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Original article

Synthesis, molecular structure, and in vitro antitumor activity of new 4-chloro-2-mercaptobenzenesulfonamide derivatives

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Abstract

The reaction of 3-amino-2-(2-alkylthio-4-chlorobenzenesulfonyl)guanidines **2a**–**j** with 1,2-dicarbonyl compounds are described. Depending on structure of 1,2-dicarbonyl reagent novel 2-alkylthio-5-chloro-*N*-(1,2,4-triazin-3-yl)benzenesulfonamides **3**–**15**, 1-(2-alkylthio-4-chlorobenzenesulfonyl)-3-(2-oxobutane-3-ylidenoimino)guanidines **16**–**18** and 2-alkylthio-4-chloro-*N*-(1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl)benzenesulfonamides **19**–**21** are obtained. The structures of these compounds were confirmed on the basis of elemental analysis, spectral data and X-ray analysis. The compounds **4**, **5**, **7**, **9**, **10**, **12**–**15**, **17**, **18** and **20** were screened at the National Cancer Institute (NCI) for their in vitro activities against a panel of 56 tumor cell lines and relationship between structure and antitumor activity are discussed. The compounds **10**, **12**, **17** and **20** were inactive, whereas the other compounds exhibited reasonable activity against one or more human tumor cell lines. The prominent compound **18** showed significant activity against cell lines of colon cancer (HCT-116), renal cancer (786-0) and melanoma (M14) (GI_{50} in the range 0.33–1.08 μM) as well as good selectivity toward non-small cell lung cancer (HOP-62) cells (GI_{50} = 0.05 μM, TGI = 0.38 μM and LC_{50} = 4.83 μM).

Keywords: 4-Chloro-2-mercapto-*N*-(1,2,4-triazin-3-yl)benzenesulfonamide; Synthesis; Crystal structures; Antitumor effect

1. Introduction

Numerous of structurally novel sulfonamide derivatives have been reported to possess anticancer or/and anti-HIV [1–5] properties. We have also described the syntheses of a number of 4-chloro-2-mercaptobenzenesulfonamide possessing bulky aromatic/heterocyclic moieties substituting the sulfonamide functionality. These compounds, depending on their structure, exhibited either anticancer [6–17] or anti-HIV-1 [6,7,15,18–20] activities and have been described by Neamati et al. [21,22] as a novel class of potent HIV-1 integrase inhibitors. We further found that *S*-substituted 4-chloro-2-mercaptobenzenesulfonamide derivatives possessing primary (unsubstituted) sulfonamide moiety or cyano group attached to the nitrogen atom of the sulfonamide moiety also showed substantial anticancer properties [23].

Recently, in search for even more potent 2-mercaptobenzenesulfonamides and for structure–activity relationship studies we synthesized a new series of arylsulfonylaminoguanidine derivatives possessing electron-withdrawing substituents, either at the N-terminal nitrogen atom of the hydrazine moiety of type **I** [24] or at the opposite nitrogen atom of guanidine moiety of type **II** and **III** [25,26] (Fig. 1), and found many of them exhibited a pronounced anticancer activity [24–26].

This prompted us to develop a method for the synthesis of their cyclic analogues. Hence, in the present study we elaborated an efficient method for syntheses of novel 2-alkylthio-4-chloro-*N*-(1,2,4-triazin-3-yl)benzenesulfonamides of type **IV** and related 2-alkylthio-4-chloro-5-methyl-*N*-(1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl)benzenesulfonamides of type **V** (Fig. 1).

2. Results and discussion

2.1. Chemistry

The previously described methods were employed for the synthesis of compounds **1a**–**j** [27] and **2a**–**c** [24]. Analo-

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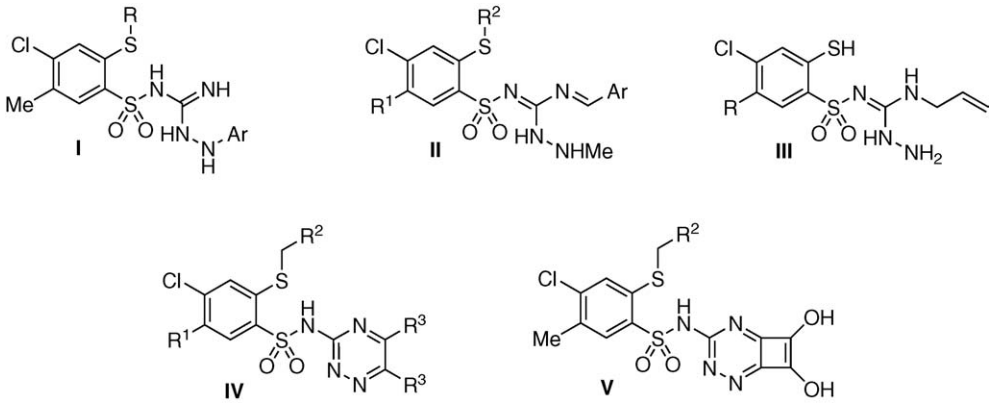
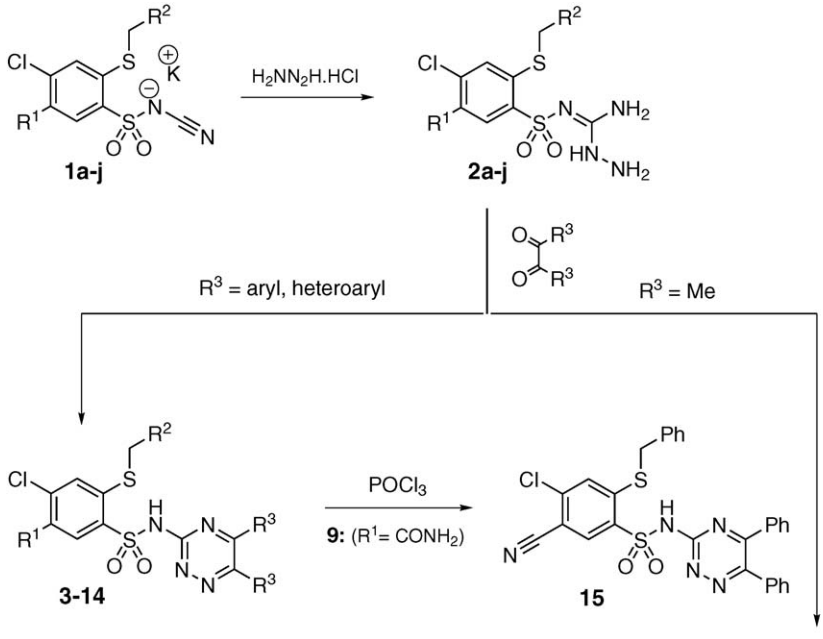


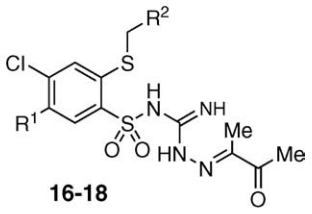
Fig. 1.

gously were prepared novel 3-amino-2-(2-alkylthio-4-chloro-5-R[1]-benzenesulfonyl)guanidines **2d–j** as shown in Scheme 1.

The synthesis of the target cyclocondensation products **3–14** were achieved by reacting the corresponding aminoguanidines **2a–c** and **2e–j** with suitable 1,2-diarylethane-1,2-diones in refluxed ethanol (**3–6**) or a mixture of ethanol and dioxane (**9–12**), as well as dry DMSO (**7–8, 13–14**) at 80–85 °C for 8–30 h (Scheme 1). Subsequent reaction of **9** with $POCl_3$ carried out at elevated temperature led to the formation of the expected 2-benzylthio-4-chloro-5-cyano-*N*-(1,2,4-triazin-3-yl)benzenesulfonamide (**15**) in 85% yield (Scheme 1).



Compounds	R^1	R^2	R^3
1a, 2a, 3	Me	COOEt	Ph
1b, 2b, 4	Me	Ph	Ph
1b, 2b, 5	Me	Ph	2-furyl
1c, 2c, 6	Me	Me	Ph
1e, 2e, 7	Me	$CONH_2$	Ph
1f, 2f, 8	H_2NCO	COOEt	Ph
1g, 2g, 9	H_2NCO	Ph	Ph
1g, 2g, 10	H_2NCO	Ph	2-furyl
1g, 2g, 11	H_2NCO	Ph	4-MeO-Ph
1h, 2h, 12	PhNHCO	Ph	Ph
1i, 2i, 13	4-Cl-PhNHCO	Ph	Ph
1j, 2j, 14	4-Me-PhNHCO	Ph	Ph



Compounds	R^1	R^2
1b, 2b, 16	Me	Ph
1d, 2d, 17	Me	H
1h, 2h, 18	PhNHCO	Ph

Scheme 1. Syntheses of the 2-alkylthio-4-chloro-5-R[1]-*N*-(1,2,4-triazin-3-yl)benzenesulfonamides **3–15** and 1-(2-alkylthio-4-chloro-5-R[1]-benzenesulfonyl)-3-(2-oxobutane-3-ylideneimino)guanidines **16–18**.

When the aminoguanidines **2b**, **d** and **2h**, in turn, were subjected to the reaction with diacetyl the corresponding 1-[2-alkylthio-4-chloro-5-(methyl or phenylcarbamoyl)benzenesulfonyl]-3-(2-oxobutane-3-ylideneimino)guanidines **16–18** were obtained as final products in 65–89% of separated yields (Scheme 1). It is worthy noting, that prolongation of the reaction time up to 24 h does not provide either the cyclocondensation product or higher yield. The first step of this reaction i.e. condensation of the terminal amino group of the hydrazine moiety with one carbonyl group, is fast. However, the intermediate product of type **16–18** adopts the stable sulfonylamino tautomeric form as shown in Scheme 1. This may results in relatively low reactivity of the opposite imino group to the reaction with second carbonyl group [25].

It is well known that the reactions of squaric acid (3,4-dihydroxy-3-cyclobutene-1,2-dione) and its esters with aliphatic or aromatic amines lead to the formation of the corresponding amide or bisamide derivatives [28–30]. As depicted in Scheme 2, treatment of aminoguanidine **2a**, **b**, **d** with 1 molar equivalent of squaric acid in refluxing ethanol afforded the 2-alkylthio-4-chloro-5-methyl-*N*-(1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl)benzenesulfonamide **19–21** in moderate (34–42%) yields. As expected, the same product **20** was formed after treatment of aminoguanidine **2b** with 1 molar equivalent of 3,4-diethoxy-3-cyclobutene-1,2-dione in ethanol, but pure product was isolated in poor yield.

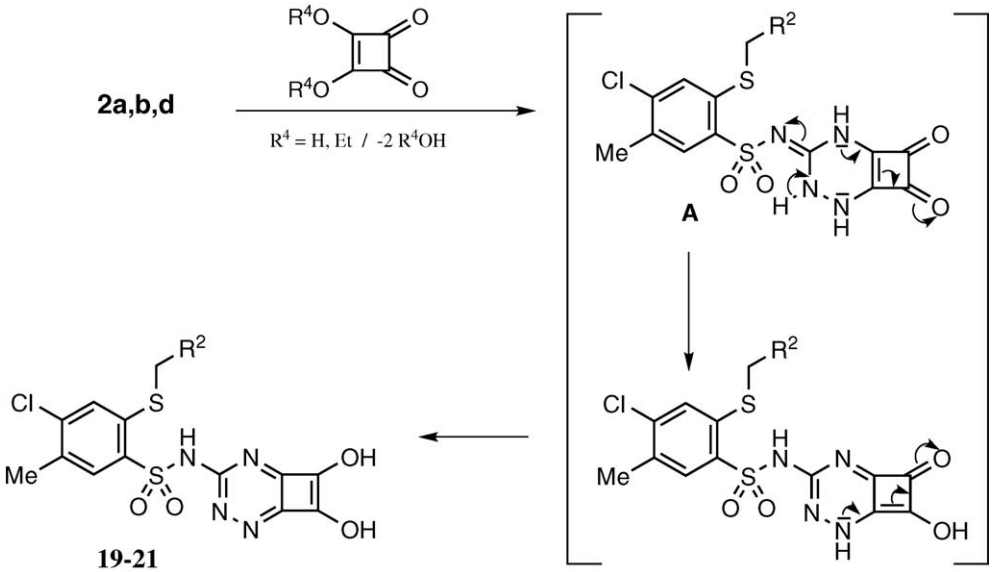
The formation of these *N*-(1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl) derivatives is believed to arise from the following two-step process: nucleophilic addition of amino groups to the double C=C bond of squaric acid with simultaneous elimination of water molecules resulting in the intermediate **A**, and finally tautomerization. A similar mechanism was proposed for the reaction with diethyl squarate (Scheme 2).

All the final products were characterized by IR and NMR spectroscopy as shown in experimental protocols. Elemental analyses were in accordance with the proposed structure.

X-ray crystallography was undertaken in order to investigate in detail tautomeric structures on representative compounds **4**, **10** and **11**. Molecular structures of compounds **4**, **10** and **11** are shown in Figs. 2–4, respectively.

Compounds **4** and **10** crystallize as sulfonamide tautomers, i.e. the hydrogen atom is bound to the sulfonamide nitrogen atom. This form was confirmed by localization of H atoms from electron-density difference maps and by geometrical parameters characteristic of the sulfonamide form. For example, the exocyclic C7–N1 bonds in **4** and **10** (1.378 and 1.381 Å, respectively), are ca. 0.06 Å longer than in **11**.

Contrary to **4** and **10**, compound **11** crystallizes in the sulfonimide form with hydrogen atom joined to N3 of the heterocycle (Fig. 4). This tautomer was confirmed by localization of the H atom in electron-density maps, by molecular geometry of **11** and by observed assembly mode of the molecules in the solid state. For example, the exocyclic C7–N1 and endocyclic N2–C9 and N4–C8 bonds of the 1,2,4-triazine fragment (1.318, 1.311 and 1.318 Å, respectively) show a substantial double-bond character pointing to a sulfonimide tautomer of **11**. Change of the tautomeric form is also reflected in the geometry of the 1,2,4-triazine cycle which



Compounds	R^2
2a, 19	COOEt
2b, 20	Ph
2d, 21	H

Scheme 2. Synthesis and proposed mechanism of the formation of 2-alkylthio-4-chloro-5-methyl-*N*-(1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl)benzenesulfonamides **19–21**.

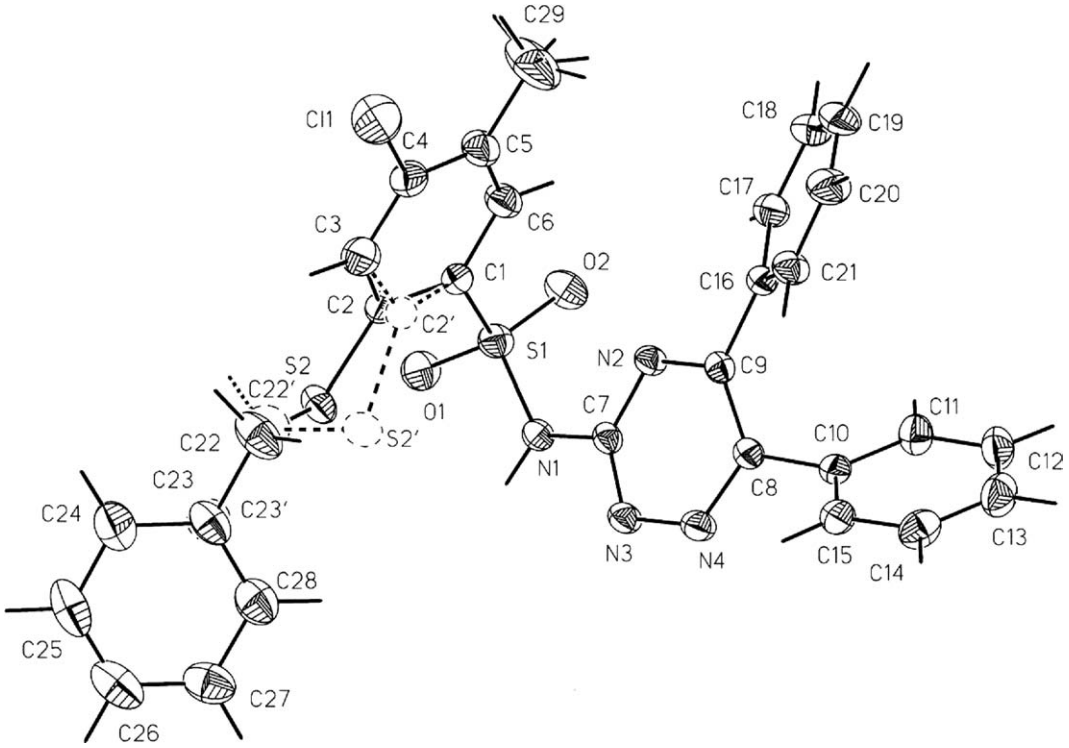


Fig. 2. ORTEP drawing [37] of **4** with labeling scheme and displacement ellipsoids at 40% probability level (dashed lines show minor conformation of the thiomethylene fragment).

has significantly spread C–N bond-lengths for the sulfonimide form of **11** (1.311–1.369 Å) whereas all C–N bonds are similar in length for the sulfonamide tautomers of **4** and **10** (1.326–1.346 and 1.329–1.334 Å, respectively).

Compound **4** which has more limited hydrogen-bonding potential, when compared with **10** and **11**, gives in crystals solely self-complementary hydrogen bond interaction shown in Fig. 5a. Compound **10**, which analogously to **11** crystallizes as the DMSO solvate and whose molecule is equipped with primary amide functionality, forms in crystals one-dimensional hydrogen-bonded assemblies via complementary interaction between primary amide group and sulfona-

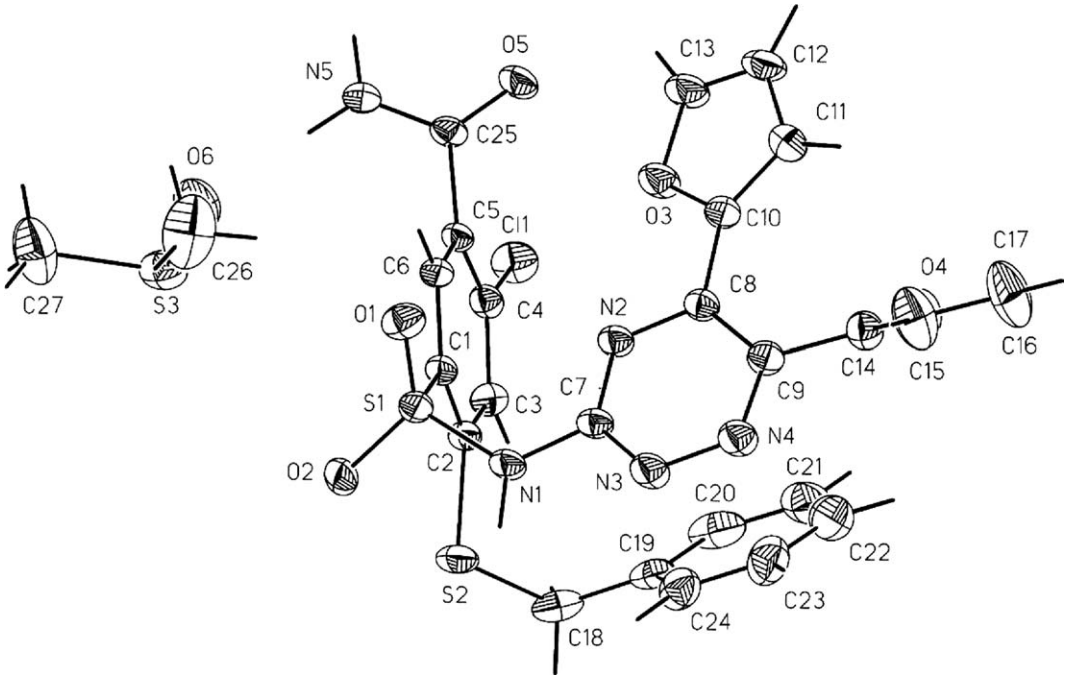


Fig. 3. ORTEP drawing [37] of **10** with labeling scheme and displacement ellipsoids at 40% probability level (only one of the two orientations of the DMSO molecule is shown).

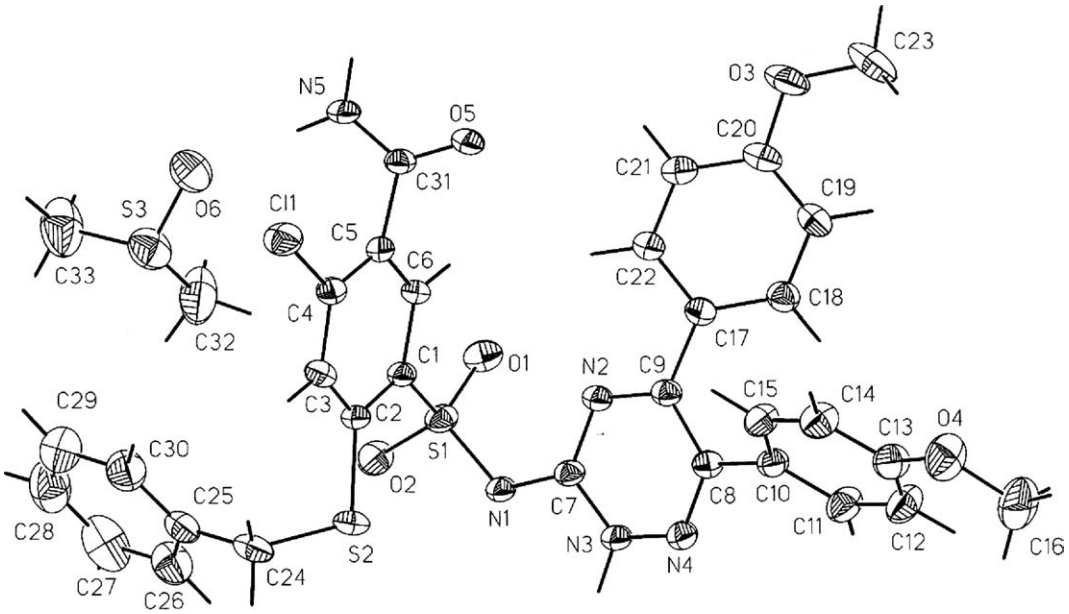


Fig. 4. ORTEP drawing [37] of **11** with labeling scheme and displacement ellipsoids at 40% probability level (only one of the two orientations of the DMSO molecule is shown).

mide moiety (Fig. 5b) and this interaction points unambiguously to sulfonamide character of **10**. On the other hand, hydrogen bond interaction observed in crystals of **11** between the primary amide group and (3*E*)-1,2,4-triazin-3(2*H*)-imine moiety, as shown in Fig. 5c, provides definitive tautomer confirmation. Hydrogen bonds between these two complementary functionalities assemble molecules of **11** into one-dimensional network, with DMSO molecules connected to the amide groups via hydrogen bonds.

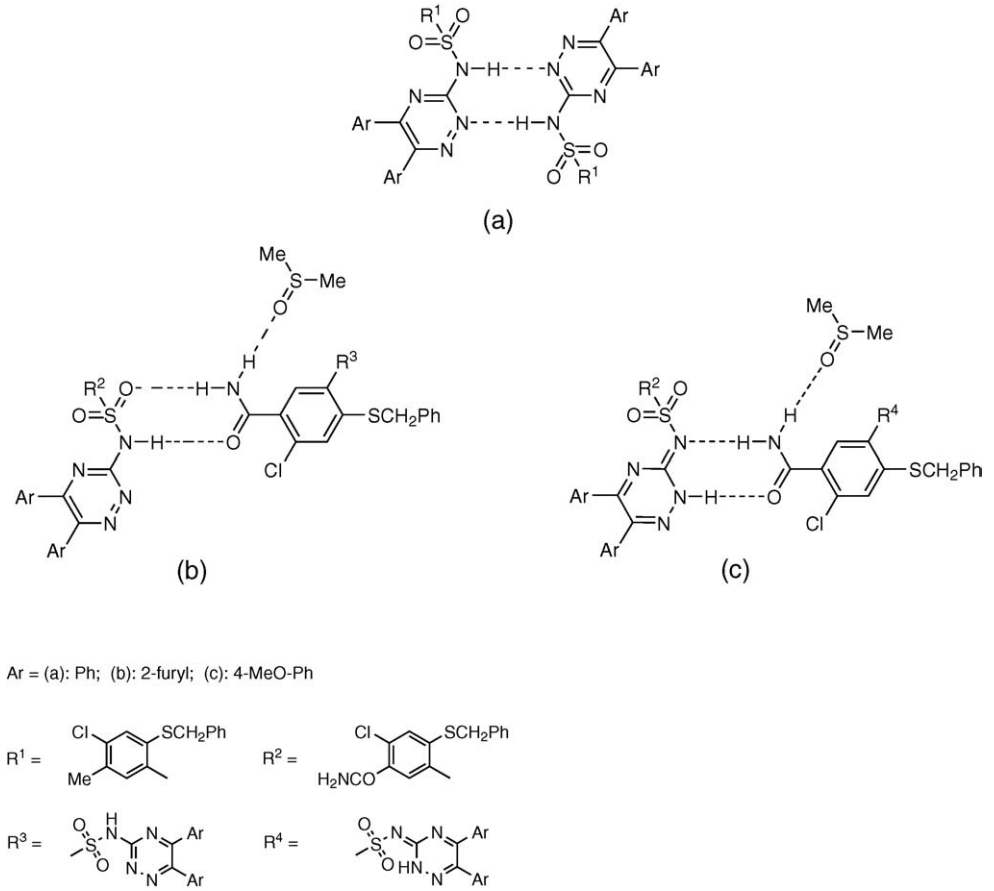


Fig. 5. Hydrogen-bonding motifs in crystals structures of (a) compound **4**, (b) compound **10** and (c) compound **11**.

Despite the fact that all three studied molecules are to a large extend flexible, the conformations which they adopt in crystals show certain common features. The aromatic substituents of 1,2,4-triazine form a propeller, i.e. they are twisted in the same direction relative to the planar heterocyclic ring. The torsion angles N2–C7–N1–S1 (–7.8, –20.8 and –1.5° for **4**, **10** and **11**, respectively) C7–N1–S1–C1 (–58.2, –66.7 and –68.1° for **4**, **10** and **11**, respectively) and N1–S1–C1–C2 (–72.0, –57.8 and –60.2° for **4**, **10** and **11**, respectively), describing orientation of the sulfonamide or sulfonimide group relative to the heterocyclic moiety and conformation of the arylsulfonamide or -sulfonimide moiety, reveal similar shape of the large molecular fragment. As could be expected, the most flexible constituent of these molecules is the benzylthio group attached to the benzene ring showing different conformations in the three studied structures.

2.2. Biology

The compounds **4**, **5**, **7**, **9**, **10**, **12–15**, **17**, **18** and **20** were submitted to the US National Cancer Institute (NCI; Bethesda, MD), for in vitro testing against a panel approximately 56 tumor cell lines, derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. The compounds were 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 system and the information which is encoded by the activity pattern over all cell lines, have been published [31–33]. The antitumor activity of tested compounds is given by three parameters for each cell line: 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 parameters over all cell lines. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested. Selectivity of the compound with respect to one or more cell lines of the screen is characterized by a high deviation (Δ) 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: (a) the compounds **10**, **12**, **17** and **20** were inactive (log GI_{50} [M] > –4), whereas the other compounds **4**, **5**, **7**, **9**, **13–15** and **18** exhibited reasonable activity against one or more human cancer cell lines (Table 1); (b) relatively broad spectrum of tumor cell growth inhibition was found for the compounds **4**, **5** and **14–15** (Table 1), while the compounds **7**, **9**, **13** and **18** demonstrated a moderate selectivity toward one or more tumor cell lines (Δ log GI_{50} ranged from 1.11 to 2.77; Table 2).

The following conclusion may be drawn from the structure–activity relationship study. In a series of 5,6-diphenyl-1,2,4-triazin-3-yl derivatives electronic character of substituent on benzene ring at position 5 is important factor influencing cytotoxicity. Thus, the presence of electron-withdrawing carbamoyl or 4-chlorophenylcarbamoyl groups at this position significantly enhances selectivity (**9**, $R^1 = CONH_2$ and **13**, 4-Cl-PhNHCO). For example, replacement of the methyl group in **4** (R^1 = Me) for carbamoyl (**9**, $R^1 = CONH_2$) caused a reasonable increase of potency against the cell lines of colon cancer (HT29), CNS (SNB-75), melanoma (SK-MEL-28) and ovarian cancer (OVCAR-4) (log GI_{50} in the range from –6.99 to –5.56), respectively (Table 2). Similarly, the presence of 4-chlorophenylcarbamoyl moiety at this position (**13**) enhances selectivity toward renal cancer RXF 393 cells (**13**, Δ log GI_{50} = 2.77) (Table 2). In contrast, the presence of unsubstituted phenylcarbamoyl group at this position (**12**, R^1 = PhNHCO) leads to total loss of cytotoxic activity. The loss in potency was also observed when the phenyl groups at five and six positions on 1,2,4-triazine ring in **9** (R^3 = Ph) was replaced for 2-furyl moieties (**10**, R^3 = 2-furyl).

Substitution of five position with electron-withdrawing cyano group (**15**, R^1 = CN) enhances activity against cell lines of leukemia HL-60(TB) and RPMI-8226, whereas the substitution of this position with 4-methylphenylcarbamoyl moi-

Table 1
Overview of the results of the anticancer screening for compounds **4**, **5**, **7**, **9**, **10**, **12–15**, **17**, **18** and **20**[a]

Compound	Number of the cell lines investigated	Number of the cell lines giving positive log GI_{50}, log TGI and log LC_{50}[b]					
		Log GI_{50} (M)		Log TGI (M)		Log LC_{50} (M)	
		Number	Range	Number	Range	Number	Range
4	55	54	–5.25 to –4.43	53	–4.60 to –4.04	31	–4.23 to –4.01
5	56	55	–4.77 to –4.41	49	–4.49 to –4.08	28	–4.22 to –4.01
7	56	41	–6.17 to –4.10	16	–4.54 to –4.06	6	–4.16 to –4.03
9	56	36	–6.99 to –4.11	20	–4.43 to –4.05	3	–4.14 to –4.07
13	55	54	–7.29 to –4.10	22	–4.44 to –4.02	3	–4.13 to –4.05
14	52	51	–4.93 to –4.31	40	–4.54 to –4.03	22	–4.24 to –4.01
15	53	51	–5.20 to –4.35	39	–4.65 to –4.04	18	–4.21 to –4.02
18	55	42	–7.26 to –4.01	7	–6.41 to –4.10	1	–5.32

Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Table 2 or Refs. [31–33] for details).

[a] Compounds **10**, **12**, **17** and **20** were inactive.

[b] The response parameters: log GI_{50}, log TGI and log LC_{50} are interpolated values representing the molar concentrations at which percentage growth is +50, 0 and –50, respectively.

Table 2
The in vitro activity and selectivity toward most sensitive tumor cell lines for compounds **4**, **5**, **7**, **9**, **13**–**15** and **18**

Compound	Most sensitive tumor cell lines	Log GI_{50} (M)[a]	Selectivity toward tumor cell lines (Δ)[b] for log GI_{50} (M). The value is shown if Δ > 1	Mean value for all tested cell lines (MG_MID)[c] for log GI_{50} (M)
4	Non-small cell lung: EKVX	–5.25		–4.68
	Non-small cell lung: NCI-H322M	–4.85		
	Leukemia: RPMI-8226	–4.94		
5	Prostate : DU-145	–4.77		–4.61
	Melanoma: SK	–4.76		
	Leukemia: MOLT	–4.75		
7	CNS: SF-539	–6.17	1.83	–4.34
	Ovarian: OVCAR-3	–4.71		
	Colon: HCT-116	–4.68		
9	Colon: HT29	–6.99	2.53	–4.45
	CNS: SNB-75	–6.30	1.85	
	Melanoma: SK-MEL-28	–6.30	1.85	
	Ovarian: OVCAR-4	–5.56	1.11	
	Breast: MCF7	–4.74		
13	Renal: RXF 393	–7.29	2.77	–4.52
	Renal: SN12C	–4.78		
	Leukemia: MOLT-4	–4.82		
14	Leukemia: RPMI-8226	–4.93		–4.64
	Melanoma: LOX IMV1	–4.88		
	Breast: MDA-MB-435	–4.80		
15	Renal: RXF 393	–5.20		–4.61
	Leukemia: HL-60(TB)	–5.15		
	Leukemia: RPMI-8226	–5.01		
18	Non-small cell lung: HOP-62	–7.26	2.60	–4.65
	Non-small cell lung: EKVX	–5.18		
	Colon: HCT-116	–6.47	1.82	
	Renal: 786-0	–6.12	1.47	
	Renal: ACHN	–5.10		
	Melanoma: M14	–5.97	1.32	
	Melanoma: LOX IMV1	–5.32		
	Leukemia: HL-60(TB)	–5.63		
	Leukemia: MOLT-4	–5.43		
	Leukemia: K-562	–5.26		
	Leukemia: SR	–5.21		
	Leukemia: RPMI-8226	–5.15		
	CNS: SF-539	–5.55		
	Prostate : DU-145	–5.46		
	Breast: MDA-MB-231/ATCC	–5.23		
	Ovarian: OVCAR-8	–5.07		
	Ovarian: OVCAR-4	–4.91		

Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Refs [31–33] for details).

[a] The response parameter: log GI_{50} is interpolated value representing the molar concentration at which percentage growth is + 50.

[b] The reported data represent the logarithmic difference between the parametric value referred to the most sensitive cell line and the same mean parameter, Δ is considered low if < 1, moderate > 1 and < 3, high if > 3.

[c] 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.

ety (**14**) results in almost equal potency (compare **14** with **4** in Tables 1 and 2). It is pertinent to note, however, that replacement of the 1,2,4-triazine ring for a fused non-aromatic 1,2-dihydroxycyclobuta[*e*]1,2,4-triazine ring system leads to inactive compound **20**.

On the other hand, replacement of the benzylthio group (**4**) at position 2 of benzene ring for carbamoylmethylthio moiety resulted in compound **7** (R^1 = Me, R^2 = $CONH_2$) (Δ log GI_{50} = 1.83, Table 2) exhibited a moderate level of selectivity toward CNS (SF-539) cells (log GI_{50} = –6.17, log TGI = –4.52 and log LC_{50} = –4.03).

The most active compound **18** (R^1 = PhNHCO, R^2 = Ph) indicating that combination of phenylcarbamoyl group at position 5 and 3-substituted aminoguanidine moiety attached to sulfonyl group results in compound with suitable properties, while its analogue **17** (R^1 = Me, R^2 = H) was inactive. The compound **18** exhibited advantageous activity against leukemia subpanel among others (Table 2). Relatively highest sen-

sitivity to **18** was also found for cell lines of colon (HCT-116), renal (786-0) and melanoma (M14), whereas a reasonable level of selectivity (Δ log GI_{50} = 2.60, Δ log TGI = 2.30 and Δ log LC_{50} = 1.29) indicated that the lung cancer HOP-62 cells were the most susceptible to inhibition by compound **18** (log GI_{50} = –7.26, log TGI = –6.41 and log LC_{50} = –5.32).

3. Conclusions

We have developed a method for the synthesis of new series of 4-chloro-2-mercaptobenzenesulfonamide derivatives with the nitrogen atom of the sulfonamide moiety attached either to 1,2,4-triazin-3-yl or 1,2-dihydroxycyclobuta[*e*]1,2,4-triazin-3-yl ring systems as well as their 'open chain' analogues. These compounds depending on their structure exhibited anticancer activity. Compounds **9**, **13** and **18** were the most potent of all derivatives tested. Moreover, the compound **18** acted as potent inhibitor against HOP-62 non-small cell lung cancer line. The results we have obtained hitherto indicated that anticancer activity of the newly synthesized compounds depends on the electronic nature of substituents.

4. Experimental protocols

4.1. Synthesis

Melting points were taken on a Bűchi SMP 20 apparatus and are reported uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer FT IR 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini (200 MHz) and Varian Unity Plus (500 MHz) spectrometer using TMS as internal standard (δ values in ppm). Mass spectra were recorded on a Finnigan MAT 95 spectrometer at 70 eV. The results of elemental analyses for C, H and N were within ±0.4% of the theoretical values.

*4.1.1. General procedure for the preparation of 3-amino-2-(2-alkylthio-4-chloro-5-R^1- benzenesulfonyl)guanidines (**2d–j**)*

To a suspension of the corresponding *N*-(benzenesulfonyl)-cyanamide potassium salt **1d–j** (5 mmol) in dry dioxane (25 ml) hydrazine hydrochloride (0.68 g, 10 mmol) was added. The reaction was stirred under reflux for 4–5 h and left to stand at room temperature overnight. The precipitate was filtered off, washed with dioxane (3 × 3 ml), dried and treated with water (50 ml). After vigorously stirring for 10 min the precipitate was collected by filtration, dried and crystallized from a mixture of ethanol and dioxane (1:1).

In this manner, the following aminoguanidines were obtained.

*4.1.1.1. 3-Amino-2-(4-chloro-5-methyl-2-methylthiobenzenesulfonyl)guanidine (**2d**).* Yield: 1.17 g, 76%, m.p. 249–251 °C dec.; IR (KBr) 3464, 3354, 3340, 3265, 3223 (NH_2, NH), 1342, 1130 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 4.51 (s, 2H, NH_2), 6.97 (s, 2H, NNH_2), 7.28 (s, 1H, H-3), 7.81 (s, 1H, H-6), 8.40 (s, 1H, NH) ppm. Anal. ($C_9H_{13}ClN_4O_2S_2$) C, H, N.

*4.1.1.2. 3-Amino-2-(2-carbamoylmethylthio-4-chloro-5-methylbenzenesulfonyl)guanidine (**2e**).* Yield: 1.37 g, 78%, m.p. 183–185 °C dec.; IR (KBr) 3447, 3355, 3216, 3162 (NH_2, NH), 1683 (C=O), 1345, 1135 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 3.68 (s, 2H, SCH_2), 4.52 (s, 2H, NH_2), 6.99 (s, 2H, NNH_2), 7.23 (s, 1H, H_aNC=O), 7.53 (s, 1H, H-3), 7.55 (s, 1H, H_bNC=O), 7.82 (s, 1H, H-6), 8.44 (s, 1H, NH) ppm. Anal. ($C_{10}H_{14}ClN_5O_3S_2$) C, H, N.

*4.1.1.3. 3-Amino-2-(5-carbamoyl-4-chloro-2-ethoxycarbonylmethylthiobenzenesulfonyl)guanidine (**2f**).* Yield: 1.78 g, 87%, m.p. 216–218 °C dec.; IR (KBr) 3448, 3406, 3354, 3336, 3218 (NH_2, NH), 1716 (C=O), 1663 (C=O), 1310, 1131 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 6.8 Hz, 3H, CH_3), 4.03 (s, 2H, SCH_2), 4.13 (q, J = 6.8 Hz, 2H, CH_2), 4.51 (s, 2H, NH_2), 7.01 (s, 2H, NNH_2), 7.41 (s, 1H, H-3), 7.67 (s, 1H, H_aNC=O), 7.87 (s, 1H, H-6), 7.97 (s, 1H, H_bNC=O), 8.48 (s, 1H, HN) ppm. Anal. ($C_{12}H_{16}ClN_5O_5S_2$) C, H, N.

*4.1.1.4. 3-Amino-2-(2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonyl)guanidine (**2g**).* Yield: 2.18 g, 95%, m.p. 219–221 °C dec.; IR (KBr) 3454, 3342 (NH_2, NH), 1684 (C=O), 1320, 1135 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 4H, dioxane), 4.35 (s, 2H, SCH_2), 4.52 (s, 2H, NH_2), 6.99 (s, 2H, NNH_2), 7.26–7.28 (m, 1H, aromatic), 7.33–7.36 (m, 2H, aromatic); 7.45–7.46 (m, 3H, aromatic, H-3), 7.65 (s, 1H, H_aNC=O), 7.87 (s, 1H, H-6), 7.94 (s, 1H, H_bNC=O), 8.48 (s, 1H, HN) ppm. Anal. ($C_{15}H_{16}ClN_5O_3S_2 \cdot 1/2C_4H_8O_2$) C, H, N.

*4.1.1.5. 3-Amino-2-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)guanidine (**2h**).* Yield: 2.40 g, 98%, m.p. 237–239 °C dec.; IR (KBr) 3448, 3348, 3213, 3101 (NH_2, NH), 1684 (C=O), 1316, 1131 (SO_2) cm^{-1}. Anal. ($C_{21}H_{20}ClN_5O_3S_2$) C, H, N.

*4.1.1.6. 3-Amino-2-[2-benzylthio-4-chloro-5-(4-chlorophenylcarbamoyl)benzenesulfonyl]guanidine (**2i**).* Yield: 1.70 g, 65%, m.p. 252–254 °C dec.; IR (KBr) 3471, 3356, 3314, 3214 (NH_2, NH), 1687 (C=O), 1333, 1133 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.51 (s, 2H, SCH_2), 4.52 (s, 2H, NH_2), 7.02 (s. 2H, NNH_2), 7.26–7.29 (m, 1H, aromatic), 7.34–7.37 (m, 2H, aromatic), 7.41 (d, J = 8.5 Hz, 2H, aromatic), 7.47–7.49 (m, 2H, aromatic), 7.56 (s, 1H, H-3), 7.71 (d, J = 8.5 Hz, 2H, aromatic), 7.98 (s, 1H, H-6), 8.51 (s, 1H, NH), 10.70 (s, 1H, NHC=O) ppm. Anal. ($C_{21}H_{19}Cl_2N_5O_3S_2$) C, H, N.

*4.1.1.7. 3-Amino-2-[2-benzylthio-4-chloro-5-(4-methylphenylcarbamoyl)benzenesulfonyl]guanidine (**2j**).* Yield: 1.89 g, 75%, m.p. 229–231 °C dec.; IR (KBr) 3466, 3313 (NH_2, NH), 1654 (C=O), 1314, 1135 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 4.38 (s, 2H, SCH_2), 4.51 (s, 2H, NH_2),

7.02 (s, 2H, NNH_2), 7.14 (d, J = 7.5 Hz, 2H, aromatic), 7.25–7.28 (m, 1H, aromatic), 7.33–7.36 (m, 2H, aromatic), 7.47 (d, J = 7.5 Hz, 2H, aromatic), 7.54–7.57 (m, 3H, aromatic), 7.95 (s, 1H, H-6), 8.50 (s, 1H, HN), 10.45 (s, 1H, HNC=O) ppm. Anal. ($C_{22}H_{22}ClN_5O_3S_2$) C, H, N.

*4.1.2. Preparation of 2-alkylthio-4-chloro-5-methyl-N-(5,6-diaryl-1,2,4-triazin-3-yl)benzenesulfonamides (**3**–**6**)*

A stirred suspension of the corresponding 3-amino-2-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)guanidine **2a**–**c** (2 mmol) and benzil (0.43 g, 2 mmol) or 2,2′-furil (0.38 g, 2 mmol) (**5**) in ethanol (10 ml) was refluxed for 24 h and left to stand in a refrigerator overnight. The precipitate that deposited was filtered off, washed with ethanol (2 × 1 ml), and dried. The product was purified by crystallization either from ethanol or from a mixture of ethanol and dioxane (4:1).

In this manner, the following benzenesulfonamides were obtained.

4.1.2.1. 4-Chloro-2-ethoxycarbonylmethylthio-5-methyl-N-*(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**3**).* Yield: 0.64 g, 58%, m.p. 170–172 °C dec.; IR (KBr) 3198 (NH), 2976, 2925, 2848 (CH_3, CH_2), 1726 (C=O), 1343, 1147 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3-Ar), 3.74 (s, 2H, SCH_2), 4.06 (m, J = 7.2 Hz, 2H, OCH_2), 7.26–7.48 (m, 11H, aromatic and NH), 7.53 (s, 1H, H-3), 8.24 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ 14.54 (CH_3), 20.0 (CH_3-Ar), 37.53 (SCH_2), 62.39 (OCH_2), 128.75, 128.89, 129.16, 129.74, 130.06, 130.58, 131.95, 132.39, 134.12, 135.18, 135.25, 135.56, 137.72, 140.29, 153.00, 155.52, 159.00 (17C, aromatic), 169.32 (C=O) ppm; EIMS: *m/z* (%) 555 (M^+, 1), 554 (M – 1, 3), 435 (13), 405 (12), 403 (30), 391 (18), 371 (23), 179 (15), 178 (100), 165 (17). Anal. ($C_{26}H_{23}ClN_4O_4S_2$) C, H, N.

4.1.2.2. 2-Benzylthio-4-chloro-5-methyl-N-*(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**4**).* Yield: 0.69 g, 62%, m.p. 204–205 °C dec.; IR (KBr) 3448 (NH), 2913, 2855 (CH_3, CH_2), 1349, 1167 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 2H, CH_3), 4.16 (s, 2H, SCH_2), 7.05–7.11 (m, 3H, aromatic), 7.24–7.28 (m, 2H, aromatic), 7.29–7.36 (m, 6H, aromatic and NH), 7.38–7.41 (m, 5H, aromatic), 7.42–7.47 (m, 1H, aromatic) 8.21 (s, 1H, H-6) ppm; EIMS: *m/z* (%) 560 (M + 1, 7), 559 (M^+, 5), 558 (M – 1, 14), 494 (11), 467 (12), 435 (10), 405 (22), 404 (15), 403 (59), 337 (37), 249 (28), 245 (29), 179 (17), 178 (100), 165 (23), 91 (65). Anal. ($C_{29}H_{23}ClN_4O_2S_2$) C, H, N.

4.1.2.3. 2-Benzylthio-4-chloro-5-methyl-N-*[5,6-di(2-furyl)-1,2,4-triazin-3-yl]benzenesulfonamide (**5**).* Yield: 0.54 g, 50%, m.p. 200–203 °C dec.; IR (KBr) 3448 (NH), 2913, 2855 (CH_3, CH_2), 1331, 1152 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.38 (s, 3H, CH_3), 4.32 (s, 2H, SCH_2), 6.50–6.52 (d, 1H, aromatic), 6.72–6.74 (m, 2H, aromatic), 6.92–6.94 (d, 1H, aromatic), 7.09–7.17 (m, 3H, aromatic), 7.28–7.33 (m, 3H, aromatic and NH), 7.56 (s, 1H, H-3), 7.91 (s, 1H, aromatic), 8.06 (s, 1H, aromatic), 8.17 (s, 1H, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 20.89 (CH_3), 37.86 (SCH_2), 110.75, 113.89, 114.16, 115.40, 121.65, 121.70, 126.67, 128.83, 129.73, 129.97, 130.74, 133.71, 135.77, 137.33, 137.96, 139.59, 146.45, 148.54, 149.06, 151.06, 152.75 (21C, aromatic) ppm. Anal. ($C_{25}H_{19}ClN_4O_4S_2$) C, H, N.

4.1.2.4. 4-Chloro-2-ethylthio-5-methyl-N-*(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**6**).* Yield: 0.65 g, 67%, m.p. 105–108 °C dec.; IR (KBr) 3401, 3189 (NH), 2966, 2925, 2860 (CH_3, CH_2), 1305, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, J = 7.3 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3-Ar), 3.02 (q, J = 7.3 Hz, 2H, SCH_2), 7.16–7.20 (m, 2H, aromatic), 7.29–7.51 (m, 10H, aromatic, and NH), 8.08 (s, 1H, H-6) ppm. Anal. ($C_{23}H_{21}ClN_4O_2S_2$) C, H, N.

4.1.3. 2-Carbamolymethylthio-4-chloro-5-methyl-N-*(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**7**)*

A stirred solution of 3-amino-2-(2-carbamoylmethylthio-4-chloro-5-methylbenzenesulfonyl)guanidine **2e** (0.70 g, 2 mmol) and benzil (0.43 g, 2 mmol) in dry DMSO (10 ml) was heated at 80–85 °C for 30 h. The reaction mixture was diluted with methanol (80 ml) then quenched with water (75 ml) and kept overnight in a refrigerator. The precipitate that deposited was filtered off, washed with methanol (3 × 1 ml) and dried. The product was purified by crystallization from ethanol to give **7** as white crystals (0.37 g, 35%); m.p. 206–208 °C. IR (KBr) 3447, 3343 (NH_2, NH), 2974, 2921, 2855 (CH_3, CH_2), 1669 (C=O), 1334, 1160 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 3.74 (s, 2H, SCH_2), 7.17–7.19 (m, 2H, aromatic), 7.21 (s, 1H, H_aN–C=O), 7.31–7.35 (m, 7H, aromatic and NH), 7.38–7.41 (m, 1H, aromatic), 7.45–7.48 (m, 1H, aromatic), 7.55 (s, 1H, H-3), 7.59 (s, 1H, H_bN–C=O), 8.06 (s, 1H, H-6) ppm. Anal. ($C_{24}H_{20}ClN_5O_3S_2$) C, H, N.

*4.1.4. 5-Carbamoyl-4-chloro-2-ethoxycarbonylmethylthio-*N-*(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**8**)*

A solution of 3-amino-2-(5-carbamoyl-4-chloro-2-ethoxycarbonylmethylthiobenzenesulfonyl)guanidine **2f** (0.92 g, 2 mmol) and benzil (0.43 g, 2 mmol) in dry DMSO (10 ml) was stirred at 80–85 °C for 8 h. The resulting mixture was diluted with methanol (70 ml) then quenched with water (30 ml) and left overnight in a refrigerator. The solid that precipitated was filtered off, washed with methanol (3 × 1 ml), dried and crystallized from ethanol to give **8** as white crystals (0.68 g, 58%); m.p. 266–269 °C dec. IR (KBr) 3466, 3331 (NH_2, NH), 2978, 2925, 2855 (CH_3, CH_2), 1728 (C=O, ester), 1699 (C=O, amide), 1331, 1152 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02 (t, J = 6.8 Hz, 3H, CH_3), 3.94–3.96 (q, J = 6.8 Hz, 2H, CH_2), 4.13 (s, 2H, SCH_2), 7.06–7.08 (m, 2H, aromatic), 7.30–7.45 (m, 9H, aromatic and NH), 7.55 (s, 1H, H-3), 7.72 (s, 1H, H_aN–C=O), 8.02 (s, 1H, H_bN–C=O), 8.14 (s, 1H, H-6) ppm. Anal. ($C_{26}H_{22}ClN_5O_5S_2$) C, H, N.

*4.1.5. Preparation of 2-benzylthio-5-(carbamoyl or phenylcarbamoyl)-4-chloro-*N*-(5,6-diaryl-1,2,4-triazin-3-yl)benzenesulfonamides (**9–12**)*

A stirred suspension of the corresponding 3-amino-2-(2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonyl)guanidine **2g** or **2h** (2 mmol) and the appropriate 1,2-diarylethane-1,2-dione (2 mmol) in a mixture prepared from ethanol (20 ml) and dioxane (10 ml) was refluxed for 12–15 h and kept overnight at room temperature. The precipitate that deposited was filtered off, washed with ethanol (2 × 1 ml) and dried. The product was purified by crystallization from a mixture of ethanol and dioxane (2:1).

In this manner, the following benzenesulfonamides were obtained.

*4.1.5.1. 2-Benzylthio-5-carbamoyl-4-chloro-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**9**).* Yield: 0.87 g, 74%, m.p. 293–294 °C dec.; IR (KBr) 3436, 3360 (NH_2, NH), 2855 (CH_2), 1646 (C=O), 1342, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.41 (s, 2H, SCH_2), 7.11–7.20 (m, 5H, aromatic), 7.31–7.45 (m, 10H, aromatic and NH), 7.65 (s, 1H, H-3), 7.72 (s, 1H, H_aNC=O), 7.99 (s, 1H, H_bNC=O), 8.12 (s, 1H, H-6) ppm. Anal. ($C_{29}H_{22}ClN_5O_3S_2$) C, H, N.

*4.1.5.2. 2-Benzylthio-5-carbamoyl-4-chloro-*N*-[5,6-di(2-furyl)-1,2,4-triazin-3-yl]benzenesulfonamide (**10**).* Yield: 0.59 g, 52%, m.p. 297–299 °C dec.; IR (KBr) 3442, 3354 (NH_2, NH), 2925, 2855 (CH_2), 1646 (C=O), 1361, 1161 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.37 (s, 2H, SCH_2), 6.42–6.43 (d, 1H, aromatic), 6.67–6.67 (m, 1H, aromatic), 6.73–6.74 (m, 1H, aromatic), 6.91–6.92 (d, 2H, aromatic), 7.11–7.15 (m, 4H, aromatic and NH), 7.31–7.33 (d, 2H, aromatic), 7.59 (s, 1H, H-3), 7.72 (s, 1H, H_aNC=O), 7.91 (s, 1H, aromatic), 7.97 (s, 1H, aromatic), 8.04 (s, 1H, H_bNC=O), 8.24 (s, 1H, H-6) ppm. Anal. ($C_{25}H_{18}ClN_5O_5S_2$) C, H, N.

*4.1.5.3. 2-Benzylthio-5-carbamoyl-4-chloro-*N*-[5,6-di(4-methoxyphenyl)-1,2,4-triazin-3-yl]benzenesulfonamide (**11**).* Yield: 0.60 g, 46%, m.p. 275–277 °C dec.; IR (KBr) 3366, 3319 (NH_2, NH), 2966, 2931, 2873 (CH_3, CH_2), 1661 (C=O), 1361, 1176 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.37 (s, 2H, SCH_2), 6.89 (d, J = 8.8 Hz, 2H, aromatic), 6.95 (d, J = 8.8 Hz, 2H, aromatic), 7.09 (d, J = 8.8 Hz, 2H, aromatic), 7.11–7.18 (m, 4H, aromatic and NH), 7.27 (d, J = 8.8 Hz, 2H, aromatic), 7.33–7.35 (m, 2H, aromatic), 7.61 (s, 1H, H-3), 7.74 (s, 1H, H_aNC=O), 8.01 (s, 1H, H_bC=O), 8.12 (s, 1H, H-6) ppm. Anal. ($C_{31}H_{26}ClN_5O_5S_2$) C, H, N.

*4.1.5.4. 2-Benzylthio-4-chloro-5-phenylcarbamoyl-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**12**).* Yield: 0.64 g, 48%, m.p. 218–221 °C dec.; IR (KBr) 3342, 3311(NH), 2966, 2923, 2857 (CH_2), 1662 (C=O), 1334, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.44 (s, 2H, SCH_2), 7.13–7.26 (m, 8H, aromatic), 7.32–7.42 (m, 11H, aromatic and NH), 7.71–7.70 (m, 3H, aromatic), 8.18 (s, 1H, H-6), 10.58 (s, 1H, HNC=O) ppm. Anal. ($C_{35}H_{26}ClN_5O_3S_2$) C, H, N.

*4.1.6. Preparation of 2-benzylthio-4-chloro-5-[(4-chloro or 4-methyl)phenylcarbamoyl]-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamides (**13–14**)*

A stirred solution of the corresponding 3-amino-2-(2-benzylthio-4-chloro-5-[(4-chloro or 4-methyl)phenylcarbamoyl]benzenesulfonyl)guanidine **2i** or **2j** (2 mmol) and benzil (0.43 g, 2 mmol) in dry DMSO (10 ml) was heated at 80–85 °C for 20 h. The reaction mixture was diluted with methanol (100 ml) and kept overnight in a refrigerator. The product that precipitated was collected by filtration, washed with methanol (3 × 2 ml) and dried. The contaminations were extracted with boiling ethanol (40 ml per 1 g of crude reaction product) to afford pure product.

In this manner, the following compounds were obtained.

*4.1.6.1. 2-Benzylthio-4-chloro-5-(4-chlorophenylcarbamoyl)-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**13**).* Yield: 0.71 g, 51%, m.p. 260–262 °C dec.; IR (KBr) 3388, 3324 (NH), 2966, 2919, 2854 (CH_2), 1669 (C=O), 1305, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.44 (s, 2H, SCH_2), 7.13–7.26 (m, 7H, aromatic), 7.32–7.45 (m, 11H, aromatic and NH), 7.73–7.75 (m, 3H, aromatic), 8.18 (s, 1H, H-6), 10.72 (s, 1H, HNC=O) ppm. Anal. ($C_{35}H_{25}Cl_2N_5O_3S_2$) C, H, N.

*4.1.6.2. 2-Benzylthio-4-chloro-5-(4-methylphenylcarbamoyl)-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**14**).* Yield: 0.77 g, 57%, m.p. 240–241 °C dec.; IR (KBr) 3389, 3354 (NH), 2919, 2855 (CH_3, CH_2), 1646 (C=O), 1314, 1164 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 4.42 (s, 2H, SCH_2), 7.12–7.26 (m, 9H, aromatic), 7.31–7.42 (m, 9H, aromatic and NH), 7.57–7.59 (d, 2H, aromatic), 7.70 (s, 1H, H-3), 8.15 (s, 1H, H-6), 10.53 (s, 1H, HNC=O) ppm. Anal. ($C_{36}H_{28}ClN_5O_3S_2$) C, H, N.

*4.1.7. 2-Benzylthio-4-chloro-5-cyano-*N*-(5,6-diphenyl-1,2,4-triazin-3-yl)benzenesulfonamide (**15**)*

A suspension of **9** (0.74 g, 1.25 mmol) in phosphorus oxychloride (12 ml) was stirred at first at room temperature for 15 min, and then the temperature was raised to 60 °C for 2.5 h. The suspension was further stirred at 65–70 °C for 8 h and allowed to stand at room temperature overnight. The resulting solution was poured onto crushed ice (130 g) with vigorously stirring for at least 1 h. The solid that precipitated was collected by filtration, washed thoroughly with several portions of cold water (pH 7), dried and crystallized from a mixture of ethanol and dioxane (4:1) to give **15** as white crystals (0.65 g, 85%); m.p. 232–234 °C. IR (KBr) 3441 (NH), 2966, 2927, 2856, 2771 (CH_2), 2234 (C≡N), 1345, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.55 (s, 4H, CH_2, dioxane), 4.45 (s, 2H, SCH_2), 7.06–7.08 (m, 2H, aromatic), 7.17–7.24 (m, 3H, aromatic), 7.29–7.36 (m, 9H, aromatic and NH), 7.39–7.43 (m, 1H, aromatic), 7.48–7.51 (m, 1H, aromatic), 7.84 (s, 1H, H-3), 8.34 (s, 1H, H-6) ppm. Anal. ($C_{29}H_{20}ClN_5O_2S_2 \cdot 1/2\ C_4H_8O_2$) C, H, N.

*4.1.8. General procedure for the preparation of 1-(2-alkylthio-4-chloro-5-R^1-benzenesulfonyl)-3-(2-oxobutane-3-ylideneimino)guanidines (**16–18**)*

To a stirred suspension of the corresponding 3-amino-2-(2-alkylthio-4-chloro-5-R^1-benzenesulfonyl)guanidine **2b**, **d** or **2h** (2 mmol) and ethanol (10 ml) diacetyl (2 mmol) was added. The resulting mixture was refluxed for 4–5 h and left overnight at room temperature. The solid that precipitated was collected by filtration, washed with ethanol (2 × 1 ml), dried and purified either by crystallization from ethanol or from a mixture of ethanol and chloroform (2:1) for **18**.

According to the above procedure, the following aminoguanidines were obtained.

*4.1.8.1. 1-(2-Benzylthio-4-chloro-5-methybenzenesulfonyl)-3-(2-oxobutane-3-ylideneimino)guanidine (**16**).* Starting from 3-amino-2-(2-benzylthio-4-chloro-5-methylbenzenesulfonyl)guanidine **2b** (0.77 g) and diacetyl (0.17 g), the title compound **16** was obtained (0.59 g, 65%); m.p. 160–162 °C. IR (KBr) 3455, 3341, 3297 (NH), 2948, 2921, 2854 (CH_3, CH_2), 1691 (C=O), 1627 (C=N), 1300, 1135 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.15 (s, 2H, SCH_2), 6.45 (br.s, 1H, C=NH), 7.05 (br.s, 1H, NH–N=C), 7.21–7.29 (m, 5H, aromatic), 7.31 (s, 1H, H-3), 7.98 (s, 1H, H-6), 9.02 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{19}H_{21}ClN_4O_3S_2$) C, H, N.

*4.1.8.2. 1-(4-Chloro-5-methyl-2-methylthiobenzenesulfonyl)-3-(2-oxobutane-3-ylideneimino)guanidine (**17**).* Starting from 3-amino-2-(4-chloro-5-methyl-2-methylthiobenzenesulfonyl)guanidine **2d** (0.62 g) and diacetyl (0.17 g), the title compound **17** was obtained (0.67 g, 89%); m.p. 190–191 °C dec. IR (KBr) 3454, 3342, 3306 (NH), 2923, 2854 (CH_3, CH_2), 1685 (C=O), 1643, 1610 (C=N), 1300, 1135 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.58 (br.s, 1H, C=NH), 7.22–7.45 (s, 2H, aromatic), 7.99 (s, 1H, NH), 9.33 (br.s, 1H, SO_2NH) ppm; ^{13}C NMR (DMSO-d_6) δ 10.39 ($\underline{C}H_3C$=N), 15.51 (SCH_3), 19.12 (CH_3-Ar), 24.98 ($\underline{C}H_3C$=O), 126.18, 130.77, 131.54, 137.51, 137.92, 138.37, 149.02, 155.29, 197.32 (C=O) ppm. Anal. ($C_{13}H_{17}ClN_4O_3S_2$) C, H, N.

*4.1.8.3. 1-(2-Benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)-3-(2-oxobutane-3-ylideneimino)guanidine (**18**).* Starting from 3-amino-2-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)guanidine **2h** (0.98 g) and diacetyl (0.17 g), the title compound **18** was obtained (0.84 g, 75%); m.p. 137–139 °C. IR (KBr) 3481, 3348, 3280 (NH), 2923, 2854 (CH_3,CH_2), 1676, 1657 (C=O), 1629, 1598 (C=N), 1316, 1129 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.18 (s, 2H, SCH_2), 6.55 (s, 1H, C=NH), 7.15–7.32 (m, 10H, aromatic), 7.62 (s, 2H, aromatic), 8.25 (s, 1H, NH), 8.33 (s, 1H, NHC=O), 9.16 (s, 1H, SO_2NH) ppm; ^{13}C NMR (DMSO-d_6) δ 10.37 ($\underline{C}H_3C$=N), 26.01 ($\underline{C}H_3C$=O), 36.05 (SCH_2), 119.92, 124.29, 127.66, 128.11, 128.73, 128.85, 129.09, 129.28, 132.59, 133.88, 136.11, 138.78, 138.93, 140.78, 149.18, 155.39, 163.74 (NHC=O), 197.33 (C=O) ppm. Anal. ($C_{25}H_{23}ClN_5O_4S_2$) C, H, N.

*4.1.9. General procedure for the preparation of 2-alkylthio-4-chloro-5-methyl-*N*-(1,2-dihydroxycyclobuta[e]1,2,4-triazin-3-yl)benzenesulfonamides (**19–21**)*

To a suspension of the corresponding 3-amino-2-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)guanidine **2a**, **b** or **2d** (2 mmol) in ethanol (10 ml) 3,4-dihydroxy-3-cyclobutene-1,2-dione (2 mmol) or 3,4-diethoxy-3-cyclobutene-1,2-dione (2 mmol) was added. The reaction mixture was stirred at reflux for 1.5–2 h, and then left overnight at room temperature. The product thus obtained was collected by filtration, washed with ethanol (2 × 1 ml) and dried. The contaminations were extracted with boiling ethanol (15 ml per 1 g of crude reaction product).

According to the above procedure, the following compounds were obtained.

*4.1.9.1. 4-Chloro-2-ethoxycarbonylmethylthio-5-methyl-*N*-(1,2-dihydroxycyclobuta[e]1,2,4-triazin-3-yl)benzenesulfonamide (**19**).* Starting from 3-amino-2-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulfonyl)guanidine **2a** (0.76 g) and 3.4-dihydroxy-3-cyclobutene-1,2-dione (0.23 g), the title compound **19** was obtained (0.31 g, 34%); m.p. 201–202 °C dec. IR (KBr) 3385, 3312, 3189, 3114 (OH, NH), 2981, 2931 (CH_3, CH_2), 1718 (C=O), 1618, 1558 (C=N), 1343, 1134 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.19 (t, J = 7.0 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3-Ar), 3.95 (s, 2H, SCH_2), 4.14 (q, J = 7.0 Hz, 2H, OCH_2), 7.20–7.60 (br.s, 2H, 2 × OH), 7.45 (s, 1H, H-3), 7.89 (s, 1H, H-6), 9.83 (s, 1H, SO_2NH) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 14.26 (CH_3), 19.12 (CH_3-Ar), 34.99 (SCH_2), 61.38 (OCH_2), 128.43, 128.65, 130.59, 132.98, 133.20, 134.55, 136.69, 140.16, 157.59, 169.49 (C=O) ppm. Anal. ($C_{16}H_{15}ClN_4O_6S_2$) C, H, N.

*4.1.9.2. 2-Benzylthio-4-chloro-5-methyl-*N*-(1,2-dihydroxycyclobuta[e]1,2,4-triazin-3-yl)benzenesulfonamide (**20**).* Starting from 3-amino-2-(2-benzylthio-4-chloro-5-methylbenzenesulfonyl)guanidine **2b** (0.77 g) and 3.4-dihydroxy-3-cyclobutene-1,2-dione (0.23 g), the title compound **20** was obtained (0.39 g, 42%); m.p. 203–204 °C dec. IR (KBr) 3376, 3307, 3189, 3110 (OH, NH), 2966, 2921, 2860 (CH_3, CH_2), 1618, 1553 (C=N), 1343, 1133 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.31 (s, 2H, SCH_2), 7.25–7.75 (m, 8H, aromatic and 2 × OH), 7.87 (s, 1H, H-6), 9.85 (s, 1H, SO_2NH) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.68 (CH_3), 38.17 (CH_2), 129.03, 129.45, 129.78, 129.94, 130.28, 130.63, 130.98, 132.08, 133.75, 137.40, 138.06, 138.20, 141.23, 159.16, 166.96 ppm. Anal. ($C_{19}H_{15}ClN_4O_4S_2$) C, H, N.

Starting from **2b** (0.77 g) and 3.4-diethoxy-3-cyclobutene-1,2-dione (0.34 g), the title compound **20** was obtained (0.19 g,

21%); m.p. 202–204 °C dec. IR and ^{1}H NMR were identical with authentic sample **20**.

*4.1.9.3. 4-Chloro-5-methyl-2-methylthio-*N*-(1,2-dihydroxy-cyclobuta[e]1,2,4-triazin-3-yl)benzenesulfonamide (**21**).* Starting from 3-amino-2-(4-chloro-5-methyl-2-methylthio-benzenesulfonyl)guanidine **2d** (0.62 g) and 3.4-dihydroxy-3-cyclobutene-1,2-dione (0.23 g), the title compound **21** was obtained (0.29 g, 37%); m.p. 215–217 °C dec. IR (KBr) 3375, 3312, 3190, 3115 (OH, NH), 2978, 2922 (CH_3), 1618, 1559 (C=N), 1343, 1134 (SO_2) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3H, CH_3), 2.46 (s, 3H, SCH_3), 7.25–7.55 (br.s, 2H, 2 × OH), 7.31 (s, 1H, H-3), 7.86 (s, 1H, H-6), 9.76 (s, 1H, SO_2NH) ppm. Anal. ($C_{13}H_{11}ClN_4O_4S_2$) C, H, N.

4.2. X-ray structure analyses

The diffraction data were collected at room temperature with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software [34]. The structures were solved by direct methods with the program SHELXS-97 [35] and refined by full-matrix least-squares method on F^2 with SHELXL-97 [36].

Crystal data for **4**: $C_{29}H_{23}ClN_4O_2S_2$, triclinic, space group $P\bar{1}$, a = 9.6195(8), b = 11.7985(9), c = 12.5981(10) Å, α = 92.024(6), β = 94.633(6), γ = 108.828(7)°, V = 1346.04(19) Å^3, Z = 2, d_x = 1.379 g cm^{-3}, T = 293 K. 10258 data were collected up to $2\theta_{max}$ = 50° for a crystal with dimensions 0.6 × 0.2 × 0.02 mm^3 (R_{int} = 0.043, R_σ = 0.062). Final R indices for 2944 reflections with $I > 2\sigma(I)$ and 389 refined parameters are: R_1 = 0.0534, wR_2 = 0.1398 (R_1 = 0.0848, wR_2 = 0.1530 for all 4725 data). Atom labeling is shown in Fig. 2. The thiomethylene fragment of the molecule is disordered and adopts two different conformations with the occupancy ratio 78:22. The hydrogen atoms of the methyl group C29 are also disordered.

Crystal data for **10**: $C_{25}H_{18}ClN_5O_5S_2{\cdot}C_2H_6OS$, triclinic, space group $P\bar{1}$, a = 9.3236(5), b = 10.5164(5), c = 15.6016(8) Å, α = 72.448(4), β = 88.733(4), γ = 81.883(4)°, V = 1443.58(13) Å^3, Z = 2, d_x = 1.487 g cm^{-3}, μ(Mo K_α) = 0.401 mm^{-1} T = 293 K. 13017 data were collected up to $2\theta_{max}$ = 50° for a crystal with dimensions 0.4 × 0.4 × 0.05 mm^3 (R_{int} = 0.034, R_σ = 0.027). Final R indices for 4562 reflections with $I > 2\sigma(I)$ and 406 refined parameters are: R_1 = 0.0462, wR_2 = 0.1173 (R_1 = 0.0516, wR_2 = 0.1216 for all 5028 data). Atom labeling is shown in Fig. 3. The DMSO molecule is disordered over two positions with the ratio of occupancy factors being 58:42.

Crystal data for **11**: $C_{31}H_{26}ClN_5O_5S_2{\cdot}C_2H_6OS$, monoclinic, space group $P2_1/n$, a = 17.7172(8), b = 9.4902(5), c = 20.7410(10) Å, β = 90.498(4)°, V = 3487.3(3) Å^3, Z = 4, d_x = 1.383 g cm^{-3}, μ(Mo K_α) = 0.266 mm^{-1}, T = 293 K. 17140 data were collected up to $2\theta_{max}$ = 50° for a crystal with dimensions 0.7 × 0.3 × 0.02 mm^3 (R_{int} = 0.051, R_σ = 0.064). Final R indices for 3579 reflections with $I > 2\sigma(I)$ and 473 refined parameters are: R_1 = 0.0461, wR_2 = 0.1056 (R_1 = 0.0933, wR_2 = 0.1260 for all 6148 data). Atom labeling is shown in Fig. 4. The DMSO molecule is disordered over two positions with the ratio of occupancy factors being 82:18.

Crystallographic data for compounds **4**, **10** and **11** have been deposited with Cambridge Crystallographic Data Center (CCDC deposition numbers CCDC 244778–244780). Copies of the data can be obtained upon request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, quoting the deposition numbers.

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