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Original article

Synthesis and in vitro antitumor activity of novel series 2-benzylthio-4-chlorobenzenesulfonamide derivatives

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Abstract

Three series of novel 2-benzylthio-4-chloro-5-R^1-benzenesulfonamides bearing the *N*-(benzoxazol-2-yl) (**10**–**19**), *N*-(benzothiazol-2-yl) (**20**–**21**) or *N*-(1,3-dihydro-2*H*-benzimidazol-2-ylidene) (**22**–**25**) moiety were synthesized by reacting *N*-(2-benzylthio-4-chloro-5-R^1-benzenesulfonyl) cyanamide potassium salts (**5**–**9**) with 2-aminophenols, 2-aminothiophenol and *o*-phenylenediamines, respectively. Compounds with carbamoyl substituent at position 5 (**14**–**16**, **21** and **25**, $R^1 = CONH_2$) were further dehydrated to the corresponding nitriles (**26**–**30**, $R^1 = CN$). The in vitro antitumor activity of the compounds obtained was determined at the National Cancer Institute (NCI), and the structure–activity relationships were discussed. *N*-(2-benzoxazolyl)-2-benzylthio-4-chloro-5-(4-fluorophenylcarbamoyl)benzenesulfonamide (**18**) is the prominent of the compounds due to its remarkable activity and selectivity toward non-small cell lung cancer (NCI-H522) and melanoma (SK-MEL-2) cell lines (GI_{50} = 0.1 μM, TGI = 0.5–0.6 μM).

Keywords: 2-Benzylthio-4-chlorobenzenesulfonamides; Benzoxazoles; Benzothiazoles; Benzimidazoles; Synthesis; Antitumor effect

1. Introduction

Various arylsulfonamides have been reported to possess anticancer [1–6] or/and anti-HIV [2–4,7] properties. Although they have a common structural motif of aromatic sulfonamide, there are a variety of mechanisms of their antitumor action. Indeed, for many of them the target is well known and the anticancer activity understood in great details, but in some other cases, particularly for very new types of leads, the molecular mechanism by which the antitumor activity is achieved are far less clear at this moment. Interestingly, one of the first sulfonamide to be recognized as antitumor agent was 4-amino-*N*-(5-chloroquinoxalin-2-yl)benzenesulfonamide (**CQS**) (Fig. 1), which demonstrates inhibition of colony formation against a variety of human solid tumors such as breast, lung, melanoma and ovarian carcinomas, and causes cell cycle arrest in the G0/G1 phase [8–10].

As a part of our research program aimed at search for new 2-mercaptobenzenesulfonamides as antitumor agents, we have previously reported the syntheses of variously substituted arylsulfonylaminoguanidine derivatives of type **I** [11], **II** [12] or **III** [13] (Fig. 1), and found that these compounds caused considerable growth inhibition on different human tumor cell lines. Recently, we have also found that *S*,*N*-disubstituted 4-chloro-2-mercaptobenzenesulfonamides of type **IV** (Fig. 1) exhibited anticancer properties [14]. These findings prompted us to synthesize a new series of sulfonamides such as **V** and **VI** depicted in Fig. 1.

Several methods for the synthesis of *N*-(2-benzoxazolyl)-, *N*-(2-benzothiazolyl)- or *N*-(1*H*-benzimidazol-2-yl)benzenesulfonamides are known. The simplest method employs the condensation of an arylsulfonyl chloride with benzothiazol-2-ylamine [15] or 1*H*-benzimidazol-2-ylamine [16]. A further method involves the reaction of either *N*-benzenesulfonyldithiocarbonimidic acid dimethyl esters [17] or benzenesulfonyl-carbonimidic acid dichlorides [18,19] with 2-aminophenol, 2-aminothiophenol or *o*-phenylenediamine, respectively. To our experience however, such 2-mercapto-benzenesulfonyl

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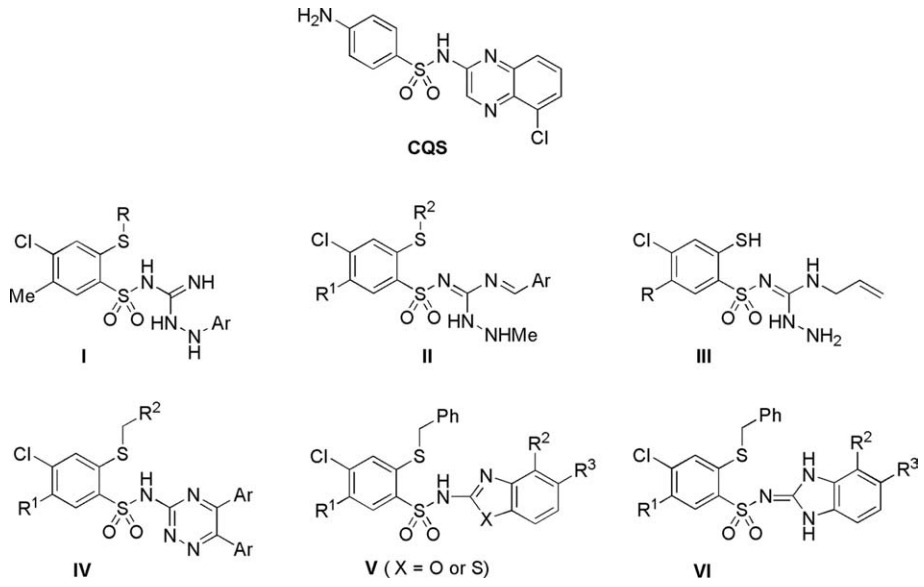


Fig. 1.

starting analogues are not attainable, due to formation of an intractable mixture of products.

2. Results and discussion

2.1. Chemistry

The starting 3-methylthiobenzodithiazines **1** [20], **2** [21] and *N*-(benzenesulfonyl)cyanamide potassium salts **5** [22], **6** and **7** [14] were prepared according to the known methods. Analogously were prepared the novel substrates **3** and **4**, and the corresponding *N*-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salts **8** and **9** (Scheme 1).

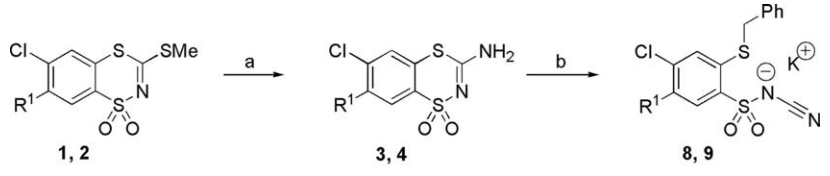
The desired *N*-(2-benzoxazolyl or 2-benzothiazolyl)-2-benzylthio-4-chlorobenzenesulfonamides (**10**–**21**) were obtained by reacting 2-aminophenols or 2-aminothiophenol with *N*-(2-benzylthio-4-chlorobenzenesulfonyl)cyanamide potassium salts (**5**–**9**) in boiling glacial acetic acid, as shown in Scheme 2. An analogous reaction of the corresponding *o*-phenylenediamines with **5** or **6** led to the formation of 2-benzylthio-4-chloro-*N*-(1,3-dihydro-2*H*-benzimidazol-2-ylidene) benzenesulfonamides (**22**–**25**). The amide compounds (**14**–**16**, **21** and **25**) were further dehydrated with phosphorus oxychloride to the target nitriles **26**–**30** in 55–75% yield (Scheme 2).

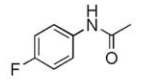
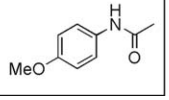
In order to shed light into the course of the reaction of **5** with dinucleophilic *o*-aminophenols, we attempted to isolate intermediates initially formed. Thus, when the reaction of **5** with 2-aminophenol was interrupted after 0.5 h, the corresponding guanidine derivative **31** was separated from the reaction mixture in 37% yield as depicted in Scheme 2. This compound was then transformed into the final benzoxazole **10** by further heating in boiling glacial acetic acid for 3 h (Scheme 2).

All the final products were characterized by IR and ^{1}H NMR spectroscopy as shown in Section 4. Elemental analyses were in accordance with the proposed structure.

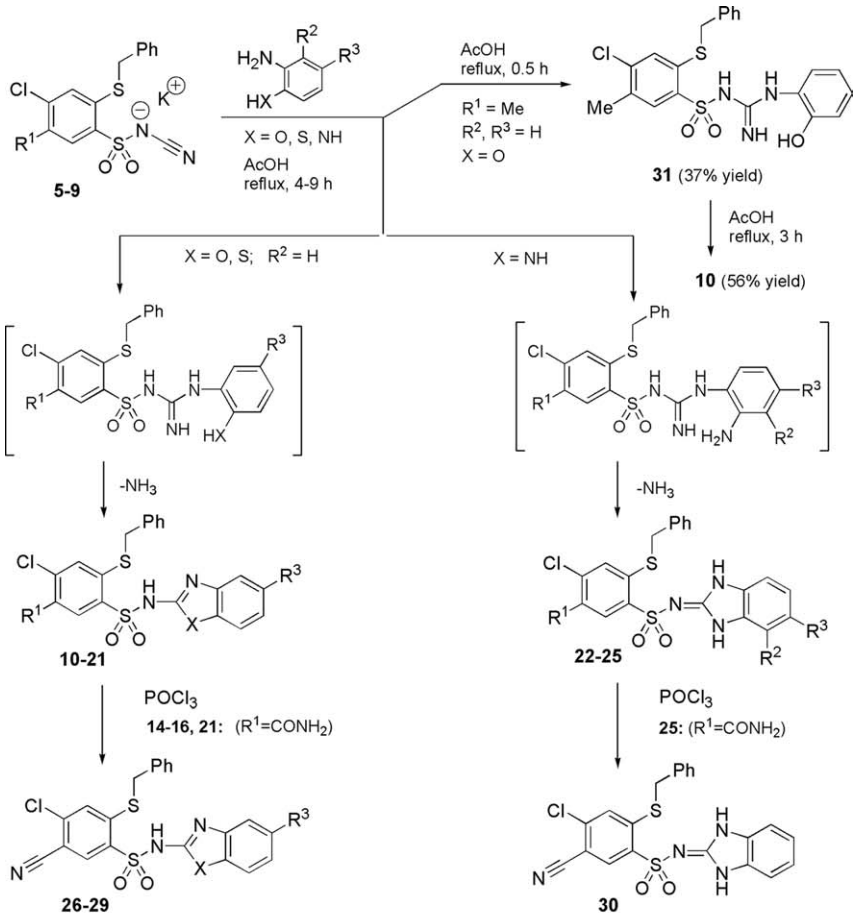
2.2. Biology

Compounds **10**, **11**, **14**, **15**, **17**, **18**, **20**–**27**, **29**–**31** were submitted to the US National Cancer Institute (NCI; Bethesda,



Compds	1, 3, 8	2, 4, 9
R^1		

Scheme 1. Synthesis of *N*-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salts (**8**, **9**). Reagents, conditions and yields: (a) 25% NH_4OH/EtOH (1.1 molar equiv.), r.t. 24 h, 65–76%; (b) anhydrous K_2CO_3 (excess), $PhCH_2Cl$ (1.1 molar equiv.), dry THF, reflux 20 h, 68–73%.



Compounds	R^1	R^2	R^3	X
5, 10	Me	H	H	O
5, 11	Me	H	Cl	O
5, 12	Me	H	Me	O
5, 13	Me	H	NO_2	O
6, 14	H_2NCO	H	H	O
6, 15	H_2NCO	H	Cl	O
6, 16	H_2NCO	H	Me	O
7, 17	PhNHCO	H	H	O
8, 18	4-F-PhNHCO	H	H	O
9, 19	4-MeO-PhNHCO	H	H	O
5, 20	Me	H	H	S
6, 21	H_2NCO	H	H	S
5, 22	Me	H	H	-
5, 23	Me	Me	H	-
5, 24	Me	H	Me	-
6, 25	H_2NCO	H	H	-
14, 26	-	-	H	O
15, 27	-	-	Cl	O
16, 28	-	-	Me	O
21, 29	-	-	H	S

Scheme 2. Synthesis of 2-benzylthio-4-chlorobenzenesulfonamide derivatives possessing benzoxazole (**10**–**19**, **26**–**28**), benzothiazole (**20**, **21**, **29**) and benzimidazole (**22**–**25**, **30**) moiety attached to the sulfonamide nitrogen atom, as well as transformation of the intermediate 3-(2-hydroxyphenyl)-1-(2-benzylthio-4-chloro-5-methylbenzenesulfonyl)guanidine (**31**) into compound **10**.

MD), for in vitro evaluation against a panel of 54–58 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, kidney, prostate, and breast. The compounds were tested at five concentrations at 10-fold dilution. A 48 h continuous drug exposure protocol was used and sulforhodamine B (SRB) protein assay was used to estimate cell growth. Details of this test system, and the information which is encoded by the activity pattern over all cell lines, have been published [23–25]. The antitumor activity of tested compounds is given by three parameters for each cell line: GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), TGI value (TGI = molar concentration of the compound leading to total inhibition) and 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 averaged activity parameters over all cell lines. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested.

Compounds **14**, **15**, **21**, **23**–**25** and **30** were inactive (GI_{50} > 100 μM), whereas the other compounds **10**, **11**, **17**, **18**, **20**, **22**, **26**, **27**, **29** and **31** exhibited either moderate or reasonable in vitro anticancer activity against one or more human cancer cell lines (Table 1).

On the basis of the data obtained, the following conclusion may be drawn from the structure–activity relationship study. Firstly, the nature of the substituent at position 5 on benzene ring is crucial factor influencing cytotoxicity. Thus, it was found that incorporation of carbamoyl moiety into benzene ring ($R^1 = CONH_2$) resulted in inactive benzoxazoles **14** (R^3 = H) and **15** (R^3 = Cl) (Table 1). Interestingly, introduction of methyl (**10**), phenylcarbamoyl (**17**), *p*-fluorophenylcarbamoyl (**18**) or cyano (**26**) substituents at this position (R^1) leads to compounds with good activity (Table 2), with the average activity order of **18** >> **17** > **10** ≥ **26**. This may suggest that the anticancer activity depending not only on the electronic nature of the substituent but also on other properties, such as for instance, its lipophilicity. Similarly, among a series of *N*-(2-benzothiazolyl)benzenesulfonamide derivatives the replacement of methyl or cyano groups in **20** (R^1 = Me) or **29** (R^1 = CN) by low lipophilic carboxamide group in **21** ($R^1 = CONH_2$) results in total loss in potency. Moreover, the presence of methyl group at position 5 on benzene ring in **20** (R^1 = Me) enhances activity over the cyano analogue **29** (R^1 = CN), probably due to relatively low lipophilic character of the cyano group (mean GI_{50} values = 16.6 and 21.8 μM, respectively) (Tables 1 and 2). The same is observed in case of *N*-(1,3-dihydro-2*H*-benzinidazol-2-ylidene)benzenesulfonamide derivatives, when **22** (R^1 = Me) is compared to inactive **25** ($R^1 = CONH_2$) (Table 1). It is worthy to mention however, that previously reported analogue (i.e. 2-benzylthio-4-chloro-*N*-(1,2,4-triazin-3-yl)benzenesulfonamide) of type **IV** (Fig. 1) bearing the carboxamide group ($CONH_2$) at position 5 on benzene ring exhibited remarkable anticancer activity and selectivity [14]. This may suggest that the mechanisms of action are different.

Secondly, the character of fused heterocyclic ring at sulfonamide functionality is the successive relevant factor influencing potency. Thus, the presence of the benzothiazole ring (**20**, **29**) substituted on the nitrogen atom of the sulfonamide moiety narrowly enhances potency over the benzoxazole analogues (**10**, **26**) (compare **20** with **10**, R^1 = Me or **29** with **26**, R^1 = CN) (Table 2). For example, **20** (X = S) exhibited fairly high activity toward renal cancer (CAKI-1), ovarian cancer (OVCAR-8) and leukemia (RPMI-8226) cell lines with GI_{50} values in the range of 4.1–9.2 μM, whereas **10** (X = O) showed comparable activity only against the non-small cell lung (HOP-92) cell lines (GI_{50} = 4.6 μM) (Table 2). On the other hand, the loss in potency was observed when the sulfonamide nitrogen atom was attached to 1,3-dihydro-2*H*-benzimidazole ring system (compounds **23**–**25** and **30**). The only exception was compound **22** (R^1 = Me, R^2, R^3 = H) which showed a weak anticancer activity against the 29 of 55 human tumor cell lines (Tables 1 and 2).

Thirdly, introduction of electron-withdrawing chlorine atom at 5-position of benzoxazole ring (**11** and **27**, R^3 = Cl) causes increase in potency (compare with **10** and **26**, R^3 = H, respectively). For example, compound **11** (R^3 = Cl) showed fairly high activity against the leukemia (CCEF-CEM), ovarian cancer (OVCAR-8) and colon cancer (HCT-15) cell lines (GI_{50} values 3.5, 4.1 and 8.2 μM, respectively), whereas compound **27** (R^3 = Cl) exhibited the higher average potency (mean GI_{50} value = 14.1 μM) when compared to its unsubstituted counterpart **26** (Table 2).

Interestingly, both the leukemia (CCRF-CEM) and ovarian (OVCAR-8) cell lines were the most sensitive of the cell lines tested to the growth inhibitory action of compounds **11** and **26** (Table 2), suggesting that benzoxazoles **11**, **26** may act by the similar mechanism. The same situation has been evidenced in the case of renal and diverse leukemia, ovarian or CNS cell lines with compounds **20** and **22** acting mainly against CAKI-1 cells with GI_{50} in the range of 2.1–4.1 μM (Table 2).

Relatively highest sensitivity to the compounds described here was found for cell lines of non-small cell lung cancer (NCI-H522), melanoma (SK-MEL-2) and ovarian cancer (IGROV1), with GI_{50} values in the low micromolar range of 0.1–0.6 for compound **18** indicating that combination of ben-

Table 1
Overview of the results of the anticancer screening for compounds **10**, **11**, **14**, **15**, **17**, **18**, **20**–**27**, **29**, **30** and **31**[a]

Compound	Number of the cell lines investigated	Number of the cell lines giving positive GI_{50}, TGI and LC_{50}[b]					
		GI_{50} (μM)		TGI (μM)		LC_{50} (μM)	
		Number	Range	Number	Range	Number	Range
10	55	54	4.6–48.9	44	20.8–91.2	17	53.7–95.4
11	57	57	3.5–45.7	52	16.5–75.8	29	60.2–95.4
17	55	55	11.4–42.6	51	28.1–91.2	29	56.2–97.7
18	54	54	0.1–46.7	50	0.5–63.1	38	51.2–97.7
20	54	54	4.1–31.6	47	17.7–93.3	25	46.7–95.4
22	55	29	2.1–77.6	8	6.1–85.1	1	50.1
26	56	56	3.3–75.8	47	31.6–75.8	18	60.2–95.4
27	58	52	10.4–18.6	58	21.3–43.6	56	47.8–81.2
29	58	58	6.1–51.2	50	29.5–95.4	18	61.6–95.4
31	58	58	3.0–33.1	53	22.9–79.4	39	52.4–83.1

Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (Table 2 or Refs. [23–25] for details).

[a] Compounds **14**, **15**, **21**, **23**–**25** and **30** were inactive.

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

Table 2
Selected in vitro tumor growth inhibition data for compounds **10**, **11**, **17**, **18**, **20**, **22**, **26**, **27**, **29** and **31**

Compound	Most sensitive tumor cell lines		GI_{50} (μM)[a]	Mean value for all tested cell lines (MG_MID)[b] for GI_{50} (μM)
	Panel	Cell line		
10	Non-small cell lung	HOP-92	4.6	22.9
	Leukemia	RPMI-8226	11.2	
	Leukemia	SR	11.5	
	Colon	HCT-116	13.8	
	Melanoma	LOX IMVI	14.9	
11	Leukemia	CCRF-CEM	3.5	20.8
	Ovarian	OVCAR-8	4.1	
	Colon	HCT-15	8.2	
	Non-small cell lung	NCI-H322M	16.7	
17	Leukemia	CCRF-CEM	11.4	19.9
	Leukemia	MOLT-4	13.3	
	Renal	TK-10	13.9	
	Melanoma	SK-MEL-5	14.1	
	Non-small cell lung	NCI-H322M	15.0	
18	Non-small cell lung	NCI-H522	0.1	14.7
	Melanoma	SK-MEL-2	0.1	
	Ovarian	IGROV1	0.6	
	Renal	RXF 393	12.8	
20	Renal	CAKI-1	4.1	16.6
	Ovarian	OVCAR-4	8.0	
	Leukemia	RPMI-8226	9.2	
	Melanoma	UACC-62	10.8	
	CNS	SF-295	11.0	
22	Renal	CAKI-1	2.1	52.4
	Leukemia	CCRF-CEM	12.3	
	Ovarian	OVCAR-3	14.2	
	CNS	U251	14.9	
26	Leukemia	CCRF-CEM	3.3	23.4
	Ovarian	OVCAR-8	6.1	
	Melanoma	SK-MEL-5	17.0	
27	Non-small cell lung	HOP-92	10.5	14.1
	Non-small cell lung	NCI-H322M	10.9	
	Non-small cell lung	NCI-H522	11.6	
	Breast	MDA-MB-231/ATCC	10.7	
	Melanoma	SK-MEL-2	12.4	
29	Ovarian	OVCAR-8	6.1	21.8
	Non-small cell lung	NCI-H522	11.3	
	Melanoma	UACC-62	11.8	
	CNS	SF-295	13.6	
31	Leukemia	MOLT-4	3.0	13.5
	Leukemia	HL-60(TB)	4.2	
	Leukemia	SR	5.8	
	Leukemia	CCRF-CEM	5.9	
	Non-small cell lung	NCI-H460	7.6	
	Non-small cell lung	NCI-H522	9.6	
	Renal	UO-31	6.9	
	Breast	BT-549	8.2	
	Melanoma	SK-MEL-2	10.6	
	Ovarian	IGROV1	11.0	

Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (Refs. [23–25] for details).
[a] The response parameter: GI_{50} is interpolated value representing the molar concentration at which percentage growth is +50.
[b] MG_MID = mean graph midpoint = arithmetical mean value 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.

zoxazole moiety at sulfonamide functionality and the most bulky and lipophilic substituent in this series (R^1 = 4-F-PhNHCO) at position 5 on benzene ring results in compound with optimal properties (Table 2).

As previously mentioned aminoguanidines of type **I**–**III** (Fig. 1) have been shown to possess a pronounced anticancer activity. It is noteworthy, that the 'open chain' analogue of **10** (R^1 = Me), guanidine derivative **31** demonstrated advantageous activity against leukemia subpanel among others, with GI_{50} values between 3.0 and 5.9 μM range (Table 2). Relatively highest sensitivity to **31** was also found for cell lines of non-small cell lung cancer (NCI-H460 and NCI-H522), renal (UO-

31), breast (BT-549), melanoma (SK-MEL-2) and ovarian cancer (IGROV1) (GI_{50} = 6.9–11.0 μM) (Table 2). The above data indicates some similarities in activity profiles (patterns of growth inhibition in the 60 cell line screen) between the guanidine (**31**) and aminoguanidines (**II**, **III**) (Fig. 1) particularly in respect of some cell lines of leukemia, melanoma and non-small cell lung cancer [12,13].

Although the mechanisms by which investigated compounds exert their antitumor effect are still unknown at this moment, some similarity in activity profiles between the most active compound **18** and chloroquinoxaline sulfonamide (**CQS**) (Fig. 1) have been found by using the COMPARE algorithm [26–29]. Thus, it seems possible that the putative mechanism of its antitumor action may involve in cell cycle arrest in the G0/G1 phase.

3. Conclusions

A number of novel 2-benzylthio-4-chlorobenzenesulfonamides possessing the *N*-(benzoxazol-2-yl), *N*-(benzothiazol-2-yl) or *N*-(1,3-dihydro-2*H*-benzimidazol-2-ylidene) moiety were synthesized by reacting *N*-(2-benzylthio-4-chlorobenzenesulfonyl)cyanamide potassium salts with 2-aminophenols, 2-aminothiophenol and *o*-phenylenediamines, respectively. The results obtained in the present investigation prove the usefulness of the 2-benzylthio-4-chlorobenzenesulfonamide scaffold in the design of new anticancer agents. The *N*-(benzoxazol-2-yl)benzenesulfonamide **18** and *N*-(benzothiazol-2-yl) benzenesulfonamide **20** may serve as useful lead compounds for the search of more potent antitumor species.

4. Experimental protocols

4.1. Synthesis

The following instruments and parameters were used: (melting points) Büchi SMP 20 apparatus and reported uncorrected; (IR spectra) KBr pellets, 400–4000 cm^{-1} Perkin–Elmer 1600 FT IR spectrometer; (^{1}H NMR spectra): Varian Gemini (200 MHz) and Varian Unity Plus (500 MHz) spectrometer using TMS as internal standard (δ values in ppm); (mass spectra) Fennigan 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. Preparation of 3-amino-6-chloro-1,1-dioxo-N-phenyl-1,4,2-benzodithiazine-7-carboxamides (**3**, **4**)

To a suspension of the corresponding 6-chloro-1,1-dioxo-3-methylthio-*N*-phenyl-1,4,2-benzodithiazine-7-carboxamide **1** or **2** (10 mmol) in ethanol (25 ml) ammonium hydroxide (25%, 1.54 g, 11 mmol) was added dropwise during 30 min. The reaction mixture was stirred at room temperature for 24 h until the evolution of methanethiol had cased [CAUTION: due to a high toxicity, methanethiol should be trapped into an aqueous NaOH solution]. The precipitate thus obtained was filtered off, washed with ethanol, dried and purified by crystallization from ethanol.

In this manner, the following compounds were obtained.

*4.1.1.1. 3-Amino-6-chloro-1,1-dioxo-N-(4-fluorophenyl)-1,4,2-benzodithiazine-7-carboxamide (**3**)*. Yield: 2.51 g, 65%, m.p. 305–307 °C; IR (KBr) 3403, 3305, 3196, 3154 (NH_2, NH), 1658 (C=O), 1315, 1174 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.17–7.26 (m, 2H, aromatic), 7.68–7.75 (m, 2H, aromatic), 8.11 (s, 2H, H-5, H-8, benzodithiazine), 9.30 (br.s, 2H, NH_2), 10.75 (s, 1H, CONH) ppm. Anal. ($C_{14}H_9ClFN_3O_3S_2$) C, H, N.

*4.1.1.2. 3-Amino-6-chloro-1,1-dioxo-N-(4-methoxyphenyl)-1,4,2-benzodithiazine-7-carboxamide (**4**)*. Yield: 3.02 g, 76%, m.p. 264–267 °C; IR (KBr) 3385, 3306, 3186 (NH_2, NH), 2995, 2965, 2930, 2830 (OCH_3), 1654 (C=O), 1313, 1163 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 6.97 (d, J = 8.9 Hz, 2H, aromatic), 7.63 (d, J = 8.9 Hz, 2H, aromatic), 8.09 (s, 1H, H-5, benzodithiazine), 8.12 (s, 1H, H-8, benzodithiazine), 9.29–9.35 (br.s, 2H, NH_2), 10.57 (s, 1H, CONH) ppm. Anal. ($C_{15}H_{12}ClN_3O_4S_2$) C, H, N.

4.1.2. Preparation of N-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salts (**8**, **9**)

To a stirred suspension of the corresponding 3-amino-6-chloro-1,1-dioxo-*N*-phenyl-1,4,2-benzodithiazine-7-carboxamide **3** or **4** (6 mmol) and anhydrous K_2CO_3 (5.0 g) in dry THF (45 ml), benzylchloride (0.84 g, 6.6 mmol) was added. The reflux condenser was plugged with anhydrous calcium chloride tube. The reaction mixture was stirred at reflux for 20 h, and then solvent was evaporated under reduced pressure. The resulting solid residue was extracted twice with boiling ethanol (2 × 40 ml). The extracts were combined and evaporated to 1/2 volumes and then left overnight in a refrigerator. The precipitate thus obtained was filtered off, washed with cold ethanol (2 × 2 ml), and dried.

In this manner, the following compounds were obtained.

*4.1.2.1. N-[2-Benzylthio-4-chloro-5-(4-fluorophenylcarbamoyl)benzenesulfonyl]cyanamide potassium salt (**8**)*. Yield: 2.34 g, 76%, m.p. 150–153 °C; IR (KBr) 3425, 3305 (NH), 2931 (CH_2), 2173 (C≡N), 1660 (C=O), 1310, 1140 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.40 (s, 2H, SCH_2), 7.17–7.41 (m, 5H, aromatic), 7.49–7.54 (m, 2H, aromatic), 7.56 (s, 1H, H-3), 7.69–7.77 (m, 2H, aromatic), 7.89 (s, 1H, H-6), 10.67 (s, 1H, CONH) ppm. Anal. ($C_{21}H_{14}ClFKN_3O_3S_2$) C, H, N.

*4.1.2.2. N-[2-Benzylthio-4-chloro-5-(4-methoxyphenylcarbamoyl)benzenesulfonyl]cyanamide potassium salt (**9**)*. Yield: 2.5 g, 68%, m.p. 230–233 °C; IR (KBr) 3371 (NH), 2953, 2925, 2833 (CH_3, CH_2), 2173 (C≡N), 1646 (C=O), 1312, 1141 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H, OCH_3), 4.37

(s, 2H, SCH_2), 6.92 (d, $J = 8.9$ Hz, 2H, aromatic), 7.28–7.40 (m, 4H, aromatic), 7.48–7.51 (m, 1H, aromatic), 7.52 (s, 1H, H-3), 7.60 (d, $J = 8.9$ Hz, 2H, aromatic), 7.85 (s, 1H, H-6), 10.45 (s, 1H, CONH) ppm. Anal. ($C_{22}H_{17}ClKN_3O_4S_2$) C, H, N.

*4.1.3. General procedure for the preparation of N-(2-benzoxazolyl)-2-benzylthio-4-chlorobenzenesulfonamides (**10**–**19**) and N-(2-benzothiazolyl)-2-benzylthio-4-chlorobenzenesulfonamides (**20**–**21**)*

To a suspension of the corresponding *N*-(benzenesulfonyl) cyanamide potassium salt **5**–**9** (4 mmol) in glacial acetic acid (12 ml) the appropriate 2-aminophenol or 2-aminothiophenol (4 mmol) was added. The reaction was stirred at reflux for 4–6 or 9 h for **13** and **18**, and then left overnight at room temperature. The precipitate was filtered off, washed with glacial acetic acid (3 × 1 ml), and dried. The contaminations were extracted with boiling ethanol (8 ml per 1 g of crude reaction product).

In this manner, the following benzenesulfonamides were obtained.

*4.1.3.1. N-(2-Benzoxazolyl)-2-benzylthio-4-chloro-5-methylbenzenesulfonamide (**10**).* Starting from *N*-(2-benzylthio-4-chloro-5-methylbenzenesulfonyl)cyanamide potassium salt **5** (1.56 g) and 2-aminophenol (0.44 g) the title compound **10** was obtained (0.99 g, 56%); m.p. 222–224 °C Dec. IR (KBr) 3089 (NH), 2919, 2858 (CH_3, CH_2), 1642, 1626 (C=N), 1310, 1156 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 7.21 (s, 3H, aromatic), 7.19–7.20 (m, 2H, aromatic), 7.22–7.26 (m, 1H, aromatic), 7.28–7.34 (m, 2H, aromatic), 7.57 (s, 1H, H-3), 7.96 (s, 1H, H-6), 12.73 (s, 1H, SO_2NH) ppm; EIMS: *m*/*z* (%) 446 (M + 1, 11), 445 (M^+, 6), 444 (M – 1, 26), 245 (75), 223 (33), 135 (26), 134 (24), 91 (100), 43 (93). Anal. ($C_{21}H_{17}ClN_2O_3S_2$) C, H, N.

*4.1.3.2. 2-Benzylthio-4-chloro-N-(5-chlorobenzoxazol-2-yl)-5-methylbenzenesulfonamide (**11**).* Starting from **5** (1.56 g) and 2-amino-4-chlorophenol (0.57 g) the title compound **11** was obtained (1.05 g, 55%); m.p. 229–231 °C. IR (KBr) 3107, 3090 (NH), 2920, 2854 (CH_3, CH_2), 1639, 1622 (C=N), 1311, 1157 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 7.12–7.13 (s, 3H, aromatic), 7.17–7.19 (m, 2H, aromatic), 7.28–7.30 (m, 2H, aromatic), 7.55–7.57 (m, 1H, aromatic), 7.59 (s, 1H, H-3), 7.94 (s, 1H, H-6), 12.80 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{16}Cl_2N_2O_3S_2$) C, H, N.

*4.1.3.3. 2-Benzylthio-4-chloro-5-methyl-N-(5-methylbenzoxazol-2-yl)benzenesulfonamide (**12**).* Starting from **5** (1.56 g) and 2-amino-4-methylphenol (0.49 g) the title compound **12** was obtained (0.89 g, 49%); m.p. 224–226 °C. IR (KBr) 3089 (NH), 2920, 2855 (CH_3, CH_2), 1641, 1622 (C=N), 1311, 1158 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 7.03–7.05 (d, 1H, aromatic), 7.12–7.14 (m, 4H, aromatic), 7.19–7.21 (m, 2H, aromatic), 7.38–7.39 (d, 1H, aromatic), 7.56 (s, 1H, H-3), 7.95 (s, 1H, H-6), 12.66 (s, 1H, SO_2NH) ppm. Anal. ($C_{22}H_{19}ClN_2O_3S_2$) C, H, N.

*4.1.3.4. 2-Benzylthio-4-chloro-5-methyl-N-(5-nitrobenzoxazol-2-yl)benzenesulfonamide (**13**).* Starting from **5** (1.56 g) and 2-amino-4-nitrophenol (0.62 g) the title compound **13** was obtained (1.08 g, 55%); m.p. 249–250 °C. IR (KBr) 3105, 3095 (NH), 2919, 2850 (CH_3, CH_2), 1648, 1633 (C=N), 1544, 1347 (NO_2), 1317, 1157 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 4.29 (s, 2H, SCH_2), 7.09–7.22 (m, 5H, aromatic), 7.62 (s, 1H, H-3), 7.75–7.79 (d, 1H, aromatic), 7.96 (s, 1H, H-6), 7.99–8.00 (d, 1H, aromatic), 8.15–8.20 (dd, 1H, aromatic) ppm. Anal. ($C_{21}H_{16}ClN_3O_5S_2$) C, H, N.

*4.1.3.5. N-(2-Benzoxazolyl)-2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonamide (**14**).* Starting from *N*-(2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonyl)cyanamide potassium salt **6** (1.68 g) and 2-aminophenol (0.44 g) the title compound **14** was obtained (0.95 g, 50%); m.p. 240–242 °C. IR (KBr) 3395, 3301, 3224 (NH_2, NH), 2913, 2854 (CH_2), 1642 (C=O) 1628, 1614 (C=N), 1330, 1144 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.41 (s, 2H, SCH_2), 7.17–7.37 (m, 8H, aromatic), 7.55–7.58 (m, 1H, aromatic), 7.66 (s, 1H, H-3), 7.75 (s, 1H, $CONH_a$), 8.03 (s, 1H, H-6), 8.04 (s, 1H, $CONH_b$), 12.80 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{16}ClN_3O_4S_2$) C, H, N.

*4.1.3.6. 2-Benzylthio-5-carbamoyl-4-chloro-N-(5-chlorobenzoxazol-2-yl)benzenesulfonamide (**15**).* Starting from **6** (1.68 g) and 2-amino-4-chlorophenol (0.57 g) the title compound **15** was obtained (0.96 g, 47%); m.p. 288–291 °C. IR (KBr) 3394, 3295, 3266, 3220 (NH_2, NH), 2925, 2854 (CH_2), 1641 (C=O), 1624, 1604 (C=N), 1317, 1141 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.40 (s, 2H, SCH_2), 7.18–7.34 (m, 7H, aromatic), 7.59–7.61 (m, 1H, aromatic), 7.67 (s, 1H, H-3), 7.74 (s, 1H, $CONH_a$), 8.00 (s, 1H, H-6), 8.04 (s, 1H, $CONH_b$) ppm. Anal. ($C_{21}H_{15}Cl_2N_3O_4S_2$) C, H, N.

*4.1.3.7. 2-Benzylthio-5-carbamoyl-4-chloro-N-(5-methylbenzoxazol-2-yl)benzenesulfonamide (**16**).* Starting from **6** (1.68 g) and 2-amino-4-methylphenol (0.49 g) the title compound **16** was obtained (0.78 g, 40%); m.p. 268–270 °C. IR (KBr) 3395, 3301, 3224 (NH_2, NH), 2978, 2925, 2860 (CH_3, CH_2), 1640 (C=O), 1622, 1607 (C=N), 1331, 1143 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 4.40 (s, 2H, SCH_2), 7.06–7.30 (m, 7H, aromatic), 7.40–7.44 (m, 1H, aromatic), 7.65 (s, 1H, H-3), 7.74 (s, 1H, $CONH_a$), 8.03 (s, 1H, H-6), 8.04 (s, 1H, $CONH_b$), 12.77 (s, 1H, SO_2NH) ppm. Anal. ($C_{22}H_{18}ClN_3O_4S_2$) C, H, N.

*4.1.3.8. N-(2-Benzoxazolyl)-2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonamide (**17**).* Starting from *N*-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salt **7** (1.98 g) and 2-aminophenol (0.44 g) the

title compound **17** was obtained (1.32 g, 60%); m.p. 271–273 °C. IR (KBr) 3301, 3277, 3236, 3177 (NH), 2920 (CH_2), 1651 (C=O), 1641, 1625 (C=N), 1316, 1146 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.43 (s, 2H, SCH_2), 7.07–7.41 (m, 11H, aromatic), 7.51–7.58 (m, 1H, aromatic), 7.68–7.72 (m, 2H aromatic), 7.95 (s, 1H, H-3), 8.13 (s, 1H, H-6), 10.63 (s, 1H, CONH), 12.85 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{27}H_{20}ClN_3O_4S_2$) C, H, N.

*4.1.3.9. N-(2-Benzoxazolyl)-2-benzylthio-4-chloro-5-(4-fluorophenylcarbamoyl)benzenesulfonamide (**18**)*. Starting from **8** (2.06 g) and 2-aminophenol (0.44 g) the title compound **18** was obtained (1.05 g, 46%); m.p. 284–286 °C. IR (KBr) 3282, 3142 (NH), 2931 (CH_2), 1642 (C=O), 1624 (C=N), 1317, 1147 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.43 (s, 2H, SCH_2), 7.16–7.30 (m, 4H, aromatic), 7.32–7.39 (m, 5H, aromatic), 7.50–7.60 (m, 2H, aromatic), 7.67–7.75 (m, 3H, aromatic), 8.13 (s, 1H, H-6), 10.68 (s, 1H, CONH), 12.85 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{27}H_{19}ClFN_3O_4S_2$) C, H, N.

*4.1.3.10. N-(2-Benzoxazolyl)-2-benzylthio-4-chloro-5-(4-methoxyphenylcarbamoyl)benzenesulfonamide (**19**)*. Starting from **9** (2.10 g) and 2-aminophenol (0.44 g) the title compound **19** was obtained (1.18 g, 51%); m.p. 305–306 °C. IR (KBr) 3278, 3125 (NH), 2931, 2837 (CH_3, CH_2), 1642 (C=O), 1622, 1584 (C=N), 1310, 1146 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.76 (s, 3H, OCH_3), 4.44 (s, 2H, SCH_2), 6.94–6.98 (m, 2H, aromatic), 7.20–7.37 (m, 9H, aromatic), 7.52–7.65 (m, 2H, aromatic), 7.74 (s, 1H, H-3), 8.13 (s, 1H, H-6), 10.50 (s, 1H, CONH), 12.85 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{28}H_{22}ClN_3O_5S_2$) C, H, N.

*4.1.3.11. N-(2-Benzothiazolyl)-2-benzylthio-4-chloro-5-methylbenzenesulfonamide (**20**)*. Starting from **5** (1.56 g) and 2-aminothiophenol (0.5 g) the title compound **20** was obtained (1.36 g, 74%); m.p. 231–233 °C. IR (KBr) 3158, 3104 (NH), 2978, 2915, 2842 (CH_3, CH_2), 1550 (C=N), 1315, 1134 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 7.09–7.15 (m, 3H, aromatic), 7.22–7.27 (m, 3H, aromatic), 7.33–7.43 (m, 2H, aromatic), 7.55 (s, 1H, H-3), 7.77–7.79 (d, 1H, aromatic), 7.91 (s, 1H, H-6), 13.25 (s, 1H, SO_2NH) ppm; EIMS: *m/z* (%) 462 (M + 1, 14), 461 (M^+, 8), 460 (M – 1, 30), 369 (20), 245 (70), 239 (44), 151 (28), 150 (34), 91 (100). Anal. ($C_{21}H_{17}ClN_2O_2S_3$) C, H, N.

*4.1.3.12. N-(2-Benzothiazolyl)-2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonamide (**21**)*. Starting from **6** (1.68 g) and 2-aminothiophenol (0.5 g) the title compound **21** was obtained (1.02 g, 52%); m.p. 290–292 °C. IR (KBr) 3460, 3325, 3254, 3155 (NH_2, NH), 2907, 2860 (CH_2), 1667 (C=O), 1547 (C=N), 1323, 1146 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.41 (s, 2H, SCH_2), 7.19–7.46 (m, 8H, aromatic), 7.64 (s, 1H, H-3), 7.75 (s, 1H, $CONH_a$), 7.82–7.86 (m, 1H, aromatic), 7.98 (s, 1H, H-6), 8.05 (s, 1H, $CONH_b$), 13.37 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{16}ClN_3O_3S_3$) C, H, N.

*4.1.4. General procedure for the preparation of 2-benzylthio-4-chloro-N-(1,3-dihydro-2H-benzimidazol-2-ylidene) benzenesulfonamides (**22**–**25**)*

To a suspension of the corresponding *N*-(benzenesulfonyl) cyanamide potassium salt **5** or **6** (4 mmol) in glacial acetic acid (12 ml) the appropriate *o*-phenylenediamine (4 mmol) was added. The reaction was stirred at reflux for 4.5–5 h and left to stand at room temperature overnight. The precipitate was filtered off, washed with glacial acetic acid (3 × 1 ml), and dried. The contaminations were extracted with boiling ethanol (8 ml per 1 g of crude reaction product).

In this manner, the following benzenesulfonamides were obtained.

*4.1.4.1. 2-Benzylthio-4-chloro-N-(1,3-dihydro-2H-benzimidazol-2-ylidene)-5-methylbenzenesulfonamide (**22**)*. Starting from **5** (1.56 g) and 1,2-diaminobenzene (0.43 g) the title compound **22** was obtained (0.85 g, 48%); m.p. 277–279 °C Dec. IR (KBr) 3311, 3201 (NH), 2918, 2884 (CH_3, CH_2), 1628, 1595 (C=N), 1305, 1135 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 4.24 (s, 2H, SCH_2), 7.11–7.15 (m, 5H, aromatic), 7.21–7.23 (m, 2H, aromatic), 7.26–7.29 (m, 2H, aromatic), 7.47 (s, 1H, H-3), 7.98 (s, 1H, H-6), 11.92 (s, 2H, 2 × NH) ppm. Anal. ($C_{21}H_{18}ClN_3O_2S_2$) C, H, N.

*4.1.4.2. 2-Benzylthio-4-chloro-5-methyl-N-(4-methyl-1,3-dihydro-2H-benzimidazol-2-ylidene) benzenesulfonamide (**23**)*. Starting from **5** (1.56 g) and 2,3-diaminotoluene (0.49 g) the title compound **23** was obtained (0.86 g, 47%); m.p. 259–261 °C. IR (KBr) 3364, 3177 (NH), 2929, 2848 (CH_3, CH_2), 1638, 1597 (C=N), 1303, 1137 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.24 (s, 2H, SCH_2), 6.93–6.95 (d, 1H, aromatic), 7.00–7.03 (t, 1H, aromatic), 7.14–7.18 (m, 4H, aromatic), 7.22–7.24 (m, 2H, aromatic), 7.47 (s, 1H, H-3), 7.99 (s, 1H, H-6), 11.65 (s, 1H, NH), 12.22 (s, 1H, NH) ppm. Anal. ($C_{22}H_{20}ClN_3O_2S_2$) C, H, N.

*4.1.4.3. 2-Benzylthio-4-chloro-5-methyl-N-(5-methyl-1,3-dihydro-2H-benzimidazol-2-ylidene) benzenesulfonamide (**24**)*. Starting from **5** (1.56 g) and 3,4-diaminotoluene (0.49 g) the title compound **24** was obtained (0.71 g, 39%); m.p. 284–287 °C Dec. IR (KBr) 3319, 3248, 3195 (NH), 2941, 2914, 2855 (CH_3, CH_2), 1624, 1590 (C=N), 1345, 1136 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.24 (s, 2H, SCH_2), 6.93–6.95 (d, 1H, aromatic), 7.07 (s, 1H, aromatic), 7.14–7.16 (m, 4H, aromatic), 7.22–7.24 (m, 2H, aromatic), 7.46 (s, 1H, H-3), 7.97 (s, 1H, H-6), 11.81 (s, 2H, 2 × NH) ppm. Anal. ($C_{22}H_{20}ClN_3O_2S_2$) C, H, N.

*4.1.4.4. 2-Benzylthio-5-carbamoyl-4-chloro-N-(1,3-dihydro-2H-benzimidazol-2-ylidene) benzenesulfonamide (**25**)*. Starting from **6** (1.68 g) and 1,2-diaminobenzene (0.43 g) the title compound **25** was obtained (0.76 g, 40%); m.p. 330–334 °C. IR (KBr) 3383, 3282, 3224 (NH_2, NH), 2964, 2889 (CH_2), 1646

(C=O), 1634, 1602 (C=N), 1326, 1144 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.36 (s, 2H, SCH_2), 7.14–7.27 (m, 5H, aromatic), 7.29–7.34 (m, 4H, aromatic), 7.55 (s, 1H, H-3), 7.70 (s, 1H, $CONH_a$), 7.99 (s, 1H, $CONH_b$), 8.08 (s, 1H, H-6), 12.00 (s, 2H, 2 × NH) ppm. Anal. ($C_{21}H_{17}ClN_4O_3S_2$) C, H, N.

*4.1.5. Preparation of N-(2-benzoxazolyl)-2-benzylthio-4-chloro-5-cyanobenzenesulfonamides (**26**–**28**) and N-(2-benzothiazolyl)-2-benzylthio-4-chloro-5-cyanobenzenesulfonamide (**29**)*

A suspension of the corresponding *N*-(2-benzoxazolyl)-2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonamide **14**–**16** (2 mmol) or *N*-(2-benzothiazolyl)-2-benzylthio-5-carbamoyl-4-chlorobenzenesulfonamide **21** (2 mmol) in phosphorus oxychloride (20 ml) was stirred at room temperature for 20 min, and then at reflux for 30 h and allowed to stand at room temperature overnight. The resulting suspension was poured onto crushed ice (170 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 6–7), dried and crystallized from ethanol.

In this manner, the following compounds were obtained.

*4.1.5.1. N-(2-Benzoxazolyl)-2-benzylthio-4-chloro-5-cyanobenzenesulfonamide (**26**)*. Yield: 0.64 g, 70%, m.p. 260–262 °C; IR (KBr) 3307, 3101 (NH), 2919, 2848 (CH_2), 2226 (C≡N), 1639, 1628 (C=N), 1316, 1149 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.48 (s, 2H, SCH_2), 7.19–7.36 (m, 8H, aromatic), 7.55–7.58 (m, 1H, aromatic), 7.86 (s, 1H, H-3), 8.40 (s, 1H, H-6), 12.95 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{14}ClN_3O_3S_2$) C, H, N.

*4.1.5.2. 2-Benzylthio-4-chloro-N-(5-chlorobenzoxazol-2-yl)-5-cyanobenzenesulfonamide (**27**)*. Yield: 0.74 g, 75%, m.p. 255–247 °C; IR (KBr) 3107 (NH), 2911 (CH_2), 2239 (C≡N), 1639, 1622 (C=N), 1313, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.49 (s, 2H, SCH_2), 7.21–7.34 (m, 7H, aromatic), 7.58–7.62 (m, 1H, aromatic), 7.89 (s, 1H, H-3), 8.39 (s, 1H, H-6) ppm. Anal. ($C_{21}H_{13}Cl_2N_3O_3S_2$) C, H, N.

*4.1.5.3. 2-Benzylthio-4-chloro-5-cyano-N-(5-methylbenzoxazol-2-yl)benzenesulfonamide (**28**)*. Yield: 0.52 g, 55%, m.p. 263–265 °C; IR (KBr) 3260, 3101 (NH), 2931, 2865 (CH_3, CH_2), 2232 (C≡N), 1649, 1626 (C=N), 1305, 1151 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 4.48 (s, 2H, SCH_2), 7.11–7.38 (m, 7H, aromatic), 7.41–7.46 (m, 1H, aromatic), 7.87 (s, 1H, H-3), 8.40 (s, 1H, H-6), 12.85 (br.s, 1H, SO_2NH) ppm. Anal. ($C_{22}H_{16}ClN_3O_3S_2$) C, H, N.

*4.1.5.4. N-(2-Benzothiazolyl)-2-benzylthio-4-chloro-5-cyanobenzenesulfonamide (**29**)*. Yield: 0.67 g, 71%, m.p. 263–264 °C; IR (KBr) 3236 (NH), 2913 (CH_2), 2236 (C≡N), 1576, 1532 (C=N), 1318, 1142 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.47 (s, 2H, SCH_2), 7.18–7.49 (m, 8H, aromatic), 7.81–7.84 (m, 1H, aromatic), 7.85 (s, 1H, H-3), 8.31 (s, 1H, H-6), 13.49 (s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{14}ClN_3O_2S_3$) C, H, N.

*4.1.6. 2-Benzylthio-4-chloro-5-cyano-N-(1,3-dihydro-2H-benzimidazol-2-ylidene)benzenesulfonamide (**30**)*

A suspension of **25** (0.71 g, 1.5 mmol) in phosphorus oxychloride (15 ml) was stirred at room temperature for 20 min, and then at reflux for 30 h and allowed to stand at room temperature overnight. The resulting suspension was poured onto crushed ice (130 g) with vigorously stirring for at least 1 h. The solid that precipitated was filtered off, washed thoroughly with several portions of cold water (pH 6–7), dried and purified by crystallization from ethanol to give **30** as a white powder (0.44 g, 65%); m.p. 300–301 °C. IR (KBr) 3342 (NH), 2955, 2878, 2831 (CH_2), 2232 (C≡N), 1625, 1592, (C=N), 1311, 1147 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.51 (s, 2H, SCH_2), 7.16–7.35 (m, 9H, aromatic), 7.79 (s, 1H, H-3), 8.46 (s, 1H, H-6), 12.12 (s, 2H, 2 × NH) ppm. Anal. ($C_{21}H_{15}ClN_4O_2S_2$) C, H, N.

*4.1.7. Synthesis of 3-(2-hydroxyphenyl)-1-(2-benzylthio-4-chloro-5-methylbenzenesulfonyl) guanidine (**31**) as intermediate product for the preparation of benzenesulfonamide (**10**) from cyanamide potassium salt (**5**)*

A suspension of **5** (1.56 g, 4 mmol) and 2-aminophenol (0.44 g, 4 mmol) in glacial acetic acid (12 ml) was stirred at reflux for 0.5 h. After cooling to room temperature the precipitate was filtered off, washed with acetic acid (2 × 1 ml), and dried. The resulting solid mixture was extracted with boiling chloroform (15 ml) for 15 min. The insoluble material was collected by filtration, dried and purified by crystallization from ethanol to give **31** as white crystals (0.68 g, 37%); m.p. 185–187 °C Dec. IR (KBr) 3471 (OH), 3297, 3260, 3141 (NH), 2970, 2919 (CH_3, CH_2), 1625, 1528 (C=N), 1343, 1139 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 4.29 (s, 2H, SCH_2), 6.59–6.63 (m, 1H, aromatic), 6.82–6.84 (m, 1H, aromatic), 6.87–6.90 (m, 1H, aromatic), 7.01 (br.s, 1H, NH), 7.21–7.26 (m, 3H, aromatic), 7.29–7.35 (m, 2H, aromatic), 7.44 (s, 1H, H-3), 7.79 (br.s, 1H, NH), 7.88 (s, 1H, H-6), 8.43 (s, 1H, OH), 9.97 (s, 1H, SO_2NH) ppm. Anal. ($C_{21}H_{20}ClN_3O_3S_2$) C, H, N.

A suspension of **31** (1.38 g, 3 mmol) in glacial acetic acid (12 ml) was stirred at reflux for 3 h. After cooling to room temperature (2 h) the crystalline product was collected by filtration and washed with acetic acid (3 × 1.5 ml), and dried to afford **10** as white crystals (0.75 g, 56%); m.p. 222–224 °C Dec. IR and ^1H NMR data were in accordance with those reported above for the authentic sample of **10**.

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