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RESEARCH ARTICLE

Synthesis and antibacterial activity of novel 4-chloro-2-mercaptobenzenesulfonamide derivatives

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Abstract

Few series of novel 4-chloro-2-mercaptobenzenesulfonamides have been synthesized by the reactions of *N*-(benzenesulfonyl)cyanamide potassium salts **7–15** with corresponding hydrazinecarbodithioic acid esters, 1-substituted carbothioic acid hydrazides, methyl 3-aminothiophene-2-carboxylate, methyl 2-aminobenzoate, 2-aminophenol or 2-aminothiophenol. The synthesized compounds (**16–49**) were screened *in vitro* for their antibacterial activity. Some of the tested compounds **16, 17, 23, 24, 31, 32** and **48** showed the promising activity against many of anaerobic Gram-positive bacteria strains.

Keywords: 2-mercaptobenzenesulfonamide, antibacterial, anti-tumour, synthesis, 1,3,4-thiadiazole

Introduction

The aryl/heteroaryl sulfonamides constitute an important class of compounds with several types of biological activities[1]. For many years, 2-mercaptobenzenesulfonamide derivatives (MBSAs) are of interest because of the various biological properties[2–12]. Depending on the modification of their chemical structure, they exhibit antitumour activity[2–7], HIV-antiviral[8–10] or inhibiting carbonic anhydrase CA both cytosolic CA I, II and transmembrane cancer-associated IX and XII isoforms[11,12].

Through investigations presented, we have also joined the trend of research on the antibacterial properties of sulfonamides. In particular, the substituted 1,3,4-thiadiazoles have attracted considerable attention due to their wide-range biological activities, including anti-bacterial, anti-tuberculosis, anaesthetic, anti-inflammatory, anti-thrombotic, anti-convulsant, anti-hypertensive, anti-ulcer, anti-viral, anti-HIV-1 or anti-cancer activities[13–20]. Therefore, for the initial chemical studies, we synthesized a series of novel 2-benzylthio-*N*-(1,3,4-thiadiazol-2-yl)benzenesulfonamide derivatives and determined their anti-bacterial activity. For further investigation, we applied various nucleophiles involving methyl 3-aminothiophene-2-carboxylate, methyl 2-aminobenzoate, 2-aminophenol or 2-aminothiophenol with *N*-(benzenesulfonyl)cyanamide potassium salts to obtain the corresponding cyclization products and to investigate their anti-bacterial properties.

Materials and methods

Chemistry

The following instruments and parameters were used: melting points Stuart SMP3 apparatus; IR spectra: KBr pellets, 400–4000 cm^{-1} Thermo Mattson Satellite FTIR spectrometer; ^1H NMR: Varian Gemini 200 apparatus at 200 MHz; chemical shifts are expressed at δ values relative to Me_4Si as standard. The results of elemental analyses for C, H, and N were in agreement with the calculated values within ± 0.4% range. Compounds **29, 34–36** were obtained in accordance with the previously described procedures[9]. The corresponding hydrazinecarbodithioic acid esters were prepared according to the known methods[21,22].

*Methyl 3-amino-6-chloro-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylate (**3**)*: To a suspension of **1** (7.43 g, 22 mmol) in ethanol (38 mL) 25% aqueous ammonium

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hydroxide solution (3.46 mL, 22.2 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 44 h. The resulting precipitate was filtered off under diminished pressure, washed with ethanol (2 × 1 mL) and dried, to give **3**. Yield: 2.95 g, 73%, mp 260°C–263°C. After crystallization from mixture of ethanol and acetonitrile (v/v 10:1), **3** presented mp 268°C–271°C dec.; IR ν_{max} (KBr)/cm^{-1} 3418, 3382, 3306, 3215 (NH), 2960, 2924 (CH_3), 1711 (C=O), 1629 (NH), 1303, 1162 (SO_2); ^{1}H NMR δ (DMSO-d_6) 3.89 (s, 3H, CH_3O), 8.12 (s, 1H, H-5), 9.34 (s, 2H, NH_2). Anal. Calcd. for $C_9H_7ClN_2O_4S_2$: C, 35.24; H, 2.30; N, 9.13. Found: C, 35.08; H, 2.19; N, 9.20%.

*5-Chloro-2-(cyanoaminosulfonyl)-4-(methoxy carbonyl) thiophenolate dipotassium salt (**5**)*: A stirred suspension of **3** (3.09 g, 10 mmol) and anhydrous K_2CO_3 (6.91 g) in dry THF (80 mL) was refluxed for 24 h. After cooling to room temperature the suspension was left in a refrigerator overnight. The resulting precipitate was filtered under diminished pressure and dried. The product was separated from a solid K_2CO_3 by extraction with boiling ethanol (2 × 80 mL). The extracts were chilled to 0°C, and left to stand in a refrigerator overnight. The precipitate was collected by filtration, washed with cold ethanol (2 × 0.5 mL) and dried at temperatures gradually increasing to 105°C, to give **5**. Yield: 1.80 g, 68%, mp 219°C–222°C dec.; IR ν_{max} (KBr)/cm^{-1} 3390 (OH), 2953, 2921, 2836 (CH_3), 2173 (C≡N), 1720 (C=O), 1280, 1112 (SO_2); ^{1}H NMR δ (DMSO-d_6) 3.73 (s, 3H, OCH_3), 7.26 (s, 1H, H-3), 8.22 (s, 1H, H-6). Anal. Calcd. for $C_9H_5ClK_2N_2O_4S_2$: C, 28.23; H, 1.32; N, 7.32. Found: C, 28.31; H, 1.10; N, 6.95%.

*N-(2-Benzylthio-4-chloro-5-methoxycarbonylbenze nesulfonyl)cyanamide potassium salt (**12**) Method A*: To a stirred solution of **5** (1.53 g, 4 mmol) in water (7 mL) benzyl chloride (0.46 mL, 4 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. After cooling to 0°C, the precipitate of crude product was filtered off, then recrystallized from methanol (11 mL), to afford **12**. Yield: 1.38 g, 80%, mp 206°C–209°C dec.; IR ν_{max} (KBr)/cm^{-1} 2952, 2836 (CH_3, CH_2), 2185 (C≡N), 1729, 1711 (CO), 1355, 1141 (SO_2); ^{1}H NMR δ (DMSO-d_6) 3.86 (s, 3H, OCH_3), 4.34 (s, 2H, SCH_2), 7.25–7.49 (m, 5H, Ph), 7.54 (s, 1H, H-3), 8.26 (s, 1H, H-6). Anal. Calcd. for $C_{16}H_{12}ClKN_2O_4S_2$: C, 44.18; H, 2.78; N, 6.44. Found: C, 44.02; H, 2.43; N, 6.29%.

Method B: To a stirred suspension of **3** (1.22 g, 4 mmol) and anhydrous K_2CO_3 (1.38 g) in dry THF (40 mL), benzyl chloride (0.46 mL, 4 mmol) was added dropwise. The reaction mixture was stirred at reflux for 22 h, then left to stand at room temperature overnight. The precipitate was filtered off and washed twice with dry THF (1 mL). The product was separated from a solid K_2CO_3 by extraction with boiling ethanol (30 mL) for 10 min. The filtrate was cooled to 0°C, and left to stand in a refrigerator overnight. The precipitate was filtered off, washed with ethanol (2 × 0.5 mL) and dried in air, to give **12**. Yield: 1.01 g, 58%, mp 197°C–199°C dec. After crystallization from methanol (7 mL), **12** presented mp 206°C–209°C dec.; IR (KBr) and ^{1}H NMR (DMSO-d_6) spectra were identical with authentic sample **12**.

*General procedure for the preparation of N-[4-chloro-5-methyl-2-(R^2-methylthio)benzenesulfonyl]cyanamide potassium salts (**13–15**):* To a suspension of 5-chloro-2-(cyanoaminosulfonyl)-4-methylthiophenolate dipotassium salt (5.08 g, 15 mmol) in water (15 mL) the appropriate alkyl halide (16.5 mmol) was added in portions at 0°C–20°C. The reaction mixture was stirred for 1–2 h and the precipitate was filtered off and dried. Crude product was purified by crystallization from ethanol.

*N-(2-Allylthio-4-chloro-5-methylbenzenesulfonyl) cyanamide potassium salt (**13**)*: Starting from **6** and allyl bromide (2.06 g), the title compound **13** was obtained. Yield: 4.98 g, 98%, mp 192°C–194°C; IR ν_{max} (KBr)/cm^{-1} 3071 (C=CH), 2921 (CH_3), 2173 (C≡N), 1631 (C=C), 1344, 1146 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.30 (s, 3H, CH_3), 3.65–3.75 (d, 2H, SCH_2), 5.10-5.40 (d, 2H, C=CH_2), 5.75-5.95 (m, 1H, CH=CH_2), 7.35 (s, 1H, H-3), 7.75 (s, 1H, H-6). Anal. Calcd. for $C_{11}H_{10}ClKN_2O_2S_2$: C, 38.76; H, 2.96; N, 8.22. Found: C, 38.40; H, 2.74; N, 8.28%.

*N-(4-Chloro-5-methyl-2-propargylthiobenzenesulfonyl) cyanamide potassium salt (**14**)*: Starting from **6** and propargyl bromide (1.96 g) the title compound **14** was obtained. Yield: 4.71 g, 93%, mp 210–212°C; IR ν_{max} (KBr) / cm^{-1} 3311, 3299 (C≡CH), 2946, 2920, 2854 (CH_3, CH_2), 2172 (C≡N), 2123 (C≡C), 1344, 1142 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.31 (s, 3H, CH_3), 3.19 (s, 1H, C≡CH), 3.87 (s, 2H, SCH_2), 7.44 (s, 1H, H-3), 7.74 (s, 1H, H-6). Anal. Calcd. for $C_{11}H_8ClKN_2O_2S_2$: C, 38.99; H, 2.38; N, 8.26. Found: C, 39.20; H, 2.34; N, 8.49%.

*N-[4-Chloro-5-methyl-2-(2-phenylsulfonylethylthio) benzenesulfonyl]cyanamide potassium salt (**15**)*: Starting from **6** and 1-chloro-2-phenylsulfonylethan (3.38 g), the title compound **15** was obtained. Yield: 6.14 g, 87%, mp 126°C–129°C; IR ν_{max} (KBr)/cm^{-1} 2924, 2854 (CH_3, CH_2), 2178 (C≡N), 1284, 1149 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.31 (s, 3H, CH_3), 3.12-3.19 (m, 2H, SCH_2), 3.35-3.62 (m, 2H, SO_2CH_2), 7.26 (s, 1H, H-3), 7.63–7.81 (m, 4H, arom.), 7.92–7.96 (m, 2H, arom). Anal. Calcd. for $C_{16}H_{14}ClKN_2O_4S_3$: C, 40.97; H, 3.01; N, 5.97. Found: C, 40.78; H, 2.90; N, 5.50%.

General procedure for the preparation of 2-benzylthio-4-chloro-5-R^1-N-(5-R^2-1,3,4-thiadiazol-2-yl)benzenesulfonamide derivatives (16–27): To a suspension of corresponding *N*-(benzenesulfonyl)cyanamide potassium salt **7**, **9–12** (2 mmol) in glacial acetic acid (6 mL), the equimolar amount of the appropiate hydrazinecarbodithioic acid esters or 1-substituted carbothioic acid hydrazides was added and then refluxed for 8–40 h. After cooling to 10°C, the precipitate was collected by filtration, washed with cold acetic acid and dried. Crude products were purified by crystallization from proper solvents: **16–18**, **22**, **23** (ethanol); **19**, **25–27** (acetonitrile); **20**, **21** (ethanol:acetonitile, v/v 19:1); **24** (ethanol:acetonitile, v/v 5:1).

*2-Benzylthio-4-chloro-5-methyl-N-(5-methylthio-1, 3,4-thiadiazol-2-yl)benzenesulfonamide (**16**)*: Starting from **7** (0.78 g) and methyl hydrazinecarbodithioate

(0.24 g) at reflux for 8 h, the title compound **16** was obtained. Yield: 0.55 g, 60%, mp 178°C–180°C dec.; IR ν_{max} (KBr)/cm^{-1} 3127 (NH), 2921, 2855 (CH_3, CH_2), 1543 (C=N), 1305, 1150 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.33 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 4.31 (s, 2H, SCH_2), 7.22-7.27 (m, 5H, Ph), 7.58 (s, 1H, H-3), 7.88 (s, 1H, H-6), 14.30 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{17}H_{16}ClN_3O_2S_4$: C, 44.58; H, 3.52; N, 9.17. Found: C, 44.21; H, 3.38; N, 8.90%.

*2-Benzylthio-4-chloro-5-methyl-N-(5-benzylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamide (**17**)*: Starting from **7** (0.78 g) and benzyl hydrazinecarbodithioate (0.40 g) at reflux for 8 h, the title compound **17** was obtained. Yield: 0.45 g, 42%, mp 194°C–196°C dec.; IR ν_{max} (KBr)/cm^{-1} 3441 (NH), 2921, 2852 (CH_3, CH_2), 1554 (C=N)), 1310, 1297, 1137 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.31 (s, 3H, CH_3), 4.26 (s, 2H, SCH_2), 4.31 (s, 2H, SCH_2), 7.27–7.35 (m, 10H, arom.), 7.42 (s, 1H, H-3), 7.79 (s, 1H, H-6). Anal. Calcd. for $C_{23}H_{20}ClN_3O_2S_4$: C, 51.72; H, 3.77; N, 7,87. Found: C, 51.40; H, 3.68; N, 7.55%.

*4-Benzylthio-2-chloro-5-(5-methylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-N-phenylbenzamide (**18**)*: Starting from **9** (0.99 g) and methyl hydrazinecarbodithioate (0.24 g) at reflux for 8.5 h, the title compound **18** was obtained. Yield: 0.50 g, 44%, mp 266°C–269°C dec.; IR ν_{max} (KBr)/cm^{-1} 3275 (NH), 2879 (CH_3, CH_2), 1659 (C=O), 1583, 1544 (C=N), 1322, 1139 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.63 (s, 3H, SCH_3), 4.45 (s, 2H, SCH_2), 7.11–7.38 (m, 8H, arom.), 7.67–7.69 (d, 2H, arom.), 7.73 (s, 1H, H-3), 7.99 (s, 1H, H-6), 10.61 (s, 1H, NHCO), 14,40 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{23}H_{19}ClN_4O_3S_4$: 49.06; H, 3.40; N, 9.95. Found: 49.02; H, 3.44; N, 9.97%.

*4-Benzylthio-2-chloro-5-(5-benzylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-N-phenylbenzamide (**19**)*: Starting from **9** (0.99 g) and benzyl hydrazinecarbodithioate (0.40 g) at reflux for 9 h, the title compound **19** was obtained. Yield: 0.66 g, 51%, mp 231°C–233°C dec.; IR ν_{max} (KBr)/cm^{-1} 3314, 3137 (NH), 2854 (CH_3, CH_2), 1663 (C=O), 1582 (C=N), 1324, 1151 (SO_2); ^{1}H NMR δ (DMSO-d_6) 4.41 (s, 4H, 2 x SCH_2), 7.08-7.39 (m, 13H, arom.), 7.66–7.71 (m, 3H, H-3 and arom.), 7.96 (s, 1H, H-6), 10.61 (s, 1H, NHCO), 14.45 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{29}H_{23}ClN_4O_3S_4$: 54.49; H, 3.63; N, 8.76. Found: 54.60; H, 3.73; N, 8.87%.

*4-Benzylthio-2-chloro-5-(5-methylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-N-(4-chlorophenyl)benzamide (**20**)*: Starting from **10** (1.06 g) and methyl hydrazinecarbodithioate (0.24 g) at reflux for 8 h, the title compound **20** was obtained. Yield: 0.55 g, 45%, mp 256°C–258°C dec.; IR ν_{max} (KBr)/cm^{-1} 3279 (NH), 2923, 2841 (CH_3, CH_2), 1659 (C=O), 1581, 1545 (C=N), 1311, 1140 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.63 (s, 3H, SCH_3), 4.45 (s, 2H, SCH_2), 7.27–7.36 (m, 5H, Ph), 7.42 (d, J = 7.8 Hz, 2H, 4-ClC_6H_4), 7.71 (d, J = 7.8 Hz, 2H, 4-ClC_6H_4), 7.74 (s, 1H, H-3), 8.01 (s, 1H, H-6), 10.75 (s, 1H, NHCO), 14.40 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{23}H_{18}Cl_2N_4O_3S_4$: C, 46.23; H, 3.04; N, 9.38. Found: C, 46.01; H, 2.89; N, 8.71%.

*4-Benzylthio-5-(5-benzylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-2-chloro-N-(4-chlorophenyl)benzamide (**21**)*: Starting from **10** (1.06 g) and benzyl hydrazinecarbodithioate (0.40 g) at reflux for 8.5 h, the title compound **21** was obtained. Yield: 0.63 g, 46%, mp 253°C–256°C dec.; IR ν_{max} (KBr)/cm^{-1} 3342, 3217 (NH), 2923, 2759 (CH_3, CH_2), 1660 (C=O), 1599, 1578, 1544 (C=N), 1313, 1143 (SO_2); ^{1}H NMR δ (DMSO-d_6) 4.40 (s, 2H, SCH_2), 4.42 (s, 2H, SCH_2), 7.20–7.36 (m, 12H, 2 x Ph and 4-ClC_6H_4), 7.71 (d, J = 7.3 Hz, 2H, 4-ClC_6H_4), 7.73 (s, 1H, H-3), 7.98 (s, 1H, H-6), 10.75 (s, 1H, NHCO), 14.40 (s, 1H, SO_2NH). Anal. Calcd. for $C_{29}H_{22}Cl_2N_4O_3S_4$: C, 51.70; H, 3.29; N, 8.32. Found: C, 51.55; H, 3.19; N, 8.24%.

*4-Benzylthio-2-chloro-5-(5-methylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-N-(4-methylphenyl)benzamide (**22**)*: Starting from **11** (1.02 g) and methyl hydrazinecarbodithioate (0.24 g) at reflux for 9 h, the title compound **22** was obtained. Yield: 0.45 g, 37%, mp 237°C–240°C dec.; IR ν_{max} (KBr)/cm^{-1} 3411, 3278 (NH); 2922 (CH_3, CH_2), 1652 (C=O), 1580, 1543 (C=N), 1318, 1141 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.27 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 4.44 (s, 2H, SCH_2), 7.16 (d, J = 8.4 Hz, 2H, 4-MeC_6H_4), 7.23–7.33 (m, 5H, Ph), 7.56 (d, J = 8.4 Hz, 2H, 4-MeC_6H_4), 7.72 (s, 1H, H-3), 7.97 (s, 1H, H-6), 10.52 (s, 1H, NHCO), 14.40 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{24}H_{21}ClN_4O_3S_4$: C, 49.94; H, 3.67; N, 9.71. Found: C, 49.75; H, 3.45; N, 9.96%.

*4-Benzylthio-5-(5-benzylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)-2-chloro-N-(4-methylphenyl)benzamide (**23**)*: Starting from **11** (1.02 g) and benzyl hydrazinecarbodithioate (0.40 g) at reflux for 8 h, the title compound **23** was obtained. Yield: 0.63 g, 48%, mp 222°C–224°C dec.; IR ν_{max} (KBr)/cm^{-1} 3286, 3137 (NH), 2921, 2847 (CH_3, CH_2), 1656 (C=O), 1583, 1545, 1518 (C=N), 1322, 1151 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.27 (s, 3H, CH_3), 4.41 (s, 4H, 2 x SCH_2), 7.16 (d, J = 8.3 Hz, 2H, 4-MeC_6H_4), 7.22–7.36 (m, 10H, 2 × Ph), 7.57 (d, J = 8.3 Hz, 2H, 4-MeC_6H_4), 7.72 (s, 1H, H-3), 7.95 (s, 1H, H-6), 10.52 (s, 1H, NH), 14,40 (br s, 1H, SO_2NH). Anal. Calcd. for $C_{30}H_{25}ClN_4O_3S_4$: C, 55.16; H, 3.86; N, 8.58. Found: C, 55.10; H, 3.82; N, 8.58%.

*Methyl-4-benzylthio-2-chloro-5-(5-methylthio-1,3,4-thiadiazol-2-yl-aminosulfonyl)benzoate (**24**)*: Starting from **12** (0.87 g) and methyl hydrazinecarbodithioate (0.24 g) at reflux for 9 h, the title compound **24** was obtained. Yield: 0.43 g, 43%, mp 171°C–173°C dec.; IR ν_{max} (KBr)/cm^{-1} 3360 (NH), 2850 (CH_3, CH_2), 1731 (C=O), 1577, 1542 (C=N), 1314, 1150 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.61 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 4.41 (s, 2H, SCH_2), 7.32 (s, 5H, Ph,), 8.32 (s, 1H, H-3), 8.34 (s, 1H, H-6), 14.40 (br s, 1H, NH). Anal. Calcd. for $C_{18}H_{16}ClN_3O_4S_4$: C, 43.06; H, 3.21; N, 8.37. Found: C, 42.99; H, 3.19; N, 8.38%.

*2-Benzylthio-4-chloro-5-methyl-N-(5-pyrrolidin-1-yl-1,3,4-thiadiazol-2-yl)benzenesulfonamide (**25**)*: Starting from **7** (0.78 g) and pyrrolidine-1-carbothiohydrazide (0.29 g) at reflux for 29 h, the title compound **25** was obtained. Yield: 0.56 g, 59%, mp 220°C–223°C dec.; IR ν_{max} (KBr)/cm^{-1} 3247 (NH), 2926, 2859 (CH_3, CH_2), 1527(C=N), 1342, 1139 (SO_2); ^{1}H NMR δ (DMSO-d_6) 1.93–1.96 (m, 4H, CH_2), 2.33 (s, 3H, CH_3), 3.30–3.34 (m, 4H, CH_2), 4.31 (s, 2H, SCH_2), 7.26–7.34 (m, 5H, Ph), 7.54 (s, 1H, H-3), 7.86 (s, 1H, H-6), 13.23 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{21}ClN_4O_2S_3$:

C, 49.93; H, 4.40; N, 11.65. Found: C, 49.83; H, 4.43; N, 11.73%.

*2-Benzylthio-4-chloro-5-methyl-N-(5-morpholin-1-yl-1,3,4-thiadiazol-2-yl)benzenosulfonamide (**26**)*: Starting from **7** (0.78 g) and morpholine-4-carbothiohydrazide (0.32 g) at reflux for 11 h, the title compound **26** was obtained. Yield: 0.19 g, 19%, mp 218°C–221°C dec.; IR ν_{max} (KBr)/cm^{-1} 3431, 3236 (NH), 2919, 2854 (CH_3, CH_2), 1532 (C=N), 1343, 1141 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.33 (s, 3H, CH_3), 3.24–3.28 (m, 4H, morpholine), 3.64–3.69 (m, 4H, morpholine), 4.31 (s, 2H, SCH_2), 7.27–7.31 (m, 5H, Ph), 7.55 (s, 1H, H-3), 7.86 (s, 1H, H-6), 13.36 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{21}ClN_4O_3S_3$: 48.33; H, 4.26; N, 11.27. Found: C, 48.10; H, 4.02; N, 10.93%.

*2-Benzylthio-4-chloro-5-methyl-N-[5-(4-phenylpiperazin-1-yl)-1,3,4-thiadiazol-2-yl]benzenosulfonamide (**27**)*: Starting from **7** (0.78 g) 4-phenylpiperazine-1-carbothiohydrazide (0.47 g) at reflux for 40 h, the title compound **27** was obtained. Yield: 0.25 g, 22%, mp 195°C–201°C dec.; IR ν_{max} (KBr)/cm^{-1} 3436 (NH), 2922, 2853 (CH_3,CH_2), 1537 (C=N), 1345, 1143 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.34 (s, 3H, CH_3), 3.24 (s, 4H, CH_2), 3.43 (s, 4H, CH_2), 4.27 (s, 2H, SCH_2), 6.83–7.40 (m, 10H, Ph), 7.56 (s, 1H, H-6), 13.36 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{26}ClN_5O_2S_3$: C, 54.58; H, 4.58; N, 12.24. Found: C, 54.47; H, 4.18; N, 11.71%.

*2-Benzylthio-4-chloro-5-methyl-N-{5-[4-(pyrimidin-2--yl)piperazin-1-yl]-1,3,4-thiadiazol-2-yl}benzenosulfonamide (**28**)*: To a suspension of **16** (0.46 g, 1 mmol) in dry toluene (14 mL), 2-(piperazin-1-yl)pyrimidine (0.73 g, 4.5 mmol) was added dropwise and then the reaction mixture was stirred at reflux for 56 h. After reaction byproducts were filtered off, the filtrate was evaporated to dryness under reduced pressure. The resulting solid was crystallized from acetonitrile, to give **28**. Yield: 0.09 g, 16%, mp 238°C–242°C dec.; IR ν_{max} (KBr)/cm^{-1} 3449, 3160 (NH), 2853 (CH_2,CH_3), 1534 (C=N), 1345, 1143 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.34 (s, 3H, CH_3), 3.37–3.39 (t, 4H, CH_2), 3.83–3.85 (t, 4H, CH_2), 4.32 (s, 1H, SCH_2), 6.7–6.72 (t, 1H, pyrimidine), 7.2–7.34 (m, 5H, Ph), 7.56 (s, 1H, H-3), 7.87 (s, 1H, H-6), 8.42-8.43 (d, 2H, pyrimidine), 13.36 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{24}ClN_7O_2S_3$: C, 50.21; H, 4.21; N, 17.08. Found: C, 49.81; H, 4.00; N, 17.75%.

*General procedure for the preparation of 2-(R^2-methylthio)-4-chloro-N-(3,4-dihydro-4-oxothieno[2,3-e] pyrimidin-2-yl)benzenesulfonamide derivatives (**30–33**):* The mixture of *N*-[4-chloro-2-(R^2-methylthio)-5-methyl benzenesulfonyl]cyanamide potassium salt **8, 13–15** (2 mmol) and the equimolar amount of methyl 3-aminothiophene-2-carboxylate (0.317 g, 2 mmol) in glacial acetic acid (7 mL) was stirred at reflux for 15 h and additional 12 h at room temperature. After cooling to 10°C, the precipitate was collected by filtration, washed with cold acetic acid and dried. Crude product was purified by crystallization from ethanol or extraction of contaminations with hot ethanol.

*2-Carbamoylmethylthio-4-chloro-N-(3,4-dihydro-4-oxothieno[2,3-e]pyrimidin-2-yl)-5-methylbenzenesulfonamide (**30**)*: Starting from **8** (0.72 g) compound **30** was obtained. Yield: 0.18 g, 20%, mp 228°C–233°C; IR ν_{max} (KBr)/cm^{-1} 3435 (NH), 2923, 2851 (CH_3, CH_2), 1655 (C=O), 1555 (C=N), 1334,1130 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3), 3.19 (s, 2H, SCH_2), 6.75–6.85 (d, 1H, thiophene), 7.15 (s,1H, NH), 7.40 (s, 1H, H-3), 7.60 (s, 1H, NH), 7.75–7.85 (d, 1H, thiophene), 7.95–8.05 (d, 2H, H-6, NH), 10.70–10.80 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{13}ClN_4O_4S_3$: C, 40.49; H, 2.94; N, 12.59. Found: C, 40.21; H, 2.85; N, 12.39%.

*2-Allylthio-4-chloro-N-(3,4-dihydro-4-oxothieno[2,3-e] pyrimidin-2-yl)-5-methylbenzenesulfonamide (**31**)*: Starting from **13** (0.68 g), compound **31** was obtained. Yield: 0.34 g, 40%, mp 183°C–185°C; IR ν_{max} (KBr)/cm^{-1} 3448, 3305 (NH), 3103 (C=CH), 2922 (CH_3, CH_2), 1685 (C=O), 1617 (C=N), 1342, 1104 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3), 3.75 (d, 2H, SCH_2), 4.95–5.25 (dd, 2H, C=CH_2), 5.55–5.80 (m, 1H, CH=C), 7.30–7.40 (d, 1H, thiophene), 7.55 (s, 1H, H-3), 7.96 (s, 1H, H-6), 8.14–8.22 (d, 1H, thiophene), 11.70 (s, 1H, NH), 12.20 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S_3$: C, 44.91; H, 3.30; N, 9.82. Found: C, 44.82; H, 3.27; N, 9.62%.

*4-Chloro-N-(3,4-dihydro-4-oxothieno[2,3-e]pyrimidin-2-yl)-5-methyl-2-propargylthiobenzenesulfonamide (**32**)*: Starting from **14** (0.68 g), compound **32** was obtained. Yield: 0.28 g, 34%, mp 222°C–224°C; IR ν_{max} (KBr)/cm^{-1} 3491, 3248 (NH), 3081 (C≡CH), 2953 (CH_3, CH_2), 1672 (C=O), 1613 (C=N), 1350, 1153 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3), 3.15 (s, 1H, C≡CH), 4.95 (d, 2H, SCH_2), 7.22–7.32 (d, 1H, thiophene), 7.60 (s, 1H, H-3), 8.00 (s, 1H, H-6), 8.13 (d, 1H, thiophene), 11.60 (s, 1H, NH), 12.20 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{12}ClN_3O_3S_3$: C, 45.12; H, 2.84; N, 9.87. Found: C, C, 45.22; H, 2.96; N, 10.02%.

*4-Chloro-N-(3,4-dihydro-4-oxothieno[2,3-e]pyrimidin-2-yl)-5-methyl-2-(2-phenylsulfonylethylthio)benzenesulfonamide (**33**)*: Starting from **15** (0.94 g), compound **33** was obtained. Yield: 0.40 g, 36%, mp 233°C–235°C; IR ν_{max} (KBr)/cm^{-1} 3447, 3071 (NH), 2921, 2851 (CH_3, CH_2), 1654 (C=O), 1553(C=C), 1336, 1152 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3), 3.07 (t, 2H, CH_2), 3.47 (t, 2H, CH_2), 6.71–6.74 (d, 1H, arom.), 7.12 (s, 1H, NH), 7.65 (t, 2H, arom.), 7.74–7.80 (m, 2H, arom.), 7.86 (d, 2H, arom.), 8.00 (s, 1H, H-6), 10.85 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{18}ClN_3O_5S_4$: C, 45.36; H, 3.26; N, 7.56. Found: C, 45.20; H, 2.99; N, 7.35%.

*General procedure for the preparation of 2-(R^2-methylthio)-4-chloro-N-(3,4-dihydro-4-oxoquinazolin-2-yl)benzenesulfonamide derivatives (**37–42**):* To a suspension of the corresponding *N*-[4-chloro-2-(R^2-methylthio)-5-methylbenzenesulfonyl]cyanamide potassium salt **8, 14–15** (2 mmol) in glacial acetic acid (7 mL) the appropriate methyl 2-aminobenzoate derivatives (2.2 mmol) was added and refluxed for 14–17 h. After cooling to 10°C, the precipitate was collected by filtration, washed with cold acetic acid and dried. Crude product was purified by crystallization from ethanol or extraction of contaminations with hot ethanol.

*2-Carbamoylmethylthio-4-chloro-N-(3,4-dihydro-4-oxoquinazolin-2-yl)-5-methylbenzenesulfonamide (**37**)*:

Starting from **8** (0.72 g) and methyl 2-aminobenzoate (0.33 g), the title compound **37** was obtained. Yield: 0.36 g, 41%, mp 270°C–272°C; IR ν_{max} (KBr)/cm^{-1} 3383, 3274, 3165 (NH, NH_2), 2922 (CH_3, CH_2), 1720 (C=O), 1707 (C=O), 1642 (C=N), 1361, 1148 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.40 (s, 3H, CH_3), 3.70 (s, 2H, SCH_2), 7.20 (s, 1H, NH_2), 7.37 (t, 1H, arom.), 7.55 (d, 2H, arom.), 7.65 (s, 1H, H-3), 7.77 (t, 1H, arom.), 7.95 (s, 1H, H-6), 8.05 (s, 1H, NH_2), 11.40 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{15}ClN_4O_4S_2$: C, 46.52; H, 3.44; N, 12.77. Found: C, 46.44; H, 3.12; N, 12.40%.

*2-Carbamoylmethylthio-4-chloro-N-(7-chloro-3-,4-dihydro-4-oxoquinazolin-2-yl)-5-methylbenzene sulfonamide (**38**)*: Starting from **8** (0.72 g) and methyl 2-amino-4-chlorobenzoate (0.41 g), the title compound **38** was obtained. Yield: 0.37 g, 39%, mp 272°C–274°C; IR ν_{max} (KBr)/cm^{-1} 3391, 3275, 3175 (NH, NH_2), 2920 (CH_3, CH_2), 1719 (C=O), 1691 (C=O), 1643 (C=N), 1360, 1149 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.20 (s, 3H, CH_3), 3.70 (s, 2H, SCH_2), 7.20 (s, 1H, NH), 7.40 (d, 1H, arom.), 7.50 (s, 1H, NH), 7.60 (d, 2H, arom.), 8.00 (s, 2H, arom.), 11.50 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{14}Cl_2N_4O_4S_2$: C, 43.14; H, 2.98; N, 11.84. Found: C, 43.20; H, 2.84; N, 10.97%.

*4-Chloro-N-(3,4-dihydro-4-oxoquinazolin-2-yl)-5-methyl-2-propargylthiobenzenesulfonamide (**39**)*: Starting from **14** (0.68 g) and methyl 2-aminobenzoate (0.33 g), the title compound **39** was obtained. Yield: 0.45 g, 54%, mp 214°C–216°C; IR ν_{max} (KBr)/cm^{-1} 3275 (C≡CH), 3211, 3091 (NH), 2926 (CH_3, CH_2), 1696 (C=O), 1633 (C=N), 1381, 1136 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.20 (s, 3H, CH_3), 3.10 (s, 1H, C≡CH), 4.00 (s, 2H, SCH_2), 7.37 (t, 1H, arom.), 7.55 (d, 1H, arom.), 7.65 (s, 1H, arom.), 7.77 (t, 1H, arom.), 8.00 (s, 1H, arom.), 11.40 (s, 1H, NH), 11.85 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_3S_2$: C, 51.49; H, 3.36; N, 10.01. Found: C, 51.02; H, 3.21; N, 9.21%.

*4-Chloro-N-(7-chloro-3,4-dihydro-4-oxoquinazolin-2--yl)-5-methyl-2-propargylthiobenzenesulfonamide (**40**)*: Starting from **14** (0.68 g) and methyl 2-amino-4-chlorobenzoate (0.41 g), the title compound **40** was obtained. Yield: 0.17 g, 26%, mp 219°C–221°C; IR ν_{max} (KBr)/cm^{-1} 3441, 3310 (NH), 3191 (C≡CH), 2924, 2853 (CH_3, CH_2), 1688 (C=O), 1642 (C=N), 1358, 1138 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.40 (s, 3H, CH_3), 3.15 (s, 1H, C≡CH), 3.95 (s, 2H, SCH_2), 7.38 (d, 1H, arom.), 7.65 (d, 2H, arom.), 8.00 (t, 2H, arom.), 11.45 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3S_2$: C, 47.58; H, 2.88; N, 9.25. Found: C, 47.50; H, 2.82; N, 9.26%.

*4-Chloro-N-(3,4-dihydro-4-oxoquinazolin-2-yl)-5-methyl-2-(2-phenylsulfonylethylthio)benzenesulfonamide (**41**)*: Starting from **15** (0.94 g) and methyl 2-aminobenzoate (0.33 g), the title compound **41** was obtained. Yield: 0.18 g, 34%, mp 207°C–209°C; IR ν_{max} (KBr)/cm^{-1} 3242, 3165, 3064 (NH), 2924 (CH_3, CH_2), 1699 (C=O), 1631 (C=N), 1364, 1337, 1149, 1116 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.40 (s, 3H, CH_3), 3.20 (t, 2H, SCH_2), 3.45 (t, 2H, SCH_2), 7.20–8.00 (m, 11H, arom.), 11.40 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{20}ClN_3O_5S_3$: C, 50.22; H, 3.66; N, 7.64. Found: C, 50.01; H, 3.32; N, 6.78%.

*4-Chloro-N-(7-chloro-3,4-dihydro-4-oxoquinazolin-2-yl)-5-methyl-2-(2-phenylsulfonylethylthio)benzenesulfonamide (**42**)*: Starting from **15** (0.94 g) and methyl 2-amino-4-chlorobenzoate (0.41 g), the title compound **42** was obtained. Yield: 0.30 g, 25%, mp 237°C–240°C; IR ν_{max} (KBr)/cm^{-1} 3436, 3189, 3067 (NH), 2924 (CH_3, CH_2), 1687 (C=O), 1640 (C=N), 1357, 1148 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.40 (s, 3H, CH_3), 3.20 (t, 2H, SCH_2), 3.45 (t, 2H, SCH_2), 7.30–8.10 (m, 11H, arom.), 11.50 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{19}Cl_2N_3O_5S_3$: C, 47.26; H, 3.28; N, 7.19. Found: C, 47.20; H, 3.32; N, 7.30%.

*General procedure for the preparation of 2-(R^2-methylthio)-N-(2-benzoxazolyl)-4-chloro-5-methylbenzenesulfonamide derivatives (**43–49**)*: To a suspension of corresponding *N*-(benzenesulfonyl)cyanamide potassium salt **8, 13–15** (2 mmol) in glacial acetic acid (6 mL) the equimolar amount of the appropriate 2-aminophenol (2 mmol) or 2-aminothiophenol (2 mmol) was added and the reaction mixture was stirred for 6–7 h at reflux, then 12 h at room temperature. After cooling to 10°C, the precipitate was collected by filtration, washed with cold acetic acid and dried. Crude product was purified by crystallization from ethanol or extraction of contaminations with hot ethanol.

N-(2-Benzoxazolyl)-2-carbamoylmethylthio-4-chloro-5-methylbenzenesulfonamide (***43***): Starting from **8** (0.72 g) and 2-aminophenol, the title compound **43** was obtained. Yield: 0.38 g, 45%, mp 124°C–125°C; IR ν_{max} (KBr)/cm^{-1} 3430 (NH), 2923 (CH_3, CH_2), 1642 (C=O), 1624 (C=N), 1344, 1115 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.38 (s, 3H, CH_3), 3.72 (s, 2H, SCH_2), 7.25 (t, 2H: 1H, arom., 1H, NH_2), 7.32 (t, 1H, arom.), 7.37 (d, 1H, arom.), 7.55 (t, 2H: 1H, arom., 1H, NH_2), 7.63 (s, 1H, arom.), 8.00 (s, 1H, arom.), 12.90 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{14}ClN_3O_4S_2$: C, 46.66; H, 3.43; N, 10.20. Found: C, 46.33; H, 3.05; N, 9.87%.

N-(2-Benzothiazolyl)-2-carbamoylmethylthio-4-chloro-5-methylbenzenesulfonamide (***44***): Starting from **8** (0.72 g) and 2-aminothiophenol, the title compound **44** was obtained. Yield: 0.35 g, 41%, mp 212°C–215°C; IR ν_{max} (KBr)/cm^{-1} 3375, 3164 (NH, NH_2), 2976, 2920, 2785 (CH_3, CH_2), 1606 (C=O), 1318, 1145 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.40 (s, 3H, CH_3), 3.70 (s, 2H, SCH_2), 7.20–8.00 (m, 8H: 6H, arom., 2H, NH_2), 13.30 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S_3$: C, 44.91; H, 3.30; N, 9.82. Found: C, 44.71; H, 3.20; N, 9.35%.

*2-Allylthio-N-(2-benzoxazolyl)-4-chloro-5-methylbenzenesulfonamide (**45**)*: Starting from **13** (0.68 g) and 2-aminophenol, the title compound **45** was obtained. Yield: 0.36 g, 47%, mp 140°C–142°C; IR ν_{max} (KBr)/cm^{-1} 3448, 3302 (NH), 3084 (C=CH_2), 2923 (CH_3, CH_2), 1644 (C=N), 1366, 1145 (SO_2); ^{1}H NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3), 3.77 (d, 2H, SCH_2), 5.00–5.05 (d, 1H, CH_2), 5.15–5.20 (d, 1H, CH_2), 5.65–5.75 (m, 1H, CH), 7.27 (t, 1H, arom.), 7.35 (t, 1H, arom.), 7.39 (d, 1H, arom.), 7.53

(d, 2H, arom.), 8.00 (s, 1H, arom.), 12.80 (br s, 1H, NH). Anal. Calcd. for $C_{17}H_{15}ClN_2O_3S_2$: C, 51.71; H, 3.83; N, 7.09. Found: C, 51.61; H, 3.74; N, 7.01%.

*2-Allylthio-N-(2-benzothiazolyl)-4-chloro-5-methylbenzenesulfonamide (**46**)*: Starting from **13** (0.68 g) and 2-aminothiophenol, the title compound **46** was obtained. Yield: 0.41 g, 50%, mp 165°C–168°C; IR ν_{max} (KBr)/cm^{-1} 3449 (NH), 3101 (C=CH$_2$), 2975, 2916 (CH$_3$, CH$_2$), 1314, 1146 (SO$_2$); ^{1}H NMR δ (DMSO-d$_6$) 2.40 (s, 3H, CH$_3$), 3.74 (d, 2H, SCH$_2$), 5.00–5.05 (dd, 2H, C=CH$_2$), 5.62–5.84 (m, 2H, C=CH), 7.20–7.45 (m, 3H, arom.), 7.50 (s, 1H, arom.), 7.81 (d, 1H, arom.), 7.94 (s, 1H, arom.), 13.22 (br s, 1H, NH). Anal. Calcd. for $C_{17}H_{15}ClN_2O_2S_3$: C, 49.68; H, 3.68; N, 6.82. Found: C, 49.72; H, 3.61; N, 6.78%.

*N-(2-Benzoxazolyl)-4-chloro-5-methyl-2-propargyl thiobenzenesulfonamide (**47**)*: Starting from **14** (0.68 g) and 2-aminophenol, the title compound **47** was obtained. Yield: 0.37 g, 47%, mp 140°C–142°C; IR ν_{max} (KBr)/cm^{-1} 3374, 3261 (NH), 3091 (C≡CH), 2938 (CH$_3$, CH$_2$), 1648 (C=N), 1303, 1164 (SO$_2$); ^{1}H NMR δ (DMSO-d$_6$) 2.40 (s, 3H, CH$_3$), 3.15 (s, 1H, C≡CH), 3.97 (d, 2H, SCH$_2$), 7.26 (t, 1H, arom.), 7.35 (t, 1H, arom.), 7.37 (d, 1H, arom.), 7.53 (d, 1H, arom.), 7.61 (s, 1H, arom.), 8.02 (s, 1H, arom.), 12.90 (s, 1H, arom.), 12.90 (br s, 1H, NH). Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S_2$: C, 51.97; H, 3.34; N, 7.13. Found: C, 52.07; H, 3.23; N, 6.96%.

*N-(2-Benzoxazolyl)-4-chloro-5-methyl-2-(2-phenylsulfonylethylthio)benzenesulfonamide (**48**)*: Starting from **15** (0.94 g) and 2-aminophenol, the title compound **48** was obtained. Yield: 0.39 g, 37%, mp 193°C–195°C; IR ν_{max} (KBr)/cm^{-1} 3436, 3062 (NH), 2928 (CH$_3$, CH$_2$), 1640 (C=N), 1313, 1155 (SO$_2$); ^{1}H NMR δ (DMSO-d$_6$) 2.38 (s, 3H, CH$_3$), 3.21 (t, 2H, CH$_2$), 3.49 (t, 2H, CH$_2$), 7.26 (t, 1H, arom.), 7.32 (t, 1H, arom.), 7.37 (d, 1H, arom.), 7.47 (s, 1H, arom.), 7.52 (d, 1H, arom.), 7.65 (t, 2H, arom.), 7.76 (d, 1H, arom.), 7.86 (d, 2H, arom.), 8.20 (s, 1H, arom.), 12.80 (br s, 1H, NH). Anal. Calcd. for $C_{22}H_{19}ClN_2O_5S_3$: C, 50.52; H, 3.66; N, 5.36. Found: C, 50.28; H, 3.43; N, 5.18%.

*N-(2-Benzothiazolyl)-4-chloro-5-methyl-2-(2-phenylsulfonylethylthio) benzenesulfonamide (**49**)*: Starting from **15** (0.94 g) and 2-aminothiophenol, the title compound **49** was obtained. Yield: 0.68 g, 64%, mp 212°C–215°C; IR ν_{max} (KBr)/cm^{-1} 3449, 3102 (NH), 2919 (CH$_3$, CH$_2$), 1546 (C=N), 1320, 1151 (SO$_2$); ^{1}H NMR δ (DMSO-d$_6$) 2.40 (s, 3H, CH$_3$), 3.20 (t, 2H, CH$_2$), 3.50 (t, 2H, CH$_2$), 7.32 (m, 4H, arom.), 7.58–7.90 (m, 6H, arom.), 7.95 (s, 1H, arom.), 13.30 (br s, 1H, NH). Anal. Calcd. for $C_{22}H_{19}ClN_2O_4S_4$: C, 49.01; H, 3.55; N, 5.20. Found: C, 49.09; H, 3.65; N, 5.37%.

Biology

Anti-bacterial activity

The investigation was carried out on 26 strains of anaerobic bacteria isolated from the oral cavity, respiratory tract and intestinal tract, as well as five standard strains. The anaerobes belonged to the following genera: *Peptostreptococcus* (2 strains), *Finegoldia* (2), *Micromonas* (1), *Actinomyces* (2), *Propionibacterium* (3), *Prevotella* (6), *Porphyromonas* (2), *Fusobacterium* (4), *Bacteroides* (4) and standard strains: *Bacteroides fragilis* ATCC 25285, *Finegoldia magna* ATCC 29328, *Fusobacterium nucleatum* ATCC 25586, *Peptostreptococcus anaerobius* ATCC 27337 and *Propionibacterium acnes* ATCC 11827. The susceptibility of the anaerobic bacteria was determinated by means of the plate dilution technique in Brucella agar supplemented with 5% sheep blood[23–25]. The compounds were dissolved in 1 mL of DMSO immediately before the experiment. Further dilutions were performed in sterile distilled water. The following concentrations of the compounds were used: 200, 100, 50, 25, 12.5 and 6.2 μg/mL. Metronidazole was applied as a reference substance. The inoculum containing 10^5 CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and compound-free ones were incubated in anaerobic jars for 48 h at 37°C in 10% CO_2, 10% H_2 and 80% N_2 atmosphere with palladium catalyst and indicator of anaerobiosis.

Aerobic bacteria (25 strains) were isolated from the oral cavity, respiratory tract and intenstinal tract as well as 5 standard strains. The bacteria were as follows: *Staphylococcus* (6), *Enterococcus* (3), *Corynebacterium* (2), *Klebsiella* (1), *Acinetobacter* (2), *Escherichia* (3), *Citrobacter* (2), *Pseudomonas* (5), *Serratia* (2), as well as standard strains: *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* ATCC 13883, *Acinetobacter baumannii* ATCC 19606 and *Escherichia coli* ATCC 25922. Amikacin was used as a reference compound. The susceptibility of the aerobic bacteria was determined by means of agar dilution technique with Mueller–Hinton agar[24–26]. Further dilutions were performed in sterile distilled water. The following concentrations of the derivatives were used: 200, 100, 50, 25, 12.5 and 6.2 μg/mL. The inoculum containing 10^5 CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and compound-free ones were incubated for 24 h at 37°C in aerobic conditions. The minimal inhibitory concentration (MIC) was defined as the lowest compound concentration, which inhibited growth of bacteria.

Results and discussion

Chemistry

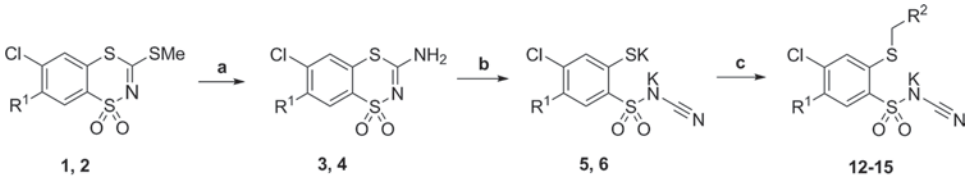
The starting 3-methylthiobenzodithiazines **1**[27], **2**[28], 3-aminobenzodithiazine **4**[29], dipotassium salt **6**[29] and *N*-(benzenesulfonyl)cyanamide potassium salts **7–11**[2,4,29] were prepared according to the known methods. The novel substrates **3** and **5** were prepared analogously and the corresponding *N*-[4-chloro-5-R^1-2-(R^2-methylthio) benzenesulfonyl]cyanamide potassium salts **12–15** (Scheme 1).

It is well known that, various 2,5-disubstituted 1,3,4-thiadiazole can be prepared in good yields by the reaction of methyl *N*-[bis(methylthio)methylene]carbamate with

either alkyl hydrazinecarbodithioates or 1-substuited thiosemicarbazides[30].

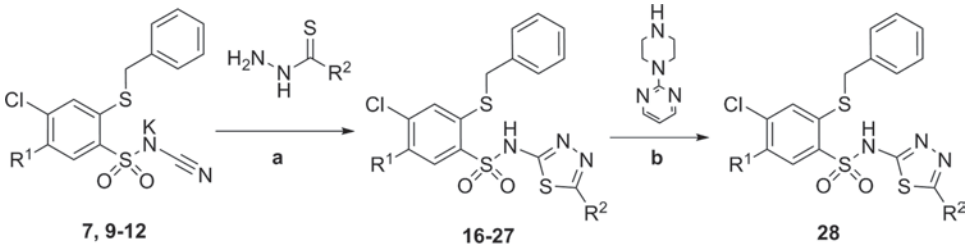
In the present study, we utilized the new method for the synthesis of 2-substituted 1,3,4-thiadiazol-2-yl derivatives **16–24** consisting in the reaction of *N*-(benzenesulfonyl) cyanamide potassium salts **7, 9–12** with either methyl- or benzyl- hydrazinecarbodithioates in boiling glacial acetic acid (Scheme 2). On the other hand, treatment of **7** with pyrrolidine-, morpholine- or 4-phenylpiperazine-1-carbothiohydrazide afforded the target thiadiazole derivatives **25–27** in 19%–59% yields. As was presented on Scheme 2 (*route B*), compound **28** could be obtained by the direct substitution of methylthio group in position 5 of **16** with 2-(piperazin-1-yl)pyrimidine in boiling dry toluene for 56 h.

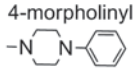
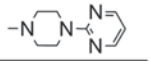
The synthesis of 4-chloro-*N*-(3,4-dihydro-4-oxothieno[2,3-*e*]pyrimidin-2-yl)-5-methylbenzenesulfonamides (**30–33**) was achieved *via* cyclization of *N*-(benzenesulfonyl)cyanamide potassium salt **8, 13–15** with methyl 3-aminothiophene-2-carboxylate, whereas desired4-chloro-*N*-(3,4-dihydro-4-oxoquinazolin-2-yl)-5-methylbenzenesulfonamides (**37–42**) were obtained from potassium salts **8**, **14**, **15** and methyl 2-aminobenzoate or methyl 2-amino-4-chlorobenzoate (Scheme 3). An analogous reaction of **8**, **13–15** with 2-aminophenol or 2-aminothiophenol guided to series of *N*-(2-benzoxazolyl- or



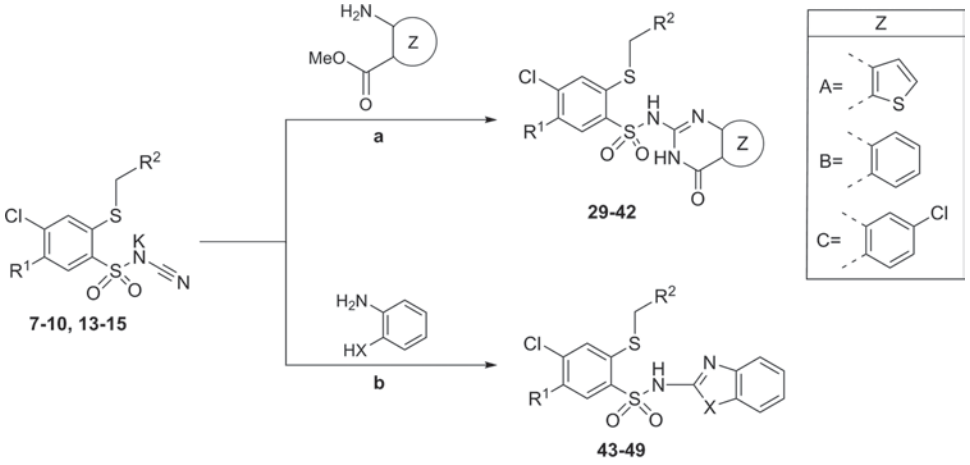
Compds	R^1	R^2
1, 3, 5, 12	CO_2Me	Ph
2, 4, 6, 13	Me	$CH{=}CH_2$
2, 4, 6, 14	Me	$C{\equiv}CH$
2, 4, 6, 15	Me	CH_2SO_2Ph

Scheme 1. Synthesis of *N*-[4-chloro-5-R^1-2-(R^2-methylthio)benzenesulfonyl]cyanamide potassium salts (**12–15**). Reagents, conditions and yields: (A) 25% NH_4OH / EtOH (1.1 molar equiv.) r.t. 44 h, 73%; (B) anhydrous K_2CO_3 (excess), dry THF, reflux 24 h, 68%–74%; (C) R^2-CH_2-X (1.0–1.1 molar equiv.) (X = Br or Cl), water, r.t., 1-2 h, 80%–98%.



Compounds	R^1	R^2
7, 16	Me	SMe
7, 17	Me	SCH_2Ph
9, 18	PhNHCO	SMe
9, 19	PhNHCO	SCH_2Ph
10, 20	4-ClPhNHCO	SMe
10, 21	4-ClPhNHCO	SCH_2Ph
11, 22	4-MePhNHCO	SMe
11, 23	4-MePhNHCO	SCH_2Ph
12, 24	CO_2Me	SMe
7, 25	Me	1-pyrrolidinyl
7, 26	Me	4-morpholinyl
7, 27	Me	
16, 28	Me	

Scheme 2. Synthesis of 2-benzylthio-4-chlorobenzenesulfonamide derivatives (**16–28**). Reagents and conditions: (A) appropriate hydrazinecarbodithioic acid esters or 1-substituted carbothioic acid hydrazides (1 molar equiv.), glacial acetic acid, reflux 8–40 h; (B) **16** (1 mmol), 2-(piperazin-1-yl)pyrimidine (4.5 mmol), dry toluene, reflux 56 h.



Compounds	R^1	R^2	Z	X	
7, 29	Me	Ph	A		Ref. [9]
8, 30	Me	$CONH_2$	A		
13, 31	Me	$CH{=}CH_2$	A		
14, 32	Me	C≡CH	A		
15, 33	Me	CH_2SO_2Ph	A		
7, 34	Me	Ph	B		Ref. [9]
9, 35	PhNHCO	Ph	B		Ref. [9]
10, 36	4-ClPhNHCO	Ph	B		Ref. [9]
8, 37	Me	$CONH_2$	B		
8, 38	Me	$CONH_2$	C		
14, 39	Me	C≡CH	B		
14, 40	Me	C≡CH	C		
15, 41	Me	CH_2SO_2Ph	B		
15, 42	Me	CH_2SO_2Ph	C		
8, 43	Me	$CONH_2$		O	
8, 44	Me	$CONH_2$		S	
13, 45	Me	$CH{=}CH_2$		O	
13, 46	Me	$CH{=}CH_2$		S	
14, 47	Me	C≡CH		O	
15, 48	Me	CH_2SO_2Ph		O	
15, 49	Me	CH_2SO_2Ph		S	

Scheme 3. Synthesis of 4-chloro-2-mercaptobenzenesulfonamide derivatives (**29–49**). Reagents and conditions: (A) *ortho*-aminocarboxylate component (1.0–1.1 molar equiv.), glacial acetic acid, reflux 15 h and 12 h at r.t. or reflux 14–17 h; (B) 2-aminophenol or 2-aminothiophenol (1 molar equiv.), glacial acetic acid, reflux 6–7 h, then 12 h r.t.

2-benothiazolyl)-4-chloro-5-methylbenzenesulfonamides (**43–49**) in 37%–64% yields.

The structure of the new compounds synthesized was confirmed by elemental analyses (C, H, N) and spectroscopic data presented in the material and methods section.

Biology

Anti-bacterial effect

The susceptibility of anaerobic and aerobic bacteria towards compounds **16–26**, **28–33**, **38–40** and **43–49** was shown in Tables 1 and 2. Twenty-six compounds exhibited anti-bacterial activity against 3–23 (12%–88%) strains of anaerobic bacteria at tested concentrations ranged from 6.2 to 100 μg/mL. Compounds **16**, **17** and **24** showed high activity towards the tested bacteria and inhibited, respectively, 23, 19, 13 (88%, 73%, 50%) strains at concentrations in the range of 6.2 to 100 μg/mL. On the other hand, among all the compounds, only **16** and **17** were more active against Gram-negative strains then Gram-positive. In series of *N*-(1,3,4-thiadiazol-2-yl) benzenesulfonamides, relatively low activity presented **20**, **22** with inhibition 6 (23%) strains of anaerobic bacteria at 6.2–50 μg/mL range. However, considering the activity at low concentrations, these compounds (**20, 22**) is interesting because of the inhibition of grows of four strains at concentration 6.2 μg/mL for each of them. It is worth noting that all *N*-(3,4-dihydro-4-oxothieno[2,3-*e*] pyrimidin-2-yl)benzenesulfonamides (**29–33**) presented moderate antibacterial activity (23%–46% strains of anaerobic bacteria in the range of 6.2–100 μg/mL) wherein **31** inhibited the growth of six bacteria strains at low concentration 6.2 μg/mL. Among the series of *N*-(3,4-dihydro-4-oxoquinazolin-2-yl)benzenesulfonamides, only three compounds (**38–40**) demonstrated activity against Gram-positive bacteria, inhibiting the growth of four to five (15%–19%) strains in range from 6.2 to 100 μg/mL. All *N*-(2-benzoxazolyl)- and *N*-(2-benzothiazolyl) benzenesulfonamides (**43–49**) exhibited influence on anaerobic bacteria that corresponded to three to seven (12%–27%) strains at concentrations 6.2–100 μg/mL. It should be emphasized that compound **48** showed

Table 1. Minimal inhibitory concentration (MIC μg/mL) of test compounds **16–24, 26, 28–33**.

	M†	16	17	18	19	20	21	22	23	24	26	28	29	30	31	32	33
Anaerobic bacteria																	
Gram-positive:																	
Peptostreptococcus anaerobius	≤ 0.4	NT	NT	50	25	≤ 6.2	50	≤ 6.2	≤ 6.2	50	25	≤ 6.2	25	50	≤ 6.2	≤ 6.2	≤ 6.2
Finegoldia magna	≤ 0.4	≤ 6.2	≤ 6.2	50	50	12.5	50	25	≤ 6.2	50	100	50	25	≤ 6.2	≤ 6.2	≤ 6.2	≤ 6.2
Micromonas micros	0.8	50	25	50	25	≤ 6.2	*	≤ 6.2	100	50	*	*	50	*	≤ 6.2	100	*
Actinomyces viscosus	6.2	NT	NT	50	*	12.5	*	≤ 6.2	*	50	25	50	50	≤ 6.2	≤ 6.2	12.5	≤ 6.2
Actinomyces odotolyticus	3.1	NT	NT	*	*	*	*	*	*	50	NT	NT	50	NT	NT	NT	NT
Actinomyces israelii	≥ 100	100	50	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Propionibacterium acnes	≥ 100	100	*	*	*	25	*	≤ 6.2	*	*	*	*	50	*	*	100	*
Propionibacterium granulosum	≥ 100	NT	NT	*	*	*	*	*	*	50	NT	NT	50	NT	NT	NT	NT
Gram-negative:																	
Prevotella bivia	≤ 0.4	100	100	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Prevotella buccalis	≤ 0.4	100	25	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Prevotella intermedia	≤ 0.4	100	100	*	*	*	*	*	*	100	*	*	*	*	*	*	*
Prevotella loescheii	≤ 0.4	*	25	*	*	*	*	*	*	50	*	*	*	*	*	*	*
Porphyromonas asaccharolytica	≤ 0.4	100	25	*	*	*	*	*	*	50	*	*	*	*	*	*	*
Fusobacterium nucleatum	≤ 0.4	*	100	*	*	*	*	*	100	50	*	*	*	*	*	*	*
Fusobacterium necrophorum	≤1.6	100	*	*	*	*	*	*	100	100	*	*	*	*	*	*	*
Bacteroides fragilis	≤ 0.4	100	100	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Bacteroides ureolyticus	≤6.2	100	50	*	*	*	*	*	100	*	*	*	50	*	*	*	*
Bacteroides vulgatus	≤ 0.4	NT	NT	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Aerobic bacteria																	
Gram-positive:	A‡																
Staphylococcus aureus	6.2	*	*	50	≤ 6.2	12.5	≤ 6.2	≤ 6.2	12,5	25	*	*	*	*	100	*	*
*Staphylococcus epidermidis*ot	6.2	NT	NT	*	*	*	*	*	*	100	*	*	*	*	*	100	*
Enterococcus faecalis	25	NT	NT	≤ 6.2	50	≤ 6.2	*	*	*	25	*	*	*	*	*	100	*
Corynebacterium spp.	50	*	*	25	*	*	25	*	≤ 6.2	*	*	*	*	*	*	≤ 6.2	*

†**M** – Metronidazole (Fluka); ‡**A** – Amikacin (Fluka); *MIC ≥ 200.
NT, not tested.

Table 2. Minimal inhibitory concentration (MIC μg/mL) of test compounds **38–40, 43–49**.

	M†	38	39	40	43	44	45	46	47	48	49
Anaerobic bacteria											
Gram-positive											
Peptostreptococcus anaerobius	≤ 0.4	100	≤ 6.2	50	25	≤ 6.2	≤ 6.2	50	*	≤ 6.2	≤ 6.2
Finegoldia magna	≤ 0.4	≤ 6.2	≤ 6.2	50	25	50	≤ 6.2	50	*	≤ 6.2	≤ 6.2
Micromonas micros	0.8	100	50	*	25	25	100	*	100	≤ 6.2	100
Actinomyces viscosus	6.2	100	12.5	*	50	≤ 6.2	50	12.5	50	≤ 6.2	≤ 6.2
Aerobic bacteria											
Gram-positive	A‡										
Staphylococcus aureus	6.2	*	*	*	*	*	*	*	50	*	*
Corynebacterium spp.	50	*	*	*	*	*	*	*	*	50	*

†**M** – Metronidazole (Fluka); ‡**A**– Amikacin (Fluka); *MIC ≥ 200NT, not tested.

(inhibition up) activity against to seven strains at low concentrations (6.2–12.5 μg/mL), while **45** and **49** suppressed three strains at above conditions.

Gram-negative anaerobic bacteria were less susceptible to the tested compounds. Only **16**, **17**, **23**, **24** and **29** inhibited the growth of 2–14 (12–82%) strains of these bacteria at concentrations 25–100 μg/mL (Table 1). Compound **16** was the most active derivative and acted on 14 strains at 100 μg/mL, while **17** inhibited 12 strains in the range of 25–100 μg/mL. Other three derivatives (**23**, **24**, **29**) had reduced activity on two to six strains in range from 50 to 100 μg/mL.

Some of the tested compounds demonstrated the same or better anti-bacterial activity than reference drugs (Tables 1, 2). Against *Actinomyces israelii* strains, **16** showed comparable activity to that displayed by metronidazole, whereas **17** demonstrated higher activity than reference drug. The higher activity against *Propionibacterium acnes* that was displayed by the metronidazole showed **20**, **22** and **29**, while **29** was also more active than reference substance against *Propionibacterium granulosum*. Comparably metronidazole activity against *Actinomyces viscosus* was demonstrated by **22**, **30**, **31**, **33**, **44**, **48** and **49.**

Activity towards aerobes was shown for 11 compounds, which acted against 1-8 (4-32%) strains, at concentrations ranged from 6.2 to 100 μg/mL. In series of *N*-(1,3,4-thiadiazol-2-yl)benzenesulfonamides, seven compounds (**18–24**) demonstrated anti-bacterial activity (three to eight strains at tested concentration range). The highest activity was exhibited by **18** with inhibition of eight (30%) strains at tested concentrations. All tested compounds had no anti-bacterial activity against Gram-negative aerobic bacteria.

Summing up, the following structure–activity relationship (SAR) can be drawn by considering data of Tables 1 and 2:

1. Anaerobic bacteria strains were susceptible to the compounds (**16–26, 28–33, 38–40** and **43–49**) in the following order: *N*-(1,3,4-thiadiazol-2-yl)- (**16–24, 26, 28**) > *N*-(3,4-dihydro-4-oxothieno[2,3-*e*]pyrimidin-2-yl)- (**29–33**) > *N*-benzoxazol-2-yl- (**43, 45, 47, 48**) > *N*-benzothiazol-2-yl- (**44, 46, 49**) > *N*-(3,4-dihydro-4-oxoquinazolin-2-yl)- (**38–40**) benzenesulfonamide derivatives (Tables 1, 2).
2. The activity towards anaerobic strains depended on both, the nature of substituents at the 5 position of benzenesulfonamide and substitution pattern of heterocyclic ring attached to the nitrogen atom of sulfonamide moiety. Thus, replacement of methylthio (R^2 = MeS) group in active **16** by either benzylthio ($PhCH_2S$) group (**17**), 4-morpholinyl (**26**) or 4-(pyrimidin-2-yl)piperazinyl (**28**) groups led to the decrease of activity, whereas introduction of 1-pyrrolidinyl (**25**) or 4-phenylpiperazinyl (**27**) moieties in this position resulted in the loss of activity. On the other hand, introducing of methoxycarbonyl group ($R^1 = CO_2Me$) (**24**) instead of methyl group (R^1 = Me) in benzene ring (**16**) resulted in lower activity by 40% (Table 1).
3. The activity against aerobic bacteria strains depended mainly on the electronic nature of substituents at the 5 position of the benzene ring in the *N*-(1,3,4-thiadiazole)benzenesulfonamide series (**16–28**). The most active compound **18** has an electron-withdrawing *N*-phenylcarbamoyl group (R^1 = PhNHCO), while other active compounds (**20–23**) bearing the similar 4-substituted *N*-phenylcarbamoyl groups inhibited growth of *Staphylococcus aureus* with MIC in the range of 6.2–12.5 μg/mL (Table 1). Most noteworthy is the greater sensitivity of *Enterococcus faecalic* and *Corynebacterium* spp strains to the above-mentioned thiadiazole derivatives (**18, 20, 21** and **23**) in comparison to the reference drug (Amikacin, Table 1).
4. Relatively broadest spectrum of anti-microbial activity (MIC ≤ 200 μg/mL) revealed compounds: **24**, **16** and **17** having 2-benzylthio-4-chloro-*N*-(5-alkylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamide scaffold.
5. Compounds that are *N*-(3,4-dihydro-4-oxoquinazolin-2-yl)benzenesulfonamide derivatives (**34–37**, **41** and **42**) showed no anti-microbial activity in the tested concentration range.

In fact, the molecular mechanism of action of investigated sulfonamides has not been elucidated. However, it seems probably that it is similar to the mechanism of action of other anti-bacterial sulfonamides and is associated with inhibition of bacterial enzymes which synthesize folic acid, essential for the production of purines, pyrimidines and amino acids[31].

Anti-proliferative effect

Compounds **16**, **17**, **21** and **27** have also been tested *in vitro* at the National Cancer Institute (Bethesda MD, USA) at a single dose (10 μM) in the full NCI 60 cell panel. None of the compounds tested, however, caused strong inhibition of cancer cell growth. The most susceptible were ovarian (IGROV1) and renal (UO-31) carcinoma cell lines whose growth was inhibited in the range of 28%–31% for compound **27**.

Conclusion

We have demonstrated that the reactions of *N*-(benzenesulfonyl)cyanamide potassium salts with either alkyl hydrazinecarbodithioates or appropriate 1-substituted carbothioic acid hydrazides led to the formation of the corresponding *N*-(5-substituted-1,3,4-thiadiazol-2-yl)benzenesulfonamide derivatives (**16–27**). Furthermore, treatment of *N*-(benzenesulfonyl)cyanamide potassium salts in boiling glacial acetic acid with nucleophiles involving methyl 3-aminothiophene-2-carboxylate, methyl 2-aminobenzoates, 2-aminophenol or 2-aminothiophenol furnished the corresponding *N*-(3,4-dihydro-4-oxothieno[2,3-*e*]pyrimidin-2-yl) (**30–33**), *N*-(3,4-dihydro-4-oxoquinazolin-2-yl) (**37–42**) and *N*-(2-benzoxazolyl- or 2-benothiazolyl)benzenesulfonamide (**43–49**) derivatives, respectively.

Most of the compounds exhibited anti-bacterial activity. Among them, compounds **16**, **17**, **23** and **24** (active mainly against anaerobes) seem to be promising lead structures for further investigation in search for better anti-bacterial activity, while others **18, 20, 21, 22, 29** and **32** are interesting due to better anti-bacterial activities against certain strains as compared to reference drugs.

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Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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