4-Benzyl- and 4-Benzoyl-3-dimethylaminopyridin-2(1*H*)-ones, a New Family of Potent Anti-HIV Agents: Optimization and in Vitro Evaluation against Clinically Important HIV Mutant Strains

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The 4-benzyl and 4-benzoyl-3-dimethylaminopyridinones **13** and **14** are representatives of a new class of highly potent non nucleoside type inhibitors of HIV-1 reverse transcriptase. To conduct SAR studies on these two lead compounds, 102 new analogues were prepared. Thirty-three compounds displayed nanomolar range activity in vitro against wild-type HIV-1, and among these, 18 were active against the 103N, Y181C, and Y188L mutant strains with IC_{50} values inferior to 1 μM. Evaluation of this group of analogues against an additional eight single [100I, 101E, 106A, 138K, 179E, 190A, 190S, 227C] and four double HIV mutant strains [100I + 103N, 101E + 103N, 103N + 181C, and 227L + 106A], which are often present in HIV infected patients, permitted the selection of eight compounds, **17x**, **18b**, **18c**, **18f**, **18g**, **27**, **30**, and **42**, which are globally more active than the lead molecules **13**/**14**, emivirine and the currently used NNRTI, nevirapine. Further comparison of the 3′-CN-substituted benzoylpyridinone compound **18c**, and the corresponding 3′-acrylonitrile-substituted analogue **30**, to efavirenz, the reference molecule in anti-HIV therapy today, revealed that the pyridinone analogues displayed a superior inhibition profile in the in vitro cellular assay system. These results form a solid basis for continued optimization of the pyridinone series.

Introduction

Combination therapy, or HAART (highly active antiretroviral therapy) has become the standard in HIV treatment. Indeed, employing this strategy spectacular advances have been made for the control of viral levels in HIV-infected patients.[1−3] Thus, in developed countries, and hopefully *soon* for the more than 30 million people in third-world countries contaminanted by HIV, one can begin to consider HIV infection to be "chronic" rather than forcibly fatal.

Combination therapy has for the most part involved the coadministration of nucleoside reverse transcriptase inhibitors (NRTI's) and protease inhibitors (PI's). However, over the past several years increasing use is being made of non nucleoside reverse transcriptase inhibitors (NNRTI's) in multiple drugs regimens[4] in order to circumvent the serious problems of toxicity, resistance, and associated side effects (lipodystrophy, hyperlipidaemia, etc.) resulting from prolonged use of NRTI + PI combinations.[5−9] Currently, three NNRTI-type inhibitors, nevirapine **1**, delavirdine **2**, and efavirenz **3** are used in clinic.[10] These compounds are noncompetitive inhibitors of RT, binding into a hydrophobic pocket in the polymerase which is proximal to the catalytic site.[11−14] NNRTI's, in general, display lower toxicity than nucleoside-based anti-HIV agents.[15,16] However, as the residues in the hydrophobic binding region are not implicated in DNA synthesis, resistance develops rapidly to this family of molecules.[17−21] Indeed, a single point mutation can result in cross resistance between compounds **1**−**3**, precluding, in situations where treatment failure occurs, new regimens where these drugs are interchanged.[22] There is thus a pressing need to develop new NNRTI type drugs which display a high level of activity against the clinically relevant HIV single and multiple mutant strains, and whose pharmacokinetic/distribution profile are such that lower doses (single dose per day) are required.

Over 30 different families of NNRTI's have been developed over the past 14 years.[10,23] The marked structural diversity that is displayed by these molecules, which in turn reflects a remarkable capacity of the hydrophobic pocket to accommodate different structural types, would suggest that there is still a good deal of opportunity to discover new highly potent non nucleoside RT inhibitors. Promising new molecules in the NNRTI group, which are currently undergoing clinicalevaluation, include DPC 083 **4**,[24] TMC125 **5**,[25] AG1549 **6**,[26] and GW8248 **7**.[27]

A contribution from our laboratories was the finding that arylthiopyridinones/benzylpyridinones of general

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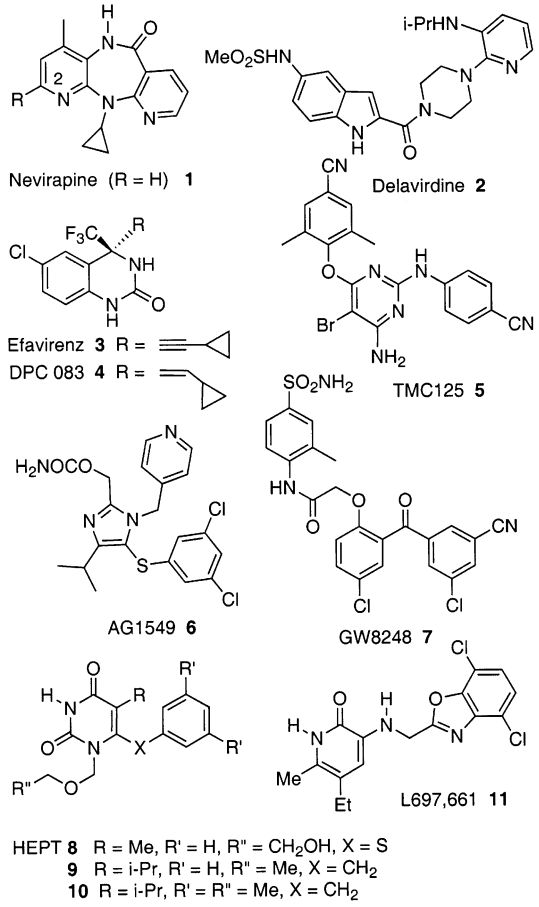
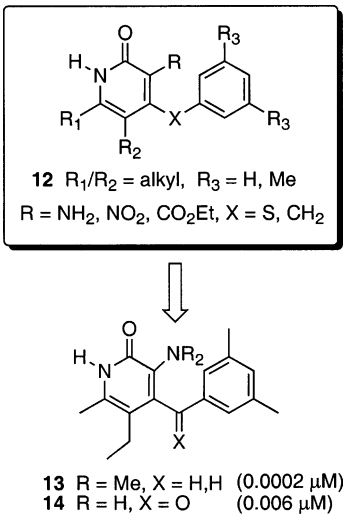


formula **12** are potent inhibitors of wild-type HIV.[28,29] Compounds **12** are in many respects hybrids of HEPT **8**[30−34] and the Merck pyridinone **11**,[35−39] since they possess the SAr/CH_2Ar group of the HEPT's and pyridinone motif of the latter.[29] The more active analogues in this series inhibit wild-type HIV-1 at nanomolar concentrations (IC_{50}'s), and recently it has been shown they may be useful as retrovirocides.[40] Preliminary SAR studies led to the identification of analogues **13** and **14** as lead compounds. Common to both of these molecules is the presence of the 5-ethyl and 6-methyl substitutuents on the pyridinone ring, and the 3,5-dimethyl substitution on the aromatic ring.



In light of the fact that development of HEPT **8**, the more recent HEPT analogue **9** (emivirine),[34] and pyridinone **11** was abandoned[22] due to the rapid appearance of drug resistant strains bearing the Y181C,[18] Y188L and K103N[20,41] mutations, a major challenge to the further optimization of compounds **13**/**14** is to find analogues which maintain potent activity against these principle mutants. As it is phenyl ring in HEPT which has been shown to interact with these residues in the hydrophobic pocket,[42] our efforts in the pyridinone series has been directed toward evaluation of the influence of aryl ring modifications in the C-4 benzyl/benzoyl substituent in **13** and **14** on anti-HIV activity in in vitro cell-based assays. Support for this strategy comes from the observation that the 3′,5′-dimethyl-substituted HEPT analogue GCA-186 **10** is more than 100 times more active in vitro against the Y181C mutant (IC_{50} = 0.18 μM) than HEPT itself.[43] At the molecular level, structural studies on the complex of GCA-186 with wild-type RT suggest that the two methyl substituents make additional hydrophobic contact with the residues in the binding pocket and in particular with the side chain of Trp229.[43] This results in the compound deriving a smaller fraction of its binding energy from the interaction with the Tyr181 side chain.

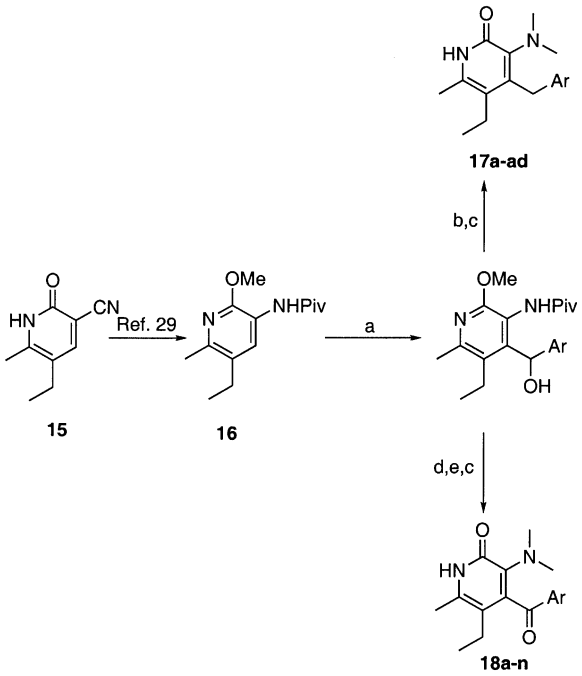
In this report we thus present the anti-HIV activity in cell-based assays of 102 new aryl ring-modified pyridinone analogues against wild-type HIV (HVTL IIIB) and the Y181C, Y188L, and K103N mutant strains (Tables 1−4). Eight compounds **17x**, **18b**, **18c**, **18f**, **18g**, **27**, **30**, and **42** were selected from this series and further evaluated (Table 5) against a larger panel of HIV mutants including 100I, 101E, 106A, 138K, 179E, 190A, 190S, and 227C, and the four double mutants, 100I + 103N, 101E + 103N, 103N + 181C, and 227L + 106A. Compounds **18c**, **27**, **30**, and **42** in particular, bearing a cyano substituent connected either directly to the phenyl ring or via an acrylonitrile type motif proved to be highly active against essentially the entire panel of HIV mutants, displaying an activity profile which is globally better than that for efavirenz and very considerably improved over that for emivirine and the currently employed NNRTI nevirapine.

Chemistry

The preparation of the 4-arylmethylpyridinones **17a**−**y** and the 4-arylketopyridinones **18a**−**k** (Scheme 1; Table 1) involved conversion of 3-cyano-5-ethyl-6-methylpyridin-2(1*H*)-one **15**[44] to the 3-pivaloylaminopyridine **16** (six steps on a 20 g scale), and reaction of the ortho-metalated species generated from this intermediate with the requisite benzaldehyde derivative.[45] Reaction of the derived carbinol with $SnCl_2 \cdot 2H_2O$[46] proved to be a very effective means to achieve reductive cleavage of the benzylic hydroxyl group and both amide and imidate hydrolysis in a single operation. The derived amines were subsequently converted in high yields to the corresponding 3-dimethylamino-substituted compounds **17** under reductive alkylation conditions (HCHO, $NaBH_3CN$). Compounds **18** were obtained by MnO_2 oxidation of the carbinol intermediate followed by treatment of the intermediate ketone with 3 N HCl and reductive alkylation.

In an identical fashion, analogues **17z**−**ad**, and **18l**−**n** (Table 2) wherein the aryl ring in the lead compounds

Scheme 1[a]



[a] Conditions: (a) *n*-BuLi, TMEDA, THF, Aryl-CHO; (b) $SnCl_2 \cdot 2H_2O$; (c) $(HCHO)_n$, Na,BH_3CN, AcOH; (d) MnO_2, toluene; (e) 3 N HCl.

13/**14** was exchanged for a thiazolyl, imidazolyl, indolyl, pyridyl, quinolyl, thienyl, and furyl motif were prepared by condensation of the anion of **16** with the appropriate heterocyclic carboxaldehyde.

To expand the study of the influence of a 3′-nitrogen substituent on the aromatic ring beyond the dimethylamino and nitro analogues **18k** and **18e**, the nitro group in **18e** was reduced under Raney Ni-catalyzed hydrogenation conditions and amine **19** was converted to compounds **20a**−**f** (Scheme 2, Table 1) by reaction, respectively, with $MeCHO/NaBH_3CN$, MeCOCl, MsCl, EtNCO, 4-chlorobutyryl chloride/*t*-BuOK, and 2,5-dimethoxytetrahydrofuran. In addition, the cyano group in **18c** was reduced using Raney Ni/H_2 giving the methylamine analogue **21**, and the corresponding acetamide **22** (after treatment with AcCl) (Scheme 3).

Using the 3′-bromo analogue **18b** as starting material for a series of Stille coupling reactions compounds **23a**−**e** containing a phenyl, 2-furyl, 2-thiazolyl, 3-pyridyl, and phenylethynyl substituent at the 3′-position of the aryl ring were readily prepared (Scheme 3; Table 1). A Pd(0)-catalyzed coupling reaction was also used to prepare the *Z*-configuration acrylonitrile-substituted analogue **24** (6% isolated yield) from **18b** and acrylonitrile. In view of the interesting activities displayed by this compound, the corresponding *E*-acrylonitriles **27** and **30**, as well as the more substituted analogues **35a**−**f**, **42**, **48** and acrylates **31**, **32**, were subsequently prepared (Scheme 4, 5; Tables 1, 3, and 4).

To prepare **27**, the dioxalane **25**, obtained by orthometalation of **16** and condensation with the monodioxalane of 1,3-phenyldicarboxaldehyde,[47] was treated with $SnCl_2 \cdot 2H_2O$, and the derived free amine was N,N-dimethylated to give compound **26**. This intermediate was then reacted with diethyl cyanomethylphosphonate. To access analogue **30**, compound **25** was oxidized to **28** and treated with 3 N HCl, and the liberated aldehyde function in **29** was engaged in the Wittig−Horner reaction with diethyl cyanomethylphosphonate to give a product which was further treated with 6 N HCl and N,N-dimethylated. In an analogous fashion the acrylate analogue **31**, the diene ester **32**, and compounds **35a** and **35d**−**f** were prepared by reaction of aldehyde **29** with the appropriate phosphonate reagent. Note that for the acrylate analogues **31** and **32** a resesterification step was required since selective *N*-pivaloyl/*O*-methyl imidate hydrolysis was not achieved. The unsubstituted styrene **34** was also obtained via a Wittig type reaction of aldehyde **33**, whereas acrylonitrile analogues **35b**,**c** were more simply accessed by a Knoevenagel condensation of **33** with malononitrile and ethyl cyanoacetate, respectively. The acrylonitrile analogues **42** and **43** bearing a methyl substitutent on the β-carbon were also prepared starting from the ketone analogue **41** via a Wittig−Horner reaction (Scheme 5).

To further complete the study of the influence of different styrene motifs on the anti-HIV activity of our pyridinones, aldehyde **29** was converted in three steps to the phosphonium salt intermediate **38** and condensed under Wittig conditions with several aliphatic aldehydes, benzaldehyde, and a range of heterocyclic aldehydes giving analogues **39a**−**u** (Table 3). Note that when *Z*/*E*-isomeric mixtures were formed, the *E* and *Z* isomers were obtained pure after column chromatography.

Compounds **44** and **45**, wherein the cyano substituent was separated from the aromatic ring by a two-carbon linker, were readily obtained by catalytic hydrogenation of the double bond in acrylonitriles **30** and **35a** (Scheme 6). The corresponding compounds **48** and **49** with a one-carbon linker were prepared by OH → Cl → CN exchange starting from **36**, and either direct treatment of **46** with hydrochloric acid and subsequent reductive amination, or alkylation of the anion of **46** with MeI prior to the hydrolysis and N,N-dimethylation steps (Scheme 7). Finally, analogues **50** and **51** were prepared by Mitsunobu reaction of **36** with phenol, and reaction of **29** with MeMgI (Scheme 8).

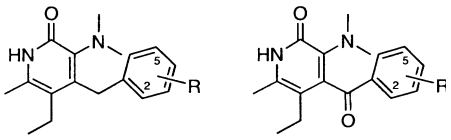
Results and Discussion

The pyridinone analogues described in Schemes 1−8 were evaluated in vitro against wild type HIV (HVTL IIIB, LAI cell line) and against the three principle mutant strains, 103N, 181C, and 188L, which confer resistance to the NNRTI's currently used in clinic.[48] The results are presented in Tables 1−5.

As the data shows, out of the 102 compounds that were tested, 67 displayed activity with an IC_{50} value inferior to 0.1 μM against wild-type HIV, and of these, 33 are active at nanomolar range concentrations. To select the most interesting molecules in this group their activities against the three mutant strains were compared.

Looking first at the data for the compounds in Table 1, one sees that the parent 4-benzylpyridinone **17a** (IC_{50} = 0.004 μM) is equipotent to both lead molecules **13** and **14** against wild type HIV and in fact has a better selectivity index (SI). However, it was poorly active against the 188L mutant. Sub-micromolar activities against wild-type HIV were observed for the mono-

Table 1. Activity (IC_{50}, μM) versus HIV-1



		IC_{50} (μM)							IC_{50} (μM)				
compd	R	LAI	SI[a]	103N	181C	188L	compd	R2	LAI	SI[a]	103N	181C	188L
13	3,5-CH_3	0.008	12589	0.032	0.1	0.251	**18a**	3-CH_3	0.002	39811	nd	nd	1.995
17a	H	0.004	25119	0.200	0.501	7.943	**18b**	3-Br	0.002	12589	0.02	0.158	0.794
17b	2-CH_3	0.025	3981	1.259	1	7.943	**18c**	3-CN	0.002	6310	0.006	0.04	0.398
17c	3-CH_3	0.002	39881	0.02	0.06	1	**18d**	4-CN	3.162	32	nd	nd	nd
17d	4- CH_3	0.316	316	12.59	10	nd	**18e**	3-NO_2	0.002	39611	0.02	0.2	3.162
17e	3-CF_3	0.010	10000	0.398	0.03	5.012	**18f**	3,5-CH_3	0.004	2512	0.01	0.063	0.158
17f	4- CF_3	1.585	6	10	10	nd	**18g**	3,5-Cl	0.002	5012	0.013	0.032	0.316
17g	4-C_6H_5	3.980	3	10	10	nd	**18h**	2,6-F	0.050	1995	nd	nd	nd
17h	2-Cl	0.006	15894	0.398	0.2	0.794	**18i**	3-F-5-CF_3	0.003	31623	nd	nd	nd
17i	2-Br	0.006	15894	0.251	0.130	1.995	**18j**	3-CH_3−4-OCH_3	0.079	200	1.585	100	100
17j	3-F	0.002	39811	0.063	0.16	1.585	**18k**	3-$N(CH_3)_2$	0.398	251	nd	nd	nd
17k	3-Cl	0.005	19953	0.04	0.08	1.585	**19**	3-NH_2	0.012	2512	0.501	10	10
17l	3-Br	0.004	25119	0.100	0.006	2.512	**20a**	3-$N(C_2H_5)_2$	1.995	50	nd	nd	nd
17m	4-Cl	0.199	50	nd	6.31	nd	**20b**	3-$NHCOCH_3$	0.126	794	nd	nd	nd
17n	4-Br	1.585	63	nd	nd	nd	**20c**	3-$NHSO_2CH_3$	1	100	nd	nd	nd
17o	3-OCH_3	0.004	12589	0.1	0.320	0.316	**20d**	3-$NHCONHC_2H_5$	1.995	50	nd	nd	nd
17p	3-OC_2H_5	0.013	794	nd	nd	nd	**20e**	3-(1-pyrrolidinyl-2-one)	0.040	2512	nd	nd	nd
17q	4-$N(CH_3)_2$	1.259	8	10	10	nd	**20f**	3-(1-pyrrolyl)	0.079	631	nd	nd	nd
17r	2,3-CH_3	0.100	200	2.512	2.512	nd	**21**	3-CH_2NH_2	0.398	251	nd	nd	nd
17s	2,5-CH_3	0.159	631	1.995	nd	nd	**22**	3-$CH_2NHCOCH_3$	0.398	251	nd	nd	nd
17t	3,4-CH_3	0.040	2512	1	0.4	nd	**23a**	3-C_6H_5	0.398	251	nd	nd	nd
17u	2,4-CH_3	10	10	100	100	nd	**23b**	3-(2-furyl)	0.063	158	nd	nd	nd
17v	2,4,6-CH_3	10	1	10	10	nd	**23c**	3-(2-thiazolyl)	0.251	40	nd	nd	nd
17w	3,5-F	0.013	7943	0.032	0.1	0.501	**23d**	3-(3-pyridyl)	0.006	126	0.05	10	10
17x	3,5-Cl	0.008	3981	0.025	0.160	0.631	**23e**	3-phenylethinyl	0.158	631	nd	nd	nd
17y	3-CH_3-4-OCH_3	0.398	251	nd	nd	nd	**33**	3-CHO	0.008	2512	0.126	1.259	10
27	3-CH=CHCN (*E*)	0.0004	25119	0.002	0.016	0.158	**37**	3-CH_2OH	0.050	2936	0.364	3.873	18.64
							41	3-$COCH_3$	0.010	3162	0.126	1.0	10
							48	3-CH_2CN	0.001	31623	0.006	0.126	1.0
							49	3-$CH(CH_3)CN$	0.003	31623	0.008	0.126	0.251
							50	3-CH_2OPh	0.039	2512	nd	nd	nd
							51	3-$CH(OH)CH_3$	0.050	1995	nd	nd	nd

[a] Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold).

methyl-substituted analogues **17b**−**d** and **18a** (IC_{50}'s = 0.316 to 0.002 μM), but only the 3′-Me compound **17c** retained acceptable activity (IC_{50} = 1 μM) toward the 188L mutant. Interestingly, with respect to wild-type HIV, the 2′-Cl- and 2′-Br-substituted analogues **17h** and **17i** were found to be equipotent to the 3′-halo-substituted analogues **17j**, **17k** and **17l**/**18b**. On further evaluation, however, the 2′-Cl compound **17h** (SI = 15894) and the 3′-Br-substituted benzoylpyridinone **18b** were the only compounds that retained activity against all three mutant strains. Of the remaining 3′-substituted analogues **17o**, **18c**, **18e**, **23d**, **27**, **48** and **49** bearing monosubstitution on the phenyl ring, the cyano compound **18c** and the 3′-CH_2(Me)CN-substituted analogue **49**, and in particular the 3′-acrylonitrile-substituted compound **27**, possessed the best profiles. All three compounds were active at nanomolar concentrations against 103N and maintaining good activity against the 181C and 188L mutants.

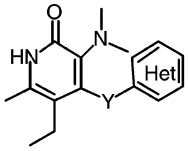
It is noteworthy that the 2′,3′-, 2′,5′-, and 3′,4′-dimethyl analogues **17r**, **17s**, and **17t** display submicromolar activities against wild type HIV. However, from the data for these compounds against the three mutant strains, and their comparatively low SI's, it is clear that these substitution patterns are not optimal compared to the 3′,5′-positioning of the methyl groups as found in lead compound **13** and the benzoylpyridinone **18f**. In fact, analogue **18f** was found to be slightly, but noticably more active than **13**. The 3′,5′-F compound **17w** and the two 3′,5′-Cl analogues **17x** and **18g** also displayed potent activities, comparable to the lead molecule **13**. Earlier SAR studies on the HEPT series similarily demonstrated that the most active analogues possessed the 3′,5′ orientation of methyl and halogen substituents.[43,49]

In previous work on related arylthiopyridinone-based anti-HIV agents a number of analogues were synthesized in which the aryl ring was exchanged for different mono and bis-heterocyclic motifs.[28] Unperturbed by the fact that none of these compounds were active, the compounds **17z**, **17aa**−**ad**, and **18l**−**n** were prepared and evaluated (Table 2). With the exception of compounds **17aa** and **17ad**, these analogues were all potent inhibitors of wild-type HIV replication. In particular the bromothiophene analogue **18m** was highly potent against wild-type HIV. Overall, however, the *N*-methylindole analogue **17ab** was the only molecule which combined activity against wild-type RT and activity against the 188L mutant.

The observation that the 3′-*E*-acrylonitrile-substituted analogue **27** is 10 times more potent than lead compound **13** in blocking the replication of wild-type HIV and the 103N and 181C mutant strains was an important finding. The corresponding benzoylpyridinone **30** was consequently tested, and found to display an almost identical RT inhibition profile (Table 3). Further, the isomeric 3′-*Z*-acrylonitrile analogue **24** was found to be less toxic and 4 times more active against the 188L mutant.

To optimize the activity of **24** and **27**/**30**, a series of *E* and *Z*-3′-vinyl-substituted benzyloxypyridinone analogues were prepared wherein the CN group was

Table 2. Activity (IC_{50}, μM) versus HIV-1



			IC_{50} (μM)				
Compd	Het	Y	LAI	SI[a]	103N	181C	188L
17z		CH_2	0.063	1,585	1.995	0.501	nd
17aa		CH_2	100	1	nd	nd	100
17ab		CH_2	0.039	2,512	0.398	0.316	0.251
17ac		CH_2	0.015	6,310	0.398	1	3.981
17ad		CH_2	5.012	20	79.43	63	nd
18l		CO	0.016	6,310	0.316	3.981	100
18m		CO	0.003	10,000	0.1	0.631	10
18n		CO	0.010	10,000	0.251	1.585	50.12

[a] See Table 1.

replaced by hydrogen, CO_2Et or its vinylogue $CH{=}CHCO_2Et$, alkyl, phenyl, benzyl, and a variety of heterocycles (pyridyl, pyridazyl, pyrrolyl, thienyl, furyl, and thiazolyl). Immediately apparent from the results presented in Table 3 for these molecules is that within a given *Z*/*E* couple of analogues, the *Z* analogue is always less active and more toxic (lower SI). Five molecules (compounds **31**, **32**, **34**, **39a** and **39i**) in this series were active at nanomolar concentrations against wild-type HIV. However, although the 3-pyridyl-substituted compound **39i** possessed the best profile, all five analogues were at least 10 times less active than the acrylonitrile leads **27**/**30** against the 103N and 181C mutants. Comparison of the activities of compounds **31**/**39i** with **34**/**39a** with respect to the 188L mutant strain highlights the importance of the presence of a polar heteroatom at the extremity of the olefin motif.

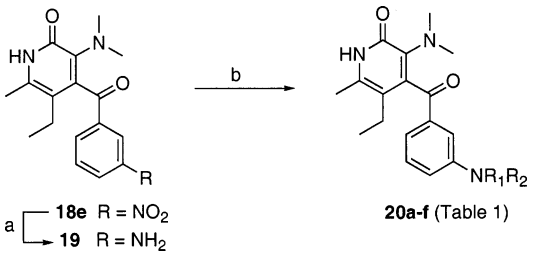
In Table 4 the data for the more highly functionalized acrylonitrile analogues **35a**−**f**, **42**, and **43** and the two double bond reduced analogues **44** and **45** is presented. Compound **42** with an additional methyl group on the β-carbon was found to be a potent inhibitor of all four HIV strains. Furthermore, the selectivity index for this analogue was remarkably high (SI = 63 090) when compared to the values for the unsubstituted acrylonitrile analogue **30** (10 000) and the unsaturated esters **31** (3162) and **32** (398). As the expected order of reactivity of these compounds in Michael type addition reactions reactions[50] is **42** < **30** < **31** < **32** the observed trend in SI values may reflect the metabolic lability of the acrylonitrile/acrylate motif in these structures. Both compounds **44** and **45** are very poor inhibitors of the 188L HIV mutant, suggesting that the acrylonitrile motif interacts with this crucial residue HIV in a structure dependent manner. It has previously been reported that introduction of sterically bulky substitutents onto the C-2 position of nevirapine gives compounds which retain their capacity to inhibit RT.[51] However, the molecular basis for binding of these large molecules in the hydrophobic pocket of RT was not detailed.

Summarizing these data, 18 analogues (**17c**, **17h**, **17o**, **17x**, **27**, **18b**, **18c**, **18f**, **18g**, **48**, **49**, **24**, **30**, **31**, **32**, **34**, **39i** and **42**) of the lead molecules **13**/**14** were found to display better than 1 μM activity against the Y181C, K103N, and Y188L mutants.

Further evaluation of this series of compounds against a larger panel of single [100I, 101E, 106A, 138K, 179E, 190A, 190S, 227C] and double mutant [100I + 103N, 101E + 103N, 103N + 181C and 227L + 106A] strains revealed that compound **17c** was inactive against the 103N + 181C double mutant strain, analogues **17c** and **17o** were inactive against the 227L + 106A double mutant, compound **24** failed against 101E + 103N, and analogues **17h**, **48**, **31**, **32**, **34**, and **39i** were essentially inactive (IC_{50} = 2−10 μM) against the 227C simple mutant (data not shown). On the basis of these observations, the eight remaining compounds, **17x**, **18b**, **18c**, **18f**, **18g**, **27**, **30**, and **42**, were selected. The results for the evaluation of these analogues against the entire panel of HIV mutant strains is presented in Table 5. Included also in this table are the data for the reference compound **13**, the closely related HEPT analogue emivirine (MKC-442), and the two NNRTI's, nevirapine and efavirenz, which are currently used in tritherapy regimens.

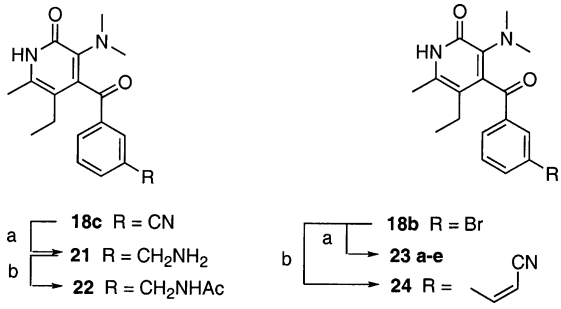
Comparing compound **13** to the corresponding benzoylpyridinone **18f**, one sees that **18f** has improved activity against all the mutant strains studied and most noticeably against 181C and the double mutant 103N + 181C. On the negative side its selectivity index is lower. The 3′,5′-Cl analogues **17x** and **18g** and the 3′-monobromo compound **18b** have profiles which are very similar to that for **13**, an approximate 10 fold gain in activity being observed for **18g** against the 181C and 100I mutants. A marked amelioration in the inhibition profile was achieved for the 3′-CN analogue **18c**. This molecule is more active than **13** against five of the mutant strains studied and is vastly superior to both emerivine and nevirapine. More importantly, it was equipotent to efavirenz against the 227L + 106A double mutant. The three new acrylonitrile-substituted analogues **27**, **30**, and **42** also largely surpass emevirine, nevirapine, and lead molecule **13** in terms of their activities. Comparing these molecules to each other one further sees that benzoylpyridinone **30** has the best overall profile against the 15 mutant strains. Indeed, this analogue is active against eight of the fifteen mutants at nanomolar concentrations. Relative to efavirenz, compound **30** was 10 times more sensitive toward the 103N, 100I, 106A, 190A, and 101E + 103N mutant strains. A substantially larger gain in activity was observed against the 190S and 100I + 103N mutants. In contrast, efavirenz is much more efficient at inhibiting the 227 + 106A double mutant strain, and

Scheme 2[a]



[a] Conditions: (a) H_2, Raney Ni; (b) CH_3CHO, $NaBH_3CN$ for **20a**; CH_3COCl for **20b**; $ClSO_2CH_3$ for **20c**; EtNCO for **20d**; 4-chlorobutyryl chloride and then t-BuOK for **20e**; 2,5-dimethoxytetrahydrofuran for **20f**.

Scheme 3



[a] Conditions (left): (a) H_2, Raney Ni; (b) CH_3COCl. [a]Conditions (right): (a) $Pd(PPh_3)_4$, $R-SnR'_3$; (b) $Pd(PPh_3)_4$, Acrylonitrile.

although **30** is a potent inhibitor of the 181C mutant ($IC_{50} = 0.016\ \mu M$), it is 10 times weaker than efavirenz against this crucial HIV mutant. Overall, the data indicates that benzoylpyridinones **18c** and **30** have a better anti-HIV profile in the cellular assays than efavirenz.

This study has permitted the identification of two new lead compounds in the 4-benzoylpyridinone series **18c** and **30**. These molecules are potent inhibitors of wild type HIV-1, as well as a large range of HIV-1 mutant strains which are responsible for the onset of resistance to the NNRTI's that are currently used in HAART therapy. Interestingly, their activity against wild-type HIV virus was not predictive of their broad spectrum, illustrating the necessity for inclusion of both wild type and mutant viruses in screening panels. It is remarkable that these compounds were found by simple modulation of the substituents on the phenyl ring in the pyridinone lead compounds **13** and **14**. These results form a solid basis for continued exploration of the pyridinone family of RT inhibitors and in particular modifications of the C-3, C-5, and C-6 centers on the pyridinone ring.

Experimental Section

Chemistry. General Remarks. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under argon. Acetonitrile and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. *N*,*N*-Dimethylformamide (DMF) was purchased from Aldrich and used without purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) using E. Merk $60F_{254}$ procoated silica gel plates. Flash column chromatography was performed with the indicated solvents and using E. Merk silica gel 60 (particle size 0.035−0.070 mm unless otherwise stated). Melting points were taken on a Kofler melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer at ambient temperature using internal deuterium lock. Chemical shifts (δ) were reported in ppm units (s, d, t, q, m, and br for singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively). Elemental analyses, performed by the "Service Central de Microanalyze du CNRS" Gif-sur-Yvette (France), were within 0.4% of the theoretical values calculated for C, H, and N.

Preparation of 4-Arylmethyl-3-dimethylaminopyridinones 17a−ad: 4-[(3-Methylphenyl)methyl]-5-ethyl-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 17c: Example of the General Method. Step 1: Lithiation/Condensation with ArCHO. *n*-Butyllithium (1.6 M in hexane, 62.5 mL, 100 mmol) was added dropwise at −78 °C to a solution of **16** (10.0 g, 40 mmol)[45] and TMEDA (15 mL, 100 mmol) in THF (150 mL) under nitrogen. The mixture was stirred at 0 °C for 1 h and then cooled to −78 °C. A solution of the *m*-tolualdehyde (10.6 g, 88 mmol) in THF (150 mL) was added dropwise, and the mixture was stirred at 0 °C for 3 h. This was followed by addition of H_2O and extraction with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was crystallized from cyclohexane. *N*-[4-[(3-Methylphenyl)hydroxymethyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropanamide (9.5 g, 62%) was obtained as a white solid mp 174 °C; ^{1}H NMR (DMSO-d_6) δ 0.73 (3 H, t, $J = 7.5$ Hz), 1.06 (9 H, s), 2.23 (3 H, s), 2.37 (3 H, s), 2.44−2.67 (2 H, m), 3.79 (3 H, s), 6.03 (1 H, d, $J = 2.6$ Hz), 6.17 (1 H, d, $J = 2.6$ Hz), 6.99 (1 H, d, $J = 7.9$ Hz), 7.02−7.18 (3 H, m), 8.60 (1 H, br s).

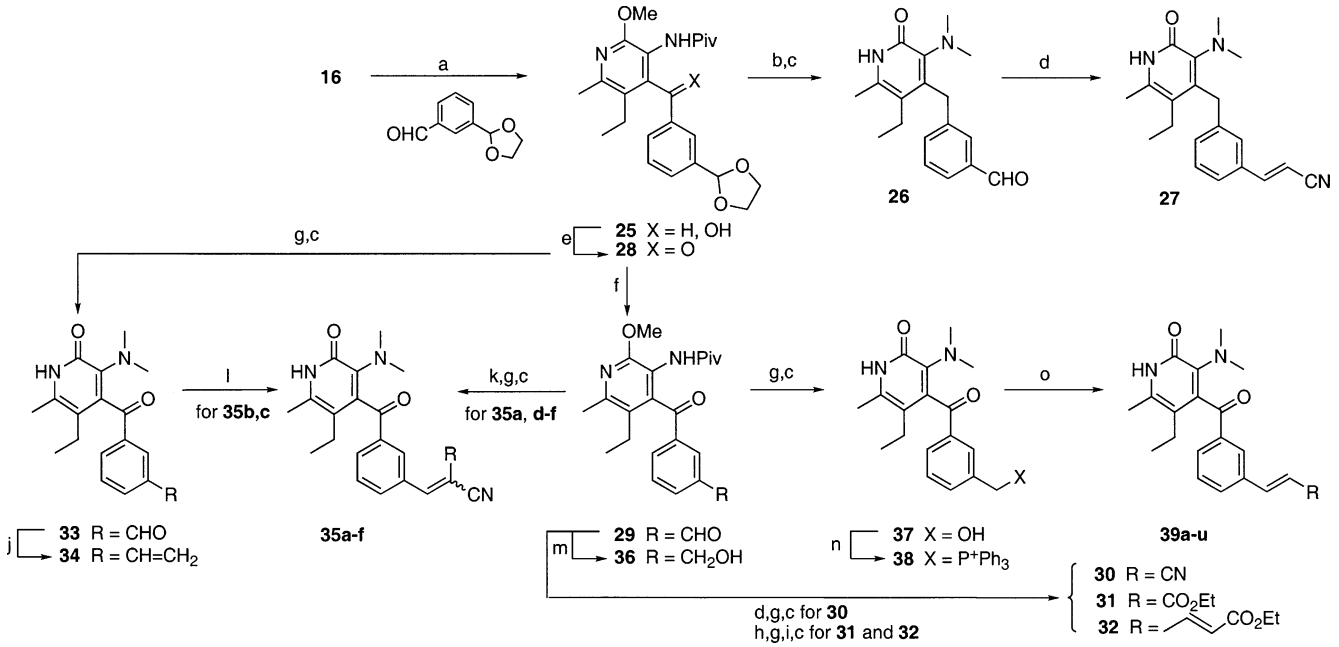
Step 2: Reaction with Tin(II) Chloride. A mixture of the above carbinol intermediate (9.2 g, 25 mmol), tin(II) chloride dihydrate (22.5 g, 100 mmol), and 12 N HCl (0.35 mL) in HOAc (80 mL) was stirred at 100 °C overnight and then poured into ice−water and basified using concentrated NH_4OH. The mixture was then filtered through Celite and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was silica gel column chromatographed (CH_2Cl_2/MeOH/NH_4OH 97/3/0.1 and 90/10/0.1), and the concentrated product fractions were triturated with Et_2O providing 3-amino-5-ethyl-6-methyl-4-[(3-methylphenyl)methyl]pyridin-2(1*H*)-one (3.5 g, 55%) as a pale yellow solid mp 207 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (3 H, t, $J = 7.5$ Hz), 2.08 (2 H, q, $J = 7.5$ Hz), 2.15 (3 H, s), 2.40 (3 H, s), 2.56 (6 H, s), 3.94 (2 H, s), 6.60 (1 H, d, $J = 7.9$ Hz), 7.00−7.10 (2 H, m), 7.20 (1 H, d, $J = 7.9$ Hz), 11.35 (1 H, br s).

Step 3: N-Methylation. Sodium cyanoborohydride (1.8 g, 29 mmol) was added at room temperature (RT) under nitrogen to a solution of the derived 3-aminopyridinone (2.5 g, 9.7 mmol) and formaldehyde (37% in H_2O, 97 mmol) in acetonitrile (65 mL). Acetic acid (1 mL) was added, and the reaction was stirred at RT for 2 h. Additional HOAc (1 mL) was then added, and stirring was continued at RT for 30 min, before pouring the mixture into H_2O and basifying with 10% aqueous K_2CO_3. The precipitate was collected, washed several times with H_2O, and dried. Compound **17c** (2.33 g, 85% step 3; 29% from **16**) was obtained as a white solid mp 165 °C; ^{1}H NMR (DMSO-d_6) δ 0.78 (3 H, t, $J = 7.4$ Hz), 2.12−2.24 (8 H, m), 2.62 (6 H, s), 4.00 (2 H, s), 6.81 (1 H, d, $J = 7.9$ Hz), 6.90 (1 H, s), 6.97 (1 H, d, $J = 7.9$ Hz), 7.13 (1 H, t, $J = 7.9$ Hz), 11.35 (1 H, br s). Anal. ($C_{18}H_{24}N_2O$) C, H, N.

Preparation of 4-Aroyl-3-dimethylaminopyridinones 18a−n: 5-Ethyl-6-methyl-3-(dimethylamino)-4-(3-methylbenzoyl)pyridin-2(1*H*)-one 18a: Example of the General Method. Step 1: Lithiation/Condensation with ArCHO. As described for **17c** (0.3 mol scale, 70% yield).

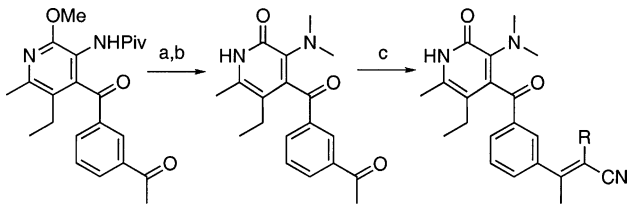
Step 2: Oxidation. MnO_2 (20 g, 230 mmol) was added portionwise at RT to a solution of *N*-[4-[(3-methylphenyl)-hydroxymethyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropanamide (16.6 g, 45 mmol) in toluene (200 mL). The mixture refluxed overnight, filtered through Celite, and concentrated under vacuum. The residue was crystallized from Et_2O to give *N*-[4-(3-methylbenzoyl)-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethyl-propanamide (15.2 g, 92%) as

Scheme 4[a]



[a] Conditions: (a) *n*-BuLi, TMEDA, THF; (b) $SnCl_2 \cdot 2H_2O$; (c) $(HCHO)_n$, $NaBH_3CN$,AcOH; (d) $(EtO)_2POCH_2CN$, *t*-BuOK; (e) $KMnO_4$, TDA-1 (f) aq HCl, 20 °C; (g) aq HCl, 100 °C; (h) $(EtO)_2POCH_2R$, *t*-BuOK; (i) $SOCl_2$, EtOH (j) CH_3PPh_3Br, *n*-BuLi; (k) $(EtO)_2POCHRCN$, *t*-BuOK; (l) RCH_2CN, LDA; (m) $NaBH_4$; (n) $SOCl_2$ and then PPh_3; (o) *t*-BuOK, RCHO.

Scheme 5[a]



[a] Conditions: (a) 6 N HCl; (b) $(HCHO)_n$, $NaBH_3CN$ HOAc; (c) $(EtO)_2POCHRCN$/*t*-BuOK.

a white powder mp 120 °C; ^{1}H NMR (DMSO-d_6) δ 0.78 (9 H, s), 0.95 (3 H, t, J = 8.8 Hz), 2.35 (8 H, m), 3.84 (3 H, s), 7.48 (4 H, m), 8.64 (1 H,br s).

Step 3: *N*-Pivaloyl/*O*-Methyl Imidate Cleavage. A solution of the propanamide intermediate (14 g, 38 mmol) in 6 N HCl (140 mL) was refluxed for 2 h and then poured into ice−water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated under vacuum. The residue was crystallized from Et_2O to give 3-amino-5-ethyl-6-methyl-4-(3-methylbenzoyl)-pyridin-2(1*H*)-one (6.36 g, 62%) as a white solid mp 202 °C; ^{1}H NMR (DMSO-d_6) δ 0.93 (3 H, t, J = 8.8 Hz), 2.23 (2 H, q, J = 8.8 Hz), 2.32 (3 H, s), 2.43 (3 H, s), 4.17 (2 H, s), 7.4 (2 H, m), 7.73 (2 H, m), 12.70 (1 H, br s).

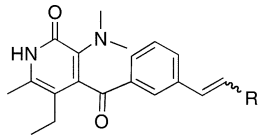
Step 4: N-Methylation. The intermediate 3-aminopyridinone (3.51 g, 13 mmol) was methylated as described for **17c**. The crude product was silica gel column chromatographed (CH_2Cl_2/MeOH/NH_4OH 98/2/0.1) and the product fractions were triturated with Et_2O to give **18a** as a pale yellow solid (1.16 g, 30%; 12% overall from **16**), mp 225 °C; ^{1}H NMR ($CDCl_3$) δ 0,95 (3 H, t, J = 7.4 Hz), 2.00−2.30 (2 H, m), 2.37 (3 H, s), 2.44 (3 H, s), 2.63 (3 H, s), 7.30−7.40 (2 H, m), 7.62 (1 H, d, J = 7.9 Hz), 7.74 (1 H, s), 13.10 (1 H, br s). Anal. ($C_{18}H_{22}N_2O_2 \cdot 0.25H_2O$) C, H, N.

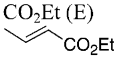
4-(3-Aminobenzoyl)-5-ethyl-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 19. A solution of **18e** (1.00 g, 3 mmol) in MeOH/NH_3 (7 N, 10 mL) was hydrogenated at RT under 3 atm of H_2 for 1 h, using Raney nickel (1 g) as the catalyst. The catalyst was then removed by filtration through Celite and washed with CH_2Cl_2, and the filtrate was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude product (1 g) was crystallized from water and triturated with Et_2O providing compound **19** (0.11 g, 12%) as a white solid mp 252 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 7.4 Hz), 1.80−2.15(2 H, m), 2.18 (3 H, s), 2.47 (6 H, s), 5.37 (2 H, s), 6.80 (1 H, d, J = 8.0 Hz), 6.90 (1 H, d, J = 8.0 Hz), 7.00 (1 H, s), 7.15 (1 H, t, J = 8.3 Hz), 11.60 (1 H, br s). Anal. ($C_{17}H_{21}N_3O_2 \cdot 0.25H_2O$) C, H, N.

5-Ethyl-4-(3-diethylaminobenzoyl)-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 20a. Sodium cyanoborohydride (130 mg, 2 mmol) was added at RT under nitrogen to a solution of **19** (200 mg, 0.67 mmol) and acetaldehyde (300 mg, 6.8 mmol) in acetonitrile (10 mL). Acetic acid (0.22 mL) was added, and the mixture was stirred at RT for 2 h. Additional HOAc (0.22 mL) was then added, and after continued stirring for 1 h, the mixture was poured into 10% aqueous K_2CO_3 and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH 97/3). Subsequent crystallization from CH_3CN afforded **20a** (106 mg, 44%) as a white solid mp 228 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.5 Hz), 1.20 (6 H, t, J = 7.1 Hz), 2.08−2.32(2 H, m), 2.36 (3 H, s), 2.67 (6 H, s), 3.42 (4 H, q, J = 7.1 Hz), 6.90 (1 H, dd), 6.99 (1 H, d, J = 8.0 Hz), 7.21−7.32 (2 H, m), 12.56 (1 H, br s). Anal. ($C_{21}H_{29}N_3O_2 \cdot 0.25H_2O$) C, H.

4-(3-Acetylaminobenzoyl)-5-ethyl-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 20b. Acetyl chloride (170 mg, 2.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 5 °C to a solution of **19** (600 mg, 2 mmol) and triethylamine (220 mg, 2.2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at RT for 4 h, followed by addition of H_2O and extraction with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 95/5/0.1). Trituration with Et_2O afforded **20b** (96 mg, 14%) as a pale yellow solid mp 268 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (3 H, t, J = 7.4 Hz), 1.80−2.20 (2 H, m), 2.04 (3 H, s), 2.46 (6 H, s), 7.40−7.50 (2 H, m), 7.85−7.95 (1 H, m), 7.99 (1 H, s), 10.11 (1 H, br s), 11.67 (1 H, br s). Anal. ($C_{19}H_{23}N_3O_3 \cdot 0.75H_2O$) C, H, N.

Table 3. Activity (IC_{50}, μM) versus HIV-1



Compd	R (Z/E form)	IC_{50} (μM) LAI	SI[a]	103N	181C	188L
24	CN (Z)	0.004	25,119	0.003	0.013	0.040
30	CN (E)	0.001	10,000	0.002	0.016	0.158
31	CO_2Et (E)	0.003	3,162	0.01	0.158	0.158
32		0.005	398	0.04	0.2	0.631
34	H	0.002	12,589	0.032	0.631	0.794
39a	CH_3 (E)	0.005	10,000	0.158	0.398	3.981
39b	CH_3CH_2 (E)	0.050	1,259	nd	nd	nd
39c	$PhCH_2$ (Z)	1.585	32	nd	nd	nd
39d	C_6H_5 (Z)	1.258	79	nd	nd	nd
39e	C_6H_5 (E)	0.251	398	nd	nd	nd
39f	 (Z)	1.585	63	nd	nd	nd
39g	 (E)	0.079	1,259	nd	nd	nd
39h	 (Z)	0.079	631	nd	nd	nd
39i	 (E)	0.003	3,162	0.02	0.063	0.158
39j	 (Z)	0.061	794	nd	nd	nd
39k	 (E)	0.010	10,000	nd	nd	nd
39l	 (Z)	0.199	501	nd	nd	nd
39m	 (E)	0.020	3,961	0.05	0.079	0.2
39n	 (E)	0.316	158	nd	nd	nd
39o	 (E)	0.079	1,259	nd	nd	nd
39p	 (E)	0.100	1,000	nd	nd	nd
39q	 (Z)	0.063	794	nd	nd	nd
39r	 (E)	0.020	5,012	nd	nd	nd
39s	 (E)	0.079	631	nd	nd	nd
39t	 (Z)	0.158	501	nd	nd	nd
39u	 (E)	0.032	3,162	nd	nd	nd

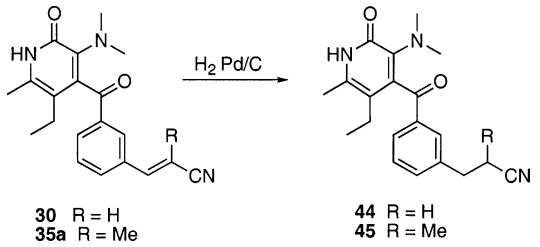
[a] See Table 1.

Following this protocol, compound **19** was reacted separately with methanesulfonyl chloride and ethyl isocyanate (triethylamine is not needed for **20d**) to give products **20c** and **20d**.

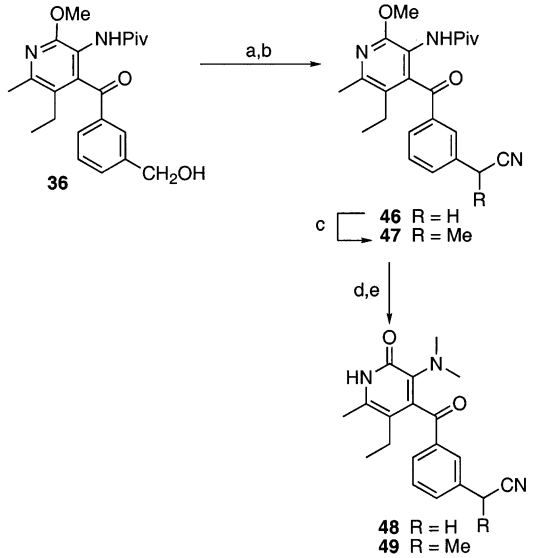
Compound **20c**: 28% yield; mp 259 °C (Et_2O); ^1H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 6.5 Hz), 1.76−2.25 (2 H, m), 2.20 (3 H, s), 2.46 (6 H, s), 3.00 (3 H, s), 7.40−7.55 (3 H, m), 7.63 (1 H, s), 9.98 (1 H, br s), 11.71 (1 H, br s). Anal. ($C_{18}H_{23}N_3O_4S\cdot0.25H_2O$) C, H, N.

Compound **20d**: 70% yield; mp > 260 °C (CH_3CN); ^1H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 7.3 Hz), 1.05 (3 H, t, J = 7.1 Hz), 1.82−2.18 (2 H, m), 2.19 (3 H, s), 2.47 (6 H, s), 3.10 (2 H, m), 6.1 (1 H, br s), 7.24−7.41 (2 H, m), 6.80 (1 H, d, J = 8.0 Hz), 7.85 (1 H, s), 8.71 (1 H, br s), 11.69 (1 H, br s). Anal. ($C_{20}H_{26}N_4O_3$) C, H, N.

Scheme 6

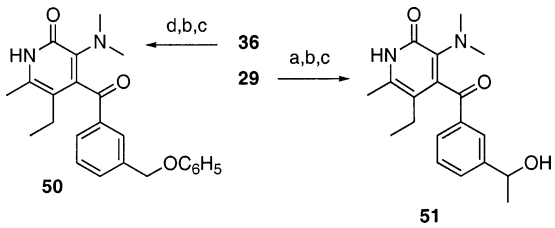


Scheme 7[a]



[a] Conditions: (a) $SOCl_2$; (b) NaCN; (c) *t*-BuOK, MeI; (d) 6 N HCl; (e) $(HCHO)_n$, $NaBH_3CN$, AcOH.

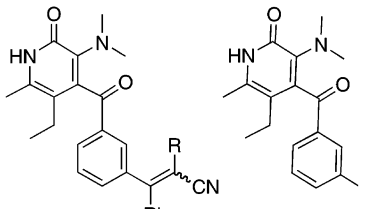
Scheme 8[a]



[a] Conditions: (a) CH_3MgI; (b) 6 N HCl; (c) $(HCHO)n$, $NaBH_3CN$, HOAc; (d) DEAD, PPh_3, C_6H_5OH.

5-Ethyl-6-methyl-3-(dimethylamino)-4-[3-(2-oxo-pyrrolidin-1-yl)benzoyl]pyridin-2(1*H*)-one 20e. A mixture of 4-chlorobutyryl chloride (410 mg, 2.9 mmol) in CH_2Cl_2 (4 mL) was added at 5 °C to a solution of **19** (600 mg, 2 mmol) in CH_2Cl_2 (26 mL) and triethylamine (0.41 mL; 2.9 mmol). The mixture was stirred at room temperature for 6 h and then poured into water. After extraction with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 90/10/0.1) to afford the chloroamide intermediate. Potassium *tert*-butoxide (0.47 g; 4.2 mmol) was added portionwise at 0°C under nitrogen to a solution of this chloroamide intermediate in THF (20 mL). The mixture was stirred at room temperature for 3 h, poured out on ice and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), concentrated, washed with diethyl ether, and dried to afford **20e** (600 mg, 82%) as a pale yellow solid mp 240 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.4 Hz), 2.05−2.35 (4 H, m), 2.36 (3 H, s), 2.63−2.70 (8 H, m), 3.90−4.00 (2 H, m), 7.48 (1 H, t, J = 8

Table 4. Activity (IC_{50}, μM) versus HIV-1



35a-f R' = H
42, 43 R' = Me

44, 45

		IC_{50} (μM)				
Cpd	R (Z/E form)	LAI	SI[a]	103N	181C	188L
35a	CH_3 (E)	0.001	6,310	nd	nd	0.631
35b	CN	0.012	3,981	nd	nd	nd
35c	$CO_2C_2H_5$ (Z)	0.158	631	nd	nd	nd
35d	C_6H_5 (Z)	1	16	nd	nd	nd
35e	 (E)	0.199	126	nd	nd	nd
35f	 (Z)	0.063	200	nd	nd	nd
42	H (E)	0.001	63,096	0.003	0.063	0.398
43	CH_3	0.006	1,585	0.025	0.126	1.585
44	H	0.003	31,632	0.013	0.251	1.995
45	CH_3	0.008	12,589	0.05	0.501	1.995

[a] See Table 1.

Hz), 7.58 (1 H, d, J = 8.0 Hz), 7.96 (1 H, s), 8.20 (1 H, d, J = 8.3 Hz), 13.00 (1 H, br s). Anal. ($C_{21}H_{25}N_3O_3$) C, H, N.

5-Ethyl-6-methyl-3-(dimethylamino)-4-[3-(1-pyrrolyl)-benzoyl]pyridin-2(1*H*)-one 20f. 2,5-Dimethoxytetrahydrofuran (80 mg, 0.6 mmol) was added at RT to a solution of **19** (150 mg, 0.5 mmol) in acetic acid (5 mL). The mixture was refluxed for 20 min and then poured into cold 10% aqueous K_2CO_3 and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.1). Trituration with Et_2O afforded **20f** (38 mg, 25%) as a white powder mp 240 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.4 Hz), 2.05−2.35 (4 H, m), 2.36 (3 H, s), 2.63−2.70 (8 H, m), 3.90−4.00 (2 H, m), 7.48 (1 H, t, J = 8.0 Hz), 7.58 (1 H, d, J = 8.0 Hz), 7.96 (1 H, s), 8.20 (1 H, d, J = 8.3 Hz), 13.00 (1 H, br s). Anal. ($C_{21}H_{25}N_3O_2$·0.33H_2O) C, H, N.

4-[3-(Aminomethyl)benzoyl]-5-ethyl-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 21. A solution of **18c** (300 mg, 1 mmol) in methanol/NH_3 (7 N, 30 mL) was hydrogenated under 3 atm of H_2 for 3 h at RT, using Raney nickel (0.3 g) as the catalyst. The catalyst was removed by filtration through Celite, washed with methanol, and the filtrate was concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 93/7/0.5). Crystallization from CH_3-CN afforded **21** (130 mg, 43%) as a pale yellow solid mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 7.4 Hz), 1.80−2.25 (2 H, m), 2.19 (3 H, s), 2.46 (6 H, s), 3.79 (2 H, s), 7.46 (1 H, t, J = 8.3 Hz), 7.52−7.62 (2 H, m), 7.83 (1 H, s). Anal. ($C_{18}H_{23}N_3O_2$) C, H, N.

4-[3-(Acetylaminomethyl)benzoyl]-5-ethyl-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 22. This compound was prepared from **21** as described for **20b** (white solid, 57% yield), mp 214 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (3 H, t, J = 7.1 Hz), 1.75−2.25 (8 H, m), 2.45 (6 H, s), 4.31 (2 H, d, J = 5.6 Hz), 7.40−7.68 (3 H, m), 7.72 (1 H, s), 8.45 (1 H, br m), 11.70 (1 H, br s). Anal. ($C_{20}H_{25}N_3O_3$·0.33H_2O) C, H, N.

5-Ethyl-6-methyl-3-(dimethylamino)-4-(3-phenylbenzoyl)pyridin-2(1*H*)-one 23a. A mixture of**18b** (510 mg, 1.4 mmol), tributylphenyltin (770 mg, 2.1 mmol), and tetrakis-(triphenylphosphine)palladium (80 mg) in dioxane (5 mL) was stirred at 80°C for 8 h. Water was then added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.1). Crystallization from CH_3CN afforded **23a** (140 mg, 28%) as a white solid mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (3 H, t, J = 7.0 Hz), 1.85−2.25 (2 H, m), 2.20 (3 H, s), 2.49 (6 H, s), 7.35−7.55 (3 H, m), 7.60−7.70 (3 H, m) 7.70−7.80 (1 H, m), 7.92−8.2 (2 H, d, J = 8.0 Hz), 11.73 (1 H, br s). Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

(*Z*)-3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acrylonitrile 24. Tetrakis(triphenylphosphine)palladium(0) (200 mg), triethylamine (33 mL), and acrylonitrile (1.9 g, 36 mmol) were sequentially added at RT under nitrogen to a solution of bromo derivative **18b** (6.7 g, 18 mmol) and triphenylphosphine (4.9 g, 18.7 mmol) in DMF (150 mL). The mixture refluxed overnight. Water was added, and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), and concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH 97/3). Crystallization from CH_3-CN provided **24** (0.35 g, 6%) as a white solid mp 107 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (3 H, t, J = 7.4 Hz), 1.85−2.15 (2 H, m), 2.19 (3H, s), 2.45 (6 H, s), 5.98 (1 H, t, J = 12.0 Hz), 7.54 (1 H, d, J = 12.0 Hz), 7.69 (1 H, d, J = 8.8 Hz), 7.80 (1 H, d, J = 8.8 Hz), 8.05 (1 H, d, J = 8.8 Hz), 8.29 (1 H, s), 11.7 (1 H, br s). Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

***N*-[4-[[3-(1,3)Dioxolan-2-yl-phenyl]hydroxymethyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide 25.** *n*-Butyllithium (1.6 M in hexane, 62.5 mL, 100 mmol) was added dropwise at −78 °C to a solution of **16** (10.0 g, 40 mmol) and TMEDA (15 mL, 100 mmol) in THF (150 mL) under nitrogen. The mixture was stirred at 0 °C for 1 h and recooled to −78 °C before dropwise addition of a solution of the 3-[(1,3)dioxolan-2-yl]benzaldehyde (19 g, 0.107 mol)[47] in THF (150 mL). The mixture was stirred at 0 °C for 3 h, followed by addition of H_2O and extraction with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was triturated with Et_2O to give **25** (11.7 g, 69% yield) as a white solid in essentially pure form mp 168 °C.

3-[(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin)-4-ylmethyl]benzaldehyde 26. Reaction of **25** (11.7 g, 27 mmol) with $SnCl_2$·$2H_2O$ as described for **17c** gave the intermediate 3-[(3-amino-5-ethyl-6-methyl-2-oxo-1,2-dihydropyridin)-4-yl-methyl]benzaldehyde (1.8 g, 24%) which was followed by N-methylation reaction gave **26** (0.4 g, 20%) as a solid; ^{1}H NMR (DMSO-d_6) δ 0.78(3 H, t, J = 7.4 Hz), 2.14 (3H, s), 2.21 (2 H, q, J = 7.4 Hz), 2.61 (6 H, s), 4.16 (2H, s), 7.44 (1 H, d, J = 8.8 Hz), 7.51 (1 H, t, J = 8.8 Hz), 7.59 (1 H, s), 7.73 (1 H, d, J = 8.8 Hz), 9.97 (1 H, s), 11.4 (1 H, br s).

(*E*)-3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-ylmethyl)phenyl]acrylonitrile 27. Potassium *tert*-butoxide (0.54 g; 4.8 mmol) was added portionwise at 5 °C under nitrogen to a mixture of diethyl cyanomethylphosphonate (0.85 g, 4.8 mmol) in THF (20 mL). The mixture was stirred at room temperature for 30 min and then the aldehyde **26** (1.3 g, 4.3 mmol) in THF (5 mL) was added. After 2 h at room temperature, water was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and concentrated. The acrylonitrile derivative **27** was crystallized from CH_3CN to give a white powder (0.36 g; 26%), mp 214 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (3 H, t, J = 7.4 Hz), 2.13 (3 H, s), 2.19 (2 H, q), 2.61 (6 H, s), 4.09 (2 H, s), 6.41 (1 H, d, J = 16.7 Hz), 7.10 (1 H, d, J = 8.8 Hz), 7.31−7.38 (2 H, m), 7.50 (1 H, d, J = 8.8 Hz), 7.64 (1 H, d, J = 16.7 Hz), 11.4 (1 H, br s). Anal. ($C_{20}H_{23}N_3O$) C, H, N.

***N*-[4-[3-(1,3)Dioxolan-2-ylbenzoyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide 28.** To a solution of **25** (8.1 g, 19 mmol) in CH_2Cl_2 (100 mL) at RT were added tri[2-(2-methoxyethoxy)ethyl]amine (1.4 mL, 4.4 mmol) and $KMnO_4$ (11.8 g, 75 mmol). The mixture was stirred at RT for 12 h, filtered through Celite, and washed with CH_2-Cl_2. The filtrate was washed with H_2O, dried over $MgSO_4$, and

Table 5. Activity (IC_{50}, μM) versus HIV-1

compd	LAI	SI[a]	103N	181C	188L	100I	101E	106A	138K	179E	190A	190S	227C	100I + 103N	101E + 103N	103N + 181C	227L + 106A
17x	0.008	3981	0.025	0.160	0.631	0.05	nd	nd	nd	nd	nd	nd	0.701	0.316	0.200	0.501	0.501
18b	0.002	12589	0.02	0.158	0.794	0.02	0.014	nd	0.005	0.005	0.007	0.003	0.264	0.075	0.074	0.974	0.1
18c	0.002	6310	0.006	0.04	0.398	0.01	0.007	nd	0.004	0.004	0.005	0.002	0.225	0.039	0.028	0.111	0.05
18f	0.004	2512	0.01	0.063	0.158	0.006	0.008	0.006	0.005	0.002	0.013	0.004	0.631	0.04	0.013	0.158	0.398
18g	0.002	5012	0.013	0.032	0.316	0.008	0.012	nd	0.017	0.014	0.011	0.003	0.631	0.501	0.040	0.158	0.06
27	0.0004	25119	0.002	0.016	0.158	0.01	0.006	0.002	0.003	0.001	0.008	0.04	0.398	0.032	0.025	0.032	3.162
30	0.001	10000	0.002	0.016	0.158	0.006	0.008	0.002	0.005	0.001	0.006	0.006	0.794	0.025	0.016	0.04	1
42	0.001	63096	0.003	0.063	0.398	0.01	0.008	0.003	0.004	0.002	0.006	0.01	1.259	0.04	0.025	0.2	1.259
13	0.008	12589	0.032	0.1	0.251	0.05	0.016	0.04	nd	nd	0.063	nd	nd	nd	nd	0.794	nd
EMV[b]	0.008	1259	0.794	1.995	39.81	0.04	0.126	1.995	0.079	0.032	1.585	7.943	79.43	25.12	7.943	100	100
NVP[b]	0.032	5012	6.310	10	100	0.316	0.316	5.012	0.050	0.195	7.943	0.044	0.135	1.452	0.509	100	0.163
EFV[b]	0.001	10000	0.04	0.002	0.158	0.04	0.006	0.04	0.002	0.005	0.01	0.251	0.158	10	0.158	0.04	0.025

[a] See Table 1. [b] EMV, emivirine; NVP, nevirapine; EFV, efavirenz.

concentrated to afford **28** (5.9 g, 73%) which was used in the next step without any further purification.

***N*-[5-Ethyl-4-(3-formylbenzoyl)-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide 29.** A solution of ketone **28** (5.9 g, 14 mmol) in 3 N HCl (60 mL) was stirred at RT for 1 h. The mixture was then poured into ice−water, basified using solid K_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated to afford **29** (5.3 g, 100%) as a white solid.

(*E*)-3-[3-(5-ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acrylonitrile 30. Step 1: Wittig−Horner Reaction. Potassium terbutoxide (0.64 g, 5.7 mmol) was added at 5 °C under nitrogen to a solution of diethyl cyanomethylphosphonate (1.0 g, 5.7 mmol) in THF (30 mL), and the mixture was stirred at 5 °C for 30 min. A solution of the benzaldehyde derivative **29** (2.0 g, 5.2 mmol) in THF (10 mL) was added dropwise, and the reaction was stirred at 5 °C for 1 h and then brought to RT before addition of H_2O and extraction with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was recrystallized from CH_3CN to afford the intermediate *N*-{4-[3-(2-cyanovinyl)benzoyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl}-2,2-dimethylpropionamide (0.85 g, 40%) as a white solid.

Step 2: *N*-Pivaloyl/*O*-Methyl Imidate Cleavage. As described for **18a**, the intermediate *N*-(2-methoxypyridin-3-yl)-dimethylpropionamide obtained above (0.79 g, 1.9 mmol) was converted to 3-[3-(3-amino-5-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acrylonitrile (0.53 g, 88%) as a white solid.

Step 3: N-Methylation. As described for **17c**, the 3-aminopyridinone intermediate (0.46 g, 1.5 mmol) obtained above was converted to **30** as a white solid (0.21 g, 42% step 3; 15% yield for the three steps), mp 240 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.4 Hz), 2.50−2.35 (2 H, m), 2.38 (3 H, s), 2.60 (6 H, s), 6.00 (1 H, t, J = 16.7 Hz), 7.48 (1 H, d, J = 16.7 Hz), 7.60 (1 H, d, J = 8.8 Hz), 7.70 (1 H, d, J = 8.8 Hz), 7.85 (1 H, d, J = 8.8 Hz), 8.03 (1 H, s), 13.10 (1 H, br s). Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

(*E*)-Ethyl 3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acrylate 31. Step 1: Wittig−Horner Reaction. Following the protocol for **30**, the potassium anion of triethyl phosphonoacetate (1.34 g, 5.9 mmol) in THF (30 mL) was condensed with **29** (1.5 g, 3.9 mmol). Crystallization of the crude product from diisopropyl ether afforded the acrylate intermediate (1.3 g, 75%), mp 115 °C.

Step 2: *N*-Pivaloyl/*O*-Methyl Imidate, and Ester Cleavage. As described for **18a**, this acrylate intermediate (1.15 g, 2.6 mmol) was converted to 3-[3-(3-amino-5-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acrylic acid (0.88 g, 100%) as a white solid.

Step 3: Esterification. Thionyl chloride (0.75 mL, 10 mmol) was added slowly to the derived acid intermediate (0.88 g, 2.7 mmol) in ethanol (50 mL) at 5 °C. The mixture was stirred at 80 °C for 2 h, poured into ice cold 10% aqueous K_2CO_3 and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to afford ethyl ester derivative (0.95 g, 99%) as a pale yellow solid.

Step 4: N-Methylation. As described for **17c**, the compound **31** (0.28 g, 38%) was obtained as a white powder (20% overall yield from dioxolane **25**), mp 221 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 4.0 Hz), 1.27 (3 H, t, J = 7.1 Hz), 1.8−2.2 (2 H, m), 2.2 (3 H, s), 2.44 (6 H, s), 4.2 (2 H, q, J = 7.1 Hz), 6.7 (1 H, d, J = 16.2 Hz), 7.6 (1 H, t, J = 7.9 Hz), 7.78 (1 H, d, J = 16.8 Hz), 7.81 (1 H, d, J = 8.8 Hz), 8.0−8.1 (2 H, m), 11.7 (1 H, br s). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

(*E*,*E*)-Ethyl 5-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]penta-2,4-dienenoate 32. Following the procedure for **31**, compound **29** was reacted with the potassium anion of triethyl 4-phosphonocrotonate, folllowed by acid treatment, reesterification, and N-methylation. Compound **32**, a white powder, was prepared in 22% overall yield from **25** mp 239 °C (CH_3CN); ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 4.0 Hz), 1.35 (3 H, t, J = 7.1 Hz), 2.00−2.35 (2 H, m), 2.37 (3 H, s), 2.62 (6 H, s), 4.26 (2 H, q, J = 7.1 Hz), 6.07 (1 H, d, J = 15.0 Hz), 6.97 (2 H, m), 7.40−7.50 (2 H, m), 7.71 (2 H, t, J = 6.5 Hz), 8.04 (1 H, s), 12.30 (1 H, br s). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

3-(5-Ethyl-6-methyl-3dimethylamino-2-oxo-1,2-dihydropyridin-4-yl carbonyl)benzaldehyde 33. Step 1: *N*-Pivaloyl,*O*-Methyl Imidate, and Dioxolane Cleavage. A solution of **28** (1.0 g, 2.3 mmol) in 6 N HCl (30 mL) was refluxed for 1 h. After dilution of the medium with H_2O, extraction with EtOAc, drying ($MgSO_4$) of the combined organic layers, and concentration, the intermediate 3-aminopyridinone (0.65 g, 97%) was obtained as a yellow solid.

Step 2: N-Methylation. As described for **17c**, the derived 3-aminopyridinone (0.65 g, 2.2 mmol) was converted to **33**, isolated as a white solid (0.30 g, 42% yield) after silica gel column chromatography (CH_2Cl_2/CH_3OH 98/2) (30% overall yield from **25**), mp 220 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.45 Hz), 2.10−2.30 (2 H, m), 2.39 (3 H, s), 2.60 (6 H, s), 7.69 (1 H, t, J = 8.0 Hz), 8.14 (2 H, t, J = 8.0 Hz), 8.34 (1 H, s), 10.15 (1 H, s), 12.80 (1 H, br s). Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

5-Ethyl-6-methyl-3-(dimethylamino)-4-(3-vinylbenzoyl)-pyridin-2(1*H*)-one 34. *n*-Butyllithium (1.6 M in hexane, 0.40 mL, 0.64 mmol) was added at −70 °C under nitrogen to a solution of methyltriphenylphosphonium bromide (230 mg, 0.64 mmol) in THF (2 mL). The mixture was brought to 0 °C, stirred for 15 min, and cooled to −70 °C. Compound **33** (100 mg, 0.32 mmol) in THF (2 mL) was added dropwise. The mixture was cooled to 0 °C and stirred for 1 h, treated with H_2O, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Crystallization from Et_2O gave **34** (40 mg, 40%) as a white solid; mp 215 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.4 Hz), 2.05−2.35 (2 H, m), 2.37 (3 H, s), 2.63 (6 H, s), 5.36 (1 H, d, J = 10.9 Hz), 5.85 (1 H, d, J = 10.9 Hz), 6.70 (1 H, m), 7.45 (1 H, t, J = 8.8 Hz), 7.60−7.75 (2 H, m), 7.95 (1 H, s), 12.70 (1 H, br s). Anal. ($C_{19}H_{22}N_2O_2 \cdot 0.25H_2O$) C, H, N.

(*E*)-3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]-2-methylacryl-

onitrile 35a. Following the procedure for **30**, compound **29** (10 mmol scale) was reacted with the potassium anion of diethyl 1-cyanoethylphosphonate, followed by acid treatment and N-methylation. Compound **35a**, a white solid, was obtained (11% overall yield from **25**); mp 196 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 7.2 Hz), 1.80−2.20 (2 H, m), 2.11 (3 H, d, J = 1.5 Hz), 2.20 (3 H, s), 2.44 (6 H, s), 7.55 (1H, s), 7.63 (1 H, t, J = 8.7 Hz), 7.77 (2 H, m), 7.85 (1 H, m), 11.70 (1 H, br s). Anal. ($C_{21}H_{23}N_3O_2$) C, H.

By reaction of **29** with the requisite diethyl phosphonates, compounds **35d**−**f** were obtained (the overall yield for the three operations is given in each case).

Compound **35d**: 28% yield; mp 105 °C (CH_3CN/*i*-Pr_2O); ^{1}H NMR (DMSO-d_6) δ 0.85 (3 H, t, J = 7.35 Hz), 1.85−2.15 (2 H, m), 2.20 (3 H, s), 2.47 (6 H, s), 7.40−7.60 (3 H, m), 7.78 (1 H, t, J = 8.8 Hz), 7.80 (2 H, d, J = 8.5 Hz), 7.90 (1 H, d, J = 8.8 Hz), 8.19 (1 H, s), 8.22 (1 H, d, J = 8.8 Hz), 8.38 (1 H, s), 11.70 (1H, br s). Anal. ($C_{26}H_{25}N_3O_2$) C, H, N.

Compound **35e**: 29% yield; mp 221 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 0.86 (3 H, t, J = 7.3 Hz), 1.85−2.15 (2 H, m), 2.16 (3 H, s), 2.48 (6 H, s), 7.17−7.22 (1 H, m), 7.48−7.53 (1 H, m), 7.70−7.76 (2 H, m), 7.90 (1 H, d, J = 8.8 Hz), 8.00 (1 H, s), 8.20 (1 H, d, J = 8.8 Hz), 8.40 (1 H, s), 11.80 (1 H, br s). Anal. ($C_{24}H_{23}N_3O_2S$) C, H, N.

Compound **35f**: 23% yield; mp 230 °C (CH_3CN/*i*-Pr_2O); ^{1}H NMR (DMSO-d_6) δ 0.85 (3 H, t, J = 7.1 Hz), 1.82−2.20 (2 H, m), 2.20 (3 H, s), 2.47 (6 H, s), 7.50−7.60 (1 H, m), 7.75 (1 H, t, J = 8.0 Hz), 7.92 (1 H, d, J = 8.8 Hz), 8.15 (1 H, d, J = 8.8 Hz), 8.25 (1 H, d, J = 8.8 Hz), 8.30 (1 H, s), 8.40 (1 H, s), 8.65 (1 H, d, J = 8.0 Hz), 8.99 (1 H, s), 11.80 (1 H, br s). Anal. ($C_{25}H_{24}N_4O_2$) C, H, N.

2-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-ylcarbonyl)benzylidene]malononitrile 35b. *n*-Butyllithium (1.6 M in hexane, 0.40 mL, 0.64 mmol) was added at −70 °C under nitrogen to a mixture of diisopropylamine (90 μL, 0.64 mmol) in THF (1 mL). The mixture was brought to 0 °C and cooled to −70 °C. A solution of malononitrile (42 mg, 0.64 mmol) in THF (1 mL) was added. The mixture was stirred at −70 °C for 1 h. A solution of **33** (100 mg, 0.32 mmol) in THF (1 mL) was added. The mixture was brought to 0 °C, stirred for 15 min, and then poured into ice−water and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.1), and the concentrated product fractions were crystallized from diisopropyl ether to give **35b** as a white powder (60 mg, 52%); mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.4 Hz), 2.05−2.30 (2 H, m), 2.37 (3 H, s), 2.59 (6 H, s), 7.71 (1 H, t, J = 8.8 Hz), 7.87 (1 H, s), 8.10 (1 H, d, J = 8.8 Hz), 8.22 (1 H, d, J = 8.8 Hz), 7.28 (1 H, s), 12.70 (1 H, br s). Anal. ($C_{21}H_{20}N_4O_2 \cdot 0.25H_2O$) C, H, N.

Following the procedure used to obtain **35b**, compound **33** was reacted with ethyl cyanoacetate. Compound **35c** was obtained as a white solid (14% yield); mp 200 °C (Et_2O); ^{1}H NMR (DMSO-d_6) δ 0.83 (3 H, t, J = 7.3 Hz), 1.32 (3 H, t, J = 7.1 Hz), 1.80−2.20 (2 H, m), 2.19 (3 H, s), 2.44 (6 H, s), 4.32 (2 H, q, J = 7.1 Hz), 7.70 (1 H, t, J = 8.8 Hz), 8.03 (1 H, d, J = 8.8 Hz), 8.27 (1 H, d, J = 8.8 Hz), 8.52 (1 H, s), 8.54 (1 H, s), 11.75 (1 H, br s). Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

***N*-[5-Ethyl-4-(3-hydroxymethylbenzoyl)-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide 36.** Sodium borohydride (0.31 g, 8.1 mmol) was added portionwise to a solution of **29** (2.6 g, 6.8 mmol) in CH_3OH (30 mL) at 5 °C. The mixture was stirred at 5 °C for 2 h, followed by addition of H_2O and extraction with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (cyclohexane/EtOAc 60/40) to afford **36** (1.2 g, 46%) as a pale yellow solid.

5-Ethyl-4-(3-hydroxymethylbenzoyl)-6-methyl-3-dimethylaminopyridin-2(1*H*)-one 37. Step 1: *N*-Pivaloyl/*O*-Methyl Imidate Cleavage. Compound **36** (1.2 g, 3.1 mmol) in 3 N HCl (15 mL) was refluxed for 2 h. The mixture was then poured into ice−water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was crystallized from EtOAc to give the free amine (0.75 g, 84%) as a pale yellow solid.

Step 2: N-Methylation. As described for **17c**, the 3-aminopyridinone intermediate (0.6 g, 2.1 mmol) was converted to **37** (0.51 g, 77%), as a white solid mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (3 H, t, J = 7,4 Hz), 1.80−2.15 (2 H, m), 2.20 (3 H, s), 2.45 (6 H, s), 4.57 (2 H, d, J = 4.4 Hz), 7.49 (1 H, t, J = 4.4 Hz), 7.55−7.65 (2 H, m), 7.80 (1 H, s), 11.7 (1 H, br s). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

Preparation of Compounds 39a−u via Phosphonium Salt 38: (*Z* and *E*) 5-Ethyl-6-methyl-3-(dimethylamino)-4-[3-(2-thiazol-2-yl-vinyl)benzoyl]pyridin-2(1*H*)-ones 39t and 39u: Example of the General Method. To **37** (1.25 g, 4 mmol) in CH_2Cl_2 (20 mL) was added dropwise thionyl chloride (0.9 mL, 12 mmol) at 5 °C. The mixture was stirred at 5 °C for 1 h and then at RT for 1 h, poured out into ice−water, and extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and concentrated to afford 4-(3-chloromethylbenzoyl)-3-(dimethylamino)-5-ethyl-6-methylpyridin-2(1*H*)-one (1.0 g, 75%) as a white solid.

A mixture of this choromethyl intermediate (1.0 g, 3 mmol) and triphenylphosphine (0.8 g, 3 mmol) in CH_3CN (28 mL) was refluxed for 48 h. The solvent was evaporated, the residue was taken up in Et_2O, filtered, washed with CH_3CN and dried to afford 3-(3-(dimethylamino)-5-ethyl-6-methyl-2-oxo-1,2-dihydropyridin)-4-yl-carbonylbenzyltriphenylphosphonium chloride **38** in quantitative yield (1.8 g).

To this intermediate (700 mg, 1.2 mmol) in THF (5 mL) under nitrogen was added portionwise potassium *tert*-butoxide (0.4 g, 3.6 mmol) at 5 °C. The mixture was stirred at 5 °C for 30 min, and then 2-thiazolecarboxaldehyde (140 mg, 1.2 mmol) in THF (5 mL) was added at 5 °C. The mixture was stirred at 5 °C for 10 min, H_2O was added, and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Compounds **39t** and **39u** were separated by silica gel column chromatography (CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.1) and crystallized from CH_3CN.

Compound **39t** (180 mg, 39%) white solid; mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.5 Hz), 2.05−2.32 (2 H, m), 2.35 (3 H, s), 2.61 (6 H, s), 6.95 (2 H, s), 7.18 (1 H, d, J = 3.3 Hz), 7.52 (1 H, t, J = 8.4 Hz), 7.70 (1 H, d, J = 8.4 Hz), 7.75 (1 H, d, J = 3.3 Hz), 7.88 (1 H, d, J = 8.4 Hz), 7.99 (1 H, s), 12.6 (1 H, br s). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

Compound **39u** (28 mg, 6%) white solid; mp > 260 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.5 Hz), 2.08−2.37 (2 H, m), 2.40 (3 H, s), 2.64 (6 H, s), 7.32 (1 H, d, J = 3.5 Hz), 7.38 (1 H, d, J = 16.0 Hz), 7.47−7.56 (2 H, m), 7.78 (1 H, d, J = 8.8 Hz), 7.81−7.88 (2 H, m), 8.03 (1 H, s), 12.8 (1 H, br s). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

***N*-[4-(3-Acetylbenzoyl)-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethyl-propionamide 40.** As described for **29**, this intermediate was obtained from **16** in three steps.

Step 1: Lithiation of **16** (6.7 g, 27 mmol)/condensation with 3-(2-methyl-[1,3]dioxolan-2-yl)benzaldehyde[54] (63% yield).

Step 2: Oxidation by MnO_2 was realized on a 17 mmol scale in 95% yield.

Step 3: Hydrolysis of dioxolane group afforded **40** in quantitative yield.

3-Dimethylamino-5-ethyl-4-[3-(1-hydroxyethyl)benzoyl]-6-methylpyridin-2(1*H*)-one 41. As described for **33**, this compound was obtained from **40** in two steps.

Step 1: *N*-Pivaloyl/*O*-methyl imidate cleavage was realized on 7 mmol scale in 84% yield.

Step 2: N-Methylation. As described for **17c**, the derived 3-aminopyridinone obtained above (1.7 g, 5.7 mmol) was converted to **41**, isolated as a white solid (0.5 g, 27% yield) after silica gel column chromatography (CH_2Cl_2/CH_3OH 97/3), mp 205 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (3 H, t, J = 7.3 Hz), 1.92−2.18 (2 H, m), 2.21 (3 H, s), 2.44 (6 H, s), 2.64 (3 H, s), 7.71 (1 H, t, J = 7.8 Hz), 8.00 (1 H, d, J = 7.8 Hz), 8.26 (1 H, d, J = 7.8 Hz), 8.29 (1 H, s), 12.80 (1 H, br s). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

(*E*)-3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]-but-2-enenitrile 42. As described for **27**, compound **42** was obtained from **41** (0.10 g, 0.3 mmol) and diethyl cyanomethylphosphonate in 64% yield as a white solid mp 204 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.4 Hz), 2.09−2.38 (2 H, m), 2.40 (3 H, s), 2.56 (3 H, d, J = 1.0 Hz), 2.63 (6 H, s), 5.74 (1 H, d, J = 1.0 Hz), 7.55 (1 H, t, J = 7.7 Hz), 7.70 (1 H, d, J = 7.7 Hz), 7.83 (1 H, d, J = 7.7 Hz), 8.09 (1 H, t, J = 1.5 Hz), 13.10 (1 H, br s). Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

(*E*)-3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]-2-methylbut-2-enenitrile 43. As described for **27**, compound **43** was obtained from **41** (130 mg, 0.4 mmol) and diethyl (1-cyanoethyl)phosphonate in 18% yield as a white solid mp 184 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.5 Hz), 1.84 (3 H, d, J = 1.4 Hz), 2.09−2.35 (2 H, m), 2.37 (3 H, s), 2.40 (3 H, d, J = 1.4 Hz), 2.61 (6 H, s), 7.39 (1 H, d, J = 8.8 Hz), 7.53 (1 H, d, J = 8.8 Hz), 7.67 (1 H, s), 7.82 (1 H, d, J = 8.8 Hz), 12.4 0(1 H, br s). Anal. ($C_{22}H_{25}N_3O_2$) C, H, N.

3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]propionitrile 44. A mixture of **30** (200 mg, 0.6 mmol) in methanol (40 mL) was hydrogenated under a 3 bar pressure for 2 h, using 10% Pd−C (100 mg) as the catalyst. The catalyst was removed by filtration through Celite and washed with methanol, and the filtrate was concentrated. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH 97/3). Crystallization from CH_3CN and *i*-Pr_2O afforded **44** (100 mg, 50%) as a white solid mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.4 Hz), 2.05−2.35 (2 H, m), 2.37 (3 H, s), 2.62 (6 H, s), 2.70 (2 H, t, J = 7.3 Hz), 3.05 (2 H, t, J = 7.3 Hz), 7.40−7.55 (2 H, m), 7.71 (1 H, d, J = 8.8 Hz), 7.79 (1 H, s), 12.50 (1 H, s). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

3-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]-2-methylpropionitrile 45. Similar preparation starting from the compound **35a** gave the corresponding analogue **45** as a pale yellow solid (20% yield), mp 162 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.4 Hz), 1.38 (3 H, d, J = 6.3 Hz), 2.05−2.35 (2 H, m), 2.37 (3 H, s), 2.62 (6 H, s), 2.87−3.10 (3 H, m), 7.42−7.53 (2 H, m), 7.70−7.80 (2 H, m), 12.80 (1 H, br s). Anal. ($C_{21}H_{25}N_3O_2$) C, H, N.

***N*-[4-(3-Cyanomethylbenzoyl)-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide 46. Step 1: Chloration by $SOCl_2$.** To **36** (4 g, 10.4 mmol) in CH_2Cl_2 (120 mL) was added dropwise thionyl chloride (2 mL, 27 mmol) at 5 °C. The mixture was stirred at 5 °C for 1 h and then at RT for 1 h, poured into ice−water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford *N*-[4-(3-chloromethylbenzoyl)-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide (4.2 g, 100%).

Step2: Cyanation. To this intermediate (3.7 g, 9.2 mmol) in EtOH (20 mL) were added water (14 mL) and then sodium cyanide (0.78 g, 15.7 mmol). The mixture was stirred at 80 °C for 2 h, poured into 10% K_2CO_3 solution, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was silica gel column chromatographed (cyclohexane/EtOAc 60/40) to give a residue which was crystallized from diisopropyl ether to afford *N*-[4-(3-cyanomethylbenzoyl)-5-ethyl-2-methoxy-6-methylpyridin-3-yl]-2,2-dimethylpropionamide **46** (2.6 g, 72%).

***N*-{4-[3-(1-Cyanoethyl)benzoyl]-5-ethyl-2-methoxy-6-methylpyridin-3-yl}-2,2-dimethylpropionamide 47.** Potassium *tert*-butoxide (0.54 g, 4.8 mmol) was added at 5 °C under nitrogen to a solution of **46** (1.72 g, 4.4 mmol) in THF (15 mL), and the mixture was stirred at 5 °C for 30 min. Iodomethane (0.30 mL, 4.8 mmol) in THF (3 mL) was then added. The mixture was stirred at 5 °C for 2 h, poured into ice−water, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was silica gel column chromatographed (CH_2Cl_2/EtOAc 93/7) to give a residue which was crystallized from CH_3CN to afford **47** (0.40 g, 22%) as a white solid mp 131 °C.

[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridin-4-yl-carbonyl)phenyl]acetonitrile 48. According to the procedure described for **18a**, the intermediate **46** (2.5 g, 6.4 mmol) was successively submitted to *N*-pivaloyl/*O*-methyl imidate cleavage (85% yield) and N-methylation to give **48**(1.2 g, 75%) as white solid mp 193 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.4 Hz), 2.05−2.35 (2 H, m), 2.38 (3 H, s), 2.62 (6 H, s), 3.85 (2 H, s), 7.52 (1 H, t, J = 8.4 Hz), 7.60 (1 H, d, J = 8.4 Hz), 7.78 (1 H, d, J = 8.4 Hz), 7.89 (1 H, s), 13.0 (1 H, br s). Anal. ($C_{19}H_{21}N_3O_2$) C, H, N.

2-[3-(5-Ethyl-6-methyl-3-(dimethylamino)-2-oxo-1,2-dihydropyridine-4-yl-carbonyl)phenyl]propionitrile 49. According to the procedure described for **18a**, the intermediate **47** (0.30 g, 0.7 mmol) was successively submitted to *N*-pivaloyl/*O*-methyl imidate cleavage (78% yield) and N-methylation to give **49** (40 mg, 23%) as a white solid mp 168 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.5 Hz), 1.71 (3 H, d, J = 7.3 Hz), 2.05−2.34 (2 H, m), 2.38 (3 H, s), 2.62 (6 H, s), 4.02 (1 H, q, J = 7.3 Hz), 7.53 (1 H, t, J = 8.8 Hz), 7.68 (1 H, d, J = 8.8 Hz), 7.79 (1 H, d, J = 8.8 Hz), 7.90 (1 H, s), 12.70 (1 H, br s). Anal. ($C_{20}H_{23}N_3O_2$·0.25H_2O) C, H, N.

5-Ethyl-6-methyl-3-(dimethylamino)-4-(3-phenoxymethylbenzoyl)pyridin-2(1*H*)-one 50. To **36** (3.8 g, 10 mmol), triphenylphosphine (3.9 g, 15 mmol), and phenol (3.7 g, 40 mmol) in THF (40 mL) under nitrogen was added dropwise diethyl azodicarboxylate (2.4 mL, 15 mmol) at 5 °C. The mixture was stirred at RT for 12 h. Water was added, and the mixture was extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was silica gel column chromatographed (CH_2Cl_2/CH_3OH 99/1) to afford *N*-[5-ethyl-2-methoxy-6-methyl-4-(3-phenoxymethylbenzoyl)pyridin-3-yl]-2,2-dimethylpropionamide (3.4 g, 75%).

This intermediate (3.4 g, 7.4 mmol) was then successively submitted to *N*-pivaloyl/*O*-methyl imidate cleavage and N-methylation as described for **18a** to give **50** (0.51 g; 18% yield); mp 186 °C; ^{1}H NMR (DMSO-d_6) δ 0.80 (3 H, t, J = 7.4 Hz), 1.80−2.14 (2 H, m), 2.19 (3 H, s), 2.44 (6 H, s), 5.21 (2 H, s), 6.90−7.03 (3 H, m), 7.28 (2 H, t, J = 8.2 Hz), 7.57 (1 H, t, J = 9.3 Hz), 7.74 (2 H, d, J = 9.3 Hz), 7.86 (1 H, s), 11.70 (1 H, br s). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

3-Dimethylamino-5-ethyl-4-[3-(1-hydroxyethyl)benzoyl]-6-methylpyridin-2(1*H*)-one 51. This compound was obtained in three steps from benzaldehyde derivative **29**.

Step 1: Grignard reaction was realized on 2.0 g, (5.2 mmol) of **29** (60% yield) with 3.3 equivalents of CH_3MgI.

Step 2: *N*-Pivaloyl/*O*-methyl imidate cleavage was realized on 3 mmol (70% yield).

Step 3: N-Methylation. The intermediate 3-aminopyridone (0.63 g, 2.1 mmol) was converted to **51** as a white solid (0.35 g, 51% yield) after silica gel column chromatography (CH_2Cl_2/CH_3OH/NH_4OH 93/7/0.5), mp 192 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (3 H, t, J = 7.4 Hz), 1.32 (3 H, d, J = 6.4 Hz), 1.85−2.18 (2 H, m), 2.20 (3 H, s), 2.46 (6 H, s), 4.80 (1 H, m), 5.31 (1 H, d, J = 4.3 Hz), 7.48 (1 H, t, J = 8.8 Hz), 7.59−7.67 (2 H, m), 7.80 (1 H, s), 11.70 (1 H, br s). Anal. ($C_{19}H_{24}N_2O_3$) C, H, N.

Biology. Evaluation of Antiviral Activity of the Compounds. Cells and Viruses. MT4 cells are human T-lymphoblastoid cells that are highly sensitive to HIV infection, producing a rapid and pronounced cytopathic effect. All cells were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum and antibiotics in a humidified incubator with a 5% CO_2 atmosphere at 37 °C.

Site-Directed Mutants. Mutant RT coding sequences were generated from a pGEM vector containing the HIV-1 LAI (clone HXB2) protease (PR) and RT coding sequence, using the QuikChange Site-Directed Mutagenesis Kit (Stratagene), and HPLC-purified primers (Genset Oligos). Plasmids were checked to confirm that they contained the desired mutations by sequencing. Mutant viruses were created by recombination of the mutant PR-RT sequence with a PR-RT deleted HIV-1 HXB2 proviral clone.[48]

Drug Sensitivity Assays. The antiviral activity of compounds against laboratory adapted strains, site-directed mutants, and clinical sample-derived recombinant viruses was

tested using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay as previously described.[48,55] Briefly, various concentrations of the test compounds were added to wells of a flat-bottom microtiter plate. Subsequently, virus and MT4 cells were added to a final concentration of 200 CCID50/well and 30 000 cells/well, respectively. To determine the toxicity of the test compound, mock-infected cell cultures, containing an identical compound concentration range, were incubated in parallel with the virus infected cell cultures. After 5 days of incubation (37 °C, 5% CO_2), the viability of the cells was determined using MTT. The results of drug susceptibility assays were expressed as an EC_{50} defined as the concentration of drug at which there was 50% infection compared with the drug-free control. In some cases a fold change in susceptibility was calculated by dividing the EC_{50} for the tested virus by the EC_{50} for the wild-type virus (HIV-1 LAI) tested in parallel. Toxicity results are expressed as CC_{50}, defined as the concentration of drug at which the cell viability was reduced by 50% compared to the drug-free control.

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Supporting Information Available: Synthetic procedure and intermediate and final product characterzation. This material is available free of charge via the Internet at http://pubs.acs.org.

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