Articles

Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles

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The development of new nonnucleoside inhibitors of human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT) active against the drug-induced mutations in RT continues to be a very important goal of AIDS research. We used a known inhibitor of HIV-1 RT, 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (TZB), as the lead structure for drug design with the objective of making more potent inhibitors against both wild-type (WT) and variant RTs. A series of structurally related 1,2-substituted benzimidazoles was synthesized and evaluated for their ability to inhibit in vitro polymerization by HIV-1 WT RT. A structure−activity study was carried out for the series of compounds to determine the optimum groups for substitution of the benzimidazole ring at the N1 and C2 positions. The best inhibitor, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**35**), has an $IC_{50} = 200$ nM against HIV-1 WT RT in an in vitro enzyme assay. Cytoprotection assays utilizing HIV-infected MT-4 cells revealed that **35** had strong antiviral activity ($EC_{50} = 440$ nM) against wild-type virus while retaining broad activity against many clinically observed HIV-1 strains resistant to nonnucleoside inhibitors. Overall, the activity of **35** against wild-type and resistant strains with amino acid substitution in RT is 4-fold or greater than that of TZB and is comparable to that of other nonnucleoside inhibitors currently undergoing clinical trials, most of which do not have the capacity to inhibit the variant forms of the enzyme.

Introduction

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 and has since become a major worldwide epidemic. A key target in the search for effective drugs useful for AIDS therapy is the viral enzymes that have critical roles in the life cycle of the human immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS. One such essential enzyme is reverse transcriptase (RT), an enzyme that contains both a DNA polymerase activity that can use either RNA or DNA as a template and a ribonuclease H activity.[1,2] These activities are essential for the conversion of retroviral genomic RNA into the double-stranded linear viral DNA that subsequently integrates into the genome of the infected host cell. Inhibition of RT should therefore provide an effective means of blocking HIV-1 replication.[3,4]

A number of inhibitors of HIV RT have been developed.[5,6] These inhibitors can be generally divided into two classes: (i) nucleoside analogues such as 3′-azido-3′-deoxythymidine (AZT) and 2′,3′-dideoxycytidine (ddC) and (ii) nonnucleoside RT inhibitors (NNRTI) such as 8-chloro-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*]-[1,4]benzodiazepin-2(1*H*)-one (8-Cl TIBO) and nevirapine. As opposed to the nucleoside drugs, the NNRTIs do not function as chain terminators and do not bind at the dNTP binding site. The results of mutational, modeling, and crystallographic studies suggest that most of these compounds share a common binding site located proximal to the RT polymerase active site.[7−10] However, in the absence of the NNRTI, the nonnucleoside binding pocket does not exist. It is only during the binding of an inhibitor that the aromatic residues Tyr181, Tyr188, and Trp229 reorient to create a hydrophobic pocket of sufficient volume to accommodate the inhibitor.[8] By binding to this allosteric site, the NNRTI increases the distance between the nucleic acid primer grip and the dNTP binding site in RT, suggesting this as a possible mechanism for the inhibition of polymerase activity.[8] The structural features that seem important for NNRTI binding include the presence of planar π-electron systems and the ability of those systems to adopt a conformation designated the "butterfly-like" orientation.[9,10] Despite these general features, the structures of different NNRTIs bound to RT vary considerably.[7,9,10] This complexity arises from the ability of the side-chain residues surrounding the pocket to adapt to each bound NNRTI in a highly specific manner, closing down around the surface of the drug to make tight van der Waals contacts. Because of this unique binding, NNRTIs do not inhibit other poly-

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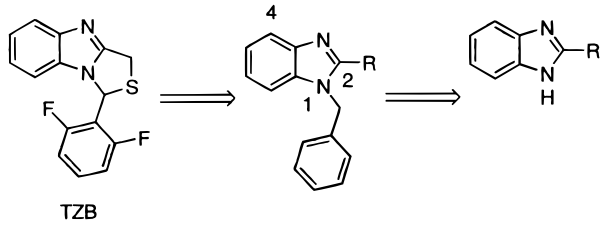


Figure 1. Retrosynthetic analysis.

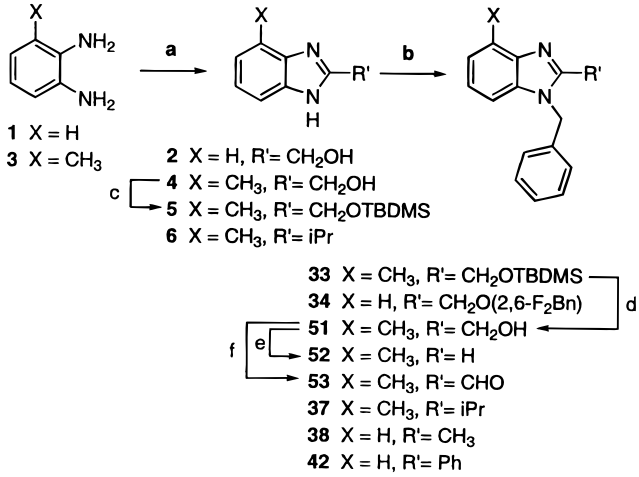
merases (not even HIV-2 RT) and are thus potentially highly effective and nontoxic drugs. The goal of our work was to determine the structural features of NNRTIs that enhance the binding to RT with a special emphasis on the structural features least affected by mutations surrounding the NNRTI binding pocket.

Although 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (TZB) was shown to be an inhibitor of HIV-1 RT, its potential therapeutic utility is hampered by a number of liabilities.[11−13] One problem is the metabolic oxidation of the thiazolo ring of TZB leading to the formation of less potent sulfoxide and sulfone metabolites.[14] A second problem with TZB is the complete loss of antiviral activity against HIV-1 variants containing amino acid substitutions in RT that arise following NNRTI treatment.[15,16] As a means to improve the RT inhibitory activity of TZB, removal of the thiazolo ring appeared to be an ideal starting point for the development of a more effective NNRTI. Retrosynthetic analysis of TZB suggested that opening of the thiazolo ring leads to *N*-benzyl-2-alkylbenzimidazoles (Figure 1). Similar to TZB, *N*-benzyl-2-alkylbenzimidazoles contain two aromatic rings that can form a butterfly-like conformation critical for binding to the NNRTI binding pocket. As indicated in Figure 1, synthesis of *N*-benzyl-2-alkylbenzimidazoles would readily be accomplished by the alkylation of 2-substituted benzimidazoles. The goal of this study was to determine substituents of *N*-benzylbenzimidazole, particularly at the C2 position, that would enhance the inhibition of HIV-1 wild-type (WT) and NNRTI resistant HIV-1 variants. The second part of this goal was especially important because the emergence of mutant forms of the virus renders most of the known NNRTIs ineffective.[17] This paper details our synthetic efforts toward achieving this goal leading to the discovery of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**35**). This compound is a better inhibitor of WT RT than TZB and appears to retain its inhibitory activity against a broad range of HIV-1 RT variants that engender resistance to many NNRTIs.

Results and Discussion

The first 2-substituted derivatives of *N*-(2,6-difluorobenzyl)benzimidazole that we examined were the methyl, hydroxymethyl, isopropyl, carboxylic, formyl, and phenyl derivatives. In the case of the methyl and phenyl compounds, commercially available benzimidazoles were allowed to react with 2,6-difluorobenzyl bromide (**27**) to give compounds **38** and **42**. Preparation of hydroxymethyl analogues was achieved by acid-catalyzed condensation−cyclization of glycolic acid with either *o*-phenylenediamine (**1**) or 2,3-diaminotoluene (**3**) via an approach similar to the one used by Chimirri et al. for the synthesis of TZB[11,12] (Scheme 1). The hydroxymethyl group was then protected with *tert*-butyldimethylsilyl (TBDMS) before N-alkylation with 2,6-difluorobenzyl bromide (**27**). Removal of TBDMS from **33** gave the desired 1-(2,6-difluorobenzyl)-2-(hydroxymethyl)-4-methylbenzimidazole (**51**).

Scheme 1[a]



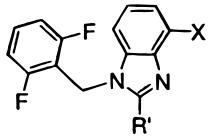
[a] Reagents: (a) glycolic or isobutyric acid, 4 N HCl, reflux; (b) 2,6-F_2BnBr (**27**); (c) *t*-BDMSCl, pyridine; (d) Bu_4NF, THF; (e) $KMnO_4$, H_2SO_4; (f) CrO_3.

Oxidation of the hydroxymethyl to the carboxylic acid, however, turned out to be problematic. When a strong oxidant ($KMnO_4$) was used, the isolated product **52** indicated that decarboxylation occurred under the acidic reaction conditions. Oxidation under basic conditions with chromium oxide also yielded **52** along with the formyl product (**53**). The carboxylic acid was never isolated in this study. The bis(2,6-difluorobenzyl) derivative (**34**) was prepared by bis-alkylation of 2-(hydroxymethyl)benzimidazole (**2**).

The ability to inhibit HIV-1 WT RT by the hydrogen (**52**), methyl (**38**), hydroxymethyl (**51**), isopropyl (**37**), formyl (**53**), phenyl (**42**), and bis(2,6-difluorobenzyl) (**34**) compounds was determined by measuring the relative nucleotide incorporation using a poly(rC)-oligo(dG) template primer at 10 mmol drug concentration to the amount of incorporation with no inhibitor present.[18] As seen in Table 1, most of the C2 alkyl compounds failed to appreciably inhibit HIV-1 RT. Only in the case of compound **42,** where C2 was phenyl, was significant RT inhibition determined. To understand the structural variation introduced by the C2 phenyl, we compared the geometry of TZB and 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole (**42**) by semiempirical quantum mechanical minimization at the AM1 level.

As seen in Figure 2, considerable similarity exists between the energy minimized butterfly-like shape of TZB and **42**. For TZB, the butterfly-like shape has been proven by crystallographic analysis.[19] In contrast to TZB, **42** has more than one butterfly-like conformation that arises by rotation of the benzyl side chain. Whereas the C2 phenyl of the AM1 energy-minimized **42** does not overlap the thiazolo ring of TZB, at least two higher energy rotational isomers result in almost complete overlap. Without an X-ray structure of **42** in a complex with HIV-1 RT, the correct butterfly-like orientation of this compound in the NNRTI binding pocket cannot be predicted. Nevertheless, since some predominant contributions to binding of NNRTI to RT involve π stacking and hydrophobic interactions, this extra aromatic ring

Table 1. Structural, Physical, and Enzyme Inhibition Data for 1-(2,6-Difluorobenzyl)-2-substituted-benzimidazoles



no.	X	R′	formula	mp, °C	anal.	% inhibn (10 μM)[a]
42	H	Ph	$C_{20}H_{14}F_2N_2$	127−129	C,H,N	77
53	CH_3	CHO	$C_{16}H_{12}F_2N_2O$	144−146	C,H,N	59
37	CH_3	*i*-Pr	$C_{18}H_{18}F_2N_2$	151−153	C,H,N	53
52	CH_3	H	$C_{15}H_{12}F_2N_2$	98−100	C,H,N	40
38	H	CH_3	$C_{15}H_{12}F_2N_2$	99−100	C,H,N	22
51	CH_3	CH_2OH	$C_{16}H_{14}F_2N_2O$	203−205	C,H,N	12
34	H	CH_2O(2,6-F_2Bn)	$C_{22}H_{16}F_4N_2O$	107−109	C,H,N	7

[a] Enzyme assay done with WT RT.

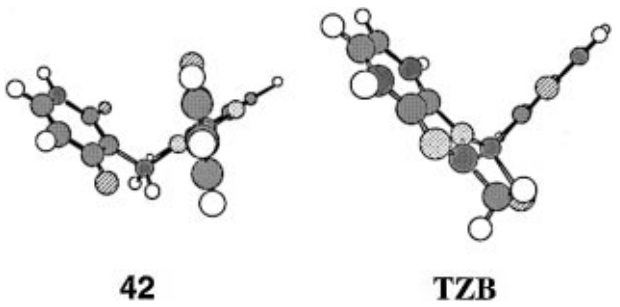


Figure 2. AM1 minimized structures of **42** and TZB.

present in **42** could significantly influence these interactions. The ability of HIV-1 RT to accommodate the extra phenyl ring led us to examine additional aromatic moieties that might further enhance binding.

The general approach used for the synthesis of 2-arylbenzimidazoles is outlined in Scheme 2. As is evident from this scheme, a variety of 2-arylbenzimidazoles can be prepared by using an appropriate acylating reagent. In most cases, high yields of the desired *N*-acylnitroaniline could be obtained from either 2-nitroaniline (**8**) or 2-methyl-6-nitroaniline (**9**). Only in the case of the 1-naphthyl derivative (**14**) was a mixture of mono- and bisacylated products formed. Subsequent reductive cyclization of compounds **10**−**17** with iron in acetic acid yielded the desired 2-arylbenzimidazoles **19**−**26**. Following coupling with 2,6-difluorobenzyl bromide (**27**), the desired 2-aryl-1-(2,6-difluorobenzyl)benzimidazoles [R_2 = 2,6-difluorophenyl (**28** and **35**); 4-cyanophenyl (**36**); 2-methylphenyl (**39**); naphthyl (**40** and **41**); pyridyl (**43** and **44**)] were obtained.

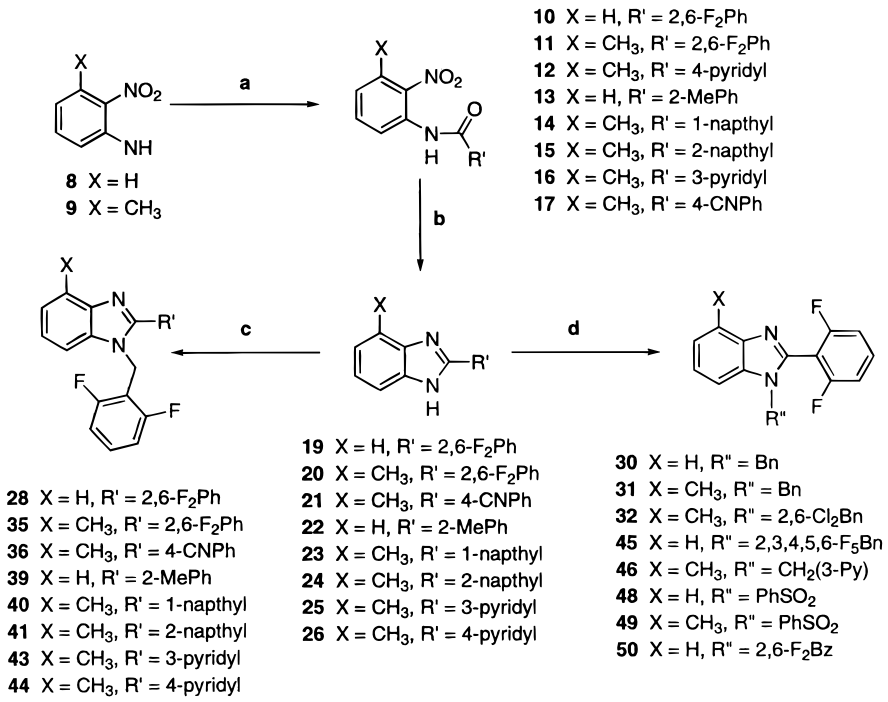
Biochemical activity of the various compounds was initially determined by examining their ability to inhibit HIV-1 WT RT at 10 mM drug concentration (Table 2). In the cases where the percent inhibition was greater than 75%, the IC_{50} (the drug quantity required to inhibit 50% of RT activity) and EC_{50} (the drug quantity required to inhibit 50% of virus-induced cell killing of CEM-SS cells in vitro by HIV-1)[20] were determined. Substitution of the phenyl group with fluorine at the 2 and 6 positions yielded the best inhibitor, **35** (IC_{50} = 200 nM and EC_{50} = 440 nM). Conservative changes, such as the addition of an *o*-methyl or a heteroatom to the 2-phenyl ring, resulted in only a small decrease in the percent inhibition (e.g. **39** and **44** vs **42**). Surprisingly, the 3-pyridyl compound (**43**) showed much less activity (over 10× lower EC_{50} as compared to the 4-pyridyl, **44**). Larger or longer aromatic moieties at C2, such as naphthyl or 4-cyanophenyl, led to loss of inhibitory activity. These results suggest that the size of the inhibitor that the NNRTI binding pocket can accommodate is limited.

We synthesized a second series of compounds to ask whether the position and nature of the substitutents on the benzyl ring at N1 were analogous to those in the TZB series. In the TZB series, the optimal anti-HIV activity was achieved when the phenyl ring was substituted at the 2 and 6 positions with fluorine. Treatment of benzimidazole **19** or **20** with benzyl bromide analogues (benzyl bromide; 2,6-dichloro-α-bromo toluene; 2,3,4,5,6-pentafluoro-α-bromo toluene) allowed us to test whether compounds with hydrogen, chlorine, or multiple fluorines on the N1 benzyl ring were better inhibitors. Since a number of NNRTIs, such as 2-nitrophenyl phenyl sulfone[21] and 5-chloro-3-(phenylsulfonyl)-indole-2-carboxamide,[22] contain sulfonyl links, we also assessed whether a sulfonyl group could replace the methylene linker in compound **35**. By allowing **19** or **20** to react with benzenesulfonyl chloride, compounds **48** and **49** were obtained in good yields. Similarly, treatment of compound **19** with 2,6-difluorobenzoyl chloride provided the *N*-(2,6-difluorobenzoate) (**50**) allowing us to examine the carbonyl group as the linker. We also tested the effect of introducing nitrogen into the *N*1-benzyl ring by synthesizing the 3-pyridyl derivative (**46**) via alkylation with α-(bromomethyl)pyridine.[23]

As seen in Table 3, the benzenesulfonyl and benzoate derivatives (**48**, **49**, **50**) did not appreciably inhibit HIV-1 RT. Substitution of the phenyl ring by a pyridine ring (**46**) similarly led to lower inhibition. Removal of the fluorines at the 2 and 6 positions (**30** or **31**) or replacement with chlorine (**32**) also resulted in decreased inhibition. Likewise, increasing the number of fluorines on the benzyl ring (**45**) yielded a compound showing greatly decreased inhibition. These findings are similar to those reported for the TZB series.[12−14]

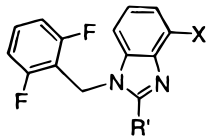
Biological evaluation of the RT inhibitory properties of the most active difluorophenyl compounds, **28** and **35,** was carried out in vitro with CEM-SS cells infected with WT or HIV-1 variants containing amino acid substitutions in RT.[24] Comparison of the methyl **35** and its desmethyl analogue **28** revealed that the methylated compound **35** was consistently 3−4-fold better at inhibiting the various viral isolates examined (Table 4). For most of the NNRTIs, π-stacking and van der Waals interactions between the inhibitor and the NNRTI binding pocket are very important. The enhanced inhibitory activity for **35** suggests that additional hy-

Scheme 2[a]



[a] Reagents: (a) aroyl chloride, pyridine/THF (1:1); (b) Fe (**18**), AcOH; (c) 2,6-F_2BnBr (**27**), NaH, THF; (d) BnBr (**29**) or $PhSO_2Cl$ (**47**) or 2,6-F_2BzCl (**7**), NaH, THF.

Table 2. Structural, Physical, and Enzyme Inhibition Data for 1-(2,6-Difluorobenzyl)-2-arylbenzimidazoles



no.	X	R′	formula	mp, °C	anal.	% inhibn (10 μM)	IC_{50} (μM)[a]	EC_{50} (mM)[b]
42	H	Ph	$C_{20}H_{14}F_2N_2$	127−129	C,H,N	77	16	6.06[c]
28	H	2,6-F_2Ph	$C_{20}H_{12}F_4N_2$	138−140	C,H,N	93	0.11	1.70[d]
35	CH_3	2,6-F_2Ph	$C_{21}H_{14}F_4N_2$	182−186	C,H,N	92	0.20	0.44[d]
39	H	2-CH_3−Ph	$C_{21}H_{16}F_2N_2$	138−140	C,H,N	71		
44	CH_3	4-Py	$C_{20}H_{15}F_2N_3$	171−172	C,H,N	70		3.5
43	CH_3	3-Py	$C_{20}H_{15}F_2N_3$	186−188	C,H,N	35		31.6
36	CH_3	4-CN−Ph	$C_{22}H_{15}F_2N_3$	207−208	C,H,N	26		
40	CH_3	1-Nap	$C_{25}H_{18}F_4N_3$	121−123	C,H,N	2		
41	CH_3	2-Nap	$C_{25}H_{18}F_4N_3$	175−176	C,H,N	8		
TZB			$C_{15}H_{10}F_2N_2S$			84	0.5[e]	0.52[f]

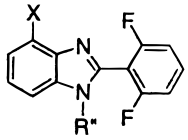
[a] The quantity of drug required to reduce WT RT enzyme activity by 50% (IC_{50}). [b] 50% cellular protection of CEM-SS cells from HIV-1 induced cytopathicity. [c] Average of two independent experiments. [d] Average of three independent experiments. [e] For ribosomal RNA by Buckheit et al.[13] [f] Yang et al.[25]

drophobic substitutents on the benzimidazole ring can significantly improve binding of this class of drugs to the NNRTI binding pocket residues.

In comparing **35** against TZB, the starting point in our drug design effort, a 3-fold increase in inhibition against WT RT has been achieved (Table 4). The EC_{50} for **35** against WT HIV-1 RT (NL4-3 isolate) in a cytopathic cell killing assay is in fact similar to the EC_{50} of TIBO. However, the real advantage of **35** over TZB involves its ability to inhibit many of the mutant HIV-1 isolates which are resistant to TZB. Likewise, **35** inhibits mutant HIV-1 RTs (i.e., A98G, L100I, V179D and Y188C isolates) which are resistant to TIBO. Additionally, our data suggest that **35** may be useful in combination drug therapy with nucleoside inhibitors since it is effective against nucleoside resistant strains (L74V and 4xAZT, an AZT drug resistant isolate). In fact, **35** inhibits strains (4xAZT/L100I and 4xAZT/Y181C) which have shown resistance to combination nucleoside/nonnucleoside treatment. Equally important, **35** is not cytotoxic at <10 mM inhibitor concentration in cell culture, resulting in an antiviral index ($AI_{50\%}$) >70.

In summary, this paper presents our initial studies in the development of a novel series of nonnucleoside HIV-1 RT inhibitors. By using standard medicinal chemistry techniques, a series of 2-substituted benzimidazoles was synthesized and tested as NNRTIs. Substitution of the C2 of benzimidazole with a 2,6-difluorophenyl ring was found to give the best HIV-1 WT RT inhibition. Biological testing using a cytopathic cell killing assay found that compound **35** yielded the best overall biological profile of this series. The substitution of an aryl group in place of the thiazolo ring of TZB produced a novel nonnucleoside HIV-1 RT inhibitor, while eliminating the metabolically labile

Table 3. Structural, Physical, and Enzyme Inhibition Data for 1-Aryl-2-(2,6-difluorophenyl)benzimidazoles



no.	X	R″	formula	mp, °C	anal.	% inhibn (10 mM)	IC_{50} (mM)	EC_{50} (mM)
28	H	2,6-F_2Bn	$C_{20}H_{12}F_4N_2$	138−140	C,H,N	93	0.11	1.70
35	CH_3	2,6-F_2Bn	$C_{21}H_{14}F_4N_2$	182−186	C,H,N	92	0.20	0.44
30	H	Bn	$C_{20}H_{14}F_2N_2$	122−125	C,H,N	71	18.6	toxic >32
31	CH_3	Bn	$C_{21}H_{16}F_2N_2$	112−117	C,H,N[a]	87	1.6	0.75
32	CH_3	2,6-Cl_2Bn	$C_{21}H_{14}Cl_2F_2N_2$	202−203	C,H,N	58		3.16
45	CH_3	2,3,4,5,6-F_5Bn	$C_{21}H_{11}F_7N_2$	155−156	C,H,N	36		
46	CH_3	CH_2(3-Py)	$C_{20}H_{15}F_4N_3$	131−132	C,H,N	43		
48	H	$PhSO_2$	$C_{19}H_{12}F_2N_2SO_2$	104−106	C,H,N	52		
49	CH_3	$PhSO_2$	$C_{20}H_{14}F_2N_2SO_2$	134−135	C,H,N	39		
50	H	2,6-F_2Bz	$C_{20}H_{10}F_4N_2O$	144−146	C,H,N	8		

[a] Anal. ($C_{21}H_{16}F_2N_2 \cdot {}^1/_4H_2O$) Calcd C, 74.43; H, 4.91; N, 8.27. Found C, 74.81; H, 4.90; N, 7.85.

Table 4. Cross-Resistance Profile with NNRTI Resistant HIV Isolates from Cytopathic Cell Killing Assay[a]

isolate	35	28	TZB	TIBO
NL4−3 (WT)	0.5	1.85	1.7	0.3
L74V	0.1	0.46	0.7	0.2
A98G	1.4	4.75	17.7	11
L100I	0.3	1.36	12.2	17.4
K101E	16.7	>20	>20	17.4
K103N	8.1	12.9	>20	17.4
V106A	20	>20	>20	12.5
V108I	2.8	10.4	9.7	2.4
V179D	0.5	2.3	3.1	6.2
Y181C	6	15.2	16.3	4.2
Y188C	2.3	11.7	>20	>17.4
4xAZT[b]	0.1	0.27	1.5	0.3
4xAZT/L100I	0.2	0.84	1.7	>17.4
4xAZT/Y181C	3.5	>20	14.5	2.0

[a] Antiviral data is reported as the average from three determinations of the quantity of drug in micromolar required to reduce cell killing or virus production by 50% (EC_{50}). [b] 4xAZT is an AZT resistant virus isolate containing four specific amino acid changes.

sulfur. In addition, our studies indicate that **35** should have broad inhibitory effects against both WT and a number of clinically important variant HIV-1 RTs. It is interesting to note that compound **35** resembles another important RT inhibitor, α-anilinophenylacetamide (α-APA),[24] that also exhibits broad spectrum inhibitory activity against variant RTs. The good activity against variant forms of RT exhibited by both compounds may reflect on their flexibility that allows them to assume a number of butterfly-like conformations in response to the spacial demands imposed by the various RT mutations.

Experimental Section

General. Where analyses are indicated by symbols of the elements, results were within 0.4% of the theoretical values. Elemental analyses were determined by Atlantic Microlab, Inc. Norcross, GA. Melting points were determined on an electrothermal apparatus using the supplied, stem-corrected thermometer and are as read. ^{1}H NMR spectra were recorded on a Varian 200 or 300 MHz spectrometer with Me_4Si as the internal standard. Yields were not optimized. Merck silica gel, 70−230 and 230−400 mesh, was used for gravity and flash chromatography, respectively. Primes used in NMR assignments are defined by R′ and R″ in the structures shown in Tables 1 and 3.

2-(Hydroxymethyl)benzimidazole (2). *o*-Phenylenediamine (**1**) (1.3 g, 12 mmol) and 85% glycolic acid (2.74 g, 36 mmol, 300 M%) were stirred in 4 N HCl (40 mL) under reflux for 4 h. After cooling to room temperature, the pH was adjusted to 7 with NaOH(solid). The resulting brown precipitate was filtered, washed with water, and dried in vacuo (0.71 g, 4.8 mmol, 40%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (m, 2H, $H_{4,7}$), 7.13 (m, 2H, $H_{5,6}$), 5.67 (t, J = 5.5 Hz, 1H, OH), 4.68 (d, J = 5.5 Hz, 2H, CH_2).

2-(Hydroxymethyl)-4-methylbenzimidazole (4). 2,3-Diaminotoluene (**3**) (2.65 g, 21.7 mmol) and 85% glycolic acid (8.20 g, 107.8 mmol, 500 M%) were stirred in 4 N HCl (80 mL) under reflux for 2 h. After cooling to room temperature, the pH was adjusted to 7 with NaOH(solid). The resulting brown precipitate was filtered, washed with water, and dried in vacuo (2.97 g, 18.3 mmol, 84% yield): ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.28 (br d, 1H, H_7), 6.98 (dd, J = 8.0, 7.3 Hz, 1H, H_6), 6.90 (m, 1H, H_5), 4.67 (s, 2H, CH_2), 2.49 (s, 3H, CH_3).

2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-methylbenzimidazole (5). To **4** (1.50 g, 9.24 mmol) dissolved in pyridine (30 mL) was added *t*-BDMSCl (2.35 g, 15.6 mmol, 170 M%). After 4 h at room temperature, the reaction was concentrated to dryness. The residue was redissolved in CH_2Cl_2 and washed with $NaHCO_3$(sat aq) and NaCl(sat aq), dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography, eluting with 4% MeOH/CH_2Cl_2, and then recrystallized from hexane (2.15 g, 7.78 mmol, 84% yield of white powder): ^{1}H NMR (300 MHz, CD_3OD) δ 7.36 (br d, J = 11.1 Hz, 1H, H_7), 7.11 (dd, J = 11.1, 10.4 Hz, 1H, H_6), 7.01 (br d, J = 10.4 Hz, 1H, H_5), 4.94 (s, 2H, CH_2O), 2.55 (s, 3H, CH_3), 0.95 (s, 9H, *t*-BuSi), 0.14 (s, 6H, $Si(CH_3)_2$).

2-Isopropyl-4-methylbenzimidazole (6). 3 (1.00 g, 8.19 mmol) and isobutyric acid (4.0 mL, 43.1 mmol, 525 M%) were dissolved in 4 N HCl (90 mL). After 2 h at reflux, the reaction was cooled in an ice bath and the pH adjusted to 7 with NaOH (solid). The resulting precipitate was filtered and washed with water (0.63 g, 3.62 mmol, 44% yield): ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.02 (br, 1H, NH), 7.26 (br, 1H, H_7), 6.99 (dd, J = 7.4, 7.7 Hz, 1H, H_6), 6.87 (ddt, J = 0.8, 1.1, 7.4 Hz, 1H, H_5), 3.14 (sep, J = 7.0, 1H, *i*-Pr), 2.48 (s, 3H, CH_3), 1.34 (d, J = 7.0 Hz, 6H, *i*-Pr).

Method A: *N*-(2,6-Difluorobenzoyl)-2-nitroanilide (10). To 2-nitroaniline (**8**) (1.1 g, 8.0 mmol) dissolved in THF (10 mL) and pyridine (2 mL) was added 2,6-difluorobenzoyl chloride (**7**) (1.11 mL, 8.8 mmol, 110 M%) dissolved in THF (15 mL). After stirring for 5 h at room temperature, the reaction was concentrated to dryness. The residue was redissolved in ethyl acetate and washed with $NaHSO_4$(5% solution), $NaHCO_3$(sat. aq) and NaCl(sat. aq). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane resulting in slightly yellow crystals (1.7 g, 6.1 mmol, 76%): mp 139 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 10.77 (s, 1H, NH), 8.89 (dd, J = 1.2, 8.5 Hz, 1H, H_3), 8.26 (dd, J = 1.5, 8.5 Hz, 1H, H_6), 7.75 (ddd, J = 1.2, 7.9, 8.5 Hz, 1H, H_5),

7.50 (m, 1H, $H_{3'}$), 7.29 (ddd, J =1.5, 7.9, 8.5 Hz, 1H, H_4), 7.07 (m, 2H, $H_{3',5'}$).

The following compounds were prepared by method A.

***N*-(2,6-Difluorobenzoyl)-2-methyl-6-nitroanilide (11).** 2-Methyl-6-nitroaniline (**9**) (2.25 g, 14.8 mmol) and **7** (1.9 mL, 15 mmol, 100 M%) after stirring overnight and purification by gravity chromatography eluting with CH_2Cl_2/hexane/diethyl ether (380 + 120 + 10) gave 2.36 g (8.1 mmol, 55%) of slightly yellow crystals: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.55 (s, 1H, NH), 7.87 (dd, J = 8.2, 0.92 Hz, 1H, H_5), 7.61 (d, J = 7.4 Hz, 1H, H_3), 7.48 (m, 1H, $H_{4'}$), 7.38 (dd, J = 7.4, 8.2 Hz, 1H, H_4), 7.05 (m, 2H, $H_{3',5'}$), 2.43 (s, 3H, CH_3).

***N*-Isonicotinoyl-2-methyl-6-nitroanilide (12).** **9** (1.52 g, 10.0 mmol) and isonicotinoyl chloride hydrochloride (2.95 g, 19.7 mmol, 200 M%) and a second addition of isonicotinoyl chloride hydrochloride (1.05 g, 5.90 mmol, 60 M%) at 4 h after stirring overnight and recrystallization from diethyl ether:hexane (3:1) gave 1.61 g (6.26 mmol, 63% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.06 (br, 1H, NH), 8.82 (m, 2H, $H_{2',6'}$), 7.93 (br d, J = 7.9 Hz, H_6), 7.77 (m, 2H, $H_{3',5'}$), 7.63 (br d, J = 8.0 Hz, 1H, H_3), 7.40 (dd, J = 7.9, 8.0 Hz, H_4), 2.38 (s, 3H, CH_3).

***N*-(2-Methylbenzoyl)-2-nitroanilide (13).** **8** (1.28 g, 9.3 mmol) and *o*-toluoyl chloride (1.52 mL, 11.6 mmol, 125 M%) gave 2.2 g (8.6 mmol, 92% yield) of yellow crystals after recrystallization from diethyl ether:hexane (1:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (s, 1H, NH), 8.98 (d, J = 8.5 Hz, 1H, H_3), 8.27 (d, J = 8.5 Hz, 1H, H_6), 7.72 (dd, J = 8.5, 7.4 Hz, 1H, H_5), 7.61 (d, J = 8.4 Hz, 1H, $H_{6'}$), 7.41 (dd, J = 8.5, 7.4 Hz, 1H, H_4), 7.32 (t, J = 7.4 Hz, 1H, $H_{4'}$), 7.31 (d, J = 7.4 Hz, 1H, $H_{3'}$), 7.23 (dd, J = 8.4, 7.4 Hz, 1H, $H_{5'}$), 2.56 (s, 3H, CH_3).

***N*-(1-Naphthoyl)-2-methyl-6-nitroanilide (14).** **9** (1.52 g, 10.0 mmol) and 1-naphthoyl chloride (2.00 mL, 13.3 mmol, 130 M%) and a second addition of 1-naphthoyl chloride (1.00 mL, 6.65 mmol, 66 M%) at 1 h after stirring for 6 h and recrystallization from ethyl acetate gave 2.79 g (9.11 mmol, 91% yield) of white powder: ^{1}H NMR (200 MHz, CD_2Cl_2) δ 8.09−7.99 (m, 2H), 7.77 (m, 1H), 7.66−7.41 (m, 5H), 7.23 (d, J = 8.3 Hz, 1H), 7.24 (dd, J = 7.3, 8.3 Hz, 1H), 2.77 (s, 3H, CH_3).

***N*-(2-Naphthoyl)-2-methyl-6-nitroanilide (15): 9** (1.52 g, 10.0 mmol) and 2-naphthoyl chloride (2.00 mL, 13.3 mmol, 130 M%) and a second addition of 2-naphthoyl chloride (1.00 mL, 6.65 mmol, 66 M%) at 1 h yielded, after 6 h and recrystallization from ethyl acetate, 2.29 g (7.48 mmol, 75% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.15 (br s, 1H, NH), 8.49 (s, 1H, $H_{1'}$), 8.06−7.86 (m, 5H, nap and H_5), 7.72−7.45 (m, 3H, nap and H_3), 7.37 (dd, J = 7.3 Hz, 1H, H_4), 2.43 (s, 3H, CH_3).

***N*-Nicotinoyl-2-methyl-6-nitroanilide (16).** **9** (1.52 g, 10.0 mmol) and nicotinoyl chloride hydrochloride (2.67 g, 15.0 mmol, 150 M%) after stirring overnight and recrystallization from diethyl ether:hexane (3:1) gave 1.41 g (5.49 mmol, 55% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.16 (dd, J = 0.8, 2.2 Hz, 1H, $H_{2'}$), 9.01 (br, 1H, NH), 8.80 (dd, J = 1.7, 4.8 Hz, 1H, $H_{6'}$), 8.23 (ddd, J = 1.7, 2.2, 8.0 Hz, 1H, $H_{4'}$), 7.92 (m, 1H, H_5), 7.62 (br d, J = 7.5 Hz, 1H, H_3), 7.48 (ddd, J = 0.8, 4.8, 8.0 Hz, 1H, $H_{5'}$), 7.39 (dd, J = 7.5, 8.5 Hz, 1H, H_4), 2.39 (s, 3H, CH_3).

***N*-(4-Cyanobenzoyl)-2-methyl-6-nitroanilide (17): 9** (2.60 g, 17.1 mmol) and 4-cyanobenzoyl chloride (3.70 g, 22.3 mmol, 130 M%) after stirring overnight and recrystallization from diethyl ether:hexane (3:1) gave 3.69 g (13.1 mmol, 77% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.00 (br, 1H, NH), 8.04 (cm, 2H, $H_{2',6'}$), 7.93 (m, 1H, H_5), 7.84 (cm, 2H, $H_{3',5'}$), 7.63 (m, 1H, H_3), 7.39 (dd, J = 7.8, 8.2 Hz, 1H, H_4), 2.60 (s, 3H, CH_3).

Method B: 2-(2,6-Difluorophenyl)benzimidazole (19). To **10** (9.31 g, 31.9 mmol) dissolved in glacial acetic acid (100 mL) was added iron powder (**18**) (4.95 g). After 30 min at reflux, the reaction was concentrated to dryness, diluted with ethyl acetate, and washed with $NaHCO_3$. The aqueous layer was back-extracted with ethyl acetate, and the combined organic solution was washed with $NaHCO_3$(sat. aq) and NaCl(sat. aq), dried (Na_2SO_4), filtered, and concentrated. The product was recrystallized from ethyl acetate (6.24 g, 27.1 mmol, 85% yield of white powder): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.92 (br, 1H, NH), 7.69 (br, 1H, $H_{4,7}$), 7.45 (m, 1H, $H_{4'}$), 7.31 (ddd, J = 3.2, 4.0, 6.0 Hz, 2H, $H_{5,6}$), 7.11 (m, 2H, $H_{3',5'}$).

The following compounds were prepared by method B.

2-(2,6-Difluorophenyl)-4-methylbenzimidazole (20). 11 (1.35 g, 4.62 mmol) and **18** (1.3 g) gave, after recrystallization from diethyl ether:hexane (3:1), 1.1 g (4.48 mmol, 97%) of colorless crystals: mp 148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.86 (s, 1H, NH), 7.66 (m, 1H, $H_{4'}$), 7.33 (m, 2H, $H_{3',5'}$), 7.27−7.18 (m, 1H, H_7), 7.15 (dd, J = 8.0, 7.2 Hz, 1H, H_6), 7.05 (d, J = 7.2 Hz, 1H, H_5), 2.55 (s, 3H, CH_3).

2-(4-Cyanophenyl)-4-methylbenzimidazole (21). 17 (3.15 g, 11.2 mmol) and **18** (2.15 g) gave, after recrystallization from methanol, 1.69 g (7.57 mmol, 68%) of colorless crystals: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (m, 2H, $H_{2',6'}$), 7.79 (m, 2H, $H_{3',5'}$), 7.46 (m, 1H, H_7), 7.21 (dd, J = 7.4, 8.1 Hz, 1H, H_6), 7.05 (m, 1H, H_5), 2.62 (s, 3H, CH_3).

2-(2-Methylphenyl)benzimidazole (22). 13 (1.9 g, 7.4 mmol) and **18** (1.2 g) gave, after recrystallization from diethyl ether:hexane (3:1) 1.2 g (5.76 mmol, 78%) of colorless crystals: mp 215 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.63 (m, 1H, $H_{6'}$), 7.58 (dd, J = 6.1, 3.2 Hz, 2H, $H_{4,7}$), 7.39−7.21 (m, 3H, $H_{3',4',5'}$), 7.25 (dd, J = 6.1, 3.2 Hz, 2H, $H_{5,6}$), 2.58 (s, 3H, CH_3).

2-(1-Naphthyl)-4-methylbenzimidazole (23). 14 (2.60 g, 11.7 mmol) and **18** (2.00 g) gave, after purification by flash chromatography eluting with 4% MeOH/CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1) 1.63 g (6.31 mmol, 54% yield) of white powder: ^{1}H NMR (200 MHz, CD_2Cl_2) δ 9.71 (br, 1H, NH), 8.80 (m, 1H), 8.01−7.89 (m, 2H), 7.81 (dd, J = 1.3, 7.3 Hz, 1H), 7.61−7.47 (m, 4H), 7.21 (dd, J = 7.3, 7.6 Hz, 1H), 7.11 (m, 1H), 2.66 (s, 3H, CH_3).

2-(2-Naphthyl)-4-methylbenzimidazole (24). 15 (2.25 g, 7.34 mmol) and **18** (1.60 g) gave, after purification by flash chromatography eluting with 4% MeOH/CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1) 1.00 g (3.88 mmol, 53% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.70 (br, 1H, NH), 8.34 (dd, J = 1.7, 8.6 Hz, 1H), 7.99−7.87 (m, 3H), 7.57−7.51 (m, 2H), 7.50−7.43 (m, 1H), 7.15 (dd, J = 7.3, 7.5 Hz, 1H, H_6), 7.04 (m, 1H, H_5), 2.67 (s, 3H, CH_3).

2-(3-Pyridyl)-4-methylbenzimidazole (25): 16 (1.00 g, 3.89 mmol) and **18** (0.75 g) and a second addition of **18** (0.75 g) at 30 min gave, after recrystallization from ethyl acetate, 0.72 g (3.44 mmol, 88% yield) of white powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (dd, J = 2.3, 0.9 Hz, 1H, $H_{2'}$), 8.67 (dd, J = 1.7, 4.8 Hz, 1H, $H_{6'}$), 8.53 (ddd, J = 1.7, 2.3, 8.0 Hz, 1H, $H_{4'}$), 7.58 (ddd, J = 0.9, 4.8, 8.0 Hz, 1H, $H_{5'}$), 7.44 (dd, J = 0.9, 8.1 Hz, 1H, H_7), 7.12 (dd, J = 7.3, 8.1 Hz, 1H, H_6), 7.02 (ddt, J = 0.8, 0.9, 7.3 Hz, 1H, H_5), 2.59 (s, 3H, CH_3).

2-(4-Pyridyl)-4-methylbenzimidazole (26). 12 (1.02 g, 3.97 mmol) and **18** (1.10 g) gave, after recrystallization from ethyl acetate, 0.70 g (3.34 mmol, 84% yield) of white powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (m, 2H, $H_{2',6'}$), 8.14 (m, 2H, $H_{3',5'}$), 7.46 (dd, J = 0.9, 8.1 Hz, 1H, H_7), 7.15 (dd, J = 7.3, 8.1 Hz, 1H, H_6), 7.05 (ddt, J = 0.8, 0.9, 7.3 Hz, 1H, H_5), 2.59 (s, 3H, CH_3).

Method C: 1-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (28). To **19** (2.00 g, 8.70 mmol) and 2,6-difluorobenzyl bromide (**27**) (2.85 g, 160 M%) dissolved in THF (20 mL) was added NaH (60% dispersion in mineral oil) (0.75 g, 215 M%). After 2 h, the reaction was quenched with MeOH and concentrated. The residue was redissolved in ethyl acetate, washed with $NaHCO_3$(sat. aq) and NaCl(sat. aq), dried (Na_2SO_4), filtered, and concentrated. The product was recrystallized from ethyl acetate:hexane (1:1) (2.62 g, 0.35 mmol, 85% yield of white powder): mp 145 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.77 (m, 1H, H_4), 7.54 (m, 1H, $H_{4'}$), 7.49 (m, 1H, H_7), 7.29 (m, 2H, $H_{5,6}$), 7.24 (m, 1H, $H_{4''}$), 7.08 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.36 (s, 2H, CH_2PhF_2). Anal. ($C_{20}H_{12}F_4N_2$) C, H, N.

The following compounds were prepared by method C.

1-Benzyl-2-(2,6-difluorophenyl)benzimidazole (30). 19 (0.50 g, 2.17 mmol) and benzyl bromide **29** (0.40 mL, 3.36 mmol, 155 M%) and a second addition of **29** (0.20 mL, 1.68 mmol, 80 M%) after 5 h gave, after stirring overnight at room temperature, aqueous workup, flash chromatography eluting with 2% methanol/CH_2Cl_2, and recrystallization from diethyl

ether, 0.57 g (1.78 mmol, 82% yield) of colorless crystals: mp 124 °C; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 7.81 (m, 1H, H_4), 7.51 (m, 1H, $H_{4'}$), 7.34−7.19 (m, 6H, $H_{5,6,7,2'',4'',6''}$), 7.06 (m, 2H, $H_{3',5'}$) 6.99 (m, 2H, $H_{3'',5''}$), 5.27 (s, 2H, CH_2). Anal. ($C_{20}H_{14}F_2N_2 \cdot {}^1/_8H_2O$) C, H, N.

1-Benzyl-2-(2,6-difluorophenyl)-4-methylbenzimidazole (31). **20** (0.50 g, 2.05 mmol) and **29** (0.35 mL, 2.94 mmol, 140 M%) gave, after 2 h and flash chromatography eluting with 2% methanol/CH_2Cl_2 and recrystallization from hexane, 0.41 g (1.23 mmol, 60% yield) of colorless crystals: mp 112−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 1H, $H_{4'}$), 7.26−7.22 (m, 3H, $H_{7,3'',5''}$), 7.18−6.98 (m, 7H, $H_{5,6,3',5',2'',4'',6''}$), 5.25 (s, 2H, CH_2), 2.74 (s, 3H, CH_3); HRMS 334.1281 (calcd), 334.1266 (found) δ 4.6. Anal. ($C_{21}H_{16}F_2N_2 \cdot {}^1/_4H_2O$) Calcd C, 74.43; H, 4.91; N, 8.27. Found: C, 74.81; H, 4.90; N, 7.85.

1-(2,6-Dichlorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (32). **20** (0.50 g, 2.05 mmol) and 2,6-dichlorobenzyl bromide (0.74 g, 3.08 mmol, 150 M%) gave, after 2 h and purification by flash chromatography eluting with 4% MeOH/CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1), 0.70 g (1.74 mmol, 85% yield) of white powder: mp 202−203 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.48 (m, 1H, $H_{4'}$), 7.26 (m, 2H, $H_{5,7}$), 7.19 (dd, J = 8.0, 8.2 Hz, 1H, H_6), 7.14−6.98 (m, 5H, $H_{3',5',3'',4'',5''}$), 5.56 (s, 2H, CH_2PhCl_2), 2.64 (s, 3H, CH_3). Anal. ($C_{21}H_{14}Cl_2F_2N_2 \cdot {}^1/_4H_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-4-methylbenzimidazole (33). **5** (3.25 g, 11.76 mmol) and **27** (3.65 g, 150 M%) gave, after 4 h and purification by flash chromatography with ethyl acetate:hexane (1:4), 4.41 g (10.96 mmol, 93% yield) of white powder: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.32 (m, 1H, $H_{4''}$), 7.17 (br d, J = 8.2 Hz, 1H, H_7), 7.08 (dd, J = 7.3, 8.2 Hz, 1H, H_6), 7.00 (br d, J = 7.3 Hz, 1H, H_5), 6.95 (m, 2H, $H_{3'',5''}$), 5.63 (s, 2H, CH_2PhF_2), 5.13 (s, 2H, CH_2O), 2.59 (s, 3H, CH_3), 0.94 (s, 9H, Si-*t*-Bu), 0.14 (s, 6H, $Si(CH_3)_2$).

1-(2,6-Difluorobenzyl)-2-[[(2,6-difluorobenzyl)oxy]-methyl]benzimidazole (34). **2** (92 mg, 0.62 mmol) and **27** (334 mg, 1.61 mmol, 260 M%) gave, after recrystallization from diethyl ether:hexane (3:1), 66 mg (0.165 mmol, 27%) of colorless crystals: mp 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 1H, H_4), 7.38 (m, 1H, H_7), 7.36−7.18 (m, 4H, $H_{5,6,4',4''}$), 6.98−6.82 (m, 4H, $H_{3',5',3'',5''}$), 5.58 (s, 2H, NCH_2PhF_2), 5.07 (s, 2H, OCH_2), 4.70 (s, 2H, OCH_2PhF_2). Anal. ($C_{22}H_{16}F_4N_2O \cdot {}^1/_2H_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (35). **20** (400 mg, 1.63 mmol) and **27** (388 mg, 1.87 mmol) gave, after stirring overnight and recrystallization with diethyl ether:hexane (3:1), 453 mg (1.22 mmol, 75% yield) of white powder: mp 182−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 1H, $H_{4'}$), 7.32 (d, J = 8.1 Hz, 1H, H_7), 7.20 (m, 1H, $H_{4''}$), 7.19 (dd, J = 8.1, 7.2 Hz, 1H, H_6), 7.09 (d, J = 7.2 Hz, 1H, H_5), 7.04 (m, 2H, $H_{3',5'}$), 6.79 (m, 2H, $H_{3'',5''}$), 5.33 (s, 2H, CH_2), 2.70 (s, 3H, CH_3). Anal. ($C_{21}H_{14}F_4N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(4-cyanophenyl)-4-methylbenzimidazole (36). **21** (0.26 g, 1.11 mmol) and **27** (0.31 g, 1.50 mmol, 135 M%) gave, after stirring overnight, flash chromatography with 2% methanol/CH_2Cl_2, and recrystallization with diethyl ether:hexane (3:1), 0.19 g (1.22 mmol, 48% yield) of white powder: mp 207−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (cm, 4H, $H_{2',3',5',6'}$), 7.32−7.03 (cm, 4H, $H_{4',5,6,7}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.51 (s, 2H, CH_2), 2.62 (s, 3H, CH_3). Anal. ($C_{22}H_{15}F_2N_3 \cdot {}^1/_2H_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-isopropyl-4-methylbenzimidazole (37). **6** (0.20 g, 1.15 mmol) and **27** (0.36 g, 1.74 mmol, 150 M%) gave, after stirring for 5 h and purification by flash chromatography eluting with 4% methanol:CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1), 0.20 g (0.67 mmol, 58% yield) of white powder: mp 151−153 °C; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 7.30 (m, 1H, $H_{4''}$), 7.15 (br d, J = 7.7 Hz, 1H, H_7), 7.04 (dd, J = 7.3, 7.7 Hz, 1H, H_6), 6.96 (br d, J = 7.3 Hz, 1H, H_5), 6.82 (m, 2H, $H_{3'',5''}$), 5.38 (s, 2H, CH_2PhF_2), 3.40 (sep, J = 6.8 Hz, 1H, *i*-Pr), 2.57 (s, 3H, CH_3), 1.38 (d, J = 6.8 Hz, 6H, *i*-Pr). Anal. ($Cl_8H_{18}F_2N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-methylbenzimidazole (38). 2-Methylbenzimidazole (204 mg, 1.54 mmol) and **27** (351 mg, 1.70 mmol) gave, after recrystallization from diethyl ether:hexane (3:1), 290 mg (1.12 mmol, 73%) of colorless crystals: mp 99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, J = 8.0, 1.1, 0.6 Hz, 1H, H_4), 7.37 (m, J = 0.6, 1.1, 8.2 Hz, 1H, H_7), 7.30 (m, 1H, $H_{4''}$), 7.20 (m, J = 8.0, 1.1, 7.3, 1H, H_5), 7.19 (m, J = 8.2, 7.3, 1.1 Hz, 1H, H_6), 6.92 (m, 2H, $H_{3'',5''}$) 5.35 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). Anal. ($C_{15}H_{12}F_2N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(2-methylphenyl)benzimidazole (39). **22** (0.10 g, 0.48 mmol) and **27** (0.15 g, 0.73 mmol, 150 M%) gave 109 mg (0.33 mmol, 68%) of colorless crystals after flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1): mp 139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 1H, H_4), 7.43−7.23 (m, 7H, $H_{5,6,7,3',4',5',6'}$), 7.21 (m, 1H, $H_{4''}$), 6.79 (m, 2H, $H_{3'',5''}$), 5.31 (s, 2H, CH_2), 2.23 (s, 3H, CH_3). Anal. ($C_{21}H_{16}F_2N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(1-naphthyl)-4-methylbenzimidazole (40). **23** (0.30 g, 1.16 mmol) and **27** (0.54 g, 2.60 mmol, 225 M%) gave, after stirring overnight and purification by flash chromatography eluting with ethyl acetate:hexane (1:4) and recrystallization from diethyl ether:hexane (3:1), 0.32 g (0.83 mmol, 72% yield) of white powder: mp 121−123 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.00 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 6.3 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.53 (dt, J = 1.3, 7.5 Hz, 1H), 7.43 (dt, J = 1.3, 7.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.11 (m, 2H), 6.67 (m, 2H), 5.28 (s, 2H, CH_2PhF_2), 2.68 (s, 3H, CH_3). Anal. ($C_{25}H_{18}F_2N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(2-naphthyl)-4-methylbenzimidazole (41). **24** (0.30 g, 1.16 mmol) and **27** (0.36 g, 1.74 mmol, 150 M%) and a second addition of **27** (0.18 g, 0.87 mmol, 75 M%) at 2 h gave, after stirring overnight and purification by flash chromatography eluting with ethyl acetate:hexane (1:4) and recrystallization from diethyl ether:hexane (3:1), 0.35 g (0.91 mmol, 78% yield) of white powder: mp 175−176 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.20 (d, J = 1.6 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.96 (m, 2H), 7.83 (dd, J = 1.7, 8.5 Hz, 1H), 7.59 (m, 2H), 7.20 (m, 2H), 7.12 (m, 1H), 7.06 (m, 1H), 6.80 (m, 2H), 5.60 (s, 2H, CH_2PhF_2), 2.66 (s, 3H, CH_3). Anal. ($C_{25}H_{18}F_2N_2$) C, H, N.

1-(2,6-Difluorobenzyl)-2-phenylbenzimidazole (42). 2-Phenylbenzimidazole (300 mg, 1.54 mmol) and **27** (1.70 mmol, 110 M%) gave, after recrystallization from diethyl ether:hexane (3:1), 300 mg (0.94 mmol, 63% yield) of colorless crystals: mp 163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 1H, H_4), 7.75 (m, 2H, $H_{3',5'}$), 7.53 (m, 3H, $H_{2',4',6'}$), 7.33 (d, J = 8.3 Hz, 1H, H_7), 7.25 (m, 3H, $H_{5,6,4''}$), 6.81 (m, 2H, $H_{3'',5''}$), 5.55 (s, 2H, CH_2). Anal. ($C_{20}H_{14}F_2N_2 \cdot {}^1/_4H_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(3-pyridyl)-4-methylbenzimidazole (43). **25** (0.30 g, 1.43 mmol) and **27** (0.49 g, 2.37 mmol, 165 M%) gave, after stirring overnight and purification by flash chromatography eluting with 4% methanol:CH_2Cl_2 and recrystallization from diethyl ether/hexane (3:1), 0.34 g (1.02 mmol, 71% yield) of white powder: mp 186−188 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.92 (dd, J = 0.9, 2.3 Hz, 1H, $H_{2'}$), 8.74 (dd, J = 1.7, 4.9 Hz, 1H, $H_{6'}$), 8.05 (dt, J = 2.0, 7.8 Hz, 1H, $H_{4'}$), 7.48 (ddd, J = 0.9, 4.9, 7.8, 1H, $H_{5'}$), 7.24 (m, 1H, $H_{4''}$), 7.22 (br d, J = 7.7 Hz, 1H, H_7), 7.15 (dd, J = 7.7, 7.2, 1H, H_6), 7.07 (dt, J = 1.0, 7.2 Hz, 1H, H_5), 6.83 (m, 2H, $H_{3'',5''}$), 5.51 (s, 2H, CH_2PhF_2), 2.64 (s, 3H, CH_3). Anal. ($C_{20}H_{15}F_2N_3$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(4-pyridyl)-4-methylbenzimidazole (44). **26** (0.30 g, 1.43 mmol) and **27** (0.45 g, 2.17 mmol, 150 M%) gave, after stirring overnight and purification by flash chromatography eluting with 4% methanol:CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1), 0.29 g (0.86 mmol, 60% yield) of white powder: mp 171−172 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.77 (dd, J = 1.6, 4.4 Hz, 2H, $H_{2',6'}$), 7.66 (dt, J = 1.4, 4.4 Hz, 2H, $H_{3',5'}$), 7.24 (m, 1H, $H_{4''}$), 7.22 (dd, J = 0.8, 8.1 Hz, 1H, H_7), 7.15 (dd, J = 7.5, 8.1 Hz, 1H, H_6), 7.07 (ddq, J = 0.4, 0.8, 7.5 Hz, 1H, H_5), 6.82 (m, 2H, $H_{3'',5''}$), 5.54 (s, 2H, CH_2PhF_2), 2.63 (s, 3H, CH_3). Anal. ($C_{20}H_{15}F_2N_3$) C, H, N.

1-(2,3,4,5,6-Pentafluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (45). **20** (0.31 g, 1.27 mmol) and 2,3,4,5,6-pentafluoro-α-bromotoluene (0.30 mL, 1.99 mmol, 155 M%) gave, after 4 h and purification by flash chromatography

eluting with 4% methanol:CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1), 0.33 g (0.77 mmol, 61% yield) of white powder: mp 155−156 °C; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 7.57 (m, 1H, $H_{4'}$), 7.29−7.23 (m, 2H, $H_{6,7}$), 7.19−7.05 (m, 3H, $H_{5,3',5'}$), 5.35 (s, 2H, CH_2PhF_5), 2.64 (s, 3H, CH_3). Anal. ($C_{21}H_{11}F_7N_2$) C, H, N.

1-(3-Pyridylmethyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (46). **20** (0.21 g, 0.86 mmol) and α-(bromomethyl)pyridine (0.22 g, 1.28 mmol, 150 M%) gave, after 1 h and purification by flash chromatography eluting with ethyl acetate:hexane (1:1) increasing to ethyl acetate (100%) and recrystallization from diethyl ether:hexane (3:1), 0.24 g (0.73 mmol, 85% yield) of white powder: mp 131−132 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 (d, J = 3.4 Hz, 1H, $H_{6''}$), 8.32 (s, 1H, $H_{2''}$), 7.53 (m, 1H, $H_{4'}$), 7.25−7.03 (m, 7H, $H_{5,6,7,3',5',4'',5''}$), 5.26 (s, 2H, CH_2Py), 2.67 (s, 3H, CH_3Ar). Anal. ($C_{20}H_{15}F_2N_3 \cdot {}^1/_2H_2O$) C, H, N.

Method D: 1-(Phenylsulfonyl)-2-(2,6-difluorophenyl)-benzimidazole (48). To **19** (0.31 g, 1.34 mmol) dissolved in THF (5 mL) was added NaH (60% dispersion in mineral oil) (0.10 g, 190 M%). After 5 min, benzenesulfonyl chloride (**47**) (0.25 mL, 0.35 g, 2.00 mmol, 150 M%) was added. After 2 h of stirring the reaction mixture was dissolved in ethyl acetate, washed with $NaHCO_3$(sat. aq) and NaCl(sat. aq), dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography eluting with 2% methanol:CH_2Cl_2 and then recrystallized from diethyl ether:hexane (3:1) (0.41 g, 1.10 mmol, 83% yield of white powder): mp 104−106 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.09 (m, 1H, $PhSO_2$), 7.77 (m, 1H, $PhSO_2$), 7.69 (m, 2H, $PhSO_2$), 7.66−7.53 (m, 2H, $H_{4,7}$), 7.51−7.39 (m, 4H, $H_{3,5}$ and $PhSO_2$), 7.07 (m, 2H, $H_{3',5'}$). Anal. ($C_{19}H_{12}F_2N_2SO_2$) C, H, N.

1-(Phenylsulfonyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (49). **20** (0.20 g, 0.82 mmol) and **47** (0.20 mL, 0.28 g, 1.58 mmol, 190 M%) gave, after purification by flash chromatography eluting with 2% methanol:CH_2Cl_2 and recrystallization from diethyl ether:hexane (3:1), 0.24 g (0.62 mmol, 76% yield) of white powder: mp 134−135 °C; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 7.89 (br d, J = 8.2 Hz, 1H), 7.73−7.38 (m, 6H), 7.34 (dd, J = 7.4, 8.1 Hz, 1H, H_6), 7.22 (br d, J = 7.4 Hz, 1H, H_5), 7.07 (m, 2H, $H_{3',5'}$), 2.59 (s, 3H, CH_3). Anal. ($C_{20}H_{14}F_2N_2SO_2$) C, H, N.

1-(2,6-Difluorobenzoyl)-2-(2,6-difluorophenyl)benzimidazole (50). To **19** (30 mg, 0.13 mmol) dissolved in pyridine (0.5 mL) and chloroform (1.2 mL) was added **7** (20 μL, 0.16 mmol, 120 M%). After 5 h at room temperature, the mixture was diluted with chloroform and washed with $NaHSO_4$(2% solution). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The solid was recrystallized from diethyl ether:hexane (19 mg of colorless crystals, 40% yield): mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (m, 1H, H_4), 7.89 (m, 1H, H_7), 7.48 (m, 2H, $H_{5,6}$), 7.31−7.18 (m, 2H, $H_{4',4''}$), 6.77 (m, 4H, $H_{3',5',3'',5''}$). Anal. ($C_{20}H_{10}F_4N_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-(hydroxymethyl)-4-methylbenzimidazole (51). To **33** (1.82 g, 4.52 mmol) dissolved in THF (20 mL) was added tetrabutylammonium fluoride (1.45 g, 4.60 mmol, 100 M%). After 30 min at room temperature, the reaction mixture was concentrated to dryness. The residue was suspended in water, filtered, and washed with water (1.28 g, 4.44 mmol, 98% yield of white powder): ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (m, 1H, $H_{4''}$), 7.18 (br d, J = 8.3 Hz, 1H, H_7), 7.09 (dd, J = 7.4, 8.3 Hz, 1H, H_6), 7.05−6.97 (m, 3H, $H_{3'',5'',5}$), 5.68 (s, 2H, CH_2PhF_2), 4.99 (s, 2H, CH_2O), 2.57 (s, 3H, CH_3). Anal. ($C_{16}H_{14}F_2N_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-4-methylbenzimidazole (52). To **51** (1.82 g, 4.52 mmol) dissolved in 1.5 M H_2SO_4 (40 mL) was added $KMnO_4$ (1.50 g, 9.49 mmol, 160 M%). After 1 h at room temperature, the reaction was filtered and washed with water. The brown solid was collected, suspended in acetone:methanol, and filtered. The filtrate was collected and purified by flash chromatography, eluting with 10% methanol/CH_2Cl_2 increasing to 50% methanol/CH_2Cl_2 (1.42 g, 4.70 mmol, 80% yield of white powder): ^{1}H NMR (200 MHz, CD_2Cl_2) δ 7.99 (br s, 1H, H_2), 7.37 (br d, J = 7.9 Hz, 1H, H_7), 7.32 (m, 1H, $H_{4''}$), 7.17 (dd, J = 7.3, 7.9 Hz, 1H, H_6), 7.03 (d, J = 7.3 Hz, 1H, H_5), 6.96 (m, 2H, $H_{3'',5''}$), 5.40 (s, 2H, CH_2PhF_2), 2.59 (s, 3H, CH_3). Anal. ($C_{15}H_{12}F_2N_2 \cdot {}^1/_4H_2O$) C, H, N.

1-(2,6-Difluorobenzyl)-2-formyl-4-methylbenzimidazole (53). To pyridine (3.4 mL) dissolved in CH_2Cl_2 (50 mL) was added CrO_3 (2.20 g). After 15 min, **51** dissolved in DMF (10 mL) was added. After 20 min, the organic solution was decanted from a tarry black deposit. The organic solution was washed with 5% NaOH, 5% HCl, $NaHCO_3$, and NaCl, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography eluting with 2% methanol/CH_2Cl_2 gave 0.55 g (1.92 mmol, 44% yield) of **53** and 0.17 g (0.66 mmol, 15% yield) of **52**: ^{1}H NMR (200 MHz, CD_3OD) δ 10.13 (s, 1H, CHO), 7.36−7.10 (cm, 4H, $H_{5,6,7,4''}$), 6.90 (m, 2H, $H_{3'',5''}$), 6.05 (s, 7H, CH_2PhF_2), 2.66 (s, 3H, CH_3). Anal. ($C_{16}H_{12}F_2N_2O \cdot {}^1/_5H_2O$) C, H, N.

RT Assay. The RNA-dependent DNA polymerase assay has been described previously.[18] Briefly, purified heterodimer RT protein (0.015 mg/mL) was incubated in the presence and absence of inhibitor at various concentrations in a 100 μL reaction mixture [25 mM Tris (pH 8.0), 75 mM KCl, 8 mM $MgCl_2$, 2 mM dithiothreitol, 0.1 units poly(rC)-oligo(dG), 0.01 mM dGTP, 0.1 mg/mL BSA, 10 mM CHAPS, 0.025 mCi [α-^{35}S]-dGTP (specific activity, 1000 Ci/mmol)] for 30 min at 37 °C. The assays were stopped by adding 1 mL of 10% trichloroacetic acid and 10 μL of denatured and sheared salmon sperm DNA (10 mg/mL) as a carrier. The labeled polymer was collected on Whatman glass GF/C filters by suction filtration. After washing sequentially with 10% trichloroacetic acid and 95% ethanol, the filter was collected and counted. The reported inhibitory values were determined as the average of three determinations.

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV-1, humans immunodeficiency virus type 1; RT, reverse transcriptase; TZB, 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo[3,4-a]benzimidazole; NNRTI, nonnucleoside reverse transcriptase inhibitor; WT, wild-type; AZT, 3′-azido-3′-deoxythymidine; ddC, 2′,3′-dideoxycytidine; 8-Cl TIBO, 8-chloro-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one.

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