Synthesis of Novel Series of 6-Chloro-1,1-dioxo-1,4,2-benzodithiazine Derivatives with Potential Biological Activity

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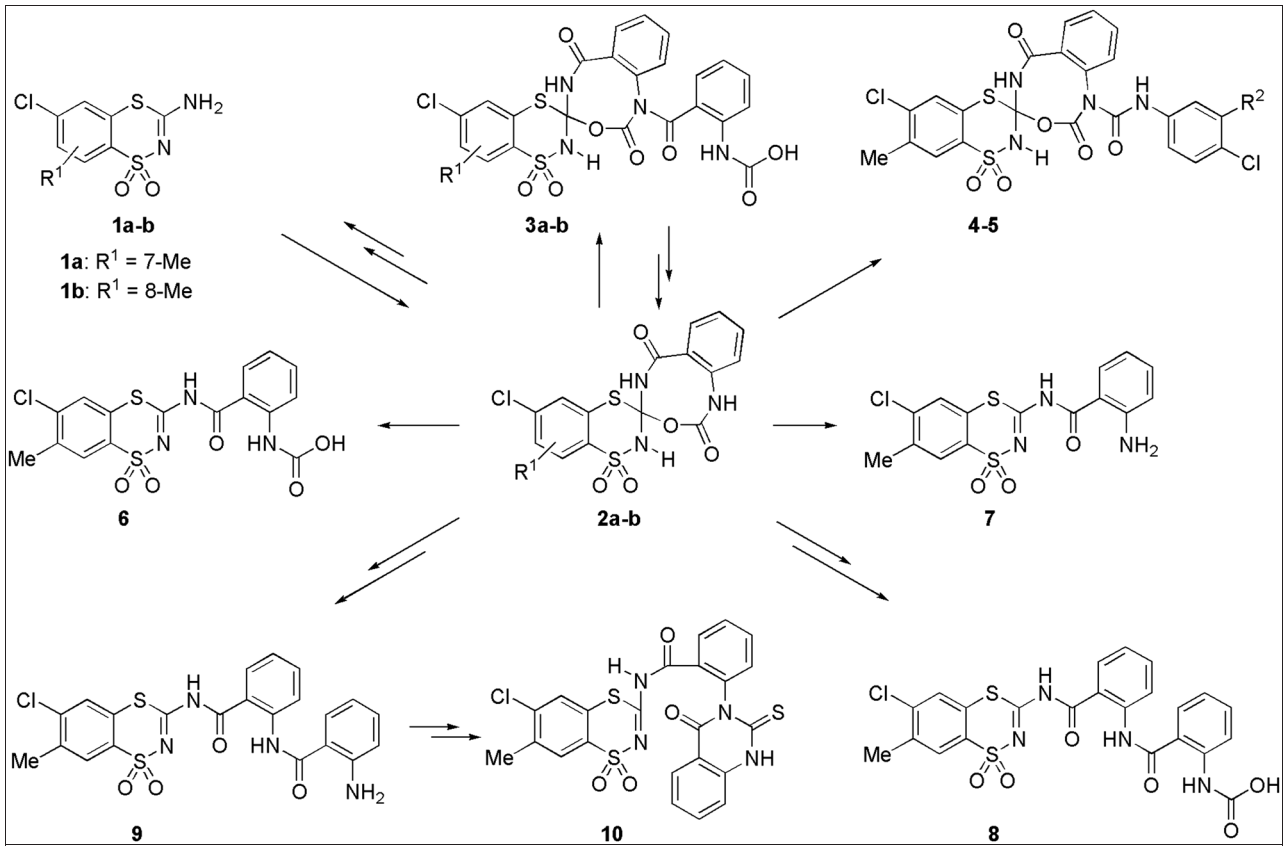


A series of 6′-chloro-1′,1′-dioxo-2′*H*-spiro[benzo[*d*][1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1*H*,5*H*)-dione derivatives **2a–b** and **3a–b** have been synthesized starting from 3-aminobenzodithiazines **1a–b** and isatoic anhydride. Subsequent reactions of **2a** with 3-chlorophenyl isocyanate gave condensation products **4** and **5**. Compound **2a** was also converted into 3-(2-aminobenzamido)-6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazine derivatives **6–10**. The mechanisms of the reactions are discussed.

INTRODUCTION

Compounds containing 1,4,2-benzodithiazine ring system were synthesized in our laboratories in 1984 and received considerable attention over the past several years because of their wide range of biological activities. Hence, 3-mercapto-1,4,2-benzodithiazine 1,1-dioxides were obtained by reacting 2-chlorobenzene\sulfonamides with carbon disulfide in the presence of potassium hydroxide [1,2]. Various 3-substituted benzodithiazine derivatives of type **I** (Fig. 1) have been prepared by the nucleophilic displacement of the preformed 3-methylthio-1,4,2-benzodithiazine 1,1-dioxides [1–3] with the respective amines [4–15], hydrazines [5,10,12,13], guanidines [5,16], or sulfonamides [17]. Alternatively, access to the 2-R-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazine-3-one (R = Me or Ph) is provided by the reaction of *N*-methyl or *N*-phenylbenzenesulfonamides with butyllithium and sulfur at −78° [18]. It has been demonstrated that many of 1,4,2-benzodithiazine derivatives possessed low acute toxicity in mice and rats and, depending on their structure, acted as potential radioprotective [1,2], hypertensive [1], diuretic [1,2,4,6,9], or cholagogue [9] agents.

Recently, it has also been shown that some 1,4,2-benzodithiazines exhibited remarkable antitumor (Fig. 1, types **I** [17,19–21] and **II** [15,22]) or anti-HIV activity (Fig. 1, types **I** [23,24], **II** [15], **III** and **IV** [25]).

Furthermore, 3-methylthio-1,4,2-benzodithiazine 1,1-dioxides have received our investigative attention with

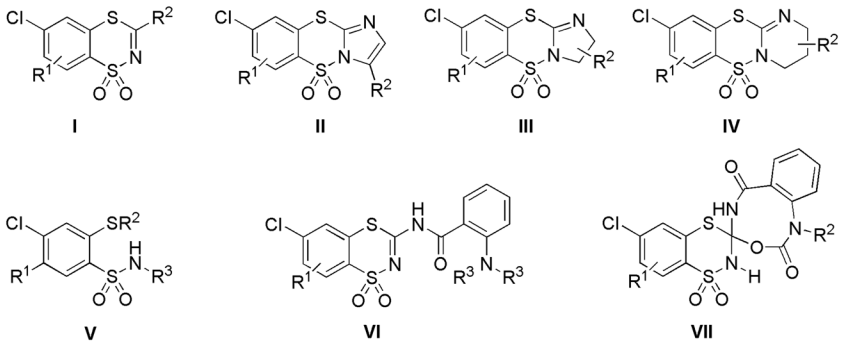


Figure 1. General structures of known benzodithiazine derivatives **I–V** with antitumor and/or anti-HIV activity, and new 1,1-dioxo-1,4,2-benzodithiazines of type **VI** and **VII** with expected biological activity.

regard to their susceptibility for chemical transformation into otherwise not readily obtainable 2-mercaptobenzenesulfonamides. This concerns the synthesis of 4-chloro-2-mercaptobenzenesulfonamides of type **V** (Fig. 1) with the nitrogen atom of the sulfonamide moiety attached to a variety of heterocyclic ring systems. These compounds exhibited structure-dependent remarkable antitumor activity [14,26–34], remarkable anti-HIV activity [13,16,26,27,35,36], or strong inhibitory activity of human carbonic anhydrase isozymes I, II, IX, and XII [37–39]. Some of the compounds were described as novel class of HIV-1 integrase inhibitors (MBSAs) [40–43]. In the present work, the possibility of using reactions of 3-amino-6-chloro-1,4,2-benzodithiazine 1,1-dioxides with isatoic anhydride to the synthesis of novel benzodithiazines of types **VI** and **VII** (Fig. 1) with expected biological activity or as useful starting materials for further chemical transformations has been surveyed.

RESULTS AND DISCUSSION

The synthesis of the target compounds **2a–b**, **3a–b**, **4**, and **5** was achieved by convenient one-step or two-step procedure starting from 3-amino-6-chloro-1,4,2-benzodithiazine 1,1-dioxides **1a–b**, as shown in Scheme 1. First, the reaction of the appropriate benzodithiazines **1a** or **1b** with isatoic anhydride carried out in boiling toluene led to the formation of spiro [benzo[*d*][1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1*H*,5*H*)-dione derivatives **2a–b**, which were obtained in 98% yield. Then, upon treatment of **2a–b** with isatoic anhydride in boiling toluene, the desired 2-(2,6-dioxo-1,2,5,6-tetrahydro-2′*H*-spiro[benzo[*d*] [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)-1-ylcarbonyl] phenylcarbamic acid derivatives **3a** and **3b** were obtained in 85 and 87% yield, respectively. An analogous reaction of spiro compound **2a** with aryl isocyanates furnished *N*-phenyl-2,6-dioxo-5,6-dihydro-2′*H*-spiro[benzo[*d*] [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-1-(2*H*)-carboxamide derivatives **4** and **5**.

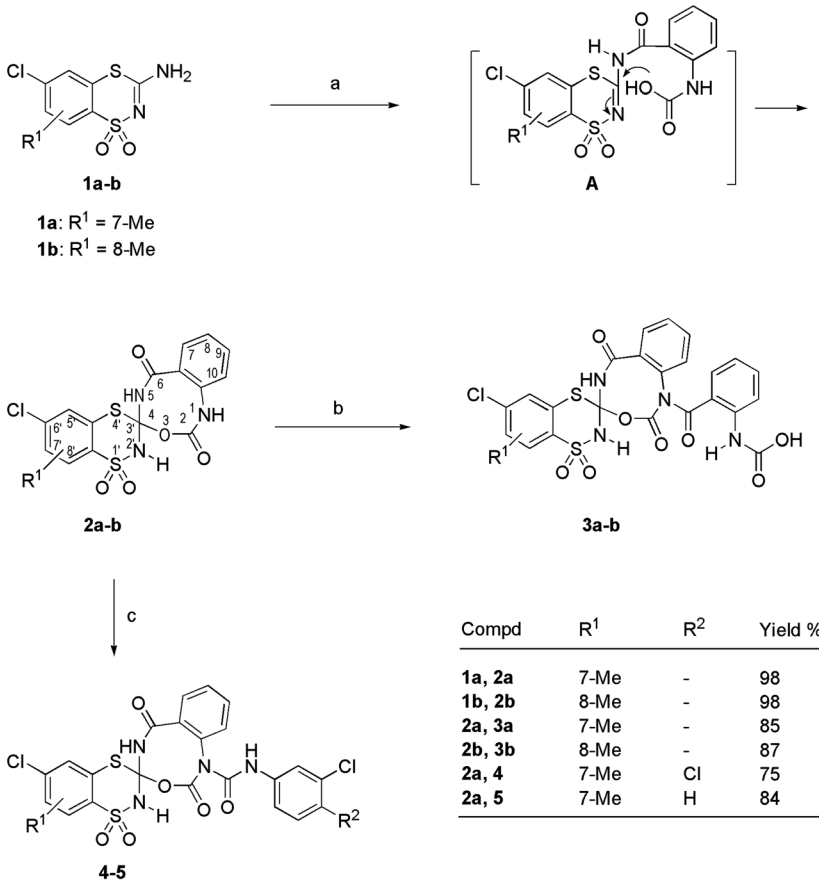
As shown in Scheme 2, compound **2a** heated in boiling *p*-dioxane (0.5 h) gave 2-(1,4,2-benzodithiazine-3-ylaminocarbamoyl)phenylcarbamic acid **6**, which was separated in 75% yield. However, the analogous transformation of **2a** carried out in tetrahydrofuran in the presence of equivalent amount of triethylamine led to the formation of 3-(2-aminobanzamido)-1,4,2-benzodithiazine **7** via initial formation of triethylaminium salts **B** and **C**. The later compound **7** upon treatment with **2a** in boiling toluene readily converted to 2-[*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzamido-2-aminocarbonyl] phenylcarbamic acid **8**. Apparently, the first step of the reaction sequence is the nucleophilic attack of amine **7** at the C-6 carbon atom of **2a** to give intermediate **D**, which, upon elimination of benzodithiazine **1a**, led to the formation of carbamic acid **8**.

In contrast, as shown in Scheme 3, the reaction of **2a** with catalytic amount of NaOH (0.075 molar equiv.) carried out in toluene under similar conditions furnished benzodithiazine **9**, which separated in 44.9% yield. The initial step is believed to be the formation of intermediate sodium salts **E** and **F**, which after decarboxylation gave benzodithiazine intermediate **G**. The latter compound reacts with a second molecule of **2a**, which is present in the reaction mixture, to give intermediate **H**, which upon subsequent elimination of benzodithiazine **1a** affords sodium salt of carbamic acid **I**, and then upon decarboxylation gave the final benzodithiazine **9**. However, the alkaline hydrolysis of **9** with a small amount of NaOH gave intermediate **G** and sodium anthranilate **J**, which upon acidification afforded anthranilic acid in 3.6% yield.

Further reaction of **9** with carbon disulfide and KOH carried out in ethanol led to the formation of the desired benzodithiazine **10**, as outlined in Scheme 4. The initial step is believed to be the formation of dithiocarbamic acid potassium salt **K** followed by intramolecular ring closure via two-step addition–elimination process, which gave rise to the insoluble potassium salt **L**. Then, upon acidification of the salt **L** with hydrochloric acid, the free benzodithiazine **10** was produced in 81% yield via its tautomeric thiol form **M**.

Spiro compounds **2a–b**, **3a–b**, and **4–5** are stable when stored at room temperature for several months. However, these compounds are relatively unstable either in DMSO or alkaline water solution. Proposed mechanisms of the

Scheme 1. Synthesis of 6′-chloro-1′,1′-dioxo-2′H-spiro[benzo[*d*][1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1H,5H)-dione derivatives **2a–b**, **3a–b**, **4**, and **5**. Reagents and conditions: (a) isatoic anhydride (1.08 molar equiv.) dry toluene, reflux, 55 h; (b) isatoic anhydride (1.14 molar equiv.), dry toluene, reflux, 48 h; (c) aryl isocyanate (1.25 molar equiv.), toluene, reflux, 32 h.



Compd	R^1	R^2	Yield %
1a, 2a	7-Me	-	98
1b, 2b	8-Me	-	98
2a, 3a	7-Me	-	85
2b, 3b	8-Me	-	87
2a, 4	7-Me	Cl	75
2a, 5	7-Me	H	84

regioselective two-step alkaline hydrolysis of compound **3a** is outlined in Scheme 5. The reaction of **3a** with equivalent amount of NaOH water solution carried out at room temperature for 8 h led to the formation of **2a** and anthranilic acid, which were isolated in 94 and 73% yields, respectively. On the other hand, upon treatment of **2a** with an excess of NaOH in water solution at room temperature for 30 h, 3-aminobenzodithiazine **1a** and isatoic anhydride could be isolated in 76 and 46% yields, respectively.

The structures of the final products were confirmed by elemental analyses as well as IR and NMR spectroscopy as evidenced in the Experimental section. Inspection of the ^{13}C NMR spectra of spirocyclic compounds **2a–b**, **3a**, **4**, and **5** revealed the characteristic signals of spiro carbon atom (C-4,3′) in the upfield region δ 110.50–111.42 ppm, whereas the presence of two carbonyl C═O groups in positions 2 and 6 of benzo[*d*][1,3,7]oxadiazocine ring was indicated by characteristic signals in the regions 160.13–164.13 and 162.27–166.27 ppm, respectively. The IR spectra of compounds **2a–b**, **3a**, **4**, and **5** showed strong absorption bands of these two carbonyl C═O groups in the regions 1720–1780 and 1770–1790 cm^{-1}.

CONCLUSION

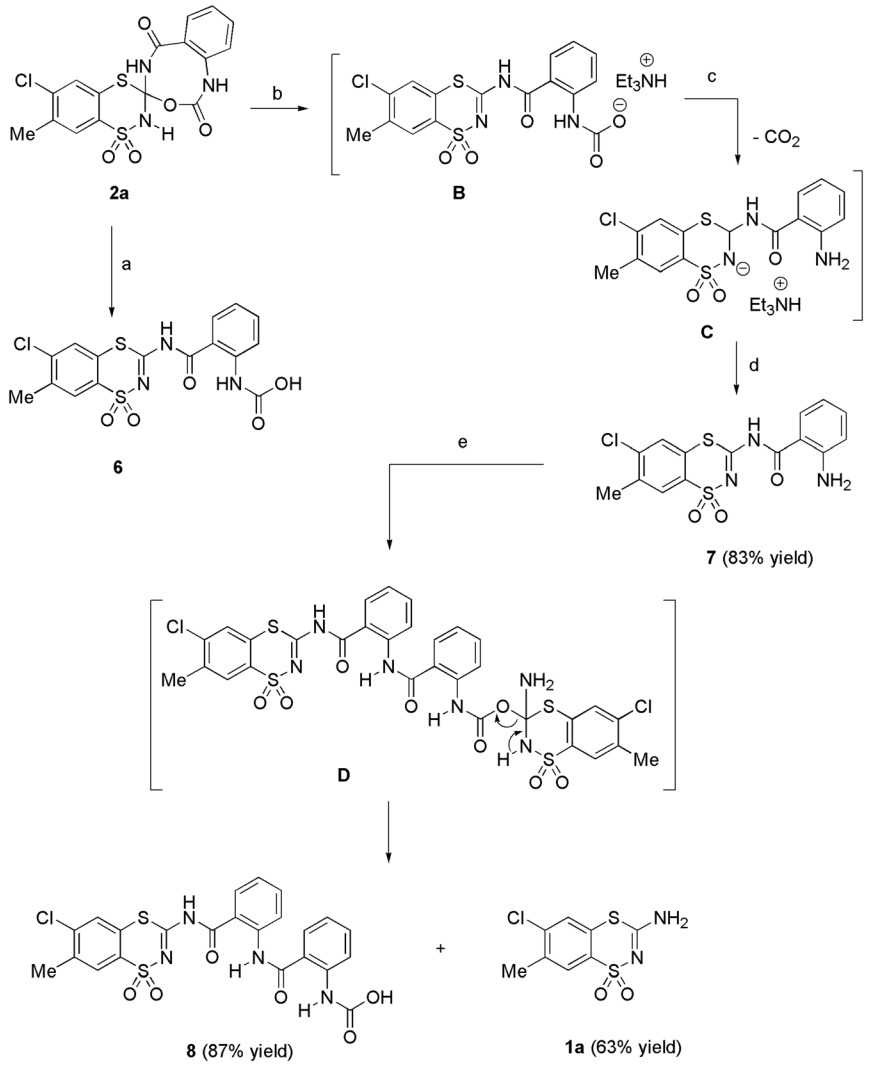
We have developed methods for the preparation of 6′-chloro-1′,1′-dioxo-2′*H*-spiro[benzo[*d*][1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1*H*,5*H*)-dione derivatives **2a–b**, **3a–b**, **4**, and **5**, representing a new type of constitutionally nonsymmetrical spirans, which in turn provide access to a variety of new 3-substituted 1,4,2-benzodithiazine 1,1-dioxide derivatives (**6–10**).

Further structural modifications and biological evaluations of these compounds are in progress and will be described elsewhere.

EXPERIMENTAL

The following instruments and parameters were used: melting points: Büchi 535 apparatus; IR spectra: KBr pellets, 400–4000 cm^{-1} Perkin Elmer 1600 FTIR spectrophotometer; ^{1}H and ^{13}C NMR: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively. Chemical shifts are expressed as δ value to Me_4Si as standard. The results of elemental analyses for C, H, and N were in agreement with the calculated values within ±0.4% range. The starting 3-amino-6-chloro-1,4,2-benzodithiazine dioxides **1a** and **1b** were prepared according to the method described previously [44].

Scheme 2. Synthesis and proposed mechanism of the formation of benzodithiazines **6–8** from compound **2a**. Reagents and conditions: (a) 1,4-dioxane, reflux 10 min; (b) TEA (1.05 molar equiv.), THF, RT, 6 h; (c) distillation of THF under reduced pressure, heating, slowly increasing temperature to 200°C, 6 h; (d) glacial acetic acid (large excess), reflux, 3 min; (e) compound **2a** (1.0 molar equiv.), dry toluene, reflux, 32 h.

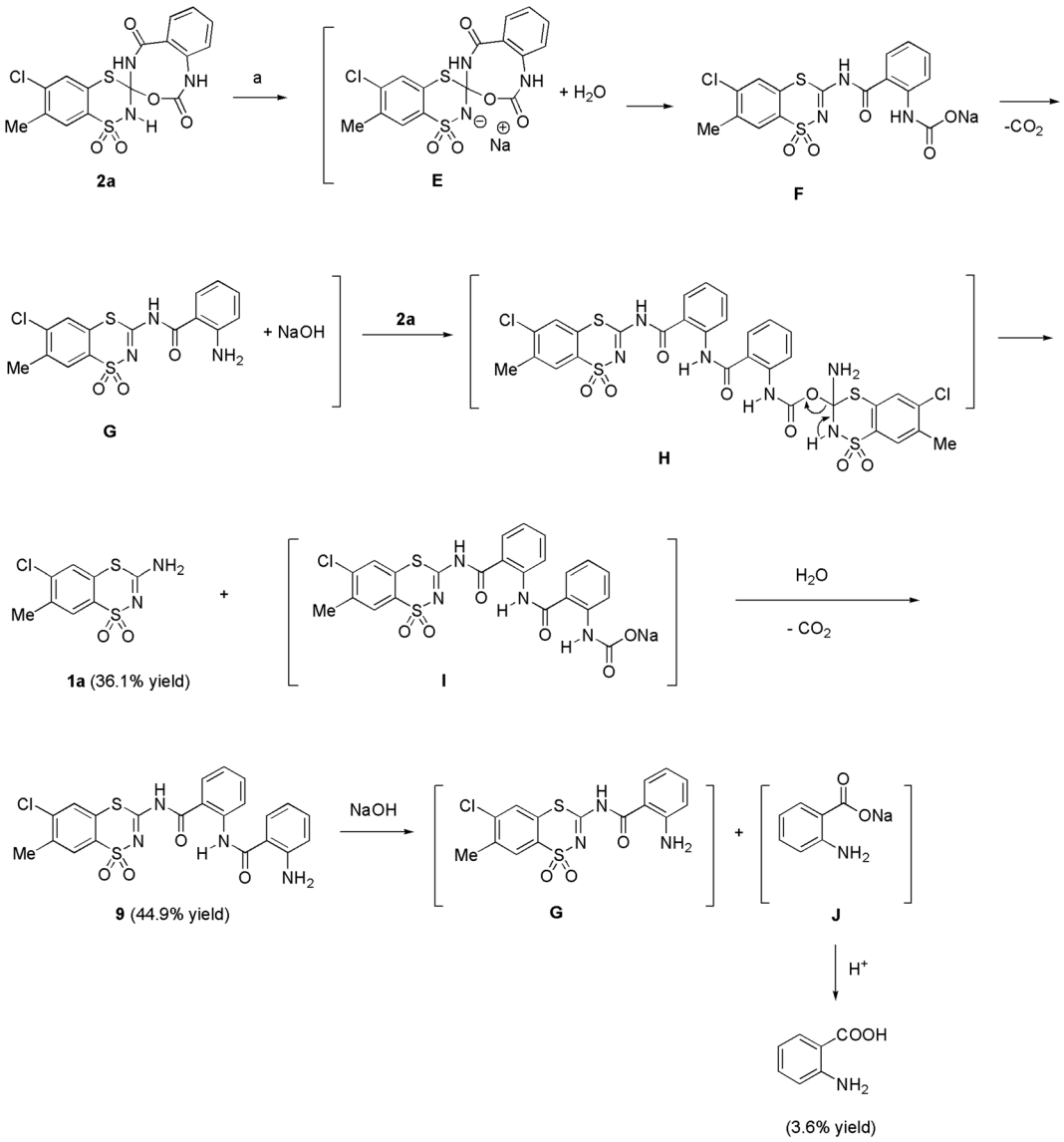


Procedures for the preparation of spiro[benzo[*d*] [1,3,7] oxadiazocine-4,3′-(1,4,2-benzodithiazine)] derivatives (2a, **2b**). A mixture of isatoic anhydride (2.82 g, 17.3 mmol) and the corresponding 3-amino-1,4,2-benzodithiaznes (16 mmol) in dry toluene (40 mL) was refluxed with stirring for 55 h. After cooling to room temperature, the precipitate was collected by filtration, washed successively with toluene (2 × 2 mL), methanol (5 × 1 mL), and petroleum ether (3 × 2 mL), and dried. In this manner, the following spiro compounds were obtained.

6′-Chloro-7′-methyl-1′,1′-dioxo-2′H-spiro[benzo[d][1,3,7] oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1H,5H)-dione (2a). Starting from 3-amino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide **1a** (4.2 g), the title compound **2a** was obtained (6.7 g, 98%): mp 231–233°C dec.; IR (KBr) 3290, 3205, 3145 (NH), 1785, 1730, 1655, 1620 (C═O), 1360, 1170, (SO_2), 1290, 1085, 1015, 935, 755, 680, 575, 480, and 460 (other strong) cm^{-1}; ^1H NMR (acetonitrile-d_3): δ 2.46 (s, 3H, CH_3), 7.10 (br.s, 2H, 2 × O═C–NH), 7.17 (d, J = 8.3 Hz, 1H, H-10), 7.28 (t, J = 7.6 Hz, 1H, H-9), 7.60 (s, 1H, H-5′), 7.73 (t, J = 7.6 Hz, 1H, H-8), 7.97 (s, 1H, H-8′), 8.00 (d, J = 7.8 Hz, 1H, H-7), 9.23 (s, 1H, H-2′) ppm; ^{13}C NMR (CD_3CN) δ 19.98, 111.42, 115.94, 124.92, 127.61, 128.36, 128.83, 130.25, 131.70, 138.04, 138.74, 139.02, 141.97, 147.94, 160.71, 166.27 ppm. *Anal*. Calcd for $C_{16}H_{12}ClN_3O_5S_2$ (425.88): C, 45.12; H, 2.84; N, 9.86. Found: C, 45.11; H, 2.91; N, 9.91.

6′-Chloro-8′-methyl-1′,1′-dioxo-2′H-spiro[benzo[d][1,3,7] oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-2,6(1H,5H)-dione (2b). Starting from 3-amino-6-chloro-8-methyl-1,4,2-benzodithiazine 1,1-dioxide **1b** (4.2 g), the title compound **2b** was obtained (6.7 g, 98%): mp 191–193°C dec.; IR (KBr): 3340, 3300, 3210 (NH), 1765, 1725, 1650, 1620 (C═O), 1360, 1165 (SO_2), 1270, 1110, 1010, 885, 765, 615, 540, 480, and 460 (other strong) cm^{-1}; ^1H NMR (acetonitrile-d_3): δ 2.68 (s, 3H, CH_3), 7.07 (br.s, 2H, 2 × O═C–NH), 7.16 (d, J = 8.3 Hz, 1H, H-10),

Scheme 3. One-pot synthesis and proposed mechanism of the formation of benzodithiazine **9** from compound **2a**. Reagents and conditions: (a) NaOH (0.075 molar equiv.), water (0.2 mL), toluene, RT, 8 h, reflux, 34 h.

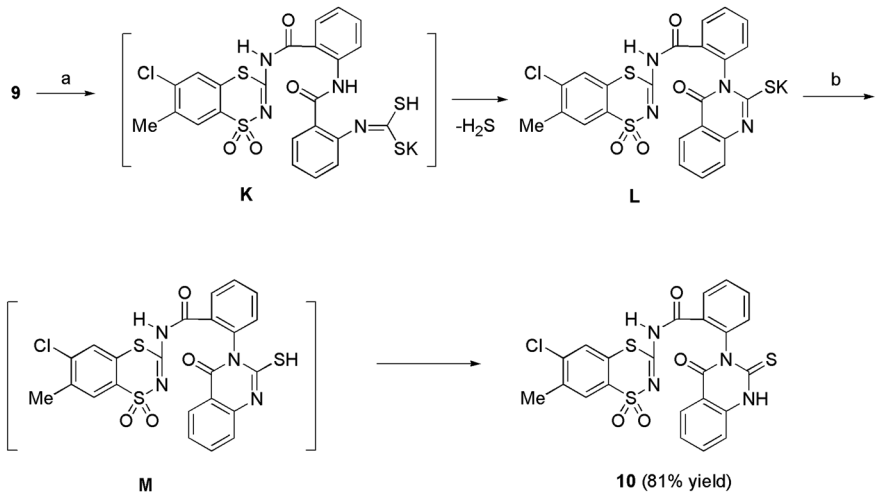


7.27 (t, $J = 7.6$ Hz, 1H, H-9), 7.40 (d, $J_{metha} = 2.9$ Hz, 1H, H-5′) 7.72 (t, $J = 7.6$ Hz, 1H, H-8), 7.75 (d, $J_{metha} = 7.6$ Hz, 1H, H-7′), 7.79 (d, $J = 7.8$ Hz, 1H, H-7), 9.35 (s, 1H, H-2′) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 21.10, 110.50, 115.59, 123.76, 125.41, 129.19, 130.44, 131.56, 131.94, 135.69, 137.18, 139.19, 141.66, 147.36, 160.13, 162.68 ppm. *Anal.* Calcd for $C_{16}H_{12}ClN_3O_5S_2$ (425.88): C, 45.12; H, 2.84; N, 9.86. Found: C, 45.20; H, 2.88; N, 9.90.

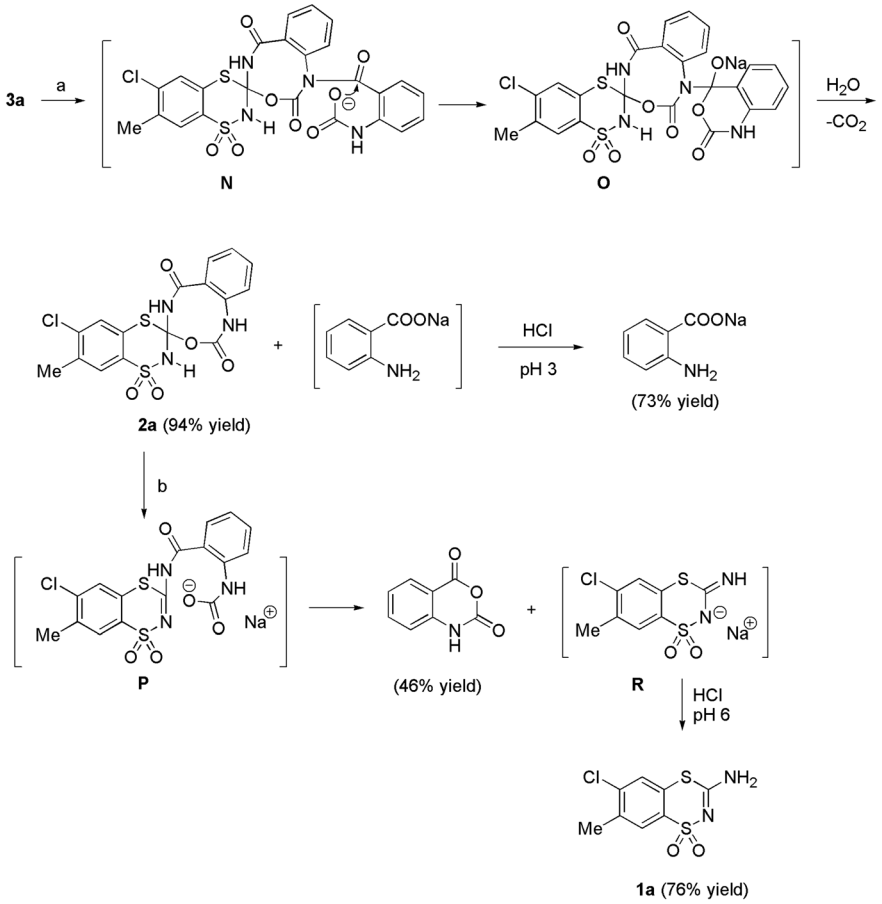
Procedures for the preparation of spiro[benzo[*d*] [1,3,7] oxadiazocine-4,3′-(1,4,2-benzodithiazine)] derivatives (3a, 3b). A mixture of isatoic anhydride (1.3 g, 8 mmol) and spiro compound **2a** or **2b** (3.0 g, 7 mmol) in dry toluene (70 mL) was refluxed with stirring for 48 h. The precipitate was filtered off when hot and washed with toluene (2 × 5 mL) and ethanol (3 × 4 mL), and then the crude product obtained was added to methanol (30 mL). After 1 h of stirring at room temperature, the precipitate was filtered off, washed with methanol (2 × 4 mL) and petroleum ether (2 × 5 mL), and dried. In this manner, the following spiro compounds were obtained.

***2-(6′-Chloro-7′-methyl-1′,1′-dioxo-2,6-dioxo-1,2,5,6-tetrahydro-2′H-spiro[benzo[d]* [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)-1-ylcarbonyl]phenylcarbamic acid (3a).** Starting from **2a**, the title compound **3a** was obtained (3.5 g, 85%): mp 270–271°C dec; IR (KBr) 3330, 3290, 3200, 3140 (NH and COOH), 2800, 2715, 2540 (COOH), 1790, 1780, 1655, 1620 (C═O), 1360, 1170 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 2.42 (s, 3H, CH_3), 7.15 (d, $J = 8.3$ Hz, 2H, arom.), 7.25 (t, $J = 7.8$ Hz, 2H, arom.), 7.74 (t, $J = 7.8$ Hz, 2H, arom.), 7.78 (s, 1H, H-5′), 7.91 (d, $J = 7.8$ Hz, 2H, arom.), 7.97 (s, 1H, H-8′), 9.10 (s, 1H, H-2′), 9.18 (br.s, 1H, HN–C═O), 11.73 (s, 2H, HN–COOH) ppm; ^{13}C

Scheme 4. Synthesis of benzodithiazine **10**. Reagents and conditions: (a) KOH (1.33 molar equiv.), CS2 (1.33 molar equiv.), 95% ethanol, RT, 4 h, reflux 34 h; (b) water, RT, 1% hydrochloric acid to pH 1.



Scheme 5. Proposed mechanism of the regioselective two-step alkaline hydrolysis of spiro compound **3a** into spiro compound **2a** and benzodithiazine **1a**. Reagents and conditions: (a) NaOH (1.0 molar equiv.) water, RT, 8 h; (b) NaOH (1.1 molar equiv.), RT, 30 h.



NMR (dimethyl sulfoxide-d_6) δ 19.54, 110.51, 115.59, 123.76, 126.54, 127.92, 128.17, 129.19, 131.09, 131.19, 137.37, 141.65, 147.36, 160.13, 164.87 ppm. *Anal*. Calcd for $C_{24}H_{17}ClN_4O_8S_2$ (589.01): C, 48.94; H, 2.21; N, 9.51. Found: C, 49.03; H, 2.94; N, 9.53.

***2-(6′-Chloro-8′-methyl-1′,1′-dioxo-2,6-dioxo-1,2,5,6-tetrahydro-2′H-spiro[benzo[d]* [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)-1-ylcarbonyl]phenylcarbamic acid (3b)**. Starting from **2b**, the title compound **3b** was obtained (3.6 g, 87%): mp 190–191°C dec.; IR (KBr): 3345, 3330, 3210, 3110 (NH and COOH), 2935, 2880, 2780, 2530 (COOH), 1770, 1730, 1650, 1620 (C═O), 1360, 1165, (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.64 (s, 3H, CH_3), 7.16 (d, J = 8.3 Hz, 2H, arom.), 7.26 (t, J = 7.6 Hz, 2H, arom.), 7.54 (s, 1H, H-7′), 7.71–7.77 (m, 4H, arom.), 7.92 (s, 1H, H-5′), 7.94 (s, 1H, H-2′), 9.04 (br.s, 1H, HN–C═O), 11.73 (s, 2H, HN–COOH) ppm. *Anal*. Calcd for $C_{24}H_{17}ClN_4O_8S_2$ (589.01): C, 48.94; H, 2.21; N, 9.51. Found: C, 48.99; H, 2.27; N, 9.60.

Procedures for the preparation of spiro[benzo[*d*] [1,3,7] oxadiazocine-4,3′-(1,4,2-benzodithiazine)] derivatives (4 and 5). A suspension of spiro compound **2a** and the corresponding phenyl isocyanate (10 mmol) in dry toluene (80 mL) was refluxed with stirring for 32 h. After cooling to room temperature, the precipitate was collected by filtration, washed successively with toluene (5 × 5 mL) and acetonitrile (4 × 4 mL) and dried.

***6′-Chloro-N*-(3,4-dichlorophenyl)-7′-methyl-1′,1′-dioxo-2,6-dioxo-5,6-dihydro-2′H-spiro[benzo[*d*] [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-1-(2H)-carboxamide (4)**. Starting from 3,4-dichlorophenyl isocyanate (1.88 g), the title compound **3a** was obtained (3.7 g, 75%): mp 201–202°C dec.; IR (KBr): 3300, 3260, 3185, (NH), 1785, 1730, 1655, 1620 (C═O), 1360, 1165 (SO_2) cm−^{1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 2.44 (s, 3H, CH_3), 7.15 (d, J = 7.8 Hz, 1H, H-10), 7.24 (t, J = 7.8 Hz, 1H, H-9), 7.41 (d, J = 8.7 Hz, 1H, H-6, 3,4-diClPh), 7.60 (d, J = 8.7 Hz, 1H, H-5, 3,4-diClPh), 7.73 (t, J = 7.8 Hz, 1H, H-8), 7.84 (s, 1H, H-5′), 7.89 (s, 1H, H-2, 3,4-diClPh), 8.00 (s, 1H, H-8′), 8.05 (s, 1H, O═C–NH-5), 9,13 (d, J = 12 Hz, 1H, H-7), 9.68 (s, 1H, H-2′), 11.72 (s, 1H, NH, 3,4-diClPh) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 19.60, 110.50, 115.59, 119.95, 121.03, 123.76, 125.81, 126.55, 128.16, 128.38, 128.98, 129.19, 129.84, 131.09, 131.51, 137.18, 137.36, 137.94, 138.61, 141.55, 150.88, 164.13, 164.85 ppm. *Anal*. Calcd for $C_{23}H_{15}Cl_3N_4O_6S_2$ (613.90): C, 45.00; H, 2.46; N, 9.13. Found: C, 45.10; H, 2.51; N, 9.20.

***6′-Chloro-N*-(3-chlorophenyl)-7′-methyl-1′,1′-dioxo-2,6-dioxo-5,6-dihydro-2′H-spiro[benzo[*d*] [1,3,7]oxadiazocine-4,3′-(1,4,2-benzodithiazine)]-1-(2H)-carboxamide (5)**. Starting from 3-chlorophenyl isocyanate (1.53 g), the title compound **4** was obtained (3.9 g, 84%): mp 186–187°C dec.; IR (KBr): 3305, 3260, 3195, (NH) 1770, 1725, 1655, 1620 (C═O), 1365, 1170, (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.44 (s, 3H, CH_3), 7.14 (d, J = 8.4 Hz, 1H, H-10), 7.23 (t, J = 8.4 Hz, 1H, H-9), 7.33–7.43 (m, 2H, H-5 and H-6, 3ClPh), 7.66 (s, 1H, H-5′), 7.73 (t, J = 8.4 Hz, 1H, H-8), 7.88 (s, 1H, H-2, 3-ClPh), 7.94 (d, J = 7.3 Hz, 1H, H-4, 3-ClPh), 8.01 (s, 1H, H-8′), 8.05 (s, 1H, O═C–NH-5), 9.13 (d, J = 14 Hz, 1H, H-7, benzoxadiazocine), 9.66 (s, 1H, H-2′), 11.73 (s, 1H, NH, 3-ClPh) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 19.60, 110.51, 115.59, 118.26, 119.18, 123.77, 123.94, 126.55, 128.39, 129.01, 129.17, 129.88, 130.94, 133.58, 137.18, 137.93, 138.59, 139.24, 141.66, 147.35, 150.80, 164.12, 164.86 ppm. *Anal*. Calcd for $C_{23}H_{16}Cl_2N_4O_6S_2$ (579.46): C, 47.67; H, 2.78; N, 9.67. Found: C, 47.64; H, 2.82; N, 9.74.

Procedure for the preparation of 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylaminocarbonyl)phenylcarbamic acid (6) from spiro compound (2a). A suspension of **2a** (2.13 g, 5 mmol) in dry 1,4-dioxane (25 mL) was refluxed with stirring for 10 min. The small amount of insoluble side products was filtered out when hot, and the filtrate left to stand at room temperature overnight. The precipitate was filtered off, washed with 1,4-dioxane (2 × 1.5 mL), dried (1.8 g), and purified by heating in boiling acetonitrile (10 mL) for 5 min. After cooling to room temperature, the precipitate of title compound **6** was collected by filtration, washed with acetonitrile (2 × 1 mL), and dried. Yield 1.6 g (75%); mp 229–230°C dec.; IR (KBr): 3345, 3285, 3195, 3145 (HN–COOH, HNC═O) 1785, 1730, 1655, (NHC═O, and COOH), 1360, 1170 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.41 (s, 3H, CH_3), 7.14 (d, J = 8.3 Hz, 1H, H-5, Ph), 7.23 (t, J = 7.6 Hz, 1H, H-4, Ph), 7.26 (t, J = 7.6 Hz, 1H, H-3, Ph), 7.88 (s, 1H, H-5, benzodithiazine), 7.90 (d, J = 8.3 Hz, 1H, H-2, Ph), 7.96 (s, 1H, H-8, benzodithiazine), 9.08 (s, 1H, NH), 9.16 (s, 1H, NH), 11.71 (s, 1H, COOH) ppm. *Anal*. Calcd for $C_{16}H_{12}Cl$ $N_3O_5S_2$ (425.88): C, 45.12; H, 2.84; N, 9.88 Found: C, 45.18; H, 2.94; N, 10.02.

Procedure for the transformation of spiro compound (2a) into 3-(2-aminobenzamido)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (7). A solution of spiro compound **2a** (4.26 g, 10 mmol) and triethylamine (1.06 g, 10.5 mmol) in tetrahydrofuran (70 mL) was stirred at room temperature for 6 h. The small amount of insoluble side products was filtered out together with charcoal added. The solvent was evaporated under reduced procedure at room temperature. The oily residue was heated at temperatures gradually increasing to 200°C for 6 h. The resulting solid residue was treated with glacial acetic acid (25 mL) and then stirred at reflux for 3 min. After cooling to room temperature, the precipitate was collected by filtration, washed successively with acetic acid (2 × 1.5 mL), water (5 × 3 mL), and methanol (3 × 2 mL), and dried. Yield 3.2 g (83%); mp 299–300°C dec.; IR (KBr): 3325, 3285, 3240 (NH, NH_2) 1725, 1700, (C═O), 1655, (C═N) 1340, 1305,1150, 1135 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 2.33 (s, 3H, CH_3), 7.38 (t, J = 7.3 Hz, 1H, H-4, Ph), 7.61 (d, J = 8.3 Hz, 1H, H-3, Ph), 7.75 (s, 1H, NH, benzodithiazine), 7.77–7.82 (m, 2H, H-5, Ph and H-5, benzodithiazine), 7.97 (d, J = 7.3 Hz, 1H, H-6, Ph), 8.06 (s, 1H, H-8, benzodithiazine), 11.48 (s, 1H, $PhNH_B$), 11.87 (s, 1H, $PhNH_A$) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 19.64, 116.44, 118.21, 125.62, 127,51, 131.51, 133.59, 135.96, 136.41, 138.84, 139.77, 149.29, 160.64 ppm. *Anal*. Calcd for $C_{15}H_{12}Cl$ $N_3O_3S_2$ (381.87): C, 47.18; H, 3.17; N, 11.00, Found: C, 47.19; H, 3.20; N, 11.01.

Synthesis of 2-[*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzamido-2-aminocarbonyl)]phenylcarbamic acid (8) and 3-amino-6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazine (1a) as by-product. A mixture of compound **2a** (1.28 g, 3 mmol) and 3-(aminobenzamido)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide **7** (1.16 g, 3 mmol) in dry toluene (40 mL) was refluxed with stirring for 32 h. After cooling to room temperature, the precipitate was collected by filtration, washed with toluene (3 × 2.5 mL), and dried. The mixture of products was thus obtained (2.2 g), and methanol (100 mL) was refluxed with stirring for 0.5 h. The precipitate of title compound **8** was filtered out when hot, washed with methanol (3 × 5 mL) and acetonitrile (3 × 3 mL), and dried. Yield 1.43 g (87%); mp 295–296°C dec.; IR (KBr): 3490, 3285, 3260 (NH and COOH) 1725, 1700, 1655, 1630 (HOC═O, HNC═O, and C═N), 1360,

1305, 1150, 1135 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 2.31 (s, 3H, CH_3), 6.07 (t, J = 7.1 Hz, 1H, arom.), 6.36 (d, J = 7.8 Hz, 1H, arom.), 6.75 (s, 1H, H-5, benzodithiazine), 6.91 (t, J = 7.1 Hz, 1H, arom.), 7.24 (t, J = 7.3 Hz, 1H, arom.), 7.35–7.73 (m, 3H, arom.), 7.94 (d, J = 7.3 Hz, 1H, arom.), 8.04 (s, 1H, H-8, benzodithiazine), 11.15 (s, 1H, NH), 11.45 (s, 1H, NH), 11.78 (s, 1H, NH), 11.85 (s, 1H, COOH) ppm. *Anal.* Calcd for $C_{23}H_{17}Cl N_4O_6S_2$ (545.0): C, 50.69; H, 3.14; N, 10.28, Found: C, 50.63; H, 3.19; N, 10.37.

The methanol–acetonitrile filtrate mixture was evaporated to one-fourth volume at reduced pressure. After cooling to room temperature, the suspension was left overnight. The precipitate of benzodithiazine **1a** thus obtained as a side product was filtered off, washed with acetonitrile (3 × 1 mL), and dried. Yield 0.5 g (63%); mp 161–162°C; IR data were in accordance with those reported previously to the authentic sample of **1a** [44].

One-pot synthesis of 3-[2-anthranilamido)benzamido]-6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazine (9) and 3-amino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine (1a) and anthranilic acid as side products. A mixture of NaOH (0.06 g, 0.0015 mol) in water (0.2 mL), toluene (160 mL), and compound **2a** (8.52 g, 0.02 mol) was stirred at room temperature for 8 h followed at reflux for 34 h. After cooling to room temperature, the precipitate was collected by filtration, washed with toluene (3 × 5 mL), dried, and mixed with water (20 mL) for 1 h. Resulting precipitate of **1a** and **9** was filtered off, washed with water (3 × 10 mL), dried, and left for further work-up (7.4 g). The water filtrate (pH ~7) was acidified with 1% hydrochloric acid to pH 1. The resulting precipitate of anthranilic acid was collected by filtration, washed with water (3 × 1 mL), and dried. Yield 0.1 g (3.6%); mp 144–146°C, and IR were identical with authentic sample of commercially available anthranilic acid.

A mixture of **1a** and **9** obtained (7.4 g) in methanol (160 mL) was stirred at reflux for 1 h. The precipitate of **9** was filtered out when hot, washed with methanol (4 × 5 mL) (methanol filtrate was left for further work-up), and dried. Yield 4.5 g (44.9%); mp 270–271°C dec.; IR (KBr): 3490, 3380, (NH_2), 3260, 3230 (NH), 1710, 1655 (C═O), 1630 (C═N), 1360, 1150 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 2.50 (s, 3H, CH_3), 6.10 (t, J = 7.1 Hz, 1H, Ph), 6.39 (d, J = 8.3 Hz, 1H, Ph), 6.78 (s, 2H, NH_2), 6.94 (t, J = 7.1 Hz, 1H, Ph), 7.26 (t, J = 7.3 Hz, 1H, Ph), 7.32 (d, J = 7.8 Hz, 1H, Ph), 7.41 (d, J = 7.8 Hz, 1H, Ph), 7.63 (t, J = 7.3 Hz, 1H, Ph), 7.72–7.80 (m, 2H, Ph and H-5, benzodithiazine), 8.18 (s, 1H, H-8, benzodithiazine), 11.17 (s, 1H, NH), 11.81 (s, 1H, NH) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6): δ 20.24, 114.71, 115.33, 115.86, 117.56, 117.80, 125.04, 125.59, 127.26, 129.28, 131.37, 135.12, 136.06, 137.43, 139.09, 139.53, 140.35, 145.21, 149.27, 150,25, 160.02, 186.68 ppm. *Anal.* Calcd for $C_{22}H_{17}Cl N_4O_4S_2$ (500.99): C, 52.74; H, 3.42; N, 11.18. Found: 52.76; H, 3.51; N, 11.20.

The methanol–filtrate mixture was evaporated to one-fifth volume at reduced pressure. After cooling to room temperature, the suspension was left overnight. The precipitate of benzodithiazine **1a** was filtered off, washed with methanol (4 × 2 mL), and dried. Yield 1.94 g (36.1%); mp 160–162°C; ^1H NMR data were in accordance with those reported previously for authentic sample of **1a** [44].

Synthesis of 6-chloro-7-methyl-1,1-dioxo-3-[2-(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-3-yl)benzamido]-1,4,2-benzodithiazine (10). To a mixture of KOH (0.23 g, 4 mmol), 95% ethanol (30 mL), and carbon disulfide (0.29 g, 4 mmol), benzodithiazine **9** (1.5 g, 3 mmol) was added with stirring. The reaction mixture was stirred at room temperature for 4 h followed at reflux until the evolution of H_2S had ceased (34–36 h)(*Caution*: because of high toxicity, H_2S should be trapped in aqueous NaOH solution). After cooling to room temperature, the suspension was left overnight. The precipitate was collected by filtration, washed with ethanol (3 × 1.5 mL), and dried. The crude potassium salt of **10** (1.7 g); mp 300–302°C dec.; IR (KBr) 3420, 3300, 3205 (NH), 1660, 1620 (C═O) 1360, 1135, (SO_2) cm^{-1} was suspended in water (15 mL) (pH ~9.5) then acidified with 1% hydrochloric acid to pH 1. After 3 h of stirring, the title compound **10** was collected by filtration, washed successively with water (5 × 3 mL), methanol (2 × 1 mL), and acetonitrile (3 × 1.5 mL), and dried. Yield 1.33 g (81%); mp 269–270°C; IR (KBr): 3285, 3240 (NH), 1725, 1700 (C═O), 1635, (C═N), 1360, 1130 (SO_2), 1100 (C═S) cm^{-1}; ^1H NMR (dimethyl sulfoxide): δ 2.30 (s, 3H, CH_3), 7.02–7.20 (m, 2H, arom.), 7.22–7.38 (m, 2H, arom.), 7.52 (s, 1H, H-5, benzodithiazine), 7.58–7.65 (m, 2H, arom.), 7.80–7.90 (m, 2H, arom.), 8.03 (s, 1H, H-8, benzodithiazine), 11.40 (br.s, 2H, 2 × NH) ppm. *Anal.* Calcd for $C_{23}H_{15}Cl N_4O_4S_3$ (543.05): C, 50.87; H, 2.78; N, 10.32. Found: C, 50.91; H, 2.87; N, 10.30.

Regioselective hydrolysis of spiro compound 3a into spiro compound 2a and anthranilic acid as side product. To a solution of NaOH (0.12 g, 3 mmol) in water (15 mL), compound **3a** (1. 76 g, 3 mmol) was added, and the reaction mixture was stirred at room temperature for 8 h. The precipitate of **2a** was filtered off, washed with water (5 × 2 mL), and dried initially at room temperature and then at temperatures gradually increasing to 100°C. Yield 1.2 g (94%): mp 231–232°C dec.; IR and ^1H NMR data were in accordance with those reported previously to the authentic sample of **2a**. The water filtrate (pH ~7.5) was acidified with 1% hydrochloric acid to pH 3. Anthranilic acid thus obtained as a side product was filtered out, washed with water (2 × 1 mL), and dried. Yield 0.3 g (73%); mp 145–147°C.

Regioselective hydrolysis of spiro compound 2a into3-amino-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxide (1a) and isatoic anhydride as side product. To a solution of NaOH (0.18 g, 4.4 mmol) in water (70 mL), compound **2a** (1.7 g, 4 mmol) was added, and the reaction mixture was stirred at room temperature for 30 h. The precipitate of isatoic anhydride thus obtained was filtered off, washed successively with water (5 × 5 mL) and petroleum ether (4 × 1 mL), and dried. Yield 0.3 g (46%); mp 235–237°C. The water filtrate (pH ~7.5) was acidified with 1% hydrochloric acid to pH 6. The precipitate of benzodithiazine **1a** was collected by filtration, washed successively with water (4 × 4 mL) and methanol (5 × 2 mL), and dried. Yield 0.8 g (76%); mp 261–262°C; IR and ^1H NMR data were in accordance with those reported previously to the authentic sample of **1a** [44].

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