Synthesis and Biological Evaluation of Certain Alkenyldiarylmethanes as Anti-HIV-1 Agents Which Act as Non-Nucleoside Reverse Transcriptase Inhibitors

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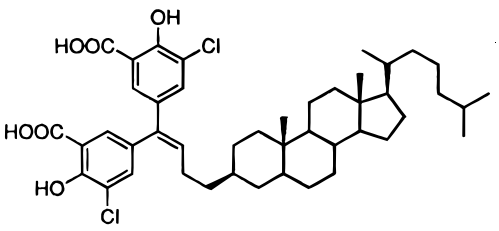
Several novel alkenyldiarylmethane (ADAM) non-nucleoside HIV-1 reverse transcriptase inhibitors were synthesized. The most potent of these proved to be 3′,3″-dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene **(8)**. ADAM **8** inhibited the cytopathic effect of HIV-1 in CEM cell culture with an EC_{50} value of 7.1 μM and was active against an array of laboratory strains of HIV-1 in CEM-SS and MT-4 cells, but was inactive as an inhibitor of HIV-2. In common with the other known non-nucleoside reverse transcriptase inhibitors, ADAM **8** was an effective inhibitor of HIV-1 reverse transcriptase (IC_{50} 1 μM) with poly(rC)·oligo(dG), but not with poly(rA)·oligo(dT), as the template/primer. ADAM **8** was inactive against HIV-1 reverse transcriptases containing non-nucleoside reverse transcriptase inhibitor resistance mutations at residues 101, 106, 108, 139, 181, 188, and 236, while it remained active against enzymes with mutations at residues 74, 98, 100, 103, and at 103/181. An AZT-resistant virus having four mutations in reverse transcriptase was more sensitive to inhibition by ADAM **8** than the wild-type HIV-1. In addition, ADAM **8** displayed synergistic activity with AZT, but lacked synergy with ddI. ADAM **8** or a structurally related analog may therefore be useful as an antiviral agent in combination with AZT or with other NNRTIs that are made ineffective by mutations at residues which do not confer resistance to ADAM **8**.

The non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) constitute a large and structurally diverse set of compounds having potential value in the treatment of AIDS.[1−5] Several of the more familiar types of compounds in this class include [(hydroxyethoxy)methyl](phenylthio)thymine (HEPT),[6] tetrahydroimidazobenzodiazepinone (TIBO),[7] dipyridodiazepinone (nevirapine),[8] pyridinone,[9] bis(heteroaryl)piperazine (BHAP),[10] (*tert*-butyldimethylsilyl)spiroaminooxathiole dioxide (TSAO),[11] and α-anilinophenylacetamide (α-APA)[12] derivatives. A number of other more recent additions to the group include oxathiin carboxanilide (OC or UNIROYAL)[13,14] and (phenylethyl)thioureidothiazole (PETT)[15] derivatives, as well as other compounds.[16−37] In addition, several natural products in the calanolide[38] and inophyllum[39] families have been identified as non-nucleoside HIV-1 reverse transcriptase inhibitors, and halogenated derivatives of the natural product gomisin *J* have displayed similar activity.[40] All of these substances inhibit HIV-1 reverse transcriptase specifically through an allosteric mechanism involving binding to a pocket close to, but separate from, the deoxyribonucleoside triphosphate binding site.[4,41] Although the initial excitement concerning the potential therapeutic use of the NNRTIs in the treatment of AIDS has waned somewhat due to the rapid emergence of resistant viral strains following their administration, more recent work has suggested several strategies by which this problem might be circumvented. These include switching to another NNRTI to which the virus has remained sensitive, using higher doses of the NNRTI against the resistant strain,[42,43] and employing combinations of agents which elicit mutations that counteract one another.[2,44] There is therefore a definite need for additional types of NNRTIs which might elicit unique patterns of resistance mutations.

During our prior work on the design and synthesis of anti-HIV agents related to cosalane **(1)**,[45−47] we observed the prevention of the cytopathic effect of HIV-1 in cell culture by an analog **8**[48] (Scheme 1) that did not fit the general structural pattern expected for active compounds in this series. In the cosalane series, antiviral activity had generally been observed for compounds having free carboxylic acid groups, and the corresponding methyl esters were inactive. Compound **8**, which does inhibit the cytopathic effect of HIV-1 in cell cultures, is obviously an exception to this rule. In addition, cosalane **(1)** appears to act, at least in part, by inhibition of gp120-CD4 binding.[46] When tested for inhibition of gp120-CD4 binding, however, compound **8** was completely inactive. It consequently seemed to act



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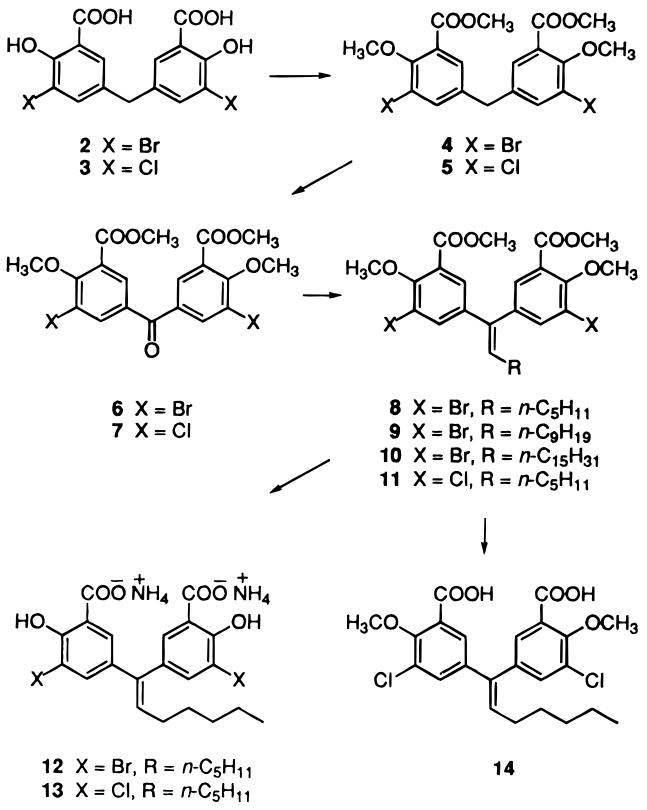
Scheme 1



by a mechanism distinct from that of cosalane, and studies were therefore undertaken to establish its mode of action and to delineate some of the structural parameters associated with its anti-HIV activity. As disclosed in the present report, compound **8** has been found to be a novel NNRTI.

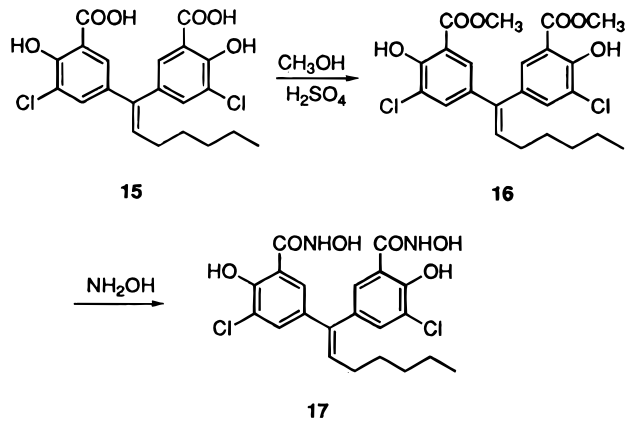
Chemistry

The syntheses of various alkenyldiarylmethanes (ADAMs) are outlined in Schemes 1−4. Methylation of the substituted diarylmethanes **2**[49] and **3**[46] with dimethyl sulfate in the presence of potassium carbonate in refluxing acetone afforded intermediates **4** and **5**, which were oxidized with chromium trioxide in acetic anhydride to yield benzophenones **6** and **7**. The brominated ADAMs **8**−**10** were synthesized from **6** using the appropriate Wittig reagents, while the chlorinated ADAM **11** was prepared similarly from **7**. Demethylation of the hexenyl compound **8** with trimethylsilyl chloride and sodium iodide in refluxing acetonitrile, followed by conversion of the resulting carboxylic acids to their ammonium salts, afforded **12**. Intermediate **11** was demethylated with boron tribromide in methylene chloride, and the resulting carboxylic acids were converted to their ammonium salts to afford **13**. The diacid **14** was obtained by selective demethylation of the two ester functionalities of **11** with potassium hydroxide in refluxing methanol.

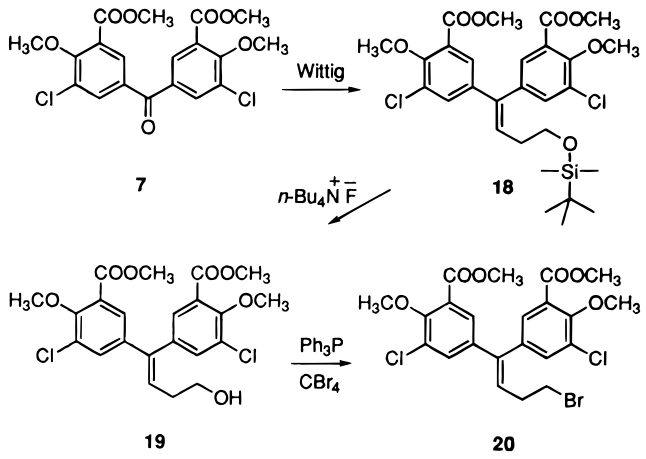
An analog **17**, containing two hydroxamic acid groups, was prepared as outlined in Scheme 2. Esterification of the two carboxylic acid groups of **15** with methanol under acidic conditions gave the diester **16**. Treatment of intermediate **16** with hydroxylamine in aqueous dioxane then yielded the desired compound **17**.

The synthesis of ADAM **20**, containing a brominated side chain, is detailed in Scheme 3. The *tert*-butyldimethylsilylated intermediate **18** was prepared from **7**

Scheme 2

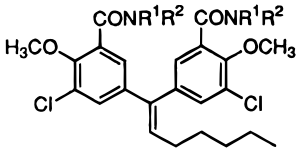


Scheme 3



by reaction with an appropriate Wittig reagent, and the *tert*-butyldimethylsilyl group was then removed with tetra-*n*-butylammonium fluoride in THF to afford compound **19**.[50] The resulting primary alcohol **19** was then converted to the desired bromide **20** with triphenylphosphine and carbon tetrabromide in boiling acetonitrile.[51]

The amides **21** and **23** were synthesized by conversion of the diacid **14** to its acid chloride with oxalyl chloride in benzene at reflux, followed by treatment with ammonia and dimethylamine, respectively. Amide **22** was prepared by treatment of the diester **11** with methylamine in refluxing aqueous methanol.



21 $R^1 = R^2 = H$
22 $R^1 = H, R^2 = CH_3$
23 $R^1 = R^2 = CH_3$

In order to investigate the effect of changing the substitution pattern of the aromatic rings on the antiviral activity, compound **28** (Scheme 4) was prepared in which the two methoxyl groups present in **8** have been moved to positions ortho to the carbon atom linking the two aromatic rings. Treatment of 5-bromosalicylic acid **(24)** with formaldehyde under acidic conditions yielded the substituted diphenylmethane **25**, which was methylated with dimethyl sulfate and potas-

Scheme 4

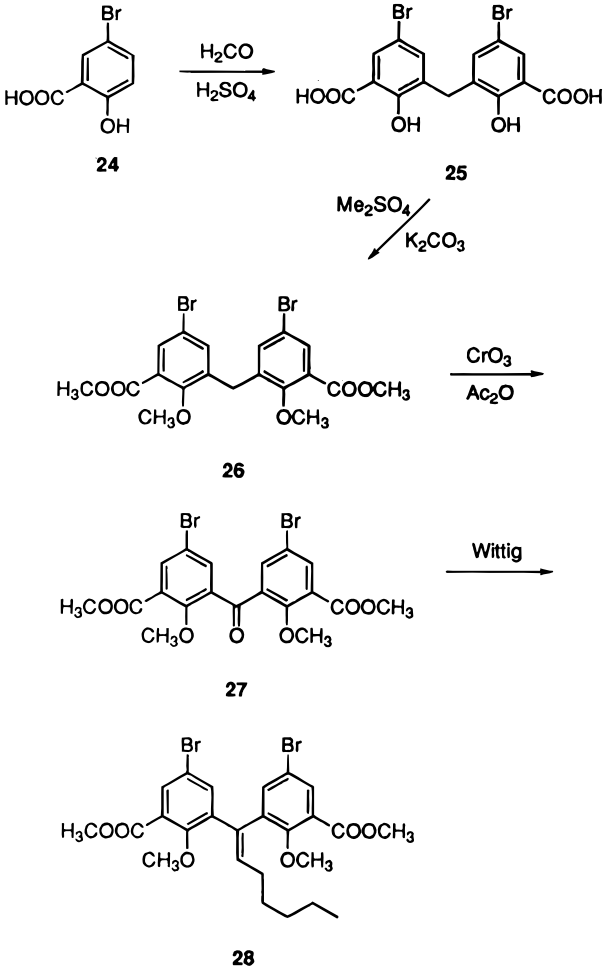


Table 1. Anti-HIV-1 Activities of 1,1-Diphenyl-1-alkenes

compd	EC_{50}[a] (μM)	IC_{50}[b] (μM)	IC_{50}/EC_{50}
8	7.1 ± 5.0	110 ± 22	15
9	>30	>30	
10	>28	>28	
11	16.0 ± 4.4	>29.1	>1.8
12	NA[c]	150 ± 10	
13	>91.5	>91.5	
14	NA[c]	84 ± 10	
17	NA[c]	37 ± 2	
20	8.0 ± 0.2	18 ± 3	2.2
21	NA[c]	31 ± 3	
22	NA[c]	21 ± 0.2	
23	NA[c]	21 ± 0.2	
28	NA[c]	44 ± 4	

[a] The EC_{50} is the 50% inhibitory concentration for cytopathicity of HIV-1_{RF} in CEM-SS cells. The values are averages of at least two determinations. [b] The IC_{50} is the 50% cytotoxic concentration for mock-infected CEM cells. The values are the averages of at least two determinations. [c] No activity shown at concentrations below the IC_{50} value.

sium carbonate to afford **26**. Oxidation of **26** with chromium trioxide in acetic anhydride gave the benzophenone derivative **27**, which was then converted to the desired product **28** using the appropriate Wittig reagent.

Biological Results and Discussion

The ADAMs **8**−**14**, **17**, **20**−**23**, and **28** were tested for prevention of the cytopathic effect of HIV-1 and for cytotoxicity in CEM-SS cells, and the results are listed in Table 1. The most potent ADAM, as well as the one with the highest "therapeutic index" (IC_{50}/EC_{50}), proved to be **8**. The EC_{50} value of 7.1 ± 5.0 μM represents an average of seven determinations, and the range of values was from 2.5 to 18 μM.

Table 2. Range of Activity of Compound **8** against HIV-1 Isolates in Cell Culture-Based Assays

cells	virus	EC_{50} (μM)[a]	IC_{50} (μM)
CEM-SS	HIV-1_{RF}	9.2 ± 2.8	138 ± 12
CEM-SS	HIV-2	Inactive	
MT-4	HIV-1_{IIIB}	16 ± 4.3	>200
MT-4	HIV-1_{A17}[b]	14 ± 0.5	>200
MT-4	HIV-1_{N119}[c]	151	>200
MT-4	HIV-1_{6R}	6.0 ± 3.4	>200
MT-4	HIV-1_{6S}	0.56 ± 0.39	>200
Mo/Ma	HIV-1_{Ba-L}	5.5 ± 3.5	>200
Mo/Ma	HIV-1_{ADA}	1.85 ± 0.9	>200
PBL	HIV-1_{WEJO}	6.6 ± 4.8	93 ± 25
MT-4	SIV	136	>200

[a] EC_{50} values were determined in an XTT-based cytopathicity assay. [b] Pyridinone-resistant. [c] Nevirapine-resistant.

Replacement of the two bromine atoms in **8** by the two chlorines in **11** resulted in a decrease in the anti-HIV-1 potency (EC_{50} 16.0 ± 4 μM). Substitution of the hexenyl chain of **11** with an ω-bromopropenyl side chain in **20** was accompanied by an increase in the anti-HIV-1 potency (EC_{50} 8.0 ± 0.2 μM), but there was also a significant increase in the cytotoxicity (IC_{50} 18 ± 3 μM). The increase in cytotoxicity seen with **20** may result from its potential ability to nonspecifically alkylate nucleophilic biological macromolecules through displacement reactions involving the primary bromide.

Various other modifications of **8** were tried, all of them resulting in inactive compounds. Lengthening the alkenyl chain from C-6 in **8** to C-10 in **9** and C-16 in **10** resulted in loss of activity. Removal of the four *O*-methyl groups of **8** and **11**, resulting in **12** and **13**, was accompanied by a complete loss of activity. Likewise, removal of the two ester methyl groups from **11**, resulting in **14**, also caused total loss of anti-HIV-1 activity. These results emphasize the importance of the *O*-methyl groups for anti-HIV-1 activity. The dihydroxamic acid derivative **17** was also inactive. Replacement of the two methyl ester groups of **8** with two carbamoyl, *N*-methylcarbamoyl, or *N*,*N*-dimethylcarbamoyl groups results in the amides **21**, **22**, and **23**, all of which were inactive. Moving the two methoxyls from the para positions relative to the bridging carbon in **8** to the ortho positions in **28** was also associated with a loss of anti-HIV-1 activity, indicating the importance of the substitution patterns of the two aromatic rings. It therefore appears that the anti-HIV activity of **8** is associated with a relatively high degree of structural specificity, since a variety of structural changes resulted in complete loss of anti-HIV-1 activity.

The range of activity of ADAM **8** was tested against a variety of laboratory strains of HIV-1 in CEM-SS and MT4 cells. As shown in Table 2, ADAM **8** was active against a wide range of HIV-1 strains, including one (HIV-1_{A17}) which is resistant to pyridinone non-nucleoside reverse transcriptase inhibitors. However, ADAM **8** was much less active against a nevirapine-resistant strain of HIV-1 (HIV-1_{N119}) as well as simian immunodeficiency virus (SIV) in MT-4 cells. The inactivity of ADAM **8** against HIV-2 is consistent with its classification as an HIV-1-specific non-nucleoside reverse transcriptase inhibitor.

ADAM **8** was tested for anti-HIV activity in combination with AZT (3′-azido-3′-deoxythymidine) using the *in*

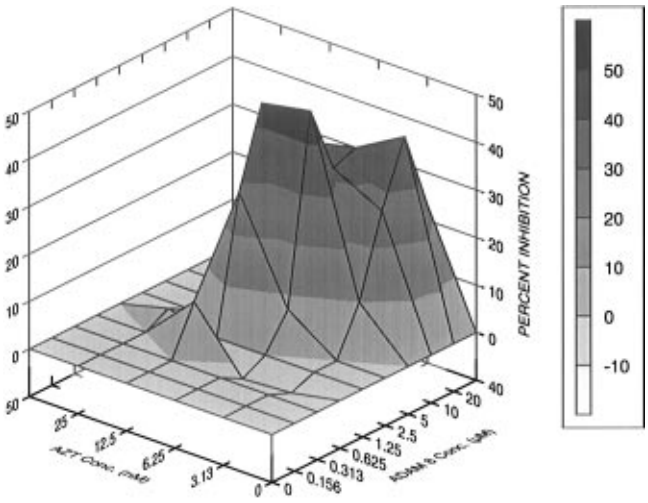


Figure 1. Combination antiviral activity of ADAM **8** with AZT in CEM-SS cells infected with HIV-1 (IIIB): the three-dimensional synergy plot demonstrating the synergistic activity of the two compounds.

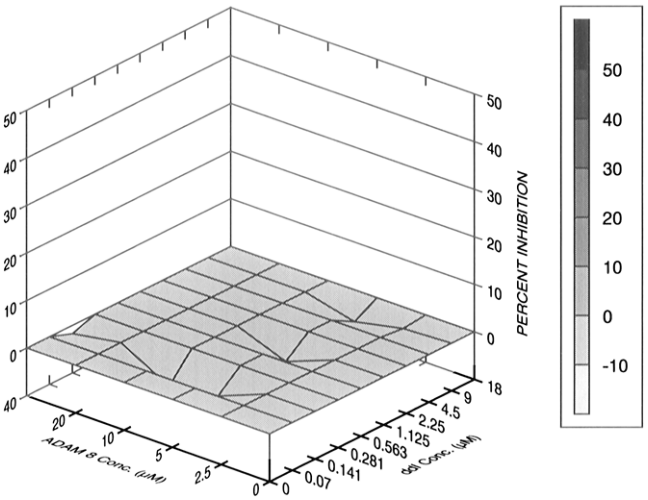
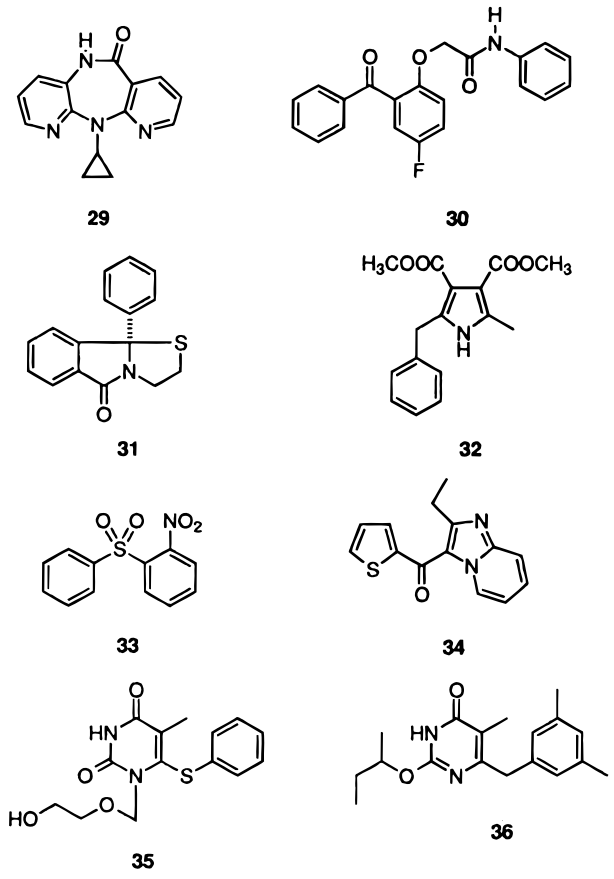


Figure 2. Combination antiviral activity of ADAM **8** with ddI in CEM-SS cells infected with HIV-1 (IIIB): the three-dimensional synergy plot demonstrating the lack of synergistic activity of the two compounds.

vitro XTT anti-HIV assay. Eight concentrations of ADAM **8** were tested in all combinations with five concentrations of AZT. Effects of the drug combination were calculated on the basis of the activity of the two compounds when tested alone. The results of these assays demonstrated that the combined antiviral activity was greater than that predicted for additivity (Figure 1). The peak above the plane represented a maximal antiviral activity (protection from HIV-induced killing) from a combination of ADAM **8** and AZT which was nearly 50% greater than would have been expected if the antiviral effects were merely additive. No antagonism was detected at any concentration tested. A similar study involving ADAM **8** and ddI demonstrated a lack of synergistic activity (Figure 2).

In order to determine the mechanism of action of ADAM **8**, it was tested in a number of assays representative of important events in the replication cycle of HIV-1. These included virus attachment to the cell, gp120-CD4 binding, syncytium formation, reverse transcription, integration, and protease. The results, which are detailed in Table 3, indicate that the mechanism of action of ADAM **8** is inhibition of HIV-1 reverse transcriptase. With poly(rC)·oligo(dG) as the template/primer, ADAM **8** inhibited HIV-1 reverse transcriptase with an IC_{50} value of 0.38 ± 0.04 μM (mean ± 1 SD, n = 3). However, it was inactive as an inhibitor of HIV-1 reverse transcriptase with poly(rA)·oligo(dT) as the template/primer. The greater sensitivity to inhibition with poly(rC)·oligo(dG) as the template/primer is characteristic of the HIV-1-specific non-nucleoside reverse transcriptase inhibitors.[7,9,52−55]

Although the non-nucleoside HIV-1 reverse transcriptase inhibitors constitute a large and structurally diverse set of compounds, there are nevertheless certain generalities that can be made with regard to their structures. Many of them possess two aromatic ring systems that have heteroatoms or functional groups attached to them that can accept hydrogen bonds. In a number of them, the two aromatic systems are attached to the same atom. Examples include the well-known inhibitor nevirapine **(29)**,[8] as well as benzophenone **30**,[33] isoindolone **31**,[19] benzylpyrrole **32**,[27] diaryl sulfone **33**,[23] diaryl ketone **34**,[31] and related compounds. In the HEPT **35**[6] and DABO **36**[56] derivatives, one of the aromatic rings is replaced by a pyrimidinedione ring. The ADAM derivative **8** also has two aromatic rings attached to one atom (carbon), and it therefore bears some resemblance to the known NNRTIs **29**−**36**.



Insight into the process of nevirapine **(29)** binding to HIV-1 reverse transcriptase has been gained through comparison of the crystal structure of the complex of nevirapine with HIV-1 reverse transcriptase[41] and the crystal structure of the unliganded enzyme.[57] The results of these studies show that a hydrophobic binding pocket is created in the p66 palm domain of HIV-1 reverse transcriptase during the binding of the inhibitor. This involves the withdrawal of Trp-229 from the

Table 3. Mechanism Studies of the Anti-HIV-1 Activity of ADAM 8

parameter	IC_{50}[a] (μM)
virion attachment	NI_{100}[b]
syncytia formation	NI_{25}
gp 120-CD4 interaction	NI_{100}
RT enzymatic activity (rAdT)	NI_{100}
(rCdG)	0.38
Integrase	>200
protease enzymatic activity (IC_{50})	37
p7 nucleocapsid protein zinc fingers ($RFU_{\%}$)[c]	NI_{25}
cell-to-cell transmission	NI

[a] Mechanistic studies were quantitated as described in Materials and Methods. IC_{50} values (drug concentration providing 50% inhibition of the indicated activity) were derived from graphs in which each point represented the mean of at least three replicates. [b] NI indicates that no inhibition of activity was observed at the indicated high test concentration. [c] The RFU% value represents the percentage decrease in the relative fluorescence intensity of the zinc finger after treatment of the p7 nucleocapsid protein with 25 μM ADAM **8** for 10 min.

Table 4. ADAM **8** Activity against HIV-1 Viruses Containing NNRTI Resistance Mutations Obtained by Site-Directed Mutagenesis (EC_{50} Values, μM)

enzyme	ADAM **8** (EC_{50})	AZT (EC_{50})	fold resistance[b]
NL4-3[a]	12.3	0.05	–
L74V	5.47	0.03	S[c]
A98G	24.1	0.03	S
K101E	>100	1	>8
K103N	23.6	0.01	S
V106A	>100	0.01	>8
V179D	>100	0.02	>8
Y181C	>100	0.003	>8
Y188C	>100	0.05	>8
4xAZT[d]	0.93	0.98	↑S

[a] Wild-type enzyme. [b] Fold resistance (the EC_{50} of ADAM **8** against the mutant virus divided by the EC_{50} of ADAM **8** against the wild-type virus) indicates the level of loss of sensitivity of the mutant virus to the antiviral action of ADAM **8**. [c] Sensitive (no resistance). [d] AZT resistant, with four mutations.

binding site as well as conformational changes of the Tyr-181 and Tyr-188 side chains. Inhibitor binding may be driven by $\pi-\pi$ interactions between the ligand and aromatic amino acid residues present at the binding site.[4] The filling of the hydrophobic binding pocket by the inhibitor is associated with domain shifts in the enzyme that may alter oligonucleotide binding. It is possible that similar processes occur during the binding of ADAM **8**, as well as the related compounds **30**–**36**, to HIV-1 reverse transcriptase. The orientations of the two aromatic systems in these compounds fit a "butterfly-like" model recently proposed on the basis of a comparison of the structures of several non-nucleoside HIV-1 reverse transcriptase inhibitors.[58] In the case of ADAM **8**, the hexenyl side chain points toward a "lipophilic site" proposed by the model.

In order to identify the amino acid residues of HIV-1 reverse transcriptase that may be involved in ADAM binding, ADAM **8** was tested for inhibitory activity against a variety of HIV-1 strains containing NNRTI resistance mutations in the reverse transcriptase enzyme. The viruses were obtained either by site-directed mutagenesis or by *in vitro* biological selection, and the results of these studies are listed in Tables 4 and 5. Comparison of these data with the published structures of the NNRTI binding pocket shows that the mutations conferring resistance to ADAM **8** are clustered within the amino acid residues comprising the pocket (see Figure 3).[4,41,59,60] In the case of α-APA, it has been documented that the commonly identified NNRTI resistance mutations are located close to the bound inhibitor,[60] and it therefore seems reasonable to assume that the NNRTI resistance mutations conferring resistance to ADAM **8** may also be located close to bound ADAM **8**. These amino acid residues are located at positions 101, 106, 108, 139, 179, 181, 188, and 236.

Table 5. ADAM **8** Activity against HIV-1 Viruses Containing NNRTI Resistance Mutations Obtained by *in Vitro* Biological Selection (EC_{50} Values, μM)

enzyme	ADAM **8** (EC_{50})	AZT (EC_{50})	fold resistance[a]
IIIB[b]	15.5	0.01	–
OC/100[c]	5.29	0.005	S[d]
Thiazol/108[e]	>100	0.008	>6
TIBO/108[f]	>100	0.004	>6
Calo/139[g]	>100	0.03	>6
DPS/181[h]	>100	0.02	>6
UC38/181[c]	>100	0.01	>6
HEPT/181[i]	85.9	0.01	5.5
A17/103/181[j]	17.9	0.002	S
HEPT/236	>100	0.01	>6
Cos/R[k]	11.2	0.005	S

[a] Fold resistance (the EC_{50} of ADAM **8** against the mutant virus divided by the EC_{50} of ADAM **8** against the wild-type virus) indicates the level of loss of sensitivity of the mutant virus to the antiviral action of ADAM **8**. [b] Wild-type enzyme. [c] Oxathiin carboxanilide resistant. [d] Sensitive (no resistance). [e] Thiazolobenzimidazole resistant. [f] Tetrahydroimidazobenzodiazepinone resistant. [g] Calanolide resistant. [h] Diphenyl sulfonate resistant. [i] (Hydroxyethoxy)methyl](phenylthio)thymine resistant. [j] Pyridinone resistant. [k] Cosalane resistant.

There are also several known NNRTI resistance mutations located in the NNRTI binding pocket that do not confer significant resistance to ADAM **8**. These include residues 98, 100, and 103. The enzyme with two mutations at residues 103 and 181 also remains sensitive to inhibition by ADAM **8**. It is generally recognized that NNRTI resistance mutations do not confer resistance to all NNRTIs, and that a potentially viable strategy for dealing with NNRTI resistance may be to simply switch to another NNRTI that remains effective against the resistant virus.[2,44] The A98G mutation is known to confer resistance to pyridinone L-697,661[61] and nevirapine,[62] while the OC/100 virus is oxathiin carboxanilide resistant. The A17/103/181 virus is resistant to nevirapine. It is of interest that the virus containing the 4xAZT enzyme, which has four mutations in its reverse transcriptase and is resistant to AZT, displayed increased sensitivity to ADAM **8** relative to the wild-type virus containing the NL4–3 enzyme.

Figure 3, which was obtained by erasing nevirapine from the structure of the nevirapine–RT complex, shows the amino acid residues in the p66 subunit surrounding the NNRTI binding pocket.[41] Mutation of the red- and yellow-colored residues in Figure 3 results in resistance to certain of the known NNRTIs. Mutation of the yellow-colored residues in Figure 3 also results in resistance to ADAM **8**, while mutation of the red-colored residues does not confer resistance to ADAM **8** (Table 4 and 5). The yellow-colored lysine residue 101 is located at the assumed entrance to the binding pocket, near the red-colored lysine residue 103. The two yellow-colored tyrosine residues are Tyr 181 and Tyr 188, while the three yellow valine residues are Val 106, Val 108, and Val 179. The yellow-colored proline residue is Pro 236. The red-colored alanine residue is Ala 98, and the red-colored leucine residue is Leu 100. The mutation at residue 139 conferring resistance to ADAM **8** is located on the p51 subunit and is not shown. Taken

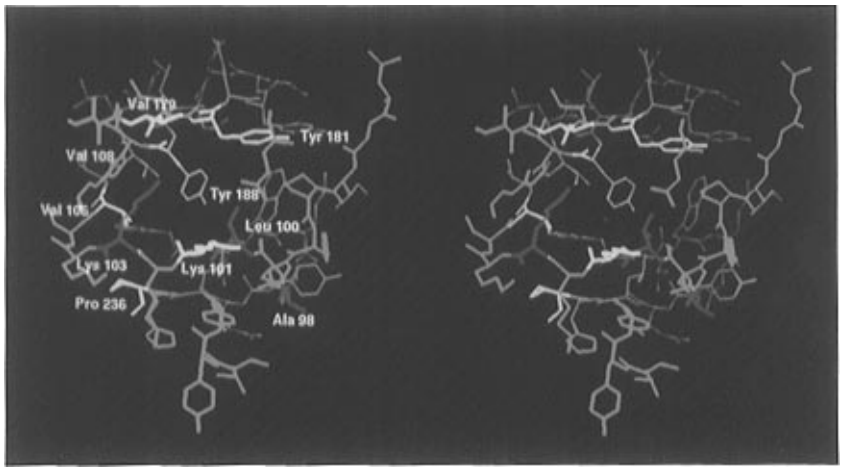


Figure 3. The non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) binding site. Mutation of the yellow- and red-colored residues results in resistance to known NNRTIs. Mutation of the yellow residues also results in resistance to ADAM **8**, while mutation of the red residues does not confer resistance to ADAM **8**.

together, the cluster of yellow amino acid residues depicted in Figure 3 indicate the geometrical relationships of the residues that are likely to be involved in ADAM **8** binding, and they circumscribe a well-defined cavity which most likely constitutes the ADAM **8** binding site.

Additional studies will be required in order to further define the structural parameters associated with the HIV-1 reverse transcriptase inhibitory activity of the compounds in the ADAM series, as well as to maximize the anti-HIV potency and therapeutic index. It will also be of interest to define the pattern of resistance mutations associated with the use of ADAM **8**.

The fact that ADAM **8** displays synergistic anti-HIV-1 activity with AZT and is actually more effective against an AZT-resistant virus suggests that ADAM **8** or a closely related analog may prove to be useful in treating HIV-1 infections in combination with AZT. It may also find some utility against viral strains that have been made resistant to other NNRTIs by mutations that do not confer resistance to ADAM **8**.

Experimental Section

General. Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Spectra were obtained as follows: CI mass spectra on a Finnegan 4000 spectrometer; FAB mass spectra and EI mass spectra on a Kratos MS50 spectrometer; ^{1}H NMR spectra on Varian VXR-500S and XL-200A spectrometers; IR spectra on a Beckman IR-33 spectrometer or on a Perkin-Elmer 1600 series FTIR. Microanalyses were performed at the Purdue Microanalysis Laboratory, and all values were within ±0.4% of the calculated compositions.

3,3′-Dibromo-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)diphenylmethane (4). 3,3′-Dibromo-5,5′-dicarboxy-4,4′-dihydroxydiphenylmethane **(2)**[49] (8.179 g, 18.34 mmol) was partially dissolved in acetone (250 mL), potassium carbonate (20.09 g) was added followed by dimethyl sulfate (9.5 mL), and the mixture was heated at reflux with stirring for 24 h. Acetone was removed *in vacuo*, water (100 mL) was added, and the mixture was extracted with methylene chloride (6 × 30 mL). The combined organic extracts were washed with 2% potassium hydroxide (50 mL), brine, dried (sodium sulfate), and evaporated to dryness. The residue was crystallized from a chloroform−hexane mixture to afford product **4** (7.75 g, 84%): mp 107−108 °C; IR (KBr) 2948, 1725, 1595, 1553, 1472, 1433, 1314, 1251, 1202, 1089, 996, 926, 876, 827, 800, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d, J = 2.2 Hz, 2 H), 7.50 (d, J = 2.2 Hz, 2 H), 3.92 (s, 6 H), 3.91 (s, 6 H), 3.88 (s, 2 H); CIMS m/e (relative intensity) 503 (MH^+, 76), 471 (100), 257 (63). Anal. ($C_{19}H_{18}Br_2O_6$) C, H.

3,3′-Dichloro-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)diphenylmethane (5). This intermediate was prepared from **3** as previously described.[46]

3,3′-Dibromo-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)diphenyl Ketone (6). Diphenylmethane **4** (6.02 g, 12 mmol) was partially dissolved in acetic anhydride (110 mL), the solution was cooled in an ice bath, and chromium trioxide (5.05 g) was added in small portions with stirring. The mixture was stirred at ambient temperature for 3 h and then for 2 h at reflux and was filtered after cooling. The chromium salts and ketone **6** were filtered off, washed with chloroform, and then extracted twice by stirring the solid with chloroform (80 mL) and refiltering the suspension. The solvents were removed *in vacuo* from the combined chloroform washings and extracts, and the residue was crystallized from a chloroform−hexane mixture to yield the product **6** (4.84 g 78%): mp 130−131 °C; IR (KBr) 2954, 1742, 1657, 1589, 1472, 1438, 1318, 1268, 1201, 1090, 986 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.16 (d, J = 2.2 Hz, 2 H), 8.12 (d, J = 2.2 Hz, 2 H), 4.03 (s, 6 H), 3.95 (s, 6 H); CIMS m/e (relative intensity) 517 (MH^+, 100), 485 (25). Anal. ($C_{19}H_{16}Br_2O_7$) C, H.

3,3′-Dichloro-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)diphenyl Ketone (7). This intermediate was prepared from **5** as previously described.[46]

3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (8). *n*-Hexyltriphenylphosphonium bromide[63] (1.43 g, 3.35 mmol) was suspended in dry THF (25 mL), the mixture was cooled in an ice bath, and sodium bis(trimethylsilyl)amide (1 M solution in THF, 3.35 mL) was added dropwise. The mixture was stirred for 20 min, and a solution of the bromo ketone **6** (1.554 g, 3.01 mmol) in THF (12 mL) was added dropwise. The ice bath was removed, and the reaction mixture was stirred 1 h at 60 °C and 20 h at ambient temperature. The reaction was quenched with ammonium chloride solution, the THF phase was separated and the aqueous phase extracted with ether. The combined organic extracts were dried (sodium sulfate) and evaporated to dryness. Flash chromatography on silica gel (hexane−ethyl acetate, 4:1) yielded solid that was recrystallized from ethanol to afford a crystalline product (1.593 g, 91%): mp 52−53 °C; IR (KBr) 2946, 2860, 1732, 1472, 1435, 1288, 1250, 1209, 1086, 997, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.53 (d, J = 2.2 Hz, 2 H), 7.495 (d, J = 2.2 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 6.06 (t, J = 7.6 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 6 H), 3.92 (s, 3 H), 2.08 (m, 2 H), 1.45 (m, 2 H), 1.26 (m, 4 H), 0.88 (t, J = 6.7 Hz, 3 H); CIMS m/e (relative intensity) 585 (MH^+, 85), 553 (100). Anal. ($C_{25}H_{28}Br_2O_6$) C, H.

3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-undecene (9). *n*-Decyltriphenylphosphonium bromide[64] (1.15 g, 2.62 mmol) was suspended in dry THF (22 mL), the mixture was cooled in an ice bath, and sodium bis(trimethylsilyl)amide (1 M solution in THF, 2.62 mL) was added dropwise. The mixture was stirred for 20 min, and a solution of ketone **6** (1.082 g, 2.096 mmol) in THF (18

mL) was added dropwise. The ice bath was removed, and the reaction mixture was stirred 24 h at ambient temperature. The reaction was quenched with ammonium chloride solution, the THF phase was separated, and the aqueous phase was extracted with ether. The combined organic extracts were dried (sodium sulfate) and evaporated to dryness, and the residue was purified by flash chromatography on silica gel (hexane−ethyl acetate, 4:1) and crystallization from ethanol to yield the product **9** (1.25 g, 93%): mp 69−70 °C; IR (KBr) 2928, 2855, 1734, 1471, 1435, 1364, 1288, 1251, 1208, 1087, 998, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.53 (m, 2 H), 7.49 (m, 2 H), 6.06 (t, J = 7.5 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 9 H), 2.08 (m, 2 H), 1.44 (m, 2 H), 1.25 (m, 12 H), 0.88 (t, J = 5.3 Hz, 3 H); CIMS *m/e* (relative intensity) 641 (MH^+, 80), 609 (100). Anal. ($C_{29}H_{36}Br_2O_6$) C, H.

3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptadecene (10). *n*-Hexadecyltriphenylphosphonium bromide[65] (1.706 g, 3.006 mmol) was dissolved in dry THF (32 mL), the solution was cooled in an ice bath, and sodium bis(trimethylsilyl)amide (1 M solution in THF, 3 mL) was added dropwise. The mixture was stirred for 20 min, and a solution of ketone **6** (1.393 g, 2.7 mmol) in THF (12 mL) was added dropwise. The ice bath was removed, and the reaction mixture was stirred for 28 h at ambient temperature. The reaction was quenched with ammonium chloride solution, the THF phase was separated, and the aqueous phase was extracted with ether. The combined organic extracts were dried (sodium sulfate) and evaporated to dryness. Flash chromatography on silica gel (hexane−ethyl acetate, 6:1) afforded an oil, which crystallized from ethanol to yield the product **10** (1.15 g, 59%): mp 43 °C (ethanol); IR (KBr) 2923, 2852, 1734, 1590, 1470, 1435, 1288, 1251, 1209, 1087, 999, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52 (d, J = 2.3 Hz, 2 H), 7.49 (d, J = 2.3 Hz, 1 H), 7.48 (d, J = 2.3 Hz, 1 H), 6.86 (t, J = 7.4 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 9 H), 2.08 (m, 2 H), 1.42 (m, 2 H), 1.25 (m, 24 H), 0.875 (t, J = 6.5 Hz, 3 H); CIMS *m/e* (relative intensity) 725 (MH^+ − MeOH, 100). Anal. ($C_{35}H_{48}Br_2O_6$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (11). Sodium hydride (54 mg, 1.35 mol, 60% dispersion in mineral oil) was washed with *n*-hexane (3 × 5 mL). Dimethyl sulfoxide (2 mL) was introduced *via* a syringe, and the mixture was heated at 75 °C until the evolution of hydrogen ceased. The clear solution was cooled in an ice−water bath, and a solution of the *n*-hexyltriphenylphosphonium bromide[63] (576 mg, 1.35 mmol) in DMSO (3 mL) was added dropwise. The resulting solution was stirred at room temperature for 15 min. A solution of the ketone **7** (0.86 mmol, 369 mg) in warm DMSO (6 mL) was added dropwise and the reaction mixture heated at 55 °C for 27 h. It was then cooled in an ice bath. A solution of ammonium chloride (143 mg) in water (5 mL) was added, and the reaction mixture was extracted with ethyl ether (5 × 5 mL). The organic extracts were washed twice with brine, dried over sodium sulfate, and evaporated *in vacuo*. Flash chromatography on silica gel (230−400 mesh), eluting with *n*-hexane−ethyl acetate, 4:1, yielded starting ketone (39 mg) and heptene **8** (320 mg, 75%): mp 88 °C; IR (KBr) 3046, 1732, 1595, 1364, 1250, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, J = 2.4 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.4 Hz, 1 H), 6.07 (t, J = 7.6 Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.08 (m, 2 H), 1.44 (m, 2 H), 1.27 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H); CIMS *m/e* (relative intensity) 495 (MH^+, 100), 463 (12). Anal. ($C_{25}H_{28}Cl_2O_6$) C, H.

Diammonium 3′,3″-Dibromo-5′,5″-dicarboxy-4′,4″-dihydroxy-1,1-diphenyl-1-heptene (12). Methoxy ester **8** (0.289 g, 0.495 mmol) and sodium iodide (0.593 g) were stirred in dry acetonitrile under argon atmosphere. Trimethylsilyl chloride (1.27 mL, 9.9 mmol, 20 equiv) was added dropwise at room temperature, and the reaction mixture was stirred under reflux for 48 h. The reaction mixture was quenched with water (3 mL) and extracted with ethyl acetate (3 × 3 mL). The combined extracts were washed with brine, 10% sodium sulfite, and 5% sodium bicarbonate (3 × 4 mL). The basic extracts were acidified with concentrated hydrochloric acid, and the product was extracted with ethyl acetate. The organic extracts were washed with brine and dried (sodium sulfate) to yield a foam (191 mg, 68%), which was crystallized from ethyl acetate: mp 159−160 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 7.44 (d, J = 2.0 Hz, 1 H), 7.36 (d, J = 1.9 Hz, 1 H), 7.18 (d, J = 2.0 Hz, 1 H), 7.10 (d, J = 1.9 Hz, 1 H), 5.75 (t, J = 7.4 Hz, 1 H), 2.02 (m, 2 H), 1.37 (m, 2 H), 1.22 (m, 4 H), 0.82 (t, J = 6.1 Hz, 3 H); FABMS *m/e* (relative intensity) 529 (MH^+, 2). Anal. ($C_{21}H_{20}Br_2O_6 \cdot 2H_2O$) C, H. The diammonium salt **12** was prepared by dissolving the diacid in ammonium hydroxide and then evaporating the water and excess ammonia.

Diammonium 3′,3″-Dichloro-5′,5″-dicarboxy-4′,4″-dihydroxy-1,1-diphenyl-1-heptene (13). A solution of methoxy ester **11** (148.6 mg, 0.3 mmol) in dry methylene chloride (2.5 mL) was added *via* septum under an argon atmosphere to a stirred solution of boron tribromide (1 M) in methylene chloride (1.6 mL) cooled in a dry ice−acetone bath. The cooling bath was removed after 2 h, and stirring continued at ambient temperature for 2 days. More BBr_3 (0.8 mL) was added on the second day. The reaction was quenched with water (2 mL), stirring was continued for 30 min, and the product was extracted with 20% aqueous KOH. The alkaline solution was acidified on cooling with concentrated hydrochloric acid and the product extracted with ethyl acetate. The organic extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo*. The product (19 mg, 32%) was crystallized from methylene chloride: mp 234−236 °C; IR (KBr) 3500−2500, 2926, 2856, 1670, 1600, 1443, 1232, 1179, 901, 799, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.68 (m, 2 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.41 (d, J = 1.6 Hz, 1 H), 6.13 (t, J = 7.2 Hz, 1 H), 2.11 (m, 2 H), 1.48 (m, 2 H), 1.28 (m, 14 H), 0.85 (t, J = 6.3 Hz, 3 H); FABMS *m/e* (relative intensity) 438 (M^+, 2), 307 (10). Anal. ($C_{21}H_{20}Cl_2O_6 \cdot {}^1/_2H_2O$) C, H. The ammonium salt **13**, mp 150 °C, was prepared by dissolving the diacid in ammonium hydroxide and evaporating the water and excess ammonia.

3′,3″-Dichloro-5′,5″-dicarboxy-4′,4″-dimethoxy-1,1-diphenyl-1-heptene (14). Diester **11** (35 mg, 0.071 mmol) was heated for 2 h under reflux in a solution of potassium hydroxide (28 mg, 0.5 mmol) in methanol (2 mL). Methanol was evaporated *in vacuo*, water was added, and the solution was acidified with hydrochloric acid (1 M, 1 mL). The white precipitate was extracted with chloroform (5 × 2 mL), and the combined extracts were washed with brine, dried (sodium sulfate), and evaporated *in vacuo* to yield a white solid (31 mg, 100%), which was crystallized from methylene chloride: mp 204 °C; IR (KBr) 3425, 3500−2500, 1696, 1597, 1555, 1296 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.58 (d, J = 2.1 Hz, 1 H), 7.58 (d, J = 2.1 Hz, 1 H), 7.49 (d, J = 2.1 Hz, 2 H), 6.28 (t, J = 7.5 Hz, 1 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 2.12 (m, 2 H), 1.5 (m, 2 H), 1.28 (m, 4 H), 0.85 (t, J = 6.6 Hz, 3 H); CIMS *m/e* (relative intensity) 467 (MH^+, 42), 449 (100). Anal. ($C_{23}H_{24}Cl_2O_6$) C, H.

3′,3″-Dichloro-4′,4″-dihydroxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (16). The diacid **15** (98 mg, 0.11 mmol), obtained by acidification of **12** with hydrochloric acid, was added to a solution of concentrated sulfuric acid (5 drops) in methanol (4 mL), and the mixture was heated at 90 °C for 5 days. The reaction mixture was cooled in an ice bath, water was added, and the product was extracted with methylene chloride (3 × 3 mL). The combined extracts were washed with 5% sodium bicarbonate solution and brine and dried (sodium sulfate). The solvent was removed *in vacuo*, and the residue was flash chromatographed on silica gel (4 g, hexane−ethyl acetate, 4:1) to yield the ester as an oil which crystallized from a mixture of methanol and ether to afford the product **16** (78 mg, 75%): mp 118 °C; IR (KBr) 3422, 3125, 2952, 2927, 2858, 1679, 1604, 1442, 1334, 1237, 1200, 1168, 797, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 11.37 (s, 1 H), 11.28 (s, 1 H), 7.53 (d, J = 2.1 Hz, 1 H), 7.50 (d, J = 2.2 Hz, 1 H), 7.38 (dd, J = 2.2, 0.3 Hz, 1 H), 7.33 (bd, J = 2.1 Hz, 1 H), 5.96 (t, J = 7.5 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 2.03 (m, 2 H), 1.43 (m, 2 H), 1.23 (m, 6 H), 0.85 (t, J = 5.1 Hz, 3 H); CIMS *m/e* (relative intensity) 467 (MH^+, 1), 465 (MH^+ − 2H, 3), 433 (3), 281 (100). Anal. ($C_{23}H_{24}Cl_2O_6$) C, H.

3′,3″-Dichloro-5′,5″-bis(hydroxycarbamoyl)-4′,4″-dihydroxy-1,1-diphenyl-1-heptene (17). A solution of 3 M sodium hydroxide (3.07 mL) was added to a solution of

hydroxylamine hydrochloride (275 mg, 3.95 mmol) in water (2.8 mL), followed by a solution of the dimethyl ester **16** (74 mg, 0.158 mmol) in dioxane (2 mL). The cloudy mixture was stirred at room temperature for 20 h, cooled in an ice bath, acidified with 3 M hydrochloric acid (2 mL), and extracted with ethyl acetate. The combined extracts were washed with brine and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue crystallized on trituration with methylene chloride to afford **17** (67 mg, 90%): mp 137−138 °C; IR (KBr) 3340, 3160, 2925, 1648, 1470, 1108, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 11.21 (bs, 2 H), 8.65 (bs, 2 H), 7.53 (d, $J = 2.1$ Hz, 1 H), 7.47 (d, $J = 2.1$ Hz, 1 H), 7.45 (d, $J = 2.1$ Hz, 1 H), 7.38 (d, $J = 2.1$ Hz, 1 H), 6.14 (t, $J = 7.5$ Hz, 1 H), 2.05 (m, 2 H), 1.49 (m, 2 H), 1.27 (m, 4 H), 0.84 (t, $J = 6.8$ Hz, 3 H); FABMS *m/e* (relative intensity) 469 (MH^+, 75), 436 ($MH^+ - NH_2OH$, 100). Anal. ($C_{21}H_{22}N_2Cl_2O_6$) C, H, N.

[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]triphenylphosphonium Bromide. 3-Bromo-3-(*tert*-butyldimethylsilyl)-1-propanol (2.7 g, 10.75 mmol) and triphenylphosphine (2.83 g, 10.75 mmol) were dissolved in hot acetonitrile (3 mL) and heated under reflux for 30 h. The reaction mixture was allowed to cool, the solvent removed *in vacuo*, and the oily residue triturated with hexane until crystallization came to completion. The white salt (4.995 g, 93%) was filtered the next day, washed with hexane (3 × 5 mL), and dried in a vacuum desiccator: mp 137−139 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 7.9−7.8 (m, 15 H), 3.68 (t, $J = 5.9$ Hz, 2 H), 3.53 (m, 2 H), 1.67 (m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H); EIMS 435 ($M^+ - Br$).

4-[(*tert*-Butyldimethylsilyl)oxy]-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-butene (18). [3-[(*tert*-Butyldimethylsilyl)oxy]propyl]triphenylphosphonium bromide (1.27 g, 2.46 mmol) was suspended in dry DME (10 mL), and *n*-butyllithium (2.4 M, 1.03 mL) was added dropwise. A solution of ketone **7** (1.05 g, 2.46 mmol) in DME (12 mL) was added dropwise to the solution of the ylide, and the mixture was stirred at 63 °C for 22 h. The cooled reaction mixture was quenched with aqueous ammonium chloride solution (250 mg in 10 mL of water). The aqueous layer was extracted with ether (5 mL), and the combined organic extracts were washed with brine and dried (sodium sulfate). The solvent was evaporated *in vacuo* to afford an oil (2.05 g), which was flash chromatographed on silica gel (90 g, hexane−ethyl acetate, 4:1) to yield a colorless oil (0.617 g, 43%) which crystallized from ethanol: mp 40 °C; IR (KBr) 2946, 2861, 1735, 1596, 1475, 1436, 1252, 1210, 1096, 1001, 842, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, $J = 2.2$ Hz, 1 H), 7.46 (d, $J = 2.0$ Hz, 1 H), 7.37 (d, $J = 2.0$ Hz, 1 H), 7.27 (d, $J = 2.2$ Hz, 1 H), 6.09 (t, $J = 7.5$ Hz, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 6 H), 3.68 (t, $J = 6.4$ Hz, 2 H), 2.30 (m, 2 H), 0.87 (s, 9 H), 0.025 (s, 6 H); FABMS *m/e* (relative intensity) 583 (MH^+, 63), 551 (90), 525 (100). Anal. ($C_{28}H_{36}Cl_2O_7Si$) C, H.

3′,3″-Dichloro-4-hydroxy-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-butene (19). The silyl ether **18** (407 mg, 0.687 mmol) was stirred at 0 °C for 2.5 h in a solution prepared by adding a 1 M solution of tetra-*n*-butylammonium fluoride in THF (1.4 mL) to THF (4 mL). The solvent was removed *in vacuo*, brine was added, and the product was extracted with benzene. The combined extracts were washed with brine, dried (sodium sulfate), evaporated *in vacuo*, and flash chromatographed on silica gel to yield a colorless oil (0.255 g, 78%): IR (neat) 3528, 3061, 2952, 2875, 2832, 1732, 1596, 1477, 1437, 1402, 1359, 1269, 1210, 1168, 1094, 999, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52 (d, $J = 2.5$ Hz, 1 H), 7.52 (d, $J = 2.2$ Hz, 1 H), 7.38 (d, $J = 2.2$ Hz, 1 H), 7.32 (d, $J = 2.5$ Hz, 1 H), 6.14 (t, $J = 7.5$ Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.92 (s, 3 H), 3.75 (m, 2 H), 2.39 (m, 2 H); CIMS *m/e* (relative intensity) 469 (MH^+, 100), 451 (35), 437 (780). Anal. ($C_{22}H_{22}Cl_2O_7$) C, H.

4-Bromo-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-butene (20). A solution of alcohol **19** (215 mg, 0.458 mmol) and carbon tetrabromide (304 mg, 0.916 mmol) in dry acetonitrile (3 mL) was heated under reflux with stirring, and a solution of triphenylphosphine (360 mg, 1.374 mmol) in acetonitrile (7 mL) was added dropwise over 2 min. The mixture was heated under reflux for 2 h and cooled, the solvent was removed *in vacuo*, and the residue was extracted with benzene (3 × 5 mL). The combined extracts were filtered, and the solvent was removed *in vacuo*. The residue was flash chromatographed on silica gel (20 g, hexane−ethyl acetate, 4:1) and recrystallized from ethanol to yield the bromide **20** (0.20 g, 82%): mp 68 °C; IR (KBr) 2949, 1730, 1476, 1437, 1297, 1254, 1214, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.51 (m, 2 H), 7.36 (d, $J = 2.1$ Hz, 1 H), 7.33 (d, $J = 2.3$ Hz, 1 H), 6.08 (t, $J = 7.2$ Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 9 H), 3.46 (t, $J = 6.6$ Hz, 2 H), 2.69 (q, $J = 6.7$ Hz, 2 H); CIMS *m/e* (relative intensity) 533 (MH^+, 94), 501 (100). Anal. ($C_{22}H_{21}BrCl_2O_6$) C, N.

3′,3″-Dicarbamoyl-5′,5″-dichloro-4′,4″-dimethoxy-1,1-diphenyl-1-heptene (21). The diacid **14** (112 mg, 0.240 mmol) was suspended in dry benzene (2 mL), oxalyl chloride (0.4 mL) was added, and the mixture was heated at reflux for 15 min. The solution was stirred for 2 h, and the solvent was removed *in vacuo*. The acid chloride was dissolved in dry benzene (4 mL), and sodium-dried ammonia was passed through the stirred solution for 2 h. Water was added, followed by chloroform, and the mixture was filtered from contaminating oxalyl amide. The organic phase was washed with a 5% solution of potassium hydroxide and then brine, dried (sodium sulfate), and evaporated to dryness. The residue was purified by preparative TLC on silica gel (ethyl acetate−ethanol, 97:3), and the amide **21** (60 mg, 54%) was crystallized from methylene chloride−hexane: mp 61−62 °C; IR (KBr) 3447, 3263, 2930, 2855, 1718, 1687, 1579, 1474, 1375, 1250, 991 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 7.66 (d, $J = 1.9$ Hz, 2 H), 7.52 (d, $J = 2$ Hz, 1 H), 7.43 (d, $J = 1.9$ Hz, 1 H), 6.32 (m, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 2.13 (m, 2 H), 1.51 (m, 2 H), 1.29 (m, 4 H), 0.87 (t, $J = 5.5$ Hz, 3 H); FABMS *m/e* (relative intensity) 465 (MH^+, 16), 448 (100). Anal. ($C_{23}H_{26}Cl_2N_2O_4$) C, H.

3′,3″-Bis(methylcarbamoyl)-5′,5″-dichloro-4′,4″-dimethoxy-1,1-diphenyl-1-heptene (22). Diester **11** (140 mg, 0.295 mmol) was dissolved in hot methanol (1 mL), and methylamine (1 mL, 40% aqueous solution) was added. The reaction mixture was heated at reflux for 5 h, cooled, and concentrated, and water (3 mL) was added. The product was extracted with ether, the organic phase was washed with water, 5% potassium hydroxide, and brine, dried (sodium sulfate), and evaporated to dryness. The residue (130 mg, 89%) was crystallized from ether−hexane to afford the product: mp 118−119 °C; IR (neat) 2930, 2863, 1642, 1556, 1475, 1390, 1264, 1165, 1085, 999, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, $J = 2.5$ Hz, 1 H), 7.76 (d, $J = 2.2$ Hz, 1 H), 7.67 (m, 2 H), 7.28 (d, $J = 2.2$ Hz, 1 H), 7.22 (d, $J = 2.5$ Hz, 1 H), 6.10 (t, $J = 7.0$ Hz, 1 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.02 (m, 6 H), 2.09 (m, 2 H), 1.42 (m, 2 H), 1.27 (m, 4 H), 0.86 (m, 3 H); FABMS *m/e* (relative intensity) 493 (MH^+, 100). Anal. Calcd ($C_{25}H_{30}Cl_2N_2O_4$) C, H.

3′,3″-Bis(dimethylcarbamoyl)-5′,5″-dichloro-4′,4″-dimethoxy-1,1-diphenyl-1-heptene (23). Compound **14** (128 mg, 0.274 mmol) was converted to the corresponding acid chloride as described in the preparation of **21**. The chloride was dissolved in dry benzene (4 mL), and anhydrous dimethylamine was bubbled through the stirred solution at 5−10 °C for 2 h. The solvent was removed *in vacuo*, water was added, and the product was extracted with methylene chloride. The combined extracts were washed with a 5% solution of potassium hydroxide and brine, dried (sodium sulfate), and evaporated to dryness. The residue was purified by flash chromatography on alumina (hexane−ethyl acetate, 1:1) to yield the product as a low-melting glass (90 mg, 63%): IR (neat) 2930, 2863, 1642, 1556, 1473, 1390, 1264, 1165, 1085, 999, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24 (bs, 1 H), 7.18 (bs, 1 H), 6.98 (bs, 1 H), 6.91 (bs, 1 H), 6.02 (t, $J = 7.3$ Hz, 1 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 2.86 (s, 6 H), 2.84 (s, 6 H), 2.06 (m, 2 H), 1.39 (m, 2 H), 1.23 (m, 4 H), 0.845 (t, $J = 5.8$ Hz, 3 H); FABMS *m/e* relative intensity 521 (MH^+, 100), 476 (82), 433 (27). Anal. ($C_{27}H_{34}Cl_2N_2O_4$) C, H.

5,5′-Dibromo-3,3′-dicarboxy-2,2′-dihydroxydiphenylmethane (25). 5-Bromosalicylic acid (**24**, 8.62 g, 40 mmol) was placed in a 250 mL three-necked, round-bottomed flask equipped with a mechanical stirrer, a 100 mL pressure-equalizing dropping funnel, and a thermometer. The solid was

dissolved in methanol (10 mL), and the mixture was vigorously stirred at dry ice−acetone bath temperature while concentrated sulfuric acid (70 mL) was added at such a rate to keep the temperature below 0 °C. The reaction mixture was stirred on an ice bath for 1 h and then cooled in a dry ice−acetone bath again. An mixture of 37% aqueous formaldehyde solution (20 mL) and methanol (20 mL) was added at such a rate to keep the temperature below 0 °C. The mixture was stirred at 0 °C for 4 h and was left overnight at room temperature. It was poured on crushed ice (0.5 kg), and the precipitate was filtered and dried, first at room temperature overnight and then in a vacuum desiccator, to afford a solid (7.00 g, 78%). The product was recrystallized from methanol: mp 230 °C dec; IR (KBr) 3500−2500, 1663, 1607, 1432, 1288, 1238, 1181, 885, 869, 802 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.88 (d, J = 2.4 Hz, 2 H), 7.55 (d, J = 2.4 Hz, 2 H), 4.00 (s, 2 H); CIMS *m/e* (relative intensity) 447 (MH^+, 100), 429 ($MH^+ - H_2O$, 84). Anal. Calcd ($C_{15}H_{10}Br_2O_6$) C, H.

5,5′-Dibromo-2,2′-dimethoxy-3,3′-bis(methoxycarbonyl)diphenylmethane (26). 5,5′-Dibromo-3,3′-dicarboxy-2,2′-dihydroxydiphenylmethane (**25**, 7.52 g, 16.86 mmol) was placed in a 500 mL three-necked, round-bottomed flask equipped with a mechanical stirrer, a 50 mL pressure-equalizing dropping funnel, and a reflux condenser connected to a drying tube. The acid was dissolved in acetone (220 mL, Mallincrodt, AR), and ground anhydrous potassium carbonate (19.00 g, 137.5 mmol) was added, followed by dimethyl sulfate (11.47 g, 8.6 mL, 90.7 mmol). The reaction mixture was stirred vigorously under reflux for 2 days. The solvent was removed *in vacuo*, and water (100 mL) was added, followed by methylene chloride (80 mL). The resulting mixture was filtered through a Celite pad, the organic phase was separated, the residue on the filtration funnel was washed twice with methylene chloride (2 × 30 mL), and the second filtrate used for re-extraction of the aqueous phase. The combined organic extracts were washed with water, dried (sodium sulfate), and evaporated *in vacuo* to yield the product as a colorless solid (8.2 g, 97%): mp 71−72 °C (hexane); IR (KBr) 2947, 1738, 1650, 1577, 1466, 1417, 1320, 1286. 1236, 1194, 997 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 2.5 Hz, 2 H), 7.32 (d, J = 2.5, 2 H), 3.99 (s, 2 H), 3.90 (s, 6 H), 3.75 (s, 6 H); CIMS *m/e* (relative intensity) 504 (M^+ + 2, 29), 502 (M^+, 46), 500 (24), 470 (M^+ − MeOH, 100). Anal. ($C_{19}H_{18}Br_2O_6$) C, H.

5,5′-Dibromo-2,2′-dimethoxy-3,3′-bis(methoxycarbonyl)benzophenone (27). 5,5′-Dibromo-2,2′-dimethoxy-3,3′-bis(methoxycarbonyl)diphenylmethane (**26**, 6.34 g, 12.63 mmol) was placed in a 250 mL one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to a drying tube. Acetic anhydride (128 mL) was added, the solution was cooled in an ice bath, and chromic anhydride (5.3 g, 5.30 mmol) was added in small portions over 10 min. The bath was removed, and the mixture was stirred at room temperature for 2 h, heated under reflux for 1 min, and then allowed to stand overnight at room temperature. The chromium salts were filtered off and washed with methylene chloride (5 × 5 mL). The solvent was removed *in vacuo*, and the solidified residue was flash chromatographed on silica gel (90 g). Elution with methylene chloride afforded the benzophenone derivative **27** (5.7 g, 88%): mp 128 °C (methylene chloride−hexane); IR (KBr) 3080, 3000, 2946, 1737, 1648, 1576, 1465, 1417, 1285, 1236, 1194, 1167, 988 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.08 (d, J = 2.7 Hz, 2 H), 7.80 (d, J = 2.7 Hz, 2 H), 3.92 (s, 6 H), 3.57 (s, 6 H); FABMS *m/e* (relative intensity) 517 (MH^+, 15), 515 (MH^+, 5), 485 (MH^+ − MeOH, 28). Anal. ($C_{19}H_{16}Br_2O_7$) C, H.

5′,5″-Dibromo-2′,2″-dimethoxy-3′,3″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (28). The compound was prepared from **27** as described for the conversion of **6** to **8** to yield the product an oil in 41% yield: IR (neat) 3071, 2951, 2854, 1723, 1571, 1462, 1437, 1413, 1284, 1195, 1167, 1145, 804, 738, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.88 (d, J = 2.6 Hz, 1 H), 7.80 (d, J = 2.6 Hz, 1 H), 7.56 (d, J = 2.6 Hz, 1 H), 7.50 (d, J = 2.6 Hz, 1 H), 6.07 (t, J = 7.4 Hz, 1 H), 3.88 (s, 3 H), 3.875 (s, 3 H), 3.52 (s, 3 H), 3.48 (s, 3 H), 2.12 (m, 2 H), 1.46 (m, 2 H), 1.28 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H); CIMS *m/e* (relative intensity) 585 (MH^+, 100), 553 (61). Anal. ($C_{25}H_{28}Br_2O_6$) C, H.

In Vitro Anti-HIV Assay. Anti-HIV screening of test compounds against various viral isolates and cell lines was performed as previously described.[66] This cell-based microtiter assay quantitates the drug-induced protection from the cytopathic effect of HIV. Data are presented as the percent control of XTT values for the uninfected, drug-free control. EC_{50} values reflect the drug concentration that provides 50% protection from the cytopathic effect of HIV-1 in infected cultures, while the IC_{50} reflects the concentration of drug that causes 50% cell death in the uninfected cultures. XTT-based results were confirmed by measurement of cell-free supernatant reverse transcriptase and p24 levels.

Mechanistic Assays. Binding of HIV-1_{RF} to PBLs was measured by a p24-based assay.[67] Briefly, 2 × 10^5 CEM-SS cells were incubated with a concentrated stock of virus for 30 min at 37 °C in the absence or presence of various concentrations of inhibitor, the unbound virus was washed away, and the cell-associated virus was solubilized in 1% Triton X-100 and 1% BSA and analyzed by the p24 antigen capture assay as previously described. The effects of inhibitors on the in vitro activity of purified RT (kind gift of Steve Hughes, NCI-FCRDC, Frederick, MD) were determined by measurement of incorporation of [^{32}P]TTP into the poly(rA):oligo(dT) (rAdT) homopolymer or [^{32}P]GTP into the poly(rC):oligo(dG) (rCdG) template/primer systems. Samples (5 μL) were blotted onto DE81 paper, washed with 5% dibasic sodium phosphate as previously described,[18] and then quantitated on a Packard Matrix 9600 direct beta counter. 3′-Azido-2′,3′-dideoxythymidine 5′-triphosphate (AZTTP) and NSC 629243 (UC38) served as a positive control for inhibition of RT.

To determine if compounds affected the HIV-1 p7 nucleocapsid protein zinc fingers, fluorescence measurements of the Trp^{37} residue in the C-terminal zinc finger of the HIV-1 p7 nucleocapsid protein were performed as previously described.[68] The p7NC protein was prepared at 20 μg/mL in 10 mM sodium phosphate buffer (pH 7.0) and treated with 25 μM of test compound, and then after indicated time intervals the samples were diluted 1/10 in 10 mM sodium phosphate buffer (pH 7.0) and the fluorescence intensity was measured. The excitation and emission wavelengths utilized with the Shimadzu RF5000 spectrofluorimeter were 280 and 351 nm, respectively. The analytical procedure employed to determine the reagent-induced inhibition of HIV-1 protease activity has been previously described.[67] Recombinant HIV-1 protease (Bachem BioScience Inc., King of Prussia, PA) and the substrate (Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-NH_2, Multiple Peptide Systems, San Diego, CA) were utilized to determine the concentration of test compound required to inhibit protease activity by 50% (IC_{50}). Briefly, HIV-1 protease (14.2 nM final) was mixed with various concentrations of test compounds in 250 mM potassium phosphate buffer, pH 6.5, 2.5% (v/v) glycerol, 0.5 mM dithiothreitol, 0.5 mM EDTA, and 375 mM ammonium sulfate, after which the substrate was added (30 nmol) and the reaction incubated at 37 °C for 30 min. Reactions were terminated by the addition of 20 μL of a mixture of 8 M guanidine hydrochloride to 10% trifluoroacetic acid (8:1), and the reaction products were separated by reverse-phase HPLC on a Nova-Pak C-18 column. Absorbance was measured at 206 nm, peak areas were quantitated, and the percentage conversion to product was used to calculate the percentage of control cleavage in the presence of inhibitors.

Screening against HIV-1 Viruses Containing NNRTI Resistance Mutations. These studies were performed as previously described.[69]

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