Journal of Medicinal Chemistry Article

J. Med. Chem. **2009,** *52,* 7473–7487 **7473**
DOI: 10.1021/jm900802y

Synthesis and Biological Evaluation of C-5 Methyl Substituted 4-Arylthio and 4-Aryloxy-3-Iodopyridin-2(1*H*)-one Type Anti-HIV Agents†

Jérôme Guillemont,*,‡ Abdellah Benjahad,§ Said Oumouch,§ Laurence Decrane,‡ Patrice Palandjian,‡ Daniel Vernier,‡ Laurence Queguiner,‡ Koen Andries,∥ Marie-Pierre de Béthune,⊥ Kurt Hertogs,⊥ David S. Grierson,§ and Chi Hung Nguyen*,§

‡*TIBOTEC, Medicinal Chemistry Department, Campus de Maigremont BP315, 27430 Val de Reuil, France,* §*UMR 176 CNRS-Institut Curie, Laboratoire de Pharmacochimie, Section de Recherche, Bâtiment 110, Centre Universitaire, 91405 Orsay, France,* ∥*Johnson&Johnson Pharmaceutical Research and Development, Virology Drug Discovery, Tumhoutseweg 30, B-2340 Beerse, Belgium, and* ⊥*TIBOTEC, Generaal De Wittelaan L 11 B3, B-2800 Mechelen, Belgium*

Received June 4, 2009

A series of C-5 methyl substituted 4-arylthio- and 4-aryloxy-3-iodopyridin-2(1*H*)-ones has been synthesized as new pyridinone analogues for their evaluation as anti-HIV inhibitors. The optimization at the 5-position was developed through an efficient use of the key intermediates 5-ethoxycarbonyl- and 5-cyano-pyridin-2(1*H*)-ones (**14** and **15**). Biological studies revealed that several compounds show potent HIV-1 reverse transcriptase inhibitory properties, for example, compounds **93** and **99** are active at 0.6−50 nM against wild type HIV-1 and a panel of major simple/double HIV mutant strains.

Introduction

Combination therapy or HAART[a] is the only effective strategy for the treatment of AIDS. However, in some patients, the long-term use of nucleoside and non-nucleoside RT inhibitors, in combination with protease inhibitors, leads ultimately to serious problems of drug resistance, toxicity, and associated side effects (lipodystrophy, hyperlipidaemia, etc.).[1−5] To treat AIDS as a chronic infection, it is thus important to continually find more potent and less toxic drugs that display a high level of activity against the clinically relevant HIV single and multiple mutant strains. This criterion is of particular importance to the development of the NNRTI class of compounds for which it has been shown that cross resistance is a major concern.

In our laboratories, it was found that 3-amino-4-phenylthiopyridinones of general structure **1** are potent inhibitors of wild type HIV-1 reverse transcriptase.[6] SAR studies on this series led to the identification of the 3-dimethylamino-4-benzyl and 4-benzoylpyridinones **2** and **3** as promising lead compounds.[7] Further systematic optimization of these molecules through modification of the substituents on the phenyl ring gave analogues **4** and **5**, displaying nanomolar range activities in vitro against a wide panel of HIV-1 mutant strains commonly encountered in HIV infected patients.[8] Preliminary indications are that analogues of **2**, such as **6**, in which the C-5 ethyl group is replaced by a longer heteroalkyl chain, will also possess promising activity profiles.[9]

Recently, we described the preparation and anti-HIV properties of a new 3-iodopyridinone based anti-HIV agent **7** in which the 3,5-dimethylphenyl motif is linked to the central heterocycle via an oxygen bridge.[10] In the optimization of this new series, we chose to first look at the influence on activity of the introduction of different heteroatoms/heterocycles into the C-5 side chain. This work is inspired from our own studies on compounds **2**/**3**[8,9] and from the large amount of background work on different HEPT systems (cf. MKC-442 and GCA-186).[11−13] In particular, Pedersen et al. recently showed that HEPT analogues bearing an allyoxy side chain at N-1 are very potent RT inhibitors.[14a]

The encouraging biological results obtained in our pyridinone series inspire new developments of this privileged scaffold. Elsewhere, very recently, a closely related family, the 4-cycloalkyloxypyridin-2(1*H*)-one derivatives, has been synthesized and good antiviral activities against mutant viral strains were reported.[14b]

In the present report, we describe an efficient strategy for the rapid synthesis of a diverse library of C-5 modified

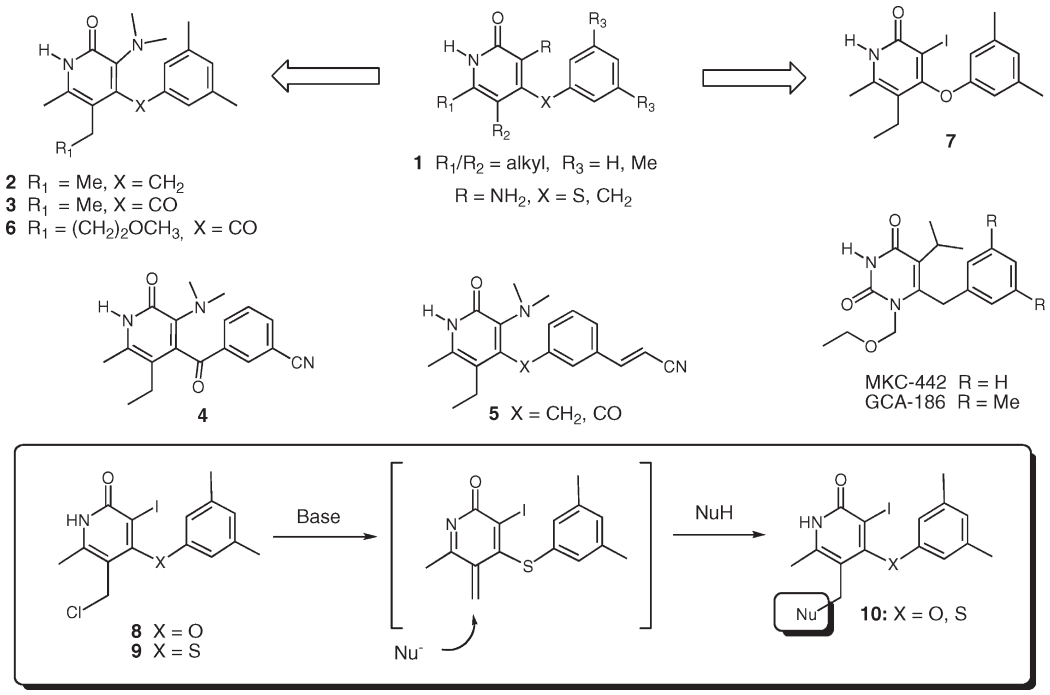
†For the 100th anniversary of the Division of Medicinal Chemistry: The research described in this paper is a prime example of the strengths of medicinal chemistry. The interplay between chemical synthesis and pharmacological testing enabled the delineation of structure−activity relationships and the rational design of improved NNRTIs. The design of better drugs is not only of pure scientific importance but may have a positive impact on the lives of large numbers of patients worldwide, which is another vital aspect of the field of medicinal chemistry. The here-described optimization of the IOPY and ISPY series of NNRTIs was based on the concerted efforts and enthusiasm of many people from many disciplines, researchers originating both from academia and the industry. The ACS Division of Chemistry plays a crucial role to facilitate this kind of collaborative research and to disseminate the findings. Moreover, the efforts of the ACS Division of Chemistry to promote the practice of medicinal chemistry are fundamental to ensure the inflow of young medicinal chemists. Therefore, we are happy for the opportunity to dedicate the research described here to the 100-year-old ACS Division of Medicinal Chemistry.

*To whom correspondence should be addressed. For J.G.: phone, 33-2-32 61 74 58; fax, 33 2 32 61 72 98; e-mail,jguillem@its.jnj.com. For C.H.N.: phone, 33-1 69 86 30 89; fax, 33-1 69 07 53 81; e-mail, chi.hung@curie.up-sud.fr.

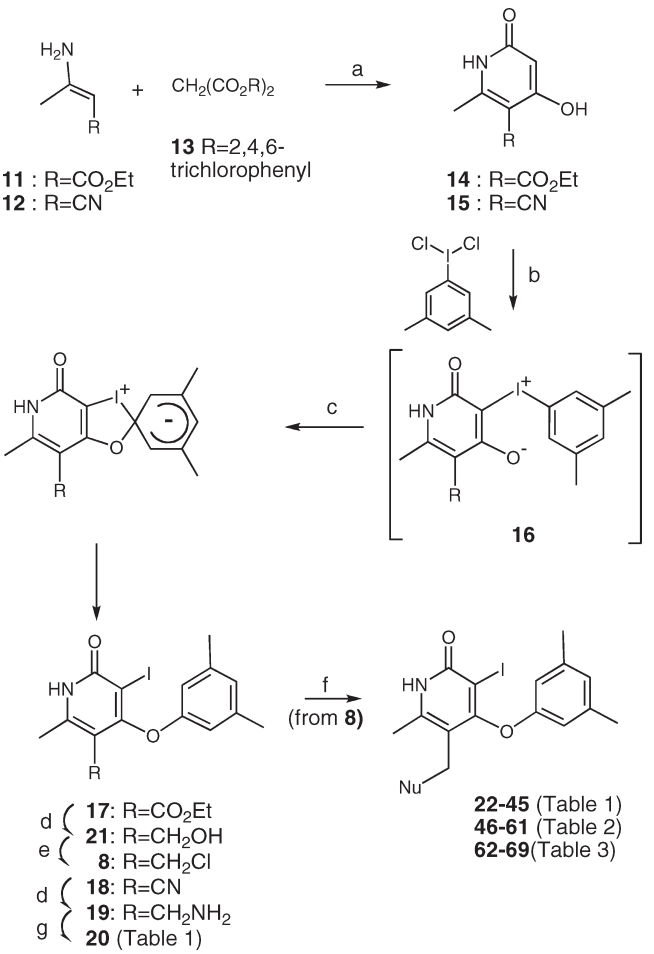
[a] Abbreviations: HIV-1, human immunodeficiency virus-1; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; RT, reverse transcriptase; NNRTI, non-nucleoside reverse transcriptase inhibitor; LAI, wild type HIV-1; Lys103Asn, K103N mutant strain; Tyr181Cys, Y188C mutant strain; Tyr188Leu, Y188L mutant strain; SAR, structure−activity relationship; IC_{50}, 50% inhibitory concentration for inhibition of viral cytopathicity; IOPY, iodoaryloxypyridinone; ISPY, iodoarylthiopyridinone; HEPT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine; DMF, dimethylformamide; DIBAL-H, diisobutylaluminum hydride; NIS, *N*-iodosuccinimide.

Published on Web 07/31/2009

Scheme 1. Structures of Lead Compounds in Various Stages of Development and Design of New 5-Methyl Substituted Analogues **10**



Scheme 2. Synthesis of 5-Methyl Substituted-4-phenoxy Derivatives[a]



[a] Conditions: (a) diglyme, 120 °C, 2 h; (b) Na_2CO_3, H_2O, rt; (c) DMF, rfx; (d) DIBAL-H; (e) $SOCl_2$; (f) Nu-H, K_2CO_3; (g) coumarilic acid, EDCI, HOBT, NEt_3.

3-iodo-4-aryloxypyridinones (IOPY's) and 3-iodo-4-arylthiopyridinones (ISPY's) (Scheme 1).

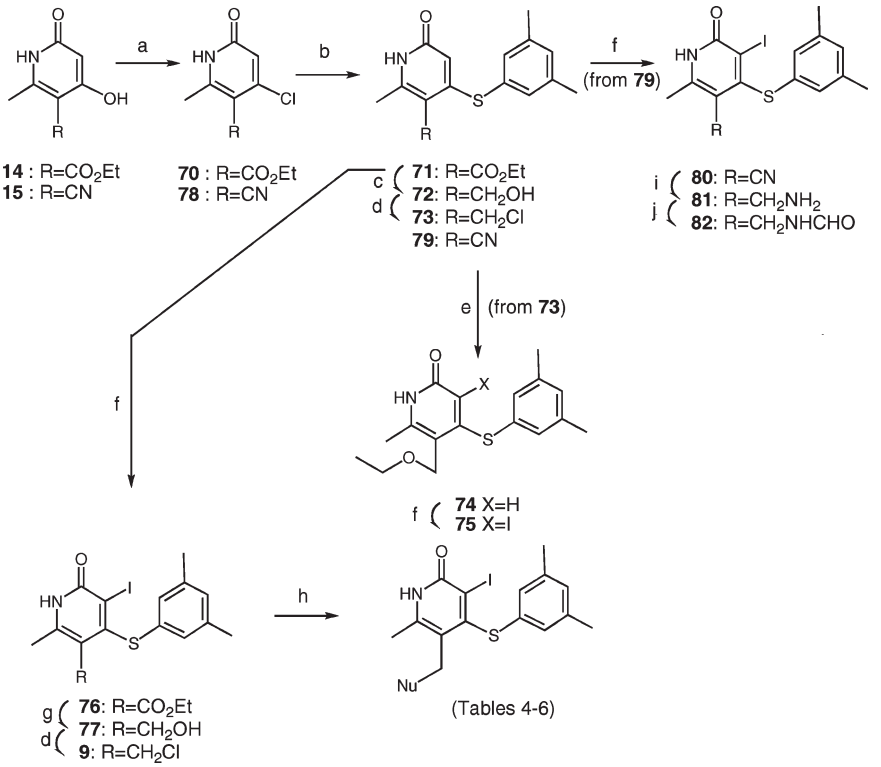
Naturally, new 5-methyl substituted **10** could be prepared by a simple SN2 pathway from **8** and **9**. However, the approach, which was based on the idea that treatment of the 5-chloromethyl substituted pyridinones **8** and **9** with mild base would lead to formation of a conjugated imine intermediate, in turn would react with a nucleophile present in the medium to give **10**.

In this paper, applying this concept, a 48-member library of new IOPY analogues was prepared from compound **8** (Scheme 2), and each component was evaluated for its anti-HIV activity in vitro. Similarly, a 43-member library of related 3-iodo-4-arylthiopyridinones (ISPY's) was prepared from the corresponding 5-chloromethyl substituted pyridinone **9** (Scheme 3) and tested. It is worth mentioning that, of the more than 300 molecules synthesized in this work, appoximately 200 displayed activity at submicromolar concentrations (IC_{50} < 100 nM) against wild type RT. Of these, 106 analogues were active in the 1−10 nM range and a selection is shown in Tables 1−6. On the basis of the further evaluation of these molecules against the three principle HIV mutant strains Y181C, Y188L, and K103N, a number were chosen for screening against a wider panel of HIV single and double mutants (Table 7). Comparison of the in vitro results for these compounds to the data for lead compounds **2**/**3** and **7**, as well as to nevirapine and efavirenz, it is clear that the optimized compounds **46**, **93**, and **99** have an activity profile that is superior to the two clinically used NNRTI drugs. Analysis of the structure for the compound **24** wild-type RT complex provided a molecular basis for understanding the contribution of the C-5 side chain substituent in these molecules to their anti-HIV activity.[15] Taken together, the biological and the structural data serve as a valuable guide to the further optimization of the anti-HIV activity of the 3-iodopyridinone (IOPY/ISPY) family.

Chemistry

The key intermediate **8** required for production of the C-5 modified IOPY library was prepared in five steps (Scheme 2).

Scheme 3. Synthesis of 5-Methyl Substituted-4-phenylthio Derivatives[a]



[a] Conditions: (a) (i) $POCl_3$, $BnNEt_3Cl$, CH_3CN reflux; (ii) NaOAc, AcOH rfx. (b) 3,5-Dimethylthiophenol. (c) LAH. (d) $SOCl_2$. (e) NaOEt, EtOH rfx. (f) NIS. (g) DIBAL-H. (h) Nu-H, K_2CO_3. (i) $BH_3 \cdot (CH_3)_2S$, THF. (j) HCO_2H, NH_2CHO.

The first step involved formation of the 5-carbethoxy substituted pyridinone **14**, which has been described in the literature.[16a]

Compound **14** was previously synthesized in 8% yield over two steps starting from ethyl 3-aminocrotonate, which was converted to ethyl 3-amino-2-(2-cyano)acetylbut-2-enoate and cyclized to form the pyridinone ring. We found that this compound **14** was conveniently prepared in 75% yield in single step through condensation of ethyl 3-aminocrotonate **11** with the activated malonate derivative **13** in the absence of added base. The reaction of **14** at room temperature with dichloroiodo-3,5-dimethylbenzene in water containing Na_2CO_3 led to rapid formation of dipole **16**.[16b] This intermediate was isolated by simple filtration, dried under vacuum, and then heated in dry DMF at reflux in order to effect rearrangement to the 3-iodo-4-phenoxysubstituted **17** (75% yield from **14**). Conversion of **17** to **8** involved ester reduction using DIBAL-H, leading to hydroxymethyl derivative **21**, which was followed by reaction with thionyl chloride. This chloromethyl intermediate **8** in either ethanol, acetonitrile or dioxane (see Experimental Section) was treated with Et_3N or K_2CO_3 and reacted with a battery of oxygen, nitrogen, and sulfur containing open chain nucleophiles (compounds **22**−**45**; Table 1), five-membered ring heterocycles (compounds **46**−**61**; Table 2), and six-membered nitrogen heterocycles (compounds **62**−**69**; Table 3).

Similarly, the pyridine-3-carbonitrile derivative **15** was prepared by condensation of aminobutenenitrile **12** with trichlorophenylmalonate **13**. Conversion of this intermediate to **18**, followed by nitrile reduction using DIBAL-H and peptide coupling of the resulting 5-aminomethyl derivative **19** with coumarilic acid, gave amide **20**.

In the ISPY series, the pivotal intermediate **71** was prepared by converting pyridinone **14** to the corresponding 4-chloro derivative **70** and reacting this compound with 3,5-dimethylthiophenol in ethanol (31% yield for the two steps) (Scheme 3).

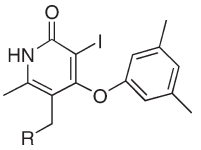
The 5-ethoxymethyl compound **75** (Table 4) was obtained from this ester via reduction to **72**, chlorination, reaction of the chloromethyl derivative **73** with NaOEt, and introduction of the 3-iodo substituent by reaction of **74** with NIS. Preparation of the chloromethyl intermediate **9** from ester **71** involved introduction of the iodo group prior to modification of the C-5 position. This intermediate was treated with K_2CO_3 in CH_3CN or Et_3N in EtOH and reacted with different oxygen, nitrogen, and sulfur containing open-chain nucleophiles (compounds **83**−**92**; Table 4), five-membered ring heterocycles (compounds **93**−**111**; Table 5), and six-membered nitrogen heterocycles (compounds **112**−**125**; Table 6).

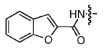
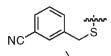
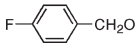
Results and Discussion

The entire collection of C-5 modified 3-iodo phenoxy and thiophenylpyridinone analogues were evaluated in vitro against wild type HIV-1 (HTLV IIIB, LAI cell line) and were further tested against the three principle mutant strains, K103N, Y181C, and Y188L, which confer resistance to the NNRTI's currently used in clinic.[17,18] The biological results for this new collection of **96** compounds are presented in Tables 1−6.

Looking at the data for IOPY **7** against the three mutant strains, one sees that it is 3- and 10-fold more active than efavirenz (see Table 7) against the Y188L and K103N mutants, respectively, but 10-fold less sensitive than this drug against the Y181C mutant strain. We thus began the analysis of the data in Tables 1−6 by identifying the analogues that inhibit the Y181C mutant with the IC_{50} value set at less than 35 nM. Of the **96** compounds, 51 in the initial list fell into this

Table 1. Biological Activity of C-5 Modified 3-Iodo Phenoxy Pyridinone (IOPY) Analogues[a]

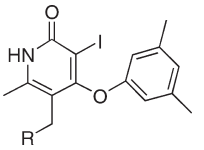


Cpd	R	IC_{50} (nM)					Chemical Synthesis			
		LAI	SI[1]	K103N	Y181C	Y188L	Method[2]	Reaction time (h)/(°C)	Purification method[3]	Yield (%)
7	CH_3	1.25	9,000	3.16	19.9	50.1	See reference 10			
20		6.3	>15,849	199	31.6	158	See experimental section			
21	OH	5.0	>19,953	158	158	3162	See experimental section			
22	OC_2H_5	0.63	>158,489	6.3	6.3	125	See experimental section			
23		1.0	>100,000	1.0	6.3	7.9	A	3/80	d	20
24		1.25	>79,433	1.0	5.0	31.6	Example of the General Method (Method A)			52
25	SC_2H_5	1.25	>79,433	6.3	6.3	31.6	A	3/80	c	53
26	$SCH_2CONHCH_3$	1.58	>60,096	3.98	19.9	158	A	16/80	a	77
27	$O(CH_2)_2OCH_3$	1.58	>63,096	50.1	10.0	158	See experimental section			77
28	$S(CH_2)_2OCH_3$	1.99	>50,119	1.58	7.94	31.6	A	3/80	c	18
29	$O(CH_2)_2OH$	1.99	>50,119	39.8	31.6	501	See experimental section			48
30		2.51	>39,811	1.0	19.9	39.8	A	3/80	d	34
31		3.16	19,953	1.58	6.3	794	A	3/80	f	29
32		5.01	12,589	31.6	39.8	251	Example of the General Method (Method B)			42
33		5.0	>19,953	25.1	25.1	100	C	18/100	d	35
34	$SCH(CH_3)_2$	5.0	>19,953	12.5	39.8	316	A	3/80	a	31
35	$SCH_2C_6H_5$	6.3	>15,849	7.94	15.8	31.6	A	3/80	b	69
36		6.3	>15,849	6.3	31.6	50.1	Example of the General Method (Method C)			38
37	$C_2H_5SO_2$	7.94	>12,589	39.8	158	794	See experimental section			
38		7.94	>12,589	31.6	39.8	501	C	15/100	f	16
39		7.94	>12,589	7.94	25.1	79.4	C	15/100	f	19
40		7.94	>12,589	25.6	63	158	A	3/80	d	10
41	$(CH_3)_2CHCH_2S$	7.94	>12,589	25.1	50.1	794	A	3/80	a	42
42		7.94	>12,589	25.1	39.8	1995	A	3/80	a	74
43	$C_6H_5CH_2O$	7.94	>12,589	31.6	31.6	125	C	18/100	c	63
44		10.0	>10,000	31.6	100.0	630	A	3/80	a	68
45	SCH_2CO_2Et	10.0	>10,000	nd	nd	nd	A	3/80	a	57

[a] [1]Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold). [2]Method A: ethanol, triethylamine, sealed tube; method B: acetonitrile, K_2CO_3, reflux; method C: dioxane, K_2CO_3, reflux. [3]a: Crystallization from EtOH; b: crystallization from *i*-Pr_2O; c: column chromatography on silica, eluent CH_2Cl_2/MeOH: 99/1; d: column chromatography on silica, eluent CH_2Cl_2/MeOH: 98/2; e: column chromatography on silica, eluent CH_2Cl_2/2-propanol: 98/2 then crystallization from Et_2O; f: column chromatography on silica, eluent CH_2Cl_2/2-propanol: 98/2 then crystallization from Et_2O.

category, indicating that a wide variation in the nature of the substitutents at C-5 was compatible with activity against this key mutant. Being more restrictive, only 16 compounds in this set (**22**, **23**, **24**, **25**, **27**, **28**, **31**, **46**, **47**, **48**, **93**, **95**, **98**, **99**, **102**, **108**) were active, like efavirenz, in the 1−10 nM concentration range. Similarly, more than half (54) of the C-5 substituted pyridinone analogues in Tables 1−6 were active against the K103N mutant in the IC_{50} range < 10 nM, indicating that modification in the nature of the substitutent at C-5 also has little effect on sensitivity toward this mutation. Looking finally at the activities against the Y188L mutant strain, the upper limit for the IC_{50} value was set at 50 nM. Twenty compounds were identified. Of these, 12 cross reference with the molecules selected as highly active against Y181C and

Table 2. Substitution of the C-5 Methyl by Azole Derivatives on the IOPY Scaffold[a]



Cpd	R	IC_{50} (nM)					Chemical Synthesis[1]		
		LAI	SI[2]	K103N	Y181C	Y188L	Reaction time (h)	Purification method[3]	Yield (%)
46		0.79	>100,000	1.4	5.9	10.3	16	c	15
47		1.99	>50,118	2.51	10.0	31.6	16	a	87
48		1.99	>50,118	3.98	10.0	100	16	a	67
49		2.51	>39,810	7.94	31.6	79.4	16	c	37
50		3.98	15,848	7.94	50.1	125	3	d	27
51		3.98	>25,118	15.8	31.6	125	2	-	24
52		5.01	>19,952	6.30	31.6	316	16	a	86
53		5.01	>19,952	10.0	31.6	125	16	c	36
54		6.3	>15,848	15.8	39.8	251	1	d	42
55		6.3	>15,848	12.5	39.8	125	16	b	64
56		6.3	>15,858	7.94	31.6	31.6	16	c	38
57		7.9	>3,981	nd	nd	Nd	16	c	20
58		7.9	>3,981	nd	nd	Nd	16	b	69
59		7.9	>12,589	39.8	39.8	125	16	c	31
60		7.94	>12,589	7.94	31.6	100.0	16	c	29
61		10.0	>10,000	31.6	199	1000	16	c	25

[a] [1]General procedure B was applied by reluxing in acetonitrile. [2]Selectivity Index or ratio of CC_{50} to IC_{50} relative to LAI (fold). [3]a: Crystallization from *i*-Pr_2O, b: crystallization from CH_3CN, c: column chromatography on silica, eluent CH_2Cl_2/MeOH/NH_4OH: gradient of elution 100/0/0 to 90/10/0.1, d: column chromatography on silica, eluent CH_2Cl_2/MeOH: 98/2 then crystallization from Et_2O.

K103N (**23**, **24**, **25**, **28**, **46**, **47**, **93**, **98**, **99**, **102**, **106**, and **108**). Note, in particular, that three of these compounds, **23**, **46**, and **99**, approach the 10 nM level for the Y188L mutant, which corresponds to a significant improvement in activity relative to efavirenz. These 12 compounds were selected for further evaluation against the larger panel of mutants (Table 7).

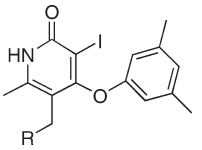
However, before analyzing this data, it is of interesting to look at the trends in substitution versus activity in the two series of analogues. Introduction of a sulfur atom into the C-5 side chain of the IOPY's, as in **25** and **28** (Table 1), results in a molecule that is comparable in activity to the 5-methoxypropyl-3-dimethylaminopyridinone analogue **6**. Indeed, the latter was active with IC_{50} (nM) values of 2, 10, 50, and 200 at LAI and 103N, 181C, and 188L mutant strains, respectively.[9]

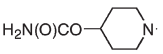
Both these analogues are significantly more active against the Y188L mutant than the corresponding oxygen containing compounds **22** and **27** and the sulfur analogue **26** with an additional terminal *N*-methyl amide motif. Note that there is a significant and even total loss of activity against this mutant Y188L when a terminal OH group is present in the C-5 side chain (cf. **21** and **29**). In contrast to **21**, the related analogue of **2** with an hydroxymethyl substituent at C-6 remains moderately active against the Y188L mutant (IC_{50} = 630 nM).[9]

Compounds **35**, **39**, and **43** with an *S*/*O*-benzyl group incorporated into the C-5 side chain were found to be potent inhibitors of the three mutant strains, even if the activities for the oxygen analogue **43** is just outside the cut off limit. The corresponding compounds **23**, **24**, **30**, and **36**, wherein the phenyl ring was replaced by a thiazole, thiophene, or furan ring, were also highly active against the three mutant strains. Indeed, thiazole **23** displays excellent acitivity against all three of the major mutants. Note, however, that the thiazole analogue **42** (and **87**) is inactive against the Y188L mutant and that there is a small loss in activity against this mutant for the isomeric thiophene analogue **33** relative to **36**.

As illustrated (Table 2), compounds **46**−**61**, where the pyridinone nucleus is separated from a second heterocyclic ring by a simple methylene linker, are all highly active against

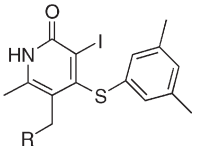
Table 3. Substitution of the C-5 Methyl by Substituted Cyclic Amines on the IOPY Scaffold[a]



Cpd	R	IC$_{50}$ (nM)					Chemical Synthesis[1]		
		LAI	SI[2]	K103N	Y181C	Y188L	Reaction time (h)	Purification method[3]	Yield (%)
62		3.98	19,953	6.30	31.6	199	2	c	10
63		6.30	>15,849	6.30	31.6	100	1	c	52
64		6.30	7,943	1.99	25.1	50.1	See experimental section		
65		6.30	>15,849	6.30	15.8	39.8	2	a	84
66		6.30	>15,849	1.99	25.1	50.1	2	a	75
67		6.30	>15,849	7.94	39.8	125	1	b	80
68		10.0	1,585	25.1	125	158	3	c	87
69		10.0	>10,000	nd	nd	nd	3	a	88

[a] [1]General procedure B was applied by reluxing in acetonitrile. [2]Selectivity index or ratio of CC$_{50}$ to IC$_{50}$ relative to LAI (fold). [3]a: Crystallization from *i*-Pr$_2$O; b: crystallization from CH$_3$CO$_2$C$_2$H$_5$; c: column chromato on silica, eluent CH$_2$Cl$_2$/MeOH/NH$_4$OH: gradient of elution 100/0/0 to 90/10/0.1.

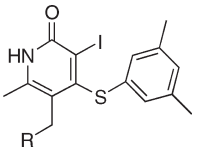
Table 4. Biological Activity of C-5 Modified 3-Iodo Thiophenoxy Pyridinone (ISPY) Analogues[a]

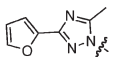


Cpd	R	IC$_{50}$ (nM)					Chemical Synthesis			
		LAI	SI[1]	K103N	Y181C	Y188L	Method	Reaction time (h)/(°C)	Purification method[2]	Yield (%)
75	O-C$_2$H$_5$	1.99	50,119	1.25	31.6	251	See experimental section			
81	NH$_2$	19.95		158	794	>10^4	See experimental section			
82	NH-CHO	1.25	>79,433	1.25	31.6	199	See experimental section			
83	SCH$_2$CONHCH$_3$	1.58	>63,096	3.98	39.8	794	A	3/80	a	61
84		1.99	>39,811	5.01	31.6	199	See experimental section			29
85	NCH$_3$(CH$_2$)$_2$CN	2.51	>31,623	6.30	63.0	1000	B	2/80	b	15
86	S-C$_2$H$_5$	3.16	>15,849	5.01	31.6	630	A	4/80	c	17
87		5.01	15,849	7.94	199	3162	A	3/80	d	29
88		6.30	>15,849	15.84	50.1	794	B	1/80	e	65
89		6.30	>12,589	5.01	39.8	1000	A	3/80	f	35
90	SCH$_2$CH(CH$_3$)$_2$	7.94	>12,589	10.0	199	2511	A	3/80	g	32
91	SCH(CH$_3$)$_2$	7.94	>12,589	31.6	630	3162	A	16/80	d	54
92		10.0	>10,000	10.0	39.8	794	A	3/80	a	61

[a] [1]Selectivity index or ratio of CC$_{50}$ to IC$_{50}$ relative to LAI (fold). [2]a: Crystallization in EtOH; b: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH: 99/1 then crystallization in *i*-Pr$_2$O; c: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH/NH$_4$OH: 95/5/0.1 then crystallization in *i*-Pr$_2$O; d: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH/NH$_4$OH: 98/2 then crystallization in *i*-Pr$_2$O; e: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH: 99/2; f: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH: 98/2 then crystallization in *i*-PrOH; g: column chromatography on silica, eluent CH$_2$Cl$_2$/MeOH: 98/2.

Table 5. Substitution of the C-5 Methyl by Azole Derivatives on the ISPY Scaffold[a]



Cpd	R	IC_{50} (nM)					Chemical Synthesis			
		LAI	SI[1]	K103N	Y181C	Y188L	Method	Reaction time (h)/(°C)	Purification method[2]	Yield (%)
93		0.63	>158,489	1.25	10.0	31.6	See experimental section			4
94		0.79	>125,893	1.99	15.8	100	See experimental section			22
95		1.0	>25,119	1.0	7.94	125	B	1.5/80	a	48
96		1.0	>31,623	nd	nd	nd	B	1/80	b	26
97		1.0	>31,623	nd	nd	nd	B	15/80	c	22
98		1.25	15,849	0.79	7.9	50.11	B	1/80	d	35
99		1.25	>79,433	0.31	7.9	15.8	See experimental section			12
100		1.25	>79,433	1.25	31.6	100	See experimental section			84
101		1.99	>12,589	15.8	31.6	316	See experimental section			17
102		1.99	>50,119	1.0	10.0	50.11	B	1.5/80	a	38
103		1.99	>50,119	12.5	31.6	31.6	See experimental section			26
104		2.51	19,953	1.0	31.6	158	See experimental section			12
105		3.16	>31,623	31.6	39.8	158	B	1.5/80	d	53
106		3.98	>25,119	0.50	10.0	50.11	See experimental section			15
107		5.01	>19,953	25.11	39.8	199	See experimental section			17
108		6.30	>15,849	7.94	10.0	39.8	See experimental section			19
109		6.30	>15,849	158	1258	3162	See experimental section			
110		10.0	>10,000	5.01	39.8	316	B	16/80	b	95
111		10.0	5,012	50.11	63.0	199	B	16/80	b	8

[a] [1]Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold). [2]a: column chromatography on silica, eluent CH_2Cl_2/MeOH/NH_4OH: 95/5/0.1 then crystallization in *i*-Pr_2O; b: column chromatography on silica, eluent CH_2Cl_2/MeOH/NH_4OH: gradient of elution 100/0/0 to 90/10/0.1; c: column chromatography on silica, eluent CH_2Cl_2 then crystallization in *i*-Pr_2O/acetone; d: column chromatography on silica, eluent CH_2Cl_2/MeOH/NH_4OH: 95/5/0.1 then crystallization in Et_2O.

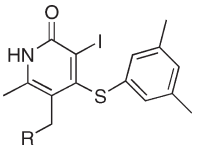
the Y181C and K03N mutants and retain significant sensitivity to the Y188L mutant strain. Indeed, the imidazole analogues **47** and **56** are included in the short list of 12 compounds for further testing. The corresponding analogues **62**−**69** with a saturated heterocyclic ring at this position also display potent activities against the three mutant strains.

We looked next at the activities for the ISPY analogues (Tables 4−6). Although many similarities exist between these pyridinone analogues and the IOPY compounds, several amazing differences were observed. Indeed, comparison of the activities of compounds **26** and **83** and **25** with **86** revealed that the phenoxy to thiophenyl modification at C-4 results in a loss of sensitivity toward the Y188L mutant. This trend was particularly noted for the furan analogue **89** relative to **24** and the thiophene analogue **92** relative to **30**.

In Table 5, one sees again that pyridinone analogues with a methylene linker at C-5 between two heteroaromatic rings display potent activities, the two isomeric tetrazoles **93** and **99** stand out as having the best profiles in this series.

Interesting also is compound **106**, where the connection is made via the C-2 carbon. This compound is highly active against the three major mutants and is possibly also more metabolically stable than the isomeric *N*-alkylation product, pyrrole **104**.

Table 6. Substitution of the C-5 Methyl by Substituted Cyclic Amines on the ISPY Scaffold[a]



Cpd	R	IC_{50} (nM)					Chemical Synthesis[1]		
		LAI	SI[2]	K103N	Y181C	Y188L	Reaction time (h)	Purification method[3]	Yield (%)
112		1.25	>50,119	1.0	25.11	125	1	c	56
113		1.25	7943	1.25	31.6	158	3	a	73
114		1.58	25,119	1.0	25.11	100	1	c	35
115		1.58	31,623	1.58	31.6	199	1	d	46
116		2.51	25,119	0.62	25.11	50	2	e	59
117		3.98	12,589	5.01	63.0	398	See experimental section		
118		3.98	10,000	12.5	199	1995	1	e	55
119		5.01	>5,012	nd	158	1000	See experimental section		
120		5.01	>19,953	3.16	25.11	125	2	b	60
121		5.01	>19,953	12.5	316	3981	4	a	16
122		5.01	>19,953	10.0	158	1258	2	a	61
123		5.01	7943	19.9	630	3162	1	c	44
124		6.30	>15,849	31.6	794	7943	2	g	51
125		10.0	398	nd	nd	nd	16	f	73

[a] [1]General procedure B was applied by reluxing in acetonitrile. [2]Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold). [3]a: Crystallization in EtOH; b: crystallization in *i*-Pr_2O; c: column chromatography on silica, eluent CH_2Cl_2/MeOH: gradient of elution 100/0 to 90/10 then crystallization in *i*-Pr_2O; d: column chromatography on silica, eluent toluene/*i*-PrOH/NH_4OH: 85/14/1 then crystallization in acetone/*i*-PrOH; e: column chromatography on silica, eluent CH_2Cl_2/MeOH: 98/2; f: column chromatography on silica, eluent CH_2Cl_2/MeOH: gradient of elution 100/0 to 90/10; g: column chromatography on silica, eluent CH_2Cl_2/MeOH: gradient of elution 100/0 to 90/10 then crystallization in acetone.

The piperidine and morpholine analogues presented in Table 6 all display strong activity against the LAI HIV strain, but many of these compounds are inactive against the Y188L mutant.

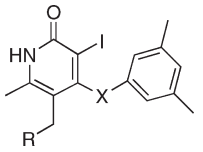
This loss in activity with respect to the Y188L mutant may reflect the expected differences in the overall geometry/conformation of the ISPY and IOPY compounds. In other words, due to the longer C−S bond length and wider C(4)−S−C(Ar) bond angle in the ISPY analogues, the change in contacts with the S−Ar substituent in the hydrophobic pocket of RT may translate into a reduction in room available to, and the contacts with, the heteroatom functionality present on the C-5 side chains.

To gain a better understanding as to why often minor structural modifications can lead to significant or complete loss of activity, the X-ray crystal structure of the **24** wild-type RT complex was obtained. In this structure, important interactions of the furan ring in **24** with P236 were revealed. It was further determined that the iodine atom engages in both donor and acceptor type interactions with the backbone NH and C=O of Gly190 and X188, respectively.[15]

In Table 7, the activities of the selected C-5 analogues against an expanded panel of HIV single and double mutants are presented along with the values for the IOPY lead compound **7**, the 3-*N*-dimethylpyridinones **2** and **3**, nevirapine, and efavirenz. Immediately evident is that the activity profile for **7** is significantly better than that for **2**/**3** and nevirapine. The discussion will therefore be restricted to a comparison of the activities of the new pyridinone analogues relative to **7** and the clinically used NNRTI efavirenz. As discussed earlier, all the new compounds and **7** are significantly more active than efavirenz against the 188L mutant. Improvement is further noted against 106A and 190S, and the majority of the new compounds are more active against 227C.

All the IOPY/ISPY compounds are also more active than efavirenz against the 100I + 103N, the 101E + 103N, and the 103N + 181 C double mutants. Indeed, tetrazole **99** is 1000-fold more sensitive to the 100I + 103N mutant than efavirenz. Equally as important, this compound and **93** are essentially equipotent to efavirenz against the 227 + 106A double mutant. This double mutant has proven to be the "achilles heal" in the development of the pyridinone based anti-HIV agents, since up until now very few compounds have been identified that inhibit this mutant at IC_{50} < 50 nM concentrations.

Table 7. Activity (IC_{50}, nM) vs HIV-1 of the Selected Compounds



Compd	X	R	LAI	SI[a]	103N	181C	188L	100I	101E	106A	138K	179E	190A	190S	227C	100I + 103N	101E + 103N	103N + 181C	227L + 106A
7	O	CH_3	1.25	9,000	3.16	19.9	50.1	6.31	6.31	5.01	3.98	1.99	6.31	1.99	63.1	19.9	15.8	39.8	398
23	O		1.0	>100,000	1.0	6.31	7.94	3.16							39.81	158			158
24	O		1.25	>79,433	1.0	5.01	31.6	6.31	6.31	1.58	1.25	1.0	3.16	1.25	39.8	31.6	3.98	5.01	125
25	O		1.25	>79,433	6.31	6.31	31.6	7.94	19.9	7.94	25.1	10.0	19.9	10.0	199	15.8	19.9	19.9	125
28	O		1.99	>50,119	1.58	7.94	31.6	10.0							199				199
46	O		0.79	>100,000	1.4	5.9	10.3	4.0	4.0	2.0	3.9	1.4	3.7	0.4	2.6	4.7	4.6	17.4	3.8
47	O		1.99	>50,118	2.51	10.0	31.6	6.31	9.2	3.7	11.2	5.1	8.0	2.2	nd	23.7	28.6	71.2	nd
93	S		0.63	>158,489	1.25	10.0	31.62	1.25	3.3	0.6	2.6	0.8	1.0	0.3	50.11	3.98	5.0	32.9	50.11
98	S		1.25	15,849	0.79	7.9	50.1												
99	S		0.8	>79,433	0.31	7.94	15.80	0.79	1.4	0.5	1.1	0.8	0.9	0.2	31.6	1.25	1.0	6.8	39.8
102	S		1.99	>50,119	1.0	10.0	50.1												
106	S		3.98	>25,119	0.50	10.0	50.1												
108	S		6.30	>15,849	7.94	10.0	39.8												
2[9]			7.94	12,589	31.6	100	251	50.1	15.8	39.8	nd	nd	63.1	nd	nd	nd	nd	794	nd
3[9]			3.98	2,512	10.0	63.1	158	6.31	7.94	6.31	6.31	2.51	12.59	3.98	631	39.81	12.6	158	398
NVP[b9]			31.6	5,012	6,310	10^4	10^5	316	316	5,012	51	195	7,943	44	135	1,452	509	10^5	163
EFV[b9]			1.0	10,000	39.8	1.99	158	3.98	6.3	39.8	1.99	5.01	10.0	251	158	1,000	158	39.8	25.1

[a] Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold). [b] NVP: nevirapine; EFV: efavirenz.

Conclusion

This work led us to elaborate different ways to obtain 3-iodo-4-phenoxy- (and 4-phenylthio-)-5-methyl substituted pyridin-2(1*H*)-one derivatives.[9] These compounds constitute new potent non-nucleoside HIV-1 RT inhibitors related both to HEPT and Merck-pyridinone series. Biological studies revealed that new 5-methyl substituted pyridinones show potent HIV-1 specific reverse transcriptase inhibitory properties. Indeed, the introduction of functionalized groups at this C5-position allowed enhancing potency against a panel of single and double mutant strains. Best results were obtained with the substitution of the C-5 methyl by azole derivatives (Tables 2 and 5). Some azoles show very good profile against the wild-type HIV, 1001E, 103N, 181C, and 188L mutant strains and proved to be as potent as efavirenz on the whole profile. Finally, the isomeric tetrazoles **46**, **93**, and **99** represent most interesting new leads for the further optimization of the IOPY/ISPY series and will be selected for in vivo pharmacokinetic studies.

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. Merck $60F_{254}$ procoated silica gel plates. Flash column chromatography was performed with the indicated solvents and using E. Merck 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 Bruker Avance 300 (300 MHz) and Bruker Avance 400 (400 MHz) spectrometers. Chemical shifts (δ) were reported in ppm units (s, d, t, q, m, and br for singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively) using internal deuterium lock DMSO (2.54 ppm) or $CDCl_3$ (7.28 ppm) and coupling constants (*J*) in Hz. Elemental analyses, realized with a Thermo Electron Corporation instruments EA 1110 or EA 1108, were within 0.4% of the theoretical values calculated for C, H, and N. LC/MS analyses were performed on a Applied Biosystems API100/Perkin-Elmer series 200 HPLC system or a Micromass LCT/Waters' Alliance 2795 HPLC system with a Kromasil 5 μm C18 column, 150 mm × 4.633 mm i.d. column from Interchim at room temperature using the following solvent system: solvent A, ammonium acetate 500 mg/L in ultrapure water; solvent B, acetonitrile; solvent C, 0.2% formic acid in ultrapure water at a flow rate of 1 mL/min. Gradient starting with 30% A/40% B/30% C from 0 to 1 min and then to 100% B from 1 to 5 min and continuing at 100% B up to 10 min. From 10 to 12 min, the gradient was reverted back to 30% A/40% B/30% C and was held until 13 min. UV detection was at 254 nm, and ionization was positive or negative ion electrospray. The molecular scan range was 100−900 amu. Samples were supplied as 0.5−1 mg/mL in methanol and/or acetonitrile with 5 μL injected on a partial loop fill.

The purity of the final compounds was determined by HPLC as described above and is 95% or higher unless specified otherwise.

5-Ethoxycarbonyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (14). A solution of ethyl 3-aminocrotonate **11** (12.6 g, 97.5 mmol) and di-(2,4,6-trichlorophenyl)malonate **13** (49.6 g, 107 mmol)[19] in diglyme (400 mL) was heated at 100 °C for 3 h, during which a precipitate was separated. After cooling, diethyl ether (1.5 L) was added and the expected 5-carbethoxypyridinone **14** was filtered (14.2 g, 75%): mp 243−245 °C (Lit. = 231−233 °C).[16a] ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7.0 Hz), 2.35 (3 H, s), 4.28 (2 H, q), 5.51 (1 H, s), 11.17 (1 H, br s), 11.53 (1 H, br s).

5-Cyyano-4-hydroxy-6-methylpyridin-2(1*H*)-one (15). The carbonitrile derivative **15** was prepared as described in the literature.[20]

5-Ethoxycarbonyl-3-iodo-6-methyl-4-(3,5-dimethylphenoxy)-pyridin-2(1*H*)-one (17). Dichloro-3,5-dimethyliodobenzene (6.6 g, 21.8 mmol), prepared from 3,5-dimethyliodobenzene and chlorine as described in the literature,[21] was suspended in water (50 mL) containing sodium carbonate (2.1 g, 20 mmol) and stirred for 30 min at room temperature. To this mixture, a solution of pyridinone **14** (3.6 g, 18 mmol) in water (50 mL) containing also sodium carbonate (2.1 g, 20 mmol) was added. After stirring for 1 h at 20 °C, the precipitate was filtered off, washed with water, dried in vacuo, and suspended in DMF (50 mL). After heating under reflux for 1 h, the solvent was removed in vacuo. The residue was crystallized in diisopropyl ether to give the titled compound (5.8 g, 75%) as yellow microcrystals, mp 190 °C. ^{1}H NMR (DMSO-d_6) δ 0.95 (3 H, t, J = 7.1 Hz), 2.21 (6 H, s), 2.30 (3 H, s), 3.35 (2 H, q, J = 7.1 Hz), 6.47 (2 H, s), 6.70 (1 H, s), 12.30 (1 H, br s). MS 428 $(M+H)^+$. Anal. ($C_{17}H_{18}INO_4$) Calcd C, 47.79; H, 4.25; N, 3.28. Found C, 47.71; H, 4.23; N, 3.56.

5-Cyano-3-iodo-6-methyl-4-(3,5-dimethylphenoxy)pyridin-2(1*H*)-one (18). Dichloro-3,5-dimethyliodobenzene (18.4 g, 60.8 mmol), prepared from 1,3-dimethyliodobenzene and chlorine as described in the literature,[21] was suspended in water (100 mL) containing sodium carbonate (6.5 g, 60.8 mmol) and stirred for 30 min at room temperature. To this mixture, a solution of pyridinone **15**[20] (8.3 g, 55.3 mmol) in water (100 mL) containing also Na_2CO_3 (6.5 g, 60.8 mmol) was added. After stirring for 1 h at 20 °C, the precipitate was filtered off, washed with water, dried in vacuo, and suspended in DMF (80 mL). After heating under reflux for 1 h, the solvent was removed in vacuo. The residue was then chromatographed on a silica gel column with CH_2Cl_2/CH_3OH (98:2) as the eluent to give the titled compound **18** (8.5 g; 41%), mp 289 °C. ^{1}H NMR (DMSO-d_6) δ 2.28 (6 H, s), 2.44 (3 H, s), 6.64 (2 H, s), 6.79 (1 H, s), 12.88 (1 H, br s). Anal. ($C_{15}H_{13}IN_2O_2$) Calcd C, 47.39; H, 3.45; N, 7.37. Found C, 47.23; H, 3.48; N,7.41.

5-Aminomethyl-4-(3,5-dimethylphenoxy)-3-iodo-6-methylpyridin-2(1*H*)-one (19). Diisobutylaluminium hydride (20 wt %, solution in toluene; 149 mL; 0.21 mol) was added at −78 °C to a solution of cyanopyridinone **18** (8 g; 21 mmol) in toluene (160 mL). The mixture was stirred at 5 °C for 4 h, hydrolyzed with the minimum of water, and filtered over celite. The celite was washed with CH_2Cl_2/MeOH (50:50). The filtrate was dried over $MgSO_4$ and concentrated. The residue was then chromatographed on a silica gel column with CH_2Cl_2/MeOH/NH_4OH (90:10:0.1) as the eluent to give the titled compound **19** (5.7 g; 71%). ^{1}H NMR (DMSO-d_6) δ 2.22 (6 H, s), 2.29 (3 H, s), 3.30 (2 H, s), 6.48 (2 H, s), 6.70 (1 H, s). MS ($C_{15}H_{17}IN_2O_2$): m/z 385 $(M + H)^+$.

***N*-[4-(3,5-Dimethylphenoxy)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-benzofuran-2-carboxylamide (20).** A solution of 5-aminomethyl-4-(3,5-dimethylphenoxy)-3-iodo-6-methylpyridin-2(1*H*)-one **19** (100 mg; 0.26 mmol), coumarilic acid (51 mg; 0.31 mmol), EDCI (60 mg; 0.39 mmol), HOBT (53 mg; 0.39 mmol), and triethylamine (0.054 mL; 0.39 mmol) in CH_2Cl_2 was stirred at room temperature for 15 h. The mixture was washed by a solution of 10% K_2CO_3, dried over $MgSO_4$, and the solvent was removed. After crystallization in diethylether, pure iodopyridinone **20** was isolated (73 mg; 53%). MS ($C_{24}H_{21}IN_2O_4$): m/z 529 $(M + H)^+$.

5-Hydroxymethyl-3-iodo-6-methyl-4-(3,5-dimethylphenoxy)-pyridin-2(1*H*)-one (21). Diisobutylaluminium hydride (20 wt %, solution in toluene; 42.5 mL, 51.5 mmol) was added at −78 °C to a solution of carbethoxypyridinone **17** (5.5 g, 12.9 mmol) in toluene (150 mL). The mixture was stirred at 5 °C for 2 h, hydrolyzed with the minimum of water, and filtered over celite. The celite was washed with CH_2Cl_2/methanol (98:2). The filtrate was dried over $MgSO_4$ and concentrated. Crystallization of the residue from diisopropyl ether to give the hydroxymethylpyridinone **21** (4.0 g; 81%) mp 248−250 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (6 H, s), 2.34 (3 H, s), 4.14 (2 H, br s), 4.72 (1 H, br s), 6.47 (2 H, s), 6.71 (1 H, s), 12.11 (1H, br s); Anal. ($C_{15}H_{16}INO_3$) Calcd C, 46.77; H, 4.19; N, 3.64. Found 46.58; H, 4.21; N, 3.56.

5-Chloromethyl-3-iodo-6-methyl-4-(3,5-dimethylphenoxy)pyridin-2(1*H*)-one (8). The heterogeneous solution of hydroxymethylpyridinone **21** (450 mg; 1.2 mmol) in CH_2Cl_2 (30 mL) became a homogeneous mixture by addition at room temperature $SOCl_2$ (2.6 mL). After 2 h on stirring at room temperature, all the volatiles were removed under reduced pressure, giving a yellow solid that corresponds to the expected chloromethyl derivative **8** in quantitative yield (470 mg) mp 256−258 °C. This compound was used for the next step without any further purification.

5-Ethoxymethyl-3-iodo-6-methyl-4-(3,5-dimethylphenoxy)pyridin-2(1*H*)-one (22). A solution of chloromethylpyridinone **8** (60 mg; 0.15 mmol) in absolute ethanol (5 mL) and K_2CO_3 (60 mg; 0.44 mmol) was heated under reflux for 16 h. After evaporation under reduced pressure, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. The colorless solid residue was then chromatographed on a silica gel column with CH_2Cl_2/ethanol (98:2) as the eluent to give the titled compound **22** (59 mg; 95%) mp 234−236 °C. ^{1}H NMR ($CDCl_3$) δ 1.04 (3 H, t, J = 7.0 Hz), 2.32 (6 H, s), 2.50 (3 H, s), 3.30 (2 H, q, J = 7.0 Hz), 4.21 (2 H, s), 6.47 (2 H, s), 6.69 (1 H, s), 12.99 (1 H, br s). MS ($C_{17}H_{20}INO_3$): m/z 414 $(M + H)^+$.

Procedure A: Synthesis of 4-(3,5-Dimethylphenoxy)-5-(furan-2-ylmethylthiomethyl)-3-iodo-6-methyl-pyridin-2(1*H*)-one (24): Example of the General Procedure. A solution of chloromethylpyridinone **8** (100 mg; 0.24 mmol), furan-2-ylmethanethiol (48 mg; 0.48 mmol), and triethylamine (0.1 mL; 0.72 mmol) in ethanol (2 mL) was heated in a sealed tube at 80 °C for 3 h. The precipitate was filtered and washed with ethanol. It was then purified by recrystallization in EtOH to give pure iodopyridinone **24** (60 mg; 52%) mp 220 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 2.15−2.27 (9 H, m), 3.43 (2 H, s), 3.71 (2 H, s), 6.17 (1 H, d, J = 3.0 Hz), 6.35−6.38 (1 H, m), 6.40 (2 H, s), 6.69 (1 H, s), 7.54(1 H, br s), 12.13 (1 H, br s). MS 482 $(M + H)^+$. Anal. ($C_{20}H_{20}INO_3S$) Calcd C, 49.90; H, 4.19; N, .2.91; S, 6.66. Found C, 49.42; H, 4.28; N, 2.92; S, 6.89.

4-(3,5-Dimethylphenoxy)-3-iodo-5-(2-methoxy-ethoxymethyl)-6-methylpyridin-2(1*H*)-one (27). A solution of chloromethylpyridinone **8** (60 mg; 0.15 mmol) in 2-methoxyethanol (5 mL) and K_2CO_3 (60 mg; 0.44 mmol) was heated at 110 °C for 16 h. After evaporation under reduced pressure, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. The residue was then chromatographed on a silica gel column with CH_2Cl_2/ethanol (98:2) as the eluent to give the titled compound **27** (51 mg; 77%) mp 184−186 °C. ^{1}H NMR ($CDCl_3$) δ 2.25 (6 H, s), 2.51 (3 H, s), 3.29 (3 H, s), 3.39 (4 H, m), 4.29 (2 H, s), 6.46 (2 H, s), 6.68 (1 H, s), 13.10 (1 H, br s). MS ($C_{18}H_{22}INO_4$): m/z 444 $(M + H)^+$. Anal. Calcd C, 48.77; H, 5,00; N, 3.16. Found C, 48,64; H, 4,94; N, 2,75.

Procedure B: Synthesis of 4-(3,5-Dimethylphenoxy)-5-[*N*-(furan-2-ylmethyl)-*N*-methyl]aminomethyl-3-iodo-6-methylpyridin-2(1*H*)-one (32): Example of the General Procedure. A solution of chloromethylpyridinone **8** (100 mg; 0.24 mmol), furfurylmethylamine[22] (55 mg; 0.48 mmol), and K_2CO_3 (100 mg; 0.72 mmol) in acetonitrile (5 mL) was heated under reflux for 2 h. Water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. After crystallization in diisopropylether, pure iodopyridinone **32** was isolated (50 mg; 42%) mp 185 °C. ^{1}H NMR (DMSO-d_6) δ 1.99 (3 H, s), 2.21 (9 H, s), 3.10 (2 H, s), 3.40 (2 H, s), 6.21 (1 H, d, J = 3.0 Hz), 6.36 (1 H, dd, J = 3.0, 1.1 Hz), 6.40 (2 H, s), 6.67 (1 H, s), 7.54 (1 H, d, J = 1.1 Hz), 12.09 (1 H, br s). MS ($C_{21}H_{23}IN_2O_3$): m/z 479 $(M + H)^+$.

Procedure C: Synthesis of 4-(3,5-Dimethylphenoxy)-3-iodo-5-(thiophen-2-yl-methoxymethyl)-6-methylpyridin-2(1*H*)-one

(36): Example of the General Procedure. A solution of chloromethylpyridinone **8** (150 mg; 0.37 mmol) and thiophen-2-ylmethanol (0.1 mL; 1.11 mmol) in dioxanne (1 mL) was heated at reflux for 15 h. The mixture is taken in K_2CO_3 10% (5 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on a silica gel column with CH_2Cl_2/propan-2-ol (98:2) as eluent. After crystallization in diethylether, pure iodopyridinone **36** was isolated (68 mg; 38%) mp 200 °C. ^{1}H NMR (DMSO-d_6) δ 2.20 (6 H, s), 2.25 (3 H, s), 4.14 (2 H, s), 4.45 (2 H, s), 6.41 (2 H, s), 6.68 (1 H, s), 6.90−7.00 (2 H, m), 7.48 (1 H, dd, J = 4.8, 1.3 Hz), 12.17 (1 H, br s). MS ($C_{20}H_{20}INO_3S$): m/z 482 $(M + H)^+$.

Most of the products showed in Tables 1−6 were prepared in the manner of either procedure A, B, or C. The yields, different reaction times, and purification methods are mentioned for each product.

4-(3,5-Dimethylphenoxy)-5-(2-hydroxy-ethoxymethyl)-3-iodo-6-methylpyridin-2(1*H*)-one (29). A solution of chloromethylpyridinone **8** (60 mg; 0.15 mmol) in 1,2-ethanediol (5 mL) and K_2CO_3 (60 mg; 0.44 mmol) was heated at 110 °C for 16 h. After evaporation under reduced pressure, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. The residue was then chromatographed on a silica gel column with CH_2Cl_2/ethanol (98:2) as the eluent to give the titled compound **29** (31 mg; 48%) mp 224−226 °C. ^{1}H NMR ($CDCl_3$) δ 2.26 (6 H, s), 2.50 (3 H, s), 3.38 (2 H, q, J = 4.5 Hz), 3.50 (2 H, q, J = 4.5 Hz), 4.28 (2 H, s), 6.47 (2 H, s), 6.69 (1 H, s), 13.10 (1 H, br s). MS ($C_{17}H_{20}INO_4$): m/z 430 $(M + H)^+$.

4-(3,5-Dimethylphenoxy)-5-(ethanesulfonylmethyl)-3-iodo-6-methylpyridin-2(1*H*)-one (37). To a solution of 4-(3,5-dimethylphenoxy)-5-(ethylthiomethyl)-3-iodo-6-methylpyridin-2(1*H*)-one **25** (0.35 g; 0.81 mmol) in CH_2Cl_2 (20 mL) was added a solution of 3-chloroperoxybenzoic acid (0.24 g; 0;97 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 1 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on a silica gel column with CH_2Cl_2/MeOH (98:2) as eluent. After crystallization in diisopropylether, pure iodopyridinone **37** was isolated (34 mg; 9%) mp > 250 °C. MS ($C_{17}H_{20c}INO_4S$): m/z 462 $(M + H)^+$.

1-[4-(3,5-Dimethylphenoxy)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]pipe ridin-4-ylcarbamate (64). A solution of chloromethylpyridinone **8** (150 mg; 0.37 mmol), piperidin-4-ol (75 mg; 0.74 mmol), and K_2CO_3 (150 mg; 1.12 mmol) in acetonitrile (5 mL) was heated under reflux for 1 h. Water (5 mL) was added, and the resulting precipitate was filtered, washed with water and then with diethyl ether, and dried to give 4-(3,5-dimethylphenoxy)-5-(4-hydroxypiperidin-1-ylmethyl)-3-iodo-6-methylpyridin-2(1*H*)-one (140 mg; 81%) mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ 1.20 (2 H, q, J = 10.5 Hz), 1.52−1.62 (2 H, m), 1.90 (2 H, t, J = 6.9 Hz), 2.22 (6 H, s), 2.29 (3 H, s), 2.48−2.55 (2 H, m), 3.02 (2 H, s), 3.28−3.40 (1 H, m), 4.45 (1 H, d, J = 2.5 Hz), 6.40 (2 H, s), 6.67 (1 H, s), 12.09 (1 H, br s). To a solution of this intermediate (140 mg; 0.3 mmol) in AcOEt (3 mL) was added dropwise chlorosulfonyl isocyanate (0.06 mL; 0.68 mmol) at −30 °C. The mixture was stirred at −30 °C for 1 h. Water (0.15 mL) was added at 5 °C and then 12 N HCl (0.15 mL) and MeOH (0.3 mL) were added. This mixture was heated at 40 °C for 2 h. The residue was poured into ice water, basified using K_2CO_3, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column with CH_2Cl_2/methanol (95:5) as the eluent to give pure iodopyridinone **64** (22 mg; 14%) mp > 250 °C. MS ($C_{21}H_{26}IN_3O_4$): m/z 512 $(M + H)^+$.

Ethyl 4-Chloro-2-methyl-6-oxo-1,6-dihydropyridin-3ylcarboxylate (70). To a solution of 4-hydroxypyridinone **14** (13.7 g; 0.0695 mol) and benzyltriethylammonium chloride (63.3 g; 0.278 mol) in acetonitrile (200 mL) was added in one portion of phosphorus oxychloride (27.9 mL; 0.298 mol). The obtained mixture was stirred at room temperature under nitrogen atmosphere for 5 min and heated under reflux for 4 h. After evaporation of all the volatiles under reduced pressure, the residue was poured into ice water and basified using NH_4OH and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the 4,6-dichloro-2-methyl-3-carbethoxypyridine (16.3 g; 100%), which was directly transformed into the chloropyridinone **70** by refluxing for 15 h in a mixture of sodium acetate (11.4 g; 0.139 mol) and acetic acid (200 mL). The acetic acid was evaporated under reduced pressure. The residue was poured into ice water, basified using K_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. The product (12.0 g) was crystallized from diisopropyl ether to give the titled 4-chloropyridinone **70** (5.9 g; 39%) mp 161−163 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (3 H, t, J = 7.2 Hz), 2.46 (3 H, s), 4.40 (2 H, q), 6.54 (1 H, s), 13.06 (1 H, br s). Anal. ($C_9H_{10}ClNO_3 \cdot 0.10$ EtOAc) Calcd C, 50.30; H, 4.85; N,.6.24. Found C, 50.68; H, 4.45; N, 6.41. MS m/z 215−217 $(M + H)^+$.

Ethyl 4-(3,5-Dimethylphenylsulfanyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl-carboxylate (71). A mixture of the 4-chloropyridinone **70** (5.9 g; 27.4 mmol) in ethanol (60 mL), triethylamine (5.9 mL), and 3,5-dimethylthiophenol (4.1 mL; 30 mmol) was heated under reflux for 16 h. After cooling, the precipitate was filtered off, washed with diisopropyl ether, and dried. The product **71** was obtained (7 g; 80%) as a colorless solid mp 233−235 °C. ^{1}H NMR ($CDCl_3$) δ 1.43 (3 H, t, J = 7.2 Hz), 2.33 (6 H, s), 2.48 (3 H, s), 4.42 (2 H, q), 5.76 (1 H, s), 7.07 (1 H, s), 7.14 (2 H, s), 12.82 (1 H, br s). MS ($C_{17}H_{19}NO_3S$) m/z 318 $(M + H)^+$.

5-Hydroxymethyl-6-methyl-4-(3,5-dimethylphenylsulfanyl)pyridin-2(1*H*)-one (72). Under nitrogen atmosphere, the ester **71** (500 mg; 1.6 mmol) was suspended in dry THF (20 mL) and $LiAlH_4$ (120 mg; 3.2 mmol) was added at 0 °C. The mixture was stirred at room temperature for 18 h and poured in ethyl acetate (50 mL) at 0 °C and a solution 10% H_2SO_4 (100 mL) was added dropwise. The mixture was extracted with ethyl acetate (2 × 100 mL), and the organic layer was removed under reduced pressure giving the hydroxymethylpyridinone **72** (310 mg; 71%) mp 268−270 °C. ^{1}H NMR (DMSO-d_6) δ 2.31 (9 H, s), 4.46 (2 H, s), 4.67 (1 H, br s), 5.46 (1 H, s), 7.07 (1 H, s), 7.11 (2 H, s), 11.36 (1 H, br s). MS ($C_{15}H_{17}NO_3S$): m/z 276 $(M + H)^+$.

5-Chloromethyl-6-methyl-4-(3,5-dimethylphenylsulfanyl)pyridin-2(1*H*)-one (73). The heterogeneous solution of hydroxymethylpyridinone **72** (275 mg; 1 mmol) in CH_2Cl_2 (10 mL) became a homogeneous mixture by addition at room temperature $SOCl_2$ (2.3 mL). After 2 h on stirring at room temperature, all the volatiles were removed under reduced pressure, giving a yellow solid that corresponds to the expected chloromethyl derivative **73** in quantitative yield (294 mg). This compound was used for the next step without any further purification.

5-Ethoxymethyl-6-methyl-4-(3,5-dimethylphenylsulfanyl)pyridin-2(1*H*)-one (74). A solution of chloromethylpyridinone **73** (250 mg; 0.85 mmol) in absolute ethanol (10 mL) and triethylamine (0.24 mL) was heated at 50 °C for 18 h. After evaporation under reduced pressure, the residue was chromatographed on a silica gel column with CH_2Cl_2/ethanol (99:1) as the eluant to give the titled compound **74** (243 mg; 94%) mp 203−205 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7.2 Hz), 2.33 (6 H, s), 2.38 (3 H, s), 3.60 (2 H, q), 4.48 (2 H, s), 5.80 (1 H, s), 7.01 (1 H, s), 7.16 (2 H, s), 12.77 (1 H, br s). Anal. ($C_{17}H_{21}NO_2S$) Calcd C, 67.29; H, 6.98; N, 4.62; S, 10.57. Found 66.98; H, 6.78; N, 4.79; S, 10.38.

5-Ethoxymethyl-3-iodo-6-methyl-4-(3,5-dimethylphenylsulfanyl)-pyridin-2(1*H*)-one (75). The compound **74** (100 mg; 0.33 mmol) was dissolved in acetic acid (2 mL) and ethyl acetate (2 mL). At room temperature and in the dark, *N*-iodosuccinimide (75 mg; 0.33 mmol) was added in one portion. After 2.5 h under stirring at room temperature, the mixture was poured into water (5 mL) and

the pH of the solution was adjusted to ca. 7 with 28% ammonia. The combined organic layers obtained by extraction with CH_2Cl_2 (3 × 10 mL) were washed with water (15 mL), dried over $MgSO_4$, and evaporated to give a solid residue. It was then chromatographed on silica gel column with CH_2Cl_2/ethanol (99:1) as the eluant to give the titled compound **75** as colorless microcrystals (96 mg; 68%) mp 220−222 °C. ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 7.2 Hz), 2.26 (6 H, s), 2.50 (3 H, s), 3.41 (2 H, q), 4.55 (2 H, s), 6.78 (2 H, s), 6.83 (s, 1H, H-4′), 12.82 (1 H, br s). Anal. ($C_{17}H_{20}INO_2S$) Calcd C, 47.56; H, 4.70; N, 3.26; S, 7.47. Found C, 47.62; H, 4.51; N,.3.48; S, 7.44.

Ethyl 4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylcarboxylate (76). *N*-Iodosuccinimide (28 g; 110 mmol) was added at room temperature to a solution of **71** (7 g; 22 mmol) in *N*,*N*-dimethylformamide (50 mL). The mixture was stirred for 48 h in darkness, poured into water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed. After crystallization from a mixture of diisopropyl ether and 2-propanol, pure iodopyridinone **76** was isolated (7.5 g; 77%) mp 210 °C. ^{1}H NMR (DMSO-d_6) δ 1.00−1.10 (3 H, m), 2.13 (3 H, br s), 2.22 (6 H, s), 3.75−3.90 (2 H, m), 6.85 (2 H, br s), 6.93 (1H, br s), 12.30 (1 H, br s). Anal. ($C_{17}H_{18}INO_3S$) Calcd C, 46.06; H, 4.09; N, 3.16; S, 7.23. Found C, 45.88; H, 4.21; N, 3.12; S, 7.27.

5-Hydroxymethyl-3-iodo-6-methyl-4-(3,5-dimethylphenylsulfanyl)-pyridin-2(1*H*)-one (77). Diisobutylaluminium hydride (20 wt %, solution in toluene; 56 mL, 67.7 mmol) was added at −78 °C to a solution of carbethoxypyridinone **76** (7.5 g, 16.9 mmol) in toluene (500 mL). The mixture was stirred at 5 °C for 2 h, hydrolyzed with the minimum of water, and filtered over celite. The celite was washed with CH_2Cl_2/methanol (98:2). The filtrate was dried over $MgSO_4$ and concentrated. Crystallization of the residue from diisopropyl ether to give the hydroxymethylpyridinone **77** (5.7 g; 84%) mp 240 °C. MS ($C_{15}H_{16}INO_2S$): m/z 402 (M + H)$^+$. This compound was used for the next step without any further purification.

5-Chloromethyl-3-iodo-6-methyl-4-(3,5-dimethylphenylsulfanyl)-pyridin-2(1*H*)-one (9). $SOCl_2$ (0.9 mL; 12.3 mmol) was added dropwise at 0 °C to a solution of hydroxymethylpyridinone **77** (800 mg; 1.9 mmol) in CH_2Cl_2 (90 mL). The mixture was stirred at room temperature overnight and all the volatiles were removed under reduced pressure, giving a yellow solid that corresponds to the expected chloromethyl derivative **9** (700 mg; 89%) mp 218 °C. This compound was used for the next step without any further purification.

4-Chloro-2-methyl-6-oxo-1,6-dihydropyridin-3ylcarbonitrile (78). To a solution of 4-hydroxypyridinone **15** (3.0 g; 0.02 mol) and benzyltriethylammonium chloride (9.1 g; 0.04 mol) in acetonitrile (120 mL) was added in one portion phosphorus oxychloride (3.7 mL; 0.04 mol). The obtained mixture was stirred at room temperature under nitrogen atmosphere for 5 min and heated under reflux for 15 h. After evaporation of all the volatiles under reduced pressure, the residue was poured into ice−water and basified using NH_4OH and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the 4,6-dichloro-2-methyl-3-cyanopyridine (3.1 g; 83%), which was directly transformed into the chloropyridinone **78** by refluxing for 15 h in a mixture of sodium acetate (3.0 g; 0.036 mol) and acetic acid (50 mL). The acetic acid was evaporated under reduced pressure. The residue was poured into ice water, basified using K_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. The product (12.0 g) was crystallized from diisopropyl ether to give the titled 4-chloropyridinone **78** (2.8 g; 100%). MS ($C_7H_5ClN_2O$): m/z 169−171 (M + H)$^+$. This unstable chloronitrile derivative was used for the next step without any further purification.

4-(3,5-Dimethylphenylsulfanyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-ylcarbonitrile (79). A mixture of the 4-chloropyridinone **78** (4 g; 23 mmol) in ethanol (100 mL), triethylamine (4 mL), and 3,5-dimethylthiophenol (3.2 mL; 23 mmol) was heated under reflux for 16 h. After cooling, the precipitate was filtered off, washed with diisopropyl ether, and dried. The product **79** was obtained (800 mg; 13%) mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ 2.33 (6 H, s), 2.40 (3 H, s), 5.23 (1 H, s), 7.25 (3 H, m), 12.32 (1 H, br s). MS ($C_{15}H_{14}N_2OS$): m/z 271 (M + H)$^+$.

4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridine-3-ylcarbonitrile (80). *N*-Iodosuccinimide (3.1 g; 12.6 mmol) was added at room temperature to a solution of **79** (680 mg; 2.5 mmol) in *N*,*N*-dimethylformamide (3 mL). The mixture was stirred for 48 h in darkness, poured into water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed. After crystallization from 2-propanol, pure iodopyridinone **80** was isolated (600 mg; 61%) mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ 2.23 (6 H, s), 2.35 (3 H, s), 6.83−6.98 (3 H, m), 12.85 (1 H, br s). MS ($C_{15}H_{13}IN_2OS$): m/z 397 (M + H)$^+$.

5-Aminomethyl-4-(3,5-dimethylphenylsulfanyl)-3-iodo-6-methyl-pyridin-2(1*H*)-one (81). Borane−methyl sulfide complex (2 M solution in tetrahydrofuran; 6.4 mL, 12.6 mmol) was added at 0 °C to a solution of cyanopyridinone **80** (0.5 g, 1.26 mmol) in THF (10 mL). The mixture was stirred at room temperature for 2 h, hydrolyzed with 3 N HCl, and then basified with 3 N NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on a silica gel column with CH_2Cl_2/methanol/NH_4OH (95:5:0.1) as the eluent to give the aminomethylpyridinone **81** (250 mg; 50%) mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ 2.21 (6 H, s), 2.35 (3 H, s), 3.43 (2 H, s), 6.71 (2 H, s), 6.88 (1 H, s), 7.50−9.50 (3 H, br s). MS ($C_{15}H_{17}IN_2OS$): m/z 401 (M + H)$^+$.

***N*-[4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]formamide (82).** A solution of 5-aminomethylpyridinone **81** (100 mg; 0.25 mmol), formic acid (0, 1 mL), and formamide (0.5 mL) was heated at 100 °C for 1 h. The mixture was neutralized by addition of a solution of 10% K_2CO_3. The resulting precipitate was filtered and chromatographed on a silica gel column with CH_2Cl_2/methanol (95:5) as the eluant to give the titled compound **82** (15 mg; 14%). MS ($C_{16}H_{17}IN_2O_2S$): m/z 429 (M + H)$^+$.

3-Iodo-4-(3,5-dimethylphenylsulfanyl)-6-methyl-5-(2-pyrazin-2-yl-ethylthiomethyl)pyridin-2(1*H*)-one (84). A solution of chloromethylpyridinone **9** (150 mg; 0.36 mmol), pyrazineethanethiol (100 mg; 0.71 mmol), and triethylamine (0.15 mL; 1.07 mmol) in ethanol (2 mL) was heated in an sealed tube at 70 °C for 2 h. The precipitate was filtered and washed with ethanol. It was then purified by chromatography on silica gel column with CH_2Cl_2/methanol (90:10) as the eluent to give, after crystallization from diisopropyl ether, pure iodopyridinone **84** (55 mg; 29%) mp 166 °C. ^{1}H NMR (DMSO-d_6) δ 2.19 (6 H, s), 2.29 (3 H, s), 2.89 (2 H, t, J = 7.0 Hz), 3.03 (2 H, t, J = 7.0 Hz), 3.84 (2 H, s), 6.70 (2 H, s), 6.83 (1 H, s), 8.47 (1 H, d, J = 2.3 Hz), 8.51−8.60 (2 H, m), 12.20 (1 H, br s). MS ($C_{21}H_{22}IN_3OS_2$): m/z 524 (M + H)$^+$.

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(tetrazol-2-ylmethyl)pyridin-2(1*H*)-one (93) and 4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(tetrazol-1-ylmethyl)pyridin-2(1*H*)-one (99). A solution of chloromethylpyridinone **9** (360 mg; 0.86 mmol), 1*H*-tetrazole (120 mg; 1.72 mmol), and K_2CO_3 (360 mg; 2.58 mmol) in acetonitrile (20 mL) was heated at 80 °C for 1 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. The compounds **93** and **99** were separated by silica gel chromatography with CH_2Cl_2/methanol/NH_4OH (90:10:0.1) as the eluent and crystallized from Et_2O.

Compound **93** (15 mg; 4%); mp > 250 °C (Et_2O). ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 2.38 (3 H, s), 5.90 (2 H, s), 6.55 (2 H, s), 6.79 (1 H, s), 8.83 (1 H, s), 12.46 (1 H, br s). MS ($C_{16}H_{16}IN_5OS$): m/z 454 (M + H)$^+$.

Compound **99** (45 mg; 12%); mp > 250 °C (Et_2O). ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 2.37 (3 H, s), 5.62 (2 H, s), 6.57 (2 H, s), 6.78 (1 H, s), 9.25 (1 H, s), 12.44 (1 H, br s).

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(3-methyl-1*H*-[1,2,4]triazol-1-ylmethyl)pyridin-2(1*H*)-one (94) and

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(5-methyl-1*H*-[1,2,4]triazol-1-ylmethyl)pyridin-2(1*H*)-one (101). A solution of chloromethylpyridinone **9** (300 mg; 0.71 mmol), 3-methyl-1*H*-[1,2,4]triazole[23] (90 mg; 1.07 mmol), and K_2CO_3 (300 mg; 2.14 mmol) in acetonitrile (15 mL) was heated at 80 °C for 1 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. After pre-purification on silica gel chromatography with CH_2Cl_2/methanol (96:4) as the eluent, the compounds **94** and **101** were separated on Hypersil C18 with methanol/H_2O (64:36) as the eluent.

Compound **94** (73 mg; 22%); mp 248 °C. ^{1}H NMR (DMSO-d_6) δ 2.13 (6 H, s), 2.33 (3 H, s), 2.40 (3 H, s), 5.22 (2 H, s), 6.45 (2 H, s), 6.76 (1 H, s), 7.68 (1 H, s), 12.40 (1 H, br s). MS ($C_{18}H_{19}IN_4OS$): m/z 467 $(M + H)^+$.

Compound **101** (57 mg; 17%); mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.17 (9 H, s), 2.37 (3 H, s), 5.27 (2 H, s), 6.58 (2 H, s), 6.80 (1 H, s), 8.21 (1 H, s), 12.36 (1 H, br s). MS ($C_{18}H_{19}IN_4OS$): m/z 467 $(M + H)^+$.

3-[4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-3*H*-imidazol-4-ylcarbonitrile (100). To a solution of **109** obtained as described below (370 mg; 0.73 mmol) in tetrahydrofuran (30 mL), 1,1′-carbonyldiimidazole (370 mg; 2.9 mmol) was added. The mixture was stirred at reflux for 15 h, poured into water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The solid residue was washed with hot acetone to give the titled compound **100** (300 mg, 84%) mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.07 (3 H, s), 2.15 (6 H, s), 2.29 (3 H, s), 5.19 (2 H, s), 6.56 (2 H, s), 6.76 (1 H, s), 7.63 (1 H, s), 12.36 (1 H, br s). MS ($C_{20}H_{19}IN_4OS$): m/z 491 $(M + H)^+$.

4-(3,5-Dimethylphenylsulfanyl)-5-(3-furan-2-yl-5-methyl-[1,2,4]-triazol-1-ylmethyl)-3-iodo-6-methylpyridin-2(1*H*)-one (103). A solution of chloromethylpyridinone **9** (300 mg; 0.71 mmol), 5-furan-2-yl-3-methyl-1*H*-[1,2,4]triazole (160 mg; 1.07 mmol,)[24] and K_2CO_3 (300 mg; 2.14 mmol) in acetonitrile (20 mL) was heated at 80 °C for 1 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. It was then purified by chromatography on silica gel column with CH_2Cl_2/methanol (97:3) as the eluent to give after crystallization from EtOH the main product, which corresponds to the title compound (100 mg; 26%); mp >250 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 2.00 (6 H, s), 2.36 (3 H, s), 2.44 (3 H, s), 5.26 (2 H, s), 6.41 (2 H, s), 6.55 (1 H, s), 6.68 (1 H, s), 6.76 (1 H, d, J = 2.5 Hz), 7.70 (1 H, s), 12.44 (1 H, br s). MS ($C_{22}H_{21}IN_4O_2S$): m/z 533 $(M + H)^+$. The byproduct (not shown) 4-(3,5-dimethylphenylsulfanyl)-5-(5-furan-2-yl-3-methyl-[1,2,4]triazol-1-ylmethyl)-3-iodo-6-methylpyridin-2(1*H*)-one was also isolated (60 mg; 16%); mp >250 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 2.10 (6 H, s), 2.15 (3 H, s), 2.37 (3 H, s), 5.52 (2 H, s), 6.31 (2 H, s), 6.70 (1 H, m), 6.74 (1 H, s), 6.95 (1 H, d, J = 2.5 Hz), 7.86 (1 H, s), 12.40 (1 H, br s). MS ($C_{22}H_{21}IN_4O_2S$): m/z 533 $(M + H)^+$.

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-pyrrol-1-ylmethylpyridin-2(1*H*)-one (104) and 4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(1*H*-pyrrol-2-ylmethyl)pyridin-2(1*H*)-one (106). A solution of chloromethylpyridinone **9** (500 mg; 1.19 mmol), pyrrole (160 mg; 2.38 mmol), and K_2CO_3 (490 mg; 3.57 mmol) in acetonitrile (20 mL) was heated at 80 °C for 2 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. It was then purified by chromatography on silica gel with CH_2Cl_2/methanol/NH_4OH (97:3) as the eluent. Two pure fractions were collected which correspond to (i) the pyrrol-1-ylmethylpyridinone derivative **104** (70 mg; 13%), MS ($C_{19}H_{19}IN_2OS$), m/z 451 $(M + H)^+$ and (ii) the pyrrol-2-ylmethylpyridinone analogue **106** (80 mg; 15%), mp 240 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 2.18 (9 H, s), 3.91 (2 H, s), 5.46 (1 H, s), 5.83 (1 H, s), 6.53 (1 H, s), 6.65 (2 H, s), 6.80 (1 H, s), 10.40 (1 H, br s), 12.18 (1 H, br s). MS ($C_{19}H_{19}IN_2OS$): m/z 451 $(M + H)^+$.

{1-[4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-1*H*-[1,2,4]triazol-3-yl}acetonitrile (107). A solution of chloromethylpyridinone **9** (300 mg; 0.71 mmol), (5-methyl-2*H*-[1,2,4]triazol-3-yl)acetonitrile[25] (180 mg; 1.43 mmol), and K_2CO_3 (300 mg; 2.14 mmol) in acetonitrile (20 mL) was heated at 80 °C for 1 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. It was then purified by chromatography on Hypersil C18 with CH_3CN/H_2O (35:65) as the eluent to give after crystallization from Et_2O/acetone the product, which corresponds to the title compound **107** (62 mg; 17%); mp 224 °C (Et_2O/acetone). ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 2.35 (3 H, s), 2.40 (3 H, s), 3.95 (2 H, s), 5.20 (2 H, s), 6.49 (2 H, s), 6.78 (1 H, s), 12.40 (1 H, br s). MS ($C_{20}H_{20}IN_5OS$): m/z 506 $(M + H)^+$. The byproduct (not shown) {2-[4-(3,5-dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-2*H*-[1,2,4]-triazol-3-yl}acetonitrile was also isolated (95 mg; 26%); mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.10 (3 H, s), 2.15 (6 H, s), 2.37 (3 H, s), 4.30 (2 H, s), 5.20 (2 H, s), 6.47 (2 H, m), 6.76 (1 H, s), 12.38 (1 H, br s). MS ($C_{20}H_{20}IN_5OS$): m/z 506 $(M + H)^+$.

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(3-phenyl-[1,2,4]triazol-1-ylmethyl)-pyridin-2(1*H*)-one (108). A solution of chloromethylpyridinone **9** (250 mg; 0.6 mmol), 5-phenyl-1*H*-[1,2,4]triazole[26] (174 mg; 1.2 mmol), and K_2CO_3 (250 mg; 1.8 mmol) in acetonitrile (20 mL) was heated at 80 °C for 1 h 30. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed. It was then purified by chromatography on silica gel column with CH_2Cl_2/methanol/NH_4OH (95:5:0.1) as the eluent to give after crystallization from Et_2O the product, which corresponds to the title compound **108** (60 mg; 19%); mp >250 °C (Et_2O). ^{1}H NMR (DMSO-d_6) δ 2.18 (6 H, s), 2.47 (3 H, s), 5.44 (2 H, s), 6.57 (2 H, s), 6.73 (1 H, s), 7.35−7.47 (3 H, m), 7.90 (2 H, d, J = 7.5 Hz), 8.40 (1 H, s), 12.40 (1 H, br s). MS ($C_{23}H_{21}IN_4OS$): m/z 529 $(M + H)^+$. The byproduct (not shown) 4-(3,5-dimethylphenylsulfanyl)-3-iodo-6-methyl-5-(3-phenyl-[1,2,4]triazol-4-ylmethyl)-pyridin-2(1*H*)-one was also isolated (60 mg; 19%); mp >250 °C (Et_2O). ^{1}H NMR (DMSO-d_6) δ 2.10(6 H, s), 2.43 (3 H, s), 5.39 (2 H, s), 6.05 (2 H, s), 6.73 (1 H, s), 7.49−7.60 (5 H, m), 7.90 (1 H, s), 12.40 (1 H, br s). MS ($C_{23}H_{21}IN_4OS$): m/z 529 $(M + H)^+$.

3-[4-(3,5-Dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-3*H*-imidazol-4ylcarbaldehyde oxime (109). Step 1: A solution of chloromethylpyridinone **9** (1.5 g; 3.57 mmol), 5-methyl-3*H*-imidazole-4-carbaldehyde (0.72 g; 6.54 mmol), and K_2CO_3 (300 mg; 9.9 mmol) in acetonitrile (80 mL) was heated at 80 °C for 15 h. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 75 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, and the solvent was removed. It was then purified by chromatography on silica gel column with CH_2Cl_2/methanol/NH_4OH (94:6:0.6) as the eluent to give the main product, which corresponds to the 3-[4-(3,5-dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-3*H*-imidazol-4-ylcarbaldehyde (0.66 g; 41%); mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.12 (6 H, s), 2.22 (3 H, s), 2.28 (2 H, s), 5.40 (2 H, s), 6.58 (2 H, s), 6.75 (1 H, s), 7.47 (1 H, s), 12.30 (1 H, br s). Besides this intermediate 3*H*-imidazol-4-ylcarbaldehyde, the byproduct 1*H*-imidazol-4-ylcarbaldehyde was also isolated (0.41 g; 26%); mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.12 (6 H, s), 2.28 (3 H, s), 2.40 (2 H, s), 5.03 (2 H, s), 6.58 (2 H, s), 6.70 (1 H, s), 7.37 (1 H, s), 12.30 (1 H, br s). Step 2: A solution of 3-[4-(3,5-dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-5-methyl-3*H*-imidazol-4-ylcarbaldehyde obtained above (600 mg; 1.2 mmol) and hydroxylamine hydrochloride (100 mg; 1.56 mmol) in ethanol (50 mL) was heated at 50 °C. A solution of 5 N NaOH (10 mL) was added dropwise. The mixture was heated at 50 °C for 2 h, poured into water, and

extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. After crystallization in diisopropylether, pure pyridinone oxime **109** was isolated (500 mg; 81%); mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 2.10 (3 H, s), 2.15 (6 H, s), 2.20 (3 H, s), 5.20 (2 H, s), 6.61 (2 H, s), 6.76 (1 H, s), 7.15 (1 H, s), 8.06 (1 H, s), 10.96 (1 H, s), 12.33 (1 H, br s). MS ($C_{20}H_{21}IN_4O_2S$): m/z 509 $(M + H)^+$.

4-(3,5-Dimethylphenylsulfanyl)-3-iodo-5-[2-(2-methoxyethyl)-morpholin-4-ylmethyl)]-6-methylpyridin-2(1*H*)-one (117). Step 1: To the 2-(4-benzylmorpholin-2-yl)ethanol[27] (1.5 g; 6.78 mmol) in 10 mL of dry DMF at 5 °C under N_2 was added NaH portionwise (60% in mineral oil; 300 mg; 7.45 mmol). The suspension was stirred at 5 °C for 10 min, after which a solution of CH_3I (0.46 mL; 7.45 mmol) in DMF (2 mL) was added. After the mixture was stirred for 30 min at 5 °C, the mixture was poured in water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed. The residue was then chromatographed on a silica gel column with cyclohexane/AcOEt (50:50) as the eluent to give the 4-benzyl-2-(2-methoxyethyl)morpholine (700 mg; 44%). ^{1}H NMR ($CDCl_3$) δ 1.60−1.78 (2 H, m), 1.89 (3 H, t, J = 10.2 Hz), 2.15 (1 H, td, J = 10.2, 3.0 Hz), 2.65 (1 H, d, J = 10.2 Hz), 2.75 (1 H, d, J = 10.2 Hz), 3.32 (3 H, s), 3.40−3.53 (4 H, m), 3.60−3.70 (2 H, m), 3.80−3.86 (1 H, m), 7.24- 7.36 (5 H, m). Step 2: After displacing the air with N_2, palladium on charcoal (10%; 100 mg) was added to a solution of 4-benzyl-2-(2-methoxyethyl)morpholine (400 mg; 1.7 mmol) in MeOH (30 mL). After hydrogenation under 3 bar at 40 °C for 3 h, the palladium catalyst was removed by filtration over a bed of celite. The celite was washed with methanol. The filtrate was evaporated to give 2-methoxyethylmorpholine (220 mg; 90%). Step 3: A solution of chloromethylpyridinone **9** (150 mg; 0.36 mmol), 2-methoxyethylmorpholine (100 mg; 0.71 mmol), and K_2CO_3 (150 mg; 1.07 mmol) in acetonitrile (5 mL) was heated at 80 °C for 1 h. Water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed. The colorless solid residue was then chromatographed on a silica gel column with CH_2Cl_2/ethanol (95:5) as the eluent to give after recrystallization from diisopropyl ether, the titled compound **117** (100 mg; 53%) mp 146 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.59−1.73 (2 H, m), 1.89 (1 H, t, J = 10.4 Hz), 2.15−2.23 (1 H, m), 2.24 (6 H, s), 2.48 (3 H, s), 2.50−2.63 (2 H, m), 3.31 (3 H, s), 3.38−3.50 (4 H, m), 3.55 (2 H, s), 3.76 (1 H, d, J = 11.1 Hz), 6.69 (2 H, s), 6.80 (1 H, s), 12.64 (1 H, br s). Anal. ($C_{22}H_{29}IN_2O_3S$) Calcd C, 50.00; H, 5.53; N,.5.30; S, 6.07. Found C, 49.84; H, 5.63; N, 5.27; S, 5.83

5-(2-Dimethylaminomethylmorpholin-4-ylmethyl)-4-(3,5-dimethylphenylsulfanyl)-3-iodo-6-methylpyridin-2(1*H*)-one (119). Step 1: A solution of chloromethylpyridinone **9** (300 mg; 0.715 mmol), *tert*-butyl morpholin-2-ylmethylcarbamate[28] (310 mg; 1.43 mmol), and K_2CO_3 (300 mg; 2.14 mmol) in acetonitrile (10 mL) was heated at 80 °C for 1 h. Water (15 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and the solvent was removed. After crystallization from Et_2O, *tert*-butyl {4-[4-(3,5-dimethylphenylsulfanyl)-5-iodo-2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl]-morpholin-2ylmethyl}-carbamate was isolated (350 mg; 80%) as an oil. ^{1}H NMR (DMSO-d_6) δ 1.37 (9 H, s), 1.70 (1 H, t, J = 10.2 Hz), 2.05 (1 H, td, J = 10.2 Hz, 2.6 Hz), 2.20 (6 H, s), 2.30 (3 H, s), 2.58 (1 H, d, J = 10.2 Hz), 2.85−2.95 (2 H, m), 3.12−3.25 (2 H, m), 3.35−3.52 (2 H, m), 3.67 (1 H, d, J = 10.2 Hz), 6.65 (2 H, s), 6.78−6.85 (2 H, m), 11.90 (1 H, br s). MS ($C_{25}H_{34}IN_3O_4S$): m/z 600 $(M + H)^+$. Step 2: A solution of this carbamate intermediate (330 mg; 0.55 mmol) in 3 N HCl (7 mL) and isopropyl alcohol (3 mL) was heated at 50 °C for 30 min. After dilution with H_2O (10 mL), the mixture was basified with K_2CO_3 and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed to afford 5-(2-aminomethylmorpholin-4-ylmethyl)-4-(3,5-dimethylphenylsulfanyl)-3-iodo-6-methylpyridin-2(1*H*)-one (260 mg; 95%), which was directly transformed into the aminomethylmorpholine derivative. Step 3: To a solution of this aminomethylmorpholine intermediate (260 mg, 0.52 mmol) and formaldehyde (37% in H_2O, 0.39 mL, 5.2 mmol) in acetonitrile (10 mL), sodium cyanoborohydride (100 mg, 1.56 mmol) was added portionwise at room temperature under nitrogen. Acetic acid (0.2 mL) was added, and the reaction was stirred at room temperature for 1 h. The mixture was poured into ice−water, basified with K_2CO_3, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. It was then chromatographed on silica gel column with CH_2Cl_2/methanol/NH_4OH (90:10:0.1) as the eluent to give, after crystallization from diisopropyl ether, the titled compound **119** (116 mg; 42%) mp 164 °C; (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 1.86 (1 H, t, J = 10.4 Hz), 2.05−2.22 (5 H, m), 2.24 (9 H, s), 2.36−2.46 (1 H, m), 2.49 (4 H, s), 2.56 (2 H, t, J = 10.4 Hz), 3.45 (2 H, t, J = 10.9 Hz), 3.56 (2 H, s), 3.80 (1 H, d, J = 10.9 Hz), 6.69 (2 H, s), 6.80 (1 H, s), 12.83 (1 H, br s). MS ($C_{22}H_{30}IN_3O_2S$): m/z 528 $(M + H^+)$.

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.[29]

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[30] 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 30000 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 IC_{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 IC_{50} for the tested virus by the IC_{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.

Acknowledgment. Financial support from "Ensemble contre le SIDA-Sidaction".

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

References

(1) Lucas, G. M.; Chaisson, R. E.; Moore, R. D. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann. Intern. Med.* **1999**, *13*, 81–87.

(2) Yerly, S.; Kaiser, L.; Race, E.; Bru, J. P.; Clavel, F.; Perrin, L. Transmission of antiretroviral-drug-resistant HIV-1 variants. *Lancet* **1999**, *354*, 729–733.
(3) Carr, A.; Samaras, C. K.; Thorisdottir, A.; Kaufmann, G. R.; Ghisholm, D. J.; Cooper, D. A. Diagnosis, prediction, and natural course of HIV-1 protease inhibitor associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* **1999**, *353*, 2093–2099.
(4) Carr, A.; Cooper, D. A. Adverse effects of antiviral therapy. *Lancet* **2000**, *356*, 1423–1430.
(5) Bastard, J.-P.; Caron, M.; Vidal, H.; Jan, V.; Auclair, M.; Vigouroux, C.; Luboinski, J.; Laville, M.; Maachi, M.; Girard, P.-M.; Rozenbaum, W.; Levan, P.; Capeau, J. Association between altered expression of adipogenic factor SREBP1 in lipotrophic adipose tissue from HIV-1 infected patients and abnormal adipocyte differentiation and insulin resistance. *Lancet* **2002**, *359*, 1026–1031.
(6) Dollé, V.; Fan, E.; Nguyen, C. H.; Aubertin, A. M.; Kirn, A.; Andreola, M. L.; Jamieson, G.; Tarrago-Litvak, L.; Bisagni, E. A new series of pyridinones derivatives as potent non-nucleoside HIV-1 specific reverse transcriptase inhibitors. *J. Med. Chem.* **1995**, *38*, 4679–4686.
(7) Dollé, V.; Nguyen, C. H.; Legraverend, M.; Aubertin, A.-M.; Kirn, A.; Andreola, M. L.; Ventura, M.; Tarrago-Litvak, L.; Bisagni, E. Synthesis and antiviral activity of 4-benzyl pyridinone derivatives as potent and selective non-nucleoside human immunodeficiency virus type 1 reverse transcriptase inhibitors. *J. Med. Chem.* **2000**, *43*, 3949–3962.
(8) Benjahad, A.; Courté, K.; Guillemont, J.; Mabire, D.; Coupa, S.; Poncelet, A.; Csoka, I.; Andries, K.; Pauwels, R.; de Béthune, M. P.; Monneret, C.; Bisagni, E.; Nguyen, C. H.; Grierson, D. S. 4-Benzyl and 4-benzoyl-3-dimethylaminopyridin-2(1*H*)-ones, a new family of potent anti-HIV. Optimization and in Vitro Evaluation against Clinically Important HIV Mutant Strains. *J. Med. Chem.* **2004**, *43*, 5501–5514.
(9) Benjahad, A.; Croisy, M.; Monneret, C.; Bisagni, E.; Mabire, D.; Coupa, S.; Poncelet, A.; Csoka, I.; Guillemont, J.; Meyer, C.; Andries, K.; Pauwels, R.; de Béthune, M.-P.; Himmel, D. M.; Das, K.; Arnold, E.; Nguyen, C. H.; Grierson, D. S. 4-Benzyl and 4-benzoyl-3-dimethylaminopyridin-2(1*H*)-ones: In vitro evaluation of new C-3 amino substituted and C-5,6 alkyl substituted analogues against clinically important HIV mutant strains. *J. Med. Chem.* **2005**, *48*, 1948–1964.
(10) Benjahad, A.; Oumouch, S.; Guillemont, J.; Pasquier, E.; Mabire, D.; Andries, K.; Nguyen, C. H.; Grierson, D.S. Structure−Activity Relationship in the 3-Iodo-4-phenoxypyridinone (IOPY) Series: The Nature of the C-3 Substituent on Anti-HIV Activity. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 712–716.
(11) Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Inouye, N.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clercq, E. A new class of HIV-1-specific 6-substituted acyclouridine derivatives: synthesis and anti-HIV-1 activity of 5- or 6-substituted analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT). *J. Med. Chem.* **1991**, *34*, 349–357.
(12) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. Synthesis and antiviral activity of 6-benzyl analogs of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) as potent and selective anti-HIV-1 agents. *J. Med. Chem.* **1995**, *38*, 2860–2865.
(13) Hopkins, A. L.; Ren, J.; Tanaka, H.; Baba, M.; Okamato, M.; Stuart, D. I.; Stammers, D. K. Design of MKC-442 (Emivirine) analogues with improved activity against drug-resistant HIV mutants. *J. Med. Chem.* **1999**, *42*, 4500–4005.
(14) (a) El-Brollosy, N. R.; Jrgensen, P. T.; Dahan, B.; Boel, A.-M.; Pedersen, E. B.; Nielsen, C. Synthesis of novel N-1 (allyloxymethyl) analogues of MKC-442 (Emivirine) with improved activity against HIV-1 and its mutants. *J. Med. Chem.* **2002**, *45*, 5721–5726. (b) Le Van, K.; Cauvin, C.; De Walque, S.; Georges, B.; Boland, S.; Martinelli, V.; Demonté, D.; Durant, F.; Hevesi, L.; Van Lint, C. New pyridinone derivatives as potent HIV-1 nonnucleoside reverse transcriptase inhibitors. *J. Med. Chem.* **2009**, *52*, 3636–3643.
(15) Himmel, D. M.; Das, K.; Clark, A. D.; Hughes, S. H., Jr.; Benjahad, A.; Oumouch, S.; Guillemont, J.; Coupa, S.; Poncelet, A.; Csoka, I.; Meyer, C.; Andries, K.; Nguyen, C. H.; Grierson, D. S.; Arnold, E. Crystal structures for HIV-1 reverse transcriptase in complexes with three pyridinone derivatives: A new class of non-nucleoside inhibitors effective against a broad range of drug-resistant strains. *J. Med. Chem.* **2005**, *48*, 7582–7591.
(16) (a) Kappe, T.; Stelzel, H. P.; Ziegler, E. Synthese von Pyridonen aus Enaminen und Cyanessigsauren. *Monatsh. Chem.* **1983**, *114*, 953–963. (b) El-Mariah, F. A. A.; Kappe, T. Potential nonsteroidal estrogens and antiestrogens. I. Synthesis of some 7-methoxy-2-(1H)-quinolone derivatives. *Croat. Chem. Acta* **1986**, *59* (1), 171–176.
(17) Carr, A.; Cooper, D. A. Adverse effects of antiretroviral therapy. *Lancet* **2000**, *356*, 1423.
(18) Iversen, A. K.; Shafer, R. W.; Wehrly, K.; Winters, M. A.; Chesebro, B.; Merigan, T. C.; Mullins, J. Multidrug-resistant human immunodeficiency virus type 1 strains resulting from combination antiretroviral therapy. *J. Virol.* **1996**, *70*, 1086.
(19) Kappe, T. A synthesis of 2-hydroxyquinolizinones-(4). *Monatsh. Chem.* **1967**, *98*, 874–886.
(20) Soliman, F. S. G.; Kappe, T. Synthesis of 1-cyano-2-hydroxy-4-quinolizinones and corresponding 5-cyano-4-hydroxy-2-pyridones. Part 187: Synthesis of heterocycles. Part 9: Quinolizines and indolizines. *Pharmazie* **1977**, *32* (5), 278–279.
(21) Lucas, H. J.; Kennedy, E. R. Iodobenzene dichloride. *Org Synth. Coll.* **1955**, *3*, 482.
(22) Beck, W.; Kaye, I. A.; Kogon, I. C.; Klein, H. C.; Burlant, W. J. 1-Phenyl-2-(*N*-methyl-*N*-benzylamino)ethanol and Related Compounds. *J. Org. Chem.* **1951**, *16* (9), 1434–1441.
(23) Jones, R. G.; Ainsworth, C. 1,2,4-Triazole-3-alanine. *J. Am. Chem. Soc.* **1955**, *77* (6), 1538.
(24) Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. A convenient synthesis of 3,5-disubstituted-1,2,4-triazoles. *Tetrahedron Lett.* **1987**, *28* (43), 5133–5136.
(25) Browne, E. J.; Polya, J. B. Triazoles. Part VII. Syntheses of substituted 1,2,4-triazoles. *J. Chem. Soc.* **1962**, 5149–5152.
(26) Atkinson, M. R.; Polya, J. B. Triazoles. Part III. Mono- and di-methyl(phenyl)-1:2:4-triazoles. *J. Chem. Soc.* **1954**, 3319–3324.
(27) Kato, S.; Morie, T.; Hino, K.; Kon, T.; Naruto, S.; Yoshida, N.; Karasawa, T.; Matsumoto, J. Novel benzamides as selective and potent gastric prokinetic agents. 1. Synthesis and structure−activity relationships of *N*-[(2-morpholinyl)alkyl]benzamides. *J. Med. Chem.* **1990**, *33* (5), 1406–1413.
(28) Kawakita, T.; Kuroita, T.; Murozono, T.; Hakira, H.; Haga, K. Benzoic acid compound and use thereof as medicine. PCT Int. Appl. WO 9526953, **1995**.
(29) Pauwels, R.; Balzarini, J.; Baba, M.; Snoek, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and automated tetrazolium-based calorimetric assay for the detection of anti-HIV compounds. *J. Virol. Methods* **1988**, *20*, 309–321.
(30) Hertogs, K.; de Bethune, M. P.; Miller, V.; Ivens, T.; Schel, P.; Van Cauwenberge, A.; Van Den Eynde, C.; Van Gerwen, V.; Azijn, H.; Van Houtte, M.; Peeters, F.; Staszewski, S.; Conant, M.; Bloor, S.; Kemp, S.; Larder, B.; Pauwels, R. A rapid method for simultaneous detection of phenotypic resistance to inhibitors of protease and reverse transcriptase in recombinant human immunodeficiency virus type 1 isolates from patients treated with antiretroviral drugs. *Antimicrob. Agents Chemother.* **1998**, *42*, 269–276.