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Research Article

Antioxidant properties of some novel derivatives thiazolo[4,5-*b*] pyridine

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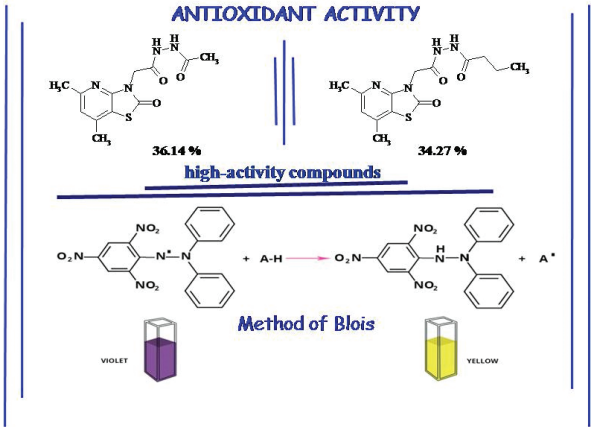
Abstract

The synthesis and determination of the antioxidant activity of some novel (5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetic acid hydrazide derivatives are described in this article. The transformation of the base heterocycle was carried out via the reactions of acylation, [2+3]cyclocondensation, Knoevenagel condencation and alkylation for the purpose to obtain substances with a satisfactory pharmacological profile. Antioxidant activity of the synthesized compounds was evaluated *in vitro* by means of the scavenging metod effect on 2,2 diphenyl-1-picrylhydrazyl (DPPH) radicals.



Keywords

antioxidant activity, 2,2 diphenyl-1-picrylhydrazyl, synthesis, thiazolo[4,5-*b*]pyridines

Introduction

Development of an effective and safe antioxidant compound is still challenging in the last few decades. There has been an increasing interest in the role of reactive oxygen species (ROS) in food, drugs, and even living system (Riley 1994). Free radical formation is associated with the normal natural metabolism of aerobic cells. They are inevitably exposed to reactive oxygen species (ROS) formed as oxygen metabolites. Oxidative stress which is largely characterized by reactive oxygen and nitrogen species is implicated in the development of a number of chronic and degenerative diseases such as atherosclerosis, cancer, cirrhosis, diabetes, wound healing and aging (Valko et al. 2005, 2006; Parthasarathy et al. 1999). Free radicals are highly reactive and therefore can attack membrane lipids, generating carbon radicals and peroxy radicals, which cause lipid peroxidation (Amarowicz et al. 2010). Therefore, scientists in various disciplines have become more interested in naturally-occurring antioxidants as well as in related synthetic derivatives that could provide active components which prevent or reduce the impact of oxidative stress.

Synthesis innovations that are enabling the development of the condensed heterocycles (Chaban et al. 2017a, 2018a) with the antioxidant efficiency are essential challenge of nowadays. In this article we described antioxidant properties investigation of thiazolo[4,5-*b*]pyridine derivatives. It should be noticed that thiazolopyridines have a wide range of biological activities on account of their iso-steric similarity to the structure of pyrine and pyrimidine bases. Some thiazolo[4,5-*b*]pyridines were described as potent antimicrobial agents (Sayed et al. 2010). They also show potent A*b* 42 fibrillization inhibitory activities in Alzheimer's disease treatment (Lee et al. 2008). Among this type of substances, several compounds were found to possess fungicidal (Marzoog and Al-Thebeiti 1978), anti-inflammatory (Chaban et al. 2016, 2017b, 2018b, 2019a, b), tuberculostatic (Chaban et al. 2014), antioxidant (Chaban et al. 2013; Klenina et al. 2013, 2017) and antitumor effects (Chaban et al. 2012a). Some of them are H3 receptor antagonists (Walczyn´ski et al. 2005), or act as antagonists of metabotropic glutamate receptors 5 (mGluR5) (Lin et al. 2009), they are of high inhibitory activity with respect to the receptors of the epidermal growth factor (Komoriya et al. 2006), and were revealed to activate the GK enzyme *in vitro* and significantly reduces glucose levels (Singh et al. 1995). Thiazolopyridine derivatives have also been used as sensitive analytical reagents (Lozynska et al. 2015; Tymoshuk et al. 2019). Thus, the research to explore different chemical modifications avenues of thiazolo[4,5-*b*]pyridine-2-ones to obtain novel active compounds should be continued.

Experimental Part

Materials and methods

All chemicals were of analytically grade and commercially available. All reagents and solvents were used without further purification and drying. Compounds' ^{1}H NMR spectra in DMSO-d6 solution were registered by means of a spectrometer Varian Mercury VX-400 (400 MHz), internal reference TMS. Experimental data elemental analysis on contents of Carbon, Hydrogen and Nitrogen correspond to calculated ones (±0.3%). Chemical shifts are reported in ppm units using a δ scale.

Ascorbic acid was purchased from a medical store.

Chemistry

*General procedure for the synthesis of N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetyl] carboxylic acids hydrazides obtained during interaction of aromatic chloroanhydrides with (5,7-dimethyl-2-oxo-thiazolo[4,5-b] pyridine-3-yl)-acetic acid hydrazide (**1d–j**).* To a solution of pyridine (20 mL) and an appropriate aromatic chloroanhydride (5 mmol) was added (5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetic acid hydrazide (5 mmol). Reaction mixture was refluxed 30 min. On cooling the crystalline precipitate was filtered off, washed with acetic acid and dried. The obtained compounds were re-crystallized from acetic acid.

1-(3,4-Dimethyl-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1d***). Yield 67%, m.p. = 174–175 °C. ^{1}HNMR (400 MHz, DMSO-d6) d 2.05 (s, 3H, C_6H_3-CH_3), 2.12 (s, 3H, C_6H_3-CH_3), 2.33 (s, 3H, CH_3), 2.45 c (3H, CH_3), 3.05 (s, 3H, triazole-CH_3), 4.82 (s, 2H, CH_2), 6.84 (d, 1H, *J* = 8.0 Hz, C_6H_3), 7.02 (s, 1H, Py), 7.12–7.15 (m, 2H, *J* = 7.2 Hz, C_6H_3), 10.40 (s, 2H, CONH), 10.51 (s, 2H, NHCO). Anal. Calculated for $C_{22}H_{23}N_7O_3S$%: C, 56.76; H, 4.98; N, 21.06. Found %: C, 56.88; H, 5.02; N, 21.25.

1-(2,4-Dimethyl-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1e***). Yield 71%, m.p. = 179–180 °C. ^{1}HNMR (400 MHz, DMSO-d6) d 1.99 (s, 3H, C_6H_3-CH_3), 2.09 (s, 3H, C_6H_3-CH_3), 2.33 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.05 (s, 3H, triazole-CH_3), 4.80 (s, 2H, CH_2), 6.94 (d, 1H, *J* = 8.1 Hz,C_6H_3), 7.02 (s, 1H, Py), 7.30–7.32 (m, 1H,C_6H_3), 7.82–7.84 (m, 1H,C_6H_3), 10.29 (s, 2H, CONH), 10.49 (s, 2H, NHCO). Anal. Calculated for $C_{22}H_{23}N_7O_3S$%: C, 56.76; H, 4.98; N, 21.06. Found %: C, 56.89; H, 4.95; N, 21.13.

1-(2-Chloro-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1f***). Yield 76%, m.p. = 164 °C. ^{1}HNMR (400 MHz, DMSO-d6) d 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.07 (s, 3H, triazole -CH_3), 4.81 (s, 2H, CH_2), 7.01 (s, 1H, Py), 6.90–6.95 (m, 1H, C_6H_3), 7.40–7.49 (m, 1H, C_6H_4), 7.54–7.57 (m, 2H, C_6H_4), 10.33 (s, 2H,CONH), 10.54 (s, 2H, NHCO). Anal. Calculated for $C_{20}H_{18}ClN_7O_3S$%: C, 50.90; H, 3.84; N, 20.78. Found %: C, 50.86; H, 3.88; N, 20.71.

4-Chloro-benzoic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1g***). Yield 78%,

m.p.= 160–161 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.05 (s, 1H, Py), 7.52 (d, 2H, *J* = 8.3 Hz, C_6H_4), 7.79 (d, 2H, *J* = 8.3 Hz, C_6H_4), 10.33 (s, 2H, CONH), 10.53 (s, 2H, NHCO). Anal. Calculated for $C_{17}H_{15}ClN_4O_3S$%: C, 52.24; H, 3.87; N, 14.33. Found %: C, 52.33; H, 3.95; N, 14.25.

4-Benzyloxy-benzoic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1h***). Yield 78%, m.p. = 160 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.30 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.82 (s, 2H, N-CH_2), 5.35 (s, 2H, CH_2), 7.03 (s, 1H, Py), 7.49 (d, 2H, *J* = 8.3 Hz, C_6H_4), 7.57–7.60 (m, 3H, C_6H_5), 7.73 (d, 2H, *J* = 8.3 Hz, C_6H_4), 7.85 (d, 2H, *J* = 8.5 Hz, C_6H_5), 10.54 (s, 2H, CONH), 10.67 (s, 2H, NHCO). Anal. Calculated for $C_{24}H_{22}N_4O_4S$%: C, 62.32; H, 4.79; N, 12.11. Found %: C, 62.17; H, 4.01; N, 12.15.

3-(4-Methoxy-phenyl)-acrylic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1i***). Yield 81%, m.p. = 162 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.29 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.57 (s, 3H, O-CH_3), 4.82 (s, 2H, CH_2), 7.03 (s, 1H, Py), 7.61 (d, 2H, *J* = 8.3 Гц, C_6H_4), 7.81 (d, 1H, *J* = 14.9 Гц, CH), 7.88 (d, 2H, *J* = 8.3 Гц, C_6H_4), 8.72 (d, 1H, *J* = 14.8 Гц, CH), 10.39 (s, 2H, CONH), 10.68 (s, 2H, NHCO). Anal. Calculated for $C_{20}H_{20}N_4O_4S$ %: C, 58.24; H, 4.89; N, 13.58. Found %: C, 58.07; H, 4.80; N, 13.65.

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***1j***). Yield 66%, m.p. = 182 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.26 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.85 (s, 2H, N-CH_2), 5.23 (s, 2H, CO-CH_2), 7.02 (s, 1H, Py.), 7.38–7.50 (m, 2H, indan), 7.80–7.85 (m, 2H, indan), 10.41 (s, 2H, CONH), 10.65 (s, 2H, NHCO). Anal. Calculated for $C_{20}H_{17}N_5O_5S$%: C, 54.66; H, 3.90; N, 15.94. Found %: C, 54.41; H, 3.87; N, 16.05.

General procedure for the synthesis of hetarylsulfanyl derivatives of N'-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetyl hydrazide acetic acid (***2a–d***). Compound **1b** (0.005 mol), appropriate thiol (0.005 mol) and ethanol (20 ml) were mixed in a round bottom flask. The reaction mixture was refluxed 1 h. The precipitate which formed on cooling was filtered off, washed with ethanol, and dried. The precipitate was re-crystallized from methanol.

[4-Amino-5-(4-methyl-furan-3-yl)-4H-pyrazol-3-ylsulfanyl]-acetic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***2a***). Yield 81%, m. p. 159 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.13 s (3H, furan-CH_3), 2.28 s (3H, CH_3), 2.43 s (3H, CH_3), 4.10 s (2H, CH_2), 4.66 s (2H, N-CH_2), 6.09 s (2H, NH_2), 7.01 s (1H, Py), 7.08 s (1H, aryl), 7.68 s (1H, aryl), 9.74 s (1H, CO-NH), 10.93 s (1H, NH-CO). Anal. Calculated for $C_{20}H_{21}N_7O_4S_2$ (%):C, 49.27; H, 4.34; N, 20.11. Found %: C, 50.05; H, 4.32; N, 19.96.

(5-Phenyl[1,3,4]oxodiazole-2-ylsulfanyl)-N'-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)- acetyl hydrazide acetic acid (***2b***). Yield 70%, m. p. 180–181 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.25 s (3H, CH_3), 2.39 s (3H, CH_3), 4.07 s (2H, CH_2), 4.68 s (2H, N-CH_2), 7.03 s (1H, Py), 7.39 s (2H, C_6H_5), 7.56 s (1H, C_6H_5), 7.83 s (2H, C_6H_5), 9.70 s (1H, CO-NH), 10.89 s (1H, NH-CO). Anal. Calculated for $C_{20}H_{18}N_6O_4S_2$ (%): C, 51.05; H, 3.86; N, 17.86. Found %: C, 51.15; H, 3.88; N, 17.98.

(Benzothiazole-2-ylsulfanyl)-N'-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)- acetyl hydrazide acetic acid (***2c***). Yield 74%, m. p. 165–167 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.18 s (3H, CH_3), 2.36 s (3H, CH_3),), 4.11 s (2H, CH_2), 4.61 s (2H, N-CH_2), 7.03 s (1H, Py), 7.39 t (1H, *J* = 7.0 Hz, *J* = 6,7 Hz, Ar), 7.50 t (1H, *J* = 7.2 Hz, *J* = 6,7 Hz, Ar), 7.84 d (1H, Ar), 8.04 d (1H, Ar), 9.74 s (1H, CO-NH), 10.95 s (1H, NH-CO). Anal. Calculated for $C_{19}H_{17}N_5O_3S_3$ (%): C, 49.66; H, 3.73; N, 15.24. Found %: C, 49.59; H, 3.69; N, 15.13.

(1-p-Tolyl-1H-tetrazol-5-ylsulfanyl)-acetic acid N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetyl]-hydrazide (***2d***). Yield 67%, m. p. 177 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.06 s (3H, aryl-CH_3), 2.25 s (3H, CH_3), 2.41 s (3H, CH_3), 4.05 s (2H, CH_2), 4.70 s (2H, N-CH_2), 7.03 s (1H, Py), 7.55 d (2H, *J*=8.8 Hz, aryl), 7.67 d (2H, *J*=8.8 Hz, aryl), 9.71 s (1H, CO-NH), 10.91 s (1H, NH-CO). Anal. Calculated for $C_{20}H_{20}N_8O_3S_2$ (%):C, 49.58; H, 4.16; N, 23.12. Found %: C, 49.71; H, 4.21; N, 23.23.

General procedure for the synthesis of N-[5-(4-arylidene)-4-oxo-2-thioxo-thiazolydine-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetamides (***5a–f***). Compound **4** (0.005 mol), an appropriate aldehyde (0.005 mmol) and a few drops of ethanolamine were added to acetic acid (15 ml). The reaction mixture was refluxed 30 min. On cooling the crystalline precipitate was filtered off, washed with water and dried. The obtained compounds were recrystallized from acetic acid. The target compounds are beige or yellow crystalline powders.

2-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-N-[5-(4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetamide (***5a***). Yield 63%, m. p. 172 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.36 s (3H, CH_3), 2.54 s (3H, CH_3), 4.87 s (2H, N-CH_2), 7.01 s (1H, Py.), 7.26 t (2H, *J* = 8.9 Hz, *J* = 8.2 Hz, C_6H_4), 7.69 t (2H, *J* = 6.5 Hz, *J* = 6.3 Hz, C_6H_4), 7.88 s (1H, CH), 10.28 s (1H , OH), 11.68 s (1H, NH). Anal. Calculated for $C_{20}H_{16}N_4O_4S_3$ (%):C, 50.83; H, 3.41; N, 11.86. Found %: C, 50.88; H, 3.36; N, 11.79.

2-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-N-[5-(4-methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetamide (***5b***). Yield 67%, m. p. 176 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.26 s (3H, C_6H_4-CH_3),2.34 s (3H, CH_3), 2.50 s (3H, CH_3), 4.84 s (2H, N-CH_2), 6.98 s (1H, Py.), 7.21 t (2H, *J* = 8.8 Hz, *J* = 8.2 Hz, C_6H_4), 7.63 t (2H, *J* = 6.6 Hz, *J* = 6.4 Hz, C_6H_4), 7.86 s (1H, CH), 11.65 s (1H , NH). Anal. Calculated for $C_{21}H_{18}N_4O_3S_3$ (%):C, 53.60; H, 3.86; N, 11.91. Found %: C, 53.73; H, 3.91; N, 11.86.

N-[5-(4-Fluoro-benzylidene)-4-oxo-2-thioxo-thiazolydine-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetamide (***5c***). Yield 72%, m. p. 186–187 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.39 s (3H, CH_3), 2.59 s (3H, CH_3), 4.90 s (2H, N-CH_2), 6.97 s (1H, Py.), 7.34 t (2H, *J* = 8.7 Hz, *J* = 8.1 Hz, C_6H_4), 7.74 t (2H, *J* = 6.4 Hz, *J* = 6.3 Hz, C_6H_4), 7.93 s (1H, CH), 11.77 s (1H , NH). Anal. Calculated for $C_{20}H_{15}FN_4O_3S_3$ (%):C, 50.62; H, 3.19; N, 11.81. Found %: C, 50.55; H, 3.23; N, 11.74.

*N-[5-(4-Chloro-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetamide (**5d**).* Yield 66%, m. p. 196 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.35 s (3H, CH_3), 2.53 s (3H, CH_3), 4.82 s (2H, N-CH_2), 6.99 s (1H, Py.), 7.29 t (2H, *J* = 8.6 Hz, *J* = 8.1 Hz, C_6H_4), 7.68 t (2H, *J* = 6.5 Hz, *J* = 6.4 Hz, C_6H_4), 7.87 s (1H, CH), 11.68 s (1H , NH). Anal. Calculated for $C_{20}H_{15}ClN_4O_3S_3$ (%):C, 48.92; H, 3.08; N, 11.41. Found %: C, 48.81; H, 3.12; N, 11.48.

*N-[5-(3,4-Dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b] pyridin-3-yl)-acetamide (**5e**).* Yield 78%, m. p. 207 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.37 s (3H, CH_3), 2.55 s (3H, CH_3), 3.76 s (3H, CH_3O) , 3.79 s (3H, CH_3O), 4.89 s (2H, N-CH_2), 7.00 s (1H, Py.), 7.04 (s, 1H, *J* = 8.5 Hz, C_6H_3), 7.42 (d, 2H, *J* = 7.7 Hz, C_6H_3), 7.91 s (1H, CH), 11.74 s (1H, NH). Anal. Calculated for $C_{22}H_{20}N_4O_5S_3$ (%):C, 51.15; H, 3.90; N, 10.84. Found %: C, 51.24; H, 3.87; N, 10.88.

*N-[5-(4-Nitro-benzylidene)-4-oxo-2-thioxo-thiazolydine-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetamide (**5f**).* Yield 75%, m. p. 193 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.38 s (3H, CH_3), 2.55 s (3H, CH_3), 4.90 s (2H, N-CH_2), 6.96 s (1H, Py.), 7.92 d (2H, *J* = 8.2 Hz, C_6H_4), 8.03 s (1H, CH), 8.36 d (2H, *J* = 8.2 Hz, C_6H_4), 11.71 s (1H , NH). Anal. Calculated for $C_{20}H_{15}N_5O_5S_3$ (%):C, 47.89; H, 3.01; N, 19.96. Found %: C, 47.77; H, 2.98; N, 13.88.

*Potassium salt of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3H-thiazolo[4,5-b]pyridine-2-one (**6**).* A mixture of water (50 mL) and potassium hydroxide (0.01 mol) was treated with compound **3** (0.01 mol) and the mixture was heated for 30 minutes to complete dissolution. The solid which was precipitated at cooling was filtered off, water-washed and dried. Re-crystallized from acetic acid. Beige crystalline powder soluble in water and alcohols, sparingly soluble in organic solvents. Yield 60%, m. p. 154–155 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.32 s (3H, CH_3), 2.44 s (3H, CH_3), 5.11 s (2H, CH_2),), 7.03 s (1H, Py.). Anal. Calculated for $C_{11}H_9KN_4O_2S_2$ (%):C, 39.74; H, 2.73; N, 16.85. Found %: C, 39.63; H, 2.78; N, 16.74.

*General procedure for the synthesis ofS-substituted3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3H-thiazolo[4,5-b]pyridine-2-ones (**7a–d, 8a–f**).* Compound **6** (0.009 mol) was dissolved in dimethylformamide (DMF) (12 mL) at heating. The obtained solution was treated with the appropriate alkylating agent (0.009 mol). Reaction mixture was refluxed 20 min. The white precipitate of the corresponding S-substituted 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one was filtered hot, washed with hot DMF and cooled to 50 °C. Water (100 mL) was added to the filtrate and the mixture was cooled to 12–15 °C. The formed precipitate was filtered off, washed with water and dried firstly at room temperature and then at 60 °C. Obtained compounds were recrystallized from acetic acid. The target compounds are beige crystalline powders, well soluble in alcohols, chloroform, dioxane, DMF, acetic acid, slightly soluble in water.

*3-(5-Allylsulfanyl-[1,3,4]oxadiazol-2-ylmethyl)-5,7-dimethyl-3H-thiazolo[4,5-b]pyridin-2-one (**7a**).* Yield 44%, m.p. = 126–127 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.60 (d, 2H, *J* = 4,8 Hz, CH_2–CH=CH_2), 5.13 (t, 2H, *J* = 4,0 Hz, *J* = 6,0 Hz, CH_2–CH=CH_2), 5.25 (s, 2H, CH_2), 5.95–5.99 (m, 1H, CH_2–CH=CH_2), 7.00 (s, 1H, Py.). Anal. Calculated for $C_{14}H_{14}N_4O_2S_2$ (%): C, 50.28; H, 4.22; N, 16.75. Found %: C, 50.31; H, 4.14; N, 16.85.

*5,7-Dimethyl-3-(5-propylsulfanyl-[1,3,4]oxadiazol-2-ylmethyl)-3H-thiazolo[4,5-b]pyridin-2-one (**7b**).* Yield 38%, m.p. = 106–107 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 0.94 (t, 3H, *J* = 7,2 Hz,-CH_2–CH_2-CH_3), 1.75–1.79 (m, 2H, CH_2–CH_2-CH_3), 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.01 (t, 2H, *J* = 6,2 Hz, CH_2–CH_2-CH_3), 5.28 (s, 2H, CH_2), 7.02 (s, 1H, Py.). Anal. Calculated for $C_{14}H_{16}N_4O_2S_2$ (%): C, 49.98; H, 4.79; N, 16.65. Found %: C, 50.11; H, 4.83; N, 16.71.

*3-(5-Isopropylsulfanyl-[1,3,4]oxadiazol-2-ylmethyl)-5,7-dimethyl-3H-thiazolo[4,5-b]pyridin-2-one (**7c**).* Yield 50%, m.p. = 98 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.53 (d, 3H, *J* = 14,7 Hz, CH_3-CH-CH_3), 1.55 (s, 3H, *J* = 14,7 Hz, CH_3-CH-CH_3), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.05–5.08 (m, 1H, CH_3-CH-CH_3), 5.32 (s, 2H, CH_2), 7.05 (s, 1H, Py.). Anal. Calculated for $C_{14}H_{16}N_4O_2S_2$ (%): C, 49.98; H, 4.79; N, 16.65. Found %: C, 50.08; H, 4.77; N, 16.63.

*5,7-Dimethyl-3-(5-pentylsulfanyl-[1,3,4]oxadiazol-2-ylmethyl)-3H-thiazolo[4,5-b]pyridin-2-one (**7d**).* Yield 42%, m.p. = 92–93 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 0.83 (t, 3H, *J* = 6,9 Hz, $CH_3(CH_2)_4$), 1.23–1.31 (m, 4H, CH_2), 1.63–1.68 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.94 т (2H, *J* = 7.2 Hz, CH_2), 5.29 (s, 2H, CH_2), 7.02 (s, 1H, Py.). Anal. Calculated for $C_{16}H_{20}N_4O_2S_2$ (%): C, 52.73; H, 5.53; N, 15.37. Found %: C, 52.55; H, 5.60; N, 15.44.

*2-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-phenyl-acetamide (**8a**).* Yield 68%, m.p. = 212 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.28 (s, 2H, S-CH_2), 5.32 (s, 2H, CH_2), 7.04 (s, 1H, Py.), 7.18–7.23 (m, 2H, C_6H_5), 7.36–7.43 (m, 3H, C_6H_5), 10.77 (s, 1H, NH). Anal. Calculated for $C_{19}H_{17}N_3O_5S_2$ (%):C, 53.38; H, 4.01; N, 16.38. Found %: C, 53.64; H, 4.95; N, 16.55.

*2-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-nitro-phenyl)-acetamide (**8b**).* Yield 55%, m.p. = 198 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.31 (s, 2H, S-CH_2), 5.26 (s, 2H, CH_2), 7.02 (s, 1H, Py.), 7,21 (d, 2H, J = 8,0 Hz, C_6H_5), 7,89 (d, 2H, J = 8,0 Hz, C_6H_5), 10.84 (s, 1H, NH). Anal. Calculated for $C_{19}H_{16}N_6O_5S_2$ (%): C, 48.30; H, 3.41; N, 17.79. Found %: C, 48.02; H, 3.36; N, 17.69.

*2-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-p-tolyl-acetamide (**8c**).* Yield 55%, m.p. = 234 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.18 (s, 3H, C_6H_4-CH_3), 2.31 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.26 (s, 2H, S-CH_2), 5.28 (s, 2H, CH_2),

7.00 (s, 1H, Py.), 7,15 (d, 2H, J=7,9 Hz, C_6H_4), 7,84 (d, 2H, J = 7,9 Hz, C_6H_4), 11.02 (s, 1H, NH). Anal. Calculated for $C_{20}H_{19}N_5O_3S_2$ (%): C, 54.41; H, 4.34; N, 15.86. Found %: C, 54.78; H, 4.29; N, 15.74.

*2-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-ethyl-phenyl)-acetamide (**8d**).* Yield 64%, m.p. = 211 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1,17 (t, 3H , J=7,3 Hz, CH_2-CH_3), 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.97 (m, 2H, CH_2-CH_3), 4.28 (s, 2H, S-CH_2), 5.24 (s, 2H, CH_2), 7.05 (s, 1H, Py.), 7,11 (d, 2H, J=7,9 Hz, C_6H_4), 7,79 (d, 2H, J = 7,9 Hz, C_6H_4), 10.82 (s, 1H, NH). Anal. Calculated for $C_{21}H_{21}N_5O_3S_2$ (%):C, 55.37; H, 4.65; N, 15.37. Found %: C, 55.41; H, 4.71; N, 15.44.

*N-(4-Chloro-phenyl)-2-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamide (**8e**).* Yield 66%, m.p. = 192 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.34 (s, 2H, S-CH_2), 5.33 (s, 2H, CH_2), 7.03 (s, 1H, Py.), 7,18 (d, 2H, J = 8,0 Hz, C_6H_4), 7,76 (d, 2H, J = 7,9 Hz, C_6H_4), 10.88 (s, 1H, NH). Anal. Calculated for $C_{19}H_{16}ClN_5O_3S_2$ (%): C, 49.40; H, 3.49; N, 15.16. Found %: C, 49.25; H, 3.41; N, 15.24.

*2-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-fluoro-phenyl)-acetamide (**8f**).* Yield 59%, m.p. = 177 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.32 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.31 (s, 2H, S-CH_2), 5.33 (s, 2H, CH_2), 6.98 (s, 1H, Py.), 7,11 (d, 2H, J = 7,9 Hz, C_6H_4), 7,72 (d, 2H, J = 7,9 Hz, C_6H_4), 10.84 (s, 1H, NH). Anal. Calculated for $C_{19}H_{16}FN_5O_3S_2$ (%):C, 51.23; H, 3.62; N, 15.72. Found %: C, 51.33; H, 3.65; N, 15.78.

Free radical scavenging assays

The Antioxidant activity was determined on basis of free radical scavenging activity of stable 2,2-Diphenyl-1-picrylhydrazyl (DPPH). Studied compounds effect on DPPH radicals was estimated according to the method of Blois (Blois 1958; Molyneux 2004) with minor modifications. The solution of DPPH in ethanol with the concentration of 150 μmoles/L (4 ml) was mixed with the compound or control solution in ethanol, its concentration was 250 μmoles/l (0.2 ml). The reaction mixture was thoroughly vortex-mixed and incubated at room temperature in the dark for 60 min. Simultaneously, a control was prepared as a mixture of DPPH solution in ethanol (4 ml) and ascorbic acid solution in ethanol (0.2 ml) without sample fraction. The Absorbance Reduction of the mixture was measured at 540 nm using ethanol as blank. Ascorbic acid was used as a standard. The absorbance of DPPH solution was also measured. The percentage of free-radical-scavenging activity was expressed as percent inhibition and it was calculated using the following formula:

$$\%\ \text{Inhibition} = \frac{\grave{A}_{DPPH} - A_c}{A_{DPPH}} \cdot 100\ \%;$$

where A_{DPPH} is the absorbance of DPPH free radicals solution, A_c is the absorbance of a sample.

Each experiment was performed in triplicate and average values were recorded. Results are expressed as the means ± S.D.

Results and discussion

Chemistry

The reasonable approach for creation of "healing" molecules from strategical and logical point of view based on modern organic and medicinal chemistry is the annelation of thiazolidon cycle to other heterocyclic compounds. This method is being used because it gives an opportunity for multifaceted modifications of parent substance with receiving new polyfunctional derivative compounds. Condensed bicyclic systems with thiazolidine core being annulated to pyridine one occupy prominent place in medicinal chemistry because of their broad spectrum of pharmacological activities.

The objective of the present work is to synthesize a series of novel thiazolo[4,5-*b*]pyridine-2-ones through structural modification of (5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetic acid hydrazide (Chaban et al. 2012b, 2016) and to subject it to pharmacological *in vitro* screening as antioxidants.

For broadening the scope of thiazolo[4,5-*b*]pyridine-2-ones we involved basic scaffold into the reaction acylation. The high yielding of compounds **1a-c** was obtained through resynthesis using the reaction proceeding in dioxane medium by introducing the equimolar amounts of (5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetic acid hydrazide and the appropriate aliphatic chloroanhydrides in the presence of triethylamine (Chaban et al. 2016). It was established that the anhydride medium is most suitable for the reaction of basic scafold with aromatic chloroanhydrides and gives the opportunity to obtain compounds **1d–j**. (Figure 1).

Chloro-acetyl hydrazides are highly reactive chemicals which being involved into alkylation reactions form the basis for creating and continuous supplement of building blocks wide collection for combinatorial chemistry including biologically active substances combinatorial libraries designing on their basis.

Compound **1b** represents a convenient intermediate in order to afford heteroarylsulfanyl derivatives of N-[2-((5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetylhydrazide acetic acid. The synthetic protocol was based on compound **1b** treatment with the appropriate heterocyclic thiols. The reaction mixture was refluxed for 30 min in 96% ethanol medium determined to be optimal conditions for formation of compounds **2a–d** in good yields (Figure 2).

For further structural modification of (5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetic acid hydrazide on account of its hydrazide center the compound

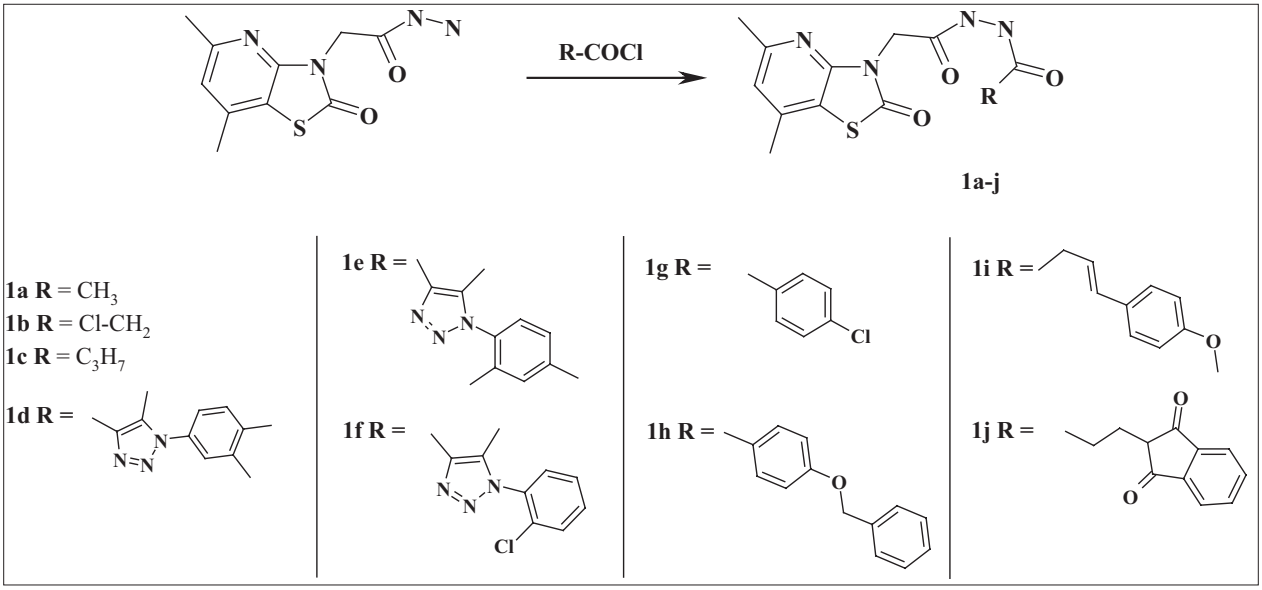


Figure 1. Synthesis of N'-[2-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetyl] carboxylic acids hydrazides under the acylation reaction.

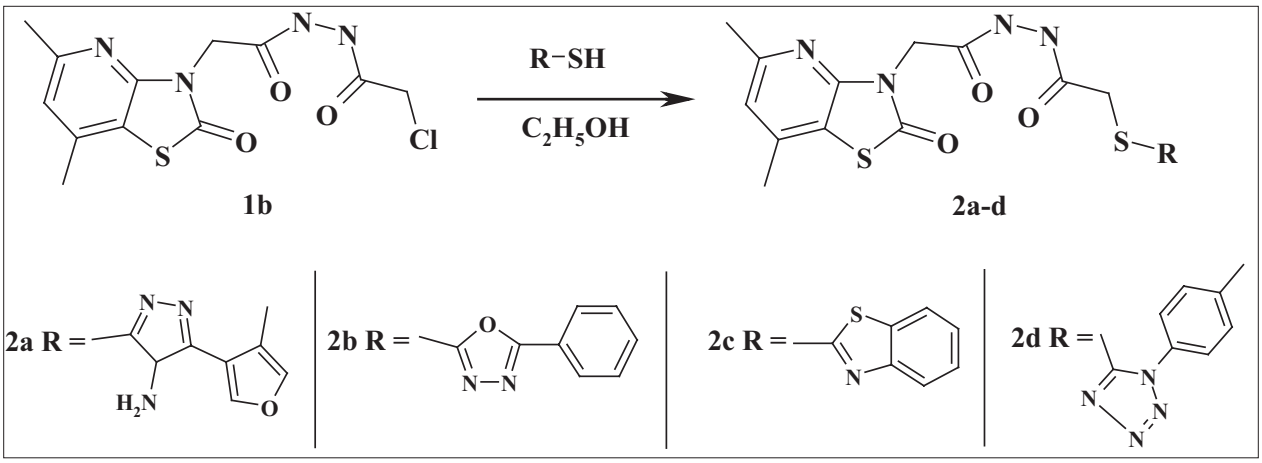


Figure 2. Synthesis of hetarylsulfanyl derivatives of N'-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetyl hydrazide acetic acid under the alkylation reaction.

was treated with thionyl-bis-glycolic acid leading to fornation of compound **3** (Chaban et al. 2016). Ethanol was found to be the most suitable medium for the reaction when equimolar amounts of reagents were refluxed for 3 hours (Figure 3).

The next hydrazide group functionalization stage was resynthesized on the synthetic protocol of N-[2-((5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetyl hydrazide acetic acid treatment with Carbon disulfide and KOH in equimolar amounts employed for compound **4** preparation(Chaban et al. 2016) (Figure 3).

The presence of active methylene group in C^5 position of the thiazolydine ring in compound **3** provided an entry for Knoevenagel condencation carried out with the respective aryliden derivatives and obtaining structures (**5a–f**). The developed synthetic strategy showed that the high yielding of the target compounds may be achieved by the reaction proceeding in acetic acid medium by introducing the equimolar amounts of compound **3** and the appropriate aromatic aldehydes. Monoamine ethanol was assayed as a catalyst for the reaction (Figure 4).

Core basic scaffold had been extensively studied as electrophilic reagent implemented on account of SH-group hydrogen atom. The good leaving property of the hydrogen atom and its strong electrophilicity advantage offered the compound **4** functionalization featuring novel S-substituted 3-(5-mercapto-[1,3,4]oxadiazol-2-yl methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*] pyridin-2-ones. Further compound **4** properties studying showed the proton acidic character in the core heterocycle SH-position which promoted the tendency of its transformation into potassium salt **6** (Figure 5) affording by potassium hydroxide treatment. The obtained salt possessed nucleophilic properties and could be

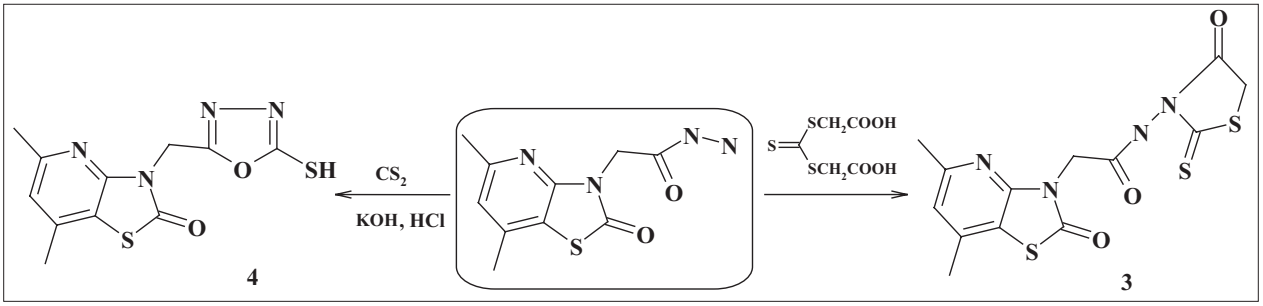


Figure 3. Resynthesis of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one and 2-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-N-(4-oxo-2-thioxo-thiazolydine-3-yl)-acetamide.

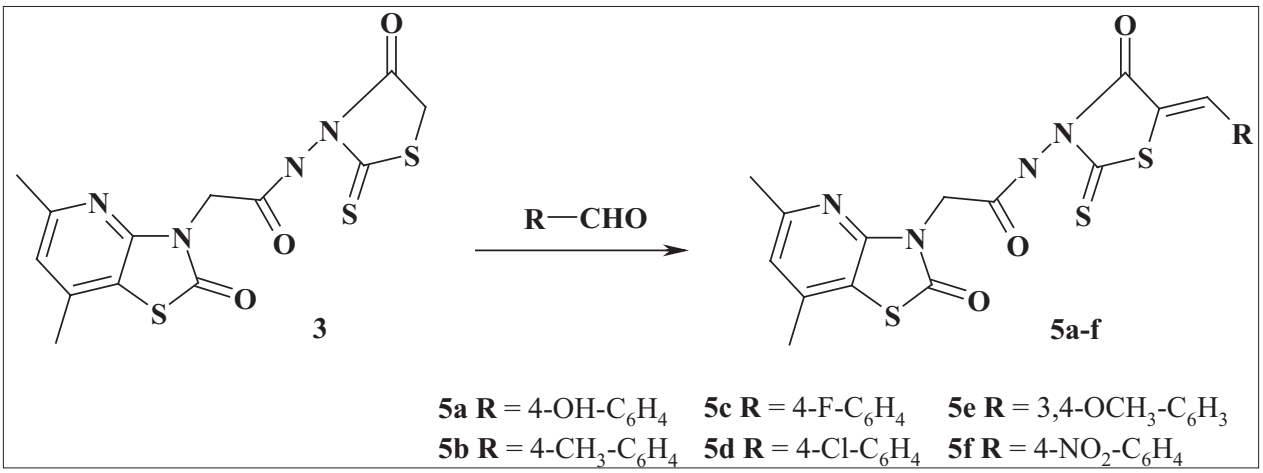


Figure 4. Synthesis of N-[5-(4-arylidene)-4-oxo-2-thioxo-thiazolydine-3-yl]-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridine-3-yl)-acetamides.

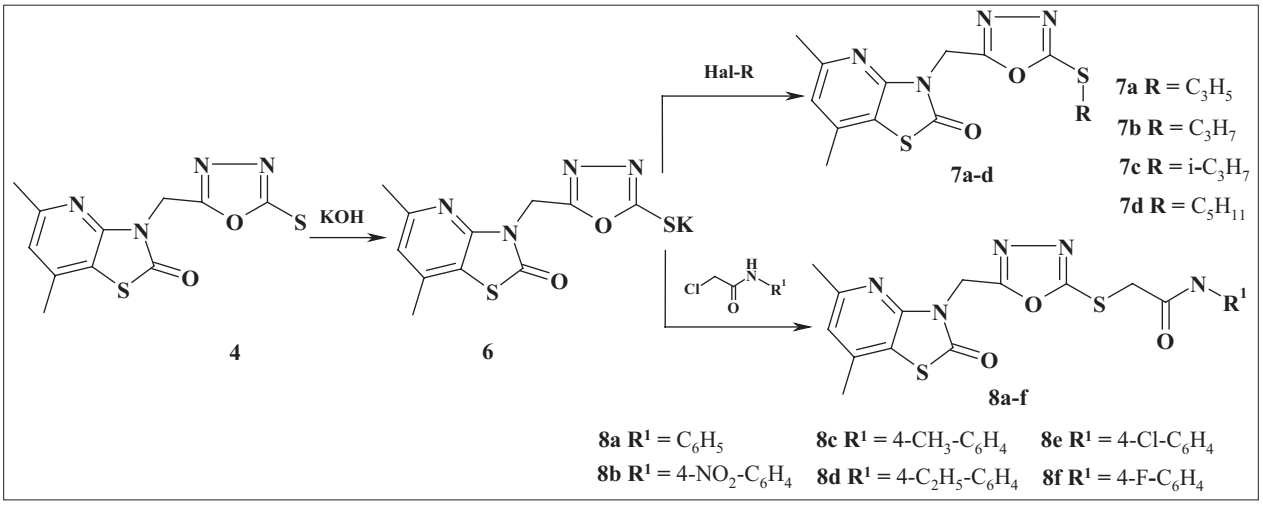


Figure 5. Synthesis of potassium salt of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one and S-substituted 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-ones.

further involved into S-alkylation reaction. The alkylation mild conditions proceeding imposed to alkyl halides and aryl acetamide moieties introduction with the generation of corresponding S[5] substituted 3-(5-mercapto-[1,3,4]oxadiazol-2-ylmethyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (**7a–d, 8a–f**) using various alkylating agents like alkyl halides and chloroacetamides (Fi gure 5).

The structures of the obtained compounds were confirmed by ^{1}H spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

Antioxidant activity in vitro evaluation

The antioxidant activity was determined on basis of free radical scavenging activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. DPPH radical has found many applications due to its high stability in a methanolic solution and intense purple color. In its oxidized form, the DPPH radical has an absorbance maximum centered at a wavelength of about 540 nm. Reducing radical by means of atioxidants, the absorbance decreases. Its reduction affords 2,2-diphenyl-1-picrylhydrazine (DPPH-H), or the corresponding anion ($DPPH^-$) in basic medium. The DPPH radical acts as a scavenger for other odd-electron species which afford *para*-substitution products at phenyl rings.

The DPPH method is described as a simple, rapid and convenient method for radical scavenging activity screening of many samples. These advantages make the DPPH method interesting for testing newly synthesized compounds to scavenge radicals and to find out promising antioxidant drug candidates.

In the present paper we demonstrate modified spectrophotometric method which allows the use of the DPPH radical and its specific absorbance properties. The free-radical-scavenging activities of each compound were assayed using a stable DPPH and were quantified by decolorization of the solution being mixed with DHHP at a wavelength of 540 nm. The absorbance of DPPH solution in ethanol (150 μmoles/L) was measured as 0.770. The absorbances and free-radical-scavenging activities % inhibitions of standard (ascorbic acid) and each compound are listed in Table 1.

Table 1. Values of absorbance and % inhibition of thiazolo[4,5-*b*] pyridine-2-ones.

The compound or standard	Absorbance of a sample, A_s	% Inhibition
Control	*0.770±0.025*	–
1a	*0.492±0.025*	36.14
1b	*0.707±0.020*	8.16
1c	*0.506±0.015*	34.27
1d	*0.684±0.020*	11.25
1e	*0.723±0.025*	6.12
1f	*0.730±0.025*	5.25
1g	*0.732±0.025*	4.95
1h	*0.706±0.020*	8.20
1i	*0.700±0.020*	9.11
1j	*0.690±0.020*	10.45
2a	*0.699±0.020*	9.25
2b	*0.702±0.020*	8.88
2c	*0.689±0.020*	10.55
2d	*0.697±0.020*	9.50
3	*0.704±0.020*	8.52
4	*0.612±0.015*	20.55
5a	*0.699±0.020*	9.20
5b	*0.707±0.020*	8.25
5c	*0.693±0.015*	10.05
5d	*0.723±0.025*	6.15
5e	*0.713±0.020*	7.43
5f	*0.695±0.020*	9.74
6	*0.584±0.015*	24.20
7a	*0.707±0.020*	8.16
7b	*0.699±0.020*	9.25
7c	*0.715±0.025*	7.15
7d	*0.691±0.020*	10.24
8a	*0.602±0.015*	21.83
8b	*0.675±0.020*	12.25
8c	*0.708±0.020*	8.11
8d	*0.716±0.025*	7.08
8e	*0.700±0.020*	8.70
8f	*0.721±0.025*	6.44
Ascorbic acid	*0.580±0.015*	24.68

The antioxidant activity evaluation results showed that, in general, most of the tested compounds possessed that their free radical scavenging effect was insignificant being in the range of 4.95% – 12.25%. On the other hand some of the new synthesized compounds (compounds **4, 6**, **8a**) possess antioxidant activity in the range of 20.55–24.20% which is comparable to the effect of ascorbic acid. When compared with existing antioxidants, some of our compounds were found to be more potent. The pharmacological screening allowed identification of lead compounds **1** and **3** whose free radical scavenging activity (36.14%, 34.24%) exceeded that for ascorbic acid.

The SAR (Structure-Activity Relationship) study revealed that acylation of hydrazide group of thiazolo[4,5-*b*]pyridines aliphatic chloroanhydrides leads to enhanced potency of compounds in compare to the products based on acylation of the aromatic chloroanhydrides. Among the four hetarylsulfanyl derivatives of N'-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridine-3-yl)-acetyl hydrazide acetic acid compounds **2a–d** showed lack of activity. When comparing the substituents nature in the hydrazide group was indicated that the presence of oxodiazole cycle (**4**) contributed to the antioxidant actions efficiency compared to the rhodanine cycle (**3**). Introduction of arylidene substituents (compounds **5a–f**) in C^5 position of rhodanine core did not influence notably their antioxidant activity. For alkyl SH-substituted compounds **7a–d, 8a–f** the presence of alkyl substituents did not essentially influence antioxidant activity compared to the unsubstituted derivatives **3** and **6.**

Conclusions

We have described that proposed approaches and developed synthetic protocols provided the possibility to design thiazolo[4,5-*b*]pyridine-2-ones diversity with a considerable chemical novelty involving acylation, alkylation, [2+3] cyclocondensation and Knoevenagel condensation reactions. Firstly antioxidant activity among 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-ones was identified. When compared with existing antioxidants, some of our compounds were found to be more potent. Thus the core fused heterocycle may be considered as a promising scaffold for antioxidant drug – like compounds development. Further structure optimization to improve their activities is currently in progress.

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