Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 3673–3681

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis, Structural Characterization and In Vitro Antitumor Activity of Novel 6-Chloro-1,1-dioxo-1,4,2-benzodithiazie Derivatives

Zdzislaw Brzozowski,[a] Franciszek Sączewski[a,*] and Maria Gdaniec[b]

[a]*Department of Chemical Technology of Drugs, Medical University of Gdańsk, Al. Gen. Hallera 107, 80-416 Gdańsk, Poland*
[b]*Faculty of Chemistry, A. Mickiewicz University, 60-780 Poznań, Poland*

Received 10 January 2003; accepted 16 May 2003

Abstract—A series of nonconventional aminium *N*-(6-chloro-7-R-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamidates **7**–**15** have been synthesized by the reactions of 6-chloro-7-*R*-3-methylthio-1,4,2-benzodithiazine 1,1-dioxides with 4-dimethylaminopyridine or Et_3N and some arylsulfonamides. The free *N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamides **16**–**18** were obtained by treatment of their aminium salts with H_2SO_4 in boiling acetic acid. The in vitro antitumor activity of the compounds **9**, **11**–**14** and **16**–**18** has been tested in the antitumor screening of the National Cancer Institute (NCI), and relationships between structure and antitumor activity are discussed. 4-Dimethylaminopyridinium 4-chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidate **9** is the prominent of the compounds due to its remarkable activity (log $GI_{50} < -8.00$, log $TGI = -5.50$) and selectivity for the leukemia SR cell line. For that reason experimental and theoretical analysis of the geometric and electronic properties of **9** was carried out.

Introduction

Compounds containing 1,4,2-benzodithiazine ring were synthesized in our laboratories in 1984 and received considerable attention over the past years due to their wide range of biological activity. Hence, 3-mercapto-1,4,2-benzodithiazine 1,1-dioxides of type **I** (Fig. 1) were obtained by reacting 2-chlorobenzenesulfonamides with carbon disulfide in the presence of potassium hydroxide.[1,2] Various 3-substituted benzodithiazine derivatives have been prepared by the nucleophilic displacement of the pre-formed 3-methylthio-1,4,2-benzodithiazine 1,1-dioxide[1–3] with the respective amines,[4–14] hydrazines[5,12–14] or guanidines.[5,15] Alternatively, access to 2-substituted 1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazine-3-ones (R = Me or Ph) is provided by the reaction of *N*-methyl or *N*-phenylbenzenesulfonamides with butyllithium and sulfur at −78 °C.[16]

It has been demonstrated that many 1,4,2-benzodithiazine derivatives possessed low acute toxicity in mice and rats and, depending on their structure, exhibited potential as radioprotective,[1,2] hypotensive,[1] diuretic,[1,2,4,6,9] or choleretic[9] agents. Previous works carried out in collaboration with the National Cancer Institute, Bethesda, USA, have also shown that some 6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylhydrazines of type **I** (Fig. 1) displayed antineoplastic properties especially against renal (U-31: $GI_{50} < 0.001$–0.034 μM) and breast (MCF-7: $GI_{50} = 0.002$–1.0 μM) cancer cell lines.[12]

Furthermore, 3-methylthio-1,4,2-benzodithiazines have received our investigative attention with regard to their potential for chemical transformations into otherwise not readily obtainable 2-mercaptobenzenesulfonamides. This concerns the synthesis of 4-chloro-2-mercaptobenzenesulfonamides of type **II** (Fig. 1) with the nitrogen atom of sulfonamide moiety attached to a variety of heterocyclic ring systems. These compounds exhibited structure-dependent anticancer[15,17–24] or anti-HIV[13–15,17,18,23,25] activity and have been described by Neamati[26] as a novel class of potent HIV-1 integrase inhibitors (Fig. 1, **MBSA**'s). Moreover, a number of different cyclic analogues of 2-mercaptobenzene-sulfonamides (Fig. 1, structure **III**[10,27] and **IV**[28]) have been shown to act as anticancer and anti-HIV agents.

*Corresponding author. Tel.: +48-58-349-3250; fax: +48-58-349-3257; e-mail: saczew@sanus.amg.gd.apl

0968-0896/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0968-0896(03)00345-6

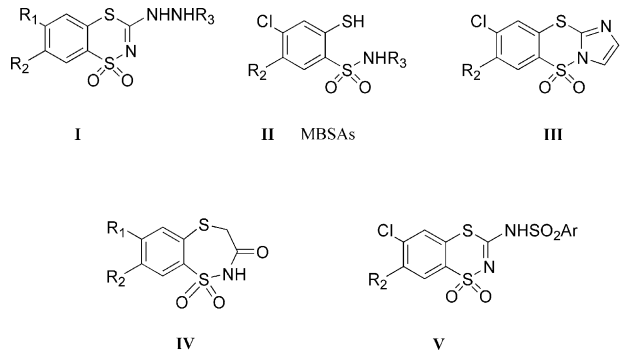


Figure 1.

Since it has been well known that sulfonamides in general have a variety of biological activities such as antibacterial, anticancer[29–42] and anti-HIV,[43–55] we considered as justified to undertake the synthesis and screening of a new group of 1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides of type **V** and their aminium salts (Fig. 1).

In addition to the synthesis and cytotoxicity evaluation, the mechanism of formation and structural elucidations on representative molecules were planned with a view to determining correlations between the structures of these molecules and their bioactivity.

Results and Discussion

The previously described methods were employed for the synthesis of compounds **1**[2] and **6**.[1,3] Analogously were prepared novel 3-methylthio-1,1-dioxo-1,4,2-benzodithiazines **5** and the corresponding substrates **3** and **4** (Scheme 1).

Preparation of aminium sulfonamidates **7–15** was achieved by reacting 3-methylthio 1,1-dioxo-1,4,2-benzodithiazines **1**, **5** and **6** with benzenesulfonamides in the presence of equimolar amount of tertiary amine such as 4-dimethylaminopyridine (DMAP) or triethylamine in refluxed toluene (Scheme 2).

The most striking property of the aminium sulfonamidates **7–15** concerns their unusual stability at low pH, as they survive in form of a salt when treated with diluted mineral acids or boiling acetic acid. This unusual acidity of the free sulfonamides may be explained by the presence of two sulfonyl groups functioning as strong electron attractors. Dissociation of sulfonamide N–H proton results in the anion formation, which counteracts the electron deficiency and keeps the molecule over a large pH range in this stable form.

In order to get a closer insight into the reaction mechanism, the reaction of 3-methylthio-1,4,2-benzodithiazine **1** with DMAP in toluene under reflux conditions was carried out and a stable betaine **19** was obtained in 23% yield as a result of an attack of tertiary amine at the electron deficient C-3 carbon atom of benzodithiazine moiety. When **19**, in turn, was refluxed in toluene in the presence of 4-chlorobenzenesulfonamide, the final aminium sulfonamidate **9** was isolated in 86% yield. Thus, our experimental results suggest that the anionic center on the N-2 nitrogen atom of the transiently formed betaine **19** may act as a strong base which, upon deprotonation of a sulfonamide present in the reaction mixture, generates the ion pair of type **A**. This process is completed by elimination of thiomethyl group (formation of **B**) and nucleophilic displacement of 4-dimethyl pyridinium group (Scheme 3).

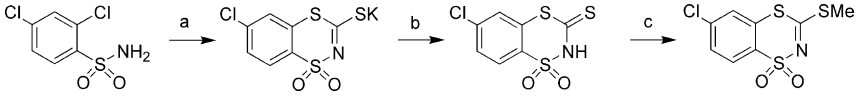
Free sulfonamides **16–18** were obtained in 87–92% yield upon treatment of the corresponding aminium sulfonamidates with 95% sulfuric acid in acetic acid under reflux.

The structures of the compounds **7–15**, **16–18** and **19** were established by spectroscopic and analytical data. For the aminium salt **9** (Fig. 2) the X-ray crystal structure analysis was carried out providing molecular geometry as the starting point for further molecular modeling studies.

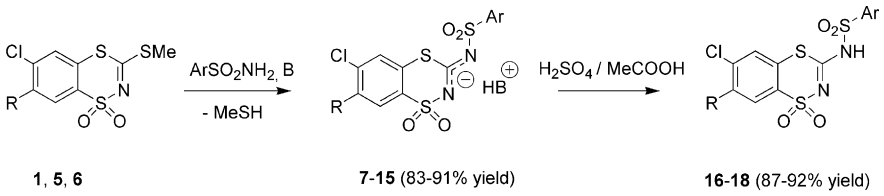
The anion moiety of **9** exhibits E configuration at the partially double C3–N15 bond (Fig. 2). The 1,4,2-dithiazine ring adopts a conformation intermediate between boat and sofa. The atoms S16, N15, C3, N2 and S4 are located nearly in one plane, with S1 displaced by 0.31 Å from their best plane. This plane forms a dihedral angle of 32.1° with the phenyl ring C5–C10 and is nearly perpendicular to the phenyl ring C19–C24 (dihedral angle of 83.0°). The two sulfonamido groups in the molecule have similar geometries with the S=O bond distances in the range 1.432–1.446 Å, that is slightly longer than the mean value of 1.428 Å for sulfonamides.[56] The bond lengths S1–N2, N2–C3, C3–N15 and N15–S16 are intermediate between single and double bonds.

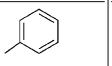
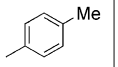
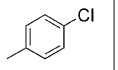
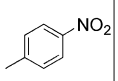
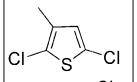
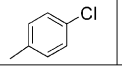
Bond lengths within the cation, showing short C2a–C3a, C5a–C6a and C4a–N7a distances (1.332–1.352 Å), and much longer C3a–C4a and C4a–C5a bonds (1.394–1.412 Å) indicate large population of the mesomeric form of the cation with the positive charge located at the dimethylamino group. Similar bond-length pattern was observed in other crystal structures with 4-dimethylaminopirydynium cations.[57–61]

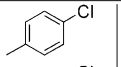
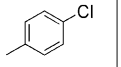
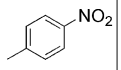
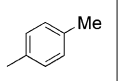
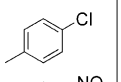
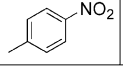
The cation binds via two hydrogen bonds, N1a–H···O11 and C6a–H···O12, to the ring sulfonyl



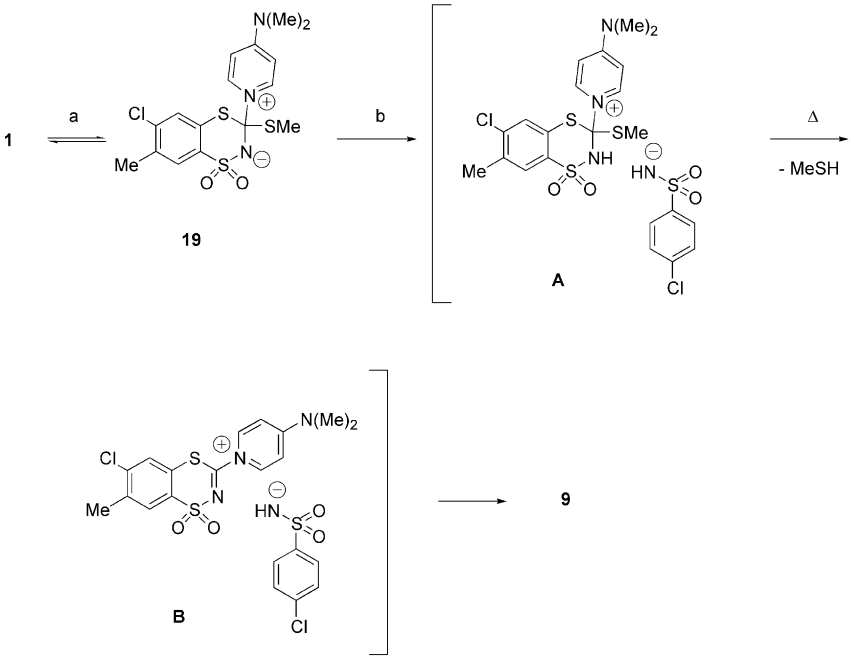
Scheme 1. Synthesis of 6-chloro-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **5**. Reagents and yields: (a) KOH (3.5 molar equiv); (b) CS_2 (1.6 molar equiv), EtOH, 0–20 °C, 68%; aqueous HCl, 20 °C, 3 h, 92%; (c) Me_2SO_4 (1,13 molar equiv), NaOH (1.25 molar equiv), H_2O, 0–20 °C, 4 h, 91%.



Compds	R	B	Ar	Solvent
1, 7	Me	DMAP		Toluene
1, 8	Me	DMAP		Toluene
1, 9	Me	DMAP		Toluene
1, 10	Me	DMAP		Toluene
1, 11	Me	DMAP		Toluene
5, 12	H	DMAP		Toluene

Compds	R	B	Ar	Solvent
6, 13		DMAP		Toluene
1, 14	Me	Et_3N		Benzene
1, 15	Me	Et_3N		Benzene
8, 16	Me	DMAP		–
14, 17	Me	Et_3N		–
15, 18	Me	Et_3N		–

Scheme 2. Synthesis of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamide derivatives **7**–**18**.



Scheme 3. Proposed mechanism of the formation of aminium sulfonamidate **9**. Reagents and yields: (a) 4-dimethylaminopyridine (1.15 molar equiv) toluene, reflux, 15 h, 23%; (b) 4-$ClPhSO_2NH_2$ (1 molar equiv), toluene, reflux, 30 h, 86%.

group of the anion. The geometries of these hydrogen bonds [N1a···O11 3.088(4) Å, N1a–H1a 0.80 Å, H1a···O11 2.44 Å, <N1a–H1a···O11 138°; C2a···O12 3.383(4) Å, C2a-H2a 0.98 Å, H2a···O12 2.46 Å, <C2a–H2a···O12 156°] point to a rather weak N–H···O interaction whereas one would expect a much stronger, 'charge-assisted' hydrogen bond[62,63] in case of the negative charge being located at the O atom of the sulfonyl group and/or positive charge being located at the pyridine N–H group.

We have generated and optimized the molecular structure in vacuo of the sulfonamidate anion of **9** using the ab initio (RHF/6-31G**) and density functional (B3LYP/3.21G**) computations.[64] The experimental and optimized calculated values of the most relevant geometrical parameters [bond distances (Å) and angles (°)] are shown in Table 1. The inspection of the data in Table 1 indicates that the geometric parameters calculated by the different methods used in this study show some differences with respect to the experimental

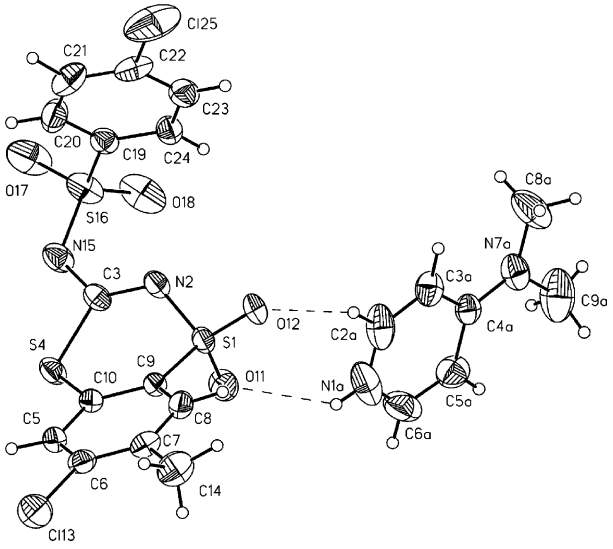


Figure 2. ORTEP drawing showing atom labeling for **9**.

Table 1. Selected theoretical and experimental bond distances (Å) and bond angles (°) for sulfonamidate anion of **9**

Bond	B3LYP /6-31G**	HF/6-31G**	Experimental
S(1)–O(11)	1.471	1.4373	1.4458 (17)
S(1)–O(12)	1.470	1.4333	1.4315 (17)
S(1)–N(2)	1.641	1.5968	1.600 (2)
N(2)–C(3)	1.318	1.3005	1.314 (3)
C(3)–S(4)	1.840	1.8058	1.786 (2)
C(3)–N(15)	1.318	1.3016	1.331 (3)
N(15)–S(16)	1.664	1.6185	1.616 (2)
S(16)–O(17)	1.472	1.4381	1.442 (2)
S(16)–O(18)	1.470	1.4371	1.437 (2)
S(1)–N(2)–C(3)	122.35	122.89	121.75 (17)
N(2)–C(3)–S(4)	123.94	123.92	125.62 (18)
S(4)–C(3)–N(15)	107.24	108.19	107.70 (17)
C(3)–N(15)–S(16)	120.61	121.19	120.52 (18)
O(11)–S(1)–O(12)	118.19	117.67	115.41 (11)
O(11)–S(16)–O(18)	118.80	118.46	116.66 (16)

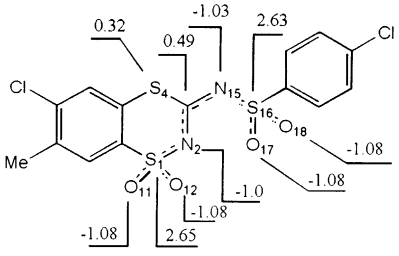


Figure 3. Molecular diagram of the anion moiety of **9** showing the natural atomic charges on selected atoms.

values, the results obtained with 6-31G** basis set at the HF level being the most similar to the experimental data.

The atomic charges were calculated using RHF/6-31G** optimized structure and the results are presented in Figure 3. From both, the theoretical and experimental analysis of geometric and electronic properties of the sulfonamidate fragment we can infer that the negative charge of the anion is extensively delocalized over oxygen atoms of the two sulfonyl groups and the two sulfonamido nitrogen atoms N2 and N15 and not localized at one atomic center.

Compounds **9**, **11**–**14** and **16**–**18** were tested in the US National Cancer Institute (Bethesda, MD, USA) for their in vitro anticancer activity using 51–58 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 sulphorhodanine 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.[65–67] The antitumor activity of a test compound is reported for each cell line by three parameters: log GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), log TGI value (TGI = molar concentration of the compound leading to total inhibition), and log LC_{50} value (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. Selectivity of a compound with respect to one or more cell lines of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG_MID value.

The following is to be noted regarding the tumor cell growth inhibition data with the tested compounds: (i) the compounds **12**, **13** and **18** were inactive (log $GI_{50} > -4$), whereas the other compounds **9**, **11**, **14**, **16** and **17** exhibited reasonable activity against one or more human tumor cell lines (Table 2), (ii) the compounds with noteworthy activity (log $GI_{50} < -8.00$; log TGI = −5.50 to −5.45) and remarkable selectivity for SR leukemia cell lines are the 4-dimethylaminopyridinium and triethylaminium 4-chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidates **9** and **14** (Tables 2 and 3).

The following conclusions may be drawn from the structure–activity (SAR) study. (i) a marked disparity in bioactivity exists between the aminium salts (**9**, **14**) and parent 4-chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamide **17**. This difference suggests that the salts **9** and **14** provide improved solubility and the charged structure of these molecules is essential for potent cytotoxicity. Moreover, a hypothesis can be put forward that the specific cancer lines show cellular uptake of **9** and **14** in form of a tight ion pair which proved to be stable in solution over a wide range of pH. (ii) in a series of aminium salts, electronic character of substituent on benzodithiazine ring is clearly the most important factor influencing cytotoxicity. Thus, the presence of electron-donating methyl group at position 7 significantly enhances cytotoxicity (**9**

Table 2. Overview of the results of the in vitro antitumor screening for compounds **9**, **11**–**14** and **16**–**18**[a]

Compd	No. of the cell lines investigated	No. of the cell lines giving positive log GI_{50}[b] (M), log TGI[c] (M) and log LC_{50}[d] (M)						MG_MID[e] for log GI50	Δ[f] for log GI50 and most sensible cell line
		Log GI50[b] (M)		Log TGI[c] (M)		Log LC50[d] (M)			
		No.	Range	No.	Range	No.	Range		
9	51	31	< −8.00 to −4.08	4	−5.50 to −4.00	2	−4.46 to 4.00	−4.33	3.67 Lukemia: SR
11	51	43	−4.63 to −4.02	6	−4.26 to −4.01	0		−4.28	0.36 Renal cancer: UO-31
14	52	31	< −8.00 to −4.01	3	−5.42 to 4.18	2	−4.04 to −4.00	−4.21	3.79 Leukemia: SR
16	58	19	−4.61 to −4.05	0		0	−4.08	−4.08	0.53 Lung cancer: HOP-92
17	54	38	−4.99 to −4.01	8	−4.52 to −4.05	2	−4.05 to −4.01	−4.28	0.71 Leukemia: SR

[a]Data obtained from the NCI's in vitro disease-oriented human tumor cells screen. Compounds **12**, **13** and **18** were inactive (log $GI_{50} > -4.00$).
[b]The log of the molar concentration that inhibits 50% net cell growth.
[c]The molar concentration giving total growth inhibition.
[d]The log of molar concentration leading to 50% net cell death.
[e]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 concentration was used for the calculation.
[f]The reported data represent the logarithmic difference between the parametric value referred to the most sensible cell line and the same mean parameter, Δ is consdered low if <1, moderate >1 and <3, high if >3.

Table 3. The in vitro activity and selectivity for leukemia cell lines by selected aminium sulfonamidates **9** and **14**, and their free sulfonamide **17**[a]

Leukemia cell line	Compound **9**			Compound **14**			Compound **17**		
	Log GI50[b] (M)	Log TGI[c] (M)	Log LC50[d] (M)	Log GI50[b] (M)	Log TGI[c] (M)	Log LC50[d] (M)	Log GI50[b] (M)	Log TGI[c] (M)	Log LC50[d] (M)
CCRF-CEM	−4.33	> −4.00	> −4.00	−4.23	> −4.00	> −4.00	−4.25	> −4.00	> −4.00
HL-60 (TB)	−4.46	> −4.00	> −4.00	−4.27	> −4.00	> −4.00	> −4.00	> −4.00	> −4.00
K-562	−5.72	> −4.00	> −4.00	−5.18	> −4.00	> −4.00	−4.38	> −4.00	> −4.00
MOLT-4	−6.18	> −4.00	> −4.00	−5.60	> −4.00	> −4.00	−4.77	−4.14	> −4.00
RPMI-8226	−4.32	> −4.00	> −4.00	−4.33	> −4.00	> −4.00	−4.24	> −4.00	> −4.00
SR	< −8.00	−5.50	−4.46	< −8.00	−5.42	−4.04	−4.99	−4.52	−4.05
MG_MID[e]	−5.50	−4.25	−4.08	−5.27	−4.24	−4.01	−4.44	−4.11	−4.01

[a]Data obtained from the NCI's in vitro disease-oriented human tumor cells screen. Compounds **12**, **13** and **18** were inactive (log $GI_{50} > -4.00$).
[b]The log of the molar concentration that inhibits 50% net cell growth.
[c]The molar concentration giving total growth inhibition.
[d]The log of molar concentration leading to 50% net cell death.
[e]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 concentration was used for the calculation.

and **14**, R = CH_3), while the introduction of hydrogen (**12**, R = H) or electron-withdrawing group (**13**, R = PhNHCO) at this position uniformly abolishes activity. As with the series of free benzenesulfonamide derivatives, the only 4-substituent which gave indisputable activity is Cl (**17**, R = Cl). Substitution of 4-position with electron donating group (**16**, R = CH_3) leads to a marked drop off in activity, and the presence of conjugative-electron-withdrawing group gives inactive compound (**18**, R = NO_2).

Conclusion

The above data prove the usefulness of the 1,1-dioxo-1,4,2-benzodithiazine ring system in the design of new active anticancer agents. The conjugation of benzodithiazine ring and benzenesulfonamido moiety results in a system which is stable in form of sulfonamidate aminium salt exhibiting a high degree of selectivity for leukemia cancer. The salts **9** and **14** may serve as useful lead compounds for the search of more powerful selective antineoplastic agents.

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 Spectrometer; (^{1}H- and ^{13}C NMR spectra) Varian Gemini 200 apparatus at 200 and 50 MHz, respectively (chemical shifts are expressed as δ values relative to Me_4Si as standard).

Potassium 6-chloro-1,1-dioxo-1,4,2-benzodithiazine-3-thiolate (3). To an ice-cold solution of KOH (17.4 g, 0.31 mol) and 2,4-dichlorobenzenesulfoamide **2** (20.35 g, 0.09 mol) in 96% ethanol (130 mL) was added with stirring carbon disulfide (10.7 g, 0.14 mol). After 0.5 h, the ice bath was removed and the reaction mixture was stirred at room temperature for 6 h, followed by reflux for 40 h. After cooling to room temperature the suspension was left overnight. The precipitate was collected by filtration, washed with ethanol (3×5 mL), dried and recrystallized from water (35 mL) to give **2** (19 g, 69%): mp 226–227 °C; IR (KBr) 1600, 1570,

1550 (C=N and benzene ring), 1395, 1365, 1160, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.47 (dd, J_{ortho} = 8.4 Hz, J_{meta} = 2.0 Hz, 1H, H-7), 7.52 (d, J_{meta} = 2.0 Hz, 1H, H-5), 7.86 (d, J_{ortho} = 8.4, 1H, H-8) ppm. Anal. ($C_7H_3ClNO_2S_3K$): C, 27.67; H, 0.99; N, 4.61. Found: C, 27.45; H, 1.22; N, 4.48.

6-Chloro-3-thioxo-2,3-dihydro-1,4,2-benzodithiazine 1,1-dioxide (4). To a suspension of potassium thiolate **3** (15.2 g, 0.05 mol) in water (45 mL) was added with stirring 36% hydrochloric acid (70 mL). The reaction mixture was stirred at room temperature for 3 h. The resulting yellow precipitate was collected by filtration washed successively with 18% hydrochloric acid (4×5 mL) and cold water (3×5 mL). Drying under vacuum gave the pure benzoditiazinethione **4** (12.2 g, 92%): mp 273–275 °C; IR (KBr) 3150 (NH), 1575, 1550, 1450 (benzene ring), 1320, 1160 (SO_2); ^1H NMR (DMSO-d_6) δ 7.37 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.1 Hz, 1H, H-7), 7.53 (d, J_{meta} = 2.1 Hz, 1H, H-5), 7.69 (d, J_{ortho} = 8.5 Hz, 1H, H-8), 12.54 (s, 1H, NH) ppm. Anal. ($C_7H_4ClN\,O_2S_3$): C, 31.63; H, 1.51; N, 5.27. Found: C, 31.50; H, 1.73; N, 5.17.

6-Chloro-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide (5). 6-Chloro-3-thioxo-2,3-dihydro-1,4,2-benzodithiazine 1,1-dioxide **4** (10.6 g, 004 mol) was dissolved in a solution of NaOH (2 g, 0.05 mol) in water (125 mL). To this ice-cooled solution $(CH_3)_2SO_4$ (5.6 g, 0.045 mol) was added dropwise. After 0.5 h, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 4 h. The title compound thus obtained was collected by filtration washed thoroughly ith water, 50% methanol (4×5 mL) and methanol (3×4 mL), and dried (10.2 g, 91%): mp 191.5–192.5 °C; IR (KBr) 1570, 1550, 1505 (benzodithiazine ring), 1320, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.69 (s, 3H, CH_3S), 7.81 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.0 Hz, 1H, H-7), 8.03 (d, J_{meta} = 2.0 Hz, 1H, H-5), 8.09 (d, J_{ortho} = 8.5 Hz, 1H, H-8) ppm. Anal. ($C_8H_6ClNO_2S_3$): C, 34.33; H, 2.16; N, 5.00. Found: C, 34.54; H, 2.11; N, 5.17.

General procedure (A) for the preparation of 4-dimethylaminopyridinum *N*-(1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamidates 7–13

A solution of 4-dimethylaminopyridine (2.5 g, 0.02 mol), the corresponding methylthiobenzodithiazine **1**, **5** or **6** (0.02 mol) and appropriate arylsulfonamide (0.02 mol) in dry toluene (50–60 mL) was refluxed with stirring until the evolution of MeSH had ceased (44–60 h) (CAUTION: due to a high toxicity, MeSH should be trapped into an aqueous NaOH solution). The precipitate thus obtained was filtered off, washed with toluene, dried and purified by crystallization from acetic acid.

In this manner, the following products were obtained.

4-Dimethylaminopyridinium *N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzo-dithiazin-3-yl)benzenesulfonamidate (7). Starting from 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **1** (5.9 g) and benzenesulfonamide (3.15 g), the title compound **7** was obtained (8.7 g, 83%): mp 201–202 °C; IR (KBr) 3230 (NH), 1985 (NH^+), 1650 (C=N), 1340, 1295, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3-7), 3.16 (s, 6H, CH_3NCH_3), 6.95 (d, J = 7.7 Hz, 2H, β-pyrid.), 7.45–7.52 (m, 3H, arom.), 7.61 (s, 1H, H-5, benzodithiazine), 7.80 (s, 1H, H-8), 7.82–7.86 (m, 2H, arom.), 8.20 (d, J = 7.7 Hz, 2H, α-pyrid), 12.9 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 19.26, 106.70, 106.90, 125.97, 126.84, 127.09, 128.08, 130.64, 131.16, 131.23, 135.45, 136.21, 139.02, 143.22, 156.50, 163.95 ppm. Anal. ($C_{21}H_{21}ClN_4O_4S_3$): C, 48.03; H, 4.03; N, 10.65. Found: C, 47.90; H, 4.18; N, 11.00.

4-Dimethylaminopyridinium 4-methyl-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidate (8). Starting from 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **1** (5.9 g) and 4-methylbenzenesulfonamide (3.42 g), the title compound **8** was obtained (9.1 g, 84%): mp 191–192 °C; IR (KBr) 3225 (NH), 2690, 1995, 1920 (NH^+), 1650 (C=N), 1345, 1298, 1150, 1134, (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3Ph), 2.35 (s, 3H, CH_3-7, benzodithiazine), 3.15 (s, 6H, CH_3NCH_3), 6.94 (d, J = 7.7 Hz, 2H, β-pyrid.), 7.25 (d, J = 8.2 Hz, 2H, Ph), 7.59 (s, 1H, H-5, benzodithiazine), 7.77 (d, J = 8.2 Hz, 2H, Ph), 7.79 (s, 1H, H-8), 8.19 (d, J = 7.7 Hz, 2H, α-pyrid.), 13.1 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 19.18, 20.91, 106.86, 125.92, 126.80, 127.17, 128.49, 130.68, 131.22, 135.37, 136.19, 139.03, 140.42, 141.12, 156.85, 163,61 ppm. Anal. ($C_{22}H_{23}ClN_4O_4S_3$): C, 49.01; H, 4.29; N, 10.39. Found: C, 49.21; H, 4.41; N, 10.29.

4-Dimethylaminopyridinium 4-chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidate (9). Starting from methylthiobenzodithiazine **1** (5.9 g) and 4-chlorobenzenesulfonamide (3.83 g), the title compound **9** was obtained (10.2 g, 91%): mp 194–195 °C; IR (KBr) 3300, 3140 (NH), 1955 (NH^+), 1645 (C=N), 1345, 1150, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 3.16 (s, 6H, CH_3NCH_3), 6.94 (d, J = 7.7 Hz, 2H, β-pyrid.), 7.49–7.56 (m, 4H, arom.), 7.62 (s, 1H, H-5, benzodithiazine), 7.80–7.86 (m, 3H, arom.), 8.16–8.22 (m, 2H, arom.); 13.2 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 19.19, 106.69, 106.87, 125.99, 126.86, 128.15, 129.18, 130.45, 130.96, 135.56, 135.96, 136.29, 138.99, 142.03, 156.87, 164.13 ppm. Anal. ($C_{21}H_{20}Cl_2N_4O_4S_3$): C, 45.08; H, 3.60; N, 10.01. Found: C, 45.17; H, 3.78; N, 9.82.

4-Dimethylaminopyridinium 4-nitro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidate (10). Starting from methylthiobenzodithiazine **1** (5.9 g) and 4-nitrobenzenesulfonamide (4.04 g), the title comound **10** was obtained (10.3 g, 90%): mp 200–201 °C; IR (KBr) 3275, 3140 (NH), 1965 (NH^+), 1645 (C=N), 1350, 1150, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 3.16 (s, 6H, CH_3NCH_3), 6.94 (d, J = 7.6 Hz, 2H, β-pyrid.), 7.64 (s, 1H, H-5, benzodithiazine), 7.80 (s, 1H, H-8), 8.05 (d. J = 8.4 Hz, 2H, arom.), 8.19 (d, J = 7.6 Hz, 2H, α-pyrid.), 8.30 (d, J = 8.4 Hz, 2H, arom.), 13.2 (br.s, 1H,

NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 19.20, 106.89, 123.5, 126.06, 126.92, 128.37, 130.20, 130.73, 135.78, 136.43, 139.07, 148.78, 148.99, 156.88, 164.67 ppm. Anal. ($C_{21}H_{20}ClN_5O_6S_3$): C, 44.24; H, 3.54; N, 12.28. Found: C, 44.33; H, 3.60; N, 12.26.

4-Dimethylaminopyridinium 2,5-dichloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-3-thiophenesulfonamidate (11). Starting from methylbenzodithiazine **1** (5.9 g) and 2,5-dichloro-3-thiophenesulfonamide (4.64 g), the title compound **11** was obtained (10.8 g, 90%): mp 230–231 °C; IR (KBr) 3220, 3110 (NH), 2700 (NH^+), 1640 (C=N), 1340, 1310, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.37 (s, 3H, CH_3), 3.16 (s, 6H, CH_3–N–CH_3), 6.85 (d, $J=7.6$ Hz, 2H, β-pyrid.), 7.22 (s, 1H, H-4, thiophene), 7.66 (s, 1H, H-5, benzodithiazine) 7.83 (s, 1H, H-8, benzodithiazine), 8.20 (d, $J=7.6$ Hz, α-pyrid.), 12.9 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 19.22, 106.68, 106.88, 123.97, 126.10, 126.95, 127.49, 128.08, 130.32, 130.70, 135.56, 136.40, 139.05, 139.95, 156.87, 164.66 ppm. Anal. ($C_{19}H_{17}Cl_3N_4O_4S_4$): C, 38.03; H, 2.85; N, 9.34. Found : C, 37.91; H, 3.05; N, 9.30.

4-Dimethylaminopyridinium 4-chloro-*N*-(6-chloro-1,1-dioxo - 1,4,2 - benzodi - thiazin - 3 - yl)benzenesulfonamidate (12). Starting from methylthiobenzodithiazine **5** (5.6 g) and 4-chlorobenzenesulfonamide (3.83 g), the title compound **12** was obtained (9.7 g, 89%): mp 191–193 °C; IR (KBr) 3230, 3120 (NH), 2695, 1940, 1920 (NH^+), 1648 (C=N), 1365, 1305, 1150, 1135 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.16 (s, 6H, CH_3NCH_3), 6.95 (d, $J=7.6$ Hz, 2H, β-pyrid.), 7.47–7.55 (m, 3H, arom.), 7.67 (d, $J=1.8$ Hz, 1H, arom.), 7.78–7.84 (m, 3H, arom.), 8.19 (d, $J=7.6$ Hz, 2H, α-pyrid.), 13.15 (br., s, 1H, NH^+), Anal. ($C_{20}H_{18}Cl_2N_4O_4S_3$): C, 43.03; H, 3.32; N, 10.27. Found : C, 44.18; H, 3.40; N, 10.11.

4-Dimethylaminopyridinium 4-chloro-*N*-(6-chloro-7-phenylcarbamoyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidate (13). Starting from methylthiobenzo dithiazine **6** (7.9 g) and 4-chlorobenzenesulfonamide (3.83 g), the title compound **13** was obtained (8.3 g, 62%): mp 231–233 °C dec; IR (KBr) 3270, 3145 (NH), 2660, 1950 (NH^+), 1680 (C=O), 1650, (C=N), 1310, 1160, 1135 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.17 (s, 6H, CH_3NCH_3), 6.96 (d, $J=6.9$ Hz, 2H, β-pyrid.), 7.12, (t, 1H, arom.), 7.35 (t, 2H, arom.), 7.53–7.91 (m, 8H, arom.), 8.20 (d, 6.9 Hz, 2H, α-piryd.), 10.62 (s, 1H, NHCO), 13.1 (br.s, 1H, NH^+) ppm. Anal. ($C_{27}H_{23}Cl_2N_5O_5S_3$): C, 48.79; H, 3.48; N, 10.53. Found : C, 48.70; H, 3.59; N, 10.70.

General procedure (B) for the preparation of triethylaminium *N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamidates 14–15

To a solution of 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **1** (5.9 g, 0.02 mol) and triethylamine (5.1 g, 0.05 mol) in dry benzene (45 mL), was added the appropriate benzenesulfonamide (0.02 mol). The reaction mixture was stirred at room temperature for 3 h followed by reflux until the evolution of MeSH had ceased (55–60 h). The precipitate thus obtained was filtered off, washed with benzene, dried and purified by crystallization from acetic acid.

In this manner, the following products were obtained.

Triethylaminium 4-chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfoamidate (14). Starting from 4-chlorobenzenesulfonamide (3.83 g), the title compound **14** was obtained (9.2 g, 85%): mp 139–140 °C; IR (KBr) 2740, 1910 (NH^+), 1345, 1150, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 (t, $J=6.8$ Hz, 9H, NEt_3), 2.36 (s, 3H, CH_3-7), 3.07 (q, 6H, $J=7.3$ Hz, NEt_3), 7.52 (d, $J=8.3$ Hz, 2H, Ph), 7.62 (s, 1H, H-5, benzodithiazine), 7.80 (s, 1H, H-8, benzodithiazine), 7.82 (d, $J=8.3$ Hz, 2H, Ph), 8.80 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 8.62, 19.19, 45.75, 126.00, 126.87, 128.16 129.18, 130.46, 130.98, 135.58, 135.96, 136.30, 142.04, 164.12 ppm. Anal. ($C_{20}H_{25}Cl_2N_3O_4S_3$): C, 44.60; H, 4.68; N, 7.80. Found : C, 44.52; H, 4.60; N, 7.82.

Triethylaminium 4-nitro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzenesulfonamide (15). Starting from 4-nitrobenzenesulfonamide (4.04 g), the title compound **15** was obtained (9.6 g, 87%): mp 157–158 °C; IR (KBr) 2630, 2515, 1940 (NH^+), 1350, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 (t, $J=7.3$ Hz, 9H, NEt_3), 2.36 (s, 3H, CH_3-7), 3.09 (q, 6H, $J=7.3$ Hz, NEt_3), 7.66 (s, 1H, H-5, benzodithiazine), 7.81 (s, 1H, H-8, benzodithiazine), 8.05 (d, $J=9.0$ Hz, 2H, Ph), 8.31 (d, $J=9.0$ Hz, 2H, Ph), 8.80 (br.s, 1H, NH^+) ppm; ^{13}C NMR (DMSO-d_6) δ 8.64, 19.20, 45.78, 123.53, 126.04, 126.94, 128.74, 130.23, 130.75, 135.79, 136.44, 148.79, 149.02, 164.69 ppm. Anal. ($C_{20}H_{25}ClN_4O_6S_3$): C, 43.74; H, 4.59; N, 10.20. Found: C, 43.78, H, 4.73; N, 10.09.

Preparation of 6-chloro-7-methyl-3-(4-dimethylamino-1-pyridinio)-3-methylthio-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-2-ate (19). A solution of methylthiobenzodithiazine **1** (5.9 g, 0.02 mol) and 4-dimethylaminopyridine (2.8 g, 0.023 mol) in dry toluene (20 mL) was refluxed with stirring for 15 h. After cooling to room temperature the reaction mixture was left overnight. The precipitate was collected by filtration, washed successively with toluene (3×2 mL) and isopropanol (3×2 mL), and dried initially at room temperature, and then at 90 °C to give the pure adduct (**19**). Yield 1.9 g (22.8%), mp 145–148 °C. IR (KBr) 3075, 3055, 2950, 2920, 2.700, 1940, 1660, 1610, 1575, 1575, 1535, 1455, 1440, 1400, 1345, 1275, 1210, 1140, 1080, cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3-7), 3.20 (s, 6H, CH_3NCH_3), 4.00 (s, 3H, CH_3S), 6.88 (d, $J=7.3$ Hz, 2H, β-pyrid.), 7.24 (s, 1H, H-5), 7.87 (s, 1H, H-8), 8.15 (d, $J=7.3$ Hz, 2H, α-pyrid.) ppm; ^{13}C NMR ($CDCl_3$) δ 20.23, 40.80, 45.54, 108.61, 124.97, 126.68, 126.96, 132.13, 133.83, 134.66, 137.18, 143.48, 158.56 ppm. Anal. ($C_{16}H_{18}ClN_3O_2S_3$): C, 46.19; H, 4.36; N, 10.10. Found: C, 46.00; H, 4.40; N, 10.26.

Preparation of sulfonamidate 9 from adduct 19. A mixture of the compound **19** (1.66 g, 0.004 mol) and 4-chlorobenzenesulfonamide (0.77 g, 0.004 mol) in dry toluene (10 mL) was refluxed with stirring until the

evolution of MeSH had ceased (30 h). The precipitate was filtered off under suction, washed with toluene and the product **9** thus obtained was purified by crystallization from acetic acid. Yield 1.93 g (86%); mp and ^{1}H NMR data were in accordance with those reported above for the authentic sample of **19**.

General procedure for preparation of free sulfonamides (16, 17 and 18)

To a solution of 95% H_2SO_4 (1.1 g, 0.01 mol) in acetic acid (18 mL) was added with stirring the appropriate sulfonamidate **8**, **14** or **15** (0.008 mol) and the reaction mixture was heated under reflux for 5 h. After cooling to room temperature and standing overnight, the product that precipitated was separated by suction, washed successively with acetic acid (4×1.5 mL) and toluene (5×1.5 mL) and dried at 90 °C.

In this manner, the following compounds were obtained.

4-Methyl-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzene-sulfonamide (16). Starting from sulfonamidate **8** (4.31 g), the title compound **16** was obtained (2.9 g, 87%): mp 212–213 °C; IR (KBr) 3150 (NH), 1590, 1555, 1450, 1370, 1345, 1315, 1170, 1150 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.23 (br.s, 1H, NH), 7.28 (d, J=8.1 Hz, 2H, Ph), 7.64 (s, 1H, H-5), 7.74 (d, J=8.1 Hz, 2H. Ph), 7.83 (s, 1H, H-8) ppm; ^{13}C NMR (DMSO-d_6) δ 19.49, 21.23, 126.31, 127.26, 127.55, 128.92, 130.76, 131.09, 135.98, 136.64, 140.21, 140.82, 163.70 ppm. Anal. ($C_{15}H_{13}ClN_2O_4S_3$): C, 43.21; H, 3.14; N, 6.72. Found ; C, 43.03; H, 3.24; N, 6.68.

4-Chloro-*N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzene-sulfonamide (17). Starting from sulfonamidate **14** (4.31 g), the title compound **17** was obtained (3.2 g, 91%): mp 223–225 °C; IR (KBr) 3180 (NH), 1575, 1560, 1445, 1370, 1350, 1320, 1165, 1150 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H, CH_3), 3.76 (br.s, 1H, NH), 7.54 (d, J=8.6 Hz, 2H, Ph), 7.64 (s, 1H, H-5), 7.81 (s, 1H, H-8), 7.84 (d, J=8.6 Hz, 2H, Ph), ppm. Anal. ($C_{14}H_{10}Cl_2N_2O_4S_3$): C, 38.44; H, 2.30; N, 6.40. Found: C, 38.21; H, 2.53; N, 6.32.

4-Nitro-N-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)benzene-sulfonamide (18). Starting from sulfonamidate **15** (4.39 g), the title compound **18** was obtained (3.30 g, 92%): mp 271–272 °C; IR (KBr) 3115 (NH), 1605, 1585, 1525, 1445, 1370, 1350, 1320, 1170, 1150 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 6.56 (br.s, 1H, NH), 7.65 (s, 1H, H-5), 7.81 (s, 1H, H-8), 8.06 (d, J=8.9 Hz, 2H, Ph), 8.30 (d, J=8.9 Hz, 2H, Ph) ppm; ^{13}C NMR (DMSO-d_6) δ 19.22, 123.55, 126.08, 126.96 128.74, 130.23, 130.74, 135.82, 136.46, 148.82, 149.00, 164.69 ppm. Anal. ($C_{14}H_{10}ClN_3O_6S_3$): C, 37.54; H, 2.25; N, 9.38. Found : C, 37.41; H, 2.37; N, 9.19.

X-ray structure analysis of 9. Crystal data for $(C_{14}H_9Cl_2N_2O_4S_3)^-(C_7H_{11}N_2)^+$: monoclinic, space group $C2/c$, a=35.6804(10), b=7.2859(3), c=18.9221(7) Å, β=99.192(3)°, V=4855.9(3) Å^3, Z=8, d_x=1.531 g cm^{-3}, T=293 K. Data were collected for a crystal with dimensions 0.4×0.4×0.3 mm on a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. Final R indices for 4013 reflections with $I > 2\sigma(I)$ and 325 refined parameters are: R_1=0.0438, wR_2=0.1089 (R_1=0.0489, wR_2=0.1045 for all 4424 data).

Acknowledgements

This work was supported by the Polish State Committee for Scientific Research (Grant No. 4 P05F 007 19). We also thank dr V. L. Narayanan from NCI (Bethesda, MD, USA) for the antitumor screenings.

References and Notes

1. Brzozowski, Z.; Sławiński, J. *Acta Polon. Pharm.* **1984**, *41*, 5.
2. Brzozowski, Z.; Sławiński, J. *Acta Polon. Pharm.* **1984**, *41*, 133.
3. Brzozowski, Z.; Gajewski, F.; Sławiński, J.; Pomarnacka, E. *Acta Polon. Pharm. Drug Res.* **1993**, *50*, 199.
4. Brzozowski, Z.; Sławiński, J.; Angielski, S.; Szczepańska-Konkiel, M. *Acta Polon. Pharm.* **1985**, *42*, 313.
5. Brzozowski, Z.; Sławiński, J. *Acta Polon. Pharm.* **1985**, *42*, 319.
6. Brzozowski, Z.; Sławiński, J.; Gajewski, F.; Angielski, S.; Hoppe, A. *Acta Polon. Pharm.* **1985**, *42*, 413.
7. Pomarnacka, E.; Brzozowski, Z. *Acta Polon. Pharm* **1986**, *43*, 8.
8. Brzozowski, Z.; Gajewski, F.; Sławiński, J.; Pomarnacka, E. *Acta Polon. Pharm.* **1986**, *43*, 291.
9. Brzozowski, Z.; Sławiński, J.; Janiec, W.; Cegła, U.; Sliwiński, L.; Sedlak, I. *Acta Polon. Pharm. Drug Res.* **1992**, *49*, 75.
10. Brzozowski, Z. *Acta Polon. Pharm.-Drug Research* **1997**, *54*, 293.
11. Brzozowski, Z.; Sączewski, F. *Eur. J. Med. Chem.* **2002**, *37*, 285.
12. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1997**, *54*, 49.
13. Pomarnacka, E. *Acta Polon. Pharm. Drug Res.* **1998**, *55*, 481.
14. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1998**, *55*, 473.
15. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1995**, *52*, 91.
16. Wright, S. W. *J. Heterocyclic Chem.* **2001**, *38*, 723.
17. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1995**, *52*, 287.
18. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1996**, *53*, 269.
19. Pomarnacka, E. *Acta Polon. Pharm. Drug Res.* **1996**, *53*, 373.
20. Pomarnacka, E.; Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1997**, *54*, 215.
21. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1998**, *55*, 233.
22. Pomarnacka, E.; Kornicka, A. *Acta Polon. Pharm. Drug Res.* **1998**, *55*, 297.
23. Brzozowski, Z. *Acta Polon. Pharm* **1988**, *55*, 375.
24. Brzozowski, Z.; Kornicka, A. *Acta Polon. Pharm. Drug Res.* **1999**, *54*, 135.
25. Brzozowski, Z. *Acta Polon. Pharm. Drug Res.* **1998**, *55*, 49.
26. Neamati, N.; Mazumder, A.; Sunder, S.; Owen, J. M.; Schultz, R. J.; Pommier, Y. *Antiviral Chem. Chemother.* **1997**, *8*, 485.
27. Brzozowski, Z.; Sączewski, F. *J. Med. Chem.* **2002**, *45*, 430.
28. Pomarnacka, E.; Kornicka, A.; Sączewski, F. *Heterocycles* **2001**, *55*, 753.
29. Howber, J.; Grossman, C. S.; Crowell, T. A.; Rider, B. J.; Harper, R. W.; Kromer, K. E.; Tao, E. V.; Aikinns, J.; Poore, G. A.; Rinzel, S. M.; Grindey, G. B.; Show, W. N.; Tood, G. C. *J. Med. Chem.* **1990**, *33*, 2393.

30. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitoh, K. *J. Med. Chem.* **1992**, *35*, 2496.
31. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Okada, T.; Koyanagi, N.; Asada, M.; Yoshimatsu, K.; Kitoh, K. *Proc. Am. Assoc. Cancer Res.* **1992**, *33*, 516.
32. Koyanagi, N.; Nagasu, T.; Fujita, F.; Watanbe, T.; Tsukahara, K.; Funahashi, Y.; Fujita, M.; Taguchi, T.; Yoshino, H.; Kitoh, K. *Cancer Res.* **1994**, *54*, 1702.
33. Yoshimatsu, K.; Yamaguchi, A.; Yoshino, H.; Koyanagi, N.; Kitoh, K. *Cancer Res.* **1997**, *57*, 3208.
34. Chern, J. W.; Leu, Y. L.; Wang, S. S.; Jou, R.; Lee, C. F.; Tsou, P. C.; Hsu, S. C.; Liaw, Y. C.; Lin, H. M. *J. Med. Chem.* **1997**, *40*, 2276.
35. Powis, G.; Gallegos, A.; Abraham, R. T.; Ashendel, C. L.; Zalkow, L. H.; Dorr, R.; Dvorakova, K.; Salomon, S.; Harrison, S.; Worzalla, J. *Cancer Chemother. Pharamocol.* **1997**, *41*, 22.
36. John, C. S.; Lim, B. B.; Vilner, B. J.; Geyer, B. C.; Bowen, W. D. *J. Med. Chem.* **1998**, *41*, 2445.
37. Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999**, *42*, 3789.
38. O'Brien, P. M.; Ortwine, D. F.; Pavlowsky, A. G.; Picard, J. A.; Sliskovic, D. R.; Roth, B. D.; Wyer, R. D.; Johnson, C. F.; Man, C. F.; Halla, K. H. *J. Med. Chem.* **2000**, *43*, 156.
39. Cheng, M.; De, B.; Pikul, S.; Almstead, N. G.; Natchus, M. G.; Anastasio, M. V.; Mc Phail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, M.; Gu, F.; Dowty, M. E.; Mieling, G. E.; Janusz, M. J.; Wang-Weigand, S. *J. Med. Chem.* **2000**, *43*, 369.
40. Supuran, C. T.; Briganti, F.; Tilli, S.; Chegwidden, W. R.; Scozzafawa, A. *Bioorg. Med. Chem.* **2001**, *9*, 703.
41. Pikul, S.; Ohler, N. E.; Ciszewski, G.; Laufersweiler, M. C.; Almsted, N. G.; De, B.; Natchus, M. G.; Hsieh, L. C.; Janusz, M. J.; Peng, S. X.; Branch, T. M.; King, S. L.; Taiwo, Y. O.; Mieling, G. E. *J. Med. Chem.* **2001**, *44*, 2449.
42. Huang, S.; Lin, Z.; Huang, J. *Eur. J. Med. Chem.* **2001**, *36*, 863.
43. Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; Colla, P. *J. Med. Chem.* **1996**, *39*, 522.
44. Artico, M. *Farmaco* **1996**, *51*, 305 [review article].
45. Nicklaus, M. C.; Neamati, N.; Hong, H.; Muzumder, A.; Sunder, S.; Chen, J.; Milne, G. W. A.; Pommier, Y. *J. Med. Chem.* **1997**, *40*, 920.
46. Skulnick, H. I.; Johson, P. D.; Aristoff, P. A.; Morris, J. K.; Lovasz, K. D.; Howe, W. J.; Watenpaugh, K. D.; Janakiraman, M. N.; Anderson, D. J.; Reischer, R. J.; Schwartz, T. M.; Banitt, L. S.; Tomich, P. K.; Lynn, J. C.; Horng, M. M.; Chong, K. T.; Hinshaw, R. R.; Dolak, L. A.; Seest, E. P.; Schwende, F. J.; Rush, B. D.; Howard, G. M.; Toth, L. N.; Wilkinson, K. R.; Kakuk, T. J.; Johnsos, C. W.; Cole, S. L.; Zaya, R. M.; Zipp, G. L.; Possert, P. L.; Dalga, R. J.; Zhong, W. Z.; Willams, M. G.; Romines, K. R. *J. Med. Chem.* **1997**, *40*, 1149.
47. Turner, S. R.; Strohbach, W. J.; Tommasi, A.; Aristoff, P. A.; Johnson, P. D.; Skulnick, H. I.; Dolak, L. A.; Seest, E. P.; Tomich, P. K.; Bohanon, M. J.; Horng, M.; Lynn, J. C.; Chong, K. T.; Hinshaw, R. R.; Watenpaugh, K. D.; Janakiraman, M. N.; Thaisrivongs, S. *J. Med. Chem.* **1998**, *41*, 3467.
48. Arraz, E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; Clercq, E.; Vega, S. *J. Med. Chem.* **1998**, *41*, 4109.
49. Turpin, J. A.; Song, Y.; Inman, J. K.; Huang, M.; Wallqvist, A.; Maynard, A.; Covell, D. G.; Rice, W. G.; Appella, E. *J. Med. Chem.* **1999**, *42*, 67.
50. Debnath, A. K.; Radigan, S.; Jiong, S. *J. Med. Chem.* **1999**, *42*, 3203.
51. Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305.
52. Boyer, F. E.; Prasad, J. V. N. V.; Domagala, J. M.; Ellsworth, E. L.; Gajda, Ch.; Hagen, S. E.; Markoski, L. J.; Tait, B. D.; Lunney, E. A.; Palovsky, A.; Ferguson, D.; Graham, N.; Holler, T.; Hupe, D.; Nauhan, C.; Tummino, P. J.; Urumov, A.; Zeikus, E.; Zeikus, G.; Gracheck, S. J.; Sanders, J. M.; Roest, S. V.; Brodfuecher, J.; Iyer, K.; Sinz, M.; Gulnik, S. V.; Erickson, J. *J. Med. Chem.* **2000**, *43*, 843.
53. Finke, P. E.; Meurer, L. C.; Oates, B.; Mills, S. G.; Mac Coss, M.; Malkowitz, L.; Springer, M. S.; Dauhherty, B. L.; Gould, S.L; De Martino, J. A.; Siciliano, S. J.; Carella, A.; Carver, G.; Holmes, K.; Danzeisen, R.; Hazuda, D.; Kassler, J.; Lineberger, J.; Miller, M.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 265.
54. Schaal, W.; Karlsson, A.; Ahlsen, G.; Lindberg, J.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultèn, J.; Hallberg, A.; Karlèn, A. *J. Med. Chem.* **2001**, *44*, 155.
55. Caler, B. W.; Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2001**, *44*, 2253.
56. Orpen A. G.; Brammer, L.; Allen, F. H.; Kennard, O.; Watson, D. G.; Taylor, R.; Bürgi, H.-B.; Dunitz, J. D., Eds.; Structure Correlations. VCH: New York, 1994; Vol. 2.
57. Chao, M.; Schempp, E.; Rosenstein, R. D. *Acta Crystallogr.* **1977**, *B33*, 1820.
58. Mayr-Stein, R.; Bolte, M. *Acta Crystallogr.* **2000**, *C56*, e19.
59. Bryant Junior, G. L.; King Junior, J. A. *Acta Crystallogr.* **1992**, *C48*, 2036.
60. Hosomi, H.; Ohba, S.; Ito, Y. *Acta Crystallogr.* **2000**, *C56*, e149.
61. Dega Szafran, Z.; Gdaniec, M.; Grunwald-Wyspiańska, M.; Kosturkiewicz, Z.; Koput, J.; Krzyżanowski, P.; Szafran, M. *J. Mol. Struct.* **1992**, *270*, 99.
62. Aakeröy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, 397.
63. Braga, D.; Maini, L.; Grepioni, F.; De Cian, A.; Felix, O.; Fischer, J.; Hosseini, M. W. *New. J. Chem.* **2000**, *24*, 547.
64. The geometry of the anion moiety of **9** was fully optimized using a molecular orbital ab initio method at the Hartree-Fock level of theory with the 6-31G** basis set, and a density functional B3LYP/6-31G** method. The ab initio calculations were carried out using the SPARTAN program distributed by Wavefunction Inc. and installed on a Silicon Graphics O2 workstation. The density functional calculations were carried out using the TITAN program distributed by Wavefunction Inc. and installed on a PC Pentium III computer.
65. Boyd, M. R. *Am. Assoc. Res.* **1989**, *30*, 652.
66. Monks, A. P.; Scudiero, D. A.; Skehan, P.; Shoemaker, R.; Poull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Cambell, H.; Mayo, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1991**, *83*, 757.
67. Weinstein, J. N.; Myers, T. G.; O'Connor, P. M.; Friend, S. H.; Fornance, A. J., Jr.; Kohn, K. W.; Fojo, T.; Bates, S. E.; Rubinstein, L. V.; Anderson, N. L.; Buolamwini, J. K.; van Osdol, W. W.; Monks, A. P.; Scudiero, D. A.; Sausiville, E. A.; Zaharevitz, D. W.; Bunow, B.; Viswanadhan, V. N.; Johnson, G. S.; Wittes, R. E.; Paull, K. D. *Science* **1997**, *275*, 343.