Benzyl Derivatives of 2,1,3-Benzo- and Benzothieno[3,2-*a*]thiadiazine 2,2-Dioxides: First Phosphodiesterase 7 Inhibitors

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The synthesis of a new family of benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]-thiadiazine 2,2-dioxides was achieved. The biological data revealed the first heterocyclic family of compounds with PDE 7 inhibitory properties appearing to be a new objective for the treatment of T-cell-dependent disorders. The IC_{50} values or percent inhibition values of the compounds against PDE 7 were calculated by testing them against human recombinant PDE 7 expressed in *S. cerevisiae*. In this expression system the only cyclic nucleotide hydrolyzing activity present in cell extracts corresponded to human PDE 7. Isoenzyme selectivity PDE 7 versus PDE 4 and PDE 3 was also measured. Considering simultaneously inhibition of the three different isoenzymes, monobenzyl derivatives **15** and **23** showed interesting PDE 7 potency (around 10 μM); although not statistically significant, a trend toward selectivity with respect to PDE 3 and PDE 4 was obtained. Benzothiadiazine **16**, although less potent at PDE 7 ($IC_{50} = 25\ \mu$M), also showed a trend of selectivity toward PDE 3 and PDE 4. These compounds are considered the best leads for further optimization.

Introduction

The interest in identifying isoenzyme-selective phosphodiesterase (PDE) inhibitors has increased in the last years. PDEs play a critical role in various biological processes by hydrolyzing the key second messengers adenosine and guanosine 3′,5′-cyclic monophosphate nucleotides (cAMP and cGMP, respectively) to the corresponding 5′-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activates specific protein phosphorylation pathways involved in a variety of functional responses.[1]

At least nine families of mammalian PDEs have been described, based on substrate specificity, affinity, sensitivity to cofactors, sequence similarity, and sensitivity to inhibitory drugs.[2−7] The seventh phosphodiesterase family is a cAMP-specific PDE, encoded by a single gene. The biochemical and pharmacological characterization of PDE 7 showed a high-affinity cAMP-specific PDE ($K_m = 0.2\ \mu$M) that was not affected by cGMP and well-known potent selective PDE isoenzyme inhibitors.[8] Subsequently, the presence of a PDE 7-like activity was described in human T-cell lines but absent in cell lines derived from B-cells.[9]

PDE 7 mRNA is highly expressed in skeletal muscle and detectable in heart, spleen, B- and T-lymphocytes, kidney, brain, uterus, and pancreas, whereas PDE 7 activity or protein is only detected in T-cell lines and several fetal tissues, suggesting that in the rest of the tissues and throughout embryonic development the translation or stability of PDE 7 protein may be highly regulated.[8,10,11]

Considering the restricted tissue expression of PDE 7, increasing cAMP levels by selective PDE 7 inhibition appears to be a potentially promising approach to specifically block T-cell-mediated immune responses. Moreover, various experimental studies have clearly demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes.[12,13] This selective approach could presumably be devoid of the secondary effects that plague the use of inhibitors selective for other isoenzymes more widely distributed (e.g. PDE 3, PDE 4). However, until now no selective PDE 7 inhibitors have been described.

Recently a functional role of PDE 7 in T-cell activation has been described, for the first time;[14] therefore, selective inhibitors of PDE 7 could be a new strategy to treat T-cell-related diseases. On the other hand, the identification of selective inhibitors of the PDE 7 isoenzyme could help to understand the functional role of this cAMP-specific PDE.

Taking into account this background and continuing with our work in the field of fused pyrimidines as PDE inhibitors,[15,16] we describe here the synthesis of benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]thiadiazine dioxides which have been proved to be the first heterocyclic inhibitors of PDE 7. Their synthesis, biological evaluation, and structure−activity relationships will be discussed.

Chemistry

The benzothienothiadiazine dioxide ring **1** was prepared by the sequential condensation of 2-nitrobenzoni-

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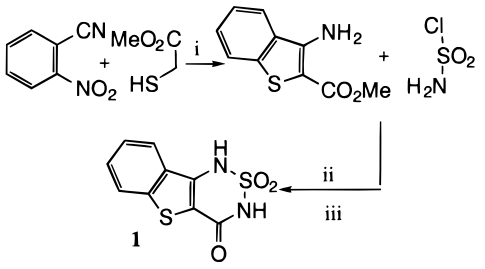
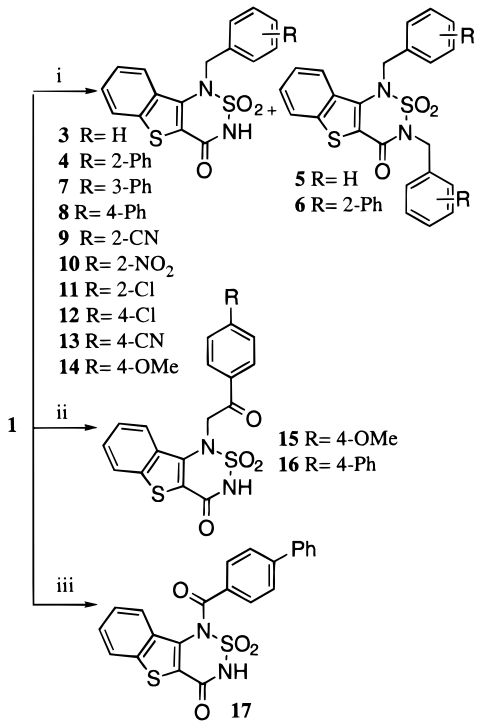
Scheme 1[a]



[a] Reagents: (i) DMF/KOH; (ii) $CH_3C_6H_5$/rt; (iii) NaOH (1 N).

Scheme 2[a]



[a] Reagents: (i) $H_2O/NaHCO_3/R\text{-}C_6H_4\text{-}CH_2X$; (ii) $DMF/NaHCO_3/R\text{-}C_6H_4\text{-}COCH_2X$; (iii) $DMF/NaHCO_3/Ph\text{-}C_6H_4\text{-}COX$.

trile and methyl thioglycolate[17] followed by reaction with sulfamoyl chloride and subsequent cyclization in basic medium (Scheme 1).

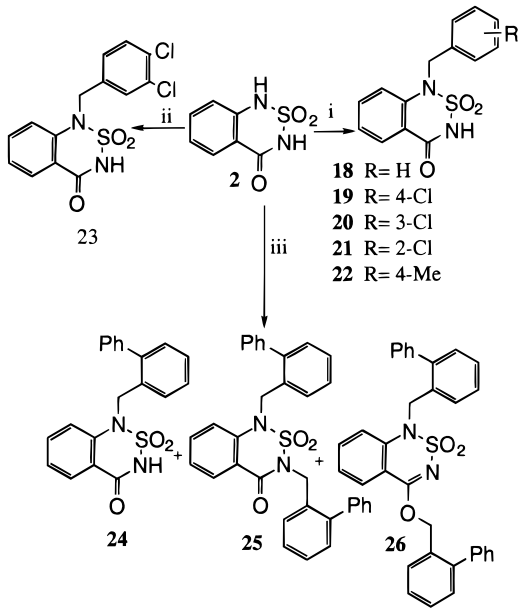
Benzothienothiadiazine derivatives **3**−**14** were prepared by reaction of the benzothienothiadiazine **1** with the appropriate benzyl derivative in aqueous bicarbonate (Scheme 2). When benzyl bromide and 2-biphenylmethyl bromide were used, mixtures of monoalkyl and dialkyl compounds were obtained which could be separated by silica gel column chromatography (Scheme 2).

In the case of compounds **15** and **16**, the reaction was achieved in DMF using an excess of sodium bicarbonate and acetophenone halide derivatives as reactants (Scheme 2). Derivative **17** was obtained by reaction of benzothienothiadiazine **1** with 4-biphenylcarbonyl bromide in DMF and sodium bicarbonate.

The benzothiadiazine dioxide ring **2** was obtained in two steps following the Cohen and Klarberg procedure[18] starting from methyl anthranylate and sulfamoyl chloride.

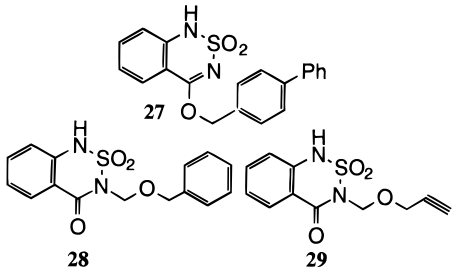
Benzyl derivatives of benzothiadiazine were obtained following a similar procedure to previous benzothienothiadiazine compounds. Thus, the reaction of benzo-

Scheme 3[a]



[a] Reagents: (i) $H_2O/NaHCO_3/R\text{-}C_6H_4\text{-}CH_2X$; (ii) $DMF/NaH/3,4\text{-}diCl\text{-}C_6H_3\text{-}CH_2X$; (iii) $DMF/NaH/2\text{-}Ph\text{-}C_6H_4\text{-}CH_2X$.

Chart 1. Benzothiadiazine Derivatives Included in the Biological Screening



thiadiazine **2** with the corresponding alkyl halides in aqueous bicarbonate leads to the monobenzothiadiazines **18**−**23**. When biphenylmethyl bromide is employed, stronger conditions were needed, using sodium hydride as base in DMF. As a result, complex mixtures of compounds **24**−**26**, including *O*-substituted derivatives, were obtained. All the isomers could be separated by column and centrifugal circular thin-layer chromatography (Scheme 3).

The structures of all new compounds were elucidated according to analytical and spectroscopic data. Unequivocal assignment of all chemical shifts (^1H and ^{13}C NMR) was done using bidimensional experimentals such COSY or HMQC for one-bond correlation. The site of alkylation was determined from ^{13}C chemical shift displacements and sequences of HMBC for long distance proton/carbon correlation experiments.

Biological Results and Discussion

In the present work, benzothieno- and benzothiadiazines dioxides **3**−**26** were synthesized and together with the previously reported *O*-derivative **27**[19] and *N3*-derivatives **28** and **29**[20] (Chart 1) were tested for their inhibitory potencies against human recombinant PDE 7 expressed in *S. cerevisiae* as described in the Experimental Section. In this expression system the only cyclic nucleotide hydrolyzing activity present in cell extracts

Table 1. Biological Activity (PDE 7, PDE 3, and PDE 4 Inhibition) of Benzothieno- and Benzothiadiazine Dioxides **1**−**29**[a]

compd	PDE 7		PDE 3		PDE 4	
1[b]	0%	(0, 0)	31%	(25, 37)	0%	(0, 0)
3	14%	(7, 21)	23%	(14, 32)	11%	(0, 25)
4	14	(9, 22)	11	(10, 12)	36	(24, 53)
5	2%	(0, 10)	18%	(0, 37)	0%	(0, 0)
6	0%	(0, 0)	13%	(0, 33)	0%	(0, 0)
7	15	(6, 35)	9	(7, 10)	14	(11, 18)
8	13	(10, 17)	8	(6, 11)	16	(13, 19)
9	29%	(24, 35)	18	(12, 27)	18%	(6, 29)
10	22	(11, 43)	12	(10, 15)	26	(13, 51)
11	28	(15, 53)	18	(14, 23)	28%	(24, 32)
12	28%	(18, 38)	35%	(18, 54)	14%	(0, 28)
13	32%	(28, 36)	36%	(20, 52)	5%	(0, 25)
14	22%	(11, 33)	43%	(28, 58)	23%	(13, 33)
15	11	(6, 22)	27	(23, 32)	30	(25, 36)
16	25	(18, 34)	15%	(6, 25)	2%	(0, 8)
17	2%	(0, 7)	11%	(0, 36)	1%	(0, 15)
18[b]	29%	(14, 44)	16%	(2, 31)	7%	(2, 13)
19	24%	(12, 36)	6%	(0, 27)	8%	(2, 15)
20	35%	(24, 45)	8%	(0, 21)	8%	(5, 12)
21	41%	(27, 56)	4%	(0, 21)	9%	(0, 29)
22	21%	(17, 26)	6%	(1, 11)	7%	(0, 21)
23	8	(3, 22)	24	(17, 34)	19	(11, 34)
24	21	(17, 25)	30	(16, 56)	20	(11, 38)
25	0%	(0, 22)	0%	(0, 0)	0%	(0, 2)
26	0%	(0, 6)	0%	(0, 2)	0%	(0, 2)
27	40%	(37, 43)	22%	(19, 24)	17%	(10, 23)
28[b]	10%	(7, 13)	0%	(0, 14)	5%	(0, 11)
29[b]	0%	(0, 3)	0%	(0, 10)	4%	(0, 17)

[a] The inhibitory potency of the synthesized compounds on the human PDE 7 activity was tested as described in the Experimental Section. Isoenzyme selectivity was determined by testing their inhibitory activity against guinea pig PDE 4 and PDE 3 enzymes. Data are indicated as IC_{50} (μM) (95% confidence interval) or percent inhibition (95% CI) at 20 μM ($n = 2-3$). No statistically significant differences were found by comparing PDE 7 values with PDE 3 and PDE 4 data. [b] Percent inhibition (95% CI) at 200 μM.

corresponded to human PDE 7. Isoenzyme selectivity was obtained by comparing the IC_{50} values or percent inhibition values of the compounds against PDE 7 with their inhibitory activity against PDE 4 and PDE 3 (Table 1).

Some of the heterocyclic compounds evaluated exhibited PDE 7 inhibitory properties (IC_{50} at micromolar level), with concurrent activity, in some cases, at PDE 4 and PDE 3 (Table 1). These data revealed that benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]thiadiazine 2,2-dioxides represent the first described heterocyclic family of compounds with PDE 7 inhibitory properties. The fact that some of these compounds also inhibit PDE 4 implies that this family could be considered as new leads in the development of drugs for asthma and other allergic airways pathologies.

Preliminary structure−activity relationships showed that monosubstitution in the thiadiazine moiety is required for activity against PDE 7. Dibenzyl derivatives assayed (compounds **5**, **6**, **25**, and **26**) completely lacked activity. Moreover, lack of activity found in modified acyclonucleoside derivatives **28** and **29** should indicate substituted benzyl compounds were required for activity. On the other hand, monosubstitution should be on the nitrogen atom as only residual activity was observed in the *O*-substituted compound **27**.

The link between the heterocyclic ring and the lipophilic *N*-substituent (phenyl moiety) is important for PDE 7 inhibition, with the methylene group being a better spacer than the carbonyl moiety (compounds **8** versus **17**). When the linker is a carbonylmethyl fragment (compound **15**) results in PDE 7 are similar to that of methylene, but there is an increase in selectivity.

Substituents on the phenyl ring of the benzyl moiety increase the PDE 7 potency in both benzothienothiadiazines and benzothiadiazines, when compared to the unsubstituted compounds (**3** and **18,** respectively). Introduction of a phenyl ring (compounds **4**, **7**, **8**, and **24**) provides good results independently of the substitution position. With respect to the chloro substitution, the *ortho* position (compounds **11** and **21**) provides better results than the *meta* or *para* position (compounds **12**, **19,** and **20**). However, surprisingly, the 3,4-disubstituted compound (**23**) showed higher potency and increased selectivity.

The nature of the heterocyclic framework slightly influences the PDE 7 inhibition. The benzothienothiadiazine moiety displays a slight increase in the inhibitory enzyme potency when compared to the benzothiadiazine (compounds **4** versus **24**, **11** versus **21**, etc.), although the benzothiadiazine derivatives showed better selectivity.

Conclusions

The synthesis of a new family of benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-*a*]thiadiazine 2,2-dioxides was achieved.

The biological data revealed that these novel compounds represent the first heterocyclic family of compounds with PDE 7 inhibitory properties appearing to be a new objective for the treatment of T-cell-dependent disorders. Additionally, the fact that some of these compounds also inhibit PDE 4 implies that this family could be considered as new leads in the development of drugs for asthma and other allergic airways pathologies.

Considering simultaneously inhibition of the three different isoenzymes (PDE 7, PDE 4, and PDE 3) compounds **15** and **23** showed interesting PDE 7 potency (around 10 μM). Although not statistically significant, a trend toward selectivity with respect to PDE 3 and PDE 4 was obtained. Benzothiadiazine **16**, although less potent at PDE 7 ($IC_{50} = 25$ μM), also showed a trend of selectivity toward PDE 3 and PDE 4. These compounds are considered the best leads for further optimization.

Experimental Section

Biological Methods. Purification and characterization of cyclic nucleotide PDE 3 and PDE 4 obtained from guinea pig ventricular tissue were performed as described previously.[21] Rolipram, SKF 94836, and zaprinast were synthesized at the Medicinal Chemistry Department of Almirall Prodesfarma. Reagents were purchased from commercial suppliers and used as received.

Cloning of hsPDE 7A cDNA. The cDNA corresponding to hsPDE 7A was generated by ligating appropiate overlapping fragments obtained by RT-PCR from total HeLa mRNA. The oligonucleotides used, designed from the published sequence information,[9] were QD1 and QR1 to amplify from position 698 to position 1535 and QD2 and QR2 from position 33 to position 923, to obtain hsPDE 7A. A *Sty*I in position 765 and *Xho*I restriction sites from the polylinker of pBS were used to join both fragments, which were sequenced twice in both directions to verify the ORF and the absence of changes according to the published sequence.[8]

hsPDE 7A was cloned into the yeast expression vector pYes2 (Invitrogen). To avoid the protein from folding improperly we fused, by PCR, the influenza hemoglutinin epitope HA1[22,11]

Primer	Sequence
QD1	^{698}CGCTGCGGATGTTACTCAGGCC^{719}
QD2	^{33}GGCAGGGCGGGCGTATTCAATG^{54}
QR1	^{1535}CCTCCAGGAGGCAGTTTGTCCC^{1514}
QR2	^{923}GCCCACTGCAGATCTCCAGTGG^{902}

at the N-terminus of the protein. TAG·PDE 7 (CT ACC GCT CGA GCC ATG TAT CCA TAC GAT GTT CCA GAT TAT GCT AGC TTA GGT GGT CCG GCG TAT TCA ATG GAA GTG) was the primer used to tag protein; this primer contains a *Xho*I restriction site, an ATG, the HA1 tag, a GGP linker, and 17 bases of hsPDE 7A cDNA, including the methionine. We amplified the hsPDE 7A tag using pBS(hsPDE 7A) as template, the TAG·PDE 7 and QR1 primers, and Vent polymerase, under the following conditions: 951C 5 min, 33 cycles of 951C 1 min, 551C 30 s, and 721C 90 s. We cloned the PCR product into the pBS(hsPDE 7A) in *Xho*I-*Sty*I restriction sites. Finally we cloned the hsPDE 7A tag into pYes using *Xho*I-*Xba*I restriction sites.

Disruption of *S. cerevisiae* PDE Genes. The two yeast PDE genes, *PDE1* and *PDE2*, were obtained from the yeast genome by PCR. The amplified fragments were cloned into pUC18. Large deletions of both genes (positions 577−1744 for the *PDE1* gene and positions 925−1325 for the *PDE2* gene) were originated by amplifying these constructs with primers Pde1·AU and Pde1·AL (*PDE1*) and Pde2·AU and Pde2·AL (*PDE2*). The missing sequences were then replaced by either the *LEU2* gene (*PDE1*) or the *TRP1* gene (*PDE2*), obtained from plasmidsYDp-L and YDp-W, respectively.[23] The amplification products of these disrupting plasmids with oligos Pde1·U and Pde1·L and Pde2·U and Pde2·L were ultimately used to disrupt both PDE genes on the protease-deficient strain BJ5459,[24] following standard procedures.[25] The double knock out (dPDEKO) was confirmed by the absence of PDE activity.

Primer	Sequence
Pde1.U	^{577}CAT CCC CTT TTT TAC C^{592}
Pde1.L	^{1759}CCG CTT TTC ATC TAC G^{1744}
Pde1.AU	^{1329}TGC GGA GAT GTT GAG C^{1345}
Pde1.AL	^{925}TTC ATT GTA TTG GCG C^{909}
Pde2.U	^{98}CTA TTG ATA TGT CCA CCC^{115}
Pde2.L	^{1671}TGC TAT TGT GGT TTC TTG^{1655}
Pde2.AU	^{1190}CCG AGG CTA TTC TGG C^{1205}
Pde2.AL	^{565}ACA TGC TTG AGT GGG G^{565}

Expression of hPDE 7A cDNA in the dPDEKO *S. cerevisiae* Strain. The construct described above, hsPDE 7A tag into pYes, was transformed into the dPDEKO yeast strain by lithium acetate precipitation.[26] Positive clones were selected in SD medium agar plates. The colonies were grown in YPD until 0.8 OD595, then were spun down, and resuspended in SD medium supplemented with galactose as carbon source. The yeast were collected and powered under liquid nitrogen to prepare protein extracts using standard protocols.

***S. cerevisiae* strains used in this study:** BJ5459, MATa pep4::HIS3 pbr1D1.6R ura3-52 trp1 lys2-801 leu2D1 his3D200 can1 GAL; dPdeKO**,** MATa pep4::HIS3 pbr1D1.6R ura3-52 trp1 lys2-801 leu2D1 his3D200 can1 GAL; pde1::LEU2 pde2::TRP1.

Measurement of PDE Activities. Cyclic nucleotide PDE 7 activity from yeast extracts was measured by a two-step procedure according to Thompson and Strada[27] at a cAMP concentration of 0.25 μM. The incubations were performed at 37 °C. The cloned PDE 7 activity was pharmacologically characterized by using different isoenzyme selective inhibitors. This PDE activity was cAMP-specific and was not inhibited by 200 μM rolipram, a selective inhibitor of PDE 4, 200 μM SKF 94836, a selective inhibitor of PDE 3, and 200 μM zaprinast, a selective inhibitor of PDE 5. Ca^{2+}/CaM, the activator of CaM-PDE (PDE 1), and cGMP, the activator of cGMP-stimulated PDE (PDE 2) and inhibitor of cGMP-inhibited PDE (PDE 3), did not modify the cloned PDE 7 activity.

PDE 3 and PDE 4 enzyme assays were performed in 96-well microtiter plates using a BIOMEK 2000 workstation (Beckman). For the automatic assay, the incubation mixtures (120 mL/well) contained 28 mM Tris-HCl (pH 8), 7 mM $MgCl_2$, 5 mM β-mercaptoethanol, 0.19 μM AMPc, 0.16 mg/mL snake venom 5′-nucleotidase, 0.06 μM [^{3}H]AMPc (16 Ci/mmol), 0.1 g/L bovine serum albumin. Reaction was started by the addition of 20 μL of the diluted enzyme preparation and incubated for 30 min at room temperature. The incubation was terminated by transferring 60 μL of the reaction mixture into a Millipore 96-well filter plate (MAHVN4550) containing 200 μL of a 50% QAE-Sephadex A-25 mixture in 20 mM CAPS, pH 10. The samples were collected by filtration into a 96-well plate (1450-401, Wallac) containing 150 μL of liquid scintillation cocktail (Supermix, Wallac) per well by using a vacuum manifold (Millipore). The total radioactivity was measured using a Wallac MicroBeta scintillation counter.

The inhibition effect of each drug on the PDE activities was evaluated using 4−5 different concentrations with duplicate determinations. IC_{50} values were obtained by nonlinear regression by use of SAS on a DEC AXP computer. Drugs were dissolved in dimethyl sulfoxide (DMSO) and the effects of this solvent on the enzyme activities were taken into consideration in the calculations.

Chemical Procedures. Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Flash column chomatography was carried out at medium pressure using silica gel (E. Merck, grade 60, particle size 0.040−0.063 mm, 230−240 mesh ASTM) with the indicated solvent as eluent. ^{1}H NMR spectra were obtained on Varian XL-300 and Gemini-200 spectrometers working at 300 and 200 MHz, respectively. Typical spectral parameters were spectral width 10 ppm, pulse width 9 μs (57°), data size 32 K. ^{13}C NMR experiments were carried out on the Varian Gemini-200 spectrometer operating at 50 MHz. The acquisiton parameters were spectral width 16 kHz, acquisition time 0.99 s, pulse width 9 μs (57°), data size 32 K. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and J values are reported in hertz. Elemental analyses were performed by the analytical departement at C.N.Q.O. (CSIC) and the results obtained were within ±0.4% of the theoretical values.

Benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(1*H*,3*H*)-one 2,2-Dioxide (1). Sulfamoyl chloride (3.46 g, 30 mmol) was added to a solution of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate[17] (2.07 g, 10 mmol) in toluene (30 mL). The reaction mixture was heated at 60 °C for 4 h. After the mixture was cooled to room temperature, the precipitated solid was collected by filtration and dissolved in 1 N NaOH (25 mL). The solution was stirred for 4 h at room temperature. After that time, the mixture was made acidic with concentrated HCl and the precipitate collected by filtration. Compound **1** was obtained (1.16 g, 45%) as a white solid: mp 234−236 °C.

General Procedure for the Synthesis of Benzyl Derivatives of Benzothienothiadiazine. The corresponding benzyl halide derivative (1 mmol) was added to a solution of benzothienothiadiazine dioxide **1** (1 mmol) in a sodium bicarbonate aqueous solution (10 mL). The reaction mixture was stirred in the indicated conditions in each case. After that, the aqueous phase was acidified using concentrated HCl and extracted with AcOEt (5 × 10 mL). The combined organic phases were dried over sodium sulfate and the solvent was eliminated under reduced pressure. The residue was chro-

matographed on silica gel column using as eluents mixtures of solvents in the portions indicated.

1-Benzylbenzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (3) and 1,3-Dibenzylbenzothieno[3,2-*a*]-1,2,6-thiadiazin-4-one 2,2-Dioxide (5). Reagents: benzothienothiadiazine dioxide **1** (0.25 g, 1 mmol), $H_2O/NaHCO_3$ (10 mL), benzyl bromide (0.17 g, 1 mmol). Conditions: room temperature, 12 h. Purification: CH_2Cl_2:MeOH (20:1), first fraction, yield of dibenzyl derivative **5**; 0.19 g (4%); mp 120−121 °C; ^{1}H NMR (DMSO-d_6) δ 4.79 (s, 2H, N_1-CH_2-Ph), 4.99 (s, 2H, N_3-CH_2-Ph), 6.92 (d, 1H, J = 7.1, Ar−H), 7.07−7.60 (m, 11H, Ar−H), 7.84 (d, 1H, J = 6.6, Ar−H), 7.90 (d, 1H, J = 7.9, Ar−H); ^{13}C NMR (DMSO-d_6) δ 46.54 (N_3-CH_2-Ph), 56.95 (N_1-CH_2-Ph), 111.72 (C-4a), 123.12, 123.98, 125.79, 128.08, 128.61, 128.92, 129.04 129.59, 129.83, 130.30, 131.81, 132.54, 135.45, 137.27 (Ar−C), 140.17 (C-9b), 158.47 (C-4). Anal. ($C_{23}H_{18}N_2S_2O_3$) C, H, N, S.

Purification: second fraction, CH_2Cl_2:MeOH (20:1), yield of monobenzyl derivative **3**; 0.28 g (81%); mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 5.12 (s, 2H, $N-CH_2-Ph$), 7.14−7.43 (m, 7H, Ar−H), 7.75 (d, 1H, J = 8.1, Ar−H), 7.92 (d, 1H, J = 8.1, Ar−H); ^{13}C NMR (DMSO-d_6) δ 52.54 ($N-CH_2-Ph$), 121.40 (C-4a), 123.14, 123.83, 124.48, 126.64, 127.00, 128.26, 132.52, 137.73, 138.45 (Ar−C), 139.53 (C-9b), 164.93 (C-4). Anal. ($C_{16}H_{12}N_2S_2O_3$) C, H, N, S.

1-[(2-Biphenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (4) and 1,3-Di[(2-biphenyl)-methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4-one 2,2-Dioxide (6). Reagents: benzothienothiadiazine dioxide **1** (0.25 g, 1 mmol), $H_2O/NaHCO_3$ (10 mL), 2-biphenylmethyl bromide (0.24 g, 1 mmol). Conditions: room temperature, 60 h. Purification: CH_2Cl_2:MeOH (20:1), first fraction, yield of compound **6;** 0.13 g (13%); mp 143−144 °C; ^{1}H NMR (DMSO-d_6) δ 4.86 (s, 2H, N_1-CH_2-Ph), 4.99 (s, 2H, N_3-CH_2-Ph), 6.87−7.80 (m, 22 H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 44.75 (N_3-CH_2-Ph), 54.35 (N_1-CH_2-Ph), 122.81 (C-4a), 123.47, 125.40, 126.54, 126.96, 127.29, 127.71, 128.17, 128.30, 128.40, 128.49, 129.31, 132.92, 138.37, 139.46, 140.05, 140.49, 141.11 (Ar−C), 141.93 (C-9b), 158.91 (C-4). Anal. ($C_{35}H_{26}N_2S_2O_3$) C, H, N, S.

Purification: second fraction, yield of monobenzyl derivative **4**; 0.07 g (18%); mp 212−215 °C; ^{1}H NMR (DMSO-d_6) δ 4.90 (s, 2H, $N-CH_2-Ph$), 7.16−7.44 (m, 11H, Ar−H), 7.80 (d, 1H, J = 8.1, Ar−H), 7.87 (d, 1H, J = 7.3, Ar−H); ^{13}C NMR (DMSO-d_6) δ 51.28 ($N-CH_2-Ph$), 120.20 (C-4a), 122.47, 123.84, 124.35, 126.59, 127.07, 127.16, 127.43, 127.72, 128.44, 129.05, 129.70, 132.09, 136.12, 137.75, 139.76, 139.79 (Ar−C), 139.86 (C-9b), 164.47 (C-4). Anal. ($C_{22}H_{16}N_2S_2O_3$) C, H, N, S.

1-[(3-Biphenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (7). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 3-biphenylmethyl bromide (0.12 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (10:1); yield 0.02 g (25%); mp 220−222 °C; ^{1}H NMR (DMSO-d_6) δ 5.19 (s, 2H, $N-CH_2-Ph$), 7.26−7.94 (m, 13H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 52.60 ($N-CH_2-Ph$), 121.35 (C-4a), 123.08, 123.76, 124.45, 125.32, 125.52, 126.08, 126.53, 126.59, 127.41, 128.79, 128.86, 132.59, 137.64, 139.00, 139.35, 139.96 (Ar−C), 140.05 (C-9b), 164.54 (C-4). Anal. ($C_{22}H_{16}N_2S_2O_3$) C, H, N, S.

1-[(4-Biphenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (8). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 4-biphenylmethyl chloride (0.10 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (10:1); yield 0.03 g (26%); mp 227−229 °C; ^{1}H NMR (DMSO-d_6) δ 5.14 (s, 2H, $N-CH_2-Ph$), 7.28−7.94 (m, 13H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 52.17 ($N-CH_2-Ph$), 123.01 (C-4a), 123.75, 124.39, 126.28, 126.43, 126.50, 126.61, 127.27, 127.54, 128.83, 132.54, 137.64, 137.81, 138.64, 139.28 (Ar−C), 139.71 (C-9b), 164.37 (C-4). Anal. ($C_{22}H_{16}N_2S_2O_3$) C, H, N, S.

1-[(2-Cyanophenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (9). Reagents: benzothienothiadiazine dioxide **1** (0.25 g, 1 mmol), $H_2O/NaHCO_3$ (10 mL), 2-cyanophenylmethyl bromide (0.19 g, 1 mmol). Conditions: room temperature, 36 h. Purification: CH_2Cl_2:MeOH (20:1); yield 0.10 g (28%); mp 228−230 °C; ^{1}H NMR (DMSO-d_6) δ 5.19 (s, 2H, $N-CH_2-Ph$), 7.26−7.98 (m, 8H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 51.55 ($N-CH_2-Ph$), 109.46 (C-4a), 117.02, 122.24, 123.95, 124.67, 126.78, 127.84, 127.98, 132.27, 132.91, 133.48, 133.56, 137.75, 139.47 (Ar−C), 142.41 (C-9b), 164.53 (C-4). Anal. ($C_{17}H_{11}N_3S_2O_3$) C, H, N, S.

1-[(2-Nitrophenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (10). Reagents: benzothienothiadiazine dioxide **1** (0.13 g, 0.5 mmol), $H_2O/NaHCO_3$ (10 mL), 2-nitrophenylmethyl bromide (0.11 g, 0.5 mmol). Conditions: room temperature, 12 h. Purification: CH_2Cl_2:MeOH (20:1); yield 0.04 g (26%); mp 245−246 °C; ^{1}H NMR (DMSO-d_6) δ 5.29 (s, 2H, $N-CH_2-Ph$), 7.20−8.17 (m, 8H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 50.65 ($N-CH_2-Ph$), 121.23 (C-4a), 122.10, 123.90, 124.60, 124.87, 126.65, 128.43, 129.24, 132.02, 134.12, 134.63, 137.80, 139.61, (Ar−C), 146.93 (C-9b), 164.23 (C-4). Anal. ($C_{16}H_{11}N_3S_2O_5$) C, H, N, S.

1-[(2-Chlorophenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (11). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 2-chlorophenylmethyl bromide (0.08 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (9:1); yield 0.04 g (40%); mp 205−206 °C; ^{1}H NMR (DMSO-d_6) δ 5.02 (s, 2H, $N-CH_2-Ph$), 7.23−7.87 (m, 8H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 50.97 ($N-CH_2-Ph$), 100.00 (C-4a), 122.15, 123.97, 124.57, 126.70, 127.43, 128.61, 128.80, 129.19, 130.74, 132.16, 136.38, 137.86 (Ar−C), 139.73 (C-9b), 164.38 (C-4). Anal. ($C_{16}H_{11}ClN_2S_2O_3$) C, H, N, S.

1-[(4-Chlorophenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (12). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 4-chlorophenylmethyl chloride (0.08 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (20:1); yield 0.04 g (48%); mp 244−245 °C; ^{1}H NMR (DMSO-d_6) δ 5.07 (s, 2H, $N-CH_2-Ph$), 7.31−7.46 (m, 6H, Ar−H), 7.73 (d, 1H, J = 8.0, Ar−H), 7.92 (d, 1H, J = 7.7, Ar−H); ^{13}C NMR (DMSO-d_6) δ 51.98 ($N-CH_2-Ph$), 122.95 (C-4a), 123.83, 124.54, 126.60, 128.17, 128.98, 131.59, 132.46, 137.35, 137.64, 139.69 (Ar−C), 144.26 (C-9b), 164.47 (C-4). Anal. ($C_{16}H_{11}ClN_2S_2O_3$) C, H, N, S.

1-[(4-Cyanophenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (13). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 4-cyanophenylmethyl bromide (0.10 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (9:1); yield 0.03 g (29%); mp 255−256 °C; ^{1}H NMR (DMSO-d_6) δ 5.14 (s, 2H, $N-CH_2-Ph$), 7.27−7.98 (m, 8H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 52.42 ($N-CH_2-Ph$), 109.82 (C-4a), 118.85, 122.77, 123.44, 123.91, 124.62, 126.67, 127.90, 132.29, 132.64, 137.70, 139.13 (Ar−C), 144.55 (C-9b), 164.33 (C-4). Anal. ($C_{17}H_{11}N_3S_2O_3$) C, H, N, S.

1-[(4-Methoxyphenyl)methyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (14). Reagents: benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol), $H_2O/NaHCO_3$ (10 mL), 4-methoxyphenylmethyl bromide (0.05 g, 0.25 mmol). Conditions: reflux, 12 h. Purification: CH_2Cl_2:MeOH (10:1); yield 0.01 g (13%); mp 222−225 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 4.88 (s, 2H, $N-CH_2-Ph$), 6.67 (d, 2H, J = 7.7, Ar−H), 6.82 (d, 2H, J = 7.7, Ar−H), 7.53 (m, 3H, J = 7.7, Ar−H), 7.89 (t, 1H, J = 8.2, Ar−H); ^{13}C NMR ($CDCl_3$) δ 52.22 ($N-CH_2-Ph$), 56.87 (OCH_3), 113.97 (C-4a), 123.48, 124.06, 124.25, 124.33, 125.94, 126.60, 128.93, 130.36, 131.96 (Ar−C), 139.66 (C-9b), 159.27 (C-4), 166.08 (C=O). Anal. ($C_{17}H_{14}N_2S_2O_4$) C, H, N, S.

1-[(4-Methoxyphenyl)carbonylmethyl]benzothieno-[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (15). To a solution of benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol) and sodium bicarbonate in excess in DMF (15 mL) was added 2-bromo-4′-methoxyacetophenone (0.12 g, 0.25 mmol). The reaction mixture was stirred at room temperature for 48 h. After that time, the reaction mixture was put over water and extracted with AcOEt (5 × 10 mL). The organic phase was dried over sodium sulfate and the solvent eliminated under

reduced pressure. The residue was purified by silica gel column chromatography CH_2Cl_2:MeOH (20:1) yielding 0.03 g (36%) of derivative **15**: mp 217−218 °C; ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H, OCH_3), 5.05 (s, 2H, N−CH_2−COPh), 7.04 (d, 1H, J = 8.9, Ar−H), 7.42 (m, 5H, Ar−H), 7.82 (d, 1H, J = 8.9, Ar−H), 8.02 (d, 1H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 41.30 (N−CH_2−Ph), 55.62 (OCH_3), 113.97 (C-4a), 121.37, 123.27, 123.87, 130.19, 130.29, 130.58, 139.33 (Ar−C), 144.34 (C-9b), 165.39 (C-4), 167.32 (C=O). Anal. ($C_{18}H_{14}N_2S_2O_5$) C, H, N, S.

1-[(4-Biphenyl)carbonylmethyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (16). Following the above procedure a solution of benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol) and 2-bromo-4′-phenylacetophenone (0.07 g, 0.25 mmol) in DMF was stirred for 48 h. at room temperature. After workup, compound **16** was obtained (0.04 g, 32%): mp 249−251 °C; ^{1}H NMR (DMSO-d_6) δ 4.09 (s, 2H, N−CH_2−COPh), 7.36−8.14 (m, 13H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 40.33 (N−CH_2−COPh), 123.27 (C-4a), 123.89, 126.95, 127.02, 127.93, 128.43, 128.54, 128.66, 128.98, 129.12, 133.94, 134.51, 138.87, 138.87, 139.38, 144.68 (Ar−C), 150.69 (C-9b), 160.57(C-4), 192.67 (C=O). Anal. ($C_{23}H_{16}N_2S_2O_4$) C, H, N, S.

1-[(4-Biphenyl)carbonyl]benzothieno[3,2-*a*]-1,2,6-thiadiazin-4(3*H*)-one 2,2-Dioxide (17). According to the method described for derivative **15** a solution of benzothienothiadiazine dioxide **1** (0.06 g, 0.25 mmol) and 2-bromo-4′-biphenylcarbonyl (0.05 g, 0.25 mmol) in DMF was stirred for 48 h. After workup compound **17** was obtained (0.01 g, 11%): mp 233−235 °C; ^{1}H NMR (DMSO-d_6) δ 7.39−8.02 (m, 13H, J = 8.9, Ar−H); ^{13}C NMR (DMSO-d_6) δ 121.35 (C-4a), 126.56, 126.91, 127.05, 128.10, 129.05, 129.89, 137.75, 139.27, 144.32, 144.78, 161.47 (C-9b), 162.97(C-4), 187.07 (C=O). Anal. ($C_{22}H_{14}N_2S_2O_4$) C, H, N, S.

General Procedure for the Synthesis of Benzyl Derivatives of Benzothiadiazine. To a solution of benzothiadiazine dioxide **2**[18] (1 mmol) in a sodium bicarbonate aqueous solution (20 mL) was added the corresponding benzyl halide (1.5 mmol). The reaction mixture was refluxed for 2 h. After cooling to room temperature, the aqueous phase was washed with CH_2Cl_2 (2 × 10 mL). The aqueous phase was cooled at 4 °C and the product was isolated and purified in each particular case.

1-Benzyl-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (18). Reagents: benzothiadiazine dioxide **2** (0.67 g, 3.3 mmol), benzyl bromide (0.86 g, 4.9 mmol). Isolation: filtration of aqueous phase. Purification: recrystallization from toluene/MeOH; yield 0.80 g (81%) as a white solid; mp 288−290 °C; ^{1}H NMR (DMSO-d_6) δ 4.95 (s, 2H, N−CH_2), 6.74 (dd, 1H, J_{H6H8} = 1.0, J_{H7H8} = 7.7, H-8), 6.87 (t, 1H, J_{H5H6} = 7.7, J_{H6H7} = 7.4, H-6), 7.23 (t, 1H, J_{H5H7} = 1.7, H-7), 7.88 (dd, 1H, H-5), 7.27−7.42 (m, 5H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 46.47 (CH_2), 113.80 (C-8), 119.28 (C-6), 119.70 (C-4a), 126.93, 126.98, 128.44, 137.88 (Ar−C), 128.85 (C-5), 131.93 (C-7), 142.22 (C-8a), 165.91 (C-4). Anal. ($C_{14}H_{12}N_2O_3S$) C, H, N, S.

1-[(4-Chlorophenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (19). Reagents: benzothiadiazine dioxide **2** (0.40 g, 2.0 mmol), 4-chlorophenylmethyl chloride (0.60 g, 3.0 mmol). Isolation: filtration of aqueous phase. Purification: recrystallization from toluene/MeOH; yield 0.41 g (63%) as a white solid; mp 285−287 °C; ^{1}H NMR (DMSO-d_6) δ 4.93 (s, 2H, N−CH_2), 6.75 (dd, 1H, J_{H6H8} = 1.0, J_{H7H8} = 8.2, H-8), 6.92 (t, 1H, J_{H5H6} = 7.7, J_{H6H7} = 7.4, H-6), 7.30 (t, 1H, J_{H5H7} = 1.7, H-7), 7.86 (dd, 1H, H-5), 7.27−7.39 (m, 4H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 46.51 (CH_2), 114.54 (C-8), 119.74 (C-4a), 120.64 (C-6), 129.01, 129.37, 129.52, 132.35 (Ar−C), 133.17 (C-5), 137.05 (C-7), 142.30 (C-8a), 167.29 (C-4). Anal. ($C_{14}H_{11}N_2O_3SCl$) C, H, N, S.

1-[(3-Chlorophenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (20). Reagents: benzothiadiazine dioxide **2** (0.21 g, 1.0 mmol), 3-chlorophenylmethyl chloride (0.26 g, 1.5 mmol). Isolation: filtration of acidified aqueous phase. Purification: silica gel column chromatrography, eluent CH_2Cl_2/MeOH (50:1); yield 0.14 g (42%) as a white solid; mp 195−197 °C; ^{1}H NMR (DMSO-d_6) δ 4.92 (s, 2H, N−CH_2), 6.71 (dd, 1H, J_{H6H8} = 1.2, J_{H7H8} = 8.3, H-8), 6.86 (t, 1H, J_{H5H6} = 7.9, J_{H6H7} = 7.0, H-6), 7.28 (t, 1H, J_{H5H7} = 1.7, H-7), 7.85 (dd, 1H, H-5), 7.22−7.41 (m, 4H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 45.97 (CH_2), 113.61 (C-8), 119.37 (C-4a), 119.40 (C-6), 125.59, 126.61, 126.89, 130.21, 133.05, 140.55 (Ar−C), 128.83 (C-5), 132.06 (C-7), 141.91 (C-8a), 165.54 (C-4). Anal. ($C_{14}H_{11}N_2O_3SCl$) C, H, N, S.

1-[(2-Chlorophenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (21). Reagents: benzothiadiazine dioxide **2** (0.50 g, 2.5 mmol), 2-chlorophenylmethyl chloride (0.61 g, 3.7 mmol). Isolation: filtration of aqueous phase. Purification: recrystallization from toluene/MeOH; yield 0.58 g (72%) as a white solid; mp 292−294 °C; ^{1}H NMR (DMSO-d_6) δ 4.99 (s, 2H, N−CH_2), 6.54 (dd, 1H, J_{H6H8} = 1.6, J_{H7H8} = 8.0, H-8), 6.92 (t, 1H, J_{H5H6} = 7.7, J_{H6H7} = 7.7, H-6), 7.29 (t, 1H, J_{H5H7} = 1.7, H-7), 7.93 (dd, 1H, H-5), 7.24−7.32 (m, 4H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 44.66 (CH_2), 113.10 (C-8), 119.43 (C-6), 119.55 (C-4a), 127.22, 128.04, 128.64, 128.93, 131.35, 134.38 (Ar−C), 129.19 (C-5), 132.07 (C-7), 142.01 (C-8a), 165.56 (C-4). Anal. ($C_{14}H_{11}N_2O_3SCl$) C, H, N, S.

1-[(4-Methylphenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (22). Reagents: benzothiadiazine dioxide **2** (0.32 g, 1.6 mmol), 4-methylphenylmethyl chloride (0.34 g, 2.4 mmol). Isolation: filtration of aqueous phase. Purification: filtration of acidified aqueous phase. Purification: silica gel column chromatrography, eluent CH_2Cl_2/MeOH (50:1); yield 0.20 g (50%) as a white solid; mp 290−292 °C; ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H, CH_3),4.91 (s, 2H, N−CH_2), 6.77 (dd, 1H, J_{H6H8} = 0.6, J_{H7H8} = 8.3, H-8), 6.88 (t, 1H, J_{H5H6} = 7.8, J_{H6H7} = 7.3, H-6), 7.26 (t, 1H, J_{H5H7} = 1.7, H-7), 7.90 (dd, 1H, H-5), 7.07−7.30 (m, 4H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 20.71 (CH_3), 46.27 (CH_2), 113.97 (C-8), 119.31 (C-6), 119.42 (C-4a), 126.93, 128.99, 136.05, 134.67 (Ar−C), 128.83 (C-5), 132.07 (C-7), 142.21 (C-8a), 166.01 (C-4). Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N, S.

1-[(3,4-Dichlorophenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (23). Reagents: benzothiadiazine dioxide **2** (0.26 g, 1.3 mmol), 3,4-dichlorophenylmethyl chloride (0.40 g, 1.9 mmol). Isolation: filtration of aqueous phase. Purification: recrystallization from toluene/MeOH; yield 0.36 g (76%) as a white solid; mp 250−252 °C; ^{1}H NMR (DMSO-d_6) δ 4.96 (s, 2H, N−CH_2), 6.74 (dd, 1H, J_{H6H8} = 0.8, J_{H7H8} = 8.1, H-8), 6.89 (t, 1H, J_{H5H6} = 7.7, J_{H6H7} = 7.2, H-6), 7.29 (t, 1H, J_{H5H7} = 1.6, H-7), 7.89 (dd, 1H, H-5), 7.41−7.67 (m, 3H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 45.42 (CH_2), 113.08 (C-8), 119.49 (C-6), 119.63 (C-4a), 127.40, 128.95, 129.48, 131.01, 139.42 (Ar−C), 130.64 (C-5), 132.08 (C-7), 141.81 (C-8a), 165.57 (C-4). Anal. ($C_{14}H_{10}N_2O_3SCl_2$) C, H, N, S.

1-[(2-Biphenyl)methyl]-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (24), 1,3-Di[(2-biphenyl)methyl]-2,1,3-benzothiadiazin-4-one 2,2-Dioxide (25), and 1-[(2-Biphenyl)methyl]-4-[(2-biphenyl)methyloxy]-2,1,3-benzothiadiazine 2,2-Dioxide (26). To a suspension of sodium hydride (0.04 g, 1.6 mmol) in DMF were added benzothiadiazine dioxide **2** (0.21 g, 1 mmol) and 2-biphenylmethyl bromide (0.38 g, 1.5 mmol). The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure. The residue was dissolved in water and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel column using CH_2Cl_2/MeOH (50:1) as eluent. From the first fraction was isolated derivative **25:** yield 0.06 g (11%) as a white solid; mp 67−68 °C; ^{1}H NMR ($CDCl_3$-d_6) δ 4.87 (s, 2H, N_1−CH_2), 5.02 (s, 2H, N_3−CH_2) 6.62 (dd, 1H, J_{H6H8} = 1.4, J_{H7H8} = 7.5, H-8), 8.04 (dd, 1H, J_{H5H6} = 7.6, J_{H5H7} = 1.5, H-5), 7.04−7.65 (m, 20H, Ar−H, H-6, H-7); ^{13}C NMR ($CDCl_3$-d_6) δ 44.64 (N_3−CH_2), 52.44 (N_1−CH_2), 121.00 (C-8), 125.81 (C-6), 127.72 (C-4a), 126.23, 127.23, 127.30, 127.50, 127.62, 127.97, 128.11, 128.32, 128.39, 128.45, 128.96, 129.26, 130.07, 130.38, 131.84, 132.96, 139.74, 139.86, 141.21, 141.61 (Ar−C), 130.44 (C-5), 134.52 (C-7), 140.50 (C-8a), 162.23 (C-4). Anal. ($C_{33}H_{26}N_2O_3S$) C, H, N, S.

From the second fraction was isolated derivative **26:** yield 0.02 g (4%) as a white solid; mp 160−162 °C; ^{1}H NMR ($CDCl_3$-

d_6) δ 5.11 (s, 2H, N_1-CH_2), 5.43 (s, 2H, $O-CH_2$), 6.51 (dd, 1H, $J_{H6H8} = 1.2$, $J_{H7H8} = 8.5$, H-8), 6.98 (t, 1H, $J_{H5H6} = 7.9$, $J_{H6H7} = 7.3$, H-6), 7.38 (t, 1H, $J_{H5H7} = 1.6$, H-7), 7.78 (dd, 1H, H-5), 7.24−7.61 (m, 18H, Ar−H); ^{13}C NMR ($CDCl_3$-d_6) δ 47.11 (N_1-CH_2), 68.88 ($O-CH_2$), 112.17 (C-4a), 115.75 (C-8), 121.66 (C-6), 126.82, 127.23, 127.53, 127.57, 127.68, 127.73, 127.79, 128.14, 128.42, 128.61, 128.96, 129.09, 130.04, 130.07, 131.65, 132.37, 140.10, 140.35, 142.57, 142.87 (Ar−C), 130.43 (C-5), 135.52 (C-7), 140.00 (C-8a), 165.41 (C-4). Anal. ($C_{33}H_{26}N_2O_3S$) C, H, N, S.

From the third fraction was isolated derivative **24:** yield 0.10 g (27%) as a syrup; ^{1}H NMR (DMSO-d_6) δ 4.77 (s, 2H, $N-CH_2$), 6.26 (dd, 1H, $J_{H6H8} = 1.0$, $J_{H7H8} = 7.8$, H-8), 6.84 (t, 1H, $J_{H5H6} = 7.8$, $J_{H6H7} = 7.3$, H-6), 7.17 (t, 1H, $J_{H5H7} = 1.7$, H-7), 7.85 (dd, 1H, H-5), 7.25−7.55 (m, 8H, Ar−H); ^{13}C NMR (DMSO-d_6) δ 44.73 (CH_2), 113.12 (C-8), 119.24 (C-6), 119.51 (C-4a), 126.62, 126.97, 127.54, 127.63, 128.56, 129.13, 134.32, 139.99, 140.44 (Ar−C), 128.84 (C-5), 131.88 (C-7), 142.08 (C-8a), 165.57 (C-4). Anal. ($C_{20}H_{16}N_2O_3S$) C, H, N, S.

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