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From β-Amino-γ-sultone to Unusual Bicyclic Pyridine and Pyrazine Heterocyclic Systems: Synthesis and Cytostatic and Antiviral Activities

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Herein we describe the first successful application of the β-amino-γ-sultone system as an intermediate for the synthesis of hitherto virtually unknown 3*H*-[1,2]-oxathiole [4,3-*b*]pyridine and pyrazine 1,1-dioxide bicyclic heterocyclic systems. All novel compounds were evaluated for their antiviral and cytostatic activities. Compounds **3a**, **15a**, and **21a** inhibited HIV-1-induced cytopathicity. Compound **7** showed remarkable cytostatic activity, and can be regarded as a potential antitumor candidate for further exploration.

Introduction

Fragment-based library screening is an alternative approach to identify novel scaffolds for compounds interacting with new or well-known targets for antiviral or anticancer research. Although such fragments usually have low affinity for their targets, they are used as a basis for a more rational design and exploration of novel drug leads. Fragments of known biologically active compounds that are further functionalized or structurally expanded are also useful to be designed, synthesized, and evaluated against potential biological targets. Sultones might be an example of such an interesting scaffold that should be further explored. Indeed, these molecules are synthetically useful heterocycles that can be readily prepared and modified in a flexible manner.[1,2] Moreover, biological activities of sultones concerning toxicological,[1c] skin sensitization,[3] and antiviral properties[4,5] have been previously reported and continue to be of interest. Indeed, 4-benzyloxy-γ-sultone derivatives were recently reported to have a selective inhibitory activity against human cytomegalovirus (HCMV) and varicella-zoster virus (VZV) replication in vitro,[5] and [2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide) nucleosides (TSAO) containing a sultone entity in their spiro moiety are reportedly potent and selective non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against human immunodeficiency virus type 1 (HIV-1).[4] Even though several examples of chemical reactions on saturated γ-sultones have been described,[6] there are fewer reported investigations on the chemistry of α,β-unsaturated γ-sultones,[2a,7] in particular the β-amino-substituted representatives of this family.[4,5,8] Recently, we reported[9] on the reactivity of the 4-amino-5*H*-1,2-oxathiole-2,2-dioxide (β-amino-γ-sultone) heterocyclic system toward electrophiles and amines on readily available model substrates. One of the interesting features of this system is its ambident nucleophilicity; nucleophilic reactions can take place either at the site of the enaminic carbon (C3) or at the primary amino nitrogen depending on the nature of the electrophile and the reaction conditions.[9] In our ongoing research on the chemistry and biological applications of this system,[4,5] we now explore for the first time the synthetic usefulness of this ambident nucleophile for the preparation of unusual fused nitrogen heterocyclic systems containing a γ-sultone moiety, and evaluate these novel structures against HIV, HCMV, VZV, and a broad variety of other DNA/RNA viruses. In spite of the poor nucleophilicity of the amino group, which is considered to have an "amide-like" character, the β-amino-γ-sultone system (**I**, Figure 1) reacts with a variety of bis-electrophilic reagents to give 3H-[1,2]-oxathiole [4,3-b]pyridine and pyrazine 1,1-dioxide bicyclic systems (pyrido- and pyrazinosultones **II** and **III**, Figure 1). The synthesized fused bicyclic ring systems may be of interest from a biological viewpoint as they contain a variety of functional groups, giving them the opportunity to afford new interactions with cellular or viral targets. It

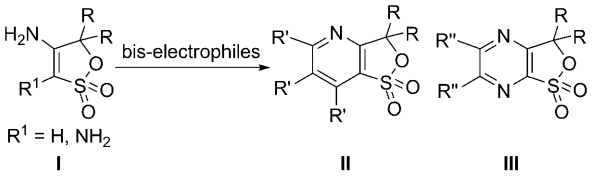

Figure 1. General structures of β-amino-γ-sultone intermediates (**I**) and target bicyclic heterocyclic systems (**II** and **III**).

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is worth noting that, to our knowledge, almost no literature exists for these type of heterocyclic systems.[10]

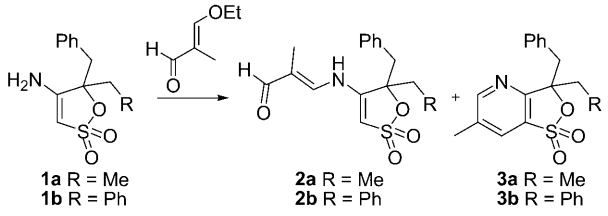
Herein we give an account on the synthetic approaches for the preparation of these new condensed heterocyclic compounds and their biological evaluation against cell proliferation and a broad panel of viruses in cell culture.

Results and Discussion

Chemistry

The β-amino-γ-sultones **1a**,**b** (Table 1), prepared from commercially available ketones as previously described,[9] were selected as simple and readily available substrates for our studies. In the beginning, we directed our efforts to the synthesis of the pyridosultone heterocyclic system **I**. We first investigated classical condensation reactions of β-amino-γ-sultones **1a**,**b** with a masked β-dialdehyde in order to prepare 6-substituted pyridosultone derivatives **3a**,**b** (Table 1). Initial attempts of condensation of **1a** with (*E*)-3-ethoxy-2-methylacrylaldehyde in acetic acid at 110 °C (entry 1) afforded a mixture of the uncyclized *N*-adduct **2a** and the target 6-methyl pyridosultone **3a** in 38 and 26% yield, respectively, together with unreacted starting material (20%). The isolation of intermediate **2a** indicates that the initial attack of the aldehyde occurs at the more nucleophilic amino group of the sultone substrate and that the reaction further proceeds to the cyclic derivative **3a** by an intramolecular condensation with the second aldehyde group. The configuration of the enamine bond of intermediate **2a** was *E*, and no compound with *Z* configuration was detected. A higher reaction temperature (140 °C, entry 2) led to lower yields of compounds **2a** and **3a**. To avoid the observed partial degradation at higher temperature, we turned to microwave activation. However, when substrate **1a** was treated with the β-dialdehyde in acetic acid under microwave irradiation (110 °C) (entry 3), the starting material underwent total decomposition and no significant spot was detected by thin-layer chromatography (TLC). The use of Lewis acids such as $BF_3{\cdot}Et_2O$ or $ZnBr_2$ instead of AcOH was not successful as well, leading either to decomposition of the starting material or to low yields of the desired pyridosultone **3a** (entries 4 and 5).

Table 1. Optimization of the reaction of β-amino-γ-sultones **1a**,**b** with (*E*)-3-ethoxy-2-methylacrylaldehyde to give 6-methyl pyridosultones **3a**,**b** (6-substituted 3*H*-[1,2]-oxathiole[4,5-*b*]pyridine 1,1-dioxide **3a**,**b**).



1a R = Me
1b R = Ph

2a R = Me
2b R = Ph

3a R = Me
3b R = Ph

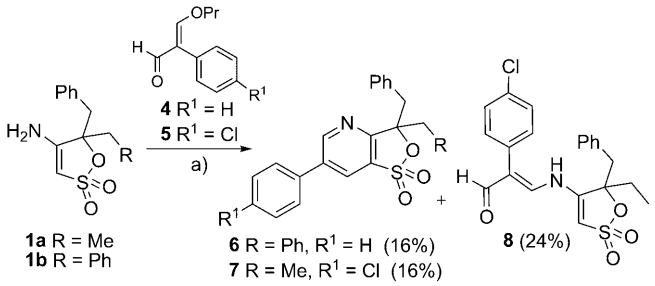
Entry	Substrate	Conditions	*T* [°C]	Yield [%][a] **2a,b**	**3a,b**
1	**1a**	AcOH	110	38	26[b]
2	**1a**	AcOH	140	22	15
3	**1a**	AcOH	110 MW[d]	decomp.	
4	**1a**	$ZnBr_2$, toluene	110	decomp.	
5	**1a**	$BF_3{\cdot}Et_2O$, DMF	110	33	12
6	**1a**	NaH, THF	100	75	8
7	**1a**	DMAP, pyridine	100	no reaction	
8	**1a**	TEA, toluene	100	no reaction	
9	**1a**	K_2CO_3, EtOH	100	–	14[c]
10	**1a**	NatBuO, EtOH	100	no reaction	
11	**1a**	KOH, EtOH, toluene	100	–	46
12	**1b**	KOH, EtOH, toluene	100	–	40

[a] Yields refer to pure isolated product. [b] 20% of starting material was recovered. [c] 40% of starting material was recovered. [d] MW: microwave activation.

Next, we performed a series of experiments exploring basic conditions and different solvents. When the reaction was carried out in THF in the presence of sodium hydride at 100 °C (entry 6), the major reaction product isolated was **2a** (75%), while the desired cyclized product **3a** was obtained in very low yield (8%). Other bases such as 4-dimethylaminopyridine (DMAP), triethylamine (TEA), or inorganic bases (K_2CO_3, Nat*Bu*O) (entries 7–10) failed to generate a reaction product or resulted in a low yield of the pyridosultone **3a**. Interestingly, the use of potassium hydroxide in a mixture of ethanol/toluene as solvent at 100 °C (entry 11) provided the desired cyclized product **3a** in a yield of 46%, nearly twice as high at the best yield obtained in previous reactions. These reaction conditions were then applied to substrate **1b** (entry 12), affording the 6-methyl pyridosultone **3b** in moderate yield (40%).

We subsequently extended the procedure to aromatic dialdehydes to obtain 6-aryl pyridosultone analogues (Scheme 1). Introduction of a 6-aryl group was also possible, although lower yields of the desired pyridosultones **6** and **7** were obtained. Initial attempts to react **1a** with (*E*)-2-phenyl-3-propoxyacrylaldehyde **4**[11] under the above optimized conditions (potassium hydroxide, ethanol, toluene, 100 °C) failed to give the desired 6-phenyl pyridosultone **6**. However, when this reaction was carried out in the presence of acetic acid and trifluoroacetic acid (TFA), **6** was obtained in low yield (16%). Similarly, treatment of **1b** with (*E*)-2-(4-chlorophenyl)-3-propoxyacrylaldehyde **5**[11] gave the 6-(4-chlorophenyl)-pyridosultone **7** together with the uncyclized compound **8** in 16 and 24% yield, respectively (Scheme 1).

To further explore the synthetic utility of β-amino-γ-sultones **1a**,**b**, we next focused on reactions with other bis-electrophiles to obtain the 5- and/or 7-substituted pyridosultone heterocy-



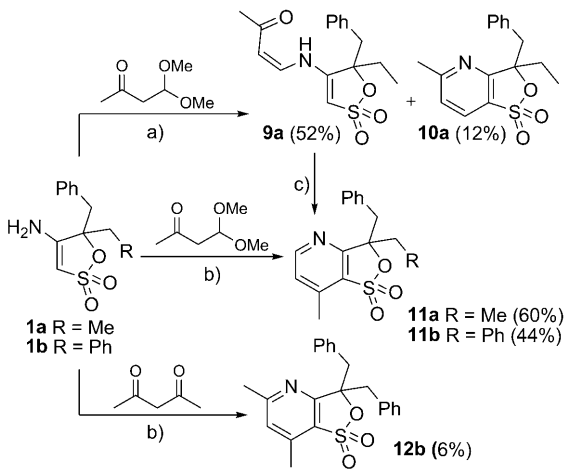
1a R = Me
1b R = Ph

6 R = Ph, R^1 = H (16%)
7 R = Me, R^1 = Cl (16%)

8 (24%)

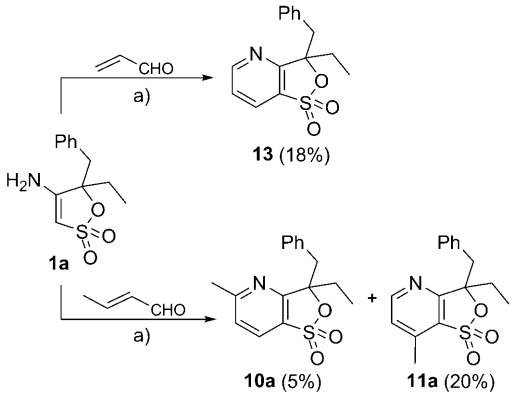
Scheme 1. Reaction of β-amino-γ-sultones **1a**,**b** with aromatic β-dialdehydes **4** and **5**: a) AcOH, TFA, 100 °C, 1 h, 80 °C, 4 h.

clic system. When **1a** was reacted with β-ketoaldehydes such as 4,4-dimethoxybutan-2-one (Scheme 2) in acetic acid at 110 °C, a mixture of the uncyclized *N*-adduct intermediate **9a** and the 5-methyl pyridosultone compound **10a** was obtained (52 and 12% yield, respectively). Subsequent treatment of intermediate **9a** with potassium hydroxide as base at 100 °C in a 5:2 mixture of toluene and ethanol afforded the 7-methyl pyridosultone compound **11a** in 44% yield. The formation of the 5-methyl and 7-methyl isomers **10a** and **11a** under these experimental conditions can be explained by a competition between both nucleophilic sites of the enamine system. Next, instead of isolating the intermediate **9a** under acidic conditions and subjecting it to a second basic cyclization step, we sought a one-pot synthesis of the 3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide system. Thus, we treated sultone **1a** with 4,4-dimethoxybutan-2-one under the above mentioned optimized basic conditions (potassium hydroxide, 100 °C) to give the 7-methyl pyridosultone compound **11a** in 60% yield. Intermediate **9a** and the 5-methyl regioisomer **10a** were not detected. Therefore, this method proved to be regioselective affording exclusively the 7-methyl analogue, in contrast to the initial results described above. Similarly, reaction of the dibenzyl sultone **1b** provided the 7-methyl pyridosultone **11b** in 44% yield as a single regioisomer under these experimental conditions (Scheme 2). Thus, this approach depicts a convenient way for the synthesis of 7-substituted pyridosultones. On the other hand, the reaction of **1b** with 1,3-diketones such as pentane-2,4-dione (Scheme 2) under the above basic conditions (potassium hydroxide, 100 °C) resulted in a complex mixture of compounds, from which the 5,7-dimethyl pyridosultone **12b** was obtained, albeit in low yield (6%).



Scheme 2. Reaction of β-amino-γ-sultones **1a**,**b** with β-ketoaldehydes and 2,4-pentanedione to give 5- and/or 7-substituted pyridosultones **9a**, **10a**, **11a**,**b**, and **12**: a) AcOH, 110 °C, 6 h; b) KOH, 100 °C, 3 h; c) KOH, 100 °C, 3 h.

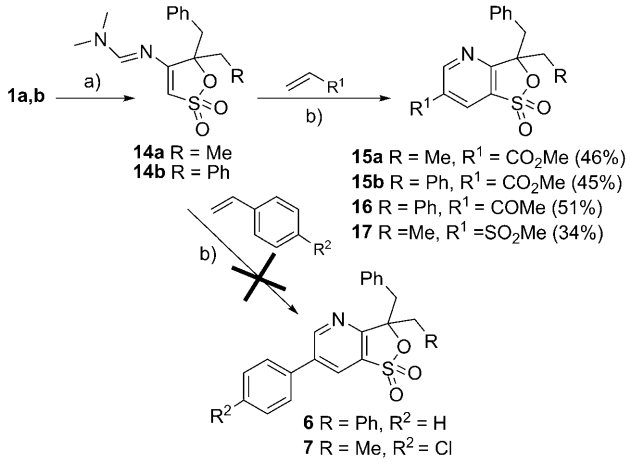
We next explored the reaction of β-amino-γ-sultone **1a** with α,β-unsaturated aldehydes (Scheme 3). We found that the reaction of **1a** with acrolein in the presence of 10% Pd/C as dehydrogenating agent[12] at 100 °C in toluene afforded the desired unsubstituted pyridosultone system **13** in 18% yield. This method did not prove to be regioselective when a substituted acrolein was used, in contrast to the results observed in the reaction of **1a**,**b** with β-keto aldehydes under the aforementioned basic conditions. Thus, when **1a** was reacted with (*E*)-but-2-enal, a mixture of the 5-methyl and 7-methyl regioisomers **10a** and **11a** was formed in 5 and 20% yield, respectively. Other reaction conditions such as the palladium-catalyzed reaction of **1a** with (*E*)-but-2-enal in the presence of $Pd(PPh_3)_4$, 10% Pd/C, and potassium carbonate[12] did neither improve the yield nor the regioselectivity of the reaction.



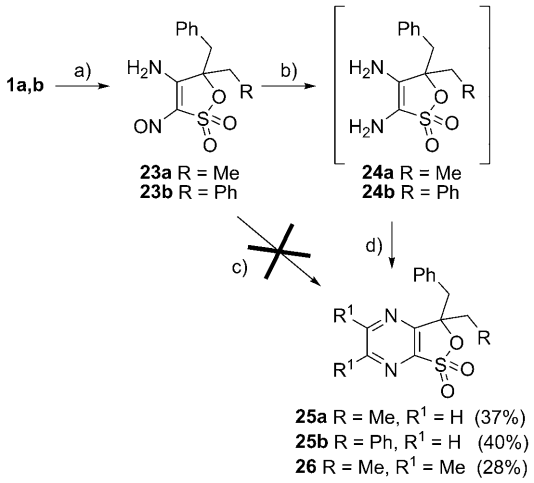
Scheme 3. Reaction of β-amino-γ-sultone **1a** with α,β-unsaturated aldehydes: a) Pd/C 10%, 100 °C, 48 or 72 h.

As it will be mentioned below, antiviral assays indicated that compound **3a**, which bears a methyl substituent at the 6-position of the pyridosultone moiety, showed a significant activity against HIV-1 infection in cell culture, while the unsubstituted analogue **13**, the 5-methyl derivative **10a**, and the 7-methyl compound **11a** were inactive. These results prompted us to examine alternative strategies for the synthesis of other 6-substituted pyridosultone derivatives. Palladium-catalyzed oxidative coupling of azavinyl intermediates with electron-deficient olefins reported by Hirota's group[13] was next attempted (Scheme 4). The required 4-(dimethylaminomethylene)amino sultone intermediates **14a**,**b** (Scheme 4) were easily prepared by condensation of **1a**,**b** with *N*,*N*-dimethylformamide dimethyl acetal (DMF–DMA) in excellent yields as previously described.[9] Reactions of **14a**,**b** with olefins such as methyl acrylate, methyl vinyl ketone, and methyl vinyl sulfone in the presence of palladium acetate in acetic acid under reflux resulted in the direct formation of the corresponding 6-substituted pyridosultones **15a**,**b**, **16**, and **17** in moderate yields (34–51%) (Scheme 4). However, an analogous treatment of **14a**,**b** with styrene or 4-chlorostyrene failed to give the desired 6-aryl derivatives **6** and **7**; instead, complex mixtures of unidentified products were detected, in contrast to a previous report by Hirota and co-workers in which successful oxidative coupling and cyclization reactions with styrene-type olefins were described.[13]

The 6-methoxycarbonyl pyridosultones **15a**,**b** were then used as starting compounds for the synthesis of a variety of 6-substituted pyridosultones (Scheme 5). The methyl ester group



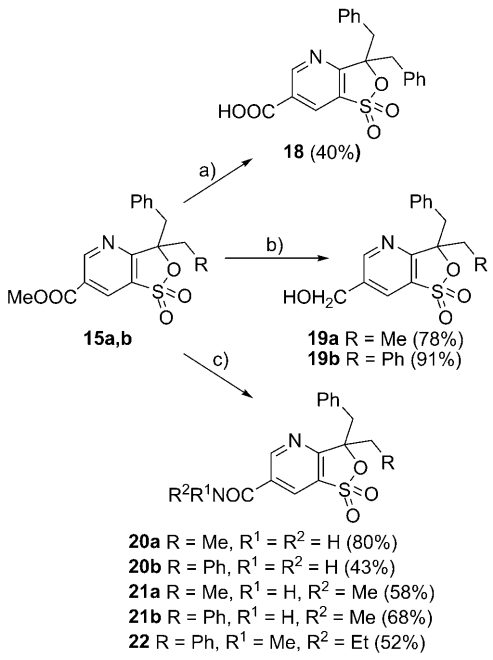
Scheme 4. Synthesis of 6-substituted pyridosultones **15a**,**b**, **16** and **17** by reaction of **14a**,**b** with electron-deficient olefins in the presence of palladium acetate: a) DMF–DMA, 40 °C, 40 min; b) $Pd(OAc)_2$, AcOH, 100 °C, 3 h.



Scheme 6. Synthesis of pyrazinosultones **25a**,**b** and **26** from 3-nitrososultone derivatives **23a**,**b**: a) $NaNO_2$, AcOH, 10 °C, 4 h; b) H_2, Pd/C 5%, DMF, 30 °C; c) R^1COCOR^1, RT, 4 h, or 40 °C, 1 h; d) R^1COCOR^1, RT.

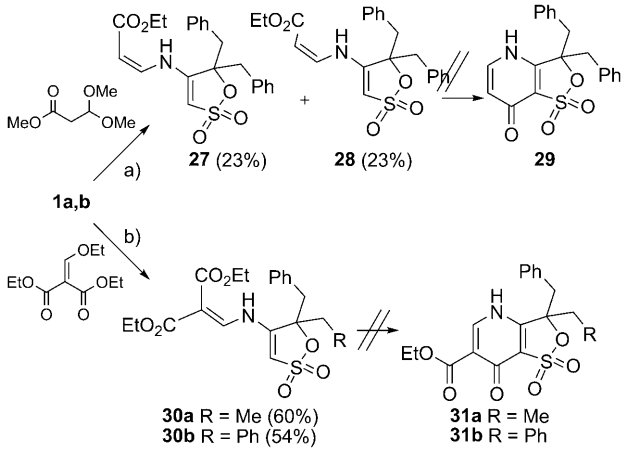
of **15a**,**b** was further transformed into the free acid **18** (40% yield) by treatment with 1 N NaOH. The reaction of **15a**,**b** with a 1 M solution of diisobutylaluminum hydride (DIBAL-H) in hexane gave the 6-hydroxymethyl derivative **19a**,**b** in 78 and 91% yield, respectively. On the other hand, reaction of **15a**,**b** with appropriate amines afforded the amides **20a**,**b**, **21a**,**b**, and **22** in moderate to good yields (43–80%) (Scheme 5).

Next, we investigated the synthesis of the pyrazinosultone heterocyclic system **II** from β-amino-γ-sultones **1a**,**b**. As shown in Scheme 6, formation of this novel bicyclic heterocyclic system was carried out in three steps: nitrosation, reduction of the nitroso group to the amine, and then ring closure with 1,2-dicarbonyl electrophiles as two-carbon source. Nitrosation of β-amino-γ-sultones **1a**,**b** was carried out as previously described[9] with sodium nitrite in acetic acid to give the required 3-nitroso sultone derivatives **23a**,**b**[9] in good yields. Quantitative reduction of the nitroso group to the amine was achieved by catalytic hydrogenation of **23a**,**b** in the presence of 5% Pd/C in DMF at 30 °C. Diamines **24a**,**b** were not isolated and used without further purification in the next step due to their instability. Reaction of **24a**,**b** with glyoxal in DMF at room temperature afforded the unsubstituted pyrazinosultone derivatives **25a**,**b** in 37 and 40% yield, respectively.[14] On the other hand, when the diketone butane-2,3-dione was condensed with diamine **24a** in a sealed tube at 40 °C, the desired disubstituted pyrazinosultone **26** was isolated in 28% yield. The direct reaction of 3-nitroso sultone intermediates (i.e., without their conversion into the diamino intermediates) with butane-2,3-dione under reflux, as previously described for the preparation of other heterocyclic systems,[15] did not afford the desired pyrazino sultone system.



Scheme 5. Synthesis of 6-substituted pyridosultones **18**, **19**–**21a**,**b**, and **22**: a) 1 N NaOH, 1,4-dioxane, RT, 4 h; b) 1 M DIBAL-H in hexane, CH_2Cl_2, RT; c) NHR^1R^2, RT, 10 min to 3 h, for **22**, 80 °C, 5 h.

Finally, the behavior of the β-amino-γ-sultone system toward β-aldehyde esters as bis-electrophiles was investigated in order to generate the new bicyclic 4-pyridone heterocyclic system (Scheme 7). The condensation of **1b** with methyl 3,3-dimethoxypropanoate in acetic acid at 110 °C yielded the *N*-adducts **27** and **28** (Scheme 7). However, all attempts to cyclize these compounds to the bicyclic 4-pyridone **29** using acidic (acetic acid or TFA), basic (potassium hydroxide or sodium hydride), or thermal cyclization conditions (PhOPh, reflux) failed and only quantitative isomerization to the more stable isomer **28** (*E* configuration) was observed. Similarly, condensation of **1a**,**b** with diethylethoxymethylenemalonate under both acidic (acetic acid, 110 °C) or basic conditions (sodium hydride or potassium hydroxide) gave intermediates **30a**,**b**, and subsequent ring closure to the 6-ethoxycarbonyl bicyclic 4-pyridones **31a**,**b** failed.



Scheme 7. Reaction of β-amino-γ-sultones **1a**,**b** with β-aldehyde esters: a) AcOH, 110 °C, 30 min; b) NaH, RT, 1 h, or TFA, reflux, 1.5 h.

Biological evaluation

All novel compounds prepared were evaluated for their inhibitory effects on the replication of a broad panel of RNA viruses including vesicular stomatitis virus (VSV), respiratory syncytial virus (RSV), Coxsackie virus B4, parainfluenza-3 virus, reovirus-1, Sindbis virus, and Punta Toro virus in Vero and/or HeLa cell cultures (Table 2), and DNA viruses such as herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), vaccinia virus (VV), HIV type 1 and 2, VZV, and HCMV (Table 3) in human embryonic lung (HEL) fibroblasts or in CEM cell cultures. Compounds were also evaluated for their cytostatic activities against malignant human T-lymphocyte (CEM) and cervical carcinoma (HeLa) cells (Table 3). The cytostatic/cytotoxic and antiviral evaluations revealed the following observations:

1) Upon microscopic inspection, compounds **3b**, **15b**, **28**, and **30b** affected HEL cell morphology at minimum cytotoxic concentrations (MCC) ranging between 16 and 50 μM, whereas their cellular toxicity was somewhat less pronounced against the other (Vero, HeLa) cell lines. The other compounds were not cytotoxic at 100 to 400 μM to the cell cultures (Table 3). A limited number of compounds were cytostatic against HEL or CEM cell proliferation. In particular, compound **7** showed the most pronounced antiproliferative activity among all tested compounds (IC_{50}: 0.88–3.4 μM). The closely related compound **6**, lacking the Cl at the aryl substituent and containing a benzyl instead of an ethyl group at the sultone moiety, was about fivefold less cytostatic.

2) Generally, none of the compounds showed an inhibitory activity against the broad panel of RNA viruses in cell culture at subtoxic concentrations (Table 2). The activity observed for compound **7** against a few RNA viruses (i.e., VSV, parainfluenza-3, Sindbis, and Coxsackie; EC_{50}: 2–6.5 μM) (Table 2) may be due to the underlying cytostatic activity of this compound (IC_{50}: 0.88–3.4 μM) (Table 3).

3) Interestingly, several compounds showed antiviral activity against DNA viruses or retroviruses (Table 3). In particular, **3a**, **15a**, and **21a** proved inhibitory to HIV-1 but not HIV-2, with EC_{50} values of 17 to 22 μM, i.e., at a concentration that is at least 10-fold lower than their cytostatic activity against CEM cell proliferation (IC_{50}: ≈183 μM or >250 μM). Their anti-HIV-1 activity is only about fivefold lower than that of reference compound tenofovir (TNF) but two to three orders of magnitude lower than the activity of TSAO-m^3T, an NNRTI consisting of an N3 methylthymidine TSAO derivative. Although the number of fused ring-sultone derivatives synthesized is still very limited, it could be concluded that the concomitant presence of a benzyl and ethyl function at the 3-position and a substituent at the 6-position on the pyridosultone ring system seems to be a pre-

Table 2. Antiviral and cytotoxic activity of the compounds against RNA viruses in cell culture.

Compd	EC_{50} [μM][a]									MCC [μM][b]	
	VSV		RSV	Coxsackie B4		Parainfluenza-3	Reovirus-1	Sindbis	Punta Toro		
	(HEL)	(HeLa)	(HeLa)	(HeLa)	(Vero)	(Vero)	(Vero)	(Vero)	(Vero)	(Vero)	(HeLa)
2a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
3a	>200	>200	>200	>200	>200	>200	120	>200	>200	>200	>200
3b	>8	>40	>40	>40	>40	>40	40	>40	>40	200	200
7	>20	4	>20	>20	6.5	3	≥20	2	≥20	100	>100
10a	>200	>200	>200	>200	>200	>200	120	>200	120	>200	>200
11a	>200	>200	>200	>200	>40	>40	>40	>40	>40	≥200	>200
13	>200	200	>40	>40	>40	>40	>40	>40	>40	200	200
15a	>40	>200	>200	>200	>40	>40	>40	>40	>40	200	≥200
15b	–	>16	>16	>16	>80	>80	>80	>80	>80	400	80
18	>100	>100	>100	>100	>100	>100	>100	>100	>100	≥100	>100
19b	>40	>200	>200	>200	>40	>40	>40	>40	>40	200	>200
22	>40	>200	>200	>200	>40	>40	>40	>40	>40	≥200	≥200
26	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
28	>40	>8	>8	>8	>8	>8	1.6	>8	>8	40	40
30a	120	>200	>200	>200	>200	>200	120	>200	>200	>200	>200
30b	>4	>4	>4	>4	>4	>4	>4	>4	>4	20	20

[a] Half-maximal effective concentration or compound concentration required to inhibit virus-induced cytopathicity by 50%. In some cases (notation ">"), the potential antiviral activity at a higher compound concentration could not be tested due to toxicity. [b] Minimal cytotoxic concentration or compound concentration required to cause a microscopically detectable alteration of normal cell morphology.

Table 3. Antiviral and cytotoxic/cytostatic activity of compounds against DNA viruses and retroviruses in cell culture.

Compd	EC_{50} [μM][a]										MCC [μM][b]	CC_{50} [μM][c]	
	HSV-1 (HEL)	HSV-2 (HEL)	VV (HEL)	HSV TK^- (HEL)	HIV-1 (CEM)	HIV-2 (CEM)	VZV OKA (HEL)	VZV 07/1 (HEL)	HCMV Davis (HEL)	HCMV AD179 (HEL)	(HEL)	(CEM)	(HEL)
2a	>100	>100	>100	>100	>50	>50	91	75	>100	>100	>100	96±12	>100
3a	>200	>200	>200	>200	17±3.5	>50	>100	>100	>100	>100	>200	183±95	50
3b	>8	>8	>8	>8	>50	>50			>100	>100	40	>250	50
6					>10	>10	-					>10	
7	>20	>20	>20	>20	>2	>2	34±6.0	≥8	3.8±3.0	0.65±0.15	100	3.4±0.07	0.88±0.22
8					>50	>50	-					16±1.4	
10a	>200	>200	>200	>200	>50	>50	67	100	>100	>100	>200	111±9.9	>50
11a	>200	>200	>200	>200	>50	>50	>80	39	>80	>80	≥200	27±0.28	52
13	>200	>200	>200	>200			117	70	>400	>80	≥400	-	200
15a	>40	>40	>40	>40	22±3.5	>250	263	271	>400	>400	≥400	>250	>250
15b	>16	>16	>16	>16	>250	>250	>20	>20	>50	>20	≥16	>250	
16					>250	>250	>20	>20	>200	>50	>200	>250	>200
18	>100	>100	>100	>100	>125	>125	>80	63	>80	>80	400	≥125	240
19a					>250	>250						>250	
19b	>40	>40	>40	>40	>250	>250	>80	>80	>80	>400	≥400	≥250	>200
20a					>250	>250						>250	
20b					>250	>250	39	32	>200	>200	>200	207±4.2	162
21a					17±2.1	>250						>250	
21b					>250	>250	93	>50	>200	>200	>200	>250	200
22	>40	>40	>40	>40	≥50	>50	>80	>80	253	>400	>400	90±2.8	>200
25a	–	–	–	–	–	–	>400	>400	>400	>400	>400	–	>200
25b	–	–	–	–	–	–	>80	>80	201	253	>400	–	>200
26	>200	>200	>200	>200	110±14	>250	280	>80	>80	>400	>400	>250	>200
28	>40	>40	>40	>40	>50	>50	10	9	9	16	50	26±3.7	30
30a	>200	>200	>200	>200	>250	>250	>100	>100	>100	>100	>200	242±12	>100
30b	>4	>4	>4	>4	>250	>250	>20	>20	>20	>20	20	>250	>100
GCV[d]	0.02	0.03	>100	1.0	>100	>100	–	–	11	13	>150	>100	250
ACV[d]	0.2	0.2	>200	>200	>200	>200	1.5	96	–	–	>200	>200	>200
CDF[d]	0.8	0.8	6.0	2.0	>100	>100	–	–	0.63	1.3	>100	>100	104
17[d]	>20	>20	>20	>20	>20	>20	5.7	7.5	6.9	9.3	≥20	≥20	48
TNF[d]	>100	>100	>100	>100	5.9	4.9	>100	>100	>100	>100	>100	>100	>100
TSAO-m^3T[d]	>100	>100	>100	>100	0.06	>100	>100	>100	>100	>100	>100	>100	>100

[a] Half-maximal effective concentration or compound concentration required to inhibit virus-induced cytopathicity by 50%. In some cases (notation">"), the potential antiviral activity at a higher concentration could not be tested due to toxicity. [b] Minimal cytotoxic concentration or compound concentration required to cause a microscopically detectable alteration of normal cell morphology. [c] 50% cytostatic concentration or compound concentration required to inhibit CEM or HEL cell proliferation by 50%. [d] Reference compounds: GCV, ganciclovir; ACV, acyclovir; CDF, cidofovir; **17**, 4-substituted γ-sultone derivative **17** from Ref. [5]; TNF, tenofovir; TSAO-m^3T, *tert*-butyldimethylsilyl aminooxathiole dioxide N3 methylthymidine.

requisite for anti-HIV-1 activity (compare anti-HIV-1 data of compound **3a** *vs.* compounds **3b**, **10a**, **11a**, and **13**). Therefore, it would be interesting to explore the effects of different substituents on the pyridine ring moiety that afforded antivirally active compounds (i.e., methyl groups and substituted amides) and on the pyrazine moiety of the pyrazinosultones, keeping the benzyl and ethyl functional groups in the sultone. In addition, the latter two groups on sultones **3a**, **15a**, and **21a** should be further functionalized in an attempt to obtain more active derivatives. On the other hand, compound **28** showed suppressive activity against HCMV and VZV at 9–16 μM. However, it should be mentioned that its cytotoxic/cytostatic activity in HEL cell cultures was between 30 and 50 μM (and 26 μM against CEM cells). Finally, compound **7** was found to markedly inhibit HCMV-induced cytopathicity in HEL cell cultures (EC_{50}: 0.65–3.8 μM); however, this activity seems to be due to its antiproliferative activity in the HEL (and CEM) cell cultures. A borderline activity was noticed for **20b** against VZV.

Conclusions

We herein report for the first time the successful application of the β-amino-γ-sultone system as an intermediate for the synthesis of unusual condensed nitrogen-containing heterocyclic compounds. The reactivity of the easily available β-amino-γ-sultone heterocyclic system with a variety of bis-electrophiles is described. Different classes of 3H-[1,2]-oxathiole [4,3-b]pyridine and pyrazine 1,1-dioxide bicyclic heterocyclic systems were obtained in a single reaction. Efficient synthetic routes for the preparation of 6- or 7-substituted pyridosultone heterocycles were developed. All novel compounds were evaluated for their antiviral and cytostatic activities. Interestingly, compounds **3a**, **15a**, and **21a** may be regarded as potential specific anti-HIV-1 lead compounds, and compound **7** as a potential antiproliferative candidate agent that may be further explored for structural optimization.

Experimental Section

Chemistry

Melting points were determined in a Reichert-Jung Thermovar hot-stage microscope equipped with a polarizer. IR spectra were obtained on a PerkinElmer Spectrum One spectrophotometer. Microanalyses were obtained on a Heraeus CHN-O-RAPID instrument. Mass spectra were measured on a quadrupole mass spectrometer equipped with an electrospray source (Hewlett–Packard, LC/MC HP 1100). ^{1}H NMR spectra were recorded on a Varian Gemini 200, a Varian XL-300, -400, or -500 spectrometer operating at 200, 300, 400 or 500 MHz with Me_4Si as the internal standard. ^{13}C NMR spectra were recorded on abovementioned spectrometers operating at 50, 75, 100 or 125 MHz. Analytical 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 (silica gel 60 PF_{254} containing gypsum (Merck), layer thickness of 1 mm, flow rate of 5 mL min^{-1}). Toluene, 1,4-dioxane, CH_2Cl_2, 1,2-dichloroethane, and CH_3CN were dried by reflux over CaH_2. THF was dried by reflux over Na.

General procedures for the reaction of β-amino-γ-sultones 1a,b with 1,3-dicarbonilic reagents: *Method A*: *Reactions in the presence of AcOH*: A solution of the corresponding β-amino-γ-sultone (0.39 mmol) and the appropriate β-dielectrophile (0.59 mmol) in AcOH (0.5 mL) was stirred at 110 °C. When the reaction was completed (monitored by TLC hexane/EtOAc, 2:1), the solvent was evaporated and the residue was purified by CCTLC.

Method B: Reactions in the presence of KOH: A solution of the corresponding β-amino-γ-sultone (0.32 mmol), the appropriate β-dielectrophile (0.85 mmol), and powdery KOH (0.43 mmol) in EtOH (2 mL) and dry toluene (5 mL) was stirred at 100 °C. Powdery KOH (0.059 mmol) was added three times every 30 min, and an extra amount of the β-dielectrophile (0.068 mmol) was added 1 h later. When the reaction was completed (monitored by TLC hexane/EtOAc, 2:1), the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with H_2O, dried, and evaporated. The residue was purified by CCTLC.

3-Benzyl-3-ethyl-6-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (3a): Compound **1a**[9] (100 mg, 0.395 mmol) was reacted with (*E*)-3-ethoxy-2-methylacrylaldehyde in AcOH according to the general procedure (Method A) for 3 h. The final residue was purified by CCTLC using hexane/EtOAc (3:1) as eluent. The fastest moving fractions afforded 31 mg (26%) of **3a** as a white solid: mp (MeOH): 103–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.81$ (m, 3H), 2.21 (m, 2H), 2.51 (s, 3H), 3.35 and 3.45 (AB system, $J = -14.3$ Hz, 2H), 7.23 (m, 5H), 7.83 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 7.6$, 20.4, 30.0, 44.4, 98.9, 124.6, 127.0, 127.2, 128.3, 130.5, 130.9, 134.1, 154.6, 159.4; MS (ES^+) *m/z* 304 $[M+1]^+$, 326.0 $[M+Na]^+$; Anal. calcd for $C_{16}H_{17}NO_3S$: C 63.34, H 5.65, N 4.62, found: C 63.30, H 5.32, N 4.55.

From the fractions with intermediate mobility 48 mg (38%) of **3-Benzyl-3-ethyl-4-[(*E*)-2-formylprop-1-enylamino]amine-5*H*-1,2-oxathiole-2,2-dioxide (2a)** was isolated as a white solid: mp (toluene): 130–131 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta = 0.92$ (m, 3H), 1.92 (m, 1H), 1.73 (s, 3H), 2.21 (m, 1H), 6.49 (s, 1H), 7.27 (m, 5H), 7.40 (d, $J = 9.3$ Hz,1H), 8.18 (d, $J = 9.3$ Hz, 1H), 9.35 (s, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 7.2$, 28.9, 29.8, 43.4, 93.6, 97.1, 121.9, 127.7, 128.6, 131.4, 134.6, 146.2, 152.7, 191.5; MS (ES^+) *m/z* 322.0 $[M+1]^+$; Anal. calcd for $C_{16}H_{19}NO_4S$: C 59.79, H 5.96, N 4.36, found: C 59.43, H 5.76, N 4.21.

From the slowest moving fractions 20 mg (20%) of unreacted starting material **1a** was recovered.

When compound **1a**[9] (100 mg, 0.395 mmol) was reacted with (*E*)-3-ethoxy-2-methylacrylaldehyde in the presence of KOH at 100 °C according to Method B for 2 h, 55 mg (46%) of **3a** was isolated after purification by CCTLC.

3,3-Dibenzyl-6-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (3b): A solution of compound **1b**[9] (100 mg, 0.32 mmol) in EtOH and dry toluene was reacted with (*E*)-3-ethoxy-2-methylacrylaldehyde in the presence of KOH at 100 °C following Method B. The final residue was purified by CCTLC on the Chromatotron (hexane/EtOAc, 3:1) to afford 47 mg (40%) of **3b** as a white solid: mp (MeOH): 151–152 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H), 3.31 and 3.45 (AB system, $J = -14.4$ Hz, 4H), 7.08 (m, 5H), 7.20 (m, 5H), 7.61 (s, 1H), 8.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 18.4, 44.9, 97.0, 127.2, 127.3, 128.1, 130.2, 130.9, 133.7, 134.4, 155.4, 156.5; MS (ES^+) *m/z* 366.3 $[M+1]^+$, 388.4 $[M+Na]^+$; Anal. calcd for $C_{21}H_{19}NO_3S$: C 69.02, H 5.24, N 3.83, found: C 68.94, H 5.00, N 3.71.

3,3-Dibenzyl-6-phenyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (6): A solution of compound **1b**[9] (100 mg, 0.32 mmol) in

AcOH (2 mL) was treated with (*E*)-2-phenyl-3-propoxyacrylaldehyde (**4**)[11] (121 mg, 0.64 mmol) in the presence of a catalytic amount of TFA (60 μL). The mixture was stirred for 1 h at 100 °C and for 4 h at 80 °C, and the solvent was evaporated to dryness. The residue was purified by CCTLC (hexane/EtOAc, 3:1) to afford 25 mg (18%) of **6** as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.35$ (AB system, $J = -14.4$ Hz, 2H), 3.50 (AB system, $J = -14.4$ Hz, 2H), 7.18 (m, 10H), 7.52 (m, 5H), 7.97 (d, $J = 2.1$ Hz, 1H), 9.12 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 44.13$, 97.33, 127.5, 128.3, 128.4, 129.6, 129.7, 131.2, 133.8, 135.5, 137.8, 154.0, 157.9; MS (ES^+) *m/z* 428.0 $[M+1]^+$; Anal. calcd for $C_{26}H_{21}NO_3S$: C 73.04, H 4.95, N 3.28, found: C 73.23, H 5.06, N 3.21.

From the slowest moving fractions 25 mg (25%) of unreacted starting material **1b** was recovered.

3-Benzyl-6-(4-chlorophenyl)-3-ethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (7): A solution of compound **1b**[9] (100 mg, 0.395 mmol) in acetic acid (2 mL) was treated with (*E*)-2-(4-chlorophenyl)-3-propoxyacrylaldehyde (**5**)[11] (178 mg, 0.79 mmol) in the presence of a catalytic amount of TFA (60 mL). The mixture was stirred at 100 °C for 1 h and at 80 °C for 4 h and the solvent was evaporated to dryness. The residue was purified by CCTLC (hexane/EtOAc, 6:1). From the fastest moving fractions 26 mg (16%) of **7** were isolated as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.55$ (t, $J = 0.55$ Hz, 3H), 1.88 (m, 1H), 1.99 (m, 1H), 3.17 (AB system, $J = -14.3$ Hz, 2H), 6.94 (m, 9H), 7.83 (d, $J = 1.95$ Hz, 1H), 8.79 (d, $J = 1.95$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 6.7$, 28.7, 29.7, 43.6, 97.9, 126.9, 127.1, 127.2, 127.6, 128.8, 129.9, 132.7, 132.8, 134.9, 135.5, 152.4, 157.3; MS (ES^+) *m/z* 401.0 $[M+1]^+$; Anal. calcd for $C_{21}H_{18}ClNO_3S$: C 63.07, H 4.54, N 3.50, found: C 63.21, H 4.46, N 3.41.

From the lowest moving fractions, 40 mg (24%) of **3-Benzyl-3-ethyl-4-[(*E*)-2-formyl-1-benzylideneamino]amine-5*H*-1,2-oxathiole-2,2-dioxide** (**8**) was isolated as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.97$ (t, $J = 7.3$ Hz, 3H), 1.99 (m, 2H), 3.20 (s, 2H), 5.97 (s, 1H), 7.24 (m, 9H), 9.74 (d, $J = 3.9$ Hz, 1H), 11.32 (d, $J = 11.1$ Hz, 1H); MS (ES^+) *m/z* 418.0 $[M+1]^+$; Anal. calcd for $C_{21}H_{20}ClNO_4S$: C 60.35, H 4.82, N 3.35, found: C 60.26, H 4.86, N 3.31.

3-Benzyl-3-ethyl-5-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (10a): Following the general procedure (Method A), compound **1a**[9] (100 mg, 0.395 mmol) was reacted with 4,4-dimethoxybutan-2-one in AcOH for 6 h. The final residue was purified by CCTLC (hexane/EtOAc, 3:1). The fastest moving fractions afforded 66 mg (52%) of 3-benzyl-4-((*Z*)-1-buten-3-ona)amine-3-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**9a**) as a white solid: mp (toluene): 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (m, 3H), 1.88 (m, 1H), 1.93 (m, 1H), 2.26 (s, 3H), 3.19 (s, 2H), 5.63 (d, $J = 8.1$ Hz, 1H), 5.88 (s, 1H), 6.77 (dd, $J = 8.1$, 10.6 Hz, 1H), 7.28 (m, 5H), 11.25 (bd, $J = 10.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.3$, 29.5, 30.5, 44.0, 92.7, 96.5, 104.3, 127.6, 128.3, 132.7, 140.5, 151.3, 201.8; MS (ES^+) *m/z* 322.1 $[M+1]^+$, 665.2 $[2M+Na]^+$; Anal. calcd for $C_{16}H_{19}NO_4S$: C 59.79, H 5.96, N 4.36, found: C 59.55, H 5.52, N 4.08.

From the slowest moving fractions 14 mg (12%) of **10a** was isolated as a white solid: mp (MeOH): 101–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.81$ (m, 3H), 2.13 (m, 1H), 2.22 (m, 1H), 2.77 (s, 3H), 3.35 and 3.44 (AB system, $J = -14.5$ Hz, 2H), 7.24 (m, 5H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 7.8$, 25.1, 30.5, 44.7, 98.7, 123.7, 125.2, 127.3, 128.2, 131.4, 131.0, 134.0, 154.7, 159.4; MS (ES^+) *m/z* 304.1 $[M+1]^+$, 326.0 $[M+Na]^+$; Anal. calcd for $C_{16}H_{17}NO_3S$: C 63.34, H 5.65, N, 4.62, found: C 63.09, H 5.40, N 4.44.

(±)-3-Benzyl-3-ethyl-7-methyl-3*H*-[1,2]-oxathiole[4,5-*b*]pyridine 1,1-dioxide (11a): To a solution of intermediate **9a** (50 mg, 0.155 mmol) in EtOH (2 mL) and dry toluene (5 mL), powdery KOH (0.43 mmol) was added. The mixture was stirred for 3 h at 100 °C and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with H_2O, dried, and evaporated. The residue was purified by CCTLC (hexane/EtOAc, 3:1) to yield 21 mg of **11a** (44%) as a white solid: mp (MeOH): 109–110 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.81$ (m, 3H), 2.16 (m, 1H), 2.22 (m, 1H), 2.63 (s, 3H), 3.36 and 3.45 (AB system, $J = -14.4$ Hz, 2H), 7.29 (m, 6H), 8.78 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 7.7$, 17.3, 30.7, 44.9, 98.4, 125.4, 127.3, 127.5, 128.2, 131.0, 134.0, 145.0, 154.7, 159.5; MS (ES^+) *m/z* 304.1 $[M+1]^+$, 326.0 $[M+Na]^+$; Anal. calcd for $C_{16}H_{17}NO_3S$: C 63.34, H 5.65, N 4.62, found: C 63.21, H 5.52, N 4.49.

One-pot reaction: When compound **1a**[9] (100 mg, 0.395 mmol) was reacted with (*E*)-3-ethoxy-2-methylacrylaldehyde in the presence of KOH at 100 °C according to the general procedure (Method B), 55 mg (46%) of **11a** was isolated after purification by CCTLC.

3,3-Dibenzyl-7-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (11b): Following the general procedure (Method B), a solution of compound **1b**[9] (100 mg, 0.32 mmol) in EtOH and dry toluene was reacted with (*E*)-3-ethoxy-2-methylacrylaldehyde in the presence of KOH at 100 °C for 3 h. The final residue was purified by CCTLC (hexane/EtOAc, 3:1) to afford 47 mg (40%) of **11b** as a white solid: mp (MeOH): 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 3.30 and 3.45 (AB system, 4H, $J = -14.4$ Hz), 7.14 (m, 11H), 8.73 (d, 1H, $J = 4.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 17.1, 43.8, 96.5, 125.3, 127.2, 128.0, 130.9, 133.6, 144.7, 154.2, 159.2; MS (ES^+) *m/z* 366.6 $[M+1]^+$, 388.3 $[M+Na]^+$; Anal. calcd for $C_{21}H_{19}NO_3S$: C 69.02, H 5.24, N 3.83, found: C 68.88, H 5.12, N 3.61.

3,3-Dibenzyl-5,7-dimethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (12): According to the general procedure (Method B), a solution of compound **1b** (150 mg, 0.48 mmol) in EtOH and dry toluene was reacted with pentane-2,4-dione in the presence of KOH at 100 °C for 3 h. The final residue was purified by CCTLC (hexane/EtOAc, 3:1) to afford 10 mg (6%) of **12** as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H), 2.77 (s, 3H), 3.36 and 3.48 (AB system, 4H, $J = -13.8$ Hz), 7.25 (m, 11H, Ph); MS (ES^+) *m/z* 380.5 $[M+1]^+$, 402.3 $[M+Na]^+$; Anal. calcd for $C_{22}H_{21}NO_3S$: C 69.63, H 5.58, N 3.69, found: C 69.45, H 5.52, N, 3.63.

General procedure for the reaction of β-amino-γ-sultones 1a with α,β-unsaturated aldehydes: A mixture of the corresponding β-amino-γ-sultone (0.39 mmol), the appropriate α,β-unsaturated aldehyde (1.6 mmol), and 10% Pd on carbon (Pd/C, 0.004 mmol) in dry toluene (3 mL) was stirred in an Ace pressure tube at 100 °C. When the reaction was completed (monitored by TLC hexane/EtOAc, 2:1), the mixture was filtered through a Celite pad and the solvent was evaporated. The residue was purified by CCTLC (hexane/EtOAc, 2:1).

(±)-3-Benzyl-3-ethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (13): Following the general procedure, compound **1a**[9] (100 mg, 0.39 mmol) was reacted with acrylaldehyde (90 mg, 1.6 mmol) and 10% Pd/C for 48 h to afford 20 mg (18%) of **13** as a white solid: mp (MeOH): 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.78 (m, 3H), 2.15 (m, 1H), 2.24 (m, 1H), 3.34 and 3.41 (AB system, $J = -14.3$ Hz, 2H), 7.29, 7.18 (2 m, 5H), 7.46 (dd, $J = 4.7$, 7.9 Hz, 1H), 8.00 (dd, $J = 1.5$, 4.7 Hz, 1H), 8.91 (dd, $J = 1.5$, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.6$, 30.7, 44.5, 98.8, 123.9, 127.2, 127.7, 128.07, 130.6, 130.8, 133.6, 154.9, 159.4; MS (ES^+) *m/z* 290.0

$[M+1]^+$ 312.0 $[M+Na]^+$, 601.1 $[2M+Na]^+$; Anal. calcd for $C_{15}H_{15}NO_3S$: C 62.26, H 5.23, N 4.84, found: C 62.01, H 4.97, N, 4.69.

3-Benzyl-3-ethyl-5-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (10a) and (±)-3-benzyl-3-ethyl-7-methyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (11a): Compound **1a**[9] (100 mg, 0.585 mmol) was reacted with (*E*)-but-2-enal (168 mg, 2.4 mmol) and 10% Pd/C according to the general procedure for 72 h. The final residue (mixture of 5-methyl and 7-methylpyridosultones **10a** and **11a**) was purified by CCTLC (hexane/EtOAc, 2:1). From the fastest moving fractions 9 mg (5%) of **10a** was isolated as a white solid. From the slowest moving fractions 24 mg (20%) of **11a** was isolated as a white solid.

General procedure for the reaction of β-amino-γ-sultones 1a,b with electron-deficient olefins in the presence of palladium acetate: To a solution of the 3-(dimethylamino)methylenenamino derivative **14a,b**[9] (1.44 mmol) in AcOH (8 mL) the corresponding electron-deficient olefin (1.73 mmol) and $Pd(OAc)_2$ (1.73 mmol) were added. The mixture was heated for 3 h at 100 °C and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (3×10 mL). The combined organic phases were washed with brine (3×10 mL), dried over Na_2SO_4, and evaporated to dryness. The final residue was purified by CCTLC.

(±)-3-Benzyl-3-ethyl-6-methoxycarbonyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (15a): According to the general procedure compound **14a**[9] (450 mg, 1.44 mmol) was treated with methyl acrylate (157 μL, 1.73 mmol) and $Pd(OAc)_2$ (388 mg, 1.73 mmol) in AcOH for 3 h at 100 °C. The final residue was purified by CCTLC (hexane/EtOAc, 3:1) to give **15a** (230 mg, 46%) as a white solid: mp (MeOH): 120–121 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=0.77$ (m, 3H), 2.17 (m, 1H), 2.32 (m, 1H), 3.45 (s, 2H), 3.99 (s, 3H), 7.16 (m, 5H), 8.76 (d, $J=1.8$ Hz, 1H), 9.51 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta=6.2$, 29.9, 43.1, 51.7, 126.3, 126.6, 127.1, 127.2, 130.1, 133.1, 155.1, 161.9, 162.8; MS (ES^+) *m/z* 348.1 $[M+1]^+$, 370.3 $[M+Na]^+$; Anal. calcd for $C_{17}H_{17}NO_5S$: C 58.78, H 4.93, N 4.03, found: C 58.49, H 4.70, N 3.83.

3,3-Dibenzyl-6-methoxycarbonyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (15b): A solution of compound **14b**[9] (450 mg, 1.22 mmol) in AcOH was reacted with methyl acrylate (132 μL, 1.46 mmol) and $Pd(OAc)_2$ (332 mg, 1.46 mmol) according to the general procedure. The final residue was purified by CCTLC (hexane/EtOAc, 4:1) to give **15b** (225 mg, 45%) as a white solid; mp: (MeOH): 179–180 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=3.41$ and 3.57 (AB system, $J=-14.5$ Hz, 4H), 3.97 (s, 3H), 7.14 (m, 10H), 8.62 (d, $J=1.8$ Hz, 1H), 9.54 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): $\delta=44.2$, 53.3, 98.0, 128.0, 128.0, 128.6, 128.9, 131.7, 132.7, 134.6, 156.5, 163.5; IR (KBr): 1783 (CO) 1356, 1182 (SO_2); MS (ES^+) *m/z* 410.1 $[M+1]^+$, 431.1 $[M+Na]^+$, 841.3 $[2M+Na]$; Anal. calcd for $C_{22}H_{19}NO_5S$: C 64.53, H 4.68, N 3.42, found: C 64.32, H 4.42, N 3.29.

3,3-Dibenzyl-6-acetyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (16): Following the general procedure, compound **14b**[9] (100 mg, 0.24 mmol) was treated with 3-buten-2-one (27 μL, 0.32 mmol) and $Pd(OAc)_2$ (73 mg, 0.32 mmol) in AcOH. The final residue was purified by CCTLC (hexane/EtOAc, 4:1) to give **16** (54 mg, 51%) as a white solid: mp (MeOH): 198–200 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=2.73$ (s, 3H), 3.40 and 3.57 (AB system, $J=-14.5$ Hz, 4H), 7.15 (m, 10H), 8.67 (d, $J=1.8$ Hz, 1H), 9.54 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): $\delta=27.2$, 44.1, 97.8, 128.0, 128.8, 128.5, 131.7, 132.5, 134.6, 136.7, 155.7, 162.5; IR (KBr): 1692 (CO), 1352 (SO_2); MS (ES^+) *m/z* 394.0 $[M+1]^+$, 416.0 $[M+Na]^+$, 809.0 $[2M+Na]^+$; Anal. calcd for $C_{22}H_{19}NO_4S$: C 67.16, H 4.87, N 3.56, found: C 67.01, H 4.57, N 3.22.

(±)-3-Benzyl-3-ethyl-6-methylsulfonyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (17): According to the general procedure, compound **14a**[9] (100 mg, 0.32 mmol) was treated with methylvinylsulfone (102 μL, 1.1 mmol) and $Pd(OAc)_2$ (87 mg, 0.39 mmol) in AcOH for 1 h at 100 °C. The final residue was purified by CCTLC (hexane/EtOAc, 3:1) to give **17** (40 mg, 34%) as a white solid: mp (MeOH): 184–185 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=0.77$ (m, 3H), 2.15 (m, 1H), 2.33 (m, 1H), 3.44 (s, 2H), 7.18 (m, 5H), 8.66 (d, $J=1.7$ Hz, 1H), 9.48 (d, $J=1.7$ Hz, 1H); MS (ES^+) *m/z* 368.0 $[M+1]^+$, 390.0 $[M+Na]^+$, 757.0 $[2M+Na]^+$; Anal. calcd for $C_{16}H_{17}NO_5S_2$: C 52.30, H 4.66, N 3.81, found: C 52.21, H 4.44, N, 3.59.

3,3-Dibenzyl-6-carboxy-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (18): To a solution of **15b** (100 mg, 0.24 mmol) in 1,4-dioxane (6 mL), a solution of 1 N NaOH in 1,4-dioxane (0.54 mL, 0.54 mmol) was added, and the mixture was stirred for 4 h at RT. Then, the mixture was neutralized with 0.1 N HCl. The resulting mixture was dissolved in EtOAc (20 mL) and was successively washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). Finally, the organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The final residue was purified by CCTLC (CH_2Cl_2/MeOH, 20:1) to give 38 mg (40%) of **18** as a white solid: mp (MeOH): > 340 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta=3.31$ (bs, 2H), 3.47 (bs, 2H), 7.20 (m, 10H), 8.71 (bs, 1H), 9.65 (bs, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta=44.1$, 97.7, 127.8, 127.7, 128.7, 128.8, 131.8, 132.7, 134.9, 157.9, 161.4; IR (KBr): 1604 (CO), 1351, 1193 (SO_2); MS (ES^+) *m/z* 396.1 $[M+1]^+$, 418.0 $[M+Na]^+$; Anal. calcd for $C_{21}H_{17}NO_5S$: C 63.79, H 4.33, N 3.54, found: C 63.54, H 4.29, N 3.30.

(±)-3-Benzyl-3-ethyl-6-hydroxymethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (19a): To a solution of **15a** (100 mg, 0.29 mmol) in dry CH_2Cl_2 (2 mL), a 1 M solution of DIBAL-H in hexane (0.56 mL, 0.56 mmol) was added. The mixture was stirred for 0.5 h at RT. Then, a saturated solution of NH_4Cl in H_2O (3 mL) was added and the mixture was stirred for 30 min at RT. The solid was filtered off and the solvent was removed under reduced pressure. The final residue was purified by CCTLC (hexane/EtOAc, 1: 2) to give **19a** (70 mg, 78%) as a white solid: mp (MeOH): 85–86 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta=0.74$ (m, 3H), 2.10 (m, 1H), 2.26 (m, 1H), 3.39 (s, 2H), 4.77 (t, $J=5.1$ Hz, 1H), 4.86 (d, $J=5.1$ Hz, 2H), 7.19 (m, 5H), 8.19 (d, $J=1.9$ Hz, 1H), 9.02 (d, $J=1.9$ Hz, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta=8.3$, 31.8, 45.5, 62.0, 99.5, 127.9, 128.4, 128.9, 129.1, 131.8, 135.3, 140.7, 155.2, 158.4; MS (ES^+) *m/z* 320.0 $[M+1]^+$, 342.0 $[M+Na]^+$; Anal. calcd for $C_{16}H_{17}NO_4S$: C 60.17, H 5.37, N 4.39, found: C 59.93, H 5.11, N 4.07.

3,3-Dibenzyl-6-hydroxymethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (19b): To a solution of **15b** (100 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL), a solution of 1 M DIBAL-H in hexane (0.48 mL, 0.48 mmol) was added. The mixture was stirred for 1 h at RT. The final residue was purified by CCTLC (hexane/EtOAc, 1:1) to give **19b** (83 mg, 91%) as a white solid: mp (MeOH): 187–188 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta=3.42$ and 3.53 (AB system, $J=-14.4$ Hz, 4H), 4.81 (s, 2H), 7.16 (m, 10H), 8.02 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): $\delta=44.1$, 61.2, 97.2, 127.5, 127.9, 128.5, 128.6, 131.5, 134.7, 140.2, 154.4, 158.0; IR (KBr): 1338 (SO_2); MS (ES^+) *m/z* 382.1 $[M+1]^+$, 404.1 $[M+Na]^+$, 785.3 $[2M+Na]^+$; Anal. calcd for $C_{21}H_{19}NO_4S$: C 66.12, H 5.02, N 3.67, found: C 66.00, H 4.82, N 3.31.

(±)-3-Benzyl-3-ethyl-6-carbamoyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (20a): A solution of **15a** (100 mg, 0.29 mmol) and MeOH saturated with ammonia (6 mL) was stirred for 2 h at

RT. The solvent was evaporated and the residue was purified by CCTLC (hexane/EtOAc, 1:1) to give **20a** (75 mg, 80%) as a white solid: mp (MeOH): 148–149 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 0.77 (m, 3H), 2.15 (m, 1H), 2.33 (m, 1H), 3.44 (s, 2H), 7.18 (m, 5H), 8.66 (d, J = 1.7 Hz, 1H), 9.48 (d, J = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 8.3, 31.9, 45.3, 99.9, 128.3, 128.8, 129.2, 131.1, 132.2, 132.3, 135.3, 156.3, 162.5, 165.9; MS (ES^+) m/z 333.1 $[M+1]^+$, 355.1 $[M+Na]^+$, 687.1 $[2M+Na]^+$; Anal. calcd for $C_{16}H_{16}N_2O_4S$: C 57.82, H 4.85, N 8.43, found: C 57.65, H 4.71, N 8.32.

3,3-Dibenzyl-6-carbamoyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (20b): A solution of **15b** (100 mg, 0.24 mmol) and MeOH saturated with ammonia (6 mL) was stirred for 3 h at RT. The solvent was evaporated and the residue was purified by CCTLC (hexane/EtOAc, 1:1) to give **20b** (41 mg, 43%) as a white solid: mp (MeOH): 200–201 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 3.40 and 3.56 (AB system, J = −14.4 Hz, 4H), 7.18 (m, 10H), 7.88 (bs, 2H), 8.50 (d, J = 1.8 Hz, 1H), 9.51 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 44.5, 98.2, 128.2, 129.1, 132.1, 128.5, 132.0, 130.7, 135.0, 156.0, 162.2, 166.6; IR (KBr): 1687 (CO), 1356, 1193 (SO_2); MS (ES^+) m/z 395.1 $[M+1]^+$, 811.2 $[2M+Na]^+$; Anal. calcd for $C_{21}H_{18}N_2O_4S$: C 63.94, H 4.60, N 7.10, found: C 63.67, H 4.29, N 6.90.

(±)-3-Benzyl-3-ethyl-6-methylcarbamoyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (21a): A solution of **15a** (100 mg, 0.29 mmol) and methylamine (8 M solution in EtOH, 7 mL) was stirred for 3 h at RT and the solvent was removed under reduced pressure. The residue was purified by CCTLC (hexane/EtOAc, 1:1) to give **21a** (58 mg, 58%) as a white foam. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ = 0.83 (m, 3H), 2.21 (m, 1H), 2.36 (m, 1H), 3.43 (s, 2H), 7.11 (m, 5H), 8.69 (d, J = 1.8 Hz, 1H), 9.51 (d, J = 1.8 Hz, 1H); MS (ES^+) m/z 347.3 $[M+1]^+$; Anal. calcd for $C_{17}H_{18}N_2O_4S$: C 58.94, H 5.24, N 8.09, found: C 58.75, H 5.31, N 8.15.

3,3-Dibenzyl-6-methylcarbamoyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (21b): A solution of **15b** (100 mg, 0.24 mmol) and methylamine (8 M solution in EtOH, 7 mL) was stirred for 10 min at RT and the solvent was removed under reduced pressure. The residue was purified by CCTLC (hexane/EtOAc, 1:1) to give **21b** (68 mg, 68%) as a white solid: mp (MeOH): 195–198 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 303 K): δ = 2.95, 2.94 (2 s, 3H), 3.42 and 3.57 (AB system, J = 14.3 Hz, 4H), 7.16 (m, 10H), 8.14 (bs, 1H), 8.45 (d, J = 1.8 Hz, 1H), 9.47 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 303 K): δ = 26.8, 44.2, 98.0, 128.0, 128.8, 132.1, 128.1, 131.8, 130.0, 135.7, 155.3, 161.6, 164.1; IR (KBr): 1671 (CO), 1341, 1194 (SO_2); MS (ES^+) m/z 409.0 $[M+1]^+$, 431.0 $[M+Na]^+$, 839.0 $[2M+Na]^+$; Anal. calcd for $C_{22}H_{20}N_2O_4S$: C 64.69, H, 4.94; N 6.86, found: C 64.83, H 4.72, N 6.65.

3,3-Dibenzyl-6-methylethylcarbamoyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyridine 1,1-dioxide (22): To a mixture of $AlCl_3$ (42 mg, 0.32 mmol) in dry 1,2-dicloroethane (4 mL) at 0 °C, a solution of ethylmethylamine (51 μL, 0.60 mmol) in 1,2-dichloroethane (2 mL) was slowly added. The reaction mixture was allowed to reach RT and compound **15b** (100 mg, 0.24 mmol) was added. The mixture was stirred in an Ace pressure tube for 5 h at 80 °C. Then, the reaction was quenched with H_2O, and the mixture was stirred for 30 min at RT and filtered through a Celite pad. The organic layer was washed with a saturated $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and evaporated to dryness. The final residue was purified by CCTLC (hexane/EtOAc, 2:1) to give **22** (54 mg, 52%) as a white solid: mp (MeOH): 150–152 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 303 K): δ = 1.10, 1.18 (2t, J = 6.8 Hz, 3H), 2.92, 3.02 (2 s, 3H), 3.18, 3.54 (2q, J = 6.8 Hz, 2H), 3.41 and 3.56 (AB system, J = −14.4 Hz, 4H), 7.15 (m, 10H), 9.10 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 303 K): δ = 12.1, 13.6, 32.3, 36.9, 42.9, 46.4, 44.3, 97.8, 127.9, 129.5, 130.0, 128.8, 131.8, 134.8, 153.6, 154.3; IR (KBr): 1639 (CO), 1353, 1182 (SO_2); MS (ES^+) m/z 437.2 $[M+1]^+$, 895.2 $[2M+Na]^+$; Anal. calcd for $C_{24}H_{24}N_2O_4S$: C 66.03, H 5.54, N, 6.42, found: C 65.84, H 5.34, N 6.26.

(±)-3-Benzyl-3-ethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyrazine 1,1-dioxide (25a): A solution of **23a**[8] (100 mg, 0.35 mmol) in DMF (4 mL) was hydrogenated at 30 psi in the presence of 5% Pd/C (2 mg, 0.001 mmol) for 1 h at 30 °C. The catalyst was removed and glyoxal (44 μL, 0.39 mmol) was added. The mixture was stirred for 4 h at RT. The solvent was evaporated to dryness and the residue was purified by CCTLC (hexane/EtOAc, 2:1) to give **25a** (50 mg, 37%) as a white solid: mp (MeOH): 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (m, 3H), 2.22 (m, 1H), 2.32 (m, 1H), 3.47 (s, 2H), 7.20 (m, 5H), 8.92 (d, J = 2.4 Hz, 1H), 9.17 (d, J = 2.4 Hz, 1H); MS (ES^+) m/z 291.0 $[M+1]^+$; Anal. calcd for $C_{14}H_{14}N_2O_3S$: C 57.92, H 4.86, N 9.65, found: C 57.70, H 4.61, N 9.42.

3,3-Dibenzyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyrazine 1,1-dioxide (25b): A solution of **23b**[9] (100 mg, 0.29 mmol) in DMF (2 mL) was hydrogenated as described for the preparation of **25a**. The catalyst was removed and glyoxal (38 μL, 0.33 mmol) was added. The mixture was stirred for 4 h at RT. The solvent was evaporated to dryness and the residue was purified by CCTLC (hexane/EtOAc, 2:1) to give **25b** (41 mg, 40%) as a white solid: mp (MeOH): 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.34 and 3.46 (AB system, J = −14.4 Hz, 2H), 7.19, 7.24 (2 m, 10H), 8.62 (d, J = 2.32 Hz, 1H), 8.86 (d, J = 2.32 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 43.8, 95.0, 127.6, 128.3, 130.9, 132.8, 145.9, 148.3, 153.9; MS (ES^+) m/z 353.0 $[M+1]^+$, 375.0 $[M+Na]^+$, 727.1 $[2M+Na]^+$; Anal. calcd for $C_{19}H_{16}N_2O_3S$: C 64.76, H 4.58, N 7.95, found: C 64.63, H 4.33, N 7.69.

(±)-3-Benzyl-3-ethyl-5,6-dimethyl-3*H*-[1,2]-oxathiole[4,3-*b*]pyrazine 1,1-dioxide (26): A solution of **23a**[9] (100 mg, 0.35 mmol) in DMF (4 mL) was hydrogenated at 30 psi in the presence of 5% Pd/C (2 mg, 0.001 mmol) for 30 min at 30 °C. The catalyst was removed and butane-2,3-dione (68 μL, 0.77 mmol) was added. The mixture was stirred in an Ace pressure tube for 14 h at 40 °C. The solvent was evaporated to dryness and the residue was purified by CCTLC (hexane/EtOAc, 2:1) to give **26** (31 mg, 28%) as a white solid: mp (MeOH): 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (m, 3H), 2.12 (m, 1H), 2.18 (m, 1H), 2.68 (s, 3H), 2.73 (s, 3H), 3.32 and 3.37 (AB system, J = −14.4 Hz, 2H), 7.23 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.7, 22.3, 23.0, 30.3, 44.4, 96.1, 127.4, 128.2, 130.9, 133.4, 142.6, 150.6, 155.7, 158.8; MS (ES^+) m/z 319.0 $[M+1]^+$, 341.0 $[M+Na]^+$, 659.2 $[2M+Na]^+$; Anal. calcd for $C_{16}H_{18}N_2O_3S$: C 60.36, H 5.70, N 8.80, found: C 60.19, H 5.49, N 8.63.

5,5-Dibenzyl-4-[(*Z*)-2-methoxycarbonylethenylamine]-1,2-oxathiole-2,2-dioxide (27) and 5,5-dibenzyl-4-[(*E*)-2-methoxycarbonylethenylamine]-1,2-oxathiole-2,2-dioxide (28): A solution of **1b**[9] (100 mg, 0.32 mmol) and methyl 3,3-dimethoxypropanoate (152 μL, 1.07 mmol) in AcOH (0.5 mL) was stirred for 30 min at 110 °C. Then, the solvent was removed under reduced pressure and the residue was purified by CCTLC (hexane/EtOAc, 3:1). The fastest moving fractions afforded **27** (30 mg, 23%) as a white solid: mp (toluene): 147–148 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ = 3.29 and 3.30 (AB system, J = −14.0 Hz, 4H), 3.78 (s, 3H), 5.23 (d, J = 8.4 Hz, 1H), 6.25 (s, 1H), 7.14 (dd, J = 8.4, 11.5 Hz, 1H), 7.26 (m, 10H), 9.92 (bd, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ = 43.3, 51.8, 92.0, 96.4, 97.0, 128.1, 129.0, 131.6, 134.4, 142.8, 151.2, 170.5; MS (ES^+) m/z 400.6 $[M+1]^+$, 422.5 $[M+Na]^+$; Anal. calcd for $C_{22}H_{23}NO_5S$: C 63.90, H 5.61, N 3.39, found: C 63.75, H 5.52, N 3.31.

The slowest moving fractions gave 30 mg (23%) of **28** as a white amorphous solid. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta = 3.20$ and 3.42 (AB system, $J = -14.0$ Hz, 4H), 3.61 (s, 3H), 5.63 (d, $J = 12.6$ Hz, 1H), 6.45 (s, 1H), 7.25 (m, 10H), 7.43 (dd, $J = 10.9$, 12.6 Hz, 1H), 9.03 (bd, $J = 10.9$ Hz, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 41.3$, 49.7, 90.5, 94.9, 100.0, 126.4, 127.3, 130.0, 133.0, 140.3, 151.0, 165.9; MS (ES^+) *m/z* 400.3 $[M+1]^+$, 422.6 $[M+Na]^+$; Anal. calcd for $C_{22}H_{23}NO_5S$: C 63.90, H 5.61, N 3.39, found: C 63.79, H 5.41, N 3.42.

(±)-5-Benzyl-5-ethyl-4-[2-diethoxycarbonylethenylamine]-5*H*-1,2-oxathiole-2,2-dioxide (30a): To a solution of **1a**[9] (100 mg, 0.39 mmol) in dry THF (7 mL), previously degassed under an argon atmosphere, NaH (31 mg, 0.79 mmol) was added. The mixture was stirred at RT for 10 min. Then, diethyl 2-(ethoxymethylene)malonate (160 μL, 0.79 mmol) was added. The mixture was stirred at RT for 1 h. When the reaction was completed (monitored by TLC hexane/EtOAc, 2:1), MeOH (2 mL) was added and the mixture was stirred at RT at 10 min. The solvent was evaporated and the residue was dissolved in EtOAc (10 mL) and washed with 0.1 N HCl (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried, filtered, and evaporated to dryness. The final residue was purified by CCTLC (hexane/EtOAc, 3:2) to give **30a** (99 mg, 60%) as a white solid: mp (toluene): 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (m, 3H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.39 (t, $J = 7.1$ Hz, 3H), 1.91 (m, 1H), 2.03 (m, 1H), 3.20 (s, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 6.11 (s, 1H), 7.24 (m, 5H), 7.92 (d, $J = 11.9$ Hz, 1H), 10.62 (bd, $J = 11.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.3$, 14.0, 14.2, 29.5, 43.9, 61.1, 61.6, 92.7, 99.2, 101.9, 127.7, 128.4, 130.7, 132.4, 149.1, 150.1, 163.6, 168.1; MS (ES^+) *m/z* 424.1 $[M+1]^+$, 446.1 $[M+Na]^+$, 869.3 $[2M+Na]^+$; Anal. calcd for $C_{20}H_{25}NO_7S$: C 56.72, H 5.95, N 3.31, found: C 56.48, H 5.88, N 3.05.

5,5-Dibenzyl-4-[2-diethoxycarbonylethenylamine]-5*H*-1,2-oxathiole-2,2-dioxide (30b): A solution of **1b**[9] (100 mg, 0.39 mmol) and diethyl 2-(ethoxymethylene)malonate (84 μL, 0.42 mmol) in TFA (0.4 mL) was held at reflux for 1.5 h. Then, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with H_2O (2 × 5 mL), dried, and evaporated. The final residue was purified by CCTLC (hexane/EtOAc, 3:1) to give **30b** (89 mg, 54%) as a white solid: mp (toluene): 152–153 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta = 1.28$ (t, 3H), 1.43 (t, 3H), 2.85 (s, 4H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.75 (s, 1H), 7.33 (m, 10H), 8.04 (bd, $J = 9.8$ Hz, 1H), 10.44 (bd, $J = 9.8$ Hz, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 12.8$, 41.7, 59.6, 60.3, 90.6, 99.4, 101.3, 126.7, 127.5, 130.0, 132.5, 148.2, 149.8, 162.7, 166.8; MS (ES^+) *m/z* 486.1 $[M+1]^+$, 993.3 $[2M+Na]^+$; Anal. calcd for $C_{25}H_{27}NO_7S$: C 61.84, H 5.60, N 2.88, found: C 61.78, H 5.55, N 2.93.

Biology

Antiviral activity assays: The compounds were evaluated against the following viruses: HSV-1 strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACVr), HSV-2 strain G, VZV strain Oka, $TK^{<M-}$ VZV strain 07-1, HCMV strains AD-169 and Davis, VV strain Lederle, HIV type 1 (III_B) and type 2 (ROD), respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, parainfluenza-3, reovirus-1, Sindbis, and Punta Toro. The antiviral assays, with the exception of anti-HIV assays, were based on the inhibition of virus-induced cytopathicity or plaque formation in HEL fibroblasts, African green monkey cells (Vero), and human epithelial cells (HeLa), according to previously established procedures.[4,5] Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) (VZV). After 1–2 h of adsorption, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation (VZV) was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or concentration (expressed in μM) required for reducing virus-induced cytopathogenicity or viral plaque formation by 50%. The methodology of the anti-HIV assays was as follows: human CEM cells (3×10^5 cells mL^{-1}) were infected with 100 $CCID_{50}$ of HIV-1 (IIIB) or HIV-2 (ROD)/mL and seeded in 200 μL wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37 °C, HIV-induced giant cell formation was examined microscopically.

Cytostatic/toxicity assays: Cytotoxicity measurements were based on the inhibition of cell growth, as described previously.[5c] Briefly, 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 cytostatic concentration (expressed in micromolar) was calculated as the CC_{50} or the compound concentration required for reducing cell proliferation 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. Alternatively, cytotoxicity of the test compounds was expressed as the MCC or the compound concentration that caused a microscopically detectable alteration of cell morphology.

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