Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 4. 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one and Analogues†

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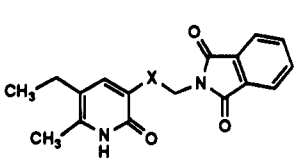
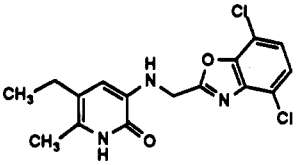
A new series of potent specific 2-pyridinone reverse transcriptase (RT) inhibitors was developed based on the preliminary development lead 3-[(phthalimido)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (**3**), a non-nucleoside derivative which exhibited weak antiviral activity in cell culture against HIV-1 strain III_B. One compound, 3-[(benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (**9**, L-696,229), which was a highly selective antagonist of the RT enzyme (IC_{50} = 23 nM) and which inhibited the spread of HIV-1 III_B infection by >95% in MT4 human T-lymphoid cell culture (CIC_{95} = 50–100 nM), was selected for clinical evaluation as an antiviral agent.

Recent communications from these laboratories disclosed a family of 2-pyridinone derivatives that are potent and selective non-nucleoside inhibitors of HIV-1 reverse transcriptase (RT).[1] Detailed structure–activity relationships (SAR) related to pyridinone **1**, a lead discovered by screening the Merck sample collection, have been reported.[2a] Although pyridinone **1** was a potent RT inhibitor (IC_{50} = 30 nM), hydrolytic instability under physiological conditions precluded demonstration of antiviral activity in cell culture. Subsequent efforts focused on improving the chemical stability of **1** yielded pyridinone **2**. This potent, specific, and hydrolytically stable inhibitor of HIV-1 RT (IC_{50} = 20 nM) had a high level of antiviral activity (CIC_{95} = 50–100 nM) as demonstrated by the inhibition of the spread of an HIV-1 strain III_B infection in MT-4 human T-lymphoid cells. Detailed SAR studies have been reported.[2b] Good antiviral activity was observed for **2** in clinical studies with HIV-positive patients, but was of short duration due to the rapid onset of viral resistance (~6–12 weeks).[3] The mutability of this virus has precluded further evaluation of pyridinone **2** as an antiviral agent for monotherapy; however, studies with combination therapies are continuing.



1 (X = NH)
3 (X = CH_2)



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In this report, we present detailed SAR studies for a series of 2-pyridinone RT inhibitors based on the hydrolytically stable ethylphthalimide **3**. Although this lead was 100-fold less active than aminopyridinone **1** as an HIV-1 RT inhibitor, weak antiviral activity was observed in cell culture. The strategy set forth here overcame these deficiencies and provided a second candidate for clinical studies.

Chemistry

The majority of compounds were synthesized following the generalized routes summarized in Scheme I. Initially, a few analogues were prepared by addition of the anions derived from 2-methylbenzothiazole, -benzoxazole, or -benzo[*b*]furan to the available 2-methoxy-5-ethyl-6-methylnicotinaldehyde (**59**) at low temperatures (–70 to –100 °C) (method A). The low temperature (–100 °C) was particularly critical for the formation and survival of the 2-methylbenzoxazole anion which is prone to self-condensation at higher temperatures (–78 °C).[4] The resultant alcohols (**v**) were dehydrated and demethylated simultaneously upon treatment with excess pyridine hydrochloride at 150 °C to afford the corresponding *trans*-vinylpyridinones (**viii**). Catalytic reduction of these olefinic intermediates gave the benzothiazolyl- (**8**), benzoxazolyl- (**9**), and benzo[*b*]furanyl- (**12**) pyridinones, respectively. Benzoxazole **55** was prepared, in a similar manner, from 2-methoxy-5-ethylnicotinaldehyde. The benzoxazole-derived olefinic intermediate **42** was also completely characterized and evaluated as an RT inhibitor.

The encouraging inhibitory activity of **9** prompted a search for alternate synthetic routes since the capricious nature of the anion formation restricted facile reaction scale-up. A Wittig approach (method B) appeared attractive since this route would permit the use of halogen-substituted 2-(chloromethyl)benzoxazoles which were available from our on-going effort in the 3-amino-2-pyridinone series.[2b] Reaction of triphenylphosphine with the appropriate chloromethyl heterocycle (i.e. 2-(chloromethyl)-4,7-dichlorobenzoxazole) in refluxing toluene gave an excellent yield of the corresponding phosphonium salt. The phosphorus ylide, generated in the presence of sodium hydride, was condensed with the desired 2-methoxynicotinaldehyde (**ii**) to afford a cis/trans mixture of vinylpyridines (**iii**). Typically, this mixture of olefins was hydrogenated to give a single saturated 2-methoxypyridine

† Dedicated to Dr. Ralph F. Hirschmann on the occasion of his 70th birthday.
‡ Medicinal Chemistry.
§ New Lead Pharmacology.
⊥ Virus and Cell Biology.

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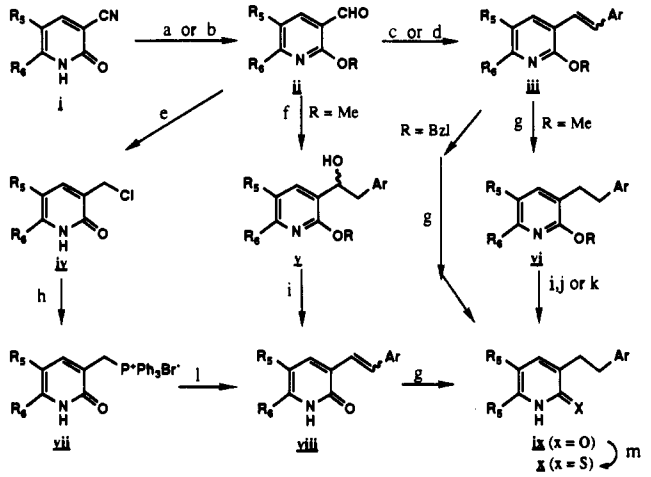
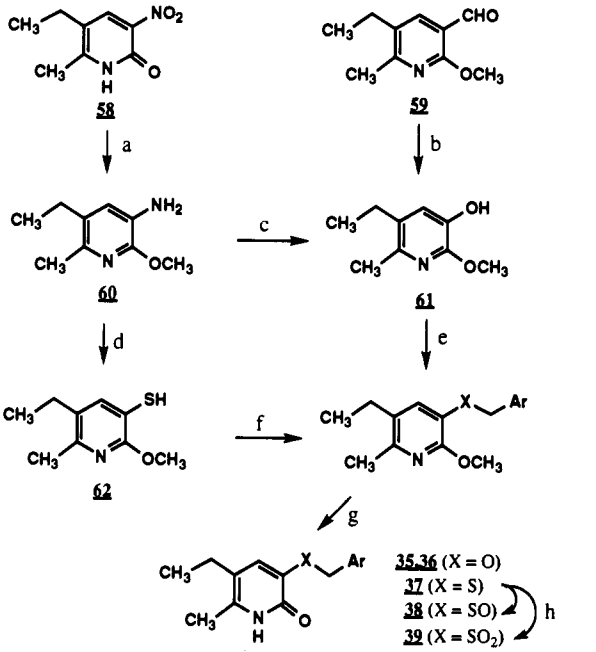
Scheme I [a,b]



[a] (a) $POCl_3$, 100 °C; MeONa, MeOH, reflux; Dibal-H, THF, 0 °C; (b) BzlBr, Ag_2CO_3, benzene; Dibal-H, THF; (c) $ArCH_2P^+Ph_3Cl^-$, NaH, THF, reflux; (d) $(EtO)_2P(O)CH_2Ar$, *n*-BuLi, THF, −10 °C; (e) $LiAlH_4$, THF; $SOCl_2$, benzene, reflux; (f) $ArCH_3$, *n*-BuLi, THF, −100 °C; (g) H_2, Pd/C, MeOH, THF; (h) $Ph_3P{\cdot}HBr$, THF, reflux; (i) pyridine hydrochloride, 150 °C, 10 min; (j) BBr_3, CH_2Cl_2, 0 °C; (k) KI, HOAc, 60 °C; (l) NaH, ArCHO, THF, reflux; (m) Lawesson's reagent, toluene, reflux. [b] R = Me, Bzl; For R_5, R_6, and Ar see Tables I, II, and III.

Scheme II [a,b]



[a] (a) PCl_5, 140 °C; MeONa, MeOH, reflux; H_2, Pd/C, MeOH, THF; (b) *m*-chloroperbenzoic acid, $CHCl_3$; HOAc, H_2O; (c) $NaNO_2$, 5% H_2SO_4, 100 °C; (d) $NaNO_2$, aqueous HCl; NaSC(S)OEt; NaOH; (e) NaH, THF, $ArCH_2Cl$; (f) Et_3N, $ArCH_2Cl$, EtOH; (g) KI, HOAc, 60 °C; (h) *m*-chloroperbenzoic acid, $CHCl_3$. [b] For **35**, Ar is benzoxazol-2-yl; **36–39**, Ar is 4,7-dichlorobenzoxazol-2-yl.

(**vi**). In one case the cis isomer derived from 2-(chloromethyl)benzoxazole and nicotinaldehyde **59** was isolated and demethylated to prepare the *cis*-vinylpyridinone **43** for comparison with the previously isolated trans isomer **42**. Initially these saturated intermediates (**vi**) were demethylated with pyridine hydrochloride at 150 °C, and benzoxazole-derived pyridinones, such as **21**, were obtained. Other analogs prepared by this method included **14**, **17**, **20**, and **57**. Significant amounts (10–15%) of a byproduct (see discussion below) were generated during workup, and alternate demethylation procedures were sought. Two milder and, in some cases, more selective procedures were subsequently found: boron tribromide in methylene chloride (0 to −10 °C), and potassium iodide in acetic acid (~60 °C). The former procedure is illustrated by the preparation of **56** and, in particular, the *cis*-vinylpyridinone **43**, while the latter procedure is described below.

Another convenient route adopted later made use of the Horner–Emmons modification of the Wittig reaction (method C). In addition, by masking the pyridinone carbonyl as a benzyloxy group instead of methoxy, the subsequent catalytic hydrogenation of the coupled olefin intermediate (**iii**) effected a simultaneous debenzylation to afford the desired pyridinone (**ix**) directly.[5] A wide variety of 2-(benzyloxy)nicotinaldehydes was coupled in this manner to obtain the following pyridinones: **10**, **11**, **15**, **16**, **18**, **19**, **22**, **23**, **24**, **25**, **48**, **49**, **51**, **52**, and **54**. 2-(Benzyloxy)nicotinaldehyde **63** was also reacted with appropriate phosphonium salts and the intermediate vinylpyridinones (**iii**) catalytically reduced and debenzylated to give pyridinones **4** and **7**. When 2-methoxynicotinaldehydes (**ii**) were condensed with appropriate phosphonates, the penultimate intermediates (**vi**) were cleanly demethylated using KI in acetic acid to afford pyridinones, such as **46** and **47**.

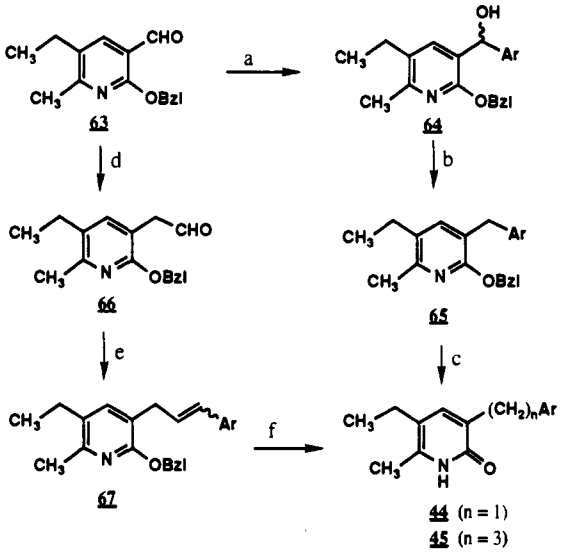
Methylation of a 5-hydroxymethyl-substituted vinylpyridine (**iii**) and catalytic reduction of this olefin with simultaneous debenzylation afforded 5-(methoxymethyl)-pyridinone **53**.

Since a number of functionally different 5-substituents on the pyridinone ring were to be evaluated, which employed a variety of synthetically incompatible approaches (see the Experimental Section for details), a mild and general method for the introduction of the benzyloxy group was needed. Reaction of 3-cyanopyridinones (**i**) with benzyl bromide and silver carbonate in benzene gave exclusively O-benzylation; subsequent reduction of the nitrile group with diisobutylaluminum hydride (Dibal-H) afforded the desired 2-(benzyloxy)nicotinaldehydes (**ii**).

In situations where a heterocyclic carboxaldehyde, such as furo[3,2-*c*]pyridine-2-carboxaldehyde, was more accessible than the chloromethyl derivative, a variation of the Wittig approach was used (method D). Reversing the components in the Wittig reaction necessitated development of methodology for the conversion of alkoxynicotinaldehyde (**ii**) into the required phosphonium salt **vii**. By first preparing the 3-(chloromethyl)pyridinone (**iv**) from a 2-alkoxynicotinaldehyde ($LiAlH_4$ reduction followed by excess thionyl chloride at reflux), the subsequent reaction with triphenylphosphine hydrobromide afforded a good yield of the phosphonium salt (**vii**). Interestingly, triphenylphosphine did not react with chloride **iv** under these conditions; apparently conversion to the more reactive bromide is necessary for phosphonium salt formation to occur. The reaction of this phosphonium salt (**vii**) with several carboxaldehydes was problematic, and mediocre yields of the corresponding vinylpyridinones (**viii**) were obtained. However, the catalytic reduction of these olefins did afford the desired pyridinones **ix**. Only the furopyridinyl (**13**), 2-pyridinyl (**6**), and 2-naphthyl (**5**) analogues were prepared by this procedure.

Completion of a study to evaluate the effect of different heteroatoms in the linker on RT inhibition required the synthesis of the oxygen and sulfur analogues corresponding to the carbon (**9** and **21**) and nitrogen (**40** and **2**) compounds (see Scheme II). The requisite 3-hydroxy- (**61**) and 3-mercapto- (**62**) pyridines were obtained by trapping the diazonium intermediate, generated from 2-methoxy-3-amino-5-ethyl-6-methylpyridine (**60**), with water or sodium

Scheme III [a,b]



[a] (a) *n*-BuLi, ArH, THF, −70 °C; (b) NaH, imidazole, CS_2, MeI, THF; *n*-Bu_3SnH, AIBN, toluene, reflux; (c) BCl_3, CH_2Cl_2, −10 °C; (d) $Me_3S^+I^-$, KOH, wet CH_3CN (phase transfer); $BF_3{\cdot}Et_2O$; (e) $(EtO)_2P(O)CH_2Ar$, *n*-BuLi, THF, −10 °C; (f) PtO, H_2, $CHCl_3$ (1 equiv)/THF.[b] Ar is benzoxazol-2-yl.

ethyl xanthate, respectively. The starting amine **60** was prepared from 3-nitropyridinone **58** by the usual sequence of chlorination and methoxylation at the 2-position, followed by catalytic reduction of the nitro group. The 3-hydroxypyridine **61** was also obtained directly from nicotinaldehyde **59** by a Baeyer–Villiger reaction. Alkylation of intermediates **61** and **62** with appropriate 2-(chloromethyl)benzoxazoles and selective demethylation with KI in acetic acid afforded oxy analogues **35** and **36** and thio analogue **37**. Oxidation of sulfide **37** with 1 or 2 equiv of peracid gave sulfoxide **38** and sulfone **39**, respectively. An example (**41**) in which the nitrogen atom was transposed relative to that in nitrogen analogue **40** was obtained from the reaction of 2-methoxy-3-(aminomethyl)-5-ethyl-6-methylpyridine with 2-chlorobenzoxazole and demethylation of the intermediate generated.

Since potency enhancements have been reported by others for thione derivatives,[6,7] several of the more potent pyridinone derivatives (**9**, **15**, **16**, **18–22**) were readily converted into the corresponding pyridinethiones **26–33** by reaction with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent).

A 2-amino analogue (**34**) of pyridinone **9** was also prepared. Selective reduction of the azidonitrile obtained from the nucleophilic addition of sodium azide to 2-chloro-5-ethyl-6-methylnicotinonitrile gave the corresponding 2-aminonicotinonitrile which was reduced directly to 2-amino-5-ethyl-6-methylnicotinaldehyde with Dibal-H without masking the amino group. Reaction of this aldehyde with the appropriate phosphonate (method C) afforded a mixture of olefins which was hydrogenated to give 2-aminopyridine **34**.

The one-carbon link analogue **44** was prepared by a slight variation of method A (Scheme III). Addition of the anion of benzoxazole to 2-(benzyloxy)nicotinaldehyde **63** afforded the benzhydryl-like alcohol **64**. To overcome a problematic hydrogenolysis to remove the hydroxyl function in **64** use was made of a Barton radical-induced cleavage of a dithiocarbonate intermediate.[8] Debenzylation of **65** (−10 °C) in the presence of boron trichloride gave **44**.

The three-carbon link analogue **45** was also obtained from 2-(benzyloxy)nicotinaldehyde **63**. Homologation of **63** via the Lewis acid catalyzed opening of an epoxide intermediate afforded acetaldehyde **66**. Condensation of **66** with the appropriate phosphonate (method C) and hydrogenation–debenzylation of olefin intermediate **67** gave pyridinone **45**.

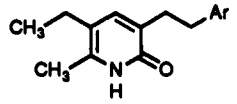
As mentioned above, demethylation of 2-methoxypyridines (vi) with pyridine hydrochloride (150 °C) followed by a water workup generated a major byproduct resulting from acid-catalyzed hydrolytic cleavage of the benzoxazole ring, a well-precedented process. For example, 10–15% yields of the corresponding phenolic amides **68** and **69** (see Table IV) were isolated during the preparation of **9** and **21**. A demethylation to afford the oxy-link analogue **35** was completely diverted to the phenolic amide **72** (see Table IV) under these conditions. The marked effect of the heteroatom in the linker on the hydrolytic stability of the benzoxazole ring was also observed during a preliminary study to evaluate the hydrolytic stability of **9**, **40**, **2**, and **35** under simulated gastric acid conditions (0.1 N HCl).[9] A more complete hydrolysis study (see Table IV) confirmed that the hydrolysis rate is accelerated by increasingly electronegative atoms in the linker, as well as by electron-withdrawing chlorine substituents on the benzoxazole ring.

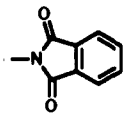
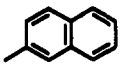
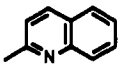
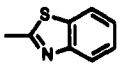
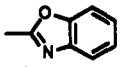
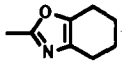
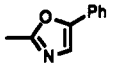
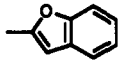
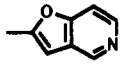
Biological Results and Discussion

The hydrolytic instability of pyridinone **1**, which precluded demonstration of antiviral activity in cell culture, was recognized to be a function of the molecule's labile aminal substructure. Strategies to eliminate this structural element evolved in two directions: replacement of the phthalimide group with other heterocycles and substitution of the exocyclic NH with a methylene unit. While the former approach yielded clinical candidate **2**, the latter strategy gave pyridinone **3**, a compound with low enzyme inhibitory activity (100-fold decrease), but with weak antiviral activity in cell culture none the less. Buoyed by the antiviral activity observed, structural modification of the phthalimide moiety was pursued with the hope that the potency loss could be overcome. As illustrated in Table I, this hope was realized with compounds **8–12**. Cognizant of the developing SAR pattern in the 3-aminopyridinone series, selected heterocyclic replacements were prepared for evaluation against the RT enzyme. It soon became evident that simple aromatic (**4**, **5**) and pyridine-based heterocyclic analogues (i.e. **6** and **7**) were much less potent (10-fold) than those in the 3-aminopyridinone series, while a benzothiazole substitution (**8**) was comparable. Unexpectedly, the benzoxazole (**9**, **10**, **11**) derivatives were 5–10 times more potent; note, in particular, the results for **9** versus **40**. Apparently an important interaction exists between the benzoxazole ring oxygen of the inhibitor and the active site of the RT enzyme/template/primer complex. The deletion of the benzoxazole ring nitrogen (i.e. benzofuran **12**) or relocation to the adjacent ring (i.e. furopyridine **13**) also adversely affected inhibitory activity relative to **9**.

Further chemical modification of this potent benzoxazole **9** was explored as illustrated in Tables II and III. However, only marginal improvements in RT inhibitory activity were achieved. In contrast to the potency-enhancing effect (10-fold) of substitutions in the 4- and/or 7-positions of the benzoxazole ring of 3-aminopyridinone analogs (i.e. **2** vs **40**), only minor improvements were

Table I. Inhibition of HIV-1 RT by Selected Heteroaryl 2-Pyridinones



no.	Ar	IC_{50}, μM[a]
3[b]		3.7 ± 0.37
4		50
5		8.4
6		260
7		2.45
8		0.37
9[c]		0.023 ± 0.001
10		0.058 ± 0.009
11		0.385
12		0.130 ± 0.021
13		13.5

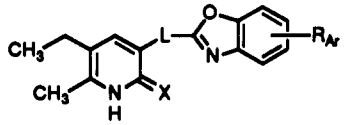
[a] The HIV-1 RT assay which used (poly)rC·(oligo)dG as the template/primer is described in ref 1. The concentration that produced 50% inhibition (IC_{50}) is stated as the mean of at least three determinations ± standard error. All other values were obtained from one or two determinations. [b] L-693,593. See ref 1a. [c] L-696,229. See ref 1a.

realized in this series from such disubstitution (i.e. **9** vs **21**, **22**). Monosubstitutions were arguably worse. Substitutions in the 5- and 6-positions (**23–25**) decreased inhibitory activity to a similar degree in both series.

In view of these differences, other SAR variations in the linker group were examined. Two trends emerged from these studies: less potent analogues containing an oxygen or nitrogen in the linker can be significantly improved by addition of substituents in the 4- and 7-positions of the benzoxazole ring (**35** and **40** vs **36** and **2**), while similar substituent modifications in the more potent carbon-containing analogues resulted in at best marginal enhancements (**9** vs **21** and **22**). The potency of the sulfur analogue **37** was similar to that of carbon analogue **21**. However, oxidation of the susceptible sulfide link in **37** (compounds **38** and **39**) reduced inhibitory activity. Apparently polar groups in this region of the inhibitor are not well tolerated. One example, in which the position of the NH in the two-atom link was transposed, had reduced potency (**41** vs **40**). As observed in earlier studies, changing the length of the link (**44** and **45**) or reducing its flexibility (**42**, **43**) also decreased inhibitory potency in this carbon series.

The one constant among these related series of pyridinones is the SAR for the substitution pattern on the pyridinone ring (see Table III). As in previous studies,

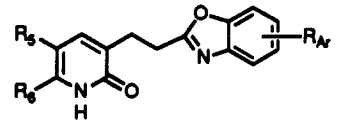
Table II. Inhibition of HIV-1 RT and Viral Infection Spread



no.	X	L	R_{Ar}	IC_{50}, μM[a]	ClC_{95}, nM[b]
9	O	$-CH_2CH_2-$	H	0.023 ± 0.001	50–100
14	O	$-CH_2CH_2-$	4-Me	0.033 ± 0.005	100
15	O	$-CH_2CH_2-$	4-Cl	0.062 ± 0.021	100
16	O	$-CH_2CH_2-$	4-F	0.015 ± 0.003	25–50
17	O	$-CH_2CH_2-$	7-Me	0.040 ± 0.003	nd
18	O	$-CH_2CH_2-$	7-Cl	0.039 ± 0.009	100
19	O	$-CH_2CH_2-$	7-F	0.037 ± 0.014	nd
20	O	$-CH_2CH_2-$	4,7-$(Me)_2$	0.028 ± 0.004	300
21	O	$-CH_2CH_2-$	4,7-Cl_2	0.014 ± 0.003	50
22	O	$-CH_2CH_2-$	4,7-F_2	0.014 ± 0.003	50
23	O	$-CH_2CH_2-$	6-Me	0.172 ± 0.025	nd
24	O	$-CH_2CH_2-$	6-F	0.442 ± 0.022	nd
25	O	$-CH_2CH_2-$	5-F	1.70	nd
26	S	$-CH_2CH_2-$	H	0.024 ± 0.004	200
27	S	$-CH_2CH_2-$	4,7-$(Me)_2$	0.052 ± 0.005	200
28	S	$-CH_2CH_2-$	4,7-Cl_2	0.030 ± 0.002	100
29	S	$-CH_2CH_2-$	4,7-F_2	0.015 ± 0.001	100–200
30	S	$-CH_2CH_2-$	4-F	0.013 ± 0.001	100
31	S	$-CH_2CH_2-$	7-F	0.043 ± 0.001	200
32	S	$-CH_2CH_2-$	4-Cl	0.030 ± 0.005	nd
33	S	$-CH_2CH_2-$	7-Cl	0.029 ± 0.006	200
34	NH_2	$-CH_2CH_2-$	H	100	nd
35	O	$-OCH_2-$	H	0.191 ± 0.030	nd
36	O	$-OCH_2-$	4,7-Cl_2	0.088 ± 0.016	200
37	O	$-SCH_2-$	4,7-Cl_2	0.011 ± 0.001	25–50
38	O	$-S(O)CH_2-$	4,7-Cl_2	1.40	nd
39	O	$-SO_2CH_2-$	4,7-Cl_2	0.205 ± 0.015	nd
40[c]	O	$-NHCH_2-$	H	0.210 ± 0.020	400–800
2[d]	O	$-NHCH_2-$	4,7-Cl_2	0.020 ± 0.004	50–100
41	O	$-CH_2NH-$	H	1.25	10 000
42	O		H	5.9	nd
43	O		H	3.0	nd
44	O	$-CH_2-$	H	45	nd
45	O	$-CH_2CH_2CH_2-$	H	16	nd

[a] See footnote *a*, Table I. [b] The MT-4 cell assay using HIV-1 strain IIIb is described in ref 1. The cell culture inhibitor concentration required to inhibit by >95% the spread of HIV-1 infection in susceptible cell culture (CIC_{95}) is stated as a range of values if multiple determinations were made. nd means not determined. [c] Refs 1, 2b. [d] L-697,661, see refs 1, 2b.

Table III. Inhibition of HIV-1 RT: Pyridinone Substituents

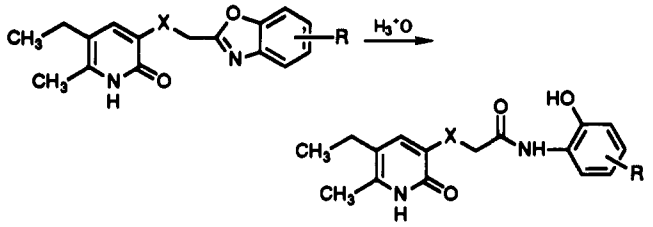


no.	R_5	R_6	R_{Ar}	IC_{50}, μM[a]
46	Me	Me	H	0.170 ± 0.073
9	Et	Me	H	0.023 ± 0.001
47	*n*-Pr	Me	H	0.083 ± 0.024
48	*i*-Pr	Me	H	0.048 ± 0.016
49	Ph	Me	H	1.10
50	N≡C	Me	H	0.310 ± 0.081
51		Me	H	41.5
52	$HOCH_2$	Me	H	3.4
53	CH_3OCH_2	Me	H	2.1
54	Me_2N	Me	H	1.85
55	Et	H	H	0.177 ± 0.032
56	Me	Me	4,7-Cl_2	0.097 ± 0.025
21	Et	Me	4,7-Cl_2	0.014 ± 0.003
57	*n*-Pr	Me	4,7-Cl_2	0.034 ± 0.003

[a] See footnote *a*, Table I.

deletion of the 6-methyl group (**55** vs **9**) or replacement of the 5-ethyl group with methyl (**46** and **56** vs **9** and **21**)

Table IV. Effect of Linker Modifications of Selected Analogues on Acid Hydrolysis Rates: HIV-RT Inhibition Activity of Cleavage Products



no.	X	R	$t_{1/2}$ (min)[a]	product no.	IC_{50} (μM)[b]
9	CH_2	H	218 + 18	68	5.4
21	CH_2	4,7-Cl_2	29 ± 1	69	>300
40	NH	H	35 ± 7	70[c]	nd
2	NH	4,7-Cl_2	17 ± 4	71	>300
35	O	H	12 ± 0.2	72[c]	nd
36	O	4,7-Cl_2	11 ± 0.2	–[d]	nd
37	S	4,7-Cl_2	34 ± 7	–[d]	nd

[a] Determinations were carried out in 90% ethanol, 10% 1 N HCl to ensure compound solubility and to maintain a final HCl concentration of 0.1 N. See Experimental Section. [b] See footnote *a*, Table I; nd means not determined. [c] Only characterized by NMR. [d] Not characterized.

decreased inhibitory potency. Again, larger hydrophobic groups in the 5-position, such as *n*-propyl (**47** and **57**) and isopropyl (**48**), were tolerated; however, a phenyl substitution (**49**) exceeded limitations for the binding site pocket. Hydrophilic (**51**, **52**) and other electron-withdrawing substituents (**50**, **54**) decreased potency; even a heteroatom substitution in the 5-*n*-propyl substituent dramatically reduced inhibitory activity (**53** vs **47**).

Another similarity with the 3-aminopyridinone series was the minimal effect of the thiocarbonyl modification (**26–33**) of pyridinones **9**, **15**, **16**, **18–22** on enzyme inhibitory activity. These results are in marked contrast to the significant potency enhancements reported for the thiono analogs of ureas and lactams in the TIBO[6] and nevirapine[7] series.

The more potent enzyme inhibitors were evaluated for antiviral activity in MT-4 human T-lymphoid cells. These data are listed in Table II as the concentration of compound necessary to prevent by >95% (CIC_{95}) the spread of an HIV-1 strain III_B infection in this cell culture. As previously reported,[1] the excellent correlation between in vitro enzyme inhibitory potency and antiviral activity in cell culture suggests that the antiviral effect of these inhibitors is mediated by direct interaction with the RT enzyme. In contrast, of those pyridinethiones (**26–33**) evaluated most were somewhat less effective in the prevention of virus spread in cell culture than would be indicated by their respective relative potencies against the RT enzyme in vitro. This may reflect poorer cell penetration.

Since so many of these benzoxazole derivatives exhibited good antiviral activity (CIC_{95} = 50–100 nM) in cell culture, several other criteria were utilized to shorten this list of candidates for further development. The susceptibility of the benzoxazole ring to hydrolysis in acidic environments (supra vide) became the basis for eliminating a number of potent inhibitors. From the data presented in Table IV, the unsubstituted benzoxazole **9** stood out from the other representative derivatives, being 10-fold more stable to acid hydrolysis.

The binding to human plasma proteins was also evaluated. Although the effect of protein binding on in vivo antiviral activity is unknown, the earlier candidate (**2**) from the 3-aminopyridinone series was very tightly bound

Table V: Human Plasma Protein Binding of Selected Analogues

no.	K_D,[a] μM	% unbound[b]	no.	K_D,[a] μM	% unbound[b]
9	21.6	4.0	19	8.16	1.4
21	0.76	0.1	15	17.6	3.0
22	18.2	3.0	18	4.16	0.7
20	1.21	0.2	14	2.45	0.4
16	24.0	4.0	2[c]	–[d]	0.4

[a] Compound plasma equilibrium dissociation constant. [b] Calculated for whole normal human plasma, a value which is extrapolated from 10% normal human plasma determinations. See Experimental Section. [c] Reference 11c. [d] Not determined.

(99.6%) to human plasma and it was hoped that subsequent candidates, which attain higher free concentrations in plasma, would possess enhanced antiviral activity in vivo. The results of protein binding measurements on selected analogues extrapolated for whole human plasma (Table V) suggest that nearly 10-fold higher free drug levels might be obtained in vivo with benzoxazole **9** than with the earlier candidate **2**. Although peak plasma levels of **9** were significantly higher (3–7-fold) than that of **2** in animals,[11] the contribution of reduced protein binding remains to be determined.

Based on the above results, as well as the equivalent potency and selectivity compared to **2**,[10] improved oral bioavailability,[11] and a somewhat different metabolic profile,[12] benzoxazole **9** was evaluated for safety and tolerability. Currently this compound is being studied clinically in HIV-positive patients. The clinical usefulness of **9** in monotherapy will depend upon the rapidity with which resistant virus emerges, as was the case with aminopyridinone **2**. Although resistance to **9** has been observed in cell culture experiments with virus cloned from clinical isolates obtained from HIV-positive patients who developed resistance to **2** (L-697,661),[3] it remains to be determined if enhanced oral bioavailability and elevated plasma drug levels of **9** will result in the delayed appearance of resistant virus. Certainly the different resistant virus variants selected for in patients undergoing therapy with different nucleoside and non-nucleoside RT inhibitors may prove susceptible to combination therapies.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.40% of the theoretical values. Routine ^1H NMR spectra, obtained on a Varian Associates XL-300 or Unity 300 using Me_4Si as an internal standard, are consistent with the structures indicated. Yields were not optimized. E. Merck silica gel, 200–400 mesh, was used for all flash chromatographies. The syntheses of all (chloromethyl)-benzoxazoles are described in the preceding paper in this series.[2b]

Method A: 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (9). To a solution of 2-methylbenzoxazole (3.1 mL, 24.9 mmol) in anhydrous THF (65 mL), cooled to −100 °C under an argon atmosphere, was added dropwise 1.6 M n-butyllithium/hexane (15.6 mL) over 35 min. After 0.5 h a solution of 2-methoxy-5-ethyl-6-methylnicotinaldehyde[2a] (4.27 g, 23.8 mmol) in dry THF (15 mL) was added dropwise. The reaction was allowed to warm to room temperature and poured onto crushed ice. This mixture was extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and the solvent was removed to give 9.0 g of crude solid. Crystallization from diethyl ether afforded 5.1 g (68%) of pure **2-[2(*R*/*S*)-hydroxy-2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethyl]benzoxazole**: mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 7.68–7.71 (m, 1 H), 7.50 (s, 1 H), 7.48–7.50 (m, 1 H), 7.29–7.33 (m, 2 H), 5.40 (dd, 1 H, J = 3, 8 Hz), 3.94 (s, 3 H), 3.44 (dd, 1 H, J = 3, 15 Hz), 3.25 (dd, 1 H, J = 8, 15 Hz), 2.55 (AB q, 2 H, J = 7.5 Hz), 2.42 (s, 3 H), 1.13 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{20}N_2O_3 \cdot 0.1H_2O$) C, H, N.

A mixture of 2-[2(*R/S*)-hydroxy-2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethyl]benzoxazole (5.13 g, 16.4 mmol) and pyridine hydrochloride (18.5 g, 16 mmol), under a nitrogen atmosphere, was placed in a preheated oil bath (150 °C) for 10 min. The reaction flask was removed, cooled, and water added to give a solid. This crude product was collected by filtration and dried. Crystallization from methanol gave 3.68 g (80%) of analytically pure ***trans*-3-[2-(benzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (42)**: mp 262–264 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1 H, *J* = 16 Hz), 7.73 (d, 1 H, *J* = 16 Hz), 7.70–7.72 (m, 1 H), 7.53 (s, 1 H), 7.50–7.53 (m, 1 H), 7.30–7.35 (m, 2 H), 2.48 (AB q, 2 H, *J* = 7.5 Hz), 2.47 (s, 3 H), 1.19 (t, 3 H, *J* = 7.5 Hz). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

A partial suspension of pure *trans*-3-[2-(benzoxazol-2-yl)-ethenyl]-5-ethyl-6-methyl-2(1*H*)-pyridinone (3.68 g, 13 mmol) in methanol/THF (175 mL, 1:1) was hydrogenated at atmospheric pressure over 5% palladium/charcoal (600 mg) for 15–24 h. After filtering off the catalyst, the solvents were evaporated and the residue triturated with methanol to give 2.89 g (78%) of nearly pure product. Crystallization from methanol afford analytically pure **3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (9)**: mp 155–156.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.66–7.70 (m, 1 H), 7.46–7.50 (m, 1 H), 7.26–7.30 (m, 2 H), 7.15 (s, 1 H), 3.30 (t, 2 H, *J* = 7.5 Hz), 3.09 (t, 2 H, *J* = 7.5 Hz), 2.31 (AB q, 2 H, *J* = 7.6 Hz), 2.27 (s, 3 H), 1.00 (t, 3 H, *J* = 7.6 Hz). Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

The following compounds were prepared by the same procedure starting from the appropriate aldehyde. **3-[2-(Benzothiazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (8)**: 14% overall yield; mp 142–143 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (dd, 1 H, *J* = 1, 8 Hz), 7.81 (dd, 1 H, *J* = 1, 8 Hz), 7.45 (dt, 1 H, *J* = 1, 8 Hz), 7.33 (dt, 1 H, *J* = 1, 8 Hz), 7.14 (s, 1 H), 3.48 (t, 2 H, *J* = 8 Hz), 3.09 (t, 2 H, *J* = 8 Hz), 2.32 (AB q, 2 H, *J* = 8 Hz), 2.27 (s, 3 H), 1.01 (t, 3 H, *J* = 8 Hz). Anal. ($C_{17}H_{18}N_2OS$) C, H, N.

3-[2-(Benzo[*b*]furan-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (12): 10% overall yield; mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.39–7.47 (m, 2 H), 7.15–7.20 (m, 2 H), 7.05 (s, 1 H), 6.38 (d, 1 H, *J* = 0.6 Hz), 3.11 (t, 2 H, *J* = 8 Hz), 2.95 (t, 2 H, *J* = 8 Hz), 2.30 (AB q, 2 H, *J* = 7.5 Hz), 2.25 (s, 3 H), 0.99 (t, 3 H, *J* = 7.5 Hz). Anal. ($C_{18}H_{19}NO_2 \cdot 0.15H_2O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-ethylpyridin-2(1*H*)-one (55): 11% overall yield; mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.63–7.69 (m, 1 H), 7.45–7.52 (m, 1 H), 7.25–7.34 (m, 2 H), 7.24 (d, 1 H, *J* = 2.4 Hz), 7.01 (d, 1 H, *J* = 2.4 Hz), 3.31 (t, 2 H, *J* = 7.4 Hz), 3.12 (t, 2 H, *J* = 7.4 Hz), 2.34 (AB q, 2 H, *J* = 7.6 Hz), 1.07 (t, 3 H, *J* = 7.6 Hz). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

Method B: 3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (21). Sodium hydride (60% in mineral oil, 3.2 g, 80 mmol) was added to a suspension of [4,7-dichlorobenzoxazol-2-yl)methyl]triphenylphosphonium chloride (37.67 g, 75.6 mmol) [prepared by heating 2-(chloromethyl)-4,7-dichlorobenzoxazole with an equimolar amount of triphenylphosphine in refluxing toluene for 15–25 h] in dry tetrahydrofuran (220 mL) under a nitrogen atmosphere at 25 °C. After 30 min, solid 2-methoxy-5-ethyl-6-methylnicotinaldehyde (13.45 g, 75.1 mmol) was added to the yellow suspension. This reaction mixture was heated at reflux for 6 h. Upon cooling, this reaction was diluted with chloroform, washed with water, dried (Na_2SO_4), and filtered and the solvent evaporated. This residue was purified by chromatography on silica gel and eluted with 5% ethyl acetate/hexanes to give some pure ***cis*-2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridine** [(1.71 g): mp 158–159 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.29 (d, 1 H, *J* = 13 Hz), 7.25 (AB q, 2 H, *J* = 8.5 Hz), 6.59 (d, 1 H, *J* = 13 Hz), 3.95 (s, 3 H), 2.61 (AB q, 2 H, *J* = 7.5 Hz), 2.48 (s, 3 H), 1.23 (t, 3 H, *J* = 7.5 Hz). Anal. ($C_{18}H_{16}Cl_2N_2O_2$) C, H, N] as well as the trans isomer (12.45 g): mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1 H, *J* = 16.4 Hz), 7.54 (s, 1 H), 7.37 (d, 1 H, *J* = 16.4 Hz), 7.26 (AB q, 2 H, *J* = 8 Hz), 4.05 (s, 3 H), 2.60 (AB q, 2 H, *J* = 7.6 Hz), 2.47 (s, 3 H), 1.22 (t, 3 H, *J* = 7.6 Hz). Anal. ($C_{18}H_{16}Cl_2N_2O_2$) C, H, N. The combined yield, including cis/trans mixtures, was 80% (21.9 g).

A solution of *cis/trans*-2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridine (5.50 g, 15.15 mmol) in methanol (60 mL) and tetrahydrofuran (60 mL) containing 5% palladium on charcoal (500 mg) was hydrogenated on a Parr apparatus at 50 psi of hydrogen for 7–10 h. The catalyst was filtered off and the solution evaporated to give a viscous oil which slowly solidified. Careful trituration of this residue with hexane yielded 3.54 g (64%) of pure **2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine**: mp 69–71 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (AB q, 2 H, *J* = 8 Hz), 7.20 (s, 1 H), 3.89 (s, 3 H), 3.28 (t, 2 H, *J* = 8 Hz), 3.12 (t, 2 H, *J* = 8 Hz), 2.49 (AB q, 2 H, *J* = 7.6 Hz), 2.39 (s, 3 H), 1.11 (t, 3 H, *J* = 7.6 Hz).

A mixture of 2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)-ethyl]-5-ethyl-6-methylpyridine (10.0 g, 27.4 mmol) and pyridine hydrochloride (19.0 g, 164 mmol) was warmed in a preheated oil bath at 150 °C for 15 min. The cooled residue was diluted with water and the precipitated product collected by filtration. This material was digested in methanol to remove a more polar impurity and the resultant solid crystallized twice from 2-propanol to give 6.08 g (63%) of pure **3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 186–187.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 1 H), 7.23 (AB q, 2 H, *J* = 5 Hz), 3.38 (t, 2 H, *J* = 7 Hz), 3.11 (t, 2 H, *J* = 7 Hz), 2.35 (AB q, 2 H, *J* = 7.5 Hz), 2.28 (s, 3 H), 1.04 (t, 3 H, *J* = 7.4 Hz). Anal. ($C_{17}H_{16}Cl_2N_2O_2$) C, H, N.

The mother liquors were combined and the solvent evaporated. The resultant residue was digested in chloroform, and the insoluble polar material isolated was crystallized from hot methanol/chloroform to give 1.26 g (12.4%) of the benzoxazole cleavage product, ***N*-(4,6-dichloro-2-hydroxyphenyl)-3-(6-methyl-5-ethyl-2-oxo-1*H*-pyridin-3-yl)propionamide (69)**: mp 219–220 °C; ^{1}H NMR ($CDCl_3$) δ 10.86 (br s, 1 H), 9.53 (s, 1 H), 7.81 (s, 1 H), 7.23 (s, 1 H), 7.19 (d, 1 H, *J* = 9.8 Hz), 6.88 (d, 1 H, *J* = 9.8 Hz), 2.89 (t, 2 H, *J* = 6.9 Hz), 2.71 (t, 2 H, *J* = 6.9 Hz), 2.36 (AB q, 2 H, *J* = 7.5 Hz), 2.22 (s, 3 H), 1.09 (t, 3 H, *J* = 7.5 Hz). Anal. ($C_{17}H_{18}Cl_2N_2O_3$) C, H, N.

The following compounds were prepared by the same procedure starting from the appropriate 2-methoxynicotinaldehyde and aralkyltriphenylphosphonium salt: **3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (57)**: 7.7% overall yield; mp 163–165 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 1 H), 7.23 (AB q, 2 H, *J* = 13 Hz), 3.66 (t, 2 H, *J* = 7 Hz), 3.13 (t, 2 H, *J* = 7 Hz), 2.32 (t, 2 H, *J* = 9 Hz), 2.30 (s, 3 H), 1.37–1.49 (m, 1 H), 0.83 (t, 3 H, *J* = 7.3 Hz). Anal. ($C_{18}H_{18}Cl_2N_2O_2$) C, H, N.

3-[2-(4,7-Dimethylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (20): 12% overall yield; mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1 H), 6.96 (AB q, 2 H, *J* = 7.5 Hz), 3.30 (t, 2 H, *J* = 7.6 Hz), 3.09 (t, 2 H, *J* = 7.6 Hz), 2.55 (s, 3 H), 2.43 (s, 3 H), 2.32 (AB q, 2 H, *J* = 7.5 Hz), 2.27 (s, 3 H), 1.02 (t, 3 H, *J* = 7.4 Hz). Anal. ($C_{19}H_{22}N_2O_2$) C, H, N.

3-[2-(4-Methylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (14): 15% overall yield; mp 170–171 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (d, 1 H, *J* = 7.5 Hz), 7.16 (s, 1 H), 7.16 (t, 1 H, *J* = 7.5 Hz), 7.08 (d, 1 H, *J* = 7.5 Hz), 3.30 (t, 2 H, *J* = 7.6 Hz), 3.08 (t, 2 H, *J* = 7.6 Hz), 2.60 (s, 3 H), 2.32 (AB q, 2 H, *J* = 7.5 Hz), 2.27 (s, 3 H), 1.02 (t, 3 H, *J* = 7.6 Hz). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

3-[2-(7-Methylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (17): 27% overall yield; mp 152–154 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1 H, *J* = 7.8 Hz), 7.18 (t, 1 H, *J* = 7.8 Hz), 7.15 (s, 1 H), 7.08 (d, 1 H, *J* = 7.8 Hz), 3.29 (t, 2 H, *J* = 7.5 Hz), 3.11 (t, 2 H, *J* = 7.5 Hz), 2.49 (s, 3 H), 2.31 (AB q, 2 H, *J* = 7.6 Hz), 2.22 (s, 3 H), 1.01 (t, 3 H, *J* = 7.6 Hz). Anal. ($C_{18}H_{20}N_2O_2 \cdot 0.5H_2O$) C, H, N.

Method C: 3-[2-(7-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (19). A mixture of 2-(chloromethyl)-7-fluorobenzoxazole (0.76 g, 4.1 mmol) and triethyl phosphite (1.4 mL, 8.2 mmol) was heated at 120 °C for 17 h. The reaction mixture was treated with toluene and concentrated under reduced pressure at 45 °C. After repeating this treatment three times, the residue was dried under high vacuum to give 1.21 g of diethyl [(7-fluorobenzoxazol-2-yl)methyl]phosphonate as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1 H, *J* = 8 Hz), 7.22–7.32 (m, 1 H), 7.18 (t, 1 H, *J* = 8 Hz), 4.16–4.32 (m, 4 H), 3.60 (d, 2 H, *J* = 21 Hz), 1.37 (t, 6 H, *J* = 7 Hz).

A solution of *n*-butyllithium in hexane (1.35 mL, 1.6 M) was added over 10 min to a solution of the phosphonate (0.58 g, 2.0 mmol) in THF (15 mL) cooled to −78 °C under argon. After stirring at −78 °C for 20 min, a solution of 2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde (0.50 g, 2.0 mmol) in THF (3 mL) was added and the reaction mixture stirred at −78 °C for 15 min and

then at room temperature for 1.5 h. The reaction mixture was poured into H_2O (100 mL) and the product extracted into $CHCl_3$. The $CHCl_3$ extracts were combined, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue over silica gel and elution with $CHCl_3$ gave 0.57 g (73%) of ***trans*-3-[2-(7-fluorobenzoxazol-2-yl)ethenyl]-2-(benzyloxy)-5-ethyl-6-methylpyridine** as an oil: ^1H NMR ($CDCl_3$) δ 7.96 (d, 1 H, J = 16.5 Hz), 7.22–7.60 (m, 9 H), 7.06 (ddd, 1 H, J = 10, 8, 0.9 Hz), 5.55 (s, 3 H), 2.60 (AB q, 2 H, J = 7.5 Hz), 2.46 (s, 3 H), 1.22 (t, 3 H, J = 7.5 Hz).

A solution of the olefin (150 mg, 0.40 mmol) in absolute EtOH (10 mL) and THF (6 mL) was hydrogenated over a 5% Pd/C catalyst (25 mg) at room temperature and atmospheric pressure for 18 h. After filtering, the solvents were removed, and the residue was flash chromatographed on silica gel. Elution with 5% MeOH–95% $CHCl_3$ gave 108 mg (52%) of **3-[2-(7-fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one**. An analytical sample, mp 160–161 °C, was obtained upon recrystallization from MeOH: ^1H NMR ($CDCl_3$) δ 7.45 (dd, 1 H, J = 8.1, 0.8 Hz), 7.22 (dd, 1 H, J = 8.1, 4.7 Hz), 7.17 (s, 1 H), 7.03 (ddd, 1 H, J = 10.1, 8.4, 0.8 Hz), 6.34 (t, 2 H, J = 7.5 Hz), 3.10 (t, 2 H, J = 7.5 Hz), 2.34 (q, 2 H, J = 7.5 Hz), 2.28 (s, 3 H), 1.02 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}FN_2O_2$) C, H, N.

The following compounds were prepared by the same procedure starting with the appropriate 2-(benzyloxy)nicotinaldehyde and diethyl (arylmethyl)phosphonate. **3-[2-(4-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (16)**: 35% overall yield; mp 155.5–156.5 °C; ^1H NMR ($CDCl_3$) δ 7.17–7.30 (m, 3 H), 7.01 (ddd, 1 H, J = 9.6, 7.9, 1.4 Hz), 3.32 (t, 2 H, J = 7.3 Hz), 3.10 (t, 2 H, J = 7.5 Hz), 2.34 (q, 2 H, J = 7.6 Hz), 2.28 (s, 3 H), 1.02 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}FN_2O_2$) C, H, N.

3-[2-(4-Chlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (15): 38% overall yield; mp 188.5–190.5 °C; ^1H NMR ($CDCl_3$) δ 7.38 (dd, 1 H, J = 7.9, 0.9 Hz), 7.19–7.40 (m, 3 H), 3.34 (t, 2 H, J = 7.5 Hz), 3.11 (t, 2 H, J = 7.3 Hz), 2.35 (q, 2 H, J = 7.6 Hz), 2.29 (s, 3 H), 1.03 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}ClN_2O_2$) H, N: C: calcd 64.45; found 63.72.

3-[2-(7-Chlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (18): 45% overall yield; mp 142–143.5 °C; ^1H NMR (DMSO-d_6) δ 7.64 (dd, 1 H, J = 7.8, 1.1 Hz), 7.44 (dd, 1 H, J = 7.8, 1.1 Hz), 7.34 (t, 1 H, J = 7.9 Hz), 7.15 (s, 1 H), 3.22 (t, 2 H, J = 7.5 Hz), 2.86 (t, 2 H, J = 7.5 Hz), 2.23 (q, 2 H, J = 7.5 Hz), 2.10 (s, 3 H), 0.91 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}ClN_2O_2$) C, H, N.

3-[2-(4,7-Difluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (22): 45% overall yield; mp 187.5–189 °C; ^1H NMR ($CDCl_3$) δ 7.2 (s, 1 H), 6.90–7.02 (m, 2 H), 3.35 (t, 2 H, J = 7.5 Hz), 3.11 (t, 2 H, J = 7.3 Hz), 2.34 (q, 2 H, J = 7.5 Hz), 2.28 (s, 3 H), 1.04 (t, 3 H, J = 7.6 Hz). Anal. ($C_{17}H_{16}F_2N_2O_2$) C, H, N.

3-[2-(6-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (24): 22% overall yield; mp 183.5–185.5 °C; ^1H NMR (DMSO-d_6) δ 7.64–7.69 (2 H, m), 7.19 (ddd, 1 H, J = 10.1, 8.9, 2.7 Hz), 7.11 (s, 1 H), 3.15 (t, 2 H, J = 7.6 Hz), 2.84 (t, 2 H, J = 7.5 Hz), 2.22 (q, 2 H, J = 7.5 Hz), 2.09 (s, 3 H), 0.90 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}FN_2O_2$) C, H, N.

3-[2-(5-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (25): 32% overall yield; mp 194.5–196.5 °C; ^1H NMR ($CDCl_3$) δ 7.26–7.42 (m, 2 H), 7.20 (s, 1 H), 7.02 (td, 1 H, J = 9.1, 2.5 Hz), 3.30 (t, 2 H, J = 7.5 Hz), 3.10 (t, 2 H, J = 7.3 Hz), 2.36 (q, 2 H, J = 7.6 Hz), 2.30 (s, 3 H), 1.03 (t, 3 H, J = 7.6 Hz). Anal. ($C_{17}H_{17}FN_2O_2$) C, H, N.

3-[2-(6-Methylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (23): 46% overall yield; mp 170.5–172 °C; ^1H NMR ($CDCl_3$) δ 7.52 (d, 1 H, J = 7.9 Hz), 7.26 (s, 1 H), 7.15 (s, 1 H), 7.11 (d, 1 H, J = 7.9 Hz), 3.27 (t, 2 H, J = 7.3 Hz), 3.08 (t, 2 H, J = 7.5 Hz), 2.46 (s, 3 H), 2.31 (q, 2 H, J = 7.6 Hz), 2.27 (s, 3 H), 1.01 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

3-[2-(5-Phenyloxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (11): 63% overall yield; mp 156–158 °C; ^1H NMR ($CDCl_3$) δ 7.64 (dd, 1 H, J = 9, 1.2 Hz), 7.46 (t, 1 H, J = 7.5 Hz), 7.38 (dd, 1 H, J = 6, 1.5 Hz), 7.33 (s, 1 H), 7.28 (br s, 1 H), 3.24 (t, 2 H, J = 6 Hz), 3.16 (t, 2 H, J = 6 Hz), 2.45 (AB q, 2 H, J = 7.5 Hz), 2.42 (s, 3 H), 1.13 (t, 3 H, J = 7.5 Hz). Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

3-[2-(4,5,6,7-Tetrahydrobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (10): 66% overall yield; mp 114–116 °C; ^1H NMR ($CDCl_3$) δ 7.14 (s, 1 H), 3.05 (t, 2 H, J = 7.2 Hz), 2.97 (t, 2 H, J = 7.2 Hz), 2.54–2.57 (m, 2 H), 2.47–2.50 (m, 2 H), 2.35 (AB q, 2 H, J = 7.5 Hz), 2.29 (s, 3 H), 1.80 (ddd, 4 H, J = 3.6, 5.1, 11.7 Hz), 1.07 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{22}N_2O_2 \cdot 0.35H_2O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-isopropyl-6-methylpyridin-2(1*H*)-one (48). In this case, 2-(benzyloxy)-5-isopropenyl-6-methylnicotinaldehyde was used and, upon hydrogenation of the penultimate olefinic intermediate, the isopropenyl substituent was reduced to isopropyl to give an 18% overall yield: mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 7.65–7.67 (m, 1 H), 7.46–7.48 (m, 1 H), 7.29–7.34 (m, 2 H), 7.28 (s, 1 H), 3.31 (t, 2 H, J = 7 Hz), 3.15 (t, 2 H, J = 7 Hz), 2.84 (m, 1 H), 2.34 (s, 3 H), 1.04 (d, 6 H, J = 7 Hz). Anal. ($C_{18}H_{20}N_2O_2 \cdot 0.35H_2O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-(dimethylamino)-6-methylpyridin-2(1*H*)-one (54): 53% overall yield; mp 118–120 °C; ^1H NMR ($CDCl_3$) δ 7.46–7.48 (m, 1 H), 7.43–7.45 (m, 1 H), 7.27–7.32 (m, 3 H), 3.30 (t, 2 H, J = 7.5 Hz), 3.09 (t, 2 H, J = 3.5 Hz), 2.41 (s, 6 H), 2.29 (s, 3 H). Anal. ($C_{17}H_{19}N_3O_2 \cdot 0.1H_2O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-(aminocarbonyl)-6-methylpyridin-2(1*H*)-one (51): 56% overall yield; mp 273–275 °C; ^1H NMR (DMSO-d_6) δ 2.38 (s, 3 H), 2.9 (t, 2 H), 3.2 (t, 2 H), 7.15 (s, NH), 7.35–7.40 (m, 2 H), 7.5 (s, NH), 7.56 (s, 1 H), 7.64 (m, 2 H). Anal. ($C_{16}H_{15}N_3O_3$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-(hydroxymethyl)-6-methylpyridin-2(1*H*)-one (52): 18% overall yield; mp 190.5–191.5 °C; ^1H NMR (DMSO-d_6) δ 7.64–7.70 (m, 2 H), 7.29–7.38 (m, 3 H), 4.83 (br s, 1 H), 4.17 (s, 2 H), 3.18 (t, 2 H, J = 7.5 Hz), 2.89 (t, 2 H, J = 7.5 Hz), 2.16 (s, 3 H). Anal. ($C_{16}H_{16}N_2O_3 \cdot 0.15H_2O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-2-amino-5-ethyl-6-methylpyridine (34): 33% overall yield; mp 81–82 °C; ^1H NMR (DMSO-d_6) δ 7.62–7.70 (m, 2 H), 7.28–7.38 (m, 2 H), 6.96 (s, 1 H), 5.50 (s, 2 H), 3.17 (t, 2 H, J = 7 Hz), 2.94 (t, 2 H, J = 7 Hz), 2.32 (AB q, 2 H, J = 7 Hz), 2.18 (s, 3 H), 0.92 (t, 3 H, J = 7 Hz). Anal. ($C_{17}H_{19}N_3O$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-phenyl-6-methylpyridin-2(1*H*)-one (49): 23% overall yield; mp 200–201 °C; ^1H NMR ($CDCl_3$) δ 7.65–7.69 (m, 1 H), 7.57 (s, 1 H), 7.46–7.50 (m, 1 H), 7.28–7.40 (m, 5 H), 7.11 (d, 2 H, J = 7.8 Hz), 3.33 (t, 2 H, J = 6 Hz), 3.24 (t, 2 H, J = 6 Hz), 2.42 (s, 3 H). Anal. ($C_{21}H_{18}N_2O_2$) C, H, N.

Method D: 3-[2-(Pyridin-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (6). A solution of 2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde (2.55 g, 10 mmol) in dry THF (13 mL) was added dropwise to a suspension of lithium aluminum hydride (0.436 g, 11.5 mmol) in dry THF (15 mL), and the mixture was stirred at ambient temperature for 2 h. The reaction was cautiously quenched with saturated aqueous sodium sulfate, the solution was diluted with diethyl ether, dried (Na_2SO_4), and filtered, and the solvent was evaporated. This residue was coevaporated from toluene to remove traces of water. **2-(Benzyloxy)-3-(hydroxymethyl)-5-ethyl-6-methylpyridine** was obtained as an oil (2.55 g, quant) and used without further purification: ^1H NMR ($CDCl_3$) δ 7.44–7.47 (m, 2 H), 7.26–7.40 (m, 3 H), 7.32 (s, 1 H), 5.43 (s, 2 H), 4.62 (br s, 2 H), 2.54 (AB q, 2 H, J = 7.6 Hz), 2.43 (s, 3 H), 1.17 (t, 3 H, J = 7.6 Hz).

Thionyl chloride (0.4 mL, 5.3 mmol) was added to a solution of 2-(benzyloxy)-3-(hydroxymethyl)-5-ethyl-6-methylpyridine (740 mg, 2.8 mmol) in dry benzene (10 mL) and refluxed, under an inert atmosphere, for 1 h. The solvent was evaporated, and the residue was coevaporated from benzene several times. The residue was triturated with diethyl ether to give solid **3-(chloromethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one** (347 mg, 65%): ^1H NMR ($CDCl_3$) δ 7.82 (s, 1 H), 4.58 (s, 2 H), 2.57 (AB q, 2 H, J = 7.6 Hz), 2.54 (s, 3 H), 1.22 (t, 3 H, J = 7.6 Hz).

The above (chloromethyl)pyridinone (347 mg, 1.87 mmol) was dissolved in THF (5 mL), triphenylphosphine hydrobromide (714 mg, 2.06 mmol) was added, and the mixture refluxed for 2 h as the salt dissolved and product precipitated. The cooled reaction mixture was diluted with diethyl ether and the product collected by filtration to give 834 mg (92%) of **[(5-ethyl-6-methyl-2-oxo-1*H*-pyridin-3-yl)methyl]triphenylphosphonium bromide**: ^1H NMR ($CDCl_3$) δ 8.53 (d, 1 H, J = 2.7 Hz), 7.80–7.92 (m, 9 H),

7.66–7.74 (m, 6 H), 5.61 (d, 2 H, J = 14.7 Hz), 2.54 (d, 3 H, J = 2.4 Hz), 2.44 (AB q, 2 H, J = 7.5 Hz), 1.01 (t, 3 H, J = 7.5 Hz).

Reaction of [(5-ethyl-6-methyl-2-oxo-1*H*-pyridin-3-yl)methyl]-triphenylphosphonium bromide with picolinaldehyde and subsequent catalytic reduction of the olefin intermediate by the procedure of method B afforded **3-[2-(pyridin-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one** (4% overall yield): mp 230–232 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.56 (br d, 1 H, J = 6 Hz), 7.57 (dt, 1 H, J = 1.8, 8 Hz), 7.16 (d, 1 H, J = 8 Hz), 7.08 (dd, 1 H, J = 1.8, 6 Hz), 7.03 (s, 1 H), 3.12 (t, 2 H, J = 8.4 Hz), 2.94 (t, 2 H, J = 8.4 Hz), 2.33 (AB q, 2 H, J = 7.8 Hz), 2.19 (s, 3 H), 1.04 (t, 3 H, J = 7.8 Hz). Anal. ($C_{15}H_{18}N_2O$) C, H, N.

Via the same procedure **3-[2-(naphth-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (5)** was prepared in 14% overall yield from naphthylene-2-carboxaldehyde: mp 140–141 °C; ^{1}H NMR ($CDCl_3$) δ 7.73–7.83 (m, 3 H), 7.64 (s, 1 H), 7.34–7.50 (m, 3 H), 6.98 (s, 1 H), 3.10 (t, 2 H, J = 8 Hz), 2.91 (t, 2 H, J = 8 Hz), 2.30 (AB q, 2 H, J = 7.5 Hz), 2.98 (s, 3 H), 0.99 (t, 3 H, J = 7.5 Hz). Anal. ($C_{20}H_{21}NO$) C, H, N.

3-[2-(Furo[3,2-*c*]pyridin-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (13): 24% overall yield from furo[3,2-*c*]-pyridine-2-carboxaldehyde:[2b] mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 8.84 (br s, 1 H), 8.45 (d, 1 H, J = 5.7 Hz), 7.44 (d, 1 H, J = 5.7 Hz), 7.06 (s, 1 H), 6.52 (br s, 1 H), 3.18 (t, 2 H, J = 7 Hz), 2.97 (t, 2 H, J = 7 Hz), 2.32 (AB q, 2 H, J = 7.5 Hz), 2.27 (s, 3 H), 1.01 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{18}N_2O_2 \cdot 0.30H_2O$) C, H, N.

3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5,6-dimethylpyridin-2(1*H*)-one (56). Via the procedure of method B, 2-methoxy-5,6-dimethylnicotinaldehyde (181 mg, 1.1 mmol) was condensed with [(4,7-dichlorobenzoxazol-2-yl)methyl]triphenylphosphonium chloride and the resultant olefin catalytically reduced to give 122 mg (32% overall yield) of **2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5,6-dimethylpyridine**: mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (AB q, 2 H, J = 9 Hz), 7.20 (s, 1 H), 3.89 (s, 3 H), 3.26 (t, 2 H, J = 8 Hz), 3.11 (t, 2 H, J = 8 Hz), 2.37 (s, 3 H), 2.15 (s, 3 H).

Boron tribromide in hexane (1 M, 1.8 mL) was added to a solution of 2-methoxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5,6-dimethylpyridine (122 mg, 0.35 mmol) in dry CH_2Cl_2 (4 mL), under an inert atmosphere, and cooled to 0 °C. After 2 h the reaction was quenched by the cautious addition of saturated aqueous $NaHCO_3$ (10 mL). The product was extracted into CH_2Cl_2, dried, and evaporated. The residue was triturated with diethyl ether, and 110 mg of crude product was collected. Crystallization from diethyl ether/methylene chloride yielded 77 mg (66%) of analytically pure **3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5,6-dimethylpyridin-2(1*H*)-one**: mp 207–208 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1 H), 7.24 (AB q, 2 H, J = 8 Hz), 3.36 (t, 2 H, J = 7.6 Hz), 3.11 (t, 2 H, J = 7.6 Hz), 2.27 (s, 3 H), 2.02 (s, 3 H). Anal. ($C_{16}H_{14}Cl_2N_2O_2$) H, N; C: calcd, 56.99; found, 56.39.

3-(2-Phenylethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (4). Essentially following the procedure of method B, 2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde was condensed with benzyltriphenylphosphonium chloride in DMSO and the resultant product olefin catalytically reduced and debenzylated to give a 77% overall yield of **3-(2-phenylethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 171–173 °C; ^{1}H NMR ($CDCl_3$) δ 7.25–7.29 (m, 2 H), 7.15–7.21 (m, 3 H), 7.03 (s, 1 H), 2.89–2.94 (m, 2 H), 2.82–2.86 (m, 2 H), 2.35 (AB q, 2 H, J = 7.5 Hz), 2.34 (s, 3 H), 1.04 (t, 3 H, J = 7.5 Hz). Anal. ($C_{16}H_{19}NO$) C, H, N.

Via this same procedure, **3-[(quinolin-2-yl)methyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (7)** was prepared in 60% overall yield to give a white solid: mp 133–135 °C; ^{1}H NMR (DMSO-d_6) δ 8.25 (d, 1 H, J = 8 Hz), 7.93 (d, 2 H, J = 8 Hz), 7.72 (t, 1 H, J = 6 Hz), 7.53 (t, 1 H, J = 6 Hz), 7.43 (d, 1 H, J = 8 Hz), 7.12 (s, 1 H), 3.15 (t, 2 H, J = 7 Hz), 2.83 (t, 2 H, J = 7 Hz), 2.24 (AB q, 2 H, J = 7 Hz), 2.09 (s, 3 H), 0.95 (t, 3 H, J = 7 Hz). Anal. ($C_{19}H_{20}N_2O$) C, H, N.

***cis*-3-[2-(Benzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (43).** Via the procedure of method B, 2-methoxy-5-ethyl-6-methylnicotinaldehyde was condensed with [(benzoxazol-2-yl)methyl]triphenylphosphonium chloride to give a 70% yield of a 3:1 trans/cis mixture of 2-methoxy-3-[2-(benzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridines. This mixture was separated by chromatography, eluting with 5% ethyl acetate/hexane to give nearly pure cis olefin as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1 H), 6.70–7.30 (m, 1 H), 7.36–7.42 (m, 1 H), 7.28–7.33 (m, 2 H), 7.15 (d, 1 H, J = 12.8 Hz), 6.56 (d, 1 H, J = 12.8 Hz), 3.94 (s, 3 H), 2.57 (AB q, 2 H, J = 7.6 Hz), 2.48 (s, 3 H), 1.20 (t, 3 H, J = 7.6 Hz). The pure trans isomer slowly solidified: mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1 H, J = 16.4 Hz), 6.70–7.30 (m, 1 H), 7.56 (s, 1 H), 7.48–7.54 (m, 1 H), 7.28–7.35 (m, 2 H), 7.26 (d, 1 H, J = 16.4 Hz), 4.04 (s, 3 H), 2.60 (AB q, 2 H, J = 7.5 Hz), 2.46 (s, 3 H), 1.22 (t, 3 H, J = 7.5 Hz).

Boron tribromide in hexane (1 M, 1.8 mL) was added to a solution of *cis*-2-methoxy-3-[2-(benzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridine (178 mg, 0.60 mmol) in dry methylene chloride (5 mL), cooled to 0 °C under a nitrogen atmosphere. A yellow precipitate rapidly formed, and after 10 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The product was extracted into methylene chloride/methanol and dried. The solvents were removed to give a yellow residue which was purified by chromatography on silica gel. Elution with a $^1/_2$–$1^1/_2$% methanol/chloroform gradient gave 61 mg (36%) of pure ***cis*-3-[2-(benzoxazol-2-yl)ethenyl]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 215–217 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1 H), 6.70–7.30 (m, 1 H), 7.40–7.46 (m, 1 H), 7.29–7.35 (m, 2 H), 7.26 (d, 1 H, J = 13 Hz), 6.57 (d, 1 H, J = 13 Hz), 2.46 (AB q, 2 H, J = 7.7 Hz), 2.35 (s, 3 H), 1.22 (t, 3 H, J = 7.7 Hz). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (47). Via the procedure of method C, 2-methoxy-5-*n*-propyl-6-methylnicotinaldehyde (202 mg, 1.04 mmol) was condensed with diethyl [(benzoxazol-2-yl)methyl]phosphonate and the resultant olefin reduced catalytically to give 207 mg (64% overall yield) of **2-methoxy-3-[2-(benzoxazol-2-yl)ethyl]-5-*n*-propyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.64–7.67 (m, 1 H), 7.44–7.48 (m, 1 H), 7.26–7.29 (m, 2 H), 7.12 (s, 1 H), 3.89 (s, 3 H), 3.20 (t, 2 H, J = 7.2 Hz), 3.12 (t, 2 H, J = 7.2 Hz), 2.43 (AB q, 2 H, J = 7.2 Hz), 2.38 (s, 3 H), 0.85 (t, 3 H, J = 7.2 Hz).

Potassium iodide (320 mg, 2.0 mmol) was added to a solution of 2-methoxy-3-[2-(benzoxazol-2-yl)ethyl]-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (183 mg, 0.59 mmol) in glacial acetic acid (5 mL), and the mixture was warmed at 60 °C for 1.5 h. The solvent was evaporated, and the residue was diluted with water. The product was extracted into $CHCl_3$ and the extract washed with saturated $NaHCO_3$ and $NaHSO_3$, dried, and evaporated. This residue was triturated with diethyl ether to give 84 mg (48%) of product. Recrystallization from ethyl acetate yielded analytically pure **3-[2-(benzoxazol-2-yl)ethyl]-5-*n*-propyl-6-methylpyridin-2(1*H*)-one**: mp 156–158 °C; ^{1}H NMR ($CDCl_3$) 7.64–7.67 (m, 1 H), 7.44–7.48 (m, 1 H), 7.26–7.30 (m, 2 H), 7.16 (s, 1 H), 3.30 (t, 2 H, J = 7.5 Hz), 3.10 (t, 2 H, J = 7.5 Hz), 2.28 (s, 3 H), 2.28 (t, 2 H, J = 7 Hz), 1.34–1.42 (m, 2 H), 0.81 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

Via the same procedure, **3-[2-(benzoxazol-2-yl)ethyl]-5,6-dimethylpyridin-2(1*H*)-one (46)** was prepared in 39% overall yield: mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 7.66–7.69 (m, 1 H), 7.46–7.49 (m, 1 H), 7.26–7.30 (m, 2 H), 7.18 (s, 1 H), 3.30 (t, 2 H, J = 7 Hz), 3.10 (t, 2 H, J = 7 Hz), 2.26 (s, 3 H), 1.99 (s, 3 H). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

3-[(Benzoxazol-2-yl)methyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (44). To a stirred solution of benzoxazole (1.0 g, 8.39 mmol) in anhydrous diethyl ether (30 mL) at −78 °C under an inert atmosphere was slowly added 1.6 M *n*-BuLi/hexane (5.27 mL). After stirring for 20 min, a solution of 2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde (2.36 g, 9.23 mmol) in anhydrous Et_2O (6 mL) was added dropwise to the mixture and stirred at room temperature for 17 h. The reaction mixture was poured into ice/H_2O and extracted with Et_2O. The combined Et_2O extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber oil, which crystallized on standing to give 0.72 g (23%) of **2-(benzyloxy)-3-[(benzoxazol-2-yl)-(*R*/*S*)-hydroxymethyl]-5-ethyl-6-methylpyridine**: mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 7.67–7.74 (m, 1 H), 7.52 (s, 1 H), 7.40–7.47 (m, 1 H), 7.29–7.35 (m, 2 H), 7.16–7.28 (m, 5 H), 6.09 (s, 1 H), 5.38 (AB q, 2 H, J = 14 Hz), 2.57 (AB q, 2 H, J = 7.8 Hz), 2.45 (s, 3 H), 1.18 (t, 3 H, J = 7.8 Hz).

A mixture of 2-(benzyloxy)-3-[(benzoxazol-2-yl)-(*R*/*S*)-hydroxymethyl]-5-ethyl-6-methylpyridine (150 mg, 0.4 mmol), 60% sodium hydride in mineral oil (40 mg), and imidazole (0.4 mg, 0.006 mmol) in dry THF (2 mL) was stirred under a nitrogen

atmosphere for 0.5 h at room temperature. Carbon disulfide (0.3 mL) was added and stirring continued for 1 h, followed by the addition of iodomethane (0.4 mL).[8] After stirring for another 0.5 h the reaction was quenched with glacial acetic acid (5 drops), and the mixture diluted with water and extracted with CH_2Cl_2. The combined organic extract was washed with dilute HCl, saturated $NaHCO_3$, and water, dried (Na_2SO_4), filtered, and concentrated to give an amber oil. This amber oil was heated to reflux under nitrogen in toluene (3 mL). To the hot solution was added α,α'-azodiisobutyronitrile (AIBN) (15 mg, 0.091 mmol) followed by the slow dropwise addition of a solution of tributyltin hydride (0.14 g, 0.48 mmol) in toluene (2 mL). After refluxing for 16 h, the reaction mixture was concentrated, and the residue was purified by chromatography on silica gel. Elution with 20% ethyl acetate/hexane gave 35.5 mg (25%) of **2-(benzyloxy)-3-[(benzoxazol-2-yl)methyl]-5-ethyl-6-methylpyridine** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.66–7.72 (m, 1 H), 7.40–7.46 (m, 1 H), 7.26–7.34 (m, 6 H), 7.20–7.23 (m, 2 H), 5.39 (s, 2 H), 4.23 (s, 2 H), 2.55 (AB q, 2 H, J = 7.8 Hz), 2.45 (s, 3 H), 1.18 (t, 3 H, J = 7.8 Hz).

To a stirred solution of 2-(benzyloxy)-3-[(benzoxazol-2-yl)-methyl]-5-ethyl-6-methylpyridine (0.20 g, 0.55 mmol) in CH_2Cl_2 (30 mL) at −10 °C and under nitrogen was added 1 M boron trichloride/CH_2Cl_2 (1.38 mmol, 1.38 mL). The solution was stirred at ambient temperature for 3 h and quenched with saturated aqueous $NaHCO_3$ (25 mL), and the layers were separated. The aqueous portion was washed with CH_2Cl_2. The combined organic organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give an amber oil. This oil was purified by chromatography on silica gel. Elution with 2.5% methanol/chloroform gave 55 mg (37%) of **3-[(benzoxazol-2-yl)methyl]-5-ethyl-6-methylpyridin-2(1*H*)-one** as a white solid: mp 193–194 °C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.69 (m, 1 H), 7.45–7.47 (m, 1 H), 7.34 (s, 1 H), 7.26–7.30 (m, 2 H), 4.17 (s, 2 H), 2.36 (AB q, 2 H, J = 7.5 Hz), 2.08 (s, 3 H), 1.08 (t, 3 H, J = 7.5 Hz). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

3-[3-(Benzoxazol-2-yl)propyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (45). A solution of 2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde (774 mg, 3.03 mmol) and trimethyl sulfonium iodide (636 mg, 3.11 mmol) in acetonitrile (9 mL) containing 3 drops of water and crushed potassium hydroxide (1.2 mg, 18.2 mmol) was vigorously stirred at 60 °C for 1.5 h. The mixture was diluted with benzene, the solids were filtered off, and the solvents were evaporated. The residue was redissolved in benzene, washed with water and saturated $NaHCO_3$, the solution was dried and filtered through a charcoal pad, and the solvent was evaporated to give 740 mg (90%) of oily **2-(benzyloxy)-3-(1,2-epoxyethyl)-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.46–7.49 (m, 2 H), 7.30–7.40 (m, 3 H), 7.18 (s, 1 H), 5.43 (s, 2 H), 4.13 (dd, 1 H, J = 2.7, 4.2 Hz), 3.12 (dd, 1 H, J = 1.8, 8.7 Hz), 2.70 (dd, 1 H, J = 3.0, 5.7 Hz), 2.53 (AB q, 2 H, J = 7.5 Hz), 2.42 (s, 3 H), 1.15 (t, 3 H, J = 7.5 Hz).

This crude epoxide (2.7 mmol) was dissolved in dry diethyl ether (30 mL), under an inert atmosphere, and boron trifluoride etherate (0.37 mL, 3.0 mmol) was added to give an immediate white precipitate. After 0.5 h the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL). The ether layer was separated, dried, filtered through a pad of charcoal, and evaporated to give 650 mg of crude product. This residue was dissolved in benzene and flash filtered through a column of silica gel to give 197 mg (26%) of purified oily **[2-(benzyloxy)-5-ethyl-6-methylpyridin-3-yl]acetaldehyde (66)**: ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1 H), 7.28–7.42 (m, 5 H), 7.18 (s, 1 H), 5.38 (s, 2 H), 3.60 (br s, 2 H), 2.55 (AB q, 2 H, J = 7.5 Hz), 2.43 (s, 3 H), 1.17 (t, 3 H, J = 7.5 Hz).

Via method C, acetaldehyde **66** was condensed with diethyl [(benzoxazol-2-yl)methyl]phosphonate to give an olefinic mixture (**67**) which was reduced and debenzylated under a hydrogen atmosphere using platinum oxide in THF containing several drops of $CHCl_3$ to give 68 mg (21% overall yield) of **3-[3-(benzoxazol-2-yl)propyl]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–7.67 (m, 1 H), 7.44–7.47 (m, 1 H), 7.26–7.32 (m, 2 H), 7.19 (s, 1 H), 3.00 (t, 2 H, J = 7.2 Hz), 2.68 (t, 2 H, J = 7.2 Hz), 2.36 (AB q, 2 H, J = 7.5 Hz), 2.27 (s, 3 H), 2.18–2.27 (m, 2 H), 1.10 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-cyano-6-methylpyridin-2(1*H*)-one (50). To a solution of 2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-6-methylpyridine-5-carboxamide (530 mg, 1.4 mmol) in dry tetrahydrofuran (50 mL) was added in portions over 2 h [(methoxycarbonyl)sulfamoyl]trimethylammonium hydroxide inner salt (Burgess reagent)[13] (880 mg, 3.7 mmol). After the mixture was stirred overnight, chloroform was added and the organic phase was washed well with water and then brine. Evaporation gave crude product. Purification by flash chromatography on silica gel using 20% ethyl acetate–methylene chloride gave pure **2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-5-cyano-6-methylpyridine** (500 mg, 97% yield): ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1 H), 7.80 (d, 1 H, J = 16.5 Hz), 7.70–7.75 (m, 1 H), 7.50–7.56 (m, 3 H), 7.30–7.45 (m, 6 H), 5.61 (s, 2 H), 2.70 (s, 3 H).

A mixture of 2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-5-cyano-6-methylpyridine (100 mg, 0.28 mmol) and 10% palladium on carbon (22 mg) in 50–50 ethanol–tetrahydrofuran (40 mL) was stirred at room temperature overnight under hydrogen at atmospheric pressure. After filtration through a pad of filtercel, the solvent was evaporated, the residue was dissolved in chloroform and refiltered, and the solvent was evaporated to give product. Recrystallization from boiling acetonitrile gave analytically pure **3-[2-(benzoxazol-2-yl)ethyl]-5-cyano-6-methylpyridin-2(1*H*)-one** (46 mg, 59% yield): mp 220–225 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–7.70 (m, 1 H), 7.45–7.51 (m, 1 H), 7.40 (s, 1 H), 7.28–7.34 (m, 2 H), 3.27 (t, 2 H, J = 7.2 Hz), 3.10 (t, 2 H, J = 7.2 Hz), 2.51 (s, 3 H). Anal. ($C_{16}H_{13}N_3O_2$) C, H, N.

3-{[(Benzoxazol-2-yl)amino]methyl}-5-ethyl-6-methylpyridin-2(1*H*)-one (41). To a solution of 2-methoxy-3-(aminomethyl)-5-ethyl-6-methylpyridine[28] (98 mg, 0.54 mmol) in methanol (1 mL) under a nitrogen atmosphere was added 2-chlorobenzoxazole (0.07 mL, 0.61 mmol), followed by triethylamine (0.076 mL, 0.55 mmol). After 2 h, product began to crystallize out. The mixture was stirred for 12 h, and the product (133 mg, 82%) was collected by filtration. This material was dissolved in diethyl ether and filtered through a charcoal pad, and hexane was added to the solution. As the ether was boiled off, solid crystallized out to give 96 mg (60%) of pure **2-methoxy-3-{[(benzoxazol-2-yl)amino]methyl}-5-ethyl-6-methylpyridine**: mp 141.5–142.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 7.37 (d, 1 H, J = 8 Hz), 7.24 (d, 1 H, J = 8 Hz), 7.16 (t, 1 H, J = 8 Hz), 7.02 (t, 1 H, J = 8 Hz), 5.47 (br t, 1 H, J = 7.2 Hz), 4.57 (d, 2 H, J = 7.2 Hz), 3.97 (s, 3 H), 2.54 (AB q, 2 H, J = 7.6 Hz), 2.42 (s, 3 H), 1.06 (t, 3 H, J = 7.6 Hz). Anal. ($C_{17}H_{19}N_3O_2$) C, H, N.

A mixture of 2-methoxy-3-{[(benzoxazol-2-yl)amino]methyl}-5-ethyl-6-methylpyridine (80 mg, 0.269 mmol) and pyridine hydrochloride (335 mg, 2.9 mmol), under a nitrogen atmosphere, was warmed in an oil bath preheated to 150 °C for 5 min. This solidified mixture was cooled and diluted with water, and the crude precipitate produced was collected by filtration. This material was dissolved in methylene chloride, filtered through a charcoal pad, and then diluted with hexane. As the methylene chloride was boiled off the product crystallized out to give 40 mg (53%) of **3-{[(benzoxazol-2-yl)amino]methyl}-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 211–213 °C; ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1 H), 7.35 (d, 1 H, J = 7.8 Hz), 7.23 (d, 1 H, J = 7.8 Hz), 7.14 (t, 1 H, J = 7.8 Hz), 7.00 (t, 1 H, J = 7.8 Hz), 6.86 (br s, 1 H), 4.54 (br s, 2 H), 2.39 (AB q, 2 H, J = 7.6 Hz), 2.32 (s, 3 H), 1.00 (t, 3 H, J = 7.6 Hz). Anal. ($C_{16}H_{17}N_3O_2$) C H, N.

3-[(Benzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridin-2(1*H*)-one (35). A mixture of 3-nitro-5-ethyl-6-methylpyridin-2(1*H*)-one[28] (0.91 g, 5.0 mmol) and phosphorus pentachloride (1.25 g, 6.0 mmol), under a nitrogen atmosphere, was heated at 140 °C for 0.5 h. The cooled mixture was diluted with chloroform and ice water. The separated chloroform layer was then washed with water and saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). After filtering through a pad of charcoal, the solvent was evaporated to yield 672 mg (67%) of **2-chloro-3-nitro-5-ethyl-6-methylpyridine** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1 H), 2.73 (AB q, 2 H, J = 7.6 Hz), 2.61 (s, 3 H), 1.31 (t, 3 H, J = 7.6 Hz).

Sodium metal (100 mg, 4.3 mmol) was dissolved in methanol (5 mL) under a nitrogen atmosphere. A solution of 2-chloro-3-nitro-5-ethyl-6-methylpyridine (677 mg, 3.37 mmol) in methanol (5 mL) was added dropwise. The reaction was warmed at 50 °C

for 4 h. The reaction was cooled and diluted with diethyl ether, and the ether layer was washed with water, dried (Na_2SO_4), filtered through a pad of charcoal, and evaporated to yield 535 mg (80%) of **2-methoxy-3-nitro-5-ethyl-6-methylpyridine** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1 H), 4.08 (s, 3 H), 2.63 (AB q, 2 H, J = 7.6 Hz), 2.51 (s, 3 H), 1.25 (t, 3 H, J = 7.6 Hz).

A solution of 2-methoxy-3-nitro-5-ethyl-6-methylpyridine (535 mg, 2.72 mmol) in methanol (8 mL) and tetrahydrofuran (8 mL) containing 5% palladium on carbon (83 mg) was hydrogenated at atmospheric pressure for 5 h. The catalyst was filtered off and the solvent evaporated to yield 436 mg (98%) of oily **2-methoxy-3-amino-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 6.71 (s, 1 H), 3.94 (s, 3 H), 3.47 (br s, 2 H, exchangable), 2.47 (AB q, 2 H, J = 7.6 Hz), 2.33 (s, 3 H), 1.13 (t, 3 H, J = 7.6 Hz).

2-Methoxy-3-amino-5-ethyl-6-methylpyridine (171 mg, 1.05 mmol) was dissolved in 5% aqueous sulfuric acid (4 mL) and cooled in an ice bath, and then a solution of sodium nitrite (78 mg, 1.13 mmol) in water (1 mL) was added dropwise. After 0.5 h, the resulting mixture was added dropwise to 5% aqueous sulfuric acid (6 mL) warmed at 110 °C. The solution was stirred for 0.5 h and cooled, and the product was extracted into chloroform, dried (Na_2SO_4), filtered, and evaporated to yield 77 mg (43%) of a phenolic smelling oil, **2-methoxy-3-hydroxy-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1 H), 5.35 (br s, exchangable H), 3.96 (s, 3 H), 2.51 (AB q, 2 H, J = 7.5 Hz), 2.35 (s, 3 H), 1.15 (t, 3 H, J = 7.5 Hz).

Sodium hydride in mineral oil (60%, 24 mg, 0.6 mmol) was added to a solution of 2-methoxy-3-hydroxy-5-ethyl-6-methylpyridine (77 mg, 0.46 mmol) in dry dimethylformamide (2 mL). After gas evolution ceased, 2-(chloromethyl)benzoxazole (100 mg, 0.6 mmol) was added and the reaction mixture warmed at 60 °C for 1 h. The reaction was then cooled and diluted with diethyl ether, and the ether extract was washed with water, dried (Na_2SO_4), filtered, and evaporated to give 151 mg of a crude mixture. This mixture was purified by flash chromatography on silica gel, eluting with 0.5% methanol/chloroform. Appropriate fractions were combined to give 46 mg (32%) of oily **2-methoxy-3-[(benzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.72–7.77 (m, 1 H), 7.53–7.58 (m, 1 H), 7.32–7.39 (m, 2 H), 7.09 (s, 1 H), 5.34 (s, 2 H), 3.97 (s, 3 H), 2.49 (AB q, 2 H, J = 7.6 Hz), 2.35 (s, 3 H), 1.12 (t, 3 H, J = 7.6 Hz).

2-Methoxy-3-[(benzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridine (140 mg, 0.47 mmol) was dissolved in methylene chloride (5 mL) and cooled in an ice bath under an atmosphere of nitrogen. Borom tribromide (1 M, 2.3 mL, 2.3 mmol) in hexane was added to this solution, and the reaction mixture was allowed to warm to room temperature over a 0.75-h period. This mixture was recooled in an ice bath, and saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The methylene chloride layer was dried (Na_2SO_4), filtered, and evaporated. The residue was triturated with diethyl ether to give 69 mg of crude product. Recrystallization from methanol yielded 60 mg (45%) of **3-[(benzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 198–200 °C; ^{1}H NMR ($CDCl_3$) δ 7.72–7.78 (m, 1 H), 7.52–7.58 (m, 1 H), 7.32–7.39 (m, 2 H), 7.00 (s, 1 H), 5.46 (s, 2 H), 2.36 (AB q, 2 H, J = 7.8 Hz), 2.27 (s, 3 H), 1.07 (t, 3 H, J = 7.8 Hz). Anal. ($C_{16}H_{16}N_2O_3$) C, H, N.

3-[(4,7-Dichlorobenzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridin-2(1*H*)-one (36). *m*-Chloroperbenzoic acid (80% pure, 1.42 g, 6.6 mmol) was added in portions to a solution of 2-methoxy-5-ethyl-6-methylnicotinaldehyde (1.08 g, 6.0 mmol) in methylene chloride (15 mL). Diethyl ether (5 mL) was added to dissolve the precipitate formed, and stirring was continued for 1.5 h. The reaction was diluted with methylene chloride and washed with saturated aqueous sodium bicarbonate. The dried organic layer (Na_2SO_4) was filtered and evaporated. The residue was suspended in 50% aqueous acetic acid and warmed to 80 °C for 1 h. This reaction was poured into water and the product extracted into diethyl ether. The ether extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. This residue (924 mg) was purified by chromatography on silica gel, eluting with chloroform to give 510 mg (50% yield) of oily **2-methoxy-3-hydroxy-5-ethyl-6-methylpyridine**.

Sodium hydride/mineral oil (60%, 59 mg, 1.5 mmol) was added to a solution of 2-methoxy-3-hydroxy-5-ethyl-6-methylpyridine (60% pure, 275 mg, 1.0 mmol) in dry dimethylformamide (3 mL) under a nitrogen atmosphere. After 1 h 2-(chloromethyl)-4,7-dichlorobenzoxazole (236 mg, 1.0 mmol) was added to the reaction and stirred for an additional hour. The reaction was neutralized with dilute (10%) hydrochloric acid and made basic with sodium bicarbonate, the product was extracted into diethyl ether, and the solution was dried (Na_2SO_4) and evaporated. The residue (288 mg) was purified by chromatography on silica gel eluting with 1% methanol/chloroform. The appropriate fractions were combined, solvents were evaporated, and the residue was triturated with diethyl ether/hexane to give 84 mg (23% yield) of crystalline **3-[(4,7-dichlorobenzoxazol-2-yl)methoxy]-2-methoxy-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 2 H), 7.16 (s, 1 H), 5.38 (s, 2 H), 3.97 (s, 3 H), 2.53 (AB q, 2 H, J = 7 Hz), 2.36 (s, 3 H), 1.16 (t, 3 H, J = 7 Hz).

Boron tribromide/hexane (1 M, 1 mL, 1.0 mmol) was added to a solution of 3-[(4,7-dichlorobenzoxazol-2-yl)methoxy]-2-methoxy-5-ethyl-6-methylpyridine (83 mg, 0.226 mmol) in anhydrous methylene chloride (3 mL) cooled in an ice bath under a nitrogen atmosphere. After 1 h, saturated aqueous $NaHCO_3$ was added and the mixture stirred for 0.5 h. The product was extracted into chloroform and dried (Na_2SO_4), and the solvent was evaporated to give a residue which was digested in warm methanol and then cooled. The collected precipitate was analytically pure, 24 mg (30% yield), **3-[(4,7-dichlorobenzoxazol-2-yl)methoxy]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 243–245 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 2 H), 7.15 (s, 1 H), 5.50 (s, 2 H), 2.40 (AB q, 2 H, J = 7.6 Hz), 2.29 (s, 3 H), 1.11 (t, 3 H, J = 7.6 Hz). Anal. ($C_{16}H_{14}Cl_2N_2O_3$) H, N; C: calcd, 54.41; found, 53.96.

3-{[(4,7-Dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methylpyridin-2(1*H*)-one (37). To a solution of 2-methoxy-3-amino-5-ethyl-6-methylpyridine (1.24 g, 7.5 mmol) in water (1.9 mL) plus concentrated HCl (1.9 mL), cooled in an ice–acetone bath, was added dropwise a solution of $NaNO_2$ (0.55 g, 7.7 mmol) in water (3 mL). The mixture was stirred for 20 min. The cold reaction mixture was added dropwise to potassium ethyl xanthate (1.4 g, 8.8 mmol) in water (1.8 mL) heated to 40–45 °C. The mixture was stirred for 20 min and then extracted three times with chloroform. The chloroform extract was washed with saturated aqueous sodium bicarbonate solution and brine and then dried ($MgSO_4$). Evaporation gave a crude residue (1.47 g) which was purified by chromatography on silica gel and eluted with a 5–20% methylene chloride/hexane gradient to give 0.34 g (17%) of purified **2-methoxy-3-[[ethoxy(thiocarbonyl)]thio]-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1 H), 4.60 (q, 2 H, J = 7.2 Hz), 3.95 (s, 3 H), 2.57 (AB q, 2 H, J = 7.5 Hz), 2.48 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz), 1.19 (t, 3 H, J = 7.5 Hz).

A mixture of 2-methoxy-3-[[ethoxy(thiocarbonyl)]thio]-5-ethyl-6-methylpyridine (0.30 g, 1.1 mmol), 1 N NaOH (3.0 mL), and ethanol (9 mL) was stirred under nitrogen for 9.5 h. HCl (1 N) was added to bring the pH to 3, and the mixture was evaporated to dryness. The residue was extracted into CH_2Cl_2 to give 0.20 g (quant yield) of crude **2-methoxy-3-mercapto-5-ethyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1 H), 4.04 (s, 3 H), 3.64 (s, 1 H), 2.52 (AB q, 2 H, J = 7.5 Hz), 2.44 (s, 3 H), 1.16 (t, 3 H, J = 7.5 Hz).

A mixture of 2-methoxy-3-mercapto-5-ethyl-6-methylpyridine (0.20 g, 1.1 mmol), 2-(chloromethyl)-4,7-dichlorobenzoxazole (0.26 g, 1.1 mmol), and diisopropylethylamine (0.16 g, 1.2 mmol) in $CHCl_3$ (5 mL) was allowed to react at room temperature under nitrogen for 3.5 h. After the extract was washed with water and dried and the solvent was evaporated, there was obtained 0.43 g of crude product which was purified by chromatography on silica gel eluting with 30% methylene chloride/hexane to give 0.35 g (83%) of solid **2-methoxy-3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methylpyridine**: mp 105–110 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1 H), 7.26 (s, 2 H), 4.26 (s, 2 H), 3.91 (s, 3 H), 2.49 (AB q, 2 H, J = 7.5 Hz), 2.42 (s, 3 H), 1.10 (t, 3 H, J = 7.5 Hz).

A mixture of 2-methoxy-3-{[(4,7-dichlorobenzoxazol-2-yl)-methyl]thio}-5-ethyl-6-methylpyridine (0.22 g, 1.2 mmol) and potassium iodide (0.191 g, 1.2 mmol) in acetic acid (10 mL) was heated at 70 °C for 7 h. Chloroform was then added and the dark solution washed with aqueous sodium thiosulfate, followed by water and brine. Evaporation gave crude product (0.21 g). After digestion with boiling acetonitrile and cooling, there was obtained

0.18 g (83% yield) of **3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 233–235 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3 H, J = 7.5 Hz), 2.14 (s, 3 H), 2.28 (q, 2 H, J = 7.5 Hz), 4.54 (s, 2 H), 7.45 (s, 1 H), 7.48 (d, 1 H, J = 8.7 Hz), 7.48 (d, 1 H, J = 8.7 Hz), 11.73 (s, 1 H). Anal. ($C_{16}H_{14}Cl_2N_2O_2S$) H, N; C: calcd 52.04; found 51.42.

3-{[(4,7-Dichlorobenzoxazol-2-yl)methyl]sulfinyl}-5-ethyl-6-methylpyridin-2(1*H*)-one (38). To a mixture of 3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methylpyridin-2(1*H*)-one (19 mg, 0.05 mmol) in methylene chloride (2 mL) cooled in an ice–acetone bath was added a solution of *m*-chloroperbenzoic acid (80%) (11 mg, 0.05 mmol) in methylene chloride (3 mL), and the mixture was stirred overnight. The solvent was evaporated, and the solid residue was washed three times with diethyl ether. After drying under vacuum, the crude product was digested with hot acetonitrile. After cooling to room temperature there was obtained upon filtration 14 mg (70%) of **3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]sulfinyl}-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 220–224 °C; ^{1}H NMR (DMSO-d_6) δ 7.52 (d, 1 H, J = 8.5 Hz), 7.48 (d, 1 H, J = 8.5 Hz), 7.20 (s, 1 H), 4.90 (d, 1 H, J = 13.5 Hz), 4.70 (d, 1 H, J = 13.5 Hz), 2.26 (AB q, 2 H, J = 7.5 Hz), 2.25 (s, 3 H), 0.72 (t, 3 H, J = 7.5 Hz). Anal. ($C_{16}H_{14}Cl_2N_2O_3S$) C, H, N.

3-{[(4,7-Dichlorobenzoxazol-2-yl)methyl]sulfonyl}-5-ethyl-6-methylpyridin-2(1*H*)-one (39). To a mixture of 3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methylpyridin-2(1*H*)-one (20.8 mg, 0.056 mmol) in methylene chloride (2 mL) cooled in an ice–acetone bath was added *m*-chloroperbenzoic acid (28 mg, 0.13 mmol) in methylene chloride (3 mL). The mixture was allowed to warm to room temperature and stirred overnight. After evaporation of solvent the residue was washed three times with excess diethyl ether. The solid remainder (15 mg) was dissolved in hot acetonitrile and filtered. Evaporation to a small volume gave 12 mg (53%) of crystalline **3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]sulfonyl}-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 312–313 °C; ^{1}H NMR (DMSO-d_6) δ 7.59 (d, 1 H, J = 8.7 Hz), 7.54 (d, 1 H, J = 8.7 Hz), 5.36 (s, 2 H), 2.38 (AB q, 2 H, J = 7.2 Hz), 2.33 (s, 3 H), 0.94 (t, 3 H, J = 7.2 Hz). Anal. ($C_{16}H_{14}Cl_2N_2O_4S$) C, H, N.

3-[2-(Benzoxazol-2-yl)ethyl]-5-(methoxymethyl)-6-methylpyridin-2(1*H*)-one (53). Excess sodium hydride in mineral oil (60%, 113 mg, 2.8 mmol) was added to a solution of 2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-5-(hydroxymethyl)-6-methylpyridine (558 mg, 1.5 mmol) in dry dimethylformamide (10 mL), under nitrogen, to give a deep purple solution. After 0.5 h, excess methyl iodide (0.22 mL, 3.8 mmol) was added, and the solution immediately became brown. After an additional hour, the reaction mixture was diluted with water and acidified with a few drops of acetic acid and the product extracted into diethyl ether. This extract was washed with water, dried, and filtered through a plug of charcoal and the solvent evaporated. The residue (367 mg) was purified by chromatography on silica gel and eluted with 20–40% ethyl acetate/hexane. The combined fractions were evaporated and the residue triturated with hexane to give 169 mg (29%) of crystalline ***trans*-2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-5-(methoxymethyl)-6-methylpyridine**: mp 94–96 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1 H, J = 16 Hz), 7.77 (s, 1 H), 7.69–7.72 (m, 1 H), 7.50–7.54 (m, 3 H), 7.23–7.42 (m, 6 H), 5.56 (s, 2 H), 4.42 (s, 2 H), 3.43 (s, 3 H), 2.50 (s, 3 H). Anal. ($C_{24}H_{22}N_2O_3$) C, H, N.

A solution of *trans*-2-(benzyloxy)-3-[2-(benzoxazol-2-yl)ethenyl]-5-(methoxymethyl)-6-methylpyridine (169 mg, 0.44 mmol) in methanol (12 mL) and THF (12 mL) containing 10% palladium/carbon (60 mg) was hydrogenated at atmospheric pressure for 4 h. The catalyst was filtered, and the solvents were evaporated. The residue was crystallized from acetonitrile/methylene chloride to give 92 mg (71%) of **3-[2-(benzoxazol-2-yl)ethyl]-5-(methoxymethyl)-6-methylpyridin-2(1*H*)-one**: mp 130–132 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–7.67 (m, 1 H), 7.45–7.48 (m, 1 H), 7.36 (s, 1 H), 7.25–7.32 (m, 2 H), 4.19 (s, 2 H), 3.28 (t, 2 H, J = 7.5 Hz), 3.24 (s, 3 H), 3.11 (t, 2 H, J = 7.5 Hz), 2.36 (s, 3 H). Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (28). A mixture of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*H*)-one (493 mg, 1.4 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) (664 mg, 1.64 mmol) in dry toluene (10 mL) was refluxed, under a nitrogen atmosphere for 5 h. Some methanol (2 mL) was added, and the solvents were evaporated. The residue was purified by chromatography on silica gel and eluted with a 0–1.25% methanol/chloroform gradient to give 458 mg (89%) of product. Several recrystallizations from diethyl ether/methylene chloride gave 378 mg of analytically pure **3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione**: mp 243–245 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.24 (AB q, 2 H, J = 7 Hz), 3.52 (t, 2 H, J = 6.5 Hz), 3.42 (t, 2 H, J = 6.5 Hz), 2.45 (s, 3 H), 2.44 (AB q, 2 H, J = 7.6 Hz), 1.09 (t, 3 H, J = 7.6 Hz). Anal. ($C_{17}H_{16}Cl_2N_2OS$) C, H, N.

The following compounds were prepared by the same procedure. **3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (26)**: 69% yield; mp 201–202 °C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.68 (m, 1 H), 7.45–7.48 (m, 1 H), 7.27–7.30 (m, 2 H), 7.28 (s, 1 H), 3.42 (m, 4 H), 2.43 (s, 3 H), 2.40 (AB q, 2 H, J = 7.5 Hz), 1.02 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{18}N_2OS$) C, H, N.

3-[2-(4,7-Dimethylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (27): 51% yield; mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1 H), 6.98 (br s, 2 H), 3.40 (br s, 4 H), 2.55 (s, 3 H), 2.48 (s, 3 H), 2.49 (AB q obscured, 2 H), 2.44 (s, 3 H), 1.07 (t, 3 H, J = 7.5 Hz). Anal. ($C_{19}H_{22}N_2OS$) C, H, N.

3-[2-(4,7-Difluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (29): 69% yield; mp 228.5–230.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.19–7.35 (m, 3 H), 3.38 (t, 2 H, J = 7.3 Hz), 3.20 (t, 2 H, J = 7.3 Hz), 2.36 (AB q, 2 H, J = 7.6 Hz), 2.30 (s, 3 H), 0.95 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{16}F_2N_2OS$) H, N; C: calcd, 61.06; found 60.36.

3-[2-(4-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (30): 38% yield; mp 200–201.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.53 (dd, H, J = 8.2, 0.8 Hz), 7.32–7.40 (m, 2 H), 7.20 (ddd, 1 H, J = 10.4, 8.3, 0.8 Hz), 3.34 (t, 2 H, J = 7.4 Hz), 3.19 (t, 2 H, J = 7.4 Hz), 2.27–2.37 (m, 5 H), 0.93 (t, 3 H, J = 7.4 Hz). Anal. ($C_{17}H_{17}FN_2OS$) C, H, N.

3-[2-(7-Fluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (31): 52% yield; mp 199–201 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (dd, 1 H, J = 7.5 Hz, 1.3 Hz), 7.23–7.33 (m, 3 H), 3.34–3.37 (m, 2 H (obscured by H_2O)), 3.18 (t, 2 H, J = 7.3 Hz), 2.28–2.36 (m, 5 H), 0.92 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}FN_2OS$) C, H, N.

3-[2-(4-Chlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (32): 63% yield; mp 206.5–208 °C; ^{1}H NMR (DMSO-d_6) δ 7.66 (dd, 1 H, J = 7.6, 0.8 Hz), 7.32–7.44 (m, 3 H), 3.35 (t, 2 H, J = 7.2 Hz), 3.19 (t, 2 H, J = 7.2 Hz), 2.30–2.37 (m, 5 H), 0.94 (t, 3 H, J = 7.4 Hz). Anal. ($C_{17}H_{17}FN_2OS$) C, H, N.

3-[2-(7-Chlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridine-2(1*H*)-thione (33): 33% yield; mp 196–198 °C; ^{1}H NMR (DMSO-d_6) δ 7.64 (dd, 1 H, J = 7.9, 0.9 Hz), 7.43 (dd, 1 H, J = 8.0, 1.1 Hz), 7.30–7.36 (m, 2 H), 3.33 (m, 2 H (obscured by H_2O peak)), 3.18 (t, 2 H, J = 7.3 Hz), 2.28–2.36 (m, 5 H), 0.90 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{17}ClN_2OS$) C, H, N.

Preparation of 2-methoxynicotinaldehydes: The following 2-methoxynicotinaldehydes were prepared according to a three-step procedure described for the synthesis of **2-methoxy-5-ethyl-6-methylnicotinaldehyde (59)**.[2a] **2-Methoxy-5,6-dimethylnicotinaldehyde**: 46% overall yield; mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1 H), 7.82 (s, 1 H), 4.03 (s, 3 H), 2.46 (s, 3 H), 2.23 (s, 3 H). Anal. ($C_9H_{11}NO_2 \cdot 0.1H_2O$) C, H, N.

2-Methoxy-5-*n*-propyl-6-methylnicotinaldehyde: 44% overall yield as an oil; ^{1}H NMR ($CDCl_3$) δ 10.05 (s, 1 H), 7.57 (s, 1 H), 3.77 (s, 3 H), 2.28 (t, 2 H, J = 7.6 Hz), 2.26 (s, 3 H), 1.25–1.41 (m, 2 H), 0.72 (t, 3 H, J = 7.4 Hz).

2-Methoxy-5-ethylnicotinaldehyde. According to an adaptation of a literature method,[14] a solution of butyraldehyde (7.2 g, 0.10 mmol), malononitrile (7.4 g, 0.11 mmol), and DL-alanine (300 mg) in benzene (300 mL) containing acetic acid (6 mL) was refluxed for 2.5 h with a Dean–Stark trap to remove water. The benzene solution was washed with water, dried (Na_2SO_4), and evaporated to give 10.7 g (89% yield) of 1,1-dicyanopentene.

This material was mixed with acetic anhydride (22 mL) and triethyl orthoformate (16 mL) containing zinc chloride (300 mg), and the mixture was heated at 145 °C for 24 h. All volatiles below 110 °C were distilled off, fresh acetic anhydride (4 mL) and triethyl orthoformate (3.4 mL) were added, and the reaction was heated at 145 °C for another 24 h. The cooled reaction was

poured into ice/water, and the product was extracted into chloroform, washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and filtered through charcoal. Evaporation of the solvent gave 15.6 g (99% yield) of crude oily 1,1-dicyano-3-ethyl-4-ethoxy-1,3-butadiene.

Hydrogen bromide/acetic acid (30%, 60 mL) was added dropwise to a solution of 1,1-dicyano-3-ethyl-4-ethoxy-1,3-butadiene (12 g, 74 mmol) in acetic acid (40 mL) and warmed at 50 °C. After 1 h, the reaction was poured into ice/water and the product extracted into a 1:1 mixture of benzene/hexane. The extract was dried (Na_2SO_4) and filtered through charcoal and the solvent evaporated. This residue (3.7 g) was purified by chromatography on silica gel, eluting with chloroform. Appropriate fractions were combined, the solvent was evaporated, and the residue was triturated with cold hexane to give 2.03 g (13% yield) of crystalline **2-bromo-5-ethylnicotinonitrile**: mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, 1 H, J = 2.5 Hz), 7.77 (d, 1 H, J = 2.5 Hz), 2.69 (AB q, 2 H, J = 7.8 Hz), 1.29 (t, 3 H, J = 7.8 Hz). Anal. ($C_8H_7BrN_2$) C, H, N.

Sodium metal (0.35 g, 15.2 mmol) was dissolved in anhydrous methanol (15 mL) under a nitrogen atmosphere, and then 2-bromo-5-ethylnicotinonitrile (2.02 g, 9.6 mmol) was added. The reaction was warmed at 55 °C for 1 h. After cooling, the reaction was diluted with diethyl ether, and the ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to give 1.52 g (98% yield) of oily **2-methoxy-5-ethylnicotinonitrile**: ^{1}H NMR ($CDCl_3$) δ 8.18 (d, 1 H, J = 2.4 Hz), 7.72 (d, 1 H, J = 2.4 Hz), 4.03 (s, 3 H), 2.62 (AB q, 2 H, J = 7.6 Hz), 1.24 (t, 3 H, J = 7.6 Hz).

A solution of 2-methoxy-5-ethylnicotinonitrile (1.52 g, 9.38 mmol) in dry tetrahydrofuran (6 mL) was added, under a nitrogen atmosphere, to 1 M diisobutylaluminum hydride/tetrahydrofuran (14 mL, 14 mmol) in an ice bath. After stirring for 4 h the yellow solution was poured into 1 N aqueous HCl (20 mL) and extracted with diethyl ether. The ethereal extract was dried (Na_2SO_4), filtered through charcoal, and evaporated. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate/hexane to give 706 mg (45% yield) of purified oily **2-methoxy-5-ethylnicotinaldehyde**: ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1 H), 8.22 (d, 1 H, J = 2.5 Hz), 7.96 (d, 1 H, J = 2.5 Hz), 4.05 (s, 3 H), 2.63 (AB q, 2 H, J = 7.6 Hz), 1.24 (t, 3 H, J = 7.6 Hz).

Preparation of 2-(Benzyloxy)nicotinaldehydes: 2-(Benzyloxy)-5-ethyl-6-methylnicotinaldehyde (63). A mixture of 3-cyano-5-ethyl-6-methylpyridin-2(1*H*)-one (4.86 g, 30 mmol), silver carbonate (9.65 g, 35 mmol), and benzyl bromide (4.2 mL, 35 mmol) in benzene (40 mL) was stirred at room temperature, in the dark and under a nitrogen atmosphere for 20 h. The gray salts were removed by filtration and rinsed with benzene, and the combined filtrate was evaporated. The viscous residue was triturated with hexane to give 7.15 g of impure product. This material was dissolved in benzene and filtered through a short column of silica gel, the solvent was evaporated, and the colorless oil was triturated with hexane to give 6.25 g (82% yield) of analytically pure **2-(benzyloxy)-3-cyano-5-ethyl-6-methylpyridine**: mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1 H), 7.48–7.51 (m, 2 H), 7.32–7.40 (m, 3 H), 5.48 (s, 2 H), 2.56 (AB q, 2 H, J = 7.5 Hz), 2.48 (s, 3 H), 1.19 (t, 3 H, J = 7.5 Hz). Anal. ($C_{16}H_{16}N_2O$) C, H, N.

To a solution of 2-(benzyloxy)-3-cyano-5-ethyl-6-methylpyridine (15.0 g, 59.5 mmol) in dry toluene (200 mL) and cooled to 0 °C, under an inert atmosphere, was added dropwise 1.5 M diisobutylaluminum hydride in toluene (46 mL, 69 mmol). After being stirred for 1 h the reaction mixture was carefully poured into ice-cooled 1.2 N hydrochloric acid (330 mL) and stirred for 2 h. The product was extracted into diethyl ether, dried, and evaporated to give 14.5 g (95% yield) of yellow oily **2-(benzyloxy)-5-ethyl-6-methylnicotinaldehyde**: ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1 H), 7.88 (s, 1 H), 7.48 (d, 2 H, J = 8 Hz), 7.32–7.41 (m, 3 H), 5.51 (s, 2 H), 2.59 (AB q, 2 H, J = 7.5 Hz), 2.50 (s, 3 H), 1.21 (t, 3 H, J = 7.5 Hz). This material was not purified further.

Via the same procedure, **2-(benzyloxy)-5-phenyl-6-methylnicotinaldehyde** was prepared from 5-phenyl-6-methylnicotinonitrile[15] in 66% overall yield as a white solid: mp 78–79 °C; ^{1}H NMR ($CDCl_3$) δ 10.44 (s, 1 H), 7.72 (s, 1 H), 7.53 (d, 2 H, J = 7.5 Hz), 7.35–7.50 (m, 6 H), 7.26–7.31 (m, 2 H), 5.55 (s, 2 H), 2.47 (s, 3 H). Anal. ($C_{20}H_{17}NO_2$) C, H, N.

2-(Benzyloxy)-5-(aminocarbonyl)-6-methylnicotinaldehyde. A mixture of ethyl 3-cyano-6-methyl-2-oxo-1-pyridine-5-carboxylate[16] (6.18 g, 30 mmol), benzyl bromide (6.16 g, 36 mmol), and silver carbonate (9.09 g, 33 mmol) in benzene (100 mL) was stirred overnight at room temperature in the dark. Filtration, followed by evaporation, gave a solid residue which was slurried with hexane and filtered to give 7.67 g (88% yield) of **ethyl 6-(benzyloxy)-5-cyano-2-methylnicotinate**: mp 130–133 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1 H), 7.49 (dd, 2 H, J = 1.5, 8 Hz), 7.30–7.40 (m, 3 H), 5.57 (s, 2 H), 4.36 (AB q, 2 H, J = 7.2 Hz), 2.83 (s, 3 H), 1.39 (t, 3 H, J = 7.2 Hz). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

A mixture of ethyl 6-(benzyloxy)-5-cyano-2-methylnicotinate (5.92 g, 20 mmol) and 1.0 N sodium hydroxide (21 mL, 21 mmol) in ethanol (125 mL) was stirred under argon overnight. The clear solution was evaporated to dryness under vacuum to give the intermediate sodium carboxylate (5.97 g). To a suspension of this sodium salt (5.97 g, 21 mmol) in tetrahydrofuran, cooled in an ice–acetone bath, was added dropwise isobutyl chloroformate (3.09 g, 23 mmol). The mixture was stirred overnight at room temperature and then added rapidly dropwise to an ice-cold solution of tetrahydrofuran (80 mL) which had been saturated with ammonia gas. The mixture was allowed to warm to room temperature and then stirred for an additional 2 h. Evaporation afforded a solid residue which was partitioned between chloroform and water. After the chloroform solution was washed with water and then brine, it was evaporated to give 3.81 g (69%) of **2-(benzyloxy)-5-(aminocarbonyl)-6-methylnicotinonitrile**: mp 160–162 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 7.49 (d, 2 H, J = 6.3 Hz), 7.30–7.41 (m, 3 H), 5.55 (s, 2 H), 2.72 (s, 3 H).

To a mixture of 2-(benzyloxy)-5-(aminocarbonyl)-6-methylnicotinonitrile (909 mg, 3.4 mmol) in toluene (50 mL), cooled in an ice–acetone bath, was added dropwise 1.5 M diisobutylaluminum hydride in toluene (5.0 mL, 7.5 mmol). After stirring for 2 h the reaction mixture was quenched into a mixture of ice and excess 1 N hydrochloric acid. The product was extracted into ethyl acetate which was then washed well with water, saturated aqueous sodium bicarbonate, and brine. After drying, evaporation of solvent gave 640 mg (70% yield) of **2-(benzyloxy)-5-(aminocarbonyl)-6-methylnicotinaldehyde**, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1 H), 8.22 (s, 1 H), 7.48 (dd, 2 H, J = 2.1, 7.5 Hz), 7.35–7.42 (m, 3 H), 5.58 (s, 2 H), 2.75 (s, 3 H).

2-(Benzyloxy)-5-(dimethylamino)-6-methylnicotinaldehyde. A mixture of 3-cyano-5-nitro-6-methylpyridin-2(1*H*)-one[17] (1.47 g, 8.0 mmol), benzyl bromide (1.55 g, 9.0 mmol), and silver carbonate (2.56 g, 9.0 mmol) in benzene (100 mL) was stirred overnight under nitrogen. After removal of silver salts by filtration and evaporation of the filtrate, there was obtained 2.27 g of crude product. This residue was purified by chromatography on silica gel and eluted with 50–80% methylene chloride/hexane to give 1.95 g (88% yield) of crystalline **2-(benzyloxy)-5-nitro-6-methylnicotinonitrile**: mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H), 7.49 (dd, 2 H, J = 1.5, 8 Hz), 7.32–7.42 (m, 3 H), 5.61 (s, 2 H), 2.90 (s, 3 H). Anal. ($C_{14}H_{12}N_3O_3$) C, H, N.

A mixture of 2-(benzyloxy)-5-nitro-6-methylnicotinonitrile (1.10 g, 4.1 mmol) and platinum oxide (0.10 g) in ethanol–THF (80 mL, 1:1) was stirred under an atmosphere of hydrogen gas for 1 h. After filtration, the filtrate was evaporated to give 0.995 g (100% yield) of brown, crystalline **2-(benzyloxy)-5-amino-6-methylnicotinonitrile**: ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 2 H, J = 7.2 Hz), 7.29–7.39 (m, 4 H), 5.43 (s, 2 H), 2.43 (s, 3 H). This material was used as is.

To a mixture of 2-(benzyloxy)-5-amino-6-methylnicotinonitrile (0.995 g, 4.1 mmol) in acetonitrile (50 mL) was added sodium cyanoborohydride (1.00 g, 16 mmol), 37% aqueous formaldehyde (2.09 mL, 25.6 mmol), and acetic acid (0.88 mL, 15 mmol). After stirring overnight, chloroform was added as well as a few drops of acetic acid to decompose excess sodium cyanoborohydride. The chloroform solution was washed with water, saturated aqueous $NaHCO_3$, and brine and then evaporated to afford 1.04 g of crude product. This material was purified by chromatography on silica gel and eluted with 50–80% methylene chloride/hexane to give 675 mg (62%) of crystalline **2-(benzyloxy)-5-(dimethylamino)-6-methylnicotinonitrile**: mp 65–68 °C; ^{1}H NMR

($CDCl_3$) δ 7.51 (s, 1 H), 7.49 (d, 2 H, J = 6.6 Hz), 7.30–7.40 (m, 3 H), 5.46 (s, 2 H), 2.64 (s, 6 H), 2.51 (s, 3 H). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

2-(Benzyloxy)-5-(dimethylamino)-6-methylnicotinonitrile (534 mg, 2.0 mmol) was reduced with diisobutylaluminum hydride by the procedure described to afford 484 mg (90%) of oily **2-(benzyloxy)-5-(dimethylamino)-6-methylnicotinaldehyde**: ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1 H), 7.81 (s, 1 H), 7.48 (dd, 2 H, J = 1.5, 7.8 Hz), 7.30–7.40 (m, 3 H), 5.49 (s, 2 H), 2.66 (s, 6 H), 2.54 (s, 3 H).

2-(Benzyloxy)-5-isopropenyl-6-methylnicotinaldehyde. A mixture of 3-cyano-5-acetyl-6-methylpyridin-2(1*H*)-one[18] (18 g, 102 mmol), benzyl bromide (12.1 mL, 102 mmol), and silver carbonate (28.1 g, 102 mmol) in benzene (500 mL) was protected from light and stirred under argon overnight. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel. Elution with $CHCl_3$ gave 25 g (94% yield) of **2-(benzyloxy)-3-cyano-5-acetyl-6-methylpyridine**: mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1 H), 7.49 (d, 2 H, J = 7.2 Hz), 7.36–7.39 (m, 3 H), 5.57 (s, 2 H), 2.77 (s, 3 H), 2.56 (s, 3 H). Anal. ($C_{16}H_{14}N_2O_2$) C, H, N.

2-(Benzyloxy)-3-cyano-5-acetyl-6-methylpyridine (10 g, 37.5 mmol) was added to a solution prepared from triphenylmethylphosphonium iodide (15.3 g, 37.9 mmol) and 1.6 M *n*-butyllithium in hexane (23.7 mL, 37.9 mmol) in THF (190 mL) at ambient temperature and stirred overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel. Elution with chloroform gave 3.0 g (30% yield) of pure **2-(benzyloxy)-5-isopropenyl-6-methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1 H), 7.50 (d, 2 H, J = 7.8 Hz), 7.35–7.49 (m, 3 H), 5.50 (s, 2 H), 5.27 (s, 1 H), 4.90 (s, 1 H), 2.49 (s, 3 H), 2.01 (s, 3 H).

2-(Benzyloxy)-5-isopropenyl-6-methylpyridine (0.80 g, 1.7 mmol) was reduced with isobutylaluminum hydride as described herein to give 270 mg (33%) of **2-(benzyloxy)-5-isopropenyl-6-methylnicotinaldehyde** as an oil: ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1 H), 7.68 (s, 1 H), 7.48 (d, 2 H, J = 7.5 Hz), 7.25–7.39 (m, 3 H), 5.53 (s, 2 H), 5.25 (s, 1 H), 4.90 (s, 1 H), 2.52 (s, 3 H), 2.03 (s, 3 H).

2-(Benzyloxy)-5-(hydroxymethyl)-6-methylnicotinaldehyde. To a solution of ethyl 6-(benzyloxy)-5-cyano-2-methylnicotinate (2.96 g, 10 mmol) in toluene (100 mL), cooled in an ice/acetone bath (−12 °C), under nitrogen, was added dropwise 1 M diisobutylaluminum hydride in toluene (34 mL, 34 mmol). After 1 h, the reaction was quenched by dropwise addition of 1 N HCl (30 mL). The reaction was extracted with chloroform, and the extract was dried, filtered, and evaporated to give 2.54 g (99% yield) of oily **2-(benzyloxy)-5-(hydroxymethyl)-6-methylnicotinaldehyde**: ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1 H), 8.07 (s, 1 H), 7.46–7.50 (m, 2 H), 7.32–7.41 (m, 3 H), 5.53 (s, 2 H), 4.68 (br s, 2 H), 2.54 (s, 3 H). No further purification was performed.

2-Amino-5-ethyl-6-methylnicotinaldehyde. A solution of 2-chloro-3-cyano-5-ethyl-6-methylpyridine[2a] (5.00 g, 27 mmol) and sodium azide (2.25 g, 34 mmol) in DMF (250 mL) was heated under nitrogen at 95 °C for 5 h. The reaction was cooled, diluted with water, and extracted with ethyl acetate. The organic phase was washed with water and saturated brine, dried over $MgSO_4$, and then filtered through a charcoal pad, and the solvent was evaporated. The crude product was recrystallized from 1:1 ethyl acetate/hexane to obtain **2-azido-3-cyano-5-ethyl-6-methylpyridine** as light tan crystals (1.63 g, 31% yield): mp 117–119 °C; ^{1}H NMR (DMSO-d_6) δ 8.58 (s, 1 H), 2.93 (s, 3 H), 2.81 (AB q, 2 H, J = 7 Hz), 1.20 (t, 3 H, J = 7 Hz).

Tin(II) chloride dihydrate (2.94 g, 13 mmol) was suspended in toluene (60 mL) and cooled to 0 °C under nitrogen. Thiophenol (4.01 mL, 39 mmol) and triethylamine (5.46 mL, 39 mmol) were added, and the bright yellow solution was stirred at 20 °C for 0.5 h.[19] A solution of 2-azido-3-cyano-5-ethyl-6-methylpyridine (1.63 g, 8.7 mmol) in toluene (90 mL) was added over a period of 10 min. The reaction was stirred at 20 °C for 1.5 h, and then 5% NaOH was added and stirring continued for 5 min. The reaction was extracted with ethyl acetate. The organic phase was washed with 10% HCl, and the aqueous extract was rendered basic and extracted with ethyl acetate. The organic phase was dried, and **2-amino-3-cyano-5-ethyl-6-methylpyridine** was obtained as a light yellow solid (1.00 g, 71% yield): mp 206–207 °C; ^{1}H NMR (DMSO-d_6) δ 7.56 (s, 1 H), 6.54 (br s, 2 H), 2.44 (AB q, 2 H, J = 7 Hz), 2.30 (s, 3 H), 1.08 (t, 3 H, J = 7 Hz).

A solution of 2-amino-3-cyano-5-ethyl-6-methylpyridine (0.990 g, 6.15 mmol) in dry toluene (100 mL) was cooled to −10 °C under nitrogen, and a solution of diisobutylaluminum hydride in toluene (1 M solution, 13.5 mL) was added slowly via syringe. After 1.5 h, the reaction was quenched with 10% HCl (20 mL) and stirred at 0 °C for 0.5 h. After extractive workup with ethyl acetate, the crude product was obtained as a pale yellow solid (1.1 g). NMR indicated the crude product was a 3:2 mixture of aldehyde and nitrile, which could not be resolved on TLC. The crude product was taken up in ethyl acetate and washed thrice with 10% $NaHSO_3$ adjusted to pH 7 with dilute NaOH. The combined aqueous phases were back extracted with ethyl acetate and then acidified to pH <1. After 20 min, the aqueous-phase pH was rendered basic and the desired aldehyde extracted with ethyl acetate. After washing with brine and drying over $MgSO_4$, the solvent was evaporated to give **2-amino-5-ethyl-6-methylnicotinaldehyde** (440 mg, 43%) as a pale yellow powder: mp 159–160 °C; ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 1 H), 7.71 (s, 1 H), 7.32 (br s, 2 H), 2.50 (AB q, 2 H, J = 7 Hz), 2.34 (s, 3 H), 1.14 (t, 3 H, J = 7 Hz). Anal. ($C_9H_{12}N_2O$) C, H, N.

Hydrolysis Studies in 0.1 N HCl. The half-lives ($t_{1/2}$) were determined for compounds **9**, **21**, **40**, **2**, **35**, **36**, and **37** in 90% ethanol, 10% 1.0 N HCl to ensure solubility and to maintain a 0.1 N HCl concentration. Stock solutions (1 mM) of each compound were prepared in ethanol and thermally equilibrated at 37 °C. The hydrolysis was initiated by the addition of an aliquot (100 μL) of stock solution to an efficiently stirred thermostated (37 °C) solution of ethanol (8.9 mL) and 1 N HCl (1.0 mL). At appropriate time intervals 100-μL aliquots were withdrawn and quenched into 200 μL of a pH 7.7 0.1 M MES (2-(*N*-morpholino)ethanesulfonic acid) buffer to neutralize the reaction before analysis by HPLC. Each half-life was calculated from duplicate hydrolysis determinations, using HPLC peak area vs time data for both the disappearance of the starting compound and the appearance of its product. Thus each half-life is the average of four values. The data are tabulated in Table IV.

Independently, the hydrolysis products were obtained on a larger scale either by hydrolysis in 10% HCl (**68**, **70**, **71**) or isolation as byproducts from the pyridine hydrochloride demethylation reactions (**68**, **69**, **72**). HPLC retention times and/or NMR spectra were used to confirm the identities of the products from kinetic studies. The following products were characterized. ***N*-(2-Hydroxyphenyl)-3-(6-methyl-5-ethyl-2-oxo-1*H*-pyridin-3-yl)propionamide (68)**: mp 229–230 °C; ^{1}H NMR ($CDCl_3$) δ 9.51 (br s, 1 H), 7.58 (s, 1 H), 7.52 (dd, 1 H, J = 1.4, 7.8 Hz), 6.98 (dt, 1 H, J = 1.4, 6.8 Hz), 6.88 (dd, 1 H, J = 1.4, 8.1 Hz), 6.78 (dt, 1 H, J = 1.4, 7.8 Hz), 2.89 (t, 2 H, J = 7.2 Hz), 2.76 (t, 2 H, J = 7.2 Hz), 2.40 (AB q, 2 H, J = 7.7 Hz), 2.33 (s, 3 H), 1.09 (t, 3 H, J = 7.7 Hz). Anal. ($C_{17}H_{20}N_2O_3 \cdot 0.35H_2O$) C, H, N.

For hydrolysis product **69**, see preparation of **21**.

***N*-(2-Hydroxyphenyl)[(6-methyl-5-ethyl-2-oxo-1*H*-pyridin-3-yl)amino]acetamide (70)**: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 9.38 (br s, 1 H), 9.14 (s, 1 H), 8.00 (d, 1 H, J = 7.2 Hz), 6.72–6.97 (m, 3 H), 6.16 (s, 1 H), 3.90 (s, 2 H), 2.32 (AB q, 2 H, J = 7.2 Hz), 2.14 (s, 3 H), 1.04 (t, 3 H, J = 7.2 Hz).

***N*-(4,6-Dichloro-2-hydroxyphenyl)[(6-methyl-5-ethyl-2-oxo-1*H*-pyridin-3-yl)amino]acetamide (71)**: mp 267–268 °C; ^{1}H NMR (DMSO-d_6) δ 9.60 (s, 1 H), 7.38 (d, 1 H, J = 0.9), 7.06 (d, 1 H, J = 0.9 Hz), 6.18 (s, 1 H), 3.93 (s, 2 H), 2.34 (AB q, 2 H, J = 7.2 Hz), 2.11 (s, 3 H), 1.09 (t, 3 H, J = 7.2 Hz). Anal. ($C_{16}H_{17}Cl_2N_3O_3$) C, H, N.

***N*-(2-Hydroxyphenyl)[(6-methyl-5-ethyl-2-oxo-1*H*-pyridin-3-yl)oxy]acetamide (72)**: ^{1}H NMR ($CDCl_3$) δ 9.47 (br s, 1 H), 7.85 (d, 1 H, J = 8.4 Hz), 6.99 (overlapping singlet and triplet, 2 H), 6.90 (d, 1 H, J = 8.4 Hz), 6.81 (t, 1 H, J = 7.2 Hz), 4.64 (s, 2 H), 2.38 (AB q, 2 H, J = 7.7 Hz), 2.20 (s, 3 H), 1.11 (t, 3 H, J = 7.7 Hz).

Human Plasma Protein Binding Measurements. The affinity of selected compounds for human plasma diluted 10-fold in pH 7.4 buffer is represented by the measured compound–plasma equilibrium dissociation constant (K_D). From this value one may also calculate the percentage of a compound which would be unbound (free) in the presence of whole human plasma in the limit of very low compound concentration. These data are listed

in Table V. The compound is dissolved in DMSO (1 mM), and 50 μL of this solution is added to 4.5 mL of pH 7.4 buffer (prepared by dissolving 1.86 g of NaH_2PO_4, 7.58 g of Na_2HPO_4, and 4.40 g of NaCl in water diluted to 1 L with the pH adjusted appropriately to 7.4) and human plasma (450 μL). An aliquot (1 mL) of this solution, in triplicate, was placed in Centrifee filtered centrifuge tubes and centrifuged for 8 min at 3000 rpm using a Sorvall SM24 rotor, and the supernatant was analyzed on a Hewlett-Packard HP 1090 HPLC at the appropriate wavelength. The dissociation constant (K_D) was calculated from $[C_f(HP_d - C_i + C_f)]/(C_i - C_f)$ where C_f is the average final compound concentration, C_i is the initial compound concentration (10 μM), and HP_d is the diluted human plasma concentration assumed to be 58 μM. The percent unbound or free compound is calculated for whole human plasma from $100(1 - [HP/(HP + K_D)])$ where HP is the concentration of whole human plasma (assumed to be 580 μM).

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