Replacement of the Metabolically Labile Methyl Esters in the Alkenyldiarylmethane Series of Non-Nucleoside Reverse Transcriptase Inhibitors with Isoxazolone, Isoxazole, Oxazolone, or Cyano Substituents

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The alkenyldiarylmethanes (ADAMs) are a unique class of non-nucleoside reverse transcriptase inhibitors that have potential value in the treatment of HIV/AIDS. However, the potential usefulness of the ADAMs is limited by the presence of metabolically labile methyl ester moieties. A series of novel ADAMs were therefore designed and synthesized in order to replace the metabolically labile methyl ester moieties of the existing ADAM lead compounds with hydrolytically stable, fused isoxazolone, isoxazole, oxazolone, or cyano substituents on the aromatic rings. The methyl ester and methoxy substituents on both of the aromatic rings in the parent compound **1** were successfully replaced with metabolically stable moieties with retention of anti-HIV activity and a general decrease in cytotoxicity.

Introduction

The HIV/AIDS epidemic remains a serious threat to human health. Despite the availability of approximately 20 approved antiretroviral drugs for treatment of HIV infection, there is a persistent demand for new anti-HIV agents to improve convenience of use and therefore compliance of the patient, to reduce adverse effects, and to maintain activity against the growing number of drug-resistant forms of HIV mutants.

Many enzymatic reactions are involved in the replication of this virus. Reverse transcriptase (RT) is a multifunctional heterodimeric enzyme that converts HIV RNA into proviral DNA. The structure of HIV-1 RT has been elucidated by X-ray crystallography in several forms, including the unliganded enzyme,[1] enzyme in complex with non-nucleoside reverse transcriptase inhibitors (NNRTIs),[2−9] and enzyme bound to a template primer with[10] or without dNTP substrate.[11] Nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors targeting HIV-1 reverse transcriptase are two classes of drugs used clinically to treat the HIV infection and AIDS. The NNRTIs (including the approved drugs nevirapine, delavirdine, and efavirenz) act as noncompetitive inhibitors that interact with an allosteric site of the enzyme, which is approximately 10 Å from the polymerase active site within RT.[12,13] The interaction of the NNRTIs with HIV-1 RT leads to a conformational change in the enzyme that inhibits the formation of a catalytically competent ternary complex.[13,14] However, the efficacy of NNRTIs is seriously compromised by the emergence of mutant, drug-resistant viral strains.[15] Therefore, the development of drugs with significantly improved resistance profiles for chronic use in anti-HIV combination therapy is still a major challenge facing medicinal chemistry.

Design

The alkenyldiarylmethanes (ADAMs) are a family of novel HIV-1 non-nucleoside reverse transcriptase inhibitors. A number of HIV strains containing AZT resistance mutations have shown enhanced sensitivity to some of the ADAMs, but in general the ADAMs, including ADAM **1**, are unstable in blood plasma because of the presence of several methyl esters groups.[16] The goal of the present research project has therefore been to explore the replacement of these methyl esters with appropriately designed bioisosteres that would increase metabolic stability and also retain the desired anti-HIV activity of the parent compound. Rather than replace all three esters at once and observe effects on activity, our strategy has been to systematically replace the esters one at a time in a sequential fashion and determine the effects. The resulting information will eventually guide the replacement of all three esters. As a step toward this objective, we previously reported the ADAMs **2**−**4**, with a 3-cyanophenyl group, that retained both enzyme inhibitory and antiviral activities.[17] Compound **5** also retained the enzyme inhibitory potency and antiviral activity of the parent compound, although it proved to be too cytotoxic to be of value as an anti-HIV agent.[17] More recently, ADAM **6** was synthesized in which one of the aryl rings with the methyl ester moiety and the adjacent methoxy group in compound **1** were replaced with a substituted benzoxazolone ring.[18] Compound **6** showed very potent anti-HIV-1 activity, with EC_{50} values of 30 nM (HIV-1_{RF} in CEM-SS cells) and 90 nM (HIV-1_{IIIB} in MT-4 cells). ADAM **6** was also active against HIV-1 reverse transcriptase (IC_{50} = 20 nM). Because compound **6** still retained an aryl ring with a metabolically labile methyl ester moiety, plans were made to replace the ester-containing aryl ring with a cyanophenyl ring.

The presently reported design strategy was also inspired by a number of existing NNRTIs that contain cyanophenyl moieties. Masuda et al. reported 2-cyanothiazolidenebenzenesulfonamide derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors. Compound YM-228855, having a 2-cyanophenyl ring, showed very potent anti-HIV activity with an EC_{50} value of 1.8 nM.[19] Several research groups have identified 6-arylsul-

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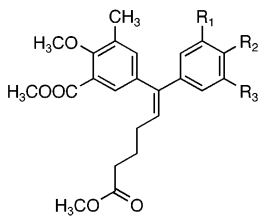
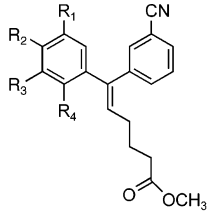
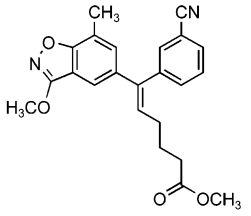


1 $R_1 = CH_3$; $R_2 = OCH_3$; $R_3 = COOCH_3$
9 $R_1 = CN$; $R_2 = R_3 = H$
10 $R_1 = R_3 = H$; $R_2 = CN$



2 $R_1 = CH_3$; $R_2 = OCH_3$; $R_3 = COOCH_3$; $R_4 = H$
3 $R_1 = Cl$; $R_2 = OCH_3$; $R_3 = COOCH_3$; $R_4 = H$
4 $R_1 = Cl$; $R_2 = R_3 = H$; $R_4 = OCH_3$



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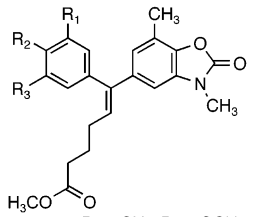
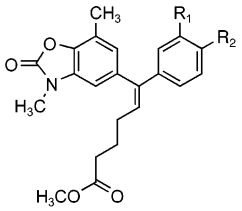
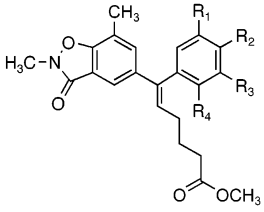


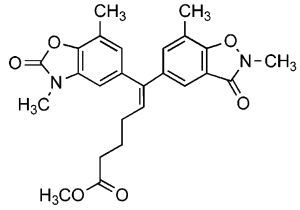
6 $R_1 = CH_3$; $R_2 = OCH_3$; $R_3 = COOCH_3$
7 $R_1 = CN$; $R_2 = R_3 = H$



8 $R_1 = CN$; $R_2 = H$
11 $R_1 = H$; $R_2 = CN$



12 $R_1 = Cl$; $R_2 = R_3 = H$; $R_4 = OCH_3$
13 $R_1 = F$; $R_2 = R_4 = H$; $R_3 = CF_3$
15 $R_1 = CH_3$; $R_2 = OCH_3$; $R_3 = COOCH_3$ $R_4 = H$



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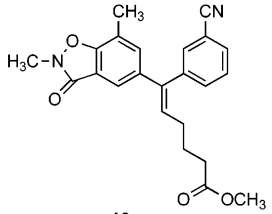

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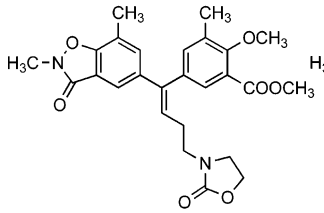

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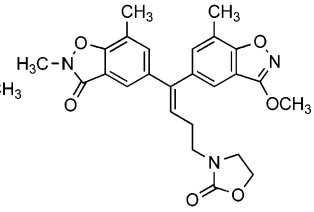
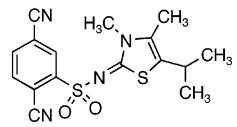
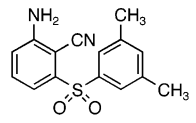


18

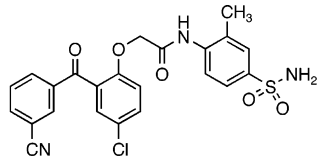
fonyl-2-aminobenzonitriles (e.g., 739W94) and related benzophenones (e.g., GW4751) having a 3-cyanophenyl ring with nanomolar EC_{50} values.[20−23] Different NNRTIs such as dapivirine (R147681 or TMC120), etravirine (R165335 or TMC125), rilpivirine (R278474 or TMC 278), and pyrazinone, with nonnucleoside HIV-1 reverse transcriptase inhibitory activity, also have a cyanophenyl ring.[24−27] On the basis of the modeling studies, the cyano group in the pyrazinone is located in a subpocket of RT in such a way that it experiences a strong dipole−dipole interaction with the backbone carbonyl of H235, while its relatively small volume allows for an excellent orientation of the inhibitor inside the protein. The cyano substituent in the 4-position of the aniline moiety is the optimal choice, similar to that observed in the TMC120/TMC125 compounds.[28,29] TMC125 is currently in phase IIB clinical trials. These findings suggested the synthesis of the ADAM analogue **7**. To further evaluate the influence of the stereochemistry of the alkene in ADAMs, isomeric compounds **8** and **9**, with exchanged aromatic rings relative to compounds **7** and **2**, were also prepared. To verify whether the cyano position could influence the inhibitory effects on RT, the syntheses of 4-cyano derivatives **10** and **11** were also planned.



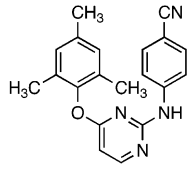
YM-228855, EC_{50} 1.8 nM



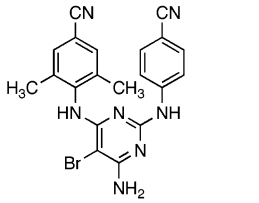
739W94 EC_{50} 10 nM



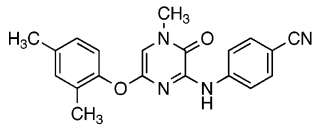
GW4751 EC_{50} 1.8 nM



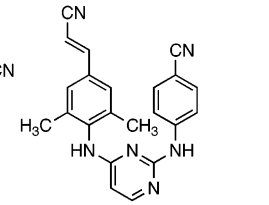
Dapivirin (R147681, TMC120) EC_{50} 1.2 nM



Etravirine (R165335, TMC125) EC_{50} 2.0 nM



Pyrazinone, EC_{50} <1.0 nM



Rilpivirine (R278474, TMC278) EC_{50} 0.4 nM

A methoxylated isoxazole (e.g., structure **5**) was previously developed to substitute for the methyl ester present in norarecoline.[30] Recently, an N-methylated isoxazolone replacement (e.g., **12**, **13**, and **15**) for a methyl ester group in PPARα/γ dual agonists has been reported by Shi and co-workers at Merck.[31] In the methoxylated isoxazoles (e.g., **5**), the nitrogen of the isoxazole mimics the carbonyl oxygen of the ester, and the methoxy group on the isoxazole mimics the methoxy group on the methyl ester. The isoxazole ring present in compounds **12**, **13**, and **15** was proposed as a metabolically stable replacement for the 4-methoxy-3-methoxycarbonyl substituents found in many of the active ADAMs. In these analogues (**12**, **13**, and **15**), the carbonyl of the isoxazolone mimics the carbonyl of a methyl ester, and the *N*-methyl moiety of the isoxazolone mimics the methoxy part of a methyl ester. All of these substances (**5**, **12**, **13**, and **15**) are obviously conformationally constrained ester mimics that may provide information about the biologically active conformation of the corresponding methyl esters in the ADAMs. ADAMs **12** and **13** eventually proved to be inactive as anti-HIV agents. This may be due to the structural modifications of these ADAMs with F/CF_3 or Cl/MeO substitution on one of the aryl rings because ADAM **14**, incorporating

a benzoxazolone ring, showed both enzyme inhibitory and antiviral activities. This led to consideration of ADAMs **15** and **16**. Compound **15** retains the methyl ester moiety and the adjacent methoxy group on the aryl ring, and compound **16** has a cyanophenyl ring. Modification of the side chain in compound **15** with an oxazolidinonyl group as shown in compound **17** was also planned. Compound **18**, in which a benzo[*d*]isoxazole ring replaced the substituted phenyl ring in **17** bearing a methyl ester, was also considered.

In this paper, the syntheses of alkenyldiarylmethanes **7**−**11** and **15**−**18** are reported, along with their activities as inhibitors of the HIV-1-induced cytopathic effect in cell culture, their cytotoxicities, and their metabolic stabilities in rat blood plasma.

Chemistry

As shown in Scheme 1, all of the alkenyldiarylmethanes were prepared by the Stille cross-coupling reaction of a vinylstannane with an aryl iodide or bromide in the presence of $Pd(PBu^t_3)_2$ and CsF at reflux temperature in toluene. No attempts were made to optimize the reaction conditions for each reaction. The syntheses of arylstannanes **19**, **22**, **25**, and **26** and aryl iodides **20**, **21**, and **27** have been reported previously.[16−18] The Sonogashira coupling of compound **27** with 3-but-3-ynyl-1,3-oxazolidin-2-one (**28**)[17] yielded the disubstituted alkyne **29**. The hydrostannation of **29** with tri-*n*-butyltin hydride in the presence of $Pd(PPh_3)_4$ afforded the regiochemically and stereochemically defined vinylstannane **30** with the side product **31**, which were separated chromatographically. Stille coupling of the stannane **30** with the iodide **21** afforded the desired ADAM **18**.

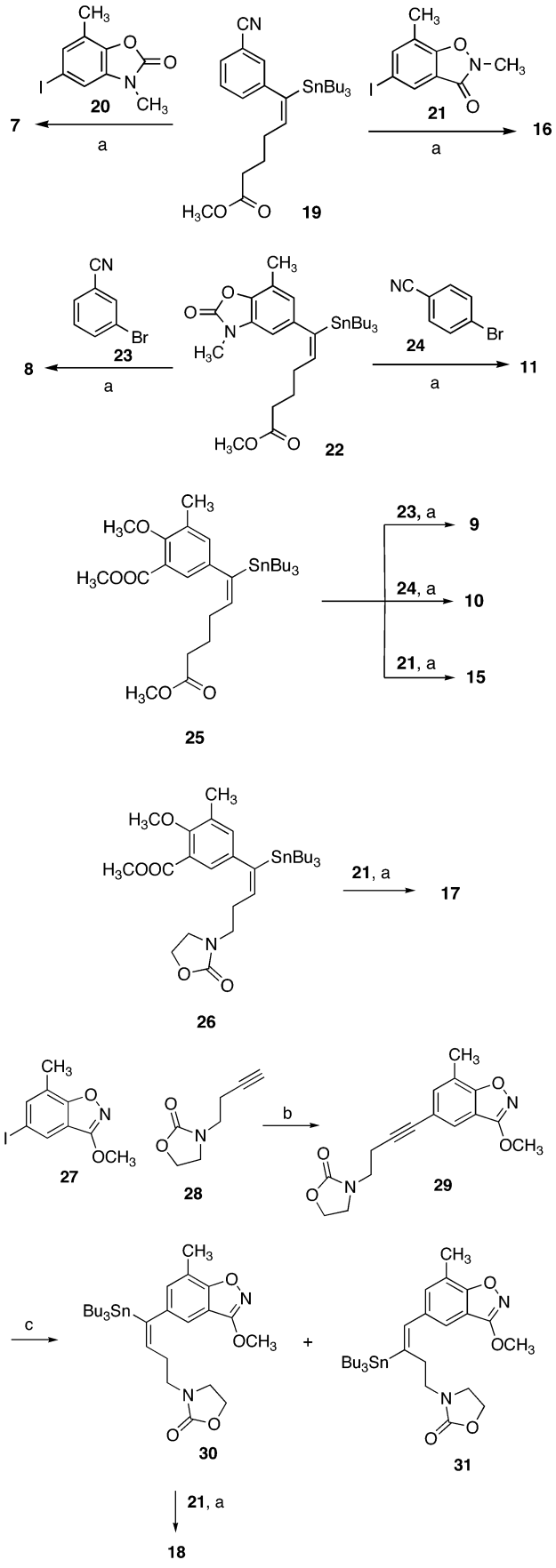
Biological Results and Discussion

The ADAMs were evaluated for cytotoxicity in CEM-SS cells and MT-4 cells, inhibition of the cytopathic effects of $HIV\text{-}1_{RF}$ in CEM-SS cells, and inhibition of the cytopathic effects of both $HIV\text{-}1_{IIIB}$ and $HIV\text{-}2_{ROD}$ in MT-4 cells. The ADAMs were also tested for inhibition of HIV-1 RT. The metabolic stabilities of the ADAMs in rat plasma (Sigma, St. Louis, MO) were also investigated. The anti-HIV activities, cytotoxicities, and metabolic stabilities of ADAM analogues are listed in Table 1. The previously reported ADAMs **1**−**5**, **12**, and **13** are included in the table for comparison. In common with other known NNRTIs, all of ADAMs tested in this series are inactive against HIV-2. Except for compounds **5**, **10**, and **18**, the reported modification of the parent compound results in decreased toxicity in MT-4 cells and CEM-SS cells.

The 10 ADAMs having a cyano substituent on one of the aryl rings (compounds **2**−**5**, **7**−**11**, and **16**) retained enzyme inhibitory activity, and 4 of the 10 compounds (compound **2**, **3**, **9**, and **10**) displayed IC_{50} values for inhibition of RT polymerase activity between 0.54 and 0.84 μM. The remaining six compounds had intermediate IC_{50} values ranging from 2.8 to 49.6 μM. Replacement of either of the aromatic rings in the lead compound **1** with a cyanophenyl group resulted in an equally or slightly more potent RT inhibitor (compare **2**, **9**, and **10** with **1**). As shown in compounds **9** and **10**, the position of the cyano group in the phenyl ring does not have much influence on the inhibitory activity on the enzyme.

Among the new cyano ADAMs, compounds **2**, **5**, and **7** were inactive against $HIV\text{-}1_{RF}$ in CEM-SS cells. Compounds **5** and **7** were also inactive against $HIV\text{-}1_{IIIB}$ in MT-4 cells. However, the replacement of the aromatic ring that is trans to the side chain in compound **1** with a cyanophenyl ring (compounds **9** and **10**) resulted in increased potency against $HIV\text{-}1_{IIIB}$ in MT-4 cells. Compared to compound **1**, compound **9** was twice as

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd(PBu^t_3)_2$, CsF, toluene, reflux; (b) $PdCl_2(PPh_3)_2$, Cu(I)I, Et_3N, THF, room temperature; (c) Bu_3SnH, $Pd(PPh_3)_4$, THF, room temperature.

Table 1. Anti-HIV Activities, Cytotoxicities, and Metabolic Stabilities of ADAM Analogues[a]

		EC_{50} (μM)[c]			CC_{50} (μM)[d]		
compd	IC_{50} (μM)[b]	HIV-1_{RF}	HIV-1_{IIIB}	HIV-2_{ROD}	CEM-SS cells	MT-4 cells	rat plasma $t_{1/2} \pm$ SD (min)
1	1.0	0.25	1.0	NA[e]	6.0	6.1	0.76 ± 0.04
2	0.84	>100	12.79	>169	23.3	153	0.71 ± 0.01
3	0.75	7.1	8.55	>223	20.2	213	0.44 ± 0.05
4	7.58	7.0	9.11	>67.6	16.3	≥45.2	0.42 ± 0.02
5	5.7	>100	>2.05	>5.63	0.8	4.69	1.16 ± 0.08
7	26.4	>100	>54.2	>54.2	12.9	54.2	1.18 ± 0.23
8	2.8	1.73	NT[f]	NT[f]	11.5	NT[f]	NT[f]
9	0.54	0.46	0.47	>10.6	10.9	10.6	1.32 ± 0.07
10	0.70	0.637	0.25	>1.40	>5.0	1.40	0.77 ± 0.06
11	1.2	0.59	1.49	>51.0	21.9	51	NT[f]
12	8.2	>100	>28.8	>28.8	13.0	28.8	0.48 ± 0.06
13	>100	>100	>35.7	43.2	16.8	39.8	0.87 ± 0.12
14	49.2	1.79	4.49	>36.5	11.1	36.5	0.46 ± 0.03
15	2.0	1.1	3.10	>27.1	>5.0	27.1	1.85 ± 0.21
16	49.6	>100	NT[f]	NT[f]	14.0	NT[f]	NT[f]
17	9.86	2.7	NT[f]	NT[f]	16.3	NT[f]	22.1 ± 0.06
18	7.6	>9.91	>1.12	>1.12	1.54	1.12	>1440

[a] All data represent mean values of at lease two separate experiments. [b] Inhibitory activity vs HIV-1 reverse transcriptase with rCdG as the template primer. [c] EC_{50} is the 50% inhibitory concentration for inhibition of cytopathicity of HIV-1_{RF}, HIV-1_{IIIB}, or HIV-2_{ROD}. [d] The CC_{50} is the 50% cytotoxic concentration for mock-infected CEM-SS cells or MT-4 cells. [e] NA, not active. [f] NT, not tested.

potent and compound **10** was four times more potent against HIV-1_{IIIB} in MT-4 cells, but they are slightly less active than compound **1** against HIV-1_{RF} in CEM-SS cells. These results indicate a moderate effect of the position of the cyano group in the phenyl ring on the antiviral activity vs HIV-1_{IIIB}, even though the position of cyano group in the ADAMs has little effect on inhibiting HIV-1_{RF} viruses. However, the position of the cyano group in compounds **8** and **11** seems to affect the inhibitory activity against HIV-1_{RF} in CEM-SS cells. Moreover, the stereochemistry of the alkene in the ADAM system has a strong influence on the anti-HIV activity. ADAM **9**, having a cyanophenyl ring trans to the side chain in the ADAM system, displays almost the same EC_{50} values for inhibition of the cytopathic effect of HIV-1 in CEM-SS cells and MT-4 cells, and it inhibits HIV-1 RT with an IC_{50} of 0.54 μM. Compound **2**, an isomer of ADAM **9**, was either inactive or displayed very low antiviral activity. A similar phenomenon was also observed with compounds **7** and **8**. Compound **8** is active ($EC_{50} = 1.73$ μM) against HIV-1_{RF} in CEM-SS cells. Compound **7**, an isomer of **8**, is inactive. In general, ADAMs having the cyanophenyl trans to the side chain retain or increase the inhibitory activity as shown in compounds **8**−**11**, compared to compounds **2**−**7** and **16**. The replacement of the methyl group in inactive ADAM **2** ($EC_{50} > 100$ μM in CEM-SS cells) with chlorine (compound **3**) results in an increased antiviral potency ($EC_{50} = 7.1$ μM). Modification of ADAM **2** by replacing the 4-methoxy-5-methoxycarbonyl-3-methylphenyl group with a substituted isoxazole ring in compounds **5** and **17** causes a significant drop in the enzyme inhibitory potency.

Except for compound **13**, having F/CF_3 substituents, all of the ADAMs containing the fused isoxazolone replacement had intermediate enzyme inhibitory activity vs HIV-1 RT with IC_{50} values ranging from 2.0 to 49.6 μM. Compounds **14**, **15**, and **17** also displayed antiviral activities. The side chain methyl ester in ADAM **15** was successfully replaced with an oxazolidinyl group in **17** with retention of the anti-HIV activity and a significant improvement of the metabolic stability in rat plasma. The half-life in rat plasma was increased from 1.85 min for compound **15** to 22.1 min for compound **17**. Compound **18** is the most stable compound in this series of ADAMs, but it was generally cytotoxic and lost the ability to inhibit the cytopathic effect of the virus at noncytotoxic concentrations.

In conclusion, a new series of ADAM non-nucleoside reverse transcriptase inhibitors were designed and synthesized with metabolically stable, fused isoxazolone, isoxazole, oxazolone, or cyano substituents on the aryl rings. Both of the aromatic rings in the parent compound **1** have been successfully replaced with hydrolytically stable moieties with retention of the anti-HIV activity as shown in compounds **4**, **8**, **11**, and **14**. In most cases, these structural modifications resulted in a decrease in cytotoxicity in MT-4 cells and CEM-SS cells. ADAM **17** displays enhanced stability ($t_{1/2} = 22.1$ min) and diminished cytotoxicity ($CC_{50} = 16.3$ μM) while maintaining moderate antiviral potency ($EC_{50} = 2.7$ μM vs HIV-1_{RF}) in CEM-SS cells. These initial results will provide a foundation for the rational replacement of all three methyl esters of the lead compound **1** with metabolically stable isosteres while maintaining antiviral potency.

Experimental Section

Unless noted otherwise, NMR spectra were obtained at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ using $CHCl_3$ as the internal standard. IR spectra were recorded using a Perkin-Elmer 1600 series FT-IR. Flash chromatography was performed with 230−400 mesh silica gel. TLC was carried out using Baker-flex silica gel IB2-F plates of a 2.5 mm thickness. Melting points are uncorrected. Unless otherwise stated, chemicals and solvents were of reagent grade and used as obtained from commercial sources without further purification. Lyophilized rat plasma (lot 052K7609) was obtained from Sigma Chemical Co., St. Louis, MO. Microanalyses were performed at the Purdue University Microanalysis Laboratory. All yields given refer to isolated yields.

General Procedure for the Synthesis of Alkenyldiarylmethanes by the Stille Cross-Coupling Reaction of Vinylstannanes with Aromatic Iodides or Bromides. A mixture of vinylstannane (1 equiv), aryl halide (1.2−1.5 equiv), cesium fluoride (3.0−4.5 equiv), and $Pd(PBu^t_3)_2$ (~10 mol %) in toluene (1 mL) was stirred under argon at different temperature for various time periods. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel (5 g), and the column was washed with ethyl acetate. The organic solution was concentrated on a rotary evaporator under vacuum.

(*Z*)-6-(3-Cyanophenyl)-6-(2,3-dihydro-3,7-dimethyl-2-oxobenzoxazol-5-yl)hex-5-enoic Acid Methyl Ester (7). The general procedure was followed using the vinylstannane **19** (300 mg, 0.579 mmol), 5-iodo-3,7-dimethyl-3*H*-benzoxazol-2-one (**20**) (266 mg,

0.920 mmol), cesium fluoride (355 mg, 2.31 mmol), and $Pd(PBu^t_3)_2$ (33 mg, 0.063 mmol) in toluene (1 mL). The mixture was stirred under argon at room temperature for 15 h, at 65 °C for 5.3 h, and at 110 °C for 23 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−30%), to afford the product **7** (82 mg) as an oil in 36% yield. IR (KBr) 2950, 2229, 1775, 1735, 1642, 1620, 1495, 1469, 1364, 1332, 1304, 1245, 1210, 1168, 1064, 880, 802, 750, 689 cm^{-1}; ^1H NMR δ 7.60 (d, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.42−7.36 (m, 2 H), 6.65 (s, 1 H), 6.53 (s, 1 H), 6.02 (t, J = 7.5 Hz, 1 H), 3.60 (s, 3 H), 3.31 (s, 3 H), 2.28 (m, 5 H), 2.09 (q, J = 7.5 Hz, 2 H), 1.76 (m, 2 H); ^{13}C NMR δ 173.46, 154.77, 140.99, 140.57, 140.01, 137.81, 134.14, 133.06, 131.35, 130.83, 130.47, 129.18, 123.49, 119.95, 118.50, 112.49, 104.36, 51.41, 33.20, 28.98, 28.06, 24.71, 14.30; ESIMS *m*/*z* (rel intensity) 412.74 (MNa^+, 100). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

(*Z*)-6-(3-Cyanophenyl)-6-(2,3-dihydro-3,7-dimethyl-2-oxobenzoxazol-5-yl)hex-5-enoic Acid Methyl Ester (8). The general procedure was followed using a stirred mixture of 6-(tributylstannanyl)-6-(2,3-dihydro-3,7-dimethyl-2-oxobenzoxazol-5-yl)-hex-5-enoic acid methyl ester (**22**) (356 mg, 0.62 mmol), 3-bromobenzonitrile (**23**) (100 mg, 0.78 mmol), cesium fluoride (395 mg, 2.57 mmol), and $Pd(PBu^t_3)_2$ (34 mg, 0.065 mmol) in toluene (1 mL) under argon at room temperature for 18 h, at 75 °C for 23 h, and at 110 °C for 24 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−20%), to afford the product **8** (7.2 mg) as an oil in 3% yield. ^1H NMR δ 7.50−7.31 (m, 4 H), 6.67 (s, 1 H), 6.52 (s, 1 H), 6.09 (d, J = 7.5 Hz, 1 H), 3.60 (s, 3 H), 3.37 (s, 3 H), 2.37 (s, 3 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.13 (q, J = 7.5 Hz, 2 H), 1.77 (dt, J = 7.5 Hz, 2 H); ESIMS *m*/*z* (rel intensity) 390.89 (MH^+, 73). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

(*E*)-5-[1-(3-Cyanophenyl)-5-methoxycarbonylpent-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (9). The general procedure was followed using the vinylstannane **25** (386 mg, 0.648 mmol), 3-bromobenzonitrile (**23**) (104 mg, 0.801 mmol), cesium fluoride (365 mg, 2.379 mmol), and $Pd(PBu^t_3)_2$ (36 mg, 0.069 mmol) in toluene (1 mL). The mixture was stirred under argon at room temperature for 29.5 h, at 60 °C for 24.5 h, and at 110 °C for 16 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−20%), to afford the product **9** (54 mg) as an oil in 20% yield. IR (KBr) 2951, 2229, 1732, 1598, 1575, 1480, 1436, 1418, 1367, 1298, 1255, 1231, 1199, 1162, 1125, 1008, 885, 799, 693 cm^{-1}; ^1H NMR δ 7.50−7.32 (m, 5 H), 7.06 (d, J = 7.06 Hz, 1 H), 6.06 (t, J = 7.5 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.60 (s, 3 H), 2.31 (s, 3 H), 2.29 (d, J = 7.5 Hz, 2 H), 2.14 (q, J = 7.5 Hz, 2 H), 1.76 (m, 2 H); ESIMS *m*/*z* (rel intensity) 430.03 (MNa^+, 100). Anal. ($C_{24}H_{25}NO_5$) C, H, N.

(*Z*)-5-[1-(4-Cyanophenyl)-5-methoxycarbonylpent-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (10). The general procedure was followed using the vinylstannane **25** (406 mg, 0.681 mmol), 4-bromobenzonitrile (**24**) (112 mg, 0.866 mmol), cesium fluoride (381 mg, 2.483 mmol), and $Pd(PBu^t_3)_2$ (36 mg, 0.069 mmol) in toluene (1 mL). The mixture was stirred under argon at room temperature for 29.5 h, at 60 °C for 24.5 h, and at 110 °C for 16 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−20%), to afford the product **10** (51 mg) as an oil in 19% yield. IR (KBr) 2951, 2226, 1732, 1603, 1503, 1480, 1436, 1370, 1302, 1257, 1231, 1196, 1168, 1126, 1008, 842, 799 cm^{-1}; ^1H NMR δ 7.53 (d, J = 8.4 Hz, 2 H), 7.37 (d, J = 2.1 Hz, 1 H), 7.26 (d, J = 8.7 Hz, 2 H), 7.06 (d, J = 1.8 Hz, 1 H), 6.14 (t, J = 7.5 Hz, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.61 (s, 3 H), 2.30 (s, 3 H), 2.29 (d, J = 7.5 Hz, 2 H), 2.15 (q, J = 7.5 Hz, 2 H), 1.77 (m, 2 H); ^{13}C NMR δ 173.55, 166.49, 157.60, 146.41, 139.94, 136.11, 133.74, 133.03, 132.43, 131.93, 130.18, 127.55, 124.53, 118.82, 110.38, 61.45, 52.13, 51.40, 33.30, 29.20, 24.63, 16.04; ESIMS *m*/*z* (rel intensity) 429.98 (MNa^+, 100). Anal. ($C_{24}H_{25}NO_5$) C, H, N.

(*Z*)-6-(4-Cyanophenyl)-6-(2,3-dihydro-3,7-dimethyl-2-oxobenzoxazol-5-yl)hex-5-enoic Acid Methyl Ester (11). The general procedure was followed using the vinylstannane **22** (416 mg, 0.719 mmol), 4-bromobenzonitrile **24** (118 mg, 0.912 mmol), cesium fluoride (398 mg, 2.594 mmol), and $Pd(PBu^t_3)_2$ (42 mg, 0.081 mmol) in toluene (1 mL). The mixture was stirred under argon at room temperature for 4 h, at 60 °C for 20 h, and at 110 °C for 7 h. The residue was purified by column chromatography on silica gel (15 g), eluting with EtOAc−hexanes (0−20%), to afford the product **11** (62 mg) as an oil in 22% yield. IR (KBr) 2950, 2225, 1778, 1735, 1642, 1618, 1602, 1495, 1469, 1356, 1299, 1245, 1209, 1159, 1123, 1062, 1030, 985, 881, 846, 750, 732 cm^{-1}; ^1H NMR δ 7.52 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H), 6.68 (s, 1 H), 6.53 (s, 1 H), 6.17 (t, J = 7.5 Hz, 1 H), 3.62 (s, 3 H), 3.36 (s, 3 H), 2.37 (s, 3 H), 2.29 (d, J = 7.5 Hz, 2 H), 2.14 (q, J = 7.5 Hz, 2 H), 1.77 (m, 2 H); ESIMS *m*/*z* (rel intensity) 390.81 (MH^+, 20). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

(*Z*)-5-[1-(2,3-Dihydro-2,7-dimethyl-3-oxobenzo[*d*]isoxazol-5-yl)-5-methoxycarbonylpent-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (15). The general procedure was followed using methyl 6-(tributylstannyl)-6-[4-methoxy-5-methoxycarbonyl-3-methylphenyl]hex-5-enoate (**25**) (391 mg, 0.6567 mmol), 5-iodo-2,7-dimethyl-benzo[*d*]isoxazol-3-one (**21**) (289 mg, 0.877 mmol), cesium fluoride (323 mg, 2.11 mmol), and $Pd(PBu^t_3)_2$ (37 mg, 0.071 mmol) in toluene (1 mL). The mixture was stirred at room temperature for 13 h, at 60 °C for 24 h, and at 110 °C for 18.5 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−30%), to afford the product **15** (223 mg) as an oil in 73% yield. IR (KBr) 2950, 1732, 1693, 1615, 1484, 1436, 1376, 1298, 1256, 1228, 1206, 1162, 1122, 1009, 882, 854, 799, 772, 655, 624 cm^{-1}; ^1H NMR δ 7.52 (m, 2 H), 7.42 (m, 1 H), 7.22 (d, J = 1.8 Hz, 1 H), 6.12 (t, J = 7.5 Hz, 1 H), 4.03 (s, 3 H), 4.01 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.47 (s, 3 H), 2.44 (s, 3 H), 2.31−2.24 (q, J = 7.2−7.5 Hz, 2 H), 1.96−1.86 (m, 2 H); ^{13}C NMR δ 173.65, 166.54, 163.00, 158.03, 157.44, 140.22, 138.50, 136.18, 134.69, 132.96, 132.78, 130.22, 129.70, 124.30, 119.89, 119.76, 115.71, 61.40, 52.02, 51.34, 33.30, 32.51, 29.02, 24.84, 16.04, 14.01; ESIMS *m*/*z* (rel intensity) 490.19 (MNa^+, 100). Anal. ($C_{26}H_{29}NO_7$) C, H, N.

(*E*)-6-(3-Cyanophenyl)-6-(2,3-dihydro-2,7-dimethyl-3-oxobenzo[*d*]isoxazol-5-yl)hex-5-enoic Acid Methyl Ester (16). The general procedure was followed using the vinylstannane **19** (316 mg, 0.61 mmol), aryl iodide **21** (224 mg, 0.774 mmol), cesium fluoride (410 mg, 2.69 mmol), and $Pd(PBu^t_3)_2$ (33 mg, 0.063 mmol) in toluene (1 mL). The mixture was stirred under argon at room temperature for 15 h, at 60 °C for 5.3 h, and at 110 °C for 23 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−30%), to afford the product **16** (23 mg) as an oil in 10% yield. IR (KBr) 2925, 2851, 2229, 1735, 1690, 1618, 1492, 1435, 1374, 1317, 1227, 1170, 880, 854, 772 cm^{-1}; ^1H NMR δ 7.61 (d, J = 7.8 Hz, 1 H), 7.50−7.34 (m, 4 H), 7.20 (s, 1 H), 6.06 (t, J = 7.5 Hz, 1 H), 3.65 (s, 3 H), 3.61 (s, 3 H), 2.33 (s, 3 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.10 (m, 2 H), 1.76 (m, 2 H); ESIMS *m*/*z* (rel intensity) 390.85 (MH^+, 19), 412.83 (MNa^+, 100). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

(*Z*)-5-[1-(2,3-Dihydro-2,7-dimethyl-3-oxobenzo[*d*]isoxazol-5-yl)-4-(2-oxooxazolidin-3-yl)but-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (17). The general procedure was followed using 1-(tributylstannanyl)-2-methoxy-3-methyl-5-[4-(2-oxooxazolidin-3-yl)-but-1-enyl]benzoic acid methyl ester (**26**) (334.7 mg, 0.55 mmol), 5-iodo-2,7-dimethylbenzo[*d*]isoxazol-3-one (**21**) (230 mg, 0.796 mmol), cesium fluoride (324 mg, 2.11 mmol), and $Pd(PBu^t_3)_2$ (31.7 mg, 0.061 mmol) in toluene (1 mL). The mixture was stirred at room temperature for 21.5 h, at 70 °C for 29 h, and at 110 °C for 21.5 h. The residue was purified by column chromatography on silica gel (20 g), eluting with EtOAc−hexanes (0−50%) to yield an oil, which was crystallized from ethyl acetate and hexanes to give the product **17** (70 mg) as a solid in 26% yield: mp 127−127.5 °C. IR (KBr) 2948, 1747, 1731, 1688, 1616, 1484, 1435, 1378, 1258, 1226, 1209, 1148, 1120, 1037, 1009, 852, 769 cm^{-1}; ^1H NMR δ 7.33 (d, J = 1.8 Hz, 1 H), 7.22 (s, 1 H), 7.04 (d, J = 2.1 Hz, 1 H), 5.92 (t, J = 7.5 Hz, 1 H), 4.19 (t, J = 7.8 Hz, 2 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.58 (s, 3 H), 3.33−3.26 (m, 4 H), 2.33 (m, 2 H), 2.29 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR δ 166.52,

162.96, 158.38, 158.21, 157.60, 141.85, 138.11, 136.09, 134.53, 133.10, 130.05, 126.27, 124.50, 120.20, 120.09, 115.67, 61.50, 60.26, 52.14, 44.30, 43.83, 32.54, 27.91, 16.08, 14.08; ESIMS *m*/*z* (rel intensity) 481.03 (MH^+, 100). Anal. ($C_{26}H_{28}N_2O_7$) C, H, N.

(*E*)-5-[1-(3-Methoxy-7-methyl-benzo[*d*]isoxazol-5-yl)-4-(2-oxooxazolidin-3-yl)but-1-enyl]-2,7-dimethylbenzo[*d*]isoxazol-3-one (18). The general procedure was followed using 3-[4-(tributylstannanyl)-4-(3-methoxy-7-methylbenzo[*d*]isoxazol-5-yl)but-3-enyl]oxazolidin-2-one (**30**) (384 mg, 0.65 mmol), 5-iodo-2,7-dimethylbenzo[*d*]isoxazol-3-one (**21**) (233 mg, 0.807 mmol), cesium fluoride (364 mg, 2.37 mmol), and $Pd(PBu^t_3)_2$ (36 mg, 0.069 mmol) in toluene (1 mL) under argon. The mixture was stirred at room temperature for 21 h, at 60 °C for 25 h, and at 110 °C for 24 h. The residue was purified by column chromatography on silica gel (30 g), eluting with EtOAc−hexanes (0−65%), to afford the product **18** (114 mg) as a solid in 38% yield: mp 202−203 °C. IR (KBr) 2925, 1775, 1618, 1548, 1496, 1448, 1426, 1359, 1333, 1305, 1267, 1226, 1153, 1104, 1065, 1043, 973, 955, 912, 881 cm^{-1}; ^1H NMR δ 7.31 (s, 1 H), 7.22 (s, 1 H), 7.18 (s, 1 H), 6.99 (s, 1 H), 5.98 (t, J = 7.5 Hz, 1 H), 4.19 (t, J = 7.8 Hz, 2 H), 4.10 (s, 3 H), 3.59 (s, 3 H), 3.34−3.26 (m, 4 H), 2.42 (s, 3 H), 2.34 (t, J = 6.9 Hz, 2 H), 2.29 (s, 3 H); ^{13}C NMR δ 167.06, 162.83, 162.47, 158.30, 158.11, 142.11, 138.27, 134.61, 132.99, 132.36, 126.14, 121.15, 120.02, 118.77, 115.63, 113.71, 61.46, 60.22, 57.26, 44.23, 43.78, 32.49, 27.86, 20.90, 14.56, 14.03; ESIMS *m*/*z* (rel intensity) 486.04 (MNa^+, 100). Anal. ($C_{25}H_{25}N_3O_6$) C, H, N.

3-[4-(3-Methoxy-7-methylbenzo[*d*]isoxazol-5-yl)but-3-ynyl]oxazolidin-2-one (29). 5-Iodo-3-methoxy-7-methylbenzo[*d*]isoxazole (**27**) (3.405 g, 11.78 mmol) and 3-but-3-ynyl-1,3-oxazolidine-2-one (**28**) (1.485 g, 10.68 mmol) were dissolved in THF (25 mL) at room temperature. Triethylamine (3.8 mL, 27 mmol), $Pd(PPh_3)_2Cl_2$ (386 mg, 0.539 mmol), and Cu(I)I (207 mg, 1.06 mmol) were added. After the resulting mixture was stirred at room temperature for 26 h, water (40 mL) was added to quench the reaction. The mixture was concentrated to remove the organic solvents, and the residue was extracted with ethyl acetate (3 × 50 mL). The combined organic solution was washed with brine (150 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (60 g), eluting with EtOAc−hexanes (0−50%) to afford the product **29** (2.816 g) as a brown solid in 88% yield: mp 94−95 °C. IR (KBr) 2943, 2238, 1751, 1613, 1549, 1497, 1426, 1390, 1312, 1268, 1223, 1091, 1042, 971, 909, 763, 693 cm^{-1}; ^1H NMR δ 7.45 (s, 1 H), 7.30 (s, 1 H), 4.34 (t, J = 8.0 Hz, 2 H), 4.13 (s, 3 H), 3.74 (t, J = 8.0 Hz, 2 H), 3.52 (t, J = 6.6 Hz, 2 H), 2.68 (t, J = 6.6 Hz, 2 H), 2.44 (s, 3 H); ^{13}C NMR δ 166.92, 162.54, 158.27, 133.99, 121.36, 121.04, 118.33, 113.67, 85.64, 81.46, 61.82, 57.35, 45.03, 43.18, 18.85, 14.37; ESIMS *m*/*z* (rel intensity) 300.93 (MH^+, 44), 600.72 ($2M+H^+$, 100). Anal. Calcd for ($C_{16}H_{16}N_2O_4$) C, H, N.

3-[4-(3-Methoxy-7-methylbenzo[*d*]isoxazol-5-yl)-4-(tributylstannanyl)but-3-enyl]oxazolidin-2-one (30). The alkyne **29** (2.746 g, 9.14 mmol) was dissolved in THF (420 mL), and then tetrakis(triphenylphosphine)palladium (108 mg, 0.092 mmol) was added. The mixture was cooled to 0 °C and degassed by gently bubbling argon for 20 min, and then tributyltin hydride (3.8 mL, 13.7 mmol) was added dropwise over 90 min. The mixture was stirred at 0 °C for 30 min and at room temperature for 160 min and then concentrated to yield a residue. The residue was purified by column chromatography on silica gel (100 g), using hexanes and EtOAc−hexanes (0−30%) to afford the product **30** (4.287 g) as an oil in 79% yield and **31** (445 mg) as oil in 8% yield. Spectral data of **30**: IR (KBr) δ 2952, 2925, 2851, 1756, 1546, 1492, 1224, 1358, 1305, 1265, 1216, 1173, 1097, 1043, 961, 910, 878, 763, 693 cm^{-1}; ^1H NMR δ 6.90 (s, 1 H), 6.84 (s, 1 H), 5.75 (t, J = 6.9 Hz, 1 H), 4.22 (t, J = 7.8 Hz, 2 H), 4.14 (s, 3 H), 3.30 (t, J = 7.8 Hz, 2 H), 3.27 (t, J = 7.2 Hz, 2 H), 2.46 (s, 3 H), 2.30−2.23 (m, 2 H), 1.45−1.35 (m, 6 H), 1.32−1.17 (m, 6 H), 0.87−0.79 (m, 9 H); ^{13}C NMR δ 167.23, 158.27, 148.31, 140.14, 137.74, 130.28, 120.53, 114.66, 113.63, 61.51, 57.28, 44.27, 43.84, 28.92, 28.04, 27.24, 14.72, 13.63, 9.92; ESIMS *m*/*z* (rel intensity) 610.84 (MNa^+, 25), 613.06 (MNa^+, 33), 614.93 (MNa^+, 40). Anal. ($C_{28}H_{44}N_2O_4Sn$) C, H, N, Sn.

3-[4-(3-Methoxy-7-methylbenzo[*d*]isoxazol-5-yl)-3-(tributylstannanyl)but-3-enyl]oxazolidin-2-one (31). Compound **31** was obtained as described above: IR (KBr) 2956, 2925, 2871, 2853, 1756, 1614, 1548, 1490, 1457, 1424, 1389, 1307, 1273, 1220, 1101, 1046, 961, 912, 807, 764, 697 cm^{-1}; ^1H NMR δ 7.19 (s, 1 H), 7.15 (s, 1 H), 6.69 (s, 1 H), 4.13 (t, J = 7.5−8.4 Hz, 2 H), 4.07 (s, 3 H), 3.31 (t, J = 7.8−8.4 Hz, 2 H), 3.24 (t, J = 7.5−8.1 Hz, 2 H), 2.66 (t, J = 8.4 Hz, 2 H), 2.42 (s, 3 H), 1.60−1.42 (m, 6 H), 1.36−1.21 (m, 6 H), 0.99−0.90 (m, 3 H), 0.85 (t, J = 7.2 Hz, 6 H); ^{13}C NMR 167.09, 161.85, 157.93, 144.73, 140.24, 133.28, 131.55, 120.44, 117.01, 113.38, 61.38, 57.09, 44.16, 44.07, 31.65, 28.90, 27.16, 14.36, 13.50, 9.79; ESIMS *m*/*z* (rel intensity) 610.98 (MNa^+, 53), 613.17 (MNa^+, 89), 615.07 (MNa^+, 100). Anal. ($C_{28}H_{44}N_2O_4Sn$) C, H, N, Sn.

RT Inhibition Assay. Analysis of the effects of the compounds on recombinant HIV-1 RT enzyme (p66/51 dimer) was performed as previously described.[33] Briefly, inhibition of purified recombinant reverse transcriptase enzyme was measured by determining the inhibition of the incorporation of [^{32}P]GTP into poly(rC)/oligo-(dG)(rCdG) homopolymer template primers.[32]

In Vitro Antiviral Assays. Evaluation of the antiviral activity of compounds against HIV-1_{RF} infection in CEM-SS cells was performed using the MTS cytoprotection assay as previously described.[33] Evaluation of the antiviral activity of the compounds against HIV-1 strain III_B and HIV-2 strain (ROD) in MT-4 cells was performed using the MTT assay as previously described.[16,34]

In Vitro Hydrolytic Stability Study in Rat Plasma. The alkenyldiarylmethanes **7**−**10** and **15**−**18** (1,1-diphenylethylene or benzophenone as internal standard) were tested for their hydrolytic stability, utilizing rat plasma in vitro using methods as previously described.[16]

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Supporting Information Available: Elemental analysis results of compounds **7**−**11**, **15**−**18**, and **29**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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