

Synthesis of a new series of biologically interesting 6'-chloro-1',1'-dioxospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives

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Abstract A series of 6'-chloro-1',1'-dioxospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives have been synthesized from isatoic anhydride and 3-(R²-amino)-1,4,2-benzodithiazine 1,1-dioxides. Some synthetic limitations are discussed on the basis of quantum chemical calculations performed by use of the Hartree–Fock method.

Keywords Benzodithiazine · Isatoic anhydride · Synthesis · RHF · Spiro compounds · Quantum chemistry

Introduction

Compounds containing the 1,1-dioxo-1,4,2-benzodithiazine ring system were synthesized in our laboratories in 1984 and have attracted much attention for several years because of their wide range of biological activity. It has been demonstrated that many 6-chloro-1,4,2-benzodithiazine derivatives (Fig. 1, type I) have low acute toxicity to mice and rats and, depending on their structure, act as potential radio-protective [1, 2], diuretic [1–5], or chologogue [5] agents. It has also been shown that some 6-chloro-1,1-dioxo-1,4,2-benzodithiazines have remarkable antitumor activity (Fig. 1, types I [6–8] and II [9, 10]) or anti-HIV activity (Fig. 1, types I [11, 12], II [9], and III [13]).

Furthermore, 6-chloro-3-methylthio-1,4,2-benzodithiazine 1,1-dioxides have attracted our investigative attention because of their suitability for chemical transformation into

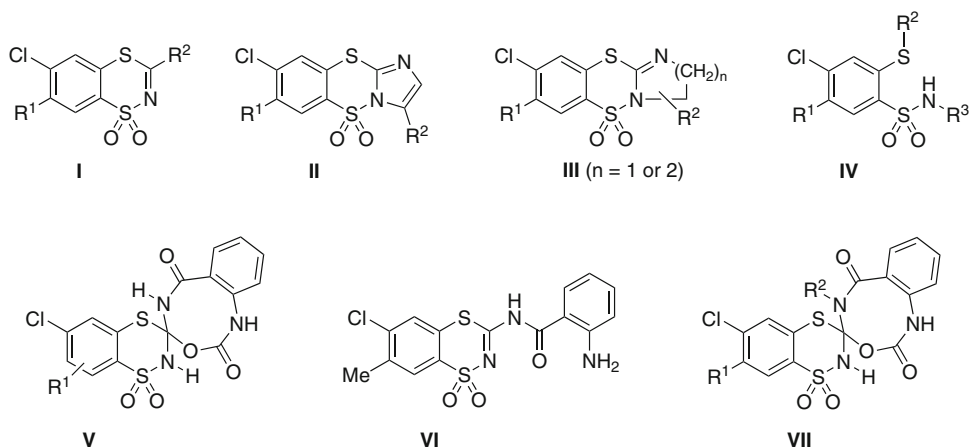
otherwise not readily obtained 4-chloro-2-mercaptobenzenesulfonamide derivatives of type IV (Fig. 1). These compounds have remarkable structure-dependent antitumor activity [14–26], anti-HIV activity [14–17, 27–30], antibacterial activity [31], or strong inhibitory activity of human carbonic anhydrase (CA) isozymes I, II, IX, and XII [32–34]. Some of the compounds have been reported to be novel HIV-1 integrase inhibitors (MBSAs) [8, 11–13].

Recently, we have reported the synthesis and some chemical properties of 6'-chloro-1',1'-dioxospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives of type V (Fig. 1) [35]. More recently the compound V (R¹ = 7'-Me) and its potential metabolite VI [35] have been tested in vitro at the National Cancer Institute (Bethesda MD, USA) at a single dose (10 μM) in the full NCI 60-cell lines panel. The most susceptible were lung cancer cells (HOP-92) and melanoma (MALME-3 M) carcinoma cell lines whose growth was inhibited by 34 and 28 % by compounds of type V (R¹ = 7'-Me) and VI, respectively. In this work, the possibility of using reaction of 3-amino-6-chloro-1,4,2-benzodithiazine 1,1-dioxide derivatives with isatoic anhydride for synthesis of novel series of spiro compounds of type VII (Fig. 1) with potential biological activity or as useful starting materials for further chemical transformation has been investigated.

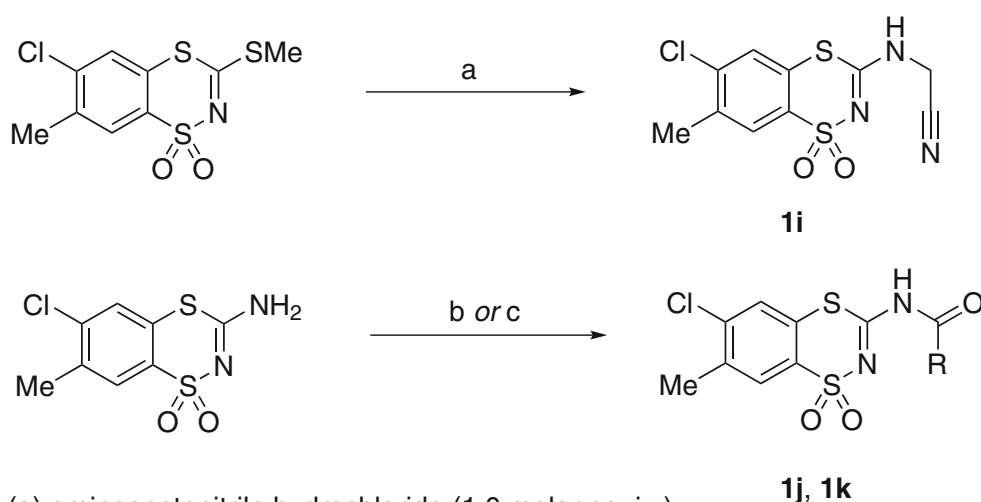
Synthesis of nitrogen-containing heterocyclic systems from isatoic anhydrides has been reported in the literature since 1981 [36, 37]. This work covers both direct transformation of the anhydrides into such heterocyclic systems, and processes leading initially to formation of anthranilic acid derivatives which are then transformed into the heterocyclic compounds in one or several stages. It is important that such transformations result in the formation of new five and six-membered heterocyclic systems. Furthermore, regioselective three-component reaction of

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Fig. 1 General structures of 6-chloro-1,4,2-benzodithiazine 1,1-dioxide derivatives **I**, **II**, **III**, and **VI**, 2-mercaptobenzene sulfonamides **IV**, and spiro [4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives **V** and **VII**



Scheme 1



(a) aminoacetonitrile hydrochloride (1.0 molar equiv.), 4-dimethylaminopyridine (1.05 molar equiv.), dry benzene, room temp. 4 h, 60 h, 81%; (b) acetic anhydride (2.0 molar equiv.) dry toluene, reflux, 10 h, 80%; (c) benzoic anhydride (2.33 molar equiv.) 170–175 °C, 3 h, dry toluene, reflux 2 h, 85%

1j, 1k

Compd	R
1j	Me
1k	Ph

isatoic anhydride, primary amines, and isatins to spirooxindole derivatives has also been reported [38].

Results and discussion

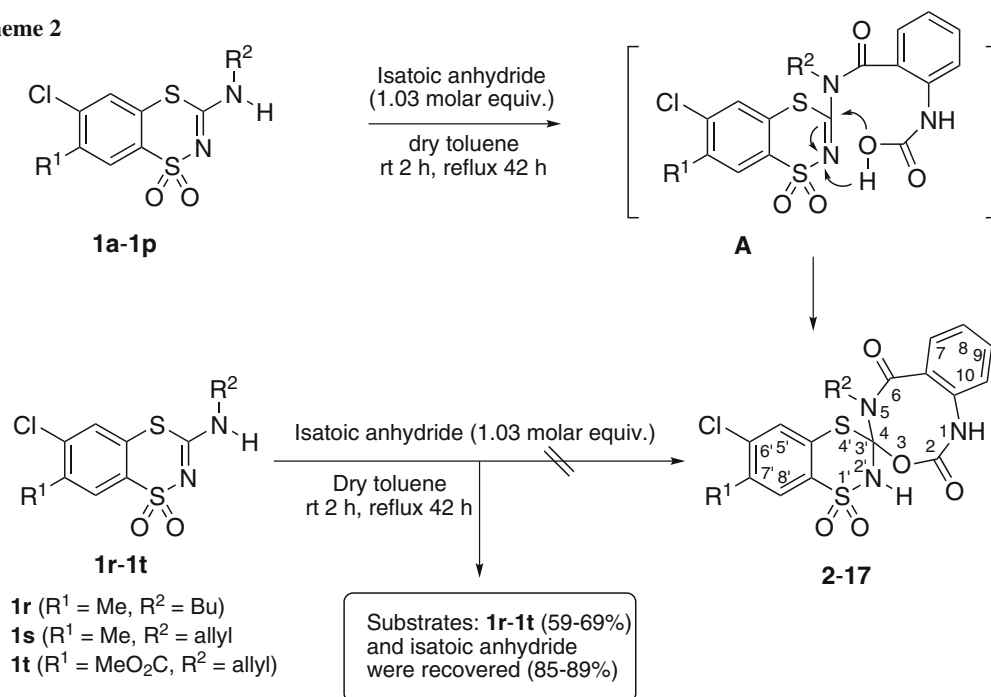
Chemistry

Previously described methods were used for synthesis of 3-amino-6-chloro-1,4,2-benzodithiazine derivatives **1a–1e** [3], **1f**, **1g** [27], **1h** [39], **1l–1p** [9], **1r** [40], **1s**, and **1t** [41]. Similar methods were used to prepare the new starting benzodithiazines **1i**, **1j**, and **1k** (Scheme 1).

As shown in Scheme 2, synthesis of the target 6'-chloro-1',1'-dioxospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives **2–17** was achieved in good to excellent yield (81–97 %) by a convenient procedure starting from isatoic anhydride and benzodithiazines **1a–1p**. However, reaction with benzodithiazines **1r**, **1s**, and **1t** failed. In these instances the substrates, only, were recovered from the resulting reaction mixture, i.e. isatoic anhydride (85–89 %) and the corresponding 3-aminobenzodithiazines **1r** (69 %), **1s** (59 %), or **1t** (69 %).

It is supposed that reaction of isatoic anhydride with benzodithiazines **1a–1t** depends on the electronic effect of

Scheme 2



Comp	R ¹	R ²	Yield /%	Comp	R ¹	R ²	Yield /%
1a, 2	Me	2-MeOPh	94	1h, 9	Me	Me ₂ N-	95
1b, 3	Me	2-BrPh	96	1i, 10	Me	NC-CH ₂ -	97
1c, 4	Me	4-ClPh	90	1j, 11	Me	Me(C=O)-	94
1d, 5	Me	2,4-diClPh	93	1k, 12	Me	Ph(C=O)-	92
1e, 6	Me		82	1l, 13	EtO ₂ C	4-FPh	97
1f, 7	Me		97	1m, 14	NC-	4-ClPh	95
1g, 8	Me		97	1n, 15	H ₂ NCO-	Ph	95
				1o, 16	H ₂ NCO-	4-ClPh	96
				1p, 17		Ph	95

their substituents R^2 . Thus, only 3-aminobenzodithiazines **1r-1t**, bearing substituents R^2 with electron-donating effects were unsuitable for formation of intermediate compounds of type **A** (Scheme 2) and further conversion to the desired spiro compounds of type **2-17** by cycloaddition reaction. Trying to understand and to explain this phenomenon we also undertook studies using ab-initio calculations for molecules **1a-1t** (in toluene), by use of the Hartree-Fock method.

The structures of the new compounds were confirmed by elemental analysis and by IR and NMR spectroscopy; the results are given in the "Experimental" section. Inspection of the ¹³C NMR spectra of spiro-cyclic compounds **2-17** revealed the characteristic signals of the spiro carbon atom

(C-4,3') in the upfield region $\delta = 110.27-110.95$ ppm, and the presence of two carbonyl groups at positions 2 and 6 of the benzo[*d*][1,3,7]oxadiazocine ring was indicated by characteristic signals in the regions 153.58–160.57 and 160.00–166.32 ppm, respectively. The ¹H NMR spectra contained characteristic signals in the regions $\delta = 7.02-7.19$ (d, $J = 7.9-8.3$ Hz) for H-10, 7.24–7.28 (t, $J = 7.1-8.1$ Hz) for H-9, 7.56–7.75 (t, $J = 7.1-8.3$ Hz) for H-8, 7.83–7.99 (d, $J = 7.1-9.0$ Hz) or 7.91 (dd, $J_{\text{ortho}} = 7.9$, $J_{\text{meta}} = 1.2$ Hz) for H-7, 8.10–12.95 as singlet for H-1, 8.10–11.82 (s) for H-2', 7.38–8.37 (s) for H-5', and 7.24 (s) for H-8'. The IR spectra of compounds **2-17** contained strong absorption bands of the two carbonyl C=O groups in the regions 1,720–1,730 and 1,765 cm^{-1} .

Molecular modeling studies

Quantum chemical calculations were performed by use of Spartan 08 software [42] to study the molecular geometry and electronic structure of 6-chloro-7- R^1 -3-(R^2 -amino)-1,4,2-benzodithiazine 1,1-dioxides **1a–1t**. The full optimized geometries of compounds **1a–1t** in toluene were calculated by use of the ab-initio restricted Hartree–Fock (RHF) method with the 6-31G* polarization basis set. The calculated relative tautomer energies with the Boltzmann distribution term equal to unity confirm experimental results that 3-(R^2 -amino)-1,4,2-benzodithiazine is a low-energy tautomer, more stable than the 3-(R^2 -imino)-1,4,2-benzodithiazine isomer.

The electrostatic atomic charges of the starting 3-aminobenzodithiazines **1a–1t** (Table 1) and electrostatic potential surface maps (Fig. 2), as affected by their R^2 substituents, provide information about the reactivity of the molecules in reactions with electrophiles.

The relative reactivity can be judged from the values of the atomic charges calculated for the nucleophilic centers of the compounds. Thus, the higher negative electrostatic charges found on the nitrogen atom of the amine groups of compounds **1a–1p** explained the different chemical behavior of 3-aminobenzodithiazines **1s–1t** in reactions with isatoic anhydride (Table 1).

The plots of electrostatic potential as maps in Fig. 2 show the electron charge density of representative compounds **1a** and **1s**. Compound **1a** has a region of high negative charge on the N atom whereas compound **1s** has less negative charge on this nitrogen atom, which explains its low reactivity.

Conclusion

We have developed a method for preparation of new series of 6'-chloro-1',1'-dioxospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-2,6(1*H*,5*H*)dione derivatives **2–17** by reaction of isatoic anhydride with 3-(R^2 -amino)-6-chloro-1,4,2-benzodithiazine 1,1-dioxide derivatives bearing R^2 substituents of diverse electronic nature. For substrates **1a–1t** geometry optimization was performed, by use of Spartan 08 software and the ab-initio restricted Hartree–Fock (RHF) method at the 6-31G* level. Theoretical studies enabled explanation of the different chemical behavior of 3-aminobenzodithiazines toward isatoic anhydride. The unreactive substrates **1r–1t** were characterized by less negative charge and greater electrostatic potential on the nitrogen atom of the amine group than the reactive compounds **1a–1p**. Further structural modification and biological evaluation of these compounds are in progress and will be reported elsewhere.

Table 1 Electrostatic atomic charges of the heterocyclic rings and amine groups of the starting 6-chloro-7- R^1 -3-(R^2 -amino)-1,4,2-benzodithiazine 1,1-dioxides **1a–1t**

Compound	SO ₂			N-2	C-3	S-4	Amine group N
	S-1	O-1	O-2				
1a	1.488	−0.677	−0.659	−0.756	0.617	−0.113	−0.550
1b	1.492	−0.676	−0.659	−0.726	0.590	−0.113	−0.599
1c	1.463	−0.670	−0.649	−0.747	0.642	−0.133	−0.637
1d	1.481	−0.669	−0.653	−0.726	0.570	−0.110	−0.534
1e	1.489	−0.676	−0.651	−0.737	0.632	−0.130	−0.614
1f	1.461	−0.667	−0.644	−0.718	0.585	−0.077	−0.599
1g	1.489	−0.674	−0.651	−0.720	0.550	−0.049	−0.572
1h	1.578	−0.704	−0.676	−0.792	0.508	−0.148	−0.197
1i	1.561	−0.699	−0.662	−0.740	0.616	−0.116	−0.341
1j	1.463	−0.656	−0.649	−0.701	0.519	−0.056	−0.674
1k	1.435	−0.651	−0.643	−0.703	0.629	−0.050	−0.600
1l	1.454	−0.653	−0.647	−0.744	0.600	−0.120	−0.586
1m	1.458	−0.661	−0.641	−0.738	0.628	−0.121	−0.628
1n	1.442	−0.663	−0.645	−0.751	0.621	−0.142	−0.607
1o	1.449	−0.671	−0.638	−0.743	0.652	−0.136	−0.647
1p	1.456	−0.674	−0.642	−0.743	0.658	−0.142	−0.651
1r	1.497	−0.682	−0.660	−0.782	0.579	−0.142	−0.386
1s	1.503	−0.680	−0.662	−0.768	0.559	−0.146	−0.390
1t	1.524	−0.685	−0.660	−0.760	0.486	−0.134	−0.260

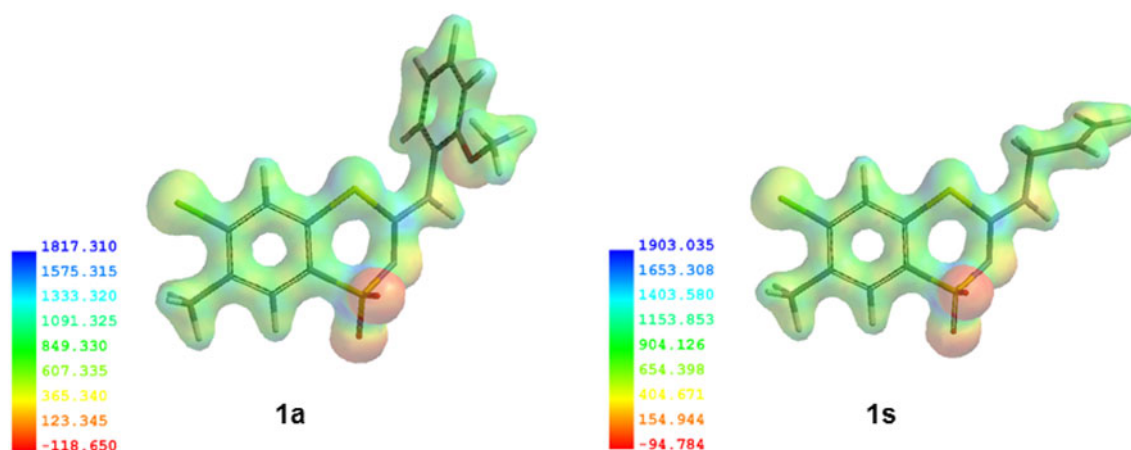


Fig. 2 Electrostatic potential maps of representative benzodithiazines **1a** and **1s**. Color ranges, in kJ mol^{-1} : **1a** from red -118.650 to blue $+1,817.310$, **1s** from red -94.784 to blue $+1,903.035$. RHF/6-31G* basis set (color figure online)

Experimental

The instrumentation and conditions used were: melting points Büchi 535 apparatus; IR spectra: KBr pellets, $400\text{--}4,000\text{ cm}^{-1}$, Perkin Elmer 1600 FT-IR spectrophotometer; ^1H NMR and ^{13}C NMR: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; spectra were recorded in dimethyl sulfoxide- d_6 (DMSO- d_6); chemical shifts are expressed as δ values relative to Me_4Si as standard; coupling constants (J) are given in hertz; multiplicity in ^1H NMR is reported as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). The results of elemental analysis for C, H, and N were in agreement with calculated values within $\pm 0.3\%$. Thin-layer chromatography (TLC) was performed on Merck silica gel 60F254 plates and visualized by UV illumination. The starting 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide and 3-amino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide were obtained by use of previously described procedures [2, 43].

2-(6-Chloro-7-methyl-1,4,2-benzodithiazin-3-ylamino)acetonitrile 1,1-dioxide (**1i**, $\text{C}_{10}\text{H}_8\text{ClN}_3\text{O}_2\text{S}_2$)

A mixture of 5.88 g 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazin 1,1-dioxide (0.02 mol), 1.85 g aminoacetonitrile hydrochloride (0.02 mol), and 2.56 g 4-dimethylaminopyridine (0.021 mol) in 50 cm^3 dry benzene was stirred at room temperature for 4 h, followed by reflux until evolution of CH_3SH had ceased (55–60 h) (CAUTION: because of high toxicity, CH_3SH should be trapped in aqueous NaOH solution). The solvent was evaporated under reduced pressure to give an oily residue and 70 cm^3 water was added, with stirring. The resulting suspension (pH ~ 7.8) was acidified to pH 2 by addition of 1 % hydrochloric acid. After stirring at room temperature for 6 h, the crude product was collected by filtration, washed with water

($6 \times 5\text{ cm}^3$), dried, and purified by recrystallization from 40 cm^3 glacial acetic acid. Yield: 4.9 g (81 %); m.p.: $228\text{--}229\text{ }^\circ\text{C}$; $R_f = 0.76$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,340$ (NH), 2,255 ($\text{C}\equiv\text{N}$), 1,560 ($\text{C}=\text{N}$), 1,345, 1,315, 1,165 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.43$ (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.96 (s, 1H, H-5), 8.03 (s, 1H, H-8), 10.34 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.58, 30.88, 116.28, 126.88, 127.25, 128.47, 130.87, 137.63, 137.94, 163.83$ ppm.

3-Acetylamino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1j**, $\text{C}_{10}\text{H}_9\text{ClN}_2\text{O}_3\text{S}_2$)

A mixture of 5.25 g 3-amino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (0.02 mol) and 4.10 g acetic anhydride (0.04 mol) in 50 cm^3 dry toluene was stirred under reflux for 10 h. After cooling to room temperature, the precipitate was collected by filtration, washed successively with toluene ($3 \times 5\text{ cm}^3$), methanol ($2 \times 5\text{ cm}^3$), and acetonitrile ($3 \times 5\text{ cm}^3$), and dried. Yield: 4.9 g (80 %); m.p.: $264\text{--}265\text{ }^\circ\text{C}$; $R_f = 0.74$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,220, 3,190$ (NH), 1,710 ($\text{C}=\text{O}$), 1,555 ($\text{C}=\text{N}$), 1,345, 1,310, 1,160 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.19$ (s, 3H, CH_3), 2.40 (s, 3H, $\text{CH}_3\text{C}=\text{O}$), 8.00 (s, 1H, H-5), 8.06 (s, 1H, H-8), 12.15 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.60, 23.95, 126.52, 128.42, 129.00, 129.35, 138.06, 138.91, 163.41, 172.27$ ppm.

3-Benzoylamino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1k**, $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}_3\text{S}_2$)

A mixture of 3.94 g 3-amino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (0.015 mol) and 7.92 g benzoic anhydride (0.035 mol) was stirred at $170\text{--}175\text{ }^\circ\text{C}$ for 3 h. After cooling to $105\text{ }^\circ\text{C}$, 60 cm^3 dry toluene was added to the reaction mixture. The resulting suspension was further stirred under reflux for 2 h. After cooling to room temperature and standing overnight, the precipitate was collected by filtration, washed with toluene

($3 \times 5 \text{ cm}^3$) and ethanol ($3 \times 5 \text{ cm}^3$), and dried. Yield: 4.7 g (85 %); m.p.: 279–280 °C; IR (KBr): $\bar{\nu} = 3,260$ (NH), 1,695 (C=O), 1,565 (C=N), 1,345, 1,305, 1,170 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.46$ (s, 3H, CH_3), 7.58 (t, $J = 7.8$ Hz, 2H, H-3 and H-5, PhC=O), 7.70 (t, $J = 7.3$ Hz, 1H, H-4, PhC=O), 8.02 (d, $J = 7.8$ Hz, 2H, H-2 and H-6, PhC=O), 8.05 (s, 1H, H-5 benzodithiazine), 8.08 (s, 1H, H-8 benzodithiazine), 12.90 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.56, 126.55, 128.47, 128.94, 129.20, 129.40, 129.64, 131.29, 134.07, 138.12, 138.96, 165.11, 168.46$ ppm.

General procedure for the preparation of spiro-[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione derivatives 2–17

A mixture of 0.84 g isatoic anhydride (5.15 mmol) and the corresponding 6-chloro-7- R^1 -3-(R^2 -amino)-1,4,2-benzodithiazine 1,1-dioxide **1a–1p** (5 mmol) in dry toluene (15 cm^3 for 1 g benzodithiazine) was stirred at room temperature for 2 h, followed by reflux for 42 h. After cooling to room temperature, the precipitate was collected by filtration, and washed successively with toluene ($3 \times 4 \text{ cm}^3$), methanol ($5 \times 3 \text{ cm}^3$), and petroleum ether ($3 \times 3 \text{ cm}^3$). In this manner, the following spiro compounds were obtained (analogous reactions with 3-(R^2 -amino)-1,4,2-benzodithiazine 1,1-dioxide **1r**, **1s**, and **1t**, bearing R^2 -substituents with strong or weak electron-donating effect, failed).

6'-Chloro-5-(2-methoxyphenyl)-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (2, $\text{C}_{23}\text{H}_{18}\text{ClN}_3\text{O}_6\text{S}_2$)

Starting from 1.85 g 6-chloro-7-methyl-3-(2-methoxyphenylamino)-1,4,2-benzodithiazine 1,1-dioxide (**1a**), the title compound **2** was obtained. Yield: 2.5 g (94 %); m.p.: 200–201 °C (dec.); TLC: $R_f = 0.95$ (CHCl_3 –MeOH 16:3); IR (KBr): $\bar{\nu} = 3,315, 3,240, 3,175$ (NH), 1,765, 1,730 (C=O), 1,340, 1,310, 1,155 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.42$ (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 7.02 (d, $J = 8.1$ Hz, 1H, H-10), 7.15–7.24 (m, 2H, arom), 7.28–7.41 (m, 3H, arom), 7.74 (t, $J = 7.6$ Hz, 1H, H-8), 7.89 (d, $J = 7.6$ Hz, 1H, H-7), 7.93 (s, 1H, H-5'), 7.99 (s, 1H, H-8'), 11.06 (br s, 1H, NH), 11.70 (br s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.56, 56.08, 110.53, 112.76, 115.59, 120.83, 123.77, 124.00, 126.70, 126.90, 127.85, 127.92, 128.41, 128.92, 129.20, 131.14, 137.19, 137.39, 137.71, 141.66, 147.36, 153.58, 160.14$ ppm.

5-(2-Bromophenyl)-6'-chloro-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (3, $\text{C}_{22}\text{H}_{15}\text{BrClN}_3\text{O}_5\text{S}_2$)

Starting from 2.09 g 3-(2-bromophenylamino)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1b**), the title compound **3** was obtained. Yield: 2.8 g (96 %); m.p.: 222–223 °C (dec.); TLC: $R_f = 0.78$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,245, 3,185$ (NH), 1,765, 1,725 (C=O), 1,365, 1,330, 1,155 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.13$ (s, 3H, CH_3), 7.15 (d, $J = 8.2$ Hz, 1H, H-10), 7.24 (t, $J = 8.1$ Hz, 1H, H-9), 7.36–7.39 (m, 1H, arom), 7.46–7.52 (m, 2H, arom), 7.68–7.71 (m, 1H, arom), 7.74 (t, $J = 7.8$ Hz, 1H, H-8), 7.91 (dd, $J_{\text{ortho}} = 7.9$ Hz, $J_{\text{meta}} = 1.2$ Hz, 1H, H-7), 7.97 (s, 1H, H-5'), 8.00 (s, 1H, H-8'), 11.46 (s, 1H, NH), 11.73 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.58, 110.53, 115.59, 123.78, 126.80, 127.52, 128.54, 129.11, 129.20, 129.79, 130.00, 130.16, 130.41, 130.87, 133.59, 137.20, 137.55, 137.95, 141.66, 147.36, 158.00, 160.14$ ppm.

6'-Chloro-5-(4-chlorophenyl)-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (4, $\text{C}_{22}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_5\text{S}_2$)

Starting from 1.87 g 6-chloro-3-(4-chlorophenylamino)-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1c**), the title compound **4** was obtained. Yield: 2.4 g (90 %); m.p.: 296–297 °C (dec.); TLC: $R_f = 0.76$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,270, 3,200, 3,125$ (NH), 1,765, 1,725 (C=O), 1,315, 1,290, 1,145 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.44$ (s, 3H, CH_3), 7.15 (d, $J = 8.1$ Hz, 1H, H-10), 7.28 (t, $J = 7.6$ Hz, 1H, H-9), 7.50 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 7.66 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 7.73 (t, $J = 8.3$ Hz, 1H, H-8), 7.91 (d, $J = 7.0$ Hz, 1H, H-7), 7.99 (s, 1H, H-5'), 8.04 (s, 1H, H-8'), 11.63 (s, 1H, NH), 11.66 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.34, 110.27, 115.34, 123.35, 123.52, 126.63, 127.53, 128.30, 128.94, 129.09, 129.67, 130.47, 136.60, 136.94, 137.40, 137.69, 141.41, 147.10, 159.88, 160.69$ ppm.

6'-Chloro-5-(2,4-dichlorophenyl)-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (5, $\text{C}_{22}\text{H}_{14}\text{Cl}_3\text{N}_3\text{O}_5\text{S}_2$)

Starting from 2.04 g 6-chloro-3-(2,4-dichlorophenylamino)-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1d**), the title compound **5** was obtained. Yield: 2.6 g (93 %); m.p.: 213–214 °C (dec.); TLC: $R_f = 0.77$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,335, 3,240, 3,175$ (NH), 1,765, 1,730 (C=O), 1,365, 1,325, 1,165 (SO_2) cm^{-1} ; ^1H NMR: $\delta = 2.43$ (s, 3H, CH_3), 7.19 (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.1$ Hz, 1H, H-9), 7.56 (s, 2H, H-5 and H-6, 2,4-diClPh), 7.73 (t, $J = 7.1$ Hz, 1H, H-8), 7.83 (s, 1H, H-3, 2,4-diClPh), 7.91 (d, $J = 7.1$ Hz, 1H, H-7), 7.99 (s, 1H, H-5'), 8.01 (s, 1H, H-8'), 11.50 (s, 1H, NH), 11.73 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.58, 110.53, 115.59, 123.79, 126.86, 128.41, 128.56, 128.64, 129.20, 130.00, 130.50, 130.75, 133.01, 133.11, 133.18, 137.20, 137.63, 138.04, 141.66, 147.36, 160.02, 163.68$ ppm.

6'-Chloro-5-(2-chloro-3-pyridinyl)-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]-benzodithiazine]-2,6(1H,5H)dione (6, C₂₁H₁₄Cl₂N₄O₅S₂)

Starting from 1.87 g 6-chloro-3-(2-chloro-3-pyridinyl-amino)-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1e**), the title compound **6** was obtained. Yield: 2.2 g (82 %); m.p.: 218–219 °C (dec.); TLC: $R_f = 0.71$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,285, 3,215, 3,175$ (NH), 1,765, 1,730 (C=O), 1,620 (C=N), 1,365, 1,155 (SO₂) cm⁻¹; ¹H NMR: $\delta = 2.43$ (s, 3H, CH₃), 7.15 (d, $J = 7.9$ Hz, 1H, H-10), 7.24 (t, $J = 7.5$ Hz, 1H, H-9), 7.58 (t, $J = 5.8$ Hz, 1H, H-5, 3-pyridinyl), 7.73 (t, $J = 7.3$ Hz, 1H, H-8), 7.90 (d, $J = 7.5$ Hz, 1H, H-7), 7.92–8.20 (m, 3H, H-4 and H-6, 3-pyridinyl, and H-5'), 8.44 (s, 1H, H-8'), 11.62 (s, 1H, NH), 11.73 (s, 1H, NH) ppm; ¹³C NMR: $\delta = 19.59, 110.51, 115.59, 123.77, 124.29, 126.89, 127.36, 128.57, 129.19, 130.66, 131.15, 137.19, 137.70, 138.11, 138.48, 141.66, 141.06, 147.36, 149.01, 160.13, 163.76$ ppm.

6'-Chloro-5-[imino(piperidin-1-yl)methyl]-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (7, C₂₂H₂₂ClN₅O₅S₂)

Starting from 1.64 g 6-chloro-7-methyl-3-(piperidine-1-carboximidamino)-1,4,2-benzodithiazine 1,1-dioxide (**1f**), the title compound **7** was obtained. Yield: 2.6 g (97 %); m.p.: 211–212 °C (dec.); TLC: $R_f = 0.75$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,370, 3,280, 3,210$ (NH), 1,765, 1,725 (C=O), 1,620 (C=N), 1,360, 1,345, 1,155 (SO₂) cm⁻¹; ¹H NMR: $\delta = 1.58$ (br s, 6H, piperidine), 2.39 (s, 3H, CH₃), 3.51 (br s, 4H, piperidine), 7.15 (d, $J = 8.0$ Hz, 1H, H-10), 7.25 (t, $J = 8.0$ Hz, 1H, H-9), 7.69 (s, 1H, H-5'), 7.73 (t, $J = 8.1$ Hz, 1H, H-8), 7.89 (s, 1H, H-8'), 7.93 (d, $J = 8.0$ Hz, 1H, H-7), 8.22 (br s, 2H, NH), 11.73 (s, 1H, C=NH) ppm; ¹³C NMR: $\delta = 19.50, 23.64, 25.51, 45.94, 110.53, 115.60, 123.77, 126.28, 127.23, 129.20, 131.09, 131.31, 133.10, 135.97, 136.78, 137.20, 141.67, 147.36, 157.20, 164.77$ ppm.

5-(N-Benzylcarbamimidoyl)-6'-chloro-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (8, C₂₄H₂₀ClN₅O₅S₂)

Starting from 1.98 g 3-(3-benzylguanidino)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1g**), the title compound **8** was obtained. Yield: 2.7 g (97 %); m.p.: 194–195 °C (dec.); TLC: $R_f = 0.74$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,425, 3,340, 3,285, 3,180$ (NH and C=NH), 1,765, 1,730 (C=O), 1,620 (C=N), 1,360, 1,330, 1,140 (SO₂) cm⁻¹; ¹H NMR: $\delta = 2.40$ (s, 3H, CH₃), 4.42 (s, 2H, PhCH₂NH), 7.15 (d, $J = 8.3$ Hz, 1H, H-10), 7.24 (t, $J = 7.6$ Hz, 1H, H-9), 7.30 (s, 5H, Ph), 7.38 (s, 1H, H-5'), 7.71 (t, $J = 7.6$ Hz, 1H, H-8), 7.74 (s, 1H, H-8'), 7.90 (d, $J = 7.6$ Hz, 1H, H-7), 8.10 (br s, 1H, NH), 8.35 (br s, 1H,

NH), 8.87 (t, $J = 6.0$ Hz, 1H, PhCH₂NH), 11.73 (s, 1H, C=NH) ppm; ¹³C NMR: $\delta = 19.52, 44.49, 110.53, 115.60, 123.77, 126.35, 127.28, 127.35, 127.47, 127.64, 127.74, 128.79, 129.20, 130.89, 131.15, 136.16, 136.96, 137.19, 141.67, 147.36, 158.42, 160.00$ ppm.

6'-Chloro-5-(dimethylamino)-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]-benzodithiazine]-2,6(1H,5H)dione (9, C₁₈H₁₇ClN₄O₅S₂)
Starting from 1.53 g 6-chloro-7-methyl-3-(2,2-dimethylhydrazino)-1,4,2-benzodithiazine 1,1-dioxide (**1h**), the title compound **9** was obtained. Yield: 2.2 g (95 %); m.p.: 207–208 °C (dec.); TLC: $R_f = 0.70$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,240, 3,170$ (NH), 1,765, 1,725 (C=O), 1,360, 1,315, 1,160 (SO₂) cm⁻¹; ¹H NMR: $\delta = 2.40$ (s, 3H, CH₃), 2.60 (s, 6H, CH₃–N–CH₃), 7.15 (d, $J = 8.3$ Hz, 1H, H-10), 7.26 (t, $J = 7.3$ Hz, 1H, H-9), 7.73 (t, $J = 7.3$ Hz, 1H, H-8), 7.83 (d, $J = 7.4$ Hz, 1H, H-7), 7.88 (s, 1H, H-5'), 7.94 (s, 1H, H-8'), 10.98 (br s, 1H, NH), 11.62 (br s, 1H, NH) ppm; ¹³C NMR: $\delta = 19.52, 46.68, 110.52, 115.59, 123.77, 126.40, 128.36, 129.04, 129.20, 130.63, 137.11, 137.19, 137.33, 141.66, 147.35, 160.01, 166.63$ ppm.

6'-Chloro-7'-methyl-1',1',2,6-tetraoxo-1,2-dihydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]-benzodithiazine]-5(6H)-acetonitrile (10, C₁₈H₁₃ClN₄O₅S₂)

Starting from 1.51 g 2-(6-chloro-7-methyl-1,4,2-benzodithiazin-3-ylamino)acetonitrile 1,1-dioxide (**1i**), the title compound **10** was obtained. Yield: 2.3 g (97 %); m.p.: 194–195 °C (dec.); TLC: $R_f = 0.70$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,345, 3,240, 3,175$ (NH), 2,245 (C≡N), 1,765, 1,725 (C=O), 1,365, 1,320, 1,165 (SO₂) cm⁻¹; ¹H NMR: $\delta = 2.43$ (s, 3H, CH₃), 4.51 (s, 2H, N≡C–CH₂N), 7.14 (d, $J = 8.1$ Hz, 1H, H-10), 7.20 (t, $J = 8.0$ Hz, 1H, H-9), 7.74 (t, $J = 8.1$ Hz, 1H, H-8), 7.91 (dd, $J_{meta} = 1.2$ Hz, $J_{ortho} = 7.9$ Hz, 1H, H-7), 7.95 (s, 1H, H-5'), 8.02 (s, 1H, H-8'), 10.32 (br s, 1H, NH), 11.72 (br s, 1H, NH) ppm; ¹³C NMR: $\delta = 19.58, 30.90, 110.53, 115.59, 116.29, 123.77, 126.89, 127.27, 128.48, 129.20, 130.90, 137.20, 137.64, 137.95, 141.66, 147.36, 160.01, 163.82$ ppm.

5-Acetyl-6'-chloro-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]-benzodithiazine]-2,6(1H,5H)dione (11, C₁₈H₁₄ClN₃O₆S₂)
Starting from 1.52 g 3-(acetylamino)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1j**), the title compound **11** was obtained. Yield: 2.2 g (94 %); m.p.: 210–211 °C (dec.); TLC: $R_f = 0.70$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,225, 3,185$ (NH), 1,765, 1,730, 1,685 (C=O), 1,365, 1,310, 1,165 (SO₂) cm⁻¹; ¹H NMR: $\delta = 2.18$ (s, 3H, CH₃), 2.44 (s, 3H, CH₃C=O), 7.14 (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.5$ Hz, 1H, H-9), 7.73 (t, $J = 7.7$ Hz, 1H,

H-8), 7.90 (d, $J = 7.7$ Hz, 1H, H-7), 8.02 (s, 1H, H-5'), 8.04 (s, 1H, H-8'), 11.72 (s, 1H, NH), 12.48 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.60, 23.97, 110.51, 115.59, 123.77, 126.53, 128.42, 129.02, 129.19, 129.39, 137.18, 138.06, 138.91, 141.66, 147.35, 160.02, 163.40, 172.29$ ppm.

5-Benzoyl-6'-chloro-7'-methyl-1',1'-dioxospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione (12, C₂₃H₁₆ClN₃O₆S₂)

Starting from 1.83 g 3-(benzoylamino)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (**1k**), the title compound **12** was obtained. Yield: 2.4 g (92 %); m.p.: 230–232 °C (dec.); TLC: $R_f = 0.77$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,240, 3,180$ (NH), 1,765, 1,730, 1,695 (C=O), 1,365, 1,170 (SO₂) cm⁻¹; ^1H NMR: $\delta = 2.46$ (s, 3H, CH₃), 7.14 (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.5$ Hz, 1H, H-9), 7.56 (t, $J = 7.4$ Hz, 1H, H-8), 7.66–7.77 (m, 3H, H-3, H-4 and H-5, PhC=O), 7.91 (d, $J = 7.8$ Hz, 1H, H-7), 8.02 (d, $J = 7.6$ Hz, 2H, H-2 and H-6, PhC=O), 8.02 (s, 1H, H-5'), 8.07 (s, 1H, H-8'), 11.73 (s, 1H, NH), 12.95 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 19.64, 110.53, 115.59, 123.77, 126.56, 128.48, 128.95, 129.20, 129.41, 129.66, 131.32, 134.07, 137.19, 138.12, 141.66, 147.36, 160.02, 165.11, 168.49$ ppm.

Ethyl 6'-chloro-5-(4-fluorophenyl)-1',1',2,6-tetraoxo-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carboxylate (13, C₂₄H₁₇ClFN₃O₇S₂)

Starting from 2.07 g ethyl 6-chloro-3-(4-fluorophenylamino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (**1l**), the title compound **13** was obtained. Yield: 2.8 g (97 %); m.p.: 216–217 °C (dec.); TLC: $R_f = 0.71$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,270, 3,265, 3,225$ (NH), 1,765, 1,725, 1,685 (C=O), 1,365, 1,325, 1,170, 1,155 (SO₂) cm⁻¹; ^1H NMR: $\delta = 1.34$ (t, $J = 7.1$ Hz, 3H, CH₃CH₂O), 4.37 (q, $J = 7.1$ Hz, 2H, CH₃CH₂O), 7.15 (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.9$ Hz, 1H, H-9), 7.33 (d, $J = 8.9$ Hz, 2H, H-2 and H-6 of 4-FPh), 7.62–7.68 (m, 2H, H-3 and H-5 of 4-FPh), 7.70 (t, $J = 8.1$ Hz, 1H, H-8), 7.91 (dd, $J_{\text{meta}} = 1.2$ Hz, $J_{\text{ortho}} = 7.9$ Hz, 1H, H-7), 8.02 (s, 1H, H-5'), 8.35 (s, 1H, H-8'), 11.61 (s, 1H, NH), 11.72 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 14.21, 62.38, 110.53, 115.59, 116.01, 116.46, 123.77, 124.39, 124.57, 126.94, 129.20, 130.54, 130.81, 130.88, 134.31, 135.82, 137.19, 141.67, 147.36, 160.00, 160.17, 163.34$ ppm.

6'-Chloro-5-(4-chlorophenyl)-1',1',2,6-tetraoxo-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carbonitrile (14, C₂₂H₁₂Cl₂N₄O₅S₂)

Starting from 1.92 g 6-chloro-3-(4-chlorophenylamino)-1,1-dioxo-1,4,2-benzodithiazine-7-carbonitrile (**1m**), the title compound **14** was obtained. Yield: 2.8 g (95 %);

m.p.: 219–220 °C (dec.); TLC: $R_f = 0.64$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,275, 3,195, 3,125$ (NH), 2,238 (C≡N), 1,765, 1,725 (C=O), 1,360, 1,320, 1,150 (SO₂) cm⁻¹; ^1H NMR: $\delta = 7.14$ (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.6$ Hz, 1H, H-9), 7.62 (d, $J = 8.7$ Hz, 2H, 4-CIPh), 7.65 (d, $J = 8.7$ Hz, 2H, 4-CIPh), 7.73 (t, $J = 7.7$ Hz, 1H, H-8), 7.90 (d, $J = 7.6$ Hz, 1H, H-7), 8.37 (s, 1H, H-5'), 8.60 (s, 1H, H-8'), 11.72 (s, 1H, NH), 11.87 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 110.81, 112.97, 114.84, 115.58, 123.77, 123.93, 129.19, 129.43, 130.01, 130.22, 130.31, 130.71, 131.33, 136.71, 137.19, 138.93, 141.65, 147.34, 159.01, 160.15$ ppm.

6'-Chloro-1',1',2,6-tetraoxo-5-phenyl-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carboxamide (15, C₂₂H₁₅ClN₄O₆S₂)

Starting from 1.84 g 6-chloro-1,1-dioxo-3-phenylamino-1,4,2-benzodithiazine-7-carboxamide (**1n**), the title compound **15** was obtained. Yield: 2.5 g (95 %); m.p.: 282–283 °C (dec.); TLC: $R_f = 0.54$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,435, 3,325, 3,255, 3,200, 3,140$ (NH₂, NH), 1,765, 1,725, 1,675 (C=O), 1,365, 1,330, 1,140 (SO₂) cm⁻¹; ^1H NMR: $\delta = 7.15$ (d, $J = 8.1$ Hz, 1H, H-10), 7.24 (t, $J = 7.4$ Hz, 1H, H-9), 7.45 (t, $J = 7.5$ Hz, 1H, H-8), 7.61 (s, 2H, O=C–NH₂), 7.65–7.77 (m, 3H, H-3, H-4, H-5 of Ph), 7.87 (d, $J = 6.6$ Hz, 2H, H-2 and H-6 of Ph), 7.95 (d, $J = 8.2$ Hz, 1H, H-7), 8.11 (s, 1H, H-5'), 8.16 (s, 1H, H-8'), 11.58 (s, 1H, NH), 11.72 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 110.53, 115.60, 122.19, 122.26, 122.44, 123.77, 124.49, 126.34, 129.20, 129.47, 129.71, 130.71, 131.51, 134.03, 137.20, 137.62, 141.66, 147.36, 160.00, 166.32$ ppm.

6'-Chloro-5-(4-chlorophenyl)-1',1',2,6-tetraoxo-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carboxamide (16, C₂₂H₁₄Cl₂N₄O₆S₂)

Starting from 2.01 g 6-chloro-3-(4-chlorophenylamino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxamide (**1o**), the title compound **16** was obtained. Yield: 2.7 g (96 %); m.p.: 286–287 °C (dec.); TLC: $R_f = 0.54$ (benzene–EtOH 4:1); IR (KBr): $\bar{\nu} = 3,455, 3,355$ (O=C–NH₂), 3,315, 3,190 (NH), 1,765, 1,730, 1,660 (C=O), 1,365, 1,315, 1,165 (SO₂) cm⁻¹; ^1H NMR: $\delta = 7.15$ (d, $J = 8.2$ Hz, 1H, H-10), 7.24 (t, $J = 7.5$ Hz, 1H, H-9), 7.52 (d, $J = 8.8$ Hz, 2H, H-3 and H-5 of 4-CIPh), 7.67 (d, $J = 8.8$ Hz, 2H, H-2 and H-6 of 4-CIPh), 7.73 (t, $J = 8.2$ Hz, 1H, H-8), 7.87 (s, 2H, O=C–NH₂), 7.95 (d, $J = 9.0$ Hz, 1H, H-7), 8.12 (s, 1H, H-5'), 8.17 (s, 1H, H-8'), 11.62 (s, 1H, NH), 11.74 (s, 1H, NH) ppm; ^{13}C NMR: $\delta = 110.53, 115.60, 123.68, 123.77, 124.55, 129.20, 129.29, 129.41, 129.73, 130.00, 130.55, 131.43, 134.11, 136.66, 137.19, 137.68, 141.66, 147.36, 160.05, 166.28$ ppm.

6'-Chloro-*N*-(4-chlorophenyl)-1',1',2,6-tetraoxo-5-phenyl-1,2,5,6-tetrahydrospiro[4*H*-benzo[*d*][1,3,7]oxadiazocine-4,3'(2'*H*)-[1,4,2]benzodithiazine]-7'-carboxamide (**17**, C₂₈H₁₈Cl₂N₄O₆S₂)

Starting from 2.40 g 6-chloro-*N*-(4-chlorophenyl)-1,1-dioxo-3-(phenylamino)-1,4,2-benzodithiazine-7-carboxamide (**1p**), the title compound **17** was obtained. Yield: 3.1 g (95 %); m.p.: 278–279 °C (dec.); TLC: *R*_f = 0.64 (benzene–EtOH 4:1); IR (KBr): $\bar{\nu}$ = 3,285, 3,280, 3,205, 3,140 (NH), 1,765, 1,730, 1,675 (C=O), 1,360, 1,310, 1,145 (SO₂) cm⁻¹; ¹H NMR: δ = 7.13 (d, *J* = 8.3 Hz, 1H, H-10), 7.21–7.24 (m, 2H, arom), 7.41–7.45 (m, 5H, arom), 7.63–7.72 (m, 5H, arom), 7.89 (d, *J* = 7.8 Hz, 1H, H-7), 8.19 (s, 1H, H-8'), 10.83 (s, 1H, NH), 11.59 (s, 1H, NH), 11.71 (s, 1H, NH) ppm; ¹³C NMR: δ = 110.95, 116.01, 122.08, 122.61, 124.19, 125.44, 126.73, 128.52, 129.48, 129.62, 129.72, 129.88, 130.17, 131.28, 132.66, 134.71, 137.41, 137.61, 138.15, 142.08, 147.79, 160.57, 160.99, 163.42 ppm.

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References

1. Brzozowski Z, Sławiński J (1984) *Acta Polon Pharm* 41:5
2. Brzozowski Z, Sławiński J (1984) *Acta Polon Pharm* 41:133
3. Brzozowski Z, Sławiński J, Angielski S, Szczepańska-Konkel M (1985) *Acta Polon Pharm* 42:313
4. Brzozowski Z, Sławiński J, Gajewski F, Angielski S, Hoppe A (1985) *Acta Polon Pharm* 42:413
5. Brzozowski Z, Sławiński J, Janiec W, Cegła M, Śliwiński L, Sedlak I (1992) *Acta Polon Pharm Drug Res* 49:75
6. Brzozowski Z, Sączewski F, Gdaniec M (2003) *Bioorg Med Chem* 11:3673
7. Brzozowski Z, Sączewski F, Gdaniec M (2003) *Eur J Med Chem* 38:991
8. Brzozowski Z, Sączewski F, Neamati N (2006) *Bioorg Med Chem* 14:2985
9. Brzozowski Z, Sączewski F, Sławiński J, Bednarski PJ, Grünert R, Gdaniec M (2007) *Bioorg Med Chem* 15:2560
10. Brzozowski Z, Sączewski F (2002) *J Med Chem* 45:430
11. Brzozowski Z, Sączewski F, Sanchez T, Kuo CL, Gdaniec M, Neamati N (2004) *Bioorg Med Chem* 12:3663
12. Brzozowski Z, Sączewski F, Sławiński J, Sanchez T, Neamati N (2009) *Eur J Med Chem* 44:190
13. Brzozowski Z, Sączewski F, Neamati N (2006) *Bioorg Med Chem* 16:5298
14. Brzozowski Z (1995) *Acta Polon Pharm Drug Res* 52:287
15. Brzozowski Z (1996) *Acta Polon Pharm Drug Res* 53:269
16. Brzozowski Z (1997) *Acta Polon Pharm Drug Res* 54:293
17. Brzozowski Z (1998) *Acta Polon Pharm Drug Res* 55:375
18. Brzozowski Z, Sączewski F (2002) *Eur J Med Chem* 37:285
19. Sławiński J (2004) *Eur J Med Chem* 39:179
20. Sławiński J, Gdaniec M (2005) *Eur J Med Chem* 40:377
21. Sławiński J, Brzozowski Z (2006) *Eur J Med Chem* 41:1180
22. Brzozowski Z, Sączewski F, Sławiński J (2007) *Eur J Med Chem* 42:1218
23. Sławiński J, Brożewicz K, Fruziński A, Główska ML (2011) *Heterocycles* 83:1093
24. Brożewicz K, Sławiński J (2012) *Monatsh Chem* 143:975
25. Brożewicz K, Sławiński J (2012) *Eur J Med Chem* 55:384
26. Sławiński J, Żołnowska B, Pirska D, Kędzia A, Kwapisz E (2012) *Monatsh Chem* 143:1705
27. Brzozowski Z (1995) *Acta Polon Pharm Drug Res* 52:91
28. Brzozowski Z (1998) *Acta Polon Pharm Drug Res* 55:49
29. Brzozowski Z (1998) *Acta Polon Pharm Drug Res* 55:473
30. Brzozowski Z, Sączewski F (2007) *J Heterocycl Chem* 44:261
31. Sławiński J, Żołnowska B, Pirska D, Kędzia A, Kwapisz E (2013) *J Enzym Inhib Med Chem* 28:41
32. Sączewski F, Sławiński J, Kornicka A, Brzozowski Z, Pomarnacka E, Innocenti A, Scozzafava A, Supuran CT (2006) *Bioorg Med Chem Lett* 16:4846
33. Sączewski F, Innocenti A, Brzozowski Z, Sławiński J, Pomarnacka E, Kornicka A, Scozzafava A, Supuran CT (2006) *J Enzym Inhib Med Chem* 21:563
34. Sączewski F, Innocenti A, Sławiński J, Kornicka A, Brzozowski Z, Pomarnacka E, Scozzafava A, Temperini C, Supuran CT (2008) *Bioorg Med Chem* 16:3933
35. Brzozowski Z, Sławiński J (2013) *J Heterocycl Chem* (in press)
36. Shvekhgeimer MGA (2001) *Chem Heterocycl Compd* 37:385
37. Kappe T, Stadlbauer W (1981) Isatoic anhydrides and their use in heterocyclic chemistry. In: *advances in heterocyclic chemistry*, vol 28. Academic Press, London, p 231
38. Mohammadi AA, Dabiri M, Qaraat H (2009) *Tetrahedron* 65:3804
39. Brzozowski Z (1997) *Acta Polon Pharm Drug Res* 54:49
40. Brzozowski Z, Sławiński J (1985) *Acta Polon Pharm* 42:319
41. Brzozowski Z, Sączewski F, Gdaniec M (2002) *Eur J Med Chem* 37:285
42. SPARTAN Wavefunction Inc, Irvine
43. Sławiński J (2001) *Polish J Chem* 75:1309