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Synthesis, structural characterization, and in vitro antitumor activity of novel *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides

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Abstract—A new series of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides **23**–**48** have been synthesized as potential anticancer agents. All compounds were screened for their cytotoxic activity against six human tumor cell lines. The selected compounds **23**–**27**, **30**, **31**, **33**, **35**, **38**, **42**, **45**, and **46** were further tested at the US National Cancer Institute for their in vitro activities against a panel of 53–59 human tumor cell lines. The compounds **23**–**26**, **30**, **31**, **33**, **38**, **42**, **45**, and **46** showed 50% growth inhibitory activity in low micromolar concentration (GI_{50} = 0.03–4.9 μM) against one or more human tumor cell lines (Table 3). The prominent compound with remarkable activity (GI_{50} = 0.03 μM, TGI = 1.3 μM) and selectivity toward melanoma UACC-257 cell line was *N*-(6-chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-*N*-(phenyl)-5-bromothiophene-2-sulfonamide **46**.

1. Introduction

Sulfonamides are among a growing list of compounds with desirable anticancer activity.[1–16] Although they have a common chemical motif of aromatic/heterocyclic sulfonamide, there are a variety of mechanisms for their anticancer action, such as disruption of microtubule assembly, cell cycle arrest in the G1 phase, functional suppression of the transcriptional activator NF-Y, angiogenesis inhibition as well as carbonic anhydrase inhibition.[1] Previously, we described the syntheses of various 4-chloro-2-mercaptobenzenesulfonamide derivatives (Fig. 1, structure **A**) with the nitrogen atom of sulfonamide moiety attached to a variety of heterocyclic ring systems. These compounds, depending on structure, exhibited either anticancer[9,15,17–22] or anti-HIV activities[17–20,23] and have been described as a novel class of potent HIV-1 integrase inhibitors.[24,25] We further found that cyclic analogues of 2-mercaptobenzenesulfonamides also showed remarkable cytotoxic properties (Fig. 1, structures **B**,[14,26,27] **C**,[28] **D**,[29], and **E**[30]). This led us to an assumption that expansion of a series of candidate anticancer agents of general formula **F** (Fig. 1) may shed light on the structural features contributing to the anticancer activity.

2. Results and discussion

2.1. Chemistry

The previously described methods were employed for the synthesis of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid **1**[31] and 3-amino-6-chloro-1,1-dioxo-1,4,2-benzodithiazines **2** and **3**,[32] **4** and **5**[33], and **6**–**8**.[34] Similarly, we prepared the new 6-chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid **9**. The syntheses of the target compounds **23**–**48** were achieved by a convenient one-, three- or four-step procedure starting from 3-amino-6-chloro-1,1-dioxo-1,4,2-benzodithiazines **2**–**9** as shown

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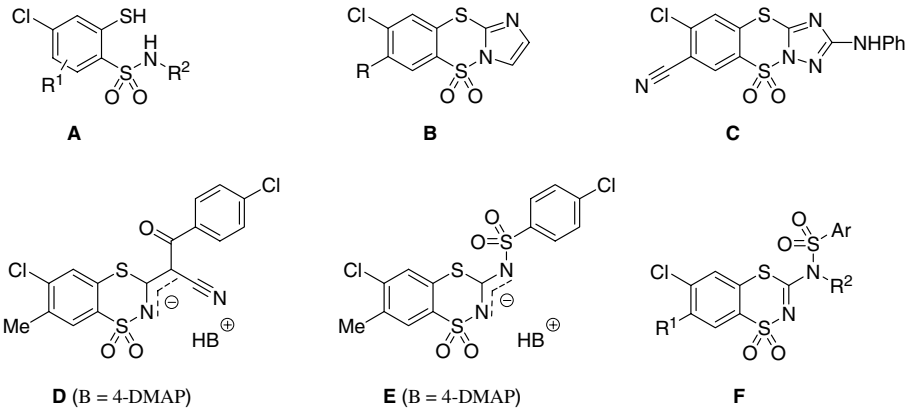


Figure 1. Lead compounds among cyclic analogues of 2-mercaptobenzene sulfonamides.

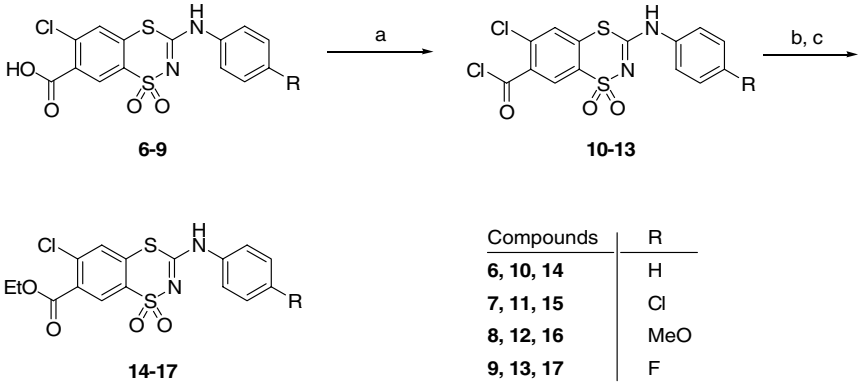
in Schemes 1–3 . First, the reaction of 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acids **6**–**9** with thionyl chloride was performed in boiling benzene to give acid chlorides **10**–**13** in 87–89% yields. Then, treatment of **10**–**13** with an excess of ethanol in the presence of triethylamine afforded the expected ethyl 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylates **14**–**17** in 78–98% yields (Scheme 1). The reaction of acid chloride **13** with 8-hydroxyquinoline carried out in *p*-dioxane at elevated temperature led to the formation of 8-quinolyl 6-chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate hydrochloride **18·HCl** in 94% yield. Then, on treatment of **18·HCl** with $KHCO_3$ in water the free ester **18** was obtained in 75% yield (Scheme 2). Second, the reaction of the 1,4,2-benzodithiazine-7-carbonyl chloride **10** and **11** with 28% ammonia aqua solution carried out in benzene at temperatures 0–20 °C led to the formation of carboxamides **19** and **20** in excellent yield. Then upon treatment of **19** and **20** with an excess of boiling phosphorus oxychloride the target 1,4,2-benzodithiazine-7-carbonitriles **20** and **21** were obtained in 90–93% yields (Scheme 2). Finally, the desired *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides **23**–**48** were obtained by reacting the benzodithiazines **2**–**18**, **21**, and **22** with the corresponding arylsulfonyl chlorides in pyridine in moderate to good yield (Scheme 3).

The structures of the compounds **9**–**22** and the final products **23**–**48** were confirmed by elemental analyses, IR and NMR spectroscopic data presented in Section 4. It is worth noting, however, that the spectroscopic data did not allow straightforward discrimination between the actual *N*-(R^2)-*N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamide structure (**23**–**48**) and the alternative 6-chloro-2-(arylsulfonyl)-3-(R^2-imino)-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazines. Therefore, X-ray crystallography was undertaken on representative compound **23** with a view to reveal some more discrete structural features of these compounds.

Molecular structure of **23** with labeling scheme and displacement ellipsoids at the 50% probability level is shown in Figure 2. This structure confirms the location of benzenesulfonyl moiety attached to the exocyclic N11 nitrogen atom.

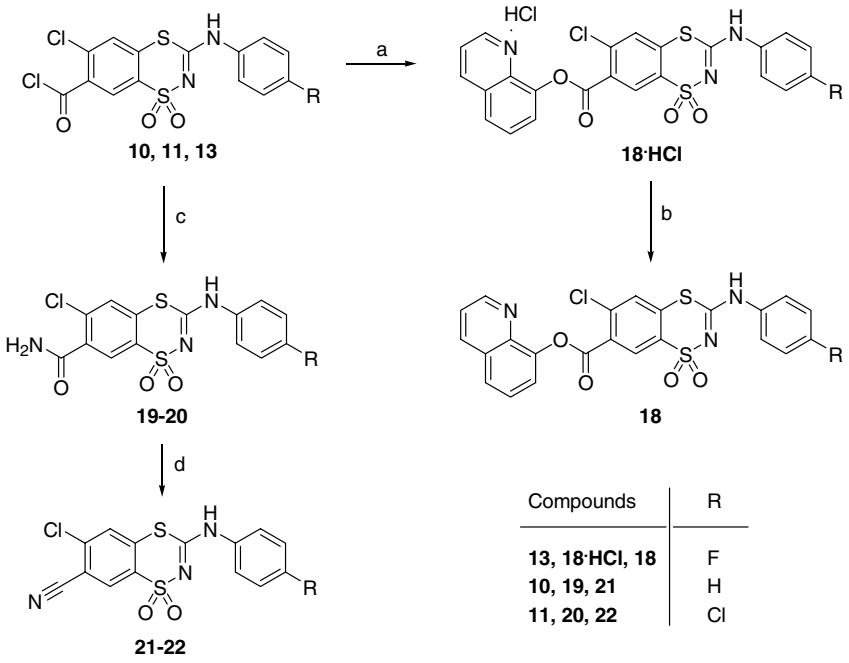
2.2. Biological Results

The in vitro cytotoxic activity of all *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides **23**–**48** was evaluated[35,36] using human bladder cancer cell lines 5637 and RT-4; human lung cancer cell lines A-427 and LCLC-103H; human pancreatic cell line DAN-G and human breast cancer cell line MCF-7. The assay was



Compounds	R
6, 10, 14	H
7, 11, 15	Cl
8, 12, 16	MeO
9, 13, 17	F

Scheme 1. Synthesis of 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chlorides (**10**–**13**) and ethyl 6-chloro-3-(arylamino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylates (**14**–**17**). Reagents, conditions, and yields: (a) $SOCl_2$ (large excess), benzene, reflux, 16 h, 87–89%; (b) ethanol (large excess), rt, 3 h; (c) Et_3N (1.1 M equiv), rt, 1 h, reflux, 3 h, 78–97%.



Scheme 2. Synthesis of 8-quinolyl 6-chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate **18** and 3-(arylamino)-6-chloro-1, 1-dioxo-1,4,2-benzodithiazine-7-carbonitriles (**21** and **22**). Reagents, conditions, and yields: (a) 8-hydroxyquinoline (1.033 M equiv), *p*-dioxane, rt, 2 h, reflux, 4 h, 94%; (b) $KHCO_3$ (1.14 M equiv), water, rt, 1 h, 75%; (c) 28% ammonia aqua solution (4 M equiv), benzene, 0–5 °C, 1 h, rt, 10 h, 95–97%; (d) $POCl_3$ (large excess), reflux, 25 h, 90–93%.

carried out in 96-well microtiter plates. Cells were seeded into the plates and after 24 h they were treated with the appropriate drug solutions. The cytotoxic effects of the compounds were measured after a 96-h continuous exposure to the substances. The cell growth inhibition values were estimated by staining the adherent cells with crystal violet. Only viable cells remained attached to the plastic surface of the wells and bind the dye. The unbound dye was washed out with water and stain remaining in the cells was redissolved with 70% ethanol. At the end, the optical density (OD) was measured with a microplate reader set at $\lambda = 570$ nm.

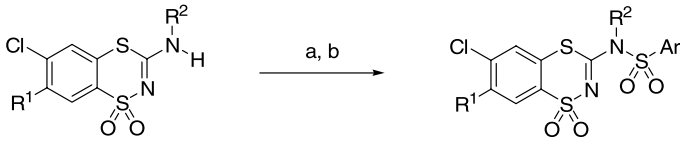
First, primary screening of the new compounds was done to indicate whether a substance possesses enough activity at the concentration of 20 μM to inhibit cell growth by 50% ($GI_{50} < 20$ μM). The human tumor cell lines used were 5637, LCLC-103H, MCF-7 and DAN-G.

Then, for sulfonamides **25**–**27**, **30**, **31**, **35**–**38**, **41**, and **42** that passed the preliminary test, a secondary screening to determine their potency was performed on a panel of six human cancer cell lines mentioned above. Table 1 lists the GI_{50} values calculated from the dose–response data obtained from 5 to 7 independent experiments and reports the average GI_{50} value and the relative standard deviation for the tested cell lines.

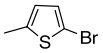
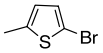
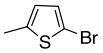
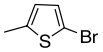
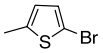
For a series of benzenesulfonamide derivatives obtained (Scheme 3), the effects of structural modifications were explored within three structural domains: substituent R^1 at 7-position of the phenyl ring, substituent R^2 at the nitrogen atom, and a variously substituted aromatic ring (Ar) attached to the sulfonyl group.

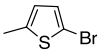
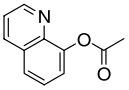
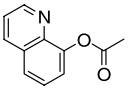
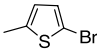
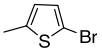
As shown in Table 1, compound **23** (R^1 = Me) with R^2 = 4-ClPh and Ar = Ph showed a moderate activity with mean GI_{50} value over all tested cancer cell lines of 11.86 μM. The most sensitive were 5637, A-427, DAN-G, and MCF-7 cell lines (GI_{50} in the range of 8.1–9.9 μM). A similar pattern was found for compound **25** incorporating R^2 = 2-ClPh and Ar = 5-Br-thienyl (mean GI_{50} = 12.01 μM). Replacement of phenyl ring at R^2 with Me_2N group resulted in compound **26** with slightly decreased antiproliferative activity (mean GI_{50} = 18.43 μM). Other compounds with $R^2 = Me_2N$, R^1 = MeOCO and a variously substituted aromatic/heteroaromatic ring at Ar-position either did not pass the preliminary test (**28** and **29**) or exhibited a moderate activity (**27** and **30**) (mean GI_{50} = 14.71 and 16.31 μM, respectively). These results indicate that lipophilic substituents are favored over Me_2N group at position R^2. Therefore, further modifications with $R^2 = Me_2N$ were not pursued.

With the goal of obtaining more SAR information we then examined the antitumor activity of compounds **31**–**40** with EtOCO group at R^1-position and lipophilic substituents R^2 and Ar. Compounds **32–34**, **36**, and **37** which incorporate aromatic/heteroaromatic rings substituted with electron-withdrawing groups (R^1 = 4-ClPh, 4-FPh, and R^2 = 4-O_2NPh, 4-ClPh, 5-Br-thienyl) were not active up to concentration of 20 μM. On the other hand, compound **31** with R^2 = Ph and Ar = 4-ClPh retained a moderate antiproliferative activity (mean GI_{50} = 15.10 μM). Likewise when R^2 or Ar were



2-5, 14-18, 21-22 23-48

Compds	R^1	R^2	Ar
2, 23	Me	4-ClPh	Ph
2, 24	Me	4-ClPh	
3, 25	Me	2-ClPh	
4, 26	Me	Me_2N	4-ClPh
5, 27	MeOCO	Me_2N	4-ClPh
5, 28	MeOCO	Me_2N	2,4-diClPh
5, 29	MeOCO	Me_2N	Ph
5, 30	MeOCO	Me_2N	
14, 31	EtOCO	Ph	4-ClPh
14, 32	EtOCO	Ph	4-O_2NPh
14, 33	EtOCO	Ph	
15, 34	EtOCO	4-ClPh	
16, 35	EtOCO	4-MeOPh	4-ClPh

Compds	R^1	R^2	Ar
16, 36	EtOCO	4-MeOPh	2,4-diClPh
16, 37	EtOCO	4-MeOPh	Ph
17, 38	EtOCO	4-FPh	4-MeOPh
17, 39	EtOCO	4-FPh	4-ClPh
17, 40	EtOCO	4-FPh	
18, 41			4-FPh	4-ClPh
18, 42			4-FPh	
21, 43	N≡C	Ph	4-O_2NPh
21, 44	N≡C	Ph	3-O_2NPh
21, 45	N≡C	Ph	4-ClPh
21, 46	N≡C	Ph	
22, 47	N≡C	4-ClPh	4-ClPh
22, 48	N≡C	4-ClPh	3-Cl-4FPh

Scheme 3. Synthesis of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides **23**–**48**. Reagents, conditions, and yields: (a) arylsulfonyl chloride (1.13 M equiv), pyridine, rt, 8 h; (b) 50–55 °C, 3 h, 33–83%.

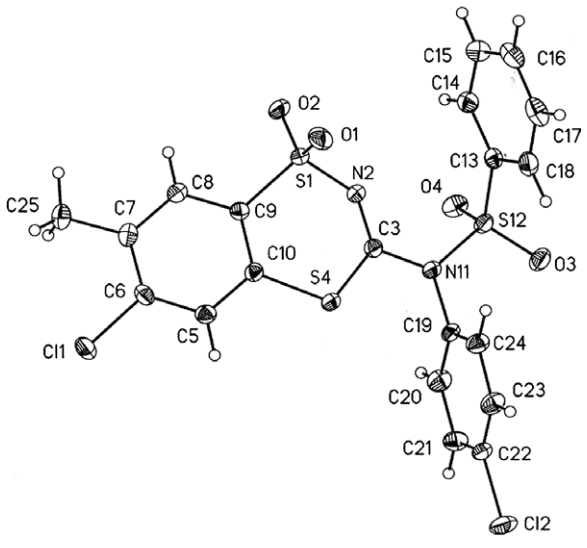


Figure 2. ORTEP drawing of **23** with atom labeling scheme. Ellipsoids are drawn at the 50% probability level.

replaced by 4-MeOPh, the resulting compounds **35**, **38**, **39**, and **40** were more active, indicating the importance of the electron-donating 4-methoxy group. Compound **39** (R^2 = 4-MeOPh, Ar = 2,4-diClPh) achieved the mean GI_{50} value of 3.50 μM.

Interestingly, compounds **41** and **42** with electron-withdrawing groups (R^2 = 4FPh, Ar = 4-ClPh or 5-Br-thienyl) carrying lipophilic quinolinoxycarbonyl group at R^1-position show a similar activity with **40** having EtO-CO at R^1, 4-MeOPh at R^2 and unsubstituted phenyl ring at Ar-position (mean GI_{50} = 7.73, 7.53, and 8.68 μM, respectively).

Compounds **23**–**27**, **30**, **31**, **33**, **35**, **38**, **42**, **45**, and **46** were also selected by the US National Cancer Institute (Bethesda, USA) and tested for their in vitro anticancer activity using 53–59 human tumor cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast. The compounds were tested at five concentrations at 10-fold dilution. A 48-h continuous drug exposure protocol was used and sulforhodamine B (SRB) protein assay was used to estimate cell growth. Details of this test system have been published.[37–39] The anticancer activity of a test compound is reported for each cell line by three parameters: GI_{50} value (GI_{50}, molar concentration of the compound that inhibits 50% net cell growth), TGI

Table 1. GI_{50} values for the inhibition of in vitro cell growth of six human cancer cell lines by compounds **23**, **25**–**27**, **30**, **31**, **35**–**38**, **41**, and **42**[a]

Compound	Mean[b]	Cell line/GI_{50} (μM)					
		5637	RT-4	A-427	LCLC-103H	DAN-G	MCF-7
23	11.86	9.6 ± 0.4	22.0 ± 8.5	9.2 ± 1.8	12.4 ± 1.9	9.9 ± 3.1	8.1 ± 2.2
25	12.01	7.5 ± 1.2	28.6 ± 21.8	8.2 ± 1.5	11.9 ± 1.4	9.4 ± 3.4	6.5 ± 1.0
26	18.43	19.2 ± 2.7	>20.0	15.6 ± 0.2	>20.0	23.5 ± 5.0	12.3 ± 0.5
27	14.71	12.6 ± 0.3	18.5 ± 2.2	10.2 ± 1.6	19.6 ± 5.1	18.7 ± 2.9	8.7 ± 0.9
30	16.31	13.7 ± 0.8	18.5 ± 1.3	12.0 ± 2.7	19.1 ± 1.2	23.7 ± 10.7	10.9 ± 1.0
31	15.10	14.3 ± 1.0	>20.0	11.7 ± 1.0	>20.0	14.8 ± 4.9	9.8 ± 1.8
35	14.31	11.9 ± 1.9	23.1 ± 8.9	11.2 ± 2.4	19.3 ± 3.3	12.3 ± 2.9	8.1 ± 1.4
36	3.50	2.3 ± 0.7	6.3 ± 0.6	4.1 ± 0.7	2.8 ± 0.4	3.1 ± 0.6	2.4 ± 0.7
37	8.68	6.5 ± 0.8	16.8 ± 8.0	7.0 ± 1.9	9.3 ± 1.3	7.6 ± 2.6	4.9 ± 1.6
38	12.46	12.1 ± 1.8	19.0 ± 5.2	8.4 ± 2.0	17.5 ± 5.2	12.0 ± 3.2	5.8 ± 1.8
41	7.73	6.2 ± 1.0	>20.0	3.1 ± 0.7	4.6 ± 1.1	9.3 ± 4.4	3.2 ± 0.5
42	7.53	5.1 ± 0.7	>20.0	3.4 ± 0.7	5.3 ± 0.5	8.2 ± 2.9	3.2 ± 1.3

[a] Values are averages ± standard deviation of five to seven independent determinations.
[b] Averaged GI_{50} values over all tested cancer cell lines.

value (TGI, molar concentration of the compound leading to total inhibition of net cell growth), and LC_{50} value (LC_{50}, molar concentration of the compound leading to 50% net cell death).

The following is to be noted regarding the tumor cell growth inhibition data with the tested compounds. All the compounds (i.e., **23**–**27**, **30**, **31**, **35**, **38**, **42**, **45**, and **46**) exhibited structure dependent high or reasonable activity (GI_{50} = 0.03–80.8 μM) against most (91–100%) of the 53–59 human tumor cell lines (Table 2). The data of the most susceptible cell lines (GI_{50} < 5.0 μM) recorded in Table 3 indicate the following rank order of potency: **23** (against 14 cell lines i.e., leukemia, lung, colon, CNS, melanoma, ovarian, renal, and breast), **45** (five cell lines i.e., lung, colon, melanoma, ovarian, and renal), **31** (five cell lines of leukemia, melanoma and breast), **33** (four cell lines of leukemia and renal, **35** (three cell lines of leukemia, lung, and breast), **24** (two cell lines of leukemia and CNS), **46** (melanoma UACC-257), **30** (melanoma SK-MEL-2), **26** (leukemia CCRF-CEM), **25** and **42** (against breast T-47D cell line).

Analysis of the structure–activity relationships suggests that electronic effects exerted by substituents R^1, R^2, and Ar affect considerably their antitumor potency, specificity, and selectivity. Thus, compound **23** exhibited the highest inhibitory activity (GI_{50} in the range of 0.3–4.5 μM) against 14 cell lines derived from eight different human cancer types (Table 3). Substitution of the phenyl ring at Ar-position with stronger electron-withdrawing 5-Br-thienyl group produced compound **24** which showed a narrowed response range against three cell lines only: RPMI-8226 of leukemia (GI_{50} = 2.1 μM) and SF-539 of CNS (GI_{50} = 2.0 μM). Further replacement of 4-ClPh at R^2-position in compound **24** by even stronger electron-withdrawing 2-ClPh yielded analogue **25** with antitumor activity limited to T-47D cell line of breast cancer (GI_{50} = 4.9 μM). A similar pattern was observed for compounds **31**, **33**, **45**, and **46**. Thus, compound **31** (R^1 = EtOCO, R^2 = Ph, Ar = 4-ClPh) exhibited a high activity against five cell lines, including leukemia CCRF-CEM (GI_{50} = 2.5 μM) and RPMI-8226 (GI_{50} = 4.2 μM), skin cancer melanoma LOX IMVI (GI_{50} = 3.1 μM) as well as breast cancer MCF-7 (GI_{50} = 4.3 μM) and T-470 (GI_{50} = 3.8 μM). Analogous

Table 2. Overview of the results of the in vitro anticancer screening for compounds **23**–**27**, **30**, **31**, **33**, **35**, **38**, **42**, **45**, and **46**[a]

Compound	No. of cell lines investigated	No. of the cell lines giving positive GI_{50}, TGI, and LC_{50}					
		GI_{50}[b] (μM)		TGI[c] (μM)		LC_{50}[d] (μM)	
		No.	Range	No.	Range	No.	Range
23	53	52	0.3–20.0	50	3.5–73.1	36	14.1-91.6
24	54	54	2.0–46.3	44	2.0–97.1	23	45.9–97.8
25	55	55	4.9–37.5	47	21.8–89.8	20	51.7–91.9
26	59	59	3.2–44.4	29	28.7–99.2	3	53.6–89.2
27	55	55	7.6–31.3	52	20.5–73.6	29	45.3–97.2
30	55	55	3.2–32.0	49	9.6–97.4	15	54.5–99.2
31	56	55	2.5–88.1	50	7.4–74.6	38	47.3–92.4
33	55	56	2.1–36.6	52	11.5–74.9	33	50.0–91.2
35	55	50	12.1–80.8	19	31.2–98.6	3	64.6–78.5
38	55	55	1.3–37.7	50	21.9–74.9	31	50.6–97.0
42	55	53	4.9–66.4	22	39.0–96.3	2	86.9–91.0
45	57	56	0.6–35.5	50	16.8–64.1	39	19.7–96.9
46	55	55	0.03–39.6	52	1.3–67.6	35	57.1–99.6

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen[37–39] (see Table 3 for details).
[b] The micromolar concentration that inhibits 50% net cell growth.
[c] The micromolar concentration giving total growth inhibition.
[d] The micromolar concentration leading to 50% net cell death.

Table 3. Inhibition of the most susceptible tumor cell lines by selected compounds **23**–**26**, **30**, **31**, **33**, **38**, **42**, **45**, and **46** (GI_{50} < 5.0 μM)[a]

Compound	Panel cell line	GI_{50}[b] (μM)	TGI[c] (μM)
23	Leukemia		
	CCRF-CEM	4.1	27.4
	RPMI-8226	2.6	14.7
	SR	0.3	12.4
	Non-small cell lung cancer		
	NCI-H226	1.5	5.9
	Colon cancer		
	COLO 205	2.8	14.8
	HCT-15	2.7	13.0
	CNS cancer		
	SF-539	1.0	3.5
	Melanoma		
	LOX IMVI	1.5	7.1
	Ovarian cancer		
	IGROVI	2.5	31.7
	OVCAR-3	1.5	7.1
	OVCAR-5	4.4	18.7
	Renal cancer		
	768-0	4.5	18.1
	ACHN	1.9	10.5
	Breast cancer		
	MDA-MB-231/ATCC	2.7	16.0
24	Leukemia		
	RPMI-8226	3.7	21.5
	CNS cancer		
	SF-539	2.0	9.9
25	Breast cancer		
	T-47D	4.9	23.0
26	Leukemia		
	CCRF-CEM	3.2	17.2
30	Melanoma		
	SK-MEL-2	3.2	8.6
31	Leukemia		
	CCRF-CEM	2.5	7.4
	RPMI-8226	4.2	19.4
	Melanoma		
	LOX IMVI	3.1	13.0
	Breast cancer		
	MCF-7	4.3	15.9
	T-47D	3.8	23.4
33	Leukemia		
	CCRF-CEM	4.5	18.8
	K-562	4.7	21.1
	MOLT-4	4.3	17.9
	Renal cancer		
	ACHN	2.1	11.5
38	Leukemia		
	CCRF-CEM	1.3	32.2
	Non-small cell lung cancer		
	HOP-92	4.8	18.3
	Breast cancer		
	T-47D	4.8	81.9
42	Breast cancer		
	T-47D	4.9	39.0
45	Non-small cell lung cancer		
	NCI-H522	3.2	17.3
	Colon cancer		
	HCT-116	3.7	18.0
	Melanoma		
	SK-MEL-2	3.6	16.8
	Ovarian cancer		
	OVCAR-3	4.9	17.9
	Renal cancer		
	TK-10	0.6	3.6
46	Melanoma		
	UACC-257	0.03	1.3

[a] Data obtained from NCI's in vitro disease-oriented human tumor cell screen.[37–39]

[b] The micromolar concentration that inhibits 50% net cell growth.

[c] The micromolar concentration giving total growth inhibition.

compound **33** with 5-Br-thienyl substituent at Ar-position exhibited different biological profile and a high antiproliferative activity against four cell lines: leukemia CCRF-CEM (GI_{50} = 4.5 μM), K-562 (GI_{50} = 4.7 μM), MOLT-4 (GI_{50} = 4.3 μM), and renal cancer ACHN (GI_{50} = 2.1 μM). Other modification of **31**, consisting in replacement of EtOCO at R^1-position by CN group with stronger electron-withdrawing properties, gave compound **45** with high activity against five cell lines: non-small cell lung cancer NCI-H522 (GI_{50} = 3.2 μM), colon cancer HCT-116 (GI_{50} = 3.7 μM), melanoma SK-MEL-2 (GI_{50} = 3.6 μM), ovarian cancer OVCAR-3 (GI_{50} = 4.9 μM), and renal cancer TK-10 (GI_{50} = 0.6 μM). Finally, when 4-ClPh at Ar-position in **45** was substituted with 5-Br-thienyl group, the resulting compound **46** demonstrated significantly enhanced potency against melanoma UACC-257 cell line (GI_{50} = 0.03 μM, TGI = 1.3 μM).

3. Conclusion

We have developed a method for the synthesis of new series of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides (**23**–**48**). The sulfonamides **23**–**26**, **30**, **31**, **33**, **38**, **42**, **45**, and **46** depending on their structure exhibited high (GI_{50} = 0.03–5.0 μM) or reasonable (GI_{50} = 5.0–80.8 μM) activity against most of the tumor cell lines investigated. Compounds **23**, **31**, **45**, and **46** were the most potent of all derivatives tested. Moreover, the compound **46** acting as a potent inhibitor against melanoma UACC-257 cell line (GI_{50} = 0.03 μM and TGI = 1.3 μM) may serve as useful lead compound for the search of more powerful selective antineoplastic agents.

4. 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; (^1H and ^{13}C NMR spectra) Varian Gemini 200 apparatus at 200 and 50 MHz, respectively (chemical shifts are expressed at δ values relative to Me_4Si as standard). The starting 6-chloro-1,4,2-benzodithiazine 1,1-dioxides **1**–**8** were obtained according to methods described previously: **1**,[31] **2** and **3**,[32] **4**–**6**[33], and **7** and **8**.[34]

4.1. 6-Chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid (9)

To an ice-cold suspension of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid **1** (48.6 g,

0.15 mol) in anhydrous methanol (180 mL) a solution of triethylamine (15.2 g, 0.15 mol) and 4-fluoroaniline (18.9 g, 0.17 mol) in anhydrous methanol (30 mL) was added dropwise with stirring. After 0.5 h the ice bath was removed and the reaction mixture was refluxed until the evolution of MeSH had ceased (30–32 h) (caution: due to a high toxicity, MeSH should be trapped into an aq NaOH solution). The solvent was evaporated under reduced pressure. The resulting residue was then dissolved in water (800 mL) and acidified to pH 6 with 1% hydrochloric acid. After 6 h of stirring, a small amount of insoluble side product was filtered out together with charcoal added, and the filtrate was slowly acidified to pH 1 with 0.5% hydrochloric acid. The title product, which precipitated, was immediately collected by filtration, washed thoroughly with water and hot (50–60 °C) 2-propanol (4× 15 mL), and dried (40.3 g, 69%): mp 317–319 °C; IR (KBr) 3265, 3220 (NH, OH), 1715 (C═O), 1620 (C═N), 1325, 1305, 1155, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.23–7.36 (m, 2H, 4-FPh), 7.56–7.68 (m, 2H, 4-FPh), 8.19 (s, 1H, H-5), 8.33 (s, 1H, H-8), 11.63 (s, 1H, NH), 13.50 (s, 1H, COOH) ppm. Anal. Calcd for $C_{14}H_8ClFN_2O_4S_2$ (386.81): C, 43.47; H, 2.08; N, 7.24. Found: C, 43.50; H, 2.19; N, 7.19.

4.2. General procedure for the preparation of 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chlorides (10–13)

To a suspension of the corresponding benzodithiazinecarboxylic acid **6**–**9** (0.06 mol) in dry benzene (80 mL) thionyl chloride (80 mL) was added. The reaction mixture was stirred at reflux for 16 h. After cooling to room temperature and standing overnight the precipitate of the adequate benzodithiazinecarbonyl chloride was filtered off washed successively with toluene (3× 8 mL) and benzene (3× 10 mL), then dried at temperatures gradually increasing to 100 °C. In this manner, the following acyl chlorides were obtained.

4.2.1. 3-Anilino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (10). Starting from benzodithiazinecarboxylic acid **6** (22.13 g), the title compound **10** was obtained (20.8 g, 89%): mp 233–235 °C; IR (KBr) 3250 (NH), 1775, 1735 (O═C—Cl), 1320, 1310, 1195 (SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_8Cl_2N_2O_3S_2$ (387.27): C, 43.42; H, 2.08; N, 7.23. Found: C, 43.47; H, 2.12; N, 7.30.

4.2.2. 6-Chloro-3-(4-chloroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (11). Starting from benzodithiazinecarboxylic acid **7** (24.2 g), the title compound **11** was obtained (22.1 g, 87%): mp 215–217 °C dec; IR (KBr) 3270 (NH), 1780 (O═C—Cl), 1315, 1295, 1195 (SO_2) cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 7.50 (d, J = 8.9 Hz, 2H, 4-ClPh), 7.78 (d, J = 8.9 Hz, 2H, 4-ClPh), 8.07 (s, 1H, H-5), 8.74 (s, 1H, H-8) ppm. Anal. Calcd for $C_{14}H_7Cl_3N_2O_3S_2$ (471.72): C, 39.87; H, 1.67; N, 6.44. Found: C, 39.76; H, 1.60; N, 6.46.

4.2.3. 6-Chloro-3-(4-methoxyanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (12). Starting from benzodithiazinecarboxylic acid **8** (23.9 g), the title compound **12** was obtained (22.6 g, 90%): mp 225–227 °C; IR (KBr) 3250 (NH), 1780, 1740 (O═C—Cl), 1340, 1315, 1155 (SO_2) cm^{-1}. Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_4S_2$ (417.30): C, 43.17; H, 2.40; N, 6.71. Found: C, 43.10; H, 2.38; N, 6.74.

4.2.4. 6-Chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (13). Starting from benzodithiazinecarboxylic acid **9** (23.2 g), the title compound **13** was obtained (21.3 g, 87%): mp 199–200 °C; IR (KBr) 3315 (NH), 1770, 1735 (O═C—Cl), 1335, 1160 (SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_7Cl_2FN_2O_3S_2$ (405.27): C, 41.49; H, 1.74; N, 6.91. Found: C, 41.41; H, 1.86; N, 6.92.

4.3. General procedure for the preparation of ethyl 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylates (14–17)

The corresponding benzodithiazinecarbonyl chloride **10**, **11**, **12** or **13** (0.03 mol) was added portionwise to 99.9% ethanol (90 mL), and this was stirred at room temperature for 3 h. Then to the stirred reaction mixture a solution of triethylamine (3.34 g, 0.033 mol) in ethanol (15 mL) was added dropwise. The resulting reaction mixture was further stirred at room temperature for 1 h, followed at reflux for 2 h. After cooling to room temperature, the precipitate of the adequate carboxylate formed was collected by filtration, washed successively with ethanol (3 mL), water (3× 15 mL), 3% aq $KHCO_3$ solution (3× 15 mL), water (5× 10 mL) and ethanol (5 mL), and dried at temperatures gradually increasing to 90 °C.

In this manner, the following carboxylates were obtained.

4.3.1. Ethyl 3-anilino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (14). Starting from benzodithiazinecarbonyl chloride **10** (11.62 g), the title compound **14** was obtained (11.6 g, 97%): mp 222–223 °C; IR (KBr) 3285 (NH), 1720 (C═O), 1315, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.36 (t, J = 7.1 Hz, 3H, CH_3), 4.39 (q, J = 7.1 Hz, 2H, CH_2), 7.29–7.67 (m, 5H, Ph), 8.22 (s, 1H, H-5), 8.38 (s, 1H, H-8), 11.67 (s, 1H, NH) ppm. Anal. Calcd for $C_{16}H_{13}ClN_2O_4S_2$ (396.87): C, 48.42; H, 3.30; N, 7.05. Found: C, 48.60; H, 3.39; N, 6.99.

4.3.2. Ethyl 6-chloro-3-(4-chloroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (15). Starting from benzodithiazinecarbonyl chloride **11** (12.65 g), the title compound **15** was obtained (12.5 g, 96%): mp 263–264 °C; IR (KBr) 3275 (NH), 1685 (C═O), 1350, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.33 (t, J = 7.3 Hz, 3H, CH_3), 4.36 (q, J = 7.3 Hz, 2H, CH_2), 7.51 (d, J = 7.8 Hz, 2H, 4-ClPh), 7,67 (d, J = 7,8 Hz, 2H, 4-ClPh), 8.19 (s, 1H, H-5), 8.35 (s, 1H, H-8), 11.27 (s, 1H, NH) ppm. Anal. Calcd for $C_{16}H_{12}Cl_2N_2O_4S_2$ (431,33): C, 44,55; H, 2.80; N, 6.49. Found: C, 44.62; H, 2.89; N, 6.47.

4.3.3. Ethyl 6-chloro-3-(4-methoxyanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (16). Starting from benzodithiazinecarbonyl chloride **12** (12.52 g), the title

compound **16** was obtained (10.1 g, 78%): mp 232–233 °C; IR (KBr) 3260 (NH), 1720 (C=O), 1305, 1160, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.34 (t, J = 7.1 Hz, 3H, CH_3), 3.77 (s, 3H, CH_3O), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 7.01 (d, J = 8.4 Hz, 2H, 4-MeOPh), 7,52 (d, J = 8.4 Hz, 2H, 4-MeOPh), 8.19 (s, 1H, H-5), 8.33 (s, 1H, H-8), 11.52 (s, 1H, NH) ppm. Anal. Calcd for $C_{17}H_{15}ClN_2O_5S_2$ (426.90): C, 47.93; H, 3.54; N, 6.56. Found: C, 47.82; H, 3.68; N, 6.60.

4.3.4. Ethyl 6-chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (17). Starting from benzodithiazinecarbonyl chloride **13** (12.16 g), the title compound **17** was obtained (11.5 g, 92%): mp 248–249 °C; IR (KBr) 3270 (NH), 1685 (C=O), 1325, 1170, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.34 (t, J = 7.1 Hz, 3H, CH_3), 4.38 (q, J = 7.1 Hz, 2H, CH_2), 7.29–7.33 (m, 2H, 4-FPh), 7.50–7.65 (m, 2H, 4-FPh), 8.22 (s, 1H, H-5), 8.35 (s, 1H, H-8), 11.66 (s, 1H, NH) ppm. Anal. Calcd for $C_{16}H_{13}ClFN_2O_4S_2$ (415.87): C, 46.21; H, 3.15; N, 6.73. Found: C, 46.32; H, 3.21; N, 6.78.

4.4. Synthesis of 8-quinolyl 6-chloro-3-(4-fluoroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (18)

To a solution of 8-hydroxyquinoline (2.25 g, 0.0155 mol) in anhyd *p*-dioxane (50 mL) benzodithiazinecarbonyl chloride **13** (6.1 g, 0.015 mol) was added portionwise with stirring. The reaction mixture was stirred at room temperature for 2 h, followed at reflux for 4 h. After cooling to room temperature and standing overnight the precipitate of the crude benzodithiazine hydrochloride (**18**·**HCl**) was collected by filtration, washed with *p*-dioxane (3× 5 mL), and dried (7.8 g, 94%); mp 171–174 °C dec; IR (KBr) 3245 (NH), 2850, 2560, 2435, 2320, 2250 (NH^+), 1760 (C=O), 1315, 1160 (SO_2) cm^{-1}. Anal. Calcd for $C_{23}H_{14}Cl_2FN_3O_4S_2$ (550.42): N, 7.63. Found: N, 7.36. The crude benzodithiazine hydrochloride **18**·**HCl** (7.7 g, 0.014 mol) was added to a solution of $KHCO_3$ (1.6 g, 0.016 mol) in water (100 mL), and the reaction mixture was stirred at room temperature for 1 h. The precipitate of title product **18** was collected by filtration, washed thoroughly with water and acetone (2× 2 mL), and dried, at temperatures gradually increasing to 100 °C (5.8 g, 75%); mp 277–278 °C dec; IR (KBr) 3265 (NH), 1760 (C=O), 1625 (C=N), 1320, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.33 (t, J = 8.3 Hz, 2H, H-3, and H-6, quinoline), 7.63–7.67 (m, 4H, 4-FPh), 8.02 (d, J = 8.3 Hz, 1H, quinoline), 8.37 (s, 1H, H-5, benzodithiazine), 8.52 (d, J = 8.3 Hz, 1H, quinoline), 8.83 (s, 1H, H-8, benzodithiazine) 8.92 (d, J = 8.3 Hz, 1H, quinoline), 11.74 (s, 1H, NH) ppm. Anal. Calcd for $C_{23}H_{13}ClFN_3O_4S_2$ (513.75): C, 53.75; H, 2.55; N, 8.17. Found: C, 53.70; H, 2.64; N, 8.19.

4.5. Procedure for the preparation of 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxamides (19 and 20)

To an ice-cold suspension of the appropriate 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride **10** and **11** (0.05 mol) in benzene (200 mL) 28% ammonia solution (25 mL) was added dropwise with stirring. After 1 h the ice-bath was removed and the reaction mixture was stirred at room temperature for 10 h. The precipitate of the adequate carboxamide formed was filtered off, washed thoroughly with water, and dried. In this manner, the following carboxamides were obtained.

4.5.1. 3-Anilino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxamide (19). Starting from benzodithiazinecarbonyl chloride **10** (19.4 g), the title compound **19** was obtained (17.5 g, 95%): mp 307–308 °C; IR (KBr) 3435, 3325, 3255, 3200 (NH_2 and NH), 1675 (C=O), 1610 (C=N), 1325, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38–7.67 (m, 5H, Ph), 7.87 (s, 1H, CON-H_a), 7.99 (s, 1H, H-5), 8.14 (s, 1H, H-8), 8.19 (s, 1H, $CONH_b$), 11.60 (s, 1H, NH) ppm. Anal. Calcd for $C_{14}H_{10}ClN_3O_3S_2$ (367.84): C, 45.71; H, 2.74; N, 11.42. Found: C, 45.66; H, 2.80; N, 11.47.

4.5.2. 6-Chloro-3-(4-chloroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carboxamide (20). Starting from benzodithiazinecarbonyl chloride **11** (21.1 g), the title compound **20** was obtained (19.5 g, 97%): mp 317–318 °C dec; IR (KBr) 3440, 3340 (NH_2), 3280 (NH), 1660 (C=O), 1610 (C=N), 1320, 1155, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.59 (d, J = 8.8 Hz, 2H, 4-ClPh), 7.69 (d, J = 8.8 Hz, 2H, 4-ClPh), 7.88 (s, 1H, $CONH_a$), 8.00 (s, 1H, H-5), 8.15 (s, 1H, H-8), 8.19 (s, 1H, $CONH_b$), 11.67 (s, 1H, NH) ppm. Anal. Calcd for $C_{14}H_9ClN_3O_3S_2$ (402.29): C, 41.80; H, 2.25; N, 10.44. Found: C, 41.76; H, 2.41; N, 10.40.

4.6. Procedure for the preparation of 3-(arylamino)-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonitriles (21–22)

A stirred mixture of the appropriate carboxamide **19** and **20** (0.04 mol) and phosphorus oxychloride (130 mL) was refluxed for 25 h. After cooling to room temperature the precipitate was collected by filtration and then was poured onto crushed ice (700 g) with vigorously stirring for at least 1 h. The precipitate of the adequate nitrile was filtered off, washed thoroughly with several portions of cold water (pH 7) and acetone (4× 3 mL), and dried.

In this manner, the following nitriles were obtained.

4.6.1. 3-Anilino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carbonitrile (21). Starting from carboxamide **19** (14.7 g), the title compound **21** was obtained (13.1 g, 93%): mp 292-294 °C; IR (KBr) 3285 (NH), 2230 (C≡N), 1610 (C=N), 1330, 1310, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.44–7.66 (m, 5H, Ph), 8.39 (s, 1H, H-5), 8.61 (s, 1H, H-8), 11,74 (s, 1H, NH) ppm. Anal. Calcd for $C_{14}H_8ClN_3O_2S_2$ (349.82): C, 48.07; H, 2.30; N, 12.01. Found: C, 48.12; H, 2.41; N, 12.02.

4.6.2. 6-Chloro-3-(4-chloroanilino)-1,1-dioxo-1,4,2-benzodithiazine-7-carbonitrile (22). Starting from carboxamide **20** (16.1 g), the title compound **22** was obtained (13.9 g, 90%): mp 281–282 °C; IR (KBr) 3275 (NH),

2235 (C=N), 1608 (C=N), 1345, 1320, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.52 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 7.66 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 8.37 (s, 1H, H-5), 8.60 (s, 1H, H-8), 11,82 (s, 1H, NH) ppm. Anal. Calcd for $C_{14}H_7Cl_2N_3O_2S_2$ (384.28): C, 43.75; H, 1.84; N, 10.93. Found: C, 43.68; H, 2.00; N, 10.90.

4.7. General procedure for the preparation of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides (23–48)

To a suspension of the corresponding 3-aminobenzodithiazine **2–5**, **14–20** (8 mmol) in dry pyridine (1.8 mL/1 g) the appropriate arylsulfonyl chloride (9 mmol) was added with stirring.

The solution obtained was stirred at room temperature for 8 h, followed at 50–55 °C for 3 h. After cooling to room temperature the suspension was left overnight. The precipitate was collected by filtration, washed successively with pyridine (2× 1 mL), and toluene (4× 4 mL), dried, and purified by crystallization from acetonitrile.

In this manner, the following sulfonamides were obtained.

4.7.1. *N*-(4-Chlorophenyl)-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamide (23). Starting from aminobenzodithiazine **2** (2.99 g) and benzenesulfonyl chloride (1.6 g) the title compound **23** was obtained (2.8 g, 68%): mp 233–235 °C; IR (KBr) 1590 (C=N), 1365, 1345, 1325, 1180, 1155 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 7.27 (d, $J = 8.7$ Hz, 2H, 4-ClPh), 7.55 (d, $J = 8.7$ Hz, 2H, 4-ClPh), 7.60–7.66 (m, 3H, $PhSO_2$ and H-5), 7.73 (t, $J = 7.4$ Hz, 1H, $PhSO_2$), 7.96 (s, 1H, H-8), 8.13 (d, $J = 7.4$ Hz, 2H, $PhSO_2$) ppm. Anal. Calcd for $C_{20}H_{14}Cl_2N_2O_4S_3$ (513.44): C, 46.78; H, 2.75; N, 5.45. Found: C, 46.71; H, 2.82; N, 5.49.

4.7.2. *N*-(4-Chlorophenyl)-*N*-(6-chloro-7-methyl-1,1-dioxo- 1,4,2-benzodithiazin-3-yl)-5-bromothiophene-2-sulfonamide (24). Starting from aminobenzodithiazine **2** (2.99 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **24** was obtained (3.8 g, 79%): mp 192–194 °C; IR (KBr) 1590 (C=N), 1385, 1355, 1335, 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.45 (s, 3H, CH_3), 7.19 (d, $J = 3.9$ Hz, 1H, H-4, thiophene), 7.25 (s, 1H, H-5, benzodithiazine), 7.35 (d, $J = 8.7$ Hz, 2H 4-ClPh), 7.54 (d, $J = 8.7$ Hz, 2H, 4-ClPh), 7.83 (d, $J = 3.9$ Hz, 1H, H-3, thiophene), 8.01 (s, 1H, H-8, benzodithiazine) ppm; ^{13}C NMR ($CDCl_3$)δ 20.34, 125.30, 127.27, 127.78, 127.89, 127.94, 131.01, 131.22, 132.11, 132.73, 136.89, 138.46, 138.85, 139.40, 139.72, 162.37 ppm.

Anal. Calcd for $C_{18}H_{11}BrCl_2N_2O_4S_4$ (598.37): C, 36.13; H, 1.85; N, 4.68. Found: C, 36.18; H, 1.96; N, 4.72.

4.7.3. *N*-(2-Chlorophenyl)-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-5-bromothiophene-2-sulfonamide (25). Starting from aminobenzodithiazine **3** (2.99 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **25** was obtained (2.4 g, 50%): mp 217–218 °C; IR (KBr) 1585 (C=N), 1385, 1350, 1335, 1180, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH_3), 7.53 (d, $J = 3.9$ Hz, 1H, H-4, thiophene), 7.60–7.62 (m, 1H, 2-ClPh), 7.70-7.74 (m, 1H, 2-ClPh), 7.79–7.82 (m, 2H, 2-ClPh), 7.84 (d, $J = 3.9$ Hz, 1H, H-3, thiophene), 7.92 (s, 1H, H-5, benzodithiazine), 8.14 (s, 1H, H-8, benzodithiazine) ppm. Anal. Calcd for $C_{18}H_{11}BrCl_2N_2O_4S_4$ (598.37): C, 36.13; H, 1.85; N, 4.68. Found: C, 36.02; H, 1.98; N, 4.63.

4.7.4. *N*-(Dimethylamino)-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-chlorobenzenesulfonamide (26). Starting from hydrazinobenzodithiazine **4** (2.4 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **26** was obtained (1.5 g, 50%): mp 170–171 °C dec; IR (KBr) 1575 (C=N), 1370, 1345, 1180, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3-7), 3.11 (s, 6H, CH_3NCH_3), 7.78 (d, $J = 8.9$ Hz, 2H, 4-ClPh), 7.95 (s, 1H, H-5), 7.98 (s, 1H, H-8), 8.08 (d, $J = 8.9$ Hz, 2H, 4-ClPh) ppm; ^{13}C NMR (DMSO-d_6)δ 19.56, 44.98, 126.86, 127.13, 128.52, 128.79, 129.83, 131.67, 136.02, 138.14, 138.84, 140.61, 164.59, ppm. Anal. Calcd for $C_{16}H_{15}Cl_2N_3O_4S_3$ (480.40): C, 40.00; H, 3.14; N, 8.75. Found: C, 40.12; H, 3.11; N, 8.90.

4.7.5. Methyl 6-chloro-3-[*N*-(dimethylamino)-4-chlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (27). Starting from hydrazinobenzodithiazine **5** (2.8 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **27** was obtained (1.5 g, 43%): mp 180–181 °C dec; IR (KBr) 1740 (C=O), 1590 (C=N), 1360, 1340, 1330, 1185, 1170 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.13 (s, 6H, CH_3NCH_3), 3.88 (s, 3H, CH_3O), 7.79 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 8.09 (d, $J = 8.8$ Hz, 2H, 4-ClPh), 8.17 (s, 1H, H-5), 8.31 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6) δ 44.98, 53.38, 127.05, 127.19, 127.51, 129.88, 130.89, 131.74, 135.47, 135.79, 136.09, 140.76, 163.54, 164.31 ppm. Anal. Calcd for $C_{17}H_{15}Cl_2N_3O_6S_3$ (524.43): C, 38.96; H, 2.88; N, 8.02. Found: C, 36.91; H, 2.90; N, 8.16.

4.7.6. Methyl 6-chloro-3-[*N*-(dimethylamino)-2,4-dichlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (28). Starting from hydrazinobenzodithiazine **5** (2.8 g) and 2,4-dichlorobenzenesulfonyl chloride (2.21 g) the title compound **28** was obtained (1.5 g, 33%): mp 236–238 °C dec; IR (KBr) 1730 (C=O), 1580 (C=N), 1375, 1345, 1335, 1175, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 3.18 (s, 6H, CH_3NCH_3), 3.87 (s, 3H, CH_3O), 7.99 (dd, $J_{ortho} = 8.8$ Hz, $J_{meta} = 2.1$ Hz, 1H, H-5, 2,4-doClPh), 8.00 (d, $J_{meta} = 2.1$ Hz, H-3, 2,4-diClPh), 8.19 (d, $J_{ortho} = 8.8$ Hz, 1H, H-6, 2,4-diClPh), 8.21 (s, 1H, H-5), 8.27 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6)δ 45.14, 53.38, 127.19, 127.57, 128.76, 130.98, 131.16, 132.04, 133.10, 134.69, 135.12, 135.21, 136.14, 141.26, 163.53, 164.83 ppm. Anal. Calcd for $C_{17}H_{14}Cl_3N_3O_6S_3$ (558.87): C, 36.53; H, 2.52; N, 7.52. Found: C, 36.54; H, 2.70; N, 7.61.

4.7.7. Methyl 6-chloro-3-[*N*-(dimethylamino)benzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (29). Starting from hydrazinobenzodithiazine **5** (2.8 g) and 2,4-dichlorobenzenesulfonyl chloride

(1.59 g) the title compound **29** was obtained (3.1 g, 79%): mp 234–236 °C dec; IR (KBr) 1740 (C=O), 1585 (C=N), 1370, 1325, 1170, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 3.14 (s, 6H, CH_3NCH_3), 3.87 (s, 3H, CH_3O), 7.68–7.87 (m, 3H, $PhSO_2$), 8.07-8.12 (m, 2H, $PhSO_2$), 8.16 (s, 1H, H-5), 8.30 (s, 1H, H-8) ppm. Anal. Calcd for $C_{17}H_{16}ClN_3O_6S_3$ (489.98): C, 46.67; H, 3.29; N, 8.57. Found: C, 46.65; H, 3.36; N, 8.56.

4.7.8. Methyl 6-chloro-3-[*N*-(dimethylamino)-5-bromothiophene-2-sulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (30). Starting from hydrazinobenzodithiazine **5** (2.8 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **30** was obtained (1.9 g, 41%): mp 185–187 °C dec; IR (KBr) 1745 (C=O), 1585 (C=N), 1380, 1330, 1175, 1165, 1135 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 3.08 (s, 6H, CH_3NCH_3), 3.89 (s, 3H, CH_3O), 7.52 (d, J = 4.2 Hz, 1H, H-4, thiophene), 7.89 (d, J = 4.2 Hz, 1H, H-3, thiophene), 8.20 (s, 1H, H-5), 8.37 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6) δ 44.75, 53.39, 125.26, 127.14, 127.58, 130.94, 131.11, 132.09, 135.56, 136.15, 137.35, 138.83, 163.56, 164.31 ppm. Anal. Calcd for $C_{15}H_{13}BrClN_3O_6S_4$ (574.90): C, 31.34; H, 2.28; N, 7.31. Found: C, 31.30; H, 2.35; N, 7.52.

4.7.9. Ethyl 6-chloro-3-[*N*-phenyl-4-chlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (31). Starting from aminobenzodithiazine **14** (3.17 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **31** was obtained (3.2 g, 70%): mp 236–237 °C; IR (KBr) 1730 (C=O), 1380, 1370, 1345, 1185, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.31 (t, J = 7.0 Hz, 3H, CH_3), 4.36 (q, J = 7.0 Hz, 2H, CH_2), 7.67 (s, 5H, Ph), 7.82 (d, J = 8.4 Hz, 2H, 4-ClPh), 8.04 (s, 1H, H-5), 8.08 (d, J = 8.4 Hz, 2H, 4-ClPh), 8.34 (s, 1H, H-8) ppm. Anal. Calcd for $C_{22}H_{16}Cl_2N_2O_6S_4$ (571.49): C, 46.23; H, 2.82; N, 4.90. Found: C, 46.32; H, 2.97; N, 4.97.

4.7.10. Ethyl 6-chloro-3-[*N*-phenyl-4-nitrobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (32). Starting from aminobenzodithiazine **14** (3.17 g) and 4-nitrobenzenesulfonyl chloride (2.0 g) the title compound **32** was obtained (3.7 g, 79%): mp 200–201 °C; IR (KBr) 1740 (C=O), 1535, 1260 (NO_2), 1380, 1350, 1185, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.74 (s, 5H, Ph), 8.07 (s, 1H, H-5), 8.35 (s, 1H, H-8), 8.37 (d, J = 8.8 Hz, 2H, 4-O_2NPh), 8.53 (d, J = 8.8 Hz, 2H, 4-O_2NPh) ppm. Anal. Calcd for $C_{22}H_{16}ClN_3O_8S_3$ (582.04): C, 45.40; H, 2.77; N, 7.22. Found: C, 45.49; H, 2.90; N, 7.11.

4.7.11. Ethyl 6-chloro-3-[*N*-phenyl-5-bromothiophene-2-sulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (33). Starting from aminobenzodithiazine **14** (3.17 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **33** was obtained (4.0 g, 80%): mp 209–210 °C; IR (KBr) 1735 (C=O), 1390, 1380, 1345, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 7.54 (d, J = 4.2 Hz, 1H, H-4, thiophene), 7.36–7.68 (m, 5H, Ph), 7.80 (d, J = 4.2 Hz, 1H, H-3, thiophene), 8.07 (s, 1H, H-5), 8.40 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{14}BrClN_2O_6S_4$ (621.95): C, 38.62; H, 2.26; N, 4.50. Found: C, 48.54; H, 2.35; N, 4.50.

4.7.12. Ethyl 6-chloro-3-[*N*-(4-chlorophenyl)-5-bromothiophene-2-sulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (34). Starting from aminobenzodithiazine **15** (3.45 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **34** was obtained (4.0 g, 76%): mp 245–246 °C dec; IR (KBr) 1730 (C=O), 1370, 1345, 1185, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 7.54 (d, J = 4.1 Hz, 1H, H-4, thiophene), 7.68 (d, J = 9.6 Hz, 2H, 4-ClPh), 7.73 (d, J = 9.6 Hz, 2H, 4-ClPh), 7.80 (d, J = 4.1 Hz, 1H, H-3, thiophene), 8.11 (s, 1H, H-5), 8.41 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{13}BrCl_2N_2O_6S_4$ (656.40): C, 35.59; H, 1.99; N, 4.26. Found: C, 35.57; H, 2.10; N, 4.28.

4.7.13. Ethyl 6-chloro-3-[*N*-(4-methoxyphenyl)-4-chlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (35). Starting from aminobenzodithiazine **16** (3.44 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **35** was obtained (3.9 g, 81%): mp 261–263 °C; IR (KBr) 1730 (C=O), 1605 (C=N), 1370, 1345, 1185, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.31 (t, J = 7.0 Hz, 3H, CH_3), 3.88 (s, 3H, CH_3O), 4.34 (q, J = 7.0 Hz, 2H, CH_2), 7.16 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.57 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.82 (d, J = 8.8 Hz, 2H, 4-ClPhSO_2), 8.04 (d, J = 8.8 Hz, 2H, 4-ClPhSO_2), 8.08 (s, 1H, H-5), 8.33 (s, 1H, H-8) ppm. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_7S_3$ (601.51): C, 45.92; H, 3.01; N, 4.65. Found: C, 45.90; H, 3.12; N, 4.71.

4.7.14. Ethyl 6-chloro-3-[*N*-(4-methoxyphenyl)-2,4-dichlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (36). Starting from aminobenzodithiazine **16** (3.44 g) and 2,4-dichlorobenzenesulfonyl chloride (2.21 g) the title compound **36** was obtained (3.3 g, 64%): mp 229–231 °C; IR (KBr) 1720 (C=O), 1600 (C=N), 1380, 1340, 1180, 1165, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.31 (t, J = 7.1 Hz, 3H, CH_3), 3.88 (s, 3H, CH_3O), 4.34 (q, J = 7.1 Hz, 2H, CH_2), 7.20 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.67 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.83 (d, J_{ortho} = 8.5 Hz, 1H, 2,4-diClPhSO_2), 7.95 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.6 Hz, 1H, 2,4-diClPhSO_2), 8.09 (s, 1H, H-5), 8.29 (d, J_{meta} = 2.6 Hz, 1H, 2,4-diClPhSO_2), 8.30 (s, 1H, H-8) ppm. Anal. Calcd for $C_{23}H_{17}Cl_3N_2O_7S_3$ (635.95): C, 43.44; H, 2.69; N, 4.40. Found: C, 43.48; H, 2.76; N, 4.50.

4.7.15. Ethyl 6-chloro-3-[*N*-(4-methoxyphenyl)benzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (37). Starting from aminobenzodithiazine **16** (3.44 g) and benzenesulfonyl chloride (1.59 g) the title compound **37** was obtained (3.8 g, 83%): mp 219–221 °C; IR (KBr) 1730 (C=O), 1605 (C=N), 1370, 1340, 1185, 1170, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.31 (t, J = 7.0 Hz, 3H, CH_3), 3.89 (s, 3H, CH_3O), 4.34 (q, J = 7.0 Hz, 2H, CH_2), 7.19 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.55 (d, J = 9.0 Hz, 2H, 4-MeOPh), 7.69–7.85 (m, 3H, $PhSO_2$), 8.04 (m, 2H, $PhSO_2$), 8.08 (s, 1H, H-5), 8.32 (s, 1H, H-8) ppm. Anal.

Calcd for $C_{23}H_{19}ClN_2O_7S_3$ (567.06): C, 48.72; H, 3.37; N, 4.94. Found: C, 48.82; H, 3.44; N, 4.87.

4.7.16. Ethyl 6-chloro-3-[*N*-(4-fluorophenyl)-4-methoxybenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (38). Starting from aminobenzodithiazine **17** (3.33 g) and 4-methoxybenzenesulfonyl chloride (1.86 g) the title compound **38** was obtained (3.3 g, 70%): mp 223–224 °C; IR (KBr) 1725 (C=O), 1590 (C=N), 1365, 1340, 1170, 1135 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 3.89 (s, 3H, CH_3O), 4.35 (q, J = 7.1 Hz, 2H, CH_2), 7.23 (d, J = 9.1 Hz, 2H, 4-MeOPh), 7.46–7.54 (m, 2H, 4-FPh), 7.66–7.73 (m, 2H, 4-FPh), 7.99 (d, J = 9.1 Hz, 2H, 4-MeOPh), 8.06 (s, 1H, H-5), 8.35 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6) δ 14.17, 56.39, 62.50, 115.02, 117.54, 118.00, 127.22, 127.46, 128.01, 131.18, 131.70, 132.49, 133.74, 133.94, 136.10, 162.44, 163.15, 164.81, 166.30 ppm. Anal. Calcd for $C_{23}H_{18}ClFN_2O_7S_3$ (585.05): C, 47.22; H, 3.10; N, 4.78. Found: C, 47.20; H, 3.16; N, 4.85.

4.7.17. Ethyl 6-chloro-3-[*N*-(4-fluorophenyl)-4-chlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (39). Starting from aminobenzodithiazine **17** (3.33 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **39** was obtained (3.0 g, 61%): mp 235–237 °C; IR (KBr) 1730 (C=O), 1605 (C=N), 1370, 1345, 1180, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.31 (t, J = 7.1 Hz, 3H, CH_3), 4.34 (q, J = 7.1 Hz, 2H, CH_2), 7.47–7.56 (m, 2H, arom.), 7.74–7.83 (m, 4H, arom.), 8.06 (d, J = 9.8 Hz, 2H, 4-ClPhSO_2), 8.09 (s, 1H, H-5), 8.34 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6)δ 14.14, 62.51, 117.61, 118.07, 127.29, 129.97, 131.18, 131.77, 133.58, 133.92, 134.12, 135.97, 136.17, 140.77, 161.45, 162.65, 163.12, 166.43 ppm. Anal. Calcd for $C_{22}H_{15}Cl_2FN_2O_6S_3$ (589.48): C, 48.82; H, 2.56; N, 4.75. Found: C, 48.79; H, 2.61; N, 4.77.

4.7.18. Ethyl 6-chloro-3-[*N*-(4-fluorophenyl)-5-bromothiophene-2-sulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (40). Starting from aminobenzodithiazine **17** (3.33 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **40** was obtained (3.2 g, 65%): mp 211–212 °C; IR (KBr) 1730 (C=O), 1600 (C=N), 1370, 1340, 1175, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 7.44–7.53 (m, 2H, 4-FPh), 7.54 (d, J = 4.2 Hz, 1H, H-4, thiophene), 7.69–7.76 (m, 2H, 4-FPh), 7.80 (d, J = 4.2 Hz, 1H, H-3, thiophene), 8.09 (s, 1H, H-5), 8.41 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{13}BrClFN_2O_6S_3$ (607.87): C, 39.52; H, 2.15; N, 4.60. Found: C, 39.49; H, 2.18; N, 4.59.

4.7.19. 8-Quinolyl 6-chloro-3-[*N*-(4-fluorophenyl)-4-chlorobenzenesulfonamido]-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (41). Starting from aminobenzodithiazine **18** (4.11 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **41** was obtained (3.0 g, 54%): mp 236–237 °C; IR (KBr) 1760 (CP=O), 1590 (C=N), 1385, 1340, 1175, 1170, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.45–7.85 (m, 8H, arom.), 7.99–8.17 (m, 4H, arom.), 8.22 (s, 1H, H-8, benzodithiazine), 8.50 (d, J = 8.3 Hz, 1H, quinoline), 8.86 (d, J = 11.4 Hz, 2H, 4-ClPhSO_2) ppm. Anal. Calcd for $C_{29}H_{16}Cl_2FN_3O_6S_3$ (688.57): C, 50.58; H, 2.34; N, 6.10. Found: C, 50.63; H, 2.29; N, 6.26.

4.7.20. 8-Quinolyl 6-chloro-3-[*N*-(4-fluorophenyl)-5-bromothiophene-2-sulfonamido]-1,1- dioxo-1,4,2-benzodithiazine-7-carboxylate (42). Starting from aminobenzodithiazine **18** (4.11 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **42** was obtained (3.3 g, 55%): mp 234–235 °C; IR (KBr) 1750 (C=O), 1600 (C=N), 1395, 1385, 1330, 1175, 1175, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.47–7.83 (m, 9H, arom.), 7.88 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 1.6 Hz, 1H, quinoline), 8.24 (s, 1H, H-5, benzodithiazine), 8.51 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 1.6 Hz, 1H, quinoline), 8.87 (s, 1H, H-8, benzodithiazine), 8.91 (dd, J_{ortho} = 4.2 Hz, J_{meta} = 1.6 Hz, 1H, quinoline) ppm. Anal. Calcd for $C_{27}H_{14}BrClFN_3O_6S_4$ (739.04): C, 43.88; H, 1.91; N, 5.68. Found: C, 43.81; H, 2.03; N, 5.75.

4.7.21. *N*-(6-Chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-*N*-phenyl-4-nitrobenzenesulfonamide (43). Starting from aminobenzodithiazine **21** (2.8 g) and 4-nitrobenzenesulfonyl chloride (2.0 g) the title compound **43** was obtained (2.7 g, 63%): mp 270–271 °C; IR (KBr) 2235 (C=N), 1605 (C=N), 1375, 1350, 1335, 1170 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.42 (s, 5H, Ph), 8.25 (s, 1H, H-5), 8.36 (d, J = 8.4 Hz, 2H, 4-O_2NPh), 8.54 (d, J = 8.4 Hz, 2H, 4-O_2NPh), 8.71 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{11}ClN_4O_6S_3$ (534.98): C, 44.90; H, 2.07; N, 10.42. Found: C, 45.06; H, 2.11; N, 10.52.

4.7.22. *N*-(6-Chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-*N*-phenyl-3-nitrobenzenesulfonamide (44). Starting from aminobenzodithiazine **21** (2.8 g) and 3-nitrobenzenesulfonyl chloride (2.0 g) the title compound **44** was obtained (3.1 g, 72%): mp 244–246 °C; IR (KBr) 2230 (CtbondN), 1375, 1355, 1340 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.74 (s, 5H, Ph), 8.05 (t, J = 8.1 Hz, 1H, 3-O_2NPh), 8.24 (s, 1H, H-5), 8.47 (dd, J_{ortho} 8.1 Hz, J_{meta} = 1.8 Hz, 1H, 3-O_2NPh), 8.68 (dd, J_{ortho} = 8.1 Hz, J_{meta} = 1.8 Hz, 1H, 3-O_2NPh), 8.71 (s, 1H, H-8), 8.77 (t, J_{meta} 1.8 Hz, 1H, 3-O_2NPh) ppm. Anal. Calcd for $C_{20}H_{11}ClN_4O_6S_3$ (534.98): C, 44.90; H, 2.07; N, 10.42. Found: C, 44.91; H, 2.10; N, 10.59.

4.7.23. *N*-(6-Chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-*N*-phenyl-4-chlorobenzenesulfonamide (45). Starting from aminobenzodithiazine **21** (2.8 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **45** was obtained (3.5 g, 83%): mp 256–258 °C; IR (KBr) 2235 (C≡N), 1380, 1345, 1335, 1175, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.69 (s, 5H, Ph), 7.85 (d, J = 8.9 Hz, 2H, 4-ClPh), 8.09 (d, J = 8.9 Hz, 2H, 4-ClPh), 8.23 (s, 1H, H-5), 8.69 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{11}Cl_2N_3O_4S_3$ (524.43): C, 45.80; H, 2.11; N, 8.01. Found: C, 45.84; H, 2.15; N, 8.20.

4.7.24. *N*-(6-Chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-*N*-phenyl-5-bromothiophene-2-sulfonamide (46). Starting from aminobenzodithiazine **21** (2.8 g) and 5-bromothiophene-2-sulfonyl chloride (2.35 g) the title compound **46** was obtained (3.3 g, 71%): mp

246–247 °C dec; IR (KBr) 2235 (C≡N), 1390, 1380, 1345, 1180, 1170 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.57 (d, J = 4.2 Hz, 1H, H-4, thiophene), 7.62–7.73 (m, 5H, Ph), 7.83 (d, J = 4.2 Hz, 1H, H-3, thiophene), 8.25 (s, 1H, H-5), 8.77 (s, 1H, H-8) ppm. Anal. Calcd for $C_{18}H_9BrClN_3O_4S_4$ (574.90): C, 37.60; H, 1.58; N, 7.31. Found: C, 37.58; H, 1.64; N, 7.33.

4.7.25. *N*-(4-Chlorophenyl)-*N*-(6-chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-chlorobenzenesulfonamide (47). Starting from aminobenzodithiazine **22** (3.07 g) and 4-chlorobenzenesulfonyl chloride (1.9 g) the title compound **47** was obtained (3.1 g, 69%): mp 280–281 °C; IR (KBr) 2235 (C≡N), 1375, 1345, 1330, 1170, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.74 (s, 4H, 4-ClPhN), 7.82 (d, J = 8.8 Hz, 2H, 4-ClPhSO_2), 8.06 (d, J = 8.8 Hz, 2H, 4-ClPhSO_2), 8.24 (s, 1H, H-5), 8.69 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_{10}Cl_3N_3O_4S_3$ (558.87): C, 42.98; H, 1.80; N, 7.52. Found: C, 43.06; H, 1.83; N, 7.54.

4.7.26. *N*-(4-Chlorophenyl)-*N*-(6-chloro-7-cyano-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-3-chloro-4-fluorobenzenesulfonamide (48). Starting from aminobenzodithiazine **22** (3.07 g) and 3-chloro-4-fluorobenzenesulfonyl chloride (2.06 g) the title compound **48** was obtained (3.3 g, 71%): mp 253–255 °C; IR (KBr) 2235 (C≡N), 1390, 1380, 1340, 1180, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6)δ 7.76 (s, 4H, 4-ClPhN), 7.83 (d, J_{ortho} = 8.8 Hz, 1H, H-5, 3-Cl-4-FPh), 8.02-8.10 (m, 1H, H-2, 3-Cl-4-FPh), 8.26 (s, 1H, H-5, benzodithiazine), 8.31 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.4 Hz, 1H, H-6, 3-Cl-4-FPh), 8.72 (s, 1H, H-8) ppm. Anal. Calcd for $C_{20}H_9Cl_3FN_3O_4S_3$ (576.86): C, 41.64; H, 1.57; N, 7.28. Found: C, 41.58; H, 1.69; N, 7.23.

4.8. X-ray structure analysis of 23

Crystal data for $C_{20}H_{14}Cl_2N_2O_4S_3$: triclinic, space group P-1, a = 9.5300 (7) Å, b = 10.5007 (7) Å, c = 12.5199 (10) Å, α = 66.112 (7)°, β = 77.284 (7)°, γ = 68.496 (7)°, V = 1062.03(14) Å^3, Z = 2, d_x = 1.605 g cm^{-3}, μ(Mo K_α) = 0.633 mm^{-1}, T = 130 K. Data were collected for a crystal with dimensions 0.5 × 0.5 × 0.3 mm with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. Final R indices for 3630 reflections with $I > 2\sigma(I)$ and 280 refined parameters are: R_1 = 0.0327, wR_2 = 0.0844 (R_1 = 0.0392, wR_2 = 0.0881 for all 4305 data). Atom labeling is shown in Fig. 2.

Supporting information available: Crystallographic data for compound **23** have been deposited at Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 619225). Copies of the data can be obtained upon request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, quoting the deposition number.

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