An Evaluation of the Antirhinoviral Activity of Acylfuran Replacements for 3-Methylisoxazoles. Are 2-Acetylfurans Bioisosteres for 3-Methylisoxazoles?

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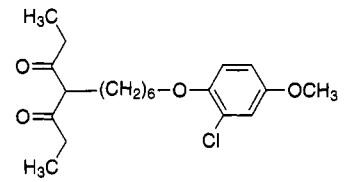
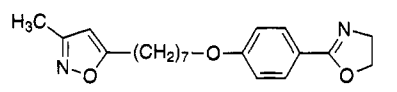
As a probe of the 3-methylisoxazole portion of our broad-spectrum antipicornaviral series, a panel of 2-acetylfuran analogues was prepared as replacements for the 3-methylisoxazole ring. Comparison of the two series showed remarkable similarity in potency, spectrum of activity, log *P*, and electrostatic parameters. X-ray studies of **21b** bound to human rhinovirus-14 showed that the 2-acetyl group adopted a *syn* conformation and the carbonyl oxygen acts as a hydrogen bond acceptor with ASN[219] in much the same way as the nitrogen of the isoxazole. The importance of the *syn* conformation and the hydrogen-bonding capability was confirmed by the reduced antiviral activity of the 2-methylfuran and 2-formylfuran analogues. From the results of this study, it is apparent that the *syn*-2-acetylfuran ring is acting as a bioisostere for the 3-methylisoxazole.

We have previously demonstrated the viability of uncoating/adsorption inhibition as a therapeutic approach to picornaviral infections. Beginning with Arildone (**1**, Figure 1) and followed by Disoxaril (**2**), WIN 54954 (**3**), and their respective analogues, we have reported increasingly broad spectrum activity against rhinoviruses[2] and enteroviruses.[3] In vivo efficacy against polio,[4] echo,[5] and coxsackie[6] viruses has also been demonstrated in mice. Furthermore, in a clinical trial, WIN 54954 was efficacious prophylactically against a human coxsackie virus-A21 infection.[7]

During the course of SAR development around disoxaril analogues, we had described the effects of substitution on the phenyl ring,[8] connecting chain length,[9] and heterocyclic replacements of the oxazoline ring.[10] In CoMFA studies, a correlation was established between steric interactions and occupied pocket volume in the virus.[11,12] Most recently, we have described efforts to optimize activity and stability by replacing the oxazoline ring with a 2-methyltetrazole moiety[13] and a 5-methyl-1,2,4-oxadiazole.[14] In this paper, we report the results of studies where the 3-methylisoxazole has been replaced by 2-acetyl-, 2-formyl-, and 5-methylfuran (Figure 2) and the compounds evaluated against 15 human rhinovirus serotypes. The activities of these analogues have been compared to their 3-methylisoxazole counterparts, and the results examined using physicochemical and electrostatic parameters. In addition, we have also explored the question of whether 2-acetylfuran is a bioisosteric replacement for the 3-methylisoxazole group.



1



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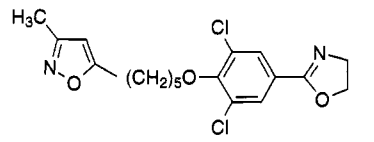
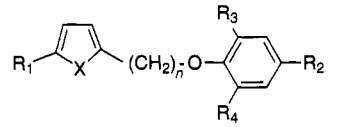


3

Figure 1. Structures of Arildone, Disoxaril, and WIN 54954.



R_1 = CH_3, CHO, and $COCH_3$
R_2 = 2-oxazoline, 2-methyltetrazole, and 5-methyl-1,2,4-oxadiazole
R_3 = H, Cl, CH_3
R_4 = H, Cl, Br, CH_3
X = O; *n* = 3 or 5

Figure 2. General structure of the furan analogues.

Chemistry

Initially, the synthesis of the 5-carbon acetylfuran side chain was performed in a linear manner as outlined in Scheme 1. Starting from the known furan alcohol **9**,[15] the requisite 2-acetyl-5-(5-chloropentyl)furan **11** was produced in 34% overall yield over four steps. An alternative approach was subsequently developed where 2-acetyl-5-(5-bromopentyl)furan **13** was obtained in 46% overall yield in just two steps (Scheme 2). As shown in Scheme 3, oxazoline phenols **14a–c**[2,8,9] could be coupled to **11** or **13** using a modified Williamson ether synthesis to provide products **15a-c**. Eventually, a convergent approach was developed for the 3-carbon chain and remaining 5-carbon chain analogues as described in Scheme 4. Beginning with readily synthesized 2-(2-furyl)-2-methyl-1,3-dioxolane,[16] **16**, metalation at −78 °C with *tert*-butyllithium followed after 10 min by alkylation with the appropriate bromochloroalkane and HMPA provided **17** in 55–62% yield. When phenols

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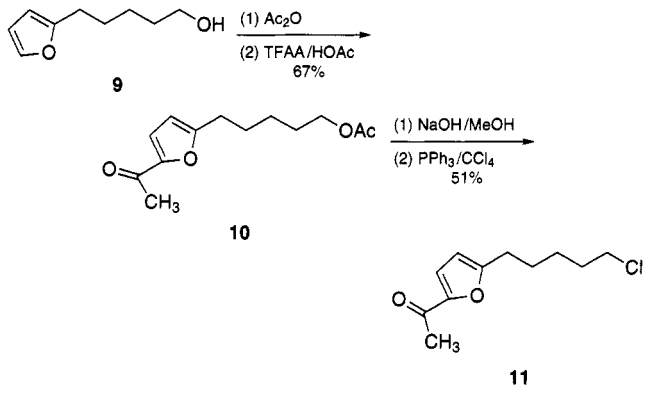
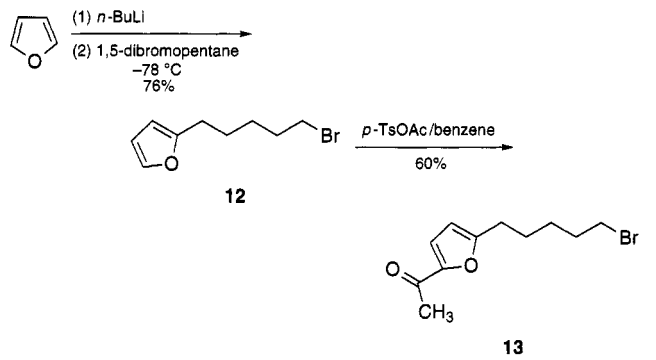
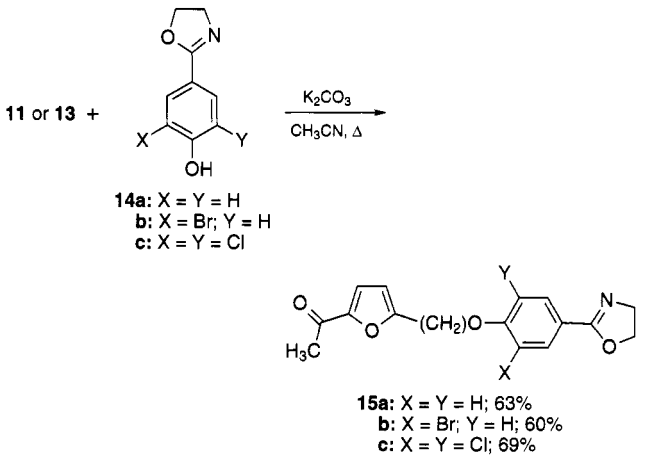
Scheme 1



Scheme 2



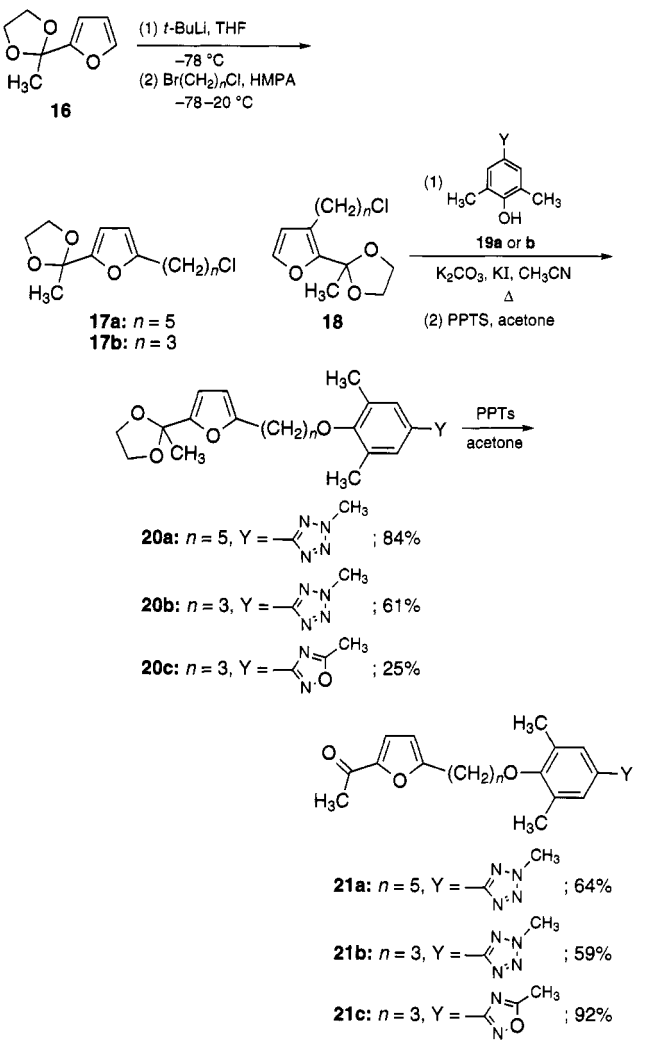
Scheme 3



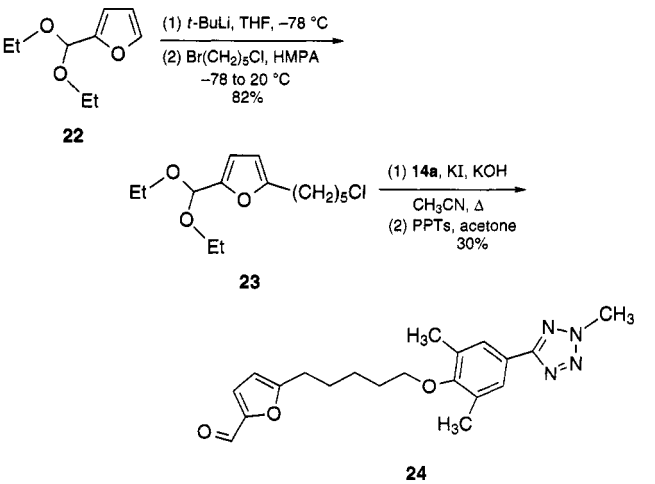
19a,**b**[13,14] were alkylated with chloroalkane **17**, the dioxolane-protected products, **20a**–**c**, were produced in good yield. Deprotection using pyridinium *p*-toluenesulfonate[17] (PPTS) in acetone provided the ketones **21a**–**c** in 59–92% yield.

In the case where $n = 5$ (Scheme 4), up to 25% of isomeric chloropentylfuran **18** was observed. It is likely that this side product is the result of chelation control by the dioxolane oxygens directing the butyllithium to the 3-position of the furan. We were subsequently able to suppress this product by shortening the metalation time from 30 to 10 min. We speculate that **18** is the thermodynamic product and that the 5-lithioanion of **16** is equilibrating to 3-lithioanion over time. Where $n = 5$, the mixture of **17** and **18** was subjected to the normal ether formation followed by deprotection using PPTS in acetone at room temperature, affording acetylfuran **21a** as the major product. Separation of the products was achieved by MPLC.

Scheme 4



Scheme 5



Employing a synthetic strategy similar to that described above, the 2-furfural analogue **24** was generated from commercially available 2-(diethoxymethyl)furan **22** through alkylation with 1-bromo-5-chloropentane, ether formation with **19a**, and deprotection with PPTs in modest yield (Scheme 5).

The 5-methylfuran analogues **26** and **27** were conveniently prepared using a Mitsunobu coupling[18] of the alcohols with phenols **19a** and **19b** in 50–68% yield as shown in Scheme 6.

Scheme 6

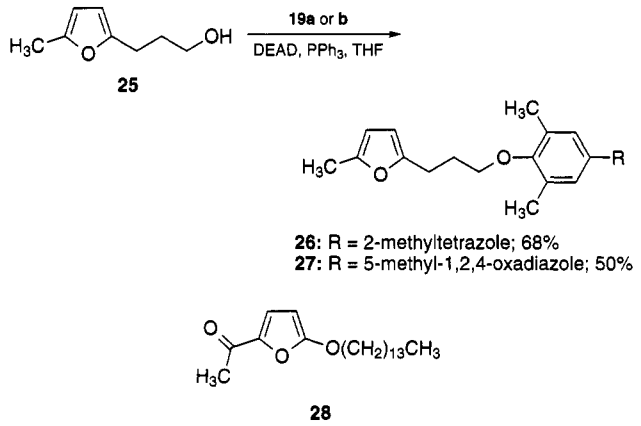


Figure 3. Structure of acetylfuran **28** (RMI 15,731).

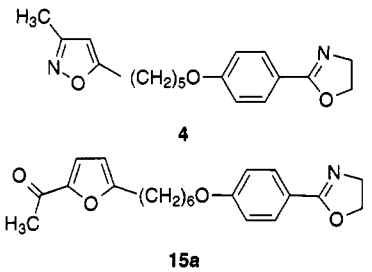


Figure 4. Structures of 3-methylisoxazole **4** and 2-acetylfuran **15a**.

Table 1. Fifteen Human Rhinovirus Serotype Comparison between Compounds 15a and 4

	MIC (μM)	
serotype	**15a**	**4**
1A	0.2	7.0
1B	0.3	inactive
2	0.5	1.1
6	0.3	0.06
14	1.0	0.7
15	0.7	1.5
21	0.4	1.2
22	1.6	0.9
25	4.5	inactive
30	0.1	0.3
41	2.2	inactive
50	0.2	1.5
67	1.0	2.4
86	0.4	0.1
89	0.05	0.4

Results and Discussion

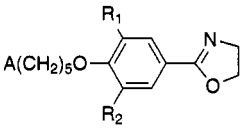
A number of factors influenced our decision to replace the 3-methylisoxazole with the 2-acetylfuran group. Predominant among these factors was an observation in an unrelated area that the 2-acetylfuran ring appeared to be bioisosteric with a 3-methylisoxazole moiety.[19] Additionally, acetylfuran **28** (Figure 3) has been reported to demonstrate antipicornaviral activity.[20] Compound **15a** (Figure 4) was screened against a panel of 15 viruses in a plaque reduction assay, and comparison with data from isoxazole **4**[3] demonstrated many similarities (Table 1). Due to the variable nature of the plaque reduction assay, 3-fold differentials in MIC were required between data comparisons before meaningful differences were attributed. The furan **15a** analogue actually showed a broader spectrum of activity by demonstrating potency against 3 serotypes (HRV-1B, -25, and -41) which were not sensitive in its 3-methylisoxazole counterpart. Encouraged by this result, a series of 2-acetylfuran analogues was then prepared and tested for antiviral activity. When further comparisons were made within this series, the similarities became more striking, particularly when comparing the MIC_{80} and mean over 15 serotypes (Table 2). Although significant differences could be seen between individual serotypes, the mean and MIC_{80} over 15 serotypes remained remarkably similar. Extension to the more potent 2-methyltetrazole[13] and 5-methyl-1,2,4-oxadiazole[14] series likewise showed very similar results (Tables 3 and 4), regardless of the connecting alkyl chain length. Comparisons were made against HRV-14, a virus for which we have X-ray data,[21,22] and very little difference in activity was seen between the 2-acetylfuran and 3-methylisoxazole analogues. It is interesting to note that both the simple 5-methyl-substituted furans and the 2-formylfuran **24** have greatly diminished activity as compared with either the 3-methylisoxazole or 2-acetylfuran analogues (see tables) even though modeling shows they should fit quite well in the viral pocket of HRV-14.

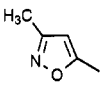
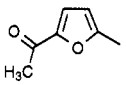
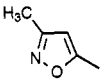
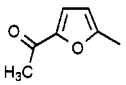
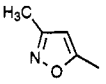
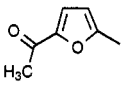
The reasons for the apparent bioisosterism between the two series were not intuitively obvious, so a number of physicochemical and electrostatic parameters were examined. Of the physicochemical properties, calculated molar refractivity (CMR) and ClogP[23] were almost identical for the 3-methylisoxazole and 2-acetylfuran rings. For confirmation, relative log *P*'s of several compounds were measured by HPLC, and the results are given in Table 5. Measured log *P*'s were indeed identical for each series. Examination of electrostatic parameters using AM1[24] in the MOPAC suite of SYBYL[25] yielded similar electrostatic potential maps and dipoles (see supplemental materials) for the 3-methylisoxazole and the *syn*-2-acetylfuran rotomer. An X-ray crystal structure of **21b** in HRV-14 (Figure 5) shows the acetyl oxygen pointing toward the NH of the ASN 219 residue at a distance (2.75 Å) suggestive of a hydrogen bond. This is reminiscent of the orientation of the 3-alkylisoxazole with respect to the ASN 219. Also similar to the isoxazole series is the apparent stacking interaction[13] of TYR 128 and TYR 152 with the furan ring. It is clear from X-ray crystallographic data that the 2-acetylfuran and isoxazole analogues occupy almost identical space within the virus pocket as shown in Figure 5.

The importance of the *syn* conformation of the carbonyl group of the 2-acetylfuran may also explain the surprising lower antiviral activity of the 2-furfural analogue **24**. Despite a measured log *P* similar to its 2-acetylfuran counterpart (Table 5), the 2-formyl furan is inactive against 6 of the 15 serotypes measured. Literature on 2-formylfuran indicates an almost exclusive preference for the *anti* conformation with an energy difference of 6.3 kJ mol^{-1} between rotamers in the vapor phase.[26] This is particularly noteworthy since we feel the gas phase approximates the hydrophobic environment of the viral pocket. It appears that the carbonyl oxygen of the acetylfuran is taking the place of the isoxazole nitrogen, something that can only be achieved with the formyl group adopting the *syn* conformation.

The poor spectrum of activity for methylfuran analogues **26** and **27** further illustrates the importance of a hydrogen bond acceptor at that end of the molecule. Furan has been reported to have a solute hydrogen bond

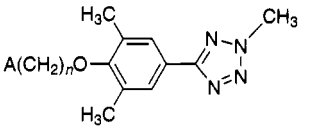
Table 2. Antipicornaviral Activity

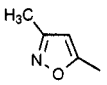
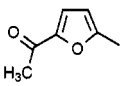
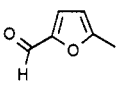
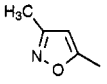
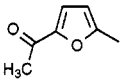
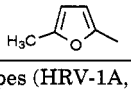


compd	A	R_1	R_2	mp, °C	formula	*in vitro* antiviral activity, μM		
						HRV-14	mean[a]	MIC_{80}
4[2]		H	H			0.7	*b*	7.0
15a		H	H	125–126	$C_{20}H_{23}NO_4$	1.1	0.9	1.0
5[2]		Br	Br			2.0	0.6	1.4
15b		Br	Br	91–92	$C_{20}H_{22}BrNO_4$	3.3	0.7	0.9
3[7]		Cl	Cl			2.3	0.7	0.9
15c		Cl	Cl	56–58	$C_{20}H_{21}Cl_2NO_4$	2.0	0.5	0.7

[a] Fifteen serotypes (HRV-1A, -1B, -2, -6, -14, -15, -21, -22, -25, -30, -41, -50, -67, -86 and -89). [b] Inactive against HRV-1B, -25, and -41.

Table 3. Antipicornaviral Activity



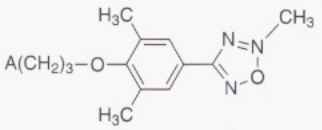
compd	A	*n*	mp, °C	formula	*in vitro* antiviral activity, μM		
					HRV-14	mean[a]	MIC_{80}
6[13]		5			0.8	0.5	0.6
21a		5	77–78	$C_{21}H_{26}N_4O_3$	1.2	0.6	0.8
24		5	63–65	$C_{20}H_{24}N_4O_3$	27	*b*	*b*[d]
7[13]		3			1.7	0.5	0.4
21b		3	77–78	$C_{19}H_{22}N_4O_3$	0.5	0.3	0.5
26		3	oil	$C_{17}H_{22}N_4O_3$	30	*c*	*c*[d]

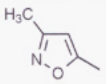
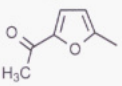
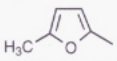
[a] Fifteen serotypes (HRV-1A, -1B, -2, -6, -14, -15, -21, -22, -25, -30, -41, -50, -67, -86, and -89). [b] Inactive against HRV-1A, -15, -22, -30, -50, -67, -86. [c] Inactive against HRV-6, -41, -67, -86. [d] Compounds were tested in a high capacity tissue culture infectious dose array as described previously.[30] Historically, results between this and the plaque reduction assay show very close agreement.

basicity identical to benzene (log $K_B^H = -0.42$)[27] whereas addition of a methyl ketone as with acetophenone strongly increases the hydrogen bond basicity (log $K_B^H = 1.27$).[27] Weak hydrogen bond acceptors like 2-methylfuran would be expected to have diminished potency.

From the data, it is apparent that the similarities in antiviral activity between the two series are more than coincidental. The similarity of the log *P*'s, CMR, electrostatic potential maps, and dipole moments suggest that the *syn*-2-acetylfuran and the 3-methylisoxazole share like physical properties. In addition, the 2-acetylfuran **21b** and 3-propylisoxazole analogue **29**[13] (despite the larger alkyl group) lie in the same area in the HRV-14 binding site, such that a hydrogen bond with ASN 219 is possible. The ability to hydrogen bond on this end of the molecule appears to be critical for broad spectrum antirhinoviral potency. This data coupled

Table 4. Antipicornaviral Activity



compd	A	mp, °C	formula	*in vitro* antiviral activity, μM		
				HRV-14	mean[a]	MIC_{80}
8[14]				0.2	0.1	0.2
21c		66–67	$C_{20}H_{22}N_2O_3$	0.5	0.2	0.4
27		47–49	$C_{19}H_{22}N_2O_3$	*b*	*b*	*b*

[a] Fifteen serotypes (HRV-1A, -1B, -2, -6, -14, -15, -21, -22, -25, -30, -41, -50, -67, -86, and -89). [b] Inactive against HRV-1A, -6, -14, -67, -86.

Table 5. Comparison of log *P* Measurements

compd no.		log P^a
3	isoxazole	4.6
15c	acetylfuran	4.6
6	isoxazole	3.6
21a	acetylfuran	3.7
24	furfural	3.5
7	isoxazole	3.2
21b	acetylfuran	3.2

[a] log *P* measurements were made by HPLC method.

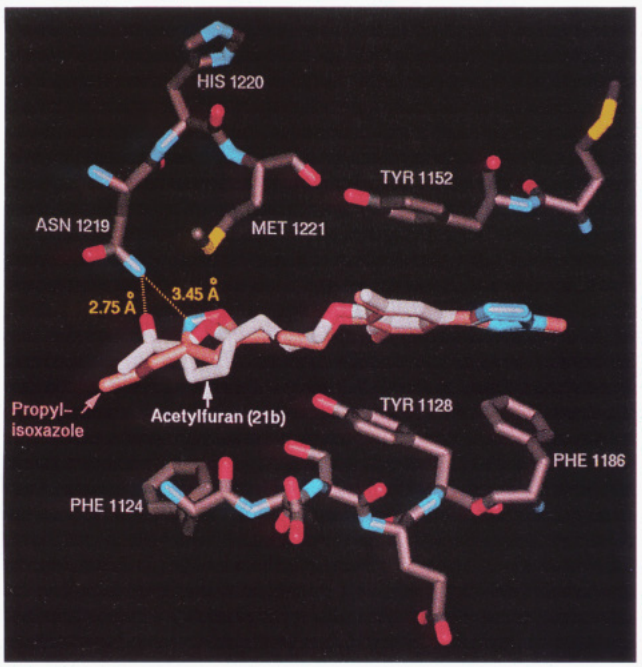


Figure 5. X-ray crystal structure comparison of **29** (mauve; WIN 61605) and 2-acetylfuran **21b** (white) bound in the viral pocket of HRV-14.

with the comparable antiviral data suggest a bioisosteric relationship between the 2-acetylfuran and 3-methylisoxazole moieties.

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 obtained in $CDCl_3$ using either a General Electric QE-300 or Bruker-AC200 FTNMR. 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. Preparative chromatography was performed using a Büchi B680 MPLC system connected to an ISCO UV detector and fraction collector. The solvents THF and HMPA were dried over molecular sieves. Anhydrous diethyl ether was purchased from Mallinckrodt and used without further purification.

1-[5-(5-Chloropentyl)-2-furanyl]ethanone (11). Alcohol **9**[15] (81.8 g, 0.53 mol) was dissolved in 100 mL of acetic anhydride containing 200 mg of 4-(dimethylamino)pyridine. The reaction exothermed to 60 °C and was allowed to stir until the temperature reached 21 °C. The solvent was evaporated *in vacuo* and the crude product distilled (74–75 °C/0.1 Torr), affording 97.0 g (93%) of the product as a clear oil. The acetate (19.6 g, 0.1 mol) was diluted with 25 mL of acetic acid and rapidly added to a solution of trifluoroacetic acid (35 g, 0.3 mol) in acetic acid (20 mL). The solution exothermed to 55 °C turning color progressively from clear, yellow, red, and finally purple. The mixture was allowed to stand for 1 h before pouring into 500 mL of water. The aqueous layer was extracted with methylene chloride (4 × 100 mL). The organic phase was concentrated and the oil subjected to Kugelrohr distillation (130–140 °C; 0.1 Torr), providing 17.1 g (72%) of the product **10** as a clear oil. Anal. ($C_{13}H_{18}O_4$) C, H. The acetylfuran **10** (6.6 g, 27.7 mmol) was combined with 200 mg of sodium methoxide in 100 mL of absolute methanol and allowed to stand at room temperature under N_2 for 20 h. The pink solution was concentrated to dryness and taken up in 100 mL of water, and the aqueous phase was extracted with methylene chloride (200 mL). The organic phase was dried over $MgSO_4$. Concentrated *in vacuo*, the orange oil was distilled on a Kugelrohr (145–150 °C; 0.025 Torr), affording 4.6 g (85%) of the alcohol as a colorless oil. The alcohol (9.8 g, 90 mmol) was combined with triphenylphosphine (13.1 g, 90 mmol) in carbon tetrachloride (100 mL) and refluxed for 4 h. Upon cooling to room temperature, the reaction mixture was concentrated to dryness. The resultant oil was triturated with diethyl ether and allowed to stand for 1 h. The triphenylphosphine was removed by filtration and the filtrate concentrated *in vacuo*. Kugelrohr distillation (120–140 °C; 0.15 Torr) provided 7.0 g (65%) of chloride **11** as a colorless oil. Anal. ($C_{11}H_{15}ClO_2$) C, H.

1-[5-[5-[4-(4,5-Dihydro-2-oxazolyl)phenoxyl]pentyl]-2-furanyl]ethanone (15a). A suspension of phenol **14a**[9] (8.15 g, 50 mmol), 5-(5-chloropentyl)-2-acetylfuran (**11**) (10.7 g, 50 mmol), K_2CO_3 (10.0 g, 72 mmol), and NaI (5.0 g, 33 mmol) in acetonitrile (100 mL) was refluxed with stirring for 24 h. Upon cooling, the reaction mixture was concentrated to dryness *in vacuo* and extracted with CH_2Cl_2. The organic phase was washed with water and dried over $MgSO_4$. Filtered and concentrated, the resultant solid was recrystallized from CH_3CN to provide 10.8 g (63%) of **15a** as a white crystalline solid:

mp 125–126 °C; ^{1}H NMR δ 7.84 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 3.4 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 6.14 (d, J = 3.4 Hz, 1H), 4.38 (t, J = 9.5 Hz, 2H), 3.95–4.04 (m, 4H), 2.71 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.65–1.85 (m, 4H), 1.45–1.56 (m, 2H). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

1-[5-[5-[2-Bromo-4-(4,5-dihydro-2-oxazolyl)phenoxy]-pentyl]-2-furanyl]ethanone (15b). Prepared as described above in 60% yield as a pale yellow solid: mp 91–92° C; ^{1}H NMR δ 8.11 (d, J = 1.7 Hz, 1H), 7.81 (dd, J = 2.0, 8.6 Hz, 1H), 7.07 (d, J = 3.9 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.15 (d, J = 3.3 Hz, 1H), 4.39 (t, J = 9.4 Hz, 2H), 3.98–4.06 (m, 4H), 2.73 (t, J = 7.4 Hz, 2H), 2.40 (s, 3H), 1.70–1.89 (m, 4H), 1.54–1.62 (m, 2H). Anal. ($C_{20}H_{22}BrNO_4$) C, H, N.

2-(5-Bromopentyl)furan (12). A solution of furan (30.3 g, 0.46 mol) in THF (500 mL) at −15 °C in a dry N_2 atmosphere was treated with 9.5 M n-butyllithium (51.5 mL, 0.49 mol) dropwise over 15 min. The resulting mixture was slowly warmed to room temperature over the course of 2 h, stirred at room temperature for an additional 90 min, and then cooled to −15 °C. In a separate flask, 1,5-dibromopentane (123 g, 0.53 mol) in THF (300 mL) containing HMPA (20 mL) was cooled to −78 °C and treated with the above anion with a wide-bore cannula using positive nitrogen pressure. The cooling bath was not replenished and the mixture stirred with slow warming to room temperature overnight (ca. 16 h). The volitiles were removed under reduced pressure at 35 °C. The reaction mixture was poured into saturated NH_4Cl (300 mL) and extracted with hexanes (3 × 150 mL). The combined hexane extracts were washed once with saturated brine, dried over anhydrous $MgSO_4$, filtered through a pad of silica while rinsing with hexane, and concentrated under reduced pressure. The resulting mobile liquid was distilled under reduced pressure (10 mmHg, bp 100–105 °C) to yield the pure product: 73.9 g (76.5%); ^{1}H NMR δ 7.05 (s, 1H), 6.05 (t, J = 2.5 Hz, 1H), 5.8 (m, 1H), 3.25 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 1.2–1.1 (m, 6H).

1-[5-(5-Bromopentyl)-2-furanyl]ethanone (13). Using the procedure of Pennanen,[28] a solution of acetyl p-toluenesulfonate[29] in anhydrous benzene at 5 °C was treated with the bromopentylfuran **12** (45.4 g, 0.21 mol) and the resulting mixture stirred at room temperature for 5 h after which time the mixture was poured into saturated $NaHCO_3$ (1 L). The organic layer was removed and the aqueous phase extracted with ethyl acetate (500 mL). The combined organic phases were washed with a saturated NaCl solution, dried over anhydrous K_2CO_3, and concentrated under reduced pressure. The resulting viscous oil was purified by flash chromatography on silica eluting with 1:2 ether/hexane to give 32.5 g (60%) of the pure desired product (along with 17 g contaminated with 10–15% TsOH): ^{1}H NMR δ 6.85 (d, J = 3.5 Hz, 1H), 5.85 (d, J = 3.5 Hz, 1H), 3.3 (t, J = 6.1 Hz, 2H), 2.6 (t, J = 7.2 Hz, 2H), 2.3 (s, 3H), 2.1–1.2 (m, 6H). This bromide was used without further purification.

1-[5-[5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]-pentyl]-2-furanyl]ethanone (15c). A solution of **14c** (dichlorophenol·HBr) (18.0 g, 67 mmol), bromide **13** (29 g, 110 mmol), and K_2CO_3 (50 g) in acetonitrile (700 mL) was heated to reflux for 90 min, cooled to room temperature, and stirred overnight. The volitiles were removed under reduced pressure, and the resulting material was slurried with ether (500 mL) and sonicated. The ether solution was washed with saturated NaCl, dried over anhydrous K_2CO_3, filtered through a pad of silica gel, and concentrated under reduced pressure to yield 41.9 g. Final purification was performed by MPLC eluting with 1:1 ether/hexane. The combined product fractions were concentrated under reduced pressure providing a white solid (28 g). Recrystallization from 2:1 hexane/ether gave **15c** (19.2 g, 69%) as a white crystalline solid: mp 56–58 °C; ^{1}H NMR δ 7.84 (s, 2H), 7.07 (d, J = 3.5 Hz, 1H), 6.15 (d, J = 3.5 Hz, 1H), 4.40 (t, J = 9.5 Hz, 2H), 4.1–3.95 (m, 4H), 2.72 (t, J = 7.4 Hz, 2H), 2.40 (s, 3H), 1.90–1.55 (m, 6H). Anal. ($C_{20}H_{21}Cl_2NO_4$) C, H, N.

General Procedure for Preparing Acetylfurans 21a–c. 2-[2-[5-(3-Chloropropyl)furanyl]]-2-methyl-1,3-dioxolane (17b). To a freshly distilled solution of 5.0 g (32 mmol) of 2-(2-furanyl)-2-methyl-1,3-dioxolane[18] in 100 mL of THF at −72 °C under N_2 was added a 30 mL (48 mmol) solution of 1.7 M t-BuLi in pentane and the mixture stirred for 10 min. A solution of 1-bromo-3-chloropropane (3.2 mL, 34 mmol) and HMPA (12 mL, 71 mmol) was added rapidly, and the reaction mixture was allowed to slowly warm to room temperature while stirring over 16 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate. The organic phase was washed with H_2O (4 × 100 mL) to remove HMPA before drying over magnesium sulfate. After filtration and removal of the solvent, the residual oil was distilled under high vacuum (0.05 Torr) to yield 2.9 g of **17b** (87–91 °C) and 1.3 g of starting 2-(2-furanyl)-2-methyl-1,3-dioxolane (32–35 °C) for a 60% yield based on unreacted starting material: ^{1}H NMR δ 6.2 (d, J = 3.1 Hz, 1H), 5.95 (d, J = 4.3 Hz, 1H), 4.00 (m, 4H), 3.59 (t, J = 6.1 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 2.70 (s, 3H), 2.10 (m, 2H).

5-Methyl-3-[3,5-dimethyl-4-[3-[2-[5-(2-methyl-1,3-dioxolane-2-yl)]furanyl]propyl]phenoxy]-1,2,4-oxadiazole (20c). To a solution of 2-[2-[5-(3-chloropropyl)furanyl]]-2-methyl-1,3-dioxolane (**17b**) (2.9 g, 13 mmol) and 2,6-dimethyl-4-(4-methyl-2-oxadiazolyl)phenol (2.7 g, 13 mmol) in acetonitrile (40 mL) was added KOH (1.0 g, 14 mmol) and KI (2.3 g, 14 mmol), and the reaction mixture was refluxed for 48 h. After cooling to room temperature, the solids were filtered, and the mother liquor was evaporated to dryness. Medium-pressure liquid chromatography on silica gel with Et_3N:EtOAc:hexanes (0.1:1:4) to give 1.3 g (25%) of **20c** as an oil: ^{1}H NMR δ 7.7 (s, 1H), 6.2 (d, J = 3.1 Hz, 1H), 5.9 (d, J = 3.7 Hz, 1H), 4.0 (m, 4H), 3.8 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 9.2 Hz, 2H), 2.6 (s, 3H), 2.3 (s, 6H), 2.05 (m, 3H), 1.7 (s, 3H); IR (film, NaBr, cm^{-1}) 1604, 1588, 1557. Anal. ($C_{22}H_{26}N_2O_5$) C, H, N.

1-[5-[3-[2,6-Dimethyl-4-(5-methyl-1,2,4-oxadiazoyl)phenoxyl]-propyl]-2-furanyl]ethanone (21c). 20c (1.3 g, 3.3 mmol) was placed in acetone (25 mL), and a catalytic amount of pyridinium p-toluenesulfonate (50 mg) was added. The mixture was stirred for 20 h at room temperature, poured into EtOAc (100 mL), washed with H_2O (2 × 100 mL), and dried over anhydrous K_2CO_3. The organic phase was filtered and concentrated *in vacuo*, and the resultant oil was crystallized in cold hexane/isopropyl acetate to give a white crystalline product, **21c** (1.1 g, 92%): mp 66–67 °C; ^{1}H NMR δ 7.72 (s, 2H), 7.13 (d, J = 3.3 Hz, 1H), 6.24 (d, J = 3.4 Hz, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.00 (t, J = 7.7 Hz, 2H), 2.65 (s, 3H), 2.45 (s, 3H), 2.31 (s, 6H), 2.22 (m, 2H); IR (KBr, cm^{-1}) 1655, 1604, 1583. Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

2-[2-[5-(3-Chloropentyl)furanyl]]-2-methyl-1,3-dioxolane (17a). Prepared in the same manner as **17b** above: yellow oil, 55%; ^{1}H NMR δ 6.20 (d, J = 3.1 Hz 1H), 5.95 (d, J = 4.3 Hz, 1H), 4.00 (m, 4H), 3.59 (t, J = 6.1 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 2.70 (s, 3H), 1.70–2.00 (m, 4H), 1.50–1.70 (m, 2H).

5-[3,5-Dimethyl-4-[5-[2-[5-(2-methyl-1,3-dioxolan-2-yl)]-furanyl]pentyl]phenoxy]-2-methyl-2*H*-tetrazole (20a). Prepared as described above for **20c**: yellow oil, 84%; ^{1}H NMR δ 7.77 (s, 2H), 6.20 (d, J = 3.1 Hz, 1H), 5.91 (d, J = 3.7 Hz, 1H), 4.48 (s, 3H), 4.02 (br s, 4H), 3.81 (t, J = 6.1 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.34 (s, 6H), 1.72 (s, 3H), 1.50–1.95 (m, 6H).

1-[5-[5-[2,6-Dimethyl-4-(2-methyl-2*H*-tetrazolyl)phenoxy]-pentyl]-2-furanyl]ethanone (21a). Prepared as described as above for **16c**: white solid, 64% yield: mp 77–78 °C; ^{1}H NMR δ 7.79 (s, 2H), 7.10 (d, J = 3.4 Hz, 1H), 6.19 (d, J = 3.4 Hz, 1H), 4.38 (s, 3H), 3.80 (t, J = 6.1 Hz, 2H), 2.77 (t, J = 7.7 Hz, 2H), 2.45 (s, 3H), 2.34 (s, 6H), 1.71–1.95 (m, 4H), 1.50–1.70 (s, 2H); ^{13}C NMR δ 185.9, 165.1, 161.6, 157.8, 151.4, 131.5, 127.3, 122.5, 119.0, 108.1, 72.0, 39.3, 30.0, 28.2, 27.6, 25.7, 25.5, 16.2; IR (KBr, cm^{-1}) 1663, 1514, 1212. Anal. ($C_{21}H_{26}N_4O_3$) C, H, N.

5-[3,5-Dimethyl-4-[3-[2-[5-(2-methyl-1,3-dioxolan-2-yl)]-furanyl]propyl]phenoxy]-2-methyl-2*H*-tetrazole (20b). Prepared as described above for **20c**: colorless oil, 61% yield; ^{1}H NMR δ 7.80 (s, 2H), 6.23 (d, J = 3.1 Hz, 1H), 5.99 (d, J = 3.7 Hz, 1H), 4.38 (s, 3H), 4.00–4.10 (m, 4H), 3.83 (t, J = 6.1 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 2.34 (s, 6H), 2.08–2.26 (m, 2H), 1.72 (s, 3H); ^{13}C NMR δ 157.8, 155.3, 152.8, 131.7, 127.4, 122.6, 107.1, 105.5, 71.2, 65.0, 39.4, 28.6, 24.7, 24.3, 16.3. Anal. ($C_{21}H_{26}N_4O_4$) C, H, N.

1-[5-[3-[2,6-Dimethyl-4-[(2-methyl-2*H*-tetrazolyl)]phenoxy]propyl]-2-furanyl]ethanone (21b). Prepared in the same manner as **21c**: pale yellow solid, 59% yield: mp 77–78 °C; ^{1}H NMR δ 7.81 (s, 2H), 7.15 (d, J = 3.4 Hz, 1H), 6.27 (d, J = 3.4 Hz, 1H), 4.38 (s, 3H), 3.86 (t, J = 6.1 Hz, 2H), 3.02 (t, J = 3.4 Hz, 2H), 2.45 (s, 3H), 2.32 (s, 6H), 2.14–2.30 (m, 2H); ^{13}C NMR 186.0, 165.0, 160.8, 157.5, 151.6, 131.5, 127.3, 127.1, 122.7, 119.0, 108.4, 70.7, 39.3, 28.4, 25.7, 25.1, 16.3, 15.9; IR (KBr, cm^{-1}) 1664.3, 1515.8, 1213.0. Anal. ($C_{19}H_{22}N_4O_3$) C, H, N.

2-(5-Chloropentyl)-5-(diethoxymethyl)furan (23). To a solution of 12.0 g (71 mmol) of 2-(diethoxymethyl)furan (Aldrich) in 100 mL of dry THF under N_2 at −70 °C was added 60 mL (105 mmol) of 1.7 M t-BuLi in pentane at such a rate as to keep the temperature below −50 °C. After 15 min at −70 °C, the very dark anion was quenched with a solution of 1-bromo-5-chloropentane (14.3 g, 77 mmol) and HMPA (27 mL, 154 mmol) in THF (90 mL). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 12 h of stirring at room temperature, the solvent was removed *in vacuo* and the residue taken up in ethyl acetate (250 mL). The organic phase was washed with water (5 × 200 mL) and dried over $MgSO_4$. The organic phase was filtered and concentrated *in vacuo*, and the crude red oil was flash chromatographed on kieselgel 60 eluting with 20% EtOAc in hexanes. Concentration provided 15.8 g (82%) of **23** as a red oil: ^{1}H NMR δ 6.30 (d, J = 3.5 Hz, 1H), 6.00 (d, J = 3.5 Hz, 1H), 5.48 (s, 1H), 3.58 (t, J = 6.2 Hz, 2H), 3.51–3.70 (m, 4H), 2.69 (t, J = 7.4 Hz, 2H), 1.56–1.97 (m, 6H), 1.25 (t, J = 6.5 Hz, 6H).

5-[5-[2,6-Dimethyl-4-[(2-methyl-2*H*-tetrazolyl)]phenoxy]pentyl]-2-furancarbaldehyde (24). A suspension of **23** (9.0 g, 33.0 mmol), **19a** (4.4 g, 21.6 mmol), KOH (2.4 g, 41.9 mmol), and KI (7.0 g, 42.2 mmol) in acetonitrile (100 mL) was refluxed under N_2 for 14 h. Upon cooling, the suspension was filted to remove the salts, and the filtrate was concentrated *in vacuo*. The dark red oil containing the product was subjected to MPLC (kieselgel 60, 30% EtOAc in hexanes) affording 7.3 g (60%) of the dioxolane product as a yellow oil: ^{1}H NMR δ 7.78 (s, 1H), 6.31 (d, J = 3.5 Hz, 1H), 5.98 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H), 4.39 (s, 3H), 3.84 (t, J = 6.4 Hz, 2H), 3.52–3.71 (m, 4H), 2.68 (t, J = 7.4 Hz, 2H), 2.33 (s, 6H), 1.55–1.96 (m, 6H), 1.25 (t, J = 6.5 Hz, 6H); ^{13}C NMR δ 165.0, 157.9, 156.1, 149.9, 131.6, 127.3, 122.4, 108.5, 105.2, 96.4, 72.2, 61.2, 39.3, 30.1, 27.9, 25.6, 16.3, 15.1. Anal. ($C_{24}H_{34}N_4O_4$). To a solution of the above dioxolane product (5.0 g, 11.3 mmol) in acetone (70 mL) was added PPTS (4.3 g, 17.1 mmol). After stirring at room temperature for 1.5 h, the reaction mixture was poured into EtOAc (100 mL) and washed with water (2 × 100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 3.0 g of crude product **24** as a yellow oil. Crystallization from i-PrOAc/hexanes provided 2.1 g (50%) of **24** as a yellow powder: mp 63–65° C; ^{1}H NMR δ 9.52 (s, 1H), 7.78 (s, 2H), 7.18 (d, J = 3.5 Hz, 1H), 6.26 (d, J = 3.5 Hz, 1H), 4.37 (s, 3H), 3.80 (t, J = 6.4 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.32 (s, 6H), 1.78–1.96 (m, 4H), 1.57–1.67 (m, 2H); ^{13}C NMR δ 176.9, 165.1, 163.6, 157.8, 151.8, 131.6, 127.3, 123.4, 122.5, 108.7, 72.0, 39.4, 30.0, 28.3, 27.5, 25.7, 16.3; IR (KBr, cm^{-1}) 1662. Anal. ($C_{20}H_{24}N_4O_3$) C, H, N.

5-[3,5-Dimethyl-4-[[3-(5-methyl-2-furanyl)propyl]oxy]phenyl]-2-methyl-2*H*-tetrazole (26). To a solution of 3-(5-methyl-2-furanyl)propan-1-ol[15] (**25**) (1.11 g, 7.92 mmol), 2,6-dimethyl-4-[5-(2-methyl-2*H*-tetrazolyl)]phenol[13] (**19a**) (1.63 g, 7.92 mmol), and triphenylphosphine (2.09 g, 7.97 mmol) in THF (50 mL) at −10 °C under N_2 was added dropwise a solution of 1.40 mL (8.82 mmol) of diethyl diazodicarboxylate in 20 mL of THF. Upon completion of the addition, the mixture was allowed to stir at room temperature for 20 min. The reaction mixture was then concentrated *in vacuo* and the resultant oil subjected to MPLC (silica gel 60, 30% EtOH in hexanes) affording 1.75 g (68%) of **26** as a white solid: mp 47–49 °C; ^{1}H NMR δ 7.76 (s, 2H), 5.89 (d, J = 2.9 Hz, 1H), 5.83 (m, 1H), 4.35 (s, 3H), 3.82 (t, J = 6.3 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 2.31 (s, 6H), 2.24 (s, 3H), 1.54–2.17 (m, 2H). Anal. ($C_{18}H_{22}N_4O_2$) C, H, N.

3-[3,5-Dimethyl-4-[[3-(5-methyl-2-furanyl)propyl]oxy]phenyl]-5-methyl-1,2,4-oxadiazole (27). Prepared as described above for **26** in 50% yield as a colorless oil: ^{1}H NMR δ 7.71 (s, 2H), 5.91 (d, J = 2.9 Hz, 1H), 5.85 (d, J = 2.9 Hz, 1H), 3.84 (t, J = 6.3 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 2.62 (s, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 2.14 (m, 2H); IR (cm^{-1}) 2923, 1584, 1420, 1352, 1208. Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

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Supplementary Material Available: Figures showing comparison of electrostatic potential maps and dipoles for 3-methylisoxazole and *syn*-2-acetylfuran (1 page). Ordering information is given on any current masthead page.

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