o J. C ., **76**, 937–944 (2002)

Syntheses of *N*-Aryl-*N*′-(4-chloro-2-alkylthio-5-methylbenzenesulphonyl)guanidines with Potential Biological Activity

by J. Sławiński

D o C o d o D , o G G . H 107, 80-416 G , o

(25 , 2002)

Syntheses of new -aryl- ′-(2-alkylthio-4-chloro-5-methylbenzenesulphonyl)guanidine **3–14** are described. The facile conversion of **1** and **8** to new 2-[(2-amino-6-dimethylamino-1,3,5-triazin-4-yl)methylthio]benzensulphonylcyanamide **16** and 2-[(2-amino-6-dimethylamino-1,3,5-triazin-4-yl)methylthio]benzensulphonylguanidine **17** respectively, was elaborated. The preliminary anticancer evaluation of **16**, **17** was performed at US National Cancer Institute.

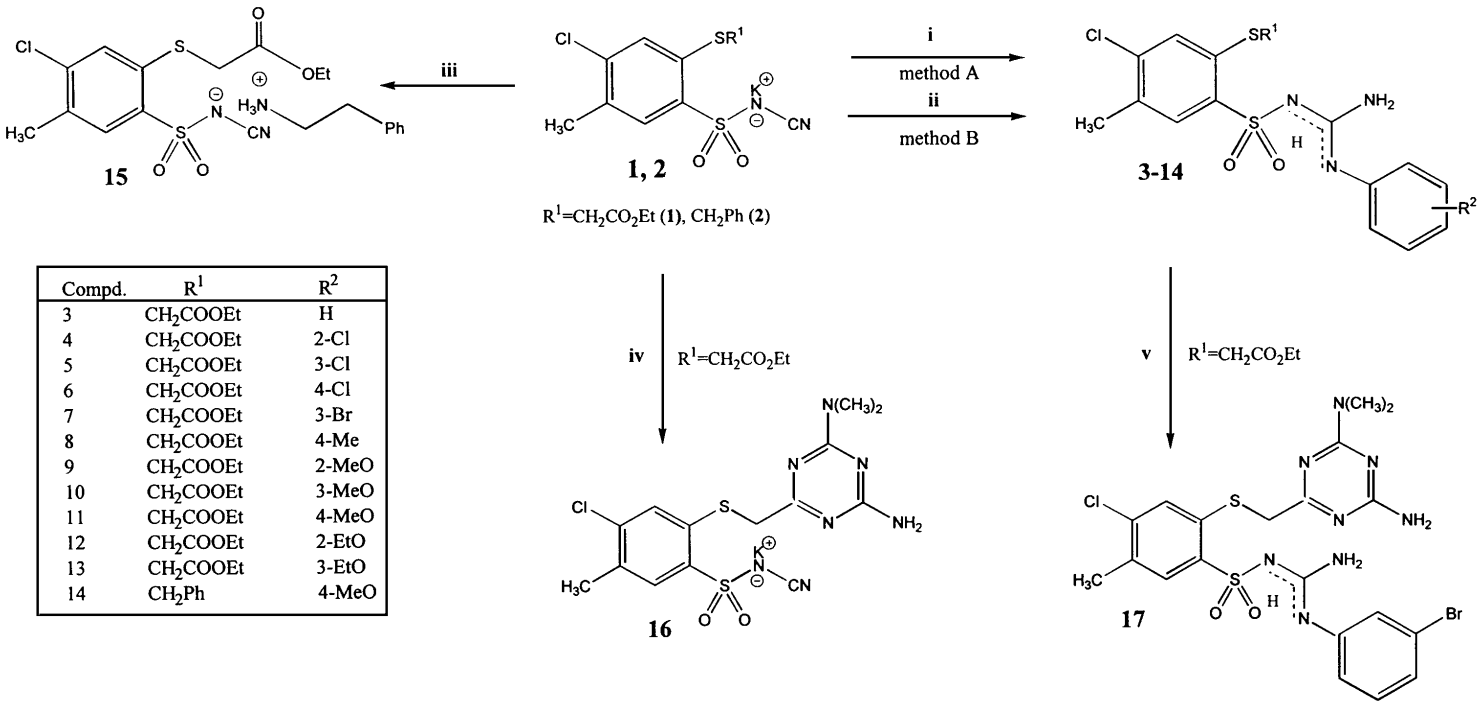
Key words: 2-mercaptobenzenesulphonylcyanamide, 2-mercaptobenzenesulphonylguanidine, 2,6-diamino-1,3,5-triazine

Interesting biological properties of compounds containing 2-mercaptobenzenesulphonamide moiety, particularly as anticancer agent [1–6] and potent inhibitors of HIV-1 integrase [7–12] prompted us to investigate further the chemistry and biological activity of the related compounds. Thus, we describe a facile synthesis of a new type of -aryl- ′-(2-mercaptobenzenesulphonyl)guanidine derivatives **3–14** and 2,6-diamino-1,3,5-triazinyl derivatives **16**,**17** with potential biological activity.

RESULTS AND DISCUSSION

Previously, we have described the synthesis of various , ′-dialkyl- ′′-(2-mercaptobenzenesulphonyl)guanidine derivatives [14–19] which consists in the reaction of 3-mercapto-1,1-dioxo-1,4,2-benzodithiazine with an excess of primary aliphatic amines [15–18]. Further method reported, was based on the reaction of 3-alkylamino-1,1-dioxo-1,4,2-benzodithiazine with an excess of primary alkyl amine [15,17–19]. This method has allowed to obtain , ′-dialkyl- ′′-(2-mercaptobenzenesulphonyl)guanidine, which possessed two different alkyl substituents, but in both methods only the aliphatic amines could be employed.

In this work, we describe the synthesis of novel -aryl- ′-(2-mercaptobenzenesulphonyl)guanidine derivatives, which could be used for further structural modifications and pharmacological examinations. Therefore, we have elaborated an efficient method for synthesis of -aryl- ′-(2-mercaptobenzenesulphonyl)guanidine **3–14**, which consists in the reaction of -(2-alkylthio-4-chloro-5-methyl-



Compd.	R^1	R^2
3	CH_2COOEt	H
4	CH_2COOEt	2-Cl
5	CH_2COOEt	3-Cl
6	CH_2COOEt	4-Cl
7	CH_2COOEt	3-Br
8	CH_2COOEt	4-Me
9	CH_2COOEt	2-MeO
10	CH_2COOEt	3-MeO
11	CH_2COOEt	4-MeO
12	CH_2COOEt	2-EtO
13	CH_2COOEt	3-EtO
14	CH_2Ph	4-MeO

Scheme 1. Reagents and yields: (**i**) R^2-C_6H_4-NH_2 (2 molar equiv.), H_2SO_4 (1 molar equiv.), CCl_4, reflux 24 h, 55–92%; (**ii**) R^2-C_6H_4-NH_2×HCl (1 molar equiv.), toluene, reflux 2 h, 76–92%; (**iii**) $PhCH_2CH_2NH_2$ (2 molar equiv.), H_2SO_4 (1 molar equiv.), CCl_4, reflux 24 h, 49%; (**iv**) 1,1-dimethylbiguanide×HCl, (2 molar equiv.), MeOK (2 molar equiv.), dry MeOH, reflux 45 h, 36.3%; (**v**) 1,1-dimethylbiguanide×HCl (2 molar equiv.), MeONa (2 molar equiv.), dry MeOH, reflux 45 h, 70.8%.

benzenesulphonyl)cyanamide potassium salt **1** or **2** with two molar equivalent of primary aryl amine in boiling carbon tetrachloride (Scheme 1, *o A*) in the presence of one molar equivalent of conc. sulfuric acid. It was also found that treatment of **1** with equimolar amount of aniline hydrochloride or *o* - and -chloroaniline hydrochloride in boiling toluene (*o B*) led to the formation of the desired guanidine derivatives **3–5** in excellent yields.

The mechanism of this reaction could be explained by the transient formation of a sulphonylcyanamide N-H acid upon mineral acid addition – followed by the nucleophilic attack of the amine nitrogen atom at the electron deficiency cyanamide carbon atom. It should be mentioned that in our hands the corresponding free N-H acid could not be isolated, apparently due to its instability [13].

The promising results prompted us to investigate the synthesis of -alkyl-'-(2-mercaptobenzenesulphonyl)guanidine, as a new pathway to the disubstituted guanidine derivative, but the reaction failed. Thus, treatment of **1** with two molar equivalents of phenethylamine in the presence of equimolar amount of conc. sulfuric acid led to the formation of the stable phenethylaminium salt **15**. It can be seen, that the phenenthylamine (relatively strong base $pK_b = 4.17$) did not react under these reaction conditions as a nucleophile, probable due to high electron density on the cyanamide carbon atom at the salt **15** initially formed.

It is well known that a number of guanidine derivatives containing substituents, such as sulphonyl group [20,21], show mainly the iminosulphonyl tautomeric form. However, some acyl derivatives are firmly in the amino form [22], while others are close to the borderline and both imino and amino forms have been isolated [23].

Compounds **3–14** can exist as three possible tautomers **3A**, **3B** and **3C** as shown in Fig. 1. We studied the tautomerism of **3** both in solution by NMR spectroscopy and by *b o* calculations for isolated molecules in the gas phase. Inspection of the ^1H NMR spectrum revealed that in DMSO solution the compounds **3–14** exist as single tautomers. The broad singlet attributable to NH_2 protons in the region δ 6.82–7.26 ppm and a sharp singlet of NH proton in the region δ 8.38–9.43 ppm, disappeared upon deuterium oxide addition. Moreover, the shielding effect of substituents such as -Cl, -OMe or -OEt at position *o* - of phenyl ring on adjacent N-H proton was observed. The signals for these N-H protons appeared in the region δ 8.38–8.74 ppm in contrast to their - or -substituted counterparts showing resonances for N-H proton in the range of δ 8.93–9.43 ppm. Therefore, it seems that iminosulphonyl tautomer **3A** could be more favoured in DMSO solution.

We have also examined tautomers of **3** using a molecular orbital *b o* method at Hartree-Fock level with the 6-31G** basis set [24].

The relative energies obtained for tautomers **3A**, **3B** and **3C** are shown in Table 1. The results indicated, that iminosulphonyl tautomer **3A** is more stable by 20,03 and 14.84 kcal/mol than aminosulphonyl tautomers **3B** and **3C** respectively.

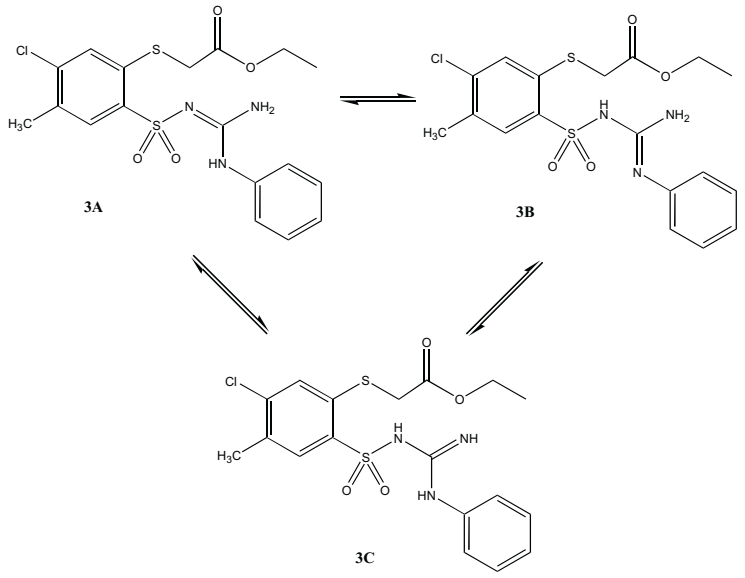


Figure 1. Possible tautomeric forms of compounds **3–14**.

Table 1. Calculated energies (E, hartrees), relative energies (ΔE, kcal/mol) of tautomers **3A**, **3B** and **3C**.

	RHF/6-31G**	
	E	ΔE
3A	–2410.5762400	0
3B	–2410.5443216	20.03
3C	–2410.5525861	14.84

Attempts were made to elaborate the synthetic procedures that would allow to obtain corresponding 2,6-diamino-1,3,5-triazin-4-yl derivative of benzenesulphonylcyanamide **16**, and benzenesulphonylguanidine **17** (Scheme 1). The cyclocondensation reaction was accomplished by treatment of **1** or **8** with two molar equivalents of 1,1-dimethylbiguanide hydrochloride in the presence of two molar equivalents of sodium or potassium methoxide in boiling dry methanol, affording the expected 1,3,5-triazinyl derivative **16** and **17** in moderate to good yields.

The structure of the new compounds obtained was established by IR, ^{1}H, ^{13}C NMR spectra and as well as elemental analyses. The anticancer activity of compounds **16** and **17** was evaluated *o* , using primary anticancer assay at concentration of 0.1 mM in the 3-cell line panel consisting of the MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS) at US National Cancer Institute (Bethesda). Compounds **16** and **17** proved to be essentially inactive. However, further studies concerning biological activity of -aryl- ′-(2-mercaptobenzenesulphonyl)guanidine derivatives are in progress.

EXPERIMENTAL

^{1}H, ^{13}C NMR spectra were recorded on a Gemini (200 MHz) and Varian Unity Plus (500 MHz) spectrometers or Tesla-Brno BS 587A (80 MHz) spectrometer, in DMSO-d_6 with TMS as internal standard. IR spectra were measured as KBr discs on a Perkin-Elmer FT IR 1600 spectrophotometer. Melting points were determined on a Büchi SMP 20 apparatus and were uncorrected. Thin-layer chromatography was performed on Merck Kieselgel 60F_{254} plates and visualised with UV or with iodine vapour.

***N*-[4-Chloro-2-(ethoxycarbonylmethyl- or benzyl)thio-5-methylbenzenesulphonyl]cyanamide potassium salt 1** and **2** were synthesized according to [13].

***N*-(Aryl)-*N′*-[4-chloro-2-(ethoxycarbonylmethyl- or benzyl)thio-5-methylbenzenesulphonyl]guanidine (3-14). General procedure.**

o A. To a stirred suspension of **1** (1.93 g, 5 mmol) or **2** (1.95 g, 5 mmol) in dry CCl_4 (35 ml) appropriate aniline derivative (10 mmol) and 96% sulfuric acid (0.14 ml, 2.5 mmol) was added. The reaction mixture was stirred at reflux for 24 h and left to stand at room temperature overnight. The resulting precipitate was filtered off, washed well with CCl_4 (3 × 1.5 ml) and dried, then treated with water (50 ml). After vigorously stirring for 20 minutes the precipitate was collected by filtration and dried, to afford crude reaction product.

***N*-Phenyl-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl)guanidine 3** was obtained without further purification. Yield 2.03 g, 91.9%, m.p. 173–176°C. IR, ν_{max} (KBr) cm^{-1}: 3395, 3283, 3136, 1725, 1622, 1343,1146. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.13 (t, 3H, CH_3), 2.33 (s, 3H, CH_3-Ar), 4.02 (s, 2H, SCH_2), 4.07 (q, 2H, OCH_2), 6.95 (br.s, 2H, NH_2), 7.0–7.1 (m, 1H, Ar), 7.21–7.31 (m. 2H, Ar), 7.36–7.43 (m, 2H, Ar), 7.47 (s, 1H, H-3), 7.92 (s, 1H, H-6), 9.13 (s, 1H, Ar-NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 13.93 (CH_3), 18.95 (CH_3-Ar), 34.24 (SCH_2), 61.08 (OCH_2), 121.42, 123.72, 127.59, 128.67, 130.60, 132.27, 134.52, 136.73, 137.67, 139.11 (C-arom.), 154.49 (C-guanid.), 168.94 (C=O). Anal. Calc. for $C_{18}H_{20}ClN_3O_4S_2$ (441.96): C, 48.93.; H, 4.52; N, 9.51. Found: C, 48.53; H, 4.70; N, 9.27.

***N*-(2-Chlorophenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 4** was obtained by crystallization of the crude product from ethanol (1:45). Yield 1.9 g, 79.8%, m.p. 197–198°C. IR, ν_{max} (KBr) cm^{-1}: 3406, 3295, 3124, 1719, 1619, 1364, 1152. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.18 (t, 3H, CH_3), 2.36 (s, 3H, CH_3-Ar), 4.11 (s, 2H, SCH_2), 4.11–4.18 (q, 2H, OCH_2), 7.15–7.34 (m, 4H, NH_2, and Ar), 7.48–7.52 (m, 1H, Ar), 7.50 (s, 1H, H-3), 7.78–7.82 (m, 1H, Ar), 7.92 (s, 1H, H-6), 8.74 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.85 (CH_3), 18.84 (CH_3-Ar), 34.47 (SCH_2), 61.05 (OCH_2), 128.28, 128.78, 129.35, 129.99, 130.63, 130.78, 132.34, 133.88, 134.34, 136.66, 139.16, 155.0 (C-guanid.), 168.85 (C=O). Anal. Calc. for $C_{18}H_{19}Cl_2N_3O_4S_2$ (476.41): C, 45.38.; H, 4.02; N, 8.82. Found: C, 44.83; H, 3.72; N, 8.35.

***N*-(3-Chlorophenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 5** was obtained by crystallization of the crude product from ethanol (1:5). Yield 1.78 g, 74.8%, m.p. 145–147°C dec. IR, ν_{max} (KBr) cm^{-1}: 3395, 3307, 3189, 1725, 1631, 1343, 1146. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.11 (t, 3H, CH_3), 2.34 (s, 3H, CH_3-Ar), 4.02 (s, 2H, SCH_2), 4.03–4.06 (q, 2H, OCH_2), 7.04 (s, 2H, NH_2), 7.04–7.08 (m, 1H, Ar), 7.25–7.29 (m, 2H, Ar), 7.48 (s, 1H, H-3), 7.7 (s, 1H, Ar), 7.94 (s, 1H, H-6), 9.23 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.77 (CH_3), 18.84 (CH_3-Ar), 34.0 (SCH_2), 60.62 (OCH_2), 129.13, 129.72, 131.59, 132.01, 133.57, 136.03, 138.0, 138.5, 139,23 (C-arom.), 154.04 (C-guanid.), 167.58 (C=O). Anal. Calc. for $C_{18}H_{19}Cl_2N_3O_4S_2$ (476.41): C, 45.38.; H, 4.02; N, 8.82. Found: C, 45.0; H, 3.7; N, 8.35.

***N*-(4-Chlorophenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 6** was obtained by crystallization of the crude product from ethanol (1:13). Yield 1.31 g, 55.2%, m.p. 168–171°C dec. IR, ν_{max} (KBr) cm^{-1}: 3401, 3295, 3201, 3166, 1736, 1634, 1340, 1140. ^{1}H NMR (80 MHz, DMSO-d_6) δ: 1.14 (t, 3H, CH_3), 2.34 (s, 3H, CH_3-Ar), 4.05 (s, 2H, SCH_2), 4.1 (q, 2H, OCH_2), 7.08 (s, 2H, NH_2), 7.3 (m, 2H, Ar), 7.48 (s, 1H, H-3), 7.53 (m, 2H, Ar), 7.95 (s, 1H, H-6), 9.43 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.85 (CH_3), 18.85 (CH_3-Ar), 34.22 (SCH_2), 61.05 (OCH_2), 122.75, 127.17, 128.42, 130.6, 132.24, 134.49, 136.77, 138.95 (C-arom.), 154.25 (C-guanid.), 168.88 (C=O). Anal. Calc. for $C_{18}H_{19}Cl_2N_3O_4S_2$ (476.41): C, 45.38.; H, 4.02; N, 8.82. Found: C, 45.6; H, 3.68; N, 8.51.

***N*-(3-Bromophenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 7** was obtained by crystallization of the crude product from ethanol (1:12). Yield 2.18 g, 83.7%, m.p. 146–148°C. IR, ν_{max} (KBr) cm^{-1}: 3395, 3301, 3183, 1725, 1634, 1343, 1146. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.11 (t, 3H, CH_3), 2.34 (s, 3H, CH_3-Ar), 4.03 (s, 2H, SCH_2), 4.02–4.06 (q, 2H, OCH_2), 7.02 (s, 2H, NH_2), 7.2–7.21 (m, 2H, Ar), 7.26–7.29 (m, 1H, Ar), 7.48 (s, 1H, H-3), 7.84 (s, 1H, Ar), 7.94 (s, 1H, H-6), 9.2 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.81 (CH_3), 18.84 (CH_3-Ar), 34.29 (SCH_2), 61.02 (OCH_2), 121.39, 122.72, 125.19, 126.66, 129.13, 129.62, 132.31, 134.41, 136.84, 138.77, 139.3 (C-arom.), 154.04 (C-guanid.), 168.7 (C=O). Anal. Calc. for $C_{18}H_{19}BrClN_3O_4S_2$ (520.86): C, 41.51; H, 3.67; N, 8.07. Found: C, 41.90; H, 4.2; N, 7.76.

***N*-(4-Methylphenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 8** was obtained by crystallization of the crude product from ethanol (1:30). Yield 1.65 g, 72.2%, m.p. 183–185°C. IR, ν_{max} (KBr) cm^{-1}: 3395, 3283, 3166, 1739, 1628, 1295, 1143. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.17 (t, 3H, CH_3), 2.26 (s, 3H, CH_3-C_6H_4-), 2.36 (s, 3H, CH_3-C_6H_2-), 4.05 (s, 2H, SCH_2), 4.05–4.17 (q, 2H, OCH_2), 6.93 (br.s, 2H, NH_2), 7.08–7.12 (m, 2H, Ar), 7.27–7.31 (m, 2H, Ar), 7.5 (s, 1H, H-3), 7.94 (s,1H, H-6), 9.03 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.85 (CH_3), 18.84 (CH_3-C_6H_2-), 20.23 (CH_3-C_6H_4) 34.58 (SCH_2), 60.94 (OCH_2), 121.87, 128.32, 128.81, 130.06, 132.29, 133.03, 134.03, 134.54, 136.51, 139.49 (C-arom.), 154.63 (C-guanid.), 168.8 (C=O). Anal. Calc. for $C_{19}H_{22}ClN_3O_4S_2$ (455.99): C, 50.05; H, 4.86; N, 9.21. Found: C, 50.32; H, 4.89; N, 8.84.

***N*-(2-Methoxyphenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 9** was obtained by crystallization of the crude product from isopropanol (1:4). Yield 1.43 g, 60.6%, m.p. 125–129°C dec. IR, ν_{max} (KBr) cm^{-1}: 3412, 3307, 3272, 3201, 1733, 1619, 1340, 1149. ^{1}H NMR (80 MHz, DMSO-d_6) δ: 1.12 (t, 3H, CH_3), 2.32 (s, 3H, CH_3-Ar), 3.82 (s, 3H, OCH_3), 4.0 (s, 2H, SCH_2), 4.08 (q, 2H, OCH_2), 6.9–7.17 (m, 5H, Ar, NH_2), 7.48 (s, 1H, H-3), 7.82 (s, 1H, Ar), 7.92 (s, 1H, H-6), 8.48 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.80 (CH_3), 18.84 (CH_3-Ar), 34.39 (SCH_2), 55.66 (OCH_3), 60.89 (OCH_2), 110.27, 125.99, 132.31, 134.34, 136.59, 139.34, 149.11 (C-arom.), 153.8 (C-guanid.), 168.85 (C=O). Anal. Calc. for $C_{19}H_{22}ClN_3O_5S_2$ (471.99): C, 48.35; H, 4.69; N, 8.90. Found: C, 47.98; H, 4.35; N, 8.58.

***N*-(3-Methoxyphenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 10** was obtained by crystallization of the crude product from ethanol (1:25). Yield 1.74 g, 73.7%, m.p. 159–163°C dec. IR, ν_{max} (KBr) cm^{-1}: 3396, 3263, 3195, 1731, 1622, 1343, 1146. ^{1}H NMR (80 MHz, DMSO-d_6) δ: 1.12 (t, 3H, CH_3), 2.35 (s, 3H, CH_3-Ar), 3.62 (s, 3H, OCH_3), 3.98 (s, 2H, SCH_2), 4.08 (q, 2H, OCH_2), 6.62 (m, 1H, Ar), 6.95–7.3 (m, 5H, Ar, NH_2), 7.5 (s, 1H, H-3), 7.92 (s, 1H, H-6), 9.07 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.81 (CH_3), 18.80 (CH_3-Ar), 34.32 (SCH_2), 54.74 (OCH_3), 61.19 (OCH_2), 107.15, 109.51, 129.56, 129.92, 130.56, 130.7, 132.42, 134.31, 136.66, 138.73, 139.3, 159.36 (C-arom.), 154.29 (C-guanid.), 168.81 (C=O). Anal. Calc. for $C_{19}H_{22}ClN_3O_5S_2$ (471.99): C, 48.35; H, 4.69; N, 8.90. Found: C, 48.7; H, 4.35; N, 8.65.

***N*-(4-Methoxyphenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 11** was obtained by crystallization of the crude product from ethanol (1:3). Yield 1.83 g, 77.5%, m.p. 168–169°C dec. IR, ν_{max} (KBr) cm^{-1}: 3418, 3283, 3166, 1742, 1622, 1302, 1140. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.15 (t, 3H, CH_3), 2.33 (s, 3H, CH_3-Ar), 3.71 (s, 3H, OCH_3), 4.02 (s, 2H, SCH_2), 4.07–4.17 (q, 2H, OCH_2), 6.84–6.86 (m, 4H, NH_2 and Ar), 7.25–7.27 (m, 2H, Ar), 7.47 (s, 1H, H-3), 7.89 (s, 1H, H-6), 8.93 (s, 1H, Ar-NH). ^{13}C NMR (20 MHz, DMSO-d_6) δ: 13.85 (CH_3), 18.84 (CH_3-Ar), 34.43 (SCH_2), 55.1 (OCH_3), 61.06 (OCH_2), 112.44, 123.6, 124.1, 130.06, 132.29, 134.03, 136.59, 156.25 (C-arom.), 154.86 (C-guanid.), 168.88. (C=O). Anal. Calc. for $C_{19}H_{22}ClN_3O_5S_2$ (471.99): C, 48.35; H, 4.69; N, 8.90. Found: C, 48.12; H, 4.8; N, 8.76.

***N*-(2-Ethoxyphenyl)-*N′*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 12** was obtained by crystallization of the crude product from ethanol (1:14). Yield 1.82 g, 74.9%, m.p. 112–114°C. IR, ν_{max} (KBr) cm^{-1}: 3418, 3318, 3171, 1733, 1616, 1340, 1299, 1146. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.17 (t, 3H, CH_3), 1.36 (t, 3H, CH_3CH_2O-Ar), 2.36 (s, 3H, CH_3-Ar), 4.04 (s, 2H, SCH_2), 4.04–4.16 (q, 4H, Ar-OCH_2, -OCH_2), 6.82–6.89 (m, 1H, Ar), 6.9–7.06 (m, 2H, Ar), 7.26 (br.s, 2H, NH_2), 7.5 (s, 1H, H-3), 7.86–7.9 (m, 1H, Ar), 7.94 (s, 1H, H-6), 8.38 (s, 1H, Ar-NH). Anal. Calc. for $C_{20}H_{24}ClN_3O_5S_2$ (486.02): C, 49.42; H, 4.97; N, 8.64. Found: N, 8.25.

***N*-(3-Ethoxyphenyl)-*N'*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl) guanidine 13** was obtained by crystallization of the crude product from ethanol (1:14). Yield 1.81 g, 74.8%, m.p. 150–153°C. IR, ν_{max} (KBr) cm^{-1}: 3401, 3265, 3201, 1742, 1622, 1302, 1143. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.15 (t, 3H, CH_3), 1.26 (t, 3H, CH_3CH_2O-Ar), 2.36 (s, 3H, CH_3-Ar), 3.72–3.82 (q, 2H, Ar-OCH_2), 4.0–4.13 (q, 2H, OCH_2), 4,02 (s, 2H, SCH_2), 6.58–6.63 (m, 1H, Ar), 6.82–6.86 (m, 1H, Ar), 6.96 (br.s, 2H, NH_2), 7.04–7.2 (m, 2H, Ar), 7.52 (s, 1H, H-3), 7.94 (s, 1H, H-6), 9.12 (s, 1H, Ar-NH). Anal. Calc. for $C_{20}H_{24}ClN_3O_5S_2$ (486.02): C, 49.42; H, 4.97; N, 8.64. Found: N, 8.55.

***N*-(4-Methoxyphenyl)-*N'*-(2-benzylthio-4-chloro-5-methylbenzenesulphonyl)guanidine 14** was obtained by crystallization of the crude product from ethanol (1:70). Yield 1.66 g, 69.7%, m.p. 208–210°C dec. IR, ν_{max} (KBr) cm^{-1}: 3426, 3312, 3207, 2960, 2919, 2813, 1575, 1525, 1340, 1143. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.32 (s, 2H, SCH_2), 6.79 (m, 2H, Ar), 6.82 (s, 2H, NH_2), 7.21–7.32 (m, 5H, Ar), 7.34–7.39 (m, 2H, Ar), 7.47 (s, 1H, H-3), 7.88 (s, 1H, H-6), 8.94 (s, 1H, Ar-NH). Anal. Calc. for $C_{22}H_{22}ClN_3O_3S_2$ (476.01): C, 55.51; H, 4.66; N, 8.83. Found: N, 8.53.

***N*-(Aryl)-*N'*-(4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonyl)guanidine (3–5)** – *o B*.

To a stirred suspension of **1** (1.93 g, 5 mmol) in dry toluene (50 ml) aniline hydrochloride, *o* -, or -chloroaniline hydrochloride (5 mmol) was respectively added. The reaction mixture was stirred at reflux for 2 h and cooled to 0°C. The resulting precipitate was filtered off, washed well with toluene (3 × 0.5 ml) and dried, then treated with water (50 ml). After vigorously stirring for 20 minutes the precipitate was collected by filtration and dried, to afford pure **3** (2.02 g, 91.7%, m.p. 173–176°C). The crude reaction product of **4** and **5** was purified by recrystallization from ethanol, to afford **4** (1.82 g, 76.4%, m.p. 197–198°C), and **5** (1.8 g, 75.6%, m.p. 145–147°C dec.). IR were identical with authentic sample **3**, **4** and **5**.

Phenethylaminium *N*-cyano-4-chloro-2-ethoxycarbonylmethylthio-5-methylbenzenesulphonamidate (15). To a stirred suspension of **1** (1.93 g, 5 mmol) in dry CCl_4 (30 ml), 2-phenylethylamine (1.21 g, 10 mmol) and 96% sulfuric acid (0.14 ml, 2.5 mmol) was added. The reaction mixture was stirred at reflux for 24 h. After cooling to ambient temperature, the resulting precipitate was filtered off and dried, then treated with water (45 ml). After vigorously stirring for 15 minutes, the precipitate was collected by filtration under diminished pressure and recrystallized from ethanol (5 ml), to give **15** (1.15 g, 49%, m.p. 140–144°C). IR, ν_{max} (KBr) cm^{-1}: 3130–3025, 2984, 2925, 2167, 1736, 1613, 1340, 1290, 1140; ^1H NMR (80 MHz, DMSO-d_6) δ: 1.20 (t, 3H, CH_3), 2.32 (s, 3H, CH_3-Ar), 2.68 (t, 2H, CH_2-Ar), 3.0 (t, 2H, $CH_2NH_3^+$), 3.93 (s, 2H, SCH_2), 4.12 (q, 2H, OCH_2), 7.35 (s, 5H, C_6H_5), 7.40 (s, 1H, H-3), 7.77 (s, 1H, H-6), 7.55–7.95 (br.s, 3H, NH_3^+). Anal. Calc. for $C_{20}H_{24}ClN_3O_4S_2$ (470.02): C, 51.11; H, 5.15; N, 8.94. Found: N, 8.93.

Potassium *N*-cyano-4-chloro-2-[(2-amino-6-dimethylamino-1,3,5-triazin-4-yl)methylthio]-5-methylbenzenesulphonamidate (16). To a stirred solution of potassium methoxide prepared from potassium (0.39 g, 10 mgram atom) and dry methanol (55 ml) **1** (1.93 g, 5 mmol) and 1,1-dimethylbiguanide hydrochloride (1.65 g, 10 mmol) was added. The reaction mixture was stirred at reflux for 45 h, then evaporated to 1/3 volume at diminished pressure. After cooling at room temperature, side precipitate of KCl was filtered off. The clear filtrate was evaporated to dryness, then the residue was extracted twice at reflux, at first with diethyl ether (50 ml) and then with petroleum ether (50 ml). The gummy product thus obtained was recrystallized from ethanol (5.5 ml) and left to stand at refrigerator at least for 48 h, then collected by suction and dried, to give **16** (0.82 g, 36.3%, m.p. 258–264°C dec.). IR, ν_{max} (KBr) cm^{-1}: 3458–3353, 3232, 2178, 1645, 1576, 1343,1140. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.31 (s, 3H, CH_3-Ar), 3.04 (s, 3H, NCH_3), 3.1 (s, 3H, NCH_3), 3.87 (s, 2H, SCH_2), 6.89 (br.s, 2H, NH_2), 7.72 (s, 1H, H-3), 7.89 (s, 1H, H-6). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 18.92 (CH_3-Ar), 35.68 (SCH_2), 37.79 (NCH_3), 117.25 (CN), 126.77, 130.76, 135.79, 136.29, 139.74, 156.69 (C-arom.), 165.0, 166.75, 173.61 (C-triazine). Anal. Calc. for $C_{14}H_{16}ClKN_7O_2S_2$ (452,0): C, 37.2; H, 3.56; N, 21.69. Found: N, 21.36.

***N*-(3-Bromophenyl)-*N'*-{4-chloro-2-[(2-amino-6-dimethylamino-1,3,5-triazin-4-yl) methylthio]-5-methylbenzenesulphonyl}guanidine (17)**. To a stirred solution of sodium methoxide prepared from sodium (0.138 g, 6 mgram atom) dry methanol (30 ml) **7** (1.56 g, 3 mmol) and 1,1-dimethylbiguanide hydrochloride (0.99 g, 6 mmol) was added. The reaction mixture was stirred at reflux for 45 h and left to stand at room temperature for 4 h. The resulting precipitate was filtered off, and dried, then treated with water (15 ml). After vigorously stirring for 20 minutes, the precipitate was collected by filtration under diminished pressure and dried, to give **17** (1.24 g, 70.8%, m.p. 242–245°C dec.). IR, ν_{max} (KBr)

cm^{-1}: 3471, 3354, 3283, 1629, 1571, 1344, 1149. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.32 (s, 3H, CH_3-Ar), 3.01 (s, 6H, $N(CH_3)_2$), 3.94 (s, 2H, SCH_2), 6.87 (s, 2H, triazine-NH_2), 7.02 (s, 2H, NH_2), 7.16–7.30 (m, 3H, Ar), 7.77 (s, 1H, Ar), 7.86 (s, 1H, H-3), 8.01 (s, 1H, H-6), 9.2 (br.s, 1H, Ar-NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 18.9 (CH_3Ar), 35.61 (SCH_2), 39.08 ($N(CH_3)_2$), 119.77, 121.4, 123.6, 126.97, 127.46, 130.43, 131.44, 136.51, 136.86, 137.93, 139.42, 154.07 (C-arom.), 164.97, 166.68, 173.34 (C-triazine). Anal. Calc. for $C_{20}H_{22}BrClN_8O_2S_2$ (585.93): C, 40.99; H, 6.76; N, 19.12. Found: N, 19.36.

REFERENCES

1. Brzozowski Z., *A o o . .-D* ., **52**, 91 (1995).
2. Brzozowski Z., *A o o . .-D* ., **53**, 269 (1996).
3. Pomarnacka E., *A o o . .-D* ., **53**, 373 (1996).
4. Pomarnacka E. and Brzozowski Z., *A o o . .-D* ., **54**, 215 (1997).
5. Brzozowski Z., Sączewski F. and Gdaniec M., *Li . J. . C* ., **37**, 285 (2002).
6. Brzozowski Z. and Sączewski F., *J. . C* ., **45**, 430 (2002).
7. Neamati N., Mazumder A., Sunder S., Owen J.M., Schultz R.J. and Pommier Y., *A C . C - o* , **8**, 485 (1997).
8. Brzozowski Z., *A o o . .-D* ., **52**, 287 (1995).
9. Brzozowski Z., *A o o . .-D* ., **55**, 49 (1998).
10. Brzozowski Z., *A o o . .-D* ., **55**, 473 (1998).
11. Pomarnacka E. and Kornicka A., *I F o* , **56**, 571 (2001).
12. Brzozowski Z., **Pol. PL 173244 B1** (Cl. CO7D 249/14) 1998, (*C.A*., **129**, 148982z 1998).
13. Sławiński J., *o J. C* ., **75**, 1309 (2001).
14. Brzozowski Z., Sławiński J., Filiczewski M. and Szymańska-Kosmala M., *A o o . .-D* ., **47**, 57 (1990).
15. Brzozowski Z., Sławiński J., Kosmala M., Olędzka K., Filiczewski M., Miłobędzka J. and Lewandowski K., *A o o . .-D* ., **48**, 39 (1991).
16. Brzozowski Z., Sławiński J., Borowik W. and Gajewski F., *A o o . .-D* ., **49**, 93 (1992).
17. Brzozowski Z. and Sławiński J., *A o o . .-D* ., **49**, 85 (1992).
18. Brzozowski Z. and Sławiński J., *A o o . .-D* ., **49**, 81 (1992).
19. Brzozowski Z., Sławiński J., Olędzka M., Kosmala M., Filiczewski M., Lewandowski K. and Miłobędzka J., *A o o . .-D* ., **50**, 345 (1993).
20. Kálmán A., Czugler M. and Argay G., *A C* ., **B37**, 868 (1981).
21. Alléaume M., Gulko A., Herbstein F.H., Kapon M. and Marsh R.E., *A C* ., **B32**, 669 (1976).
22. Kruger G.J. and Gofner G., *A C* ., **B28**, 272 (1972).
23. Costakis E., Conone P. and Tsatsas G., *C . J. C* ., **7**, 4483 (1969).
24. Molecular modelling studies were performed using a molecular orbital *b o* method at the Hartree-Fock level with 6-31G** basis set modules as implemented into TITAN program Version 1,0,5 (2000), Wavefunction Inc. Schrödinger Inc.