Antirhinoviral Activity of Heterocyclic Analogs of Win 54954

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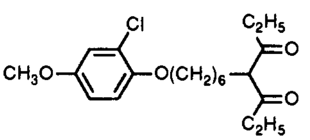
A variety of heterocyclic analogs of Win 54954 have been synthesized and tested in vitro against human rhinovirus type 14 (HRV-14) in a plaque reduction assay. The more active compounds were tested against 14 additional serotypes, and the concentration which inhibited 80% of the serotypes tested (MIC_{80}) was measured. One compound, **37**, exhibited activity comparable to Win 59454. Physicochemical as well as electrostatic parameters were calculated and the results subjected to a QSAR analysis in an effort to explain differences in activity observed between these compounds; however, no meaningful correlation with biological activity was found with any of these parameters.

During the past several years, we have been investigating the inhibition of uncoating as a viable approach to the chemotherapy of picornavirus infections. Arildone (**1**) was first shown to prevent replication of polio virus type 2,[1] and disoxaril (**2**) was subsequently found to inhibit the



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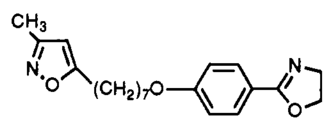

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replication of rhinovirus type 2 (HRV-2) by this mechanism.[2] The significance of this approach in the chemotherapy of enteroviral infections has been demonstrated with the prevention of paralysis and death when several of these compounds were administered to mice infected with either polio or ECHO virus, as late as 72 h postinfection.[3-10]

The determination of the three-dimensional structure of human rhinovirus-14 (HRV-14)[11] subsequently resulted in the elucidation of the binding site of disoxaril and related compounds which is located in a hydrophobic pocket on the surface of the capsid protein.[12] This discovery has allowed for the study of the molecular interaction of these compounds in the binding site which has assisted in some degree in explaining the emerging structure-activity relationships for this series of compounds.[13-15] Two factors which appeared to be critical in the inhibition of viral replication were the affinity of the compounds for the virus[16] and the resultant conformational changes induced by the drugs within the binding site. Studies with HRV-1A have shown similar conformational changes although not to the same extent.[17]

One of the most surprising results from the mechanism of action studies was the discovery that although HRV-14 and HRV-1A have similar drug binding sites, they are affected differently by this series of compounds with respect to the inhibition of viral replication. All of the compounds studied thus far block uncoating of HRV-1A but prevent adsorption of HRV-14.[18] Since HRV-14 is a member of the major serotype group while HRV-1A is

(1) Diana, G. D.; McKinlay, M. A.; Otto, M. J.; Akullian, V.; Oglesby, R. C. [[(4,5-Dihydro-2-oxazolyl)phenoxy]alkyl]isoxazoles. Inhibitors of Picornavirus Uncoating. *J. Med. Chem.* 1985, *28*, 1906-1915.

(2) Otto, M. J.; Fox, M. P.; Fancher, M. J.; Kuhrt, M. F.; Diana, G. D.; McKinlay, M. A. In Vitro Activity of Win 51711, a New Broad-Spectrum Antipicornavirus Drug. *Antimicrob. Agents Chemother.* 1985, *27*, 883-886.

(3) Diana, G. D.; Oglesby, R. C.; Akullian, V.; Carabateas, P. M.; Cutcliffe, D.; Mallamo, J. P.; Otto, M. J.; McKinlay, M. A.; Maliski, E. G.; Michalec, S. J. Activity Studies of 5-[[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]alkyl]-3-methylisoxazole: Inhibition of Picornavirus Uncoating. *J. Med. Chem.* 1987, *30*, 383-388.

(4) Diana, G. D.; Cutcliffe, D.; Oglesby, R. C.; Otto, M. J.; Mallamo, J. P.; Akullian, V.; McKinlay, M. A. Synthesis and Structure-Activity Studies of Some Disubstituted Phenylisoxazoles against Human Picornavirus. *J. Med. Chem.* 1989, *32*, 450-455.

(5) Wilfert, C. M.; Zeller, J. R.; Schauber, L. E.; McKinney, R. L. Activity of Win 51711 Against Echovirus. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1984; Abstract No. 430.

(6) Fox, M. P.; Otto, M. J.; Shave, W. J.; McKinlay, M. A. Prevention of Rhinovirus and Poliovirus Uncoating by Win 51711, a New Antiviral Drug. *Antimicrob. Agents Chemother.* 1986, *30*, 110.

(7) McSherry, J. J.; Caliguiri, L. A.; Eggers, H. J. Inhibition of Uncoating of Polio by Arildone, a New Antiviral Drug. *Virology* 1979, *97*, 307-315.

(8) Steinberg, B. A.; Viskosky, A. A.; McKinlay, M. A. Win 51711-2 Prevents ECHO-9 Induced Paralysis in Suckling Mice. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1984; Abstract No. 432.

(9) McKinlay, M. A.; Steinberg, B. A. Oral Efficacy of Win 51711 in Mice Infected with Human Poliovirus. *Antimicrob. Agents Chemother.* 1986, *29*, 30-32.

(10) Woods, M. G.; Diana, G. D.; Roggi, M. C.; Otto, M. J.; Dutko, F. J.; McKinlay, M. A. In Vitro and In Vivo Activity of Win 54954, a New Broad Spectrum Antipicornavirus Drug. *Antimicrob. Agents Chemother.* 1989, *33*, 2069-2074.

(11) Rossmann, M. G.; Arnold, E.; Erickson, J. W.; Frankenberger, E. A.; Griffith, J. P.; Hecht, H. J.; Johnson, J. E.; Kramer, J. E.; Lou, M.; Mosser, A. G.; Rueckert, R. R.; Sherry, B.; Vriend, G. Structure of a Common Cold Virus and Functional Relationship to other Picornaviruses. *Nature* 1985, *317*, 145.

(12) Smith, T. J.; Kremer, M. J.; Luo, M.; Vriend, G.; Arnold, E.; Kramer, G.; Rossmann, M. G.; McKinlay, M. A.; Diana, G. D.; Otto, M. J. The Site of Attachment in Human Rhinovirus-14 for Antiviral Agents that Inhibit Uncoating. *Science* 1986, *233*, 1286.

(13) Diana, G. D.; Otto, M. J.; Treasurywala, A. M.; McKinlay, M. A.; Oglesby, R. C.; Maliski, E. G.; Rossmann, M. G.; Smith, T. J. Enantiomeric Effects of Analogues of Disoxaril on the Inhibitory Activity Against Human Rhinovirus-14. *J. Med. Chem.* 1988, *31*, 540-544.

(14) Diana, G. D.; Treasurywala, A. M.; Bailey, T. R.; Oglesby, R. C.; Pevear, D. C.; Dutko, F. J. A Model for Compounds Active Against Human Rhinovirus-14 Based on X-ray Crystallography Data. *J. Med. Chem.* 1989, *33*, 1306-1311.

(15) Diana, G. D.; Mallamo, J. P.; Pevear, D. C.; Dutko, F. J. A Comparison of the Compound Binding Sites on Human Rhinovirus-14 and -1A. Fifth International Conference on Antiviral Research, Vancouver, B.C. Canada, March 8-13, 1992; Paper No. 86.

(16) Fox, M. P.; McKinlay, M. A.; Diana, G. D.; Dutko, F. J. Affinities of Structurally Related Human Rhinovirus Capsid Binding Compounds are Related to Their Activities Against Human Rhinovirus Type 14. *Antimicrob. Agents Chemother.* 1991, *35*, 1040-1047.

(17) Kim, S.; Smith, T. J.; Chapman, M. S.; Rossmann, M. G.; Pevear, D. C.; Dutko, F. J.; Felock, P. J.; Diana, G. D.; McKinley, M. A. Crystal Structure of Human Rhinovirus Serotype 1A (HRV-1A). *J. Biol. Chem.* 1989, *210*, 91-111.

(18) Pevear, D. C.; Fancher, M. J.; Felock, P. J.; Rossmann, M. G.; Miller, M. S.; Diana, G. D.; Treasurywala, A. M.; McKinlay, M. A.; Dutko, F. J. Conformational Change in the Floor of the Human Rhinovirus Canyon Blocks Adsorption to Hela Cell Receptors. *J. Virol.* 1989, *23*, 2002.

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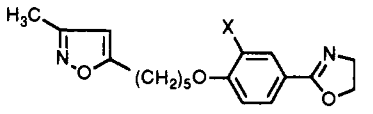
from the minor group, it appears that the mechanism of inhibition of viral replication may be group dependent. Studies are currently under way to investigate this possibility. The difference in the mode of action appears to lie in the conformational changes occurring in amino acid residues lying at the base of the putative cell receptor binding site of HRV-14 which interferes with cell affinity.[18]

Many structural modifications of disoxaril have been made. The monosubstituted phenyl analogs **3** were evaluated as antipicornaviral compounds and a quantitative structure–activity relationship (QSAR) study was performed which resulted in a strong correlation of activity



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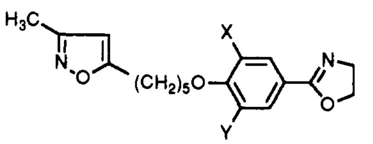
with log *P* and bulk (MW) with some contribution from σ_m.[3] A similar analysis was performed with the 2,6-disubstituted series **4** which resulted in a good correlation of activity with log *P* and a negative contribution from molecular weight reflecting a bulk effect associated with substituents on the phenyl ring.[4] Win 54954 (**4**, X = Y = Cl) emerged from this latter series as a broad-spectrum antipicornavirus agent.

In this study, we have prepared analogs of Win 54954 where the oxazoline ring has been replaced with a variety



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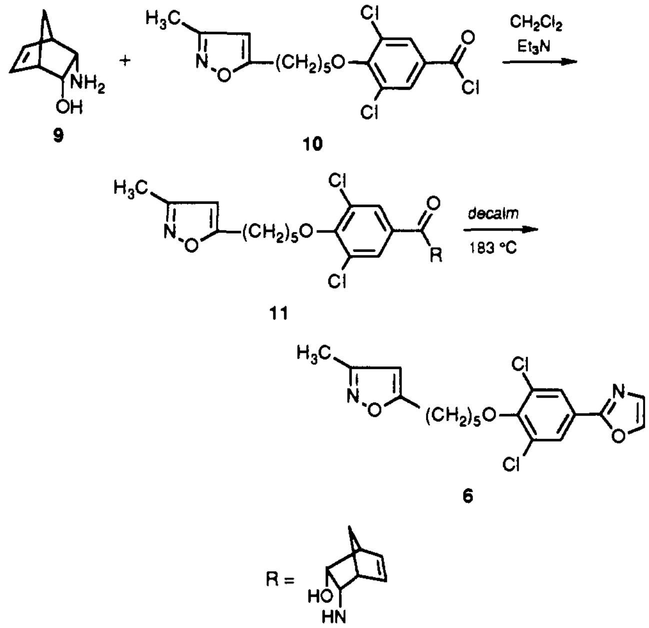
of heterocyclic rings and the compounds evaluated against HRV-14 and then against 14 additional serotypes. A number of physicochemical as well as electrostatic parameters have been calculated, and their correlation with the minimum inhibitory activity of the compounds was examined.

Chemistry

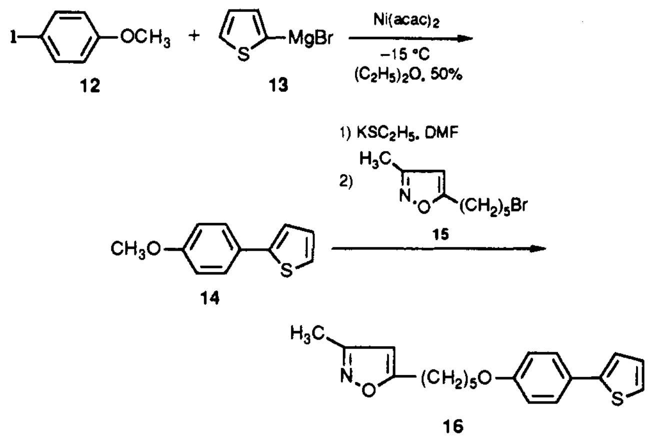
The syntheses of oxazoles **5** and **7** and thiazole **8** (Table I) have been previously reported.[19] The preparation of the 2-oxazole **6** proved difficult. However, this compound was eventually synthesized by employing a retro-Diels–Alder reaction shown in Scheme I. Acylation of amine **9**[20] with acid chloride **10** gave amide **11** in 74% yield. Heating a slurry of **11** in decalin to 183 °C provided **6** in 85% yield.[21]

To construct the remaining heteroaryl-substituted analogs, a convergent synthesis was required. Initially, we employed a Ni-catalyzed cross-coupling approach[22] as outlined in Scheme II. The heterobiaryl cross-coupling between *p*-indoanisole (**12**) and the Grignard **13** proceeded

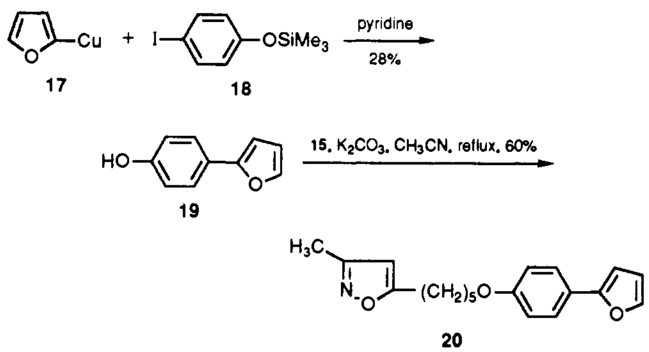
Scheme I



Scheme II



Scheme III



in a modest 50% yield. Subsequent deprotection and alkylation of anisole **14** provided **16** in only 12% yield.

An improvement in overall yield was achieved when a more classical, modified Ullmann approach was utilized (Scheme III). The known 4-(2-furyl)phenol (**19**) was synthesized from 2-furylcopper (**17**) and trimethylsilyl-protected 4-iodophenol **18** in 28% yield.[23] Alkylation of phenol **19** with the bromopentylisoxazole **15** was accom-

(19) Diana, G. D.; Treasurywala, A. M.; Oglesby, R. C.; Pevear, D. C.; Dutko, F. J. CoMFA Analysis of the Interaction of Antipicornavirus Compounds with the Binding Pocket of Human Rhinovirus-14. *J. Med. Chem.* **1992**, *35*, 1002–1008.

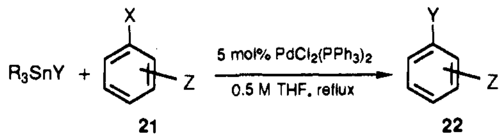
(20) Scholz, K. H.; Heine, H. G.; Hartmann, W. Diels–Alder Reaction with 3-Acetyloxazolin-2-one. *Liebigs Ann. Chem.* **1977**, 2027–2035.

(21) The scope of this approach to the synthesis of oxazoles will be discussed in a separate manuscript (M. Eissenstat et al., in preparation).

(22) Clough, R. L.; Mison, P.; Roberts, J. D. Coupling of Non Equivalent Aromatic Rings by Soluble Nickel Catalyst. *J. Org. Chem.* **1976**, *41*, 2252.

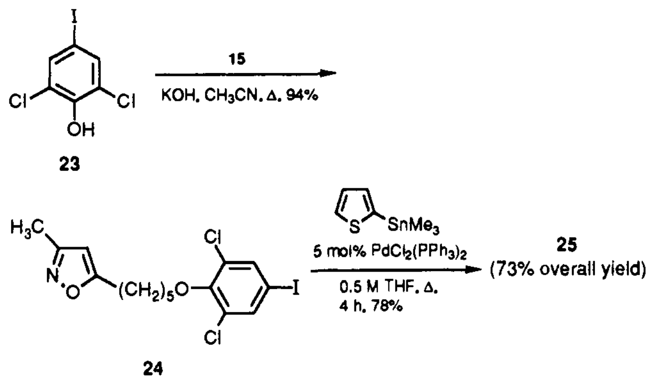
(23) King, F. D.; Walton, D. R. Protection of Amine and Hydroxy Groups in The Ullmann Reaction and Related Organocopper Couplings. *Synthesis* **1976**, 40–42.

Scheme IV

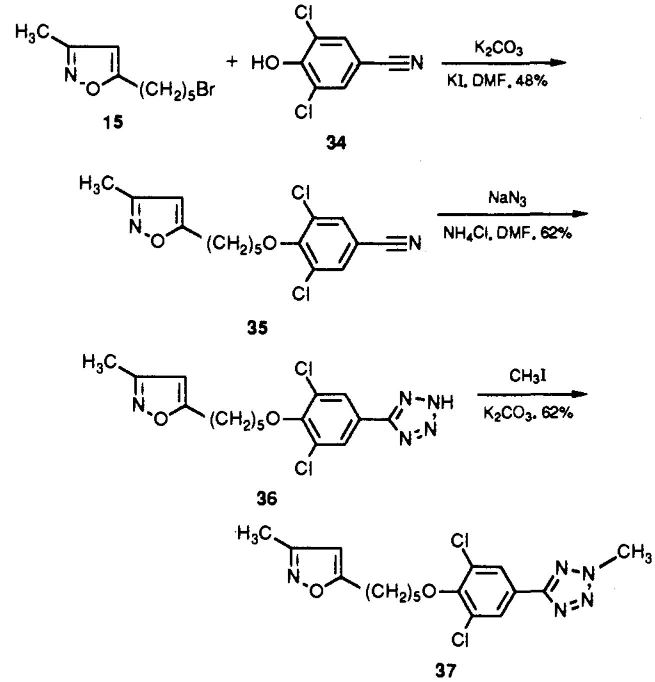


X = Br, I
Y = furyl, thienyl, pyridyl, 2-pyrryl, phenyl, imidazole
R = CH_3, *n*-butyl

Scheme V



Scheme VI



plished in 60% yield. The overall yield of **20** for this process was 17%.

In need of a general, efficient unsymmetrical heterobiaryl synthesis, a novel Pd^0-catalyzed cross-coupling methodology was developed (Scheme IV) in which a number of compounds were prepared in high yield from substituted aryl halides and 2-(trialkylstannyl) heterocycles.[24] This process has demonstrated several advantages over existing cross-coupling methodology. Similar approaches have concurrently[25] and since been reported.[26,27]

Application of this efficient cross-coupling procedure in convergent syntheses of the target antiviral agents required construction of the appropriate aryl iodides and heteroarylstannanes. The aryl iodides were prepared by alkylation of the known 4-iodophenol **23**[28] with 5-(5-bromopentyl)-3-methylisoxazole (**15**)[4] affording ether **24** in 94% yield (Scheme V). The heteroarylstannanes were efficiently generated either by direct metalation or by halogen–metal exchange followed by alkylation with trimethylstannyl chloride. Aryl iodide **24** was reacted with 1.1 equiv of the heteroarylstannane in refluxing THF (0.5 M) using 5 mol% $PdCl_2(PPh_3)_2$ as a catalyst to give **25** in an overall yield of 73% in contrast to a 24% yield using the Ullmann procedure. It should be noted that when the coupling was performed between aryl iodide **24** and heteroarylstannanes with substituents at the 3- or 4-position of the heterocyclic ring, a much longer reaction time was required and 1 equiv of HMPA was used. Exclusion of HMPA significantly retarded the reaction rate. The results of the heterobiaryl cross-coupling reactions are shown in Table I.

Finally, compound **37** was prepared by the procedure outlined in Scheme VI. Alkylation of 3,5-dichloro-4-hydroxybenzonitrile with bromide **15**[4] provided nitrile **35** in 48% yield. Treatment of **35** with sodium azide in DMF gave a 62% yield of tetrazole **36** which was alkylated with methyl iodide in DMF to provide **37** in 62% yield along with a 14% yield of the 1-positional isomer **38**. Structural assignment of these isomers was based on literature precedent where the 2-isomer has been shown to predominate in the alkylation of 5-aryltetrazoles.[29]

Results and Discussion

All of the compounds were screened in a plaque reduction assay previously described, using Hela-Ohio cells.[1] The minimum inhibitory concentration, MIC, was the concentration (μM) which reduced the number of plaques by 50%. The MIC_{80} is the concentration of compound which inhibits 80% of the serotypes. On the basis of previous mechanistic studies,[1-10] it was known that these compounds would function as uncoating/adsorption inhibitors. The results are shown in Table I and are compared to Win 54954, compound **4** (X = Y = Cl). The 2-furyl analog **29** and Win 54954 exhibited comparable activity against HRV-14. Replacement of the oxazoline with a 2-oxazole ring, compound **6**, slightly lowered activity; however, replacing the 2-oxazole with a 5-oxazole ring, compound **5**, significantly reduced activity. Replacing the 2-furyl with a 2-thiophene ring, **25** resulted in a 10-fold reduction in activity, and in both instances, the corresponding 3-substituted heterocyclic analogs **30**

(24) Bailey, T. R. Unsymmetrical Heterobiaryl Synthesis. A Highly Efficient Palladium-Catalyzed Cross-Coupling Reaction of Heteroaryl Trialkylstannanes with Aryl Halides. *Tetrahedron Lett.* **1986**, *27*, 4407–4410.

(25) Kosugi, M.; Koshiba, M.; Atok, A.; Sano, H.; Migata, T. Palladium Catalyzed Coupling between Organic Halides and Organotin Compounds Involving C-N Unsaturated Bonds at the Reaction Centers. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677–679.

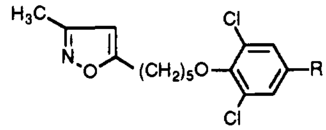
(26) Yamamoto, Y.; Ozuma, Y.; Mitoh, H. General Method for Synthesis of Bipyridines: Palladium Catalyzed Cross-Coupling Reaction of Trimethylstannylpyridines with Bromopyridines. *Synthesis* **1986**, 564–565.

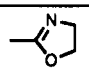
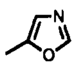
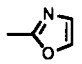
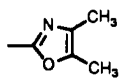
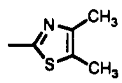
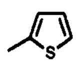
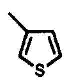
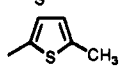
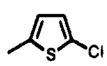
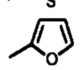
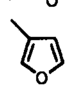
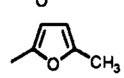
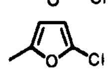
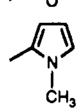
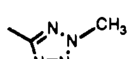
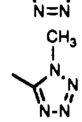
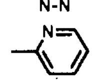
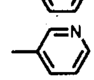
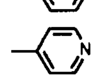
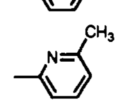
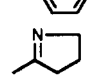
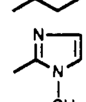
(27) (a) Dondoni, A.; Fogagnola, M.; Medici, A.; Negrini, E. Palladium Mediated Cross-Coupling Reaction Between Stannyl- and Bromothiazoles. *Synthesis* **1987**, 185–186. (b) Peters, D.; Hornfeldt, A. B.; Gronowitz, S. Synthesis of 5-Substituted Uracils. *J. Heterocycl. Chem.* **1990**, *27*, 2165.

(28) Brazier, S. A.; McCombre, H. The Chlorination of Iodophenols. Part I. The Chlorination of p-Iodophenol. *J. Chem. Soc.* **1912**, *101*, 968–977.

(29) Elpern, B.; Nachod, F. C. Adsorption Spectra and Structure of Some Tetrazoles. *J. Am. Chem. Soc.* **1950**, *72*, 3379–3382. Hebry, R. A. Methylation of 5-Phenyltetrazole. *Ibid.* **1951**, *73*, 4470. Elpern, B. The Dialkylation of Some 5-Monosubstituted Tetrazoles. *Ibid.* **1953**, *75*, 661–662.

Table I. In Vitro Antirhinoviral Activity



compd	R	% yield	mp °C	formula[b]	in vitro activity[a] MIC (μmol) HRV-14	MIC$_{80}$[f]
Win 54954		*c*	42–43	$C_{18}H_{20}Cl_2N_2O_3$	1.2	0.33
5		*d*	113–115	$C_{18}H_{18}Cl_2N_2O_3{\cdot}CH_3SO_3H$	12.76	2.24
6		85	39–41	$C_{18}H_{18}Cl_2N_2O_3$	1.83	1.71
7		*d*	61–62	$C_{20}H_{22}Cl_2N_2O_3$	2.79	1.30
8		*d*	57–58	$C_{20}H_{22}Cl_2N_2O_2S$	2.59	2.14
25		73	45–47	$C_{19}H_{18}Cl_3NO_2S$	7.32	1.11
26		84[e]	43–44	$C_{19}H_{19}Cl_2NO_3$	NA[g]	2.88
27		82	43–45	$C_{20}H_{21}Cl_2NO_2S$	5.2	1.71
28		83	53–55	$C_{19}H_{18}Cl_3NO_2S$	5.3	3.13
29		94	29–30	$C_{19}H_{19}Cl_2NO_3$	0.71	1.05
30		67[d,e]	37–39	$C_{20}H_{23}Cl_2NO_2$	NA	2.90
31		73	51–53	$C_{20}H_{21}Cl_2NO_3$	2.64	1.27
32		84	59–60	$C_{19}H_{18}Cl_3NO_2S$	2.0	1.69
33		89	46–47	$C_{20}H_{22}Cl_2N_2O_2$	NA	–
37		62	47–49	$C_{17}H_{19}Cl_2N_5O_2$	0.38	0.25
38		14	75–76	$C_{17}H_{19}Cl_2N_5O_2$	2.04	7.02
39		50	70.5–71	$C_{20}H_{20}Cl_2N_2O_2$	6.64	1.38
40		29	84–85	$C_{20}H_{20}Cl_2N_2O_2$	6.60	–
41		42	79.5–80	$C_{20}H_{20}Cl_2N_2O_2$	0.97	–
42		83	54–55	$C_{21}H_{22}Cl_2N_2O_2$	5.88	1.93
43		38	56–58	$C_{19}H_{22}Cl_2N_2O_2$	NA	–
44		61	oil	$C_{19}H_{21}Cl_2N_3O_2$	3.14	–

[a] Confidence limits $p = 75\%$. [b] Elemental analyses (C, H, N) for all new compounds were within ±0.4%. [c] See ref 4. [d] See ref 19. [e] HMPA used as an additive. [f] Concentration which inhibits 80% of the serotypes tested. The serotypes used were HRV-1A, 1B, −2, −6, −14, −15, −21, −22, −25, −30, −41, −50, −67, −86, and −89. [g] NA = not active.

Table II. A Comparison of Win 54954 and Compound 37 against 15 Human Rhinovirus Serotypes

	MIC (μmol)			MIC (μmol)	
serotype	Win 54954	compound 37	serotype	Win 54954	compound 37
2	0.023	0.025	25	0.29	0.08
1A	2.51	0.38	30	0.09	0.23
1B	0.17	0.05	50	0.06	0.06
6	0.23	0.23	67	0.18	0.18
14	1.20	0.38	89	0.02	0.01
21	0.02	0.02	86	0.21	0.24
22	0.02	0.008	41	0.89	0.63
15	0.41	0.25			

and **26**, respectively, were completely inactive. The 2-methyltetrazole **37** displayed the highest level of activity against this serotype. It is interesting to note that the 1-positional isomer **38** was considerably less active against HRV-14 and displayed a higher MIC_{80} than **37**.

When screened against 14 additional serotypes, there was some change in the relative potency of some compounds as measured by the MIC_{80}, however compound **37** was still the most potent with an MIC_{80} of 0.25 μM followed by the 2-furyl analogue **29**. A comparison of the activity of compounds Win 54954 and **37** is shown in Table II.

Bulk at the modified heterocycle end of the molecule does not appear to affect broad-spectrum activity since the unsubstituted oxazole **6** and the 4,5-dimethyl analog **7** exhibited comparable MIC_{80}'s. In the furyl and thiophene series, the 5-methyl analogues **31** and **27** had marginally higher MIC_{80}'s than the corresponding unsubstituted analogs **29** and **25**, respectively.

We had attempted to explain some of the differences in activity which we observed among the diverse heterocycles by correlating the antiviral activity with several semiempirically calculated physicochemical parameters such as log P, M_r, dipole moment, atomic point charge, HOMO, and LUMO, using the AM1 Hamiltonian available in the AMPAC suite of programs.[31] In consideration of the size and conformational flexibility of the molecules being studied, calculations were restricted to the biaryl portion of the molecule since the remaining fragment was constant in each case. The geometry for each heteroaryl system was optimized within AMPAC. The dipole moment, point charges, HOMO, and LUMO were calculated for each phenylheteroaryl system (see supplementary material). A QSAR analysis using these parameters individually or in combination and attempted correlation with either the MIC against HRV-14 or the MIC_{80} (using log 1/MIC) proved unsuccessful.

The lack of correlation between the physicochemical parameters and antiviral activity suggests that other factors may be responsible for the diversity of activity.

Experimental Section

Melting points were determined according to the USP procedure and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Analyses were performed by Galbraith Laboratories, Knoxville, TN. NMR spectra were determined on a Bruker 200 spectrophotometer and Varian Unity 300. Shifts for ^{1}H NMR are reported in ppm downfield from TMS (δ). Infrared spectra were recorded on a Nicolet 10-SX FT spectrometer.

5-[4-[[5-(3-Methyl-5-isoxazolyl)pentyl]oxy]-3,5-dichlorobenzamido]bicyclo[2.2.1]hept-2-en-6-ol (11). To 3.58 g (10.0 mmol) of 3,5-dichloro-4-[[5-(3-methyl-5-isoxazolyl)pentyl]-oxy]benzoic acid in 50 mL of CH_2Cl_2 was added 24.5 g (205 mmol) of $SOCl_2$. After 16 h, the reaction was concentrated in vacuo and dissolved in 12 mL of CH_2Cl_2. The CH_2Cl_2 solution was added dropwise to a solution of 1.25 g (10.0 mmol) of amino alcohol **9** in 10 mL of CH_2Cl_2 and 3 mL of triethylamine. After 1 h at 0 °C, the reaction mixture was concentrated in vacuo and partitioned between 1 N HCl and ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated in vacuo and chromatographed on silica gel using 4:1 ethyl acetate–hexane as an eluent providing **11** in 74% yield. The compound was recrystallized from ether–hexane: mp 84.5–88.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 2 H), 6.43 (d, J = 7 Hz, 1 H), 6.28 (m, 2 H), 5.82 (s, 1 H), 4.59 (m, 1 H), 4.34 (m, 1 H), 4.03 (t, J = 6 Hz, 2 H), 3.24 (br s, 1 H), 3.11 (br s, 1 H), 2.76 (t, J = 7 Hz, 2 H), 2.59 (br d, 1 H), 2.27 (s, 3 H), 1.32–1.95 (m, 8 H). Anal. ($C_{23}H_{26}Cl_2N_2O_4$) C, H, N.

5-[5-[2,6-Dichloro-4-(2-oxazolyl)phenoxy]pentyl]-3-methylisoxazole (6). A slurry of amide **11** and 20 mL of decalin was heated to 183 °C during which time the amide dissolved. After 4.5 h at this temperature, the reaction mixture was cooled to room temperature and directly applied to a silica gel column and eluted with 12% ethyl acetate in hexane. Product fractions crystallized from ether–hexane to provide 2.39 g (85%) of **6**: mp 39–41 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 2 H), 7.72 (s, 1 H), 7.23 (s, 1 H), 5.84 (s, 1 H), 4.07 (t, J = 6 Hz, 2 H), 2.77 (t, J = 7 Hz, 2 H), 2.27 (s, 3 H), 1.53–1.99 (m, 6 H). Anal. ($C_{18}H_{18}Cl_2N_2O_3$) C, H, N, Cl.

3,5-Dichloro-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]-benzonitrile (35). A mixture of 23.2 g (0.1 mol) of 5-(5-bromopentyl)-3-methylisoxazole[4] (**15**), 13.4 g (0.071 mol) of 3,5-dichloro-4-hydroxybenzonitrile, 20.7 g (0.15 mol) of K_2CO_3, and 15 g (0.1 mol) of KI in 250 mL of DMF was heated to 100 °C for 24 h. The mixture was concentrated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was washed with 2 N NaOH and water and dried. Removal of the solvent gave an oil which was purified by column chromatography on silica gel and eluted with hexane–ethyl acetate, 4:1. The solid which was obtained was recrystallized from methanol–hexane to give 11.6 g (48%) of **35**: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.50–1.70 (m, 2 H), 1.70–1.95 (m, 4 H), 2.30 (s, 3 H), 2.75 (t, J = 8 Hz), 4.00 (t, J = 6 Hz), 5.85 (s, 3 H), 7.60 (s, 2 H). Anal. ($C_{16}H_{16}Cl_2N_2O_2$) C, H, N.

5-[3,5-Dichloro-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]-phenyl]-1*H*-tetrazole (36). A mixture of 14.7 g (43.3 mmol) of **35**, 2.96 g (55.8 mmol) of NH_4Cl, and 3.2 g (60.4 mmol) of NaN_3 in 150 mL of DMF was heated with stirring at 100 °C for 24 h. The solvent was removed in vacuo, and the residue was desolved in ethyl acetate and the solution extracted with water and 2 N HCl. After drying, the organic layer was concentrated to dryness. The crystalline residue was recrystallized from ethyl acetate providing 10.3 g (62%) of **36**: mp 122–123 °C; ^{1}NMR ($CDCl_3$) δ 1.6–2.0 (m, 6 H), 2.3 (s, 3 H), 2.8 (t, J = 8 Hz, 2 H), 4.1 (t, J = 6 Hz, 2 H), 5.85 (s, 1 H), 8.1 (s, 2 H). Anal. ($C_{16}H_{17}Cl_2N_5O_2$) C, H, N.

5-[3,5-Dichloro-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]-phenyl]-2-methyl-2*H*-tetrazole (37). To a mixture of 6.4 g (16.7 mmol) of **36** and 3.0 g (22 mmol) of milled K_2CO_3 in 200 mL of acetonitrile was added 2.8 g (20 mmol) of CH_3I and the mixture stirred at room temperature for 18 h. After removal of the inorganic solids by filtration, the resulting solution was concentrated to dryness and the residual oil was purified by column chromatography on silica gel by eluting with hexane–ethyl acetate, 1:1. After recrystallization from hexane–ethyl acetate, compound **37** was obtained in 64% yield as a white solid: mp 47–49; ^{1}H NMR ($CDCl_3$) δ 1.50–2.00 (m, 6 H), 2.28 (s, 3 H), 2.77 (t, J = 8 Hz, 2 H), 4.11 (t, J = 6 Hz, 2 H), 4.40 (s, 3 H), 5.83 (s, 1 H), 8.10 (s, 2 H). Anal. ($C_{17}H_{19}Cl_2N_5O_2$) C, H, N. Further elution provided 0.89 g (14%) of the positional isomer **38**: mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 1.55–2.00 (m, 6 H), 2.28 (s, 3 H),

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2.77 (t, $J = 6$ Hz, 2 H), 4.11 (t, $J = 8$ Hz, 2 H), 4.21 (s, 3 H), 5.83 (s, 1 H), 7.72 (s, 2 H). Anal. ($C_{17}H_{19}Cl_2N_5O_2$) C, H, N.

5-[5-[2,6-Dichloro-4-(4,5-dihydro-3*H*-pyrrol-2-yl)phenoxy]-pentyl]-3-methylisoxazole (43). Using a modified procedure of Feringa,[30] a solution of 5.0 g (11.4 mmol) of iodide **24** in 75 mL of dry ether under N_2 at −78 °C was treated with 1.4 mL (1.2 equiv) of 9.5 M *n*-BuLi. The lithium salt immediately precipitated, and after 15 min at −78 °C, a solution of 1.8 g (11.4 mmol) of 1-(trimethylsilyl)pyrrolidin-2-one in 10 mL of dry ether was added dropwise. The reaction mixture was slowly allowed to warm to room temperature over a 2-h period. The reaction was diluted with ether (50 mL) and washed with water (75 mL). The organic layer was dried over K_2CO_3. Concentration followed by medium pressure liquid chromatography (26-mm i.d. Kieselgel column; 3:1 hexane–ethyl acetate) provided 1.8 g (42%) of the product as a clear, viscous oil. Crystallization from *i*-propyl acetate–hexane afforded white crystals: mp 57–59 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 2 H), 7.26 (br s, 1 H), 5.82 (s, 1 H), 4.05 (t, $J = 6.4$ Hz, 2 H), 2.86 (dt, $J = 1.3, 6.0$ Hz, 2 H), 2.75 (t, $J = 7.5$ Hz, 2 H), 2.25 (s, 3 H), 2.02–2.07 (m, 2 H), 1.81–1.91 (m, 2 H), 1.70–1.81 (m, 2 H), 1.59–1.65 (m, 2 H); IR (KBr) 1605 cm^{-1}. Anal. ($C_{19}H_{22}Cl_2N_2O_2$) C, H, N.

General Procedure for Palladium-Catalyzed Heterobiaryl Cross-Coupling: 5-[5-[2,6-Dichloro-4-(5-methyl-2-thienyl)phenoxy]pentyl]-3-methylisoxazole (27). A suspension of 5.4 g (12.3 mmol) of aryl iodide **24**, 5.8 g (14.8 mmol; 1.2 equiv) of 2-methyl-5-(tributylstannyl)thiophene, and 0.45 g (5 mol%) of $PdCl_2[(C_6H_5)_3P]_2$ in 10 mL of THF was refluxed under nitrogen for 20 h. Upon cooling, the crude reaction mixture was filtered through neutral alumina eluting with 9:1 (hexane–ethyl acetate). Concentration followed by MPLC of the residual oil (50-mm i.d. column, Kieselgel 60; 9:1 hexane–ethyl acetate) provided 4.1 g (82%) of the product as a colorless oil. Crystallization from *i*-propyl acetate–hexane at dry ice temperature provided 2.4 g of product as a white solid: mp 43–45 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 2 H), 7.04 (d, $J = 4$ Hz, 1 H), 6.70 (d, $J = 4$ Hz, 2 H), 5.83 (s, 1 H), 4.02 (t, $J = 6$ Hz, 2 H), 2.77 (t, $J = 8$ Hz, 2 H), 2.77 (t, $J = 8$ Hz, 2 H), 2.50 (s, 3 H), 2.26 (s, 3 H), 1.50–2.00 (m, 6 H). Anal. ($C_{20}H_{21}Cl_2NO_2S$) C, H, N.

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Supplementary Material Available: Tables of physicochemical parameters and ^{1}H NMR data (3 pages). Ordering information is given on any current masthead page.