NOVEL AZOLYLALKYLTHIO, -SULFOXY, AND -SULFONYL COMPOUNDS WITH ANTIPICORNAVIRAL ACTIVITY

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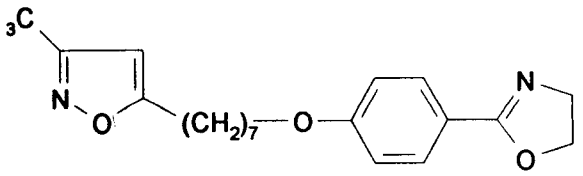
Abstract

A novel series of azolylalkylthio, -sulfoxy, and-sulfonyl compounds was designed, synthesized, and evaluated for antipicornaviral activity. Two compounds (**4i** and **41**) exhibited significant activity against various serotypes of human rhinovirus (HRV). It was found that incorporation of hydrophobic azoles such as 3-methylisoxazole or 4-methylthiazole led to increased activity. In addition, activity markedly improved when the size of the thio substituent was increased. Oxidation of the thio derivatives to the corresponding sulfoxides and sulfones resulted in less active compounds. 2-[6-[(5-chlorobenzimidazol-2-yl)thio]hexyl]-4-methylthiazole (**41**) was found to exhibit activity against HRV comparable to Disoxaril, and was also effective against the Coxsackie B1 virus.

Introduction

Among the most common of all viral infections are se due to picornaviruses. The picornavirus family is nprised of the rhino- and enteroviruses. Approximately f the cases of common cold are due to human rhinovirus RV), of which there are over 120 serotypes. Enteroviruses h as poliovirus, echovirus, coxsackievirus, and hepatitis re responsible for a multitude of clinical illnesses.

The discovery of Disoxaril **1**, which was active against ariety of picornaviruses *in vitro* and *in vivo* [1], led to the synthesis of numerous analogs from which structure-activity relationships were determined [2-7]. The three-dimensional crystal structure of HRV-14 demonstrated the existence of "canyons" on the viral capsid surface [8]. Disoxaril and related compounds bind reversibly to a hydrophobic pocket beneath the base of each canyon. Access to these pockets is via a pore on the canyon floor [9]. Once bound, these drugs exert their antiviral effect through one of two modes of action. They either block viral replication by inhibiting uncoating of the virion after it penetrates the host [1], or they inhibit adsorption of the virus to the host cells [10]. Important considerations for an agent's effectiveness include flexibility and hydrophobicity to allow passage into, and retention by, the binding pocket and suitable steric bulk for a comfortable fit therein.



1; Disoxaril

rwords: Antiviral; Azolylalkylthio compounds; Enterovirus; novirus

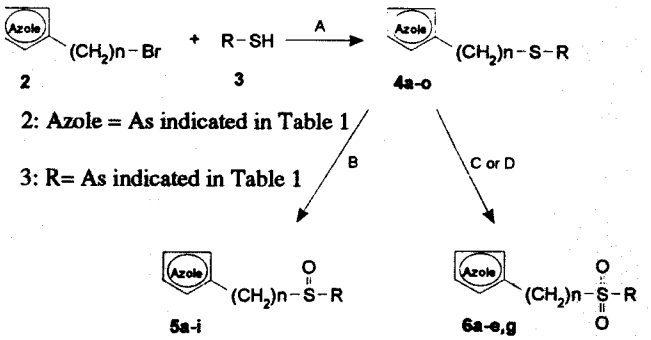
We have previously reported our work on antipicornaviral azolylalkyloxy compounds [11]. In conjunction with this work, and since sulfur is a known bioisostere of oxygen, we have synthesized and evaluated a series of azolylalkylthio compounds with the goals of obtaining effective broad spectrum antipicornavirus agents

and increasing our understanding of structure-activity relationships of these and related compounds. Sulfoxy and sulfonyl derivatives were also prepared to investigate the effects of oxidation, and the resulting altered hydrophobicity, on antipicornaviral activity.

Results

Chemistry

The synthesis of the title compounds is depicted in Scheme 1. Preparation of the azolylalkyl bromides **2** has been described previously [11]. Treatment of various



Scheme 1. Methods: A=K_2CO_3/acetone/reflux; B=1eq. MCPBA/CH_2Cl_2/25°C; C= 2eq. MCPBA/CH_2Cl_2/25°C; D=2eq. $KMnO_4$/ aq. acetic acid/25°C.

thiols **3** with an azolylalkyl bromide **2** in the presence of potassium carbonate in refluxing acetone resulted in azolylalkylthio compounds **4a-o**, with yields ranging from 55% to 85% (Table 1). Subsequent oxidation with one or two equivalents of *m*-chloroperbenzoic acid (MCPBA) resulted in the corresponding sulfoxides **5a-i** (Table 2) and sulfones **6a,c,d** (Table 3), respectively. In certain cases where oxidation to the sulfone proved difficult, treatment of a sulfide with two equivalents of potassium permanganate in aqueous acetic acid resulted in sulfones **6b,e,g** (Table 3). Sulfoxides were obtained in yields of 20% to 63%, while the yields of sulfones ranged from 20% to 53%.

Virology

The *in vitro* evaluation of the title compounds was carried out using a cytopathic effect inhibition method and a dye uptake assay. Compounds were initially screened against HRV-1A and HRV-39 with the results indicated in Tables 1-3. Compounds **4i** and **4l** which exhibited activity comparable to Disoxaril were then tested against an expanded panel of twenty rhinovirus serotypes to evaluate their range of activity (Table 4). To evaluate spectrum of activity, **4i** and **4l** were further tested against a panel of enteroviruses (Table 5). No activity was observed for **4i**, while **4l** was only effective against the Coxsackie B1 virus.

Molecular Modeling

The structures of an HRV-14 complex with the antiviral agent WIN V(S) and of an HRV-1A complex were obtained from the Protein Data Bank (Chemistry Department, Bldg. 555, Brookhaven National Laboratory, P.O. Box 5000, Upton, NY, 11973-5000, USA). To obtain the initial inhibitor placement, several of the conserved residues in the active sites of the two proteins were superimposed. Various azolylalkylthio, -sulfoxy, and -sulfonyl compounds were first template-forced onto the structure of WIN V(S) and then placed into the binding pocket of HRV-1A. Each inhibitor and the 17 nearest residues (the same 17 in each case) were allowed to move. Average interaction energies between the protein and inhibitors were determined from 20 cycles of molecular dynamics (300 ps at 400°K) and subsequent minimization (steepest descent + conjugate gradient until the gradient was less than 1.0 Kcal/Angstrom).

All of the compounds were easily accommodated within the binding pocket, however, no correlation was found between log[1/MIC (nM)] and the computed interaction energies. It should be noted, however, that this was only a very preliminary study which assumed that all of the compounds orient themselves in the binding pocket in the same manner as WIN V(S). This assumption is quite possibly incorrect, and thus the study could only lead to general observations. In addition, since the compounds were placed into the active site, the experiment did not consider how the compounds access the binding pocket which may play a major role in determining activity.

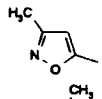
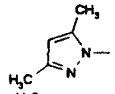
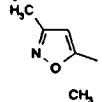
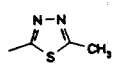
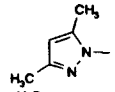
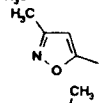
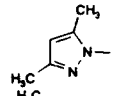
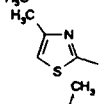
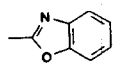
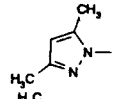
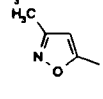
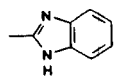
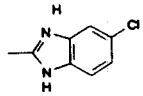
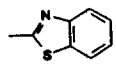
Discussion

X-ray crystallography studies have previously determined that analogs of Disoxaril can orient themselves in the binding pocket in either of two ways [5]. The isoxazole ring is either positioned directly below the pore with the rest of the molecule extending into the pocket, or the opposite can occur with the isoxazole found deep within the pocket and the oxy substituent positioned beneath the pore. It has been reported that an attempt to use a method of overlapping molecules to predict the relative orientation within the binding pocket proved unsuccessful [12]. Thus, without crystallographic data, the exact orientation that is adopted by each molecule we studied was not known. As a result, establishing structure-activity relationships is extremely difficult.

Examination of the *in vitro* data in Tables 1-3 led to several observations. The effect of the azole incorporated into the molecule was significant. The compounds that exhibited notable activity (**4g, 4i, 4l**) contained either a 3-methylisoxazolyl or 4-methylthiazolyl moiety. Conversely, those compounds containing isothiazole or 3,5-dimethylpyrazole were routinely inactive.

The nature of the thio substituent is extremely important

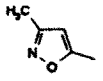
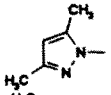
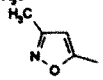
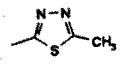
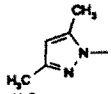
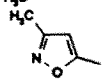
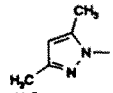
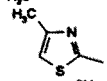
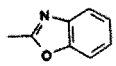
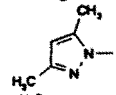
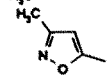
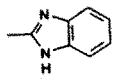
Table 1. Activity of azolylalkylthio compounds (4) Azole $-(CH_2)n-S-R$

No.	Azole	n	R	TD_{50}[a] (μg/mL)	MIC_{50} (μg/mL)[b] HRV-1A	HRV-39
4a		7		10	>10	>10
4b		6	〃	>50	>50	>50
4c		7		100	>100	>100
4d		6		100	>100	>100
4e		7		50	25	25
4f		6		>50	>50	>50
4g		7		50	25	10
4h		6		50	>50	10
4i		7		25	10	5
4j		7		25	>25	>25
4k		7		25	>25	>25
4l		6		25	10	10
4m		6		50	>50	>50
4n		6		10	>10	>10
4o		7		50	>50	10
1	Disoxaril			50	10	5

[a] Concentration at which there was a 50% reduction in cell viability compared to cell controls. [b] All tests were carried out in duplicate and MIC_{50} values were determined both visually and by a dye uptake method. Variability of results between duplicate runs and methods of determination was no more than one dilution. In the event of differing results, the higher value was reported.

Table 2. Activity of azolylalkylsulfoxy compounds (5)

Azole–$(CH_2)n$–S(=O)–R

No.	Azole	n	R	TD_{50}[a] (μg/mL)	MIC_{50} (μg/mL)[b] HRV-1A	HRV-39
5a		-		1	>1	>1
5b		6		>50	>50	>50
5c		-		100	>100	>100
5d		6		50	>50	>50
5e		-		50	>50	>50
5f		6		>50	>50	>50
5g		7		25	>25	>25
5h		6		5	>5	>5
5i		7		50	25	10
1	Disoxaril			50	10	5

[a] Concentration at which there was a 50% reduction in cell viability compared to cell controls. [b] All tests were carried out in duplicate and MIC_{50} values were determined both visually and by a dye uptake method. Variability of results between duplicate runs and methods of determination was no more than one dilution. In the event of differing results, the higher value was reported.

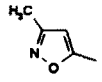
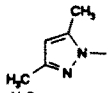
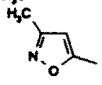
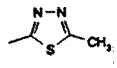
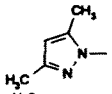
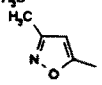
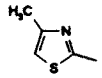
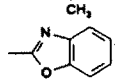
for antiviral activity. In general, little or no activity was observed with the use of the relatively small tetrazole, thiadiazole, and imidazole moieties. In addition, several of the methyltetrazole derivatives (**4a, 5a, 6a**) were quite toxic in comparison to analogous compounds. As the size of the thio substituent was increased, antiviral activity increased. Compounds **4g**, **4i** and **4l** with benzoxazole, benzimidazole, and 5-chlorobenzimidazole respectively, were the most active compounds tested. It has been reported that steric or van der Waals interactions with the binding pocket are generally the most important factors for determining biological activity [6]. Thus, it seems likely that these larger moieties better fit the pocket and presumably are better retained there.

It has also been reported that a chain length of seven carbon atoms is optimal for the oxygen-linked analogs of Disoxaril [5]. However, in the case of **4k** and **4l**, which differ only in the length of their carbon chains, **4k**, with a heptyl chain, was inactive, whereas **4l**, with a hexyl chain, was highly effective, and indeed, the best overall compound in the series. This result is a clear indication of the existence of differences in structure-activity relationships for the oxy- and thio-substituted analogs.

Finally, oxidation of the thio compounds (**4**) to the corresponding sulfoxides (**5**) and sulfones (**6**) routinely led to decreased activity. For example, **4g** had MIC_{50} values of 25 μg/mL and 10 μg/mL against HRV-1A and HRV-39 respectively, while **5g** and **6g** were both completely inactive at their toxic concentration of 25 μg/mL. Molecular modeling studies, which assumed that all three compounds are oriented in the active site in the same manner, showed only a very slight difference between the positions of the sulfoxide (**5g**) and sulfone (**6g**) derivatives and the corresponding sulfide (**4g**). The interaction energies of the

Table 3. Activity of azolylalkylsulfonyl compounds (6)

Azole–$(CH_2)n$–$\overset{O}{\overset{\|}{S}}$(=O)–R

No.	Azole	n	R	TD_{50}[a] (μg/mL)	MIC_{50} (μg/mL)[b] HRV-1A	HRV-39
6a		7		10	>10	>10
6b		6		50	>50	>50
6c		7		100	>100	>100
6d		6		100	>100	>100
6e		7		50	50	>50
6g		7		25	>25	>25
1	Disoxaril			50	10	5

[a] Concentration at which there was a 50% reduction in cell viability compared to cell controls. [b]All tests were carried out in duplicate and MIC_{50} values were determined both visually and by a dye uptake method. Variability of results between duplicate runs and methods of determination was no more than one dilution. In the event of differing results, the higher value was reported.

Table 4. Antirhinoviral activity of **4i** and **4l**

	MIC_{50}(μg/mL)[a,b]				MIC_{50}(μg/mL)[a,b]		
HRV	**4i**	**4l**	Disoxaril	HRV	**4i**	**4l**	Disoxaril
1A	10	10	10	**32**	-	1	10
1B	>25	8	25	**36**	-	>25	>25
2	-	10	>25	**39**	5	10	5
4	>25	1	0.5	**44**	1	>25	<0.5
15	-	1	5	**49**	>25	5	>25
17	-	>25	<0.5	**53**	>25	5	25
23	5	3	10	**56**	5	5	25
29	-	10	10	**63**	>25	10	25
30	5	>25	0.5	**86**	4	<0.5	0.5
31	>25	5	25	**88**	<0.5	>25	<0.5

[a] All tests were carried out in duplicate and MIC_{50} values were determined both visually and by a dye uptake method. Variability of results between duplicate runs and methods of determination was no more than one dilution. In the event of differing results, the higher value was reported. [b]MIC_{50} values greater than 25 μg/mL were considered inactive.

Table 5. Activity of **4i** and **4l** against selected enteroviruses

Enterovirus	MIC_{50}(μg/mL)[a,b]		
	4i	**4l**	Disoxaril
CoxsackieA9	>25	>25	5
CoxsackieA21	>25	>25	5
CoxsackieB1	>25	1	10
CoxsackieB4	>25	>25	10
Echo7	>25	>25	5
Echo11	>25	>25	5
Poliol	>25	>25	5

[a] All tests were carried out in duplicate and MIC_{50} values were determined both visually and by a dye uptake method. Variability of results between duplicate runs and methods of determination was no more than one dilution. In the event of differing results, the higher value was reported.
[b] MIC_{50} values greater than 25 μg/mL were considered inactive.

three compounds did not appear to be significantly different. The limitations of the modeling experiments discussed previously may be a factor in the lack of an apparent explanation for the decrease in activity observed upon oxidation.

When compounds **4i** and **4l**, which exhibited activity comparable to Disoxaril in the initial screen, were further tested against an expanded panel of rhinovirus serotypes (Table 4), **4i** was found to be effective against eight of 14 serotypes while **4l** was effective against 15 of 20. Thus, in terms of range of activity against HRV, **4l** compared favorably to Disoxaril which was active against 17 of 20. However, when tested against enteroviruses (Table 5), **4i** was completely inactive while **4l** was only effective against the Coxsackie B1 virus, indicating a narrow spectrum of activity for these compounds.

Thus, compound **4l** represents an effective agent against human rhinoviruses, *in vitro*. Future work will center on incorporating larger, more hydrophobic thio substituents into the molecule and varying the carbon chain length in attempting to improve efficacy and broaden the spectrum of activity to include the enteroviruses.

Materials and Methods

Chemistry

Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. NMR spectra were acquired on a Bruker AC-E 200 FTNMR spectrometer. Infrared spectra were acquired on a Shimadzu IR-460 spectrophotometer. Elemental analyses were performed by the Chemistry Department of The University of Alberta, Edmonton, Alberta, Canada. Silica gel used was Kieselgel 60, 230-400 mesh, from Merck.

Method A: 5-[7-[(1-Methyltetrazol-5-yl) thio]heptyl] 3-methylisoxazole (4a)

7-(3-Methylisoxazol-5-yl) heptyl bromide (0.52 g, 2. mmol) was added, while stirring, to a mixture of 5 mercapto-1-methyltetrazole (0.232 g, 2.0 mmol) and K_2CC (0.276 g, 2.0 mmol) in anhydrous acetone (20 mL). Th mixture was heated to reflux for three hours, then coole and filtered. The acetone was evaporated under reduce pressure and the residue dissolved in 50 mL CH_2Cl_2 an washed sequentially with two portions water, 5% aqueou KOH and two additional portions water. After drying ove sodium sulfate, the CH_2Cl_2 was evaporated and the residu purified by elution through a silica gel column usin methanol/dichloromethane (5:95 v/v) as eluent to giv 0.472 g (80%) of **4a** as a colorless oil.

Method B: 1-[6-[(1-Methylimidazol-2-yl) sulfoxy heptyl]-3, 5-dimethylpyrazole (5f)

4f (1.63 g, 5.5 mmol) was dissolved in 50 mL CH_2C and the solution cooled to 0°C. m-Chloroperbenzoic aci (MCPBA) (1.20 g, 5.5 mmol) was added with stirring, an the solution brought to room temperature and stirred a additional 30 minutes. Sodium bisulfite (0.5 g) was adde and the mixture washed sequentially with 5% aqueou sodium bicarbonate (50 mL), and water (2×50 mL). Th organic layer was dried over sodium sulfate and the solver evaporated to give an oily yellow residue. The residue wa eluted through a silica gel column using methano dichloromethane (5.95 v/v) as eluent to give 0.93 g (55% of **5f** as a pale yellow oil.

Method C: 5-[7-[(1-Methyltetrazol-5-yl)sulfonyl heptyl]-3 -methylisoxazole (6a)

Table 6. Physical Data of Compounds Synthesized

No.	Method[a]	Yield (%)	mp (°C)	Formula[b]	^{1}H NMR ($CDCl_3$) δ
4a	A	80	-	$C_{13}H_{21}N_5OS$	1.3-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.35 (t, J= 8Hz, 2H), 3.9 (s, 3H), 5.8 (s, 1H)
4b	A	79	-	$C_{13}H_{22}N_6S$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 3.3 (t, J=8Hz, 2H), 3.9 (s, 3H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H)
4c	A	55	62-63	$C_{14}H_{21}N_3OS_2$	1.3-2.0 (m, 10H), 2.3 (s, 3H), 2.7 (s, 3H), 2.7 (t, J=9Hz, 2H), 3.3 (t, J= 9Hz, 2H), 5.8 (s, 1H)
4d	A	72	40-42	$C_{14}H_{22}N_4S_2$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 2.7 (s, 3H), 3.3 (t, J=8Hz, 2H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H)
4e	A	58	-	$C_{15}H_{23}N_3OS$	1.5-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.05 (t, J= 8Hz, 2H), 3.6 (s, 3H), 5.8 (s, 1H), 6.85 (d, J=2Hz, 1H), 7.05 (d, J=2Hz, 1H)
4f	A	63	-	$C_{15}H_{24}N_4S$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 3.05 (t, J=8Hz, 2H), 3.6 (s,3H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H), 6.85 (d, J=2Hz, 1H), 7.05 (d, J=2Hz, 1H)
4g	A	80	-	$C_{18}H_{22}N_2OS_2$	1.4-1.9 (m, 10H), 2.45 (s, 3H), 3.00 (t, J=8Hz, 2H), 3.30 (t, J= 8Hz, 2H), 6.75 (s, 1H), 7.25-7.65 (m, 4H)
4h	A	68	-	$C_{18}H_{23}N_3OS$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 3.30 (t, J=8Hz, 2H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H), 7.15-7.75 (m, 4H)
4i	A	72	84-85	$C_{18}H_{23}N_3OS$	1.30-1.75 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 5.8 (s, 1H), 7.10-7.20 (m, 4H), 7.5 (s, 1H)
4j	A	56	-	$C_{18}H_{22}ClN_3OS$	1.3-1.75 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 5.8 (s, 1H), 7.10(d, J=2Hz, 1H), 7.18 (d, J=2Hz, 1H), 7.25 (s, 1H)
4k	A	85	110-112	$C_{18}H_{22}ClN_3S_2$	1.3-1.9 (m, 10H), 2.45 (s, 3H), 3.0 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 6.75 (s, 1H), 7.10 (d, J=2Hz, 1H), 7.18 (d, J=2Hz, 1H), 7.25 (s, 1H)
4l	A	64	106-107	$C_{17}H_{20}ClN_3S_2$	1.3-1.8 (m, 8H), 2.45 (s, 3H), 3.0 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 6.75 (s, 1H), 7.10 (d, J=2Hz, 1H), 7.18 (d, J=2Hz, 1H), 7.25 (s, 1H)
4m	A	72	129-130	$C_{17}H_{20}ClN_3S_2$	1.3-1.8 (m, 8H), 2.15 (s, 3H), 2.8 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 7.10 (d, J=2Hz, 1H), 7.18 (d, J=2Hz, 1H) 7.25 (s, 1H), 8.15 (s, 1H), 9.25 (br, 1H)
4n	A	64	86-87	$C_{16}H_{18}ClN_3S_2$	1.3-1.8 (m, 8H), 2.80 (t, J=8Hz, 2H), 3.3 (t, J= 8Hz, 2H), 6.95 (d, J=2Hz, 1H), 7.10 (d, J=2Hz, 1H), 7.18 (d, J=2Hz, 1H), 7.25 (s, 1H), 8.35(d, J=2Hz, 1H)
4o	A	70	54-57	$C_{18}H_{22}N_2OS_2$	1.30-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3. 3 (t, J= 8Hz, 2H), 5.8 (s, 1H), 7.24-7.88 (m, 4H)
5a	B	40	-	$C_{13}H_{21}N_5O_2S$	1.5-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.45 (t, J= 8Hz, 2H), 4.35 (s, 3H), 5.8 (s, 1H)
5b	B	20	-	$C_{13}H_{22}N_6OS$	1.5-1.9 (m, 8H), 2.2 (s, 6H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 4.35 (s, 3H), 5.75 (s, 1H)
5c	B	40	80-82	$C_{14}H_{21}N_3O_2S_2$	1.5-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 2.9 (s, 3H), 3.45 (t, J= 9Hz, 2H), 5.8 (s, 1H)
5d	B	24	-	$C_{14}H_{22}N_4OS_2$	1.5-1.9 (m, 8H), 2.2 (s, 6H), 2.9 (s, 3H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H)
5e	B	40	-	$C_{15}H_{23}N_3O_2S$	1.5-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.45 (t, J= 9Hz, 2H), 4.0 (s, 3H), 5.8 (s, 1H), 7.05 (d, J=2Hz, 1H) 7.15 (d, J=2Hz, 1H)
5f	B	55	-	$C_{15}H_{24}N_4OS$	1.3-1.8 (m, 8H), 2.2 (s, 6H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 4.0 (s, 3H), 5.75 (s, 1H), 7.1 (d, J=2Hz, 1H) 7.2 (d, J=2Hz, 1H)

Table 6. Physical Data of Compounds Synthesized (cont'd)

No.	Method[a]	Yield (%)	mp (°C)	Formula[b]	^{1}H NMR ($CDCl_3$) δ
5g	B	63	-	$C_{18}H_{22}N_2O_2S_2$	1.4-1.9 (m, 10H), 2.45 (s, 3H), 3.00 (t, J=8Hz, 2H), 3.45 (t, J= 9Hz, 2H), 6.75 (s, 1H), 7.45-7.90 (m, 4H)
5h	B	40	-	$C_{18}H_{23}N_3O_2S$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H), 7.50-8.00 (m, 4H)
5i	B	23	56-58	$C_{18}H_{23}N_3O_2S$	1.30-1.90 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.45 (t, J= 9Hz, 2H), 5.8 (s, 1H), 7.30-7.50 (m, 4H), 7.75 (br, 1H)
6a	C	53	58-60	$C_{13}H_{21}N_5O_3S$	1.3-1.9 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.45 (t, J= 8Hz, 2H), 4.3 (s, 3H), 5.8 (s, 1H)
6b	D	20	-	$C_{13}H_{22}N_6O_2S$	1.3-1.9 (m, 8H), 2.2 (s, 6H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 4.30 (s, 3H), 5.75 (s, 1H)
6c	C	45	80-81	$C_{14}H_{21}N_3O_3S_2$	1.3-1.9 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 2.9 (s, 3H), 3.45 (t, J= 9Hz, 2H), 5.8 (s, 1H)
6d	C	23	50-51	$C_{14}H_{22}N_4O_2S_2$	1.3-1.8 (m, 8H), 2.2 (s, 6H), 2.9 (s, 3H), 3.45 (t, J=9Hz, 2H), 3.95 (t, J= 8Hz, 2H), 5.75 (s, 1H)
6e	D	41	54-55	$C_{15}H_{23}N_3O_3S$	1.5-1.8 (m, 10H), 2.3 (s, 3H), 2.7 (t, J=8Hz, 2H), 3.45 (t, J= 9Hz, 2H), 4.0 (s, 3H), 5.8 (s, 1H), 7.00 (d, J=2Hz, 1H), 7.10 (d, J=2Hz, 1H)
6g	D	42	-	$C_{18}H_{22}N_2O_3S_2$	1.4-1.9 (m, 10H), 2.45 (s, 3H), 3.00 (t, J=8Hz, 2H), 3.45 (t, J= 9Hz, 2H), 6.75 (s, 1H), 7.50-8.05 (m, 4H)

[a] Methods are as described in the experimental section. [b]All analyses were within ±0.4 % of the calculated values.

A mixture of **4a** (0.59 g, 2.00 mmol) and MCPBA (0.82 g, 4.00 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for three hours. The mixture was then washed sequentially with 2N NaOH (20 mL) and water (2×50 mL). The organic phase was dried over sodium sulfate and the solvent evaporated. The residue was treated with 20 mL hexane/ethyl acetate (4:1 v/v) and filtered. The remaining solid was recrystallized from ether to provide 0.35 g (53%) of **6a** as colorless prisms.

Method D: 2- [7-[(Benzoxazol-2-yl) sulfonyl] heptyl]-4 -methylthiazole (6g)

4g (1.362 g , 3.90 mmol) was dissolved in 25 mL glacial acetic acid. After the addition of 5 mL water, potassium permanganate (1.24 g, 7.80 mmol) was added to the solution, while stirring at room temperature. The mixture was stirred 30 minutes and then 10 mL 30% H_2O_2 added, followed by 10 mL ice water. The water and acetic acid were evaporated under reduced pressure to give 1.50 g of a dark yellow oil. Elution through a silica gel column using hexane/ethyl acetate (3:2 v/v) gave 0.586 g (42%) of **6g** as a pale yellow oil.

Using methods A-D, compounds **4**, **5**, and **6** as indicated in Tables 1-3 were prepared. Physical data for all compounds synthesized is summarized in Table 6.

Virology

The experiments were performed by a cytopathic effect inhibition method and a crystal violet dye uptake assay as described previously [11].

Molecular Modeling

Computational results were obtained using software programs from Biosym Technologies Inc. of San Diego. Molecular dynamics and molecular mechanics calculations were carried out with the Discover program using the CVFF forcefield. The Insight II molecular modeling system was used to view the results.

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