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Synthesis and antibacterial activity of new (2,4-dioxothiazolidin-5-yl/ylidene)acetic acid derivatives with thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin moieties

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ABSTRACT

A series of new (2,4-dioxothiazolidin-5-yl/ylidene)acetic acid derivatives with thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin moiety (**28**–**65**) were synthesized by the reaction of (2,4-dioxothiazolidin-5-yl/ylidene)acetic acid chlorides with 5-(hydroxybenzylidene) thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin derivatives. Obtained compounds (**28**–**65**) were tested on reference strains of Gram-positive bacteria and ones of the Gram-negative bacteria. The antibacterial activity of target compounds was determined by broth microdilution method. These derivatives showed antibacterial activity generally against Gram-positive bacterial strains. Most active compounds possess MIC = 3.91 mg/L. Our results suggest that presence of electron-withdrawing substituent at phenyl ring is favorable while geometry of molecule does not play important role in antibacterial response. It was confirmed the lack of direct influence of substitution pattern at phenyl ring on antibacterial activity of closely related compounds of series 1–3. The antibacterial activity of some compounds was similar or higher than the activity of commonly used reference drugs such as oxacillin and cefuroxime.

1. Introduction

The increasing resistance of bacteria to currently available antibiotics is an extremely serious problem in the treatment of infections. In the world, the emergence of bacteria with multiple genes for resistance has been reported, which may result in insensitivity to all available classes of antibiotics. Therefore, search of new antibacterial agents and investigation of new targets for antimicrobial drugs is an alternative to existing antimicrobial drugs (Trojanowski et al., 2014).

Thiazolidine-2,4-diones is a well-known class of biologically active compounds due to the group of antidiabetic drugs (Pioglitazone, Rosiglitazone etc.). Besides, the thiazolidine-2,4-dione is the ring with wide application as biologically active substances. It poses a broad spectrum of biological activity, including antibacterial (Heerding et al., 2003; Ibrahim et al., 2011; Liu et al., 2011; Bozdağ-Dündar et al., 2007; Aneja et al., 2011; Purohit et al., 2012; Desai et al., 2014a, 2014b; Shaikh et al., 2013; Trotsko et al., 2017), anticancer (Liu et al., 2010; Patil et al., 2010; Salamone et al., 2012), anti-inflammatory (Koppireddi et al., 2013; Barros et al., 2010), antifungal (Tuncbilek and Altanlar, 2006; Marc et al., 2017), antioxidant (Jeong et al., 2004).

One of the directions of the search for new bioactive compounds used in medicinal chemistry is combination two biologically active heterocyclic systems into single molecule. It is known that the combination of different pharmacophore or bioactive fragments with different mechanisms of the action often showed synergistic effects (Asati et al., 2014).

Such bioactive fragment may be a thiazolidine-2,4-dione and it structural analogues: rhodanine (2-thioxothiazolidine-4-one) and 2-thiohydantoin (2-thioxoimidazolidine-4-one) due to their broad spectrum of biological activity (anticancer (Moorthy et al., 2010; Min et al., 2013; Wu et al., 2015), anti-inflammatory (Cutshall et al., 2005; Irvine et al., 2008), anticonvulsant (Gangadhar et al., 2013), antiviral (Rajamaki et al., 2009; Jiang et al., 2011), antifungal

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(Sortino et al., 2007; Chauhan et al., 2012), particularly antibacterial activity (Zvarec et al., 2012; Song et al., 2014; Miao et al., 2013; Villain–Guillot et al., 2007; Hardej et al., 2010; Zheng et al., 2012; El Hady, 2012).

The aim of the present research was to synthesize new thiazolidine-2,4-dione derivatives modified in position 5 by 5-benzylidene derivatives of thiazolidine-2,4-dione and it structural analogues 5-benzylidene derivatives of rhodanine and 2-thiohydantoin and to evaluate *in vitro* their potential as antibacterial agents.

2. Experimental

2.1. Materials and methods

Melting points were determined by using Fischer-Johns apparatus (Fisher Scientific, Schwerte, Germany) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded by a Bruker Avance 300 MHz instrument using DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts were expressed as δ (ppm). The purity of the compounds was checked by TLC on plates with silica gel Si 60 F_{254}, produced by Merck Co. (Darmstadt, Germany). Elemental analyses were performed by AMZ 851 CHX analyser and the results were within ±0.4% of the theoretical value.

*2.2. General method for the synthesis of (2,4-dioxo-1,3-thiazolidin-5-yl/ylidene)acetate derivatives (**28-65**)*

The solution of 0.01 mol acid chloride (**3**, **4**) in 3 mL of anhydrous dioxane was added to a solution of 0.01 mol of corresponding 5-benzylidene derivatives of thiazolidine-2,4-dione (**8**–**14**), rhodanine (**15**–**21**) or 2-thiohydantoin (**22**–**27**) in 5 mL anhydrous pyridine. After 2 h, water was added and the mixture was acidified of diluted hydrochloric acid solution to pH = 3–4 and left at room temperature for 24 h. The precipitate was filtered off and then crystallized from n-butanol. For the compounds **50**, **51**, **57** and **58** mixture of DMF:water (2:1) was used as the solvent for crystallization.

*2.2.1. 2-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(28)***

Yield 74%, mp = 232–234 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.51–3.54 m (2H, CH—C**H$_2$**); 4.85 dd (1H, C**H**—CH_2, *J* = 5.4, 6.7 Hz); 7.31 d, 7.42–7.59 m (4H, C_6H_4, *J* = 8.1 Hz); 7.67 s (1H, CH=); 12.19 s, 12.70 s (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.3; 46.7; 123.8; 125.1; 126.5; 127.3; 127.6; 128.9; 132.1; 149.5; 167.4; 168.2; 169.4; 172.5; 175.8. Anal. calc. for $C_{15}H_{10}N_2O_6S_2$ (%): C 47.61; H 2.66; N 7.40. Found: C 47.49; H 2.60; N 7.36.

*2.2.2. 3-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(29)***

Yield 77%, mp = 238–240 °C. CAS Registry Number: 938,870-16-7. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.44–3.47 m (2H, CH—C**H$_2$**); 4.86 dd (1H, C**H**—CH_2, *J* = 5.3, 7.0 Hz); 7.25–7.38 m, 7.51–7.63 m (4H, C_6H_4); 7.80 s (1H, CH=); 12.32 bs (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.4; 46.8; 123.1; 124.0; 125.5; 128.2; 130.9; 131.1; 135.1; 151.0; 167.7; 168.2; 169.5; 172.6; 175.9. Anal. calc. for $C_{15}H_{10}N_2O_6S_2$ (%): C 47.61; H 2.66; N 7.40. Found: C 47.29; H 2.65; N 7.34.

*2.2.3. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(30)***

Yield 73%, mp = 248–250 °C. CAS Registry Number: 938,740-39-7. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.44–3.47 m (2H, CH—C**H$_2$**); 4.84 dd (1H, C**H**—CH_2, *J* = 5.1, 7.0 Hz); 7.30 d, 7.66 d (4H, 4-O—C_6H_4, *J* = 8.7 Hz); 7.81 s (1H, CH=); 12.24 s, 12.60 s (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.4; 46.8; 123.1; 124.2; 131.3; 131.5; 131.9; 151.7; 167.8; 168.3; 169.4; 172.6; 175.9. Anal. calc. for $C_{15}H_{10}N_2O_6S_2$ (%): C 47.61; H 2.66; N 7.40. Found: C 47.55; H 2.70; N 7.38.

*2.2.4. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-methoxyphenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(31)***

Yield 86%, mp = 230–233 °C. CAS Registry Number: 938,895-02-4. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.42–3.44 m (2H, CH—C**H$_2$**); 3.82 s (3H, OCH_3); 4.83 dd (1H, C**H**—CH_2, *J* = 5.3, 6.8 Hz); 7.17 dd, 7.26 d, 7.38 d (3H, C_6H_3, *J* = 1.8, 8.4 Hz); 7.80 s (1H, CH=); 12.35 bs (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.1; 46.9; 56.5; 115.2; 122.5; 124.0; 124.4; 131.6; 132.8; 140.7; 151.5; 167.8; 168.3; 168.8; 172.7; 175.8. Anal. calc. for $C_{16}H_{12}N_2O_7S_2$ (%): C 47.06; H 2.96; N 6.86. Found: C 47.03; H 2.92; N 6.83.

*2.2.5. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-ethoxyphenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(32)***

Yield 61%, mp = 238–240 °C. CAS Registry Number: 938,740-47-7. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.32 t (3H, OCH_2C**H$_3$**, *J* = 7.0 Hz); 3.42 d (2H, CH—C**H$_2$**, *J* = 6.0 Hz); 4.05 q (2H, OC**H$_2$**CH_3, *J* = 7.0 Hz); 4.84 t (1H, C**H**—CH_2, *J* = 6.0 Hz); 7.16–7.36 m (3H, C_6H_3); 7.79 s (1H, CH=); 12.16 s, 12.57 s (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 14.8; 35.9; 46.7; 64.7; 115.9; 122.5; 123.9; 124.4; 131.6; 132.7; 140.9; 150.7; 167.7; 168.2; 168.6; 172.6; 175.7. Anal. calc. for $C_{17}H_{14}N_2O_7S_2$ (%): C 48.34; H 3.34; N 6.63. Found: C 48.25; H 3.33; N 6.60.

*2.2.6. 2-chloro-4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(33)***

Yield 80%, mp = 234–236 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.51–3.54 m (2H, CH—C**H$_2$**); 4.86 dd (1H, C**H**—CH_2, *J* = 5.3, 6.7 Hz); 7.47 d, 7.59 dd, 7.86 d (3H, C_6H_3, *J* = 2.0, 8.5 Hz); 7.80 s (1H, CH=); 12.16 s, 12.68 s (2H, 2NH, thiazolidine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.0; 46.6; 125.4; 126.0; 127.1; 129.6; 129.8; 132.3; 133.4; 147.5; 167.5; 167.9; 168.6; 172.5; 175.6. Anal. calc. for $C_{15}H_9ClN_2O_6S_2$ (%): C 43.64; H 2.20; N 6.79. Found: C 43.66; H 2.18; N 6.77.

*2.2.7. 2-bromo-4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(34)***

Yield 82%, mp = 243–245 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.51–3.53 m (2H, CH—C**H$_2$**); 4.87 dd (1H, C**H**—CH_2, *J* = 5.5, 6.5 Hz); 7.46 d, 7.64 dd, 7.99 d (3H, C_6H_3, *J* = 2.1, 8.4 Hz); 7.79 s (1H, CH=); 12.34 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.2; 46.6; 116.8; 125.3; 126.2; 129.6; 130.1; 133.8; 135.4; 148.8; 167.8; 168.1; 168.7; 172.5; 175.7. Anal. calc. for $C_{15}H_9BrN_2O_6S_2$ (%): C 39.40; H 1.98; N 6.13. Found: C 39.31; H 1.94; N 6.11.

*2.2.8. 2-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(35)***

Yield 73%, mp = 212–214 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.52–3.55 m (2H, CH—C**H$_2$**); 4.87 t (1H, C**H**—CH_2, *J* = 6.6 Hz); 7.31–7.35 m, 7.47–7.59 m (5H, C_6H_4—CH=); 12.14 s (1H, NH, thiazolidine), 13.88 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.4; 46.7; 124.0; 124.7; 126.4; 127.7; 129.1; 129.3; 132.5; 149.7; 169.4; 169.7; 172.5; 175.8; 196.1. Anal. calc. for $C_{15}H_{10}N_2O_5S_3$ (%): C 45.68; H 2.56; N 7.10. Found: C 45.61; H 2.55; N 7.02.

*2.2.9. 3-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate **(36)***

Yield 74%, mp = 207–209 °C. CAS Registry Number: 938,740-53-5. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.45–3.48 m (2H, CH—C**H$_2$**); 4.85

dd (1H, C**H**-CH_2, *J* = 5.6, 6.8 Hz); 7.26–7.39 m, 7.51–7.61 m (4H, C_6H_4); 7.65 s (1H, CH=); 12.16 s (1H, NH, thiazolidine), 13.89 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.5; 46.8; 123.5; 124.4; 127.4; 128.7; 130.8; 131.2; 135.0; 151.1; 169.5; 169.8; 172.6; 175.9; 196.0. Anal. calc. for $C_{15}H_{10}N_2O_5S_3$ (%): C 45.68; H 2.56; N 7.10. Found: C 45.59; H 2.53; N 7.11.

2.2.10. 4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(37)***

Yield 76%, mp = 236–238 °C. CAS Registry Number: 924,860-04-8. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.44–3.47 m (2H, CH—C**H$_2$**); 4.85 dd (1H, C**H**—CH_2, *J* = 5.2, 7.0 Hz); 7.31 d, 7.67 d (4H, 4-O—C_6H_4, *J* = 8.7 Hz); 7.65 s (1H, CH=); 12.17 s (1H, NH, thiazolidine), 13.80 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.4; 46.8; 123.3; 126.1; 130.9; 131.5; 132.4; 151.9; 169.3; 170.1; 172.6; 175.9; 196.2. Anal. calc. for $C_{15}H_{10}N_2O_5S_3$ (%): C 45.68; H 2.56; N 7.10. Found: C 45.62; H 2.49; N 7.03.

2.2.11. 2-methoxy-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene) methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(38)***

Yield 92%, mp = 242–243 °C. CAS Registry Number: 938,740-45-5. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.42–3.44 m (2H, CH-C**H$_2$**); 3.83 s (3H, OCH_3); 4.83 dd (1H, C**H**—CH_2, *J* = 5.3, 6.8 Hz); 7.18 dd, 7.27 d, 7.38 d (3H, C_6H_3, *J* = 1.8, 8.4 Hz); 7.65 s (1H, CH=); 12.13 s (1H, NH, thiazolidine), 13.85 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.0; 46.8; 56.5; 115.5; 123.1; 124.2; 126.6; 131.2; 132.8; 140.9; 151.6; 168.7; 170.2; 172.6; 175.7; 196.3. Anal. calc. for $C_{16}H_{12}N_2O_6S_3$ (%): C 45.27; H 2.85; N 6.60. Found: C 45.29; H 2.82; N 6.61.

2.2.12. 2-ethoxy-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene) methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(39)***

Yield 85%, mp = 236–238 °C. CAS Registry Number: 938,895-04-6. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.33 t (3H, OCH_2C**H$_3$**, *J* = 6.5 Hz); 3.42 d (2H, CH—C**H$_2$**, *J* = 5.75 Hz); 4.07 q (2H, O**CH$_2$**CH_3, *J* = 6.5 H z); 4.84 t (1H, C**H**—CH_2, *J* = 5.75 Hz); 7.17 dd, 7.27 d, 7.36 d (3H, C_6H_3, *J* = 1.8, 8.4 Hz); 7.65 s (1H, CH=); 12.12 s (1H, NH, thiazolidine), 13.81 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 14.9; 35.9; 46.8; 64.8; 116.2; 123.1; 124.1; 126.4; 131.4; 132.7; 141.3; 150.8; 168.6; 169.9; 172.6; 175.7; 196.1. Anal. calc. for $C_{17}H_{14}N_2O_6S_3$ (%): C 46.57; H 3.22; N 6.39. Found: C 46.61; H 3.18; N 6.37.

2.2.13. 2-chloro-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(40)***

Yield 81%, mp = 228–231 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.52–3.55 m (2H, CH—C**H$_2$**); 4.87 dd (1H, C**H**—CH_2, *J* = 5.2, 6.9 Hz); 7.49 d, 7.59 dd, 7.89 d (3H, C_6H_3, *J* = 2.1, 8.4 Hz); 7.65 s (1H, CH=); 12.17 s (1H, NH, thiazolidine), 13.92 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.1; 46.6; 125.5; 127.2; 128.1; 129.4; 130.0; 132.8; 133.4; 147.7; 168.6; 170.2; 172.5; 175.7; 195.9. Anal. calc. for $C_{15}H_9ClN_2O_5S_3$ (%): C 42.01; H 2.12; N 6.53. Found: C 41.83; H 2.01; N 6.55.

2.2.14. 2-bromo-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene) methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(41)***

Yield 79%, mp = 225–226 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.51 d (2H, CH—C**H$_2$**, *J* = 5.75 Hz); 4.89 t (1H, C**H**—CH_2, *J* = 5.75 Hz); 7.46 d, 7.62–7.66 m, 8.01 d (4H, C_6H_3—CH=, *J* = 2.0, 8.5 Hz); 12.17 s (1H, NH, thiazolidine), 13.78 s (1H, NH, rhodanine). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.3; 46.6; 117.0; 125.4; 128.0; 129.7; 130.5; 133.7; 135.9; 149.4; 168.6; 169.9; 172.5; 175.7; 195.9. Anal. calc. for $C_{15}H_9BrN_2O_5S_3$ (%): C 38.06; H 1.92; N 5.92. Found: C 38.08; H 1.91; N 5.91.

2.2.15. 2-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(42)***

Yield 76%, mp = 228–230 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.46 d (2H, CH-C**H$_2$**, *J* = 5.0 Hz); 4.85 t (1H, C**H**-CH_2, *J* = 5.0 Hz); 6.34 s (1H, CH=); 7.20–7.50 m, 7.79–7.82 m (4H, C_6H_4); 12.12 s, 12.18 s, 12.44 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.3; 46.7; 104.3; 123.1; 125.7; 127.0; 130.1; 130.8; 130.9; 149.0; 165.8; 169.4; 172.5; 175.8; 180.0. Anal. calc. for $C_{15}H_{11}N_3O_5S_2$ (%): C 47.74; H 2.94; N 11.13. Found: C 47.63; H 2.82; N 11.04.

2.2.16. 3-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(43)***

Yield 75%, mp = 238–240 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.44–3.46 m (2H, CH—C**H$_2$**); 4.84 dd (1H, C**H**—CH_2, *J* = 5.3, 6.7 Hz); 6.48 s (1H, CH=); 7.14–7.17 m, 7.45–7.65 m (4H, C_6H_4); 12.20 bs, 12.44 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.4; 46.8; 110.5; 122.9; 123.0; 128.6; 128.8; 130.4; 134.4; 150.8; 166.2; 169.5; 172.7; 175.9; 180.0. Anal. calc. for $C_{15}H_{11}N_3O_5S_2$ (%): C 47.74; H 2.94; N 11.13. Found: C 47.80; H 2.89; N 11.11.

2.2.17. 4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(44)***

Yield 72%, mp = 253–255 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.42–3.45 m (2H, CH—C**H$_2$**); 4.84 dd (1H, C**H**—CH_2, *J* = 5.2, 7.0 Hz); 6.50 s (1H, CH=); 7.17 d, 7.79 d (4H, 4-O—C_6H_4, *J* = 8.7 Hz); 12.18 s, 12.26 s, 12.41 s (3H, 3xNH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.5; 46.9; 110.9; 113.4; 123.8; 128.3; 130.8; 151.0; 166.2; 169.4; 172.7; 176.0; 179.8. Anal. calc. for $C_{15}H_{11}N_3O_5S_2$ (%): C 47.74; H 2.94; N 11.13. Found: C 47.57; H 2.79; N 11.16.

2.2.18. 2-methoxy-4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(45)***

Yield 81%, mp = 238–244 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.41–3.43 m (2H, CH—C**H$_2$**); 3.86 s (3H, OCH_3); 4.83 dd (1H, C**H**—CH_2, *J* = 5.4, 6.6 Hz); 6.50 s (1H, CH=); 7.13 d, 7.35–7.39 m (3H, C_6H_3, *J* = 8. 1 Hz); 12.24 bs, 12.41 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.1; 46.9; 56.6; 111.4; 123.4; 123.6; 128.3; 132.1; 140.1; 151.2; 166.2; 168.8; 172.7; 175.8; 179.8. Anal. calc. for $C_{16}H_{13}N_3O_6S_2$ (%): C 47.17; H 3.22; N 10.31. Found: C 46.99; H 3.17; N 10.34.

2.2.19. 2-ethoxy-4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(46)***

Yield 65%, mp = 242–244 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.31 t (3H, OCH_2C**H$_3$**, *J* = 6.9 Hz); 3.41 d (2H, CH-C**H$_2$**, *J* = 6.0 Hz); 4.11 q (2H, O**CH$_2$**CH_3, *J* = 6.9 Hz); 4.84 t (1H, C**H**-CH_2, *J* = 6.0 Hz); 6.48 s (1H, CH=); 7.13–7.37 m (3H, C_6H_3); 12.13 s, 12.23 s, 12.41 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 15.0; 36.3; 46.9; 64.8; 124.2; 125.6; 128.2; 132.0; 140.4; 147.4; 149.4; 150.5; 166.2; 168.7; 172.6; 175.8; 179.8. Anal. calc. for $C_{17}H_{15}N_3O_6S_2$ (%): C 48.45; H 3.59; N 9.97. Found: C 48.55; H 3.61; N 9.93.

2.2.20. 2-bromo-4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-yl)acetate ***(47)***

Yield 82%, mp = 258–260 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.49 d (2H, CH—C**H$_2$**, *J* = 6.6 Hz); 4.88 t (1H, C**H**—CH_2, *J* = 6.6 Hz); 6.47 s (1H, CH=); 7.32 d, 7.75 dd, 8.11 d (3H, C_6H_3, *J* = 2.1, 8.4 Hz); 12.18 s, 12.34 s, 12.46 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 36.3; 46.7; 109.1; 116.5; 124.6; 129.2; 131.4; 133.0; 134.2; 148.1; 166.1; 168.7; 172.6; 175.7; 180.1. Anal. calc. for $C_{15}H_{10}$-$BrN_3O_5S_2$ (%): C 39.48; H 2.21; N 9.21. Found: C 39.38; H 2.03; N 9.18.

2.2.21. 2-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(48)***

Yield 78%, mp = 267–269 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.17 s (1H, =CH—COO); 7.43–7.62 m (4H, C_6H_4); 7.67 s (1H, CH=); 12.78

bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 115.9; 123.9; 124.6; 126.1; 127.3; 127.9; 128.9; 132.2; 146.4; 149.3; 164.1; 166.6; 167.5; 168.1; 169.3. Anal. calc. for $C_{15}H_8N_2O_6S_2$ (%): C 47.87; H 2.14; N 7.44. Found: C 47.92; H 2.11; N 7.34.

2.2.22. 3-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(49)***

Yield 84%, mp = 268–270 °C. CAS Registry Number: 938,895-12-6. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.09 s (1H, =CH—COO); 7.35–7.39 m, 7.49–7.66 m (4H, C_6H_4); 7.80 s (1H, CH=); 12.75 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 116.8; 123.3; 124.0; 125.5; 128.2; 131.0; 131.1; 135.2; 145.3; 150.8; 164.2; 166.4; 167.7; 168.2; 169.4. Anal. calc. for $C_{15}H_8N_2O_6S_2$ (%): C 47.87; H 2.14; N 7.44. Found: C 48.01; H 2.10; N 7.40.

2.2.23. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(50)***

Yield 82%, mp = 298–299 °C. CAS Registry Number: 938,894-98-5. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.06 s (1H, =CH—COO); 7.40 d, 7.67 d (4H, 4-O—C_6H_4, J = 8.7 Hz); 7.81 s (1H, CH=); 12.76 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 116.6; 123.0; 124.4; 131.2; 131.8; 131.9; 145.6; 151.5; 164.0; 166.5; 167.7; 168.2; 169.3. Anal. calc. for $C_{15}H_8N_2O_6S_2$ (%): C 47.87; H 2.14; N 7.44. Found: C 47.67; H 1.99; N 7.36.

2.2.24. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-methoxyphenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(51)***

Yield 86%, mp = 292 °C. CAS Registry Number: 938,740-43-3. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.83 s (3H, OCH_3); 7.08 s (1H, =CH—COO); 7.19 dd, 7.36 d, 7.42 d (3H, C_6H_3, J = 1.8, 8.4 Hz); 7.82 s (1H, CH=); 12.75 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 56.6; 115.3; 115.7; 122.5; 124.1; 124.6; 131.6; 133.2; 140.3; 146.3; 151.4; 163.6; 166.5; 167.7; 168.2; 169.3. Anal. calc. for $C_{16}H_{10}N_2O_7S_2$ (%): C 47.29; H 2.48; N 6.89. Found: C 47.38; H 2.50; N 6.83.

2.2.25. 4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-ethoxyphenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(52)***

Yield 74%, mp = 262–264 °C. CAS Registry Number: 938,740-49-9. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.27 t (3H, $OCH_2C\mathbf{H_3}$, J = 6.9 Hz); 4.08 q (2H, $OC\mathbf{H_2}CH_3$, J = 6.9 Hz); 7.09 s (1H, =CH—COO); 7.21 dd, 7.38 d, 7.41 d (3H, C_6H_3, J = 1.8, 8.4 Hz); 7.81 s (1H, CH=); 12.77 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 14.9; 64.8; 115.8; 116.1; 122.5; 124.0; 124.5; 131.6; 133.1; 140.7; 146.1; 150.6; 163.5; 166.5; 167.7; 168.2; 169.3. Anal. calc. for $C_{17}H_{12}N_2O_7S_2$ (%): C 48.57; H 2.88; N 6.66. Found: C 48.39; H 2.78; N 6.67.

2.2.26. 2-chloro-4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(53)***

Yield 79%, mp = 280–282 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.14 s (1H, =CH—COO); 7.62–7.63 m, 7.90 d (3H, C_6H_3, J = 1.25 Hz); 7.82 s (1H, CH=); 12.78 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 115.3; 125.4; 126.2; 127.0; 129.7; 129.8; 132.4; 133.8; 146.9; 147.3; 163.3; 166.2; 167.5; 167.9; 169.0. Anal. calc. for $C_{15}H_7ClN_2O_6S_2$ (%): C 43.86; H 1.72; N 6.82. Found: C 43.77; H 1.68; N 6.79.

2.2.27. 2-bromo-4-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(54)***

Yield 83%, mp = 278–279 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.12 s (1H, =CH—COO); 7.56 d, 7.65 dd, 8.01 d (3H, C_6H_3, J = 2.0, 8.5 Hz); 7.81 s (1H, CH=); 12.67 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 115.5; 116.7; 125.3; 126.1; 129.8; 130.3; 134.0; 135.4; 146.9; 148.7; 163.4; 166.3; 167.5; 168.0; 169.0. Anal. calc. for $C_{15}H_7BrN_2O_6S_2$ (%): C 39.57; H 1.55; N 6.15. Found: C 39.62; H 1.59; N 6.09.

2.2.28. 2-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(55)***

Yield 86%, mp = 240–242 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.19 s (1H, =CH—COO); 7.44–7.67 m (5H, C_6H_4—CH=); 13.54 s (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 116.1; 124.0; 124.1; 126.0; 128.1; 129.1; 129.4; 132.5; 146.2; 149.5; 164.1; 166.4; 169.2; 169.6; 196.0. Anal. calc. for $C_{15}H_8N_2O_5S_3$ (%): C 45.91; H 2.05; N 7.14. Found: C 45.83; H 1.97; N 7.11.

2.2.29. 3-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(56)***

Yield 84%, mp = 272–274 °C. CAS Registry Number: 938,816-44-5. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.09 s (1H, =CH—COO); 7.37–7.41 m, 7.50–7.66 m (5H, C_6H_4—CH=); 13.48 s (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 116.9; 123.5; 124.2; 127.4; 128.8; 130.6; 131.2; 135.0; 145.2; 150.9; 164.2; 166.3; 169.3; 169.7; 196.0. Anal. calc. for $C_{15}H_8N_2O_5S_3$ (%): C 45.91; H 2.05; N 7.14. Found: C 45.78; H 2.01; N 7.09.

2.2.30. 4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(57)***

Yield 87%, mp = 290–292 °C. CAS Registry Number: 938,740-41-1. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.07 s (1H, =CH—COO); 7.41 d, 7.69 d (4H, C_6H_4, J = 8.7 Hz); 7.68 s (1H, CH=); 13.51 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 116.6; 123.2; 126.3; 131.0; 131.7; 132.4; 145.5; 151.7; 164.0; 166.4; 169.3; 169.9; 196.1. Anal. calc. for $C_{15}H_8N_2O_5S_3$ (%): C 45.91; H 2.05; N 7.14. Found: C 46.00; H 2.03; N 7.14.

2.2.31. 2-methoxy-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(58)***

Yield 91%, mp = 276–278 °C. CAS Registry Number: 938,895-00-2. ^{1}H NMR δ (ppm) (DMSO-d_6): 3.84 s (3H, OCH_3); 7.08 s (1H, =CH—COO); 7.20 dd, 7.38 d, 7.42 d (3H, C_6H_3, J = 1.8, 8.4 Hz); 7.67 s (1H, CH=); 13.47 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 56.6; 115.5; 115.7; 123.1; 124.2; 126.7; 131.3; 133.1; 140.6; 146.3; 151.5; 163.5; 166.5; 169.3; 169.9; 196.1. Anal. calc. for $C_{16}H_{10}N_2O_6S_3$ (%): C 45.49; H 2.39; N 6.63. Found: C 45.55; H 2.41; N 6.59.

2.2.32. 2-ethoxy-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(59)***

Yield 84%, mp = 266–268 °C. CAS Registry Number: 938,816-38-7. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.28 t (3H, $OCH_2C\mathbf{H_3}$, J = 6.9 Hz); 4.10 q (2H, $OC\mathbf{H_2}CH_3$, J = 6.9 Hz); 7.09 s (1H, =CH—COO); 7.20 dd, 7.37–7.41 m (3H, C_6H_3, J = 1.8, 8.4 Hz); 7.67 s (1H, CH=); 13.49 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 14.9; 64.9; 115.8; 116.4; 123.2; 124.1; 126.5; 131.4; 133.0; 140.9; 146.1; 150.7; 163.5; 166.4; 169.3; 169.8; 196.0. Anal. calc. for $C_{17}H_{12}N_2O_6S_3$ (%): C 46.78; H 2.77; N 6.42. Found: C 46.66; H 2.48; N 6.38.

2.2.33. 2-chloro-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(60)***

Yield 85%, mp = 269–272 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.13 s (1H, =CH—COO); 7.38 dd, 7.62–7.67 m (3H, C_6H_3, J = 2.1, 8.4 Hz); 7.56 s (1H, CH=); 13.61 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 117.9; 121.3; 123.2; 125.7; 127.1; 130.8; 131.4; 133.5; 142.7; 156.1; 166.6; 166.7; 169.8; 170.2; 195.8. Anal. calc. for $C_{15}H_7ClN_2O_5S_3$ (%): C 42.21; H 1.65; N 6.56. Found: C 42.04; H 1.47; N 6.61.

2.2.34. 2-bromo-4-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(61)***

Yield 86%, mp = 271–273 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 7.09 d, 7.41 dd, 7.79 d (3H, C_6H_3, J = 2.1, 8.4 Hz); 7.13 s (1H, =CH—COO); 7.55 s (1H, CH=); 13.63 bs (2H, 2NH). ^{13}C NMR δ (ppm) (DMSO-d_6):

110.8; 117.6; 118.9; 123.1; 126.1; 131.3; 136.5; 142.6; 146.8; 157.1; 166.2; 166.7; 169.8; 170.2; 195.7. Anal. calc. for $C_{15}H_7BrN_2O_5S_3$ (%): C 38.23; H 1.50; N 5.94. Found: C 38.40; H 1.51; N 5.83.

2.2.35. 2-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(62)***

Yield 78%, mp = 264–266 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 6.32 s (1H, CH=); 7.14 s (1H, =CH—COO); 7.36–7.52 m, 7.81–7.89 m (4H, C_6H_4); 12.25 s, 12.44 s, 12.98 bs (3H, 3NH).

^{13}C NMR δ (ppm) (DMSO-d_6): 103.7; 116.0; 123.1; 125.5; 127.2; 127.4; 130.2; 130.9; 146.1; 148.8; 164.2; 166.0; 166.4; 169.3; 180.0. Anal. calc. for $C_{15}H_9N_3O_5S_2$ (%): C 47.99; H 2.42; N 11.19. Found: C 47.81; H 2.34; N 11.21.

2.2.36. 3-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(63)***

Yield 76%, mp = 282–284 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 6.49 s (1H, CH=); 7.10 s (1H, =CH—COO); 7.24–7.28 m, 7.50 t, 7.64–7.67 m (4H, C_6H_4, J = 9.6 Hz); 12.19 s, 12.44 s, 12.95 bs (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 110.4; 116.5; 122.7; 122.9; 128.8; 129.1; 130.5; 134.4; 145.7; 150.7; 164.3; 166.2; 166.6; 169.5; 180.0. Anal. calc. for $C_{15}H_9N_3O_5S_2$ (%): C 47.99; H 2.42; N 11.19. Found: C 47.84; H 2.39; N 11.17.

2.2.37. 2-ethoxy-4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(64)***

Yield 65%, mp = 224–226 °C. ^{1}H NMR δ (ppm) (DMSO-d_6): 1.25 t (3H, $OCH_2C\mathbf{H_3}$, J = 6.9 Hz); 4.11 q (2H, $OC\mathbf{H_2}CH_3$, J = 6.9 Hz); 6.50 s (1H, CH=); 7.07 s (1H, =CH—COO); 7.24–7.26 m, 7.38–7.42 m (3H, C_6H_3); 12.06 s, 12.25 s, 12.43 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 15.0; 64.8; 115.9; 116.3; 123.5; 124.2; 125.5; 128.3; 132.3; 140.1; 145.9; 150.4; 163.7; 166.3; 166.5; 169.4; 179.9. Anal. calc. for $C_{17}H_{13}N_3O_6S_2$ (%): C 48.68; H 3.12; N 10.02. Found: C 48.73; H 3.09; N 9.97.

2.2.38. 2-bromo-4-[(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl] phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate ***(65)***

Yield 73%, mp = 276–278 °C. ^{1}H NMR δ (ppm) (DMSO-d_6):6.48 s (1H, CH=); 7.12 s (1H, =CH—COO); 7.44 d, 7.77 dd, 8.13 d (3H, C_6H_3, J = 2.1, 8.4 Hz); 12.17 s, 12.38 s, 12.47 s (3H, 3NH). ^{13}C NMR δ (ppm) (DMSO-d_6): 109.1; 115.6; 116.3; 124.5; 125.5; 129.2; 131.5; 133.2; 134.2; 146.7; 147.8; 163.4; 169.1; 172.5; 180.1. Anal. calc. for $C_{15}H_8BrN_3O_5S_2$ (%): C 39.66; H 1.78; N 9.25. Found: C 39.70; H 1.82; N 9.26.

2.3. Microbiology tests

The following reference strains of bacteria from American Type Culture Collection (ATCC) were used in the study: Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 10876, *Micrococcus luteus* ATCC 10240) and Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Pseudomonas aeruginosa* ATCC 9027). Microbial suspensions were prepared in sterile 0.85% NaCl with an optical density of 0.5 McFarland standard – 150×10^6 CFU/mL (CFU - colony forming units).

All stock solutions of detected compounds were dissolved in dimethyl sulfoxide (DMSO) at final concentration with no inhibitory effect on the growth of bacteria (negative control). The medium with DMSO at the final concentration and without the tested compounds served as negative control. A ciprofloxacin and oxacillin were used as reference antimicrobials.

The tested compounds (**28–65**) antibacterial activity was assayed in two steps. Firstly, it was screened using the agar dilution method on the basis of the microbial growth inhibition. Preliminary antibacterial effect of all compounds was screened on the Petri plates with the Mueller-Hinton agar medium with the tested compounds at concentrations 1000 mg/L. Then the antibacterial activity of the selected compounds with inhibitory effect with 1000 mg/L concentration was determined by broth microdilution technique using 96-well microplates with series of twofold dilution of the tested compounds, as well as the ciprofloxacin and oxacillin in the range of final concentrations from 0.007 to 1000 mg/L, according to described earlier (Trotsko et al., 2012).

The activity was expressed as the minimal inhibitory concentration (MIC) of the compound that inhibits the visible growth of the bacteria. MIC was assayed spectrophotometrically by optical density determination (OD_{600}) using a broth microdilution technique. The MBC (minimal bactericidal concentration), defined as the lowest concentration of each compound that resulted in >99.9% reduction in CFU of the initial inoculum, was also determined. MBC was determined by plating out the contents of wells (5 μL) that showed no visible growth of bacteria, onto Mueller-Hinton agar plates and incubating at 35 °C for 18 h. The compounds were classified as bacteriostatic when the MBC/MIC ratio was greater than or equal to 8 and bactericidal when the MBC/MIC ratio is less than or equal to 4 (Jones, 2006).

2.4. Computational part

Conformational search was performed using the RM1 semiempirical parametrization as implemented in HyperChem 8.0.3. (2007) and default convergence criteria.

3. Results and discussion

3.1. Chemistry

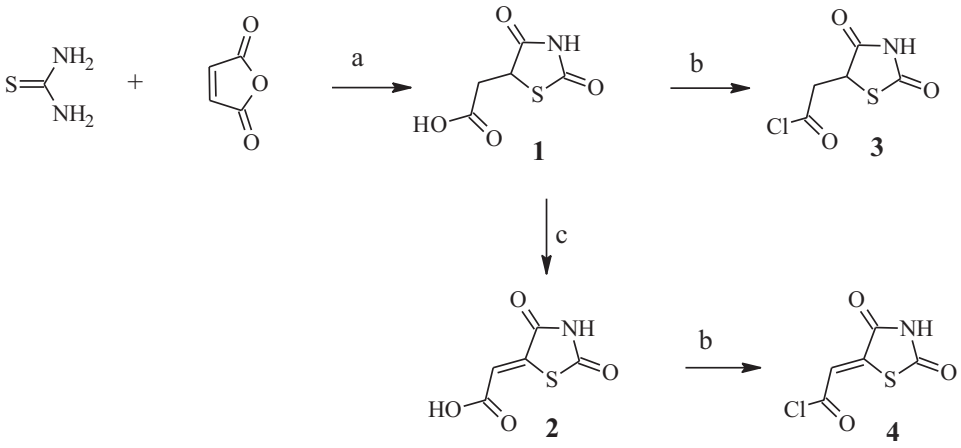
In the present research as a starting material were (2,4-dioxo thiazolidin-5-yl)acetic acid (**1**) and (2,4-dioxothiazolidin-5-yli dene)acetic acid (**2**). The (2,4-dioxothiazolidin-5-yl)acetic acid was synthesized by the reaction of cyclocondensation of thiourea with maleic anhydride in presence of concentrated hydrochloric acid (Lesyk et al., 2001). (2,4-Dioxothiazolidin-5-ylidene)acetic (**2**) was prepared by the reaction of compound (**1**) with bromine in acetic acid medium (Deghenghi and Daneault, 1960). The acids (**1**, **2**) by the reaction with thionyl chloride in anhydrous 1,4-dioxane medium were transformed into acid chlorides (**3**, **4**). Scheme 1 illustrates reactions' pathway.

Next step of synthesis was obtaining of 5-benzylidene derivatives of thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin. These compounds (**8–27**) were synthesized by Knoevenagel condensation of thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin with corresponding hydroxybenzaldehydes. The reactions are shown in Scheme 2.

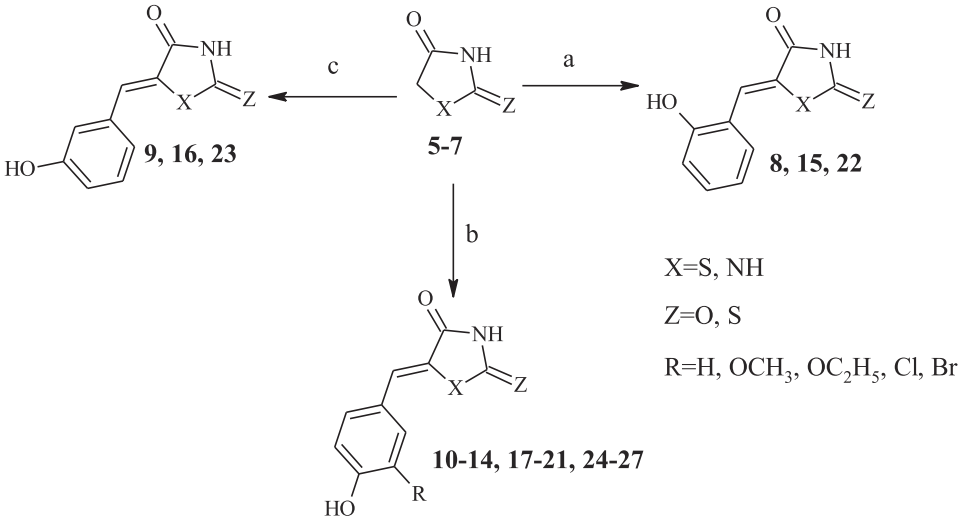
Final step of synthesis was a connection 5-benzylidene derivatives (**8**–**27**) with acid chlorides (**3**, **4**). Target compounds **28**–**65** were prepared from acetic acid chlorides (**3**, **4**) and series of hydroxybenzylidene derivatives of thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin. Reaction was provided in anhydrous 1,4-dioxane medium in the presence of anhydrous pyridine. The synthesis of these compounds (**28**–**65**) was achieved through synthetic route outlined in Scheme 3.

The structure of target compounds (**28**–**65**) was confirmed by elemental analysis, ^{1}H NMR and ^{13}C NMR spectra.

The fragment CH_2CH of compounds (**28**–**47**) that are derivatives of 2-(2,4-dioxothiazolidin-5-yl)acetic acid appeared on ^{1}H NMR spectra as two multiplets in 3.41–3.61 and 4.83–4.97 ppm ranges. For the compounds **32**, **39**, **41**, **42**, **46** and **47** signals of protons of



Scheme 1. Synthesis of (2,4-dioxothiazolidin-5-yl/ylidene)acetic acid chlorides. *Reagents and conditions*: (a) HCl, reflux; (b) $SOCl_2$, DMF, 1,4-dioxane, reflux 1 h; (c) Br_2, CH_3COOH, reflux.



Scheme 2. Synthesis of 5-benzylidene derivatives of thiazolidine-2,4-dione, rhodanine and 2-thiohydantoin. *Reagents and conditions*: (a) salicylaldehyde, sodium acetate and acetic acid, reflux; (b) 4-hydroxybenzaldehyde, vanillin, 3-ethoxy-4-hydroxybenzaldehyde, 3-chloro-4-hydroxybenzaldehyde or 3-bromo-4-hydroxybenzaldehyde, sodium acetate and acetic acid, reflux; (c) 3-hydroxybenzaldehyde, sodium acetate and acetic acid, reflux.

the fragment CH_2CH were visible as doublet in 3.43–3.52 ppm and triplet in 4.84–4.91 ppm ranges.

The proton CH═ benzylidene group appeared in the 7.55–7.87 ppm range as singlet. For the 2-thiohydantoin derivatives (**42**–**47** and **62**–**65**) proton of CH═ group was visible at δ ~6.34–6.56 ppm.

Protons signals of ═CH—COO group of compounds **48**–**65** were visible as a singlet at 7.06–7.21 ppm range.

Protons of NH group of heterocyclic rings appeared in the spectra as singlet or broad singlet in the range 12.06–13.63 ppm. For the compounds (**35**–**41**) that are rhodanine derivatives, proton signal of NH group was observed at 13.78–13.92 ppm range.

The presence of all carbon atoms for compounds (**28**–**65**) is confirmed by ^{13}C NMR spectra. For the compounds **28**–**47**, that are derivatives of 2-(2,4-dioxothiazolidin-5-yl)acetic acid, carbon signal of all C═O groups appeared in the 167.4–176.0 ppm region. Signals of all C═O groups for the 2-(2,4-dioxothiazolidin-5-ylilidene) acetic acid derivatives **48**–**65** were visible at δ ~163.3–169.3 ppm range. Signals of C═S groups of rhodanine ring (**35**–**41** and **55**–**61**) were observed at 195.7–196.3 ppm range but 2-thiohydantoin derivatives (**42**–**47** and **62**–**65**) signals of C═S groups appeared in the 179.8–180.1 ppm region.

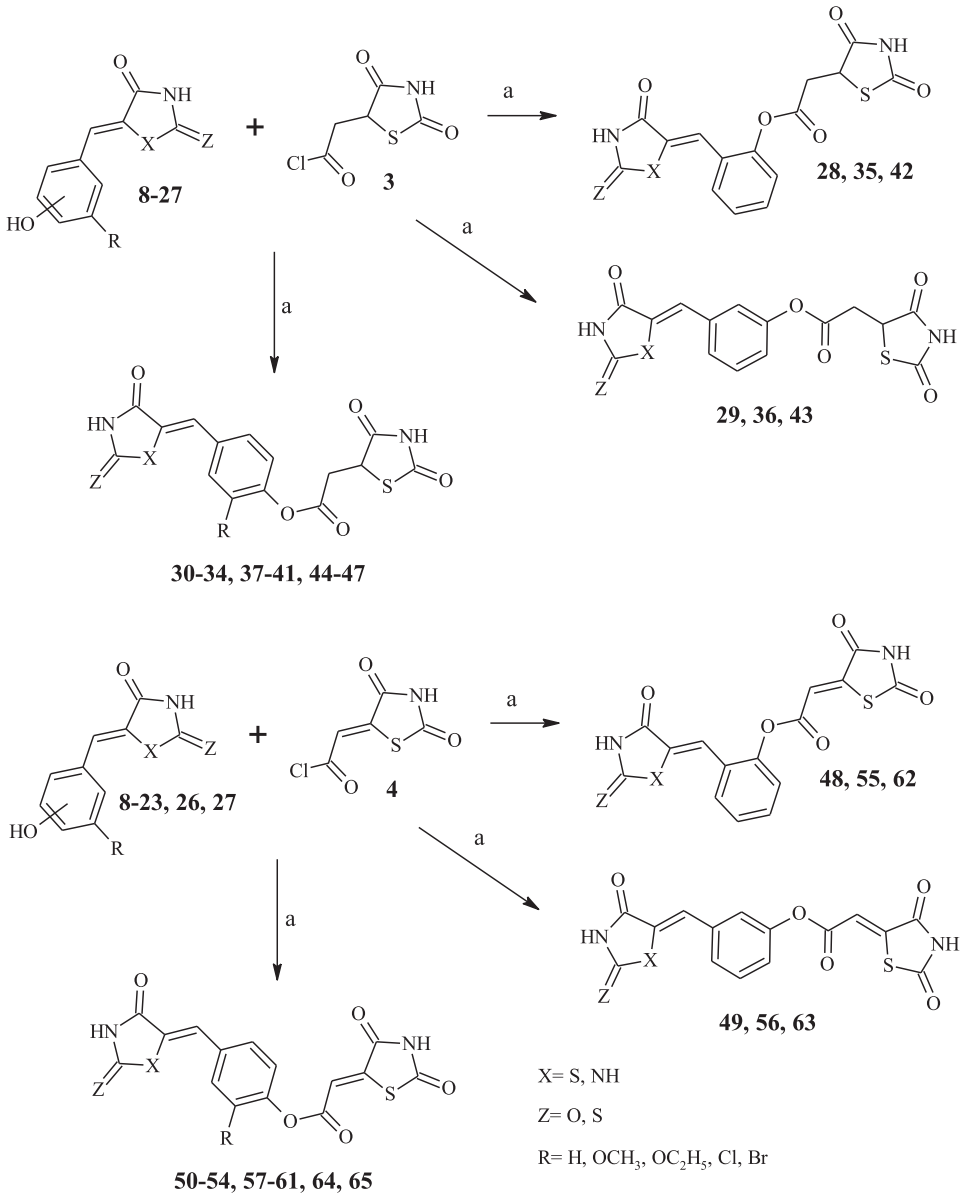
The detailed results of ^1H NMR and ^{13}C NMR spectra are presented in the experimental part.

3.2. Antimicrobial activity

Using the agar broth dilution method, it was shown that most tested compounds inhibited the growth of one to several reference species of bacteria at 1000 mg/L concentration. Only **32**, **46**, **48**–**50** and **55** compounds had no activity against all the tested bacteria.

Next, the compounds with potential inhibitory effect against bacteria was determined using broth dilution method. The variable antibacterial *in vitro* activity against the growth of the tested reference species of Gram-positive bacteria was shown as both concentration and species dependent (Table 1). The tested derivatives had mainly bacteriostatic effect (MBC/MIC > 4) towards the sensitive bacteria.

Among Gram-negative species only *P. mirabilis* ATCC 12453 had moderate sensitivity on **35**, **44**, **45** compounds with MIC = 125 mg/L, and on **62** and **63** compounds with MIC = 250 mg/L. None of the tested compound had inhibitory effect against the growth of Gram-negative *E. coli*, *K. pneumoniae* and *P. aeruginosa* reference species.



Scheme 3. Synthesis of target compounds (**28**–**65**) 2-(2,4-dioxothiazolidin-5-yl/ylidene)acetic acids derivatives. *Reagents and conditions*: (a) pyridine, 1,4-dioxane, rt, after 2 h acidified of solution of hydrochloric acid.

In the absence of detailed information about the molecular target, in order to identify the privileged scaffold for antibacterial activity among various thiazolidine-2,4-dione-based derivatives, we selected five compounds representing series of thiazolidine-2, 4-dione-phenyl-thiazolidine-2,4-dione hybrids (series 1). As indicate from results collected in Table 1, the compound **30** was inactive against all tested Gram-positive bacteria. Adding electron-donating methoxy group to phenyl ring provided compound **31** with potent activity against *S. epidermidis* (MIC 15.63 mg/L) and mild to weak inhibitory activity against remaining Gram-positive bacteria (MICs range from 62.5 to 250 mg/L). Increasing the carbon chain from methyl to ethyl (compound **32**) completely reduced the activity. In turn, the replacement of methoxy group in **31** with electron-withdrawing chloro group as in **33** improved the activity by twofold against *S. aureus* and fourfold against *B. subtilis*. Important to note, **33** inhibited the growth of *B. cereus* at MIC of 3.91 mg/L thereby indicating more effective action than those standard drugs oxacillin and cefuroxime. Finally, incorporation of bromo group within phenyl ring furnished compound **34** with the best activity among all compounds series 1. Indeed, as seen from results collected in Table 1, 34 exhibited antibacterial potency at MIC of 3.91 and 7.81 mg/L against *S. aureus* and *S. epidermidis* reference strains. Moreover, it had activity equipotent to that of oxacillin and cefuroxime against *B. cereus*. These results collectively suggest that the presence of electron-withdrawing substituent at phenyl ring is favorable while geometry of molecule does not play important role in antibacterial response. Indeed, as illustrated in Fig. 1 for representative model compounds, the superposition of the most stable conformers of active and inactive revealed only minor deviations.

Taking into consideration the results highlighted above, the next set of structures included adding double bond between thiazolidine-2,4-dione and ester core. Hence, compounds **50**–**54** (series 2) were synthesized. Within series 2 the best antibacterial response was noted both for compounds with electron-donating ethoxy group **52** and for ones with electron-withdrawing bromo group **54** with MICs in the range from 7.81 to 125 mg/L against all Gram-positive bacterial strains tested, following by **53** with MICs at 31.25 mg/L against *S. aureus* and *S. epidermidis* and **51** with

Table 1
The antibacterial activity of (2,4-dioxo-1,3-thiazolidin-5-yl/ylidene)acetate derivatives (**28**–**65**).

Compound	Gram-positive bacteria												Gram-negative bacteria	
	Sa ATCC 6538		*Sa* ATCC 25,923		*Se* ATCC 12,228		*Bs* ATCC 6633		*Bc* ATCC 10,876		*Ml* ATCC 10,240		*Pm* ATCC 12,453	
	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM	MIC mg/L μM	MBC mg/L μM
28	>1000 >2642.8	nd	>1000 >2.642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	1000 2642.8	>1000 >2642.8
29	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	1000 2642.8	1000 2642.8
30	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	>1000 >2642.8	nd	500 1321.4	>1000 >2642.8
31	125 306.1	250 612.1	250 612.1	250 612.1	15.63 38.3	250 612.1	250 612.1	250 612.1	62.5 153.8	500 1224.3	125 306.1	500 1224.3	>1000 >2448.5	nd
33	125 302.8	>1000 >2422.3	125 302.8	>1000 >2422.3	125 302.8	>1000 >2422.3	62.5 151.4	>1000 >2422.3	3.91 9.5	>1000 >2422.3	125 302.8	>1000 >2422.3	>1000 >2422.3	nd
34	3.91 8.6	>1000 >2186.9	250 546.7	>1000 >2186.9	7.81 17.1	500 1093.4	62.5 136.7	500 1093.4	31.25 68.3	>1000 >2186.9	250 546.7	500 1093.4	>1000 >2186.9	nd
35	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	125 316.9	250 633.8
36	>1000 > 2535.2	nd	>1000 > 2535.2	nd	>1000 > 2535.2	nd	>1000 > 2535.2	nd	>1000 > 2535.2	nd	>1000 > 2535.2	nd	500 1267.6	>1000 > 2535.2
37	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	>1000 >2535.2	nd	1000 2535.2	>1000 >2535.2
38	62.5 147.2	125 294.5	125 294.5	250 589.0	250 589.0	500 1177.9	125 294.5	500 1177.9	62.5 147.2	250 589.0	125 294.5	500 1177.9	>1000 >2355.9	nd
39	125 285.1	>1000 >2280.5	62.5 142.5	>1000 >2280.5	62.5 142.5	>1000 >2280.5	62.5 142.5	>1000 >2280.5	62.5 142.5	>1000 >2280.5	62.5 142.5	>1000 >2280.5	>1000 >2280.5	nd
40	>1000 >2331.6	nd	>1000 >2331.6	nd	>1000 >2331.6	nd	>1000 >2331.6	nd	>1000 >2331.6	nd	>1000 >2331.6	nd	1000 2331.6	1000 2331.6
41	3.91 8.3	1000 2112.6	15.63 33.0	500 1056.3	15.63 33.0	500 1056.3	31.25 66.0	125 264.1	15.63 33.0	>1000 >2112.6	3.91 8.3	250 528.2	>1000 >2112.6	nd
42	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	500 1324.9	1000 2649.7
43	250 662.4	>1000 >2649.7	500 1324.9	>1000 >2649.7	250 662.4	>1000 >2649.7	62.5 165.6	1000 2649.7	500 1324.9	>1000 >2649.7	125 331.2	>1000 >2649.7	>1000 >2649.7	nd
44	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	>1000 >2649.7	nd	125 331.2	>1000 >2649.7
45	>1000 >2454.5	nd	>1000 >2454.5	nd	>1000 >2454.5	nd	>1000 >2454.5	nd	>1000 >2454.5	nd	>1000 >2454.5	nd	125 306.8	>1000 >2454.5
47	7.81 17.1	31.25 68.5	1000 2191.6	1000 2191.6	31.25 68.5	1000 2191.6	3.91 8.6	250 547.9	31.25 68.5	1000 2191.6	250 547.9	1000 2191.6	>1000 >2191.6	nd
51	250615.2	>1000 >2460.7	500 1230.3	>1000 >2460.7	62.5 153.8	>1000 >2460.7	125 307.6	>1000 >2460.7	31.25 76.9	1000 2460.7	62.5 153.8	>1000 >2460.7	>1000 >2460.7	nd
52	15.63 37.2	125 297.3	125 297.3	>1000 > 2378.6	62.5 148.7	>1000 > 2378.6	15.63 37.2	>1000 > 2378.6	31.25 74.3	>1000 > 2378.6	31.25 74.3	>1000 > 2378.6	>1000 > 2378.6	nd
53	31.25 76.1	>1000 >2434.2	125 304.3	1000 2434.2	31.25 76.1	1000 2434.2	125 304.3	500 1217.1	125 304.3	>1000 >2434.2	125 304.3	>1000 >2434.2	>1000 >2434.2	nd
54	62.5 137.3	>1000 >2196.5	31.25 68.6	>1000 >2196.5	7.81 17.2	>1000 >2196.5	125 274.6	>1000 >2196.5	31.25 68.6	>1000 >2196.5	31.25 68.6	500 1098.3	>1000 >2196.5	nd
56	31.25 79.6	1000 2548.2	7.81 19.9	1000 2548.2	125 318.5	500 1274.1	250 637.1	500 1274.1	15.63 39.8	500 1274.1	15.63 39.8	500 1274.1	>1000 >2548.2	nd
57	125 318.5	>1000 >2548.2	62.5 159.3	>1000 >2548.2	31.25 79.6	>1000 >2548.2	62.5 159.3	>1000 >2548.2	125 318.5	>1000 >2548.2	31.25 79.6	>1000 >2548.2	>1000 >2548.2	nd
58	62.5 147.9	250 591.8	31.25 74.0	500 1183.6	15.63 37.0	250 591.8	31.25 74.0	500 1183.6	15.63 37.0	500 1183.6	15.63 37.0	500 1183.6	>1000 > 2367.1	nd
59	15.63 35.8	1000 2291.0	62.5 143.2	>1000 >2291.0	125 286.4	1000 2291.0	31.25 71.6	1000 2291.0	15.63 35.8	>1000 >2291.0	15.63 35.8	>1000 >2291.0	>1000 >2291.0	nd
60	7.81 18.3	500 1171.3	62.5 146.4	250 585.7	31.25 73.2	250 585.7	250 585.7	1000 2342.6	31.25 73.2	1000 2342.6	250 585.7	>1000 >2342.6	>1000 >2342.6	nd
61	31.25 66.3	>1000 >2121.7	62.5 132.6	>1000 >2121.7	125 265.2	>1000 >2121.7	62.5 132.6	250 530.4	62.5 132.6	1000 2121.7	125 265.2	>1000 >2121.7	>1000 > 2121.7	nd
62	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	250 666.0	>1000 >2664.0
63	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	>1000 >2664.0	nd	250 666.0	>1000 >2664.0
64	31.25 74.5	1000 2384.2	500 1192.1	>1000 >2384.2	31.25 74.5	>1000 >2384.2	500 1192.1	>1000 >2384.2	62.5 149.0	>1000 >2384.2	15.63 37.3	>1000 >2384.2	>1000 >2384.2	nd
65	1000 2201.3	>1000 >2201.3	1000 2201.3	>1000 >2201.3	500 1100.7	>1000 >2201.3	500 1100.7	>1000 >2201.3	500 1100.7	>1000 >2201.3	1000 2201.3	500 1100.7	>1000 >2201.3	nd

(*continued on next page*)

Table 1 (*continued*)

Compound	Gram-positive bacteria												Gram-negative bacteria	
	Sa ATCC 6538		*Sa* ATCC 25,923		*Se* ATCC 12,228		*Bs* ATCC 6633		*Bc* ATCC 10,876		*Ml* ATCC 10,240		*Pm* ATCC 12,453	
	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM	MIC mg/L µM	MBC mg/L µM
Oxacillin	0.06 0.15	0.06 0.15	nd	nd	0.12 0.3	0.12 0.3	0.06 0.15	0.12 0.3	62.5 155.7	62.5 155.7	0.98 2.4	0.98 2.4	0.24 0.6	0.49 1.2
Ciprofloxacin	0.49 1.5	0.49 1.5	nd	nd	0.49 1.5	0.49 1.5	0.015 0.05	0.12 0.4	0.12 0.4	0.12 0.4	0.98 3.0	1.95 5.9	0.015 0.05	0.24 0.7
Cefuroxime[a]	nd	nd	0.49 1.2	nd	0.24 0.6	nd	15.63 36.8	nd	31.25 73.6	nd	0.98 2.3	nd	nd	nd

Abbreviations: *Sa* ATCC 25,923 - *Staphylococcus aureus* ATCC 25,923, *Sa* ATCC 6538 - *Staphylococcus aureus* ATCC 6538, *Se* ATCC 12,228 - *Staphylococcus epidermidis* ATCC 12,228, *Bs* 6633 - *Bacillus subtilis* ATCC 6633, *Bc* ATCC 10,876 – *Bacillus cereus* ATCC 10,876, *Ml* 10,240 - *Micrococcus luteus* ATCC 10,240, *Pm* ATCC 12,453- *Proteus mirabilis* ATCC 12,453; nd - not determined.

[a] Data derived from Plech et al. (2013).

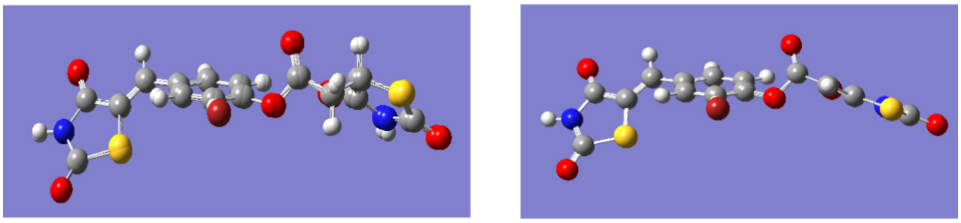


Fig. 1. Superposition diagram of compounds active **34** and inactive **30** (left) and active **54** and inactive **50** (right). Remaining compounds within series 1, 4 and 5 share geometry of molecule very similar to that of compounds **34** and **30** while all compounds series 2 and 3 share geometry of molecule very similar to that of compounds **54** and **50**.

MIC = 31.25 mg/L against *B. cereus*. Again, no antibacterial response was detected for compound without substitution at phenyl ring (**50**) suggesting that such core is not tolerated. The second important result of these studies is that geometry of molecule is not detrimental for activity; in spite of the fact that compounds of series 2 differ in the geometry of the molecule from the compounds of series 1, their activity is not uniquely favorable.

Subsequently, series 3, structurally very similar to that of series 2 was synthesized. The compounds were obtained by replacement thiazolidine-2,4-dione with rhodanine ring. Again, the observed trend in antibacterial activity cannot be not easily explain. In contrast to series 2, within this chemical series the best antibacterial response (MIC = 7.81 mg/L) was detected for compound with electron-withdrawing chloro substitution (**60**). However, the potent antibacterial effect for **60**, even comparable to oxacillin and cefuroxime, was observed only against *S. aureus* and *B. cereus*; remaining Gram-positive bacterial strains were able to grow at high concentrations (MICs from 31.25 to 62.50 mg/L) or even were almost insensitive to **60** (MICs = 250 mg/L). In turn, compound **58** with electron-donating methoxy substitution showed fourfold better activity than oxacillin and twofold better than cefuroxime against *B. cereus*. The same level of its activity with MIC at 15.63 mg/L was also observed against *M. luteus*. In contrast to series 1, increasing the carbon chain from methyl to ethyl gave compound **59** with comparable activity to **58**; MICs in the range from 15.63 to 62.5 mg/L. Surprisingly, for the first time antibacterial response was also observed for derivative with phenyl core, compound **57**. Important to note, although activity of **57** was not impressive, MICs in the range from 31.25 to 125 mg/L, it was still comparable to these obtained for **61** with bromo substitution. This is very important result, because it further confirms the lack of direct influence of substitution pattern at phenyl ring on antibacterial activity of closely related compounds of series 1–3. Unfortunately, the results for series 4 exclude the direct relationship between geometry and antibacterial activity as well. Indeed, although two compounds of series 4 were inactive (**37** and **40**) and two other had only marginal activity (**38** and **39**; MICs at 62.5 mg/L or higher), this series still contains bromo derivative **41** ranked among the most potent antibacterial agents tested so far. It is important to note that also within series 1, that is structurally closely related to series 4, the best antibacterial activity was found also for bromo derivative **34**.

Next, the rhodanine ring of series 4 was replacement with 2-thiohydantoin ring and compounds series 5 were obtained. Similar to the SAR with series 1 and 4, compound with bromo substitution **47** was effective against most of the Gram-positive strains tested with MICs in the range from 3.91 to 31.25 mg/L. Remaining compounds with this chemical series were inactive even at high concentration. A point worth highlighting is that adding double bond to compound **47** significantly reduced antibacterial activity of the compound **65** (MICs = 500–1000 mg/L), which is consistent with the results highlighted above.

Finally, in order to clearly exclude phenyl core from future research, two series of regioisomerics, series 6 with *meta* substitution and series 7 with *ortho* substitution were obtained and subsequently tested. As we expected, with the exception of **56** with MICs in the range from 7.81 to 15.63 mg/L against most of the tested Gram-positive bacteria and **43** with marginal activity, no antibacterial response was observed.

To the same conclusion are provided by the analysis of structure-activity relationships of studied compounds in terms of their micromolar concentrations.

4. Conclusions

A series of new thiazolidine-2,4-dione-phenyl-azoles hybrids were synthesized. These derivatives were assayed for antibacterial activity. Most tested compounds were shown antibacterial activity against Gram-positive bacteria. As a result of antibacterial evaluation our research showed that the presence of electron-

withdrawing substituent at phenyl ring for thiazolidine-2,4-dione-phenyl-azoles hybrids is favorable while geometry of molecule does not play important role in antibacterial response. The second important result of these studies is that geometry of molecule is not detrimental for activity. Further confirmed the lack of direct influence of substitution pattern at phenyl ring on antibacterial activity of closely related compounds of series 1–3. Unfortunately, the results for series 4 exclude the direct relationship between geometry and antibacterial activity as well. The antibacterial activity of some compounds was similar or higher than the activity of commonly used reference drugs such as oxacillin and cefuroxime.

Conflict of interest

None.

References

Aneja, D.K., Lohan, P., Arora, S., Sharma, C., Aneja, K.R., Prakash, O., 2011. Synthesis of new pyrazolyl-2, 4-thiazolidinediones as antibacterial and antifungal agents. Org. Med. Chem. Lett. 1, 15. https://doi.org/10.1186/2191-2858-1-15.

Asati, V., Mahapatra, D.K., Bharti, S.K., 2014. Thiazolidine 2,4-diones as multi-targed scaffold in medicinal chemistry: Potential anticancer agents. Eur. J. Med. Chem. 87, 814–833.

Barros, C.D., Amato, A.A., De Oliveira, T.B., Iannini, K.B.R., Da Silva, A.L., Da Silva, T.G., Leite, E.S., Marcelo Zaldini Hernandes, M.Z., De Lima, M.C.A., Galdino, S.L., Neves, F.A.R., Pitta, I.R., 2010. Synthesis and anti-inflammatory activity of new arylidene-thiazolidine-2,4-diones as PPARγ ligands. Bioorg. Med. Chem. 18, 3805–3811.

Bozdağ-Dündar, O., Özgen, Ö., Menteşe, A., Altanlar, N., Atlı, O., Kendi, E., Ertan, R., 2007. Synthesis and antimicrobial activity of some new thiazolyl thiazolidine-2,4-dione derivatives. Bioorg. Med. Chem. 15, 6012–6017.

Chauhan, K., Sharma, M., Singh, P., Kumar, V., Shukla, P.K., Siddiqi, M.I., Chauhan, P. M.S., 2012. Discovery of a new class of dithiocarbamates and rhodanine scaffold as potent antifungal agent: synthesis, biology and molecular docking. Med. Chem. Commun. 3, 1104–1110.

Cutshall, N.S., O'Day, C., Prezhdo, M., 2005. Rhodanine derivatives as inhibitors of JSP-1. Bioorg. Med. Chem. Lett. 15, 3374–3379.

Deghenghi, R., Daneault, G., 1960. Orotic acid and its analogues: part II. On the alkaline rearrangement of 5-carboxymethylidenehydantoin. Can. J. Chem. 38, 1255–1260.

Desai, N.C., Satodiya, H.M., Rajpara, K.M., Joshi, V.V., Bhatt, K., Vaghani, H.V., 2014b. Synthesis and evaluation of *N*-substituted thiazolidine-2,4-dione containing pyrazole as potent antimicrobial agents. Anti-Infective Agents 12, 85–94.

Desai, N.C., Satodiya, H.M., Kotadiya, G.M., Vaghani, H.V., 2014a. Synthesis and antibacterial and cytotoxic activities of new N-3 substituted thiazolidine-2,4-dione derivatives bearing the pyrazole moiety. Arch. Pharm. Chem. Life Sci. 347, 523–532.

El Hady, H.A., 2012. Syntheses and antimicrobial activity of some new thiohydantoin and thiazole derivatives. Der Pharma Chemica 4, 2202–2207.

Gangadhar, S.P., Ramesh, D.K., Mahajan, S.K., 2013. Synthesis, characterisation and anticonvulsant activity of 3-substituted 2-thiohydantoin derivatives. Int. J. Res. Pharm. Chem. 3, 793–796.

Hardej, D., Ashby, C.R., Khadtare, N.S., Kulkarni, S.S., Singh, S., Talele, T.T., 2010. The synthesis of phenylalanine-derived C5-substituted rhodanines and their activity against selected methicillin-resistant *Staphylococcus aureus* (MRSA) strains. Eur. J. Med. Chem. 45, 5827–5832.

Heerding, D.A., Christmann, L.T., Clark, T.J., Holmes, D.J., Rittenhouse, S.F., Takata, D. T., Venslavsky, J.W., 2003. New benzylidenethiazolidinediones as antibacterial agents. Bioorg. Med. Chem. Lett. 13, 3771–3773.

HyperChem 8.0.3. HyperCube Inc., Gainsville, FL, USA, 2007.

Ibrahim, M.A., Abdel-Megid Abdel-Hamed, M., El-Gohary, N.M., 2011. A new approach for the synthesis of bioactive heteroaryl thiazolidine-2,4-diones. J. Braz. Chem. Soc. 22, 1130–1139.

Irvine, M.W., Patrick, G.L., Kewney, J., Hastings, S.F., MacKenzie, S.J., 2008. Rhodanine derivatives as novel inhibitors of PDE4. Bioorg. Med. Chem. Lett. 18, 2032–2037.

Jeong, T.-S., Kim, J.-R., Kim, K.S., Cho, K.-H., Bae, K.-H., Lee, W.S., 2004. Inhibitory effects of multi-substituted benzylidenethiazolidine-2,4-diones on LDL oxidation. Bioorg. Med. Chem. 12, 4017–4023.

Jiang, S., Tala, S.R., Lu, H., Abo-Dya, N.E., Avan, I., Gyanda, K., Lu, L., Katritzky, A.R., Debnath, A.K., 2011. Design, synthesis, and biological activity of novel 5-((arylfuran/1H-pyrrol-2-yl)methylene)-2-thioxo-3-(3-(trifluoromethyl)phenyl) thiazolidin-4-ones as HIV-1 Fusion Inhibitors Targeting gp41. J. Med. Chem. 54, 572–579.

Jones, R.N., 2006. Microbiological features of vancomycin in the 21st century: Minimum inhibitory concentration creep, bactericidal/static activity and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin. Infect. Dis. 42, S13–S24.

Koppireddi, S., Komsani, J.R., Avula, S., Pombala, S., Vasamsetti, S., Kotamraju, S., Yadla, R., 2013. Novel 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides as antioxidant and/or anti-inflammatory compounds. Eur. J. Med. Chem. 66, 305–313.

Lesyk, R.B., Zimenkovsky, B.S., Golota, S.M., Leb'yak, M.M., 2001. Synthesis of 2,4-dioxothiazolidine-5-acetic acid and its amides - perspective synthons for obtaining combinatorial libraries of biologically active substances. Farm. Zh. (Kiev) 5, 57–62.

Liu, X., Xie, H., Luo, C., Tong, L., Wang, Y., Peng, T., Ding, J., Jiang, H., Li, H., 2010. Discovery and SAR of thiazolidine-2,4-dione analogues as insulin-like growth factor-1 receptor (IGF-1R) inhibitors via hierarchical virtual screening. J. Med. Chem. 53, 2661–2665.

Liu, X.-F., Zheng, C.-J., Sun, L.-P., Liu, X.-K., Piao, H.-R., 2011. Synthesis of new chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties as potential anti-bacterial agents. Eur. J. Med. Chem. 46, 3469–3473.

Marc, G., Ionuț, I., Pîrnău, A., Vlase, L., Vodnar, D.C., Duma, M., Tiperciuc, B., Oniga, O., 2017. Microvawe assisted synthesis of 3,5-disubstituted thiazolidine-2,4-diones with antifungal activity. Design, synthesis, virtual and *in vitro* antifungal screening. Farmacia 65, 414–422.

Miao, J., Zheng, C.-J., Sun, L.-P., Song, M.-X., Xu, L.-L., Piao, H.-R., 2013. Synthesis and potential antibacterial activity of new rhodanine-3-acetic acid derivatives. Med. Chem. Res. 22, 4125–4132.

Min, G., Lee, S.K., Kim, H.N., Han, Y.M., Lee, R.H., Jeong, D.G., Han, D.C., Kwon, B.M., 2013. Rhodanine-based PRL-3 inhibitors blocked the migration and invasion of metastatic cancer cells. Bioorg. Med. Chem. Lett. 23, 3769–3774.

Moorthy, B.T., Ravi, S., Srivastava, M., Chiruvella, K.K., Hemlal, H., Joy, O., Raghavan, S.C., 2010. Novel rhodanine derivatives induce growth inhibition followed by apoptosis. Bioorg. Med. Chem. Lett. 20, 6297–6301.

Patil, V., Tilekar, K., Mehendale-Munj, S., Mohan, R., Ramaa, C.S., 2010. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives. Eur. J. Med. Chem. 45, 4539–4544.

Plech, T., Wujec, M., Majewska, M., Kosikowska, U., Malm, A., 2013. Microbiologically active Mannich bases derived from 1,2,4-triazoles. The effect of C-5 substituent on antibacterial activity. Med. Chem. Res. 22, 2531–2537.

Purohit, S.S., Alman, A., Shewale, J., 2012. Synthesis & antimicrobial activity of a new series of 3, 5-disubstituted thiazolidine-2, 4-diones. Int. J. Pharm. Pharm. Sci. 4 (Suppl. 3), 273–276.

Rajamaki, S., Innitzer, A., Falciani, C., Tintori, C., Christ, F., Witvrouw, M., Debyser, Z., Massa, S., Botta, M., 2009. Exploration of novel thiobarbituric acid-, rhodanine- and thiohydantoin-based HIV-1 integrase inhibitors. Bioorg. Med. Chem. Lett. 19, 3615–3618.

Salamone, S., Colin, C., Grillier-Vuissoz, I., Kuntz, S., Mazerbourg, S., Flament, S., Martin, H., Richert, L., Chapleur, Y., Boisbrun, M., 2012. Synthesis of new troglitazone derivatives: Anti-proliferative activity in breast cancer cell lines and preliminary toxicological study. Eur. J. Med. Chem. 51, 206–215.

Shaikh, F.M., Patel, N.B., Rajani, D., 2013. Synthesis of new thiazolidine-2,4-dione derivatives and their antimicrobial and antitubercular activity. Indian J. Res. Pharm. Biotechnol. 1, 496–503.

Song, M.-X., Zheng, C.-J., Deng, X.-Q., Wei, Z.-Y., Piao, H.-R., 2014. The synthesis and antibacterial activities of N-carboxymethyl rhodanines. Med. Chem. 4, 441–448.

Sortino, M., Delgado, P., Juárez, S., Quiroga, J., Abonía, R., Insuasty, B., Nogueras, M., Rodero, L., Garibotto, F.M., Enriz, R.D., Zacchino, S.A., 2007. Synthesis and antifungal activity of (Z)-5-arylidenerhodanines. Bioorg. Med. Chem. 15, 484–494.

Trojanowski, D., Skut, P., Hołówka, J., Szafran, M.J., 2014. Searching for new antibiotics – inhibitors of bacterial chromosome replication. Postepy Hig. Med. Dosw. (online) 68, 701–714.

Trotsko, N., Król, J., Siwek, A., Wujec, M., Kosikowska, U., Malm, A., 2012. Synthesis and antimicrobial evaluation of new 1-{[4-(4-halogenophenyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetyl-4-substituted thiosemicarbazides and products of their cyclization. Heteroatom Chem. 23, 117–121.

Trotsko, N., Wujec, M., Kosikowska, U., Malm, A., 2017. Synthesis of new (2,4-dioxothiazolidin-5-yl)acetic acid derivatives with piperazine and 1,2,4-triazole substitutes and their antimicrobial activity evaluation. Int. J. Med. Chem. Anal. 7, 41–47.

Tuncbilek, M., Altanlar, N., 2006. Synthesis of new 3-(substituted phenacyl)-5-[3′-(4*H*-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinediones and their antimicrobial activity. Arch. Pharm. 339, 213–216.

Villain-Guillot, P., Gualtieri, M., Bastide, L., Roquet, F., Martinez, J., Amblard, M., Pugniere, M., Leonetti, J.P., 2007. Structure-activity relationships of phenyl-furanyl-rhodanines as inhibitors of RNA polymerase with antibacterial activity on biofilms. J. Med. Chem. 50, 4195–4204.

Wu, F., Jiang, H., Zheng, B., Kogiso, M., Yao, Y., Zhou, C., Li, X.-N., Song, Y., 2015. Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases by 2-thiohydantoin compounds. J. Med. Chem. 58, 6899–6908.

Zheng, C.J., Song, M.X., Sun, L.P., Wu, Y., Hong, L., Piao, H.R., 2012. Synthesis and biological evaluation of 5-aryloxypyrazole derivatives bearing a rhodanine-3-aromatic acid as potential antimicrobial agents. Bioorg. Med. Chem. Lett. 22, 7024–7028.

Zvarec, O., Polyak, S.W., Tieu, W., Kuan, K., Dai, H., Pedersen, D.S., Morona, R., Zhang, L., Booker, G.W., Abell, A.D., 2012. 5-Benzylidenerhodanine and 5-benzylidene-2,4-thiazolidinedione based antibacterials. Bioorg. Med. Chem. Lett. 22, 2720–2722.