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Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity

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A series of 1,2,4-oxadiazoles has been prepared as ester bioisosteres and tested against 15 human rhinovirus serotypes, and the MIC_{80}, the concentration which inhibits 80% or 12 of the serotypes tested, was determined. Homologation of the alkyl group attached to the oxadiazole ring resulted in a reduction in activity with increased chain length. Introduction of hydrophilic groups in this position rendered the compounds inactive. Increasing the length of the side chain attached to the isoxazole ring resulted in an increase in activity. Replacement of the methyl with alkoxyalkyl substituents retained activity; however, introduction of a hydroxyl group on to the side chain reduced activity. Compound **8a**, where both the isoxazole and oxadiazole rings were substituted with methyl groups, was one of the most active compounds in the series. A comparison was made between **8a** and the two isomeric oxadiazoles **41** and **46**, and an attempt was made to explain the difference in activity by examining electrostatic potential maps and by an energy profiling study. No conclusive results were obtained from these studies.

The antipicornaviral activity of compounds related to disoxaril (1) (Figure 1) has been well documented.[1] This series of compounds emanated from the ester **2**[1a] which had been shown to be active against human rhino- and enteroviruses but which exhibited very low oral bioavailability in mice due to hydrolysis of the ester. The corresponding acid was inactive. Initial efforts to improve upon the activity and stability of this molecule led to the synthesis of disoxaril and WIN 54954 (**3**),[1c] where the ester moiety was replaced with an oxazoline ring as an ester bioisostere. Both of these compounds were evaluated clinically. Disoxaril was removed from clinical studies due to the appearance of crystallurea at high dose levels. WIN 54954 was evaluated in phase 2 against three rhinovirus serotypes as well as an enterovirus, coxsackievirus A-21. No statistical effect was seen against the rhinoviruses;[2] however, a positive effect resulted from the coxsackievirus A-21 trial.[3] WIN 54954, however, had a very short half-life, partially due to the acid lability of the oxazoline ring, which may have been responsible for the poor clinical results.

Other variations of the oxazoline ring were prepared with the intent of discovering more hydrolytically stable analogues with comparable activity.[4] This study resulted in the synthesis and evaluation of the 2-methyltetrazole analogues[5] which were acid stable while maintaining potent broad spectrum activity. WIN 61605 (**48**), which resulted from this study, was considered a clinical candidate for the treatment of rhino- and enteroviral infections. Unfortunately, this compound caused an increase in the liver production of cytochrome P450 when administered to beagles. As a result of this study, WIN 61605 was dropped from further consideration. The assumption was made that the hepatotoxic effects may have resulted from the tetrazole ring or a metabolic product thereof. Consequently, the search for other ester bioisosteres was undertaken.

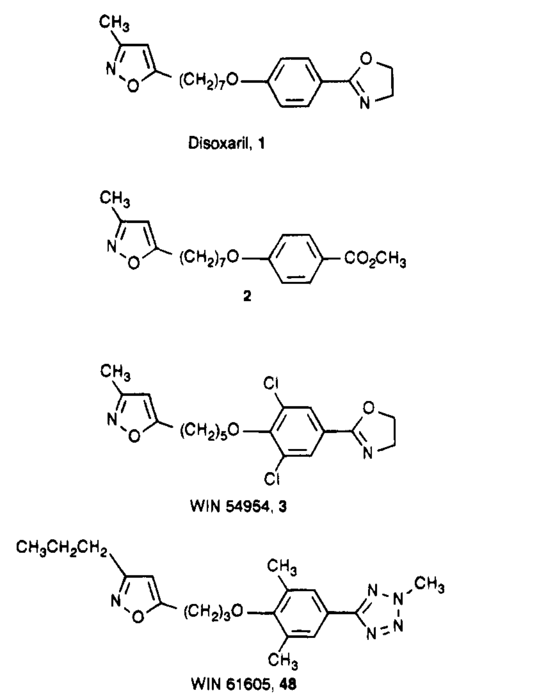

Figure 1. Structures of disoxaril, ester **2**, WIN 54954, and WIN 61605.

Oxadiazoles were first proposed as ester bioisosteres in conjunction with muscarinic agonist activity[6,7] and benzodiazopine receptor partial agonist activity.[8] Consequently, we pursued this avenue and prepared some 1,2,4-oxadiazoles.

Chemistry

Several methods were developed to synthesize analogues in this series, depending upon the substitution pattern. Those compounds with various functionalities on the oxadiazole ring and a methyl group on the isoxazole ring were synthesized according to Schemes 1–3. The (chloroalkyl)isoxazole **5** was treated with the benzonitrile **4** which gave nitrile **6a**.[5] Treatment of **6a**

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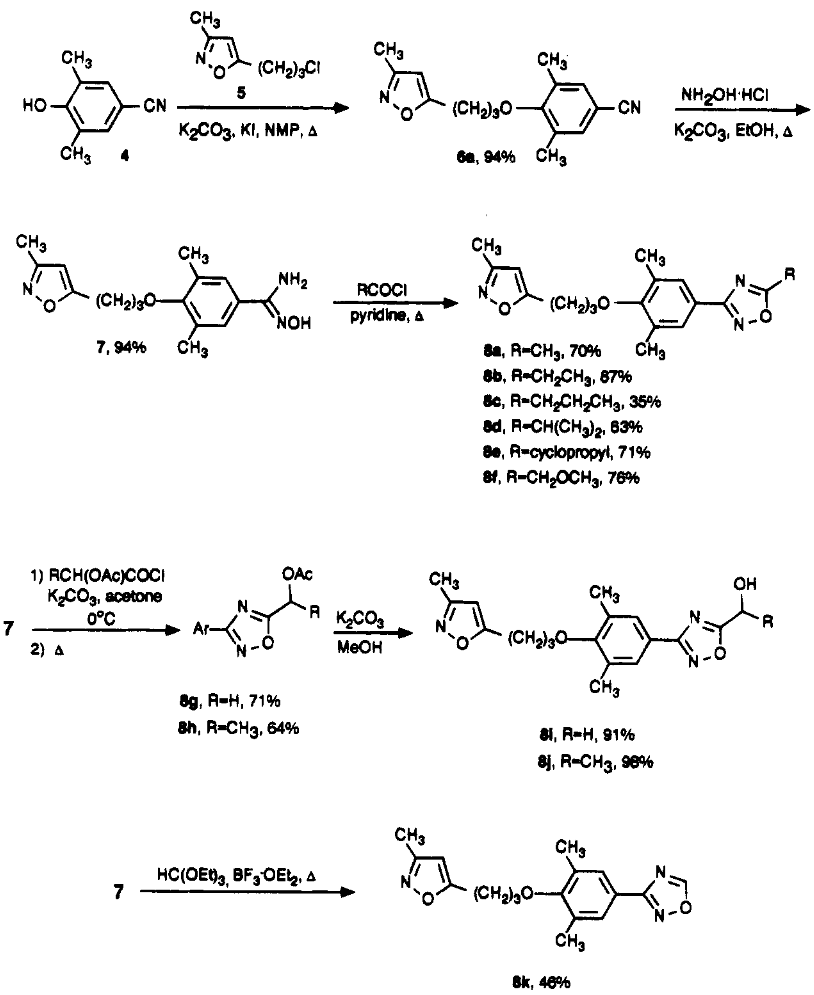
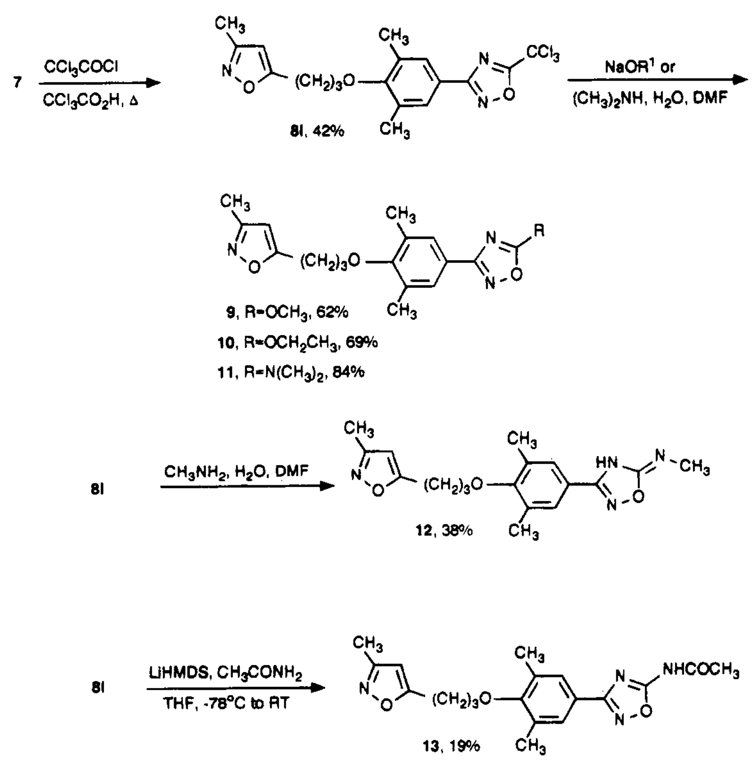
Scheme 1

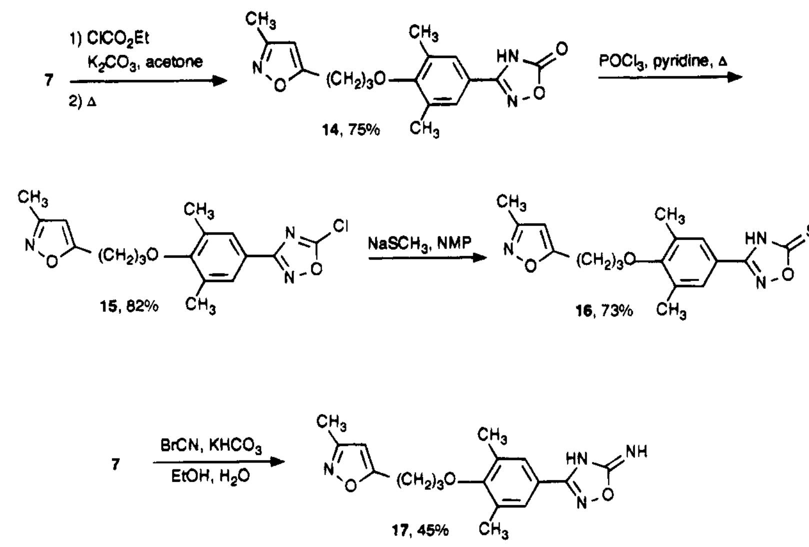


Scheme 2

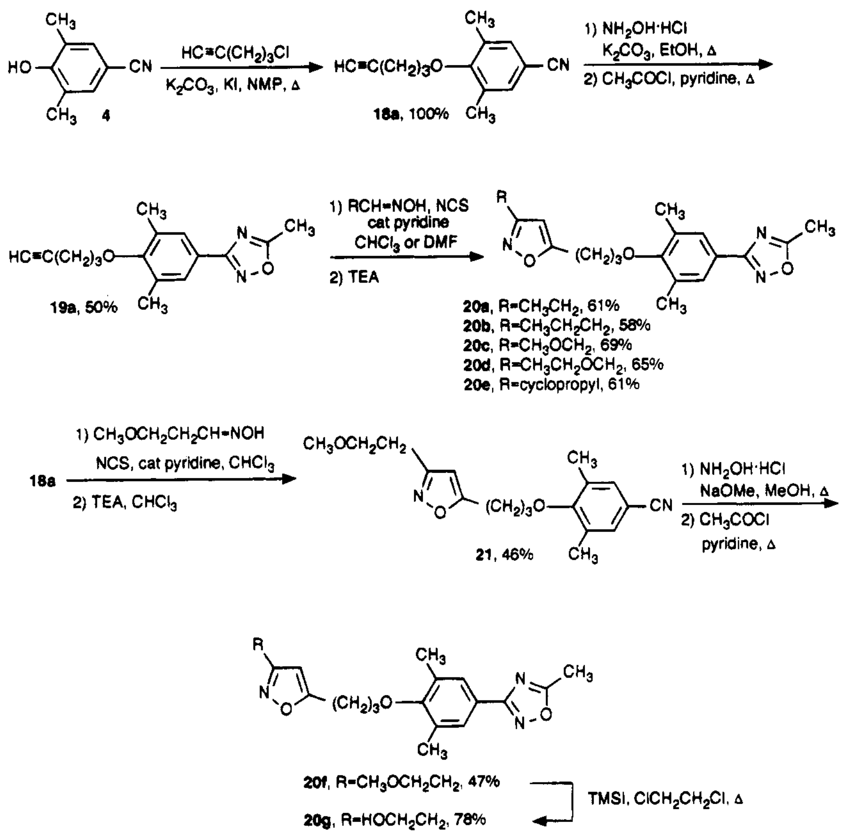


with hydroxylamine hydrochloride and potassium carbonate gave amidoxime **7** which was acylated with the appropriate acid chloride to give the 5-substituted oxadiazoles **8a–f**. Compounds **8g** and **8h** were pre-

Scheme 3



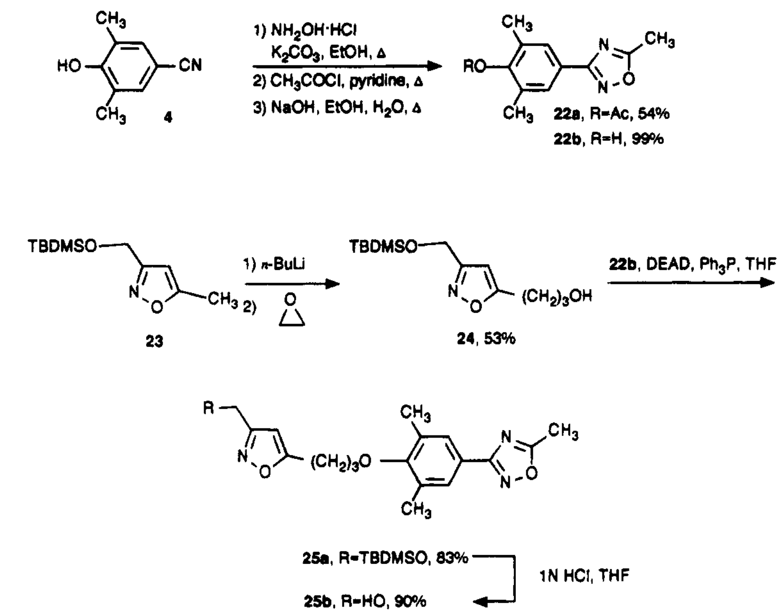
Scheme 4



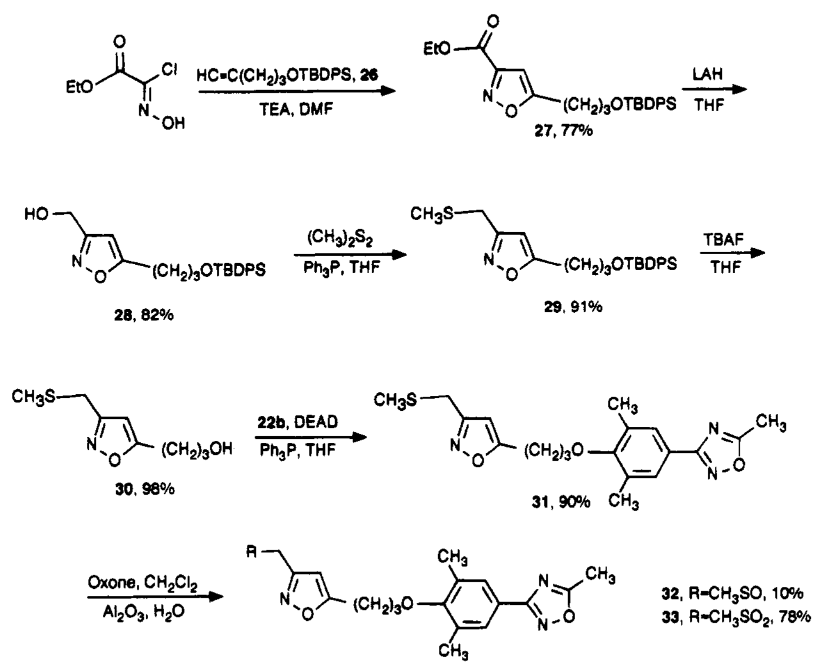
pared by thermolysis of the O-acylated amidoxime. Methanolysis of **8g** and **8h** provided alcohols **8i** and **8j** in 91% and 98% yield, respectively. The desmethyl analogue **8k** was prepared by treatment of **7** with triethyl orthoformate and boron trifluoride etherate. The alkoxy analogues **9** and **10** and dimethylamino (**11**), methylamino (**12**), and acetamido (**13**) oxadiazoles were obtained by displacement of the trichloromethyl group of **8l** with the appropriate nucleophile[9] (Scheme 2). The oxadiazolone **14** was prepared by treatment of amidoxime **7** with ethyl chloroformate and thermolysis of the resulting O-acylated amidoxime (Scheme 3). Treatment of **14** with $POCl_3$ gave chlorooxadiazole **15** which reacted with excess sodium thiomethoxide to give the thio analogue **16**. The iminooxadiazole **17** was prepared from **7** and CNBr.

To functionalize the 3-position of the isoxazole ring, the chemistry described in Scheme 4 was employed. Nitrile **18a**, prepared from **5** and 5-chloropentyne, was converted to oxadiazole **19a** via the amidoxime as described in Scheme 1. The desired isoxazoles **20a–e** were obtained from a [3 + 2] cycloaddition reaction of **19a** and the nitrile oxide derived from the appropriate hydroxamoyl chloride and triethylamine.[10] Demethylation of **20f** provided **20g**. The hydroxymethyl analogue **25b** was prepared according to Scheme 5. Formation of the oxadiazole phenol **22b** was achieved by treatment of nitrile **4** with hydroxylamine followed by

Scheme 5



Scheme 6

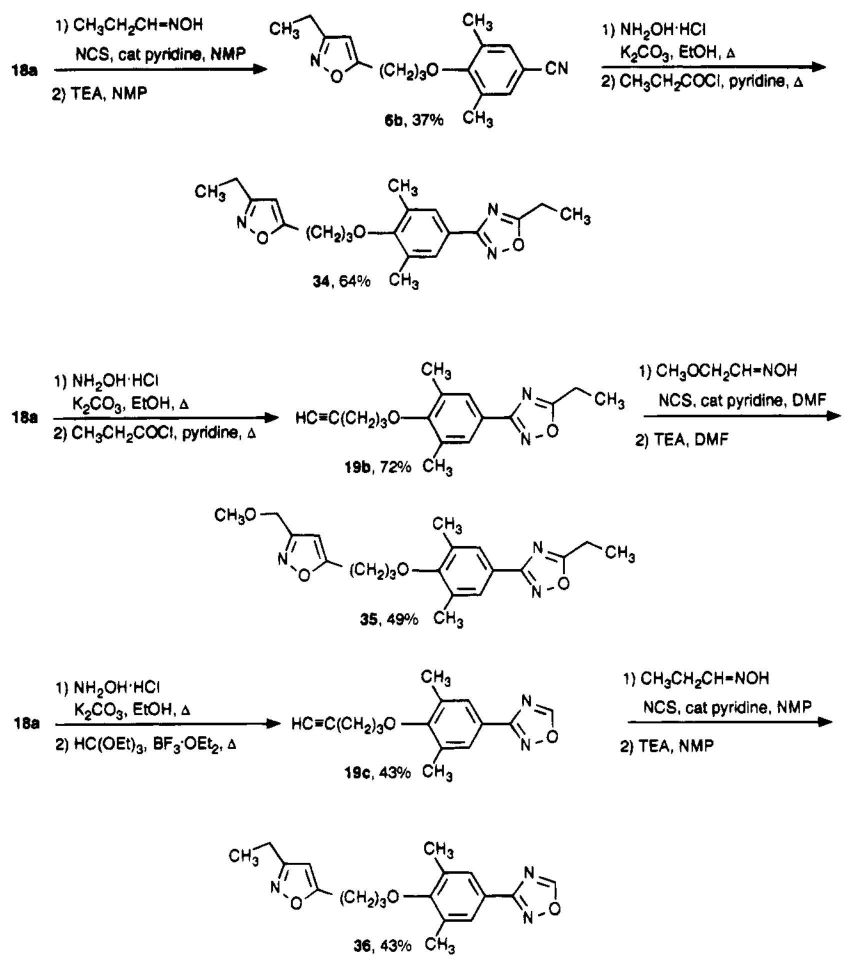


acylation of the resultant amidoxime with acetyl chloride and basic hydrolysis of the derived acetate. Phenol **22b** was then coupled with alcohol **24**, prepared from **23** and ethylene oxide in 53% yield. Removal of the protecting group of **25a** was accomplished by treatment with 1 N HCl in THF to give **25b** in 90% yield. The methylthio analogue **31** was synthesized by the method described in Scheme 6. Reaction of the nitrile oxide prepared from ethyl chlorooximidoacetate with diphenyl-*tert*-butylsilyl ether **26** gave isoxazole **27** in 77% yield. Reduction of the resultant ester with LAH gave alcohol **28** which was reacted with the reagent prepared from dimethyl disulfide and triphenylphosphine[11] to give the thio ether **29** in 91% yield. Removal of the protecting group was accomplished with tetrabutylammonium fluoride in 98% yield. Mitsunobu[12] coupling of alcohol **30** with phenol **22b** gave **31** in 90% yield. Compound **31** was oxidized with oxone in the presence of wet alumina[13] resulting in a mixture of sulfoxide **32** and sulfone **33** in 10% and 78% yield, respectively. Compounds **34–36** (Scheme 7) and dichlorophenyl analogues **37–39** (Scheme 8) were prepared by employing the chemistry described in Schemes 1 and 4. The syntheses of the two isomeric oxadiazoles **41** and **46** are described in Scheme 9. Hydrolysis of nitrile **6a** resulted in a 64% yield of amide **40** which was converted to the acylamidine with dimethylacetamide dimethyl acetal (DMADMA).[14] Cyclization with hydroxylamine gave **41** in 42% yield. Oxadiazole **46** was obtained by the cyclodehydration of the diacylhydrazine **45**.[15]

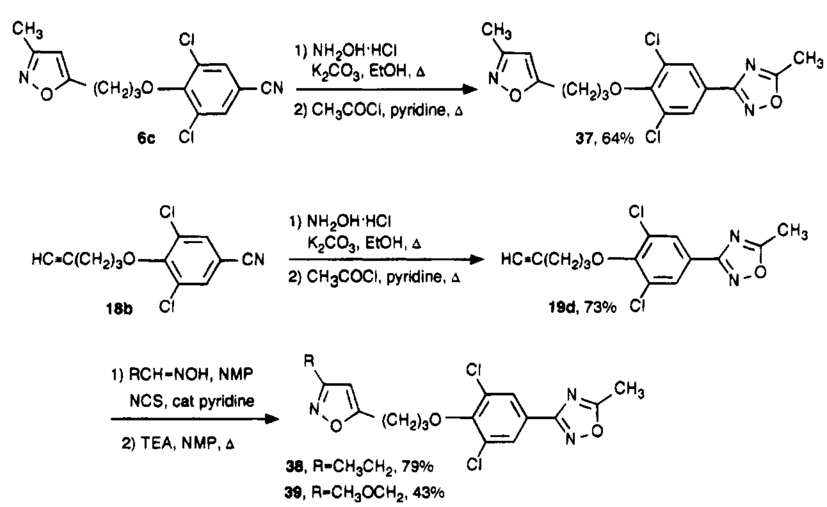
Results and Discussion

Compounds were tested against 15 human rhinovirus serotypes in a $TCID_{50}$ assay (see the Experimental Section). The MIC_{80} was determined as the concentration of drug which inhibits 80% of the serotypes tested.

Scheme 7



Scheme 8



The results of varying the substituents on the oxadiazole ring are shown in Table 1. The methyl homologue **8a** demonstrated excellent activity against the 15 serotypes. When compared to the corresponding tetrazole **47**[5] (Table 5), compound **8a** was approximately 3-fold more potent as measured by the MIC_{80}. Increasing the side chain to *n*-propyl resulted in a progressive decrease in activity, while removal of the side chain entirely (**8k**) rendered the compound only weakly active. The hydroxymethyl analogue **8i** was considerably less active than **8a**; however, the corresponding methyl ether **8f** was only slightly less active. This effect is understandable when considering the hydrophobic nature of the drug-binding pocket. Similarly, the addition of a hydroxyl group to the ethyl analogue **8b** drastically reduced activity. Replacement of the methyl group of **8a** with a methoxy (**9**) moderately reduced activity; however, the ethoxy analogue **10** had activity comparable to that of **8a**. Finally, the introduction of hydrophilic groups such as hydroxy (**14**), amino (**17**), and thio (**16**) resulted in compounds which were completely inactive.

Modifications of the methyl group on the isoxazole ring are shown in Tables 2 and 3. The results of

Scheme 9

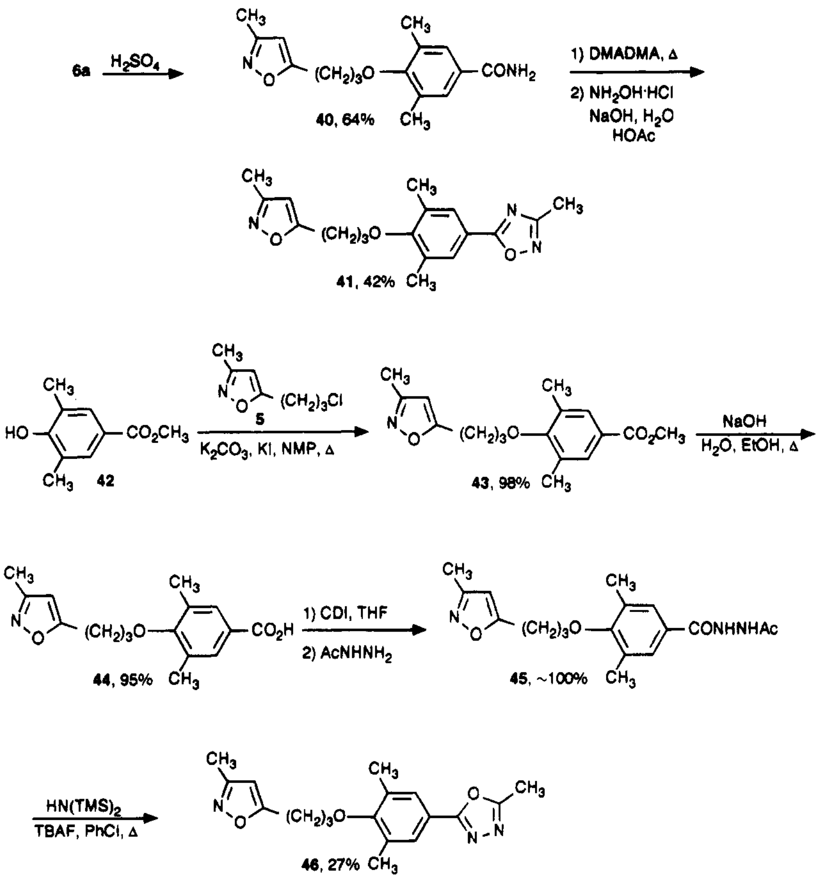
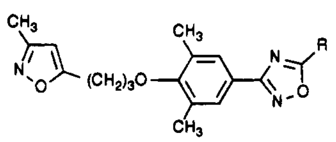


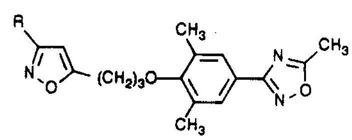
Table 1. Antirhinovirus Activity of Oxadiazole 5-Position Analogues



compd	R	mp (°C)	formula[a]	in vitro activity (μM) MIC$_{80}$[b]
8a	CH_3	82.5–84	$C_{18}H_{21}N_3O_3$	0.26
8b	C_2H_5	67.5–68	$C_{19}H_{23}N_3O_3$	0.32
8c	*n*-C_3H_7	74–75	$C_{20}H_{25}N_3O_3$	0.79
8d	*i*-C_3H_7	72–73	$C_{20}H_{25}N_3O_3$	0.93
8e	cyclopropyl	85–86	$C_{20}H_{23}N_3O_3$	0.54
8k	H	62.5–63	$C_{17}H_{19}N_3O_3$	*c*
8f	CH_3OCH_2	63–64	$C_{19}H_{23}N_3O_4$	0.43
8i	$HOCH_2$	116–117	$C_{18}H_{21}N_3O_4$	3.6
8g	$CH_3CO_2CH_2$	77–78	$C_{21}H_{25}N_3O_5$	2.1
8j	CH_3CHOH	83–87	$C_{19}H_{23}N_3O_4$	*c*
14	HO	194–95	$C_{17}H_{19}N_3O_4$	*c*
9	CH_3O	64.5–65.5	$C_{18}H_{21}N_3O_4$	0.39
10	C_2H_5O	70–72.5	$C_{19}H_{23}N_3O_4$	0.23
17	NH_2	175–183	$C_{17}H_{20}N_4O_3$	*c*
12	CH_3NH	126.5–127	$C_{18}H_{22}N_4O_3$	0.95
11	$(CH_3)_2N$	123–127	$C_{19}H_{24}N_4O_3$	0.80
13	CH_3CONH	137–138	$C_{19}H_{22}N_4O_4$	*c*
16	HS	162–165	$C_{17}H_{19}N_3O_3S$	*c*
WIN 54954				0.90

[a] Satisfactory analyses were obtained. [b] Concentration which inhibits 80% (12) of the serotypes tested. Values were determined from 15 serotypes. [c] Inactive against the majority of serotypes.

Table 2. Antirhinovirus Activity of Isoxazole 3-Position Analogues

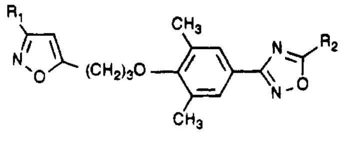


compd	R	mp (°C)	formula[a]	MIC$_{80}$ (μM)[b]
8a	CH_3	82.5–84	$C_{18}H_{21}N_3O_3$	0.26
20a	C_2H_5	80–81	$C_{19}H_{23}N_3O_3$	0.26
20b	*n*-C_3H_7	69–70	$C_{20}H_{25}N_3O_3$	0.21
20c	CH_3OCH_2	50–50.5	$C_{19}H_{23}N_3O_4$	0.22
20d	$C_2H_5OCH_2$	45.5–46	$C_{20}H_{25}N_3O_4$	0.19
20f	$CH_3O(CH_2)_2$	oil	$C_{20}H_{25}N_3O_4$	0.24
20e	cyclopropyl	50.5–51	$C_{20}H_{23}N_3O_3$	0.20
25b	$HOCH_2$	87–87.5	$C_{18}H_{21}N_3O_4$	0.73
20g	$HO(CH_2)_2$	68–69.5	$C_{19}H_{23}N_3O_4$	1.5
31	CH_3SCH_2	91–91.5	$C_{19}H_{23}N_3O_3S$	0.32
32	CH_3SOCH_2	82–83	$C_{19}H_{23}N_3O_4S$	1.0
33	$CH_3SO_2CH_2$	135–136	$C_{19}H_{23}N_3O_5S$	0.77

[a] Satisfactory analyses were obtained. [b] The minimum concentration which inhibits 80% (12) of the serotypes tested in a TCID$_{50}$ test. The values were determined using 15 serotypes.

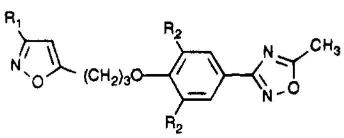
increasing the side chain were comparable to those seen in the corresponding tetrazole series. A gradual increase in activity was observed against the 15 serotypes. Replacement of the methyl group with either a methoxymethyl (**20c**), ethoxymethyl (**20d**), methoxyethyl (**20f**), or methylthio (**31**) retained activity. The corresponding sulfoxide **32** and sulfone **33** were less active. Hydroxylation of the methyl group (**25b**) reduced activity, and the hydroxyethyl homologue **20g** exhibited a further reduction in activity. Replacing the methyl groups on both the isoxazole and oxadiazole rings with ethyl groups (**34**) (Table 3) reduced activity slightly; however, when the ethyl group on the isoxazole ring of **34** was replaced with a methoxymethyl (**35**), a substan-

Table 3. Antirhinovirus Activity of 3-Ethylisoxazole and 5-Ethyloxadiazole Analogues



compd	R_1	R_2	mp (°C)	formula	MIC_{80} (μM)
8a	CH_3	CH_3			0.26
20a	C_2H_5	CH_3	80–81	$C_{19}H_{23}N_3O_3$	0.26
8b	CH_3	C_2H_5	67.5–68.5	$C_{19}H_{23}N_3O_3$	0.32
34	C_2H_5	C_2H_5	oil	$C_{20}H_{25}N_3O_3$	0.40
35	CH_3OCH_2	C_2H_5	oil	$C_{20}H_{25}N_3O_4$	0.21
36	C_2H_5	H	53–54	$C_{18}H_{21}N_3O_3$	3.2

Table 4. Antirhinovirus Activity of Phenyl Dimethyl and Dichloro Analogues



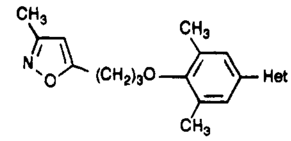
			MIC_{80} (μM)	
compd	R_1	R_2	15 serotypes	54 serotypes
8a	CH_3	CH_3	0.26	0.30
37	CH_3	Cl	0.19	0.30
20b	CH_3CH_2	CH_3	0.26	0.26
38	CH_3CH_2	Cl	0.22	0.23
20c	CH_3OCH_2	CH_3	0.22	0.45
39	CH_3OCH_2	Cl	0.18	0.19

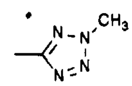
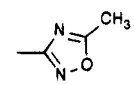
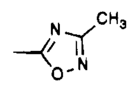
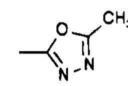
tial improvement in activity was observed. Removal of the ethyl group attached to the oxadiazole ring (**36**) resulted in a dramatic decrease in activity.

The results which we have observed reinforce observations previously reported with regard to the binding site of these compounds on the viral capsid. Although at the present time the X-ray structure of only three rhinovirus serotypes have been reported,[16–18] the SAR particularly around the oxadiazole ring strongly suggests that space constraints generally exist around the toe end of the binding pocket and that extensions off of the isoxazole ring enhance hydrophobic interactions and consequently improve activity. These results are in agreement with conclusions obtained from volume map[19] and CoMFA studies[20] associated with related series of compounds bound to HRV-14. A comparison of the binding sites of HRV-14 and -1A has also revealed the hydrophobic nature of the pocket as well as the space constraints which exist in both serotypes.[21,22] It is also interesting to note that the introduction of hydrophilic groups on the oxadiazole ring, which is situated in the hydrophobic toe of the binding sites of HRV-14 and -1A, is extremely detrimental to antiviral activity.

We have found in related series that the dimethyl- and dichlorophenyl compounds display comparable antirhinovirus activity.[5,6] We have chosen to explore the SAR in the dimethylphenyl series due to the greater bioavailability of the latter. A comparison of the MIC_{80} values for compounds **8a**, **20b**, and **20c** with their corresponding dichloro analogues **37–39** is shown in Table 4. The MIC_{80} values for 54 serotypes[1e] as well as for the original 15 are included. For the methyl and ethyl analogues, the differences are slight with the

Table 5. Comparative Evaluation of Isomeric Oxadiazoles



Compd	Het	MIC_{80} (N=15)	HRV-14	E (kcals/mol)[a]
47		0.71	2.3	342.541[b]
8a		0.26	0.070	318.086[c]
41		0.73	0.19	360.354[c]
46		3.70	8.9	306.968[c]

[a] Charges calculated from the Gasteiger and Marsili method.[32] [b] Ring conformation obtained from X-ray crystallography of compound bound to HRV-14. [c] Ring conformation obtained by modeling using compound **47** as a template.

dichloro analogues exhibiting some improvement. However in the case of compounds **20c** and **39**, greater than a 2-fold difference is seen between these analogues after screening against 54 serotypes. Compound **20c** is being evaluated further.

The antipicornaviral activity of compound **8a** was compared to the other two isomeric oxadiazoles **41** and **46** as well as the tetrazole analogue **47**[5] (Table 5). The relative antirhinovirus potency of the two 1,2,4- and the 1,3,4-oxadiazoles parallels the analysis performed in the muscarinic antagonist area.[7] It has been shown that the location of the electrostatic potential in these two cases differs in that the regions of negative potential are symmetrical in the case of the 1,3,4-oxadiazole and not in the case of the 1,2,4-oxadiazole. The latter result is similar to the electrostatic potential map of the methyl ester. These results support the conclusions that the 1,2,4-oxadiazoles more closely approximate the bioisosteric role of ester. In our case, there is a dramatic difference in the MIC_{80} between the two oxadiazole regioisomers.

In order to explore the significance of these results, we examined the electrostatic potentials of the three oxadiazoles and the complementary area surrounding these rings in the binding site of HRV-14, in search of some positive or negative interaction which could possibly explain this phenomenon. The complementary maps[23] shed no light on the question. Despite the increase in the negative potential on atom 3 of the 1,3,4-oxadiazole as compared to the 1,2,4-oxadiazoles and the slight reduction in the potential at atom 5, there does not appear to be any major repulsive effects within the binding site. In addition, there appears to be no difference in the electrostatic complementarity between the three oxadiazoles and the receptor-binding site, perhaps due to the low charge potential on the rings. The result is not surprising in view of previous studies which have shown that the effects of electrostatics on antiviral activity of these compounds are minimal.

Furthermore, calculation of the energy of each compound within the binding site using WIN 61605 (**48**) as a template (Figure 2) suggested that in their bound conformations, all three isomeric oxadiazoles exhibited energies which were not dramatically different (Table 5). An energy profiling study also demonstrated that the compounds are in their lowest energy conformations within the binding site as modeled from the X-ray crystallography results of the tetrazole analogue. We have previously reported other anomalies with respect to divergence in biological activity within analogous heterocyclic series.[4] Again, attempts to explain these differences were unsuccessful.

One can only conclude that the interactions of these molecules in their bound conformations are not the only critical factors determining the extent of binding and hence biological activity. The existence of closely related recognition sites distinct from the binding site for each serotype is a strong possibility, and such a recognition site has been recently suggested for HRV-14.[24] However, in view of the diversity of the chemical structures which have been examined against this serotype and the fact that there are over 100 distinct serotypes, it would be difficult to determine the nature of this recognition site, let alone its location.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20SX FTIR. NMR spectra were acquired in the indicated solvent on a JEOL-FX270, a General Electric QE-300, or a Bruker-AC200 FTNMR. HETCOR ($^1H-^{13}C$ correlation) and DEPT experiments were utilized to assist in peak assignments. Mass spectra were recorded on a Nermag R10/10 spectrometer coupled to a Varian 3400 gas chromatograph or on a JEOL JMS-01SC spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or Quantitative Technologies Inc., Whitehouse, NJ. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Thin layer chromatography (TLC) was performed on E. Merck 1 × 3, Kieselgel 60 F-254 plates. Flash[25] and medium pressure liquid chromatography (MPLC) were performed with E.M. Science silica gel 60 (40–63 μm, 230–400 mesh). Dry flash chromatography[26] was performed with E.M. Science silica gel 60H. High-boiling solvents (DMF, NMP) were stage-dried over molecular sieves, chloroform was passed through a column of silica gel 60 and dried (Na_2SO_4) prior to use, and THF and ether were distilled from sodium–benzophenone ketyl. Organic extracts were dried with $MgSO_4$ unless otherwise noted. All moisture sensitive reactions were performed in dried glassware under a nitrogen or argon atmosphere.

$TCID_{50}$ Assay. MIC values were determined by an automated tissue culture infectious dose of 50%. HeLa cells in monolayers in 96-well cluster plates were infected with a dilution of virus which had been shown empirically to produce 80–100% cytopathic effect (CPE) in 3 days in the absence of drug. The compound to be tested was serially diluted through 10 2-fold cycles and added to the infected cells. After a 3 day incubation at 33 °C and 2.5% carbon dioxide, the cells were fixed with a 5% solution of glutaraldehyde followed by staining with a 0.25% solution of crystal violet in water. The plates were then rinsed and dried, and the amount of stain remaining in the well (a measure of intact cells) was determined to be the concentration of compound which protected 50% of the cells from virus-induced CPE relative to an untreated virus control. The compounds were tested against a panel of 15 serotypes, namely, HRV-1A, -1B, -2, -6, -14, -15, -21, -22, -25, -30, -41, -50, -67, -86, and -89. The MIC_{80} value is the minimum concentration of compound required to inhibit 80% of the serotypes.

3,5-Dichloro-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzonitrile (6c). A mixture of 3,5-dichloro-4-hydroxybenzonitrile (1.00 g, 5.32 mmol), **5**[4] (0.92 g, 5.9 mmol), NMP (10 mL), finely divided K_2CO_3 (1.4 g, 10 mmol), and KI (0.10 g, 0.60 mmol) was heated at 60 °C for 60 h. The cooled reaction mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic phases were washed with water, 10% NaOH (2×), and brine, dried, and filtered through a short column of Florisil to provide 1.78 g of a yellow oil. Flash chromatography (20% ethyl acetate in hexanes) provided 1.34 g (80.7%) of pure **6c** as a colorless oil. Crystallization from methanol provided **6c** as a fine white solid: mp 69.5–70.5 °C; IR (KBr, cm^{-1}) 3134, 2958, 2234, 1605, 1460, 1441, 1383, 1270, 1027, 903, 883, 815; ^1H NMR ($CDCl_3$) δ 7.62 (s, 2H), 5.91 (s, 1H), 4.15 (t, J = 6.2 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.34 (s, 6H), 2.26 (m, 2H); ^{13}C NMR (ppm) 171.66, 159.78, 155.53, 132.50, 130.68, 116.18, 109.25, 101.92, 72.76, 27.96, 23.13, 11.39. Anal. ($C_{14}H_{12}Cl_2N_2O_2$) C, H, N.

***N*-Hydroxy-3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzenecarboxamide Imine (7).** A mixture of **6a**[5] (18.4 g, 68.1 mmol), absolute ethanol (200 mL), finely divided K_2CO_3 (46.9 g, 0.340 mol), and hydroxylamine hydrochloride (23.6 g, 0.340 mol) was refluxed for 18 h. The hot mixture was filtered, and the remaining solids were washed with hot ethanol. The combined filtrates were concentrated in vacuo to provide 19.4 g (93.9%) of **7** as a white powder which was of sufficient purity to be used in subsequent steps: IR (KBr, cm^{-1}) 3438, 3368, 3200, 1662, 1601, 1375, 1210, 1038, 1001, 918; ^1H NMR ($CDCl_3$) δ 7.28 (s, 2H), 5.88 (s, 1H), 4.85 (s, 1H), 3.81 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.27 (s, 9H), 2.18 (m, 2H); ^{13}C NMR (ppm) 172.39, 159.82, 157.21, 152.56, 131.22, 127.95, 101.80, 70.66, 28.30, 23.44, 16.39, 11.45.

An analytical sample was obtained by recrystallization from ethanol: mp 129–130.5 °C. Anal. ($C_{16}H_{21}N_5O_3$) C, H, N.

General Synthesis for Oxadiazoles 8a–f. To a solution of amidoxime **7** in dry pyridine was added 2.0 equiv of acid chloride at a rate to maintain a gentle reflux. The mixture was refluxed an additional 0.5–18 h, cooled to room temperature, and diluted with water. For **8a–e**, the solids obtained were washed with water, dried in vacuo, and purified by recrystallization (**8d**) or chromatography (**8a–c,e**, 15–40% ethyl acetate in hexanes). For **8f**, the reaction mixture was concentrated in vacuo and the residue obtained was partitioned between ethyl acetate (50 mL) and water (25 mL). The organic phase was separated, washed with 1 N HCl (2 × 10 mL), saturated $NaHCO_3$, and brine, dried, and concentrated in vacuo. The crude product obtained was purified by MPLC (20% ethyl acetate in hexanes).

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (8a). From **7** (3.90 g, 12.8 mmol), pyridine (3.75 mL), and acetyl chloride (1.83 mL, 25.7 mmol) was obtained 2.79 g (69.8%) of pure **8a** as a white solid: mp 82.5–84 °C (methanol); IR (KBr, cm^{-1}) 1604, 1582, 1419, 1351, 1210, 996; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 5.89 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H); ^{13}C NMR (ppm) 176.26, 172.26, 168.04, 159.72, 158.18, 131.55, 127.96, 122.08, 101.73, 70.62, 28.25, 23.36, 16.25, 12.31, 11.36. Anal. ($C_{18}H_{21}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-5-ethyl-1,2,4-oxadiazole (8b). From **7** (2.05 g, 6.74 mmol), pyridine (2.0 mL), and propionyl chloride (1.17 mL, 13.2 mmol) was obtained 2.01 g (87.0%) of pure **8b** as a white solid: mp 67.5–68.5 °C (methanol); IR (KBr, cm^{-1}) 1608, 1576, 1418, 1337, 1211, 1046, 922; ^1H NMR ($CDCl_3$) δ 7.74 (s, 2H), 5.89 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H); ^{13}C NMR (ppm) 180.49, 172.29, 167.96, 159.74, 158.15, 131.52, 128.01, 122.25, 101.74, 70.63, 28.27, 23.38, 20.28, 16.26, 11.38, 10.32. Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-5-propyl-1,2,4-oxadiazole (8c). From **7** (2.56 g, 8.44 mmol), pyridine (5.0 mL), and butyryl chloride (1.75 mL, 16.9 mmol) was obtained 1.06 g (35.3%) of pure **8c** as a white solid: mp 74–75 °C (methanol); IR (KBr, cm^{-1}) 3116,

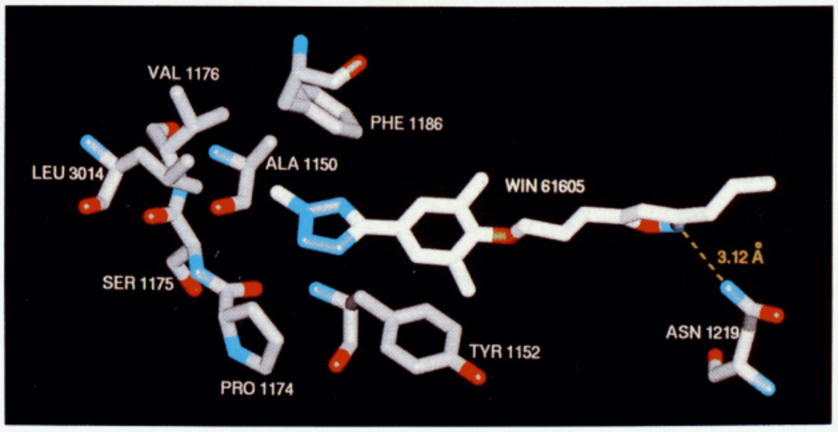


Figure 2. WIN 61605 bound to HRV-14 as determined by X-ray crystallography, showing residues within close proximity of the tetrazole ring.[31] The conformations of **8a**, **41**, and **46** were assigned using WIN 61605 as a template. The residues in the hydrophobic end of the pocket consist of Phe 1186, Pro 1174, Ser 1175, Tyr 1152, Ala 1150, and Val 1176. Energy profiling studies were performed by rotating the heterocyclic ring in 10° increments along the axis joining the phenyl ring.

2962, 2930, 1605, 1576, 1415, 1355, 1207, 1047, 924; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 2H), 5.89 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H), 1.90 (dt, J = 7.5 and 7.4 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (ppm) 179.65, 172.28, 167.92, 159.74, 158.14, 131.53, 128.01, 122.26, 101.74, 70.63, 28.44, 28.26, 23.37, 20.20, 16.26, 13.58, 11.38. Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-5-(methylethyl)-1,2,4-oxadiazole (8d). From **7** (2.00 g, 6.59 mmol), pyridine (2.0 mL), and isobutyryl chloride (1.38 mL, 13.2 mmol) was obtained 1.48 g (63.2%) of pure **8d** as a white solid: mp 72−73 °C (methanol); IR (KBr, cm^{-1}) 3128, 2970, 2935, 1606, 1566, 1419, 1355, 1211, 1113, 1047, 1000, 928, 929; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 2H), 5.89 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.28 (heptet, J = 7.0 Hz, 1H), 3.01 (t, J = 7.6 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H), 1.45 (d, J = 7.0 Hz, 6H); ^{13}C NMR (ppm) 183.70, 172.31, 167.89, 159.75, 158.11, 131.49, 128.05, 122.38, 101.75, 70.64, 28.28, 27.51, 23.39, 20.19, 16.27, 11.39. Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-5-cyclopropyl-1,2,4-oxadiazole (8e). From **7** (0.86 g, 2.8 mmol), pyridine (1.0 mL), and cyclopropanecarbonyl chloride (0.51 mL, 5.7 mmol) was obtained 0.71 g (71.0%) of pure **8f** as a white solid: mp 85−88 °C (methanol); IR (KBr, cm^{-1}) 1608, 1578, 1419, 1343, 1211, 1050, 922, 768; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 2H), 5.88 (s, 1H), 3.84 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.31 (s, 6H), 2.28 (s, 3H), 2.24 (m, 3H), 1.27 (m, 4H); ^{13}C NMR (ppm) 181.24, 172.28, 167.88, 159.71, 158.07, 131.43, 127.98, 122.28, 101.72, 70.60, 28.24, 23.36, 16.24, 11.36, 9.92, 7.70. Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-5-(methoxymethyl)-1,2,4-oxadiazole (8f). From **7** (2.28 g, 7.50 mmol), pyridine (12.0 mL), and methoxyacetyl chloride (1.4 mL, 15 mmol) was obtained 2.05 g (76.1%) of pure **8f** as a white solid: mp 63−64 °C (ether/hexane); IR (KBr, cm^{-1}) 3125, 2933, 1603, 1581, 1490, 1452, 1419, 1352, 1208, 1111, 1039, 998, 973, 926, 910; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 2H), 5.89 (s, 1H), 4.74 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.56 (s, 3H), 3.01 (t, J = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); ^{13}C NMR (ppm) 175.62, 172.23, 168.03, 159.70, 158.34, 131.58, 128.12, 121.69, 101.71, 70.61, 65.09, 59.52, 28.22, 23.32, 16.22, 11.34. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

General Procedure for the Syntheses of 8g,h and 14. To a chilled (0 °C) suspension of **7** (1 equiv), dry acetone (3.0 mL/mmol of **7**), and finely divided K_2CO_3 (1.1 equiv) was added dropwise a solution of acid chloride in acetone (0.50 mL/mmol of acid chloride). After stirring at 0 °C for 1 h, the reaction mixture was diluted with water (100 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were washed with brine, dried, filtered through a short column of Florisil, and concentrated in vacuo to give the crude O-acylated amidoximes as off-white solids. Heating at 120−130 °C for 5−60 min provided the crude oxadiazoles.

Acetic Acid, [3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazol-5-yl]methyl Ester (8g). From **7** (4.55 g, 15.0 mmol) and acetoxyacetyl chloride (1.77 mL, 16.5 mmol) was obtained 4.90 g of crude **8g** which was purified by MPLC (35% ethyl acetate in hexanes) to give 4.12 g (71.3%) of pure **8i** as a pale yellow oil which solidified upon standing: mp 71−73 °C (ether/hexanes); IR (KBr, cm^{-1}) 1749, 1604, 1475, 1421, 1378, 1339, 1232, 1209, 1031, 925; ^{1}H NMR δ ($CDCl_3$) 7.74 (s, 2H), 5.89 (s, 1H), 5.34 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.24 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (ppm) 173.70, 172.22, 169.76, 168.22, 159.70, 157.42, 131.62, 128.12, 121.49, 101.71, 70.82, 56.33, 28.22, 23.32, 20.34, 16.23, 11.33. Anal. ($C_{20}H_{23}N_3O_5$) C, H, N.

Acetic Acid, α-Methyl-[3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazol-5-yl]-methyl Ester (8h). From **7** (4.55 g, 15.0 mmol) and 2-acetoxypropionyl chloride[27] (2.48 g, 16.5 mmol) was obtained 7.52 g of crude **8h** which was purified by MPLC (30% ethyl acetate in hexanes) to give 3.87 g (64.6%) of pure **8k** as a white solid: mp 77−77.5 °C (ethanol); IR (KBr, cm^{-1}) 1748, 1604, 1580, 1420, 1374, 1331, 1225, 1221, 1090, 985, 953, 772; ^{1}H NMR δ ($CDCl_3$) 7.74 (s, 2H), 6.07 (q, J = 6.8 Hz, 1H), 5.89 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H), 2.19 (s, 3H), 1.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR (ppm) 177.34, 172.32, 169.76, 168.17, 159.82, 158.41, 131.66, 128.22, 121.73, 101.82, 70.67, 64.07, 29.30, 23.41, 20.77, 18.64, 16.32, 11.45. Anal. ($C_{21}H_{25}N_3O_5$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-1,2,4-oxadiazol-4*H*-5-one (14). From **7** (3.03 g, 10.0 mmol) and ethyl chloroformate (1.05 mL, 11.0 mmol) was obtained 3.48 g of crude **14** which was recrystallized from methanol to give 2.38 (75.4%) of pure **14** as white needles: mp 194−195 °C; IR (KBr, cm^{-1}) 3280−2400, 3122, 2928, 1771, 1611, 1512, 1472, 1449, 1422, 1203, 1046, 1008, 964, 919, 736; ^{1}H NMR (DMSO-d_6) δ 12.69 (br, 1H), 7.50 (s, 2H), 6.17 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.27 (s, 6H), 2.20 (s, 3H), 2.11 (m, 2H); ^{13}C NMR (ppm) 172.15, 159.92, 159.38, 158.53, 157.00, 131.75, 126.64, 118.50, 101.95, 70.67, 27.82, 22.64, 15.98, 10.94. Anal. ($C_{17}H_{19}N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-1,2,4-oxadiazole-5-methanol (8i). A mixture of **8g** (4.12 g, 10.7 mmol) and finely divided potassium carbonate (1.48 g, 10.7 mmol) in dry methanol (40 mL) was stirred at room temperature for 15 min and partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (1 × 25 mL), and the combined organic phases were washed with brine, dried, and concentrated in vacuo. MPLC (50% ethyl acetate in hexanes) provided 3.35 g (91.2%) of pure **8i** as a white solid: mp 116.5–117 °C (ether); IR (KBr, cm^{-1}) 3335, 3124. 2969, 2933, 1605, 1570, 1420, 1380, 1346, 1209, 1048, 996, 920, 900, 865, 810, 745; ^1H NMR ($CDCl_3$) δ 7.72 (s, 2H), 5.90 (s, 1H), 4.95 (2, 2H), 3.82 (s, 1H), 3.82 (t, J = 6.0 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H), 2.18 (m, 2H); ^{13}C NMR (ppm) 178.03, 172.34, 167.81, 159.82, 158.35, 131.62, 128.08, 121.59, 101.81, 70.60, 56.39, 28.20, 23.34, 16.23, 11.33. Anal. ($C_{18}H_{21}N_3O_4$) C, H, N.

α-Methyl-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)-propyl]oxy]phenyl]-1,2,4-oxadiazole-5-methanol (8j). A mixture of **8h** (3.60 g, 9.00 mmol) and finely divided K_2CO_3 (1.24 g, 9.00 mmol) in dry methanol (36 mL) was stirred at room temperature for 30 min and partitioned between water (250 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phases were washed with brine, dried, and concentrated in vacuo. MPLC (40% ethyl acetate in hexanes) provided 3.15 g (97.8%) of pure **8j** as a white solid: mp 83–87 °C (ether); IR (KBr, cm^{-1}) 3331, 2991, 2928, 1607, 1563, 1447, 1419, 1378, 1205, 1133, 1114, 1093, 1044, 1033, 1001, 926, 824, 778; ^1H NMR ($CDCl_3$) δ 7.72 (s, 2H), 5.89 (s, 1H), 5.16 (q, J = 6.8 Hz, 1H), 3.82 (t, J = 6.1 Hz, 2H), 3.54 (br s, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H), 2.18 (m, 2H), 1.70 (d, J = 6.8 Hz, 3H); ^{13}C NMR (ppm) 180.99, 172.38, 167.82, 159.87, 158.35, 131.66, 128.17, 121.77, 101.87, 70.65, 63.17, 28.26, 23.40, 21.48, 16.31, 11.43. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-1,2,4-oxadiazole (8k). To a suspension of **7** (2.42 g, 8.00 mmol) in triethyl orthoformate (17 mL) was added $BF_3{\cdot}OEt_2$ (0.35 mL, 2.8 mmol). A pale yellow solution formed which was refluxed for 1 h. The reaction mixture was concentrated in vacuo and the residue filtered. The solids were washed with ethyl acetate. The combined filtrate and washings were washed with water and brine, dried, and concentrated in vacuo to give 1.53 g of yellow oil which was chromatographed (30% ethyl acetate in hexanes) to provide 1.15 g (45.9%) of pure **8k** as a colorless oil. Crystallization occurred from ethanol: mp 62.5–63.5 °C; IR (KBr, cm^{-1}) 3095, 1608, 1536, 1448, 1419, 1386, 1337, 1206, 1124, 1037, 1005, 918, 805, 730; ^1H NMR ($CDCl_3$) δ 8.73 (s, 1H), 7.78 (s, 2H), 5.89 (s, 1H), 3.87 (t, J = 6.1 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.33 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); ^{13}C NMR (ppm) 172.25, 167.39, 164.48, 159.75, 158.44, 131.70, 128.21, 121.54, 101.75, 70.65, 28.25, 23.36, 16.30, 11.38. Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-5-(α,α,α-trichloromethyl)-1,2,4-oxadiazole (8l). Trichloroacetic acid (22.8 g, 140 mmol) was added to **7** (10.6 g, 34.8 mmol) and heated at 85 °C until a thick solution was obtained. Trichloroacetyl chloride (14.5 mL, 69.6 mmol) was added in three equal portions. A vigorous reaction ensued after addition of the first portion. The mixture was heated an additional hour at 94 °C. The cooled mixture was diluted with water and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with saturated $NaHCO_3$ and brine, dried, and concentrated in vacuo to give 10.1 g of orange oil. Chromatography (methylene chloride) provided 6.94 g of a yellow oil which was crystallized from methanol to give 5.03 g of pure **8l** as white needles: mp 77–77.5 °C; IR (KBr, cm^{-1}) 1602, 1575, 1469, 1446, 1419, 1383, 1345, 1207, 1046, 1004, 924, 872, 842, 823, 798, 746; ^1H NMR ($CDCl_3$) δ 7.78 (s, 2H), 5.89 (s, 1H), 3.87 (t, J = 6.1 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.34 (s, 2H), 2.29 (s, 3H), 2.22 (m, 2H); ^{13}C NMR (ppm) 174.18, 172.23, 166.89, 159.78, 158.97, 131.91, 128.36, 120.72, 101.79, 70.72, 28.28, 23.37, 16.32, 11.41. Anal. ($C_{18}H_{18}Cl_3N_3O_3$) C, H, N.

An additional 1.23 g of pure **8l** was obtained from the mother liquor for a combined yield of 6.26 g (41.7%).

General Procedure for the Syntheses of 9–12. Freshly prepared sodium alkoxide (1.5 equiv for **9** and **10**) or 40% aqueous amine (5 mL for **11** and **12**) was added to dry DMF (3–5 mL); **8l** was added and the mixture stirred at room temperature (15–30 min for **9**, **11**, and **12** and 18 h for **10**). The reaction mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic phases were washed with water and brine, dried, and concentrated in vacuo. The crude products were purified by chromatography.

5-Methoxy-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)-propyl]oxy]phenyl]-1,2,4-oxadiazole (9). From **8l** (627 mg, 1.46 mmol) and $NaOCH_3$ was obtained 0.64 g of crude product which was first chromatographed with 2% methanol in methylene chloride followed by 5% ethyl acetate in methylene chloride to give 308 mg (61.6%) of pure **9** as a colorless oil. Crystallization occurred from methanol: mp 64.5–65.5 °C; IR (KBr, cm^{-1}) 2953, 1616, 1606, 1595, 1418, 1370, 1319, 1211, 1045, 1003, 924, 768; ^1H NMR ($CDCl_3$) δ 7.67 (s, 2H), 5.89 (s, 1H), 4.25 (s, 3H), 3.85 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.31 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H); ^{13}C NMR (ppm) 173.81, 172.28, 168.66, 159.75, 158.26, 131.45, 127.70, 122.42, 101.74, 70.63, 60.16, 28.26, 23.37, 16.27, 11.38. Anal. ($C_{18}H_{21}N_3O_4$) C, H, N.

5-Ethoxy-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)-propyl]oxy]phenyl]-1,2,4-oxadiazole (10). From **8l** (905 mg, 2.10 mmol) and NaOEt was obtained 0.82 g of crude product which was chromatographed with 2% ethyl acetate in methylene chloride to give 0.52 g (69%) of pure **10** as a yellow solid: mp 70–72.5 °C (ethanol); IR (KBr, cm^{-1}) 1610, 1481, 1441, 1418, 1379, 1356, 1311, 1210, 1126, 1050, 1023, 1001, 931, 769; ^1H NMR ($CDCl_3$) δ 7.66 (s, 2H), 5.89 (s, 1H), 4.64 (q, J = 7.1 Hz, 2H), 3.85 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.31 (s, 6H), 2.28 (s, 6H), 2.20 (m, 2H), 1.52 (t, J = 7.1 Hz, 3H); ^{13}C NMR (ppm) 173.18, 172.29, 168.81, 159.75, 158.21, 131.41, 127.69, 122.55, 101.74, 70.63, 70.17, 28.26, 23.37, 16.27, 14.30, 11.38. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

***N,N*-Dimethyl-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazol-5-amine (11).** From **8l** (0.97 g, 2.2 mmol) and dimethylamine was obtained 0.75 g of crude **13** which was chromatographed with 50% ethyl acetate in hexanes to give 0.70 g (84%) of pure **11** as a pale yellow solid: mp 123–124 °C (ethanol); IR (KBr, cm^{-1}) 3112, 2937, 2912, 1654, 1607, 1446, 1420, 1380, 1348, 1275, 1208, 1120, 1044, 927, 811, 767; ^1H NMR ($CDCl_3$) δ 7.67 (s, 2H), 5.88 (s, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.20 (s, 6H), 3.01 (t, J = 7.6 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H), 2.19 (m, 2H); ^{13}C NMR (ppm) 172.34, 171.64, 168.45, 159.73, 157.77, 131.15, 127.79, 123.23, 101.72, 70.58, 38.04, 28.26, 23.39, 16.24, 11.38. Anal. ($C_{19}H_{24}N_4O_3$) C, H, N.

***N*-Methyl-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)-propyl]oxy]phenyl]-1,2,4-oxadiazol-4*H*-5-imine (12).** From **8l** (1.00 g, 2.32 mmol) and 40% aqueous methylamine was obtained 0.54 g of crude **11** which was first chromatographed with 2% methanol in methylene chloride and then 50% ethyl acetate in hexanes to give 300 mg (37.5%) of pure **12** as a yellow solid: mp 126.5–127 °C (ethanol); IR (KBr, cm^{-1}) 3225, 3200, 3168, 2940, 1676, 1604, 1536, 1478, 1436, 1417, 1378, 1327, 1211, 1203, 1131, 1043, 983, 922, 772; ^1H NMR ($CDCl_3$) δ 7.65 (s, 2H), 5.89 (s, 1H), 5.63 (br q, J = 5.1 Hz, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.13 (d, J = 5.1 Hz, 3H), 3.01 (t, J = 7.6 Hz, 2H), 2.28 (s, 6H), 2.20 (m, 2H); ^{13}C NMR (ppm) 172.30, 171.66, 168.02, 159.74, 157.87, 131.26, 127.70, 122.89, 101.73, 70.58, 29.78, 28.21, 23.34, 16.22, 11.34. Anal. ($C_{18}H_{22}N_4O_3$) C, H, N.

***N*-[3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl][5-(1,2,4-oxadiazolyl)]]acetamide (13).** To a cold (−78 °C) solution of acetamide (109 mg, 1.84 mmol) in THF (20 mL) was added 1 M lithium bis(trimethylsilyl)amide in THF (1.84 mL, 1.84 mmol). The solution was stirred at −78 °C for 40 min and −10 °C for 15 min and recooled to −78 °C. A solution of **8l** (529 mg, 1.23 mmol) in THF (2 mL) was added. The reaction mixture was allowed to gradually warm to room temperature and stirred for 96 h, afterwhich 0.5 M HCl (20 mL) was added and the whole extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Dry flash chromatography (hexanes to ethyl acetate) provided 249 mg of a white solid which was further purified by reverse phase dry flash chromatography[28] (50–80% aqueous methanol). Recrystallization from CH_2Cl_2 provided 85 mg (18.7%) of pure **13** as a white solid: mp 137–138 °C; IR (KBr, cm^{-1}) 3230, 3143, 3048, 2956, 1700, 1621, 1418, 1375, 1247, 1208, 1044, 1009, 766; ^1H NMR ($CDCl_3$) δ 8.62 (br s, 1H), 7.68 (s, 2H), 5.88 (s, 1H), 3.86 (t, J = 6.2 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.53 (s, 3H), 2.31 (s, 6H), 2.28 (s, 3H), 2.20 (m, 2H). Anal. ($C_{19}H_{22}N_4O_4$·0.25H_2O) C, H, N.

5-Chloro-3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)-propyl]oxy]phenyl]-1,2,4-oxadiazole (15). Dry pyridine (0.59 mL, 7.5 mmol) and **14** (2.47 g, 7.50 mmol) were added to phosphorus oxychloride (7.0 mL, 75 mmol). The mixture was heated at 128 °C for 7 h, cooled to 0 °C, and poured onto crushed ice (125 mL). After the excess phosphorus oxychloride was hydrolyzed, the aqueous mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with saturated $NaHCO_3$ (3 × 50 mL) and brine, dried, and concentrated in vacuo. The red oil obtained (2.63 g) was filtered through a pad of Florisil (methylene chloride) to give a yellow oil (2.34 g) which was chromatographed (MPLC, 12% ethyl acetate in hexanes) to provide pure **15** (2.13 g, 81.6%) as a white solid: mp 71–72 °C (methanol); IR (KBr, cm^{-1}) 2957, 2930, 2875, 1607, 1539, 1419, 1341, 1213, 1113, 1032, 994, 928, 898, 859, 791, 748; ^1H NMR ($CDCl_3$) δ 7.75 (s, 2H), 5.89 (s, 1H), 4.74 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); ^{13}C NMR (ppm) 172.26, 169.98, 163.59, 159.80, 158.90, 131.87, 128.00, 120.94, 101.81, 70.71, 28.29, 23.39, 16.33, 11.42. Anal. ($C_{17}H_{18}ClN_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-1,2,4-oxadiazole-4*H*-5-thione (16). To a suspension of NaH (48 mg, 2 mmol) in dry, degassed NMP (2 mL) was condensed CH_3SH. Gas evolution ensued, and a golden solution was obtained to which was added a solution of **15** (348 mg, 1.00 mmol) in the same solvent (2 mL). After 2 h, saturated NH_4Cl (0.5 mL) and water (25 mL) were added. The mixture was washed with ether (2 × 25 mL). The aqueous phase was acidified with concentrated HCl and filtered. The solids were washed with water and ether to provide pure **16** (251 mg, 72.7%) as a white powder: mp 162–165 °C (ethyl acetate); IR (KBr, cm^{-1}) 3062, 2935, 2852, 1613, 1605, 1568, 1475, 1296, 1205, 1154, 1024, 885, 719; ^1H NMR (DMSO-d_6) δ 7.60 (s, 2H), 6.19 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.27 (s, 6H), 2.20 (s, 3H), 2.11 (m, 2H); ^{13}C NMR (ppm) 187.55, 172.16, 159.42, 158.93, 158.56, 131.98, 127.49, 116.85, 102.01, 70.71, 27.83, 22.65, 16.02, 11.00. Anal. ($C_{17}H_{19}N_3O_3S$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]-oxy]phenyl]-1,2,4-oxadiazol-4*H*-5-imine (17). Cyanogen bromide (1.17 g, 11.0 mmol) was added in portions to a mixture of **7** (3.03 g, 10.0 mmol) and potassium bicarbonate (1.10 g, 11.0 mmol) in 50% aqueous ethanol (8 mL). After 15 min, the thick yellow suspension was diluted with water and filtered. The yellow solid obtained was washed with water and ether to give 1.48 g (45.1%) of pure **17** as a yellow powder: IR (KBr, cm^{-1}) 3412, 3316, 3265, 3224, 1736, 1682, 1645, 1599, 1577, 1421, 1358, 1213, 1123, 1042, 1034, 1006, 983, 916, 646; ^1H NMR (DMSO-d_6) δ 7.48 (s, 2H), 6.79 (br s, 1H), 6.52 (br s, 1H), 6.17 (s, 2H), 3.80 (t, J = 6.1 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.23 (s, 6H), 2.20 (s, 3H), 2.09 (m, 2H); ^{13}C NMR (ppm) 172.22, 159.40, 157.08, 156.44, 153.64, 130.28, 127.23, 126.67, 101.96, 70.50, 27.87, 22.70, 16.00, 10.96.

An analytical sample of **17** was obtained by crystallization from methanol and ethanol trituration: mp 175–183 °C dec. Anal. ($C_{17}H_{20}N_4O_3$·1.0H_2O) C, H, N.

3,5-Dimethyl-4-(4-pentyn-1-yloxy)benzonitrile (18a). A mixture of **4** (7.36 g, 50.0 mmol), NMP (100 mL), finely divided K_2CO_3 (13.8 g, 100 mmol), KI (0.84 g, 5.0 mmol), and 5-chloro-1-pentyne (7.95 mL, 75.0 mmol) was stirred at 65 °C for 24 h. After cooling to room temperature, the mixture was partitioned between water (400 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water and brine, dried, and concentrated in vacuo to provide 13.6 g of a brown oil which was filtered through a short column of Florisil with CH_2Cl_2. MPLC (5% ethyl acetate in hexanes) provided 9.28 g (86.7%) of pure **18a** as a colorless oil which solidified upon standing: mp 47–49 °C; IR (KBr, cm^{-1}) 3301, 2966, 2118, 1596, 1474, 1441, 1378, 1299, 1218, 1139, 1044, 914, 888, 879, 798, 650; ^1H NMR ($CDCl_3$) δ 7.32 (s, 2H), 3.91 (t, J = 6.0 Hz, 2H), 2.49 (dt, J = 6.8 and 2.6 Hz, 2H), 2.30 (s, 6H), 2.02 (m, 2H), 1.99 (d, J = 2.6 Hz, 1H); ^{13}C NMR (ppm) 159.65, 132.78, 132.64, 119.07, 107.32, 83.26, 70.30, 69.17, 28.99, 16.20, 15.09. Anal. ($C_{14}H_{15}NO$) C, H, N.

3,5-Dichloro-4-(4-pentyn-1-yloxy)benzonitrile (18b). 3,5-Dichloro-4-hydroxybenzonitrile (10.0 g, 53.2 mmol) was treated as described above. The crude oil obtained (11.8 g) following workup was first filtered through a short column of silica gel 60 (10% ethyl acetate in hexanes) and then purified by MPLC (10% ethyl acetate in hexanes) to give 7.03 g (62.0%) of pure **18b** as a colorless oil. A white solid was obtained by crystallization from methanol: mp 58–59 °C; IR (KBr, cm^{-1}) 3296, 2232, 2118, 1455, 1390, 1270, 1027, 813, 654, 615; ^1H NMR ($CDCl_3$) δ 7.61 (s, 2H), 4.20 (t, J = 6.0 Hz, 2H), 2.51 (dt, J = 7.0 and 2.6 Hz, 2H), 2.02 (m, 2H), 1.99 (d, J = 2.6 Hz, 1H). Anal. ($C_{12}H_9Cl_2NO$) C, H, N.

3-[3,5-Dimethyl-4-(4-pentyn-1-yloxy)phenyl]-5-methyl-1,2,4-oxadiazole (19a). A mixture of **18a** (13.0 g, 60.9 mmol), absolute ethanol (150 mL), finely divided K_2CO_3 (42.1 g, 0.305 mol), and hydroxylamine hydrochloride (21.2 g, 0.305 mol) was refluxed for 18 h. The hot mixture was filtered, and the remaining solids were washed with hot ethanol. The combined filtrates were concentrated in vacuo to provide 14.9 g of the amidoxime.

The above amidoxime (7.40 g, 30.0 mmol) was dissolved in pyridine (9 mL). Acetyl chloride (4.3 mL, 60 mmol) was added at a rate to maintain a gentle reflux. The mixture was refluxed for 1 h, cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with water and brine, dried, filtered through a short column of Florisil, and concentrated in vacuo. Two flash columns (CH_2Cl_2 for the first and 20% ethyl acetate in hexanes for the second) provided 4.09 g (50.4%) of pure **19a** as a white solid. Crystallization from methanol gave a white powder: mp 54–55 °C; IR (KBr, cm^{-1}) 3258, 2115, 1579, 1474, 1419, 1348, 1211, 1045, 943, 868, 749, 669; ^1H NMR ($CDCl_3$) δ 7.71 (s, 2H), 3.90 (t, J = 6.1 Hz, 2H), 2.63 (s, 3H), 2.50 (dt, J = 6.9 and 2.6 Hz, 2H), 2.32 (s, 6H), 2.02 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H); ^{13}C NMR (ppm) 176.16, 167.96, 158.13, 131.61, 127.81, 121.88, 83.40, 69.99, 68.87, 29.01, 16.15, 15.05, 12.25. Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

5-Ethyl-3-[3,5-dimethyl-4-(4-pentyn-1-yloxy)phenyl]-1,2,4-oxadiazole (19b). The amidoxime derived from **18a** (4.33 g, 20.3 mmol) was treated with propionyl chloride as described above. MPLC (20% ethyl acetate in hexanes) provided 4.70 g (71.9%) of pure **19b** as a colorless oil. Crystallization from methanol gave a white powder: mp 37–38 °C; IR (KBr, cm^{-1}) 3268, 2930, 1575, 1471, 1419, 1355, 1208, 1044, 945, 866, 656; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 3.90 (t, J = 6.1 Hz, 2H), 2.95 (q, J = 7.5 Hz, 2H), 2.49 (dt, J = 6.9 and 2.7 Hz, 2H), 2.33 (s, 6H), 2.02 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.44 (t, J = 7.5 Hz, 3H); ^{13}C NMR (ppm) 180.38, 167.90, 158.12, 131.60, 127.90, 122.07, 83.43, 70.03, 68.87, 29.04, 20.23, 16.18, 15.09, 10.79. Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

3-[3,5-Dimethyl-4-(4-pentyn-1-yloxy)phenyl]-1,2,4-oxadiazole (19c). The amidoxime derived from **18a** (5.00 g, 23.5 mmol) was suspended into triethyl orthoformate (50 mL), and BF_3·OEt_2 (1 mL) was added. The mixture was refluxed for 45 min, stirred at room temperature for 60 h, and refluxed an additional 3 h. The ethanol was removed in vacuo, 2 N HCl was added, and the whole reconcentrated in vacuo. The oily residue remaining was extracted with ethyl acetate (3×). The combined organic phases were washed with water, 5% $NaHCO_3$, and brine, dried, and concentrated in vacuo to a brown oil which was filtered through a short column of silica gel 60 (20% ethyl acetate in hexanes). MPLC (15% ethyl acetate in hexanes) provided 2.60 g (43.2%) of **19c** as a colorless oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.79 (s, 2H), 3.92 (t, J = 6.1 Hz, 2H), 2.52 (dt, J = 6.9 and 2.6 Hz, 2H), 2.35 (s, 6H), 2.02 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H); MS (CI) m/z 257 (MH^+).

3-[3,5-Dichloro-4-(4-pentyn-1-yloxy)phenyl]-1,2,4-oxadiazole (19d). The amidoxime derived from **18b** (6.00 g, 23.6 mmol) was treated with acetyl chloride as described for **19a**. After dilution with water, the crude product was filtered and washed with water. The tan solid remaining was dissolved in methylene chloride, dried, and filtered through a short column of silica gel 60 with methylene chloride. The oil obtained (5.71 g) was twice chromatographed (MPLC, 10–20% ethyl acetate in hexanes). There was obtained 5.34 g (72.8%) of pure **19d** as a colorless oil which crystallized from methanol as a white solid: mp 52–52.5 °C; IR (KBr, cm^{-1}) 3305, 3296, 1593, 1455, 1398, 1337, 1263, 1251, 1030, 916, 805, 748, 643; ^{1}H NMR (CDCl$_3$) δ 8.02 (s, 2H), 4.19 (t, J = 6.0 Hz, 2H), 2.66 (s, 3H), 2.54 (dt, J = 7.0 and 2.6 Hz, 2H), 2.09 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H); ^{13}C NMR (ppm) 177.05, 166.36, 153.62, 130.20, 127.81, 124.03, 83.52, 72.39, 68.83, 29.11, 15.19, 12.41. Anal. ($C_{14}H_{12}Cl_2N_2O_2$) C, H, N.

General Procedure for the Syntheses of 6b, 20a–e, 21, 35, 36, 38, and 39. To a solution of *N*-chlorosuccinimide (NCS, 1.8–3.0 equiv) in dry DMF or NMP (1.6–3.0 mL/mmol of NCS) and 1–2 drops of pyridine was added dropwise a solution of oxime (1.8–3.0 equiv) in the same solvent (0.40–0.80 mL/mmol of oxime). The internal temperature was maintained at 25–30 °C with a 25 °C water bath. After 1 h at room temperature, a solution of **18** or **19** (1 equiv) in the same solvent (0.80 mL/mmol) was added. The reaction mixture was heated to 85–95 °C, and a solution of triethylamine (TEA, 1.8–3.0 equiv) in the same solvent (0.80–1.6 mL/mmol of TEA) was added dropwise over 45–90 min. After an additional hour at 85–95 °C, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% KHSO$_4$, water, and brine, dried, and concentrated in vacuo. The crude products were purified by MPLC (15–40% ethyl acetate in hexanes).

4-[[3-(3-Ethyl-5-isoxazolyl)propyl]oxy]-3,5-dimethylbenzonitrile (6b). From propionaldehyde oxime (8.60 g, 118 mmol) and **18a** (10.0 g, 46.9 mmol) was obtained 4.90 g (36.8%) of pure **6b** as a white powder: mp 50–51 °C (ethanol); IR (KBr, cm^{-1}) 3132, 2972, 2921, 2226, 1610, 1476, 1302, 1221, 1211, 1202, 1041, 916, 814; ^{1}H NMR (CDCl$_3$) δ 7.32 (s, 2H), 5.91 (s, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.68 (q, J = 7.6 Hz, 2H), 2.28 (s, 6H), 2.21 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H); ^{13}C NMR (ppm) 171.86, 165.14, 159.50, 132.71, 132.42, 118.87, 107.32, 100.39, 70.77, 28.14, 23.25, 19.48, 16.13, 12.57. Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]-phenyl]-5-methyl-1,2,4-oxadiazole (20a). From propionaldehyde oxime (1.28 g, 17.6 mmol) and **19a** (2.38 g, 8.79 mmol) was obtained 1.82 g (60.7%) of pure **20a** as a white powder: mp 80–81 °C (ethanol); IR (KBr, cm^{-1}) 3127, 2972, 2959, 1603, 1579, 1460, 1423, 1393, 1351, 1271, 1211, 1202, 1017, 994, 908, 896, 868, 814, 776, 751; ^{1}H NMR (CDCl$_3$) δ 7.73 (s, 2H), 5.92 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.68 (q, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.21 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-propyl-5-isoxazolyl)propyl]-oxy]phenyl]-5-methyl-1,2,4-oxadiazole (20b). From butyraldehyde oxime (2.60 g, 30.0 mmol) and **19a** (2.70 g, 10.0 mmol) was obtained 2.06 g (58.0%) of pure **20b** as white needles: mp 69–70 °C (methanol); IR (KBr, cm^{-1}) 3123, 2960, 2931, 1603, 1578, 1422, 1351, 1272, 1209, 1199, 1013, 993, 908, 869, 805, 775, 752; ^{1}H NMR (CDCl$_3$) δ 7.44 (s, 2H), 5.90 (s, 1H), 3.86 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 7.4 Hz, 2H), 2.64 (s, 3H), 2.62 (t, J = 7.4 Hz, 2H), 2.31 (s, 6H), 2.22 (m, 2H), 1.69 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

3-[3,5-Dimethyl-4-[[3-[3-(methoxymethyl)-5-isoxazolyl]-propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (20c). From methoxyacetaldehyde oxime (1.32 g, 14.8 mmol) and **19a** (2.00 g, 7.40 mmol) was obtained 1.59 g (60.2%) of pure **20c** as a colorless oil: IR (NaCl film, cm^{-1}) 3123, 2930, 1603, 1583, 1474, 1421, 1381, 1353, 1273, 1207, 1108, 1032, 907, 867, 774, 751; ^{1}H NMR (CDCl$_3$) δ 7.73 (s, 2H), 6.12 (s, 1H), 4.51 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.40 (s, 3H), 3.06 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.24 (m, 2H); ^{13}C NMR (ppm) 176.28, 172.98, 168.03, 161.32, 158.14, 131.53, 127.96, 122.10, 100.24, 70.53, 65.79, 58.43, 28.20, 23.45, 16.24, 12.30. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-[3-(ethoxymethyl)-5-isoxazolyl]-propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (20d). From ethoxyacetaldehyde oxime (1.53 g, 14.8 mmol) and **19a** (2.00 g, 6.17 mmol) was obtained 1.79 g (65.1%) of pure **20d** following MPLC. Recrystallization from methanol provided a white powder: mp 45.5–46 °C; IR (NaCl film, cm^{-1}) 3123, 2930, 1603, 1583, 1474, 1421, 1381, 1352, 1273, 1207, 1111, 1032, 995, 907, 867, 775, 750; ^{1}H NMR (CDCl$_3$) δ 7.73 (s, 2H), 6.13 (s, 1H), 4.55 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.56 (q, J = 7.0 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.24 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (ppm) 176.27, 172.87, 168.05, 161.69, 158.16, 131.55, 127.97, 122.11, 100.37, 70.55, 66.22, 63.90, 28.20, 23.46, 16.25, 15.00. Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-cyclopropyl-5-isoxazolyl)propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (20e). From cyclopropylcarboxaldehyde oxime (0.33 g, 3.9 mmol) and **19a** (0.53 g, 2.0 mmol) was obtained 0.42 g (60.9%) of pure **20e** as a colorless oil following MPLC. Crystallization from methanol gave a fine white powder: mp 50.5–51 °C; IR (KBr, cm^{-1}) 3130, 2931, 1604, 1584, 1438, 1354, 1270, 1205, 1115, 1051, 1047, 996, 927, 906, 893, 822, 748; ^{1}H NMR (CDCl$_3$) δ 7.72 (s, 2H), 5.70 (s, 1H), 3.84 (t, J = 6.1 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.31 (s, 6H), 2.20 (m, 2H), 1.98 (dt, J = 4.9 and 3.5 Hz, 1H), 1.07–0.99 (m, 2H), 0.83–0.75 (m, 2H); ^{13}C NMR (ppm) 176.27, 172.16, 168.05, 166.38, 158.19, 131.56, 127.96, 122.08, 98.39, 70.60, 28.23, 23.41, 16.25, 12.32, 7.88, 7.32. Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

3,5-Dimethyl-4-[[3-[3-(methoxyethyl)-5-isoxazolyl]propyl]oxy]benzonitrile (21). From 3-methoxypropionaldehyde oxime (1.94 g, 18.8 mmol) and **18a** (2.20 g, 10.3 mmol) was obtained 0.89 g (40.4%) of recovered **18a** and 1.51 g (46.5%) of pure **21** as a colorless oil following MPLC. Crystallization from ethanol provided finte white needles of **21**: mp 64–64.5 °C; IR (KBr, cm^{-1}) 3109, 2899, 2223, 1603, 1479, 1222, 1115, 994, 820; ^{1}H NMR (CDCl$_3$) δ 7.32 (s, 2H), 5.99 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 3.38 (s, 3H), 3.01 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H), 2.28 (s, 6H), 2.20 (m, 2H); ^{13}C NMR (ppm) 172.08, 161.66, 159.59, 132.83, 132.50, 119.00, 107.44, 101.41, 70.84, 70.35, 58.70, 28.19, 26.74, 23.36, 16.23. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

5-Ethyl-3-[3,5-dimethyl-4-[[3-[3-(methoxymethyl)-5-isoxazolyl]propyl]oxy]phenyl]-1,2,4-oxadiazole (35). From methoxyacetaldehyde oxime (2.50 g, 28.1 mmol) and **19b** (2.00 g, 7.40 mmol) was obtained 2.57 g (49.0%) of pure **35** as a colorless oil: IR (NaCl film, cm^{-1}) 2930, 1602, 1578, 1475, 1420, 1356, 1207, 1108, 1024, 909, 865; ^{1}H NMR (CDCl$_3$) δ 7.74 (s, 2H), 6.12 (s, 1H), 4.51 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.40 (s, 3H), 3.06 (t, J = 7.6 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 2.32 (s, 6H), 2.27 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H); ^{13}C NMR (ppm) 180.49, 173.00, 167.93, 161.33, 158.09, 131.50, 128.00, 122.26, 100.25, 70.53, 65.80, 58.44, 28.22, 23.47, 20.27, 16.25, 10.81. Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]-phenyl]-1,2,4-oxadiazole (36). From propionaldehyde oxime (1.30 g, 17.4 mmol) and **19c** (1.50 g, 5.86 mmol) was obtained 0.81 g (42%) of pure **36** as a colorless oil which slowly solidified upon standing: mp 53–54 °C; IR (KBr, cm^{-1}) 3127, 2972, 1605, 1544, 1420, 1336, 1206, 1109, 1047, 926, 896, 754; ^{1}H NMR (CDCl$_3$) δ 8.71 (s, 1H), 7.79 (s, 2H), 5.92 (s, 1H), 3.88 (t, J = 6.1 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 2.68 (q, J = 7.6 Hz, 2H), 2.33 (s, 6H), 2.21 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H). Anal. ($C_{18}H_{21}N_3O_3$) C, H, N.

3-[3,5-Dichloro-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]-phenyl]-5-methyl-1,2,4-oxadiazole (38). From propionaldehyde oxime (0.92 g, 13 mmol) and **19d** (1.96 g, 6.30 mmol) was obtained 1.90 g (79.2%) of pure **38** as a colorless oil which crystallized as a white solid from methanol: mp 57–58 °C; IR (KBr, cm^{-1}) 3135, 2968, 1610, 1600, 1458, 1404, 1390, 1376, 1334, 1267, 1255, 1031, 921, 889, 807, 746; ^{1}H NMR (CDCl$_3$) 8.00 (s, 2H), 5.92 (s, 1H), 4.12 (t, J = 5.9 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 2.65 (s, 3H), 2.24 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (ppm) 177.09, 172.14, 166.32, 165.30, 153.50, 130.14, 127.85, 124.11, 100.56, 72.37, 28.07, 23.37, 19.60, 12.68, 12.41. Anal. ($C_{17}H_{17}Cl_2N_3O_3$) C, H, N.

3-[3,5-Dichloro-4-[[3-[3-(methoxymethyl)-5-isoxazolyl]-propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (39). From methoxyacetaldehyde oxime (1.07 g, 12.1 mmol) and **19d** (1.80 g, 5.78 mmol) was obtained 1.05 g (58.3%) of recovered **20d**

and 0.99 g (43%) of pure **39** as a colorless oil following MPLC. Crystallization from methanol provided a white solid: mp 55.5–56 °C; IR (1% KBr, cm^{-1}) 1603, 1587, 1453, 1407, 1342, 1258, 1247, 1107, 1036, 956, 912, 880, 807, 771, 747; ^1H NMR ($CDCl_3$) δ 8.02 (s, 2H), 6.13 (s, 1H), 4.51 (s, 2H), 4.14 (t, J = 5.9 Hz, 2H), 3.40 (s, 3H), 3.12 (t, J = 7.6 Hz, 2H), 2.66 (s, 3H), 2.27 (m, 2H); ^{13}C NMR (ppm) 177.09, 172.98, 166.31, 161.38, 153.44, 130.14, 127.86, 124.20, 100.44, 72.25, 65.87, 58.51, 28.02, 23.41, 12.41. Anal. ($C_{17}H_{17}Cl_2N_3O_4$) C, H, N.

3-[3,5-Dimethyl-4-[[3-[3-(methoxyethyl)-5-isoxazolyl]-propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (20f). Sodium (0.45 g, 20 mg atom) was dissolved in dry methanol (20 mL) contained in an addition funnel. This solution was added dropwise to a solution of hydroxylamine hydrochloride (1.39 g, 20.0 mmol) in dry methanol (25 mL). A fine white precipitate formed. After 1 h, **21** (1.26 g, 4.00 mmol) was added and the mixture heated at reflux for 2.5 h. The hot reaction mixture was filtered, the filter cake was washed with methanol, and the combined filtrates were concentrated in vacuo. The white oily solid obtained (1.54 g) was dissolved in pyridine (3 mL), and acetyl chloride (0.57 mL, 8.0 mmol) was added at a rate to maintain a gentle reflux. The mixture was heated at reflux for an additional hour, cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% $KHSO_4$, water, and brine, dried, and concentrated in vacuo to give 1.35 g of yellow oil. Flash chromatography (20% ethyl acetate in hexanes) provided pure **20f** as a colorless oil: IR (NaCl film, cm^{-1}) 2928, 1604, 1581, 1422, 1352, 1207, 1117, 906, 750; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 6.00 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 3.38 (s, 3H), 3.03 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.20 (m, 2H); ^{13}C NMR (ppm) 176.33, 172.36, 168.10, 161.60, 158.24, 131.62, 128.01, 122.13, 101.33, 70.66, 70.58, 58.69, 28.25, 26.75, 23.48, 16.31, 12.38. Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

5-[3-[2,6-Dimethyl-4-[3-(5-methyl-1,2,4-oxadiazolyl)]phenoxy]propyl]-3-isoxazoleethanol (20g). A solution of **20f** (1.17 g, 3.15 mmol), dry 1,2-dichloroethane (9.5 mL), and trimethylsilyl iodide (1.79 mL, 12.6 mmol) was refluxed for 3 h. To the cooled reaction mixture was added methanol (8 mL). The mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% $NaHSO_3$, saturated $NaHCO_3$, and brine, dried, and concentrated in vacuo. Flash chromatography (75% ethyl acetate in hexanes) provided 0.88 g (77.9%) of pure **20g** as a colorless oil. Crystallization from methanol gave **20g** as a white, crystalline solid: mp 68–69.5 °C; IR (KBr, cm^{-1}) 3342, 3111, 1597, 1426, 1353, 1204, 1053; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 5.98 (s, 1H), 3.96 (q, J = 5.9 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.20 (m, 2H); ^{13}C NMR (ppm) 176.36, 172.62, 168.09, 161.75, 158.20, 131.62, 128.03, 122.13, 101.37, 70.63, 60.57, 29.69, 28.27, 23.47, 16.33, 12.41. Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

4-[3-(5-Methyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenyl Acetate (22a). To a mixture of hydroxylamine hydrochloride (19.3 g, 0.277 mol) and finely divided K_2CO_3 (38.4 g, 0.277 mol) in ethanol (250 mL) was added **4** (8.17 g, 55.5 mmol). The mixture was refluxed for 18 h and filtered hot, the filter cake was washed with ethanol, and the combined filtrates were concentrated in vacuo to give 14.4 g of crude amidoxime as a yellow solid. This material was dissolved in pyridine (20 mL), and acetyl chloride (19.7 mL, 0.278 mol) was added at such a rate as to maintain a gentle reflux. The mixture was refluxed for an additional hour, cooled to room temperature, diluted with water, and extracted with ethyl acetate (2×). The combined organic phases were washed with water and brine, dried, and filtered through a short column of Florisil. Flash chromatography (20% ethyl acetate in hexanes) of the yellow oil obtained (15.4 g) provided 7.41 g (54.2%) of pure **22a**: mp 126–126.5 °C (ethanol); IR (KBr, cm^{-1}) 1766, 1614, 1591, 1428, 1372, 1352, 1268, 1208, 1171, 1106, 1000, 916, 860, 805, 676, 648; ^1H NMR ($CDCl_3$) δ 7.79 (s, 2H), 2.64 (s, 3H), 2.37 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (ppm) 176.48, 168.46, 167.91, 150.51, 131.12, 127.68, 124.30, 20.45, 16.33, 12.40. Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

4-[3-(5-Methyl-1,2,4-oxadiazolyl)]-2,6-dimethylphenol (22b). A mixture of **22a** (4.05 g, 16.4 mmol), NaOH (0.80 g, 20 mmol), and 50% aqueous ethanol (60 mL) was refluxed for 2 h. An additional 1.3 g (32 mol) of NaOH was added, and reflux was continued for 1.5 h. The deep yellow solution was diluted with water (300 mL), acidified with 6 N HCl, and extracted with ethyl acetate (3×). The combined organic phases were washed with water and brine, dried, and concentrated in vacuo to give 3.34 g (99.4%) of **22b** as an off-white crystalline solid: mp 166–168 °C; IR (KBr, cm^{-1}) 3350, 1595, 1480, 1419, 1352, 1232, 1182, 11189, 946, 912, 754; ^1H NMR ($CDCl_3$) δ 7.67 (s, 2H), 5.06 (br s, 1H), 2.60 (s, 3H), 2.26 (s, 6H); HRMS calcd for $C_{11}H_{13}N_2O_2$ (M + H^+), 205.09770; found, 205.09672.

Dimethyl(dimethylethyl)[[(5-methyl-3-isoxazolyl)methyl]oxy]silane (23). To a chilled (5 °C) solution of 5-methyl-3-isoxazolemethanol[29] (16.8 g, 148 mmol) and *tert*-butyldimethylsilyl chloride (24.6 g, 163 mmol) in dry CH_2Cl_2 (100 mL) was added over 15 min a solution of TEA (22.7 mL, 163 mmol) in CH_2Cl_2 (25 mL). 4-(Dimethylamino)pyridine (1.81 g, 14.8 mmol) was added, and the thick reaction mixture was stirred at room temperature for 48 h. Water (100 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine, dried, filtered through a pad composed of a layer of Florisil and a layer of silica gel 60, and concentrated in vacuo. The yellow oil obtained (36.6 g) was purified by flash chromatography (2% ethyl acetate in hexanes) to give 27.7 g (81.9%) of pure **23** as a pale yellow oil: IR (NaCl film, cm^{-1}) 2956, 2930, 2886, 2858, 1608, 1473, 1364, 1258, 1131, 1103, 1006, 894, 840, 780; ^1H NMR ($CDCl_3$) δ 6.03 (s, 1H), 4.72 (s, 2H), 2.41 (d, J = 0.7 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (ppm) 169.23, 164.20, 100.62, 57.44, 25.74, 18.21, 12.17, −5.43. Anal. ($C_{11}H_{21}NO_2Si$) C, H, N.

3-[[[Dimethyl(dimethylethyl)silyl]oxy]methyl]-5-isoxazolepropanol (24). To a cold (−78 °C) solution of **23** (13.0 g, 57.0 mmol) and TMEDA (1.2 mL, 7.9 mmol) in dry THF (150 mL) was added over 5 min *n*-butyllithium (31.3 mL, 2.0 M in hexane). The bright orange-yellow anion solution was stirred for 25 min. Ethylene oxide (50.0 mL of 7.6 M solution in dry THF) was added over 10 min. After 1.5 h, saturated NH_4Cl (30 mL) was added. The mixture was allowed to warm to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate (3×). The combined organic phases were washed with brine, dried, filtered through a short column of silica gel 60, and concentrated in vacuo. MPLC (20% ethyl acetate in hexanes) gave 3.44 g of recovered **23** and 8.18 g (52.7%) of pure **24** as a colorless oil: IR (NaCl film, cm^{-1}) 3420, 2960, 2930, 2859, 1600, 1472, 1257, 1104, 839, 780; ^1H NMR ($CDCl_3$) δ 6.06 (s, 1H), 4.72 (s, 2H), 3.72 (t, J = 6.1 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.96 (m, 2H), 1.80 (s, 1H), 0.91 (s, 9H), 0.10 (s, 6H). Anal. ($C_{13}H_{25}NO_3Si$) C, H, N.

[[3-[5-[3-[2,6-Dimethyl-4-[3-(5-methyl-1,2,4-oxadiazolyl)]-phenoxy]propyl]isoxazolyl]]methoxy]dimethyl(dimethylethyl)silane (25a). A solution of **24** (1.00 g, 3.67 mmol), **22b** (0.82 g, 4.0 mmol), and TPP (1.06 g, 4.04 mmol) in dry THF (10 mL) was chilled to 0 °C. A solution of DEAD (0.61 mL, 1.04 mmol) in dry THF (15 mL) was added dropwise over 20 min. The solution was stirred for 30 min at 0 °C and 18 h at room temperature, diluted with water, and extracted with ethyl acetate (2×). The combined organic phases were washed with 10% NaOH (3×) and brine, dried, filtered through a short column of silica gel 60, and concentrated in vacuo to give 3.44 g of a yellow oil. MPLC (10% ethyl acetate in hexanes) provided 1.54 g (83.2%) of pure **25a** as a colorless oil: IR (NaCl film, cm^{-1}) 2954, 2930, 2857, 1604, 1584, 1472, 1421, 1352, 1257, 1207, 1103, 840, 780; ^1H NMR ($CDCl_3$) δ 7.72 (s, 2H), 6.11 (s, 1H), 4.73 (s, 2H), 3.85 (t, J = 6.1 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.31 (s, 6H), 2.22 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (ppm) 176.29, 172.48, 168.10, 164.12, 158.21, 131.60, 128.00, 122.12, 100.20, 70.58, 57.48, 28.28, 25.77, 23.48, 18.25, 16.28, 12.35, −5.37. Anal. ($C_{24}H_{36}N_3O_4Si$) C, H, N.

5-[3-[2,6-Dimethyl-4-[3-(5-methyl-1,2,4-oxadiazolyl)]phenoxy]propyl]-3-isoxazolemethanol (25b). A solution of **25a** (1.03 g, 2.25 mmol), THF (80 mL), and 1 N HCl (10.3 mL) was stirred at room temperature for 18 h. The pH was adjusted to pH 7 (pH paper) with solid $NaHCO_3$, diluted with water (100 mL), and extracted with ethyl acetate (3×). The combined organic phases were washed with brine, dried, and concentrated in vacuo to give 1.13 g of yellow oil which was purified by flash chromatography (50% ethyl acetate in hexanes) to provide 0.69 g (90%) of pure **25b** as a white solid: mp 87–87.5 °C (white powder from ethanol); IR (KBr, cm^{-1}) 3341, 3120, 1601, 1585, 1486, 1356, 1272, 1207, 1048, 1038, 928, 836, 776, 752, 631; ^1H NMR ($CDCl_3$) δ 7.72 (s, 2H), 6.13 (s, 1H), 4.74 (d, J = 5.8 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.59 (t, J = 5.8 Hz, 1H), 2.31 (s, 6H), 2.22 (m, 2H); ^{13}C NMR (ppm) 176.35, 173.14, 168.07, 163.52, 158.18, 131.58, 128.03, 122.14, 99.85, 70.58, 57.07, 28.26, 23.52, 16.30, 12.35. Anal. ($C_{18}H_{21}N_3O_4$) C, H, N.

(4-Pentynyloxy)(dimethylethyl)diphenylsilane (26). A solution of imidazole (9.29 g, 136 mmol), dry DMF (50 mL), *tert*-butyldiphenylchlorosilane (17.7 mL, 68.2 mmol), and 4-pentyn-1-ol (5.77 mL, 62.0 mmol) was stirred at room temperature for 2 h, diluted with water (300 mL), and extracted with ethyl acetate (3×). The combined organic extracts were washed with water and brine, dried, and concentrated in vacuo to a yellow oil (22.7 g). Flash chromatography (hexanes followed by 3% ethyl acetate in hexanes) provided 17.4 g (86.8%) of pure **26** as a colorless oil: IR (NaCl film, cm^{-1}) 3308, 3071, 2956, 2932, 2855, 1472, 1428, 1110, 823, 701; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.38, (m, 6H), 3.74 (t, J = 5.9 Hz, 2H), 2.34 (dt, J = 7.1 and 2.6 Hz, 2H), 1.89 (t, J = 2.6 Hz, 1H), 1.77 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (ppm) 135.55, 133.78, 129.57, 127.61, 84.17, 68.31, 62.22, 31.40, 26.82, 19.21, 14.95; MS (CI) m/z 323 (MH^+).

Ethyl 5-[3-[[(Dimethylethyl)diphenylsilyl]oxy]propyl]-3-isoxazolecarboxylate (27). A solution of **26** (12.0 g, 37.3 mmol) in dry DMF (20 mL) was added dropwise over 20 min to a solution of ethyl chlorooximidoacetate (17.0 g, 112 mmol) in DMF (50 mL). After 45 min, the solution was warmed to 80–90 °C and a solution of TEA (15.6 mL, 112 mmol) in DMF (30 mL) was added over a 2.5 h period. After an additional hour, the solution was cooled to room temperature, diluted with water (200 mL), and extracted with ethyl acetate (3×). The combined organic phases were washed with water, 10% $KHSO_4$ (2×), water (2×), and brine and dried. Filtration through a short column of silica gel 60 provided 22.0 g of a red-brown oil. Flash chromatography (2% ethyl acetate in hexanes) gave 18.0 g of a yellow oil which was further purified by MPLC (10% ethyl acetate in hexanes). There was obtained 12.5 g (76.6%) of pure **27** as a colorless oil: IR (NaCl film, cm^{-1}) 2958, 2931, 2858, 1732, 1592, 1472, 1428, 1211, 1111, 823, 779, 741, 703; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.38 (m, 6H), 6.36 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.71 (t, J = 5.9 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 1.95 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (ppm) 175.23, 160.18, 156.32, 135.50, 133.48, 129.73, 127.72, 101.60, 62.26, 62.00, 30.12, 26.83, 23.24, 19.20, 14.16. Anal. ($C_{25}H_{31}NO_4Si$) C, H, N.

5-[3-[[(Dimethylethyl)diphenylsilyl]oxy]propyl]-3-isoxazolemethanol (28). A solution of **27** (7.19 g, 16.4 mmol) in dry THF (40 mL) was added slowly to a suspension of LAH (1.00 g, 26.3 mmol) in THF (35 mL). After 5 min, the mixture was chilled to 0 °C (ice/water bath) and treated sequentially with water (1.0 mL), 15% NaOH (1.0 mL), and water (3.0 mL), dried (K_2CO_3), and filtered. The filter cake was washed with ether, and the combined filtrates were concentrated in vacuo to give 6.83 g of a pale yellow oil which was purified by flash chromatography (30% ethyl acetate in hexanes). Pure **28** was obtained as a colorless oil: IR (NaCl film, cm^{-1}) 3396, 2957, 2931, 2857, 1601, 1472, 1427, 1111, 1063, 999, 964, 823, 741, 703; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.38 (m, 6H), 5.97 (s, 1H), 4.67 (d, J = 5.8 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H), 2.92 (br s, 1H), 2.87 (t, J = 7.6 Hz, 2H), 1.92 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (ppm) 173.74, 163.51, 135.52, 133.59, 129.68, 127.69, 99.70, 62.45, 56.94, 30.20, 26.83, 23.23, 19.20. Anal. ($C_{23}H_{29}NO_3Si$) C, H, N.

[[3-[5-[3-[(Methylthio)methyl]isoxazolyl]]propyl]oxy]-(dimethylethyl)diphenylsilane (29). Dimethyl disulfide (4.88 mL, 54.2 mmol) was added to a solution of **28** (4.29 g, 10.8 mmol) and triethylphosphine (8.00 mL, 54.2 mmol) in THF (45 mL). The solution was refluxed for 3.5 h, cooled to room temperature, and concentrated in vacuo. The residue obtained was diluted with water and extracted with ethyl acetate (3×). The combined organic phases were washed with water (3×) and brine, dried, and concentrated in vacuo to give 6.42 g of a yellow oil containing a white solid. Flash chromatography (hexane followed by 20% ethyl acetate in hexanes) provided 4.21 g (91.1%) of pure **29** as a pale yellow oil: IR (NaCl film, cm^{-1}) 2957, 2930, 2857, 1601, 1472, 1428, 1111, 998, 963, 823, 742, 703; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.38 (m, 6H), 5.95 (s, 1H), 3.71 (t, J = 6.0 Hz, 2H), 3.61 (s, 2H), 2.87 (t, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.97 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (ppm) 173.69, 161.42, 135.52, 133.61, 129.68, 127.69, 100.39, 62.48, 30.17, 28.30, 26.83, 23.28, 19.21, 15.08. Anal. ($C_{24}H_{31}NO_2SiS$) C, H, N.

3-[(Methylthio)methyl]-5-isoxazolepropanol (30). TBAF (1 N in THF, 17.2 mL, 17.2 mmol) was added to a solution of **29** (3.67 g, 8.62 mmol) in THF (20 mL) and stirred at room temperature for 18 h. The solvent was removed in vacuo, and the oil remaining was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine, dried, and concentrated in vacuo to a yellow oil (4.97 g) which was purified by MPLC (50% ethyl acetate in hexanes) to provide 1.57 g (97.5%) of pure **30** as a pale yellow oil: IR (NaCl film, cm^{-1}) 3393, 2919, 2875, 1600, 1477, 1431, 1057; ^1H NMR ($CDCl_3$) δ 6.06 (s, 1H), 3.71 (t, J = 6.2 Hz, 2H), 3.63 (s, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.03 (s, 3H), 2.20 (br s, 1H), 2.05 (s, 3H), 1.96 (m, 2H); ^{13}C NMR (ppm) 173.54, 161.55, 100.60, 61.33, 30.23, 28.28, 23.21, 23.28, 15.13. Anal. ($C_8H_{13}NO_2S$) C, H, N.

3-[3,5-Dimethyl-4-[[3-[3-[(methylthio)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (31). A solution of DEAD (1.35 mL, 8.56 mmol) in THF (5 mL) was added dropwise to a chilled (0 °C) solution of **30** (1.46 g, 7.80 mmol), **22b** (1.75 g, 8.56 mmol), and TPP (2.25 g, 8.56 mmol) in THF (15 mL). The solution was stirred for 18 h at room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic phases were washed with 10% NaOH, water, and brine, dried, and concentrated in vacuo to a yellow, oily solid (6.86 g) which was taken up into 20% ether in hexanes and filtered to remove triphenylphosphine oxide. The filtrate was concentrated in vacuo, and the oil remaining (4.35 g) was purified by flash chromatography (25% ethyl acetate in hexanes). Pure **31** was obtained as a white, fluffy solid: mp 91–91.5 °C (white needles from methanol); IR (NaCl film, cm^{-1}) 3126, 2961, 2921, 1604, 1578, 1478, 1421, 1352, 1271, 1208, 991, 812, 775, 751; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 6.10 (s, 1H), 3.86 (t, J = 6.0 Hz, 2H), 3.65 (s, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.32 (s, 6H), 2.24 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (ppm) 176.35, 173.08, 168.10, 161.58, 158.19, 131.63, 128.03, 122.15, 100.67, 70.57, 28.33, 28.21, 23.56, 16.32, 15.10, 12.41. Anal. ($C_{19}H_{23}N_3O_3S$) C, H, N.

3-[3,5-Dimethyl-4-[[3-[3-[(methylsulfenyl)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (32) and 3-[3,5-Dimethyl-4-[[3-[3-[(methylsulfonyl)methyl]-5-isoxazolyl]propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (33). A mixture of **31** (1.20 g, 3.21 mmol), wet alumina (3.2 g), CH_2Cl_2 (16 mL), and oxone (1.97 g, 3.2 mmol) was stirred at room temperature for 96 h, filtered, and concentrated in vacuo to a white solid (1.68 g). Flash chromatography (40% ethyl acetate in hexanes) provided 1.01 g (77.7%) of pure **33**. Elution with 2% methanol in CH_2Cl_2 gave 160 mg of **32** which was subjected to a second chromatography (1% methanol in CH_2Cl_2) to give 131 mg (10.5%) of pure **32** as a colorless oil. Trituration with ether gave **33** as a white powder. **32**: mp 82–83 °C; IR (KBr, cm^{-1}) 3105, 2957, 2928, 1590, 1474, 1444, 1420, 1384, 1352, 1272, 1207, 1045, 931, 916, 869; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 6.23 (s, 1H), 4.12 (d, J = 13.7 Hz, 1H), 3.90 (d, J = 13.7 Hz, 1H), 3.87 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.57 (s, 3H), 2.32 (s, 6H), 2.28 (m, 2H); ^{13}C NMR (ppm) 176.38, 174.53, 168.04, 158.09, 154.07, 131.57, 128.02, 122.21, 102.35, 70.43, 60.37, 39.69, 28.08, 23.62, 16.30, 12.41. Anal. ($C_{19}H_{23}N_3O_4S$) C, H, N. **33**: mp 135.5–136 °C; IR (KBr, cm^{-1}) 3127, 2977, 2929, 1599, 1579, 1472, 1443, 1418, 1355, 1307, 1271, 1220, 1144, 1118, 1032, 993, 937, 832; ^1H NMR ($CDCl_3$) δ 7.73 (s, 2H), 6.34 (s, 1H), 4.34 (s, 2H), 3.88 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.91 (s, 3H), 2.65 (s, 3H), 2.32 (s, 6H), 2.28 (m, 2H); ^{13}C NMR (ppm) 176.38, 174.61, 167.90, 158.10, 154.08, 131.58, 128.06, 122.24, 102.33, 70.44, 52.10, 39.67, 28.10, 23.66, 16.32, 12.41. Anal. ($C_{19}H_{23}N_3O_5S$) C, H, N.

5-Ethyl-3-[3,5-dimethyl-4-[[3-(3-ethyl-5-isoxazolyl)propyl]oxy]phenyl]-1,2,4-oxadiazole (34). The amidoxime derived from **6b** (1.12 g, 3.90 mmol) was treated with acetyl chloride as described for **19a**. MPLC (10% ethyl acetate in hexanes) provided 0.89 g (64%) of pure **34** as a colorless oil: IR (NaCl film, cm^{-1}) 2975, 2940, 1604, 1578, 1461, 1421, 1356, 1206, 1032, 891, 801; ^1H NMR ($CDCl_3$) δ 7.74 (s, 2H), 5.92 (s, 1H), 3.86 (t, J = 6.9 Hz, 2H), 2.98 (m, 4H), 2.68 (q, J = 7.6 Hz, 2H), 2.32 (s, 6H), 2.21 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H), 1.27 (t, J = 7.6 Hz, 3H); ^{13}C NMR (ppm) 180.49, 172.19, 167.96, 165.19, 158.16, 131.54, 128.01, 122.25, 100.38, 70.63, 28.27, 23.44, 20.29, 19.54, 16.27, 12.63, 10.83. Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

3-[3,5-Dichloro-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (37). The amidoxime derived from **6c** (1.00 g, 3.21 mmol) was treated with acetyl chloride as described for **19a**. Flash chromatography provided 683 mg (63.8%) of pure **37** as a colorless oil which crystallized from methanol to afford a white powder: mp 89–90 °C; IR (KBr, cm^{-1}) 1605, 1590, 1441, 1381, 1339, 1263, 1032, 997, 803, 748; ^1H NMR ($CDCl_3$) δ 8.02 (s, 2H), 5.91 (s, 1H), 4.13 (t, J = 5.9 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.66 2.66 (s, 3H), 2.31 (s, 3H), 2.24 (m, 2H); ^{13}C NMR (ppm) 177.04, 172.19, 166.27, 159.75, 153.44, 130.08, 127.80, 124.13, 101.87, 72.32, 28.01, 23.25, 12.35, 11.40. Anal. ($C_{16}H_{15}Cl_2N_3O_3$) C, H, N.

3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzamide (40). A solution of **6a** (6.00 g, 22.2 mmol) in concentrated H_2SO_4 (15 mL) was stirred at room temperature for 90 min. The solution was poured into 400 mL of ice/water and extracted with ethyl acetate (2 × 300 mL). The combined organic phases were washed with water and brine, dried, charcoaled, and concentrated in vacuo. There was obtained 4.10 g (64.1%) of **40** which was used without further purification. A white, crystalline solid was obtained from methanol: mp 162–163 °C; IR (KBr, cm^{-1}) 3441, 3380, 3157, 2932, 1675, 1623, 1603, 1441, 1374, 1209, 1124, 1034, 999, 980, 810, 795; ^1H NMR ($CDCl_3$) δ 7.48 (s, 2H), 6.10 (br s, 2H), 5.88 (s, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H), 2.21 (m, 2H); ^{13}C NMR (ppm) 172.16, 169.54, 159.67, 158.70, 132.66, 130.96, 128.69, 128.18, 101.69, 70.52, 28.14, 23.23, 16.24, 11.28. Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

5-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-3-methyl-1,2,4-oxadiazole (41). A solution of **40** (6.00 g, 20.8 mmol) and dimethylacetamide dimethyl acetal (33 mL) was refluxed for 3 h. The volatiles were removed in vacuo, and the resultant brown oil was treated with a solution comprised of $NH_2OH{\cdot}HCl$ (1.75 g, 25.0 mmol), 5 N NaOH (5 mL), and 70% HOAc (17 mL). After 30 min, water (10 mL) was added and the biphasic mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic phases were washed with water and brine, dried, charcoaled, and concentrated in vacuo to a yellow oil (5.50 g). Flash chromatography provided 3.50 g (41.9%) of pure **41** as a colorless oil. A white solid was obtained by crystallization from isopropyl acetate and hexanes: mp 55.5–56.5 °C; IR (KBr, cm^{-1}) 1604, 1566, 1474, 1419, 1346, 1240, 1202, 1045; ^1H NMR ($CDCl_3$) δ 7.79 (s, 2H), 5.90 (s, 1H), 3.87 (t, J = 6.1 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.46 (s, 3H), 2.33 (s, 6H), 2.29 (s, 3H), 2.24 (m, 2H); ^{13}C NMR (ppm) 175.29, 172.13, 167.55, 159.75, 159.59, 131.98, 128.78, 119.55, 101.77, 70.74, 28.25, 23.34, 16.29, 11.65, 11.38. Anal. ($C_{18}H_{21}N_3O_3$) C, H, N.

Methyl 3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzoate (43). Methyl 4-hydroxy-3,5-dimethylbenzoate[30] (**42**) (19.7 g, 109 mmol) was alkylated with **5**[4] (25.5 g, 160 mmol) according to the procedure described for **18a**. MPLC (20% ethyl acetate in hexanes) afforded 32.5 g (98.2%) of pure **43** as a colorless oil: IR (NaCl film, cm^{-1}) 2951, 1718, 1605, 1436, 1318, 1233, 1201, 1018, 904, 773; ^1H NMR ($CDCl_3$) δ 7.71 (s, 2H), 5.88 (s, 1H), 3.89 (s, 3H), 3.84 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.29 (s, 6H), 2.28 (s, 3H), 2.24 (m, 2H); ^{13}C NMR (ppm) 172.15, 166.82, 159.66, 130.86, 130.37, 125.35, 101.68, 70.51, 51.78, 28.18, 23.25, 16.21, 11.27. Anal. ($C_{17}H_{21}NO_4$) C, H, N.

3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzoic Acid (44). A solution of **44** (7.58 g, 25.0 mmol), ethanol/water, 1:1 (80 mL), and NaOH (1.2 g, 30 mmol) was refluxed for 1 h and cooled to room temperature and the ethanol removed in vacuo. The aqueous solution was washed with ether (20 mL), and HOAc (1.7 mL, 30 mmol) was added. The chilled mixture was filtered, and solids obtained were washed with water and dried in vacuo to give 6.90 g (95.4%) of pure **44** as a white powder: mp 156–157 °C (isopropyl acetate and hexanes); IR (KBr, cm^{-1}) 3320–2080, 1676, 1602, 1419, 1311, 1207, 1118, 1032, 999, 923, 790, 740, 700; ^1H NMR ($CDCl_3$) δ 11.20 (br s, 1H), 7.84 (s, 2H), 5.90 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.31 (s, 6H), 2.29 (s, 3H), 2.21 (m, 2H); ^{13}C NMR (ppm) 172.22, 160.46, 159.78, 131.11, 124.67, 101.81, 70.62, 51.78, 28.24, 23.33, 16.32, 11.36. Anal. ($C_{16}H_{19}NO_4$) C, H, N.

3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]benzoic Acid 2-Acetylhydrazide (45). A solution of **44** (8.30 g, 28.8 mmol), THF (80 mL), and CDI (5.14 g, 31.7 mmol) was refluxed for 2 h. After cooling to room temperature, acetic hydrazide (2.35 g, 31.7 mmol) was added and the reflux resumed. After 4 h, additional acetic hydrazide (1.5 g) was added. The solution was refluxed for 18 h, cooled to room temperature, and concentrated in vacuo. The resultant yellow oil was partitioned between water and ethyl acetate; the organic phase was dried, charcoaled, and concentrated in vacuo. There was obtained 10.2 g of **45** which was used without further purification. An analytical sample was obtained by recrystallization from ethyl acetate and hexanes: mp 141–142 °C; IR (KBr, cm^{-1}) 3215, 1603, 1583, 1463, 1207, 1158, 1039, 999, 910; ^1H NMR ($CDCl_3$) δ 9.60 (br s, 2H), 7.54 (s, 2H), 5.90 (s, 1H), 3.82 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.30 (s, 3H), 2.23 (s, 6H), 2.21 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (ppm) 172.16, 168.54, 165.12, 159.72, 159.18, 131.20, 128.21, 126.40, 101.74, 70.58, 28.22, 23.31, 20.64, 16.24, 11.36. Anal. ($C_{18}H_{23}N_3O_4$) C, H, N.

2-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-5-methyl-1,3,4-oxadiazole (46). A mixture of **45** (10.0 g, 29.0 mmol), chlorobenzene (120 mL), 1,1,1,3,3,3-hexamethyldisilazane (12.2 mL, 58.0 mmol), and 1 N TBAF (1.7 mL) was heated at 100 °C for 96 h. The residue obtained following in vacuo removal of the volatiles was partitioned between water and ethyl acetate. The organic phase was washed with water, dried, charcoaled, and concentrated in vacuo to a yellow oil (6.10 g). Filtration through a short column of silica gel 60 with 25% ethyl acetate in hexanes followed by ethyl acetate provided 4.00 g of a yellow oil which was crystallized from isopropyl acetate. There was obtained 2.41 g (27.0%) of pure **46** as white prisms: mp 99–100 °C; IR (KBr, cm^{-1}) 1604, 1583, 1556, 1479, 1445, 1416, 1280, 1230, 1187, 1044, 1004, 923; ^1H NMR ($CDCl_3$) δ 7.70 (s, 2H), 5.90 (s, 1H), 3.88 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.59 (s, 3H), 2.34 (s, 6H), 2.28 (s, 3H), 2.24 (m, 2H); ^{13}C NMR (ppm) 172.16, 164.71, 163.23, 159.72, 158.53, 131.82, 127.34, 119.33, 101.74, 70.69, 28.22, 23.30, 16.29, 11.36, 11.00. Anal. ($C_{18}H_{21}N_3O_3$) C, H, N.

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