4-Benzyloxy-γ-Sultone Derivatives: Discovery of a Novel Family of Non-Nucleoside Inhibitors of Human Cytomegalovirus and Varicella Zoster Virus

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Received November 21, 2008

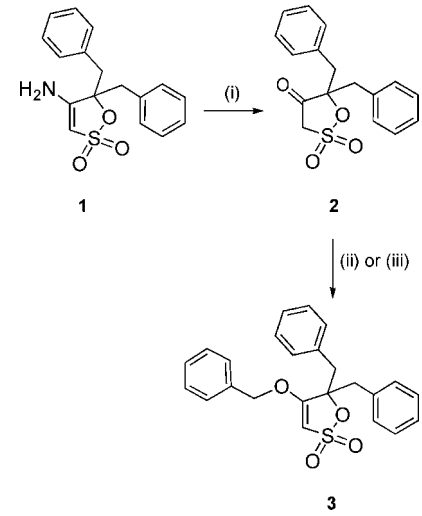
We report the synthesis and antiviral activity of a new family of non-nucleoside antivirals, derived from the 4-keto-1,2-oxathiole-2,2-dioxide (β-keto-γ-sultone) heterocyclic system. Several 4- and 5-substituted-5*H*-1,2-oxathiole-2,2-dioxide derivatives were found to have a selective inhibitory activity against human cytomegalovirus (HCMV) and varicella zoster virus (VZV) replication in vitro, being inactive against a variety of other DNA and RNA viruses. A structure−activity relationship (SAR) study showed that the presence of a benzyl at the 5 position and a benzyloxy substituent at the 4 position are a prerequisite for anti-HCMV and VZV activity. The novel compounds do not show cross-resistance against a wide variety of mutant drug-resistant HCMV strains, pointing to a novel mechanism of antiviral action.

Introduction

Herpes virus infections in humans are found worldwide and are among the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients. Although generally benign in the immunocompetent host, human cytomegalovirus (HCMV[a]) infection is associated with clinical symptoms such as pneumonia, retinitis, and gastrointestinal disease in the immunocompromised, as well as congenital birth defects in neonates.[1−3] Other herpesviruses such as varicella zoster virus (VZV) are widespread among the human population, and VZV is known to be responsible for a primary infection of varicella (chicken pox) in young children.[4,5] Reactivation of latent VZV infection in the ganglia is associated with herpes zoster (shingles), a highly debilitating illness characterized by persistent neuropathic pain.[6,7] There are currently five FDA-approved drugs used for the treatment of HCMV infections, namely ganciclovir or its prodrug valganciclovir, cidofovir, foscarnet, and the antisense oligonucleotide fomivirsen, whereas the drug of choice for the treatment of VZV infections is acyclovir.[8,9] However, the currently available compounds suffer from a number of limitations including poor oral bioavailability and/or toxicity as well as the emergence of single and multiple drug resistance.[10,11] All of the licensed compounds (with the exception of fomivirsen) are nucleoside-based antivirals that act by targetting the viral DNA polymerase. There are a number of nucleoside analogues in preclinical development (i.e., the (β-L-ribofuranosyl)benzimidazole derivative maribavir or 1263-W94[12] and the (β-D-ribofuranosyl)benzimidazole derivatives BDCRB and TCRB[13]) that act as "non-nucleoside inhibitors" of HCMV by targetting processing, synthesis, and/or maturation of viral DNA. The lipophilic alkyl furano pyrimidine dideoxynucleosides act against HCMV by inhibiting an early event in the HCMV infection process.[14] Also, several non-nucleoside analogues are described as HCMV (and VZV) inhibitors, such as the 4-*oxo*-4,7-dihydrothieno[2,3-β]pyridines,[15] 4-hydroxyquinoline carboxamides,[16] and 4-*oxo*-dihydroquinolines.[17] These classes of compounds inhibit the viral DNA polymerases. The non-nucleoside inhibitor BAY 38-4766 (tomeglovir) inhibits HCMV by targetting HCMV DNA maturation via the UL89 and UL59 gene products.[18,19] Current progress on the development of human herpesvirus inhibitors have been recently reviewed.[20−25]

We previously reported[26] studies on the reactivity toward electrophiles and amines on simple model substrates of the scarcely explored 4-amino-1,2-oxathiole-2,2-dioxide (β-amino-γ-sultone) heterocyclic system **1** (Scheme 1). We found that acid hydrolysis worked smoothly in this system, leading to the

Scheme 1[a]



[a] Reagents and conditions: (i) 4.5 N HCl methanol, rt; (ii) BnBr, NaH, THF, rt; (iii) BnBr, K_2CO_3, TEBAI, acetonitrile, rt.

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[a] Abbreviations: HCMV, human cytomegalovirus; VZV, Varicella zoster virus; SAR, structure−activity relationship; BDCRB, 2-bromo-5,6-dichloro-1-(β-D-ribofuranosy)benzimidazole; TCRB, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole; TEBAI, tetrabutylammonium iodide; HSV-1, herpes simplex virus type 1; TK−, thymidine kinase-deficient; ACV, acyclovir; HSV-2, herpes simplex virus type 2; HEL, human embrionic lung; MCC, minimal cytotoxic concentration; GCV or DHPG, ganciclovir; PFA, foscarnet; HPMPC, cidofovir; PMEDAP, 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine; HPMPA, 9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine; HPFC, High performance flash chromatography.

10.1021/jm8014662 CCC: $40.75
Published on Web 02/18/2009

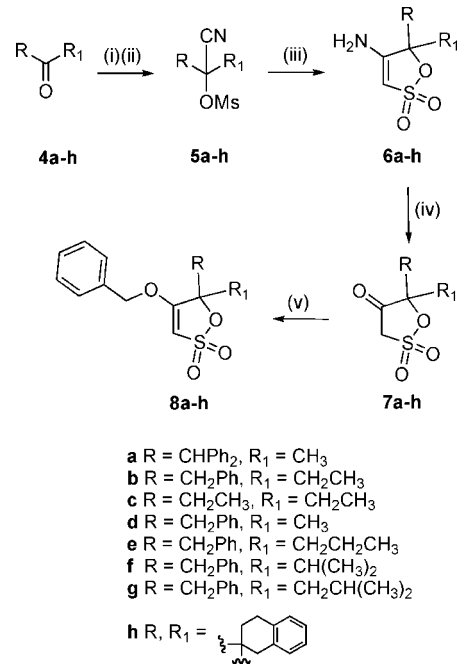
β-keto-γ-sultone compound **2**.[26] Alternative reported methods for the synthesis of the β-keto-γ-sultone heterocycle involved cyclization of α-(carboxyethyl)alkyl alkanesulfonates.[27] Alkylation of **2** with benzyl bromide in the presence of a base (Scheme 1) gave the 4-benzyloxy sultone derivative **3**. This compound showed a very limited inhibitory activity against HCMV ($EC_{50} \geq 50$ μM) and VZV ($EC_{50} \geq 5$ μM) replication in cell culture, being inactive against a variety of other DNA and RNA viruses. These results prompted us to explore the biological potential of this readily available heterocyclic system. We describe herein the results of this work that has led to the discovery of an entirely new class of non-nucleoside inhibitors of human cytomegalovirus (HCMV) and varicella zoster virus (VZV). Structure−activity relationships (SAR) were focused on the substituents at the C-4 and C-5 positions of the sultone moiety. These studies showed that the presence of aromatic rings at both positions are a prerequisite for anti-HCMV and VZV activity. The synthesis, biological evaluation, and SAR studies of this new family of compounds is reported.

Results and Discussion

Chemistry. The known β-keto-γ-sultone intermediate **2** was prepared, as previously described by our group,[26] by acid hydrolysis of the enamine derivative **1** with 4.5 N HCl in methanol (Scheme 1). Alkylation of intermediate **2** with benzyl bromide in the presence of a base to give **3** was explored under different reaction conditions. Thus, when **2** was reacted, at room temperature, with 2 equiv of benzyl bromide in dry THF in the presence of 2 equiv of NaH, the 4-*O*-benzyl derivative **3** was isolated in 40% yield, together with unreacted starting material (27%), after 24 h. Increasing amounts of benzyl bromide (3 equiv) and base (3 equiv) slightly improved the yield of **3** (53% vs 40%). However, reaction of **2** with benzyl bromide (1 equiv) in acetonitrile under phase-transfer-catalyzed conditions,[28] K_2CO_3 (1.5 equiv) as base, and tetrabutylammonium iodide (TEBAI) as catalyst, afforded the desired compound **3** in 70% yield, after 3 h. Thus, under these alkylation conditions, the yield of **3** was significantly improved by using lower amounts of base and benzyl bromide and shorter reaction times.

Initial structure−activity relationship studies on this sultone template were focused on the C-5 substituents (Scheme 2). The number and position of benzyl groups at the 5 position was first explored. Compounds **8a**−**c** were prepared from the corresponding β-keto-γ-sultone derivatives **7a**−**c.** The synthesis of intermediates **7a**−**c** was carried out by starting from the appropriate commercially available ketones **4a**−**c** following a four-step procedure involving cyanohydrin formation, mesylation, base-cyclization, and hydrolysis as previously described.[26] Thus, treatment of **4a**−**c** with trimethylsilyl cyanide in the presence of equimolecular amounts of $BF_3 \cdot Et_2O$ afforded the corresponding cyanohydrines, which upon treatment with mesyl chloride in the presence of triethylamine, as base, yielded the desired alkyl sulfonate derivatives **5a**−**c** in 63%, 74%, and 73% yields, respectively. Reaction of **5a**−**c** with Cs_2CO_3 gave the desired β-amino-γ-sultone derivatives **6a**−**c** in moderate to good yields (52−81%). Acid hydrolysis (4.5 N HCl in methanol) of compounds **6a**−**c** proceeded also in good yields to provide the β-keto-γ-sultone derivatives **7a**−**c**. These keto compounds (**7a**−**c**) were then treated with benzyl bromide under the optimized phase-transfer-catalyzed alkylation conditions described above, to afford the target 4-benzyloxy derivatives **8a**−**c** in 31%, 53%, and 57% yields, respectively. Antiviral studies indicated that the presence of both a benzyl and an ethyl group at the 5-position of the sultone moiety (compound **8b**) improved

Scheme 2[a]



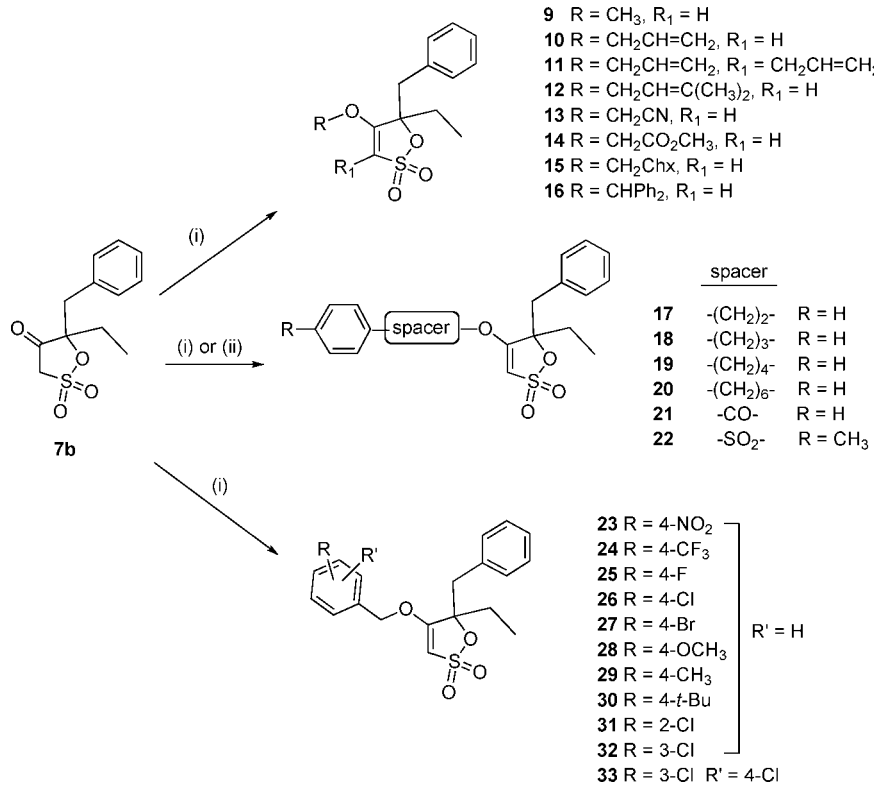
[a] Reagents and conditions: (i) TMSCN, $BF_3 \cdot Et_2O$, dichloromethane, rt; (ii) MsCl, dichloromethane, TEA, 0 °C; (iii) Cs_2CO_3, acetonitrile, rt; (iv) 4.5 N HCl methanol, rt; (v) BnBr, K_2CO_3, TEBAI, acetonitrile, rt.

the inhibitory potency against HCMV and VZV. Thus, replacement of the 5-ethyl group of compound **8b** by alkyl groups of different length (compounds **8d**,**e**) and by branched-alkyl groups (compounds **8f**,**g**) was next undertaken. The synthesis of compounds **8d**−**g** (Scheme 2) was carried out by following a similar four-step procedure to that described for the synthesis of **8a**−**c**, starting from the appropriate commercially available ketones **4d**−**g** in good yields. Similarly, compound **8h** (the conformationally restricted analogue of **8b**) was prepared from the commercially available β-tetralone **4h** (Scheme 2). Substitution of the 5-ethyl group of **8b** by other alkyl groups resulted in inactive compounds as will be mentioned below.

Further structural modifications were focused on the 4-benzyloxy substituent of **8b** while the 5-benzyl and 5-ethyl substituents were maintained (Scheme 3). To determine the role of the phenyl group at the 4 position in the biological activity, a first series of 4-substituted alkyloxy sultone derivatives was prepared in which the phenyl group was absent (compound **9**) or replaced by a variety of groups of different nature (compounds **10**−**15**). Other aromatic substituents such as diphenylmethyl at this position were also introduced (compound **16**). Compounds **9**−**16** were prepared from the keto precursor **7b**, following the optimized alkylation procedure described above for the synthesis of compound **3**. Thus, treatment of **7b** with the corresponding alkyl bromides in the presence of K_2CO_3 (1.5 equiv) as base and TEBAI as catalyst afforded, exclusively, the 4-*O*-alkylated derivatives **9**, **12**−**16** (Scheme 3) in moderate to good yields (32−67%). However, in the reaction of **7b** with allyl bromide, the 4-*O*-allylated derivative **10** together with the C,*O*-diallylated compound **11** were isolated in 70% and 12% yield, respectively. All of these compounds were inactive against HCMV and VZV replication, which indicated a key role for a phenyl group at the 4 position.

Modifications of the length and nature of the methylene spacer between the phenyl group and the oxygen attached to the 4-position of the sultone moiety of compound **8b** were next carried out (Scheme 3). Thus, methylene spacers of different

Scheme 3[a]



[a] Reagents and conditions: (i) RBr, K_2CO_3, TEBAI, acetonitrile, 40 °C; (ii) PhCOCl or *p*-CH_3PhSO_2Cl, NaH 60%, THF, rt.

length (compounds **17**−**20**) or spacers of different nature (compounds **21**, **22**) were explored. Treatment of **7b** with phenylethyl bromide, 3-phenylpropyl bromide, 4-phenylbutyl bromide, or 6-phenyl hexyl bromide under the optimized phase-transfer-catalyzed conditions (K_2CO_3, TEBAI), as described above, gave compounds **17**−**20** in moderate to good yields (40−76%). The 4-*O*-acyl derivatives **21** and **22**, in which the methylene spacer of compound **8b** was replaced by a −CO− or by a $-SO_2-$ spacer, were synthesized in moderate yields (41% and 30% yields, respectively) by reaction of the keto intermediate **7b** with benzoyl chloride or *p*-toluensulfonyl chloride in dry THF in the presence of NaH.

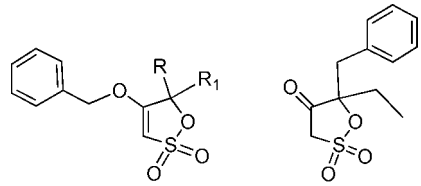
Finally, a variety of substituents of different electronic and steric properties were incorporated at the phenyl ring of the 4-benzyloxy moiety of compound **8b** to determine the role of such substitution on HCMV and VZV inhibition. The target compounds **23**−**33** (Scheme 3) were prepared in moderate to good yields (40−81%) by reaction of **7b**, with the appropriate commercially available substituted benzyl bromides following the optimized alkylation procedure described above for compound **3**.

Antiviral Activity. Compounds **8b**, **17**, **26**, and **28** lacked inhibitory activity against a wide variety of viruses, including parainfluenza-3 virus, reovirus-3, Sindbis virus, Coxackie virus B4, Punta Toro virus in Vero cell cultures, and vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncitial virus in HeLa cell cultures, and herpes simplex virus type 1 (HSV-1) (KOS) and a thymidine kinase-deficient (TK−) acyclovir-resistant (ACV^r) strain, HSV-2, vaccinia virus, and vesicular stomatitis in HEL cell cultures. However, they showed antiviral activity against human cytomegalovirus (HCMV) and varicella zoster virus (VZV). Therefore, a variety of novel 4- and 5-substituted-γ-sultone derivatives and the 4-keto-γ-sultone intermediate **2** were evaluated against HCMV and VZV strains in human embryonic lung (HEL) cells,[30] and the results were compared to those obtained for the reference compounds ganciclovir, cidofovir, acyclovir, and brivudin (Tables 1 and 2). Several of the compounds showed pronounced anti-HCMV and anti-VZV activity. Dual anti-HCMV and anti-VZV activity has been also recently described for a series of bicyclic furanopyrimidine deoxynucleosides,[31,32] 1-acylazetidine derivatives,[33] and substituted imidazo[1,2-*a*]pyridine derivatives.[34]

The following structure−activity relationships were observed. The substituents at the C-5 position on 4-benzyloxy-γ-sultone derivatives had a pronounced influence on antiviral activity (Table 1). As shown in Table 1, the 5-dibenzyl-substituted derivative **3** weakly blocked HCMV- or VZV-induced plaque formation with an EC_{50} value of ≥ 50 μM or ≥ 5 μM, respectively, and a minimal cytotoxic concentration (MCC) or 50% cytostatic concentration (CC_{50}) values of ≥ 200. Interestingly, replacement of one of the benzyl groups by an ethyl group (compound **8b**) markedly enhanced the antiviral activity against both HCMV strains (EC_{50} = 13 and 9.3 μM) and VZV strains (EC_{50} = 6.4 and 5.6 μM) while retaining a relatively low cytotoxicity (MCC $\geq$ 50). Thus, the therapeutic index (ratio $CC_{50}/EC_{50} \geq 5-10$) of compound **8b** was improved compared to that of the 5-dibenzyl-substituted derivative **3** (ratio $CC_{50}/EC_{50} \leq 4$). Substitution of both benzyl groups by ethyl groups (compound **8c**) led to a marked decrease in antiviral activity. Replacement of the 5-ethyl group of compound **8b** by alkyl groups of different length (compounds **8d,e**) or by branched-alkyl groups (compounds **8f**,**g**) annihilated the antiviral activity. Also, the conformationally restricted analogue of **8b** (compound **8h**) was inactive. From these results, it appears that the concomitant presence of a benzyl and an ethyl group at the C-5 position is required for antiviral activity.

It was also observed that the benzyloxy moiety at the 4 position of **8b** was essential or preferable for its antiviral activity

Table 1. Activity of 5-Substituted 4-Benzyloxy-γ-sultone Derivatives **3**, **8a**−**h**, and 4-Keto γ-Sultone Intermediate **2** against Human Cytomegalovirus (HCMV) and Varicella Zoster Virus (VZV) in HEL Cell Cultures



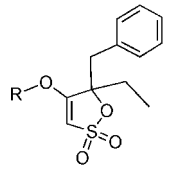
3, 8a-h **2**

			EC_{50} (μM)					
			anti-HCMV activity[a]		anti-VZV activity[b]		Cytotoxicity (μM)	
Compd	R	R_1	AD-169	Davis	OKA (TK^+)	07/1 (TK^-)	MCC[c]	CC_{50}[d]
3	CH_2Ph	CH_2Ph	50	>50	>5	5	200	>200
8a	$CHPh_2$	CH_3	>80	>400	>80	>80	≥400	>200
8b	CH_2Ph	CH_2CH_3	13	9.3	6.4 (YS strain 3.6)	5.6	≥50	>200
8c	CH_2CH_3	CH_2CH_3	>400	234	175	155	>400	>200
8d	CH_2Ph	CH_3	>200	>200	306	>400	>400	68
8e	CH_2Ph	$CH_2CH_2CH_3$	>400	>400	>80	>400	≥400	>200
8f	CH_2Ph	$CH(CH_3)_2$	>400	>400	>80	>16	≥80	>200
8g	CH_2Ph	$CH_2CH(CH_3)_2$	>400	>400	>80	>80	≥80	102
8h			>400	>80	80	>16	≥80	131
2	-	-	>400	400	10.0	10.5	>100	>200
ganciclovir			2.0	3.6			>400	134
cidofovir			0.3	0.5			>150	74
acyclovir					1.1	72	>200	733
brivudin					0.015	140	>150	600

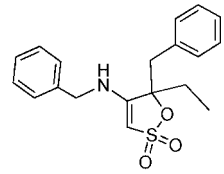
[a] Effective concentration required to inhibit by 50% the HCMV-induced cytopathicity in human embryonic lung (HEL) fibroblast cell cultures at 7 days post infection, as described in refs 14 and 30, virus input was 100 plaque-forming units (PFU). [b] Effective concentration required to reduce VZV plaque formation after 5 days in HEL cell cultures by 50%, as compared to untreated controls. [c] Compound concentration required to cause a microscopically visible alteration of normal cell morphology. [d] Cytotoxic concentration required to reduce cell growth by 50%.

because the 4-keto-γ-sultone intermediate **2** displayed no (for HCMV) or less (2-fold) activity (for VZV) (Table 1). Thus, the next phase of SAR investigations focused on modifications at the 4-benzyloxy substituent of **8b** (Table 2). Substitution of the phenyl group at the 4 position by other groups of different nature (compounds **9**−**16**) invariably annihilated the activity against HCMV or markedly weakened the activity against VZV. Regarding the length and nature of the methylene spacer between the phenyl group and the oxygen attached to the 4-position, compounds **17** and **18**, bearing an ethyl and a propyl spacer, respectively, retained the potency of the methylene analogue **8b** against HCMV and VZV but with a slightly

Table 2. Activity of 4-Substituted γ-Sultone Derivatives **9**−**34** against Human Cytomegalovirus (HCMV) and Varicella Zoster Virus (VZV) in HEL Cell Cultures



9,10,12-33



34

		EC_{50} (μM)					
		anti-HCMV activity[a]		anti-VZV activity[b]		cytotoxicity (μM)	
compd	R	AD-169	Davis	OKA (TK^+)	07/1 (TK-)	MCC[c]	CC_{50}[d]
9	CH_3	>400	>400	168	285	>400	>200
10	$CH_2CH{=}CH_2$	>400	>400	>16	>16	80	>200
12	$CH_2CH{=}C(CH_3)_2$	>80	>80	59	52	400	112
13	CH_2CN	>80	235	199	199	>400	>200
14	$CH_2CO_2CH_3$	>400	>400	>400	>400	>400	>200
15	CH_2Ch_x	>200	>200	20	7.0	≥200	>200
16	$CHPh_2$	>400	>400	>80	>80	≥80	>200
17	$(CH_2)_2Ph$	6.9	9.3	5.7	7.5	≥20	48
18	$(CH_2)_3Ph$	9.0	8.7	>3.2	6.5	≥20	133
19	$(CH_2)_4Ph$	>3.2	7.8	6.2	>20	≥20	99
20	$(CH_2)_6Ph$	<3.2	6.4	8.7	8.4	≥20	<200
21	COPh	>400	179	>400	>400	>400	>200
22	$SO_2Ph(4\text{-}CH_3)$	>80	>80	>80	>80	400	109
23	$CH_2Ph\ (4\text{-}NO_2)$	>400	>80	80	54	≥80	<200
24	$CH_2Ph\ (4\text{-}CF_3)$	12	8	7.7	6.7	≥16	99
25	$CH_2Ph\ (4\text{-F})$	15	7	8.6 (YS strain 10.4)	8.6 (YS-R strain 9.3)	>50	>50
26	$CH_2Ph\ (4\text{-Cl})$	10.4	9.7	7.6 (YS strain 10)	5.7	≥50	<200
27	$CH_2Ph\ (4\text{-Br})$	10	6	8.3	6.3	80	171
28	$CH_2Ph\ (4\text{-}OCH_3)$	200	142	120	106	>200	>200
29	$CH_2Ph\ (4\text{-}CH_3)$	7.2	5.9	6.4	5.9	≥16	41.5
30	$CH_2Ph\ (4\text{-}t\text{-Bu})$	20[e]	≥5[e]	6.4[e]	7.3[e]	≥400	>200
31	$CH_2Ph\ (2\text{-Cl})$	>4	>4	8.7 (YS strain >5)	10	≥20	38
32	$CH_2Ph\ (3\text{-Cl})$	>16	8	7.3	6.7	≥20	50
33	$CH_2Ph(3,4\text{-diCl})$	6.5	7.2	>3.2	>3.2	≥20	36.7
34[f]		>80	>80	37	32	≥80	92
ganciclovir		2.3	4.6			>400	134
cidofovir		0.3	0.5			>150	74
acyclovir				1.1	74	>200	733
brivudin				0.015	≥150	>150	600

[a] Effective concentration required to inhibit by 50% the HCMV-induced cytopathicity in human embryonic lung (HEL) fibroblast cell cultures at 7 days post infection, as described in refs 14 and 30. Virus input was 100 plaque-forming units (PFU). [b] Effective concentration required to reduce VZV plaque formation after 5 days in HEL cell cultures by 50%, as compared to untreated controls. [c] Compound concentration required to cause a microscopically visible alteration of normal cell morphology. [d] Cytotoxic concentration required to reduce cell growth by 50%. [e] No complete inhibition at higher drug concentration. [f] The synthesis of compound **34** has been described in ref 26.

increased cytostatic activity. Longer methylene linkers (i.e., $n > 3$, compounds **19** and **20**) showed further increased cytotoxicity (MCC values for these compounds were in the same range as their EC_{50} values). Substitution of the methylene spacer of **8b** by a carbonyl or sulfoxide group (compounds **21** and **22**) resulted in inactive compounds.

Finally, the influence of substitutions on the 4-benzyloxy aromatic ring on the antiviral activity and cytotoxicity was examined. Among the 4-substituted derivatives, the tested compounds can be classified in three groups: a group of (virtually) inactive compounds (**23** and **28** with a NO_2 or a OCH_3 group), a group of active compounds, with an EC_{50} between 6 and 15 μM, bearing electron-withdrawing substituents such as CF_3 or F (compounds **24** and **25**) or alkyl groups (**29** and **30** with a CH_3 or a *t*-Bu) that were more cytotoxic than the unsubstituted derivative **8b**, and the 4-chloro and 4-bromo derivatives **26** and **27** that show antiviral activity at ca. 6−10 μM with relatively low cytotoxicity. Thus, the selectivity indices (ratio CC_{50} to EC_{50}) for compounds **26** and **27** were similar to that of the unsubstituted analogue **8b**. On the other hand, an increased toxicity was noticed when a chlorine atom at the 3-position or disubstitution at the 3- and 4-positions were present (compounds **32** and **33**).

Compound **26** was also evaluated against a panel of mutant HCMV strains that had been selected for resistance against a wide variety of anti-HCMV compounds including DHPG (ganciclovir), PFA (foscarnet), (*S*)-HPMPC (cidofovir), PMEDAP, (*S*)-HPMPA, and ACV (acyclovir). Interestingly, **26** kept full antiviral sensitivity against all strains evaluated (Table 3). Similar observations were made for compound **24**, suggesting that the novel compounds most likely act through another antiviral target than the currently existing antiviral compounds (Table 3). It is, however, unclear which stage in the infection cycle of HCMV and VZV the compounds are targetting. (Cross)-resistance studies against mutant HCMV strains that are resistant to the currently existing benzimidazoles and non-nucleoside inhibitors may reveal whether the compounds share a similar or a different mechanism of antiviral action.

Conclusions

In conclusion, we report on the discovery of a new family of non-nucleoside anti-HCMV and anti-VZV agents based upon

Table 3. Anti-HCMV Activity of **26** against Drug-Resistant HCMV Strains[a]

	wild-type HCMV		mutant HCMV (AD169) virus strains					
compd	Davis	AD169	AD/DHPG^R clone 4	AD/PFA^R clone C	AD/HPMPC^R clone 5	AD/PMEDAP^R clone 4	AD/HPMPA^R clone 2	AD/ACV^R clone 1
26	11 ± 0.71	11 ± 1.3	11 ± 2.1	9.6 ± 0.64	11 ± 8.2	12 ± 5.6	9.9 ± 0.98	11 ± 1.8
GCV (DHPG)	0.66 ± 0.34	0.7 ± 0.39	4.3 ± 1.5	2.6 ± 0.85	4.0 ± 2.0	3.5 ± 3.1	1.2 ± 0.75	0.69 ± 0.26
foscarnet (PFA)	11 ± 0.71	13 ± 4.2	20 ± 9.2	95 ± 6.6	11 ± 4.1	63 ± 24	13 ± 0.75	35 ± 21
cidofovir (HPMPC)	0.069 ± 0.026	0.076 ± 0.028	0.74 ± 0.85	0.045 ± 0.007	1.0 ± 0.76	0.092 ± 0.075	0.55 ± 0.29	0.095 ± 0.022
PMEDAP	7.7 ± 0.35	8.4 ± 2.7	1.9 ± 0.99	25 ± 13	3.5 ± 1.8	37 ± 12	0.82 ± 0.040	>50
HPMPA	0.2 ± 0	0.17 ± 0.11	2.1 ± 1.5	0.036 ± 0.006	2.1 ± 1.7	0.12 ± 0.097	1.9 ± 1.4	0.080 ± 0.014
acyclovir (ACV)	7.5 ± 3.5	15 ± 6.5	4.3 ± 0.87	176 ± 34	7.6 ± 2.2	125 ± 106	1.0 ± 0.87	200 ± 0

[a] 50% Effective concentration or compound concentration required to inhibit virus-induced cytopathicity by 50%.

the easily available β-keto-γ-sultone template. We have shown that substituents at the 4 and 5 positions of the γ-sultone moiety strongly influence the activity/toxicity of these compounds. The presence of a benzyl group at the 5 position and a benzyloxy substituent at the 4 position are a prerequisite for anti-HCMV and VZV activity. From the synthesized compounds, the 4-chloro and 4-bromobenzyloxy sultone derivatives **26** and **27** and the unsubstituted analogue **8b** ranked among the most potent and selective inhibitors against HCMV and VZV. All compounds showed similar activity against TK+ and nucleoside drug-resistant TK− VZV strains, thus indicating a mechanism of action independent of the virus-encoded thymidine kinase as expected from their non-nucleoside structure. Also, compounds **24** and **26** were equally inhibitory against a wide variety of drug-resistant HCMV strains, suggesting another antiviral target than that of the currently existing compounds. These compounds rank among the few classes of non-nucleoside inhibitors with dual anti-HCMV and VZV activity described so far.

Experimental Section

Chemical Procedures. Melting points were determined in a Reichert−Jung Thermovar hot-stage microscope equipped with a polarizer. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. The purity of the compounds was ascertained through combustion analysis. Microanalyses were obtained a Heraeus CHN-O-RAPID instrument. The analytical results are within ±0.4% of the theoretical values. Mass spectra were measured on a quadropole mass spectrometer equipped with an electrospray source (Hewlett-Packard, LC/MC HP 1100). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker 300 Avance and a Varian XL-500 spectrometer operating at 300 and 500 MHz and at 75 and 125 MHz, respectively, with Me_4Si as the internal standard. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck). Separations on silica gel were performed by preparative centrifugal circular thin-layer chromatography (CCTLC) on a Chromatotron (Kiesegel 60 PF_{254} gypsum-based (Merck), layer thickness of 1 mm, flow rate of 5 mL/min). Flash column chromatography was performed with silica gel 60 (230−400 mesh)(Merck). Liquid chromatography was performed using a force flow (flash chromatography) HPFC Horizon system (Biotage) with Flash 25 M cartridges (KP-Sil Silica, 60 Å, 40−63 μM). Triethylamine, dichloromethane, and acetonitrile were dried by refluxing over calcium hydride. Tetrahydrofurane was dried by refluxing over sodium.

Synthesis of Compounds 5a−h: General Procedure. To a solution of the corresponding ketone **4a−h** (4 mmol) in dichloromethane (10 mL), trimethylsilyl cyanide (0.80 mL, 6 mmol) and boron trifluoride diethyl etherate (20 mL, 4 mmol) were added. The mixture was stirred at room temperature for 1−24 h. Volatiles were removed and the residue was dissolved in ethyl acetate (20 mL) and washed with brine (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. To a solution of this residue in dry dichloromethane, Et_3N (4 mL, 28 mmol) was added. The mixture was cooled to −30 °C, and methanesulfonyl chloride (0.92 mL, 12 mmol) was slowly added. The mixture was stirred at −20 °C for 1 h and at 0 °C for an additional hour. Volatiles were removed and the residue was dissolved in ethyl acetate (10 mL) and washed successively with water (1 × 10 mL) and brine (2 × 10 mL). The organic phase was filtered, dried (Na_2SO_4), and evaporated to dryness. The final residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1) to give the target products **5a−h**.

(±)-1-Diphenylmethyl-2-(methanesulfonyloxy)propionitrile (5a). 1,1-Diphenyl-2-propanone (0.84 g, 4 mmol) was treated with trimethylsilyl cyanide for 2 h and then with methanesulfonyl chloride for 2 h to give 0.80 g (63%) of **5a** as a white amorphous solid. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.95 (s, 3H, CH_3), 3.17 (s, 3H, CH_3SO_2), 4.66 (s, 1H, CH), 7.31, 7.62 (2m, 5H, Ph). MS (ES^+) *m/z* 316.2 $[M + 1]^+$. Anal. ($C_{17}H_{17}NO_3S$): C, H, N, S.

(±)-2-Benzyl-2-(methanesulfonyloxy)butyronitrile (5b).[26] 1-Phenyl-2-butanone **1b** (0.30 g, 2 mmol) was treated with trimethylsilyl cyanide for 2 h and then with methanesulfonyl chloride for 2 h to give 0.37 g (74%) of **5b** as a white amorphous solid. IR (film): 2536 cm^{-1}. MS (ES^+) *m/z* 254.6 $[M + 1]^+$.

(±)-2-Ethyl-2-(methanesulfonyloxy)butyronitrile (5c).[29] 3-Pentanone (0.34 g, 4 mmol) was reacted with trimethylsilyl cyanide for 3 h. The mixture was reacted with methanesulfonyl chloride for 2 h to give 0.52 g (73%) of **5c** as a white amorphous solid. MS (ES^+) *m/z* 192.3 $[M + 1]^+$.

(±)-2-Benzyl-2-(methanesulfonyloxy)propionitrile (5d). 1-Phenyl-2-propanone (0.74 g, 4 mmol) was treated with trimethylsilyl cyanide for 2 h. The mixture was reacted with methanesulfonyl chloride for 2 h to afford compound **5d** (0.80 g, 63%) as a white amorphous solid. MS (ES^+) *m/z* 240.7 $[M + 1]^+$. Anal. ($C_{11}H_{13}NO_3S$): C, H, N, S.

(±)-2-Benzyl-2-(methanesulfonyloxy)pentanenitrile (5e). 1-Phenyl-2-pentanone (0.64 g, 4 mmol) was reacted with trimethylsilyl cyanide for 2 h. Reaction of the mixture with methanesulfonyl chloride for 2 h gave 0.54 g (51%) of **5e** as a white amorphous solid. MS (ES^+) *m/z* 268.7 $[M + 1]^+$. Anal. ($C_{13}H_{17}NO_3S$): C, H, N, S.

(±)-2-Benzyl-3-methyl-2-(methanesulfonyloxy)butyronitrile (5f). 1-Phenyl-3-methyl-2-butanone (0.64 g, 4 mmol) was treated with trimethylsilyl cyanide for 2 h and then with methanesulfonyl chloride for 2 h to yield compound **5f** (0.76 g, 72%) as a white amorphous solid. MS (ES^+) *m/z* 268.9 $[M + 1]^+$. Anal. ($C_{13}H_{17}NO_3S$): C, H, N, S.

(±)-1-Benzyl-5-methyl-2-(methanesulfonyloxy)pentanenitrile (5g). 1-Phenyl-4-methyl-2-pentanone (0.70 g, 4 mmol) was treated with trimethylsilyl cyanide for 2 h and then with methanesulfonyl chloride for 2 h to give 0.72 g (65%) of **5g** as a white amorphous solid. MS (ES^+) *m/z* 282.4 $[M + 1]^+$. Anal. ($C_{14}H_{19}NO_3S$): C, H, N, S.

(±)-2-Cyano-2-(methanesulfonyloxy)-1,2,3,4-tetrahydronaphthalene (5h). β-Tetralone (0.52 mL, 4 mmol) was reacted with trimethylsilyl cyanide for 2 h and then with methanesulfonyl chloride for 1 h to afford compound **5h** (0.50 g, 50%) as a white

amorphous solid. MS (ES^+) *m/z* 252.5 $[M + 1]^+$. Anal. ($C_{12}H_{13}NO_3S$): C, H, N, S.

Synthesis of Compounds 6a−h: General Procedure. A suspension of the corresponding cyanomesylate **5a−h** (2 mmol) in dry acetonitrile (6 mL) was treated with cesium carbonate (0.98 g, 3.0 mmol) and the mixture was stirred at room temperature for 2−7 h. Solvent was removed and the residue was dissolved in ethyl acetate (20 mL) and washed, successively, with water (10 mL) and brine (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by flash column chromatography (hexane/ethyl acetate, 3:1) to give the final products **6a−h.**

(±)-4-Amino-5-diphenylmethyl-5-methyl-5*H*-1,2-oxathiole-2,2-dioxide (6a). Compound **5a** (0.62 mL, 2 mmol) was treated with cesium carbonate for 4 h to give compound **6a** (0.32 g, 52%) as a white solid; mp (ethanol/water) 233−234 °C. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.65 (s, 3H, CH_3), 4.68 (s, 1H, CH), 5.27 (s, 1H, H-3), 6.28 (bs, 2H, NH_2), 7.30, 7.61 (2m, 10H, 2Ph). ^{13}C NMR [75 MHz, $(CD_3)_2CO$]δ: 24.2 (CH_3), 55.6 (CH), 87.0 (C-3), 90.0 (C-5), 126.1, 126.3, 127.2, 127.7, 128.8, 129.1, 139.1, 138.5 (2Ph), 158.3 (C-4). MS (ES^+) *m/z* 316.0 $[M + 1]^+$, 333.0 $[M + H_2O]^+$, 338.0 $[M + Na]^+$, 631.2 $[2M + 1]^+$, 653.3 $[2M + Na]^+$. Anal. ($C_{17}H_{17}NO_3S$): C, H, N, S.

(±)-4-Amino-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (6b).[26] Compound **5b** (0.25 g, 1 mmol) was reacted with cesium carbonate (0.49 g, 1.5 mmol) for 2 h to give **6b** (0.20 g, 81%) as a white solid; mp (toluene) 164−166 °C (lit.[26] 165−166 °C). IR (film): 3503, 3408 cm^{-1}.

4-Amino-5,5-diethyl-5*H*-1,2-oxathiole-2,2-dioxide (6c).[29] A solution of **5c** (0.36 g, 2 mmol) in dry acetonitrile was treated with cesium carbonate for 2 h to give 0.24 g (70%) of **6c** as a white solid; mp (ethanol/water) 163−164 °C (lit.[29] 162−164 °C).

(±)-4-Amino-5-benzyl-5-methyl-5*H*-1,2-oxathiole-2,2-dioxide (6d). Compound **5d** (0.64 g, 2 mmol) was reacted with cesium carbonate for 3 h to give 0.36 g (76%) of **6d** as a white solid; mp (ethanol/water) 199−200 °C. MS (ES^+) *m/z* 240.1 $[M + 1]^+$, 257.0 $[M + H_2O]^+$, 262.0 $[M + Na]^+$, 479.2 $[2M + 1]^+$, 501.2 $[2M + Na]^+$. Anal. ($C_{11}H_{13}NO_3S$): C, H, N, S.

(±)-4-Amino-5-benzyl-5-propyl-5*H*-1,2-oxathiole-2,2-dioxide (6e). Compound **5e** (0.54 mL, 2 mmol) was reacted with cesium carbonate for 2 h to afford compound **6e** (0.26 g, 50%) as a white solid; mp (ethanol/water) 180−181 °C. Anal. ($C_{13}H_{17}NO_3S$): C, H, N, S.

(±)-4-Amino-5-benzyl-5-isopropyl-5*H*-1,2-oxathiole-2,2-dioxide (6f). A solution of **5f** (0.54 g, 2 mmol) was treated with cesium carbonate for 3 h to give 0.32 g (62%) of **6f** as a white solid;mp (ethanol/water) 185−186 °C. MS (ES^+) *m/z* 268.0 $[M + 1]^+$, 285.0 $[M + H_2O]^+$, 290.0 $[M + Na]^+$, 535.2 $[2M + 1]^+$, 557.3 $[2M + Na]^+$. Anal. ($C_{13}H_{17}NO_3S$):C, H, N, S.

(±)-4-Amino-5-benzyl-5-isobutyl-5*H*-1,2-oxathiole-2,2-dioxide (6g). Compound **5g** (0.56 g, 2 mmol) was reacted with cesium carbonate for 3 h to yield 0.36 g (66%) of **6g** as a white solid; mp (ethanol/water) 201−202 °C. MS (ES^+) *m/z* 282.0 $[M + 1]^+$, 299.2 $[M + H_2O]^+$, 304.0 $[M + Na]^+$, 563.2 $[2M + 1]^+$, 585.3 $[2M + Na]^+$. Anal. ($C_{14}H_{19}NO_3S$): C, H, N, S.

(±)-1,2,3,4-Tetrahydronaphthalene-2-spiro-5′-(4′-amino-5′*H*-1′,2′-oxathiole-2′,2′-dioxide) (6h). A solution of **5h** (0.50 g, 2 mmol) in dry acetonitrile was treated with cesium carbonate for 7 h to give 0.36 g (70%) of **6h** as a white solid; mp (ethanol/water) 194−195 °C. MS (ES^+) *m/z* 252.1 $[M + 1]^+$, 269.0 $[M + H_2O]^+$, 274.0 $[M + Na]^+$, 503.12 $[M + 1]^+$, 525.0 $[2M + Na]^+$. Anal. ($C_{12}H_{13}NO_3S$): C, H, N, S.

Synthesis of Compounds 7a−h: General Procedure. A solution of the appropriate β-amino-γ-sultone derivative **6a−h** (1.1 mmol) in 4.5 N HCl in methanol (1.6 mL, 7.2 mmol) was stirred at room temperature for 16 h. Then, a solution of 1 N NaOH in methanol was added until pH ∼ 6, salts were filtered, and the solvent was evaporated. The final residue was purified by flash column chromatography (hexane/ethyl acetate, 1:5) to give the final products **7a−h.**

(±)-5-Diphenylmethyl-5-methyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7a). Compound **6a** (0.32 g, 1 mmol) was reacted with 4.5 N HCl in methanol to give 0.17 g (54%) of **7a** as a white solid; mp (ethanol/water) 143−144 °C. ^{1}H NMR [300 MHz, $CDCl_3$] δ: 1.67 (s, 3H, CH_3), 2.59, 3.59 (AB system, 2H, $J = -16.8$ Hz, H-3), 4.29 (s, 1H, CH), 7.29, 7.54 (2m, 8H, 2Ph). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 22.3 (CH_3), 52.8 (CH), 58.4 (C-3), 100.3 (C-5), 127.7, 127.9, 129.0, 129.3, 129.8, 137.2, 137.3 (2Ph), 201.2 (C-4). MS (ES^+) *m/z* 317.0 $[M + 1]^+$, 334.0 $[M + H_2O]^+$, 338.9 $[M + Na]^+$, 655.0 $[2M + Na]^+$. Anal. ($C_{17}H_{16}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7b).[26] Compound **6b** (0.10 g, 0.39 mmol) was reacted with 4.5 N HCl in methanol (2 mL, 9 mmol) for 14 h to afford **7b** (0.08 g, 76%) as a white solid; mp (ethanol/water) 103−104 °C (mp lit.[26] 102−104 °C). IR (film): 1769 cm^{-1}.

5,5-Diethyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7c).[29] Compound **6c** (0.18 g, 1 mmol) was reacted with 4.5 N HCl in methanol to yield compound **7c** (0.14 g, 77%) as a viscous colorless oil. MS (ES^+) *m/z* 193.0 $[M + 1]^+$, 215.0 $[M + Na]^+$.

(±)-5-Benzyl-5-methyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7d). Compound **6d** (0.24 g, 1 mmol) was reacted with 4.5 N HCl in methanol to give compound **7d** (0.21 g, 88%) as a viscous colorless oil. MS (ES^+) *m/z* 241.1 $[M + 1]^+$, 236.0 $[M + Na]^+$, 529.3 $[2M + Na]^+$. Anal. ($C_{11}H_{12}O_4S$): C, H, S.

(±)-5-Benzyl-5-propyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7e). Compound **6e** (0.26 g, 1 mmol) was reacted with 4.5 N HCl in methanol to afford 0.22 g (81%) of **7e** as a white solid; mp (ethanol/water) 90−91 °C. MS (ES^+) *m/z* 269.0 $[M + 1]^+$, 291.0 $[M + Na]^+$, 559.2 $[2M + Na]^+$. Anal. ($C_{13}H_{16}O_4S$): C, H, S.

(±)-5-Benzyl-5-isopropyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7f). Compound **6f** (0.36 g, 1 mmol) was reacted with 4.5 N HCl in methanol to give 0.11 g (81%) of **7f** as a white solid; mp (ethanol/water) 88−89 °C. MS (ES^+) *m/z* 269.0 $[M + 1]^+$, 291.0 $[M + Na]^+$, 559.2 $[2M + Na]^+$. Anal. ($C_{13}H_{16}O_4S$): C, H, S.

(±)-5-Benzyl-5-isobutyl-4-*oxo*-1,2-oxathiolane-2,2-dioxide (7g). Compound **6g** (0.28 g, 1 mmol) was treated with 4.5 N HCl in methanol to afford compound **7g** (0.21 g, 73%) as a white solid; mp (ethanol/water) 118−119 °C. MS (ES^+) *m/z* 283.0 $[M + 1]^+$, 300.0 $[M + H_2O]^+$, 305.0 $[M + Na]^+$, 587.3 $[2M + Na]^+$. Anal. ($C_{14}H_{18}O_4S$): C, H, S.

(±)-1,2,3,4-Tetrahydronaphthalene-2-spiro-5′-(4′-*oxo*-1′,2′-oxathiolane-2′,2′-dioxide) (7h). Compound **6h** (0.36 g, 1 mmol) was reacted with 4.5 N HCl in methanol to give 0.15 g (58%) of **7h** as a viscous colorless oil. MS (ES^+) *m/z* 253.1 $[M + 1]^+$, 270.0 $[M + H_2O]^+$, 275.0 $[M + Na]^+$, 527.0 $[2M + Na]^+$. Anal. ($C_{12}H_{12}O_4S$): C, H, S.

Alkylation of β-Keto-γ-sultone Derivatives: General Procedure. A mixture of the corresponding ketone **2**, **7a−h** (1 equiv), K_2CO_3 (1.5 equiv), and tetrabuthylamonium iodine (0.1 equiv) in dry acetonitrile (5 mL) was stirred at room temperature for 15 min. Then, the appropriate alkylbromide (1−6 equiv) was added and the mixture was stirred at 40 °C for 3−24 h. The solvent was evaporated to dryness and the residue was purified by flash column chromatography or by HPFC on a Horizon system to give the target compounds.

4-Benzyloxy-5,5-dibenzyl-5*H*-1,2-oxathiole-2,2-dioxide (3). Compound **2**[26] (0.17 g, 0.55 mmol) was treated with benzyl bromide (63 μL, 0.55 mmol) for 3 h. Purification of the residue by flash column chromatography (hexane/ethyl acetate, 6:1) gave compound **3** (0.15 g, 70%) as a white solid; mp (ethanol/water) 122−123 °C. ^{1}H NMR [300 MHz, $CDCl_3$] δ: 3.04, 3.16 (AB system, 2H, $J = -14.3$ Hz, CH_2Ph), 4.77 (s, 2H, CH_2O), 5.49 (s, 1H, H-3), 7.26−7.43 (m, 15H, 3Ph). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 42.4 (2 CH_2), 74.7 (CH_2O), 92.4 (C-5), 96.2 (C-3), 128.2, 127.4, 128.5, 129.0, 130.7, 133.3, 133.2 (Ph). MS (ES^+) *m/z* 407.1 $[M + 1]^+$, 424.1 $[M + H_2O]^+$, 853.3 $[2M + Na]^+$. Anal. ($C_{24}H_{22}O_4S$): C, H, S.

Method B. A solution of **2**[26] (0.12 g, 0. 39 mmol) and a sodium hydride 60% dispersion in mineral oil (0.03 g, 1.17 mmol) in dry THF (2 mL), previously degassed under an argon atmosphere, was stirred at room temperature for 15 min. Then, benzyl bromide (135

μL, 1.17 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction was quenched with acetic acid until the pH of the mixture was ∼7, and ethyl acetate was added (5 mL). The resulting mixture was washed with water (2 × 5 mL) and brine (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by CCTLC on a Chromatotron (hexane/ethyl acetate, 3:1) to give **3** (0.06 g, 53%) as a white solid; mp (ethanol/water) 123−124 °C.

(±)-4-Benzyloxy-5-diphenylmethyl-5-methyl-5*H*-1,2-oxathiole-2,2-dioxide (8a). Compound **7a** (0.17 g, 0.55 mmol) was reacted with benzyl bromide (63 μL, 0.55 mmol) for 5 h. The residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.07 g (31%) of **8a** as a white solid; mp (ethanol/water): 146−147 °C. ^{1}H NMR [300 MHz, $CDCl_3$] δ: 1.72 (s, 3H, CH_3), 4.30 (s, 1H, CH), 4.75, 4.91 (AB system, 2H, J = −10.9 Hz, CH_2Ph), 5.62 (s, 1H, H-3), 7.29−7.62 (m, 15H, 3Ph). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 24.5 (CH_3), 57.3 (CH), 75.0 (CH_2O), 92.4, 95.3 (C-3, C-5), 127.5, 127.7, 128.5, 128.9, 129.2, 129.6, 129.8, 133.4, 138.2, 138.5 (3Ph), 168.9 (C-4). MS (ES^+) *m*/*z* 407.0 $[M + 1]^+$, 424.2 $[M + H_2O]^+$, 429.0 $[M + Na]^+$, 835.2 $[2M + Na]^+$. Anal. ($C_{24}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzyloxy-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (8b). **7b**[26] (0.10 g, 0.39 mmol) was reacted with benzyl bromide (45 μL, 0.39 mmol) for 3 h. The residue was purified by CCTLC on a Chromatotron (hexane/ethyl acetate, 3:1) to give **8b** (0.09 g, 70%) as a white solid; mp (ethanol/water) 107−109 °C. MS (ES^+) *m*/*z* 345.1 $[M + 1]^+$, 362.2 $[M + H_2O]^+$, 367.1 $[M + Na]^+$, 711.2 $[2M + Na]^+$. Anal. ($C_{19}H_{20}O_4S$): C, H, S.

4-Benzyloxy-5,5-diethyl-5*H*-1,2-oxathiole-2,2-dioxide (8c). A solution of **7c** (0.10 g, 0.55 mmol) in dry acetonitrile was treated with benzyl bromide (63 μL, 0.55 mmol) for 3 h. After the workup, the residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.08 g (57%) of **8c** as a white solid; mp (ethanol/water) 95−98 °C. MS (ES^+) *m*/*z* 283.0 $[M + 1]^+$, 305.0 $[M + Na]^+$, 587.0 $[2M + Na]^+$. Anal. ($C_{14}H_{18}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzyloxy-5-methyl-5*H*-1,2-oxathiole-2,2-dioxide (8d). A solution of **7d** (0.13 g, 0.55 mmol) in dry acetonitrile was treated with benzyl bromide (63 μL, 0.55 mmol) for 3 h. After the workup, the residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.09 g (52%) of **8d** as a white solid; mp (ethanol/water) 139−140 °C. MS (ES^+) *m*/*z* 331.0 $[M + 1]^+$, 348.0 $[M + H_2O]^+$, 353.0 $[M + Na]^+$, 683.3 $[2M + Na]^+$. Anal. ($C_{18}H_{18}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzyloxy-5-propyl-5*H*-1,2-oxathiole-2,2-dioxide (8e). Compound **7e** (0.15 g, 0.55 mmol) was treated with benzyl bromide (63 μL, 0.55 mmol) for 3 h. The final residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.10 g (54%) of **8e** as a white solid; mp (ethanol/water) 105−107 °C. MS (ES^+) *m*/*z* 359.0 $[M + 1]^+$, 376.3 $[M + H_2O]^+$, 381.0 $[M + Na]^+$, 739.2 $[2M + Na]^+$. Anal. ($C_{20}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzyloxy-5-isopropyl-5*H*-1,2-oxathiole-2,2-dioxide (8f). A solution of **7f** (0.15 g, 0.55 mmol) in dry acetonitrile was treated with benzyl bromide (63 μL, 0.55 mmol) for 4 h. After the workup, the residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.12 g (63%) of **8f** as a white solid; mp (ethanol/water) 114−115 °C. MS (ES^+) *m*/*z* 359.0 $[M + 1]^+$, 376.3 $[M + H_2O]^+$, 381.0 $[M + Na]^+$, 739.2 $[2M + Na]^+$. Anal. ($C_{20}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzyloxy-5-isobutyl-5*H*-1,2-oxathiole-2,2-dioxide (8g). Compound **7g** (0.15 g, 0.55 mmol) was treated with benzyl bromide (63 μL, 0.55 mmol) for 3 h. Purification of the final residue by flash column chromatography (hexane/ethyl acetate, 6:1) gave **8g** (0.09 g, 45%) as a white solid; mp (ethanol/water) 114−115 °C. MS (ES^+) *m*/*z* 373.3 $[M + 1]^+$, 390.2 $[M + H_2O]^+$, 395.2 $[M + Na]^+$, 767.5 $[2M + Na]^+$. Anal. ($C_{21}H_{24}O_4S$): C, H, S.

(±)-1,2,3,4-Tetrahydronaphthalene-2-spiro-5′-(4′-benzyloxy-5′*H*-1′,2′-oxathiole-2′,2′-dioxide) (8h). Compound **7h** (0.14 g, 0.55 mmol) was reacted with benzyl bromide (63 μL, 0.55 mmol) for 4 h. The final residue was purified by flash column chromatography (hexane/ethyl acetate, 6:1) to give 0.08 g (44%) of **8h** as a white solid; mp (ethanol/water) 220−221 °C. MS (ES^+) *m*/*z* 343.0 $[M + 1]^+$, 360.1 $[M + H_2O]^+$, 365.0 $[M + Na]^+$, 707.2 $[2M + Na]^+$. Anal. ($C_{19}H_{18}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-methoxy-5*H*-1,2-oxathiole-2,2-dioxide (9). Compound **7b**[26] (0.10 g, 0.39 mmol) was treated with methyl iodide (24 μL, 0.39 mmol) for 3 h. Purification of the final residue by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) gave compound **9** (0.07 g, 63%) as a white solid; mp (ethanol/water) 103−104 °C. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 0.92 (m, 3H, CH_3CH_2), 1.87 (m, 2H, CH_3CH_2), 3.17 (s, 2H, CH_2Ph), 3.97 (s, 3H, CH_3O), 6.25 (s, 1H, H-3), 7.32 (m, 4H, Ph). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 7.6 (CH_3CH_2), 29.2 (CH_3CH_2), 43.2 (CH_2Ph), 59.6 (CH_3O), 93.7 (C-5), 95.6 (C-3), 127.5, 128.3, 130.8, 133.6 (Ph), 168.7 (C-4). MS (ES^+) *m*/*z* 269.0 $[M + 1]^+$, 291.0 $[M + Na]^+$, 559.2 $[2M + Na]^+$. Anal. ($C_{13}H_{16}O_4S$): C, H, S.

(±)-4-Allyloxy-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide and (±)-3-Allyl-4-allyloxy-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (10 and 11). Compound **7b**[26] (0.10 g, 0.39 mmol) was reacted with allyl bromide (51 μL, 0.58 mmol) for 4 h. The final residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1). The faster running fractions afforded **11** (0.02 g, 12%) as a viscous colorless oil. MS (ES^+) *m*/*z* 335.0 $[M + 1]^+$, 353.0 $[M + H_2O]^+$, 691.0 $[2M + Na]^+$. Anal. ($C_{18}H_{22}O_4S$): C, H, S.

The slowest moving fractions afforded 0.08 g (72%) of **10** as a viscous colorless oil. MS (ES^+) *m*/*z* 295.0 $[M + 1]^+$, 312.3 $[M + H_2O]^+$, 317.0 $[M + Na]^+$, 611.2 $[2M + Na]^+$. Anal. ($C_{15}H_{18}O_4S$). C, H, S.

(±)-5-Benzyl-5-ethyl-4-dimethylallyloxy-5*H*-1,2-oxathiole-2,2-dioxide (12). A solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with dimethylallyl bromide (68 μL, 0.39 mmol) for 3 h. After the workup, the residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) to give 0.03 g (32%) of **12** as a viscous colorless oil. MS (ES^+) *m*/*z* 323.3 $[M + 1]^+$, 340.3 $[M + H_2O]^+$, 345.2 $[M + Na]^+$, 667.5 $[2M + Na]^+$. Anal. ($C_{17}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-4-cyanomethyloxy-3-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (13). Compound **7b**[26] (0.10 g, 0.39 mmol) was treated with bromoacetonitrile (27 μL, 0.39 mmol) for 3 h. Purification of the final residue by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), gave compound **13** (0.07 g, 60%) as a white solid; mp (ethanol/water) 111−114 °C. MS (ES^+) *m*/*z* 294.2 $[M + 1]^+$, 311.2 $[M + H_2O]^+$, 316.0 $[M + Na]^+$, 609.2 $[2M + Na]^+$. Anal. ($C_{14}H_{15}NO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-methoxycarbonylmethoxy-5*H*-1,2-oxathiole-2,2-dioxide (14). Compound **7b**[26] (0.10 g, 0.39 mmol) was reacted with methyl bromoacetate (37 μL, 0.39 mmol) for 3 h. The final residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), to give 0.085 g (67%) of **14** as a white solid; mp (ethanol/water) 145−146 °C. MS (ES^+) *m*/*z* 327.0 $[M + 1]^+$, 344.0 $[M + H_2O]^+$, 349.0 $[M + Na]^+$, 675.3 $[2M + Na]^+$. Anal. ($C_{15}H_{18}O_6S$): C, H, S.

(±)-5-Benzyl-4-cyclohexylmethoxy-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (15). A solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with bromomethylcyclohexane (55 μL, 0.39 mmol) for 3 h. After the workup, the residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), to give 0.048 g (35%) of **15** as a white solid; mp (ethanol/water) 110−111 °C. MS (ES^+) *m*/*z* 351.2 $[M + 1]^+$, 368.3 $[M + H_2O]^+$, 373.3 $[M + Na]^+$, 723.5 $[2M + Na]^+$. Anal. ($C_{19}H_{26}O_4S$): C, H, S.

(±)-5-Benzyl-4-diphenylmethoxy-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (16). A solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with diphenylbromomethane (0.096 g, 0.39 mmol) for 3 h. The residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), to give 0.064 g (39%) of **16** as a white solid; mp (ethanol/water) 173−174 °C. MS (ES^+) *m*/*z* 421.0 $[M + 1]^+$, 438.1 $[M + H_2O]^+$, 443.0 $[M + Na]^+$, 863.3 $[2M + Na]^+$. Anal. ($C_{25}H_{24}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(2′-phenylethoxy)-5*H*-1,2-oxathiole-2,2-dioxide (17). Compound **7b**[26] (0.10 g, 0.39 mmol) was treated with 2-phenylethyl bromide (46 μL, 0.39 mmol) for 5 h. Purification of the final residue by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), gave compound **17** (0.072 g, 52%) as a white solid;

mp (ethanol/water) 56−57 °C. MS (ES^+) *m/z* 359.2 $[M + 1]^+$, 376.3 $[M + H_2O]^+$, 381.0 $[M + Na]^+$, 739.2 $[2M + Na]^+$. Anal. ($C_{20}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(3′-phenylpropoxy)-5*H*-1,2-oxathiole-2,2-dioxide (18). Compound **7b**[26] (0.10 g, 0.39 mmol) was reacted with 3-phenylpropyl bromide (59 μL, 0.39 mmol) for 5 h. The final residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) to give 0.058 g (40%) of **18** as a viscous colorless oil. MS (ES^+) *m/z* 373.3 $[M + 1]^+$, 395.2 $[M + Na]^+$, 767.3 $[2M + Na]^+$. Anal. ($C_{21}H_{24}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-phenylbutoxy)-5*H*-1,2-oxathiole-2,2-dioxide (19). **7b**[26] (0.10 g, 0.39 mmol) was treated with 4-phenylbutyl bromide (83 μL, 0.39 mmol) for 5 h. Purification of the residue by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) gave compound **19** (0.114 g, 76%) as a viscous colorless oil. MS (ES^+) *m/z* 387.2 $[M + 1]^+$, 404.2 $[M + H_2O]^+$, 795.5 $[2M + Na]^+$. Anal. ($C_{22}H_{26}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(6′-phenylhexyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (20). **7b**[26] (0.10 g, 0.39 mmol) was treated with 6-phenylhexyl bromide (0.094 g, 0.39 mmol) for 4 h. The residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) to give 0.09 g (56%) of **20** as a viscous colorless oil. MS (ES^+) *m/z* 415.3 $[M + 1]^+$, 437.3 $[M + Na]^+$, 851.5 $[2M + Na]^+$. Anal. ($C_{24}H_{30}O_4S$): C, H, S.

(±)-5-Benzyl-4-benzoyloxy-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (21). A solution of **7b**[26] (0.10 g, 0.39 mmol) and a sodium hydride 60% dispersion in mineral oil (0.028 g, 1.14 mmol) in dry THF (5 mL) was stirred at room temperature for 10 min. Then, benzoyl chloride (136 μL, 1.17 mmol) was added and the mixture was stirred at room temperature for 5 h. The reaction was quenched with acetic acid to pH ∼ 7, and ethyl acetate was added (5 mL). The reaction mixture was successively washed with water (2 × 5 mL) and brine (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1) to give **21** (0.057 g, 41%) as a white solid; mp (ethanol/water) 139−140 °C. MS (ES^+) *m/z* 359.0 $[M + 1]^+$, 381.0 $[M + Na]^+$, 739.2 $[2M + Na]^+$. Anal. ($C_{19}H_{18}O_5S$): C, H, S.

The slowest moving fractions afforded 0.05 g (50%) of unreacted starting material.

(±)-5-Benzyl-5-ethyl-4-(*p*-toluensulfonyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (22). Via the procedure describe for **21**, compound **7b**[26] (0.10 g, 0.39 mmol) was reacted with *p*-toluensulfonyl chloride (0.074 g, 0.39 mmol) and sodium hydride for 24 h. After the workup, the residue was purified by flash column chromatography (hexane/ethyl acetate, 3:1) to give 0.046 g (30%) of **22** as a white solid; mp (ethanol/water) 89−90 °C. MS (ES^+) *m/z* 409.2 $[M + 1]^+$, 426.2 $[M + H_2O]^+$, 431.2 $[M + Na]^+$, 839.3 $[2M + Na]^+$. Anal. ($C_{19}H_{20}O_6S_2$): C, H, S.

The slowest moving band afforded 0.057 g (57%) of unreacted starting material.

(±)-5-Benzyl-5-ethyl-4-(4′-nitrobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (23). Via the general alkylation procedure, a solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with 4-nitrobenzyl bromide (0.067 g, 0.39 mmol) for 5 h. After the workup, the residue was purified by HPFC on a Horizon system (hexane/ethyl acetate, 3:1), to give 0.094 g (62%) of **23** as a white solid; mp (ethanol/water) 115−118 °C. MS (ES^+) *m/z* 390.0 $[M + 1]^+$, 407.0 $[M + H_2O]^+$, 412.0 $[M + Na]^+$, 801.0 $[2M + Na]^+$. Anal. ($C_{19}H_{19}NO_6S$): C, H, N, S.

(±)-5-Benzyl-5-ethyl-4-(4′-trifluorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (24). According to the procedure described for **23**, **7b**[26] (0.10 g, 0.39 mmol) was reacted with 4-trifluoromethylbenzyl bromide (0.093 g, 0.39 mmol) for 3 h to give 0.10 g (65%) of **24** as a white solid; mp (ethanol/water) 82−84 °C. MS (ES^+) *m/z* 413.0 $[M + 1]^+$, 430.0 $[M + H_2O]^+$, 434.9 $[M + Na]^+$, 846.8 $[2M + Na]^+$. Anal. ($C_{20}H_{19}F_3O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-fluorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (25). The procedure described for **23** was followed with **7b**[26] (0.10 g, 0.39 mmol) and 4-fluorobenzyl bromide (49 μL, 0.39 mmol) for 3 h to give compound **25** (0.078 g, 54%) as a white solid; mp (ethanol/water) 114−115 °C. MS (ES^+) *m/z* 363.0 $[M + 1]^+$, 385.0 $[M + Na]^+$, 747.2 $[2M + Na]^+$. Anal. ($C_{19}H_{19}FO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-chlorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (26). Via the procedure described for **23**, a solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with 4-chlorobenzyl bromide (0.08 g, 0.39 mmol) for 3 h to give 0.068 g (47%) of **26** as a white solid; mp (ethanol/water) 75−77 °C. MS (ES^+) *m/z* 379.1 $[M + 1]^+$, 396.1 $[M + H_2O]^+$, 401.1 $[M + Na]^+$, 779.2 $[2M + Na]^+$. Anal. ($C_{19}H_{19}ClO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-bromobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (27). The procedure described for **23** was followed with **7b**[26] (0.10 g, 0.39 mmol) and 4-bromobenzyl bromide (0.097 g, 0.39 mmol) for 3 h to give 0.086 g (52%) of **27** as a white solid; mp (ethanol/water): 118−120 °C. MS (ES^+) *m/z* 423.0 $[M + 1]^+$, 445.0 $[M + Na]^+$, 867.0 $[2M + Na]^+$. Anal. ($C_{19}H_{19}BrO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-methoxybenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (28). Following the procedure described for **23**, **7b**[26] (0.10 g, 0.39 mmol) was reacted with 4-methoxybenzyl bromide (53 μL, 0.39 mmol) for 6 h to give compound **28** (0.058 g, 40%) as a white solid; mp (ethanol/water) 80−81 °C. MS (ES^+) *m/z* 375.0 $[M + 1]^+$, 392.2 $[M + H_2O]^+$, 397.0 $[M + Na]^+$, 771.3 $[2M + Na]^+$. Anal. ($C_{20}H_{22}O_5S$). C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-methylbenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (29). According to procedure described for **23**, **7b**[26] (0.10 g, 0.39 mmol) was reacted with 4-methylbenzyl bromide (0.072 g, 0.39 mmol) for 3 h to yield 0.059 g (42%) of **29** as a viscous colorless oil. MS (ES^+) *m/z* 359.0 $[M + 1]^+$, 376.0 $[M + H_2O]^+$, 381.0 $[M + Na]^+$, 739.0 $[2M + Na]^+$. Anal. ($C_{20}H_{22}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(4′-*tert*-butylbenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (30). The procedure described for **23** was followed with **7b**[26] (0.10 g, 0.39 mmol) and 4-*tert*-butylbenzyl bromide (72 μL, 0.39 mmol) for 3 h to give 0.126 g (81%) of **30** as a viscous colorless oil. MS (ES^+) *m/z* 401.2 $[M + 1]^+$, 418.0 $[M + H_2O]^+$, 491.2 $[M + 2Na]^+$, 823.3 $[2M + Na]^+$, 423.0 $[M + Na]^+$. Anal. ($C_{23}H_{28}O_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(2′-chlorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (31). Following the procedure described for **23**, **7b**[26] (0.10 g, 0.39 mmol) was treated with 2-chlorophenyl bromide (51 μL, 0.39 mmol) for 3 h to afford compound **31** (0.064 g, 60%) as a white solid; mp (ethanol/water) 102−104 °C. MS (ES^+) *m/z* 379.0 $[M + 1]^+$, 779.2 $[2M + Na]^+$. Anal. ($C_{19}H_{19}ClO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(3′-chlorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (32). The procedure described for **23** was followed with **7b**[26] (0.10 g, 0.39 mmol) and 3-chlorobenzyl bromide (51 μL, 0.39 mmol) for 3 h to give 0.098 g (66%) of **32** as a viscous colorless oil. MS (ES^+) *m/z* 379.0 $[M + 1]^+$, 396.0 $[M + H_2O]^+$, 401.0 $[M + Na]^+$, 779.0 $[2M + Na]^+$. Anal. ($C_{19}H_{19}ClO_4S$): C, H, S.

(±)-5-Benzyl-5-ethyl-4-(3′,4′-dichlorobenzyloxy)-5*H*-1,2-oxathiole-2,2-dioxide (33). Via the procedure described for **23**, a solution of **7b**[26] (0.10 g, 0.39 mmol) was treated with 3,4-dichlorobenzyl bromide (0.094 g, 0.39 mmol) for 4 h to yield 0.069 g (43%) of **33** as a white solid; mp (ethanol/water) 115−116 °C. MS (ES^+) *m/z* 413.2 $[M + 1]^+$, 435.1 $[M + Na]^+$, 848.9 $[2M + Na]^+$. Anal. ($C_{19}H_{18}Cl_2O_4S$): C, H, S.

Antiviral Assays. HCMV. Confluent human embryonic lung (HEL) fibroblasts were grown in 96-well microtiter plates and infected with the human cytomegalovirus (HCMV) strains Davis and AD-169 at 100 PFU per well. Also, a variety of relevant drug-resistant HCMV strains, mutated in the DNA polymerase gene, were included in the infection and sensitivity studies. After a 2 h incubation period, residual virus was removed and the infected cells were further incubated with medium containing different concentrations of the test compounds (in duplicate). After incubation for 7 days at 37 °C, virus-induced cytopathogenicity was monitored microscopically after ethanol fixation and staining with Giemsa. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathogenicity by 50%.

EC_{50} values were calculated from graphic plots of the percentage of cytopathogenicity as a function of concentration of the compounds.

VZV. The laboratory wild-type VZV strain Oka and the thymidine kinase-deficient VZV strain 07/1 were used. Confluent HEL cells grown in 96-well microtiter plates were inoculated with VZV at an input of 20 PFU per well. After a 2 h incubation period, residual virus was removed and varying concentrations of the test compounds were added (in duplicate). Antiviral activity was expressed as the 50% effective concentration required to reduce viral plaque formation after 5 days by 50% as compared with untreated controls.

Cytotoxicity Assays. Cytotoxicity measurements were based on the inhibition of HEL cell growth. HEL cells were seeded at a rate of 5×10^3 cells/well into 96-well microtiter plates and allowed to proliferate for 24 h. Then, medium containing different concentrations of the test compounds was added. After 3 days of incubation at 37 °C, the cell number was determined with a Coulter counter. The 50% cytostatic concentration (CC_{50}) was calculated as the compound concentration required to reduce cell growth by 50% relative to the number of cells in the untreated controls. CC_{50} values were estimated from graphic plots of the number of cells (percentage of control) as a function of the concentration of the test compounds. Cytotoxicity was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that causes a microscopically detectable alteration of cell morphology.

Acknowledgment. We thank Lies Van den Heurck, Anita Camps, and Steven Carmans for excellent technical assistance. We also thank the Spanish MEC/MCINN (project SAF2006-12713-C02), the European Commission [project HPAW-CT-2002-90001 (René Descartes Prize 2001)] for financial support, and the K. U. Leuven (GOA project no. 05/19).

Supporting Information Available: Elemental analysis data of compounds **3**, **5a**,**d**−**h**, **6a**,**d**−**h**, **7a**,**d**−**h**, **8a**−**h**, and **9**−**33**. ^{1}H NMR and ^{13}C NMR data of compounds **5b**−**h**, **6b**−**h**, **7b**−**h**, **8b**−**h**, and **10**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM8014662