Novel derivatives of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide: synthesis, lipophilicity and *in vitro* antimicrobial activity screening

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SUPPLEMANTARY MATERIALS

Materials and methods

2.1. Chemistry

All reagents used for the experiments in this research were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and used without further purification. They had class of the purity declared by the manufacturer. The purity of the obtained compounds was assessed by means of thin layer chromatography (TLC) on plates covered with silica gel (aluminum oxide 60 F-254) delivered by Merck Co. Chloroform-ethanol mixture in the 10:1 (v/v) ratio was used as the mobile phase. The spots were detected by irradiation with UV light at a wavelength of λ = 254 nm. The FT-IR spectra were recorded on a Nicolet 6700 spectrometer (Thermo Scientific, USA); in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on the Bruker Avance 300 and 600 apparatus (Bruker BioSpin GmbH, Germany). The melting points of the obtained compounds were determined with a Fisher-Johns apparatus (Fisher Scientific, Germany), and presented without any correction. The compounds were dissolved in dimethylsulfoxide (DMSO-d_6) for the analysis. Tetramethylsilane (TMS) was used as an internal standard. Chemical shift values are given in ppm. The elemental analysis was determined by a Perkin Elmer 2400 series II CHNS/O analyzer (Waltham, MA, USA), and the results were within ± 0.4% of the theoretical value.

Detailed physico-chemical properties of new derivatives of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**2**-**16**)

N-[(2-chlorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**2**)

White powder, Yield: 87%, M.p.: 236°C; IR: 3031 (N-H), 2970 (CH, arom.), 2936 (CH, aliph.), 1652 (C=O), 1513 (C=N), 1272, 1045 (C-OC), 1022 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.51-7.54 (m, 1H, ArH), 7.56-7.60 (m, 2H, ArH), 8.13-8.14 (m, 1H, ArH), 8.63 (s, 1H, =CH), 12.56 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 15.47 (CH_3), 127.95, 128.55, 130.61, 131.11, 132.51, 134.02, 135.71 (7C_{ar}), 142.46 (=CH), 160.52 (C_{ar}), 163.88 (C=O). Anal. calc. for $C_{11}H_9ClN_4OS$ (280.73) (%): C 47.06; H 3.23; N 19.96. Found: C 49.25; H 3.31; N 19.50.

N-[(3-chlorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**3**)

White powder, Yield: 86%, M.p.: 204°C; IR: 3024 (N-H), 2970 (CH, arom.), 2840 (CH, aliph.), 1657 (C=O), 1515 (C=N), 1217, 1071 (C-OC), 1022 (N-N); ^{1}H NMR (600 MHz,

DMSO-d_6): 2.98 (s, 3H, CH_3), 7.57-7.59 (m, 2H, ArH), 7.84-7.85 (m, 2H, ArH), 8.21 (s, 1H, =CH), 12.51 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 15.48 (CH_3), 126.44, 127.89, 130.65, 131.53, 134.27, 135.67, 136.02 (7C_{ar}), 144.88 (=CH), 160.53 (C_{ar}), 163.86 (C=O). Anal. calc. for $C_{11}H_9ClN_4OS$ (280.73) (%):C 47.06; H 3.23; N 19.96. Found: C 48.25; H 3.21; N 19.72.

N-[(4-chlorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**4**)

White powder, Yield: 96%, M.p.: 260°C; IR: 3016 (N-H), 2970 (CH, arom.), 2844 (CH, aliph.), 1659 (C=O), 1592 (C=N), 1208, 1085 (C-OC), 1007 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.61-7.62 (d, 2H, ArH, J = 6 Hz), 7.86-7.87 (d, 2H, ArH, J = 6 Hz), 8.22 (s, 1H, =CH), 12.46 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.50 (CH_3), 129.74, 129.87, 132.77, 135.54, 135.78 (7C_{ar}), 145.20 (=CH), 160.52 (C_{ar}), 163.84 (C=O). Anal. calc. for $C_{11}H_9ClN_4OS$ (280.73) (%):C 47.06; H 3.23; N 19.96. Found: C 47.45; H 3.31; N 19.82.

N-[(2-fluorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**5**)

Yellowish powder, Yield: 98%, M.p.: 222°C; IR: 3016 (N-H), 2970 (CH, arom.), 2942 (CH, aliph.), 1739 (C=O), 1513 (C=N), 1217, 1091(C-OC), 1017 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.35-7.38 (m, 1H, ArH), 7.42-7.44 (m, 1H, ArH), 7.55-7.59 (m, 1H, ArH), 8.05-8.08 (m, 1H, ArH), 8.43 (s, 1H, =CH), 12.50 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.48 (CH_3), 116.57, 121.48, 125.87, 127.65, 133.09, 135.74 (6C_{ar}), 139.31 (=CH), 159.71, 160.49 (2C_{ar}), 163.89 (C=O). Anal. calc. for $C_{11}H_9FN_4OS$ (264.28) (%): C 49.99; H 3.43; N 21.20. Found: C 49.25; H 3.51; N 21.50.

N-[(3-fluorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**6**)

White powder, Yield: 80%, M.p.: 240°C; IR: 3016 (N-H), 2970 (CH, arom.), 2935 (CH, aliph.), 1739 (C=O), 1520 (C=N), 1216, 1072 (C-OC), 1021 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.34-7.37 (m, 1H, ArH), 7.58-7.63 (m, 2H, ArH), 7.70-7.71 (d, 1H, ArH, J = 6 Hz), 8.23 (s, 1H, =CH), 12.51 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.49 (CH_3), 114.39, 124.30, 135.72, 136.34, 137.55 (5C_{ar}), 145.10 (=CH), 152.62, 160.58, 161.27 (3C_{ar}), 163.88 (C=O). Anal. calc. for $C_{11}H_9FN_4OS$ (264.28) (%): C 49.99; H 3.43; N 21.20. Found: C 49.45; H 3.53; N 21.56.

N-[(4-fluorophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**7**)

White powder, Yield: 75%, M.p.: 260°C; IR: 3056 (N-H), 2936 (CH, arom.), 2842 (CH, aliph.), 1652 (C=O), 1596 (C=N), 1290, 1092 (C-OC), 1022 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.37-7.40 (t, 2H, ArH, J = 6 Hz, J = 12 Hz), 7.88-7.91 (m, 2H, ArH), 8.21 (s, 1H, =CH), 12.42 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 15.49 (CH_3), 116.66, 130.47, 135.81 (5C_{ar}), 145.29 (=CH), 160.42, 162.96, 163.78 (3C_{ar}), 164.61 (C=O). Anal. calc. for $C_{11}H_9FN_4OS$ (264.28) (%): C 49.99; H 3.43; N 21.20. Found: C 49.75; H 3.56; N 21.57.

N-[(3-ethoxy-4-hydroxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**8**)

Yellow powder, Yield: 79%, M.p.: 170°C; IR: 3405 (N-H), 2970 (CH, arom.), 2940 (CH, aliph.), 1738 (C=O), 1500 (C=N), 1208, 1036 (C-OC), 1015 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 1.35-1.37 (t, 3H, CH_3, J = 6 Hz), 2.98 (s, 3H, CH_3), 4.08-4.11 (q, 2H, CH_2, J = 6 Hz), 6.92-6.93 (d, 1H, ArH, J = 6 Hz), 6.96-6.98 (d, 1H, ArH, J = 12 Hz), 7.37-7.39 (m, 1H, ArH), 8.11 (s, 1H, =CH), 9.76 (s, 1H, OH), 12.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.15 (CH_3), 15.52 (CH_3), 64.21 (CH_2), 111.76, 116.34, 122.74, 125.06, 135.86 (5C_{ar}),

146.67 (=CH), 147.65, 150.12, 160.09 (3C_{ar}), 163.66 (C=O). Anal. calc. for C13H14N4O3S (306.34) (%): C 50.97; H 4.61; N 18.29. Found: C 49.25; H 4.51; N 18.50.

N-[(2-bromo-6-hydroxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**9**)

Yellow powder, Yield: 57%, M.p.: 270°C; IR: 3016 (N-H), 2970 (CH, arom.), 2850 (CH, aliph.), 1739 (C=O), 1595 (C=N), 1217, 1106 (C-OC), 1025 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 6.92-6.93 (d, 1H, ArH, *J* = 6 Hz), 7.46-7.48 (d, 1H, ArH, *J* = 12 Hz), 7.93-7.94 (d, 1H, ArH, *J* = 6 Hz), 8.47 (s, 1H, =CH), 10.60 (s, 1H, OH), 12.42 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 15.47 (CH_3), 111.32, 119.15, 122.51, 128.71, 134.65, 135.71 (6C_{ar}), 141.32 (=CH), 156.62, 160.29 (2C_{ar}), 163.77 (C=O). Anal. calc. for $C_{11}H_9BrN_4O_2S$ (341.18) (%): C 38.72; H 2.66; N 16.42. Found: C 39.15; H 2.51; N 16.52.

N-[(3-iodo-4-hydroxy-5-methoxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**10**)

Yellow powder, Yield: 70%, M.p.: 254°C; IR: 3120 (N-H), 2900 (CH, arom.), 2835 (CH, aliph.), 1652 (C=O), 1570 (C=N), 1274, 1042 (C-OC), 1015 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 7.44-7.45 (d, 1H, ArH, *J* = 6 Hz), 7.70-7.71 (d, 1H, ArH, *J* = 6 Hz), 8.08 (s, 1H, =CH), 10.27 (s, 1H, OH), 12.38 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.52 (CH_3), 75.48 (OCH_3), 110.03, 118.80, 126.98, 135.75, 136.72 (5C_{ar}), 145.20 (=CH), 147.82, 149.31, 160.20 (3C_{ar}), 163.76 (C=O). Anal. calc. for $C_{12}H_{11}IN_4O_3S$ (418.21) (%): C 34.46; H 2.65; N 13.40. Found: C 36.65; H 2.53; N 13.05.

N-[(2-chloro-6-nitrophenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**11**)

Yellowish powder, Yield: 59%, M.p.: 220°C; IR: 3015 (N-H), 2970 (CH, arom.), 2856 (CH, aliph.), 1739 (C=O), 1526 (C=N), 1217, 1050 (C-OC), 1017 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.99 (s, 3H, CH_3), 7.90-7.91 (d, 1H, ArH, *J* = 6 Hz), 8.30-8.32 (d, 1H, ArH, *J* = 12 Hz), 8.62 (s, 1H, =CH), 8.83-8.84 (d, 1H, ArH, *J* = 6 Hz), 12.74 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.47 (CH_3), 111.39, 122.37, 126.17, 132.28, 132.62, 135.49 (6C_{ar}), 140.62 (=CH), 147.32, 160.73 (2C_{ar}), 164.14 (C=O). Anal. calc. for $C_{11}H_8ClN_5O_3S$ (325.73) (%): C 40.56; H 2.48; N 21.50. Found: C 41.25; H 2.51; N 21.59.

N-[(2,3-dimethoxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**12**)

Yellowish powder, Yield: 95%, M.p.: 200°C; IR: 3155 (N-H), 2931 (CH, arom.), 2834 (CH, aliph.), 1656 (C=O), 1575 (C=N), 1267, 1062 (C-OC), 1004 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.21-7.23 (t, 1H, ArH, *J* = 12 Hz), 7.27-7.29 (m, 1H, ArH), 7.39-7.41 (m, 1H, ArH), 8.52 (s, 1H, =CH), 12.87 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.49 (CH_3), 54.86 (OCH_3), 55.68 (OCH_3), 117.96, 125.33, 127.30, 135.85 (4C_{ar}), 142.22 (=CH), 147.46, 148.90, 153.23, 160.08, 160.37 (4C_{ar}), 163.76 (C=O). Anal. calc. for $C_{13}H_{14}N_4O_3S$ (306.34) (%): C 50.97; H 4.61; N 18.29. Found: C 53.25; H 4.51; N 18.40.

N-[(2,4-dimethoxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**13**)

Yellow powder, Yield: 96%, M.p.: 248°C; IR: 2999 (N-H), 2935 (CH, arom.), 2835 (CH, aliph.), 1664 (C=O), 1599 (C=N), 1209, 1099 (C-OC), 1026 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.68-6.69 (d, 1H, ArH, *J* = 6 Hz), 6.76-6.78 (m, 1H, ArH), 7.91-7.92 (d, 1H, ArH, *J* = 6 Hz), 8.47 (s, 1H, =CH),

12.31 (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 15.50 (CH_3), 56.02 (OCH_3), 56.38 (OCH_3), 98.82, 107.46, 114.66, 128.11, 130.28, 135.96 ($6C_{ar}$), 142.11 (=CH), 160.08, 163.41 ($2C_{ar}$), 163.58 (C=O). Anal. calc. for $C_{13}H_{14}N_4O_3S$ (306.34) (%): C 50.97; H 4.61; N 18.29. Found: C 49.95; H 4.55; N 18.66.

N-[(3,4-dimethoxyphenyl)methylidene]-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (**14**)

Yellow powder, Yield: 82%, M.p.: 228°C; IR: 3027 (N-H), 2970 (CH, arom.), 2832 (CH, aliph.), 1655 (C=O), 1578 (C=N), 1261, 1132 (C-OC), 1023 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.99 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.10-7.11 (d, 1H, ArH, *J* = 6 Hz), 7.34-7.36 (d, 1H, ArH, *J* = 12 Hz), 7.43-7.44 (d, 1H, ArH, *J* = 6 Hz), 8.14 (s, 1H, =CH), 12.35 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.53 (CH_3), 55.87 (OCH_3), 56.10 (OCH_3), 109.71, 112.22, 122.62, 126.48, 135.82 ($5C_{ar}$), 146.29 (=CH), 149.54, 151.50, 160.21 ($3C_{ar}$), 163.71 (C=O). Anal. calc. for $C_{13}H_{14}N_4O_3S$ (306.34) (%): C 50.97; H 4.61; N 18.29 Found: C 50.05; H 4.53; N 18.50.

4-methyl-*N*-[(5-nitrofuran-2-yl)methylidene]-1,2,3-thiadiazole-5-carbohydrazide (**15**)

Yellow powder, Yield: 96%, M.p.: 246°C; IR: 3143 (N-H), 2942 (CH, aliph.), 1739 (C=O), 1527 (C=N), 1217, 1151 (C-OC), 1017 (N-N); ^{1}H NMR (600 MHz, DMSO-d_6): 2.98 (s, 3H, CH_3), 7.40-7.41 (d, 1H, ArH, *J* = 6 Hz), 7.84-7.85 (d, 1H, ArH, *J* = 6 Hz), 8.14 (s, 1H, =CH), 12.82 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.54 (CH_3), 110.86, 115.03, 117.03, 132.94 ($4C_{ar}$), 135.59 (=CH), 151.11, 161.07 ($2C_{ar}$), 164.04 (C=O). Anal. calc. for $C_9H_7N_5O_4S$ (281.25) (%): C 38.43; H 2.51; N 24.90. Found: C 39.25; H 2.55; N 23.50.

4-methyl-*N*-[(1*H*-pyrrol-2-yl)methylidene]-1,2,3-thiadiazole-5-carbohydrazide (**16**)

Yellow powder, Yield: 85%, M.p.: 250°C; IR: 3366 (N-H), 2826 (CH, aliph.), 1608 (C=O), 1543 (C=N), 1245, 1089 (C-OC), 1036 (N-N); 1H NMR (600 MHz, DMSO-d_6): 2.97 (s, 3H, CH_3), 6.23-6.24 (m, 1H, ArH), 6.68-6.69 (m, 1H, ArH), 7.06-7.07 (m, 1H, ArH), 8.06 (s, 1H, =CH), 11.28 (s, 1H, NH), 12.10 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 15.45 (CH_3), 110.44, 114.25, 123.96, 126.63, 136.29 ($5C_{ar}$), 138.50 (=CH), 159.92 (C_{ar}), 163.31 (C=O). Anal. calc. for $C_9H_9N_5O_4S$ (235.27) (%): C 45.95; H 3.86; N 29.77. Found: C 42.25; H 3.61; N 29.50.

List of reagents.

Compound	Provider	Catalog number	Purity %	CAS number
4-Methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide	Sigma-Aldrich	546399	97	75423-15-3
2-Chlorobenzaldehyde	Sigma-Aldrich	124974	99	89-98-5
3-Chlorobenzaldehyde	Sigma-Aldrich	C23403	97	587-04-2
4-Chlorobenzaldehyde	Sigma-Aldrich	112216	97	104-88-1
2-Fluorobenzaldehyde	Sigma-Aldrich	F4807	97	446-52-6
3-Fluorobenzaldehyde	Sigma-Aldrich	F5005	97	456-48-4
4-Fluorobenzaldehyde	Sigma-Aldrich	128376	98	459-57-4
3-Ethoxy-4-hydroxybenzaldehyde	Sigma-Aldrich	128090	99	121-32-4
5-Bromosalicylaldehyde	Sigma-Aldrich	137286	98	1761-61-1
5-Iodovanillin	Sigma-Aldrich	129488	97	5438-36-8
2-Chloro-5-nitrobenzaldehyde	Sigma-Aldrich	139033	97	6361-21-3
2,3-Dimethoxybenzaldehyde	Sigma-Aldrich	D130206	98	86-51-1
2,4-Dimethoxybenzaldehyde	Sigma-Aldrich	D130400	98	613-45-6
3,4-Dimethoxybenzaldehyde	Sigma-Aldrich	143758	99	120-14-9
5-Nitro-2-furaldehyde	Sigma-Aldrich	170968	99	698-63-5
Pyrrole-2-carboxaldehyde	Sigma-Aldrich	P73404	98	1003-29-8
Ethyl alcohol	Pure P.A BASIC	BA6420113	96	64-17-5

2.3. Lipohilicity

The experimental lipophilicity of new derivatives of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**2-6**, **8-16**) was determined with the use of reversed-phase thin-layer chromatography. on 10×20 cm RP18 F_{254} plates from Merck Co. (Darmstadt, Germany). The chromatograms were developed to a distance of 9 cm from the origin of the plate at temperature of 24 ± 0.5°C, in a horizontal teflon chamber with an eluent distributor (DS Chromdes Lublin, Poland). After developing chromatograms, the spots of the substances were located under ultraviolet illumination at 254 nm. The reference substances (acetaminophen, salicylamide, nitrophenol, ethyl hydroxybenzoate, thymol, phenyl salicylate) were purchased from Sigma-Aldrich (USA). The mobile phases were prepared by mixing appropriate amounts of water and respective polar modifier (50-75% of acetone, 50-75% of acetonitrile, 50-70% of 1,4-dioxane and 60-80% of methanol). All solvents were of analytical grade purity and were purchased from POCh Gliwice (Poland). The new synthesized compounds (**2-6**, **8-16**) and the reference substances with known lipophilicity [1] were dissolved in methanol to obtain the concentrations of 2.0 mg/mL and the volumes of 0.2 μL were applied onto the plates. On the basis of the obtained retardation coefficients (R_F) values, the R_M values were calculated for the references substances as well as for the tested compounds, using a known chromatographic formula:

$$R_M = \log\frac{1-R_F}{R_F}$$

The R_{M0} values equivalent to the retention of the compound extrapolated to pure water as a mobile phase were calculated on the basis of the equation: $R_M = R_{M0} - S\varphi$, where φ was the volume fraction of the organic modifier in the mobile phase. The calculated R_{M0} values for six reference substances were correlated with their log P values and appropriate calibration curves for further lipophilicity estimation (log P_{EXP}) were obtained. Experimental lipophilicity of the synthesized new derivatives of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**2-6**, **8-16**) was calculated on the basis of the obtained calibration equations and their R_{M0} values.

References:

1. Komsta, Ł.; Skibiński, R.; Berecka, A.; Gumieniczek, A.; Radkiewicz, B.; Radoń, M. Revisiting thin-layer chromatography as a lipophilicity determination tool-A comparative study on several techniques with a model solute set. *J. Pharm. Biomed. Anal.* **2010**, *53*, 911–918, doi:10.1016/j.jpba.2010.06.024.