Research on Potentially Bioactive Aza and Thiaza Polycyclic Compounds Containing a Bridgehead Nitrogen Atom. III. Synthesis and Antimicrobial Activity of some 1,4-Benzothiazines and Pyrrolobenzothiazines

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Cyclization reactions of *N*-(2,2-dialkoxyethyl)-1,4-benzothiazine lactams **2** and 1,4-benzothiazine-sulfones **10** lead to the corresponding pyrrolo[1,2,3-*de*]-1,4-benzothiazines **4** and **12**, respectively, by using the dioxane/*p*-toluenesulfonic acid or polyphosphoric acid/chloroform systems. In contrast, in the same reaction conditions, 1,4-benzothiazines **5a-h** do not provide the expected pyrrolobenzothiazines **7**, and as for **5c-h** considerable amount of the 2-amino-phenyl-sulfide **8** was obtained. The results of microbiological assays are reported.

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Introduction.

In previous papers [1-3] we reported that acid catalyzed cyclizations of both 3-alkyl- and 3-aryl-substituted *N*-(2,2-dialkoxyethyl)-3,4-dihydro-2*H*-benzo[1,4]thiazines **A** lead to 2,3-dihydro-pyrrolo[1,2,3-*de*]benzo[1,4]thiazines **B** (Chart 1). These reactions were performed by using the dioxane/*p*-toluenesulfonic acid [1-3] and/or polyphosphoric acid/chloroform [3] systems. Compounds **A**, in turn, were obtained by *N*-alkylation of the corresponding 2,3-dihydro-4*H*-benzo[1,4]thiazines **C** by deprotonation with sodium hydride followed by the reaction with bromoacetaldehyde dialkylacetal. As a continuation of these studies, to explore the scope and limitations of these synthetic methods, at first we wished to evaluate the effect of the change of the benzo[1,4]thiazine nitrogen function from an aminic type (such as in compounds **A**) to that lactam and enaminic occurring in compounds **2** and **6**, respectively. Cyclization of these compounds using the above systems could lead to compounds **4** and **7**, respectively.

For the reasons reported below, we next extended our investigation to the cyclization of sulfones **10** in order to prepare compounds **12**.

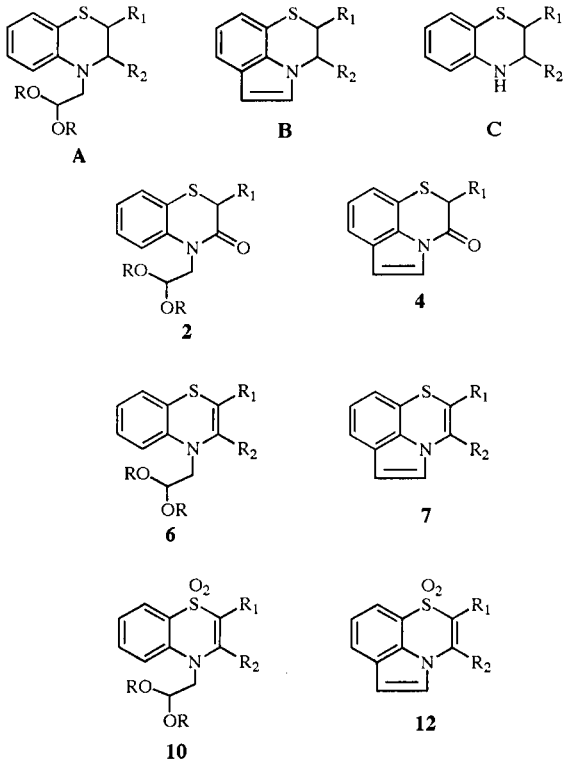
Besides our interest from a chemical point of view, further aim of this study was to explore the antimicrobial activity of these bi- and tri-cyclic azasulfurated heterocycles. In this regard, interesting antimicrobial activity has previously been observed for some derivatives [2,3].

Results and Discussion.

Chemistry.

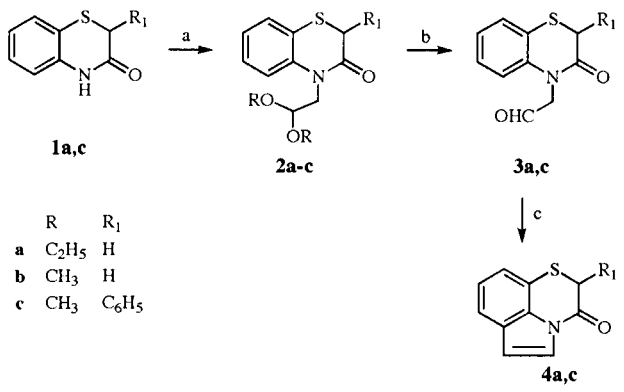
As shown in Scheme 1, the lactam **2a** was prepared by treatment of benzothiazinone **1a** [4] with bromoacetaldehyde diethylacetal in the presence of sodium hydride in *N,N*-dimethylformamide. Similarly, the dimethylacetals **2b** [5], **c** were obtained starting from **1a** and **1c** [6], respectively. Hydrolytic cleavage of acetals **2a** or **2b** [5] using dioxane/*p*-toluenesulfonic acid system yielded the aldehyde **3a** (81% yield) which, in turn, was converted to pyrrolo[1,2,3-*de*]-benzo[1,4]thiazine-3-one **4a** (16% yield) employing the polyphosphoric acid/chloroform system. In similar way, starting from **2c**, in turn prepared as **2b**, the aldehyde **3c** was obtained and then cyclized to **4c** (50% yield). Therefore, on the basis of the obtained results, it can be concluded that, even though working in moderate yields, our synthetic sequence allows the preparation of both lactam dialkylacetals **2** and pyrrolobenzothiazinones **4**.

Chart 1



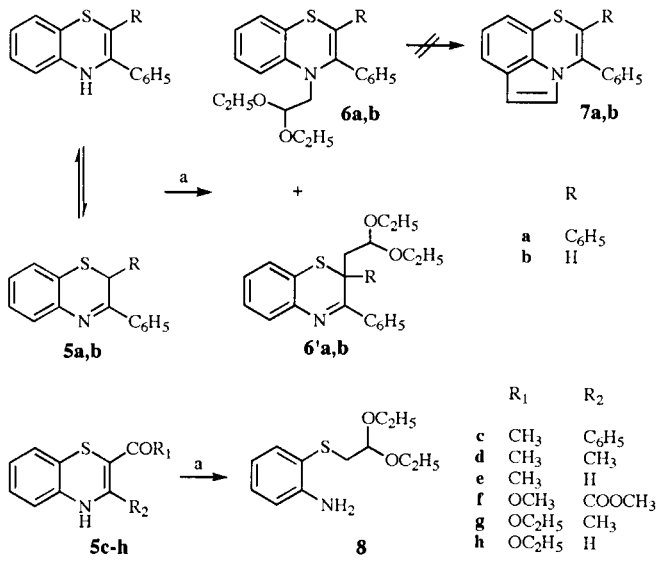
To evaluate the behaviour of enaminosulfide compounds, we prepared at first the 3-phenyl-substituted-benzothiazine **5a** [7], **b** [8] (Scheme 2).

Scheme 1



Reagents: a) NaH, $BrCH_2CH(OR)_2$, DMF; b) Dioxane/PTSA; c) PPA/$CHCl_3$

Scheme 2

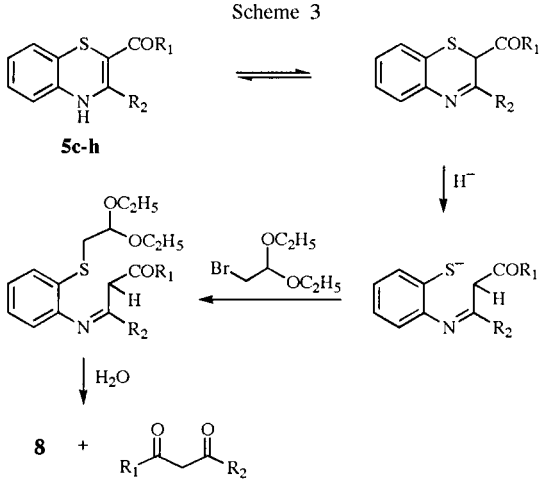


Reagents: a) NaH, $BrCH_2CH(OC_2H_5)_2$, DMF

Both compounds **5a** and **5b** are known to exist in solution as a mixture of 2*H* and 4*H* tautomers [7,8]. Treatment of **5a** with bromoacetaldehyde diethylacetal gave a complex mixture containing the expected *N*-(2,2-diethoxyethyl)-4*H*-benzo[1,4]thiazine **6a**, which was isolated by column chromatography together with the isomeric 2*H*-benzothiazine **6'a**. Clearly, **6'a** arises from the alkylation at C-2 of the 2,3-diphenyl-2*H*-benzo-[1,4]thiazine tautomer 2*H* of **5a**. Reaction of **5b** with bromoacetaldehyde diethylacetal afforded a mixture of compounds **6b** and **6'b** as revealed by gas-mass analysis. Successive treatment of **6a** with the dioxane/*p*-toluenesulfonic acid or polyphosphoric acid/chloroform system gave complex mixtures from which the expected pyrrolobenzothiazine compound **7a** was not isolated. Similarly, by reacting the mixture of **6b** and **6'b** with the dioxane/*p*-toluenesulfonic acid or polyphosphoric acid/chloroform system, the expected pyrrolobenzothiazine compound **7b** was not obtained.

Next, we decided to examine 1,4-benzothiazines existing only as the 4*H* form. However, attempts to prepare *N*-alkylate compounds of 4*H*-benzothiazines **5c** [9], **d** [10], **e** [11], **f** [9], **g** [12], **h** [9] with bromoacetaldehyde diethylacetal under the usual conditions failed providing in each case considerable amount of a degradation product, namely S-(2,2-diethoxyethyl)-2-amino-phenyl-sulfide **8**. The structure of **8** was deduced from spectrographic [ir, ^1H nmr, mass (ms: m/z 241 M^+, base)] and microanalytical data and confirmed by comparison with an authentic sample prepared following the procedure reported in literature (bp, ir, ^1H nmr, elemental analyses) [7]. In Scheme **3** is shown a possible reaction mechanism accounting for the formation of **8**. The failure to obtain the required compounds starting from **5a-h** supports the hypothesis that they are very sensitive under the reaction conditions employed and, for this reason, no further investigation was performed on the enaminosulfide series.

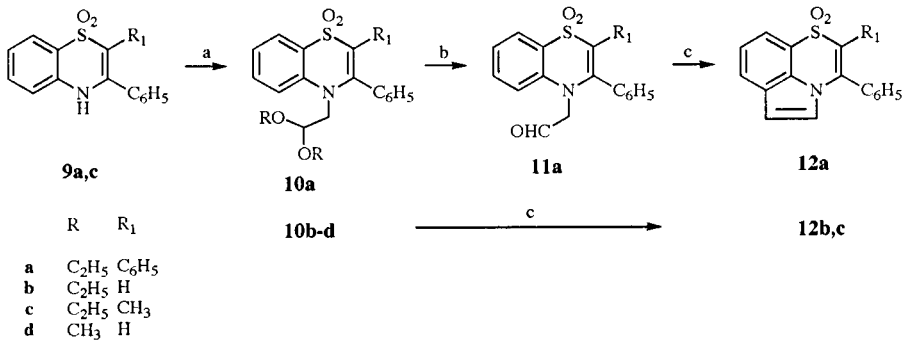
Scheme 3



Finally, it appeared of interest to examine the behavior of compounds characterized by sulfur atom in the highest oxidation state such as benzo[1,4]thiazine-S,S-dioxide **9a-c** (Scheme 4) which, likely, would be less sensitive than the corresponding sulfides under the conditions used.

All these benzothiazinesulfones **9a-c** were prepared by literature [13] proceedures. Treatment of compound **9a** with bromoacetaldehyde diethylacetal following the usual method [1] with a modification (toluene:*N*,*N*-dimethylformamide 1:2 v:v in place of toluene alone as solvent) that improved the overall yield, gave compound **10a** in 80% yield. In a similar way compounds **10b,c** were prepared. Compound **10d** was prepared by reaction of **9b** with bromoacetaldehyde dimethylacetal. Hydrolytic cleavage of **10a** in aqueous dioxane containing *p*-toluenesulfonic acid and acetic acid yielded the aldehyde **11a** (yield 96%), which was

Scheme 4



Reagents: a) NaH, $BrCH_2CH(OR)_2$, DMF; b) Dioxane/PTSA; c) PPA/$CHCl_3$

then cyclized in low yield (11%) to the pyrrolobenzothiazinesulfone **12a** with the polyphosphoric acid/chloroform system. It should be noted that cleavage of **10b-d** using the dioxane/*p*-toluenesulfonic acid system did not yield the corresponding aldehydes, but starting materials were mainly recovered. The pyrrolobenzothiazinesulfones **12b,c** were obtained both in satisfactory yield by a one-step procedure starting from benzothiazines **10b-d**, respectively, using the polyphosphoric acid/chloroform system, without isolation of an aldehyde intermediate. Therefore, it can be stated that, overall, our synthetic sequence again proceeds successfully with enaminosulfone compounds.

The structures of new compounds are fully supported by microanalytical and spectrographic (ir, ^1H nmr, and mass) data.

Microbiology.

Benzo[1,4]thiazine compounds are known to exhibit a wide range of pharmacological properties including antidepressant, anxiolytic, and calcium antagonist activity [14]. In our search devoted to explore the antimicrobial properties of 1,4-benzothiazine compounds, all the prepared compounds were tested against some Gram-positive, Gram-negative bacteria, and the fungus *Saccharomyces cerevisiae*. The obtained results are summarized in Table 1 in which the most significant findings only are listed (*i.e.*, compounds showing MIC ≤ 250 μg/ml).

In conclusion, as shown in Table 1, all of the compounds, except for **1a** and **5b**, showed only weak or poor activity against the tested organisms. Compound **1a** in fact, displayed an interesting antibacterial activity against

Table 1

Antibacterial and Antifungal Activities Against Gram-positive, Gram-negative Bacteria and *Saccharomyces Cerevisiae*. (MIC, μg/ml) [a]

Compounds	Gram +						Gram -		Fungus
	S. lutea	*S. subflava*	*B. subtilis*	*B. cereus*	*S. aureus*	*M. luteus*	*A. faecalis*	*E. coli*	*S. cerevisiae*
1a						31,2			
2b									250
3a		62.5	125					125	
4a				125					
5b	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	125
5c	125	125	250	125	62.5			250	
5d	62.5	250	62.5		125		250	250	250
5e	250				250				
5f	125				125				
5g	125				125		250	250	
5h	250				62.5		250		
9b	250	125	125	250	250		250	250	250
10a									250
10c	250	250	250	250	250		250	250	250
Penicillin V		125	250	250	1.9				
Gentamicin	<1.9	<1.9	<1.9	<1.9	<1.9	<1.9			
Piperacillin	250	31.2	31.2	125	125	<1.9			
Chloramph.							3.9	1.9	
Sulfamethazine							125	125	
Nalidixic Acid							3.9		
Miconazole									15.6
Sorbic acid									250

[a] Only MIC values ≤ 250 μg/ml were reported.

strains of *Micrococcus luteus* with a MIC value of 31.2 μg/ml. Compound **5b** showed moderate activity (MIC 62.5 μg/ml) against all the organisms tested.

EXPERIMENTAL

Chemistry.

Melting points were determined in open capillary tubes with a Büchi apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer 283 spectrophotometer (nujol mull for liquids or potassium bromide pellets for solids). ^{1}H nmr spectra were recorded on a Varian EM-390 instrument operating at 90 MHz. Chemical shifts are given in δ values downfield from tetramethylsilane as internal standard. Mass spectra were recorded on a Hewlett-Packard 5995c GC-MS low resolution spectrometer. All compounds showed appropriate ir, ^{1}H nmr and mass spectra.

Elemental analyses were carried out with a Carlo Erba mod. 1106 analyzer and the results were within ± 0.40% of the theorical values. Column chromatography on silica gel 60 (Merck 70-230 mesh) was carried out using light petroleum ether (bp 40-70°):ethyl acetate (v:v) as eluent, the ratio being in each case specified.

N-(2,2-Diethoxyethyl)-2,3-dihydro-4*H*-benzo[1,4]thiazin-3-one (**2a**).

A mixture of 3,4-dihydro-2*H*-benzo[1,4]thiazine-3-one **1a** [4] (1.0 g, 6.05 mmol) and sodium hydride (0.15 g, 6.25 mmol) in dry *N,N*-dimethylformamide (18 ml) under nitrogen atmosphere was stirred for 1.5 hours and then a solution of 2-bromoacetaldehyde diethylacetal (1.20 g, 6.09 mmol in 2.5 ml of dry *N,N*-dimethylformamide) was slowly added. The mixture was heated at 100° for 1 hour. After cooling, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. Column chromatography (eluent 7:3) of the residue gave compound **2a** as a yellow oil. R_f 0.76 (tlc petroleum ether:ethyl acetate 7:3). Yield 25%, ir (nujol) *v* 1670 (amide C=O), 1150-1030 (C-O-C) cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 1.18 (t, 6 H, *J* = 7.5 Hz, 2 x CH_3), 3.32 (s, 2 H, S-CH_2), 3.4-3.8 (m, 4 H, 2 x CH_2-CH_3), 3.95 (d, 2 H, *J* = 6.0 Hz, N-CH_2), 4.75 (t, 1 H, *J* = 4.5 Hz, CH_2-*CH*), 6.8-7.7 (m, 4 H, aromatics). ms: m/z 281 (M$^+$), 103 (base), 75, 47.

Anal. Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59,92; H, 6,78; N, 4,77.

N-(2,2-Dimethoxyethyl)-2-phenyl-2,3-dihydro-4*H*-benzo[1,4]-thiazin-3-one (**2c**).

A mixture of 2-phenyl-3,4-dihydro-2*H*-benzo[1,4]thiazine-3-one **1c** [6] (0.75 g, 3.11 mmol) and sodium hydride (0.075 g, 3.11 mmol) in dry *N,N*-dimethylformamide (10 ml) under nitrogen atmosphere was stirred for 1.5 hours and then a solution of 2-bromoacetaldehyde dimethylacetal (0.53 g, 3.11 mmol in 1.3 ml of dry *N,N*-dimethylformamide) was slowly added. The mixture was heated at 100° for 1 hour. After cooling, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. Column chromatography (eluent 7:3) of the residue gave compound **2c** as a yellow oil. R_f 0.91 (tlc petroleum ether:ethyl acetate 7:3). Yield 15%, ir (nujol) *v* 1660 (amide C=O), 1120-1070 (C-O-C) cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 3.45 and 3.50 (s, 6 H, 2 x CH_3), 4.08-4.28 (m, 2 H, N-CH_2), 4.81 (t, 1 H, *J* = 4.5 Hz, N-CH_2-*CH*), 4.69 (s, 1 H, S-CH), 6.7-7.6 (m, 9 H, aromatics). ms: m/z 329 (M$^+$), 75 (base).

Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.40; H, 6.03; N, 4.12.

(3-Oxo-2,3-dihydrobenzo[1,4]thiazin-4-yl)-acetaldehyde (**3a**).

To a solution of **2a** (0.40 g, 1.42 mmol) in dioxane (3 ml), a mixture of *p*-toluensulfonic acid (0.20 g, 1.05 mmol) in water (0.26 ml) was added. The mixture was stirred at room temperature for 72 hours, then diluted with water and extracted with toluene (4 x 10 ml). The toluenic layers were separated, dried (sodium sulfate), and evaporated *in vacuo*. Column chromatography of the residue (eluent 7:3) gave the aldehyde **3a** as a violet solid. R_f 0.47 (tlc petroleum ether:ethyl acetate 7:3). Yield 75%, mp 86-87°, ir (nujol) *v* 3400 (vinyl OH), 1720 (aldehyde C=O), 1660 (amide C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 2.1 (s, 0.33 H, br, OH, exchangeable with deuterium oxide, 33,3% enol form), 3.5 (s, 2 H, S-CH_2), 4.70 (s, 1.34 H, N-CH_2), 6.8-7.5 (m, 4.66 H, 4 aromatics + 0.66 CH=CH), 9.70 (s, 0.67 H, C*H*O, 67% aldehyde form). ms: m/z 207 (M$^+$), 179, 150 (base), 109.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76. Found: C, 57.72; H, 4.46 ; N, 6.50.

Starting from **2b** [5] (1 g, 3.95 mmol), dioxane (8 ml), *p*-toluensulfonic acid (1.13 g, 5.94 mmol), water (1.4 ml), and following the above procedure, compound **3a** (yield 80%) was obtained resulting identical in all respect to that obtained *via* **2a**.

(3-Oxo-2-phenyl-2,3-dihydrobenzo[1,4]thiazin-4-yl)-acetaldehyde (**3c**).

To a solution of **2c** (0.3 g, 0.91 mmol) in dioxane (2 ml), a mixture of *p*-toluensulfonic acid (0.123 g, 0.647 mmol) in water (0.17 ml) was added. By working up as described above for the preparation of **3a**, the aldehyde **3c** (eluent 7:3) was obtained as a brown oil. R_f 0.28 (tlc petroleum ether:ethyl acetate 7:3). Yield 58%, ir (nujol) *v* 3680-3080 (vinyl OH), 1725 (aldehyde C=O), 1660 (amide C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 3.5 (s, 0.5 H, br, OH, exchangeable with deuterium oxide, 50% enol form), 4.56 (d, 0.5 H, N-*CH*=CH), 4.76 (s, 1 H, S-CH), 4.88 (s, 1 H, N-CH_2), 5.10 (d, 0.5 H, N-CH=*CH*), 6.8-7.6 (m, 9 H, aromatics), 9.80 (s, 0.5 H, C*H*O, 50% aldehyde form). ms: m/z 283 (M$^+$), 226 (base).

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.63; N, 4.94. Found: C, 67.69; H, 4.70; N, 4.82.

2,3-Dihydropyrrolo[1,2,3-*de*]benzo[1,4]thiazin-3-one (**4a**).

To a solution of aldehyde **3a** (0.55 g, 2.65 mmol) in chloroform (100 ml) polyphosphoric acid (16.5 g) was added and the biphasic system was stirred at room temperature for 7 days. The organic layer was separated, the polyphosphoric acid extracted with chloroform and the combined organic solutions washed with water, dried (sodium sulfate), and evaporated *in vacuo*. The residue was the essentially pure benzothiazinone **4a** which was obtained as a yellow oil. R_f 0.54 (tlc petroleum ether:ethyl acetate 9:1). Yield 16%, ir (neat) *v* 1660 (amide C=O), 790 (vinyl CH=CH) cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 3.90 (s, 2 H, S-CH_2), 6.73 (d, 1 H, *J* = 3.0 Hz, N-CH=*CH*), 7.2-7.5 (m, 3 H, aromatics), 7.80 (d, 1 H, *J* = 3.0 Hz, N-*CH*=CH). ms: m/z 189 (M$^+$), 160 (base), 144.

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.50; H, 3.88; N, 7.12.

2-Phenyl-2,3-dihydropyrrolo[1,2,3-*de*]benzo[1,4]thiazin-3-one (**4c**).

Starting from aldehyde **3c** (0.25 g, 0.88 mmol) in chloroform (30 ml) polyphosphoric acid (2.5 g) and following the procedure described to prepare compound **4a**, the benzothiazinone **4c** was obtained as a yellow oil. Yield 50%, ir (neat) ν 1650 (amide C=O), 750 (vinyl CH=CH) cm^{-1}; ^1H nmr (chloroform) δ 5.10 (s, 1 H, S-CH), 6.72 (d, 1 H, J = 3.0 Hz, N-CH=*CH*), 7.2-7.7 (m, 8 H, aromatics), 7.75 (d, 1 H, J = 3.0 Hz, N-*CH* =CH). ms: m/z 265 (M^+, base), 236, 144.

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.27; H, 4.39; N, 5.01.

Reaction of Benzothiazine **5a** with 2-Bromoacetaldehyde Diethylacetal.

A tautomeric mixture of compound **5a** [7] (1.4 g, 4.60 mmol) and sodium hydride (0.84 g, 34.90 mmol) in dry toluene (40 ml) under a nitrogen atmosphere was refluxed for 4 hours and then 2-bromoacetaldehyde diethylacetal (4.6 g, 23.50 mmol) was added dropwise. The reflux was prolonged for 21 hours. After cooling, the reaction mixture was diluted by adding with caution ethanol 95% and extracted with toluene:water (3:1). The toluene layer was separated, dried (sodium sulfate), and evaporated *in vacuo*. Column chromatography of the residue (eluent 98:2) gave in order the following compounds, as pale yellow oils:

N-(2,2-Diethoxyethyl)-2,3-diphenyl-4*H*-benzo[1,4]thiazine (**6a**).

Yield 8%, ir (neat) ν 1120-1100 (C-O-C) cm^{-1}; ^1H nmr (deuteriochloroform) δ 1.16 (t, 6 H, J = 9.0 Hz, 2 x CH_3), 2.90 (d, 2 H, J = 4.5 Hz, N-CH_2), 3.60 (q, 4 H, J = 3.0 Hz, 2 x O-*CH_2*-CH_3), 4.62 (t, 1 H, J =4.5 Hz, CH_2-*CH*), 6.2-8.2 (m, 14 H, aromatics). ms: m/z 417 (M^+), 386, 385, 282, 103 (base), 75, 47.

Anal. Calcd. for $C_{26}H_{27}NO_2S$: C, 74.79, H, 6.52; N, 3.35. Found: C, 74.52; H, 6.89; N, 3.07.

2-(2,2-Diethoxyethyl)-2,3-diphenyl-2*H*-benzo[1,4]thiazine (**6'a**).

Yield 29%, ^1H nmr (deuteriochloroform) δ 0.93 (t, 3 H, J = 6.0 Hz, CH_3), 1.06 (t, 3 H, J = 6.0 Hz, CH_3), 2,59 (d, 2 H, J = 4.5 Hz, N-CH_2), 2.9-3.6 (m, 4 H, 2 x O-*CH_2*-CH_3), 4.50 (t, 1 H, J = 4.5 Hz, CH_2-*CH*), 7.0-7.6 (m, 14 H, aromatics). ms: m/z 417 (M^+), 212, 103 (base), 75.

Anal. Calcd. for $C_{26}H_{27}NO_2S$: C, 74.79; H, 6.52; N, 3.35. Found: C, 74.50; H, 6.73; N, 3.00.

N-(2,2-Diethoxyethyl)-2,3-diphenyl-4*H*-benzo[1,4]thiazine-S,S-dioxide (**10a**).

A mixture of sulfone **9a** [13] (0.5 g, 1.50 mmol) and sodium hydride (0.27 g, 11.3 mmol) in dry *N,N*-dimethylformamide (20 ml) and toluene (10 ml) under a nitrogen atmosphere was refluxed for 4 hours and then 2-bromoacetaldehyde diethylacetal (1.48 g, 7.50 mmol) dropwise added. The reflux was prolonged for 26 hours. After cooling, the reaction mixture was diluted by adding with caution ethanol 95% (10 ml) and extracted with toluene:water (3:1). The toluene layer was separated, dried (sodium sulfate), and evaporated *in vacuo*. Column chromatography of the residue (eluent 1:1) gave compound **10a** as a pale yellow solid. R_f 0.74 (tlc petroleum ether:ethyl acetate 1:1). Yield 80%, mp 183-185°, ir (potassium bromide) ν 1290 (SO_2), 1120-1040 (C-O-C) cm^{-1}; ^1H nmr (deuteriochloroform) δ 1.10 (t, 6 H, J = 7.5 Hz, 2 x CH_3), 3.2-3.7 (m, 4 H, 2 x O-CH_2), 3.97 (d, 2 H, J = 6.0 Hz, N-CH_2), 4.45 (t, 1 H, J = 4.5 Hz, CH_2-*CH*), 7.1-8.2 (m, 14 H, aromatics). ms: m/z 449 (M^+), 375, 103 (base), 75, 47.

Anal. Calcd. for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.25; H, 6.27; N, 3.08

N-(2,2-Diethoxyethyl)-3-phenyl-4*H*-benzo[1,4]thiazine-S,S-dioxide (**10b**).

This compound was prepared similarly to benzothiazine **10a**. A mixture of sulfone **9b** [13] (0.39 g, 1.5 mmol) and sodium hydride (0.04 g, 1.56 mmol) in dry *N,N*-dimethylformamide (20 ml) and toluene (10 ml) under a nitrogen atmosphere was refluxed for 4 hours and then 2-bromoacetaldehyde diethylacetal (0.90 g, 4.55 mmol) was added dropwise. The reflux was prolonged for 26 hours. By working up as above (eluent 1:1) compound **10b** was obtained as a pale yellow solid. R_f 0.71 (tlc petroleum ether:ethyl acetate 1:1). Yield 53%, mp 110-112°, ir (nujol) ν 1270 (SO_2), 1120-1040 (C-O-C) cm^{-1}; ^1H nmr (deuteriochloroform) δ 1.10 (t, 6 H, J = 7.5 Hz, 2 x CH_3), 3.1-3.7 (m, 4 H, 2 x O-CH_2), 4.05 (d, 2 H, J = 6.0 Hz, N-CH_2), 4.98 (t, 1 H, J = 4.5 Hz, CH_2-*CH*), 5.90 (s, 1 H, SO_2-CH), 7.1-8.2 (m, 9 H, aromatics). ms: m/z 373 (M^+), 103 (base), 75, 47.

Anal. Calcd. for $C_{20}H_{23}NO_4S$: C, 64,32; H, 6.21; N, 3.75. Found: C, 64.50; H, 6.38; N, 3.43.

N-(2,2-Diethoxyethyl)-2-methyl-3-phenyl-4*H*-benzo[1,4]thiazine-S,S-dioxide (**10c**).

This compound was prepared similarly to benzothiazine **10a**. A mixture of sulfone **9c** [13] (0.41 g, 1.5 mmol) and sodium hydride (0.27 g, 11.30 mmol) in dry *N,N*-dimethylformamide (20 ml) and toluene (10 ml) under a nitrogen atmosphere was refluxed and then 2-bromoacetaldehyde diethylacetal (2.96 g, 15.0 mmol),was added dropwise in two identical portions (after 4 and 36 hours of reflux). The reflux was prolonged further 72 hours. By working up as above (eluent 1:1) compound **10c** was obtained as a yellow oil, which slowly solidified on standing. R_f 0.83 (tlc petroleum ether:ethyl acetate 1:1). Yield 70%, mp 84-87°, ir (potassium bromide) ν 1270 (SO_2), 1120-1040 (C-O-C) cm^{-1}; ^1H nmr (deuteriochloroform) δ 1.08 (t, 6 H, J = 6.0 Hz, 2 x O-CH_2-*CH_3*), 1.95 (s, 3 H, C-CH_3), 3,2-3.7 (m, 4 H, 2 x O-CH_2), 3.80 (d, 2 H, J = 6.0 Hz, N-CH_2), 4.40 (t, 1 H, J = 4.5 Hz, N-CH_2-*CH*), 7.2-8.2 (m, 9 H, aromatics). ms: m/z 387 (M^+), 103 (base), 75,

Anal. Calcd. for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.62. Found: C, 64.81; H, 6.72; N, 3.56.

N-(2,2-Dimethoxyethyl)-3-phenyl-4*H*-benzo[1,4]thiazine-S,S-dioxide (**10d**).

This compound was prepared similarly to benzothiazine **10a**. A mixture of sulfone **9b** [13] (0.5 g, 1.50 mmol) and sodium hydride (0.27 g, 11.30 mmol) in dry *N,N*-dimethylformamide (20 ml) and toluene (10 ml) under a nitrogen atmosphere was refluxed for 4 hours and then 2-bromoacetaldehyde dimethylacetal (0.76 g, 4.48 mmol) was added dropwise. The reflux was prolonged for 26 hours. By working up as above (eluent 1:1) compound **10d** was obtained as a yellow oil. R_f 0.79 (tlc petroleum ether:ethyl acetate 7:3). Yield 60%, ir (nujol) ν 1270 (SO_2), 1130-1040 (C-O-C) cm^{-1}; ^1H nmr (deuteriochloroform) δ 3.28 and 3.32 (s, 6 H, 2 x CH_3), 4.04 (d, 2 H, J = 6.0 Hz, N-CH_2), 4.31 (t, 1 H, J = 4.5 Hz, CH_2-*CH*), 5.90 (s, 1 H, SO_2-CH), 7.1-8.2 (m, 9 H, aromatics). ms: m/z 345 (M^+), 284, 75 (base).

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.34; H, 5.72; N, 3.87.

(2,3-Diphenyl-4*H*-benzo[1,4]thiazin-4-yl)-acetaldehyde-S,S-dioxide (**11a**).

To a solution of **10a** (0.15 g, 0.33 mmol) in dioxane (15ml), glacial acetic acid (0.2 g, 3.33 mmol) in water (0.06 ml, 3.33 mmol) was added a small amount of *p*-toluensulfonic acid. The mixture was stirred at room temperature for 72 hours. By working up, as reported above for **3a**, gave the aldehyde **11a** as a yellow oil. R_f 0.30 (tlc petroleum ether:ethyl acetate 1:1). Yield 96%, ir (nujol) ν 3400 (vinyl OH), 1725 (aldehyde C=O), 1270 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform) δ 4.1-4.4 (s, 0.75 H, br, OH, exchangeable with deuterium oxide, 75% enol form), 4.40 (s, 0.5 H, N-CH_2), 6.2-8.2 (m, 15.5 H, 14 aromatics + 1.5 C*H*=C*H*), 9.45 (s, 0.25 H, C*H*O, 25% aldehyde form). ms: m/z 375 (M^+), 346, 282 (base).

Anal. Calcd. for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73. Found: C, 70.10; H, 4.67; N, 3.61.

2,3-Diphenylpyrrolo[1,2,3-*de*]benzo[1,4]thiazine-S,S-dioxide (**12a**).

To a solution of aldehyde **11a** (0.22 g, 0.59 mmol) in chloroform (20 ml) polyphosphoric acid (3.60 g) was added and the biphasic system was stirred at room temperature for 96 hours. By working up, as reported above for **4a**, gave a residue which was the essentially pure sulfone **12a** as a yellow oil. Yield 11%; ^1H nmr (deuteriochloroform) δ 6.68 (d, 1 H, J = 3.0 Hz, N-CH=*CH*), 6.92 (d, 1 H, J = 3.0 Hz, N-*CH* =CH), 7.0-8.2 (m, 13 H, aromatics). ms: m/z 357 (M^+, base), 291, 252, 105.

Anal. Calcd. for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23, N, 3.92. Found: C, 73,63; H, 4.34; N, 3.81.

3-Phenylpyrrolo[1,2,3-*de*]benzo[1,4]thiazine-S,S-dioxide (**12b**).

To a solution of **10b** (0.15 g, 0.40 mmol) in chloroform (10 ml) polyphosphoric acid (0.675 g) was added and the biphasic system was stirred at room temperature for 17 hours. The organic layer was separated, the polyphosphoric acid extracted with chloroform and the combined organic solutions washed with water, dried (sodium sulfate) and evaporated *in vacuo*. Column chromatography of the residue (eluent 1:1) gave **12b** as a yellow solid. R_f 0.61 (tlc petroleum ether:ethyl acetate 1:1). Yield 45%, mp 147-149°, ir (nujol) ν 1270 (SO_2), 790 (vinyl CH=CH) cm^{-1}; ^1H nmr (deuteriochloroform) δ 6.20 (s, 1 H, SO_2-CH), 6.70 (d, 1 H, J = 3.0 Hz, N-CH=*CH*), 7.15 (d, 1 H, J = 3.0 Hz, N-*CH*=CH), 7.3-8.2 (m, 8 H, aromatics). ms: m/z 281 (M^+, base), 252, 105.

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.31; H, 3.94; N, 4.98. Found: C, 68.04; H, 4.12; N, 4.73.

Starting from compound **10d** and following the above reported procedure, compound **12b** was obtained and the results are identical in all respects to that obtained *via* **10b**.

2-Methyl-3-phenylpyrrolo[1,2,3-*de*]benzo[1,4]thiazine-S,S-dioxide (**12c**).

Starting from **10c** and following the procedure to obtain **12b**, except for the reaction time (44 hours instead of 17 hours), compound **12c** was obtained as an orange solid. R_f 0.92 (tlc petroleum ether:ethyl acetate 1:1). Yield 90%, mp 178-181°, ir (potassium bromide) ν 1280 (SO_2), 790 (vinyl CH=CH) cm^{-1}; ^1H nmr (deuteriochloroform) δ 2.15 (s, 3 H, CH_3), 6.63 (d, 1 H, J = 3.0 Hz, N-CH=*CH*), 6.83 (d, 1 H, J = 3.0 Hz, N-*CH* =CH), 7.3-8.1 (m, 8 H, aromatics). ms: m/z 295 (M^+, base), 252, 105.

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74. Found: C, 69.40; H, 4.50; N, 4.55.

Microbiology.

The *in vitro* antimicrobial screening of prepared benzothiazine compounds was carried out against a variety of Gram-positive (*Sarcina lutea* ATCC 15957, *Sarcina subflava* ATCC 7468, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 10876, *Staphylococcus aureus* ATCC 25923, *Micrococcus luteus* ATCC 49732) and Gram-negative (*Alcaligenes faecalis* ATCC 8750, *Escherichia coli* ATCC 12795) bacteria as well as against the *Saccharomyces cerevisiae* ATCC 4125, fungus. Details on the experimental procedures were previously reported [1-3].

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