Antipicornavirus Activity of Tetrazole Analogues Related to Disoxaril

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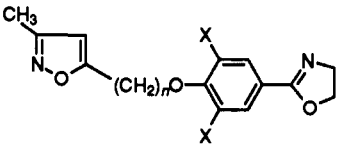
A series of tetrazole analogues of Win 54954, a broad-spectrum antipicornavirus compound, has been synthesized to address the acid lability of the oxazoline ring of this series of compounds. The results of X-ray crystallography studies of several members of the oxazoline series bound to human rhinovirus type 1A and 14 have been used to design compounds in the tetrazole series with a broad spectrum of activity. Compound **16b**, which has a three-carbon linkage between the isoxazole and phenyl rings and a propyl chain extending from the isoxazole ring, exhibiting an MIC_{80} for 15 rhinovirus serotypes of 0.20 μM as compared to 0.40 μM for Win 54954. X-ray studies of **16b** bound to human rhinovirus-14 show that the propyl side chain extends into a pore in the binding site with the possibility of hydrophobic interactions with a pocket formed by Leu^{106} and a portion of Ser^{107}.

The antipicornavirus activity of oxazolines of shown in Figure 1 has been well established.[1] Disoxaril and Win 54954 (Figure 1) have demonstrated broad-spectrum activity in vitro against both rhinoviruses[2,3] and enteroviruses[4] and were also effective in vivo when administered as late as 72 h postinfection to mice infected with polio,[5] echo,[6] and coxsackie[7] viruses. Although Win 54954 did not demonstrate a statistically significant clinical effect against rhinovirus 23 and 39,[8] a prophylactic effect was demonstrated in the prevention of human coxsackie A21 infection.[9] This lack of clinical efficacy against the rhinoviruses, although disappointing, suggests that poor pharmacokinetics could account for the inactivity.

The oxazoline ring structure suffers from acid lability which was seen to a large extent with WIN 54954. Three hydrolysis products are formed: aminoethyl ester **2**, hydroxyethyl amide **3**, and carboxylic acid **4** (Figure 2), all of which were found to be completely devoid of antirhinovirus activity. Consequently, Win 54954 exhibited a short half-life which could be attributed to the instability of the molecule. In view of the chemical instability associated with the oxazoline ring, we examined heterocyclic replacements with comparable or enhanced antirhinovirus activity and which were considerably more stable to acid hydrolysis.

We recently reported that one of the most promising replacements for the oxazoline ring which we have examined is 2-methyltetrazole.[10] This compound, **5** (Figure 3), was found to exhibit activity comparable to Win 54954 and on the basis of these results we have prepared and evaluated a series of analogues of **5**, where the chlorines have been replaced with methyl groups (Figure 4). We previously reported that a similar replacement in the oxazoline series resulted in a compound with comparable activity[10] and subsequently found that the dimethyl analogues displayed enhanced bioavailability.



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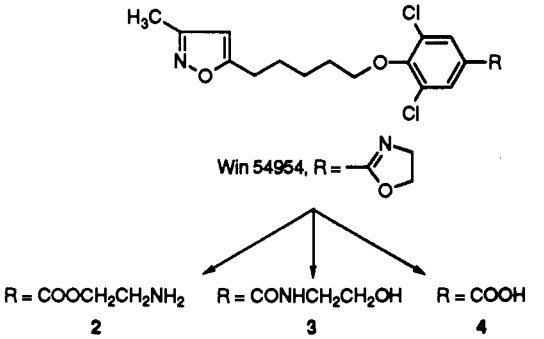
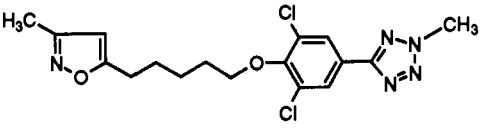
DISOXARIL; $n = 7$, X = H
WIN 54954; $n = 5$, X = Cl

Figure 1. Disoxaril and Win 54954 have shown broad-spectrum activity against a variety of picornaviruses. Win 54954 demonstrated activity against coxsackie A21 infections in humans.



2 **3** **4**

Figure 2. A description of the products resulting from the acid hydrolysis of Win 54954. The extent of and nature of the products is dependent upon the treatment and time.



5

Figure 3. The 2-methyltetrazole analogue of Win 54954. This compound has demonstrated activity comparable to Win 54954.

Chemistry

Several methods were used to synthesize the compounds described. The three-carbon chain analogues **10a–d**, with homologation of the alkyl group on the tetrazole ring, were prepared by the procedure outlined in Scheme I. Reaction of 3,5-dimethylisoxazole with 1-bromo-2-chloroethane gave the (chloropropyl)isoxazole **6**[10] which was treated with 3,5-dimethyl-4-hydroxybenzonitrile **7**[11] to give nitrile **8**. Treatment of **8** with sodium azide provided a 92% yield of tetrazole **9**, which on treatment with the appropriate alkyl iodide gave a mixture of the 1- and 2-substituted tetrazoles in a ratio of approximately 4:1, dependent upon the alkyl substituent. These isomers were separated by MPLC.[10]

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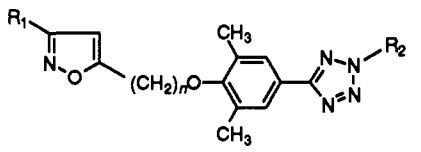
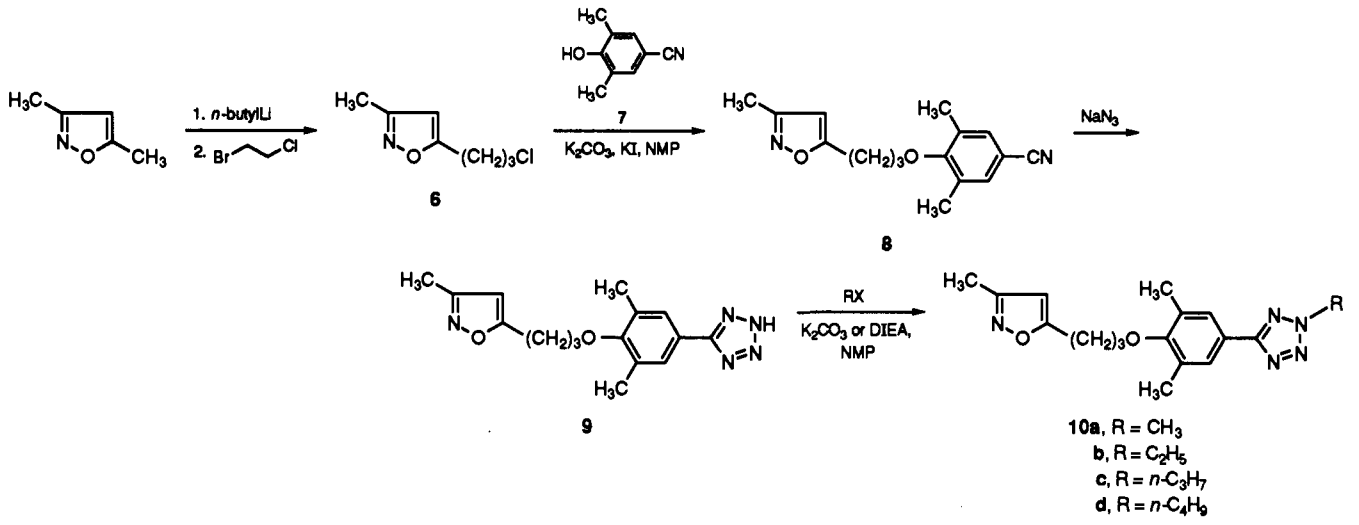


Figure 4. A general structure of analogues of compound **5** which are described in this paper.

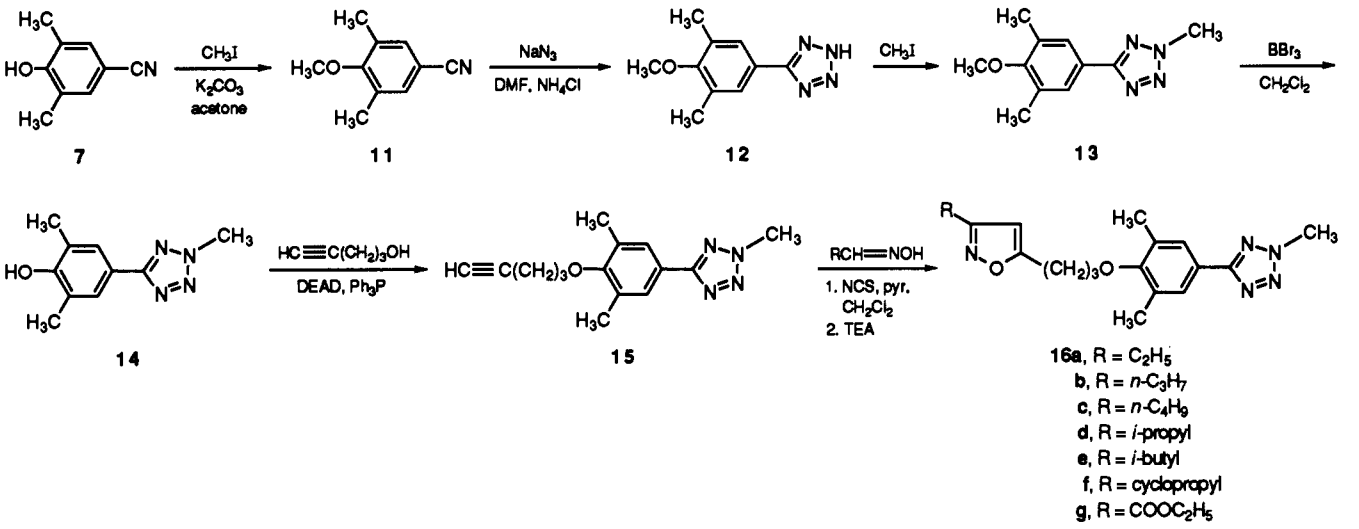
Modifications on the isoxazole ring were accomplished using the procedures outlined in Schemes II–V. Tetrazole **14**, was prepared in four steps from 3,5-dimethyl-4-hydroxybenzonitrile (Scheme II). The DEAD coupling[12] of **14** with 4-pentyn-1-ol provided **15** which on treatment with the appropriate oxime in the presence of *N*-chlorosuccinimide and pyridine, followed by triethylamine, provided compounds **16a–g** in 30–40% yield. The hydroxypropyl analogue **20** was prepared from ester **16g** in five steps (Scheme III). Reduction of ester **16g** with lithium aluminum hydride gave alcohol **17** which was converted with triphenylphosphine and bromine in methylene chloride[11] to bromide **18**. Treatment of **18** with the anion of *tert*-butyl acetate[13] gave the *tert*-butyl ester **19** which was reduced with DIBAL to **20**. Alcohols **24a,b**

Scheme I



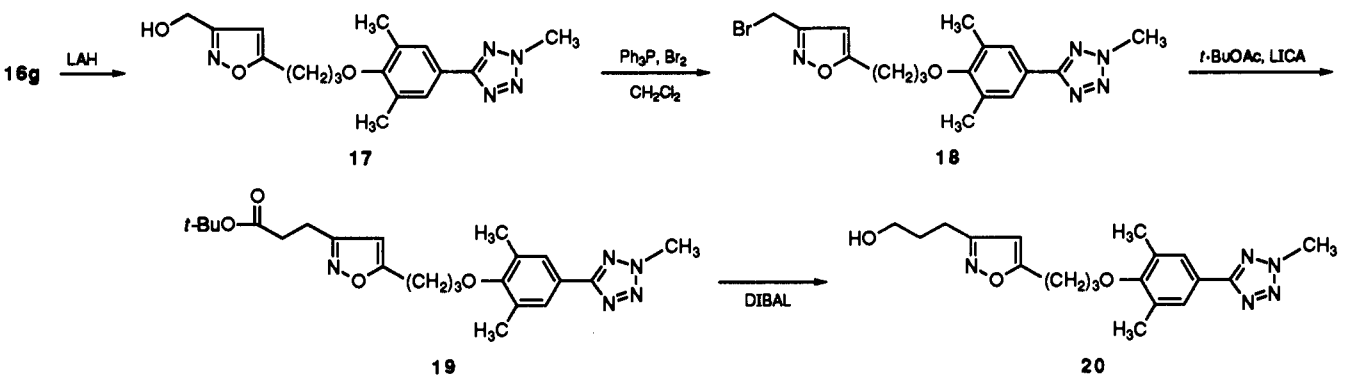
10a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7
d, R = n-C_4H_9

Scheme II

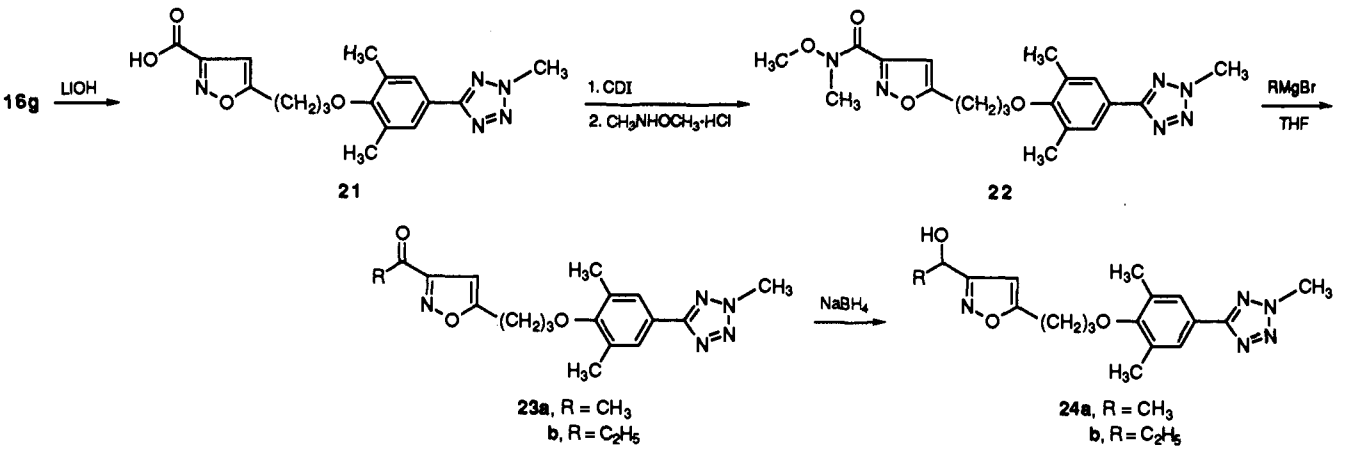


16a, R = C_2H_5
b, R = n-C_3H_7
c, R = n-C_4H_9
d, R = i-propyl
e, R = i-butyl
f, R = cyclopropyl
g, R = $COOC_2H_5$

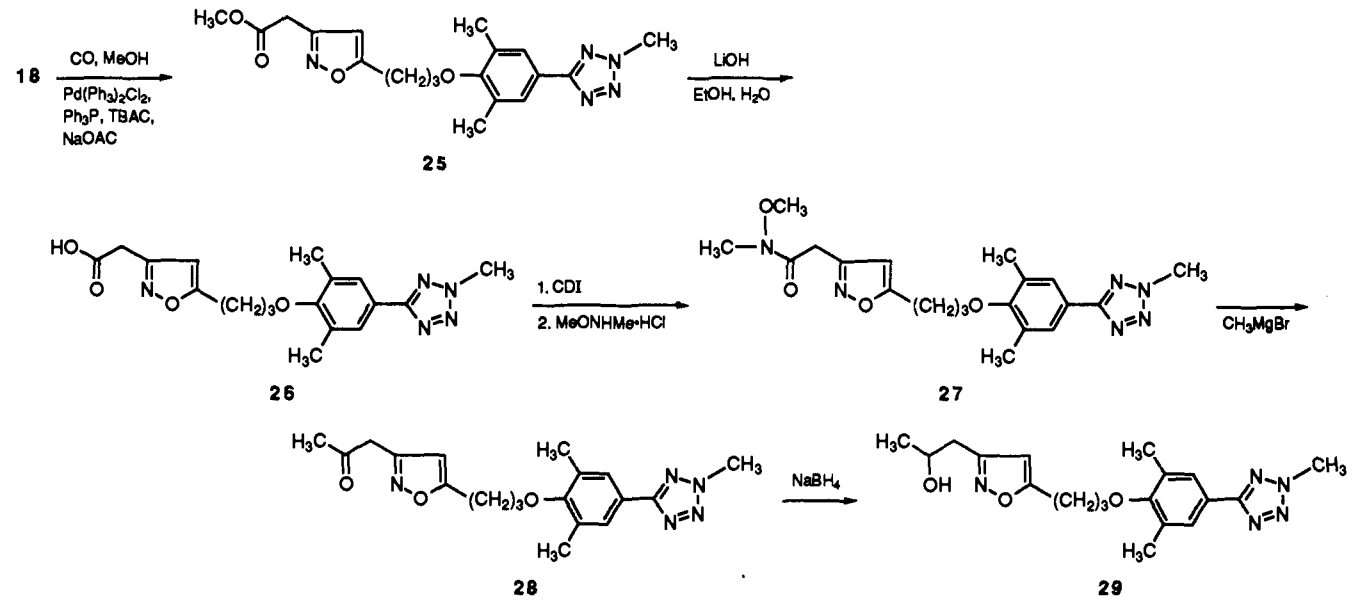
Scheme III



Scheme IV



Scheme V

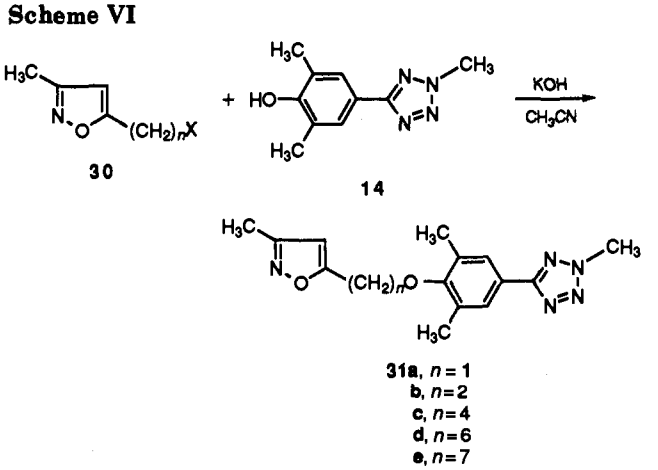


were also prepared from ester **16g** according to the procedure shown in Scheme IV. Conversion of acid **21** with CDI and *N,O*-dimethylhydroxylamine[14] to amide **22** followed by treatment with the appropriate alkyl Grignard gave ketones **23** which were reduced to alcohols **24a,b**. The homologated alcohol **29** was prepared in a similar sequence of reactions (Scheme V) from ester **25**.

Variation in the length of the connecting chain was accomplished according to Scheme VI. This procedure was used for the preparation of the compounds **31a–e**.

Modification of the alkyl groups on the tetrazole ring in the 5-carbon chain series was achieved by the procedure described in Scheme VII. The requisite nitrile **35**, was prepared from aldehyde **33** via oxime formation followed by dehydration with acetic anhydride. The synthesis of the hydroxymethyl and alkoxymethyl analogues in this series is described in Scheme VIII. Finally the displacement of bromide from **44** with the appropriate alcohol[15] gave the alkoxy isoxazoles **45a–c** (Scheme IX).

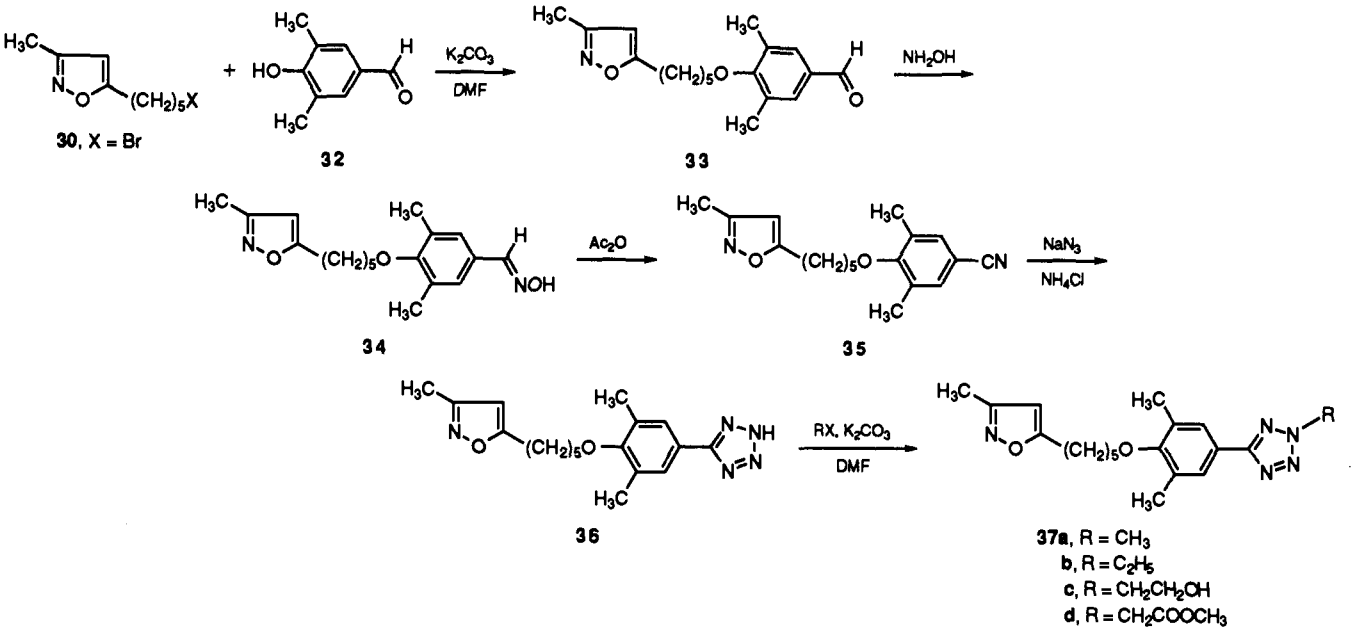
Scheme VI



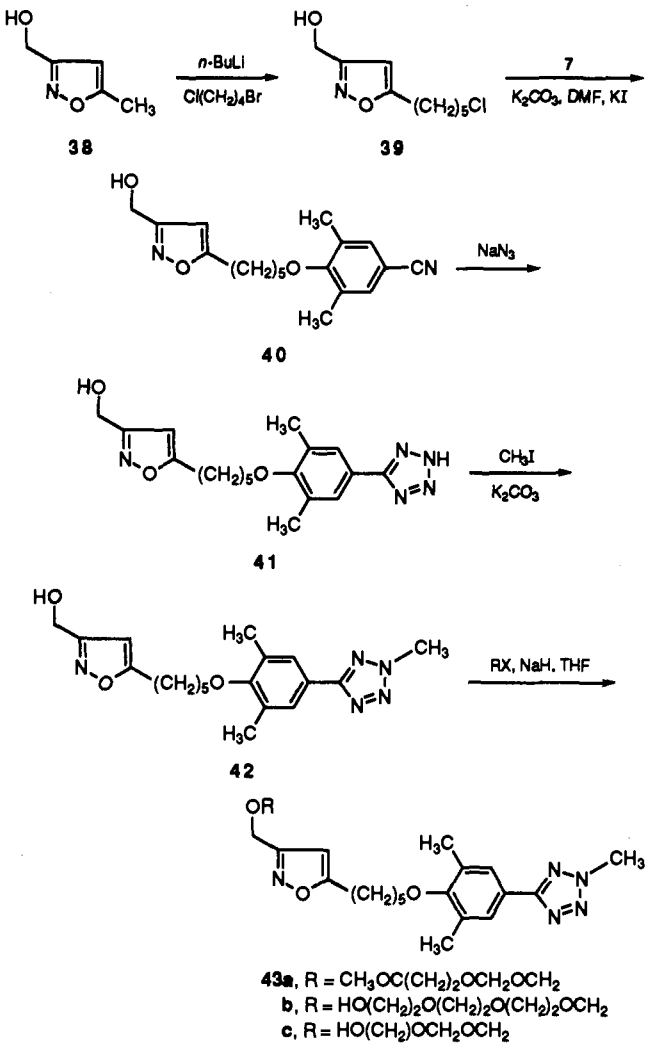
Results and Discussion

Compounds were initially screened against human rhinovirus types 1A and 14 in a plaque reduction assay.[16] These serotypes were used because their three-dimensional structure had been determined with and without drug bound to the viral capsid.[17,18] Those compounds which were active against both serotypes were screened against an additional 13 serotypes, and the MIC_{80} (the concentration which inhibits 80% of the serotypes) was determined. Although the dichlorophenyl analogue **5** demonstrated potent activity comparable to Win 54954, it had been found that the dimethylphenyl analogues in related series exhibited greater bioavailability than the corresponding dichlorophenyl counterparts (unpublished results). Consequently, we chose to examine the structure–activity relationships in the dimethyl series commencing

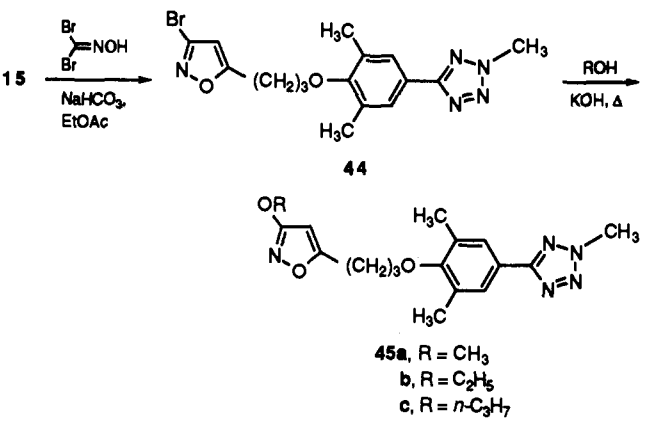
Scheme VII



Scheme VIII



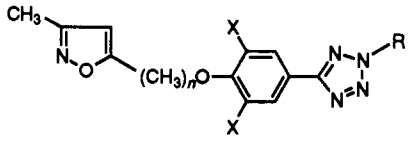
Scheme IX



with compound **37a**, which exhibited activity comparable to **5**. Variation in the chain length from one to five carbon atoms (Table I) resulted in an interesting pattern of activity. The three- and five-carbon homologues, **10a** and **37a** respectively, showed a similar MIC_{80}, despite the difference in activity against HRV-14. This difference was not unexpected since it had been shown that in analogous series, longer compounds were routinely more active against this HRV-14.[19] X-ray studies have shown that the compound binding site in HRV-14 is longer than HRV-1A.[20] Increasing the length of the alkyl substituent on the tetrazole ring from methyl to ethyl, in the case of the five-carbon homologue (compounds **37a,b**), resulted in a reduction in activity against both HRV-14 and -1A with a corresponding increase in MIC_{80}. Replacement of the methyl group on the isoxazole ring with a hydroxymethyl, compound **42** (Table IV), provided a slight improvement in activity against HRV-1A with a corresponding reduction against HRV-14 as well as an increase in MIC_{80}.

Our goal was to achieve broad-spectrum activity as exemplified by the MIC_{80}. It had been shown in previous studies with HRV-14 that the activity of compounds in this series appeared to correlate with the ability to occupy optimum space in the compound binding site and consequently maximize binding energy through hydrophobic interactions.[21] Chain extension from methyl to propyl on the isoxazole ring in the oxazoline series resulted in a corresponding increase in activity, and a further chain extension was detrimental to activity. These results were in agreement with the space occupancy theory resulting

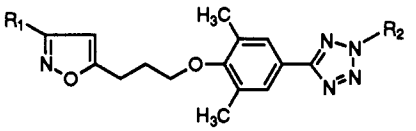
Table I. Antirhinovirus Activity



compd	n	X	R	mp, °C	formula[a]	in vitro antiviral activity, μM[b] HRV-1A	HRV-14	MIC_{80}[c]
5	5	Cl	Cl	47–49	$C_{17}H_{19}Cl_2N_5O_2$[d]	0.38	0.38	0.25
31a	1	CH_3	CH_3	118–119	$C_{15}H_{17}N_5O_2$	NA[e]	NA[e]	-
31b	2	CH_3	CH_3	77–79	$C_{18}H_{19}N_5O_2$	2.14	NA[e]	-
10a	3	CH_3	CH_3	97–98	$C_{17}H_{21}N_5O_2$	0.11	1.74	0.40
31c	4	CH_3	CH_3	41–43	$C_{18}H_{23}N_5O_2$	0.10	2.43	0.66
37a	5	CH_3	CH_3	63–65	$C_{19}H_{25}N_5O_2$	0.34	0.45	0.39
31e	6	CH_3	CH_3	66–68	$C_{20}H_{27}N_5O_2$	0.24	1.91	0.73
31f	7	CH_3	CH_3	53–54	$C_{21}H_{29}N_5O_2$	0.76	3.0	1.6
37b	5	CH_3	C_2H_5	56–57	$C_{20}H_{27}N_5O_2$	0.73	0.73	0.65
37c	5	CH_3	$HOCH_2CH_2$	69–70	$C_{20}H_{27}N_5O_3$	NA[e]	4.35	-
37d	5	CH_3	CH_3OOCCH_2	52–53	$C_{21}H_{27}N_5O_4$	NA[e]	NA[e]	-

[a] Satisfactory analysis were obtained. [b] Minimum inhibitory concentration which reduces the number of viral plaques by 50%. [c] Values determined from 15 serotypes. [d] See ref 10. [e] Not active.

Table II. Antirhinovirus Activity



compd	R_1	R_2	mp, °C	formula	in vitro antiviral activity, μM HRV-1A	HRV-14	MIC_{80}
10a	CH_3	CH_3	97–98	$C_{17}H_{21}N_5O_2$	0.11	1.7	0.40
10b	CH_3	C_2H_5	77–78	$C_{18}H_{23}N_5O_2$	0.67	0.80	0.25
10c	CH_3	n-C_3H_7	80–81	$C_{19}H_{25}N_5O_2$	6.5	1.6	1.27
10d	CH_3	n-C_4H_9	65–66	$C_{20}H_{27}N_5O_2$	6.5	NA	-
16a	C_2H_5	CH_3	54–55	$C_{18}H_{23}N_5O_2$	0.05	0.50	0.41
16b	C_3H_7	CH_3	49–50	$C_{19}H_{25}N_5O_2$	0.12	0.12	0.20
16c	C_4H_9	CH_3	oil	$C_{20}H_{27}N_5O_2$	0.54	0.11	0.54
16d	i-C_3H_7	CH_3	81–82	$C_{19}H_{25}N_5O_2$	0.28	0.73	0.73
16e	i-C_4H_9	CH_3	66–67	$C_{20}H_{27}N_5O_2$	0.46	0.32	1.5
16f	cyclopropyl	CH_3	69–70	$C_{19}H_{23}N_5O_2$	0.19	0.48	0.48

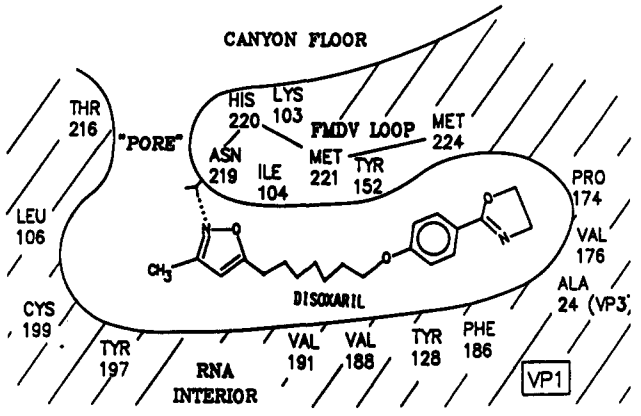


Figure 5. A schematic of the compound binding site in HRV-14 as determined by X-ray crystallography by T. Smith and coworkers (see ref 18), showing the hydrophobic "toe" and the pore area leading to the canyon floor. The canyon has been determined to be the cell receptor binding site which attaches to domains 1 and 2 of ICAM-1.

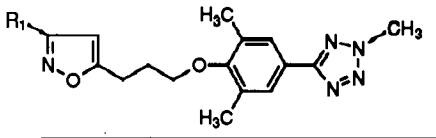
from the volume map[22] and CoMFA[21] studies which we had previously reported. These studies suggest that activity correlated with a compound's ability to optimally occupy space in the binding site, particularly in the pore area (Figure 5). It had also been shown that the size of the HRV-1A and -14 binding sites differ, the HRV-1A binding site being shorter and wider, suggesting that some flexibility in a molecule would be desirable for broad-spectrum activity. Consequently, we extended the side chain on the isoxazole ring of compound **10a** (Table II). Increasing the chain length to ethyl, **16a**, improved activity against both HRV-1A and -14, although the MIC_{80} was essentially unchanged. The propyl homologue **16b** showed a substantial improvement in potency against HRV-14, retained activity against HRV-1A, and demonstrated a broader spectrum of activity (lower MIC_{80}). Further extension of the side chain to butyl, **16c**, resulted in a general reduction in activity.

The results of introducing an oxygenated side chain on the isoxazole ring are shown in Table III. The hydroxylmethyl analogue **17** was considerably less active than the parent compound. Increasing the size of the chain to ethyl, **48**, and propyl, **20**, resulted in improved activity; the latter compound was comparable in activity to **10a**. Replacement of the methyl group with a methoxyethyl, **47**, retained activity against HRV-1A but demonstrated a substantial improvement in activity against HRV-14.

Compound **16b** was selected for further evaluation since it appeared to demonstrate broad-spectrum activity. A comparison of the activity of **16b**, Win 54954, and **10a** against 15 serotypes is shown in Table V. Compound **16b** is more potent against the majority of serotypes tested.

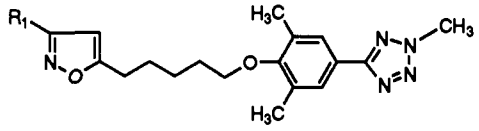
The X-ray structure of **16b** in HRV-14 has been determined (Figure 6). The compound is in the same orientation in the pocket as Win 54954, with the phen-

Table III. Antirhinovirus Activity



compd	R	mp, °C	formula	in vitro antiviral activity, μM HRV-1A	HRV-14	MIC_{80}
10a	CH_3	97–98	$C_{17}H_{21}N_5O_2$	0.11	1.74	0.40
17	$HOCH_2$	88–90	$C_{18}H_{21}N_5O_3$	0.20	3.4	3.4
48	$HO(CH_2)_2$	75–76	$C_{18}H_{23}N_5O_3$	0.14	2.0	1.09
20	$HO(CH_2)_3$	61–63	$C_{19}H_{25}N_5O_3$	0.20	0.17	0.40
23a	CH_3CO	99–100	$C_{18}H_{21}N_5O_3$	0.12	0.96	–
24a	CH_3CHOH	90–92	$C_{18}H_{23}N_5O_3$	0.14	1.4	1.1
24b	CH_3CH_2CHOH	64–65	$C_{19}H_{25}N_5O_3$	NA	0.13	–
29	$CH_3CHOHCH_2$	oil	$C_{19}H_{25}N_5O_3$	0.71	1.8	–
44	$HOCH_2CHOHCH_2$	oil	$C_{19}H_{25}N_5O_4$	0.67	NA	–
47	$CH_3O(CH_2)_2$	oil	$C_{19}H_{25}N_5O_3$	0.12	0.05	0.30
45a	CH_3O	100–101	$C_{17}H_{21}N_5O_3$	0.11	1.4	0.33
45b	C_2H_5O	86–87	$C_{18}H_{23}N_5O_3$	0.15	0.10	0.70
45c	C_3H_7O	90–91	$C_{19}H_{25}N_5O_3$	0.39	0.08	0.60

Table IV. Antirhinovirus Activity



compd	R	mp, °C	formula	in vitro antiviral activity, μM HRV-1A	HRV-14	MIC_{80}
42	$HOCH_2$	82–83	$C_{19}H_{25}N_5O_3$	0.18	0.62	1.59
49	COOH	112–113	$C_{19}H_{23}N_5O_4$	1.4	30.4	–
43a	$CH_3O(CH_2)_2OCH_2OCH_2$	oil	$C_{23}H_{33}N_5O_5$	2.89	0.33	–
43b	$HO(CH_2)_2O(CH_2)_2O(CH_2)_2OCH_2$	oil	$C_{25}H_{37}H_5O_8$	4.9	1.05	–
43c	$HO(CH_2)_2OCH_2OCH_2$	oil	$C_{22}H_{31}N_5O_5$	4.03	0.06	–

Table V. Comparative Evaluation of Win 54954, Compound 10a, and Compound 16b against 15 Human Rhinovirus Serotypes

serotype	in vitro antiviral activity, μM Win 54954	compound 10a	compound 16b
1A	2.51	0.11	0.12
1B	0.17	0.03	0.03
2	0.02	0.02	0.04
6	0.23	2.20	0.15
14	1.20	1.70	0.12
15	0.41	0.18	0.68
21	0.02	0.02	0.02
22	0.02	0.05	0.08
25	0.29	0.06	0.006
30	0.09	0.07	0.20
41	0.89	0.40	0.93
50	0.30	0.23	0.09
67	0.18	0.14	0.22
86	0.21	2.05	0.12
89	0.02	0.01	0.02
MIC_{80}	0.41	0.40	0.20

yltetrazole group in a stacking conformation with Tyr^{128} and Tyr^{152}. The propyl chain is in close proximity to a hydrophobic pocket formed by Leu^{106} and a portion of Ser^{107}. This type of interaction has been previously described for other analogues in this series[19] and may account for the enhancement in activity with increased chain length in the pore area of the compound binding site.

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, 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 coupled to a Varian 3400 gas chromatograph or on a JEOL JMS-01SC spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. 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. Preparative chromatography was performed using a Buchi B680 MPLC system coupled to an ISCO UV detector and fraction collector. 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.

3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]-benzonitrile (8). A mixture of 7 (7.36 g, 50.0 mmol), finely divided K_2CO_3 (13.8 g, 100 mmol), KI (0.84 g, 5.0 mmol), 6[10] (12.0 g, 75.0 mmol), and *N*-methylpyrrolidinone (100 mL) was heated at 60 °C for 18 h. The cooled mixture was diluted with H_2O (200 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with H_2O (3 × 50 mL) and brine, dried ($MgSO_4$), filtered through a short column of Florisil, and concd in vacuo to an oil (18.3 g) which was purified by MPLC (Silica Gel 60, 25% EtOAc in hexanes) to give 12.7 g (94.1%) of pure 8 as a white solid: mp 46–8 °C (CH_3OH); ^1H NMR ($CDCl_3$) δ 2.20 (m, 2H), 2.28 (s, 9H), 2.99 (t, J = 7.6 Hz, 2H), 3.84 (t, J = 6.1 Hz, 2H), 5.88 (s, 1H), 7.32 (s, 2H). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]-phenyl]-2*H*-tetrazole (9). A mixture of 8 (8.53 g, 31 mmol), NaN_3 (2.5 g, 38 mmol), tetraethylamine hydrochloride (6.9 g, 50 mmol), and *N*-methylpyrrolidinone (75 mL) was gradually heated to 150 °C and stirred at this temperature for 5 h. After cooling, the mixture was poured into cold H_2O and a solution of 20%

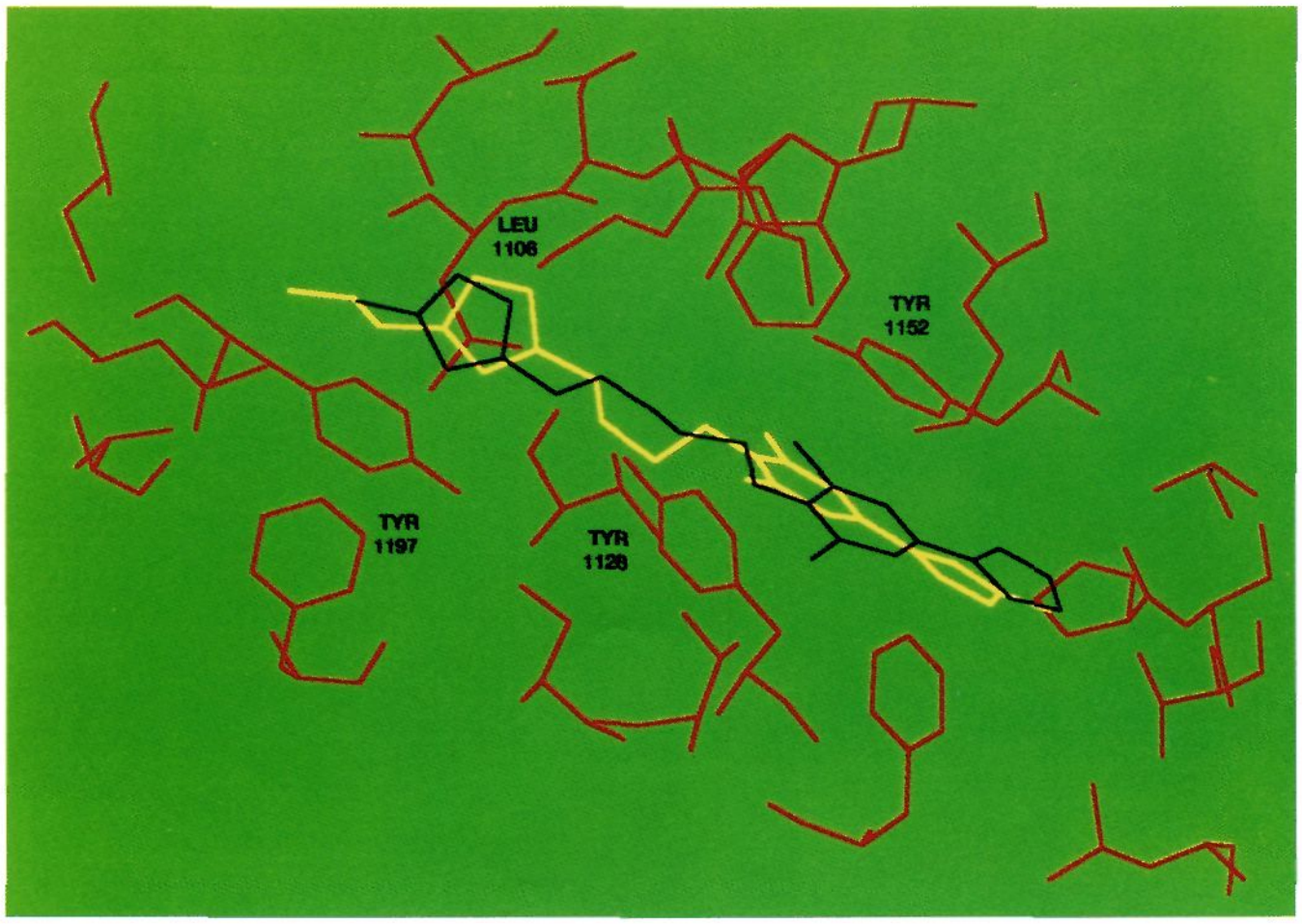


Figure 6. Compound **16b** (yellow) and Win 54954 (blue) bound to HRV-14 with the methyltetrazole and oxazoline rings in the hydrophobic toe region of the binding site. The phenyl rings are in a stacking conformation with Tyr^{128} and Tyr^{152}. The propyl side chain of **16b** is in close proximity to Leu^{106} and Tyr^{197} in the pore area suggesting possible hydrophobic interactions with these residues.

$NaNO_2$ was added until a positive starch–iodide test resulted. Acidification of the resultant solution caused the precipitation of an off-white solid which was collected, washed with H_2O, and dried. Recrystallization from CH_3OH gave 8.79 g (89%) of **9**: mp 185–186 °C; ^1H NMR (DMSO-d_6) δ 2.12 (m, 2H), 2.21 (s, 3H), 2.30 (s, 6H), 2.97 (t, J = 7.6 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 6.20 (s, 1H), 7.73 (s, 2H). *Anal.* ($C_{16}H_{19}N_5O_2$) C, H, N.

2-Ethyl-5-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy]phenyl]-2*H*-tetrazole (10b). A solution of **9** (4.7 g, 15 mmol), C_2H_5I (1.6 mL, 20 mmol), *N*,*N*-diisopropylethylamine (5.2 mL, 30 mmol), and *N*-methylpyrrolidinone (50 mL) under nitrogen was stirred at rt for 24 h. Water (150 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were dried, and the solvent was removed to give 4.71 g of an oil which was crystallized from CH_3OH. Recrystallization from CH_3OH gave 3.45 g (67%) of **10b**: mp 77–78 °C; ^1H NMR ($CDCl_3$) δ 1.65 (t, J = 6 Hz, 3H), 2.20 (m, 2H), 2.25 (s, 3H), 2.30 (s, 6 H), 3.05 (t, J = 6 Hz, 2H), 3.85 (t, J = 4 Hz, 2H), 4.70 (q, J = 6 Hz, 2H), 5.90 (s, 1H), 7.80 (s, 2H). Anal. ($C_{18}H_{23}N_5O_2$) C, H, N.

4-Methoxy-3,5-dimethylbenzonitrile (11). A mixture of **7** (14.7 g, 100 mmol), finely divided K_2CO_3 (16.6 g, 120 mmol), and dry acetone (200 mL) was stirred at rt for 30 min, after which CH_3I (7.5 mL, 120 mmol) was added. The mixture was refluxed for 18 h, cooled, and concd in vacuo. The pasty residue was partitioned between H_2O (100 mL) and ether (50 mL). The aqueous layer was extracted with ether (25 mL). The combined ethereal layers were washed with 10% NaOH (2 × 25 mL), H_2O (25 mL), and brine, dried ($MgSO_4$), and concd in vacuo to an off-white solid (17.3 g). MPLC (Silica Gel 60, 5% EtOAc in hexanes) provided 15.0 g (93.2%) of pure **11** as a white solid: mp 51–2 °C (pentane); ^1H NMR ($CDCl_3$) δ 2.30 (s, 6H), 3.76 (s, 3H), 7.32 (s, 2H). Anal. ($C_{10}H_{11}NO$) C, H, N.

5-(4-Methoxy-3,5-dimethylphenyl)-2*H*-tetrazole (12). To a solution of **11** (8.25 g, 51 mmol) in DMF (50 mL) under nitrogen was added NaN_3 (3.64 g, 56 mmol) and NH_4Cl (0.69 g, 13 mmol). The mixture was heated carefully to 110 °C for 24 h. The cooled solution was poured into H_2O (150 mL) and extracted with melthylene chloride (2 × 50 mL). The aqueous solution was chilled in ice and acidified carefully with 6 N HCl. A white solid precipitated which was collected and dried. Recrystallization from CH_3CN afforded 6.44 g (62%) of **12**: mp 235–236 °C; ^1H NMR ($CDCl_3$) δ 2.27 (s, 6H), 3.68 (s, 3H), 7.78 (s, 3H). Anal. ($C_{10}H_{12}N_4O$) C, H, N.

5-(4-Methoxy-3,5-dimethylphenyl)-2-methyl-2*H*-tetrazole (13). A suspension of **12** (7.15 g, 35 mmol), K_2CO_3 (5.52 g, 40 mmol), and CH_3I (2.5 mL, 40 mmol) in CH_3CN (100 mL) was refluxed for 1 h then stirred at rt for 12 h. The reaction mixture was concd in vacuo and the residue partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), concd in vacuo and the resultant oil purified by MPLC (Silica Gel 60, 20% EtOAc in hexanes) providing 5.11 g (67%) of **13**: mp 75–76 °C (white needles from hexanes); ^1H NMR ($CDCl_3$) δ 2.3 (s, 6H), 3.8 (s, 3H), 4.4 (s, 3H), 7.8 (s, 2H). Anal. ($C_{11}H_{14}N_4O$) C, H, N.

2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenol (14). To a solution of **13** (11.34 g, 52 mmol) in dry methylene chloride (100 mL) under nitrogen was added BBr_3 (9.9 mL, 105 mmol) at a rate to cause gentle reflux. After stirring for an additional h at rt, the solution was cautiously poured into ice–water and the resultant white precipitate was collected and recrystallized from C_2H_5OH to yield 10.23 g (96%) of **14** as a tan solid: mp 194–195 °C; ^1H NMR ($CDCl_3$) δ 2.28 (s, 6H), 4.35 (s, 3H), 7.60 (s, 2H), 8.72 (s, 1H). Anal. ($C_9H_{12}N_4O$) C, H, N.

5-[3,5-Dimethyl-4-(4-pentyn-1-yloxy)phenyl]-2-methyl-2*H*-tetrazole (15). To a chilled (0 °C) solution of **14** (15.32 g, 75 mmol), 4-pentyn-1-ol (7.5 mL, 81 mmol), and triphenylphosphine (23.61 g, 90 mmol) in methylene chloride (200 mL) under nitrogen was added dropwise a solution of DEAD (15 mL, 90 mmol) in methylene chloride (50 mL). After stirring for 12 h, the mixture was concd to dryness and the residue was filtered through a column of Silica Gel 60, eluting with methylene chloride. The oil obtained was purified by MPLC (Silica Gel 60, 25% EtOAc in hexanes) to give a viscous oil which crystallized from methanol. A pale yellow solid (17.02 g, 84%) was obtained: mp 46–48 °C; ^1H NMR ($CDCl_3$) δ 2.00 (m, 1H), 2.05 (m, 2 H), 2.35 (s, 6H), 2.55 (dt, J = 7, 6.5 Hz, 2H), 3.95 (t, J = 6 Hz, 2H), 4.40 (s, 3H), 7.80 (s, 2H). Anal. ($C_{15}H_{18}N_4O$) C, H, N.

5-[3,5-Dimethyl-4-[[3-(3-propyl-5-isoxazolyl)propyl]oxy]-phenyl]-2-methyl-2*H*-tetrazole (16c). To a solution of NCS (2.67 g, 20 mmol) in $CHCl_3$ (20 mL) was added 4 drops of pyridine followed by a solution of pentanal oxime (1.46 g, 20 mmol) in $CHCl_3$ (7 mL) while maintaining the temperature at 25–30 °C with a rt water bath. A solution of **15** (2.7 g, 10 mmol) in $CHCl_3$ (5 mL) was added dropwise followed by a solution of triethylamine

(2.8 mL, 20 mmol) in $CHCl_3$ (10 mL). The reaction mixture was heated to 40–50 °C for 1 h and then refluxed for 20 h. The cooled mixture was diluted with H_2O and extracted with ether (4×). The combined ether layers were washed with 1 N HCl, dried ($MgSO_4$), and concd in vacuo to give an oil which was purified by MPLC (Silica Gel 60, 20% EtOAc in hexanes). There was obtained 98 mg (27%) of **16c** as an oil: ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 8 Hz, 3H), 1.30–1.48 (m, 2H), 1.57–1.72 (m, 2H), 2.22 (m, 2H), 2.33 (s, 6H), 2.65 (t, J = 6 Hz, 2H), 3.02 (t, J = 7 Hz, 2H), 3.86 (t, 2H, J = 5 Hz), 4.38 (s, 3H), 5.90 (s, 1H), 7.98 (s, 2H). Anal. ($C_{20}H_{27}N_5O_2$) C, H, N.

Ethyl 5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolecarboxylate (16g). A solution of triethylamine (5.0 mL, 35.8 mmol) in $CHCl_3$ (75 mL) was added dropwise over 1 h to a solution of ethyl chlorooximidoacetate (5.43 g, 35.8 mmol) and **15** (14.5 g, 53.6 mmol) in $CHCl_3$ (100 mL). The reaction mixture was stirred at rt for 72 h. Additional ethyl chlorooximidoacetate (5.43 g, 35 mmol) and triethylamine (5.0 mL, 35.8 mmol) in $CHCl_3$ (75 mL) were added. The reaction mixture was heated to reflux for 18 h and cooled to rt, and H_2O (300 mL) was added. The organic layer was separated and washed with 1 N HCl and water, dried ($MgSO_4$), and concd in vacuo. Column chromatography (Silica Gel 60, 25% EtOAc in hexanes) provided 5.17 g (37.5%) of **16g** as a white solid: mp 101.5–103 °C; ^1H NMR ($CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 2.22 (m, 2H), 2.33 (s, 6H), 3.14 (t, J = 7.6 Hz, 2H), 3.87 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 4.45 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 6.51 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{23}N_5O_4$) C, H, N.

5-[3-[2,5-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolemethanol (17). To a suspension of LAH (2.46 g, 64.8 mmol) in THF (50 mL) was added dropwise a solution of **16g** (15.6 g, 40.5 mmol) in THF (100 mL) at such a rate as to maintain a gentle reflux. After 30 min at rt, the mixture was chilled (−20 °C) and treated dropwise sequentially with H_2O (2.5 mL), 15% NaOH (2.5 mL), and H_2O (7.4 mL) and dried ($MgSO_4$). The mixture was filtered, the filter cake was washed with ether, and the combined filtrates were concd in vacuo to an oil (15.0 g) which was filtered through a short column on Silica Gel 60 with *i*-PrOAc to give 12.0 g (86.2%) of pure **17**: mp 88–89 °C (*i*-PrOAc and hexanes); ^1H NMR ($CDCl_3$) δ 1.70 (br s, 1H), 2.25 (m, 2H), 2.35 (s, 6H), 3.10 (t, J = 6 Hz, 2H), 3.90 (t, J = 5 Hz, 2H), 4.40 (s, 3H), 4.80 (s, 2H), 6.15 (s, 1H), 7.85 (s, 2H). Anal. ($C_{17}H_{21}N_5O_3$) C, H, N.

5-[4-[[3-[3-(Bromomethyl)-5-isoxazolyl]propyl]oxy]-3,5-dimethylphenyl]-2-methyl-2*H*-tetrazole (18). To a chilled (0 °C) solution of triphenylphosphine (24.44 g, 93.2 mmol) in dry CH_2Cl_2 (250 mL) was added dropwise a solution of bromine (4.77 mL, 93.2 mmol) in CH_2Cl_2 (100 mL). A solution of **17** (26.45 g, 77 mmol) in CH_2Cl_2 (150 mL) was added dropwise and stirred an additional 10 min. Saturated K_2CO_3 (20 mL) was added and the mixture was partitioned between H_2O (500 mL) and ether (500 mL). The organic layer was separated and the aqueous layer was extracted with ether (1 × 200 mL). The combined organic layers were dried ($MgSO_4$), diluted with an equal volume of hexanes, and passed through a short column of Silica Gel 60. Removal of the solvent gave 28.86 g (92.2%) of **18** as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.17 (m, 2H), 2.33 (s, 6H), 3.07 (t, J = 7.6 Hz, 2H), 3.87 (t, J = 6.1 Hz, 2H), 4.38 (s, 3H), 4.41 (s, 2H), 6.17 (s, 1H), 7.80 (s, 2H). Anal. ($C_{17}H_{20}BrN_5O_2$) C, H, N.

1,1-Dimethylethyl 5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolepropanoate (19). To a cold (−78 °C) solution of LICA, prepared from *N*-isopropylcyclohexylamine (0.27 mL, 1.7 mmol) in dry THF (5 mL) and 2.5 M *n*-butyllithium in hexanes (0.66 mL, 1.7 mmol) at 0 °C, was added dropwise *t*-BuOAc (0.22 mL, 1.7 mmol).[13] After 30 min the solution was introduced by cannulation into a rt solution of bromide **18** (450 mg, 1.1 mmol) in dry DMSO (6 mL). After 1 h, the mixture was treated with saturated NH_4Cl (1 mL) and partitioned between H_2O (50 mL) and ether (50 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concd in vacuo. The oil obtained was purified by column chromatography (Silica Gel 60, 40% EtOAc in hexanes) to give 240 mg (50%) of **19** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.17 (m, 2H), 2.33 (s, 6H), 2.62 (t, J = 5.7 Hz, 2H), 2.94 (t, J = 7.7 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 4.38 (s, 3H), 5.94 (s, 1H), 7.80 (s, 2H). Anal. ($C_{23}H_{31}N_5O_4$) C, H, N.

5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolepropanol (20). To a chilled (0 °C) solution of **19** (1.03 g, 2.3 mmol) in THF (20 mL) was added dropwise over 10 min 1 M DIBAL in hexanes (9.33 mL, 9.3 mmol). The reaction mixture was stirred at rt for 72 h, chilled (0 °C), treated with saturated Rochelle's salt (2 mL), and warmed to rt. Following dispersal of the gel, the organic layer was decanted and the salt residue washed with ether (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through a short column of Silica Gel 60. Purification of the oil obtained by column chromatography on Silica Gel 60 (40% EtOAc in hexanes) afforded 840 mg (90.6%) of **20** as a pale yellow solid: mp 61–63.5 °C; ^1H NMR ($CDCl_3$) δ 1.71 (s, 1H), 1.87–2.01 (m, 2H), 2.22 (m, 2H), 2.33 (s, 6H), 2.77 (t, J = 7.4 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 3.72 (t, J = 6.2 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 4.38 (s, 3H), 5.93 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{25}N_5O_3$) C, H, N.

5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolecarboxylic Acid (21). Ester **16g** (5.00 g, 13 mmol) was dissolved in EtOH/H_2O 9:1 (75 mL). LiOH (340 mg, 14 mmol) was added and the mixture stirred at rt for 12 h and then heated to reflux for 2 h. The solution was diluted with water (400 mL) and extracted with ether. The aqueous layer was acidified with CH_3COOH (1.0 mL). The solid which separated was filtered, washed with H_2O, dried, and recrystallized from ether to give 3.36 g (72.3%) of **21**: mp 138.5–140 °C; ^1H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 3.13 (t, J = 7.6 Hz, 2H), 3.88 (t, J = 6.0 Hz, 2H), 4.39 (s, 3H), 6.20 (s, 1H), 6.48 (s, 1H), 7.80 (s, 2H). Anal. ($C_{17}H_{19}N_5O_3$) C, H, N.

***N,O*-Dimethyl-*N*-hydroxy-5-[3-[2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolecarboxamide (22).** To a suspension of **21** (2.0 g, 5.6 mmol) in $CHCl_3$ (25 mL) was added 1,1'-carbonyldiimidazole (1.0 g, 6.2 mmol). The resultant solution was stirred until the evolution of carbon dioxide ceased and then *N,O*-dimethylhydroxylamine hydrochloride (600 mg, 6.2 mmol) was added. The solution was stirred for 12 h, H_2O (50 mL) was added, and the mixture was extracted with ether (2 × 100 mL). The ethereal layers were combined, washed with H_2O and 1 N HCl (2 × 50 mL), and dried ($MgSO_4$). Removal of the solvent gave a pale yellow solid which was purified by MPLC (40% EtOAc in hexanes) to afford 1.23 g (61.2%) of **22**: mp 94.5–97.5 °C; ^1H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.34 (s, 6H), 3.13 (t, J = 7.6 Hz, 2H), 3.41 (br s, 3H), 3.80 (s, 3H), 3.88 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.43 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{24}N_8O_4$) C, H, N.

1-[5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolyl]ethanone (23a). To a chilled (0 °C) solution of **22** (3.76 g, 9.38 mmol) in THF (20 mL) was added ethereal 3 M CH_3MgBr (6.72 mL, 20.2 mmol). The solution was stirred for 1 h and then treated with saturated NH_4Cl (3 mL) and partitioned between H_2O (50 mL) and ether (25 mL). The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic extracts were dried ($MgSO_4$) and concd in vacuo. The white solid obtained (3.4 g) was purified by MPLC (Silica Gel 60, 30% EtOAc in hexanes) to give 3.18 g (93.5%) of pure **23a**: mp 99.5–100.5 °C (EtOH); ^1H NMR ($CDCl_3$) δ 2.24 (m, 2H), 2.33 (s, 6 H), 2.65 (s, 3H), 3.13 (t, J = 7.6 Hz, 2H), 3.88 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.45 (s, 1H), 7.80 (s, 2H). Anal. ($C_{18}H_{21}N_5O_3$) C, H, N.

α-Methyl-5-[3-[2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolemethanol (24a). To a solution of **23a** (1.62 g, 4.6 mmol) in C_2H_5OH (75 mL) and methanol (10 mL) was added $NaBH_4$ (130 mg, 3.4 mmol). After stirring for 10 min, 1 N NaOH (5 mL) was added followed by H_2O (250 mL) and EtOAc (175 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concd in vacuo to dryness, and purified by MPLC (Silica Gel 60, 20% EtOAc in hexanes). Compound **24a** was obtained in nearly quantitative yield after recrystallization from a mixture of ether and hexanes: mp 89.5–91.5 °C NMR ($CDCl_3$) δ 1.56 (d, J = 6.6 Hz, 3H), 2.22 (m, 2H), 2.33 (s, 6H), 2.42 (d, J = 4.7 Hz, 1H), 3.06 (t, J = 7.6 Hz, 2H), 3.87 (t, J = 6.1 Hz, 2H), 4.38 (s, 3H), 5.02 (dq, J = 6.6, 4.7 Hz, 1H), 6.10 (s, 1H), 7.78 (s, 2H). Anal. ($C_{18}H_{23}N_5O_3$) C, H, N.

α-Ethyl-5-[3-[2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolemethanol (24b). Prepared in the same fashion as **24a** according to Scheme IV in 92% yield: mp 64.5–66 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3H), 1.85 (m, 2H), 2.22 (m, 2H), 2.33 (s, 6H), 2.37 (d, J = 4.7, 1H), 3.05 (t, J = 7.6 Hz, 2H), 3.86 (t, J = 6.1, 2H), 4.38 (s, 3H), 4.78 (dt, J = 7.6, 4.7 Hz, 1H), 6.08 (s, 1H), 7.79 (s, 2H). Anal. ($C_{19}H_{25}N_5O_3$) C, H, N.

Methyl 5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazoleacetate (25). Bis(triphenylphosphine)palladium(II) chloride (0.17 g, 0.24 mmol) was added to dry CH_3OH (150 mL) which was pretreated with carbon monoxide for 15 min. After 15 min and with continuous addition of CO, triphenylphosphine (0.32 g, 1.2 mmol), triethylbenzylammonium chloride (0.55 g, 2.4 mmol), and NaOAc (2.14 g, 26.1 mmol) were added and heated with an oil bath to 60 °C. After 1 h, 18 (10.0 g, 24.6 mmol) was added and heated for 18 h with continuous addition of CO. The reaction mixture was partitioned between H_2O (100 mL), ether (100 mL), and CH_2Cl_2 (50 mL). The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and filtered through a short column of Silica Gel 60. The solvent was removed in vacuo and the resulting oil (10.2 g) was purified by MPLC (Silica Gel 60, 30% EtOAc in hexanes) to give 9.45 g (99.6%) of pure **25**: mp 71.5–73 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 3.06 (t, J = 7.6 Hz, 2H), 3.73 (s, 2H), 3.75 (s, 3H), 3.87 (t, J = 6.1 Hz, 2H), 4.38 (s, 3H), 6.14 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{23}N_5O_4$) C, H, N.

5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazoleacetic Acid (26). A mixture of **25** (2.20 g, 5.70 mmol), LiOH (0.18 g, 7.4 mmol), and EtOH/H_2O 9:1 (30 mL) was stirred at rt for 1 h, diluted with H_2O (250 mL), and washed with ether (2 × 50 mL). The aqueous phase was acidified with CH_3COOH (2.0 mL), chilled with an ice bath, and filtered. The solids obtained were washed with cold H_2O (2 × 50 mL) and dried to give 2.03 g (94.9%) of pure **26**: mp 118.5–119 °C (ether and CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 3.06 (t, J = 7.6 Hz, 2H), 3.81 (s, 2H), 3.86 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.16 (s, 1H), 7.79 (s, 2H), 9.42 (s, 1H). Anal. ($C_{18}H_{21}N_5O_4$) C, H, N.

***N,O*-Dimethyl-*N*-hydroxy-5-[3-[2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazoleacetamide (27).** To a solution of **26** (2.0 g, 5.5 mmol) in $CHCl_3$ (25 mL) was added 1,1′-carbonyldiimidazole (1.0 g, 6.2 mmol). After CO_2 evolution had ceased, *N,O*-dimethylhydroxylamine hydrochloride (0.60 g, 6.2 mmol) was added. After 18 h, the solution was partitioned between H_2O (100 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined ethereal layers were washed with 1 N HCl and brine and dried ($MgSO_4$). Removal of the solvent in vacuo provided 1.5 g (64%) of **27** which was used without further purification. An analytical sample of **27** was obtained by column chromatography (Silica Gel 60, 50% ethyl acetate in hexanes): mp 79.5–80.5 °C (CH_2Cl_2 and ether); ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 3.05 (t, J = 7.6 Hz, 2H), 3.23 (s, 3H), 3.73 (s, 3H), 3.86 (s, 2H), 3.87 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.17 (s, 1H), 7.79 (s, 2H). Anal. ($C_{20}H_{26}N_8O_4$), C, H, N.

1-[5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolyl]-2-propanone (28). To a chilled (0 °C) solution of **27** (1.18 g, 2.85 mmol) in THF (15 mL) was added 2.8 M ethereal CH_3MgBr (2.0 mL, 5.7 mmol). After 2 h at 0 °C and 1 h at rt, the mixture was treated with saturated NH_4Cl (2 mL) and partitioned between H_2O (50 mL), 1 N HCl (1 mL), and ether (20 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with 1 N HCl and brine, dried ($MgSO_4$), and concd in vacuo. The oil obtained (0.71 g) was purified by MPLC (Silica Gel 60, 50% EtOAc in hexanes). There was obtained 0.22 g (20%) of **28** and 0.51 g (43%) of recovered **27**. For **28**: mp 96–96.5 °C (CH_2Cl_2, ether, and hexanes); ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.26 (s, 3H), 2.33 (s, 6 H), 3.06 (t, J = 7.6 Hz, 2H), 3.80 (s, 2H), 3.87 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.06 (s, 1H), 7.80 (s, 2H).

α-Methyl-5-[3-[2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazoleethanol (29). To a chilled (0 °C) suspension of **28** (0.16 g, 0.51 mmol) in EtOH/H_2O 1:1 (10 mL) was added $NaBH_4$ (0.16 g, 4.2 mmol). After 2 h, H_2O (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concd in vacuo, and purified by MPLC (Silica Gel 60, 50% EtOAc in hexanes) to provide 0.12 (75%) of pure **29** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 6.2 Hz, 3H), 2.22 (m, 2H), 2.33 (s, 6H), 2.79 (ddd, J = 15.0, 7.2, 4.8 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 3.86 (t, J = 6.1 Hz, 2H), 4.17 (m, 1 H), 4.38 (s, 3H), 5.99 (s, 1H), 7.79 (s, 2H). Anal. ($C_{19}H_{25}N_5O_3 \cdot 0.25H_2O$) C, H, N.

5-[3,5-Dimethyl-4-[[4-(3-methyl-5-isoxazolyl)butyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (31c). A suspension of **30**[1] (n = 4, X = Cl, 4.7 g, 27 mmol), 14 (5.0 g, 25 mmol), powdered KOH (1.7 g, 30 mmol), and KI (4.56 g, 27 mmol) in CH_3CN (150 mL) was refluxed under nitrogen for 12 h. Upon cooling, the reaction was filtered and concd in vacuo. The crude oil was taken up in EtOAc (200 mL) and washed with H_2O. The organic phase was dried ($MgSO_4$), decolorized (charcoal), and concd to provide an orange oil which solidified on standing. Recrystallization from *i*-ProAc and hexanes provided 4.75 g (56%) of **31c**: mp 41–43 °C; ^{1}H NMR ($CDCl_3$) δ 1.85–2.06 (m, 4H), 2.27 (s, 3H), 2.33 (s, 6H), 2.82 (t, J = 7.1 Hz, 2H), 3.83 (t, J = 5.8 Hz, 2H), 4.37 (s, 3H), 5.85 (s, 1 H), 7.79 (s, 2H). Anal. ($C_{18}H_{23}N_5O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[(3-methyl-5-isoxazolyl)methyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (31a) was prepared in 75% yield by the same procedure used for **31c**: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 9H), 4.41 (s, 3H), 4.94 (s, 2H), 6.22 (s, 1H), 7.82 (s, 2H). Anal. ($C_{15}H_{17}N_5O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[6-(3-methyl-5-isoxazolyl)hexyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (31d) was prepared as above in 51% yield: mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 1.45–1.65 (m, 4H), 1.66–1.90 (m, 4H), 2.26 (s, 3H), 2.33 (s, 6H), 2.73 (t, J = 7.4 Hz, 2H), 3.80 (t, J = 6 Hz, 2H), 4.37 (s, 3H), 5.8 (s, 1H), 7.79 (s, 2H). Anal. ($C_{20}H_{27}N_5O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[7-(3-methyl-5-isoxazolyl)heptyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (31e) was prepared as above in 32% yield: mp 53–54 °C; ^{1}H NMR ($CDCl_3$) δ 1.39–1.75 (m, 8H), 1.76–1.92 (m, 2H), 2.26 (s, 1H), 2.33 (s, 6H), 2.71 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 6.4 Hz, 2H), 4.37 (s, 3H), 5.80 (s, 1H), 7.79 (s, 2H). Anal. ($C_{21}H_{29}N_5O_2$) C, H, N.

3,5-Dimethyl-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]benzaldehyde (33). A solution of 4-hydroxy-3,5-dimethylbenzaldehyde **32** (8.7 g, 58 mmol), **30**[1] (n = 5, X = Br, 14.4 g, 62 mmol), and K_2CO_3 (3.9 g, 98 mmol) in CH_3CN (100 mL) was refluxed for 5 h. The mixture was filtered, concd in vacuo, and filtered through a short column of Silica Gel 60, eluting with *i*-ProAc. Concentration of the solvent in vacuo gave 14.3 g (82%) of **33** as a pale yellow solid: mp 51–53 °C (*i*-ProAc and hexanes); ^{1}H NMR ($CDCl_3$) δ 1.58–1.92 (m, 6H), 2.27 (s, 3H), 2.36 (s, 6H), 2.80 (t, J = 7 Hz, 2H), 3.82 (t, J = 6 Hz, 2H), 5.85 (s, 1H), 7.55 (s, 2H), 9.82 (s, 1H). Anal. ($C_{18}H_{23}NO_3$), C, H, N.

3,5-Dimethyl-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]benzaldehyde Oxime (34). A solution of **33** (49.4 g, 164 mmol), hydroxylamine hydrochloride (50.5 g, 730 mmol), and pyridine (50 mL, 620 mmol) was heated to reflux for 1 h and then concd to dryness. Water (600 mL) was added and the precipitated solid was collected. Recrystallization from EtOAc and hexanes provided 43.9 g (85%) of **34**: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 1.61–1.83 (m, 6H), 2.28 (s, 9H), 2.77 (t, J = 7 Hz, 2H), 3.78 (t, J = 6 Hz, 2H), 5.83 (s, 1H), 7.25 (s, 2H), 8.05 (s, 2H). Anal. ($C_{18}H_{24}N_2O_3$) C, H, N.

3,5-Dimethyl-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]benzonitrile (35). A solution of **34** (82.3 g, 260 mmol) in acetic anhydride (1 L) was refluxed for 12 h. The solution was concd to dryness and the residue was partitioned between H_2O and EtOAc. The organic layer was dried and concd in vacuo leaving a dark oil which was filtered through a short column of Silica Gel 60, eluting with EtOAc. Removal of the solvent and recrystallization from ether and hexanes gave 66.8 g (86%) of **35** as a brown solid: mp 50–51 °C; ^{1}H NMR ($CDCl_3$) δ 1.62–1.85 (m, 6H), 2.28 (s, 9H), 2.75 (t, J = 8 Hz, 2H), 3.78 (t, J = 6 Hz, 2H), 5.83 (s, 1H), 7.32 (s, 2H). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]phenyl]-2*H*-tetrazole (36). A solution of **35** (33 g, 110 mmol), NaN_3 (13.3 g, 200 mmol), and NH_4Cl (3.6 g, 70 mmol) in DMF (250 mL) was heated at 100 °C for 72 h. Water was added and the mixture concd in vacuo. The residue was dissolved in EtOAc

(3 L) and washed with 1 N HCl, dried, and concd in vacuo. The solid obtained was washed with hexanes and recrystallized from EtOAc to give 35 g (93%) of **36**: mp 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 1.62–1.85 (m, 6H), 2.30 (s, 9H), 2.80 (t, J = 6 Hz, 2H), 3.80 (t, J = 5 Hz, 2H), 5.90 (s, 1H), 7.82 (s, 2H). Anal. ($C_{18}H_{23}N_5O_2$) C, H, N.

5-[3,5-Dimethyl-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (37a). A mixture of **36** (27.1 g, 79.4 mmol), methyl iodide (7 mL, 110 mmol), and K_2CO_3 (20 g, 150 mmol) in CH_3CN (150 mL) was refluxed for 1 h. The solids were removed by filtration, and the filtrate was concd to dryness. The residue was partitioned between H_2O and EtOAc. The organic layer was dried and concd to dryness to give an oil which was purified by column chromatography (Silica Gel 60, 50% EtOAc in hexanes). Recrystallization from ether gave 16.1 g (57%) of **37a**: mp 63–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 6H), 2.30 (s, 9H), 2.78 (t, J = 8 Hz, 2H), 3.82 (t, J = 8 Hz, 2H), 4.40 (s, 3H), 5.84 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{25}N_5O_2$) C, H, N.

3,5-Dimethyl-4-[[5-[3-(hydroxymethyl)-5-isoxazolyl]pentyl]oxy]benzonitrile (40). A mixture of **39**[21] (35.7 g, 175 mmol), **7** (20 g, 136 mmol), K_2CO_3 (20 g, 145 mmol), and a catalytic amount of KI in DMF (100 mL) was heated at 100 °C for 18 h. After cooling, the mixture was diluted with H_2O (100 mL) and extracted with ether. The combined ether extracts were dried and filtered through Silica Gel 60 with 50% EtOAc in hexanes which provided 36.3 g (66%) of **40** as a light brown solid: mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 2H), 1.74–1.89 (m, 4H), 2.33 (s, 6H), 2.38 (m, 1H), 2.82 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 6.1 Hz, 2H), 4.24 (d, J = 5.8 Hz, 2H), 6.07 (s, 1H), 7.32 (s, 2H). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

5-[5-[2,6-Dimethyl-4-[5-(2*H*-tetrazolyl)phenoxy]pentyl]-3-isoxazolemethanol (41). A mixture of **40** (15 g, 47.7 mmol), NaN_3 (6.4 g, 98.5 mmol), and NH_4Cl (500 mg, 9.4 mmol) in DMF (150 mL) was heated at 100 °C for 72 h. The cooled mixture was diluted with water (1 L), acidified with 2 N HCl, and cooled in an ice bath. The solid which separated was collected, dried in vacuo, and heated with EtOAc (400 mL). The undissolved material was removed by filtration and the filtrate passed through a column of Silica Gel 60, eluting with 50% EtOAc in hexanes. Recrystallization of the solid obtained from EtOAc and hexanes gave pure **41** as a white solid in 62%: mp 127–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.50–1.61 (m, 6H), 2.30 (s, 6H), 2.78 (t, J = 7.1 Hz, 2H), 3.8 (t, J = 5.9 Hz, 2H), 4.46 (s, 2H), 6.23 (s, 1H), 7.72 (s, 2H). Anal. ($C_{18}H_{23}N_5O_3$) C, H, N.

5-[5-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]pentyl]-3-isoxazolemethanol (42). A mixture of **41** (9.6 g, 26.9 mmol), K_2CO_3 (5.0 g, 36 mmol), and CH_3I (3.0 mL, 48 mmol) in CH_3CN (250 mL) was heated at 60 °C for 1 h. The solvent was removed in vacuo and the residual oil dissolved in EtOAc, washed with H_2O, and dried. Removal of the solvent gave an oil which was purified by column chromatography (Silica Gel 60, 20% EtOAc in hexanes) providing a light brown solid which after recrystallization from ether gave 6.08 g (61%) of **42**: mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 1.61–1.83 (m, 6H), 2.36 (s, 6H), 2.81 (t, J = 7.2 Hz, 2H), 3.81 (t, J = 6.3 Hz, 2H), 4.38 (s, 3H), 4.72 (d, J = 7 Hz, 2H), 6.06 (s, 1H), 7.79 (s, 2H). Anal. ($C_{19}H_{25}N_5O_3$) C, H, N. A second chromatography fraction gave 2.7 g (27%) of the 1-methyl positional isomer as an amorphous solid.

5-[3,5-Dimethyl-4-[[5-[3-[(methoxyethoxymethoxy)methyl]-5-isoxazolyl]pentyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (43a). A mixture of **42** (2.0 g, 5.38 mmol) and NaH (186 mg, 7.75 mmol) in THF (12 mL) was stirred under nitrogen at rt for 1 h. A solution of MEM chloride (960 mg, 7.7 mmol) in THF (2 mL) was added. After 12 h, the mixture was poured onto ice and extracted with ether. The combined ethereal extracts were dried and concd in vacuo to an oil which was purified by MPLC (Silica Gel 60, 60% EtOAc in hexanes) to give 1.5 g (61%) of **43a** as colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.70–1.90 (m, 6H), 2.34 (s, 6H), 2.82 (t, J = 7.2 Hz, 2H), 3.41 (s, 3H), 3.58 (dd, J = 8.4 and 6.0 Hz, 2H), 3.76 (dd, J = 8.4 and 6.0 Hz, 2H), 3.82 (t, J = 6.0 Hz, 2H), 4.40 (s, 3H), 4.66 (s, 2H), 4.86 (s, 2H), 6.09 (s, 1H), 7.78 (s, 2H). Anal. ($C_{23}H_{33}N_5O_5$) C, H, N.

5-[4-[[3-(3-Bromo-5-isoxazolyl)propyl]oxy]-3,5-dimethylphenyl]-2-methyl-2*H*-tetrazole (44). A mixture of dibromoformaldoxime[24] (5.95 g, 29.3 mmol), **21** (3.45 g, 12.8 mmol), and $NaHCO_3$ (5.35 g, 63.7 mmol) in dry EtOAc (50 mL) was stirred at rt for 72 h and filtered and the filtrate concd in vacuo leaving an oil which was purified by column chromatography (Silica Gel 60, 20% EtOAc in hexanes). A white crystalline solid (4.6 g, 92%) was obtained after recrystallization from CH_3OH: mp 80.5–81 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 3.09 (t, J = 7.6 Hz, 2H), 3.86 (t, J = 6.0 Hz, 2H), 4.38 (s, 3H), 6.17 (s, 1H), 7.80 (s, 2H). Anal. ($C_{18}H_{18}BrN_5O_2$) C, H, N.

5-[4-[[3-(3-Methoxy-5-isoxazolyl)propyl]oxy]-3,5-dimethylphenyl]-2-methyl-2*H*-tetrazole (45a). Bromide **44** (1.14 g, 2.9 mmol) was added to a saturated methanolic KOH solution (5 mL) and refluxed for 6 h. The reaction was diluted with H_2O (10-fold) and extracted with EtOAc. The combined organic extracts were washed with H_2O and 1 N HCl, dried ($MgSO_4$), and passed through a short column of Silica Gel 60. Removal of the solvent and recrystallization from CH_3OH provided 810 mg (81%) of **45a**: mp 100.5–101 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H), 2.33 (s, 6H), 2.94 (t, J = 7.6 Hz, 2H), 3.85 (t, J = 6.0 Hz, 2H), 3.97 (s, 3H), 4.37 (s, 3H), 5.68 (s, 1H), 7.79 (s, 2H). Anal. ($C_{17}H_{21}N_5O_3$) C, H, N.

3-[5-[3-[2,6-Dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-3-isoxazolyl]-1,2-propanediol (46). This compound was prepared in two steps according to Scheme II from **15** and 2,2-dimethyl-1,3-dioxolanecarboxaldehyde oxime and acid hydrolysis of the ketal with 1 N HCl in THF in overall yield of 43%; ^{1}H NMR ($CDCl_3$) δ 2.21 (m, 2H), 2.33 (s, 6H), 2.53 (br s, 2H), 2.84 (d, J = 6.2 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 3.58 (dd, J = 11.1, 6.4 Hz, 1H), 3.74 (dd, J = 11.1, 3.5 Hz, 1H), 3.87 (t, J = 6.1 Hz, 2H), 4.10 (m, 1H), 4.38 (s, 3H), 6.01 (s, 1H), 7.80 (s, 2H). Anal. ($C_{19}H_{25}N_5O_4$) C, H, N.

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