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Short communication

Synthesis of a new series of 4-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives with potential antitumor activity

Jarosław Sławiński

Department of Chemical Technology of Drugs, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdansk, Poland

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Abstract

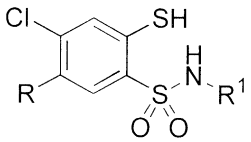
The syntheses of *S*-(5-chloro-4-methyl-2-sulfamoylphenyl)alkanethio (or benzothio)hydrazonates (**3a–3o**) and potassium *S*-(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)alkanethio (or benzothio)hydrazonates (**4–10**) are described. The compounds **3e, 3i–3o, 7** and **8** were screened at the National Cancer Institute (NCI) for their activities against a panel of 59 tumor cell lines and relationships between structure and antitumor activity in vitro are discussed. The compounds **3e, 3j, 3l–3o** and **7** exhibited reasonable activity against numerous human tumor cell lines. The prominent compound **3l** showed significant activity against some cell lines of leukemia (SR), melanoma (SK-MEL-5), CNS cancer (SF-539), ovarian cancer (OVCAR-3, OVCAR-4) and breast cancer (MDA-MB-231/ACTT) (GI_{50} values in the range 0.3–0.9 μM). Furthermore, compound **8** exhibited the high selectivity against renal cancer (A498) cells ($GI_{50} < 0.01$ μM, TGI = 2.3 μM and $LC_{50} = 35.7$ μM).

Keywords: 4-Chloro-2-mercapto-5-methylbenzenesulfonamide derivatives; *S*-(5-Chloro-4-methyl-2-sulfamoylphenyl)alkanethio (or benzothio)hydrazonates; Synthesis; Structures; Antitumor effect

1. Introduction

Various arylsulfonamides have been reported to possess anticancer [1–4] or/and anti-HIV [2–7] properties. We have previously described the syntheses a number of 4-chloro-2-mercaptobenzensulfonamide derivatives with the nitrogen atom of the sulfonamide moiety attached to a variety of heterocyclic ring systems or acyclic polynitrogen substituents. These compounds, depending on the structure, exhibited either anticancer [8–22] or anti-HIV [8–11,17,18,23–25] activities and have been described [26] as a novel class of potent HIV-1 integrase inhibitors (MBSAs, Fig. 1).

The aim of the present investigation was to extend our studies in this class of compounds. Thus, we elaborated the syntheses and anticancer evaluations in vitro of a new *S*-substituted 2-mercaptobenzenesulfonamides bearing either the unsubstituted sulfonamide moiety or cyano group attached to the sulfonamide nitrogen atom.



MBSAs

Fig. 1. General structure of novel class of potent HIV-1 integrase inhibitors – **MBSAs** (R = H or Me, R^1 = heteroaryl).

2. Results and discussion

2.1. Chemistry

The syntheses of the target compounds **3a–3o** were achieved by a convenient procedure starting from 2-mercaptobenzenesulfonamide **1a** and the corresponding hydrazonyl bromides **2a–2o** as shown in Fig. 2.

Thus, treatment of the substrate **1a** with equimolar amount of triethylamine in methylene chloride at room temperature, and then with 1 M equivalent of the corresponding hydrazonyl bromides **2a–2o**, initially at room temperature for 1 h, and then at reflux for further 7.5 h, leads to the formation of the desired *S*-(5-chloro-4-methyl-2-sulfamoylphenyl) *N*-(4-

E-mail address: jaroslaw@amg.gda.pl (J. Sławiński).

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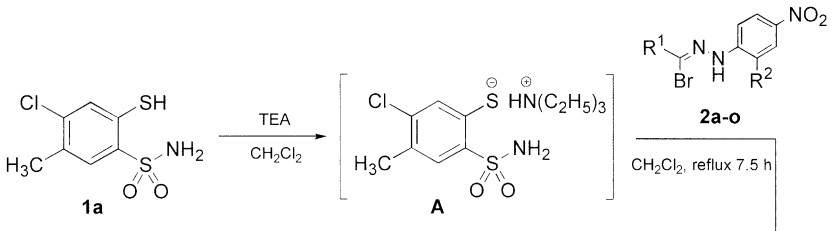


Compounds	R^1	R^2
2a, 3a	C_2H_5	H
2b, 3b	C_3H_7	H
2c, 3c	*i*-C_3H_7	H
2d, 3d	*i*-C_3H_7	NO_2
2e, 3e	*i*-C_4H_9	H
2f, 3f	*t*-C_4H_9	H
2g, 3g	C_5H_{11}	H
2h, 3h	CH_2CH_2Ph	H
2i, 3i	Ph	H
2j, 3j	4-Cl-Ph	H
2k, 3k	4-NO_2-Ph	H
2l, 3l	4-CH_3-Ph	H
2m, 3m	4-CH_3O-Ph	H
2n, 3n	3-Br,4-HO-Ph	H
2o, 3o	2-naphthyl	H

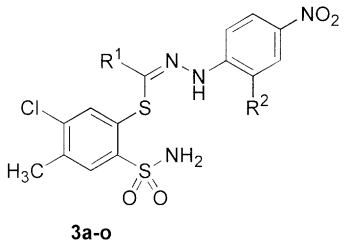


Fig. 2. Synthesis of the *S*-(5-chloro-4-methyl-2-sulfamoylphenyl)thiohydrazonate derivatives **3a–o**.

nitrophenyl)alkanethiohydrazonates (**3a–3h**), and corresponding benzothiohydrazonates (**3i–3o**) in good to high yields. The product was easily separated from the reaction mixture because of their low solubility. The plausible oxidation of the mercapto group furnished *bis*(5-chloro-4-methyl-2-sulfamoylphenyl)disulfide or typical hydrazonyl bromide intermolecular transformations products, for instance corresponding hydrazides or 1,3,4,6-tetrasubstituted-1,2,4,5-tetrazines [27,28] were not observed.

The question of what determines nucleophilicity and how to treat nucleophilic reactivity in a quantitative way intrigued chemists for many years. It has been pointed out that sulfur nucleophiles are often "much more reactive than would be expected from their basicity" [29]. Moreover, notable reactivity of sulfur nucleophiles is observed in substitution reactions at vinylic centers [30]. On the other hand, benzenesulfonamides should be considered as N–H acids and their relatively low nucleophilicity by an electron withdrawal due to mutual interaction of the inductive and mesomeric effect of neighboring sulfonyl group. Thus, it could be supposed that the nucleophilicity of thiophenolate group is distinguished higher than that of the benzenesulfonamide nitrogen atom.

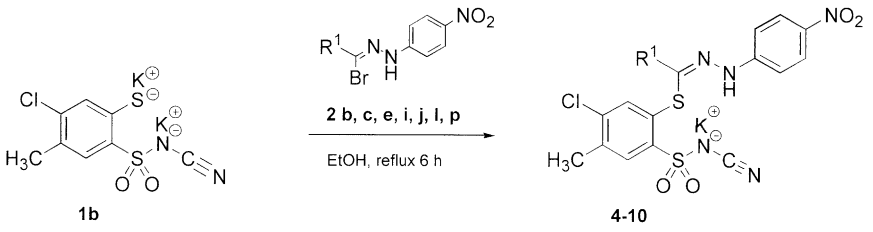
Thiophenols are the relatively stronger acids (pK_a 7.47) [31] than benzenesulfonamides (pK_a in the range 9.4–10.2) [32]. Thus, treatment of the 2-mercaptobenzenesulfonamide **1a** in methylene chloride with 1 M equivalent of triethylamine leads unambiguously to the formation of triethylaminium 2-sulfamoylphenylthiolate **A** (as shown in Fig. 2.), then upon treatment with hydrazonyl bromides salt **A** undergoes *S*-alkylation reaction, exclusively.

Therefore, in our investigations the competition reaction between *S*- and *N*-alkylation was not observed. Inspection of the ^{1}H NMR spectrum of the products obtained (**3i–3o**) revealed singlet attributable to the protons of SO_2NH_2 group in the region δ = 7.71–7.99 ppm. This signal integrating for two protons was disappeared upon deuterium oxide addition.

A series of potassium *S*-(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl) *N*-(4-nitrophenyl)alkanethiohydrazonates (**4–6**) and corresponding benzothiohydrazonates (**7–10**) were synthesized from dipotassium 5-chloro-2-cyanoamidatesulfonyl-4-methylphenylthiolate (**1b**) by the reaction with 1 M equivalent of corresponding hydrazonyl bromides **2b, 2c, 2e, 2i, 2j, 2l**, and **2p** in ethanol at reflux, as shown in Fig. 3. The desired *S*-alkylated product was separated either in good yields (67–84%) for (**7–10**) or in moderate yields (47–53%) for (**4–6**).

Compound **1b** represents an interesting example of *N*-substituted benzenesulfonamide possess two anionic centers. However, the nucleophilicity of the sulfonamide nitrogen atom was markedly decreased as a result of electron withdrawal caused by neighboring sulfonyl and cyano groups [33,38]. Under these reaction conditions the *S*-alkylation proceed exclusively. It is pertinent to note that an attempt was made to introduce both *S*- and *N*-alkyl substituents, but the reaction failed.

The structures of the final products were confirmed by elemental analyses as well as by IR and NMR spectroscopy as shown in experimental protocols. The presence of the 4-nitrophenylhydrazonyl moiety was indicated by characteristic signals of NH proton in the downfield region δ = 10.01–11.38 ppm, integrating for one proton, as well as typical



Copmounds	R^1
2b, 4	C_3H_7
2c, 5	*i*-C_3H_7
2e, 6	*i*-C_4H_9
2i, 7	Ph
2j, 8	4-Cl-Ph
2l, 9	4-CH_3-Ph
2p, 10	4-Br-Ph

Fig. 3. Synthesis of the potassium *S*-(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl) thiohydrazonate derivatives **4–10**.

aromatic AA`XX` system, while the IR spectra showed the absorption of the polar NO_2 group in the regions 1495–1528 and 1316–1331 cm^{-1}, however, this last was partially overlapped with antisymmetric vibration band of SO_2 group in a similar region 1302–1318 cm^{-1}. The IR spectra of compounds **4–10** showed strong absorption band of the C≡N group in the region 2172–2184 cm^{-1} and sharp adsorption band of the NH group in the region 3195–3236 cm^{-1}. ^1H NMR spectra of all compounds revealed characteristic singlets of H-6 and H-3 of the benzenesulfonamide protons in the region δ = 6.94–7.56 ppm and δ = 7.84–8.53 ppm, respectively.

2.2. Biology

The compounds **3e, 3i–3o, 7** and **8** were submitted to the US National Cancer Institute (NCI; Bethesda, MD), for in vitro testing against a panel approximately 59 tumor cell lines. 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 [34–36]. The antitumor activity of tested compounds is given by three parameters for each cell line: GI_{50}, molar concentration of the compound that inhibits 50% net cell growth; TGI molar concentration of the compound leading to total inhibition; and LC_{50}, molar concentration of the compound leading to 50% net cell death.

Compounds **3i** and **3k** were inactive (GI_{50} >100 μM), whereas the other compounds **3e, 3j, 3l–3o, 7** and **8** exhibited reasonable activity against most of the 59 human cancer cell lines (Table 1).

Relatively highest sensitivity to the compounds described here was found for cell lines of melanoma (SK-MEL-5, SK-MEL-28), leukemia (SR), CNS cancer (SF-539), ovarian cancer (OVCAR-3, OVCAR-4), breast cancer (MDA-MB-231/ACTT, T-47D) and renal cancer (A498, RXF-393) (Tables 2 and 3).

Different cancer cell lines of the same tumor type possessed a variable response to inhibition of growth in the presence of the new derivatives. For example, the renal cancer A498 cells were susceptible to inhibition by **7** and **8** (GI_{50} <0.01 μM) whereas the other cell lines (such as RFX-

Table 1
Overview of the results of the anticancer screening for compounds **3e, 3i–3o, 7** and **8** [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)	
		No.	Range	No.	Range	No.	Range
3e	56	56	1.8–18.8	54	5.7–97.0	46	19.7–96.0
3j	56	56	0.5–44.3	45	3.4–77.9	20	6.9–71.8
3l	56	56	0.3–19.5	54	4.1–46.3	46	4.8–86.3
3m	56	56	0.03–21.1	55	1.3–86.9	48	4.3–86.3
3n	56	56	0.6–51.6	52	1.8–53.3	41	6.1–76.4
3o	57	54	<0.01–84.0	34	8.8–83.7	16	48.6–98.3
7	57	51	<0.01–44.7	48	22.5–83.1	38	47.5–96.0
8	57	49	<0.01–77.6	21	2.3–98.3	5	35.7–98.3

Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Tables 2 and 3 or Refs. [34–36] for details).

[a] Compounds **3i** and **3k** 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 **3e, 3j, 3n, 3o, 7** and **8** [a]

Tumor cell lines	GI_{50} (μM) [b]					
	3e	**3j**	**3n**	**3o**	**7**	**8**
Leukemia						
K-562	5.8	3.4	2.7	28.0	15.2	35.2
RPMI-8226	2.5	2.5	1.6	37.7	19.5	30.5
SR	1.8	2.9	51.6	42.6	NT [c]	NT [c]
Non-small cell lung cancer						
NCI-H226	2.8	2.2	2.6	18.4	16.3	18.5
NCI-H460	4.0	2.1	2.9	18.5	18.7	26.7
NCI-H23	3.7	2.2	2.4	16.4	15.4	77.6
Colon cancer						
KM12	3.3	1.9	1.9	25.2	16.6	24.6
SW-620	8.8	3.2	3.5	33.4	17.1	21.1
CNS cancer						
SF-268	7.2	2.3	2.2	10.1	19.2	26.0
SF-295	2.3	2.1	2.0	20.0	15.9	22.7
Melanoma						
LOX IMVI	5.8	2.1	2.1	20.3	15.4	30.1
MALME-3M	12.5	1.5	1.7	11.7	16.5	24.4
SK-MEL-28	13.9	0.5	2.6	35.1	17.2	31.2
Ovarian cancer						
OVCAR-3	3.1	1.7	2.0	17.5	14.2	21.2
OVCAR-4	5.0	1.7	3.4	61.1	13.9	20.9
SK-OV-3	13.7	1.9	4.3	20.4	>100	17.9
Renal cancer						
A498	NT [c]	4.3	7.5	NT [c]	<0.01	<0.01
RXF-393	4.1	1.7	0.6	8.6	23.5	34.4
TK-10	2.9	1.7	2.0	7.4	16.0	25.0
Breast cancer						
MCF7	2.3	2.0	2.1	19.9	14.7	15.9
HS-578T	11.9	4.8	2.9	2.1	16.2	17.2
MDA-MB-435	2.9	2.2	1.8	22.2	32.7	64.3
T-47D	3.0	3.0	2.5	<0.01	>100	3.9

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen [34–36].
[b] Molar concentration of the compound that inhibits 50% net cell growth.
[c] Not tested.

393, TK-10) showed a substantial lower level of inhibition (GI_{50} ranged from 16.0 to 34.4 μM). Similarly, the breast cancer T-47D cells were high sensitive to compound **3o** (GI_{50} <0.01 μM) while other cell lines (such as HS-578T, MDA-MB-435) showed GI_{50} in the range from 2.1 to 22.2 μM (Table 2). The same situation has been evidenced in the case of diverse melanoma cell lines with compound **3m** acting mainly against SK-MEL-5 cells (GI_{50} = 0.03 μM) but the other melanoma cell lines showed a much lower level of inhibition (GI_{50} in the range 1.9–11.1 μM) (Table 3).

It could be stated, that the electronic nature of the substituent essentially influence anticancer activity of derivatives and differentiate sensitivity of tumor cell lines. The presence, for instance, R^1 = 4-methylphenyl **3l** or 4-methoxyphenyl **3m** essentially increased the activity as seen in the series of structural analogues **3i–3o** tested. Introduction either 4-chlorophenyl **3j** or 3-bromo-4-hydroxyphenyl group **3n** led to the slight decrease of activity, while the presence of relatively more electron withdrawing substituent in this series i.e. R^1 = 4-nitrophenyl group in **3k** resulted in the total loss of activity.

In contrast, compound **3e** bearing electron donating 2-methylpropyl substituent (R^1) showed a moderate activity (Table 2).

It is noteworthy, that replacement of sulfonamide hydrogen atoms in **3j** by both cyano group and potassium ion resulted in compound **8** exhibited a high degree of selectivity against renal cancer (A498) cells (GI_{50} <0.01 μM,

Table 3
In vitro anticancer data for selected compounds **3l** and **3m** [a]

Panel cell lines	Response parameters: GI_{50}, TGI and LC_{50} [b]					
	Compound **3l**			Compound **3m**		
	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
Leukemia						
K-562	4.3	14.8	38.4	3.8	12.2	35.0
MOLT-4	3.3	12.3	35.0	3.7	13.7	37.1
RPMI-8226	1.9	5.0	21.4	2.4	6.5	23.4
SR	0.9	3.5	>100	2.1	5.4	>100
Non-small cell lung cancer						
A549/ATCC	3.1	12.9	45.5	3.7	16.8	81.6
EKVX	4.0	16.0	61.0	3.1	10.4	36.2
HOP-62	2.5	6.6	23.3	3.0	10.0	31.3
HOP-92	1.4	3.6	9.1	1.2	35.5	9.8
NCI-H226	1.4	3.3	7.6	2.4	5.2	42.7
NCI-H23	1.2	2.7	6.2	1.9	4.0	8.2
NCI-H322M	1.7	5.0	17.9	2.3	7.1	25.8
NCI-H460	2.3	9.7	86.3	4.7	22.0	87.5
NCI-H522	6.5	>100	>100	11.3	27.8	68.6
Colon cancer						
COLO 205	1.8	5.3	>100	4.0	22.1	>100
HCC-2998	1.2	2.7	5.8	1.6	3.2	6.1
HCT-116	1.1	2.3	4.8	1.7	3.2	6.1
HCT-15	3.8	24.6	>100	4.6	16.7	40.8
HT29	1.3	3.1	7.4	2.0	4.0	7.9
KM12	1.0	2.6	7.0	2.2	5.8	20.0
SW-620	2.5	10.5	47.3	3.0	10.9	33.0
CNS cancer						
SF-268	1.2	5.6	32.6	2.8	10.8	46.2
SF-295	1.4	2.9	6.0	2.0	4.0	7.8
SF-539	0.6	2.1	6.6	2.2	4.7	11.0
SNB-19	1.5	4.1	15.3	3.1	9.6	36.7
U251	1.5	3.7	>100	3.0	11.8	>100
Melanoma						
LOX IMVI	1.0	2.6	6.5	2.0	4.9	15.2
MALME-3M	1.6	4.7	17.3	2.2	6.7	24.7
M14	1.3	3.1	7.3	2.7	9.2	30.4
SK-MEL-2	7.4	46.3	>100	8.6	20.8	45.6
SK-MEL-28	3.4	12.2	36.6	3.4	10.2	32.0
SK-MEL-5	0.8	2.2	5.4	0.03	1.3	4.3
UACC-257	7.4	20.1	44.8	11.1	23.0	48.0
UACC-62	1.5	3.4	7.4	1.9	4.5	11.6
Ovarian cancer						
IGROV1	2.4	14.6	>100	3.3	86.9	>100
OVCAR-3	0.9	2.2	5.2	1.6	3.3	6.6
OVCAR-4	0.7	3.4	>100	1.9	4.6	>100
OVCAR-5	1.9	5.5	20.2	3.1	11.1	33.3
OVCAR-8	7.3	>100	>100	14.6	>100	>100
SK-OV-3	1.4	3.2	7.3	2.6	5.8	17.6
Renal cancer						
786-0	1.7	3.2	6.1	3.2	12.3	35.1
A498	1.8	4.5	13.0	0.1	2.6	13.4
ACHN	2.0	5.0	15.8	3.3	12.0	34.7

(continued on next page)

Table 3
(continued)

Panel cell lines	Response parameters: GI_{50}, TGI and LC_{50} [b]					
	Compound **3l**			Compound **3m**		
	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
CAKI-1	1.3	2.7	5.4	1.8	3.8	8.0
RXF-393	1.7	4.2	12.3	1.6	4.5	>100
SN12C	1.6	3.9	9.2	2.2	4.2	8.3
TK-10	1.4	3.3	7.6	2.1	4.5	9.6
UO-31	2.5	10.7	32.7	4.8	17.4	42.4
Prostate cancer						
PC-3	1.9	5.4	19.5	2.7	11.5	33.8
DU-145	1.4	3.5	8.2	2.2	4.5	9.2
Breast cancer						
MCF7	1.7	4.6	21.2	2.6	7.6	26.8
NCI/ADR-RES	1.6	4.1	11.8	2.1	5.4	>100
MDA-MB-231/ATCC	0.3	1.5	4.9	2.1	4.2	8.5
HS-578T	1.4	5.5	55.7	1.1	3.5	21.5
MDA-MB-435	1.5	3.8	9.4	2.5	7.8	27.7
BT-549	19.5	34.8	62.0	21.1	38.5	70.3
T-47D	2.2	5.3	19.1	3.6	9.0	38.7

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cell screen [34–36].
[b] The responses parameters: GI_{50}, TGI and LC_{50} are interpolated values representing the molar concentrations at which percentage growth is +50, 0 and –50, respectively.

TGI = 2.3 μM and LC_{50} = 35.7 μM), whereas the other cancer cell lines showed a substantial lower level of inhibition (GI_{50} in the range 3.9–77.6 μM).

3. Conclusions

We have developed a method for the synthesis of a new series of 4-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives containing either unsubstituted sulfonamide moiety or cyano group attached to sulfonamide nitrogen atom, which exhibited anticancer activity. Compounds **3l** and **3m** were the most potent of all derivatives tested. On the other hand, compound **8** displayed a high degree of selectivity against renal cancer (A498) cells. The results we have obtained hitherto indicated that anticancer activity of the newly obtained compounds depends on the electronic nature of substituents.

4. Experimental protocols

4.1. Synthesis

Melting points were taken on a Büchi SMP 20 apparatus and are reported uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 1600 FTIR 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). The results of elemental analyses for C, H and N were within ±0.4% of the theoretical values. The starting 4-chloro-2-mercapto-5-methylbenzenesulfonamide **1a** [37] and dipotassium 5-chloro-2-cyanoamidatesulfonyl-4-methylphenylthiolate **1b** [38] were obtained according to methods described previously. The hydrazonyl bromides **2a** [39], **2b** [40], **2c–2f** [39], **2i–2l, 2p** [41] and **2m** [42] were prepared as previously described. The hydrazonyl bromides not yet reported such as **2g**: yield 55%, m.p. 92–94 °C dec.; IR (KBr) 3272 (NH), 2951, 2854 (CH_3, CH_2), 1600 (C=N), 1504, 1315 (NO_2) cm^{-1}; Anal. ($C_{12}H_{16}BrN_3O_2$) C, H, N; **2h**: yield 83%, m.p. 124–126 °C; IR (KBr) 3282 (NH) 2942, 2920, 2854 (CH_2), 1601 (C=N), 1500, 1322 (NO_2) cm^{-1}; Anal. ($C_{15}H_{14}BrN_3O_2$) C, H, N.; **2n**: yield 70%, m.p. 193–195 °C dec.; IR (KBr) 3406 (br, OH) 3297 (NH), 1594 (C=N), 1495, 1320 (NO_2) cm^{-1}; Anal. ($C_{13}H_9Br_2N_3O_3$) C, H, N; and **2o**: yield 80%, m.p. 196–198 °C dec.; IR (KBr) 3271 (NH), 1595 (C=N), 1498, 1325 (NO_2) cm^{-1}; Anal. ($C_{17}H_{12}BrN_3O_2$) C, H, N were obtained in a similar manner according to the literature methods [39,41].

4.1.1. General procedure for the preparation of S*-(5-chloro-4-methyl-2-sulfamoylphenyl)* N*-(4-nitrophenyl)alkanethiohydrazonates (**3a–3h**)*

To a suspension of 4-chloro-2-mercapto-5-methylbenzenesulfonamide **1a** (1.19 g, 5 mmol) in dry CH_2Cl_2 (45 ml) the equimolar amount of dry TEA (0.69 ml, 5 mmol) was added with stirring. After the reaction mixture became a clear solution the corresponding hydrazonyl bromides **2a–2h** (5 mmol) was added gradually. The resulting suspension was stirred at room temperature for 1 h, and then refluxed for further 7.5 h. After cooling the precipitate was filtered off, washed successively with CH_2Cl_2 (3 × 3 ml) and water (3 ×

5 ml). The product was purified by recrystallization from ethanol.

In this manner, the following alkanethiohydrazonates were obtained.

4.1.1.1. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl).* N-*(4-nitrophenyl)propanethiohydrazonate (**3a**)* Yield: 52%, m.p. 168–170 °C; IR (KBr) 3351, 3293, 3252 (NH_2, NH), 2967, 2930, 2866 (CH_3, CH_2), 1595 (C=N), 1500, 1319 (NO_2), 1308, 1163 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 7.3 Hz, 3H, CH_3), 2.35 (q, J = 7.3 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3–Ar), 7.27 (d, 2H, aromat.), 7.60 (s, 1H, H-6), 7.71 (s, 2H, SO_2NH_2), 7.99 (s, 1H, H-3), 8.13 (d, 2H, aromat.), 10.21 (s, 1H, NH) ppm. Anal. ($C_{16}H_{17}ClN_4O_4S_2$) C, H, N.

4.1.1.2. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)butanethiohydrazonate (**3b**).* Yield: 54%, m.p. 195–197 °C dec.; IR (KBr) 3364, 3317, 3280, 3190 (NH_2, NH), 2958, 2925, 2868 (CH_3, CH_2), 1600 (C=N), 1502, 1330 (NO_2), 1318, 1161 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 0.84 (t, J = 7.3 Hz, 3H, CH_3), 1.65 (m, J = 7.3 Hz, 2H, CH_2), 2.33 (t, J = 7.3 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3–Ar), 7.26 (d, 2H, aromat.), 7.56 (s, 1H, H-6), 7.71 (s, 2H, SO_2NH_2), 7.99 (s, 1H, H-3), 8.12 (d, 2H, aromat.), 10.24 (s, 1H, NH) ppm. Anal. ($C_{17}H_{19}ClN_4O_4S_2$) C, H, N.

4.1.1.3. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-2-methylpropanethiohydrazonate (**3c**).* Yield: 52%, m.p. 198–199 °C dec.; IR (KBr) 3354, 3241 (NH_2, NH), 2966, 2931, 2866 (CH_3, CH_2), 1594 (C=N), 1502, 1323 (NO_2), 1303, 1160 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 1.17 (d, J = 6.8 Hz, 6H, CH_3), 2.62 (m, J = 6.8 Hz, 1H, CH), 2.38 (s, 3H, CH_3–Ar), 7.27 (d, 2H, aromat.), 7.35 (s, 1H, H-6), 7.76 (s, 2H, SO_2NH_2), 7.96 (s, 1H, H-3), 8.12 (d, 2H, aromat.), 10.24 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.28 (CH_3–Ar), 21.13 (2 × CH_3), 36.27 (CH), 112.45, 125.84, 128.42, 130.71, 132.87, 136.17, 136.98, 139.28, 142.46, 146.13 (10C, aromatic), 150.57 (S–C=N) ppm. Anal. ($C_{17}H_{19}ClN_4O_4S_2$) C, H, N.

4.1.1.4. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(2,4-dinitrophenyl)-2-methylpropanethiohydrazonate (**3d**).* Yield: 79%, m.p. 238–239 °C dec.; IR (KBr) 3348, 3260, 3113 (NH_2, NH), 2962, 2931, 2872 (CH_3, CH), 1616 (C=N), 1495, 1331 (NO_2), 1307, 1158 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 1.19 (d, J = 6.8 Hz, 6H, 2 × CH_3), 2.41 (s, 3H, CH_3–Ar), 2.50–2.68 (m, J = 6.8 Hz, 1H, CH), 7.54 (s, 1H, H-6), 7.78 (s, 2H, SO_2NH_2), 7.91–7.95 (m, 1H, aromat.), 8.00 (s, 1H, H-3), 8.41–8.51 (m, 1H, aromat.), 8.88–8.89 (m, 1H, aromat.), 11.38 (s, 1H, NH) ppm. Anal. ($C_{17}H_{18}ClN_5O_6S_2$) C, H, N.

4.1.1.5. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-3-methylbutanethiohydrazonate (**3e**).* Yield: 52%, m.p. 189–190 °C dec.; IR (KBr) 3385, 3336, 3296, 3233 (NH_2, NH), 2955, 2924, 2868 (CH_3, CH_2, CH), 1598 (C=N), 1500, 1328 (NO_2), 1304, 1161 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 0.85 (d, J = 6.6 Hz, 6H, 2 × CH_3), 2.08 (m, J = 6.6 Hz, 1H, CH), 2.25 (d, J = 6.6 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3–Ar), 7.26 (d, 2H, aromat.), 7.52 (s, 1H, H-6), 7.72 (s, 2H, SO_2NH_2), 7.98 (s, 1H, H-3), 8.13 (d, 2H, aromat.), 10.27 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.35 (CH_3–Ar), 22.03 (2 × CH_3), 25.82 (CH), 112.23, 125.87, 127.44, 130.65, 134.54, 136.83, 136.10, 139.90, 141.90, 143.28 (10C, aromatic), 150.68 (S–C=N) ppm. Anal. ($C_{18}H_{21}ClN_4O_4S_2$) C, H, N.

4.1.1.6. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-2,2-dimethylpropanethiohydrazonate (**3f**).* Yield: 47%, m.p. 222–224 °C; IR (KBr) 3345, 3329 (NH_2, NH), 2963, 2928, 2865 (CH_3), 1594 (C=N), 1500, 1325 (NO_2), 1304, 1160 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 1.30 (s, 9H, *t*-butyl, 2.32 (s, 3H, CH_3–Ar), 6.95 (s, 1H, H-6), 7.23 (d, 2H, aromat.), 7.86 (s, 2H, SO_2NH_2), 7.91 (s, 1H, H-3), 8.11 (d, 2H, aromat.), 10.01 (s, 1H NH) ppm. Anal. ($C_{18}H_{21}ClN_4O_4S_2$) C, H, N.

4.1.1.7. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)hexanethiohydrazonate (**3g**).* Yield: 66%, m.p. 180–182 °C; IR (KBr) 3357, 3297, 3266, 3221 (NH_2, NH), 2952, 2923, 2854 (CH_3, CH_2, CH), 1599 (C=N), 1504, 1324 (NO_2), 1309, 1157 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 0.81 (t, J = 6.8 Hz, 3H, CH_3), 1.19 (m, J = 6.8 Hz, 4H, CH_2–CH_2), 1.58 (m, J = 6.8 Hz, 2H, CH_2), 2.35 (t, J = 6.8 Hz, 2H, CH_2–C=), 2.41 (s, 3H, CH_3–Ar), 7.25 (d, 2H, aromat.), 7.56 (s, 1H, H-6), 7.71 (s, 2H, SO_2NH_2), 7.99 (s, 1H, H-3), 8.13 (d, 2H, aromat.), 10.21 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 13.84, 19.36, 21.78, 26.07, 30.49, 36.33 (6C, aliphatic), 112.19, 125.85, 127.23, 130.67, 134.90, 136.93, 136.97, 139.03, 143.03, 143.52 (10C, aromatic), 150.78 (S–C=N) ppm. Anal. ($C_{19}H_{23}ClN_4O_4S_2$) C, H, N.

4.1.1.8. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-3-phenylpropanethiohydrazonate (**3h**).* Yield: 49%, m.p. 189–191 °C; IR (KBr) 3370, 3237 (NH_2, NH), 2954, 2920, 2854 (CH_3, CH_2), 1594 (C=N), 1503, 1326 (NO_2), 1306, 1153 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 2.65 (t, J = 7.8 Hz, 2H, CH_2), 2.92 (t, J = 7.8 Hz, 2H, CH_2–C=N), 7.14–7.16 (m, 3H, aromat.), 7.22–7.25 (m, 4H, aromat.), 7.55 (s, 1H, H-6), 7.74 (s, 2H, SO_2NH_2), 7.99 (s, 1H, H-3), 8.11 (d, 2H, aromat.), 10.28 (s, 1H, NH) ppm. Anal. ($C_{22}H_{21}ClN_4O_4S_2$) C, H, N.

4.1.2. General procedure for the preparation of S-*(5-chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)benzothiohydrazonates (**3i–3o**)*

To a suspension of 4-chloro-2-mercapto-5-methylbenzenesulfonamide **1a** (1.19 g, 5 mmol) in dry CH_2Cl_2 (80 ml) the equimolar amount of dry TEA (0.69 ml, 5 mmol) was added with stirring. After the reaction mixture became a clear solution the corresponding hydrazonyl bromides **2i–2o** (5 mmol) was added gradually. The resulting suspension was stirred at room temperature for 1 h, and then refluxed for

further 7.5 h. After cooling the precipitate was filtered off, washed successively with CH_2Cl_2 (3 × 3 ml) and water (3 × 5 ml). The contaminations were extracted with boiling ethanol (100 ml per 1 g of crude reaction product).

In this manner, the following benzothiohydrazonates were obtained.

4.1.2.1. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)benzothiohydrazonate (**3i**).* Yield: 80%, m.p. 253–255 °C dec.; IR (KBr) 3342, 3218 (NH_2, NH), 2919 (CH_3), 1595 (C=N), 1498, 1322 (NO_2), 1302, 1148 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 6.96 (s, 1H, H-6), 7.36–7.38 (m, 3H, aromat.), 7.51 (d, J = 9.0 Hz, 2H, aromat.), 7.87 (s, 1H, H-3), 7.92–7.95 (m, 4H, 2H, aromat. and SO_2NH_2), 8.18 (d, J = 9.0 Hz, 2H, aromat.), 10.99 (br.s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.08 (CH_3), 113.38, 125.77, 127.47, 128.67, 129.38, 129.99, 130.43, 134.80, 135.97, 136.53, 136.84, 140.07, 141.02 (13C, aromatic), 149.78 (S–C=N) ppm. Anal. ($C_{20}H_{17}ClN_4O_4S_2$) C, H, N.

4.1.2.2. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-4-chlorobenzothiohydrazonate (**3j**).* Yield: 75%, m.p. 278–281 °C dec.; IR (KBr) 3340, 3242, 3216 (NH_2, NH), 2921 (CH_3,), 1594 (C=N), 1528, 1326 (NO_2), 1305, 1151 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 7.01 (s, 1H, H-6), 7.44 (d, J = 8.4 Hz, 2H, aromat.), 7.55 (d, J = 9.0 Hz, 2H aromat.), 7.92 (s, 1H, H-3), 7.99 (m, 4H, 2H, aromat. and SO_2NH_2), 8.22 (d, J = 9.0 Hz, 2H aromat.), 11.08 (br.s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.08 (CH_3), 113.49, 125.71, 128.64, 129.02, 129.70, 130.32, 130.49, 133.89, 134.98, 135.08, 136.95, 140.22, 141.01 (13C, aromatic) 149.58 (S–C=N) ppm. Anal. ($C_{20}H_{16}Cl_2N_4O_4S_2$) C, H, N.

4.1.2.3. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-4-nitrobenzothiohydrazonate (**3k**).* Yield: 78%, m.p. 268–270 °C dec.; IR (KBr) 3354, 3236, 3206 (NH_2, NH), 2923, 2851 (CH_3,), 1592 (C=N), 1507, 1331 (NO_2), 1305, 1155 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.99 (s, 1H, H-6), 7.61 (d, J = 9.0 Hz, 2H, aromat.), 7.90 (s, 1H, H-3), 7.99 (s. 2H, SO_2NH_2), 8.16–8.23 (m, 6H, aromat.), 11.33 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.14 (CH_3), 114.09, 123.79, 125.74, 128.19, 129.52, 130.18, 130.70, 133.76, 135.25, 137.16, 140.82, 141.02, 142.36, 147.23 (14C, aromatic), 149.24 (S–C=N) ppm. Anal. ($C_{20}H_{16}ClN_5O_6S_2$) C, H, N.

4.1.2.4. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-4-methylbenzothiohydrazonate (**3l**).* Yield: 82%, m.p. 253–254 °C dec.; IR (KBr) 3348, 3218 (NH_2, NH), 2919, 2872 (CH_3), 1595 (C=N), 1501, 1324 (NO_2), 1304, 1146 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 6H, 2 × CH_3), 6.96 (s, 1H, H-6), 7.19 (d, J = 7.8 Hz, 2H, aromat.), 7.49 (d, J = 9.0 Hz, 2H, aromat.), 7.85–7.88 (m, 3H, aromat.), 7.95 (br.s, 2H, SO_2NH_2), 8.19 (d, J = 9.0 Hz, 2H, aromat.), 10.92 (br.s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 19.09 (CH_3), 20.83 (CH_3), 113.29, 125.79, 127.38, 129.34, 130.16, 130.24, 130.43, 133.32, 134.74, 136.54, 136.86, 139.18, 139.97, 140.97 (14C, aromatic), 149.78 (S–C=N) ppm. Anal. ($C_{21}H_{19}ClN_4O_4S_2$) C, H, N.

4.1.2.5. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-4-methoxybenzothiohydrazonate (**3m**).* Yield: 76%, m.p. 242–245 °C dec.; IR (KBr) 3361, 3230 (NH_2, NH), 2952, 2919, 2842 (CH_3, CH_3O), 1594 (C=N), 1499, 1323 (NO_2), 1307, 1155 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.77 (s, 3H, CH_3O), 6.93 (d, J = 9.0 Hz, 2H, aromat.), 6.97 (s, 1H, H-6), 7.47 (d, J = 9.15 Hz, 2H, aromat.), 7.89 (s, 1H, H-3), 7.93–7.96 (m, 4H, 2H, aromat. and SO_2NH_2), 8.18 (d, J = 9.15 Hz, 2H, aromat.), 10.86 (s, 1H, NH) ppm. Anal. ($C_{21}H_{19}ClN_4O_5S_2$) C, H, N.

4.1.2.6. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-3-bromo-4-hydroxybenzothiohydrazonate (**3n**).* Yield: 63%, m.p. 264–267 °C dec.; IR (KBr) 3442 (OH), 3283, 3289, 3236 (NH_2, NH), 2919, 2854 (CH_3), 1592 (C=N), 1496, 1322 (NO_2), 1307, 1158 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.90–6.92 (m, 1H, aromat.), 6.98 (s, 1H, H-6), 7.46 (d, J = 8.8 Hz, 2H, aromat.), 7.75–7.77 (m, 1H, aromat.), 7.88 (s, 1H, H-3), 7.95 (s, 2H, SO_2NH_2), 8.06–8.07 (m, 1H, aromat.), 8.17 (d, J = 8.8 Hz, 2H, aromat.), 10.72 (s, 1H, OH), 10.85 (s, 1H, NH) ppm. Anal. ($C_{20}H_{16}BrClN_4O_4S_2$) C, H, N.

4.1.2.7. S-*(5-Chloro-4-methyl-2-sulfamoylphenyl)* N-*(4-nitrophenyl)-2-naphthothiohydrazonate (**3o**).* Yield: 61%, m.p. 245–247 °C dec.; IR (KBr) 3336, 3207 (NH_2, NH), 2919, 2854 (CH_3), 1592 (C=N), 1495, 1316 (NO_2), 1316, 1149 (SO_2) $cm^{-1;}$ ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 7.03 (s, 1H, H-6), 7.05–7.62 (m, 4H, aromat.), 7.92–8.25 (m, 9H, 7H, aromat. and SO_2NH_2), 8.53 (s, 1H, H-3), 11.13 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.05 (CH_3), 113.55, 124.15, 125.78, 126.05, 127.52, 127.76, 128.25, 128.62, 130.14, 130.27, 130.44, 132.78, 133.15, 133.54, 134.85, 136.38, 136.92, 140.19, 141.07 (20C, aromatic), 149.65 (S–C=N) ppm. Anal. ($C_{24}H_{19}ClN_4O_4S_2$) C, H, N.

4.1.3. General procedure for the preparation of potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)alkanethiohydrazonates (**4–6**)*

To a suspension of dipotassium 5-chloro-2-cyanoamidatesulfonyl-4-methylphenylthiolate **1b** (1.69 g, 5 mmol) in ethanol (17 ml) the corresponding hydrazonyl bromides **2b, 2c** or **2e** (5 mmol) was added. The reaction mixture was stirred at reflux for 6 h, after then the side potassium bromide was filtered off. The clear filtrate was concentrated under diminished pressure to volume and left to stand in a refrigerator, overnight. The precipitate thus obtained was filtered out and purified by recrystallization from ethanol.

In this manner, the following alkanethiohydrazonates were obtained.

4.1.3.1. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)butanethiohydrazonate (**4**).* Yield: 53%, m.p. 235–237 °C dec.; IR (KBr) 3207 (NH), 2931, 2872 (CH_3, CH_2), 2173 (CN), 1598 (C=N), 1516, 1325 (NO_2), 1309, 1111 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 0.95 (t, J = 7.2 Hz, 3H, CH_3), 1.62–1.73 (m, 2H, CH_2), 2.40 (s, 3H, CH_3–Ar), 2.48 (t, J = 7.2 Hz, 2H, CH_2–C=N), 7.26 (d, J = 9.2 Hz, 2H, aromat.), 7.44 (s, 1H, H-6), 7.94 (s, 1H, H-3), 8.13 (d, J = 9.2 Hz, 2H, aromat.), 10.27 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 13.60 (CH_3), 19.58 (CH_2), 20.18 (CH_3–Ar), 38.54 (CH_2–C=N), 112.38, 117.43 (CN), 126.10, 128.30, 131.06, 133.93, 136.16, 136.23, 139.22, 143.52, 144.50 (10C, aromatic), 150.91 (S–C=N). Anal. ($C_{18}H_{17}ClKN_5O_4S_2$) C, H, N.

4.1.3.2. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)-2-methylpropanethiohydrazonate (**5**).* Yield: 47%, m.p. 157–160 °C; IR (KBr) 3236 (NH), 2925, 2872 (CH_3, CH_2), 2172 (CN), 1595 (C=N), 1516, 1325 (NO_2), 1302, 1111 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 1.25 (d, J = 6.7 Hz, 6H, 2 × CH_3), 2.38 (s, 3H, CH_3–Ar), 2.76–2.83 (m, 1H, CH), 7.24 (d, J = 9.2 Hz, 2H, aromat.), 7.28 (s, 1H, H-6), 7.91 (s, 1H, H-3), 8.12 (d, J = 9.2 Hz, 2H, aromat.), 10.21 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.58 (CH_3–Ar), 21.22 (2 × CH_3), 37.19 (CH), 112.57, 117.37 (CN), 126.10, 129.28, 130.99, 132.37, 135.68, 136.26, 139.25, 143.67, 147.34 (10C, aromatic), 150.87 (S–C=N). Anal. ($C_{18}H_{17}ClKN_5O_4S_2$) C, H, N.

4.1.3.3. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)-3-methylbutanethiohydrazonate (**6**).* Yield: 53%, m.p. 176–78 °C; IR (KBr) 3236 (NH), 2925, 2866 (CH_3, CH_2, CH), 2178 (CN), 1598 (C=N), 1516, 1328 (NO_2), 1305, 1111 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 0.88 (d, J = 6.5 Hz, 6H, 2 × CH_3), 2.05–2.25 (m, 1H, CH), 2.36 (br.s, 5H, CH_3, CH_2), 7.22 (d, J = 8.9 Hz, 2H, aromat.), 7.37 (s, 1H, H-6), 7.90 (s, 1H, H-3), 8.10 (d, J = 8.9 Hz, 2H, aromat.), 10.25 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.56 (CH_3–Ar), 22.33 (2 × CH_3), 26.23 (CH), 46.73 (CH_2), 112.41, 117.41 (CN), 126.12, 128.54, 131.02, 133.62, 136.06, 136.16, 139.27, 142.65, 144.29 (10C, aromatic), 150.81 (S–C=N) ppm. Anal. ($C_{19}H_{19}ClKN_5O_4S_2$) C, H, N.

4.1.4. General procedure for the preparation of potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)benzothiohydrazonates (**7–10**)*

To a suspension of dipotassium 5-chloro-2-cyanoamidatesulfonyl-4-methylphenylthiolate **1b** (1.69 g, 5 mmol) in ethanol (30 ml) the corresponding hydrazonyl bromides **2i–2j, 2l** or **2p** (5 mmol) was added. The reaction mixture was stirred at reflux for 6 h. The resulting precipitate of the desired product and KBr was filtered off and dried, then treated with water (30 ml). After vigorously stirring for 20 min the pure product was collected by filtration and dried.

In this manner, the following benzothiohydrazonates were obtained.

4.1.4.1. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)benzothiohydrazonate (**7**).* Yield: 72%, m.p. 262–264 °C dec.; IR (KBr) 3198 (NH), 2921, 2854 (CH_3), 2182 (CN), 1598 (C=N), 1527, 1329 (NO_2), 1305, 1112 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H, CH_3), 6.95 (s, 1H, H-6), 7.38–7.41 (m, 3H, aromat.), 7.48 (d, J = 9.2 Hz, 2H, aromat.), 7.84 (s, 1H, H-3), 8.03–8.07 (m, 2H, aromat.), 8.16 (d, J = 9.2 Hz, 2H, aromat.), 10.90 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.37 (CH_3), 113.49, 117.28 (CN), 126.07, 127.64, 129.06, 129.61, 130.35, 130.76, 134.93, 136.22, 136.81, 138.06, 140.25, 142.79 (13C, aromatic), 149.98 (S–C=N) ppm. Anal. ($C_{21}H_{15}ClKN_5O_4S_2$) C, H, N.

4.1.4.2. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)-4-chlorobenzothiohydrazonate (**8**).* Yield: 72%, m.p. 278–280 °C dec.; IR (KBr) 3195 (NH), 2919, 2848 (CH_3), 2184 (CN), 1595 (C=N), 1528, 1331 (NO_2), 1305, 1111 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 6.97 (s, 1H, H-6), 7.47 (d, J = 8.7 Hz, 2H, aromat.), 7.53 (d, J = 9.3 Hz, 2H, aromat.), 7.87 (s, 1H, H-3), 8.09 (d, J = 8.7 Hz, 2H, aromat.), 8.20 (d, J = 9.3 Hz, 2H, aromat.), 11.02 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.39 (CH_3), 113.64, 117.28 (CN), 126.04, 129.03, 129.25, 130.11, 130.74, 130.87, 134.11, 135.06, 135.73, 136.28, 136.81, 140.39, 142.77 (14C, aromatic), 149.87 (S–C=N) ppm. Anal. ($C_{21}H_{14}Cl_2KN_5O_4S_2$) C, H, N.

4.1.4.3. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)-4-methylbenzothiohydrazonate (**9**).* Yield: 84%, m.p. 268–270 °C dec.; IR (KBr) 3200 (NH), 2920, 2852 (CH_3), 2181 (CN), 1595 (C=N), 1528, 1328 (NO_2), 1305, 1112 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.94 (s, 1H, H-6), 7.22 (d, J = 8.0 Hz, 2H, aromat.), 7.45 (d, J = 9.0 Hz, 2H, aromat.), 7.84 (s, 1H, H-3), 7.95 (d, J = 8.0 Hz, 2H, aromat.), 8.15 (d, J = 9.0 Hz, 2H, aromat.), 10.83 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.39 (CH_3), 21.11 (CH_3), 113.37, 117.29 (CN), 126.08, 127.57, 129.72, 130.50, 130.64, 130.77, 134.12, 134.89, 136.24, 138.24, 139.39, 140.11, 142.74 (14C, aromatic), 150.00 (S–C=N) ppm. Anal. ($C_{22}H_{17}ClKN_5O_4S_2$) C, H, N.

4.1.4.4. Potassium S-*(5-chloro-2-cyanoamidatesulfonyl-4-methylphenyl)* N-*(4-nitrophenyl)-4-bromobenzothiohydrazonate (**10**).* Yield: 67%, m.p. 280–282 °C dec.; IR (KBr) 3196 (NH), 2920, 2852 (CH_3), 2184 (CN), 1595 (C=N), 1528, 1331 (NO_2), 1305, 1111 (SO_2) $cm^{-1;}$ ^1H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 6.96 (s, 1H, H-6), 7.52 (d, J = 8.1 Hz, 2H, aromat.), 7.60 (d, J = 9.0 Hz, 2H, aromat.), 7.87 (s, 1H, H-3), 8.02 (d, J = 8.1 Hz, 2H, aromat.), 8.20 (d, J = 9.0 Hz, 2H, aromat.), 11.01 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 19.39 (CH_3), 113.65, 117.29 (CN), 122.90, 126.04, 129.49, 130.13, 130.71, 130.88, 131.94, 135.07, 136.11, 136.29, 136.87, 140.40, 142.76 (14C, aromatic), 149.85 (S–C=N) ppm. Anal. ($C_{21}H_{14}BrClKN_5O_4S_2$) C, H, N.

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