Synthesis and Biological Evaluation of Alkenyldiarylmethane HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors That Possess Increased Hydrolytic Stability

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Non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs), albeit not the mainstays of HIV/AIDS treatment, have become increasingly important in highly active antiretroviral therapy (HAART) due to their unique mechanism of action. Several years ago our group identified the alkenyldiarylmethanes (ADAMs) as a potent and novel class of NNRTIs; however, the most active compounds were found to be metabolically unstable. Subsequent work has led to the synthesis of 33 analogues, with improved metabolic profiles, through the replacement of labile esters with various heterocycles, nitriles, and thioesters. As a result, a number of hydrolytically stable NNRTIs were identified with anti-HIV activity in the nanomolar concentration range. Furthermore, an improved pharmacophore model has been developed based on the new ADAM series, in which a salicylic acid-derived aryl ring is oriented cis to the side chain and the aryl ring that is trans to the side chain contains a hydrogen bond acceptor site within the plane of the ring.

Introduction

In the 25 years since the initial discovery that acquired immunodeficiency syndrome (AIDS[a]) is caused by the human immunodeficiency virus (HIV), the disease has grown into a global pandemic. At the end of 2005, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported more than 4 million new cases of HIV infection for the year, bringing the worldwide number of HIV-infected individuals up to more than 40 million.[1] Given the rate at which HIV infection is spreading, despite the current number of AIDS therapeutics and vast resources being poured into AIDS research, it is quite clear that curbing the spread of AIDS is becoming one of the most challenging medical problems of the century.

Highly active antiretroviral therapy (HAART) is the first line of defense against development of AIDS. The regimen has been successful in reducing the morbidity and mortality associated with AIDS progression to a level at which the disease can be treated as a chronic ailment with associated drug toxicities.[2−4] The success of HAART lies in the combined use of an HIV protease inhibitor and several reverse transcriptase inhibitors (RTIs). Typically, the RTIs employed are nucleoside or nucleotide analogues (NRTIs) that act as chain terminators for developing viral DNA chains being reverse transcribed by reverse transcriptase (RT). However, another class of RTIs, the non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been experiencing increased use in HAART over the past several years.[5]

The NNRTI class of HIV-1 antiretroviral agents is reported to consist of over thirty different scaffolds, which exhibit immense structural diversity;[6] however, only three NNRTIs (nevirapine,[7] delavirdine,[8] and efavirenz[9]) have been approved for clinical use by the FDA. NNRTIs exert their antiretroviral effects through binding at an allosteric site close to (approximately 10 Å away), but separate from the nucleoside binding site (polymerase active site). This dual mode of inhibition available for RT typically results in a synergistic, therapeutic effect when NNRTIs are coupled with NRTIs in retroviral therapy.[10] Unfortunately, aggressive treatment with NNRTIs results in the rapid emergence of RT mutants that exhibit cross-resistance to multiple NNRTIs.[11] Should a patient relapse after HAART fails to halt the progression of AIDS, treatment of the resulting multi-drug-resistant (MDR) HIV is problematic in that extreme dosing and constant exchange of antiretrovirals is required, which produces serious side effects and severe, acute toxicities.[12] The emergence of MDR HIV strains, as a result of antiretroviral therapy, has developed into a serious medical issue because there are no efficient therapeutics to combat them. In response, potent NNRTIs capable of inhibiting MDR forms of RT are urgently needed, and this area of research has the potential to make great contributions to AIDS therapy.

Several years ago, our group discovered a novel class of NNRTIs based on an alkenyldiarylmethane (ADAM) scaffold while investigating the ability of cosalane analogues to inhibit the attachment of HIV-1 to $CD4^+$ cells.[13−15] The initial lead compounds exhibited low micromolar inhibition of HIV-1 cytopathicity, and, after a few years of investigation, ADAMs **1** and **2** were identified as sub-micromolar inhibitors of HIV-1 RT, which also exhibited minimal losses in potency against clinically relevant RT mutants K103N and L100I.[16] Unfortunately, it was discovered that conversion of the methyl esters present in the ADAMs to carboxylic acids results in complete loss of antiviral activity, which compromises the ADAMs as potential therapeutic agents because ester hydrolysis is expected to occur readily in vivo.[15−17] The focus of the project therefore shifted toward improving the hydrolytic stability of the ADAMs

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[a] Abbreviations: AIDS, acquired immunodeficiency syndrome; AZT, azidothymidine; DIAD, diisopropylazodicarboxylate; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase.

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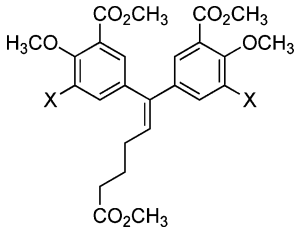
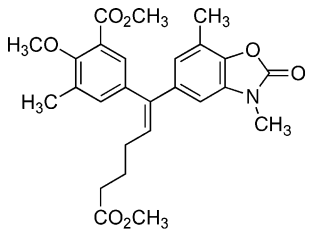


1 X= Br
2 X= Cl

while maintaining their antiviral potency, and we have been making progress toward this objective.[18−20]

Design

Given the recent assertion that performing molecular modeling studies on novel NNRTIs without an experimentally determined NNRTI-RT crystal structure complex is problematic, and because our own attempts to explain the SAR of ADAMs based on hypothetical models of protein complexes have been frustrating,[18,21] we opted to forego traditional structure-based drug design in favor of synthesizing an array of compounds that incorporate several of our current leads for improving the hydrolytic stability of ADAMs. Past SAR work on ADAMs indicated that conversion of the labile esters to traditional bioisosteres, such as amides,[15,22] ketones,[16,18] carbamates,[16] and oxazolidinones,[19,22] usually yielded analogues with significantly reduced or no detectable antiviral activity. In contrast, thioester replacements on the aryl rings surprisingly provide the desired increase in hydrolytic stability at the expense of only a 6-fold loss in potency.[18] We have also reported that replacing the esters and adjacent methoxy groups on the aryl rings with a number of hydrolytically stable heterocycles (as shown in ADAMs **3** and **4**) or a simple nitrile moiety effectively increases the half-



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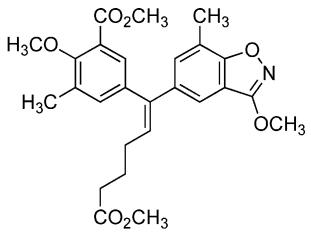

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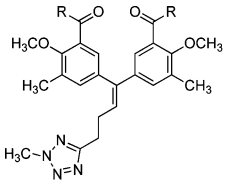
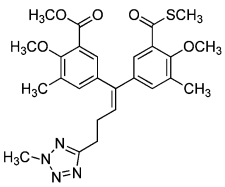
lives of analogues in rat plasma and occasionally maintains the anti-HIV potency of the parent compounds.[20,23] The side chain ester SAR indicates that this region of the ADAMs is more amenable to change, relative to the rest of the molecule; however, conservation of electrostatic potential and hydrogen bond acceptor sites appears to be necessary for achieving high potency. As such we sought to replace the remaining side chain ester with a hydrolytically stable heterocycle (such as an alkylated tetrazole or 1,3,4-oxadiazole), which possesses a similar electrostatic potential surface, volume, and number of hydrogen bond acceptor sites as an ester. Although the antiviral activity of the target compounds may not necessarily be governed by the "sum of the fragments" composing them, we believed that the serial array strategy was the best option available for combining our various leads to produce potent antiviral agents.

Herein we report the synthesis of a serial array of 33 new ADAMs **5**−**37**, which led to the discovery of several antiviral agents with low micromolar and sub-micromolar activities. The new ADAMs were evaluated for their ability to inhibit HIV-1



5 R= OCH_3
6 R= SCH_3



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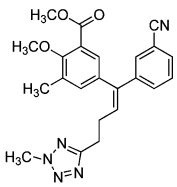

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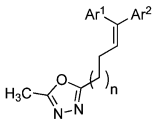
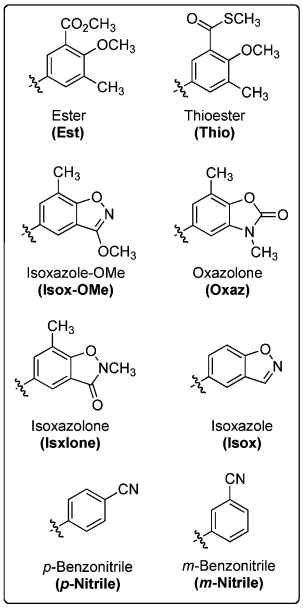


9 n = 1, Ar^1 = Ar^2 = Est
10 n = 1, Ar^1 = Est, Ar^2 = Thio
11 n = 1, Ar^1 = Est, Ar^2 = *m*-Nitrile
12 n = 1, Ar^1 = Est, Ar^2 = *p*-Nitrile
13 n = 1, Ar^1 = Est, Ar^2 = Isxlone
14 n = 1, Ar^1 = Est, Ar^2 = Isox-OMe
15 n = 1, Ar^1 = Est, Ar^2 = Oxaz
16 n = 1, Ar^1 = Ar^2 = Thio
17 n = 1, Ar^1 = Thio, Ar^2 = Isox-OMe
18 n = 1, Ar^1 = Thio, Ar^2 = Isxlone
19 n = 1, Ar^1 = Thio, Ar^2 = Oxaz
20 n = 1, Ar^1 = Thio, Ar^2 = *m*-Nitrile
21 n = 1, Ar^1 = Thio, Ar^2 = *p*-Nitrile
22 n = 1, Ar^1 = Thio, Ar^2 = Isox
23 n = 1, Ar^1 = Oxaz, Ar^2 = Thio
24 n = 1, Ar^1 = Isox-OMe, Ar^2 = Thio
25 n = 1, Ar^1 = Isxlone, Ar^2 = Thio
26 n = 1, Ar^1 = *m*-Nitrile, Ar^2 = Thio
27 n = 1, Ar^1 = *p*-Nitrile, Ar^2 = Thio
28 n = 2, Ar^1 = Ar^2 = Thio
29 n = 2, Ar^1 = Thio, Ar^2 = Isox-OMe
30 n = 2, Ar^1 = Thio, Ar^2 = Isxlone
31 n = 2, Ar^1 = Thio, Ar^2 = *m*-Nitrile
32 n = 2, Ar^1 = Thio, Ar^2 = *p*-Nitrile
33 n = 2, Ar^1 = Oxaz, Ar^2 = Thio
34 n = 2, Ar^1 = Isox-OMe, Ar^2 = Thio
35 n = 2, Ar^1 = Isxlone, Ar^2 = Thio
36 n = 2, Ar^1 = *m*-Nitrile, Ar^2 = Thio
37 n = 2, Ar^1 = *p*-Nitrile, Ar^2 = Thio



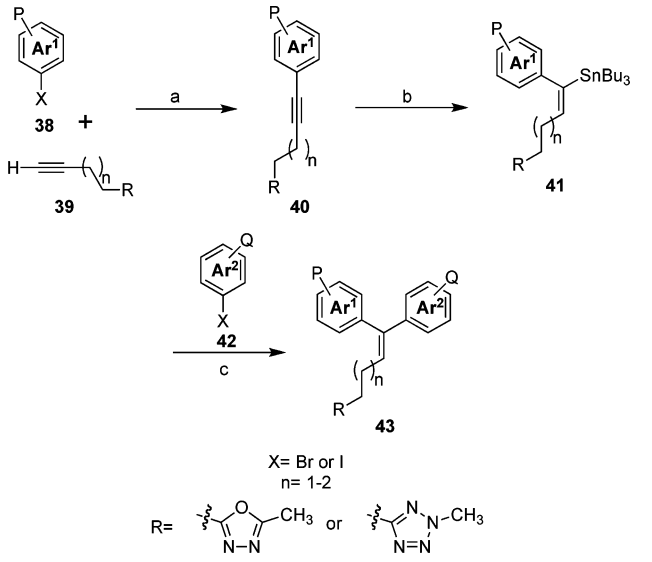
RT and to protect infected cells from the cytopathic effects of three HIV strains (HIV-1 strains RF and III_B, and HIV-2 strain ROD). The more potent analogues identified in the series were also tested for cytoprotective activity against HIV-1 strains bearing the K103N and Y181C mutations. In addition, the metabolic half-lives of a subset of ADAMs in rat plasma were determined to ensure that the hydrolytic stability of the proposed compounds had, in fact, increased relative to the parent compounds.

Results and Discussion

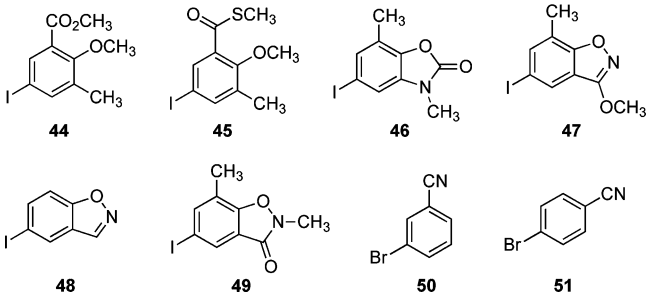
Chemistry. Over the course of the project, a variety of routes have been established for the synthesis of ADAMs, including a solid-phase based strategy.[16,23,24] Of the options available we chose the route that utilized a series of metal-mediated cross-coupling reactions to stitch ADAMs together from a series of simple, common precursors because it particularly suited our array design. All of the ADAMs reported here were synthesized from common precursors via the same methodology; thus a general, rather than a detailed, scheme is presented for the synthesis of ADAMs **5**−**37** (Scheme 1). Briefly, Sonogashira coupling of aryl halide **38** with terminal alkyne **39** afforded the highly functionalized alkyne intermediate **40**, which when treated with tributyltin hydride and a catalytic amount of $Pd(PPh_3)_4$ yields stannane **41**. To complete the synthesis of the ADAM scaffold, a Stille coupling between stannane **41** and aryl halide **42** provided the desired target compound **43**.

The conditions reported for all reactions in Scheme 1 were general and provided the desired products in good yields (typically >70%), regardless of the substrates used. With respect

Scheme 1[a]



Ar^1 / Ar^2 "Building Blocks"

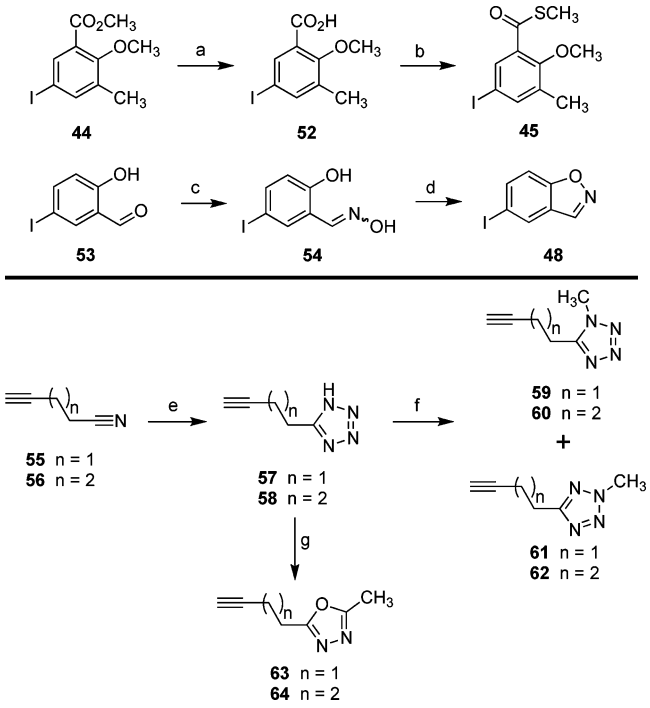


[a] Reagents and conditions: (a) cat. $PdCl_2(PPh_3)_2$, cat. CuI, Et_3N, THF, rt; (b) cat. $Pd(PPh_3)_4$, Bu_3SnH, THF, 0 °C to rt; (c) cat. CuI or 1 equiv. of CuI, cat. $Pd(PPh_3)_4$, CsF, DMF, 60 °C.

to the Stille coupling, it was found that the cross-coupling could be performed in the presence of copper(I) iodide in either catalytic or stoichiometric amounts; however, the two conditions required reaction times of 4−24 h (depending on the substrates) or 15 min, respectively. Although copper is a heavy metal and use of its associated reagents in excess amounts should be avoided due to toxicity concerns, the Stille couplings were performed on a sufficiently small scale that using stoichiometric amounts of the metal did not present a significant hazard. As such, the majority of the Stille couplings utilized a full equivalent of copper(I) iodide in an effort to enhance coupling yields and reaction times.

Of the common aryl "building blocks" presented in Scheme 1, the syntheses of intermediates **44**,[19] **46**,[23] **47**,[19] and **49**[19] have been previously reported and benzonitriles **50** and **51** are commercially available. The syntheses of aryl intermediates **45** and **48** are presented in Scheme 2, in addition to the alkyne intermediates **59**−**64**, which were required for the initial Sonogashira couplings, as depicted by alkyne **39**. Access to thioester **45** was conveniently achieved through another aryl building block, ester **44**. Saponification of **44** was effected through heating a mixture of the ester and potassium hydroxide in methanol at reflux to afford benzoic acid **52**. Treatment of acid **52** with thionyl chloride to obtain the corresponding acyl chloride intermediate, followed by esterification with sodium thiomethoxide in benzene, afforded thioester **45**. Synthesis of isoxazole **48** began with formation of oxime **54** from salicylic aldehyde **53** via condensation with hydroxylamine. Cyclization

Scheme 2[a]



[a] Reagents and conditions: (a) KOH, MeOH, reflux; (b) (i) $SOCl_2$, reflux; (ii) $NaSCH_3$, benzene, rt; (c) H_2NOH−HCl, EtOH, reflux; (d) PPh_3, DIAD; (e) NaN_3, Et_3N−HCl, toluene, reflux; (f) cat. Bu_4NBr, K_2CO_3, Me_2SO_4, EtOAc/H_2O; (g) Ac_2O, reflux.

of oxime intermediate **54** was accomplished with triphenylphosphine and DIAD to afford isoxazole **48**.

Alkynes **59**−**64** were synthesized from their corresponding nitriles, **55** and **56**, via tetrazole intermediates. Treatment of commercially available nitriles **55** and **56** with triethylamine hydrochloride and sodium azide afforded the cycloaddition products **57** and **58**, respectively. The tetrazole intermediates **57** and **58** conveniently served as common precursors for both the methylated tetrazole and oxadiazole-bearing side chains via application of different reaction conditions. Alkylation of tetrazoles **57** and **58** proceeded smoothly with dimethyl sulfate and potassium carbonate under biphasic catalysis conditions to afford mixtures of the 1*H* and 2*H* methylated products (**59** mixed with **61** and **60** mixed with **62**), which were easily separated via chromatography on silica and distinguished by ^{1}H NMR chemical shifts of the methyl groups. Alternatively, a mixture of acetic anhydride and tetrazole **57** or **58** could be heated at reflux to obtain the desired oxadiazole intermediates **63** and **64**, respectively.

Biological Results and Discussion. The antiviral activity of the ADAMs was evaluated by determining their ability to inhibit the enzymatic activity of HIV-1 RT *in vitro* and protect HIV-infected cells from the cytopathic effects of three viral strains (HIV-1 strains RF and III_B, and HIV-2 strain ROD). In addition, cytotoxicities for the ADAMs were recorded and their metabolic half-lives in rat plasma (Sigma, St. Louis, MO) were determined. The results of the antiviral and metabolic investigations on ADAMs **5**−**37** are presented in Table 1. Associated data for ADAMs **1**−**4** and two clinically approved NNRTIs (nevirapine and efavirenz) are included for comparison.

Unsurprisingly, a wide range of inhibitory activities were exhibited by the array of ADAMs; however, the array design was surprisingly successful at affording a large number of moderately potent NNRTIs. Of the 33 ADAMs under investigation, 74% of the compounds displayed IC_{50} values lower than

Table 1. Antiviral Activity and Hydrolysis Half-Lives of ADAMs **1**−**37**

		EC_{50} (μM)[b]			CC_{50} (μM)[c]		
compound	IC_{50} (μM)[a]	HIV-1_{RF}	HIV-1_{IIIB}	HIV-2_{ROD}	CEM-SS	MT-4	half-life $t_{1/2} \pm$ SD (min)[d]
1	0.30	0.001	0.30	NA[e]	13	91	6.2 ± 0.4
2	0.30	0.01	0.60	25	32	160	5.8 ± 0.9
3	0.02	0.03	0.09	NA[e]	5.1	17	1.3 ± 0.09
4	0.91	0.04	0.02	NA[e]	0.50	1.1	NT[f]
5	53	NA[e]	NA[e]	NA[e]	9.6	5.0	24 ± 3.2
6	67	2.9	NA[e]	NA[e]	33	7.0	NT[f]
7	95	NA[e]	NA[e]	NA[e]	1.6	1.4	NT[f]
8	7.7	2.4	1.5	NA[e]	7.4	34	42 ± 3.2
9	71	2.3	3.2	NA[e]	40	37	3.3 ± 0.07
10	32	NA[e]	NA[e]	NA[e]	13	3.9	78 ± 4.1
11	29	NA[e]	NA[e]	NA[e]	4.5	8.1	113.5 ± 0.7
12	24	3.0	2.0	NA[e]	28	16	45 ± 1.4
13	7.4	3.0	2.7	NA[e]	7.7	41	219.5 ± 9.2
14	0.39	0.36	0.42	NA[e]	2.8	6.4	331 ± 20
15	1.0	0.43	0.44	NA[e]	3.2	13	NT[f]
16	> 100	NA[e]	NA[e]	NA[e]	8.1	5.9	NT[f]
17	0.90	0.52	0.81	NA[e]	2.1	4.4	1090 ± 302
18	9.2	6.4	3.7	NA[e]	18	19	NT[f]
19	2.6	0.60	0.69	4.7	5.9	12	739 ± 25
20	9.3	NA[e]	1.4	NA[e]	2.7	8.4	221 ± 43
21	6.3	2.1	3.2	NA[e]	5.5	45	NT[f]
22	7.7	2.6	NT[f]	NT[f]	38	NT	NT[f]
23	90	NA[e]	NA[e]	5.9	6.6	14	NT[f]
24	33	NA[e]	NA[e]	NA[e]	1.2	1.6	NT[f]
25	> 100	NA[e]	NA[e]	NA[e]	17	37	NT[f]
26	55	NA[e]	NA[e]	NA[e]	1.3	3.8	NT[f]
27	48	NA[e]	NA[e]	NA[e]	1.2	3.2	NT[f]
28	6.7	2.2	1.3	NA[e]	5.3	4.4	76 ± 4.2
29	0.47	0.05	0.14	NA[e]	5.7	7.0	864 ± 29
30	> 100	0.97	0.76	NA[e]	6.0	9.9	NT[f]
31	0.52	0.50	0.83	NA[e]	12	36	221 ± 43
32	3.2	0.60	0.36	NA[e]	8.9	36	45 ± 7.1
33	36	NA[e]	NA[e]	NA[e]	5.5	7.7	NT[f]
34	5.2	NA[e]	NA[e]	NA[e]	0.78	1.1	NT[f]
35	> 100	NA[e]	NA[e]	NA[e]	12	25	NT[f]
36	7.7	NA[e]	NA[e]	NA[e]	7.2	8.2	NT[f]
37	0.45	NA[e]	NA[e]	NA[e]	4.8	7.6	41.5 ± 2.1
nevirapine	NT	0.015	0.053	NA[e]		15	NT[f]
efavirenz	NT	0.005	0.001	NA[e]		6.0	NT[f]

[a] Inhibitory activity versus HIV-1 RT with poly(rC).oligo(dG) as the template primer. [b] EC_{50} is the 50% inhibitory concentration for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cells, HIV-1_{IIIB} in MT-4 cells, or HIV-2_{ROD} in MT-4 cells. [c] CC_{50} is the cytotoxic concentration required to induce cell death for 50% of the mock infected CEM-SS or MT-4 cells. [d] The metabolic half-life of the compound when it was incubated with rat plasma; determined from a minimum of two replicates. [e] Not Active. [f] Not Tested.

50 μM. Even more encouraging was the observation that 53% of the array displayed RT IC_{50} values in the low micromolar to nanomolar range (less than 10 μM), with the lowest IC_{50} of 0.39 μM being assigned to ADAM **14**. Unfortunately, although 53% of the compounds in the array were at least low micromolar inhibitors of HIV-1 RT enzymatic activity *in vitro*, many failed to satisfactorily protect HIV-infected cells from the cytopathic effects of the virus because either they were less potent in a cellular system (example: ADAM **37**) or possessed pronounced cytotoxicities (example: ADAM **34)**. Despite the overall drawbacks observed for many of the compounds, ADAMs **14** and **29** exhibited sub-micromolar antiviral and RT inhibitory activities. Yet, **14** and **29** were both 5- to 400-fold less potent in the cytoprotective assays than the clinically approved NNRTIs nevirapine and efavirenz, indicating that the potency of the ADAMs still has room for improvement. As is typical of most NNRTIs, all of the target compounds were inactive against HIV-2, with the exception of ADAMs **19** and **23**.

Over the course of this project, the ADAMs have exhibited undesirable cytotoxic properties, which narrow their therapeutic windows; unfortunately, as ADAM RT inhibitory activity has improved, the compounds have typically become more cytotoxic. Also, compounds have occasionally been identified that poorly inhibit RT activity *in vitro*, such as **6** and **9**, but are relatively potent antivirals in the cellular assays. These observations led to the conclusion that ADAMs likely interact with additional cellular and/or viral entities to produce their cytotoxic and antiviral effects. In the development of new therapeutics, emergence of drug-related toxicities is expected; however, when the toxicity increases along with the drug potency, the therapeutic target and source of toxicity likely possess similar pharmacophores, which complicates drug development efforts. In regard to non-RT, antiviral therapy targets, there are several other HIV replication proteins, such as integrase or TaT, and HIV-associated cellular pathways through which ADAMs might be affecting the HIV lifecycle. To address these issues, additional investigations are being performed to identify other molecular entities through which ADAMs may exert their antiviral and cytotoxic effects.

During prior investigations, ADAMs **1** and **2** displayed zero- to 5-fold loss in antiviral activity against NNRTI-resistant HIV-1 bearing the K103N and Y188C RT mutations, yet their potency was significantly reduced (20-fold or more) when in the presence of the Y181C mutation. It was believed that, in general, other ADAM analogues would exhibit similar patterns in antiviral activity against these same mutations. In light of

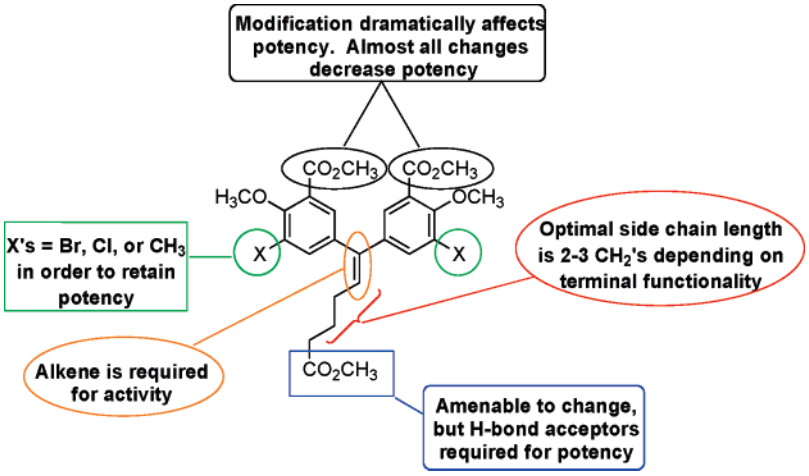


Figure 1. The general SAR observed for ADAMs as generated from past studies.

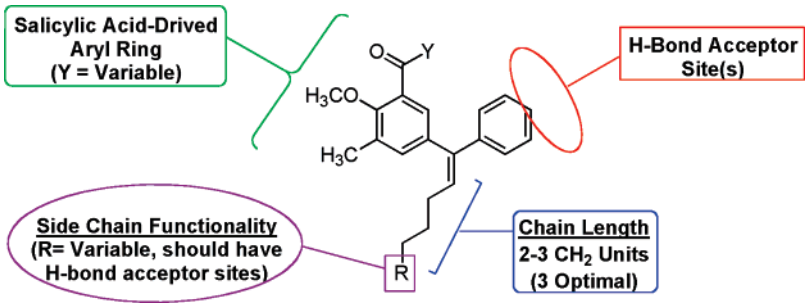


Figure 2. New pharmacophore model for the design of potent ADAM-based NNRTIs.

this information, cytoprotective activities for ADAMs **11**, **13**−**15**, **17**−**19**, **21**, **22**, **28**, **29**, **31**, **32**, **34**, and **37**, the fifteen most potent RT inhibitors in this study, were determined for CEM-SS cells that had been infected with NNRTI-resistant HIV-1 strains, which were engineered to express the K103N and Y181C RT mutations.[25,26] As expected, all fifteen analogues were inactive (EC_{50} > 100 μM) in the cytoprotection assay for the Y181C mutant, mirroring the attenuation in antiviral activity reported for ADAMs **1** and **2**. Unexpectedly, only ADAMs **14**, **19**, **29**, **31**, and **32** were found to inhibit the cytopathic effects of the K103N HIV-1 mutant with EC_{50} values of 0.8, 1.0, 0.4, 1.2, and 2.3 μM, respectively, which reflected only a 2- to 8-fold loss in antiviral potency for these analogues relative to their activities against wild-type $HIV\text{-}1_{RF}$ in CEM-SS cells. The remaining analogues showed no cytoprotective activity against the K103N mutant (EC_{50}'s > 50 μM). The antiviral potency of nevirapine was reduced by four and five times in the Y181C and K103N mutant assays, respectively.

After noting the salient information obtained from the antiviral evaluations, a closer examination of the data yields a new pharmacophore model for potent ADAM-based NNRTIs (Figure 2). In comparing the structures of the most potent RT inhibitors in the array (ADAMs **14**, **15**, **17**, **29**, and **31**) with earlier leads **3** and **4**, one notices that the compounds share many structural similarities. First, the inhibitors contain a salicylic acid-derived aryl ring cis to the side chain. Second, the compounds have chain lengths of either two or three methylene units, although the longer three methylene unit side chain is optimal. Third, the aryl ring trans to the side chain contains a pendant functional group, at the three or four position, with a hydrogen bond acceptor site in the plane of the ring. In addition, on the basis of past and current SAR data, the side chain must contain a small functional group capable of accepting hydrogen bonds. This new model more narrowly defines the structural features that are required for potent RT inhibitory in the ADAM series; however, the accuracy of the new model needs to be validated by future work.

Metabolic Stability Studies. The basis of our research has been toward improving the metabolic stability of the lead compounds, so that we may continue the development of new, potential antivirals. To ensure that the ester bioisosteres were, in fact, improving the hydrolytic stability of the array, a metabolic stability assay was employed to determine the ADAM half-lives in rat plasma.[18] Rat plasma was utilized because esterase activity in rodents is reported to be significantly higher than that of humans, so ADAMs displaying moderately short or longer half-lives in the assay should, a fortiori, be particularly stable to similar forms of metabolism in humans. A panel of ADAMs, which included the most active compounds from the array, was subjected to the metabolism assay, and the calculated half-lives are presented in Table 1, along with the antiviral data.

After surveying the metabolism data, it is evident that the ester bioisosteres successfully increased the metabolic half-lives of the analogues relative to the lead compounds, albeit to varying degrees. In some cases, incorporation of the bioisosteres afforded ADAMs with several hour long half-lives (example: ADAM **17**), but for others the increase in half-life was modest at best, resulting in compounds whose metabolic profiles are not much better than those of the original leads (example: ADAM **37**). However, many of the potent inhibitors, notably nanomolar inhibitor **29**, exhibited half-lives of at least 3 h, which should translate into a longer half-life in a human system with similar metabolic processes.

The inclusion of ester bioisosteres in the ADAM system clearly does not render all compounds resistant to hydrolysis, and the rate of metabolism for each compound appears to be based on its individual structure. This observation is not surprising because the metabolic enzymes would be expected

to have their own sets of structure−activity relationships for the ADAM class of compounds. However, for the ADAM−rat esterase system, ester stability is modulated by the overall ADAM structure to the extent that an ADAM bearing an ester (ADAM **13**) can exhibit a longer metabolic half-life than one whose esters have been replaced with bioisosteres (ADAM **32**). In fact, compounds with very similar structures can have significantly different metabolic half-lives (ADAM **31** versus **32**).

Conclusions

The incorporation of ester bioisosteres into an array of ADAMs led to the successful development of several low micromolar and sub-micromolar inhibitors of HIV-1 reverse transcriptase that exhibited increased metabolic stability in rat plasma relative to their parent analogues. Among the inhibitors synthesized, ADAM **14** proved to be the most potent inhibitor of RT *in vitro*, exhibiting an IC_{50} of 0.39 μM. However, ADAM **29** displayed similar RT inhibitory activity (IC_{50} = 0.47 μM) to **14**, yet also exhibited superior cytoprotective and metabolic stability profiles, making it a better candidate for future development. Unfortunately, the ADAM class of NNRTIs exhibit cytotoxic properties and the relative cytotoxicity of the compounds tends to increase as the RT inhibitory potency increases. Regardless of the apparent toxicities associated with the analogues produced in this study, the antiviral activity of the ADAMs still falls short of current FDA-approved NNRTIs, and additional studies are required to improve their potencies.

Additionally, the ADAMs produced in this study were incapable of inhibiting the cytopathic effects of HIV-1 bearing the Y181C RT mutation, clearly indicating that these analogues are not suitable for treating drug-resistant HIV bearing this particular mutation. However, in relation to the K103N RT mutation, five compounds were identified that retained antiviral activity, exhibiting only 2- to 8-fold reductions in potency. On the basis of this investigation and past ADAM studies, another viral or cellular entity may play a role in the antiviral properties of the ADAMs, and therefore additional studies are being performed to identify other potential mechanisms for the antiviral activity and cytotoxicity of the ADAMs. Antiviral data obtained for the array also led to the development of a new pharmacophore model, which will serve an important role in the development of future ADAM-based NNRTIs.

Experimental Section

Unless noted, all ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$, using the deuterated solvent as the internal standard for chemical shifts. In the cases where a solvent other than $CDCl_3$ was utilized, the alternative solvent was used as the internal standard, with the calibration set according to the residual solvent peak as reported by Nudelman and co-workers.[27] A Perkin-Elmer 1600 series FT-IR spectrometer was used to record infrared spectra of all compounds, and flash chromatography was performed on 230−400 mesh silica. Preparative TLC separations utilized Analtech Uniplates with glass supported silica (20 × 20 cm, 2000 μm thickness) and UV indicator (254 nm). The progress of reactions was monitored with Baker-flex silica gel IB2-F plates (0.25 mm thickness). Melting points are uncorrected. Unless specifically mentioned, chemicals and solvents were of minimum reagent grade and used as obtained from commercial sources without further purification. Anhydrous tetrahydrofuran was prepared by distillation from sodium ketyl radical. The hydrolytic stability assay utilized lyophilized rat plasma (LOTs 052K7609 and 065K7555) from Sigma Chemical Co., St. Louis, MO. Elemental analyses were performed at the Purdue University Microanalysis Laboratory. High-resolution mass spectra for all ionization techniques were obtained from a FinniganMAT XL95. Analytical HPLC analyses performed to aid in the establishment of compound purity were completed on a Waters binary HPLC system (model 1525, 20 μL injection loop) equipped with a Waters dual wavelength absorbance UV detector (model 2487) set for 254 nM. The mobile phases consisted of 8:2 (v/v) acetonitrile−water or 8:2 (v/v) THF−water, and the Symmetry HPLC column (4.6 mm × 150 mm) was packed with C_{18} silica from Waters. All yields reported refer to isolated yields. The structures of all of the intermediates for the general synthetic scheme (Scheme 1) that are referenced in experimental procedures, but are not explicitly shown in the body of the paper, can be found in the Supporting Information.

General Procedure for the Synthesis of Alkenyldiarylmethanes via Stille Cross-Coupling of Stannanes with Aryl Halides. A mixture of stannane **41** (1 equiv) and aryl halide **42** (1.2 equiv) in anhydrous DMF (2−3 mL) was sparged with argon for 10 min and maintained under an argon atmosphere. Cesium fluoride (3.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and copper(I) iodide (0.2−1 equiv) were quickly added to the reaction mixture, which was again placed under an argon atmosphere. The reaction mixture was stirred at 60 °C, under an argon atmosphere, for 1−24 h until the stannane starting material had been consumed. The system was allowed to cool to room temperature, and the reaction mixture was sonicated at room temperature for 30 s, after being diluted with a mixture of ethyl acetate (5 mL), methanol (1 mL), and water (1 mL). The reaction mixture was loaded onto a short column of silica (10−20 mL), and the products were eluted with ethyl acetate (50−75 mL). The eluate was then washed with a basic, aqueous solution (pH = 10) of 1 M EDTA (2 × 20 mL) and an aqueous solution saturated with ammonium chloride (2 × 20 mL). The phases were separated, and the organic phase was dried over magnesium sulfate, filtered, and condensed in vacuo to afford the crude products. The crude products were separated by column chromatography to obtain the desired ADAM product, and, if necessary, additional purification methods were applied.

Methyl 2-Methoxy-5-[1-(4-methoxy-3-methyl-5-methoxycarbonyl-phenyl)-4-(2-methyl-2*H*-tetrazol-5-yl)-but-1-enyl]-3-methylbenzoate (5). The general Stille coupling procedure was followed using stannane **69** (375 mg, 0.619 mmol), iodide **44** (255 mg, 0.833 mmol), cesium fluoride (338 mg, 2.23 mmol), $Pd(PPh_3)_4$ (75 mg, 0.065 mmol), and copper(I) iodide (26 mg, 0.137 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred for 17 h. The crude products were separated by column chromatography (100 mL of silica gel, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−80%). The product was isolated and purified again by column chromatography (80 mL of silica gel, 2 in. diameter) using an ethyl acetate−hexanes gradient (20−66%). The desired ADAM product was isolated as a clear oil (255 mg, 83%): IR (neat) 2951, 2862, 2004, 1729, 1600, 1577, 1480, 1436, 1379, 1298, 1260, 1228, 1173, 1135, 1123, 1008 cm^{-1}; ^{1}H HMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 2.4 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.08 (d, J = 1.8 Hz, 1 H), 7.06 (d, J = 1.8 Hz, 1 H), 6.01 (t, J = 7.5 Hz, 1 H), 4.30 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.00 (t, J = 7.5 Hz, 2 H), 2.57 (q, J = 7.5 Hz, 2 H), 2.30 (s, 3 H), 2.25 (s, 3 H); ESIMS *m*/*z* (relative intensity) 517 (MNa^+, 100). Anal. ($C_{26}H_{30}N_4O_6$) C, H, N.

2-Methoxy-5-[1-(4-methoxy-3-methyl-5-methylsulfanylcarbonyl-phenyl)-4-(2-methyl-2*H*-tetrazol-5-yl)-but-1-enyl]-3-methylthiobenzoic Acid *S*-Methyl Ester (6). The general Stille coupling procedure was followed using stannane **73** (144 mg, 0.232 mmol), iodide **45** (95 mg, 0.299 mmol), cesium fluoride (135 mg, 0.889 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), and copper(I) iodide (15 mg, 0.079 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred for 15 h. The crude products were absorbed onto silica gel (2 mL) and separated by column chromatography (80 mL of silica gel, 2 in. diameter) using an ethyl acetate−hexanes gradient (33−66%). The desired product was isolated as a highly viscous, pale yellow oil (57 mg, 47%): IR (neat) 2298, 2857, 2824, 1673, 1644, 1593, 1574, 1478, 1417, 1379, 1307, 1244, 1199, 1156, 1133, 1039, 1001 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 2.4 Hz, 1 H), 7.32 (d, J = 2.1 Hz, 1 H), 7.08 (dd, J = 2.1, 0.6 Hz, 1

H), 7.05 (dd, $J = 2.1$, 0.6 Hz, 1 H), 6.02 (t, $J = 7.2$ Hz, 1 H), 4.30 (s, 3 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.02 (t, $J = 7.5$ Hz, 2 H), 2.59 (q, $J = 7.5$ Hz, 2 H), 2.44 (s, 3 H), 2.43 (s, 3 H), 2.32 (s, 3 H), 2.26 (s, 3 H); ESIMS *m/z* (relative intensity) 549 (MNa^+, 9), 526 (MH^+, 37), 497 ($MH^+ - SCH_3 + H_2O$, 100), 479 ($MH^+ - SCH_3$, 24). Anal. ($C_{26}H_{30}N_4O_4S_2$) C, H, N.

(*Z*)-Methyl 2-Methoxy-5-[1-(4-methoxy-3-methyl-5-methylsulfanylcarbonyl-phenyl)-4-(2-methyl-2*H*-tetrazol-5-yl)-but-1-enyl]-3-methylbenzoate (7). The general Stille coupling procedure was followed using stannane **69** (225 mg, 0.372 mmol), iodide **45** (183 mg, 0.568 mmol), cesium fluoride (199 mg, 1.30 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol), and copper(I) iodide (18 mg, 0.096 mmol) in anhydrous DMF (4 mL). The reaction mixture was stirred for 16 h. The crude products were absorbed onto silica (3 mL) and separated by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (20−50%). The product was isolated as a yellow oil (141 mg, 74%): IR (neat) 3642, 2950, 2004, 1729, 1675, 1646, 1594, 1575, 1479, 1435, 1379, 1296, 1253, 1229, 1208, 1150, 1125, 1051, 1005 cm^{-1}; ^1H HMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1 H), 7.37 (s, 1 H), 7.08 (d, $J = 1.8$ Hz, 1 H), 7.06 (d, $J = 1.8$ Hz, 1 H), 6.02 (t, $J = 7.2$ Hz, 1 H), 4.30 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.00 (t, $J = 7.2$ Hz, 2 H), 2.58 (q, $J = 7.2$ Hz, 2 H), 2.43 (s, 3 H), 2.31 (s, 3 H), 2.26 (s, 3 H); ESI HRMS *m/z* calcd for $C_{26}H_{30}N_4O_5S$ [MNa^+] 533.1835, found 533.1840; ESIMS *m/z* (relative intensity) 533 (MNa^+, 100), 481 ($MH^+ - SCH_3 + H_2O$, 76).

(*Z*)-5-[1-(3-Cyanophenyl)-4-(2-methyl-2*H*-tetrazol-5-yl)-but-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (8). The general Stille coupling procedure was followed using stannane **69** (155 mg, 0.256 mmol), bromide **50** (65 mg, 0.357 mmol), cesium fluoride (161 mg, 1.06 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and copper(I) iodide (11 mg, 0.058 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 13.5 h. The crude products were absorbed onto silica (5 mL) and separated by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (33−50%). The product was isolated as a clear oil (94 mg, 88%): IR (neat) 3063, 2951, 2858, 2229, 1728, 1597, 1575, 1480, 1436, 1418, 1396, 1380, 1300, 1256, 1231, 1199, 1154, 1125, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dt, $J = 7.2$, 1.5 Hz, 1 H), 7.44−7.34 (m, 4 H), 7.04 (d, $J = 1.8$ Hz, 1 H), 6.14 (t, $J = 7.5$ Hz, 1 H), 4.30 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.02 (t, $J = 7.5$ Hz, 2 H), 2.61 (q, $J = 7.5$ Hz, 2 H), 2.32 (s, 3 H); ESIMS *m/z* (relative intensity) 440 (MNa^+, 100), 364 ($MH^+ - C_2H_2N_2$, 67). Anal. ($C_{23}H_{23}N_5O_3$) C, H, N.

Methyl 2-Methoxy-5-[1-(4-methoxy-3-methyl-5-methoxycarbonylphenyl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-3-methylbenzoate (9). The general Stille coupling procedure was followed using stannane **71** (522 mg, 0.862 mmol), iodide **44** (356 mg, 1.16 mmol), cesium fluoride (461 mg, 3.03 mmol), $Pd(PPh_3)_4$ (99 mg, 0.086 mmol), and copper(I) iodide (47 mg, 0.247 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred for 17 h. The crude products were separated by column chromatography (125 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (20−100%). The desired product was further purified by preparative thin layer chromatography using 50% ethyl acetate−hexanes as the eluant (developed 4 times). The desired ADAM product was isolated as a pale, yellow oil (284 mg, 67%): IR (neat) 3000, 2950, 2851, 1729, 1596, 1570, 1480, 1436, 1298, 1260, 1228, 1173, 1135, 1123, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, $J = 2.4$ Hz, 1 H), 7.38 (d, $J = 2.1$ Hz, 1 H), 7.08 (d, $J = 2.1$ Hz, 1 H), 7.05 (d, $J = 2.1$ Hz, 1 H), 5.98 (t, $J = 7.2$ Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 2.91 (t, $J = 7.5$ Hz, 2 H), 2.56 (dt, $J = 7.5$, 7.2 Hz, 2 H), 2.47 (s, 3 H), 2.30 (s, 3 H), 2.24 (s, 3 H); CIMS *m/z* (relative intensity) 495 (MH^+, 100), 463 ($MH^+ - HOCH_3$, 73). Anal. ($C_{27}H_{30}N_2O_7$) C, H, N.

(*Z*)-Methyl 2-Methoxy-5-[1-(4-methoxy-3-methyl-5-methylsulfanylcarbonylphenyl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-3-methylbenzoate (10). The general Stille coupling procedure was followed using stannane **71** (433 mg, 0.715 mmol), iodide **45** (312 mg, 1.02 mmol), cesium fluoride (383 mg, 2.52 mmol), $Pd(PPh_3)_4$ (85 mg, 0.074 mmol), and copper(I) iodide (28 mg, 0.143 mmol) in anhydrous DMF (7 mL). The reaction mixture was stirred for 21 h. The crude products were separated by column chromatography (110 mL of silica gel, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−100%), and the desired product was further purified by preparative thin layer chromatography using 50% ethyl acetate−hexanes as the eluant (developed twice). The product was isolated as a very viscous, opaque oil (239 mg, 65%): IR (neat) 2930, 2866, 2004, 1730, 1679, 1645, 1595, 1570, 1479, 1435, 1379, 1296, 1253, 1229, 1125, 1049, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 2.1$ Hz, 1 H), 7.36 (d, $J = 2.4$ Hz, 1 H), 7.09 (d, $J = 2.1$ Hz, 1 H), 7.06 (d, $J = 2.4$ Hz, 1 H), 6.00 (t, $J = 7.5$ Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 2.92 (t, $J = 7.5$ Hz, 2 H), 2.57 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.43 (s, 3 H), 2.32 (s, 3 H), 2.27 (s, 3 H); ESIMS *m/z* (relative intensity) 511 (MH^+, 94), 481 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{27}H_{30}N_2O_6S$) C, H, N.

(*Z*)-Methyl 5-[1-(3-Cyanophenyl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-2-methoxy-3-methylbenzoate (11). The general Stille coupling procedure was followed using stannane **71** (200 mg, 0.330 mmol), bromide **50** (83 mg, 0.429 mmol), cesium fluoride (177 mg, 1.17 mmol), $Pd(PPh_3)_4$ (6 mg, 0.033 mmol), and copper(I) iodide (13 mg, 0.066 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 16 h. The crude products were absorbed onto silica (2 mL) and purified by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The product was isolated as a clear oil (103 mg, 75%): IR (neat) 3065, 2950, 2851, 2229, 2003, 1728, 1596, 1571, 1480, 1436, 1379, 1299, 1256, 1230, 1199, 1154, 1125, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, $J = 7.2$, 1.5 Hz, 1 H), 7.46−7.35 (m, 4 H), 7.05 (d, $J = 1.8$ Hz, 1 H), 6.12 (t, $J = 7.2$ Hz, 1 H), 3.97 (s, 3 H), 3.90 (s, 3 H), 2.94 (t, $J = 7.2$ Hz, 2 H), 2.61 (q, $J = 7.2$ Hz, 2 H), 2.48 (s, 3 H), 2.33 (s, 3 H); ESI HRMS *m/z* calcd for $C_{24}H_{23}N_3O_4$ [MNa^+] 440.1586, found 440.1580; ESIMS *m/z* (relative intensity) 440 (MNa^+, 100).

(*Z*)-Methyl 5-[1-(4-Cyanophenyl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-2-methoxy-3-methylbenzoate (12). The general Stille coupling procedure was followed using stannane **71** (541 mg, 0.894 mmol), bromide **51** (213 mg, 1.17 mmol), cesium fluoride (481 mg, 3.17 mmol), $Pd(PPh_3)_4$ (104 mg, 0.090 mmol), and copper(I) iodide (34 mg, 0.178 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred for 15 h. The crude products were purified by column chromatography (100 mL of silica gel, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−100%), and the desired product was isolated as a very viscous, pale yellow oil (363 mg, 87%): IR (neat) 2950, 2868, 2225, 1731, 1599, 1570, 1503, 1480, 1435, 1409, 1380, 1300, 1258, 1230, 1195, 1169, 1126, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (dt, $J = 8.4$, 1.8 Hz, 2 H), 7.33 (dt, $J = 8.7$, 1.8 Hz, 2 H), 7.27 (d, $J = 2.4$ Hz, 1 H), 7.13 (d, $J = 1.8$ Hz, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 2.99 (t, $J = 7.2$ Hz, 2 H), 2.59 (dt, $J = 7.5$, 7.2 Hz, 2 H), 2.44 (s, 3 H), 2.31 (s, 3 H); CIMS *m/z* (relative intensity) 418 (MH^+, 100), 386 ($MH^+ - OCH_3$, 69). Anal. ($C_{24}H_{23}N_3O_4$) C, H, N.

(*Z*)-5-[1-(2,7-Dimethyl-3-oxo-2,3-dihydrobenzo[*d*]isoxazol-5-yl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (13). The general Stille coupling procedure was followed using stannane **71** (160 mg, 0.264 mmol), iodide **49** (98 mg, 0.339 mmol), cesium fluoride (154 mg, 1.01 mmol), $Pd(PPh_3)_4$ (31 mg, 0.027 mmol), and copper(I) iodide (13 mg, 0.068 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 20 h. The crude products were absorbed onto silica (4 mL) and separated by column chromatography (80 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The product was isolated as an off-white solid (76 mg, 60%): mp 135−136 °C; IR ($CHCl_3$) 3469, 2949, 2862, 2236, 1997, 1729, 1690, 1614, 1596, 1570, 1490, 1437, 1399, 1378, 1298, 1257, 1227, 1168, 1147, 1121, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, $J = 2.1$ Hz, 1 H), 7.36 (d, $J = 1.8$ Hz, 1 H), 7.28 (s, 1 H), 7.05 (d, $J = 1.5$ Hz, 1 H), 6.02 (t, $J = 7.2$ Hz, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.66 (s, 3 H), 2.92 (t, $J = 7.5$ Hz, 2 H), 2.59 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.35 (s, 3 H), 2.31 (s, 3 H); ESI HRMS *m/z* calcd for $C_{26}H_{27}N_3O_6$ [MNa^+] 500.1798, found 500.1797;

ESIMS *m/z* (relative intensity) 500 (MNa^+, 100), 464 ($MH^+ - OCH_3 + OH$, 33). Anal. ($C_{26}H_{27}N_3O_6$) C, H, N.

(*Z*)-2-Methoxy-5-[1-(3-methoxy-7-methyl-benzo[*d*]isoxazol-5-yl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-1-enyl]-3-methylbenzoic Acid Methyl Ester (14). The general Stille coupling procedure was followed using stannane **71** (144 mg, 0.238 mmol), iodide **47** (106 mg, 0.367 mmol), cesium fluoride (142 mg, 0.935 mmol), $Pd(PPh_3)_4$ (29 mg, 0.024 mmol), and copper(I) iodide (13 mg, 0.068 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred for 20 h. The crude products were absorbed onto silica (3 mL) and separated by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (33−100%). The product was isolated as a clear oil (106 mg, 93%): IR (neat) 2948, 1730, 1596, 1570, 1547, 1495, 1436, 1395, 1318, 1284, 1256, 1202, 1143, 1120, 1048, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 2.1$ Hz, 1 H), 7.17 (s, 1 H), 7.15 (s, 1 H), 7.06 (d, $J = 2.1$ Hz, 1 H), 6.01 (t, $J = 7.2$ Hz, 1 H), 4.13 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.93 (t, $J = 7.2$ Hz, 2 H), 2.59 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 2.31 (s, 3 H); ESIMS *m/z* (relative intensity) 500 (MNa^+,100). Anal. ($C_{26}H_{27}N_3O_6$) C, H, N.

(*E*)-5-[1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzooxazol-5-yl)-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-but-2-enyl]-2-methoxy-3-methylbenzoic Acid Methyl Ester (15). The general Stille coupling procedure was followed using stannane **71** (197 mg, 0.325 mmol), iodide **46** (136 mg, 0.470 mmol), cesium fluoride (178 mg, 1.17 mmol), $Pd(PPh_3)_4$ (42 mg, 0.036 mmol), and copper(I) iodide (14 mg, 0.066 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 22 h. The crude products were absorbed onto silica (5 mL) and purified by column chromatography (60 mL of silica, 1 in. diameter) using ethyl acetate as the eluant. The desired product was further purified by preparative thin layer chromatography using ethyl acetate as the eluant (developed twice). The product was isolated from the plate and purified again by preparative thin layer chromatography using 66% ethyl acetate−hexanes as the eluant (developed three times). The pure product was isolated as a glassy, amber solid (80 mg, 52%): mp 43−47 °C; IR ($CHCl_3$) 2949, 1776, 1728, 1641, 1619, 1596, 1570, 1475, 1437, 1368, 1334, 1299, 1229, 1196, 1141, 1120, 1064, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 2.1$ Hz, 1 H), 7.06 (d, $J = 2.4$ Hz, 1 H), 6.73 (s, 1 H), 6.56 (d, $J = 2.0$ Hz, 1 H), 5.98 (t, $J = 7.2$ Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.34 (s, 3 H), 2.94 (t, $J = 7.2$ Hz, 2 H), 2.59 (q, $J = 7.2$ Hz, 2 H), 2.47 (s, 3 H), 2.32 (s, 6 H); ESI HRMS *m/z* calcd for $C_{26}H_{27}N_3O_6$ [MNa^+] 500.1798, found 500.1794; ESIMS *m/z* (relative intensity) 500 (MNa^+, 100).

***S*,*S*′-Dimethyl 5,5′-(4-(5-Methyl-1,3,4-oxadiazol-2-yl)but-1-ene-1,1-diyl)bis(2-methoxy-3-methylbenzothioate) (16).** The general Stille coupling procedure was followed using stannane **75** (165 mg, 0.266 mmol), iodide **45** (114 mg, 0.354 mmol), cesium fluoride (160 mg, 1.05 mmol), $Pd(PPh_3)_4$ (32 mg, 0.029 mmol), and copper(I) iodide (17 mg, 0.089 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 18.5 h. The crude products were purified by column chromatography (100 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The product was isolated as a beige oil (81 mg, 59%): IR (neat) 2928, 2867, 1995, 1793, 1674, 1644, 1595, 1570, 1476, 1419, 1378, 1362, 1307, 1244, 1193, 1159, 1133, 1045, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, $J = 6.6$, 2.4 Hz, 2 H), 7.09 (m, 1 H), 7.06 (m, 1 H), 6.01 (t, $J = 7.5$ Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.93 (t, $J = 7.5$ Hz, 2 H), 2.58 (q, $J = 7.5$ Hz, 2 H), 2.49 (s, 3 H), 2.43 (s, 3 H), 2.39 (s, 3 H), 2.33 (s, 3 H), 2.27 (s, 3 H); ESIMS *m/z* (relative intensity) 549 (MNa^+, 100), 497 ($MH^+ - SCH_3 + H_2O$, 59). Anal. ($C_{27}H_{30}N_2O_5S_2$) C, H, N.

(*Z*)-*S*-Methyl 2-Methoxy-5-(1-(3-methoxy-7-methylbenzo[*d*]-isoxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-3-methylbenzothioate (17). The general Stille coupling procedure was followed using stannane **75** (140 mg, 0.225 mmol), iodide **47** (84 mg, 0.291 mmol), cesium fluoride (127 mg, 0.836 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), and copper(I) iodide (13 mg, 0.068 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 14 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The desired product was isolated as a pale, yellow oil (67 mg, 62%): IR (neat) 2929, 2862, 2230, 1775, 1675, 1641, 1610, 1596, 1570, 1547, 1495, 1477, 1448, 1418, 1394, 1316, 1284, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, $J = 2.1$ Hz, 1 H), 7.17 (s, 1 H), 7.16 (s, 1 H), 7.05 (d, $J = 2.1$ Hz, 1 H), 6.01 (t, $J = 7.5$ Hz, 1 H), 4.13 (s, 3 H), 3.87 (s, 3 H), 2.95 (t, $J = 7.5$ Hz, 2 H), 2.61 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 2.44 (s, 3 H), 2.32 (s, 3 H); ESIMS *m/z* (relative intensity) 516 (MNa^+, 100). Anal. ($C_{26}H_{27}N_3O_5S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(2,7-Dimethyl-3-oxo-2,3-dihydrobenzo[*d*]-isoxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (18). The general Stille coupling procedure was followed using stannane **75** (162 mg, 0.261 mmol), iodide **49** (99 mg, 0.342 mmol), cesium fluoride (150 mg, 0.987 mmol), $Pd(PPh_3)_4$ (29 mg, 0.024 mmol), and copper(I) iodide (16 mg, 0.084 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 15 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using ethyl acetate as the eluant. The desired product was recrystallized from acetone−hexanes (1:3) to afford an off-white solid (84 mg, 65%): mp 123−124 °C; IR ($CHCl_3$) 2929, 2868, 2238, 1689, 1643, 1615, 1596, 1592, 1490, 1436, 1377, 1308, 1243, 1226, 1192, 1155, 1126, 1042, 1000 cm^{-1}; ^1H NMR (300 MHz, methanol-d_4) δ 7.47 (s, 1 H), 7.29 (s, 1 H), 7.24 (d, $J = 1.8$ Hz, 1 H), 7.16 (s, 1 H), 6.19 (t, $J = 7.5$ Hz, 1 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.01 (t, $J = 7.2$ Hz, 2 H), 2.60 (q, $J = 7.5$ Hz, 2 H), 2.46 (s, 3 H), 2.43 (s, 3 H), 2.38 (s, 3 H), 2.34 (s, 3 H); ESIMS *m/z* (relative intensity) 516 (MNa^+, 100), 464 ($MH^+ - SCH_3 + H_2O$, 81). Anal. ($C_{26}H_{27}N_3O_5S$) C, H, N.

(*E*)-*S*-Methyl 5-(1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]-oxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (19). The general Stille coupling procedure was followed using stannane **75** (118 mg, 0.190 mmol), iodide **46** (68 mg, 0.235 mmol), cesium fluoride (107 mg, 0.704 mmol), $Pd(PPh_3)_4$ (23 mg, 0.020 mmol), and copper(I) iodide (8 mg, 0.042 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 14 h. The crude products were purified by preparative thin layer chromatography using 66% ethyl acetate−hexanes as the eluant (developed 4 times). The product was isolated as a clear oil (39 mg, 43%): IR ($CHCl_3$) 2925, 2853, 2252, 1772, 1641, 1597, 1571, 1463, 1376, 1318, 1246, 1153, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, $J = 2.1$ Hz, 1 H), 7.05 (d, $J = 1.8$ Hz, 1 H), 6.73 (s, 1 H), 6.56 (d, $J = 1.5$ Hz, 1 H), 5.98 (t, $J = 7.5$ Hz, 1 H), 3.87 (s, 3 H), 3.34 (s, 3 H), 2.95 (t, $J = 7.5$ Hz, 2 H), 2.61 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 2.32 (s, 6 H); ESIMS *m/z* (relative intensity) 516 (MNa^+, 100). Anal. ($C_{26}H_{27}N_3O_5S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(3-Cyanophenyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (20). The general Stille coupling procedure was followed using stannane **75** (138 mg, 0.222 mmol), bromide **50** (61 mg, 0.340 mmol), cesium fluoride (132 mg, 0.869 mmol), $Pd(PPh_3)_4$ (90 mg, 0.078 mmol), and copper(I) iodide (33 mg, 0.173 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 14 h. The crude products were purified by column chromatography (100 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%), and the desired product was further purified by preparative thin layer chromatography using 2:1 ethyl acetate−hexanes as the eluant. The product was isolated as a clear film (21 mg, 22%): IR (neat) 3065, 2928, 2851, 2229, 1674, 1643, 1596, 1570, 1478, 1416, 1390, 1374, 1313, 1278, 1239, 1178, 1133, 1041, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54−7.32 (m, 5 H), 7.04 (d, $J = 1.8$ Hz, 1 H), 6.12 (t, $J = 7.5$ Hz, 1 H), 3.88 (s, 3 H), 2.95 (t, $J = 7.5$ Hz, 2 H), 2.62 (q, $J = 7.5$ Hz, 2 H), 2.49 (s, 3 H), 2.43 (s, 3 H), 2.34 (s, 3 H); ESIMS *m/z* (relative intensity) 456 (MNa^+, 100), 404 ($MH^+ - SCH_3 + H_2O$, 23). Anal. ($C_{24}H_{23}N_3O_3S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(4-Cyanophenyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (21). The general Stille coupling procedure was followed using stannane **75** (162 mg, 0.261 mmol), bromide **51** (64 mg, 0.340 mmol), cesium fluoride (179 mg, 1.18 mmol), $Pd(PPh_3)_4$ (33 mg, 0.031 mmol),

and copper(I) iodide (18 mg, 0.091 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 24 h. The crude products were purified by column chromatography (80 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%), and the desired product was further purified by preparative thin layer chromatography using 50% ethyl acetate−hexanes as the eluant. The product was isolated as colorless, opaque oil (20 mg, 17%): IR (neat) 2929, 2226, 1674, 1641, 1597, 1570, 1502, 1476, 1409, 1312, 1231, 1136, 1040, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, $J = 8.4$ Hz, 2 H), 7.32−7.25 (m, 3 H), 7.04 (d, $J = 2.1$ Hz, 1 H), 6.19 (t, $J = 7.5$ Hz, 1 H), 3.87 (s, 3 H), 2.95 (t, $J = 7.5$ Hz, 2 H), 2.63 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 2.33 (s, 3 H); ESI HRMS *m/z* calcd for $C_{24}H_{23}N_3O_3S$ [MNa^+] 456.1358, found 456.1362; ESIMS *m/z* (relative intensity) 456 (MNa^+, 100), 404 ($MH^+ - SCH_3 + H_2O$, 21).

(*Z*)-*S*-Methyl 5-(1-(Benzo[*d*]isoxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (22). The general Stille coupling procedure was followed using stannane **75** (118 mg, 0.190 mmol), iodide **48** (75 mg, 0.306 mmol), cesium fluoride (112 mg, 0.737 mmol), $Pd(PPh_3)_4$ (24 mg, 0.021 mmol), and copper(I) iodide (40 mg, 0.210 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 45 min. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The product was isolated as yellow oil (20 mg, 23%): IR ($CDCl_3$) 2928, 2862, 2227, 1672, 1643, 1598, 1569, 1508, 1473, 1416, 1301, 1244, 1226, 1139 cm^{-1}; ^1H NMR (300 MHz, methanol-d_4) δ 7.30 (d, $J = 2.1$ Hz, 1 H), 7.28 (d, $J = 2.4$ Hz, 1 H), 7.24 (d, $J = 2.4$ Hz, 2.4 Hz), 7.21 (d, $J = 1.8$ Hz, 1 H), 7.12 (dd, $J = 2.1$, 0.6 Hz, 1 H), 6.86 (d, $J = 8.7$ Hz, 1 H), 6.08 (t, $J = 7.5$ Hz, 1 H), 3.84 (s, 3 H), 2.98 (t, $J = 7.2$ Hz, 2 H), 2.55 (q, $J = 7.2$ Hz, 2 H), 2.45 (s, 3 H), 2.43 (s, 3 H), 2.33 (s, 3 H); ESI HRMS *m/z* calcd for $C_{24}H_{23}N_3O_4S$ [MH^+] 450.1488, found 450.1490; ESIMS *m/z* (relative intensity) 450 (MH^+, 51), 420 ($MH^+ - SCH_3 + H_2O$, 100).

(*Z*)-*S*-Methyl 5-(1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]-oxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (23). The general Stille coupling procedure was followed using stannane **79** (213 mg, 0.362 mmol), iodide **45** (139 mg, 0.434 mmol), cesium fluoride (202 mg, 1.33 mmol), $Pd(PPh_3)_4$ (46 mg, 0.040 mmol), and copper(I) iodide (15 mg, 0.070 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 3.5 h. The crude products were absorbed onto silica (15 mL) and purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The desired product was further purified by preparative thin layer chromatography using 70% ethyl acetate−toluene as the eluant. The product was isolated as a white, microcrystalline solid after being exposed to high vacuum conditions (92 mg, 51%): mp: 50−53 °C; IR (neat) 2928, 2857, 1779, 1674, 1640, 1618, 1595, 1473, 1420, 1375, 1350, 1298, 1248, 1220, 1177, 1156, 1121, 1057, 1030, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, $J = 2.4$ Hz, 1 H), 7.12 (d, $J = 2.4$ Hz, 1 H), 6.68 (s, 1 H), 6.52 (s, 1 H), 6.04 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 3.37 (s, 3 H), 2.92 (t, $J = 7.5$ Hz, 2 H), 2.57 (q, $J = 7.5$ Hz, 2 H), 2.43 (s, 3 H), 2.39 (s, 3 H), 2.27 (s, 3 H); ESIMS *m/z* (relative intensity) 516 (MNa^+, 100), 494 (MH^+, 29), 464 ($MH^+ - SCH_3 + H_2O$, 81). Anal. ($C_{26}H_{27}N_3O_5S$) C, H, N.

(*E*)-*S*-Methyl 2-Methoxy-5-(1-(3-methoxy-7-methylbenzo[*d*]-isoxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-3-methylbenzothioate (24). The general Stille coupling procedure was followed using stannane **83** (164 mg, 0.278 mmol), iodide **45** (178 mg, 0.553 mmol), cesium fluoride (153 mg, 1.01 mmol), $Pd(PPh_3)_4$ (33 mg, 0.029 mmol), and copper(I) iodide (55 mg, 0.288 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 45 min. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (55−66%). The product was isolated from the column as an orange, amorphous solid (115 mg, 84%): IR (neat) 2928, 2862, 1675, 1644, 1614, 1595, 1570, 1547, 1498, 1475, 1423, 1389, 1350, 1311, 1251, 1233, 1195, 1181, 1157, 1121, 1042, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 2.4$ Hz, 1 H), 7.19 (s, 1 H), 7.10 (d, $J = 1.5$ Hz, 1 H), 7.00 (s, 1 H), 6.06 (t, $J = 7.5$ Hz, 1 H), 4.17 (s, 3 H), 3.80 (s, 3 H), 2.92 (t, $J = 7.5$ Hz, 2 H), 2.56 (q, $J = 7.5$ Hz, 2 H), 2.49 (s, 3 H), 2.47 (s, 3 H), 2.41 (s. 3 H), 2.26 (s, 3 H); ESI HRMS *m/z* calcd for $C_{26}H_{27}N_3O_5S$ [MH^+] 494.1750, found 494.1742; ESIMS *m/z* (relative intensity) 516 (MNa^+, 13), 494 (MH^+, 15), 464 ($MH^+ - SCH_3 + H_2O$, 100).

(*E*)-*S*-Methyl 5-(1-(2,7-Dimethyl-3-oxo-2,3-dihydrobenzo[*d*]-isoxazol-5-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (25). The general Stille coupling procedure was followed using stannane **87** (134 mg, 0.228 mmol), iodide **45** (88 mg, 0.273 mmol), cesium fluoride (123 mg, 0.810 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), and copper(I) iodide (49 mg, 0.257 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (40 mL of silica, 1.5 in. diameter) using ethyl acetate as the eluant. The product was isolated from the column as an orange oil (86 mg, 76%): IR (neat) 2926, 2855, 1778, 1692, 1615, 1595, 1570, 1493, 1477, 1438, 1376, 1301, 1251, 1224, 1193, 1121, 1047 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J = 1.2$ Hz, 1 H), 7.33 (d, $J = 2.4$ Hz, 1 H), 7.09 (d, $J = 2.4$ Hz, 2 H), 6.05 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 2.92 (t, $J = 7.5$ Hz, 2 H), 2.56 (q, $J = 7.5$ Hz, 2 H), 2.49 (s, 3 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 2.26 (s, 3 H); ESIMS *m/z* (relative intensity) 516 (MNa^+, 8), 494 (MH^+, 48), 464 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{26}H_{27}N_3O_5S$) C, H, N.

(*E*)-*S*-Methyl 5-(1-(3-Cyanophenyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (26). The general Stille coupling procedure was followed using stannane **91** (138 mg, 0.261 mmol), iodide **45** (128 mg, 0.397 mmol), cesium fluoride (157 mg, 1.03 mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol), and copper(I) iodide (54 mg, 0.284 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (50 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The desired product was isolated as a yellow oil (85 mg, 75%): IR (neat) 3063, 2929, 2860, 2229, 1674, 1639, 1595, 1570, 1477, 1418, 1356, 1304, 1227, 1183, 1130, 1049, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (dt, $J = 7.8$, 1.5 Hz, 1 H), 7.52 (t, $J = 7.8$ Hz, 1 H), 7.39 (tt, $J = 7.8$, 1.5 Hz, 2 H), 7.30 (d, $J = 2.4$ Hz, 1 H), 7.07 (d, $J = 1.8$ Hz, 1 H), 6.11 (t, $J = 7.5$ Hz, 1 H), 3.81 (s, 3 H), 2.94 (t, $J = 7.5$ Hz, 2 H), 2.55 (q, $J = 7.5$ Hz, 2 H), 2.50 (s, 3 H), 2.43 (s, 3 H), 2.27 (s, 3 H); ESIMS *m/z* (relative intensity) 434 (MH^+, 8), 404 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{24}H_{23}N_3O_3S$) C, H, N.

(*E*)-*S*-Methyl 5-(1-(4-Cyanophenyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)but-1-enyl)-2-methoxy-3-methylbenzothioate (27). The general Stille coupling procedure was followed using stannane **95** (118 mg, 0.223 mmol), iodide **45** (102 mg, 0.317 mmol), cesium fluoride (131 mg, 0.862 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), and copper(I) iodide (43 mg, 0.226 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The desired product was isolated as an orange oil (74 mg, 77%): IR (neat) 2929, 2856, 2227, 1733, 1674, 1643, 1595, 1570, 1503, 1476, 1421, 1357, 1303, 1251, 1222, 1178, 1136, 1109, 1048, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.1$ Hz, 2 H), 7.30 (d, $J = 2.4$ Hz, 1 H), 7.24 (d, $J = 8.1$ Hz, 2 H), 7.08 (d, $J = 2.1$ Hz, 1 H), 6.10 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 2.93 (t, $J = 7.5$ Hz, 2 H), 2.56 (q, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.42 (s, 3 H), 2.27 (s, 3 H); ESI HRMS *m/z* calcd for $C_{24}H_{23}N_3O_3S$ [MH^+] 434.1538, found 434.1529; ESIMS *m/z* (relative intensity) 434 (MH^+, 16), 404 ($MH^+ - SCH_3 + H_2O$, 100).

***S,S′*-Dimethyl 5,5′-(5-(5-Methyl-1,3,4-oxadiazol-2-yl)pent-1-ene-1,1-diyl)bis(2-methoxy-3-methylbenzothioate) (28).** The general Stille coupling procedure was followed using stannane **77** (213 mg, 0.335 mmol), iodide **45** (131 mg, 0.402 mmol), cesium fluoride (215 mg, 1.42 mmol), $Pd(PPh_3)_4$ (78 mg, 0.067 mmol), and copper(I) iodide (13 mg, 0.068 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 13.5 h. The crude products were

purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The product was isolated as an orange oil (126 mg, 70%): IR (neat) 2929, 2866, 1675, 1644, 1595, 1570, 1476, 1421, 1378, 1362, 1308, 1244, 1228, 1192, 1154, 1133, 1043, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 2.4$ Hz, 1 H), 7.36 (d, $J = 1.8$ Hz, 1 H), 7.08 (m, 2 H), 5.99 (t, $J = 7.5$ Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.80 (t, $J = 7.5$ Hz, 2 H), 2.47 (s, 3 H), 2.45 (s, 3 H), 2.43 (s, 3 H), 2.32 (s, 3 H), 2.27 (s, 3 H), 2.22 (q, $J = 7.5$ Hz, 2 H), 1.93 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 563 (MNa^+, 100), 533 (MH^+, 9). Anal. ($C_{28}H_{32}N_2O_5S_2$) C, H, N.

(*Z*)-*S*-Methyl 2-Methoxy-5-(1-(3-methoxy-7-methylbenzo[*d*]-isoxazol-5-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-3-methylbenzothioate (29). The general Stille coupling procedure was followed using stannane **77** (411 mg, 0.647 mmol), iodide **47** (231 mg, 0.779 mmol), cesium fluoride (443 mg, 2.92 mmol), $Pd(PPh_3)_4$ (78 mg, 0.067 mmol), and copper(I) iodide (29 mg, 0.152 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred for 15 h. The crude products were absorbed onto silica (20 mL) and purified by column chromatography (100 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The desired product was isolated as an amorphous, yellow solid (212 mg, 65%): IR (neat) 2930, 2867, 1675, 1642, 1614, 1596, 1570, 1547, 1494, 1477, 1455, 1424, 1394, 1315, 1275, 1240, 1223, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, $J = 2.1$ Hz, 1 H), 7.19 (s, 1 H), 7.18 (s, 1 H), 7.09 (d, $J = 2.1$ Hz, 1 H), 6.01 (t, $J = 7.5$ Hz, 1 H), 4.15 (s, 3 H), 3.89 (s, 3 H), 2.83 (t, $J = 7.5$ Hz, 2 H), 2.48 (s, 3 H), 2.47 (s, 3 H), 2.46 (s, 3 H), 2.33 (s, 3 H), 2.26 (q, $J = 7.5$ Hz, 2 H), 1.95 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 508 (MH^+, 5), 478 ($MH^+ - SCH_3 + H_2O$, 100), 460 ($MH^+ - SCH_3$, 13). Anal. ($C_{27}H_{29}N_3O_5S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(2,7-Dimethyl-3-oxo-2,3-dihydrobenzo[*d*]-isoxazol-5-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (30). The general Stille coupling procedure was followed using stannane **77** (154 mg, 0.242 mmol), iodide **49** (90 mg, 0.311 mmol), cesium fluoride (134 mg, 0.882 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and copper(I) iodide (50 mg, 0.263 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The desired product was isolated as a yellow oil (90 mg, 73%): IR (neat) 3479, 2929, 2868, 1693, 1681, 1646, 1596, 1570, 1489, 1434, 1401, 1377, 1242, 1226, 1126, 1043 cm^{-1}; ^1H NMR (300 MHz, methanol-d_4) δ 7.47 (s, 1 H), 7.30 (s, 2 H), 7.18 (s, 1 H), 6.17 (t, $J = 7.5$ Hz, 1 H), 3.84 (s, 3 H), 3.70 (s, 3 H), 2.86 (t, $J = 7.5$ Hz, 2 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.39 (s, 3 H), 2.33 (s, 3 H), 2.24 (q, $J = 7.5$ Hz, 2 H), 1.95 (p, $J = 7.5$ Hz, 2 H); ESI HRMS *m/z* calcd for $C_{27}H_{29}N_3O_5S$ [MH^+] 508.1906, found 508.1904; ESIMS *m/z* (relative intensity) 530 (MNa^+, 100).

(*Z*)-*S*-Methyl 5-(1-(3-Cyanophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (31). The general Stille coupling procedure was followed using stannane **77** (92 mg, 0.145 mmol), bromide **50** (41 mg, 0.225 mmol), cesium fluoride (87 mg, 0.572 mmol), $Pd(PPh_3)_4$ (18 mg, 0.018 mmol), and copper(I) iodide (16 mg, 0.084 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 30 min. The crude products were purified by column chromatography (60 mL of silica, 1 in. diameter) using an ethyl acetate−hexanes gradient (50−66%), and the desired product was further purified via preparative thin layer chromatography using 66% ethyl acetate−hexanes as the eluant (developed twice). The pure product was obtained as a light, yellow oil (33 mg, 51%): IR (neat) 3063, 2930, 2866, 2228, 1995, 1726, 1675, 1643, 1595, 1570, 1478, 1416, 1394, 1378, 1239, 1175, 1133, 1043, 1000 cm^{-1}; ^1H NMR (300 MHz, methanol-d_4) δ 7.61−7.55 (m, 2 H), 7.47−7.45 (m, 2 H), 7.29 (s, 1 H), 7.18 (s, 1 H), 6.26 (t, $J = 7.5$ Hz, 1 H), 3.84 (s, 3 H), 2.85 (t, $J = 7.5$ Hz, 2 H), 2.45 (s, 3 H), 2.43 (s, 3 H), 2.33 (s, 3 H), 2.25 (q, $J = 7.5$ Hz, 2 H), 1.96 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 470 (MNa^+, 52), 418 ($MH^+ - SCH_3 + H_2O$, 100), 400 ($MH^+ - SCH_3$, 76). Anal. ($C_{25}H_{25}N_3O_3S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(4-Cyanophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (32). The general Stille coupling procedure was followed using stannane **77** (171 mg, 0.269 mmol), bromide **51** (71 mg, 0.390 mmol), cesium fluoride (173 mg, 1.14 mmol), $Pd(PPh_3)_4$ (36 mg, 0.031 mmol), and copper(I) iodide (26 mg, 0.135 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 30 min. The crude products were purified by column chromatography (100 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The product was isolated from the column as a yellow oil (71 mg, 59%): IR (neat) 2931, 2867, 2226, 1674, 1643, 1599, 1570, 1503, 1476, 1409, 1231, 1179, 1136, 1043, 1000 cm^{-1}; ^1H NMR (300 MHz, methanol-d_4) δ 7.64 (dd, $J = 6.9$, 1.8 Hz, 2 H), 7.37 (dd, $J = 6.6$, 1.8 Hz, 2 H), 7.28 (d, $J = 2.1$ Hz, 1 H), 7.17 (d, $J = 2.1$ Hz, 1 H), 6.33 (t, $J = 7.5$ Hz, 1 H), 3.84 (s, 3 H), 2.85 (t, $J = 7.5$ Hz, 2 H), 2.46 (s, 3 H), 2.42 (s, 3 H), 2.33 (s, 3 H), 2.25 (q, $J = 7.5$ Hz, 2 H), 1.96 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 448 (MH^+, 11), 418 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{25}H_{25}N_3O_3S$) C, H, N.

(*Z*)-*S*-Methyl 5-(1-(3,7-Dimethyl-2-oxo-2,3-dihydrobenzo[*d*]-oxazol-5-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (33). The general Stille coupling procedure was followed using stannane **81** (160 mg, 0.266 mmol), iodide **45** (127 mg, 0.394 mmol), cesium fluoride (144 mg, 0.948 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol), and copper(I) iodide (56 mg, 0.294 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1.5 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−80%). The desired product was isolated as a yellow oil (81 mg, 60%): IR (neat) 3534, 2929, 2865, 1779, 1771, 1674, 1641, 1618, 1570, 1471, 1421, 1389, 1375, 1351, 1298, 1242, 1229, 1171, 1153, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, $J = 2.7$ Hz, 1 H), 7.11 (d, $J = 2.7$ Hz, 1 H), 6.71 (s, 1 H), 6.55 (s, 1 H), 6.02 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 3.38 (s, 3 H), 2.79 (t, $J = 7.5$ Hz, 2 H), 2.46 (s, 3 H), 2.43 (s, 3 H), 2.39 (s, 3 H), 2.27 (s, 3 H), 2.18 (q, $J = 7.5$ Hz, 2 H), 1.92 (p, $J = 7.5$ Hz, 2 H); ESI HRMS *m/z* calcd for $C_{27}H_{29}N_3O_5S$ [MH^+] 508.1906, found 508.1908; ESIMS *m/z* (relative intensity) 508 (MH^+, 14), 478 ($MH^+ - SCH_3 + H_2O$, 100), 460 ($MH^+ - SCH_3$, 33).

(*E*)-*S*-Methyl 2-Methoxy-5-(1-(3-methoxy-7-methylbenzo[*d*]-isoxazol-5-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-3-methylbenzothioate (34). The general Stille coupling procedure was followed using stannane **85** (123 mg, 0.204 mmol), iodide **45** (106 mg, 0.329 mmol), cesium fluoride (125 mg, 0.823 mmol), $Pd(PPh_3)_4$ (25 mg, 0.022 mmol), and copper(I) iodide (42 mg, 0.221 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The desired product was isolated as a yellow, amorphous solid (81 mg, 60%): IR (neat) 2930, 1675, 1596, 1570, 1548, 1498, 1389, 1233, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, $J = 2.1$ Hz, 1 H), 7.22 (s, 1 H), 7.09 (d, $J = 2.1$ Hz, 1 H), 7.04 (s, 1 H), 6.05 (t, $J = 7.5$ Hz, 1 H), 4.17 (s, 3 H), 3.80 (s, 3 H), 2.77 (t, $J = 7.5$ Hz, 2 H), 2.47 (s, 3 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.26 (s, 3 H), 2.12 (q, $J = 7.5$ Hz, 2 H), 1.91 (p, $J = 7.5$ Hz, 2 H); ESI HRMS *m/z* calcd for $C_{27}H_{29}N_3O_5S$ [MH^+] 508.1906, found 508.1905; ESIMS *m/z* (relative intensity) 508 (MH^+, 8), 408 ($MH^+ - SCH_3 + H_2O$, 100).

(*E*)-*S*-Methyl 5-(1-(2,7-Dimethyl-3-oxo-2,3-dihydrobenzo[*d*]-isoxazol-5-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (35). The general Stille coupling procedure was followed using stannane **89** (127 mg, 0.211 mmol), iodide **45** (116 mg, 0.360 mmol), cesium fluoride (138 mg, 0.908 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), and copper(I) iodide (45 mg, 0.236 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 45 min. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−100%). The desired product was isolated as a yellow oil (80 mg, 75%): IR (neat) 2929, 2865, 1694, 1682, 1644, 1615, 1596, 1570, 1493, 1477, 1439, 1422, 1395, 1365,

1303, 1251, 1224, 1191, 1173, 1154, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, $J = 0.9$ Hz, 1 H), 7.34 (d, $J = 2.4$ Hz, 1 H), 7.11 (s, 1 H), 7.08 (d, $J = 1.8$ Hz, 1 H), 6.03 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 2.77 (t, $J = 7.5$ Hz, 2 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 2.35 (s, 3 H), 2.26 (s, 3 H), 2.19 (q, $J = 7.5$ Hz, 2 H), 1.91 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 530 (MNa^+, 27), 478 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{27}H_{29}N_3O_5S$) C, H, N.

(*E*)-*S*-Methyl 5-(1-(3-Cyanophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (36). The general Stille coupling procedure was followed using stannane **93** (86 mg, 0.159 mmol), iodide **45** (68 mg, 0.211 mmol), cesium fluoride (106 mg, 0.698 mmol), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol), and copper(I) iodide (40 mg, 0.210 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The product was isolated from the column as an orange, viscous oil (51 mg, 72%): IR (neat) 3060, 2930, 2862, 2229, 1995, 1674, 1643, 1596, 1570, 1478, 1418, 1307, 1252, 1227, 1173, 1130, 1048, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (dt, $J = 7.5$, 1.5 Hz, 1 H), 7.51 (t, $J = 7.5$ Hz, 1 H), 7.43−7.38 (m, 2 H), 7.32 (d, $J = 2.4$ Hz, 1 H), 7.06 (d, $J = 1.8$ Hz, 1 H), 6.08 (t, $J = 7.5$ Hz, 1 H), 3.81 (s, 3 H), 2.79 (t, $J = 7.5$ Hz, 2 H), 2.77 (s, 3 H), 2.48 (s, 3 H), 2.27 (s, 3 H), 2.18 (q, $J = 7.5$ Hz, 2 H), 1.93 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 470 (MNa^+, 41), 448 (MH^+, 18), 418 ($MH^+ - SCH_3 + H_2O$, 100). Anal. ($C_{25}H_{25}N_3O_3S$) C, H, N.

(*E*)-*S*-Methyl 5-(1-(4-Cyanophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)pent-1-enyl)-2-methoxy-3-methylbenzothioate (37). The general Stille coupling procedure was followed using stannane **97** (179 mg, 0.330 mmol), iodide **45** (158 mg, 0.490 mmol), cesium fluoride (222 mg, 1.46 mmol), $Pd(PPh_3)_4$ (42 mg, 0.036 mmol), and copper(I) iodide (50 mg, 0.352 mmol) in anhydrous DMF (3 mL). The reaction mixture was stirred for 1 h. The crude products were purified by column chromatography (60 mL of silica, 1.5 in. diameter) using an ethyl acetate−hexanes gradient (50−66%), and the desired product was isolated as a highly viscous, yellow oil (103 mg, 70%): IR (neat) 2930, 2868, 2227, 1674, 1643, 1596, 1570, 1500, 1476, 1418, 1305, 1251, 1221, 1136, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, $J = 6.6$, 1.5 Hz, 2 H), 7.31 (d, $J = 2.4$ Hz, 1 H), 7.26 (dd, $J = 6.6$, 1.5 Hz, 2 H), 7.06 (d, $J = 1.8$ Hz, 1 H), 6.09 (t, $J = 7.5$ Hz, 1 H), 3.80 (s, 3 H), 2.79 (t, $J = 7.5$ Hz, 2 H), 2.47 (s, 3 H), 2.43 (s, 3 H), 2.26 (s, 3 H), 2.19 (q, $J = 7.5$ Hz, 2 H), 1.93 (p, $J = 7.5$ Hz, 2 H); ESIMS *m/z* (relative intensity) 448 (MH^+, 42) 447 (M^+, 51), 418 ($MH^+ - SCH_3 + H_2O$, 100), 400 ($MH^+ - SCH_3$, 37). Anal. ($C_{25}H_{25}N_3O_5S$) C, H, N.

General Procedure for the Synthesis of Stannane Intermediates via Palladium-Catalyzed Hydrostannation of Alkynes. A solution of alkyne **40** (1 equiv) in anhydrous THF (0.02−0.05 M) was cooled in an ice bath, sparged with argon for 15 min, and maintained under an inert atmosphere at 0 °C. The catalyst, $Pd(PPh_3)_4$ (0.01 equiv), was added to the THF solution, followed by tributyltin hydride (1.2−1.5 equiv). The heterogeneous reaction mixture was stirred at 0 °C, under an argon atmosphere, for 30 min to 2 h. If the reaction had not reached completion after approximately 2 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1−24 h. The reaction mixture was concentrated in vacuo, and the remaining residue was absorbed onto silica. The products were separated by column chromatography to obtain the stannane product, and, if necessary, additional purification methods were applied.

General Procedure for the Synthesis of Functionalized Alkyne Intermediates via the Sonogashira Coupling Reaction of Aryl Halides with Terminal Alkynes. A mixture of alkyne **39** (1.2−1.5 equiv), aryl halide **38** (1 equiv), and triethylamine (2.5 equiv) in anhydrous THF (0.1−0.5 M) was cooled in an ice bath, sparged with argon for 15 min, and maintained under an inert atmosphere. After being allowed to warm back to room temperature, $PdCl_2(PPh_3)_2$ (0.1 equiv) and copper(I) iodide (0.2 equiv) were added. The heterogeneous reaction mixture was stirred at room temperature, under an argon atmosphere, for 3−24 h. The reaction mixture was concentrated in vacuo, and the remaining residue was absorbed onto silica. The products were separated by column chromatography to obtain the desired alkyne product, and, if necessary, additional purification methods were applied.

5-Iodo-2-methoxy-3-methylthiobenzoic Acid *S*-Methyl Ester (45). A flask was charged with benzoic acid **52** (251 mg, 0.859 mmol) and thionyl chloride (3.4 mL). The flask was fitted with a condenser and the system heated at reflux, under argon, for 40 min. The system was allowed to cool to room temperature, and the reaction mixture was azeotropically condensed in vacuo with benzene (2 mL). More benzene (3 mL) was added, and the reaction mixture was concentrated again to azeotrope any remaining thionyl chloride (this step was repeated two more times). A white solid was obtained after concentrating the reaction mixture (occasionally the material is a yellow oil). The solid was dissolved in benzene (3 mL), and sodium thiomethoxide (77 mg, 1.10 mmol) was added to the solution. The heterogeneous mixture was stirred at room temperature for 15 h and was then diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). Organic extracts were combined, dried over magnesium sulfate, filtered, and condensed in vacuo to afford an oil. The product was purified by column chromatography (30 mL of silica, 0.5 in. diameter) using 5% ethyl acetate−hexanes as the eluant. The product was isolated as a clear oil (215 mg, 78%): IR (neat) 3066, 2926, 1995, 1674, 1642, 1565, 1465, 1414, 1255, 1173, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, $J = 2.4$, 0.6 Hz, 1 H), 7.65 (dd, $J = 2.4$, 0.6 Hz, 1 H), 3.80 (s, 3 H), 2.46 (s, 3 H), 2.28 (s, 3 H); EIMS *m/z* (relative intensity) 322 (M^+, 2), 275 (M^+ - SCH_3, 100). Anal. ($C_{10}H_{11}IO_2S$) C, H.

5-Iodobenzo[*d*]isoxazole (48). An oven-dried flask (25 mL) was charged with oxime **54** (180 mg, 0.684 mmol), triphenylphosphine (192 mg, 0.720 mmol), and anhydrous THF (4 mL). The flask was maintained under an argon atmosphere, and diisopropylazodicarboxylate (DIAD) (0.14 mL, 0.719 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h before more triphenylphosphine (30 mg) and DIAD (0.5 mL) were added. After the reaction mixture was stirred for another hour, the mixture was condensed in vacuo and the remaining residue was loaded onto a short column of silica (20 mL, 0.5 in. diameter). The product was eluted with 20% ethyl acetate−hexanes (80 mL), and the eluate was condensed in vacuo to afford a yellow solid. The material was recrystallized from acetone and hexanes to afford the product as a white, crystalline solid (77 mg, 46%): mp 102−103 °C; IR ($CDCl_3$) 3085, 3056, 1995, 1896, 1782, 1755, 1724, 1621, 1597, 1506, 1435, 1417, 1269, 1254, 1224, 1167, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, $J = 0.9$ Hz, 1 H), 8.10 (d, $J = 1.8$ Hz, 1 H), 7.82 (dd, $J = 8.7$, 1.5 Hz, 1 H), 7.42 (d, $J = 8.7$ Hz, 1 H); CIMS *m/z* (relative intensity) 246 (MH^+, 100). Anal. (C_7H_4INO) C, H, N.

5-Iodo-2-methoxy-3-methylbenzoic Acid (52). A flask was charged with ester **44**[19] (266 mg, 0.869 mmol) and methanol (40 mL). Solid potassium hydroxide (506 mg, 9.02 mmol) was added, and the reaction mixture was stirred until all of the solids had dissolved. The flask was fitted with a condenser, and the system was heated at reflux, under an argon atmosphere, for 19 h. The system was allowed to cool to room temperature, and the reaction mixture was condensed in vacuo to afford a yellow oil. The oil was partitioned between water (10 mL) and ethyl acetate (20 mL), followed by separation of the two phases. The aqueous phase was cooled in an ice bath and acidified to a pH of 1, via slow addition of concentrated hydrochloric acid, to produce a white precipitate. The precipitate was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL), dried over magnesium sulfate, filtered, and condensed in vacuo to afford a white, fluffy solid (248 mg, 85%): mp 163−165 °C; IR (KBr) 3434, 2947, 2560, 1673, 1567, 1467, 1299, 1252, 1223, 1170, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 2.4$ Hz, 1 H), 7.76 (d, $J = 1.8$ Hz, 1 H), 3.92 (s, 3 H), 2.34 (s, 3 H); ESIMS *m/z* (relative intensity) 291 (M− - H, 100). Anal. ($C_9H_9IO_3$) C, H.

2-Hydroxy-5-iodobenzaldehyde Oxime (54). A solution of aldehyde **53** (472 mg, 1.90 mmol) in ethanol (10 mL) was heated at 70 °C, and an aqueous solution of hydroxylamine hydrochloride (3.70 g, 53.3 mmol in 15 mL of water) was added. The reaction mixture was stirred for 1 h and then cooled to room temperature. The reaction mixture was diluted with water (50 mL), and the resulting heterogeneous mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and condensed in vacuo to afford the product as a white solid (489 mg, 98%): mp 134−135 °C; IR ($CDCl_3$) 3416, 3137, 2945, 2225, 1873, 1769, 1640, 1616, 1555, 1477, 1429, 1359, 1288, 1255, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 8.14 (s, 1 H), 7.55 (dd, J = 8.7, 2.1 Hz, 1 H), 7.47 (d, J = 2.1 Hz, 1 H), 7.19 (s, 1 H), 6.76 (d, J = 8.7 Hz, 1 H); EIMS m/z (relative intensity) 263 (M^+, 100), 245 ($M^+ - H_2O$, 27). Anal. ($C_7H_6NIO_2$) C, H, N.

5-But-3-ynyl-1*H*-tetrazole (57). A flask was charged with nitrile **55** (8.449 g, 0.107 mol) and toluene (100 mL). Triethylamine hydrochloride (29.49 g, 0.214 mol) was added to the flask, followed by sodium azide (14.05 g, 0.216 mol). The flask was fitted with a condenser, and the system was heated at reflux for 9.5 h. During the course of the reaction a second, black layer formed at the bottom of the flask. The system was allowed to cool to room temperature, and the reaction mixture was diluted with water (35 mL). The phases were separated, and the organic phase was extracted with water (3 × 10 mL). Aqueous extracts were combined and acidified to a pH of 1 through the addition of concentrated hydrochloric acid. The acidified extracts were stored at 5 °C for several hours to obtain a white precipitate. The precipitate was extracted with ethyl acetate (200 mL), and the organic phase was dried over magnesium sulfate, filtered, and condensed in vacuo to afford the product as an off-white solid (5.734 g, 49%). An analytical sample was prepared by recrystallization from ethyl acetate−hexanes (1:4): mp 59−61 °C; IR ($CHCl_3$) 3684, 3617, 3412, 3308, 3020, 2978, 2897, 2400, 2243, 1885, 1602, 1520, 1476, 1423, 1219 1046, 929 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.20 (t, J = 7.2 Hz, 2 H), 2.73 (dt, J = 7.2, 2.7 Hz, 2 H), 2.41 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 123 (MH^+, 100). Anal. ($C_6H_6N_4$) C, H, N.

5-Pent-4-ynyl-1*H*-tetrazole (58). A flask (100 mL) was charged with nitrile **56** (1.12 mL, 0.011 mol) and toluene (20 mL). Triethylamine hydrochloride (4.41 g, 0.032 mol) and sodium azide (2.06 g, 0.032 mol) were added to the solution, and the resulting mixture was heated at reflux for 9 h. As the reaction progressed, a black liquid formed at the bottom of the reaction vessel. The system was allowed to cool to room temperature, and the reaction mixture was extracted with water (4 × 10 mL). Aqueous extracts were combined and acidified to a pH of 1 by adding concentrated hydrochloric acid. The aqueous phase was extracted with ethyl acetate (4 × 20 mL), and the combined organic extracts were dried over magnesium sulfate, filtered, and condensed in vacuo to afford a yellow oil that, when triturated with hexanes, solidified to a low melting point solid (1.259 g, 84%): mp 24−26 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.31 (s, 1 H), 2.95 (t, J = 7.5 Hz, 2 H), 2.84 (t, J = 2.7 Hz, 1 H), 2.25 (dt, J = 7.2, 2.7 Hz, 2 H), 1.87 (p, J = 7.2 Hz, 2 H); CIMS m/z (relative intensity) 137 (MH^+, 100). Anal. ($C_6H_8N_4$) C, H, N.

5-But-3-ynyl-1-methyl-1*H*-tetrazole (59) and 5-But-3-ynyl-2-methyl-2*H*-tetrazole (61). A flask was charged with tetrazole **57** (1.504 g, 12.3 mmol) and ethyl acetate (30 mL). Tetrabutylammonium bromide (419 mg, 1.30 mmol) and dimethyl sulfate (1.74 mL, 18.4 mmol) were added to the flask, followed by an aqueous solution (30 mL) saturated with potassium carbonate (14.40 g). The biphasic mixture was stirred vigorously for 16 h, and then the phases were separated. The organic phase was dried over magnesium sulfate, filtered, and condensed in vacuo to afford a yellow oil. The products were separated by column chromatography (75 mL of silica gel, 2 in. diameter column) using 50% ethyl acetate−hexanes as eluant. Two methylated tetrazole products were isolated after column chromatography: solid **59** (553 mg, 33%) and liquid **61** (792 mg, 47%). The physical constants determined for **59**: mp 47−49 °C; IR ($CHCl_3$) 3684, 3622, 3019, 2977, 2895, 2400, 1520, 1476, 1424, 1218, 1046, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 3 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.78 (dt, J = 7.2, 2.7 Hz, 2 H), 2.02 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 137 (MH^+, 100). Anal. ($C_6H_8N_4$) C, H, N.

5-But-3-ynyl-2-methyl-2*H*-tetrazole (61). IR (neat) 3290, 2958, 2925, 2119, 1497, 1440, 1395, 1330, 1194 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (s, 3 H), 3.12 (t, J = 7.5 Hz, 2 H), 2.69 (dt, J = 7.5, 2.7 Hz, 2 H), 1.98 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 137 (MH^+, 100). Anal. ($C_6H_8N_4$) C, H, N.

1-Methyl-5-pent-4-ynyl-1*H*-tetrazole (60) and 2-Methyl-5-pentyl-4-ynyl-2*H*-tetrazole (62). A saturated aqueous solution of potassium carbonate (25 mL) was added to a mixture of tetrazole **58** (1.52 g, 0.011 mol), tetrabutylammonium bromide (373 mg, 1.16 mmol), and dimethyl sulfate (1.60 mL, 0.017 mol) in ethyl acetate (25 mL). The biphasic mixture was stirred vigorously at room temperature for 7 h. The phases were separated, and the organic phase was washed with water (1 × 20 mL) and brine (1 × 20 mL), dried over magnesium sulfate, filtered, and condensed in vacuo to afford a brown oil. The products were purified by column chromatography (40 mL of silica, 1 in. diameter) using 50% ethyl acetate−hexanes as the eluant. Tetrazoles **60** (593 mg, 36%) and **62** (825 mg, 50%) were isolated as clear oils. The physical constants determined for **60**: IR (neat) 3920, 3465, 3285, 2955, 2873, 2116, 1633, 1526, 1468, 1455, 1434, 1415, 1349, 1332, 1286, 1239, 1152, 1095, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 3.00 (t, J = 7.5 Hz, 2 H), 2.35 (dt, J = 6.6, 2.7 Hz, 2 H), 2.06 (p, J = 6.6 Hz, 2 H), 2.02 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 151 (MH^+, 100). Anal. ($C_7H_{10}N_4$) C, H, N.

2-Methyl-5-pentyl-4-ynyl-2*H*-tetrazole (62). IR (neat) 3921, 3291, 2957, 2870, 2116, 1496, 1435, 1395, 1348, 1329, 1295, 1191, 1078, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (s, 3 H), 3.01 (t, J = 7.5 Hz, 2 H), 2.31 (dt, J = 6.9, 2.7 Hz, 2 H), 2.01 (p, J = 7.2 Hz, 2 H), 1.99 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 151 (MH^+, 100). Anal. ($C_7H_{10}N_4$) C, H, N.

2-But-3-ynyl-5-methyl-[1,3,4]oxadiazole (63). A flask was charged with tetrazole **57** (1.50 g, 12.3 mmol) and acetic anhydride (25 mL). The flask was fitted with a condenser, and the system was heated at reflux for 20 h. The system was allowed to cool to room temperature, and the reaction mixture was concentrated in vacuo to afford a black-yellow residue. The residue was dissolved in ethyl acetate (30 mL), and the organic solution was washed with an aqueous solution saturated with sodium bicarbonate (3 × 20 mL) and brine (1 × 10 mL). The organic phase was dried over magnesium sulfate, filtered, and condensed in vacuo to afford a brown oil. The product was purified by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (50−66%). The desired product was isolated as a clear oil (834 mg, 50%): IR ($CHCl_3$) 3690, 3606, 3309, 3155, 2984, 2902, 2254, 1817, 1793, 1732, 1643, 1598, 1572, 1471, 1382, 1096, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03 (t, J = 7.3 Hz, 2 H), 2.67 (dt, J = 7.2, 2.7 Hz, 2 H), 2.46 (s, 3 H), 2.43 (t, J = 2.7 Hz, 1 H); CIMS m/z (relative intensity) 137 (MH^+, 100). Anal. ($C_7H_8N_2O$) C, H, N.

2-Methyl-5-pent-4-ynyl-[1,3,4]oxadiazole (64). A solution of tetrazole **58** (3.16 g, 0.023 mol) in acetic anhydride (22 mL) was heated at reflux for 24 h and then allowed to cool to room temperature. The mixture was diluted with water (30 mL) and basified to a pH of 8 through the addition of concentrated ammonium hydroxide. The mixture was extracted with ether (3 × 40 mL) and ethyl acetate (1 × 30 mL). The organic extracts were combined, washed with brine (1 × 40 mL), dried over magnesium sulfate, and condensed in vacuo to afford a yellow oil. The crude products were purified by column chromatography (100 mL of silica, 2 in. diameter) using an ethyl acetate−hexanes gradient (33−50%). The product was isolated as a yellow oil (2.44 g, 91%): IR (neat) 3453, 3290, 2942, 2873, 2648, 2117, 1725, 1702, 1597, 1571, 1435, 1394, 1367, 1348, 1330, 1278, 1224, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, J = 7.5 Hz, 2 H), 2.50 (s, 3 H), 2.34 (dt, J = 6.9, 2.7 Hz, 2 H), 2.06−1.99 (m, 3 H); CIMS m/z (relative intensity) 151 (MH^+, 100). Anal. ($C_8H_{10}N_2$) C, H, N.

RT Inhibition Assay. The ability of target compounds to inhibit the enzymatic activity of recombinant HIV-1 RT (p66/51 dimer) was evaluated as previously described.[15,28] Briefly, inhibition of purified HIV-1 reverse transcriptase was determined by the amount of ^{32}P labeled GTP incorporated into a nascent DNA strand, with a poly(rC)oligo(dG) homopolymer primer, in the presence of increasing concentrations of the target compounds.

In Vitro Antiviral Assays. The antiviral activities of the target compounds were determined for the HIV strains HIV-1_{RF}, HIV-1_{IIIB}, and HIV-2_{ROD}. Evaluation of antiviral activity against HIV-1_{RF} was determined in infected CEM-SS cells while using the XTT cytoprotection assay, as previously described.[28] Evaluation of antiviral activity against the HIV-1_{IIIB} and HIV-2_{ROD} strains was performed in infected MT-4 cells using the previously described MTT assay.[18,29] Cytoprotective evaluations against the engineered HIV strains bearing Y181C and K103N RT mutations were performed as previously reported.[25,26]

In Vitro Hydrolytic Stability Assay Utilizing Rat Plasma. The compounds of interest were tested for their hydrolytic stability in solutions of reconstituted rat plasma using methods that have been previously reported.[18] The internal standard used was 1,1-diphenylethylene, and two different batches of rat plasma had to be utilized for the experiments (LOTs 052K7609 and 065K7555). A control compound was tested in both batches of rat plasma to ensure that the hydrolysis rates of the two batches were approximately equivalent. The aliquot supernatants were analyzed using a Waters binary HPLC system (model 1525, 20 μL injection loop) and a Waters dual wavelength absorbance UV detector (model 2487) set for 254 nM. Data were collected and processed using the Waters Breeze software (version 3.3) on a Dell Optiplex GX280 personal computer. The mobile phase consisted of 8:2 (v/v) acetonitrile/water, and the Symmetry HPLC column (4.6 mm x 150 mm) was packed with C_{18} Silica from Waters. The column was maintained at room temperature during the analyses. The reported half-lives for the compounds are averages calculated from a minimum of two replicates. Half-lives for the individual replicates were calculated from regression curves fitted to plots of the compound concentration versus time.

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Supporting Information Available: Schemes and experimental procedures pertaining to synthetic intermediates not presented; synthesis of compound **4**; analytical HPLC traces and data; elemental analysis results for compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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