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

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Abstract A series of 6′-chlo-ro-1′,1′-dioxospiro[4H-
benzo[d][1,3,7]oxadiazocine-4,3′(2′H)-[1,4,2]benzodithiazine]-
2,6(1H,5H)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-benzodithia-
zone 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-benzodithia-
zone 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 cholal-
gogue [5] agents. It has also been shown that some
6-chloro-1,1-dioxo-1,4,2-benzodithiazines have remark-
able 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-benzodithia-
zone 1,1-dioxides have attracted our investigative attention
because of their suitability for chemical transformation into
otherwise not readily obtained 4-chloro-2-mercaptobenze-
sulfonamide derivatives of type IV (Fig. 1). These
compounds have remarkable structure-dependent antitumor
activity [14–26], anti-HIV activity [14–17, 27–30], anti-
bacterial 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′-chlo-ro-1′,1′-dioxospiro[4H-benzo
[d][1,3,7]oxadiazocine-4,3′(2′H)-[1,4,2]benzodithiazine]-
2,6(1H,5H)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 sus-
ceptible 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 trans-
formation of the anhydrides into such heterocyclic systems,
and processes leading initially to formation of anthranilic
acid derivatives which are then transformed into the het-
erocyclic compounds in one or several stages. It is
important that such transformations result in the formation
of new five and six-membered heterocyclic systems. Fur-
thermore, regioselective three-component reaction of
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′-dioxospir[4H-benzo[d][1,3,7]oxadiazocine-4,3′(2′H)-[1,4,2]benzodithiazine]-2,6(1H,5H)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...
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 $^{13}$C 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, $J_{ortho} = 7.9, J_{meta} = 1.2$ 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\textsuperscript{-1-3-(R\textsuperscript{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\textsuperscript{2-amino})-1,4,2-benzodithiazine is a low-energy tautomer, more stable than the 3-(R\textsuperscript{2-imino})-1,4,2-benzodithiazine isomer.

The electrostatic atomic charges of the starting 3-amino benzodithiazines 1a–1t (Table 1) and electrostatic potential surface maps (Fig. 2), as affected by their R\textsuperscript{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\textsuperscript{-chloro-1',1'-dioxospiro[4H-benzo[d]1,3,7]oxadiazone-4,3'(2'H)-[1,4,2]benzodithiazine]-2,6(1H,5H)dione derivatives 2–17 by reaction of isatoic anhydride with 3-(R\textsuperscript{2-amino})-6-chloro-1,4,2-benzodithiazine 1,1-dioxide derivatives bearing R\textsuperscript{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

| Compound | SO\textsubscript{2} | O-1 | O-2 | N-2 | C-3 | S-4 | Amine group N |
|----------|----------------|-----|-----|-----|-----|-----|--------------|
| 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 |
The instrumentation and conditions used were: melting points Büchi 535 apparatus; IR spectra: KBr pellets, 400–4,000 cm\(^{-1}\), Perkin Elmer 1600 FT-IR spectrophotometer; \(^1\)H NMR and \(^{13}\)C NMR: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; spectra were recorded in dimethyl sulfoxide-
\(\text{d}_6\) (DMSO-
\(\text{d}_6\)); chemical shifts are expressed as \(\delta\) values relative to Me\(^4\)Si as standard; coupling constants (\(J\)) are given in hertz; multiplicity in \(^1\)H 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 ±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 (\(\text{Ii}, \text{C}_{10}\text{H}_{8}\text{ClN}_{3}\text{O}_{2}\text{S}_{2}\))
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\(_3\)SH had ceased (55–60 h) (CAUTION: because of high toxicity, CH\(_3\)SH 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 \(~\sim 7.8\)) 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 cm\(^3\)), dried, and purified by recrystallization from 40 cm\(^3\) glacial acetic acid. Yield: 4.9 g (81 %); m.p.: 228–229 °C; \(R_f = 0.76\) (benzene–EtOH 4:1); IR (KBr): \(\tilde{\nu} = 3,340\) (NH), 2,255 (C=N), 1,560 (C=N), 1,345, 1,315, 1,165 (SO\(_2\)) cm\(^{-1}\); \(^1\)H 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 (\(\text{Ij}, \text{C}_{10}\text{H}_{9}\text{ClN}_{2}\text{O}_{3}\text{S}_{2}\))
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 cm\(^3\)), methanol (2 \times 5 cm\(^3\)), and acetonitrile (3 \times 5 cm\(^3\)), and dried. Yield: 4.9 g (80 %); m.p.: 264–265 °C; \(R_f = 0.74\) (benzene–EtOH 4:1); IR (KBr): \(\tilde{\nu} = 3,220, 3,190\) (NH), 1,710 (C=O), 1,555 (C=N), 1,345, 1,310, 1,160 (SO\(_2\)) cm\(^{-1}\); \(^1\)H NMR: \(\delta = 2.19\) (s, 3H, CH\(_3\)), 2.40 (s, 3H, CH\(_3\)C=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 (\(\text{Ik}, \text{C}_{15}\text{H}_{11}\text{ClN}_{2}\text{O}_{3}\text{S}_{2}\))
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 170–175 °C for 3 h. After cooling to 105 °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.
A mixture of 0.84 g isatoic anhydride (5.15 mmol) and the corresponding 6-chloro-7-R=1-3-(R2-amino)-1,4,2-benzodithiazine 1,1-dioxide 1a-1p (5 mmol) in dry toluene (15 cm³) 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 × 4 cm³), methanol (5 × 3 cm³), and petroleum ether (3 × 3 cm³). In this manner, the spiro compounds were obtained (analogous reactions with 3-(R2-amino)-1,4,2-benzodithiazine 1,1-dioxide 1r, 1s, and 1t, bearing R2-substituents with strong or weak electron-donating effect, failed).

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: Rf = 0.78 (benzene–EtOH 4:1); IR (KBr): ν = 3,245, 3,185 (NH), 1,765, 1,725 (C=O), 1,365, 1,330, 1,155 (SO2) cm⁻¹; 1H NMR: δ = 2.13 (s, 3H, CH3); 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). 

Starting from 1.87 g 6-chloro-3-(4-chlorophenylamino)-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (1e), the title compound 4 was obtained. Yield: 2.4 g (90 %); m.p.: 296–297 °C (dec.); TLC: Rf = 0.76 (benzene–EtOH 4:1); IR (KBr): ν = 3,270, 3,240, 3,175 (NH), 1,765, 1,725 (C=O), 1,315, 1,290, 1,145 (SO2) cm⁻¹; 1H NMR: δ = 2.44 (s, 3H, CH3); 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; 13C NMR: δ = 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.

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: Rf = 0.77 (benzene–EtOH 4:1); IR (KBr): ν = 3,335, 3,240, 3,175 (NH), 1,765, 1,730 (C=O), 1,365, 1,325, 1,165 (SO2) cm⁻¹; 1H NMR: δ = 2.43 (s, 3H, CH3); 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; 13C NMR: δ = 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, 137.18, 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′-dioxo[d][1,3,7]oxadiazocine-4,3(2′H)-[1,4,2]-benzodithiazine]-2,6(1H,5H) dione (6, C2H4Cl3N2O5S2)

Starting from 1.87 g 6-chloro-3-(2-chloro-3-pyridylamino)-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: Rt = 0.71 (benzene–EtOH 4:1); IR (KBr): ν = 3,285, 3,215, 3,175 (NH), 1,765, 1,730 (C=O), 1,620 (C=O), 1,365, 1,155 (SO2) cm−1; 1H NMR: δ = 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), 7.93 (t, J = 7.2 Hz, 1H, H-8), 7.90 (d, J = 6.0 Hz, 1H, H-9), 11.73 (s, 1H, C=NH) ppm; 13C NMR: δ = 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-(dimethylaminol)-7′-methyl-1′,1′-dioxo[d][1,3,7]oxadiazocine-4,3(2′H)-[1,4,2]-benzodithiazine]-2,6(1H,5H) dione (9, C13H13Cl2N5O5S2)

Starting from 1.53 g 6-chloro-7-methyl-3-(2,2-dimethyl-hydrazino)-1,4,2-benzodithiazine 1,1-dioxide (1b), the title compound 9 was obtained. Yield: 2.2 g (95 %); m.p.: 207–208 °C (dec); TLC: Rt = 0.70 (benzene–EtOH 4:1); IR (KBr): ν = 3,240, 3,170 (NH), 1,765, 1,725 (C=O), 1,360, 1,315, 1,160 (SO2) cm−1; 1H NMR: δ = 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: δ = 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.

5′-Acetyl-6′-chloro-7′-methyl-1′,1′-dioxo[d][1,3,7]oxadiazocine-4,3(2′H)-[1,4,2]-benzodithiazine]-2,6(1H,5H) dione (11, C13H13Cl3N3O6S2)

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: Rt = 0.70 (benzene–EtOH 4:1); IR (KBr): ν = 3,225, 3,185 (NH), 1,765, 1,730, 1,685 (C=O), 1,365, 1,310, 1,165 (SO2) cm−1; 1H NMR: δ = 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; 13C NMR: δ = 19.60, 23.97, 110.51, 115.59, 123.77, 126.53, 128.42, 129.02, 129.19, 129.37, 138.18, 138.06, 138.91, 141.66, 147.35, 160.32, 163.40, 172.29 ppm.

5-Benzoyl-6'-chloro-7'-methyl-1',1'-dioxo[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]-benzodithiazine]-2,6(1H,5H)diione (12, C_{22}H_{24}Cl_{10}N_{3}O_{7}S_{2})

Starting from 1.83 g 3-(benzoylamino)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (11), 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): ν = 3,240, 3,180 (NH), 1,765, 1,730, 1,695 (C=O), 1,365, 1,170 (SO_{2}) cm^{-1}; 1H NMR: δ = 2.46 (s, 3H, CH_{3}), 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), 9.71 (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; 13C NMR: δ = 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-tetraaxo-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carboxylate (13, C_{23}H_{18}Cl_{12}F_{2}N_{3}O_{7}S_{2})**

Starting from 2.07 g ethyl 6-chloro-3-(4-fluorophenylamino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (11), 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): ν = 3,270, 3,265, 3,225 (NH), 1,765, 1,725, 1,685 (C=O), 1,365, 1,325, 1,170, 1,155 (SO_{2}) cm^{-1}; 1H NMR: δ = 1.34 (t, J = 7.1 Hz, 3H, CH_{3}CH_{2}O), 3.47 (q, J = 7.1 Hz, 2H, CH_{2}CH_{2}O), 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_{meta} = 1.2 Hz, J_{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; 13C NMR: δ = 14.21, 26.38, 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-fluorophenyl)-1',1',2,6-tetraaxo-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3'(2'H)-[1,4,2]benzodithiazine]-7'-carbonylchloride (14, C_{23}H_{18}Cl_{2}F_{2}N_{3}O_{7}S_{2})**

Starting from 1.92 g 6-chloro-3-(4-fluorophenylamino)-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): ν = 3,275, 3,195, 3,125 (NH), 2,238 (C=O), 1,765, 1,725 (C=O), 1,360, 1,320, 1,150 (SO_{2}) cm^{-1}; 1H NMR: δ = 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; 13C NMR: δ = 110.81, 112.97, 114.84, 115.58, 123.77, 129.33, 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-N-(4-chlorophenyl)-1′,1′,2,6-tetraoxo-5-phenyl-1,2,5,6-tetrahydrospiro[4H-benzo[d][1,3,7]oxadiazocine-4,3′(2H)-[1,4,2]benzodithiazine]-7-carboxamide (17, C_{28}H_{18}Cl_{2}N_{4}O_{6}S_{2})

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): ν = 3,285, 3,280, 3,205, 3,140 (C=O), 1,765, 1,730, 1,675 (C=O), 1,360, 1,310, 1,145 (SO_{2}) cm⁻¹; ^{1}H 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-80), 10.83 (s, 1H, NH), 11.59 (s, 1H, NH), 11.71 (s, 1H, NH) ppm; ^{13}C 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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