Synthesis and Anti-HIV Activity of New Metabolically Stable Alkenyldiarylmethane Non-Nucleoside Reverse Transcriptase Inhibitors Incorporating *N*-Methoxy Imidoyl Halide and 1,2,4-Oxadiazole Systems

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The alkenyldiarylmethanes (ADAMs) are a unique class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are capable of inhibiting HIV-1 reverse transcriptase (RT) through an allosteric mechanism. However, the potential usefulness of the ADAMs is limited by the presence of metabolically labile methyl ester moieties that are hydrolyzed by nonspecific esterases present in blood plasma, resulting in the formation of the inactive carboxylic acid metabolites. Therefore, to discover metabolically stable ADAMs, the design and synthesis of a new class of ADAMs with *N*-methoxy imidoyl halide and 1,2,4-oxadiazole systems were attempted. The resulting new ADAM **6** displayed enhanced metabolic stability in rat plasma ($t_{1/2}$ = 61 h) along with the ability to inhibit HIV-1 reverse transcriptase and the cytopathic effect of HIV-1_{RF} and HIV-1_{IIIB} at submicromolar concentrations.

Introduction

The human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), was identified in the early 1980s. The AIDS epidemic has spread throughout the world and today an estimated 39.5 million people are living with HIV/AIDS.[1] The potent therapeutic agents that have been developed to combat the progression of AIDS are based on four classes of drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion inhibitors (enfuvirtide). Treatment with combinations of these antiviral agents that target the viral enzymes reverse transcriptase (RT) and protease, termed highly active antireteroviral therapy (HAART), has been more successful than monotherapeutic regimens.[2] There are, however, problems with drug toxicity and multidrug resistance after prolonged therapy. NNRTIs have the advantage that they are minimally toxic; however, there are significant problems with the development of NNRTI resistance. Therefore, the development of new NNRTIs with less severe side effects and more favorable drug resistance profiles will be essential to the future management of HIV infection.

Among NNRTIs, the alkenyldiarylmethanes (ADAMs) are a relatively new class of inhibitors that are active at submicromolar concentrations.[3−14] In addition, ADAMs have displayed synergistic activity with AZT and enhanced activity when tested against AZT-resistant strains of HIV-1.[4,5,7,8] Certain ADAMs, for example, compounds **1** and **2**, have been found to inhibit HIV-1 RT and the cytopathic effect of HIV-1 in cell culture. ADAM **1** inhibited HIV-1 RT, with an IC_{50} value of <1.0 μM and displayed an EC_{50} value of 1.0 μM for inhibition of HIV-1_{IIIB} in MT-4 cells[11,13] (Table 1). The more recently synthesized ADAM **2** features an oxazolone replacement for one of the methyl esters and an adjacent methyl ether present in **1**.[3] ADAM **2** showed very potent anti-HIV-1 activity, with EC_{50} values of 0.03 μM (HIV-1_{RF} in CEM-SS cells) and 0.09 μM (HIV-1_{IIIB} in MT-4 cells). Also, ADAM **2** was active against HIV-1 RT, with an IC_{50} = 0.02 μM, establishing it as the most potent RT inhibitor among ADAM analogues. However, the methyl ester moieties of the ADAMs are hydrolyzed to biologically inactive acids by nonspecific esterases present in blood plasma, which is unfavorable for their potential therapeutic use. Therefore, we have focused on searching for hydrolytically stable and pharmacologically active bioisosteres of the methyl esters on the ADAM phenyl rings and side chain.

Results and Discussion

Design. The *N*-methoxy imidoyl fluoride and 3-methyl-1,2,4-oxadiazol-5-yl systems have been previously reported as metabolically stable bioisosteres for methyl esters in azabicyclic ring systems.[15−17] Examination of electrostatic potential maps revealed broad similarities between a methyl ester and these bioisosteres. These results encouraged the design of new ADAM analogues in which the methyl esters were replaced by *N*-methoxy imidoyl fluoride and 3-methyl-1,2,4-oxadiazol-5-yl bioisosteres.

We envisaged new ADAMs **3** and **6** as metabolically stable analogues of ADAM **2** with potent anti-HIV-1 activity. In these ADAMs, the methyl esters on the phenyl rings and side chains of **1** and **2** are replaced with *N*-methoxy imidoyl fluoride or 3-methyl-1,2,4-oxadiazol-5-yl systems (Chart 1). In addition, the new ADAMs **4** and **5** were proposed to examine the effect of halide size on anti-HIV activity. The synthesis of ADAM **7** was also planned to evaluate the effect of the *N*-methoxy imidoyl fluoride replacement on anti-HIV activity by direct comparison with the ADAM **2**.

Chemistry. Our previous work has already established a general and practical method to synthesize ADAMs using Pd-catalyzed reactions (Sonogashira reaction, hydrostannation, and Stille coupling; Scheme 1).[12−14] First, the synthesis of ADAM

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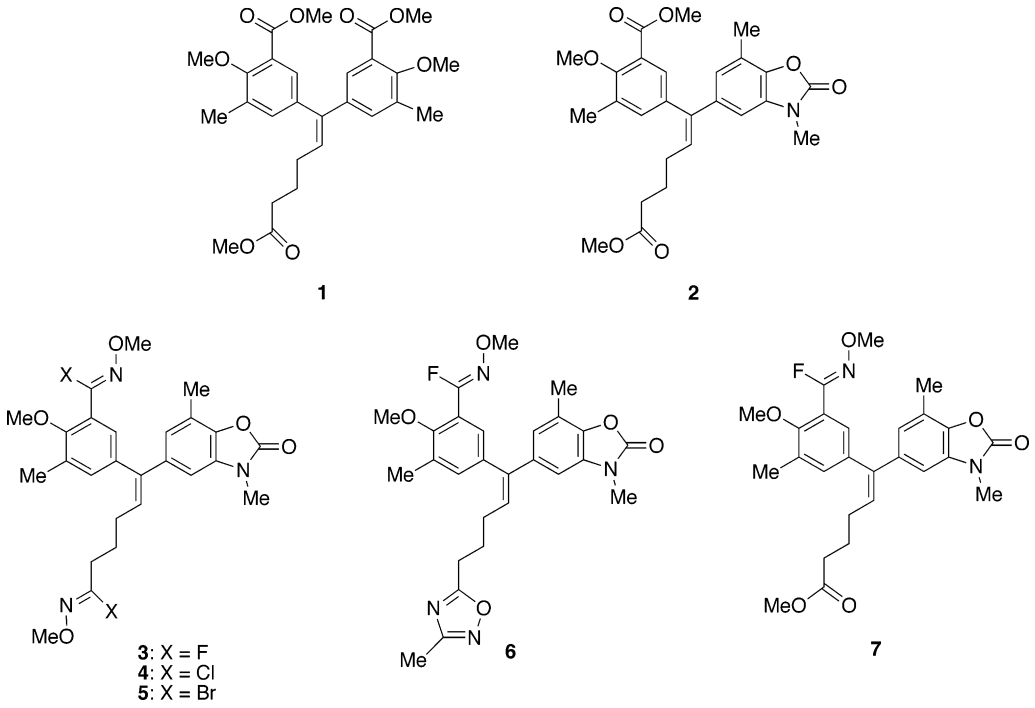
Table 1. Anti-HIV Activities, Cytotoxicities, and Metabolic Stabilities of ADAM Analogues[a]

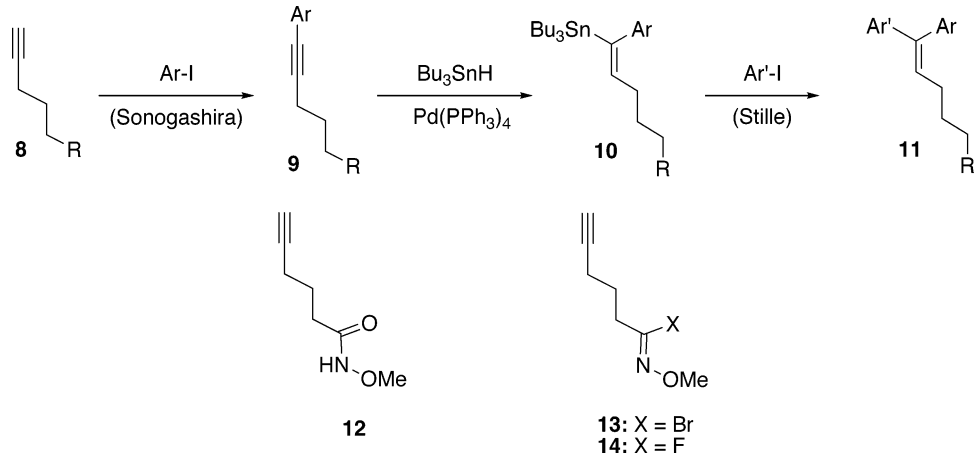
cmpd	IC_{50}[b] (μM)	EC_{50}[c] (μM)			CC_{50}[d] (μM)		
		HIV-1_{RF}	HIV-1_{IIIB}	HIV-2_{ROD}	CEM-SS cells	MT-4 cells	rat plasma $t_{1/2} \pm$ SD (min)
1	1.0	0.25	1.0	NA[e]	6.0	6.1	0.76 ± 0.04
2	0.02	0.02	0.09	NA[e]	5.1	16.86	1.30 ± 0.09
4	0.60	NA[e]	1.2	NA[e]	1.3	3.9	4970 ± 795
5[f]	0.85	NA[e]	6.3	NA[e]	2.1	13.3	156 ± 21
6	0.67	0.7	0.24	NA[e]	2.9	12.4	3641 ± 14.1
7	0.55	0.5	0.29	NA[e]	3.9	21.0	9.2 ± 1.5
22	>100	NA[e]	NA[e]	NA[e]	5.2	16.8	NT[g]
24	>100	NA[e]	NA[e]	NA[e]	5.4	18.4	NT[g]

[a] All data represent mean values of at least two separate experiments. [b] Inhibitory activity versus HIV-1 reverse transcriptase with poly(rC).oligo(dG) as the template primer. [c] EC_{50} is the 50% effective concentration for inhibition of cytopathicity of HIV-1_{RF} in CEM-SS cells, HIV-1_{IIIB} in MT-4 cells, or HIV-2_{ROD} in MT-4 cells. [d] CC_{50} is the 50% cytotoxic concentration for the mock-infected CEM-SS cell or MT-4 cells. [e] Not active. [f] A mixture (1:1) of *E*- and *Z*-isomers. [g] Not tested.

Chart 1

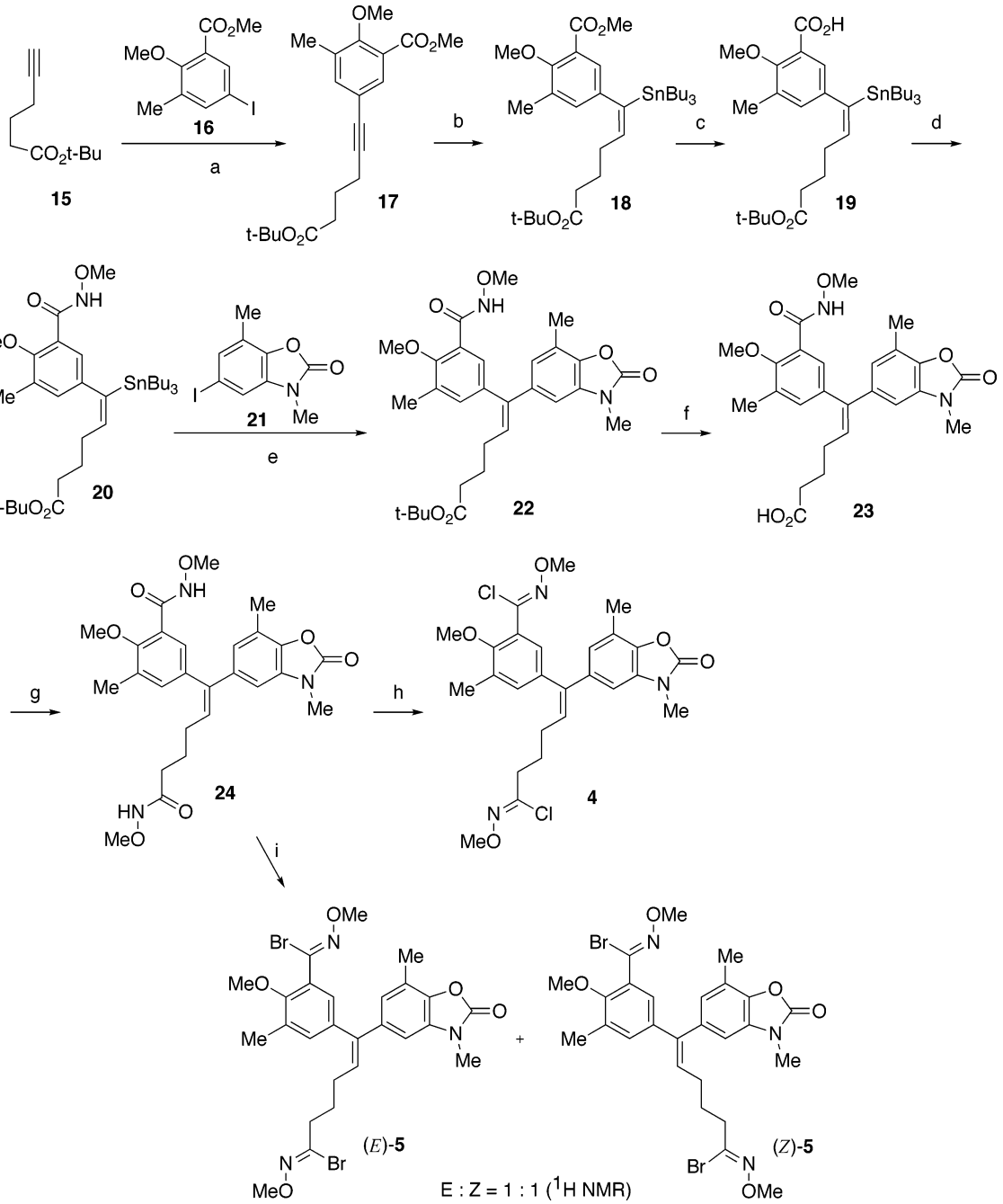


Scheme 1



3 was undertaken. The *N*-methoxy imidoyl fluoride **14** was a key intermediate corresponding to the general intermediate **8** in Scheme 1. To prepare intermediate **14**, two previously reported methods were applied.[17] One was the fluorination of *N*-methoxyamide **12** with bis(diethyl)aminosulfur trifluoride (DAST)[17,18] or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),[19] and the other was the replacement reaction of *N*-methoxy imidoyl bromide **13** with calcium fluoride-supported alkali metal fluorides ($KF-CaF_2$ and $CsF-CaF_2$).[17,20] However, these reactions afforded complex mixtures and attempts to synthesize imidoyl fluoride **14** were all unsuccessful. The difficulty of the synthesis can probably be attributed to the low nucleophilicity and high Lewis basicity of fluoride ions, which are capable of abstracting the α-hydrogens of imidoyl groups. The

Scheme 2[a]



[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, TEA, THF, room temperature, 12 h; (b) Bu_3SnH, $Pd(PPh_3)_4$, THF, room temperature, 2 h; (c) LiOH, dioxane−H_2O (6:1), 60 °C, 22 h; (d) H_2NOMe, EDCI, DMAP, CH_2Cl_2, room temperature, 15 h; (e) $Pd(PPh_3)_4$, CuI, CsF, DMF, 60 °C, 0.5 h; (f) TFA−CH_2Cl_2 (1:1), 0 °C, 3 h; (g) H_2NOMe, EDCI, DMAP, CH_2Cl_2, room temperature, 24 h; (h) PPh_3, CCl_4, CH_3CN, reflux 3.5 h; (i) PPh_3, CBr_4, CH_3CN, reflux, 2 h.

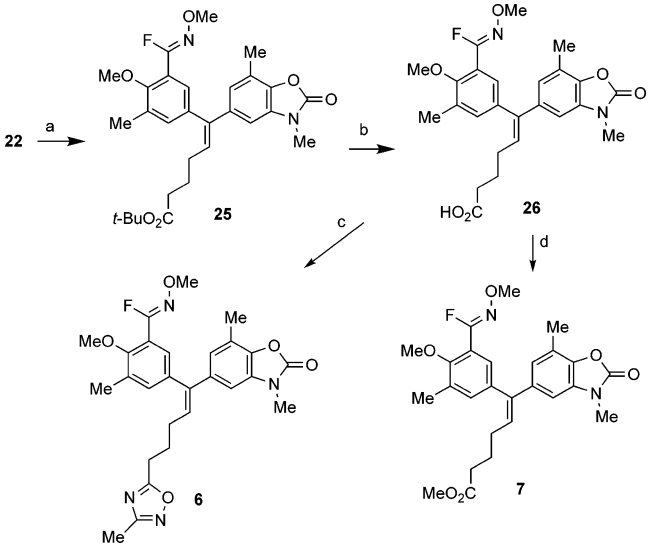
difficulties encountered in the synthesis of ADAM **3** led us to focus on the imidoyl fluorides **6** and **7**, as well as the higher molecular weight halides **4** and **5**.

ADAMs **4** and **5** were synthesized as outlined in Scheme 2. The key functional groups, *N*-methoxy imidoyl chloride and bromide, were introduced after the construction of the ADAM framework to avoid the risk of Pd-catalyzed reactions with the imidoyl halides. As a related example, Chang et al. have reported that an *N*-methoxy imidoyl bromide was successfully employed as an efficient coupling partner in the Pd-catalyzed Stille coupling reaction with various organotin compounds.[21]

The syntheses of intermediates **16** and **21**, which are the precursors of the two aromatic rings of ADAMs **4** and **5**, have been previously reported.[12,13] The Sonogashira coupling of starting materials **15** with **16** and the hydrostannation of **17** were carried out on a large scale. Chemoselective cleavage of methyl ester **18** with LiOH in dioxane−H_2O afforded the corresponding carboxylic acid **19**.[22] Subsequent EDCI-promoted coupling of **19** with methoxyamine gave *N*-methoxyamide **20**.

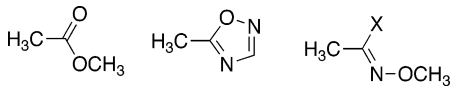
In the next step, the Stille coupling of **20** with **21**[13] was attempted using the reaction conditions previously described by Mee et al.[23] The significant feature of their conditions is that addition of a catalytic amount of cuprous iodide accelerates the reaction rate in a highly polar solvent such as DMF. However, in the case of the reaction of **20** with **21**,[13] no reaction was observed, probably due to the chelation of the *N*-

Scheme 3[a]



[a] Reagents and conditions: (a) DAST, CH_2Cl_2, 0 °C, 0.5 h; (b) TMOSTf, TEA, dioxane, room temperature, 2 h; (c) acetamide oxime, TBTU, HOBt, DIPEA, DMF, room temperature, 0.5 h, then heated at 110 °C, 3 h; (d) $TMSCHN_2$, toluene−MeOH (2:1), room temperature.

Chart 2



27 **28**

29, X = F
30, X = Cl
31, X = Br

methoxyamide group of **20** and the neighboring methoxy group to Pd^{II}-complexes. In this case, the *N*-methoxyamide group could be deprotonated by cesium fluoride and act as a ligand for palladium.[24] To improve this reaction, 1.2 equiv of cuprous iodide were used. Surprisingly, addition of a large amount of cuprous iodide afforded the coupling product **22** quantitatively.

The *tert*-butyl protecting group of **22** was removed with trifluoroacetic acid to give carboxylic acid **23**. EDCI coupling of **23** with methoxyamine provided di-*N*-methoxyamide **24**. Finally, chlorination of **24** with PPh_3-CCl_4 afforded ADAM **4** in 71% yield. Similarly, bromination of **24** with PPh_3-CBr_4 was attempted. However, the reaction unfortunately afforded a nearly equimolar mixture of mixture of *Z* and *E* isomers of ADAM **5** in 75% yield. The isomeric mixture was tested for anti-HIV activity because separation by column chromatography was unsuccessful. The isomerization of the olefin was probably caused by Br_2 or Br^+, which was generated from the decomposition of $[Br_3C-PPh_3]^+Br^-$ complex in refluxing acetonitrile.

The syntheses of ADAMs **6** and **7** were performed according to Scheme 3. Fluorination of **22** with DAST afforded imidoyl fluoride **25**. Cleavage of the *tert*-butyl ester of **25** was achieved using $TMSOTf-Et_3N$ to give carboxylic acid **26**.[25] ADAM **6**, incorporating the 3-methyl-1,2,4-oxadiazole system, was synthesized in 46% yield from carboxylic acid **26** and acetamide oxime using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU).[26] Also, carboxylic acid **26** was converted into ADAM **7** with (trimethylsilyl)diazomethane in 82% yield.

Biological Results and Discussion. Compounds **4**−**7**, **22**, and **24** are a new family of ADAMs characterized by the presence of *N*-methoxy imidoyl halide, *N*-methoxyamide, and 3-methyl-1,2,4-oxadiazole moieties. To visualize the size and electronic character of these methyl ester replacements, compounds **27**−**31** (Chart 2) were modeled using Sybyl 7.1. The models were constructed and then energy minimized using the MMFF94s force field and MMFF94 charges, and the electrostatic potentials were mapped onto the Connolly surfaces. The results displayed in Figure 1 document a significant variation in the sizes and electronic characters of these replacements relative to a methyl ester itself, but in spite of this fact, the potencies of ADAMs **4**, **5**, **6**, and **7** as inhibitors of HIV-1 reverse transcriptase are all very close, with submicromolar IC_{50} values. This may reflect the well-known ability of the flexible NNRTI binding pocket to mold itself to the shape of the inhibitor.

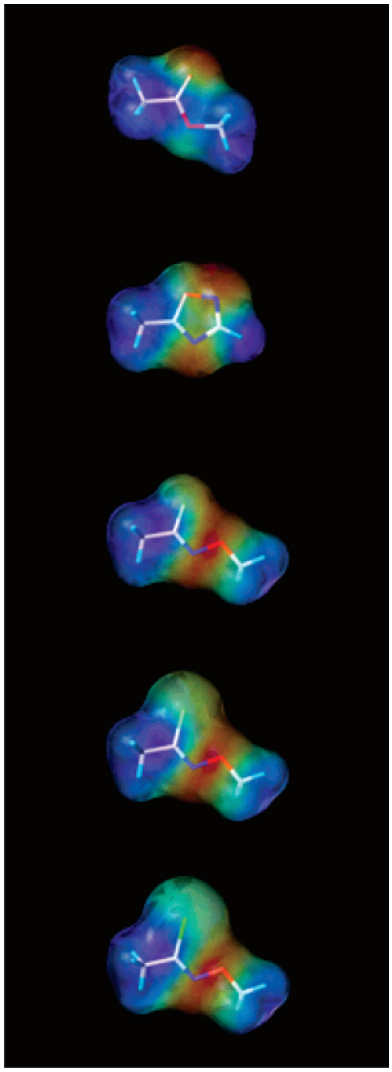


Figure 1. Electrostatic potentials mapped onto Connolly surfaces of models **27** (top), **28**, **29**, **30**, and **31** (bottom). Red, electronegative; blue, electropositive.

In the cellular assays for inhibition of the cytopathic effect of the virus, ADAMs **6** and **7** displayed anti-$HIV\text{-}1_{RF}$ activity in the submicromolar range. Also, the ADAMs **4**−**7** produced EC_{50} values versus $HIV\text{-}1_{IIIB}$ between 0.24 and 6.3 μM. Comparison between ADAMs **2** and **7** indicates that the *N*-methoxy imidoyl fluoride system retained the desired anti-HIV activity, although the potency of **7** was somewhat lower, both with regard to RT inhibition as well as prevention of the cytopathic effect of the virus. However, ADAMs **22** and **24**, having *N*-methoxyamide groups, were inactive both in the enzymatic and in the cellular tests. Similar to other known

NNRTIs, all of the ADAMs in this series were inactive against HIV-2. Regarding metabolic stabilities in rat plasma, the half-lives of ADAMs **4**−**6**, in which all of the esters were replaced to *N*-methoxy imidoyl halide or 3-methyl-1,2,4-oxadiazole moieties, increased significantly in comparison with the previously reported ADAMs **1** and **2**.

According to previous reports, (*Z*)-*N*-methoxy imidoyl halides isomerize to the *E*-isomers in HCl-benzene at 40 °C within a few days.[27] However, attempted thermal isomerization of the *Z*-isomers in benzene in the absence of HCl at 50 °C failed to result in any significant isomerization within a period of 1 week.[27] Also, in polar protic solvents at elevated temperatures, imidoyl halides hydrolyze to the corresponding *N*-methoxy-amides rather than undergoing isomerization.[28] Johnson and Cornell previously reported that imidoyl halides hydrolyze thermally at >80 °C in dioxane−water at pH 7.[28] In the present case, neither the NMR spectra of the imidoyl halides nor the HPLC traces recorded during the hydrolysis studies in rat plasma provided any evidence for isomerization, indicating that they are stable under the mild, neutral assay conditions.

The overall results revealed that *N*-methoxy imidoyl halide, especially *N*-methoxy imidoyl fluoride, and 3-methyl-1,2,4-oxadiazole systems were metabolically stable, biologically active bioisosteres for methyl esters in the ADAM series. In particular, ADAM **6** is the best lead compound in this series, having a 2801-fold increase in plasma half-life and maintaining anti-HIV activities with submicromolar EC_{50} values. Future studies will be directed toward modifying the heterocycle on the side chain of ADAM **6**.

Experimental Section

Unless noted otherwise, ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent and internal standard at 300 and 75 MHz, respectively. ^{19}F NMR spectra were obtained at 282 MHz in $CDCl_3$, and chemical shifts are reported in δ values, relative to CF_3CO_2H (external standard) at δ 0.00 ppm. IR spectra were recorded using a Perkin-Elmer 1600 series FT-IR. Flash chromatography was performed with 230−400 mesh silica gel and TLC was carried out using Baker-flex silica gel IB2-F plates of 0.25 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 065K7555) was obtained from Sigma Chemical Co., St. Louis, MO. Microanalyses were performed at the Purdue Microanalysis Laboratory. All yields refer to yields of isolated compounds.

***tert*-Butyl 5-Hexynate (15).**[29] Di-*tert*-butyl-dicarbonate (29.2 g, 134 mmol) was added portionwise over 1 h to a solution of 5-hexynoic acid (5.00 g, 44.6 mmol) and 4-dimethylaminopyridine (0.550 g, 4.46 mmol) in *t*-BuOH (100 mL), and the reaction mixture was stirred for 2 h at room temperature. The mixture was evaporated and diluted with ethyl acetate (80 mL). The organic solvent was washed with 5% HCl (2 × 30 mL), 5% aq $NaHCO_3$ (2 × 30 mL), brine (2 × 20 mL), and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using an ethyl acetate−hexanes gradient (0−10%) to afford the product **15** (4.65 g, 62%) as a colorless oil: IR (neat) 3306, 1730, 1149 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (t, J = 7.2 Hz, 2 H) 2.25 (dt, J = 7.2, 2.4 Hz, 2 H), 1.94 (t, J = 2.4 Hz, 1 H), 1.78 (q, J = 7.2 Hz, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.31, 83.38, 80.16, 68.86, 34.11, 28.00, 27.79, 23.72, 21.36, 17.37; GC-CIMS *m*/*z* (rel intensity) 169 (3, MH^+), 113 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, H.

Methyl 5-(5-*tert*-Butoxycarbonyl-pent-1-ynyl)-2-methoxy-3-methylbenzonate (17). A solution of alkyne **15** (1.648 g, 9.800 mmol), iodide **16** (2.500 g, 8.167 mmol), cuprous iodide (0.156 g, 0.817 mmol), and triethylamine (2.30 mL, 16.3 mmol) in THF (50 mL) was cooled to 0 °C and degassed for 10 min with argon. $PdCl_2(PPh_3)_2$ (0.585 g, 0.817 mmol) was added to the solution. After stirring for 12 h at room temperature under argon, the mixture was evaporated and diluted with ethyl acetate (15 mL). The mixture was filtered through a small pad of silica gel, concentrated, and purified by column chromatography on silica gel using an ethyl acetate−hexanes gradient (2−5%) to afford the product **17** (2.23 g, 79%) as a pale yellow oil: IR (Neat) 2973, 1731, 1256, 1215, 1148 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 2.0 Hz, 1 H), 7.34 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 2.34−2.25 (m, 4 H), 2.25 (s, 3 H), 1.84 (q, J = 7.2 Hz, 2 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.43, 166.13, 157.80, 137.77, 132.84, 132.31, 124.41, 119.13, 88.99, 80.24, 79.91, 61.51, 52.16, 34.34, 28.04, 23.99, 18.70, 15.83; ESIMS *m*/*z* (rel intensity) 369 (100, MNa^+). Anal. Calcd for $C_{20}H_{26}O_5$: C, H.

(*E*)-Methyl 5-(6-*tert*-Butoxy-6-oxo-1-(tributylstannyl)hex-1-enyl)-2-methoxy-3-methylbenzoate (18). A solution of alkyne **17** (2.55 g, 7.36 mmol) in THF (90 mL) was cooled to 0 °C and degassed for 10 min with argon, and $Pd(PPh_3)_4$ (0.850 g, 0.736 mmol) was added. Tributyltin hydride (2.93 mL, 11.0 mmol) was added dropwise to the mixture at room temperature and the reaction mixture was stirred for 2 h under argon. The mixture was evaporated and diluted with ethyl acetate (50 mL). The mixture was filtered through a small pad of silica gel, concentrated, and purified by column chromatography on silica gel using an ethyl acetate−hexanes gradient (2−4%) to afford the product **18** (4.15 g, 89%) as a colorless oil: IR (neat) 2928, 2871, 1732, 1148, 1014 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 2.0 Hz, 1 H), 6.85 (d, J = 2.0 Hz, 1 H), 5.70 (t, J = 6.6 Hz, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 2.26 (s, 3 H), 2.13 (t, J = 7.3 Hz, 2 H), 1.98−2.08 (m, 2 H), 1.36 (s, 9 H), 1.16−1.68 (m, 14 H), 0.83 (t, J = 7.4 Hz, 9 H), 0.71−0.96 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.89, 166.83, 155.68, 144.69, 141.52, 140.13, 133.63, 132.09, 127.39, 123.81, 77.86, 61.37, 51.92, 34.98, 29.31, 28.91, 27.94, 27.21, 25.11, 16.04, 13.60, 9.87; ESIMS *m*/*z* (rel intensity) 657/659/661 (41/78/100, MNa^+). Anal. Calcd for $C_{32}H_{54}O_5Sn$: C, H.

(*E*)-5-(6-*tert*-Butoxy-6-oxo-1-(tributylstannyl)hex-1-enyl)-2-methoxy-3-methylbenzoic Acid (19). Lithium hydroxide monohydrate (0.328 g, 7.86 mmol) was added to a solution of methyl ester **18** (4.152 g, 6.513 mmol) in dioxane−H_2O (6:1, 60 mL). The reaction mixture was stirred for 22 h at 60 °C. The mixture was concentrated in vacuo, acidified with 5% HCl, and diluted with water (60 mL). The mixture was extracted with ethyl acetate (2 × 40 mL). The combined organic solvent was washed with brine (2 × 40 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel using 30% ethyl acetate−hexanes to give the product **19** (2.56 g, 63.0%) as an oil: IR (neat) 2967, 2928, 1732, 1696, 1255, 1149 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1 H), 7.48 (d, J = 2.1 Hz, 1 H), 6.94 (d, J = 2.1 Hz, 1 H), 5.72 (t, J = 7.4 Hz, 1 H), 3.89 (s, 3 H), 2.31 (s, 3 H), 2.11 (t, J = 7.4 Hz, 2 H), 2.00 (t, J = 7.4 Hz, 2 H), 1.61 (quint, J = 7.4 Hz, 2 H), 1.36 (s, 9 H), 1.14−1.46 (m, 12 H), 0.83 (t, J = 7.2 Hz, 9 H), 0.71−0.97 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.89, 167.15, 155.19, 144.30, 141.87, 141.73, 135.23, 131.12, 128.65, 121.48, 79.93, 62.00, 34.95, 29.35, 28.89, 27.94, 26.99, 25.04, 16.47, 13.60, 9.90; ESIMS *m*/*z* (rel intensity) 643/645/647 (15/28/35, MNa^+); negative ion ESIMS *m*/*z* (rel intensity) 619/621/623 (39/76/100, $M - H^+$). Anal. Calcd for $C_{31}H_{52}O_5Sn$: C, H.

(*E*)-*tert*-Butyl 6-(4-Methoxy-3-(methoxycarbamoyl)-5-methylphenyl)-6-(tributylstannyl)hex-5-enoate (20). EDCI (2.26 g, 11.8 mmol) was added to a mixture of carboxylic acid **19** (2.45 g, 3.92 mmol), methoxyamine hydrochloride (0.983 g, 11.8 mmol), 4-dimethylaminopyridine (0.240 g, 1.96 mmol), and triethylamine (2.20 mL, 15.7 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for 15 h at room temperature. After the reaction was complete, the mixture was diluted with ethyl acetate (100 mL). The organic solution was washed with 5% HCl (2 × 30 mL), 5% aq $NaHCO_3$ (2 × 30 mL), and brine (2 × 30 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using 30% ethyl acetate−hexanes to give the product **20** (1.56 g, 61%) as an oil:

IR (neat) 3340, 1730, 1683, 1464, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (br s, 1 H), 7.37 (d, J = 2.3 Hz, 1 H), 6.82 (d, J = 2.3 Hz, 1 H), 5.70 (t, J = 7.4 Hz, 1 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 2.26 (s, 3 H), 2.12 (t, J = 7.4 Hz, 2 H), 2.10 (q, J = 7.4 Hz, 2 H), 1.60 (quint, J = 7.4 Hz, 2 H), 1.36 (s, 9 H), 1.14−1.46 (m, 12 H), 0.83 (t, J = 7.2 Hz, 9 H), 0.71−0.95 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.99, 164.37, 153.38, 144.62, 141.56, 133.37, 130.85, 127.23, 124.03, 79.93, 64.31, 61.37, 34.97, 29.36, 28.90, 27.95, 27.20, 25.08, 15.95, 13.62, 9.89; ESIMS *m*/*z* (rel intensity) 672/674/676 (42/94/100, MNa^+). Anal. Calcd for $C_{32}H_{55}NO_5Sn$: C, H, N.

(*E*)-*tert*-Butyl 6-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(4-methoxy-3-(methoxycarbamoyl)-5-methylphenyl)-hex-5-enoate (22). A mixture of aryl iodide **21**[13] (56 mg, 0.188 mmol), organostannane **20** (147 mg, 0.225 mmol), and cesium fluoride (104 mg, 0.675 mmol) in DMF (5 mL) was cooled to 0 °C and degassed for 10 min with argon. $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) and cuprous iodide (43 mg, 0.255 mmol) were added to the mixture. The reaction mixture was stirred for 0.5 h at 60 °C under argon. After the reaction was complete, the reaction mixture was diluted with dichloromethane (20 mL) and water (10 mL). After vigorous shaking, the mixture was filtered through celite with ethyl acetate (80 mL). The organic layer was separated, washed with brine (3 × 30 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel using 30% ethyl acetate−hexanes to give the product **22** (100 mg, 100%) as an oil: IR (neat) 3308, 2975, 2934, 1777, 1726, 1674, 1470, 1151, 1001, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (br s, 1 H), 7.61 (d, J = 1.2 Hz, 1 H), 7.05 (d, J = 1.2 Hz, 1 H), 6.70 (d, J = 1.0 Hz, 1 H), 6.55 (d, J = 1.0 Hz, 1 H), 5.92 (t, J = 7.5 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.32 (s, 3 H), 2.29 (s, 6 H), 2.20 (t, J = 7.5 Hz, 2 H), 2.08 (q, J = 7.5 Hz, 2 H), 1.70 (quint, J = 7.5 Hz, 2 H), 1.37 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.81, 164.10, 155.15, 154.97, 140.59, 140.40, 138.76, 136.33, 135.98, 131.54, 131.16, 129.98, 124.52, 123.62, 119.77, 104.60, 80.11, 64.33, 61.37, 34.95, 29.14, 28.13, 27.93, 25.13, 16.00, 14.36; ESIMS *m*/*z* (rel intensity) 547 (100, MNa^+); negative ion ESIMS *m*/*z* (rel intensity) 523 [100, $(M - H^+)^-$]. Anal. Calcd for $C_{29}H_{36}NO_7$: C, H, N.

(*E*)-6-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(4-methoxy-3-(methoxycarbamoyl)-5-methylphenyl)hex-5-enoic Acid (23). Trifluoroacetic acid (2 mL) was added to a solution of the *tert*-butyl ester **22** (99 mg, 0.189 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 3 h at 0 °C. After the reaction was complete, the solvent was evaporated at room temperature and the residue was diluted with ethyl acetate (40 mL). The organic solution was washed with brine (2 × 20 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using 75% ethyl acetate−hexanes to give the product **23** (71 mg, 80%) as an oil: IR (neat) 3271, 1771, 1645, 1471, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1 H), 8.65 (br s, 1 H), 7.63 (d, J = 1.6 Hz, 1 H), 7.04 (d, J = 1.6 Hz, 1 H), 6.69 (d, J = 1.0 Hz, 1 H), 6.56 (d, J = 1.0 Hz, 1 H), 5.92 (t, J = 7.4 Hz, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.31 (s, 3 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.28 (s, 6 H), 2.12 (q, J = 7.4 Hz, 2 H), 1.76 (quint, J = 7.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.82, 164.12, 155.09, 154.95, 140.74, 140.33, 138.62, 136.24, 136.05, 131.57, 131.07, 129.95, 129.61, 124.19, 123.55, 119.70, 104.55, 64.24, 61.31, 33.18, 28.84, 28.05, 24.55, 15.90, 14.26; ESIMS *m*/*z* (rel intensity) 491 (100, MNa^+); negative ion ESIMS *m*/*z* (rel intensity) 467 [100, $(M - H^+)^-$]. Anal. Calcd for $C_{25}H_{28}N_2O_7$: C, H, N.

(*E*)-5-(1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(methoxyamino)-6-oxohex-1-enyl)-*N*,2-dimethoxy-3-methylbenzamide (24). EDCI (58 mg, 0.304 mmol) was added to a solution of carboxylic acid **23** (71 mg, 0.152 mmol), methoxyamine hydrochloride (25 mg, 0.304 mmol), 4-dimethylaminopyridine (4 mg, 0.030 mmol), and triethylamine (0.06 mL, 0.456 mmol) in dichloromethane (4 mL). The reaction mixture was stirred for 24 h at room temperature. After the reaction was complete, the mixture was diluted with ethyl acetate (40 mL). The organic solution was washed with 2% HCl (2 × 15 mL), 5% aq $NaHCO_3$ (2 × 15 mL), and brine (2 × 15 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using 3% methanol−ethyl acetate to give the product **24** (40 mg, 53%) as an oil: IR (neat) 3435, 1772, 1648, 1471, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.34 (br s, 1 H), 8.76 (br s, 1 H), 7.61 (s, 1 H), 7.02 (s, 1 H), 6.69 (s, 1 H), 6.56 (s, 1 H), 5.94 (t, J = 7.6 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 3.31 (s, 3 H), 2.28 (s, 6 H), 2.14−1.99 (m, 4 H), 1.73−1.87 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.40, 164.30, 155.25, 154.97, 140.65, 140.36, 138.60, 136.06, 135.93, 131.80, 131.12, 129.80, 129.59, 124.43, 123.56, 119.73, 104.58, 64.21, 63.90, 61.32, 32.31, 29.11, 28.10, 25.26, 15.97, 14.30; ESIMS *m*/*z* (rel intensity) 498 (100, MH^+), 520 (70, MNa^+); negative ion ESIMS *m*/*z* (rel intensity) 496 [86, $(M - H^+)^-$]. Anal. Calcd for $C_{26}H_{31}N_3O_7$: C, H, N.

(*Z*)-5-((1*E*,6*Z*)-6-Chloro-1-(3,7-dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(methoxyimino)hex-1-enyl)-*N*,2-dimethoxy-3-methylbenzimidoyl Chloride (4). Carbon tetrachloride (0.16 mL, 1.61 mmol) was added to a solution of di-*N*-methoxyamide **24** (40 mg, 0.080 mmol) and triphenylphosphine (84 mg, 0.322 mmol) in acetonitrile (5 mL). The reaction mixture was stirred for 0.5 h at room temperature and for 3.5 h at reflux. Additional triphenylphosphine (42 mg, 0.161 mol) and carbon tetrachloride (0.1 mL, 1.01 mmol) were added, and the mixture was stirred for 1 h at reflux. After the reaction was complete, the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel using 20% ethyl acetate−hexanes to give the product **4** (30 mg, 71%) as an oil: IR (neat) 2938, 1779, 1464, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 2.0 Hz, 1 H), 6.99 (d, J = 2.0 Hz, 1 H), 6.76 (d, J = 1.1 Hz, 1 H), 6.57 (d, J = 1.1 Hz, 1 H), 5.93 (t, J = 7.4 Hz, 1 H), 4.07 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.33 (s, 3 H), 2.47 (t, J = 7.4 Hz, 2 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.16 (q, J = 7.4 Hz, 2 H), 1.79 (quint, J = 7.4 Hz, 2 H); ESIMS *m*/*z* (rel intensity) 556/558/560 (100/65/11, MNa^+). Anal. Calcd for $C_{26}H_{29}Cl_2N_3O_5$: C, H, N.

Stereoisomeric Mixture of (*Z*)-5-((1*E*,6*Z*)-6-Bromo-1-(3,7-dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(methoxyimino)hex-1-enyl)-*N*,2-demethoxy-3-methylbenzimidoyl Bromide (*E*-5) and (*Z*)-5-((1*Z*,6*Z*)-6-Bromo-1-(3,7-dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(methoxyimino)hex-1-enyl)-*N*,2-demethoxy-3-methylbenzimidoyl Bromide (*Z*-5). Carbon tetrabromide (893 mg, 2.47 mmol) was added to a solution of di-*N*-methoxyamide **24** (123 mg, 0.247 mmol) and triphenylphosphine (342 mg, 1.24 mmol) in acetonitrile (15 mL). The reaction mixture was stirred for 0.5 h at room temperature and for 2 h at reflux. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel using 25% ethyl acetate−hexanes to give an equimolar mixture of *E* and *Z* isomers of ADAM **5** (115 mg, 75%) as an oil: IR (neat) 2936, 1778, 1757, 1640, 1469, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 2 H), 7.00 (s, 1 H), 6.97 (s, 1 H), 6.77 (s, 1 H), 6.71 (s, 1 H), 6.58 (s, 1 H), 6.52 (s, 1 H), 5.99 (t, J = 7.4 Hz, 1 H), 5.93 (t, J = 7.5 Hz, 1 H), 4.11 (s, 3 H), 4.09 (s, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 2.94−2.64 (m, 4 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.23 (s, 3 H), 2.22−2.05 (m, 4 H), 1.87−1.69 (m, 4 H); ESIMS *m*/*z* (rel intensity) 644/646/648 (47/100/49, MNa^+).

(*E*)-*tert*-Butyl 6-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(3-((*Z*)-fluoro(methoxyimino)methyl)-4-methoxy-5-methylphenyl)hex-5-enoate (25). (Diethylamino)sulfur trifluoride (0.07 mL, 0.510 mmol) was added to a solution of *N*-methoxyamide **22** (134 mg, 0.255 mmol) in dichloromethane (7 mL) at 0 °C under argon, and the mixture was stirred for 0.5 h. After quenching the reaction with 5% aq $NaHCO_3$, the mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic solvent was washed with brine (2 × 25 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using an ethyl acetate−hexanes gradient (10−13%) to give the product **25** (80 mg, 60%) as an oil: IR (neat) 2939, 1779, 1727, 1472, 1149, 1051 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.19 (d, $J = 2.0$ Hz, 1 H), 7.04 (s, 1 H), 6.73 (s, 1 H), 6.56 (s, 1 H), 5.93 (t, $J = 7.4$ Hz, 1 H), 3.94 (s, 3 H), 3.84 (s, 3 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.21 (t, $J = 7.5$ Hz, 2 H), 2.12 (t, $J = 7.5$ Hz, 2 H), 1.72 (quint, $J = 7.5$ Hz, 2 H), 1.38 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.70, 156.16 (d, $J = 75.2$ Hz), 151.65, 147.35, 140.46, 138.72, 135.40, 132.56, 131.22, 129.97, 128.76, 128.75, 123.58, 120.22, 119.84, 104.56, 80.07, 63.06, 60.92, 35.00, 29.16, 28.15, 27.96, 25.19, 16.09, 14.40; ^{19}F NMR (282 MHz, $CDCl_3$) δ 10.95 (s, 1 F); ESIMS *m/z* (rel intensity) 494 (100, M-methanol), 495 (30). Anal. Calcd for $C_{29}H_{35}FN_2O_5$: C, H, N.

(*E*)-6-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(3-((*Z*)-fluoro(methoxy-imino)methyl)-4-methoxy-5-methylphenyl)hex-5-enoic Acid (26). Trimethylsilyl trifluoromethanesulfonate (0.59 mL, 3.27 mmol) was added to a solution of *tert*-butyl ester **25** (862 mg, 1.64 mmol) and triethylamine (0.46 mL, 3.27 mmol) in dioxane (25 mL) at room temperature under argon. The reaction mixture was stirred for 2 h at room temperature. After the reaction was complete, water (50 mL) was added to the mixture. The mixture was extracted with ethyl acetate (2 × 35 mL). The combined organic solvent was washed with brine (2 × 35 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel using an ethyl acetate−hexanes gradient (30−70%) to give the product **26** (626 mg, 81%) as an oil: IR (neat) 3200, 2941, 1778, 1708, 1471, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, $J = 1.4$ Hz, 1 H), 7.03 (d, $J = 1.4$ Hz, 1 H), 6.73 (d, $J = 1.1$ Hz, 1 H), 6.55 (d, $J = 1.1$ Hz, 1 H), 5.93 (t, $J = 7.4$ Hz, 1 H), 3.94 (s, 3 H), 3.84 (s, 3 H), 3.32 (s, 3 H), 2.34 (t, $J = 7.3$ Hz, 2 H), 2.30 (s, 3 H), 2.29 (s, 3 H), 2.15 (q, $J = 7.3$ Hz, 2 H), 1.77 (quint, $J = 7.3$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.02, 155.67 ($J = 89.9$ Hz,), 151.80, 147.80, 140.94, 140.40, 138.64, 135.35, 135.33, 132.69, 131.27, 129.47, 128.71, 123.62, 120.10, 119.97, 140.85, 63.12, 60.98, 33.35, 29.06, 28.21, 24.69, 16.14, 14.46; ^{19}F NMR (282 MHz, $CDCl_3$) δ 11.29; ESIMS *m/z* (rel intensity) 470.97 (100, MH^+); negative ion ESIMS *m/z* (rel intensity) 469 [100, $(M - H^+)^-$]. Anal. Calcd for $C_{25}H_{27}FN_2O_5$: C, H, N.

(*Z*)-5-((*E*)-1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)pent-1-enyl)-*N*,2-dimethoxy-3-methylbenzimidoyl Fluoride (6). TBTU (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; 71 mg, 0.213 mmol) was added to a mixture of carboxylic acid **26** (100 mg, 0.213 mmol), acetamide oxime (16 mg, 0.213 mmol), HOBt (6 mg, 0.043 mmol), and DIPEA (0.19 mL, 1.07 mmol) in DMF (4 mL). The mixture was stirred for 0.5 h at room temperature and for 3 h at 110 °C. The mixture was diluted with ethyl acetate (50 mL), and the organic solution was washed with brine (4 × 20 mL), dried over sodium sulfate, and concentrated. The residue was purified by preparative TLC using 50% ethyl acetate−hexanes to give the product **6** (50 mg, 46%) as an oil. IR (neat) 2956, 1778, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, $J = 2.0$ Hz, 1 H), 7.10 (d, $J = 2.0$ Hz, 1 H), 6.71 (d, $J = 0.8$ Hz, 1 H), 6.54 (d, $J = 0.8$ Hz, 1 H), 5.93 (t, $J = 7.4$ Hz, 1 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.32 (s, 3 H), 2.83 (t, $J = 7.7$ Hz, 2 H), 2.33 (s, 3 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.21 (q, $J = 7.4$ Hz, 2 H), 1.95 (quint, $J = 7.5$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.12, 166.91, 155.61 (d, $J = 98.3$ Hz), 151.60, 147.30, 141.34, 140.56, 138.44, 135.25, 135.16, 132.72, 131.26, 128.76, 128.65, 123.56, 120.28, 119.92, 104.52, 63.10, 60.95, 28.93, 28.17, 26.47, 16.13, 14.42, 11.44; ^{19}F NMR (282 MHz, $CDCl_3$) δ 10.99 (s, 1 F); ESIMS *m/z* (rel intensity) 509 (100, MH^+). Anal. Calcd for $C_{27}H_{29}FN_4O_5$: C, H, N.

(*E*)-Methyl 6-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-6-(3-(*Z*)-fluoro-(methoxyimino)methyl)-4-methoxy-5-methylphenyl)hex-5-enoate (7). (Trimethylsilyl)diazomethane (0.17 mL of 2 M solution in hexanes, 0.340 mmol) was added to a solution of the carboxylic acid **26** (80 mg, 0.170 mmol) in toluene−methanol (2:1, 4.5 mL). After stirring for 10 min at room temperature, the excess (trimethylsilyl)diazomethane was quenched by dropwise addition of acetic acid. The solvent was evaporated, and the residue was purified by column chromatography using an ethyl acetate−hexanes gradient (20−40%) to give the product **7** (67 mg, 82%) as an oil: IR (neat) 2944, 1778, 1737, 1471, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, $J = 1.8$ Hz, 1 H), 7.03 (d, $J = 1.8$ Hz, 1 H), 6.72 (s, 1 H), 6.55 (s, 1 H), 5.92 (t, $J = 7.4$ Hz, 1 H), 3.94 (s, 3 H), 3.84 (s, 3 H), 3.61 (s, 3 H), 3.32 (s, 3 H), 2.32 (s, 3 H), 2.29 (s, 3 H), 2.28 (t, $J = 7.4$ Hz, 2 H), 2.12 (q, $J = 7.4$ Hz, 2 H), 1.77 (quint, $J = 7.4$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.74, 155.56 (d, $J = 93.2$ Hz), 151.62, 147.31, 140.70, 140.46, 138.64, 135.35, 132.57, 131.22, 129.64, 128.70, 123.55, 120.20, 119.89, 104.53, 63.04, 60.92, 51.41, 33.38, 29.90, 28.13, 24.92, 16.08, 14.38; ^{19}F NMR (282 MHz, $CDCl_3$) δ 10.86 (s, 1 F); ESIMS *m/z* (rel intensity) 485 (100, MH^+). Anal. Calcd for $C_{26}H_{29}FN_2O_6$: C, H, N.

RT Inhibition Assay. Inhibition of purified recombinant reverse transcriptase was measured by the incorporation of [^{32}P]GTP into poly(rC)/oligo(dG) (rCdG) homopolymer template primers, as previously described.[4,30]

In Vitro Antiviral Assays. Evaluation of the antiviral activity of compounds against HIV-1_{RF} infection in CEM-SS cells was performed using the XTT cytoprotection assay, as previously described.[30] 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.[31,32]

In Vitro Hydrolytic Stability Study in Rat Plasma. The alkenyldiarylmethanes **4**−**7** (with 1,1-diphenylethylene or benzophenone as internal standards) were tested for their hydrolytic stability, utilizing rat plasma and in vitro methods, as previously described.[11]

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Supporting Information Available: HPLC analysis results of compound **5** and elemental analysis data for all other compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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