



Pergamon

Synthesis and Anticancer Activity of 2-Amino-8-chloro-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine Derivatives

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Abstract—A new series of 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-arylsemicarbazides (**4–16**) were obtained. Intramolecular ring closure in semicarbazides **4–16** upon treatment with phosphorus oxychloride resulted in the formation of 2-amino-8-chloro-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29** with potential antitumor activity. The structures of these compounds were confirmed on the basis of elemental analysis, spectral data and X-ray analysis. Compounds **17–29** were screened at the US National Cancer Institute (NCI) for their activities against a panel of 59 tumor cell lines, and relationships between structure and antitumor activity in vitro are discussed. The benzodithiazines **18**, **19**, **23**, **28** and **29** were inactive, whereas the other compounds exhibited reasonable activity against numerous human tumor cell lines. The prominent compound **17** showed significant activity against the leukemia SR cell line (log GI₅₀ = −7.67, log TGI = −6.90 and log LC₅₀ = −4.77).

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Introduction

The sulfonamides constitute an important class of therapeutic agents in current medicinal science and various structurally novel sulfonamide derivatives have recently been reported to show substantial antitumor and anti-HIV activities.^{1–4} Although they have a common chemical motif of an 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- κ B, angiogenesis inhibition as well as carbonic anhydrase inhibition.⁵ Our systematic studies on the synthesis of 1,4,2-benzodithiazine 1,1-dioxides, and their subsequent transformation into *N*-(azolyl or azinyl)-2-mercaptobenzenesulfonamides (**I**, **MBSAs**) resulted in promising anticancer agents^{6–13} or potent inhibitors of HIV-1 integrase.^{14–17} We also found that cyclic sulfonamide derivatives of 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine of type **II** possessed interesting anticancer properties (Fig. 1).^{18,19} This prompted us to investigate further the chemistry and biological activity of the related new heterocyclic ring system **III**.

Results and Discussion

The reaction of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine **1–3** with the appropriate 4-arylsemicarbazides²⁰ were performed in boiling methanol to give 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-arylsemicarbazides **4–16**. When the semicarbazides **4–16**, in turn, were subjected to the reaction with POCl₃ the target 8-chloro-2-arylamino-5,5-dioxo-7-*R*¹-[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29** were obtained in 27–56% of separated yields (Scheme 1). A probable mechanism of the reaction course is shown in Scheme 2. First, upon treatment of semicarbazides **4–16** with POCl₃ imidoyl chloride of type **A** is formed, which undergoes intramolecular ring closure with evolution of HCl to give triazolo[4,3-*b*][1,4,2]benzodithiazine **B**. Under acidic conditions, a scission of SO₂–N bond takes place with formation of a sulfonyl chloride **D**, which, in turn cyclizes to a more stable triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29**. The structures of the compounds **4–16** and the final products **17–29** were confirmed by elemental analyses, IR, ¹H NMR and ¹³C NMR spectrophotometry. It is worth noting, however, that the spectroscopic data did not allow straightforward discrimination between the actual triazolo[2,3-*b*][1,4,2]benzodithiazine structure and the

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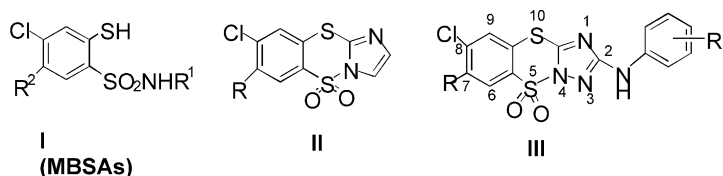
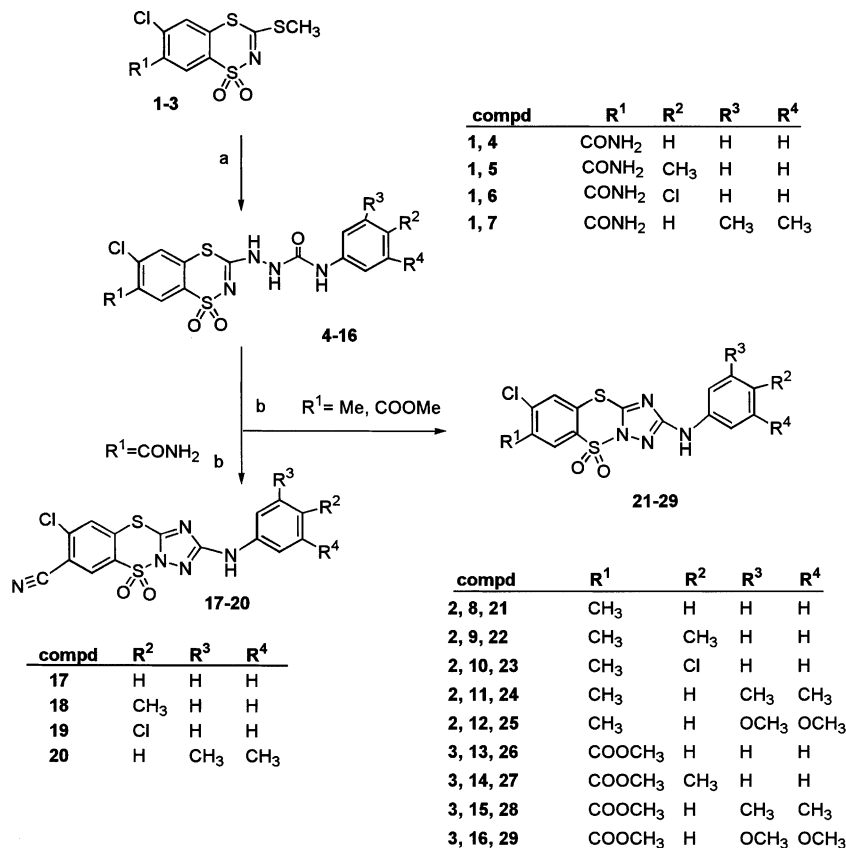


Figure 1.



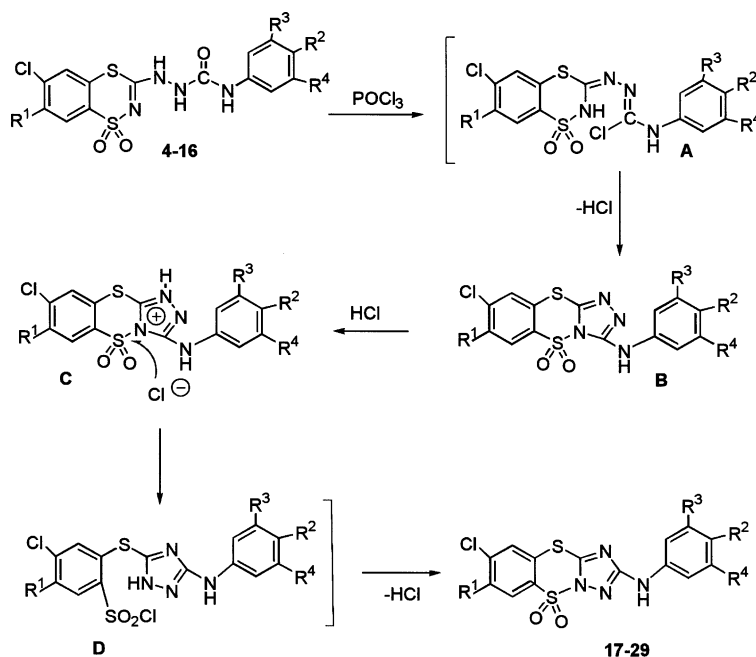
Scheme 1. Synthesis of 8-chloro-2-arylmino-5,5-dioxo[1,24]triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29**. Reagents: (a) 4-arylsulfonamide, MeOH, reflux; (b) (1) POCl₃, reflux/18 h; (2) ice/H₂O, pH = 7; (3) recrystallization from DMF.

alternative triazolo[4,3-*b*][1,4,2]benzodithiazine **B** (Scheme 2). Therefore, X-ray crystallography was undertaken on representative compound **26** with a view to reveal some more discrete structural features of these compounds.

The molecule of **26** has a butterfly shape due to the conformation of the central 1,4,2-dithiazine ring which is intermediate between boat and chair and to the virtually coplanar arrangement of the phenyl and triazole moieties (dihedral angle of 16.7°) stabilized by weak intramolecular C20–H20···N13 interaction (H20···N13 2.35 Å, <C20–H20···N13 117°). The C–S and C–N bond lengths [1.728(2) and 1.676(2) Å, respectively] of the sulfonamido group are slightly shorter than the corresponding bond lengths of similar, however acyclic, arylsulfonamides.^{21–23} The C3–N1 and C12–N13 bonds of 1.316(3) and 1.305(3) Å are the shortest of the triazole moiety and show considerable double-bond character. In crystals the molecules of **26** form centrosymmetric dimers via a pair of weak N–H···N hydrogen bonds [N14···N1' 3.249(3) Å, N14–H14.

079(3) Å, H14···N1' 2.46(3) Å, <N14–H14···N1' 178°]. The dimer structure leads to a pair of short C–H···S contacts [C16···S4' 3.638(2) Å, C16–H16 0.96(3) Å, H16···S4' 2.83(3) Å, <C16–H16···S4' 178°] between the two molecules (Fig. 2).

All the 5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29** synthesized were submitted to the US National Cancer Institute (Bethesda, MD, USA) for in vitro testing against a panel approximately 60 tumor cell lines. 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 sulphorhodamine B (SRB) protein assay was used to estimate cell growth. Details of this test system and the information which is encoded by the activity pattern over all cell lines, have been published.^{24,25} The antitumor activity of a test compound is given by three parameters for each cell line: GI₅₀, molar concentration of the compound that inhibits 50% net cell growth; TGI molar concentration



Scheme 2. Proposed mechanism of the formation of the 2-arylmino-5,5-dioxo[1,24]triazolo[2,3-*b*][1,4,2]benzodithiazines **17–29**.

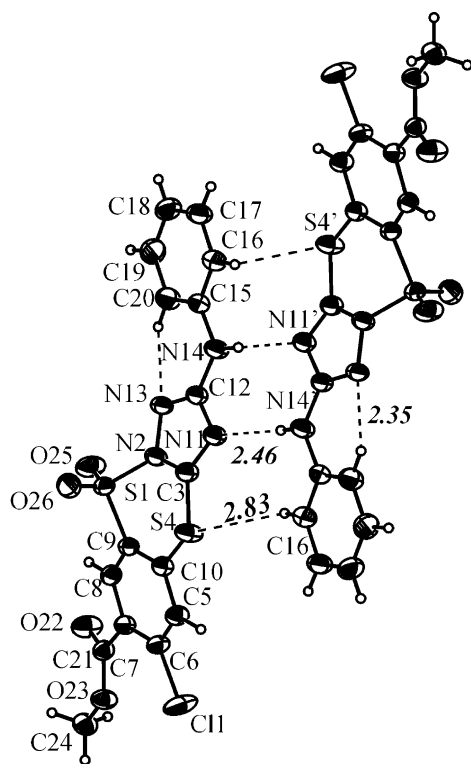


Figure 2. View of the hydrogen-bonded dimer of **26** showing short intra- and intermolecular contacts (Å) and atom labeling.

of the compound leading to total inhibition; and LC_{50} , molar concentration of the compound leading to 50% net cell death. Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity parameter over all cell lines. For the calculation of the MG_MID,

insensitive cell lines are included with the highest concentration tested. The discovery of compounds with new selectivity patterns is one of the intentions of the screening program.

The following is to be noted regarding the tumor cell growth inhibition data with the tested compounds. Compounds **18**, **19**, **23**, **28** and **29** were inactive ($\log \text{GI}_{50} > -4$), whereas the other compounds **17**, **20**, **21**, **22** and **24–27** exhibited reasonable antineoplastic activity against most of the human cell lines (Table 1). Relatively highest sensitivity to the compounds described here was found for leukemia (SR, CCRF-CEM), ovarian cancer (IGROVI, OVCAR-3), CNS cancer (SF-539) and lung cancer (HOP-92). The nature and location of substituents essentially influence cytotoxic activity of derivatives and differentiate sensitivity of tumor cell lines. The presence of the nitrile group at the position 7 essentially increased the cytotoxicity, as seen in the series of structural analogues **17**, **21**, **26** and **20**, **24**, **28** varied by R^1 (CN, CH_3 or COOCH_3). Generally, the most active compounds were **17**, **20** and **26** (Table 2). Different cancer cell lines of the same tumor type possessed a variable response to inhibition of growth in the presence of the new derivatives. For example, the SR leukemia cells were susceptible to inhibition by **17** ($\log \text{GI}_{50} = -7.67$, $\log \text{TGI} = -6.90$ and $\log \text{LC}_{50} = -4.77$), whereas other leukemia cell lines (such as CCRF-CEM, HL-60, KL-562, etc.) showed a lower level of inhibition ($\log \text{GI}_{50}$ ranged from -5.70 to -5.88). The same situation has been evidenced in the case of diverse ovarian cancer cell lines, with compound **26** acting as a potent inhibitor against the IGROVI line ($\log \text{GI}_{50} = -7.16$, $\log \text{TGI} = -5.84$ and $\log \text{LC}_{50} = -5.32$). Furthermore, the substitution of the arylamino group at the position 2 by the electron-withdrawing chlorine atom led to inactive compounds **19** and **23**.

Table 1. Overview of the results of the in vitro antitumor screening for compounds **17–29**^{a–d}

Compd	No. of the cell lines investigated	No. of the cell lines giving positive log GI ₅₀ ^b (M), log GTI ^c (M), and log LC ₅₀ ^d (M)					
		log GI ₅₀ ^b (M)		log GTI ^c (M)		log LC ₅₀ ^d (M)	
		No.	Range	No.	Range	No.	Range
17	59	59	–7.67 to –5.08	58	–6.90 to –4.73	50	–5.30 to –4.18
20	52	52	–6.30 to –4.79	50	–5.53 to –4.28	41	–5.18 to –4.07
21	53	53	–5.70 to –4.49	48	–5.16 to –4.15	23	–4.47 to –4.02
22	53	53	–5.77 to –4.45	40	–5.36 to –4.06	2	–4.35 to –4.19
24	58	58	–6.50 to –4.75	40	–5.03 to –4.04	5	–4.31 to –4.07
25	56	56	–5.66 to –4.21	35	–5.20 to –4.02	7	–4.40 to –4.01
26	55	55	–7.16 to –4.97	54	–5.84 to –4.60	52	–5.32 to –4.16
27	57	57	–5.93 to –4.74	57	–5.33 to –4.40	48	–5.14 to –4.07

^aData obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Table 2 and refs 24 and 25 for details). Compound **18**, **19**, **23**, **28** and **29** were inactive.

^bThe log of the molar concentration that inhibits 50% net cell growth.

^cThe log of the molar concentration giving total growth inhibition.

^dThe log of the molar concentration leading to 50% net cell death.

Conclusion

We have therein described an efficient procedure for obtaining derivatives of 5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine, a novel tricyclic ring system useful as a lead structure for the design of antitumor agents. Compounds **17** and **20** were the most potent of all derivatives tested. At the present stage, we may infer that the anticancer activity of the new compounds depends on the electronic character of all substituents. The mechanism of the antitumor activity and further variations of the parent structure are currently being investigated to improve both potency and selectivity and to get more detailed information on the SAR.

Experimental

Melting points are uncorrected and were determined on a Buchi SMP-20 apparatus. The IR spectra were recorded on 1600 FTIR Perkin-Elmer spectrometer as potassium bromide pellets and frequencies are expressed in cm^{–1}. The ¹³C NMR and ¹H NMR spectra were obtained on a Tesla BS-587 spectrometer (80 MHz)* and Varian Gemini (200 MHz) spectrometer in dimethyl sulfoxide-*d*₆. The chemical shift values δ are expressed in ppm relative to tetramethylsilane as internal standard and coupling constants (*J*) are in Hertz. Abbreviations are as follows: s, singlet; d, doublet; br, broad; m, multiplet. The analytical results for C, H, and N were within $\pm 0.4\%$ of the theoretical values. Mass spectrum was recorded on Finnigan MAT 95 (DCI) spectrometer at 70 eV. The starting 6-chloro-1,1-dioxo-3-methylthio-1,4,2-benzodithiazines **1–3** were obtained according to methods described previously: **1**,²⁶ **2**,²⁷ **3**,²⁸

General procedure for preparation of 1-(6-chloro-1,1-dioxo-7-*R*¹-1,4,2-benzodithiazin-3-yl)-4-(4-*R*²,3-*R*³,5-*R*⁴-phenyl)semicarbazides (4–16). A stirred mixture of the appropriate 3-methylthiobenzodithiazine **1–3** (10 mmol), the proper 4-arylsemicarbazide (10 mmol), and

methanol (100 mL) was refluxed until the evolution of MeSH had ceased (40–50 h) [CAUTION: because of high toxicity, MeSH should be trapped in an aqueous NaOH solution]. The precipitate was filtered off, washed with methanol and dried.

In this manner, the following semicarbazides were obtained.

1-(6-Chloro-1,1-dioxo-7-carbamoyl-1,4,2-benzodithiazin-3-yl)-4-phenylsemicarbazide (4). 3.0 g (70%), mp 264–265 °C; IR (KBr) 3439, 3350, 3206 (NH), 1688 (CONH), 1668 (CONH₂), 1650 (C=N), 1319, 1165 (SO₂) cm^{–1}; ¹H NMR (DMSO-*d*₆) δ 6.94–7.53 (m, 5H, ar.), 7.84 (s, 1H, NH), 7.94 (s, 1H, H-5), 8.08 (s, 1H, H-8), 8.15 (s, 1H, NH), 8.98 (s, 1H, HN-2), 9.42 (s, 1H, HN-4), 11.37 (br.s, 1H, HN-1); ¹³C NMR (DMSO-*d*₆) δ 119.23, 122.95, 124.28, 129.03, 129.65, 130.15, 131.54, 133.76, 137.65, 139.20 (ar.), 154.66 (C=N), 166.35 (CONH₂), 169.73 (CONH). Anal. calcd for C₁₅H₁₂ClN₅O₄S₂: C, 42.30; H, 2.83; N, 16.44. Found: C, 42.39; H, 3.01; N 16.37.

1-(6-Chloro-1,1-dioxo-7-carbamoyl-1,4,2-benzodithiazin-3-yl)-4-(4-methylphenyl)semicarbazide (5). 3.6 g (82%), mp 275–277 °C; IR (KBr) 3350, 3206 (NH), 1688 (CONH), 1655 (CONH₂), 1625 (C=N), 1310, 1160 (SO₂) cm^{–1}; ¹H NMR (DMSO-*d*₆) δ 2.24 (s, 3H, CH₃), 7.02–7.40 (m, 4H, ar.), 7.84 (s, 1H, NH₂), 7.93 (s, 1H, H-5), 8.07 (s, 1H, H-8), 8.15 (s, 1H, NH₂), 8.92 (s, 1H, HN-2), 9.31 (s, 1H, HN-4), 11.34 (br.s, 1H, HN-1). Anal. calcd for C₁₅H₁₄ClN₅O₄S₂: C, 43.68; H, 3.20; N, 15.92. Found: C, 43.79; H, 3.10; N 15.69.

1-(6-Chloro-1,1-dioxo-7-carbamoyl-1,4,2-benzodithiazin-3-yl)-4-(4-chlorophenyl)semicarbazide (6). 3.6 g (78%), mp 276–278 °C; IR (KBr) 3350, 3205 (NH), 1688 (CONH), 1655 (CONH₂), 1615 (C=N), 1310, 1165 (SO₂) cm^{–1}; ¹H NMR (DMSO-*d*₆) δ 7.28–7.57 (m, 4H, ar.), 7.85 (s, 1H, NH₂), 7.94 (s, 1H, H-5), 8.07 (s, 1H, H-8), 8.15 (s, 1H, NH₂), 9.09 (s, 1H, HN-2), 9.59 (s, 1H, HN-4), 11.38 (br.s, 1H, HN-1). Anal. calcd for C₁₅H₁₁Cl₂N₅O₄S₂: C, 39.13; H, 2.40; N, 15.21. Found: C, 39.19; H, 2.50; N 15.41.

Table 2. Inhibition of in vitro cancer cell lines by selected 8-chloro-2-arylamino-5,5-dioxo[1,2,4]triazolo[2,3-b][1,4,2]benzodithiazines **17**, **20** and **26^a**

Panel cell line	Response parameters: (A) log GI ₅₀ ^b (M), (B), log TGI ^c (M), (C) log LC ₅₀ ^d (M) and MG_MID ^e								
	Compd 17			Compd 20			Compd 26		
	A	B	C	A	B	C	A	B	C
Leukemia									
CCRF-CEM	−5.77	^e	^e	−5.97	−5.36	−4.47	−5.60	−5.05	−4.11
HL-60 (TB)	−5.70	−5.30	−4.60	−5.77	−4.71	^e	−5.58	−5.20	−4.10
K-562	−5.84	−4.95	−4.18	−5.83	^e	^e	−5.49	^e	^e
MOLT-4	−5.88	−5.39	^e	−5.95	−4.28	^e	−5.61	−5.14	^e
RPMI-8226	−6.36	−4.73	^e	nt	nt	nt	−5.75	−5.33	−4.10
SR	−7.67	−6.90	−4.77	−6.29	−5.47	^e	−5.69	−5.27	−4.10
Non-small cell lung cancer									
A 549/ATCC	−5.49	−4.95	−4.47	−4.79	−4.48	−4.18	−5.41	−4.83	−4.42
EKVX	−5.35	−4.77	−4.34	−5.06	−4.67	−4.32	−5.19	−4.73	−4.36
HOP-62	−5.71	−5.39	−5.06	−5.56	−5.03	^e	−5.70	−5.34	−4.94
HOP-92	−6.45	−5.24	^e	nt	nt	nt	−5.85	−5.43	−5.00
NCI-H226	−5.57	−4.99	−4.40	−4.97	−4.58	−4.20	−5.61	−4.83	−4.30
NCI-H23	−5.75	−5.43	−5.11	−5.75	−5.36	−4.91	−5.76	−5.35	−4.86
NCI-H322M	5.57	−5.04	−4.50	nt	nt	nt	−5.36	−4.79	−4.40
NCI-H460	−5.54	−4.95	−4.27	−5.50	−4.91	−4.43	−5.03	−4.64	−4.27
NCI-H522	−5.71	−5.30	−4.64	−5.73	−5.34	−4.88	—	−5.62	−5.28
Colon cancer									
COLO 205	−5.72	−5.43	−5.14	−4.96	−4.46	^e	−5.45	−4.84	−4.42
HCC-2998	−5.81	−5.52	−5.24	nt	nt	nt	−5.65	−5.22	−4.67
HCT-116	−5.65	−5.31	−4.88	−5.66	−5.20	−4.42	−5.47	−4.90	−4.43
HCT-15	−5.79	−5.44	−5.10	−5.60	−5.09	−4.24	−5.80	−5.53	−5.27
HT29	−5.78	−5.24	^e	−5.74	−5.30	−4.50	−5.71	−5.42	−5.13
KM12	−5.78	−5.48	−5.17	−5.72	−5.35	−4.93	−5.65	−5.23	−4.66
SW-620	−5.89	−5.5	−5.30	−5.62	−5.31	−5.01	nt	nt	nt
Melanoma									
LOX IMVI	−5.77	−5.38	^e	−5.54	−5.04	^e	nt	nt	nt
MALME 3M	−5.84	−5.53	−5.22	−5.95	−5.53	−5.12	−5.68	−5.13	−4.57
M14	−5.63	−5.23	−4.61	−5.25	−4.55	^e	−5.36	−4.77	−4.37
SK-MEL-2	−5.70	−5.24	−4.63	−5.12	−4.71	−4.31	nt	nt	nt
SK-MEL-28	−5.66	−5.28	−4.68	−5.49	−4.85	−4.37	−5.53	−4.99	−4.49
SK-MEL-5	−5.44	−4.84	−4.42	−5.12	−4.68	−4.31	−5.12	−4.69	−4.35
UACC-257	−5.85	−5.55	−5.25	−5.84	−5.48	−5.11	−4.93	−4.61	−4.28
UACC-62	−5.78	−5.49	−5.19	−5.40	−4.81	−4.31	−5.41	−4.87	−4.41
Prostate cancer									
PC-3	−5.79	−5.49	−5.19	nt	nt	nt	−5.51	−4.91	−4.41
DU-145	−5.77	−5.41	−5.05	−5.50	−4.90	−4.41	−5.82	−5.48	−5.41
CNS cancer									
SF-268	−5.59	−5.01	−4.48	−5.66	−5.26	−4.72	−5.70	−5.30	−4.80
SF-295	−5.75	−5.39	−5.04	−5.55	−5.04	−4.48	−5.57	−5.06	−4.53
SF-539	−5.65	−5.34	−5.04	−5.72	−5.40	−5.08	−5.85	−5.54	−5.23
SNB-19	−5.73	−5.34	−4.86	−5.17	−4.67	−4.27	−5.44	−4.82	−4.23
SNB-75	−5.46	−4.85	−4.33	−5.63	−5.12	−4.51	nt	nt	nt
U251	−5.74	−5.45	−5.16	−5.71	−5.37	−5.03	−5.67	−5.22	−4.66
Ovarian cancer									
IGROV1	−5.64	−5.20	−4.61	−6.30	−5.77	−5.39	−7.16	−5.84	−5.32
OVCAR-3	−5.95	−5.61	−5.27	−5.80	−5.48	−5.15	−5.79	−5.49	−5.20
OVCAR-4	−5.44	−4.85	−4.36	−5.10	−4.66	−4.27	−5.84	−5.44	−5.03
OVCAR-5	−5.69	−5.42	−5.14	−5.55	−5.02	−4.43	−5.31	−4.76	−4.38
OVCAR-8	−5.79	−5.45	−5.11	nt	nt	nt	−5.52	−4.96	−4.39
SK-OV-3	−5.32	−4.80	−4.39	−5.18	−4.66	−4.24	−5.42	−4.82	−4.41
Renal cancer									
768-0	−5.66	−4.95	−4.20	−5.65	^e	^e	−5.48	−4.86	−4.39
A498	−5.08	−4.68	−4.34	−4.79	−4.50	−4.22	−4.97	−4.65	−4.33
ACHN	−5.76	−5.47	−5.18	−5.51	−4.97	−4.37	−5.94	−5.63	−5.31
CAKI-1	−5.85	−5.57	−5.28	−5.49	−4.90	−4.41	−5.62	−5.14	−4.59
RXF 393	−5.76	−5.26	−4.49	−5.80	−5.49	−5.18	−5.71	−5.26	−4.69
SN12C	−5.76	−5.47	−5.19	−5.59	−5.15	−4.50	−5.09	−4.65	−4.28
TK-10	−5.54	−5.08	−4.51	nt	nt	nt	−5.54	−5.05	−4.53
UO-31	−5.78	−5.44	−5.09	−5.31	−5.36	−4.39	−5.70	−5.25	−4.69

(continued on next page)

Table 2 (continued)

Panel cell line	Response parameters: (A) log GI ₅₀ ^b (M), (B), log TGI ^c (M), (C) log LC ₅₀ ^d (M) and MG_MID ^e								
	Compd 17			Compd 20			Compd 26		
	A	B	C	A	B	C	A	B	C
Breast cancer									
MCF 7	−5.58	−4.79	^e	−5.73	−5.18	−4.53	−5.64	−5.13	−4.53
NCI/ADR-RES	−5.74	−5.45	−5.16	−5.61	−5.19	−4.07	−5.09	−4.60	−4.16
MDA-MB-231/ATCC	−5.68	−5.19	−4.54	−5.51	−4.89	−4.32	−5.45	−4.82	−4.31
HS 578T	−5.73	−5.17	^e	−5.57	−4.80	^e	−5.49	−4.74	^e
MDA-MB-435	−5.76	−5.43	−5.10	−5.52	−4.98	−4.41	−5.31	−4.76	−4.38
MDA-N	nt	nt	nt	nt	nt	nt	−5.27	−4.72	−4.32
BT 549	−5.61	−5.09	−4.53	−5.67	−5.22	−4.60	−5.87	−5.20	−4.57
T-47D	−5.81	−5.19	^e	−5.49	−4.50	^e	−5.77	−5.43	−5.09
MG_MID	−5.74	−5.25	−4.69	−5.54	−4.97	−4.44	−5.56	−5.06	−4.56

^aData obtained from the NCI's in vitro disease-oriented human tumor cells screen (see refs. 24 and 25 for details).

^bThe log of the molar concentration that inhibits 50% net cell growth.

^cThe log of the molar concentration giving total growth inhibition.

^dThe log of the molar concentration leading to 50% net cell death. MG_MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

^eThe values log TGI or log LC₅₀ > −4.00; nt, not tested.

1-(6-Chloro-1,1-dioxo-7-carbamoyl-1,4,2-benzodithiazin-3-yl)-4-(3,5-dimethylphenyl)semicarbazide (7). 3.1 g (68%), mp 222–224 °C; IR (KBr) 3445, 3310, 3210 (NH), 1688 (CONH), 1660 (CONH₂), 1610 (C=N), 1325, 1165 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.28 (s, 6H, 2×CH₃), 6.66 (s, 1H, ar.), 7.12 (brs, 2H, ar.), 7.86 (s, 1H, NH), 7.95 (s, 1H, H-5), 8.08 (s, 1H, H-8), 8.16 (s, 1H, NH), 8.93 (s, 1H, HN-2), 9.25 (s, 1H, HN-4), 11.34 (br.s, 1H, HN-1); ¹³C NMR (DMSO-*d*₆) δ 21.37 (2×CH₃), 117.0, 124.26, 124.51, 129.64, 130.16, 131.58, 133.74, 137.63, 137.97, 139.03 (ar.), 154.58 (C=N), 166.34 (CONH₂), 169.78 (CONH). Anal. calcd for C₁₇H₁₆ClN₅O₄S₂: C, 44.98; H, 3.55; N, 15.42. Found: C, 44.79; H, 3.50; N 15.63.

1-(6-Chloro-1,1-dioxo-7-methyl-1,4,2-benzodithiazin-3-yl)-4-phenylsemicarbazide (8). 3.15 g (79%), mp 216–218 °C; IR (KBr) 3324, 3284, 3218 (NH), 1695 (CONH), 1349, 1155 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.42 (s, 3H, 7-CH₃), 6.97–7.53 (m, 5H, Ph), 7.94 (s, 1H, H-5), 8.01 (s, 1H, H-8), 8.94 (s, 1H, HN-2), 9.39 (s, 1H, HN-4), 11.23 (s, 1H, HN-1). Anal. calcd for C₁₅H₁₃ClN₄O₃S₂: C, 45.39; H, 3.30; N, 14.12. Found: C, 45.15; H, 3.54; N 14.26.

1-(6-Chloro-1,1-dioxo-7-methyl-1,4,2-benzodithiazin-3-yl)-4-(4-methylphenyl)semicarbazide (9). 3.0 g (73%), mp 225–227 °C; IR (KBr) 3283, 3189 (NH), 1684 (CONH), 1320, 1152 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.23 (s, 3H, CH₃), 2.43 (s, 3H, 7-CH₃), 7.07–7.39 (m, 4H, Ph), 7.95 (s, 1H, H-5), 8.0 (s, 1H, H-8), 8.88 (s, 1H, HN-2), 9.27 (s, 1H, HN-4), 11.21 (s, 1H, HN-1). Anal. calcd for C₁₆H₁₅ClN₄O₃S₂: C, 46.76; H, 3.68; N, 13.65. Found: C, 46.53; H, 3.49; N 13.74.

1-(6-Chloro-1,1-dioxo-7-methyl-1,4,2-benzodithiazin-3-yl)-4-(4-chlorophenyl)semicarbazide (10). 3.8 g (88%), mp 237–239 °C; IR (KBr) 3271, 3189 (NH), 1689 (CONH), 1313, 1152 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.42 (s, 3H, 7-CH₃), 7.25–7.65 (m, 4H, Ph), 7.95 (s,

1H, H-5), 8.0 (s, 1H, H-8), 9.05 (s, 1H, HN-2), 9.52 (s, 1H, HN-4), 11.21 (s, 1H, HN-1)*. Anal. calcd for C₁₅H₁₂Cl₂N₄O₃S₂: C, 41.77; H, 2.80; N, 12.99. Found: C, 41.85; H, 3.05; N 12.90.

1-(6-Chloro-1,1-dioxo-7-methyl-1,4,2-benzodithiazin-3-yl)-4-(3,5-dimethylphenyl)semicarbazide (11). 3.5 g (83%), mp 246–248 °C; IR (KBr) 3279, 3126 (NH), 1690 (CONH), 1620 (C=N), 1281, 1160 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.24 (s, 6H, 2×CH₃), 2.45 (s, 3H, CH₃), 6.64–6.67 (m, 1H, ar.), 7.08–7.18 (m, 2H, ar.), 7.97 (s, 1H, H-5), 8.03 (s, 1H, H-8), 8.90 (s, 1H, HN-2), 9.23 (s, 1H, HN-4), 11.23 (br.s, 1H, HN-1); ¹³C NMR (DMSO-*d*₆) δ 19.57 (7-CH₃), 21.37 (2×CH₃), 116.97, 124.45, 126.59, 128.48, 130.29, 137.36, 137.74, 137.79, 137.93, 139.06 (ar.), 154.29 (C=N), 169.94 (CONH). Anal. calcd for C₁₇H₁₇ClN₄O₃S₂: C, 48.05; H, 4.03; N, 13.18. Found: C, 48.09; H, 4.15; N, 13.31.

1-(6-Chloro-1,1-dioxo-7-methyl-1,4,2-benzodithiazin-3-yl)-4-(3,5-dimethoxyphenyl)semicarbazide (12). 3.85 g (83%), mp 225–226 °C; IR (KBr) 3289, 3170 (NH), 1695 (CONH), 1616 (C=N), 1346, 1150 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 2.44 (s, 3H, CH₃), 3.70 (s, 6H, 2×OCH₃), 6.14–6.20 (m, 1H, ar.), 6.75 (d, *J* = 2.3 Hz, 2H, ar.), 7.95 (s, 1H, H-5), 8.01 (s, 1H, H-8), 8.94 (s, 1H, HN-2), 9.37 (s, 1H, HN-4), 11.22 (br.s, 1H, HN-1); ¹³C NMR (DMSO-*d*₆) δ 19.57 (7-CH₃), 55.31 (2×OCH₃), 94.84, 97.39, 126.59, 127.84, 128.49, 130.27, 137.38, 137.83, 140.98, 160.78 (ar.), 154.54 (C=N), 169.88 (CONH). Anal. calcd for C₁₇H₁₇ClN₄O₅S₂: C, 44.68; H, 3.75; N, 12.26. Found: C, 44.59; H, 4.05; N, 12.21.

1-(6-Chloro-1,1-dioxo-7-methoxycarbonyl-1,4,2-benzodithiazin-3-yl)-4-phenylsemicarbazide (13). 3.6 g (82%), mp 225–227 °C; IR (KBr) 3326, 3215 (NH), 1738, 1718, 1703 (CO), 1670 (CONH), 1600 (C=N), 1325, 1165 (SO₂) cm^{−1}; ¹H NMR (DMSO-*d*₆) δ 3.89 (s, 3H, OCH₃), 6.8–7.54 (m, 5H, ar.), 8.17 (s, 1H, H-5), 8.36 (s, 1H, H-8), 9.0 (s, 1H, HN-2), 9.44 (s, 1H, HN-4), 11.46

(br.s, 1H, HN-1). Anal. calcd for $C_{16}H_{13}ClN_4O_5S_2$: C, 43.59; H, 2.97; N, 12.70. Found: C, 45.73; H, 3.15; N, 12.92.

1-(6-Chloro-1,1-dioxo-7-methoxycarbonyl-1,4,2-benzodithiazin-3-yl)-4-(4-methylphenyl)semicarbazide (14). 3.6 g (79%), mp 224–225 °C; IR (KBr) 3324, 3205 (NH), 1740, 1721 (CO), 1666 (CONH), 1605 (C=N), 1314, 1165 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 2.24 (s, 3H, CH₃), 3.9 (s, 3H, OCH₃), 7.05–7.42 (m, 5H, arom.), 8.18 (s, 1H, H-5), 8.37 (s, 1H, H-8), 8.94 (s, 1H, HN-2), 9.32 (s, 1H, HN-4), 11.44 (br.s, 1H, HN-1). Anal. calcd for $C_{17}H_{15}ClN_4O_5S_2$: C, 44.88; H, 3.32; N, 12.31. Found: C, 44.99; H, 3.15; N, 12.39.

1-(6-Chloro-1,1-dioxo-7-methoxycarbonyl-1,4,2-benzodithiazin-3-yl)-4-(3,5-dimethylphenyl)semicarbazide (15). 3.3 g (70%), mp 205–207 °C; IR (KBr) 3350, 3283 (NH), 1737, 1721 (CO), 1680 (CONH), 1615 (C=N), 1317, 1165 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 2.21 (s, 6H, 2×CH₃), 3.9 (s, 3H, OCH₃), 6.62–6.67 (m, 1H, ar.), 7.05–7.14 (m, 2H, ar.), 8.17 (s, 1H, H-5), 8.36 (s, 1H, H-8), 8.93 (s, 1H, HN-2), 9.24 (s, 1H, HN-4), 11.42 (br.s, 1H, HN-1); ¹³C NMR (DMSO-*d*₆) δ 21.35 (2×CH₃), 53.32 (OCH₃), 117.03, 124.57, 127.04, 130.2, 130.86, 134.55, 135.64, 137.99, 138.95, 139.24 (ar.), 154.56 (C=N), 163.77 (CO), 169.4 (CONH). Anal. calcd for $C_{18}H_{17}ClN_4O_5S_2$: C, 46.10; H, 3.65; N, 11.94. Found: C, 46.23; H, 3.75; N, 12.12.

1-(6-Chloro-1,1-dioxo-7-methoxycarbonyl-1,4,2-benzodithiazin-3-yl)-4-(3,5-dimethoxyphenyl)semicarbazide (16). 4 g (80%), mp 178–180 °C; IR (KBr) 3300, 3170 (NH), 1734 (CO), 1685 (CONH), 1616 (C=N), 1307, 1156 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 3.69 (s, 6H, 2×OCH₃), 3.9 (s, 3H, OCH₃), 6.14–6.21 (m, 1H, ar.), 6.68–6.77 (m, 2H, ar.), 8.17 (s, 1H, H-5), 8.36 (s, 1H, H-8), 8.99 (s, 1H, HN-2), 9.42 (s, 1H, HN-4), 11.44 (br.s, 1H, HN-1). Anal. calcd for $C_{18}H_{17}ClN_4O_7S_2$: C, 43.16; H, 3.42; N, 11.18. Found: C, 42.99; H, 3.65; N, 11.27.

General procedure for the preparation of 8-chloro-2-aryl-amino-7-*R*¹-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines (17–29). A stirred mixture of the appropriate semicarbazide 4–16 (10 mmol) and phosphorus oxychloride (70 mL) was refluxed for 18 h. After cooling, the solution obtained was poured onto crashed ice (300 g) and stirred at room temperature for 10 h. The precipitated solid was collected by filtration, washed thoroughly with water (pH = 7), dried and recrystallized from dimethylformamide (10–15 mL).

In this manner, the following benzodithiazines were obtained.

8-Chloro-2-phenylamino-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carbonitrile (17). 1.12 g (29%), mp 215–217 °C; IR (KBr) 3312 (NH), 2238 (CN), 1618 (C=N), 1376, 1180 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 6.98 (t, *J* = 7.3 Hz, 1H, ar.), 7.28–7.41 (m, 2H, ar.), 7.57 (d, *J* = 7.69 Hz, 2H, ar.), 8.62 (s, 1H, H-9), 9.06 (s, 1H, H-6), 10.17 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 113.05 (CN), 114.4, 117.35, 121.73, 129.27, 131.06,

131.36, 132.33, 134.98, 139.91, 141.19 (ar.), 152.1, 161.51 (C=N). Anal. calcd for $C_{15}H_8ClN_5O_2S_2$: C, 46.21; H, 2.06; N, 17.96. Found: C, 46.10; H, 2.15; N, 17.70.

8-Chloro-2-(4-methylphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carbonitrile (18). 1.1 g (27%), mp 213–214 °C; IR (KBr) 3360 (NH), 2234 (CN), 1602 (C=N), 1363, 1190 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 2.25 (s, 3H, CH₃), 7.14 (d, *J* = 8.06 Hz, 2H, ar.), 7.44 (d, *J* = 8.06 Hz, 2H, ar.), 8.59 (s, 1H, H-9), 9.03 (s, 1H, H-6), 10.04 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 20.63 (CH₃), 113.05 (CN), 114.42, 117.41, 129.65, 130.58, 131.03, 131.33, 132.32, 134.94, 137.42, 141.19 (ar.), 152.14, 161.64 (C=N). Anal. calcd for $C_{16}H_{10}ClN_5O_2S_2$: C, 47.58; H, 2.49; N, 17.34. Found: C, 47.39; H, 2.34; N, 17.15.

8-Chloro-2-(4-chlorophenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carbonitrile (19). 1.3 g (30%), mp 238–239 °C; IR (KBr) 3383 (NH), 2233 (CN), 1601 (C=N), 1361, 1190 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 7.40 (d, *J* = 8.7 Hz, 2H, ar.), 7.57 (d, *J* = 8.7 Hz, 2H, ar.), 8.6 (s, 1H, H-9), 9.05 (s, 1H, H-6), 10.03 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 113.07 (CN), 114.39, 118.85, 125.3, 129.15, 131.07, 131.33, 132.32, 134.96, 138.89, 141.23 (ar.), 152.16, 161.2 (C=N). Anal. calcd for $C_{15}H_7ClN_5O_2S_2$: C, 42.46; H, 1.66; N, 16.50. Found: C, 42.25; H, 1.55; N, 16.27.

8-Chloro-2-(3,5-dimethylphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carbonitrile (20). 1.16 g (28%), mp 237–238 °C; IR (KBr) 3320 (NH), 2238 (CN), 1616 (C=N), 1370, 1185 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 2.26 (s, 6H, 2×CH₃), 6.62 (s, 1H, ar.), 7.18 (s, 2H, ar.), 8.61 (s, 1H, H-9), 9.04 (s, 1H, H-6), 10.0 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 21.56 (2×CH₃), 113.07 (CN), 114.40, 115.14, 123.45, 130.99, 131.30, 132.25, 134.93, 138.2, 139.78, 141.17 (ar.), 152.0, 161.57 (C=N). Anal. calcd for $C_{17}H_{12}ClN_5O_2S_2$: C, 48.86; H, 2.89; N, 16.75. Found: C, 48.79; H, 2.65; N, 16.80.

8-Chloro-7-methyl-2-phenylamino-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine (21). 2.1 g (55%), mp 229–231 °C; IR (KBr) 3375 (NH), 1601 (C=N), 1335, 1165 (SO₂) cm^{-1} ; ¹H NMR (CD₃)₂CO δ 2.59 (s, 3H, CH₃), 6.96–7.74 (m, 5H, ar.), 8.09 (s, 1H, H-9), 8.29 (s, 1H, H-6), 9.02 (s, 1H, NH). Anal. calcd for $C_{15}H_{11}ClN_4O_2S_2$: C, 47.55; H, 2.92; N, 14.79. Found: C, 47.61; H, 2.98; N, 14.77.

8-Chloro-7-methyl-2-(4-methylphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine (22). 2.2 g (56%), mp 216–218 °C; IR (KBr) 3335 (NH), 1609 (C=N), 1360, 1180 (SO₂) cm^{-1} ; ¹H NMR (DMSO-*d*₆) δ 2.25 (s, 3H, CH₃Ph), 2.55 (s, 3H, 8-CH₃), 7.04–7.61 (m, 4H, ar.), 8.25 (s, 1H, H-9), 8.39 (s, 1H, H-6), 9.98 (s, 1H, NH)*. Anal. calcd for $C_{16}H_{13}ClN_4O_2S_2$: C, 48.91; H, 3.33; N, 14.26. Found: C, 48.99; H, 3.45; N, 14.37.

8-Chloro-2-(4-chlorophenylamino)-7-methyl-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine (23). 2.06 g (50%), mp 240–241 °C; IR (KBr) 3359 (NH), 1604

(C=N), 1350, 1180 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.55 (s, 3H, 8-CH₃), 7.36–7.62 (m, 4H, ar.), 8.26 (s, 1H, H-9), 8.39 (s, 1H, H-6), 10.28 (s, 1H, NH); MS (70 eV) *m/z*: 412 (M⁺, 100%). Anal. calcd for C₁₅H₁₀Cl₂N₄O₂S₂: C, 43.59; H, 2.43; N, 13.56. Found: C, 43.70; H, 2.55; N, 13.68.

8-Chloro-2-(3,5-dimethylphenylamino)-7-methyl-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine (24). 1.8 g (44%), mp 234–235 °C; IR (KBr) 3315 (NH), 1615 (C=N), 1365, 1180 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.26 (s, 6H, 2×CH₃), 2.55 (s, 3H, 8-CH₃), 6.61 (s, 1H, ar.), 7.19 (s, 2H, ar.), 8.25 (s, 1H, H-9), 8.37 (s, 1H, H-6), 9.94 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 19.52 (7-CH₃), 21.56 (2×CH₃), 115.10, 123.32, 125.85, 127.88, 129.77, 130.57, 138.15, 138.33, 139.93, 140.08 (ar.), 153.08 (C=N), 161.56 (C=N). Anal. calcd for C₁₇H₁₅ClN₄O₂S₂: C, 50.18; H, 3.71; N, 13.76. Found: C, 50.23; H, 3.65; N, 13.67.

8-Chloro-2-(3,5-dimethoxyphenylamino)-7-methyl-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine (25). 1.8 g (41%), mp 220–221 °C; IR (KBr) 3400 (NH), 1609 (C=N), 1354, 1150 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ, 2.50 (s, 3H, 8-CH₃), 3.73 (s, 6H, 2×OCH₃), 6.15 (t, *J* = 2.13 Hz, 1H, ar.), 6.80 (d, *J* = 2.18 Hz, 2H, ar.), 8.25 (s, 1H, H-9), 8.37 (s, 1H, H-6), 10.05 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 19.52 (CH₃), 55.31 (2×OCH₃), 93.14, 96.32, 125.88, 127.92, 129.82, 130.56, 138.35, 140.09, 141.57, 161.11 (ar.), 153.02 (C=N), 161.35 (C=N). Anal. calcd for C₁₇H₁₅ClN₄O₄S₂: C, 46.52; H, 3.44; N, 12.76. Found: C, 46.60; H, 3.55; N, 12.67.

Methyl 8-chloro-2-phenylamino-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carboxylate (26). 1.45 g (34%), mp 232–233 °C; IR (KBr) 3320 (NH), 1709 (CO), 1616 (C=N), 1370, 1150 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ, 3.92 (s, 3H, OCH₃), 6.97 (t, *J* = 7.3 Hz, 1H, ar.), 7.34 (t, *J* = 7.8 Hz, 2H, ar.), 7.57 (d, *J* = 7.9 Hz, 2H, ar.), 8.46 (s, 1H, H-9), 8.65 (s, 1H, H-6), 10.15 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 53.55 (OCH₃), 117.33, 121.68, 128.45, 129.25, 130.25, 130.61, 132.04, 132.63, 138.19, 139.95 (ar.), 152.49, 161.53 (C=N), 163.25 (CO). Anal. calcd for C₁₆H₁₁ClN₄O₄S₂: C, 45.44; H, 2.62; N, 13.24. Found: C, 45.950; H, 2.65; N, 13.20.

Methyl 8-chloro-2-(4-methylphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carboxylate (27). 1.65 g (38%), mp 209–210 °C; IR (KBr) 3350 (NH), 1736 (CO), 1606 (C=N), 1366, 1165 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ, 2.26 (s, 3H, CH₃), 3.94 (s, 3H, OCH₃), 7.15 (d, *J* = 8.42 Hz, 2H, ar.), 7.46 (d, *J* = 8.42 Hz, 2H, ar.), 8.45 (s, 1H, H-9), 8.65 (s, 1H, H-6), 10.05 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 20.62 (CH₃), 53.55 (OCH₃), 117.40, 128.43, 129.63, 130.25, 130.51, 130.61, 132.02, 132.61, 137.46, 138.17 (ar.), 152.51, 161.66 (C=N), 163.26 (CO). Anal. calcd for C₁₇H₁₃ClN₄O₄S₂: C, 46.73; H, 2.99; N, 12.82. Found: C, 46.90; H, 3.13; N, 12.83.

Methyl 8-chloro-2-(3,5-dimethylphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carboxylate (28). 1.4 g (31%), mp 207–208 °C; IR (KBr) 3345 (NH),

1725 (CO), 1616 (C=N), 1370, 1185 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ, 2.24 (s, 6H, 2×CH₃), 3.92 (s, 3H, OCH₃), 6.59 (s, 1H, ar.), 7.17 (s, 2H, ar.), 8.44 (s, 1H, H-9), 8.63 (s, 1H, H-6), 9.97 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 21.57 (2×CH₃), 53.57 (OCH₃), 115.13, 123.42, 128.42, 130.21, 130.50, 130.61, 132.02, 132.63, 138.2, 139.84 (ar.), 152.45, 161.59 (C=N), 163.26 (CO). Anal. calcd for C₁₈H₁₅ClN₄O₄S₂: C, 47.94; H, 3.35; N, 12.42. Found: C, 47.99; H, 3.61; N, 12.25.

Methyl 8-chloro-2-(3,5-dimethoxyphenylamino)-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carboxylate (29). 1.6 g (33%), mp 194–196 °C; IR (KBr) 3345 (NH), 1737 (CO), 1612 (C=N), 1363, 1180 (SO₂) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ, 3.72 (s, 6H, 2×OCH₃), 3.92 (s, 3H, OCH₃), 6.15 (s, 1H, ar.), 6.75–6.87 (m, 2H, ar.), 8.45 (s, 1H, H-9), 8.63 (s, 1H, H-6), 10.09 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 53.57 (OCH₃), 55.32 (2×OCH₃), 93.24, 96.34, 128.44, 130.27, 130.64, 132.07, 132.67, 138.17, 141.49, 161.12 (ar.), 152.38, 161.37 (C=N), 163.27 (CO). Anal. calcd for C₁₈H₁₅ClN₄O₆S₂: C, 44.76; H, 3.14; N, 11.60. Found: C, 44.79; H, 3.05; N, 11.52.

X-ray structure analysis

Crystal data for C₁₆H₁₁ClN₄O₄S₂: triclinic, space group *P* $\bar{1}$, *a* = 7.6220(7), *b* = 7.8922(9), *c* = 16.1453(10) Å, α = 91.099(7), β = 99.906(6), γ = 114.945(10)°, *V* = 862.89(14) Å³, *Z* = 2, *d*_x = 1.627 g cm⁻³, *T* = 293 K. Data were collected for a crystal with dimensions 0.5×0.3×0.2 mm on a KumaCCD diffractometer using graphite monochromated Mo *K*_α radiation. Final *R* indices for 2724 reflections with *I* > 2σ(*I*) and 289 refined parameters are: *R*₁ = 0.0365, *wR*₂ = 0.0914 (*R*₁ = 0.0408, *wR*₂ = 0.0951 for all 3026 data). Atom labeling is shown in Figure 1. Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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