

## Notes

## [(Biaryloxy)alkyl]isoxazoles: Picornavirus Inhibitors

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Received October 1, 1994<sup>®</sup>

A series of biphenyl analogs, **6**, of 5-[5-(2,6-dichloro-5-oxazolylphenoxy)pentyl]-3-methylisoxazole (**2**) have been synthesized and tested in vitro against 10 human rhinovirus serotypes in a TCID<sub>50</sub> assay. The most potent compound in the series **6s**, 3-[3-[2,6-dimethyl-4-(4-fluorophenyl)phenoxy]propyl]-3-methylisoxazole, was screened against an additional 84 serotypes. It was found to be active against 64 of the serotypes, while 87 serotypes were sensitive to **2** at <3 μg/mL. On comparison of the active serotypes, **6s** exhibited greater potency versus **2**. Analogs **6a-c,s** were examined for in vitro metabolic stability by monkey liver microsomal assay. These analogs exhibited a greater than 7-fold improvement ( $t_{1/2} > 200$  min) in metabolic stability compared with **2** ( $t_{1/2} > 27$  min).

## Introduction

Disoxaril (**1**) and analog **2** (Figure 1) are representatives of a series of (phenoxyalkyl)isoxazoles which have demonstrated broad spectrum antipicornavirus activity.<sup>1</sup> These compounds have been shown by X-ray crystallography<sup>2-4</sup> to bind to the viral capsid protein and occupy a common hydrophobic area below the cell receptor binding site or "canyon". Mode of action studies have revealed that in the case of the major serotypes such as human rhinovirus-14 (HRV-14), these compounds prevent adsorption of the virus to ICAM-1.<sup>5</sup> A different mechanism of action is operative in the case of human rhinovirus-1A (HRV-1A) (minor group) where viral uncoating appears to be the primary mode of action.<sup>6</sup> It appears that the different mechanism of viral inhibition can be attributed to the extent of conformational changes which occur within the binding sites of the respective serotypes upon entry of the compounds. The binding site of HRV-14 is considerably narrower than that of HRV-1A, and consequently the conformational changes which occur during the binding process are more extensive (3-5 Å) than with the latter. These changes extend into the base of the canyon causing significant movement of residues which are essential to the cellular binding process.<sup>7</sup> Only minimal conformational changes result from compounds binding to the HRV-1A pocket, and consequently, the cell receptor binding site is unaffected. The resultant inhibition of uncoating may be due to stabilization of the capsid protein at the binding site, preventing disruption of the protein coat which is necessary for the uncoating process to occur. It has been reported that X-ray studies of native HRV-16 have revealed a substance residing in the pocket which is displaced by capsid-binding compounds.<sup>8</sup> This material, referred to as a "pocket factor", has also been reported from studies performed with

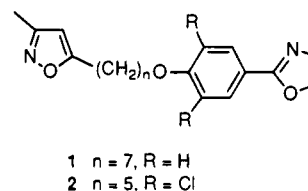


Figure 1.

poliovirus type 3.<sup>9</sup> The function of this factor is at present unknown but may be responsible for stabilizing the capsid protein prior to uncoating.

As a result of our continued interest in this approach to picornaviral inhibition, we have synthesized and evaluated a series of biphenyl analogs, **6**, where the oxazoline ring has been replaced with a phenyl ring. This replacement addresses the chemical and metabolic instability issues associated with predecessors in this series.<sup>10</sup>

## Chemistry

Two general methods, the Ullman reaction<sup>11</sup> and Pd-Sn couplings,<sup>12,13</sup> have been successfully utilized for the preparation of biaryls. Earlier work from these laboratories<sup>1b</sup> exploited a novel Pd(0)-catalyzed cross-coupling method for the synthesis of novel antiviral heterobiaryls. This strategy has now been further adapted to provide a highly convergent method for the preparation of our desired biaryl targets. The modified process relies upon the synthesis of late stage synthetic intermediate **5**, which was found to couple with numerous commercially available aryl iodides in the presence of a Pd(0) catalyst.

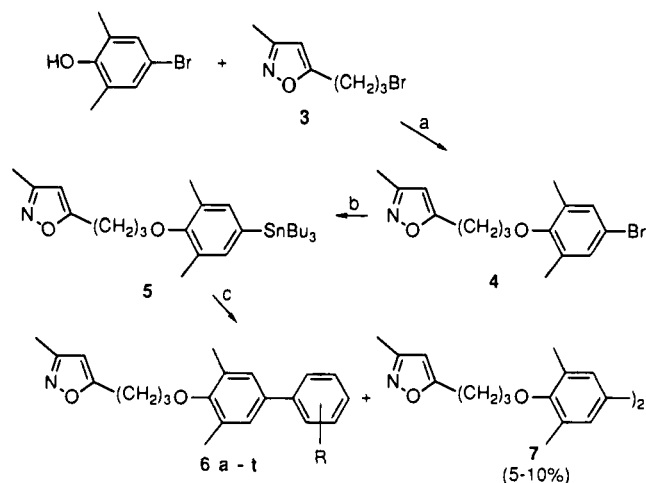
4-Bromo-2,6-dimethylphenyl was O-alkylated with 5-(3-bromopropyl)-3-methylisoxazole (**3**) in the presence of potassium carbonate and potassium iodide to yield the highly functionalized aryl bromide **4**.<sup>14</sup> Bromide-lithium exchange of **4** at -78 °C in tetrahydrofuran followed by addition of tributylstannyl chloride provided the arylstannane **5** in excellent yield. We observed that exposure of the aryl bromide intermediate to alkyl-

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® Abstract published in *Advance ACS Abstracts*, July 1, 1995.

Scheme 1<sup>a</sup>

<sup>a</sup> Reagents: (a)  $K_2CO_3$ , KI, NMP, 60 °C; (b) *t*-BuLi, THF, -78 °C,  $Bu_3SnCl$ ; (c) ArI, DMF,  $\Delta$ ,  $PdCl_2(PPh_3)_2$  (cat.).

**Table 1.** Physicochemical Properties of [(Biaryloxy)alkyl]isoxazoles **6a-7**

compd	R	yield (%)	mp (°C)	formula
<b>6a</b>	H	78	65-67	$C_{21}H_{23}NO_2$
<b>6b</b>	3-Me	35	72-74	$C_{22}H_{25}NO_2$
<b>6c</b>	4-Me	50	105-106	$C_{22}H_{25}NO_2$
<b>6d</b>	3-OMe	44	54-55	$C_{22}H_{25}NO_3$
<b>6e</b>	4-OMe	46	96-97	$C_{22}H_{25}NO_3$
<b>6f</b>	3-OH	18	161-162	$C_{21}H_{23}NO_3$
<b>6g</b>	4-OH	50	148-149	$C_{21}H_{23}NO_3$
<b>6h</b>	3-CH <sub>2</sub> OH	28	83-85	$C_{22}H_{25}NO_3$
<b>6i</b>	4-NMe <sub>2</sub>	11	110-111	$C_{23}H_{28}N_2O_2$
<b>6j</b>	3-Cl	65	44-45	$C_{21}H_{22}ClNO_2$
<b>6k</b>	4-Cl	47	124-125	$C_{21}H_{22}ClNO_2$
<b>6l</b>	3-NO <sub>2</sub>	76	70-71	$C_{21}H_{22}N_2O_4$
<b>6m</b>	4-NO <sub>2</sub>	24	135-136	$C_{21}H_{22}N_2O_4$
<b>6n</b>	4-CF <sub>3</sub>	47	93-95	$C_{22}H_{22}F_3NO_2$
<b>6o</b>	3-CN	41	128-129	$C_{22}H_{22}N_2O_2$
<b>6p</b>	4-CN	26	75-76	$C_{22}H_{22}N_2O_2$
<b>6q</b>	2-F	27	36-37	$C_{21}H_{22}FNO_2$
<b>6r</b>	3-F	43	43-44	$C_{21}H_{22}FNO_2$
<b>6s</b>	4-F	53	105-106	$C_{21}H_{22}FNO_2$
<b>6t</b>	3-F, 4-F	41	65-67	$C_{21}H_{21}F_2N$
<b>7</b>		6	119-121	$C_{30}H_{36}N_2O_4$

lithium reagents for extended periods of time, or higher temperatures, frequently caused side reactions to occur.

In a typical coupling experiment, the aryl iodide was heated at 80 °C in DMF with 0.9 equiv of the arylstannane and 5-10 mol %  $PdCl_2(PPh_3)_2$  as catalyst for 8-24 h. A common side product, **7**, which resulted from homocoupling of the aryltin was routinely isolated from the reaction in 5-10% yield. The results of the biaryl cross-coupling reactions are shown in Table 1.

## Results and Discussion

The compounds were tested against 10 human rhinoviruses in a TCID<sub>50</sub> (tissue culture infectious dose) assay.<sup>8</sup> The MIC<sub>50</sub> was determined as the concentration of compound which inhibits 50% of the serotypes tested to 50% of the viral concentration of untreated controls, following 72 h of exposure (Table 2).

All of the compounds in this series were inactive (MIC<sub>50</sub> > 3.0  $\mu$ g/mL) against HRV-3, -4, and -5 regardless of the nature of the substituents or the substitution pattern. The 4-Cl, 4-F, and 4-CH<sub>3</sub> analogs along with the 2-F analog were the most active compounds discovered. The 3-OH and 3-NO<sub>2</sub> analogs **6f,l**, respectively,

**Table 2.** TCID<sub>50</sub> Assay

compd	R	MIC <sub>50</sub> ( $\mu$ mol) <sup>a</sup>
<b>2</b> (WIN 54954)		0.78
<b>6a</b>	H	0.16
<b>6b</b>	3-Me	0.23
<b>6c</b>	4-Me	0.12
<b>6d</b>	3-OMe	0.23
<b>6e</b>	4-OMe	0.28
<b>6f</b>	3-OH	0.44
<b>6g</b>	4-OH	0.77
<b>6h</b>	3-CH <sub>2</sub> OH	0.23
<b>6i</b>	4-NMe <sub>2</sub>	0.66
<b>6j</b>	3-Cl	0.27
<b>6k</b>	4-Cl	0.12
<b>6l</b>	3-NO <sub>2</sub>	0.35
<b>6m</b>	4-NO <sub>2</sub>	0.76
<b>6n</b>	4-CF <sub>3</sub>	1.7
<b>6o</b>	3-CN	> 8.9
<b>6p</b>	4-CN	0.26
<b>6q</b>	2-F	0.11
<b>6r</b>	3-F	0.32
<b>6s</b>	4-F	0.11
<b>6t</b>	3-F, 4-F	0.16

<sup>a</sup>  $n = 2$  determinations against HRV-3-5, -9, -16, -18, -38, -66, -67, and -75. Concentration which inhibits 50% of the serotypes tested.

exhibited improved activity over their 4-substituted counterparts. Among the 4-position analogs, the least active were the CF<sub>3</sub>, OH, NO<sub>2</sub>, and NMe<sub>2</sub> compounds **6n,g,m,i**, respectively, while the remainder of the compounds in this series were of comparable activity, and all exhibited greater potency than compound **2** (MIC<sub>50</sub> = 0.78  $\mu$ M).

Extensive metabolism of compound **2** has previously plagued the utility of this agent and similar agents.<sup>1b,c</sup> One of the major goals toward designing a therapeutic agent was to improve metabolic stability. The metabolic stability was monitored by an in vitro liver microsomal assay.<sup>15</sup> The half-life values for several analogs of **6** which were incubated with liver microsomes are shown in Table 4. A comparison between the oxazoline analog **2** and the phenyl analogs was made. All the phenyl analogs examined displayed significantly greater stability than oxazoline analog **2**,  $t_{1/2} > 200$  min vs 27 min, respectively. As a result of this improved performance, compound **6s**, the most potent analog, was screened against an additional 94 serotypes. Compound **6s** was found to be active against only 64 of these serotypes, while 87 serotypes were sensitive to WIN 54954 at <3  $\mu$ g/mL. A comparison of the activity of compound **6s** and WIN 54954 against the 64 serotypes is shown in Table 3. Generally speaking, **6s** exhibited greater potency against the set of 64 serotypes in Table 3. In addition, comparison using the insensitive serotypes (MIC > 3  $\mu$ g/mL) revealed that all of the WIN 54954 insensitive serotypes were in common with the **6s** insensitive serotypes.<sup>16</sup>

The reason for the disparity in activity between WIN 54954 and **6s** is surprising. The sharp demarcation of the MICs between the sensitive and insensitive serotypes had not been seen previously. Since the binding site on the capsid protein of several human rhinovirus serotypes for a related series of compounds has been

**Table 3.** Comparative Antirhinovirus Activity of Compounds **6s** and **2**

HRV	MIC ( $\mu\text{g/mL}$ ) <sup>a</sup>		fold difference <sup>b</sup>
	<b>6s</b>	<b>2</b>	
55	0.003	0.020	6.7
83	0.004	0.018	4.5
88	0.006	0.084	14.0
7	0.006	0.035	5.8
11	0.007	0.102	14.6
21	0.009	0.031	3.4
51	0.009	0.033	3.7
2	0.009	0.058	6.4
36	0.009	0.073	8.1
68	0.009	0.032	3.6
76	0.009	0.102	11.3
89	0.012	0.034	2.8
58	0.013	0.028	2.1
92	0.014	0.002	-7.0
38	0.015	0.078	5.2
78	0.018	0.081	4.5
33	0.019	0.107	5.6
20	0.019	0.037	1.9
34	0.020	0.072	3.6
85	0.020	0.043	2.1
22	0.020	0.027	1.3
47	0.021	0.015	-1.4
35	0.021	0.036	1.7
1B	0.024	0.105	4.4
57	0.024	0.156	6.5
61	0.024	0.127	5.3
90	0.024	0.191	7.9
71	0.025	0.018	-1.4
30	0.028	0.156	5.6
19	0.030	0.178	5.9
29	0.030	0.295	9.8
80	0.031	0.124	4.0
96	0.031	0.091	2.9
40	0.033	0.053	1.6
44	0.033	0.119	3.6
T39	0.035	0.299	8.5
24	0.036	0.175	4.9
49	0.037	0.160	4.3
75	0.037	0.157	4.2
56	0.038	0.099	2.6
50	0.040	0.470	11.7
84	0.042	>3.0	>7.1
23	0.046	0.451	9.8
73	0.049	0.242	4.9
79	0.056	0.028	-2.0
46	0.058	0.143	2.5
16	0.058	0.639	11.0
64	0.070	0.497	7.1
43	0.072	0.283	3.9
25	0.077	0.072	
39	0.078	0.347	4.4
9	0.080	0.187	2.3
32	0.098	0.269	2.7
67	0.118	0.169	1.4
100	0.120	0.025	-4.8
81	0.125	0.416	3.3
63	0.139	0.101	-1.4
28	0.140	0.116	-1.2
62	0.154	0.115	-1.3
1A	0.155	0.419	2.7
66	0.161	0.069	-2.3
82	0.187	0.245	1.3
15	0.492	0.490	
53	0.889	0.355	-2.5

<sup>a</sup>  $n = 2$  determinations. <sup>b</sup> Fold difference determined by dividing less active analog by more active analog; positive difference reflects **6s** as being more active than WIN 54954.

identified by X-ray crystallography, one may assume that sites on the insensitive serotypes are unable to accommodate the inhibitors due to either the rigidity or the size of these molecules.

**Table 4.** Inhibition of in Vitro P450 Metabolism

compd	$t_{1/2}$ (min) <sup>a</sup>
<b>2</b>	27
<b>6a</b>	>200
<b>6b</b>	>200
<b>6c</b>	>200
<b>6s</b>	>200

<sup>a</sup>  $n = 2$  determinations.

## Conclusion

In summary, it is demonstrated that a series of biphenyl analogs, **6**, where the oxazoline ring has been replaced with a phenyl ring, exhibit improved metabolic stability and potency over the oxazoline analog **2**. These new biphenyl analogs, while slightly narrower in spectrum, offer a new opportunity for development as antirhinovirus agents.

## Experimental Section

Melting points were determined according to the USP procedure and are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results are within  $\pm 0.4\%$  of the theoretical values. Analysis was performed by Galbraith Laboratories, Knoxville, TN. NMR spectra were determined on a Varian Unity 300. Shifts for <sup>1</sup>H NMR are reported in ppm downfield from TMS ( $\delta$ ).

**3-[3-(2,6-Dimethyl-4-bromophenoxy)propyl]-3-methylisoxazole (4).** A mixture of 4-bromo-2,6-dimethylphenol (5.0 g, 24.87 mmol), finely divided K<sub>2</sub>CO<sub>3</sub> (3.8 g, 37.3 mmol), KI (6.2 g, 37.3 mmol), **3**<sup>5</sup> (5.95 g, 37.3 mmol), and *N*-methylpyrrolidinone (20 mL) was heated at 60 °C for 18 h. The cooled mixture was diluted with H<sub>2</sub>O (75 mL) and EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2  $\times$  50 mL). The combined organic phases were washed with H<sub>2</sub>O (3  $\times$  50 mL) and brine, dried (MgSO<sub>4</sub>), filtered through a short column of Florisil, and concentrated *in vacuo* to an oil (8.6 g), which was recrystallized from ether (-78 °C) to give 5.6 g (69.5%) of slender white needles: mp 35–37 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.13 (s, 2H), 5.88 (s, 1H), 3.84 (t, 2H,  $J = 6.2$  Hz), 3.01 (t, 2H,  $J = 7.5$  Hz), 2.37 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.20 (m, 2H,  $J = 7.5$  Hz). Anal. (C<sub>16</sub>H<sub>18</sub>NO<sub>2</sub>), C, H, N.

**3-[3-(2,6-Dimethyl-4-(tributylstannyl)phenoxy)propyl]-3-methylisoxazole (5).** To a stirred solution of **4** (10.0 g, 30.8 mmol) in THF at -78 °C was added *t*-BuLi (19 mL of a 1.7 M solution in hexanes, 32.4 mmol). After 5 min, chlorotributyltin (8.8 mL, 32.4 mmol) was added to the magenta-colored solution. The solution was stirred for an additional 2 h followed by addition of saturated NH<sub>4</sub>Cl (75 mL), H<sub>2</sub>O (75 mL), and hexane (75 mL). The layers were separated, and the aqueous layer was extracted with hexane (3  $\times$  75 mL). The combined organic phases were washed with H<sub>2</sub>O (3  $\times$  50 mL) and brine, dried (K<sub>2</sub>CO<sub>3</sub>), and concentrated *in vacuo* to an oil (16 g). The oil was purified by reverse phase chromatography (SiO<sub>2</sub>, C18, eluent: CH<sub>3</sub>CN) to give 10.5 g (65.5%) of the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.07 (s, 2H), 5.88 (s, 1H), 3.84 (t, 2H,  $J = 6.2$  Hz), 3.01 (t, 2H,  $J = 7.5$  Hz), 2.37 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.20 (m, 2H,  $J = 7.5$  Hz), 1.5 (m, 6H), 1.3 (m, 6H), 1.05 (m, 6H), 0.9 (t, 9H,  $J = 6.3$  Hz). Anal. (C<sub>27</sub>H<sub>45</sub>NO<sub>2</sub>Sn), C, H, N.

**General Procedure for Palladium-Catalyzed Biaryl Cross-Coupling: 3-[3-(2,6-Dimethyl-4-phenylphenoxy)propyl]-3-methylisoxazole (6a).** A suspension of iodobenzene (0.3 g, 1.4 mmol), arylstannane **5** (0.63 g, 1.2 mmol), and 45 mg (5 mol %) of PdCl<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P]<sub>2</sub> in 3 mL of DMF was heated at 100 °C under nitrogen for 16 h. Upon cooling the crude reaction mixture was diluted with 10 mL of ether and 3 mL of KF (saturated) and stirred for 1 h. The mixture was filtered through a pad of Celite and the ether filtrate (20 mL) washed with water (2  $\times$  10 mL) and then brine (10 mL). The organic layer was dried over K<sub>2</sub>CO<sub>3</sub>. Concentration followed by medium pressure liquid chromatography (26-mm i.d. Kie-

selgel column, 5:1 hexane-ethyl acetate) provided 0.3 g (78%) of the desired product as a white solid. Crystallization from hexane at 0 °C provided slender white needles: mp 65–67 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (d, 2H, *J* = 6.99 Hz), 7.40 (t, 2H, *J* = 7.1 Hz), 7.23 (m, 3H), 5.88 (s, 1H), 3.84 (t, 2H, *J* = 6.2 Hz), 3.01 (t, 2H, *J* = 7.5 Hz), 2.37 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.20 (m, 2H, *J* = 7.5 Hz). Anal. (C<sub>21</sub>H<sub>23</sub>NO<sub>2</sub>) C, H, N.

The mother liquors were concentrated and resubjected to liquid chromatography as above. The major bands were concentrated and upon sitting provided 40 mg of slender needles corresponding to the homocoupling product **7**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.11 (s, 2H), 5.88 (s, 1H), 3.84 (t, 2H, *J* = 6.2 Hz), 3.01 (t, 2H, *J* = 7.5 Hz), 2.37 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.20 (m, 2H, *J* = 7.5 Hz). Anal. (C<sub>30</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**Acknowledgment.** The authors wish to thank Dr. Tom Bailey for helpful discussions and Eva Clinton, Guy Russo, Mark Hafner, Christopher Aldi, Guy Gendron, and Richard Czerniak for biological assay assistance.

**Supporting Information Available:** <sup>1</sup>H NMR data (1 page). Ordering information is given on any current masthead page.

## References

- (1) (a) Diana, G. D.; McKinlay, M. A.; Brisson, C. J.; Zalay, E. S.; Miralles, J. V.; Salvador, U. J. Isoxazoles with Antipicornavirus Activity. *J. Med. Chem.* **1985**, *28*, 748–752. (b) 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 Picornaviruses. *J. Med. Chem.* **1989**, *32*, 450–455. (c) Woods, M. G.; Diana, G. D.; Rogge, M. C.; Otto, M. J.; Dutko, F. J.; McKinlay, M. A. In Vitro and In Vivo Activities of Win 54954, A New Broad Spectrum Antipicornavirus Drug. *Antimicrob. Agents Chemother.* **1989**, *33*, 2069–2074. (d) Schiff, G. M.; Sherwood, J. R.; Young, E. C.; Mason, L. J.; Gamble, J. N. Prophylactic Effect of Win 54954 in Prevention of Experimental Human Coxsackie A21 Infection and Illness. *Antiviral Res. Suppl.* **1992**, *17S* (1), Abstract 92. (e) Turner, R. B.; Hayden, F. G. Efficacy of Oral WIN 54954 for the Prophylaxis of Experimental Rhinovirus Infections. *Antiviral Res. Suppl.* **1992**, *17S* (1), Abstract 91.
- (2) 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.
- (3) Badger, J.; Minor, I.; Kremer, M. J.; Oliveira, M. A.; Smith, T. J.; Griffith, J. P.; Guerin, D. M. A.; Krishnasawamy, S.; Luo, M.; Rossmann, M. G.; McKinlay, M. A.; Diana, G. D.; Dutko, F. J.; Fancher, M.; Rueckert, R. R.; Heinz, B. A. Structural Analysis of A Series of Antiviral Agents Complexed With Human Rhinovirus 14. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *3304*–3308.
- (4) Kim, K. H.; Willingmann, P.; Gong, Z. X.; Kremer, M. J.; Chapman, M. S.; Minor, I.; Oliveira, M. A.; Rossmann, M. G.; Andries, K.; Diana, G. D.; Dutko, F. J.; McKinlay, M. A.; Pevear, D. C. A Comparison of the Antirhinoviral Drug Binding Pocket in HRV-14 and HRV-1A. *J. Mol. Biol.* **1993**, *230*, 206–227.
- (5) Staunton, D. E.; Merluzzi, V. J.; Rothlein, R.; Barton, R.; Marlin, S. D.; Springer, T. A. ICAM-1 is the Major Surface Receptor for Rhinovirus. *Cell* **1989**, *56*, 849–853.
- (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*, 110–114.
- (7) 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*, 2002–2007.
- (8) Oliveira, M. A.; Zhao, R.; Lee, W.; Kremer, M. J.; Minor, I.; Rueckert, R. R.; Diana, G. D.; Pevear, D. C.; Dutko, F. J.; McKinlay, M. A.; Rossmann, M. G. The Structure of Human Rhinovirus 16. *Structure* **1993**, *1*, 51–68.
- (9) Hogle, J. M.; Chow, M.; Filman, D. J. The Three-dimensional Structure of Poliovirus at 2.9 Å Resolution. *Science* **1985**, *229*, 1358–1365.
- (10) Diana, G. D.; Volkots, D. M.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity. *J. Med. Chem.* **1994**, *37*, 2421–2436.
- (11) Fuson, R. C.; Cleveland, E. A. *Org. Synth.* **1955**, *3*, 339.
- (12) Bailey, T. R. *Synthesis* **1991**, *3*, 242.
- (13) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Couplings of Aryl Triflates with Organoanions. *J. Am. Chem. Soc.* **1987**, *109*, 5478. For recent examples of Sn–Pd couplings, see: Farina, V.; Marshal, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. Jutand, A.; Mosleh, A. *SYNLETT* **1993**, 568.
- (14) Bailey, T. R.; Diana, G. D.; Kowalczyk, P. J.; Akullian, V.; Eissenstat, M. A.; Cutcliffe, D.; Mallamo, J. P.; Carabateas, P. M.; Pevear, D. C. Antirhinoviral Activity of Heterocyclic Analogs of WIN 54954. *J. Med. Chem.* **1992**, *35*, 4628–4633.
- (15) Diana, G. D.; Rudewicz, P.; Volkots, D. M.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Aldous, D. J.; Robinson, D. T.; Draper, T.; Aldi, C.; Gendron, G.; Oglesby, R. C.; Reuman, M.; Czerniak, R.; Block, T.; Roland, R.; Oppermann, J.; Pevear, D. C.; Dutko, F. J. Picornavirus Inhibitors: Trifluoromethyl Substitution Provides a Global Protective Effect Against Hepatic Metabolism. *J. Med. Chem.*, in press.
- (16) Insensitive serotypes (MIC > 3 μg/mL): 3–6, 10, 12–14, 17, 18, 26, 27, 31, 37, 41, 48, 54, 59, 60, 65, 70, 72, 77, 86, 91, 94, and 95.

JM940576X