Novel Benzophenones as Non-nucleoside Reverse Transcriptase Inhibitors of HIV-1

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GW4511, GW4751, and GW3011 showed IC_{50} values ≤2 nM against wild type HIV-1 and <10 nM against 16 mutants. They were particularly potent against NNRTI-resistant viruses containing Y181C-, K103N-, and K103N-based double mutations, which account for a significant proportion of the clinical failure of the three currently marketed NNRTIs. The antiviral data together with the favorable pharmacokinetic data of GW4511 suggested that these benzophenones possess attributes of a new NNRTI drug candidate.

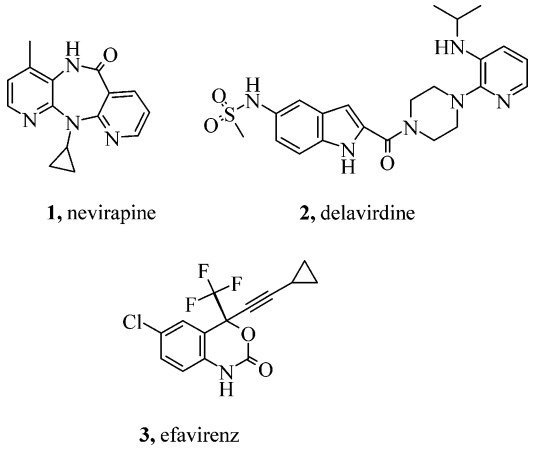
Introduction

Highly active antiretroviral therapy (HAART) combination regimens have dramatically decreased the morbidity and mortality among patients with human immunodeficiency virus (HIV) infections.[1] HAART regimens typically consist of two nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) as a third agent, or three NRTIs. The NNRTI class is the least extensive in terms of approved agents, consisting of only three, nevirapine,[2] delavirdine,[3] and efavirenz[4] (Figure 1).

NNRTIs bind in a region of HIV-1 RT which is approximately 10 Å away from the catalytic site. Unlike the nucleosides, which require anabolism to the triphosphate to become chain-terminating substrates, NNRTIs bind directly to the enzyme and inhibit catalytic function by distorting the three-dimensional structure of HIV-1 RT.[5] Hampered by the rapid emergence of resistant viruses in monotherapy, the therapeutic usefulness of NNRTIs was not fully realized until combination therapy with NRTIs and PIs proved successful in lowering viral load.[6,7] Subsequently, there has been a revived interest in developing NNRTIs to treat HIV infections and AIDS.

Current NNRTIs have a relatively low genetic barrier to mutations, and consequently resistance emerges quite rapidly. This and high cross-resistance within the class dictate that a new generation NNRTI should exhibit high potency against both wild-type and resistant strains of the virus.

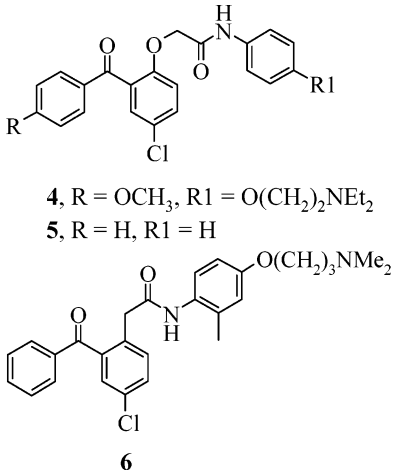
To date, several attempts to describe such a compound have been made. A series of benzophenone analogues with potent activity against wild-type HIV-1 has been reported.[8] From an initial structure **4** (Figure 2), compound **5** (Figure 2) was identified as having the requisite pharmacophore for antiviral activity. Unfortunately, passage experiments with analogue **6** (Figure 2) resulted in the rapid emergence of an HIV-1 resistant strain. Although the observed mutation was not the highly cross-resistant Y181C, nonetheless, these benzophenones were precluded from considerations as therapeutics because of the rapid emergence of that mutation.[8]



1, nevirapine **2,** delavirdine

3, efavirenz

Figure 1. Currently approved NNRTIs.



4, R = OCH_3, R1 = $O(CH_2)_2NEt_2$

5, R = H, R1 = H

6

Figure 2. Early benzophenones.

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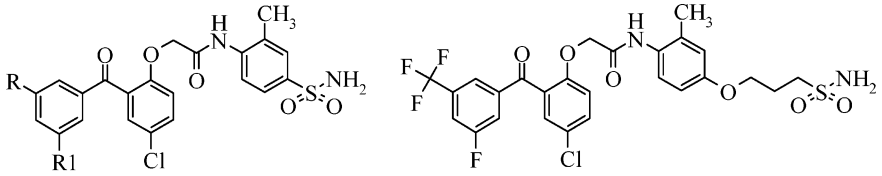
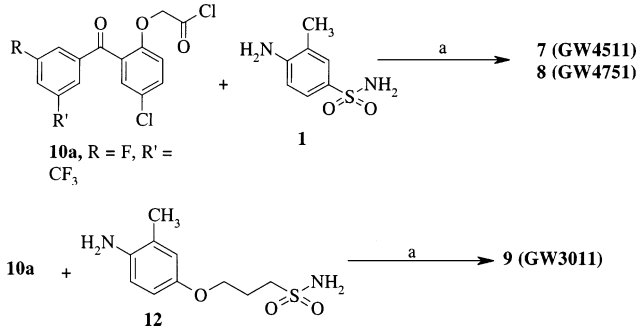


7, R = CF_3, R1 = F (GW4511)
8, R = H, R1 = CN (GW4751)

9, GW3011

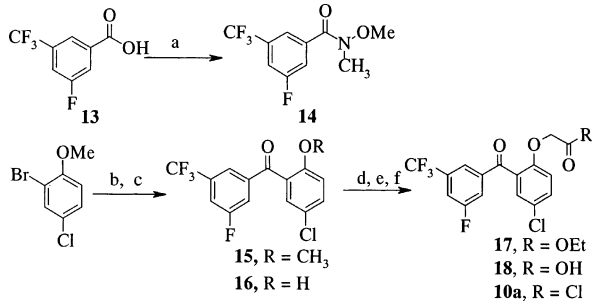
Figure 3. Current potent benzophenones.

Scheme 1[a]



[a] Conditions: (a) $NaHCO_3$, acetone, H_2O, reflux.

Scheme 2[a]



[a] Conditions: (a) CDI, NH(OMe)Me·HCl, TEA, THF, 0 °C to rt; (b) n-BuLi, THF, 78 °C, **14**; (c) BBr_3, CH_2Cl_2, −78 °C to rt; (d) K_2CO_3, DMF, $BrCH_2CO_2Et$, reflux; (e) LiOH, H_2O, EtOH, rt; (f) $(COCl)_2$, DMF, $CHCl_3$, 0 °C to rt.

In this paper we describe synthetic work and structure−activity relationship studies, aided by computer modeling of the X-ray crystal structures of the benzophenone-RT complex.[9] This work had resulted in the identification of a series of analogues that were potent against wild-type HIV-1 and a panel of NNRTI-resistant HIV-1 strains. GW4511, GW4751, and GW3011 (Figure 3) were examples of such analogues, which showed broad-spectrum potency and could be considered important lead molecules in the discovery of a new generation NNRTI.

Chemistry

The key step in the synthesis involved the coupling of acid chloride **10a**, **10b**, and aniline **11** for the synthesis of benzophenones **7** and **8**, and the coupling of acid chloride **10a** and aniline **12** for the synthesis of compound **9**, as depicted in Scheme 1.[8]

Acid chloride **10a** (R = F, R′ = CF_3) for the synthesis of **7** was synthesized according to procedures summarized in Scheme 2. The first step involved the synthesis of Weinreb amide **14** from benzoic acid **13** with *N*,*O*-dimethylhydroxylamine hydrochloride using carbonyldiimiazole (CDI) and triethylamine. Intermediate **14** was then reacted with the lithium salt of 2-bromo-4-chloroanisole resulting in **15**. Demethylation using boron tribromide in methylene chloride led to hydroxy benzophenone **16** that was then reacted with ethyl bromoacetate to give ester **17**. On saponification, **17** led to acid **18** from which acid chloride **10a** was generated in situ by the reaction of **18** with a Vilsmeier−Haack reagent generated from oxalyl chloride and DMF.[10]

The synthesis of aniline **11** is depicted in Scheme 3 and began by protection of 2-aminotoluene-5-sulfonic acid with acetic anhydride, leading to pyrdinium salt **19**. Salt exchange of **19** with sodium hydroxide led to **20**. Sulfonyl chloride **21** was generated in situ after reacting sodium salt **20** with thionyl chloride in DMF. **21** was then reacted with ammonium hydroxide in THF to afford **22**.[11] Deprotection with concentrated hydrochloric acid in refluxing aqueous ethanol led to **11**.

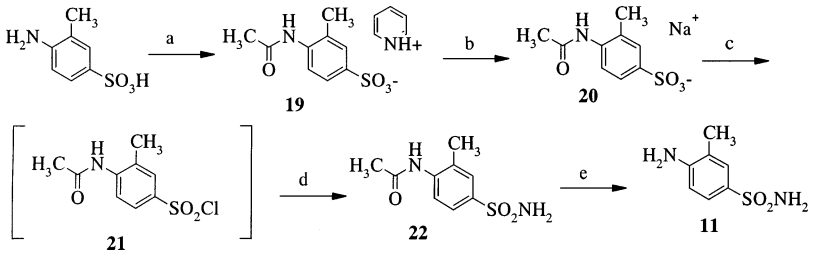
The acid chloride **10b** for the synthesis of compound **8** was synthesized as shown in Scheme 4. 3-Cyanobenzoyl chloride, prepared from commercially purchased 3-cyanobenzoic acid with oxalyl chloride in methylene chloride and catalytic DMF, was reacted with *N*,*O*-dimethylhydroxylamine hydrochloride in chloroform and triethylamine to afford the desired Weinreb amide **23**. The amide was reacted, as before, with the lithium salt of 2-bromo-4-chloroanisole leading to intermediate **24**. Demethylation with boron tribromide resulted in phenol **25**, which was then reacted with ethyl bromoacetate using potassium carbonate as the base leading to ester **26**. Hydrolysis of the ester group with lithium hydroxide led to the carboxylic acid **27**. Acid chloride **10b** was generated in situ under conditions similar to those described above for **10a**.

Finally, the synthesis of aniline **12** followed the procedures described in Scheme 5. Commercially purchased 3-methyl-4-nitrophenol was reacted with 1,3-propane sultone using sodium hydride as the base. This resulted in intermediate **28**, which was then reacted with thionyl chloride to give chloride **29**. Upon reacting with ammonium hydroxide in THF, **30** was formed, which was hydrogenated in a Parr bomb leading to aniline **12**.

Results and Discussion

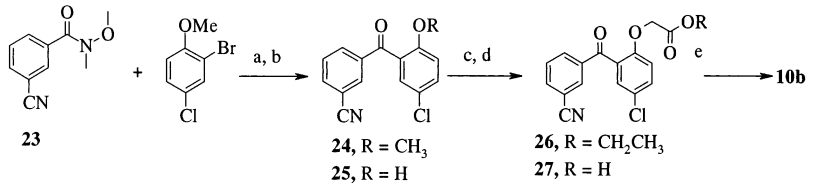
During the initial stages of our search for a lead molecule, we routinely evaluated compounds in an MT4 cell assay infected with wild-type virus or Y181C, a nevirapine- and delavirdine-resistant strain.[12] Benzophenones GW4751, GW4511, and GW3011 were evaluated initially for their antiviral activity in such an assay,

Scheme 3[a]



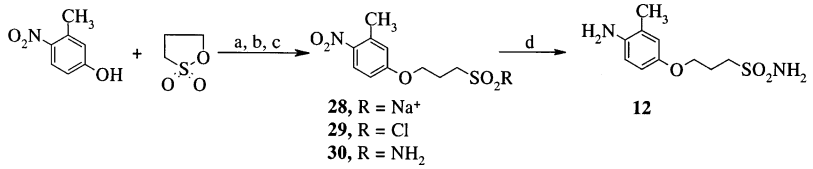
[a] Conditions: (a) Ac_2O, pyridine, rt; (b) 1 N NaOH, 0 °C; (c) $SOCl_2$, DMF, −4 °C; (d) NH_4OH, THF, rt; (e) concd HCl, EtOH, H_2O, reflux.

Scheme 4[a]



[a] Conditions: (a) n-BuLi, Et_2O, −78 °C to rt; (b) BBr_3, CH_2Cl_2, −78 °C to rt; (c) $BrCH_2CO_2Et$, K_2CO_3, acetone, reflux; (d) LiOH, THF, EtOH, H_2O, rt; (e) $(COCl)_2$, DMF, $CHCl_3$, 0 °C to rt.

Scheme 5[a]



[a] Conditions (a) NaH, THF, 0 °C to reflux; (b) SO_2Cl_2, 0 °C to rt; (c) NH_4OH, THF_3, 0 °C; (d) H_2, Pd/C, EtOH, rt.

Table 1. Antiviral Activity of GW4751, GW4511, GW3011, and Marketed NNRTIs in MT4 Cells Infected with HIV-1

	IC_{50} values (nM) vs wild-type HIV-1 and Y181C strain					
virus	GW4751	GW4511	GW3011	nevirapine	delavirdine	efavirenz
wild-type	1.8	0.5	7.2	96	160	3.5
Nev-R	1.4	1.6	4.5	17200	2400	2.7

Table 2. Activity of GW4511, GW4751, and GW3011 against Wild-Type Reverse Transcriptase

	IC_{50} values [nM] (n)[a]					
RT enzyme	GW4511	GW4751	GW3011	efavirenz	nevirapine	delavirdine
wild-type	3.0 (4)	1.7 (4)	4.7 (4)	0.75 (4)	230 (4)	21 (3)

[a] Efavirenz, nevirapine, and delavirdine are included for comparison purposes.

and the results are summarized in Table 1. Nevirapine, delavirdine, and efavirenz are included in the table for comparison purposes.

The results of this preliminary assay suggest that all three benzophenone analogues were potent compounds. Indeed, GW4751, GW4511, and GW3011 were much more potent than nevirapine and delavirdine and equivalent to efavirenz against both the wild-type virus and Y181C. We next assayed the three compounds against HIV-1 reverse transcriptase, and the data are listed in Table 2.

The inhibitory activity against HIV-1 RT indeed showed the mechanism of action of those three compounds was via the inhibition of HIV-1 RT and the enzyme activity consistent with the antiviral activity shown in Table 1.[13] These results warranted further evaluation against a more extensive panel of NNRTI-resistant strains, including those highly resistant to efavirenz using a HeLa MAGI luciferase reporter assay.[12]

The NNRTI-resistant strains (Table 3) were constructed using the procedure of Kellam and Larder[14] and encode both single and double mutations surrounding the NNRTI binding site. Some of these mutations are known to manifest high NNRTI cross-resistance. For example, K103N and Y181C confer a high degree of cross-resistance to the currently available NNRTIs and signal the loss of clinical efficacy.[15]

Resistance to nevirapine is directly linked to K103N and Y181C mutations, as well as mutants encoding the G190A, Y188C/I, L100I, and V106A mutations.[16,17] Delavirdine is limited in use by K103N, Y181C, and P236L mutations.[18] This background information and that obtained from the resistance profiles of other NNRTIs[19] were used to construct the 20 mutant viruses shown in Table 3.

GW4751, GW4511, and GW3011 were found to be extremely potent against the wild-type virus with IC_{50} values ≤2 nM. Against 16 of the 20 mutants, the three compounds showed IC_{50} values of <10 nM. Four of these

Table 3. Antiviral Activity of GW4511, GW4751, and GW3011 against Wild-type HIV-1 and a Panel of Resistant HIV-1 Strains

	IC_{50} Values [nM] (*n*)[a]					
HIV-1 type	GW4511	GW4751	GW3011	efavirenz	nevirapine	delavirdine
wild-type	1.4 (30)	1.4 (12)	2.4 (8)	0.9 (30)	100 (14)	200 (9)
K103N	1.9 (25)	2.0 (10)	3.3 (9)	27 (34)	6600 (11)	2700 (7)
V106A	10.0 (25)	30.0 (6)	16 (4)	1.5 (22)	9000 (10)	,900 (4)
V106I	2.5 (9)	2.7 (4)	3.2 (3)	0.8 (10)	150 (4)	55 (3)
V108I	1.9 (8)	1.0 (4)	3.5 (3)	2.1 (11)	290 (7)	78 (3)
K101E	3.4 (3)	3.4 (4)	7.2 (3)	2.5 (8)	520 (3)	29 (2)
L100I	1.2 (6)	0.8 (4)	2.0 (3)	21 (14)	500 (3)	920 (2)
G190A	4.2 (8)	5.2 (4)	5.6 (3)	7 (13)	>10 000 (6)	35 (2)
P225H	0.7 (7)	0.5 (3)	1.8 (3)	1.7 (7)	1200 (1)	11 (3)
*P*236L	5.1 (6)	21 (2)	7.8 (2)	0.8 (9)	56 (2)	1,600 (2)
Y181C	3.1 (11)	6.5 (3)	6.6 (2)	1.8 (17)	9400 (13)	2300 (1)
Y188C	0.4 (9)	0.3 (6)	0.6 (4)	1.4 (11)	2300 (10)	170 (4)
E138K	3.0 (6)	3.9 (3)	6.1 (3)	0.9 (8)	65 (6)	10 (1)
K103N/Y181C	3.6 (14)	8.1 (6)	7.6 (6)	46 (21)	>10 000 (11)	>8400 (5)
K103N/P225H	1.5 (12)	3.0 (4)	7.9 (5)	150 (14)	9800 (6)	2300 (4)
K103N/G190A	16.0 (10)	26 (5)	15 (3)	490 (11)	>10 000 (3)	2700 (3)
K103N/L100I	3.0 (10)	4.0 (5)	6.6 (5)	1,500 (18)	8000 (8)	> 8400 (5)
K103N/V108I	3.6 (10)	5.6 (5)	4.8 (6)	93 (14)	15000 (7)	3500 (3)
V106A/Y181C	16 (14)	28 (4)	21 (5)	3.1 (8)	>10 000 (2)	>10 000 (2)
V106I/Y181C	11 (12)	34 (5)	11 (4)	3.6 (8)	>10 000 (3)	4500 (4)
V108I/Y181C	3.4 (12)	4.1 (2)	6.2 (3)	3.1 (6)	>10 000 (3)	>10 000 (1)

[a] Efavirenz, nevirapine, and delavirdine are included for comparison purposes.

Table 4. Protein Binding Studies in HeLa MAGI Assay

	fold change in IC_{50}					
	HXB2			K103N		
NNRTI	AAG[a]	HuS[b]	AAG + HuS	AAG	HuS	AAG + HuS
GW4751	1.1	6.4	3.7	1.9	4.5	2.4
GW4511	1.9	7.7	6.5	1.4	5.8	5.5
GW3011	1.7	5.5	7.7	1.5	5.7	5.3
EFV	2.4	24	20	1.3	5.1	5.8
NEV	1.0	2.5	2.0	0.8	1.0	1.2

[a] AAG, 0.8 mg/mL a1 acid glycoprotein. [b] HuS, 45% human serum.

mutants are K103N-based including K103N/P225H and K103N/L100I, which are highly resistant to efavirenz. The highest IC_{50} values in the entire panel were 16 nM for GW4511 (vs K103N/G190A and V106A/Y181C), 21 nM for GW3011 (vs V106A/Y181C), and 34 nM for GW4751 (vs V106I/Y181C).

The effect of protein binding on the antiviral activity of GW4751, GW4511, and GW3011 versus both the wild-type virus (strain HXB2) and the K103N resistant strain was tested in the presence of acid glycoprotein, human serum, and a combination of both acid glycoprotein and human serum. The results are summarized in Table 4, together with those for efavirenz and nevirapine. As shown in the table, the presence of acid glycoprotein had limited affect on the antiviral activity of GW4751, GW4511, and GW3011 versus both the wild-type virus and the K103N resistant strain, similar to that observed for both efavirenz and nevirapine. In the presence of human serum, the fold change in IC_{50} was still within a reasonable range, albeit slightly higher than that in acid glycoprotein. The combination of acid glycoprotein and human serum did not have a dramatic effect on the antiviral activity.

In an effort to establish putative developability of the benzophenone class, GW4511 was administered to rats, dogs, and monkeys to determine its pharmacokinetic characteristics. The results of those experiments are summarized in Table 5. Each species provided evidence of absoprtion with both solutions and suspensions. The solutions of drug in PEG400 consistently demonstrated

Table 5. Mean Pharmacokinetic Parameter Values for GW4511 Following Single Oral Dose Administration to Rats, Dogs, and Monkeys

species	dose (mg/kg)	formulation	C_{max}[a] (ng/mL)	C_{24h}[b] (ng/mL)	AUC[c] (ng h/mL)	F[d] (%)
rat	10	solution	357	32	4146	27
		suspension	60	nd[e]	438	3
dog	1	solution	80	nd	650	29
		suspension	22	7	451	20
monkey	1	solution	95	8	988	58
		suspension	4	nd	57	3

[a] C_{max}, maximum observed concentration in plasma. [b] C_{24h}, concentration in plasma at 24 h postdose. [c] AUC, area under the plasma concentration−time curve. [d] F, oral bioavailability [$(AUC_{po}/AUC_{iv}) \times 100$]. [e] nd, not determined or not detected (i.e., <1 ng/mL).

advantage in C_{max} and exposures relative to the suspensions (compound suspended in aqueous 5% hydroxypropylmethylcellulose (HPMC):Tween-80). The total body clearance values (Cl), determined from single intravenous administration were 11, 7, and 10 mL/min/kg for the rat, dog, and monkey, respectively. The calculated Cl values were consistently less than one-third of hepatic blood flow for all three species, indicating an acceptable metabolic fate and clearance of the drug from the body. The oral bioavailability (F) ranged from 27 to 58% when the drug was administered as a solution and 3−20% when it was dosed as a suspension.

In summary, we have identified a benzophenone scaffold, analogues of which showed potent broad-spectrum antiviral activity against both wild type and relevant NNRTI-resistant mutant viruses. GW4751, GW4511, and GW3011 were three of the analogues that manifested potency against the wild type HIV-1 and the panel of NNRTI-resistant mutants. Of particular significance was their potency against the Y181C-, K103N-, and K103N-containing double mutation NNRTI-resistant viruses, which account for a significant proportion of the clinical failure of the three currently marketed NNRTIs. The pharmacokinetic data, together with the potency and broad-spectrum antiviral activity, suggested that these benzophenones are potentially important lead molecules for a new generation NNRTI.

Experimental Section

^{1}H NMR spectra were recorded on a Varian XL200, Varian Unity Plus 400, or Varian Unity Plus 200 MHz spectrometers. Elemental analyses were carried out by Atlantic Microlabs, Inc., Atlanta, GA. All purchased starting materials were used without further purifications. All solvents were reagent grades. Procedures for the MT4 cell assay and the HeLa MAGI assay followed that described in ref 12.

3-Fluoro-*N*-methoxy-*N*-methyl-5-(trifluoromethyl)-benzamide (14). Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed *N*,*O*-dimethylhydroxylamine hydrochloride (2.8 g, 28.7 mmol), Et_3N (9.0 mL, 64.57 mmol), and $CHCl_3$ (50 mL). The solution was cooled to 0 °C, and 3-trifluoromethyl-5-fluorobenzoyl chloride (5.0 g, 22.07 mmol) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to room temperature and stirred for an additional 30 min. The mixture was then poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and washed with water and brine. After drying ($MgSO_4$) and solvent removal, **14** was obtained as a clear oil, which was used without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.65 (d, J = 9 Hz, 1H), 7.46 (d, J = 9 Hz, 1H), 3.59 (s, 3H), 3.42 (s, 3H).

(5-Chloro-2-methoxyphenyl)[3-fluoro-5-(trifluoromethyl)phenyl]methanone (15). Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (4.05 g, 18.29 mmol) and Et_2O (75 mL). The solution was cooled to −78 °C, and n-BuLi (13 mL of a 1.6 M solution in hexane, 20.8 mmol) was added dropwise. The resulting mixture was allowed to stir at −78 °C for 15 min, after which **14** (5.04 g, 20.07 mmol) was added dropwise. After stirring for an additional 30 min at − 78 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 2 h. The mixture was then poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and was washed with water and brine. After drying ($MgSO_4$) and solvent removal, **15** was obtained as a yellow solid (6.14 g, 92%), which was used in the following reaction without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.68 (d, J = 9 Hz, 1H), 7.58−7.51 (m, 2H), 7.44 (d, J = 3 Hz, 1H), 7.00 (d, J = 9 Hz, 1H), 3.74 (s, 3H).

(5-Chloro-2-hydroxyphenyl)[3-fluoro-5-(trifluoromethyl)phenyl]methanone (16). Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **15** (6.14 g, 18.46 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to −78 °C, and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol) was added dropwise over several min. The resulting dark mixture was allowed to stir at −78 °C for 30 min and was then allowed to warm to room temperature and stir for an additional 1 h. The mixture was carefully poured over ice, and the two-phase mixture was stirred for 30 min. The mixture was then poured into a separatory funnel containing CH_2Cl_2 and H_2O. The organic layer was collected and washed with water and brine. After drying ($MgSO_4$) and solvent removal, **16** was obtained as a yellow solid (5.68 g, 96%), which was used without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.61 (s, 1H), 7.77 (s, 1H), 7.65−7.54 (m, 3H), 7.47 (d, J = 3 Hz, 1H), 7.12 (d, J = 9 Hz, 1H).

Ethyl [4-Chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)-phenoxy]acetate (17). Into a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed **16** (5.68 g, 17.83 mmol), ethyl bromoacetate (2 mL, 18.03 mmol), K_2CO_3 (9.61 g, 69.53 mmol), and acetone. The resulting mixture was heated to reflux for 5 h, after which it was allowed to cool to room temperature and was poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and was washed with water and brine. After drying ($MgSO_4$) and solvent removal, **17** was obtained as an oil, which was used in the following reaction without further purification.

[4-Chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)-phenoxy]acetic Acid (18). A round-bottom flask was equipped with a stir bar and nitrogen on demand and was flushed with N_2. To the flask were added LiOH (1.42 g, 33.84 mmol), H_2O (20 mL), THF (50 mL), and EtOH (20 mL). The resulting suspension was stirred vigorously, and **17** (6.83 g, 16.88 mmol) was added in one portion. The mixture was allowed to stir at room temperature for 2 h, after which the pH was adjusted to approximately pH 5 by the slow addition of 1 N aq HCl. The mixture was then poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and was washed with water and brine. After drying ($MgSO_4$) and solvent removal, **18** was obtained as a white solid. The solid was used in the following reaction without further purification.

[4-Chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)-phenoxy]acetyl Chloride (10a). Into a round-bottom flask were placed carboxylic acid **18** (11.24 g, 29.84 mmol), CH_2Cl_2 (250 mL), and DMF (5 mL). The mixture was cooled to 0 °C, and oxalyl chloride (3.9 mL, 44.7 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 2 h. The solvents were then removed under reduced pressure, and the remaining residue was dried in vacuo. The acid chloride thus obtained was used without further purification

Pyridinium 4-(Acetylamino)-3-methylbenzenesulfonate (19). Into a round-bottom flask with argon on demand and an overhead stirrer were placed 2-aminotoluene-5-sulfonic acid (250 g, 1.34 mol) and pyridine (1.7 L). Acetic anhydride (205 mL, 2.17 mol) was added dropwise from an addition funnel, and the resulting mixture was allowed to stir for 2 h. The solvents were removed in vacuo and further azeotroped with several portions of EtOH. EtOH was re-added and the resulting suspension was cooled in an ice water bath and filtered. The solid obtained was washed with cold EtOH and Et_2O and then dried in vacuo to afford **19** as a pink solid (366.80 g, 89%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 2.17 (s, 3H), 7.35 (s, 2H), 7.41 (s, 1H), 8.04 (t, J = 7 Hz, 2H), 8.57 (t, J = 8 Hz, 1H), 8.91 (d, J = 5 Hz, 2H), 9.27 (s, 1H).

Sodium 4-(Acetylamino)-3-methylbenzenesulfonate (20). NaOH (1 N) (1.25 L) was added to a around-bottom flask and cooled to 0 °C. **19** (367 g, 1.2 mol) was added portionwise, and the resulting mixture was allowed to warm to room temperature. EtOH was added, and the mixture was concentrated under reduced pressure by 75%. An additional portion of EtOH was added, and the mixture was then concentrated to dryness in vacuo. The solid was triturated with EtOH, filtered, washed with Et_2O, and dried in vacuo overnight to afford **20** as an off-white solid (296 g, 99%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.04 (s, 3H), 2.18 (s, 3H), 7.37 (s, 2H), 7.43 (s, 1H), 9.30 (s, 1H).

***N*-[4-(Aminosulfonyl)-2-methylphenyl]acetamide (22).** **20** (205 g, 820 mmol) and DMF (1.6 L) were added to a round-bottom flask that was equipped with a stir bar and N_2 on demand and was cooled to −4 °C in an ice−brine bath. Thionyl chloride (180 mL, 2.5 mol) was added dropwise from an addition funnel at a rate that the temperature of the reaction mixture did not exceed 0 °C. When the addition was complete, the mixture was kept below 0 °C and allowed to stir for an additional 2 h. The mixture was then poured into a beaker containing crushed ice and H_2O (3 L). The resulting yellow solid was collected by filtration, washed with several portions of H_2O, and dried under a stream of nitrogen. The solid was then added portionwise to a stirred solution of THF (1.6 L) and concentrated NH_4OH (850 mL). The reaction was then stirred for 20 min. and concentrated in vacuo and triturated with cold H_2O. The solid obtained was filtered and washed with Et_2O. After drying in vacuo, **22** was obtained as a tan solid (189.48 g, crude product). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.09 (s, 3H), 2.27 (s, 3H), 7.25 (s, 2H), 7.58 (dd, J = 2, 8 Hz, 1H), 7.64 (d, J = 2 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 9.44 (s, 1H).

4-Amino-3-methylbenzenesulfonamide (11). Into a round-bottom flask equipped with a stir bar and N_2 on demand were placed **22** (127 g, 560 mmol), H_2O (65 mL), and EtOH (1200

mL). Concentrated HCl (500 mL) was added, and the mixture was brought to reflux for 1 h. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with EtOAc (3×). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **11** (70.24 g, 68%) as a tan solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.07 (s, 3H), 5.57 (s, 2H), 6.61 (d, J = 8 Hz, 1H), 6.85 (s, 2H), 7.32 (dd, J = 2, 8 Hz, 1H), 7.36 (d, J = 2 Hz, 1H).

***N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide (7).** Into a round-bottom flask were placed sulfonamide **11** (5.12 g, 27.49 mmol), $NaHCO_3$ (11.12 g, 132 mmol), acetone (300 mL), and H_2O (10 mL). **10a** was added dropwise as a solution in acetone (10 mL), and the reaction mixture was allowed to stir at room temperature for 24 h. When judged to be complete, the mixture was poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and was washed with water and brine. After drying ($MgSO_4$) and solvent removal, **7** was obtained as a white solid (9 g, 60%) after crystallization from a mixture of CH_3CN/H_2O. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.47 (s, 1H), 8.05 (d, J = 9 Hz, 1H), 7.93−7.90 (m, 2H), 7.73−7.50 (m, 5H), 7.30−7.26 (m, 3H), 4.84 (s, 2H), 2.19 (s, 3H). Anal. Calcd for $C_{23}H_{17}ClF_4N_2O_5S$: C, 50.70; H, 3.14; N, 5.14. Found: C, 50.75; H, 3.10; N, 5.21.

3-(5-Chloro-2-methoxybenzoyl)benzonitrile (20). To a round-bottom flask equipped with an overhead stirrer, an addition funnel, and N_2 on demand were placed 2-bromo-4-chloroanisole (75.3 g, 0.34 mol) and Et_2O (800 mL). The mixture was cooled to −78 °C, and n-BuLi (148 mL of a 2.5 M solution in hexane, 0.37 mol) was added dropwise via the addition funnel. The reaction was then allowed to stir at −78 °C for 1 h. **19** (65 g, 0.34 mol) was added dropwise as a solution in Et_2O (150 mL) over 30 min. The reaction was warmed to room temperature and stirred for an additional 1 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing H_2O (800 mL). The organic layer was separated, washed with brine, and then dried over $MgSO_4$. After solvent removal, a yellow solid was obtained, which was recrystallized from methanol to afford **20** as a yellow solid (54.2 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (m, 2H), 7.92 (d, J = 8 Hz, 1H), 7.68 (t, J = 8 Hz, 1H), 7.58 (dd, J = 4, 8 Hz, 1H), 7.41 (d, J = 4 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 3.61 (s, 3H).

3-(5-Chloro-2-hydroxybenzoyl)benzonitrile (21). Into a round-bottom flask equipped with an overhead stirrer and N_2 on demand were placed **20** (100 g, 0.37 mmol) and CH_2Cl_2 (1 L). The solution was cooled to −78 °C and boron tribromide (100 g, 0.4 mol) was added dropwise over 30 min. The resulting dark mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was carefully poured over ice, and the two-phase mixture was stirred for 30 min. The organic layer was collected and dried over $MgSO_4$. After solvent removal subsequent drying in vacuo for 2 days, **21** was obtained as a yellow solid (92 g, 97%), which was used without any further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.41 (s, 1H), 8.05 (m, 1H), 7.95 (d, J = 8 Hz, 1H), 7.68 (t, J = 8 Hz, 1H), 7.43 (dd, J = 4, 9 Hz, 1H), 7.34 (m, 1H), 6.94 (d, J = 8 Hz, 1 H).

Ethyl [4-Chloro-2-(3-cyanobenzoyl)phenoxy]acetate (22). Into a three-neck round-bottom flask equipped with an overhead stirrer, reflux condenser, and N_2 on demand were placed **21** (91 g, 0.35 mol), acetone (1 L), K_2CO_3 (97 g, 0.7 mol), and ethyl bromoacetate (62 g, 0.37 mol). The resulting mixture was heated to reflux for 2.5 h, after which it was allowed to cool to room temperature and was poured into a separatory funnel containing EtOAc and H_2O. The organic layer was collected and was dried over $MgSO_4$. After solvent removal and drying in vacuo overnight, **22** (149 g, crude) was obtained as an oil, which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (m, 2H), 8.00 (d, J = 8 Hz, 1H), 7.67 (t, J = 8 Hz, 1 H), 7.55 (dd, J = 4, 8 Hz, 1 H), 7.45 (d, J = 4 Hz, 1 H), 7.09 (d, J = 12 Hz, 1H), 4.71 (s, 2H).

[4-Chloro-2-(3-cyanobenzoyl)phenoxy]acetic Acid (23). A round-bottom flask was flushed with N_2 and equipped with a stir bar and N_2 on demand. To the flask were added **22** (120 g, 0.35 mol), H_2O (200 mL), THF (800 mL), EtOH (200 mL), and lithium hydroxide (120 g, 0.35 mol). The resulting suspension was stirred vigorously for 2 h, after which the pH was adjusted to approximately 3 by the slow addition of concentrated HCl. The mixture was then poured into a separatory funnel containing EtOAc. The organic layer was collected and was dried over $MgSO_4$. After solvent removal, a crude solid was obtained, which was triturated with pentane and then dried in a vacuum oven at room temp for 2 h. This resulted in **23** (103 g, 94%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (bs, 1H), 8.09 (s, 1H), 8.04 (m, 2H), 7.66 (t, J = 8 Hz, 1 H), 7.55 (dd, J = 4, 8 Hz, 1 H), 7.43 (m,1 H), 7.08 (d, J = 8 Hz, 1H), 4.62 (s, 2H).

***N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide (8).** Into a round-bottom flask were placed **23** (100 g, 320 mmol) and CH_2Cl_2 (1 L). The mixture was cooled in an ice water bath. Oxalyl chloride (44.4 g, 350 mmol) was added dropwise. After 15 min, DMF (1 mL) was added, and the reaction mixture was allowed to stir at room temperature for 2 h. An additional amount of oxalyl chloride (2 equiv) and DMF (1 mL) were added, and the reaction again was stirred at room temperature for 2 h. When judged to be complete, the homogeneous solution was concentrated in vacuo. Into another round-bottom flask were placed **11** (54 g, 290 mmol), acetone (1 L), $NaHCO_3$ (134 g, 1.6 mol), and H_2O (∼80 mL). The acid chloride from above was dissolved in reagent grade acetone (250 mL) and added dropwise over 30 min. The reaction was allowed to stir at room temperature overnight before the mixture was poured into a separatory funnel containing EtOAc (500 mL) and H_2O (500 mL). The white solid formed was filtered. The organic layer was separated, dried over $MgSO_4$,and filtered. Concentration of the organic layer afforded an off-white solid. The desired product was obtained by combining the two solids, recrystallization from a mixture of CH_3CN/ H_2O (3:2), and vacuum-drying to provide **8** as a white solid (71.25 g, 46%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.41 (s, 1H), 8.20 (t, J = 2 Hz, 1H), 8.09 (td, J = 2, 8 Hz, 2H), 7.71 (t, J = 8 Hz, 1H), 7.65 (m, 3H), 7.59 (dd, J = 2, 8 Hz, 1H), 7.51 (d, J = 3 Hz, 1H), 7.26 (s, 2 H), 7.24 (d, J = 9 Hz, 1H), 4.80 (s, 2H), 2.17 (s, 3H). Anal. Calcd for $C_{23}H_{18}ClN_3O_5S$: C, 57.08; H, 3.75; N, 8.68. Found: C, 57.23; H, 3.75; N, 8.68.

Sodium 3-(3-Methyl-4-nitrophenoxy)propane-1-sulfonate (28). To a round-bottom flask equipped with an overhead stirrer, an addition funnel, and N_2 on demand were placed NaH (7.8 g of 60 wt % in mineral oil, 0.20 mol) and anhydrous THF (300 mL). The mixture was cooled to 0 °C, and 2-methyl-3-nitrophenol (30 g, 0.20 mol) was added dropwise as a solution in THF (100 mL). The reaction was then allowed to warm to room temperature, heated to 40 °C for 15 min, and then allowed to cool to room temperature. 1,3-Propane sultone (25.6 g, 0.21 mol) in THF (100 mL) was added dropwise, and the reaction was heated to reflux for 4−6 h. When judged to be complete, the reaction mixture was filtered, and the resulting solid was washed with absol EtOH and Et_2O, and dried in a vacuum oven. A solid precipitated out of the mother liquor that was filtered, washed with absol EtOH and Et_2O, and dried in a vacuum oven to afford a combined yield of **28** as a pale yellow solid (27 g, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J = 9 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.98 (dd, J = 2.7, 9.3 Hz, 1H), 4.22 (t, J = 6.6 Hz, 2H), 2.58 (m, 2H), 2.52 (s, 3H), 2.04 (m, 2H).

3-(3-Methyl-4-nitrophenoxy)propane-1-sulfonyl Chloride (29). To a round-bottom flask equipped with a stir bar, an addition funnel, and N_2 on demand were added **28** (11 g, 0.037 mol) and DMF (250 mL), and the reaction was cooled to 0 °C. Thionyl chloride (8.0 mL, 13.0 g, 0.11 mol) was added dropwise, and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which it was allowed to warm to room temperature and stir for an additional 3 h. When judged to be complete, the reaction mixture was poured into a beaker of

ice, and the resulting white precipitate was filtered and placed in a vacuum oven to afford **29** as a white solid (8.7 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J = 9 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.98 (dd, J = 2.7, 9.3 Hz, 1H), 4.22 (t, J = 6.3 Hz, 2H), 2.61 (m, 2H), 2.57 (s, 3H), 2.04 (m, 2H).

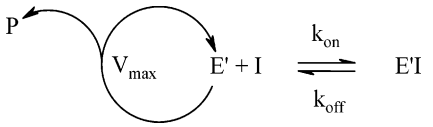
3-(3-Methyl-4-nitrophenoxy)propane-1-sulfonamide (30). To a round-bottom flask equipped with a stir bar, an addition funnel, and N_2 on demand were added NH_4OH (10 mL) and THF (20 mL), and the reaction was cooled to 0 °C. Sulfonyl chloride **29** (2 g, 6.8 mmol) in THF (20 mL) was added dropwise, and the reaction was allowed to stir at 0 °C for 15 min, after which the reaction was poured into a beaker of ice and extracted with EtOAc. The organic layer was collected, washed with H_2O, dried over $MgSO_4$, and filtered. After solvent removal, **30** was obtained as a white solid (1.4 g, 77%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (d, J = 9 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 7.00 (dd, J = 2.7, 9 Hz, 1H), 6.91 (s, 2H), 4.24 (t, J = 6 Hz, 2H), 3.16 (t, J = 7.5 Hz, 2H), 2.56 (s, 3H), 2.18 (m, 2H).

3-(4-Amino-3-methylphenoxy)propane-1-sulfonamide (12). To a plastic-coated reaction vessel, equipped with a stir bar, were added **30** (0.29 g, 1.1 mmol), absol EtOH (25 mL), and palladium on charcoal (29 mg of 10% Pd/C, 10 wt %). The vessel was placed on a hydrogenation apparatus at 60 psi for 3 h. When judged to be complete, the reaction was filtered through a Celite plug, and the EtOH was removed under reduced pressure to provide **12** (0.25 g, 98%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 2H), 6.54 (s, 1H), 6.49 (s, 2H), 4.34 (s, 2H), 3.89 (t, J = 6 Hz, 2H), 2.58 (m, 2H), 3.05 (m, 2H), 1.99 (m, 5H).

***N*-{4-[3-(Aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]-phenoxy}acetamide (9). 10a** (obtained from the reaction of **16** (13 g, 0.035 mol), oxalyl chloride (7.0 mL, 9.8 g, 0.077 mol), DMF (1 drop), and CH_2Cl_2 (100 mL) according to the procedure described above), **12** (7.81 g, 0.032 mol), $NaHCO_3$ (15 g, 0.18 mol), acetone (125 mL), and H_2O (10 mL) were used according to the procedure described for the synthesis of **7**. The product was crystallized from MeOH to afford **9** as a white solid (10.5 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J = 2.7, 9 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.13 (d, J = 9 Hz, 1H), 6.88 (s, 2H), 6.80 (d, J = 2.7 Hz, 1H), 6.73 (dd, J = 2.7, 9 Hz, 1H), 4.74 (s, 2H), 4.07 (t, J = 6 Hz, 2H), 3.13 (m, 2H), 2.13 (m, 2H), 2.03 (s, 3H). MS (ES): 602 (M−H)$^-$, 603 (M$^+$). Anal. Calcd for $C_{26}H_{23}N_2O_6ClF_4S$: C, 51.79; H, 3.84; N, 4.65. Found: C, 51.91; H, 3.88; N, 4.66.

RT Enzyme Assay: Continuous Time-Resolved Fluorescence. Reactions contained 100 nM Cy5-dUTP, 40 nM Eu-labeled template primer, 1 nM purified recombinant RT, 47 mM Tris-HCl, 75 mM KCl, 9.3 mM $MgCl_2$, 0.003% NP40, 9.3 mM dithiothreitol (DTT), and 2% dimethyl sulfoxide (DMSO). Test compound or control solvent (15 μL) was added to each well containing 25 μL of substrate solution. Wells in column 12 contained substrate solution and control solvent without inhibitor and served as uninhibited controls. The assay was initiated by adding 10 μL of diluted RT to each well using a RapidPlate 96-well pipetting station. Incorporation of Cy5-dUTP into the Eu-labeled template primer was monitored over 40 min by time-resolved fluorescence with a Victor 1420 Multilabel Counter (Wallac). Refer to RR1999/0040/00 for additional details regarding materials and data analysis. GW678248X and GW695634A were each tested over a final concentration range of 0.002 to 2.0 μM, and efavirenz was tested over a final concentration range of either 0.001 to 1.0 μM or 0.002 to 2.0 μM.

IC_{50} Determinations with Purified RT Enzymes: Continuous Time-Resolved Fluorescence Assay. All data reduction was done with SigmaPlot (Jandel Scientific, Corte Madera, CA). Background fluorescence was subtracted from all fluorescence readings. Data analyses were based on the following scheme:



where E′ is a mixture of free enzyme, enzyme−nucleotide complex, enzyme−template primer complex, and enzyme−nucleotide−template primer complex, I is inhibitor, k_{on} is the inhibitor on rate constant, k_{off} is the inhibitor off rate constant, V_{max} is the uninhibited reaction rate, and P is product.

If reactions were linear over 40 min, then IC_{50} values were determined by fitting

$$y = V_{max} \times IC_{50} \times t/(IC_{50} + [I]) \quad (1)$$

to the data where y was the observed fluorescence at time t (minutes), V_{max} was the uninhibited rate (fluorescence min^{-1}), and [I] was the inhibitor concentration (molar). If the data indicated that the reaction could not be completely inhibited by increasing [I], the IC_{50} value was determined by fitting eq 1 to only the data from reactions containing low [I]. Limited inhibition was attributed to inhibitor insolubility.

If inhibited reactions were not linear over 40 min, indicating slow time-dependent inhibition, kinetic constants k_{on} and k_{off} were determined by nonlinear least-squares fit of the equation

$$y = (V_{max} \times k_{off}/(k_{on}[I] + k_{off}))t) + (V_{max}k_{on}[I]/((k_{on}[I] + k_{off})^2))(1 - \exp(-(k_{on}[I] + k_{off})t)$$

where y, V_{max}, and I were defined as above, k_{off} was the off rate constant (min^{-1}), and k_{on} was the on rate constant (M^{-1} min^{-1}). IC_{50} was determined by

$$IC_{50} = k_{off}/k_{on}\ (M)$$

Again, if the data indicated that the reaction could not be completely inhibited by increasing [I], the IC_{50} value was determined by fitting eq 2 to only the data from reactions containing low [I].

RT Enzyme Assay: Continuous Time-Resolved Fluorescence. Reactions contained 100 nM Cy5-dUTP, 40 nM Eu-labeled template primer, 1 nM purified recombinant RT, 47 mM Tris-HCl, 75 mM KCl, 9.3 mM $MgCl_2$, 0.003% NP40, 9.3 mM dithiothreitol (DTT), and 2% dimethyl sulfoxide (DMSO). Test compound or control solvent (15 μL) was added to each well containing 25 μL of substrate solution. The assay was initiated by adding 10 μL of diluted RT to each well using a RapidPlate 96-well pipetting station. Incorporation of Cy5-dUTP into the Eu-labeled template primer was monitored over 40 min by time-resolved fluorescence with a Victor 1420 Multilabel Counter (Wallac). Data reduction was performed with SigmaPlot (Jandel Scientific, Corte Madera, CA).

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