatives **5** and **7**–**9** indicates that there is a limit to the size of the substituent tolerated at the 2-position. The 2,4-dimethyl derivative **5** is the most potent member of this series, and inhibition decreases steadily as the size of the 2-substituent increases. This steric constraint is also apparent in comparing the 2-pyrrolidinyl and 2-piperidinyl derivatives **27** and **30**, where there is a substantial decrease in potency with the larger substituent.

Only a few compounds in this first phase of the SAR study inhibited the Y181C RT to a significant extent.

The 2-chloro derivative **16** (IC_{50} = 0.21 μM) and the 2-(*N*-pyrrolyl) derivative **33** (IC_{50} = 0.21 μM) were the most effective inhibitors. In comparing the activity of the 2-chloro derivatives **14**–**17** against the Y181C RT, it is clear that the cyclopropyl substituent at N-11 has a detrimental effect on potency and that nucleus C confers better activity than does nucleus B. The Y181C RT, selected on exposure of the HIV-1 virus to nevirapine, is less tolerant of the 4-methyl-11-cyclopropyl substitution pattern preferred against the wild-type RT.

The greater potency against the Y181C RT of the pyrrole **33**, when compared to the pyrrolidine **27** or the pyrroline **28**, indicated to us that 2-aryl substitution might confer combined activity against wild-type and mutant enzymes. Although activity against the wild-type enzyme is moderately attenuated, the aromatic pyrrolyl derivative **33** is more potent than **27** or **28** against the Y181C RT.

With few exceptions, the 2-aryl substitution yields good to excellent inhibitors of both the wild-type RT and Y181C RT. In general the 5-membered aromatic ring systems are more effective than the 6-membered systems, which is consistent with the observation above on the 2-pyrrolidine and 2-piperidine derivatives. The pyrrolyl derivatives **41**–**43** and the 4-pyrazolyl derivatives **53** and **54** are particularly effective inhibitors of both wild-type and mutant enzymes. The furanyl derivatives **39** and **40** and the thienyl derivatives **44** and **45** are slightly less potent. The 2-phenyldipyridodiazepinone **55** displays moderate inhibition of wild-type RT but is only weakly active against the Y181C RT, whereas the three pyridyl isomers **63**, **64**, and **68** are more or less equipotent against wild-type RT, but the 2-pyridyl isomer **63** is less effective against the mutant enzyme.

Substitution on the phenyl ring of **55** can improve activity against both wild-type and Y181C enzymes. An amino or hydroxyl group at the *meta* or *para* position of the phenyl ring, as in compounds **58**, **59**, **61**, and **62**, is most effective, although even with these preferred substituents potency still trails the pyrrolyl and pyrazolyl derivatives. Potency is also improved with the *p*-amino substitution in the 3-pyridyl series, compare derivatives **64** and **67**, consistent with the result in the phenyl series. The unexpectedly low activity of the analogous hydroxyl-substituted compound **66** may arise because the pyridone rather than the hydroxypyridine tautomer is preferred.

Secondary Evaluation. Although viral resistance to nevirapine is due mainly to the Y181C mutation, resistance to other members of the non-nucleoside class can result from alternative mutations around the binding pocket. It has been suggested that a combination therapy involving agents with complimentary resistance profiles might be an effective strategy against the virus,[36a,b] but this remains to be demonstrated.[36c-e] In this regard it was of particular interest to profile the more potent inhibitors against other mutant RT enzymes. The results of these secondary evaluations against K103N RT resistant to the pyridinones,[20a] L100I RT resistant to TIBO,[37] P236L RT resistant to BHAP,[20b] and E138K RT resistant to TSAO[37] are presented in Table 3.

Nevirapine (**1**) and also the 2-chloro lead compound **16** are potent inhibitors of the P236L RT and E138K RT enzymes but are less effective against the K103N RT. This result is not surprising since the K103N mutation has been seen clinically after nevirapine treatment.[19b] Derivatives **53** and **54** are less effective against the L100I RT although they have good activity against the other mutant enzymes. Derivatives **42**, **61**, **62**, and **67** have good activity against all the enzymes with each compound having a distinct profile with respect to effectiveness.

Table 3. Secondary Evaluation of Dipyridodiazepinones

	IC_{50} (μM)				
no.	cell culture[a]	L100I	K103N	P236L	E138K
1	0.04	0.13	1.9	0.08	0.11
16	0.16	*b*	1.1	0.02	0.12
42	0.04	0.41	0.05	0.13	0.07
53	0.04	2.5	0.08	0.13	0.05
54	0.12	1.5	0.42	0.34	0.46
61	0.30	0.50	0.01	0.001	0.06
62	0.55	0.57	0.26	0.26	0.06
67	0.24	0.24	0.41	0.04	0.02

[a] Human T-cell line c8166, HIV-1 IIIB strain. [b] Not determined.

Conclusion

The potency of the dipyridodiazepinone class against the wild-type RT has been enhanced, and inhibition has been extended to the Y181C RT and other mutant RT enzymes by substitution at the 2-position of the dipyridodiazepinone ring system. Excellent activity against wild-type RT can be achieved with methyl or methoxy substituents, although in these cases there is only moderate activity against the Y181C mutant enzyme. Potency against both wild-type RT and the Y181C RT can be achieved with chloro, pyrrolyl, pyrazolyl, substituted phenyl, and substituted pyridyl groups. In addition, some of these substitutions confer activity against mutant RT enzymes resistant to other classes of non-nucleoside RT inhibitors. It remains to be seen whether or not new mutations in the RT enzyme can confer resistance to these more potent analogs of nevirapine.

Experimental Section

Experimental Details. For general experimental details, see ref 21. Mutant HIV-1 RT clones were constructed by a site-directed mutagenesis method[38] and expressed from the vector pKK233-2 (Pharmacia) in *Escherichia coli* strain JM109.[39] The heterodimeric form (p66/p51) of mutant RTs was purified to near homogeneity as previously described,[40] or alternatively, *E. coli* lysates containing mutant RTs were used[39] for the enzyme assays. The details of the enzyme assay have been previously described.[21] *J* values are reported in hertz (Hz).

General Procedure for the Reaction of 15[41] with Amines. 5,11-Dihydro-2-[*N*-(hydroxyethyl)-*N*-methylamino]-11-ethyl-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (26). A mixture of **15** (0.764 g, 2.65 mmol) and *N*-methylethanolamine (5 mL) was heated at 180 °C in a sealed pressure tube for 5 h. The mixture was cooled and diluted with EtOAc/water. The organic phase was separated, washed, dried ($MgSO_4$), filtered, and evaporated to a volume of 5 mL. The title compound crystallized on standing (0.371 g, 1.13 mmol, 43%): mp 139–142 °C; ^{1}H NMR (DMSO-d_6) δ 9.55 (1H, s, NH), 8.40 (1H, dd, *J* = 2, 5), 7.97 (1H, dd, *J* = 2, 8), 7.11 (1H, dd, *J* = 5, 8), 6.24 (1H, s), 4.64 (1H, t, *J* = 5, OH), 3.99 (2H, q, *J* = 7), 3.51 (4H, br m), 2.98 (3H, s), 2.23 (3H, s), 1.15 (3H, t, *J* = 7); MS (CI) 328 (MH^+). Anal. ($C_{17}H_{21}N_5O_2$) C, H, N.

Displacement of the 2-Chloro Substituent with Methylthiolate. Synthesis of 38. A mixture of **15** (1.00 g, 3.47 mmol) and MeSNa (0.350 g, 5 mmol) in sulfolane (20 mL) was heated at 150 °C for 2 h. The mixture was cooled and

poured onto water. The yellow precipitate was collected by filtration, dried, and recrystallized from ethanol to give **38** (0.60 g, 2 mmol, 57%): ^{1}H NMR ($CDCl_3$) δ 8.45 (1H, dd, J = 2, 5), 8.12 (1H, dd, J = 2, 8), 7.38 (1H, br s, NH), 7.02 (1H, dd, J = 5, 8), 6.80 (1H, s), 4.22 (2H, q, J = 7), 2.53 (3H, s), 2.29 (3H, s), 1.24 (3H, t, J = 7); MS (CI) 301 (MH^+). Anal. ($C_{15}H_{16}N_4OS$) C, H, N.

Synthesis of the Triflate 78. 3-Amino-2-bromo-6-methoxypyridine (70). To a stirred mixture of 5-amino-2-methoxypyridine (2.5 g, 20.2 mmol) and NaOAc (1.6 g, 19.5 mmol) in AcOH (15 mL) was added Br_2 (3.0 g, 18.75 mmol) dropwise. After 20 min the reaction mixture was added to 10% aqueous NaOH (100 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was fractionated on silica gel to give **70** (2.7 g, 13.3 mmol, 60%). An analytical sample crystallized from EtOAc/hexane: mp 44–45 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (1H, d, J = 8), 6.58 (1H, d, J = 8), 3.86 (3H, s), 3.71 (2H, br s). Anal. ($C_6H_7N_2OBr$) C, H, N.

***N*-(2′-Bromo-6′-methoxy-3′-pyridyl)-2-chloro-3-pyridinecarboxamide (73).** To a solution of **70** (2.7 g, 13.3 mmol) in CH_2Cl_2 (20 mL) were added pyridine (1 mL) and 2-chloronicotinoyl chloride (2.2 g, 12.6 mmol). The mixture was stirred at room temperature for 20 min and then diluted with CH_2Cl_2 (100 mL), washed, dried ($MgSO_4$), filtered, and evaporated. The semisolid residue was triturated with hexane, filtered, and dried to give **73** (4.1 g, 12 mmol, 90%). Recrystallization from EtOAc/$CHCl_3$ provided an analytical sample: mp 174–176 °C; ^{1}H NMR (DMSO-d_6) δ 10.41 (1H, s, NH), 8.55 (1H, dd, J = 2, 5), 8.09 (1H, dd, J = 2, 8), 7.90 (1H, d, J = 9), 7.59 (1H, dd, J = 5, 8), 6.97 (1H, d, J = 9), 3.88 (3H, s); MS (CI) 342 (MH^+). Anal. ($C_{12}H_9N_3O_2BrCl$) C, H, N.

***N*-(2′-Bromo-6′-methoxy-3′-pyridinyl)-2-chloro-*N*-methyl-3-pyridinecarboxamide (75).** To DMSO (10 mL) stirred under argon was added NaH (50% in oil, 0.3 g, 6.25 mmol). The mixture was heated at 50 °C until H_2 evolution ceased. The amide **73** (2.0 g, 5.8 mmol) was added followed by MeI (0.4 mL). After 30 min the mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was fractionated on silica gel (CH_2Cl_2/EtOH) to give **75** (1.9 g, 5.4 mmol, 86%) as an oil: ^{1}H NMR (DMSO-d_6) δ 8.33 (1H, dd, J = 2, 5), 7.94 (1H, d, J = 9), 7.91 (1H, dd, J = 2, 8), 7.37 (1H, dd, J = 5, 8), 6.85 (1H, d, J = 9), 3.78 (3H, s), 3.28 (3H, s); MS (CI) 356 (MH^+). Anal. ($C_{13}H_{11}N_3O_2BrCl$) C, H, N.

***N*-(2′-Bromo-6′-methoxy-3′-pyridinyl)-2-(ethylamino)-*N*-methyl-3-pyridinecarboxamide (76).** A solution of **75** (1.9 g, 5.4 mmol) and ethylamine (0.7 g) in xylene (5 mL) was sealed in a pressure tube and heated at 150 °C for 4 h. The mixture was cooled, diluted with EtOAc, washed, dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue over silica gel (EtOAc/hexane) gave **76** (1.5 g, 4.1 mmol, 76%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.03 (1H, dd, J = 2, 5), 7.29 (1H, d, J = 8), 7.09 (1H, br d), 6.62 (1H, d, J = 8), 6.35 (1H, br s), 6.24 (1H, br t), 3.91 (3H, s), 3.50 (2H, m), 3.32 (3H, s), 1.26 (3H, t, J = 7); MS (CI) 365 (MH^+). Anal. ($C_{15}H_{17}N_4O_2Br$) C, H, N.

5,11-Dihydro-11-ethyl-2-methoxy-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (36). To a solution of **76** (1.4 g, 3.8 mmol) in xylene was added NaH (50% in oil, 0.9 g, 9.4 mmol). The mixture was heated at 150 °C (bath temperature) for 2 h. After cooling, excess NaH was decomposed with MeOH. The mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was chromatographed over silica gel (EtOAc/hexane) to give **36** (0.82 g, 2.9 mmol, 76%): mp 116–118 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 8.42 (1H, dd, J = 2, 5), 8.03 (1H, dd, J = 2, 8), 7.79 (1H, d, J = 9), 7.16 (1H, dd, J = 5, 8), 6.68 (1H, d, J = 9), 4.08 (2H, q, J = 7), 3.83 (3H, s), 3.37 (3H, s), 1.22 (3H, t, J = 7); MS (EI) 284 ($M^{\cdot+}$). Anal. ($C_{15}H_{16}N_4O_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-hydroxy-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (35). To a solution of **36** (0.30 g, 1.06 mmol) in AcOH (2 mL) was added hydrobromic acid (48% aqueous solution, 2 mL). The mixture was heated at reflux for 5 min, cooled, and added to 10% aqueous NaOH (10 mL). The mixture was extracted with EtOAc, and the organic phase was washed, dried, filtered, and evaporated to give **35** (0.28 g, 1.04 mmol, 98%): mp 215–218 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 10.84 (1H, br s), 8.41 (1H, dd, J = 2, 5), 8.01 (1H, dd, J = 2, 8), 7.70 (1H, d, J = 9), 7.15 (1H, dd, J = 5, 8), 6.48 (1H, d, J = 9), 4.02 (2H, br), 3.56 (3H, s), 1.17 (3H, t, J = 7); MS (EI) 270 ($M^{\cdot+}$). Anal. ($C_{14}H_{14}N_4O_2$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-2-[[(trifluoromethyl)sulfonyl]oxy]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (78). To a stirred solution of **35** (2.602 g, 9.64 mmol) in $CHCl_3$ (50 mL) cooled on ice under nitrogen was added diisopropylethylamine (2.0 mL) followed by triflic anhydride (1.65 mL, 10 mmol) added dropwise over 5 min. The mixture was allowed to warm to room temperature and then diluted with EtOAc (150 mL), washed, dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed over silica gel (EtOAc/hexane) to give the triflate (2.974 g, 7.47 mmol, 77%): mp 92–93 °C (^{i}Pr$_2$O/hexane); ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, dd, J = 2, 5), 8.13 (1H, dd, J = 2, 8), 7.62 (1H, d, J = 8), 7.07 (1H, dd, J = 5, 8), 6.06 (1H, d, J = 8), 4.13 (2H, q, J = 7), 3.52 (3H, s), 1.27 (3H, t, J = 7). Anal. ($C_{15}H_{13}N_4O_4SF_3$) C, H, N.

Typical Procedure for the Displacment of the Triflate Group by Amines. 5,11-Dihydro-11-ethyl-5-methyl-2-morpholino-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (31). To the triflate **78** (0.15 g, 0.37 mmol) in a pressure tube was added morpholine (0.5 mL). The tube was sealed, and the mixture was heated at 110 °C for 1 h. The mixture was cooled, diluted with CH_2Cl_2, washed, dried (Na_2SO_4), filtered, and evaporated. The residue was fractionated by chromatography over silica gel (EtOAc/hexane) to give **31** (0.091 g, 0.27 mmol, 72%): mp 157–160 °C (^{i}Pr$_2$O); ^{1}H NMR (DMSO-d_6) δ 8.40 (1H, dd, J = 2, 5), 8.00 (1H, dd, J = 2, 8), 7.64 (1H, d, J = 9), 7.13 (1H, dd, J = 5, 8), 6.66 (1H, d, J = 9), 4.01 (2H, q, J = 7), 3.69 (4H, m), 3.41 (4H, m), 3.35 (3H, s), 1.18 (3H, q, J = 7); MS (CI) 340 (MH^+). Anal. ($C_{18}H_{21}N_5O_2$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-2-(1′-pyrazolyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (34). A mixture of **16** (0.169 g, 0.59 mmol) and hydrazine hydrate (0.35 g) in dioxane (1 mL) was heated at 150 °C in a sealed tube for 48 h. The reaction mixture was diluted with $CHCl_3$, washed with water, dried, filtered, and evaporated. The residue was fractionated on silica gel ($CHCl_3$/EtOH) to give the 2-hydrazino derivative as an oil (0.144 g) which was used directly in the next reaction. A mixture of the hydrazine (0.141 g), malonaldehyde diethyl acetal (0.5 mL), acetic acid (0.4 mL), and water (1 mL) in dioxane (10 mL) was heated under reflux for 10 h. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was purified by chromatography over silica gel (EtOAc/hexane) followed by crystallization to give **34** (0.045 g, 0.14 mmol, 24%): mp 145–147 °C (^{i}Pr$_2$O); ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, m), 8.41 (1H, dd, J = 2, 5), 8.13 (1H, dd, J = 2, 8), 7.75 (1H, d, J = 9), 7.71 (1H, m), 7.62 (1H, d, J = 9), 7.05 (1H, dd, J = 5, 8), 6.45 (1H, dd, J = 2, 3), 4.23 (2H, q, J = 7), 3.53 (3H, s), 1.31 (3H, t, J = 7); MS (CI) 321 (MH^+). Anal. ($C_{17}H_{16}N_6O$) C, H, N.

Typical Procedures for the Pd-Catalyzed Cross-Coupling Reactions of the Triflates. 5,11-Dihydro-11-ethyl-5-methyl-2-[2-(methoxycarbonyl)vinyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (10). To a solution of **78** (0.120 g, 0.30 mmol) in Et_3N were added methyl acrylate (0.20 g) and $Pd(Ph_3P)_2Cl_2$ (0.011 g). The mixture was heated at 120 °C in a pressure tube for 5 h, cooled, diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was purified by flash chromatography over silica gel (EtOAc/hexane) to give recovered **78** (0.026 g) and **10** (0.059 g, 57%): mp 138–139 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, dd, J = 2, 5), 8.11 (1H, dd, J = 2, 8), 7.58 (1H, d, J = 14), 7.47 (1H, d, J = 8), 7.17 (1H, d, J = 8), 7.03 (1H, dd, J = 5, 8), 6.92 (1H, d, J = 14), 4.24 (2H, q, J = 7), 3.82 (3H, s), 3.51 (3H, s), 1.28 (3H, t, J = 7); MS (CI) 339 (MH^+). Anal. ($C_{18}H_{18}N_4O_3$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-2-(3-aminophenyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (59). A mixture of the triflate **78** (0.200 g, 0.50 mmol), 3-(tributylstannyl)-aniline[1] (0.227 g), LiCl (0.088 g), and $Pd(Ph_3P)_2Cl_2$ (0.031 g) in DMF (2 mL) was heated at 130 °C for 2 h. The mixture was cooled, treated with aqueous potassium fluoride for 2 h,

diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was purified by flash chromatography over silica gel (EtOAc/hexane) to give **59** (0.148 g, 0.43 mmol, 85%): mp 155–157 °C ($^iPr_2O$/EtOAc); ^1H NMR ($CDCl_3$) δ 8.40 (1H, dd, J = 2, 5), 8.11 (1H, dd, J = 2, 8), 7.51 (2H, s), 7.44–7.19 (3H, m), 7.01 (1H, dd, J = 5, 8), 6.74 (1H, m), 4.31 (2H, q, J = 7), 3.78 (2H, br, NH_2), 3.54 (3H, s), 1.32 (3H, t, J = 7); MS (CI) 346 (MH^+). Anal. ($C_{20}H_{19}N_5O$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-2-(5-imidazolyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (51). (a) 1-(*N*,*N*-Dimethylsulfonamido)-5-iodoimidazole. To a solution of 1-(*N*,*N*-dimethylsulfonamido)imidazole[34b] (3.516 g, 20 mmol) in THF (100 mL) cooled below −60 °C (internal temperature) was added BuLi (1.4 M in hexanes, 15.2 mL) at such a rate that the internal temperature remained below −60 °C. After 30 min Et_3SiCl (3.7 mL) was added all at once, and the reaction mixture was allowed to warm to room temperature. After 3 h the mixture was cooled to −50 °C, and ^{s}BuLi (1.3 M in cyclohexane, 20 mL) was added at such a rate that the internal temperature remained below −50 °C. The mixture was stirred for 1 h, and iodine (6.73 g, 26.3 mmol) in THF (15 mL) was added all at once. The reaction mixture was allowed to warm to room temperature, diluted with EtOAc, washed with aqueous sodium thiosulfate, dried, filtered, and evaporated. The residue was dissolved in THF (100 mL), and tetrabutylammonium fluoride (1 M in THF, 25 mL) was added. After 15 min, the mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was purified by chromatography over silica gel (EtOAc/hexane) to give the 1-(*N*,*N*-dimethylsulfonamido)-5-iodoimidazole (2.68 g, 8.6 mmol, 42%): ^1H NMR ($CDCl_3$) 8.09 (1H, d, J = 1), 7.18 (1H, d, J = 1), 3.00 (6H, s).

(b) To a solution of the 1-(*N*,*N*-dimethylsulfonamido)-5-iodoimidazole (1.222 g, 3.9 mmol) in CH_2Cl_2 (20 mL) at room temperature under nitrogen was added EtMgBr (1 M in Et_2O, 4.5 mL)[34c] dropwise. After 10 min $ZnCl_2$ (1 M in Et_2O, 12 mL) was added followed by $Pd(Ph_3P)_4$ (0.280 g, 0.40 mmol), triflate **78** (1.502 g, 3.7 mmol), and THF (30 mL), and the mixture was heated under reflux for 6 h. On cooling the reaction mixture was diluted with EtOAc, washed dried, filtered, and evaporated. The residue was fractionated over neutral alumina (grade II) (hexane/CH_2Cl_2 to CH_2Cl_2/EtOH gradient) to give 5,11-dihydro-11-ethyl-5-methyl-2-[1-(*N*,*N*-dimethylsulfonamido)-5-imidazolyl]-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (0.35 g, 22%) which was directly deprotected. To a solution of the above product (0.319 g, 0.75 mmol) in EtOH (20 mL) was added KOH (0.14 g), and the mixture was heated at 85 °C for 2 h. The reaction mixture was diluted with $CHCl_3$, washed with water, dried, filtered, and evaporated. Fractionation of the residue over deactivated basic alumina ($CHCl_3$/EtOH) gave **51** (0.134 g, 0.42 mmol, 55%): mp 177–180 °C; ^1H NMR (DMSO-d_6) δ 12.35 (1H, s), 8.44 (1H, dd, J = 5), 8.04 (1H, dd, J = 2, 8), 7.86–7.58 (4H, m), 7.16 (1H, dd, J = 5, 8), 4.16 (2H, m), 3.43 (3H, s), 1.22 (3H, t, J = 7). Anal. ($C_{17}H_{16}N_6O\cdot0.5H_2O$) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-2-(2-thiazolyl)-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (46). To a mixture of butyllithium (1.6 M in hexane, 1.25 mL, 2.0 mmol) in THF (5 mL) cooled to −70 °C under nitrogen was added thiazole (0.095 g, 1.12 mmol). The mixture was stirred at −70 °C for 10 min, $ZnCl_2$ (1 M in ether, 3.3 mL) was added, and the reaction mixture was allowed to warm to room temperature. $Pd(Ph_3P)_4$ (0.010 g, 0.014 mmol) and triflate **78** (0.150 g, 0.37 mmol) were added, and the mixture was heated under reflux for 2 h. Further catalyst (0.010 g) was added, and heating was continued for 1 h. The mixture was cooled, diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was purified by chromatography over silica gel (EtOAc/CH_2Cl_2) to give **46** (0.080 g, 63%): mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 8.43 (1H, dd, J = 2, 5), 8.14 (1H, dd, J = 2, 8), 7.96 (1H, d, J = 8), 7.89 (1H, d, J = 3), 7.59 (1H, d, J = 8), 7.43 (1H, d, J = 3), 7.04 (1H, dd, J = 5, 8), 4.28 (2H, q, J = 7), 3.55 (3H, s), 1.33 (3H, t, J = 7). Anal. ($C_{17}H_{15}N_5OS$) C, H, N.

Synthesis of 2-Bromo-11-cyclopropyl-5,11-dihydro-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (18). ***N*-(6′-Bromo-2′-chloro-3′-pyridinyl)-2-chloro-3-pyridinecarboxamide (74).** To a solution of 3-amino-6-bromo-2-chloropyridine (**72**) (10.72 g, 51.8 mmol) in CH_2Cl_2 (100 mL) was added pyridine (5 mL) followed by 2-chloronicotinoyl chloride (8.75 g, 50 mmol) added portionwise over 30 min. The mixture was stirred for 18 h, diluted with CH_2Cl_2, washed, dried, filtered, and evaporated. The residue was crystallized from EtOAc/CH_2Cl_2 to give **74** (11.49 g, 33.2 mmol, 64%): mp 184–185 °C; ^1H NMR ($CDCl_3$) δ 8.98 (1H, s), 8.81 (1H, d, J = 8), 8.58 (1H, dd, J = 2, 5), 8.32 (1H, dd, J = 2, 8), 7.51 (1H, d, J = 8), 7.47 (1H, dd, J = 5, 8). Anal. ($C_{11}H_6N_3OCl_2Br$) C, H, N.

***N*-(6′-Bromo-2′-chloro-3′-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (80).** A mixture of **74** (7.00 g, 20.2 mmol) and cyclopropylamine (2.9 g, 50.8 mmol) in dioxane (15 mL) was heated at 95 °C for 72 h. The mixture was diluted with EtOAc and washed with water. The organic phase was extracted with 3 N aqueous HCl which on standing gave a crystalline precipitate (the hydrochloride salt of **80**). The precipitate was collected by filtration, redissolved in aqueous KOH, and extracted with EtOAc. The organic phase was dried, filtered, and evaporated to give **80** (2.21 g, 6 mmol, 30%): mp 135–137 °C; ^1H NMR ($CDCl_3$) δ 8.67 (1H, d, J = 8), 8.44 (1H, dd, J = 2, 5), 8.19 (1H, s), 8.09 (1H, s), 7.75 (1H, dd, J = 2, 8), 7.47 (1H, d, J = 8), 6.67 (1H, dd, J = 5, 8), 2.90 (1H, m), 0.86 (2H, m), 0.13 (2H, m). Anal. ($C_{14}H_{12}N_4OClBr$) C, H, N.

2-Bromo-11-cyclopropyl-5-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (18). To a solution of **80** (1.274 g, 3.5 mmol) in pyridine (7 mL) was added NaHMDS (1 M in THF, 7.5 mL). The mixture was heated at 95 °C (bath temperature) under nitrogen for 30 min. Ethanol (1 mL) was added, and the mixture was evaporated to dryness. Treatment of the residue with water (25 mL) gave **81** which was collected by filtration, dried, and used without further purification in the next step (yield: 0.996 g, 3.0 mmol, 86%). To a suspension of **81** (0.979 g, 2.96 mmol) in DMSO (4 mL) stirred under nitrogen was added KO^{t}Bu (1 M in THF, 4.0 mL). After 3 min iodomethane (0.30 mL) was added, and the mixture was stirred at room temperature for 25 min. The reaction mixture was diluted with EtOAc, washed, dried, filtered, and evaporated to give **18** (0.684 g, 1.98 mmol, 67%). An analytical sample was crystallized from EtOAc/CH_2Cl_2: mp 232–233 °C; ^1H NMR ($CDCl_3$) δ 8.47 (1H, dd, J = 2, 5), 8.08 (1H, dd, J = 2, 8), 7.32–7.25 (2H, m), 7.07 (1H, dd, J = 5, 8), 3.68 (1H, m), 3.44 (3H, s), 1.02 (2H, m), 0.53 (2H, m). Anal. ($C_{15}H_{13}N_4OBr$) C, H, N.

11-Cyclopropyl-5-methyl-2-(4-pyridinyl)-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (68). To 4-bromopyridine hydrochloride (0.200 g, 1.02 mmol) in THF (5 mL) at 0 °C was added BuLi (2 M in cyclohexane, 0.5 mL). The mixture was cooled to −70 °C, and further BuLi was added (0.5 mL). After 5 min, tributyltin chloride (0.27 mL, 1 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, washed, dried, filtered, and evaporated to give crude 4-(tributylstannyl)pyridine which was used without further purification in the next step. To the crude stannane dissolved in NMP (3 mL) were added **18** (0.170 g, 0.5 mmol) and $Pd(Ph_3P)_2Cl_2$ (0.040 g, 0.057 mmol). The mixture was heated under nitrogen at 100 °C for 3 h, cooled, diluted with EtOAc, washed, dried, filtered, and evaporated. Fractionation over silica gel (EtOAc/hexane) gave **68** (0.030 g, 0.087 mmol, 17%): mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 8.70 (2H, m), 8.50 (1H, dd, J = 2, 5), 8.13 (1H, dd, J = 2, 8), 7.93 (2H, m), 7.67 (1H, d, J = 8), 7.57 (1H, d, J = 8), 7.08 (1H, dd, J = 5, 8), 3.86 (1H, m), 3.52 (3H, s), 1.26 (2H, m), 0.61–0.50 (2H, m). Anal. ($C_{20}H_{17}N_5O\cdot0.75H_2O$) C, H, N.

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(41) Compound **15** was synthesized in a manner analogous to that described in detail for **14**; see ref 24.

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