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THE SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF NEW 2-(R-PHENYLIMINO)-1,3-THIAZOLINE DERIVATIVES CONTAINING THE *N*-METHYLPIPERAZINE MOIETY

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Abstract. New derivatives of *N*-(R-phenyl)-3-(4-methyl-1-piperazinyl)-1,3-thiazole-2(3*H*)- imine with the medium to high yields were synthesized by the Hantzsch reaction in the ethanol medium. The structure of target compounds was confirmed by elemental analysis and NMR spectroscopy. The antimicrobial activity of 1,3-thiazoline derivatives with the *N*-methylpiperazine moiety against sulfate-reducing bacteria of *Desulfovibrio* sp. M.4.1 strain was studied. It was found that substances containing the halo- and unsubstituted phenyl fragment in the position 4 of the thiazoline cycle showed the potent antimicrobial activity.

Keywords: 2-(R-phenylimino)-1,3-thiazoline, *N*-methyl-piperazine, Hantzsch synthesis, antimicrobial activity, sulfate-reducing bacteria.

1. Introduction

Metal microbial corrosion is a part of current topical issue – biodegradation, which causes substantial economic loses [1]. At present, the primary role of microorganisms in metal corrosion has been proven. The main agents of the anaerobic corrosion are sulphate-reducing bacteria (SRB), which are responsible for the reduction of sulphates to hydrogen sulphide [2]. A possible solution to the problem of metal construction protection against microbial corrosion is the search of substances with the biocidal activity, which can inhibit the SRB growth.

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The moieties of 2-imino-1,3-thiazoline and *N*-methylpiperazine are important pharmacophores when developing drugs. The antibacterial [3], antifungal [4, 5], anti-inflammatory, analgesic and kinase CDK1 inhibition [6, 7] activities are reported for iminothiazole-containing heterocyles. *N*-methylpiperazine derivatives containing the azole nucleus possess the antifungal [8], anti-tuberculosic [9, 10] and antimicrobial [9] activities.

The nucleus of iminothiazole-containing heterocyles – 2-iminothiazole – is generally prepared by the single-stage reaction of thiourea and α-halocarbonyls where thiourea should be disubstituted at both nitrogen atoms [9-13]. Unsymmetric thioureas can be synthesized from amines. By the reaction of amines with carbon disulfide in ethanol reflux the symmetrical 1,3-disubstituted thioureas can be easily obtained [14], while the unsymmetric thioureas are obtained by the reaction of amines with isothiocyanates [15-18]. Isothiocyanates are obtained from amines by the interaction of triethylamine with different reagents, such as [bis(acetoxy)iodo]benzene or dithiocarbamates [19] in acetonitrile, dithiocarbamates and lead nitrate solution [20] or iodine [21]; carbon disulfide and tosyl chloride [22]. The thiophosgene method is also applied; it involves the interaction of thiophosgene and aromatic amines in dry acetone [23], and in dichloromethane [24].

Our earlier research of new biologically active substances among the derivatives of 2-R-phenylimino-1,3-thiazoline completed successfully. Substances with the analgesic [25, 26], anti-inflammatory [27, 28] activity were protected by the patents of Ukraine. The search for substances with the antioxidant activity among 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives continues [29].

The results obtained prompted us to synthesize new derivatives of 1,3-thiazoline with a fragment of *N*-methyl-piperazine.

The aim of this work was to synthesize a series of 4- and 5-(un)substituted *N*-(R`-phenyl)-3-(4'-methyl-1-

piperazinyl)-1,3-thiazol-2(3*H*)-imine derivatives by the Hantzsch reaction and to study their antimicrobial activity againist sulfate-reducing bacteria of *Desulfovibrio* sp. M.4.1 strain.

2. Experimental

2.1. Chemistry

All solvents were purified before use. *N*-methylpiperazin-N^1-amine, 3-chloropentane-2,4-dione, 3-chlorohexane-2,4-dione were purchased from Acros Organics and used without purification. α-Bromoacetophenones were obtained by bromination of the corresponding acetophenones by standard methods [30-34]. Reactions were monitored by a thin-layer chromatography (TLC) using Fluka silica gel (60F 254) plates (0.25 mm). Visualization was made with the help of UV light. Elemental analysis was performed on a EuroEA 3000 elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Gemini 400 MHz device in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a Varian MR-400 device in DMSO-d_6 using TMS as an internal standard. Chemical shifts were reported in ppm units using δ scale.

2.2. Synthesis

Synthesis of N-(4'-methylpiperazine-1-yl)-N'-(R-phenyl)thioureas **5a-e.** To the suspension of 0.05 mol the corresponding N^1-aryl-*N,N*-dimethylthiourea **3a-e** in 50 ml of dioxane 0.05 mol of *N*-methyl-N^1-aminopiperazine **4** was added. The reaction mixture was refluxed while stirring for 5 h. After cooling the resulting precipitate was filtered, washed with dioxane, and dried. The constants of compounds **5a, 5b, 5d** and **5e** correspond to the literary ones [10].

N-(4-methylpiperazine-1-yl)-N'-(2,3-dimethylphenyl)thiourea **5c** was obtained according to the general method from 10.4 g (0.05 mol) of N^1-(2,3-dimethylphenyl)-*N,N*-dimethylthiourea and 5.76 g (0.05 mol) of *N*-methyl-N^1-aminopiperazine **4**. The yield was 12.4 g (89 %), m.p. 461–462 K (ethanol). Found, %: N = 19.8 $C_{14}H_{22}N_4S$. Calculated, %: N = 20.1. ^{1}H NMR spectrum (DMSO-d_6, TMS): 2.04 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.29 (s, 3H, NCH_3), 2.25+2.70 (m+m, 4H, CH_2NCH_2), 2.84 (m, 4H, CH_2NCH_2), 7.00–7.28 (m, 3H, C_6H_3), 9.01 (s, 1H, NH), 9.28 (s, 1H, NH).

Synthesis of hydrobromide N,4-diphenyl-3-(4'-methylpiperazine-1-yl)-1,3-thiazol-2(3H)-imine **7af.** To the solution of 1.99 g (0.01 mol) of α-bromoacetophenone **6f** in 50 ml ethanol while stirring 2.50 g (0.01 mol) of *N*-(4'-methyl-1-piperazine-1-yl)-*N'*-phenylthiourea **5a** was added and boiled for 2 h. The precipitate formed was filtered, washed with a small amount of ethanol, and dried. The yield was 3.36 g (78 %), m.p. 486–487 K (ethanol). Found, %: N = 13.3, S = 6.21 $C_{20}H_{23}BrN_4S$. Calculated, %: N = 13.0, S = 6.27. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.76 (s, 3H, NCH_3), 2.89 (m, 4H, CH_2NCH_2), 3.31 (m, 4H, CH_2NCH_2), 6.49 (s, 1H, CH), 7.03–7.47 (m, 10H, Ph+NPh), 9.86 (br. s., 1H, HBr). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 43.12, 48.03, 48.05, 52.16, 52.21, 121.3, 122.1, 125.5, 127.2, 128.1, 129.8, 133.5, 133.6, 148.6, 149.7, 156.1.

Hydrobromide 4-[4-(2^1-methyl-2^1-propanyl) phenyl]-3-(4'-methylpiperazine-1-yl)-N-phenyl-1,3-thiazol-2(3H)-imine **7ah** was obtained similarly to hydrobromide **7af** from 2.55 g (0.01 mol) of α-bromo-4-(*t*-butylacetophenone) **6h** and 2.50 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-phenylthiourea **5a.** The yield was 3.71 g (76 %), m.p. 533 K (sublimates) (propanol-2). Found, %: N = 11.7, S = 6.71 $C_{24}H_{31}BrN_4S$. Calculated, %: N = 11.5, S = 6.58. ^{1}H NMR spectrum (DMSO-d6, TMS): 1.19 (s, 9H, $C(CH_3)_3$), 2.80 (s, 3H, CH_3), 2.89 (m, 4H, CH_2NCH_2), 3.34 (m, 4H, CH_2NCH_2), 6.45 (m, 1H, CH), 7.02 and 7.23 (d-d, 4H, C_6H_4), 7.17–7.37 (m, 5H, Ar-H). 9.95 (br. s, 1H, HBr). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 31.15, 34.41, 43.09, 47.90, 48.00, 51.91, 51.95, 121.5, 122.3, 125.6, 126.6, 128.1, 131.3, 133.6, 148.5, 149.6, 156.2.

Hydrobromide 4-(4^1-chlorophenyl)-N-(2,3-dimethylphenyl)-3-(4'-methylpiperazine-1-yl)-1,3-thiazol-2(3H)-imine **7cj** was obtained similarly to hydrobromide **7af** from 2.33 g (0.01 mol) of α-bromo-4-chloroacetophenone **6j** and 2.78 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(2',3'-dimethylphenyl)thiourea **5c.** The yield was 3.75 g (76 %), m.p.= 543 K (ethanol). Found, %: N = 11.4, S = 6.57 $C_{22}H_{26}ClBrN_4S$. Calculated, %: N = 11.3, S = 6.49. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.03 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.79 (s, 3H, NCH_3), 2.95 (m, 4H, CH_2NCH_2), 3.42 (m, 4H, CH_2NCH_2), 6.28 (s, 1H, CH), 6.86–7.12 (m, 3H, C_6H_3), 7.03 and 7.15 (d-d, 4H, C_6H_4), 10.6 (br. s, 1H, HBr). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 13.72, 19.97, 43.21, 48.09, 48.14, 52.23, 52.28, 120.8, 122.2, 122.8, 125.7, 128.4, 129.3, 132.1, 133.6, 134.8, 149.6, 147.2, 156.3.

Hydrobromide 4-(4^1-chlorophenyl)-N-(4^1-ethoxyphenyl)-3-(4'-methylpiperazine-1-yl)-1,3-thiazol-2(3H)-imine **7ej** was obtained similarly to hydrobromide **7af** from 2.33 g (0.01 mol) of α-bromo-4-chloroacetophenone **6j** and 2.94 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(4-ethoxyphenyl)thiourea **5e.** The yield was 4.23 g (83 %), m.p. 502–503 K (ethanol). Found, %: N = 11.2, S = 6.17 $C_{22}H_{26}BrClN_4OS$. Calculated, %: N = 11.0, S = 6.29. ^{1}H NMR spectrum

(DMSO-d6, TMS): 1.30 (t, 3H, CH_3), 2.80 (s, 3H, NCH_3), 2.87 (m, 4H, CH_2NCH_2), 3.35 (m, 4H, CH_2NCH_2), 3.98 (kv, 2H, OCH_2), 6.51 (s, 1H, CH), 6.86 and 7.08 (d-d, 4H, C_6H_4), 7.13 and 7.31 (d-d, 4H, C_6H_4), 9.71 (br. s, 1H, HBr). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 14.97, 43.22, 48.13, 48.18, 51.91, 51.96, 63.59, 114.5, 122.6, 128.4, 128.5, 129.3, 131.9, 132.1, 133.6, 142.8, 148.6, 153.6, 156.2.

Hydrobromide 4-(4^1-bromophenyl)-N-(3-methylphenyl)-3-(4'-methylpiperazine-1-yl)-1,3-thiazol-2(3H)-imine **7bk** was obtained similarly to hydrobromide **7af** from 2.78 g (0.01 mol) of α-bromo-4-bromoacetophenone **6k** and 2.64 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(3-methylphenyl)thiourea **5b.** The yield was 4.30 g (82 %), m.p. 549 K (sublimates) (ethanol). Found, %: N = 10.8, S = 6.24 $C_{21}H_{24}Br_2N_4S$. Calculated, %: N = 10.7, S = 6.12. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.29 (s, 3H, CH_3), 2.80 (s, 3H, NCH_3), 2.97 (m, 4H, -CH_2NCH_2-), 3.45 (m, 4H, CH_2NCH_2), 6.30 (s, 1H, CH), 6.99 and 7.32 (d-d, 4H, C_6H_4), 6.93–7.22 (m, 4H, Ar-H), 10.5 (br. s, 1H, HBr). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 21.46, 43.15, 48.19, 48.23, 52.21, 52.25, 119.3, 119.8, 121.3, 124.0, 128.2, 129.2, 129.3, 131.7, 131.8, 132.0, 133.6, 138.0, 147.4, 148.7, 156.0.

Synthesis of 4-(4'-chlorophenyl)-3-(4'-methylpiperazine-1-yl)-N-phenyl-1,3-thiazol-2(3H)-imine **8aj.** To the solution of 2.33 g (0.01 mol) of α-bromo-4-chloroacetophenone **6j** in 50 ml of ethanol while stirring 2.50 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-phenylthiourea **5a** was added and boiled for 2 h. The reaction mixture was evaporated to the volume of 15–20 ml and neutralized by adding 10 ml of 10% ammonia solution. The precipitate formed was filtered washed with water, and dried. The yield was 2.66 g (69 %), m.p. 471–472 K (heptane). Found, %: N = 14.7, S = 8.46 $C_{20}H_{21}ClN_4S$. Calculated, %: N = 14.6, S = 8.33.^{1}H NMR spectrum (DMSO-d6, TMS): 2.24 (s, 3H, NCH_3), 2.62 (m, 4H, -CH_2NCH_2-), 3.10 (m, 4H, -CH_2NCH_2-), 6.35 (s, 1H, CH), 7.09 and 7.24 (d-d, 4H, C_6H_4), 7.15–7.33 (m, 5H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 43.01, 48.01, 48.07, 52.11, 52.15, 121.4, 121.9, 122.0, 128.2, 128.3, 128.5, 128.6, 129.3, 131.8, 132.1, 133.4, 148.6, 149.8, 156.1.

4-(2^1,4^1-dichlorophenyl)-3-(4'-methylpiperazine-1-yl)-N-phenyl-1,3-thiazol-2(3H)-imine **8al** was obtained similarly to the compound **8aj** from 2.68 g (0.01 mol) of α-bromo-2,4-dichloroacetophenone **6l** and 2.50 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-phenylthiourea **5a.** The yield was 2.81 g (67 %), m.p. 434–435 K (heptane). Found, %: N = 13.6, S = 7.57 $C_{20}H_{20}Cl_2N_4S$. Calculated, %: N = 13.4, S = 7.65. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.19 (s, 3H, NCH_3), 2.65 (m, 4H, CH_2NCH_2), 3.16 (m, 4H, CH_2NCH_2), 6.30 (s, 1H, CH), 7.11–7.43 (m, 8H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 42.95, 47.89, 47.93, 51.89, 51.93, 121.2, 122.0, 122.1, 127.2, 128.0, 128.1, 130.6, 130.8, 132.2, 134.2, 136.1, 148.5, 149.7, 151.1.

4-(4^1-ethoxyphenyl)-3-(4'-methylpiperazine-1-yl)-N-phenyl-1,3-thiazol-2(3H)-imine **8ai** was obtained similarly to the compound **8aj** from 3.95 g (0.01 mol) of α-bromo-4-ethoxyacetophenone **6i** and 2.50 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-phenylthiourea **5a.** The yield was 2.49 g (63 %), m.p. 445–446 K (propanol-2). Found, %: N = 14.4, S = 8.04 $C_{22}H_{26}N_4OS$. Calculated, %: N = 14.2, S = 8.13. ^{1}H NMR spectrum (DMSO-d6, TMS): 1.26 (t, 3H, CH_3), 2.16 (s, 3H, NCH_3), 2.61 (m, 4H, CH_2NCH_2), 3.24 (m, 4H, CH_2NCH_2), 3.94 (kv, 2H, OCH_2), 6.24 (s, 1H, CH), 6.74 and 7.00 (d-d, 4H, C_6H_4), 7.14–7.31 (m, 5H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 15.20, 43.29, 48.17, 48.22, 52.20, 52.23, 64.15, 116.1, 116.2, 121.5, 122.1, 122.3, 125.4, 127.7, 127.8, 128.0, 128.1, 133.5, 148.6, 149.6, 156.1, 158.4.

N-(4^1-methoxyphenyl)-3-(4'-methylpiperazine-1-yl)-4-phenyl-1,3-thiazol-2(3H)-imine **8df** was obtained similarly to the compound **8aj** from 1.99 g (0.01 mol) of α-bromoacetophenone **6f** and 2.80 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(4^1- methoxyphenyl)thiourea **5d.** The yield was 2.54 g (66 %), m.p. 505–506 K (heptane). Found, %: N = 14.7, S = 8.26 $C_{21}H_{24}N_4OS$. Calculated, %: N = 14.8, S = 8.43. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.17 (s, 3H, NCH_3), 2.61 (m, 4H, CH_2NCH_2), 3.25 (m, 4H, -CH_2NCH_2-), 3.79 (s, 3H, OCH_3), 6.27 (s, 1H, CH), 6.70 and 7.01 (d-d, 4H, C_6H_4), 7.11–7.33 (m, 5H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 43.03, 48.06, 48.11, 52.13, 52.18, 55.43, 113.6, 113.7, 122.9, 123.0, 125.4, 125.5, 127.1, 127.2, 129.7, 133.4, 133.5, 142.9, 148.6, 154.8, 156.2.

Synthesis of ethyl 2-[(2^1,3^1-dimethylphenyl)imino]-4-methyl-3-(4'-methyl-1-piperazinyl)-2,3-dihydro-1,3-thiazole-5-carboxylate **11cn.** To the solution of 1.65 g (0.01 mol) of ethyl 2-chloroacetoacetate **9n** in 50 ml of ethanol while stirring 2.78 g (0.01 mol) of *N'*-(4'-methylpiperazine-1-yl)-*N*-(2^1,3^1-dimethylphenyl)thiourea was added and boiled for 2 h. The reaction mixture was evaporated to the volume of 15–20 ml and neutralized by adding 10 ml of 10% ammonia solution. The precipitate formed was filtered, washed with water, and dried. The yield was 2.29 g (59 %), m.p. 405–406 K **(**propanol-2). Found, %: N = 14.6, S = 8.18 $C_{20}H_{28}N_4O_2S$. Calculated, %: N = 14.4, S = 8.25. ^{1}H NMR spectrum (DMSO-d6, TMS): 1.35 (t, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.43 (m, 4H, CH_2NCH_2), 2.60 (m, 4H, CH_2NCH_2), 4.23 (kv, 2H, OCH_2), 6.98–7.25 (m, 3H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 13.71, 14.05, 16.13, 19.96, 43.10, 47.99, 48.03, 52.11, 52.14, 61.55, 121.0, 121.5, 122.2, 122.8, 125.7, 134.8, 146.3, 147.1, 148.4, 166.7.

Ethyl 2-[(4[1]-methoxyphenyl)imino]-4-methyl-3-(4'-methyl-1-piperazinyl)-2,3-dihydro-1,3-thiazole-5-carboxylate **11dn** was obtained similarly to the compound **11cn** from 1.65 g (0.01 mol) of ethyl 2-chloroacetoacetate **9n** and 2.50 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(4[1]-methoxyphenyl)thiourea **5d.** The yield was 2.19 g (56 %), m.p. 404–405 K (heptane). Found, %: N = 14.5, S = 8.34 $C_{19}H_{26}N_4O_3S$. Calculated, %: N = 14.4, S = 8.21. ^{1}H NMR spectrum (DMSO-d6, TMS): 1.27 (t, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.40 (m, 4H, CH_2NCH_2), 2.56 (m, 4H, CH_2NCH_2), 3.83 (s, 3H, OCH_3), 4.20 (kv, 2H, OCH_2), 7.03 and 7.23 (d-d, 4H, C_6H_4). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 14.81, 16.22, 43.08, 47.92, 47.95, 51.87, 51.93, 55.39, 61.45, 113.5, 113.6, 121.5, 123.1, 142.7, 146.3, 147.9, 154.7, 166.8.

Synthesis of hydrochloride 1-[2(4[1]-methoxyphenylimino)-4-methyl-3-(4[2]-methylpiperazine-1-yl)-2,3-dihydrothiazol-5-yl]ethanone **10dm.** To the solution of 1.35 g (0.01 mol) of 3-chloropentane-2,4-dione **9m** in 50 ml of ethanol while stirring 2.80 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(4[1]-methoxyphenyl)thiourea **5d** was added and boiled for 2 h. The reaction mixture was evaporated to the volume of 15–20 ml and neutralized by adding 10 ml of 10% ammonia solution. The precipitate formed was filtered, washed with a small amount of ethanol, and dried. The yield was 2.66 g (67 %), m.p. 451–453 K **(**propanol-2). Found, %: N = 14.3, S = 8.20 $C_{18}H_{25}ClN_4O_2S$. Calculated, %: N = 14.1, S = 8.08. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.16 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.86 (m, 4H, CH_2NCH_2), 3.12 (m, 4H, CH_2NCH_2), 3.82 (s, 3H, OCH_3), 7.06 and 7.25 (d-d, 4H, C_6H_4), 10.9 (m, 1H, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 15.91, 27.11, 43.18, 47.85, 47.91, 52.08, 52.11, 55.39, 113.7, 113.8, 123.5, 123.6, 130.7, 142.2, 146.0, 147.7, 154.8, 191.9.

Synthesis of 1-[2-[(2[1],3[1]-dimethylphenyl)imino]-4-methyl-3-(4'-methyl-1-piperazinyl)-2,3-dihydro-1,3-thiazol-5-yl]ethanone **11cm.** To the solution of 1.49 g (0.01 mol) of 3-chloropentane-2,4-dione **9m** in 50 ml of ethanol while stirring 2.78 g (0.01 mol) of *N*-(4'-methylpiperazine-1-yl)-*N'*-(2[1],3[1]-dimethylphenyl)thiourea **5c** was added and boiled for 2 h. The reaction mixture was evaporated to the volume of 15–20 ml and neutralized by adding 10 ml of 10% ammonia solution. The precipitate formed was filtered, washed with a small amount of ethanol, and dried. The yield was 2.29 g (64 %), m.p. 421–423 K (heptane). Found, %: N = 15.9, S = 8.86 $C_{19}H_{26}N_4OS$. Calculated, %: N = 15.6, S = 8.94. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.00 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.44 (m, 4H, CH_2NCH_2), 2.60 (m, 4H, CH_2NCH_2), 6.99–7.26 (m, 3H, Ar-H). ^{13}C NMR spectrum (100 MHz, DMSO-d6) δ: 13.70, 16.01, 20.03, 27.15, 43.12, 48.06, 48.11, 52.18, 52.20, 121.7, 121.8, 125.7, 130.8, 134.8, 146.1, 146.8, 148.6, 191.7.

2,2,3,3-Tetrafluoropropyl ester 4-[2-(2[1],3[1]-dimethylphenylimino)-3-(4'-methylpiperazine-1-yl)-2,3-dihydrothiazol-4-yl]-benzenesulfonic acid **16** was obtained similarly to the compound ***8aj*** from 1.97 g (0.005 mol) of 1-(α-bromoacetyl)-4-(2[1],2[1],3[1],3[1]-tetrafluoropropyl)ester of benzenesulfonic acid **15** and 1.39 g (0.005 mol) of *N'*-(4'-methylpiperazine-1-yl)-*N*-(2[1],3[1]- dimethylphenyl)thiourea **5c.** The yield was 1.52 g (53 %), m.p. 430–431 K (heptane). Found, %: N = 9.61, S = 5.81 $C_{25}H_{28}F_4N_4O_3S_2$. Calculated, %: N = 9.78, S = 5.93. ^{1}H NMR spectrum (DMSO-d6, TMS): 2.10 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.43 (m, 4H, -CH_2NCH_2-), 2.64 (m, 4H, -CH_2NCH_2-), 4.42 (t, 2H, OCH_2CF_2), 6.24 (t-t, 1H, CF_2CHF_2, J = 52 Hz,), 6.47 (s, 1H, CH), 6.83–7.10 (m, 3H, C_6H_3), 7.27 and 7.72 (d-d, 4H, C_6H_4).

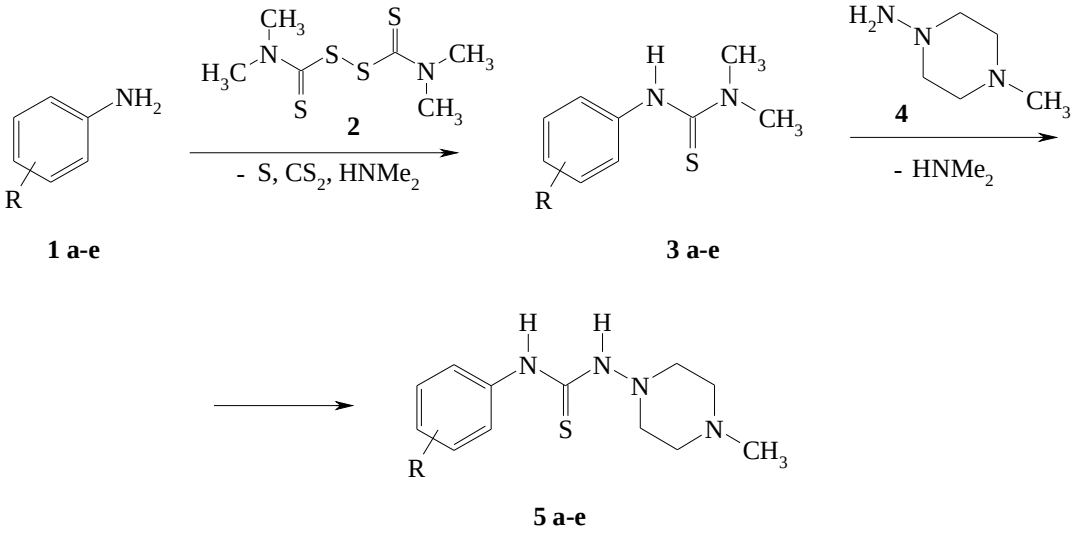
2.3. Antimicrobial Activity

Sulfate-reducing bacteria of *Desulfovibrio sp.* M.4.1 strain gathered previously from corroded iron coating of the subterranean gas pipeline were used as test microorganisms and identified by molecular-biological methods [35].

Substances in the concentration of 0.1 and 1.0 % were added to a Postgate "B" nutrient medium inoculated with SRB. The number of cells in the inoculum was 10^6 cell/ml. The cultivation was performed at the temperature of 301±2 K for 7 days. After the cultivation period, the bacterial count was determined using the decimal dilution method when inoculating the corresponding cell suspension on the liquid elective nutrient medium – Postgate "B" [36]. All experiments were accompanied by the corresponding control tests: the medium sterility control and the culture growth control in the medium without compounds.

3. Results and Discussion

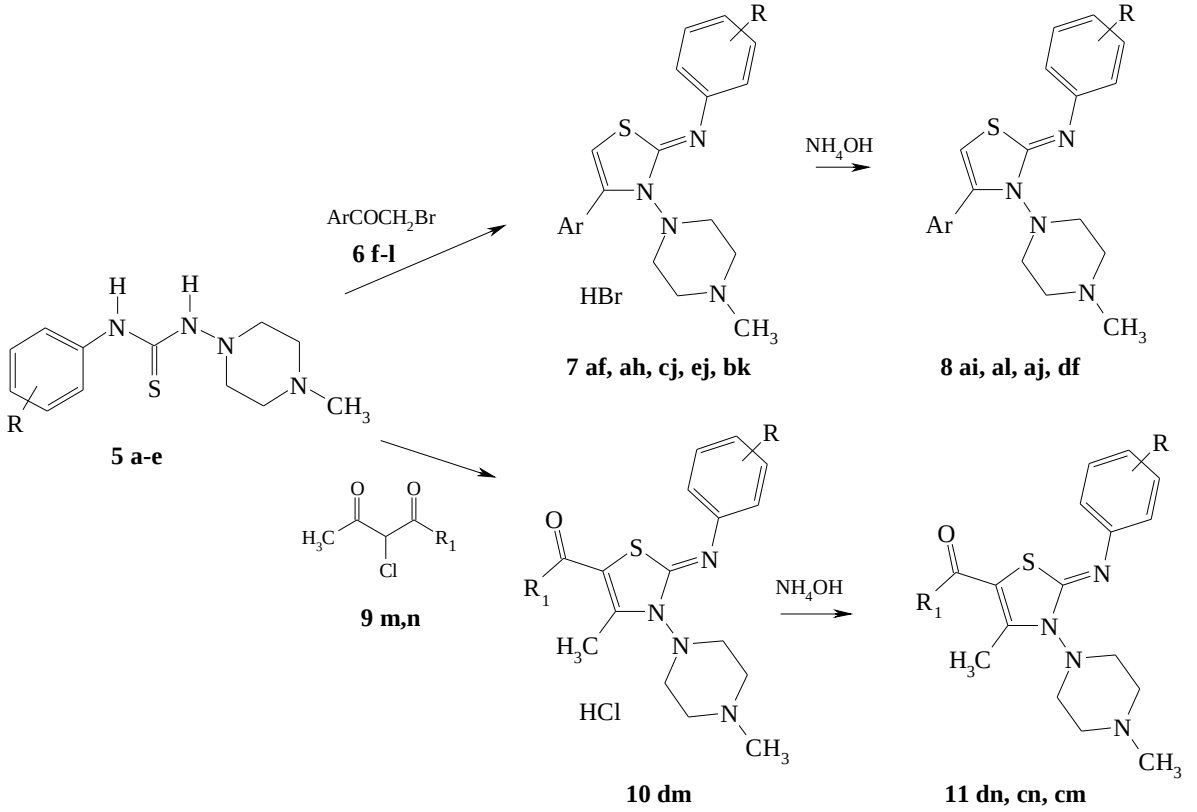
The synthesis of all asymmetric thioureas with the fragment of *N*-methylpiperazine is based on the classical reaction of the interaction *N*-methyl-*N*[1]-aminopiperazine with the corresponding aromatic isothiocyanates [9, 10]. We have shown that asymmetric thioureas **5a-e** can be obtained by the condensation of *N*-methyl-*N*[1]-aminopiperazine **4** with the corresponding *N*[1]-aryl-*N*,*N*-dimethylthioureas **3a-e**. The thioureas **3a-e** were obtained by the treatment of aromatic amines **1a-e** with tetramethylthiouram disulfide (TMTD) **2** by the method [37] (Scheme 1).



1 a-e **2** **3 a-e** **4** **5 a-e**

where R = H (**a**), 3-CH_3 (**b**), 2,3$(CH_3)_2$ (**c**), 4-OCH_3 (**d**) and 4-OC_2H_5 (**e**)

Scheme 1



5 a-e **7 af, ah, cj, ej, bk** **8 ai, al, aj, df** **9 m,n** **10 dm** **11 dn, cn, cm**

where R = H (**a**), 3-CH_3 (**b**), 2,3-$(CH_3)_2$ (**c**), 4-OCH_3 (**d**) and 4-OC_2H_5 (**e**); Ar = Ph (**f**), 4-MeC_6H_4 (**g**), 4-*t*-BuC_6H_4 (**h**), 4-$EtOC_6H_4$ (**i**), 4-ClC_6H_4 (**j**), 4-BrC_6H_4 (**k**) and 2,4-$Cl_2C_6H_3$ (**l**); R_1 = CH_3 (**m**) and OC_2H_5 (**n**)

Scheme 2

Formation of 1-(4-methylpiperazine-1-yl)-3-arylthioureas **5a-e** was the result of the interaction of boiling the equimolar amounts of N^1-aryl-*N*,*N*-dimethylthioureas **3a-e** and *N*-methyl-N^1-aminopiperazine **4** in a dry dioxane. The reaction was accompanied with dimethylamine release due to the transamination reaction.

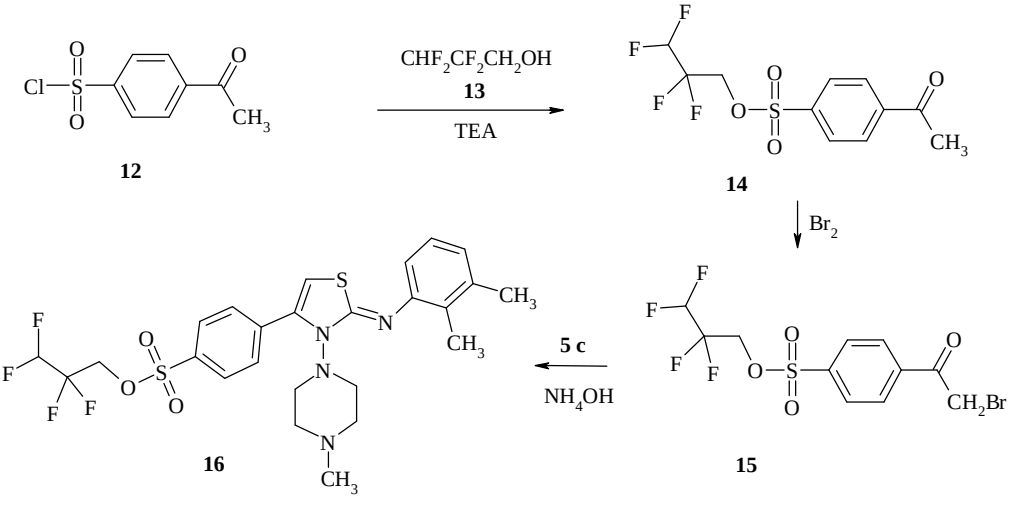
The ^{1}H NMR-spectra of unsymmetric thioureas **5a-e** showed downfield signals at δ = 8.95–9.40 ppm as two singlets attributed to both NH-groups, and general resonance signals of the aromatic protons at δ = 6.81–7.86 ppm as multiplets. The signals of *N*-methylpiperazine residue protons for all compounds were presented on the spectra as multiplets at δ = 2.20–2.95 ppm for piperazine and as singlets δ = 2.20 ppm for the methyl group of piperazine.

We have shown that the condensation of asymmetric thioureas **5a-e** with substituted aromatic α-bromoketons **6f-l** and with aliphatic chloroketones **9m-n** leads to the formation of the corresponding substituted thiazoles **7-11** (Scheme 2) by the Hantzsch reaction.

The synthesis of 2,2,3,3-tetrafluoropropyl ester 4-[2-(2^1,3^1-dimethylphenylimino)-3-(4'-methylpiperazine-1-yl)-2,3-dihydrothiazol-4-yl]-benzenesulfonic acid **16** was performed on the basis of 4-acetylbenzenesulfonyl chloride **12** [38] according to Scheme 3 without intermediate identification of compounds **14** and **15**.

The results of the study of the SRB sensitivity in relation to 4- and 5-(un)substituted derivatives of N-(R'-phenyl)-3-(4-methyl-1-piperazinyl)-1,3-thiazole-2(3*H*)-imine are shown in Fig.

The tests have shown that practically all compounds studied demonstrate the marked antibacterial activity against SRB compared to the control group. With the concentration of 0.5 % the number of bacteria cells decreases by 5–7 orders. It should be mentioned that with the increase of the concentration there is no change in the antimicrobial activity for substances **8ai**, **10dm**, **7ah** and **16**, while the biocidal activity enhances for substances **7bk**, **8al**, **8aj**, **7aj**, **7af**, **7cj**, **8df**, **11cm** and **16**. In addition, substances **7bk**, **8al**, **7af** and **7cj** completely inhibit the SRB growth in the concentration of 1.0 %.



Scheme 3

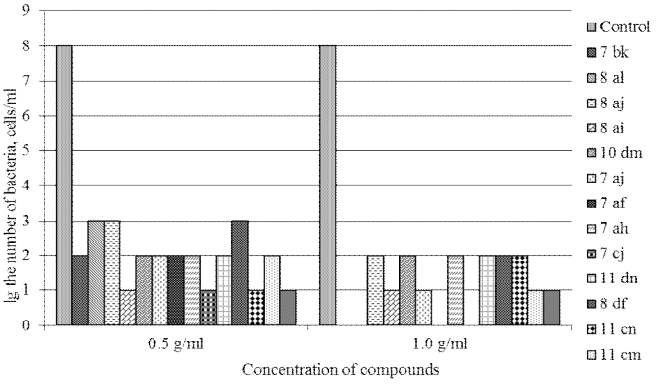


Fig. The number of SRB cells under the action of 4- and 5-(un)substituted derivatives of *N*-(R'-phenyl)-3-(4-methyl-1-piperazinyl)-1,3-thiazole-2(3*H*)-imine

4. Conclusions

The synthesis of initial substances for the synthesis of 1,3-thiazoline derivatives with the *N*-methylpiperazine moiety – *N*-(4-methylpiperazine-1-yl)-*N'*-(R-phenyl) thioureas – has been performed by the one-stage condensation of *N*-methyl-N^1-aminopiperazine with the corresponding N^1-aryl-*N*,*N*-dimethylthioureas formed by the treatment of aromatic amines with TMTD. The synthesis of new 4- and 5-(un)substituted derivatives of N-(R'-phenyl)-3-(4-methyl-1-piperazinyl)-1,3-thiazole-2(3*H*)-imine in good to high yields has been performed by the cyclization reaction of *N*-piperazine-4-yl-*N'*-(R-phenyl)thioureas and various α-bromoacetophenones and α-chlorodiketones in the ethanol medium. The structure and individuality of the compounds synthesized have been confirmed by ^{1}H, ^{13}C NMR-spectroscopy and elemental analysis. The pharmacological screening for the antimicrobial activity of the compounds synthesized reveals that substances contain electroacceptor substituents and the unsubstituted phenyl fragment in position 4 of the thiazoline cycle, electrodonor substitutes and the unsubstituted phenyl fragment in position 2 of the thiazoline cycle; they exhibit the potent antimicrobial activity against sulfate-reducing bacteria of *Desulfovibrio* sp. M.4.1 strain. Some of the synthesized compounds are promising for further study as antimicrobial agents.

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СИНТЕЗ ТА ВЛАСТИВОСТІ НОВИХ ПОХІДНИХ 2-(R-ФЕНІЛІМІНО)-1,3-ТІАЗОЛІНУ, ЩО МІСТЯТЬ ФРАГМЕНТ *N*-МЕТИЛПІПЕРАЗИНУ

Анотація. *На основі несиметричних тіосечовин синтезовані нові похідні N-(R`-феніл)-3-(4-метил-1-піперазиніл)-1,3-тіазол-2(3H)-іміну за реакцією Ганча. Структуру цільових компонентів підтверджено елементим аналізом та ЯМР спектроскопією. Досліджено антимікробну активність похідних 1,3-тіазоліну з N-метилпіперазиновим фрагментом щодо сульфатвідновлювальних бактерій штаму Desulfovibrio sp. M 4.1. Встановлено, що сполуки з галогензаміщеним та незаміщеним фенільним фрагментом в 4-му положенні тіазолінового циклу виявляють виразну протимікробну активність.*

Ключові слова: *2-(R-феніліміно)-1,3-тіазолін, N-метилпіперазин, синтез Ганча, антимікробна активність, сульфатвідновлювальні бактерії.*