A Model for Compounds Active against Human Rhinovirus-14 Based on X-ray Crystallography Data

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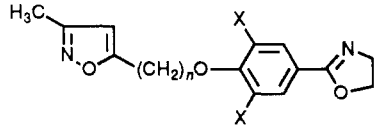
A number of (oxazolinylphenyl)isoxazoles have been synthesized and tested against human rhinovirus-14 (HRV-14). Several of the more active compounds have been examined by X-ray crystallography and their orientation in the compound binding site on the capsid protein of HRV-14 has been determined. Based on the minimum inhibitory concentration against HRV-14 and the X-ray conformation of the compounds, a model has been developed which distinguishes between the space-filling properties of the active and inactive compounds in this series. The model was generated by overlaying composite structures and comparing the van der Waals generated volume maps. The results of this study indicate that inactive compounds display areas of excessive bulk particularly around the phenyl ring, while the active compounds occupy space below the pore area of the compound binding site.

Extensive structure–activity studies have been performed on (oxazolinylphenyl)isoxazoles (I) with respect to their antipicornavirus activity. Several compounds in this



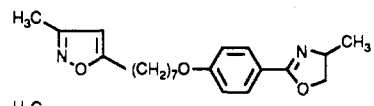
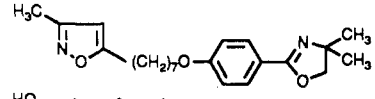
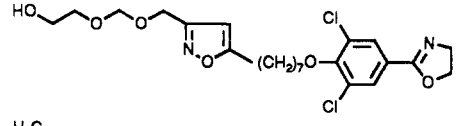
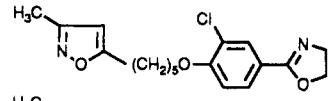
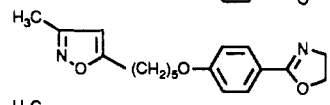
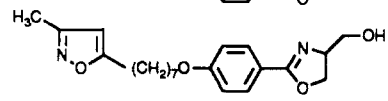
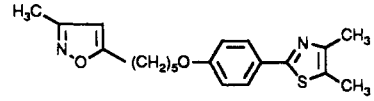
I

series have been shown to exhibit excellent activity against a wide range of human rhinoviruses, as well as enteroviruses in vitro.[1-5] These compounds inhibit viral replication by binding to the viral capsid. Although the mode of action against human rhinovirus-2 (HRV-2) and polio-2 has been reported to involve the inhibition of uncoating,[6] it has recently been found that several of these compounds inhibit adsorption of rhinovirus-14 to target cells, presumably by causing a conformational change in the putative cell-receptor binding site on the viral capsid.[7]

In addition to the results of structure–activity studies which have been previously reported, the elucidation of the 3-dimensional structure of HRV-14,[8] the identification of the compound-binding site on the capsid protein and the X-ray structure of the compound–virus complex[9] have allowed for the development of a model representing the steric requirements for activity against HRV-14 for this series of compounds.

Previous structure–activity studies have provided extensive information concerning the effect of physicochemical parameters as well as enantiomeric effects on antiviral activity. In the monosubstituted (I, X = H) series, the major parameter which affected biological activity was log *P* with some contribution from bulk and inductive effects (Hammett σ).[4] A somewhat similar result was obtained with the disubstituted series I, except that the inductive contributions were minimal and the bulk term correlated negatively with activity.[5] This latter result was explained by the presence of space constraints within the drug-binding site on the capsid protein, which would preclude entry of excessively bulky molecules. Also, enantiomeric effects were observed with substituents on the 4-position of the oxazoline ring, the *S* conformers being more active than the *R*.[10] Energy profiling studies based on calculations performed on a VAX 11/785 using a 6-12 function suggested that the torsion angle between the phenyl and oxazoline rings of 15–25° appeared to be of importance with respect to activity. This conformation of the two rings

Table I. Compounds Active against HRV-14

no.	structure	MIC, μmol, for HRV-14
1[a]		0.05
2[a]		0.16
3		0.06
4[b]		2.41
5[a]		0.51
6		0.16
7		0.14

[a] See ref 1. [b] See ref 4.

(1) Diana, G. D.; McKinlay, M. A.; Otto, M. J.; Akullian, V.; Oglesby, R. C. *J. Med. Chem.* **1985**, *28*, 1906.
(2) Otto, M. J.; Fox, M. P.; Fancher, M. J.; Kuhrt, M. F.; Diana, G. D.; McKinlay, M. A. *Antimicrob. Agents Chemother.* **1985**, *27*, 883.
(3) Wilfert, C. M.; Zeller, J. R.; Schauber, L. E.; McKinney, R. L. Abstract No. 430, 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1984.
(4) 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. *J. Med. Chem.* **1987**, *30*, 383.
(5) Diana, G. D.; Cutcliffe, D.; Oglesby, R. C.; Otto, M. J.; Mallamo, J. P.; Akullian, V.; McKinlay, M. A. *J. Med. Chem.* **1989**, *32*, 450.
(6) Fox, M. P.; Otto, M. J.; Shave, W. J.; McKinlay, M. A. *Antimicrob. Agents Chemother.* **1986**, *30*, 110.
(7) Pevaer, D. C.; Fancher, M. J.; Felock, P. J.; Rossmann, M. A.; Dutko, F. J. *J. Virol.* **1989**, *63*, 2002.
(8) Rossmann, M. J.; Arnold, E.; Erickson, J. W.; Frankenberger, E. A.; Griffith, J. P.; Hecht, H. J.; Johnson, J. E.; Kramer, G.; Luo, M.; Mosser, A. G.; Reuckert, R. R.; Sherry, B.; Vriend, G. *Nature* **1985**, *317*, 145.
(9) Smith, T. J.; Kremer, M. J.; Luo, M.; Vriend, G.; Arnold, E.; Kamer, G.; Rossmann, M. G.; McKinlay, M. A.; Diana, G. D.; Otto, M. J. *Science* **1986**, *233*, 1286.
(10) Diana, G. D.; Otto, M. T.; Treasurywala, A. M.; McKinlay, M. A.; Oglesby, R. C.; Maliski, E. G.; Rossmann, M. G.; Smith, T. J. *J. Med. Chem.* **1988**, *31*, 540.

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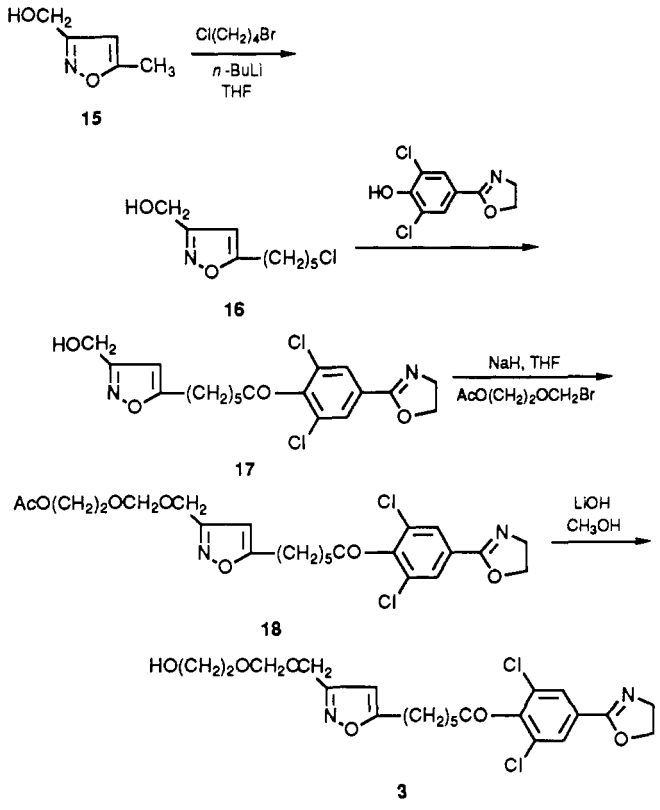
Scheme I



permits the alkyl groups on the oxazoline ring to assume a position suitable for a hydrophobic interaction with a Leu[106] residue.

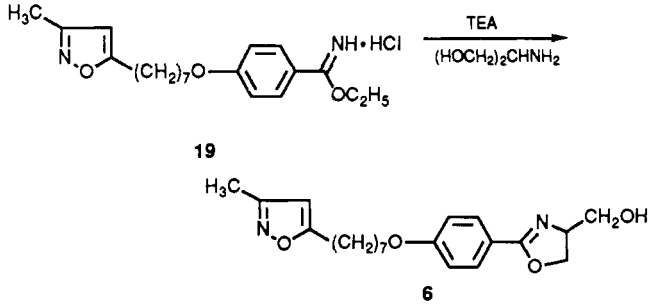
Recent X-ray crystallographic studies performed on compounds in this series having five- and seven-carbon chains connecting both ends of the molecules have shown that the compounds bind in the pocket in one of two orientations.[11] Compounds with a seven-carbon chain and a substituent on the oxazoline ring are bound in one orientation, while those with a five-carbon chain, regardless of the substitution pattern, are bound in the opposite orientation (Figure 1).

The results reported thus far suggest the importance of particular interactions of these compounds with the residues within the compound-binding site. With these results in hand and the orientation of several analogues in the binding site established by X-ray crystallography, a model was developed which took into consideration all of these parameters.

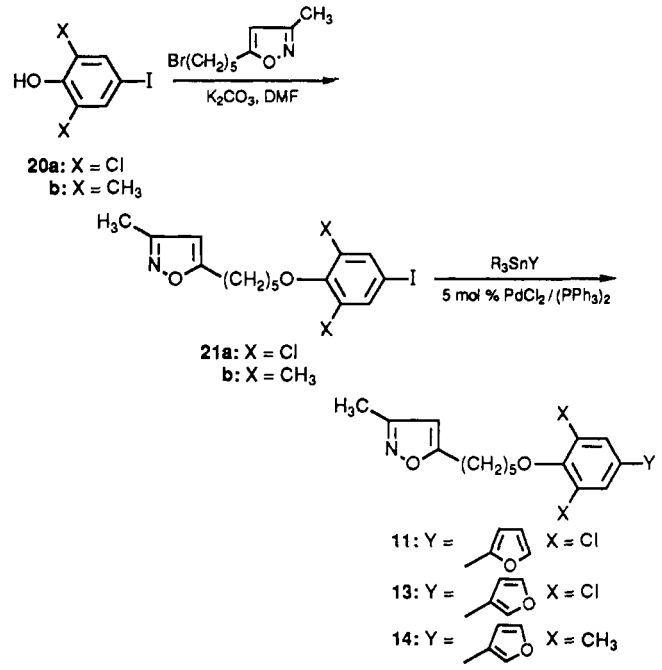
Chemistry

The synthesis of compounds **1**, **2**, **4**, and **5** in Table I and compounds **8**, **10**, and **12** in Table II were previously reported.[1,4,5] The synthesis of compound **3** is shown in Scheme I. Alkylation of 3-(hydroxymethyl)-5-methylisoxazole[5] with 1-bromo-4-chlorobutane provided (chloropentyl)isoxazole **16** in 79% yield. Alkylation of 2,6-dichloro-4-oxazolinylphenol[5] with **16** provided **17** in 38% yield, as an oil. The hydroxylated side chain of **3** was introduced by alkylation of **17** with (2-acetoxyethoxy)methyl bromide,[12] to produce **18**, which was subsequently hydrolyzed to **3** in an overall yield from **17** of 46%.

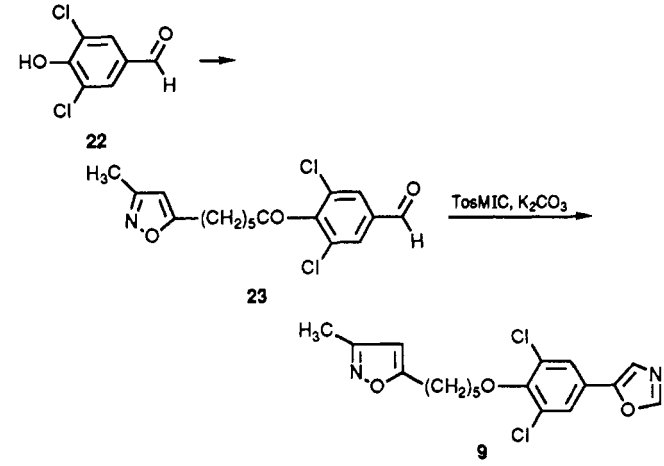
Scheme II



Scheme III



Scheme IV



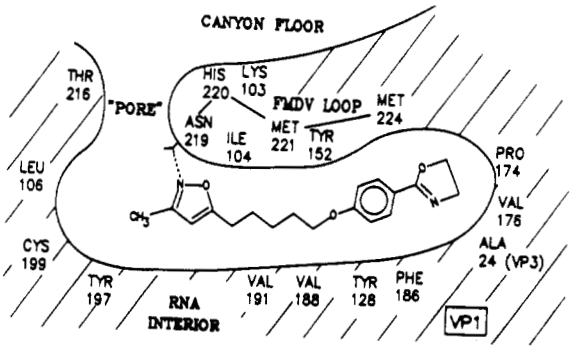
Compound **6** was prepared from the imino ester **19**[1] and 2-amino-1,3-propanediol (Scheme II) in 73% yield. Compound **7** (Table I) resulted from the alkylation of 4-(4,5-dimethylthiazolyl)phenol with 5-(5-bromopentyl)-3-methylisoxazole according to a published procedure.[1]

Compounds **11**, **13**, and **14** (Table II) were synthesized by using the heterobiaryl cross-coupling procedure[13,14]

(11) Badger, J.; Minor, I.; Kremer, M. J.; Oliveria, M. A.; Smith, T. J.; Griffith, J. P.; Guerin, D. M. A.; Krishnaswamy, S.; Luo, M.; Rossmann, M. J.; McKinlay, M. A.; Diana, G. D.; Dutko, F. J.; Fancher, M.; Reuckert, R. R.; Heinz, B. A. *Proc. Natl. Acad. Sci.* U.S.A. **1988**, *85*, 3304.

(12) Robbins, M. J.; Hatfield, P. *Can. J. Chem.* **1982**, *60*, 54.

(13) Bailey, T. R. *Tetrahedron Lett.* **1986**, *27*, 4407.



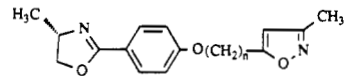
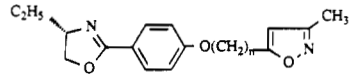
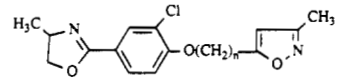
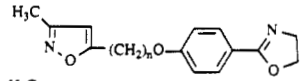
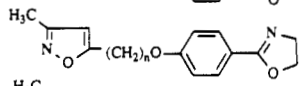
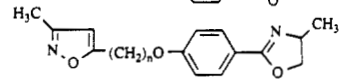
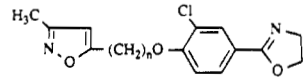
Cmpd #	ORIENTATION	n	MIC μmol
1		7	0.06
30		7	0.023
31		7	2.4
32		7	0.41
5		5	0.56
33		5	0.70
4		5	2.4

Figure 1. The orientation shown of the compounds bound to HRV-14 as determined by X-ray crystallography.

shown in Scheme III. The aryl iodides **21a** and **21b** were prepared by alkylation of the known 4-iodophenols **20a**[15] and **20b**[16] with 3-(5-bromopentyl)-5-methylisoxazole in 94% and 96% yield, respectively. Heterobiarylstannanes were generated either by direct metalation or halogen/metal exchange of the parent heterocycle followed by alkylation with trimethylstannyl chloride.

Oxazole **9** (Table II) was prepared from benzaldehyde **22** as shown in Scheme IV. Alkylation of **22** according to the conditions shown in Scheme III gave aldehyde **23** in 29% yield. Treatment of **23** with TosMIC in methanol provided **9** in 59% yield.

Compounds **27–29** were synthesized according to Scheme V. The reaction of 6-heptyn-1-ol (**24**) with oxazolinylphenol **25** in the presence of diethyl azidodicarboxylate (DEAD) and triphenylphosphine in methylene chloride produced **26** in 83% yield. Compound **26** was treated with the appropriate nitroalkane to give compounds **27–29** in yields of 10–12%.

(14) Bailey, T. R.; Diana, G. D.; McKinlay, M. J.; Otto, M. J.; Akullian, V. 193rd National ACS meeting, Denver CO, 1987.
(15) Kamitani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043.
(16) Brazier, S. A.; McCombie, H. *J. Chem. Soc.* **1912**, *101*, 974.
(17) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333.
(18) Herada, K.; Kaji, E.; Zen, S. *Chem. Pharm. Bull.* **1980**, *28*, 3296.
(19) Schmtiz, H.; DeVault, R. L.; McDonnel, C. D.; Godfrey, J. C. *J. Antibiot.* **1968**, *21*, 603.
(20) Charpentier-Marize, M.; Doukhan, R.; Sanaoulet, J. *Bull. Soc. Chim. Fr.* **1968**, 685.
(21) Bredereck, H.; Grompper, R. *Chem. Ber.* **1954**, *87*, 700.

Table II. Compounds Inactive[a] against HRV-14

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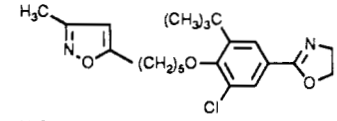
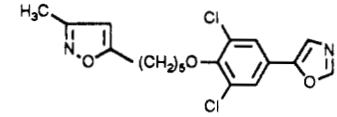
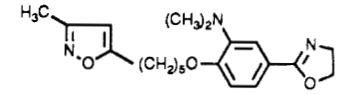
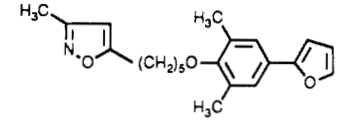
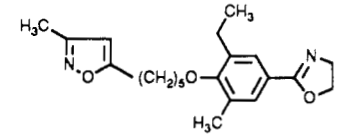
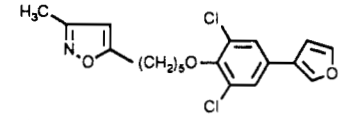
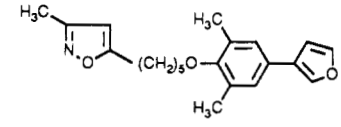
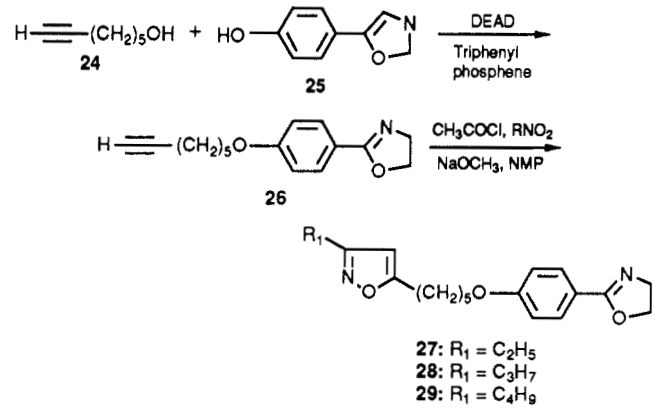
8[b]	
9	
10[c]	
11	
12[b]	
13	
14	

[a] These compounds were inactive at the highest level tested, i.e. 10 μmol. [b] See ref 5. [c] See ref 4.

Scheme V



27: $R_1 = C_2H_5$
28: $R_1 = C_3H_7$
29: $R_1 = C_4H_9$

Model Development

In order to determine the requirements for compounds active against HRV-14, seven active compounds were chosen with some variation in structure. The compounds were restricted to those whose conformation in HRV-14 had been determined by X-ray crystallography or which were structurally closely related to these compounds so that their orientation could be assumed to be the same. These assumptions were made on the basis of the X-ray data of the compounds shown in Figure 1. Our conclusions from these results were that compounds with a seven-carbon bridge between the isoxazole and phenoxy moieties and with alkyl substituents on the oxazoline ring were in the orientation with the oxazoline ring below the pore of the binding site. When no substituent was present on the ring as in the case of disoxaril (32), the compound was in

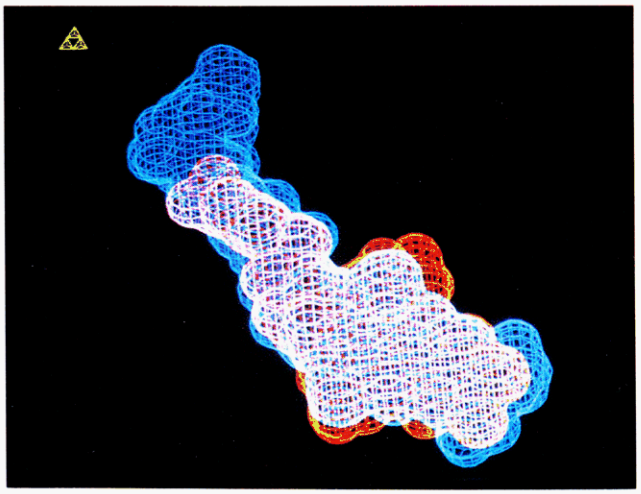


Figure 2. Overlay of the volume maps of active compounds (blue) and inactive compounds (red).

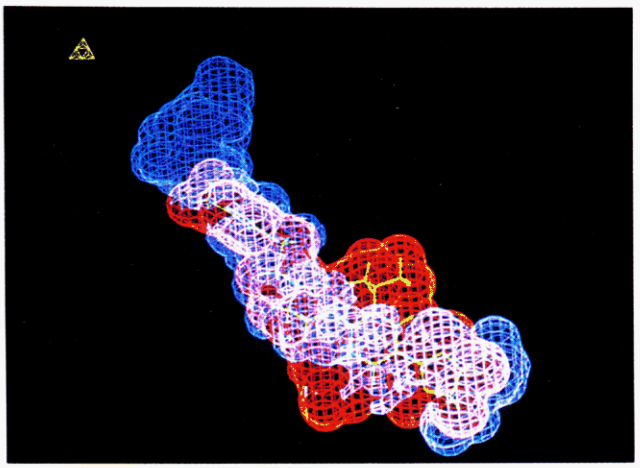


Figure 3. Boolean "minus" displaying the volume occupied by the inactive compounds in red with compound **12** inserted.

the opposite orientation. However, in the case of those compounds with a five-carbon-chain spacer, all of the analogues examined were in the same orientation with the isoxazole ring below the pore as depicted in the drawing. Since a considerable number of compounds have been examined, all of which behaved predictably, it was assumed that the conclusions drawn with respect to the orientation of these compounds in the drug-binding site would apply to other analogues in this series of compounds. Consequently, compound **7**, whose orientation was not determined, was modeled from **5**, and likewise, compound **6** was constructed from **1**.

Since the X-ray coordinates of the inactive compounds were not available, the same rules were applied to these structures with regard to their orientation. In this case, compound **5** from Table I was used as a template for all of the inactive compounds.

In order to perform the volume calculations, a database was created of the active molecules whose conformations were obtained from the crystal structures in the compound binding site, with the program SYBYL (version 5.0). Each of the compounds was overlapped so that it corresponded to a similar position in the binding site (Figure 1), as determined by X-ray crystallography. A volume was then calculated of the Boolean "union" of all active and inactive compounds which were then overlayed as shown in Figure 2. Finally, the difference between these two maps (Boolean "minus") in both directions was calculated (Figures 3 and 4).

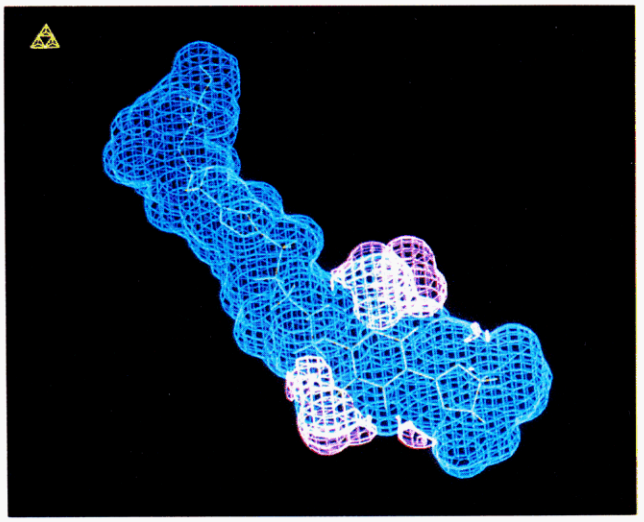
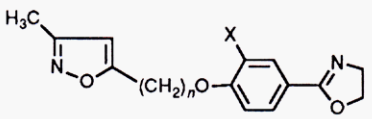


Figure 4. Difference between the inactive (red) and active (blue) volume maps (Boolean "minus") showing the space occupied by active compounds with compound **1** inserted.

Table III. In Vitro Activity against HRV-14 (MIC, μmol)



	n				
X[a]	4	5	6	7	8
H	NA	0.73	2.9	0.41	3.92
Cl	9.2	2.41	3.86	1.06	14.32

[a] See ref 4.

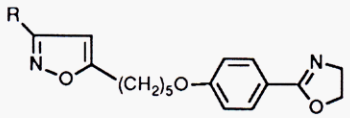
Results and Discussion

The overlay of the volume maps generated from the active and inactive compounds revealed two major differences. Inactive compounds displayed bulk around the phenyl ring. This is demonstrated clearly in Figure 3, by the red area representing the space occupied by the inactive compounds. Although some bulk is desirable, exceeding certain limits (compounds **8**, **10**, and **12**) results in inactive compounds. The second major difference is illustrated in Figure 4 by the blue area representing a space-filling requirement. The most active compounds (**1** and **3**) extended well beyond the area occupied by the other less active analogues. It should be pointed out that compound **1**, as determined by X-ray crystallography, is in the opposite orientation to compound **3** in the compound binding site such that the methyl group on the oxazoline ring of **1** and the hydroxylated side chain of **3** occupy the same area (Figure 4).

In support of our conclusions resulting from the model development that a space-filling requirement exists, a series of unsubstituted and monochloro-substituted analogues with variations in the bridging chain were evaluated against HRV-14 (Table III). In both series, a chain length of seven carbon atoms was required for optimum activity, a result which appears to be in agreement with the proposed model. Increasing the bridge to eight carbon atoms results in a corresponding reduction in activity, which may be the result of steric crowding.

In a related series, the bridge connecting both ends of the molecule was maintained at five carbon atoms and the methyl group attached to the isoxazole ring was extended to butyl (Table IV). The orientation of the methyl homologue **5** in the binding site was determined by X-ray crystallography. By lengthening the side chain, the mol-

Table IV. In Vitro Activity against HRV-14



compd	R	MIC, μmol
5	CH_3	1.27
27	C_2H_5	0.43
28	C_3H_7	0.16
29	C_4H_9	0.56

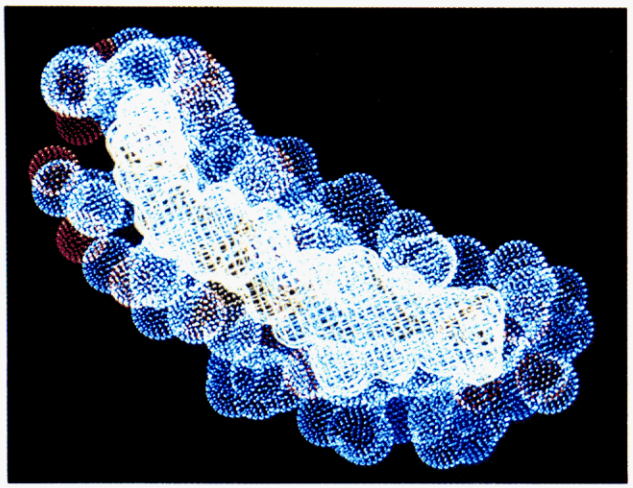


Figure 5. The compound binding site in HRV-14 highlighted by van der Waals surfaces with compound **3** inserted.

ecules should extend into the area of the compound-binding site which was predicted by the model to be an area where the presence of bulk was considered to be associated with good activity. This effect was attributed to increased binding energy due to the additional hydrophobic interactions in this area. On the basis of our model, one would predict an increase in activity with increasing chain length. The results in Table IV show that a 4-fold increase in activity resulted with each corresponding increase in chain length to propyl homologue **28** and a drop in activity with butyl compound **29**. The latter effect may be due to an increase in steric effects or an increase in log *P* beyond that desirable for optimum activity.[4,5]

Conclusions

The results of this study become more significant in view of the nature of the compound binding site below the surface of viral capsid protein. This binding site is shown in Figure 5 highlighted by van der Waals surfaces and is characterized by a pore area terminating in a hydrophobic pocket. Compound **3** is shown in the binding site in Figure 5, as determined by X-ray crystallography. The hydroxylated side chain extends into the pore area while the oxazolyldichlorophenyl ring rests in the hydrophobic region. The introduction of a bulky group on the phenyl ring would cause severe steric interactions with the surrounding residues. These potential interactions would prevent entry of these compounds into the pocket. Consequently, although bulk is important, the location of the bulk is the most critical factor which affects 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 JOEL FX-270 spectrophotometer and the mass spectrophotometer was operated by Dr. S. Clemens.

5-(5-Chloropentyl)-3-(hydroxymethyl)isoxazole (16). To a solution of 5.0 g (44.2 mmol) of 3-(hydroxymethyl)-5-methylisoxazole[5] in 200 mL of dry THF under nitrogen at −78 °C was added 11.0 mL (2.3 equiv) of 9 M *n*-butyllithium. After 15 min, the homogeneous yellow dianion was quenched with 9.1 g (1.1 equiv) of 1-bromo-4-chlorobutane and the reaction mixture was slowly allowed to warm to ambient temperature. The reaction mixture was diluted with an equal volume of diethyl ether and the organic phase was washed successively with saturated NH_4Cl solution and brine. The ether layer was dried over anhydrous K_2CO_3. Concentration of the solution followed by flash chromatography (Kieselgel 60) using hexane as an eluent provided 7.1 g (79%) of the desired product as an orange oil; ^1H NMR ($CDCl_3$) δ 5.8 (s, 1 H), 4.4 (s, 2 H), 3.4 (t, 2 H, *J* = 6 H), 2.7 (t, 2 H, *J* = 6 H), 1.5–2.0 (m, 6 H).

5-[5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentyl]-3-(hydroxymethyl)isoxazole (17). A suspension of 3.3 g (16.2 mmol) of **16**, 4.6 g (17.0 mmol) of 2,6-dichloro-4-(4,5-dihydro-2-oxazolyl)phenol hydrochloride,[5] 2.5 g (16.2 mmol) of NaI, and 2.0 g (35.6 mmol) of powdered KOH in 150 mL of acetonitrile was refluxed for 48 h. Upon cooling, the solution was filtered and the filtrate was concentrated in vacuo. The crude, dark brown gum was subjected to MPLC (50 mm i.d. Kieselgel 60) column and eluted with hexane/EtOAc 9:1, providing 2.5 g of **17** as an orange oil in 38% yield. Crystallization from isopropyl acetate/hexane afforded 1.5 g of **17** as a white powder: mp 65–66 °C; ^1H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 6.07 (s, 1 H), 4.73 (s, 2 H), 4.45 (t, 2 H, *J* = 8 Hz) 4.05 (m, 4 H), 2.9 (br s, 1 H), 2.81 (t, 2 H, *J* = 7 Hz), 1.55–2.00 (m, 6 H). Anal. ($C_{18}H_{20}Cl_2N_2O_4$) C, H, N.

2-[[[5-[5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentyl]-3-isoxazolyl]methoxy]methoxy]ethanol (3). To a solution of **17** (4.0 g, 10.0 mmol) in 50 mL of THF was added 0.29 g (12.0 mmol) of dry NaH. After hydrogen evolution had ceased, the reaction mixture was cooled to 0 °C and a solution of 2.0 g (12.0 mmol) of (2-acetylethoxy)methyl bromide[12] in 5 mL of THF was added. The reaction was stirred for 48 h at room temperature, after which the reaction mixture was diluted with an equal volume of diethyl ether and the organic phase was washed with water. After concentration in vacuo, the reaction mixture was subjected to MPLC (50-mm, i.d. Kieselgel 60 column; 2:1 EtOAc/hexane), affording the acetoxy derivative as a colorless oil. The oil was dissolved in 30 mL of MeOH, 15 mL of H_2O, and 0.25 g (11 mmol) of LiOH. The cloudy solution became transparent within 15 min and was allowed to stir at room temperature for 12 h. The crude mixture was concentrated in vacuo and extracted with diethyl ether, and the organic phase was washed with saturated NaCl solution. The ethyl layer was dried over K_2CO_3. After removal of the solvent, 2.2 g (46%) of compound **3** was obtained as a pale oil: ^1H NMR ($CDCl_3$) δ 7.88 (s, 2 H), 6.05 (s, 1 H), 4.82 (s, 2 H), 4.64 (s, 2 H), 4.45 (t, 2 H, *J* = 8 Hz) 4.06 (m, 4 H) 3.73 (m, 4 H), 2.80 (t, 2 H, *J* = 7 Hz), 2.39 (br s, 1 H), 1.55–2.00 (m, 6 H). Anal. ($C_{21}H_{26}Cl_2N_2O_6$) C, H, N.

4,5-Dihydro-2-[4-[[7-(3-methyl-5-isoxazolyl)heptyl]oxy]phenyl]-4-oxazolemethanol (6). A mixture of 11.0 g (30 mmol) of ethyl 4-[[7-(3-methyl-5-isoxazolyl)heptyl]oxy]benzimidate hydrochloride[1] (19) and 3.0 g (30 mmol) of 2-amino-1,3-propanediol was heated in an oil bath to 100 °C for 2.5 h and the resultant viscous oil was dissolved in 100 mL of H_2O and allowed to cool to room temperature. The pink platelets were collected and washed with H_2O. The damp material was dissolved in CH_2Cl_2, dried, and decolorized with charcoal. Removal of the solvent and recrystallization from *i*-PrOAc/hexane afforded 8.2 g (73%) of **6**, mp 76–77 °C. Anal. ($C_{21}H_{28}N_2O_4$) C, H, N.

5-[5-(2,6-Dimethyl-4-iodophenoxy)pentyl]-3-methylisoxazole (21b). This compound was prepared from 2,6-dimethyl-4-iodophenol (**20b**) and 5-(5-bromopentyl)-3-methylisoxazole in 60% yield by a procedure previously described.[1] The material was purified by MPLC (5:1 hexane/EtOAc) and isolated as a colorless oil. Anal. ($C_{17}H_{22}INO_2$) C, H, N.

5-[5-[4-(2-Furanyl)-2,6-dimethylphenoxy]pentyl]-3-methylisoxazole (11). A solution of 5.7 g (14.3 mmol) of aryl iodide **21b**, 0.41 g (5 mol %) of $PdCl_2(PPh_3)_2$, and 3.8 g (15.7 mmol) of 2-(trimethylstannyl)furan in 20 mL of dry THF was

refluxed under N_2 for 5 h. The reaction mixture was diluted with diethyl ether and washed twice with water. The ether phase was dried over K_2CO_3. Concentration and MPLC (50-mm i.d. Kieselgel 60 column; 5:1 hexane/EtOAc) provided 3.0 g of a clear, viscous oil. Crystallization from *i*-PrOAc/hexane afforded 2.6 g (54%) of **11** as a pale pink solid: mp 51–53 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1 H, J = 2 Hz), 7.32 (s, 2 H), 6.53 (d, 1 H, J = 3 Hz), 6.43 (m, 1 H), 5.83 (s, 1 H), 3.77 (t, 2 H, J = 6 Hz), 2.76 (t, 2 H, J = 6 Hz), 2.29 (s, 6 H), 2.28 (s, 3 H), 1.80 (m, 4 H), 1.60 (m, 2 H). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

3,5-Dichloro-4-[[5-(3-methyl-5-isoxazolyl)pentyl]oxy]-benzaldehyde (23). This compound was prepared from 3,5-dichloro-4-hydroxybenzaldehyde[22] and 5-(5-bromopentyl)-3-methylisoxazole and purified by MPLC by eluting with hexane/EtOAc 5:1 and was used without further purification.

5-[5-[2,6-Dichloro-4-(4-oxazolyl)phenoxy]pentyl]-3-methylisoxazole (9). A suspension of 3.8 g (11.1 mmol) of **23**, 3.0 g (2 equiv) of K_2CO_3, and 2.4 g (12.3 mmol) of TosMIC[23] in 30 mL of MeOH was refluxed under nitrogen for 1.5 h. The suspension was concentrated in vacuo, taken up in CH_2Cl_2, and washed with water. The organic phase was concentrated and the crude oil was subjected to flash chromatography (Kieselgel 60; 2:1 hexane/EtOAc). The purified oil was dissolved in *i*-PrOAc and treated with 1.8 g (12.5 mmol) of 70% methanesulfonic acid. The resultant gum was crystallized from *i*-PrOH/*i*-PrOAc, providing 3 g (59%) of the product as a mesylate hemihydrate salt: mp 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (br s, 1 H), 7.69 (s, 1 H), 7.65 (s, 2 H), 5.86 (s, 1 H), 4.07 (t, 2 H, J = 8 Hz), 2.99 (br s, 3 H), 2.77 (t, 2 H, J = 6 Hz), 2.28 (s, 3 H), 1.50–2.00 (m, 6 H). Anal. ($C_{18}H_{18}N_2O_3 \cdot CH_3SO_3H \cdot {}^1/_2H_2O$) C, H, N.

2-[4-(6-Heptyn-1-yloxy)phenyl]-4,5-dihydrooxazole (26). A solution of 4.42 g (39 mmol) of 6-heptyn-1-ol[17] and 10.23 g (39 mmol) of triphenylphosphine in 100 mL of CH_2Cl_2 was chilled in an ice bath and 6.1 mL (39 mmol) of diethyl azidodicarboxylate dissolved in 75 mL of dry CH_2Cl_2 was added dropwise. After the addition was complete, the reaction mixture was warmed to room temperature and stirred overnight. The mixture was filtered and the filtrate was concentrated to dryness. The residual oil was purified by MPLC on a silica gel column by elution with EtOAc and hexane (8:2) to provide 7.5 g (83%) of **26**. Recrystallization from *i*-PrOAc/hexane yielded colorless crystals: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 2 H), 6.9 (d, 2 H), 4.4 (t, 2 H), 4.05 (t, 2 H), 3.95 (t, 2 H), 2.2–2.3 (m, 2 H), 1.95 (t, 1 H), 1.7–1.9 (m, 4 H). Anal. ($C_{16}H_{19}NO_2$) C, H, N.

3-Ethyl-5-[5-[[4-(4,5-dihydro-2-oxazolyl)phenyl]oxy]-pentyl]isoxazole (27). To a magnetically stirred solution of 1-nitropropane (1 mL, 11 mmol) in 50 mL of *N*-methylpyrrolidinone at room temperature under nitrogen was added 11 mL of 1.0 N $NaOCH_3$ in MeOH (11 mL, 11 mmol).[18] The resulting milky suspension was chilled in an ice bath and then 0.8 mL (11 mmol) of acetyl chloride was added, followed by 1.45 g (5.6 mmol) of **26**. The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into 400 mL of H_2O and extracted twice with EtOAc, and the combined extracts were washed successively with H_2O and a saturated NaCl solution. After drying, the solution was concentrated to dryness, providing a yellow oil, which was purified by MPLC on silica gel and eluting with EtOAc and hexane (8:2) to give 220 mg (12%) of compound **27**: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 2 H), 6.9 (d, 2 H), 5.8 (s, 1 H), 4.4 (t, 2 H), 4.05 (t, 2 H), 3.95 (t, 2 H), 2.75 (t, 2 H), 2.65 (q, 2 H), 1.5–1.9 (t, 3 H). Anal. ($C_{19}H_{24}N_2O_3$) C, H, N.

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