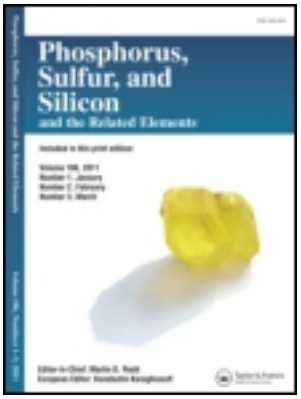

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Synthesis and Antioxidant Activity Evaluation of Novel 5,7-dimethyl-3H-Thiazolo[4,5-B]Pyridines

Taras I. Chaban [a], Volodymyr V. Ogurtsov [a], Ihor G. Chaban [a], Olena V. Klenina [a] & Josef D. Komarytsia [a]
[a] Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
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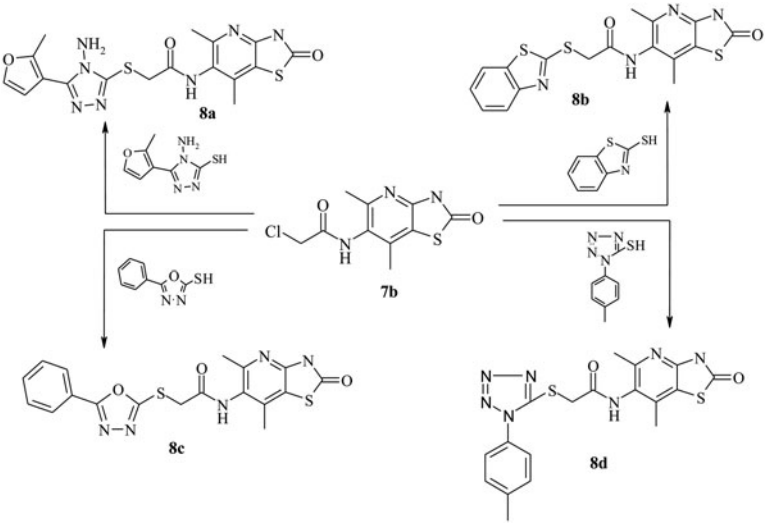
SYNTHESIS AND ANTIOXIDANT ACTIVITY EVALUATION OF NOVEL 5,7-DIMETHYL-3*H*-THIAZOLO[4,5-b]PYRIDINES

Taras I. Chaban, Volodymyr V. Ogurtsov, Ihor G. Chaban, Olena V. Klenina, and Josef D. Komarytsia
Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

GRAPHICAL ABSTRACT



Abstract *5,7-Dimethyl-3H-thiazolo[4,5-b]pyridine-2-one was obtained under the reaction of 4-iminothiazolidin-2-one with acetylacetone. Further structural modifications include the introduction of diversity at the N^3 and C^6 positions. The antioxidant activity of the synthesized compounds was evaluated in vitro by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the following free supplemental files: Additional figures]*

Keywords Thiazolo[4,5-b]pyridines; DPPH; antioxidant activity

Received 15 November 2012; accepted 15 February 2013.
Address correspondence to Olena V. Klenina, Danylo Halytsky Lviv National Medical University, Pekarska Str., 69, Lviv 79010, Ukraine. E-mail: olena_klenina@yahoo.com

INTRODUCTION

Different environmental stress factors like pollution, drought, temperature, excessive light intensities, and nutritional limitation are able to increase the production of reactive oxygen species (ROS) (e.g., superoxide, hydroxyl, peroxyl, and alkoxy radicals).[1,2] Their highly reactive potential is discussed to be responsible for some human diseases, for example, cancer and cardiovascular diseases, and is able to cause oxidative damages to proteins, DNA, and lipids in both humans and microorganisms.[3]

Antioxidants can interfere with the oxidation process by reacting with free radicals, and also by acting as reactive species scavenger. Several enzymes like superoxide dismutase, catalase peroxidase are able to scavenge ROS.[4] Carotenoids, fatty acids, tocopherol, flavonoids, alkaloids, Selenium, and ascorbic acid, are the examples for nonenzymatic classes of natural substances, which are able to protect the organism from oxidative damage.[5] There are also a few synthetical antioxidative compounds (butylated hydroxyl anisole, butylated hydroxyrotoluene, propyl gallate, tertiary butyl hydroquinone, and nordihydro guaretic acid) used as drugs.[6]

The antioxidant activities of the individual compounds may depend on their structural features.

4-Azolidone is widely used in modern medical chemistry as a scaffold for molecular rational design of drug candidates. The thiazolidine-based heterocycles and their analogs fused to the pyridine ring were shown to posses the wide range of biological actions. Some of thiazolo[4,5-b] pyridines were described as potent antimicrobial agents.[7] They also show potent inhibitory activities for Aβ42 fibrillization for Alzheimer's disease treatment.[8] Among substances of this type, several compounds were found to possess fungicidal, antiexcudative, antimicrobial, and antitumor actions.[9–12] Some of them are H3 receptor antagonists,[13,14] or act as antagonists of metabotropic glutamate receptors 5 (mGluR5),[15] they are of high inhibitory activity with respect to the receptors of the epidermal growth factor,[16] and were revealed to activate the GK enzyme in vitro and significantly reduce glucose levels.[17]

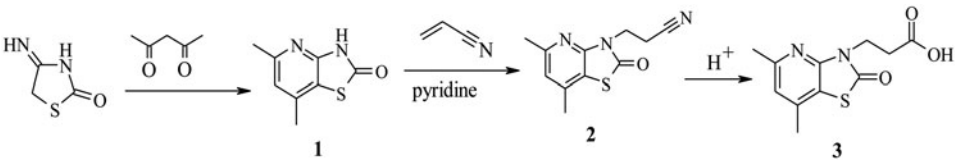
The objective of the present work was to synthesize a series of novel 3*H*-thiazolo[4,5-*b*]pyridine-2-ones by the structural modification of the core heterocycle in its N^3 and C^6 positions for further pharmacological screening in vitro as antioxidants.

RESULTS AND DISCUSSION

Chemistry

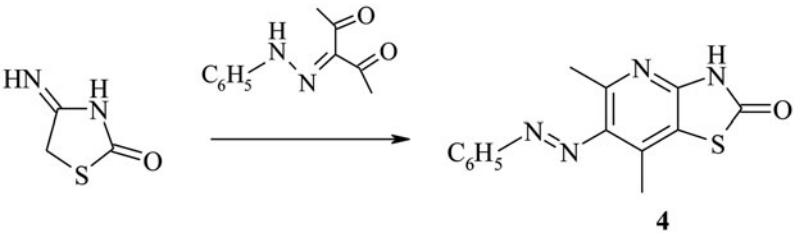
One of the efficient synthetic approaches for thiazolo[4,5-*b*]pyridine system construction used in modern medial chemistry is the protocol based on [3+3] cyclocondensation of 4-iminothiazolidone-2[18] on account of its N,C-binucleophylic properties with dielectrophylic reagents like acetylacetone forming the above-mentioned fused heterocycle (**1**).[19]

For broadening the scope of N^3-substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-ones, we involved compound **1** into cynoethylation reaction taking the advantage of the good leaving hydrogen atom property of the NH-group. We discovered that the high yield of the product can be achieved by introducing the equimolar amounts of the compound **1** and acrylonitrile in pyridine–water medium 5:1; 3-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-propionitryl (**2**) prepared in this way was subjected to hydrolysis leading to 3-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-propionic acid formation (**3**) (Scheme 1).



Scheme 1

The next stage of our strategy includes the core heterocycle structural modification in its C^6 position. The direct functionalization proceeding has exposed to be of a small introducing possibility owing to the low nucleophilic activity of the compound **1** in the C^6 position. However, 5,7-dimethyl-6-arylazo-3*H*-thiazolo[4,5-*b*]pyridine-2-one (**4**) was yielded by α-arylazoacetone[20] treatment with 4-iminothiazolidone-2 (Scheme 2).



Scheme 2

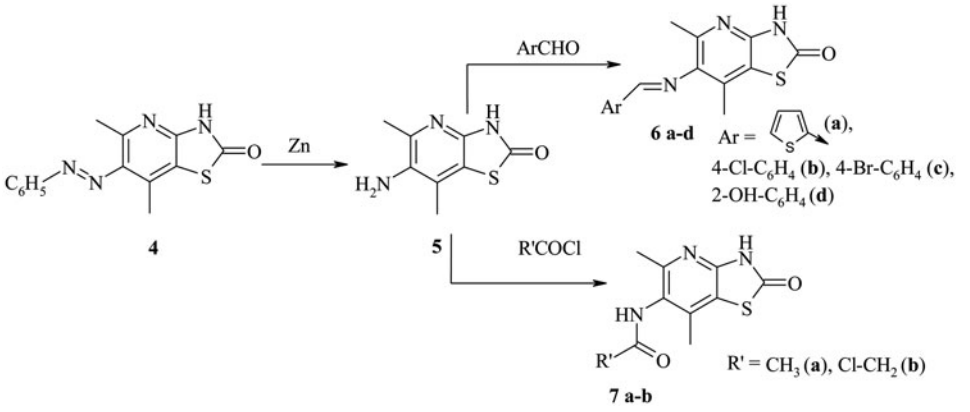
Compound **4** represents a convenient intermediate in order to afford 6-amino-5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-one (**5**) as a building block for more elaborate functionalizations of thiazolo[4,5-b]pyridine-2-one moiety in its C^6 position. The reductive cleavage of compound **4** was proceeded leading to obtaining of compound **5**. The synthetic strategy developed showed the compound **5** high yielding may be achieved in acetic acid–pyridine medium by using zinc dust as a reduction agent.

The amine group presence in C^6 position of compound **5** provides an entry for 6-arylidenamino- (**6a-d**) and 6-acetylamino derivatives (**7a-b**) generation. Acetic acid was found to be the most suitable medium for the reaction of compound **5** with aromatic aldehydes and dioxane—for the reaction of compound **5** with chloroanhydrides of aliphatic acids (Scheme 3).

Chloroacetamides are highly reactive chemicals, which, on being involved into alkylation reactions form the basis for creating and continuous supplementing of building blocks, a wide collection for combinatorial chemistry including biologically active substances and combinatorial libraries designed on their basis.

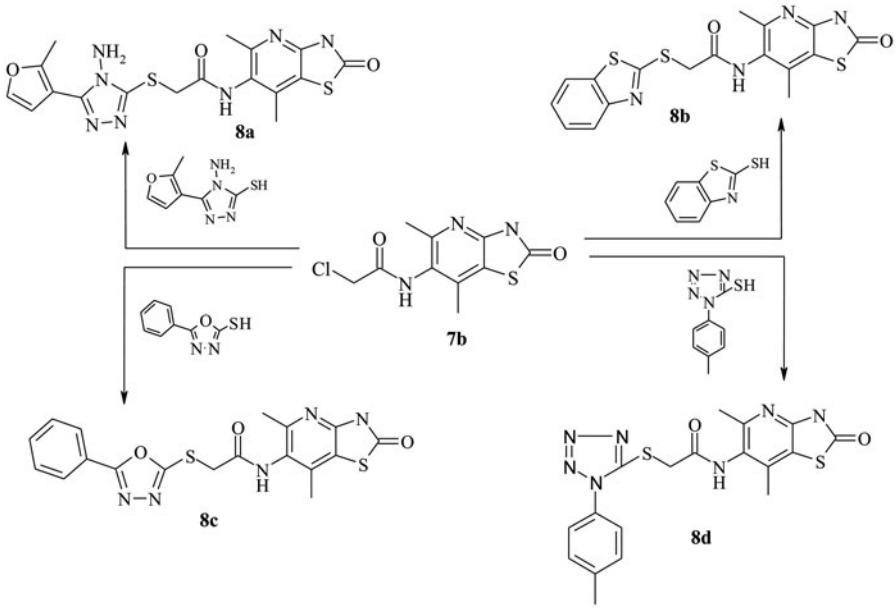
Compound **7b** may be considered as a key intermediate in 6-sulfanylacetamide derivatives of 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-one that are obtained on being treated with appropriate thiols. The reaction mixture reflux for 30 min and in 96% ethanol medium were optimal conditions for compounds **8a–d** formation proceeding in good yields (Scheme 4).

Thus, the series of thiazolo[4,5-b]pyridin-2-one acetamides has been diversified by alkylation reactions applying N-substituted 2-chloroacetamide **7b** as alkylating agent, employing it into the reactions with heteryl moiety thiols, which can be considered an effective and general route to a wide range of acetamides preparation.



4 5 6 a-d 7 a-b

Scheme 3



8a 8b 7b 8c 8d

Scheme 4

The structures of the obtained compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures. The ^{1}H NMR spectra of all compounds show the protons signals of methyl groups in pyridine ring as singlets in the δ 2.42–2.57 and 2.61–2.64 ppm. The compound **4** spectrum shows the signal of phenyl radical as two duplets at 7.53–7.63 and 7.75–7.92 ppm. The $N^{3}H$ proton was not resolved for the compound **2** that proves the cyanoethylation reaction. The ^{1}H NMR spectrum of the compound **2** hydrolysis product (**3**) contains the signal of COOH-group as singlet at 12.47 ppm while its reductive cleavage product (**5**) spectrum contains a singlet signal at 4.67 ppm, which indicates the presence of aminogroup at C^{6} position of thiazolopyridine ring. However the absence of

Table 1 Values of absorbance and % inhibition of 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-ones

The compound or standard	Absorbance of a sample, A_s	% Inhibition	The compound or standard	Absorbance of a sample, A_s	% inhibition
Ascorbic acid	0.580 ± 0.015	24.68	6c	0.685 ± 0.020	11.04
1	0.730 ± 0.030	5.19	6d	0.690 ± 0.020	10.39
2	0.740 ± 0.020	3.90	7a	0.425 ± 0.015	44.81
3	0.720 ± 0.015	6.49	7b	0.720 ± 0.030	6.49
4	0.715 ± 0.025	7.14	8a	0.700 ± 0.025	9.01
5	0.465 ± 0.020	39.61	8b	0.710 ± 0.020	7.80
6a	0.480 ± 0.015	37.67	8c	0.699 ± 0.015	9.25
6b	0.690 ± 0.025	10.39	8d	0.710 ± 0.020	8.10

aminogroup signal in compounds **7a,b** proves both Schiff bases formation and the reaction of their acylation. ^{1}H NMR spectra of the compounds **8a–d** contain characteristic aromatic signals, which prove 6-sulfanylacetamido derivatives of 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-one formation.

In Vitro Antioxidant Assay

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 about 520 nm. The absorbance decreases when the radical is reduced by antioxidants. 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 screening of many samples for radical-scavenging activity. 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 that modified spectrophotometric method makes 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 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.

CONCLUSIONS

A series of novel 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-one derivatives possessing antioxidant activity were prepared by the structural modification of the core heterocycle in N^3 and C^6 positions. Therefore we have shown that the proposed approaches provide the possibility to design 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-ones diversity with a considerable chemical novelty; first identified antioxidant activity among 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine-2-ones. 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 candidate development. Further optimization of the structure to improve their activities is currently in progress.

EXPERIMENTAL

Materials

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying.

Chemistry

^{1}H and ^{13}C NMR spectra of compounds in DMSO-d6 solution were registered on a spectrometer Varian Mercury VX-400 (400 MHz), internal reference tetramethylsilane (TMS). The elemental analysis experimental data on contents of nitrogen and sulfur correspond to the calculated ones (±0.3%).

5,7-Dimethyl-3*H*-Thiazolo[4,5-b]Pyridin-2-One (1). Sodium (2.5 g, 109 mmol) was dissolved in anhydrous methanol (125 mL), and to the solution obtained 4-iminothiazolidin-2-one (6.8 g, 50 mmol) and acetylacetone (8 mL) were added at 20°C. The mixture was left standing for 5 days with the intermittent stirring, then it was acidified with acetic acid to pH ∼5, five-fold diluted with water, the precipitate was filtered off, washed with water, and dried. Compound **1** was obtained as a white crystalline powdered solid, well soluble in dimethylformamide (DMF), DMSO, solutions of alkali and mineral acids, sparingly soluble in the other organic solvents.

Yield 74%, melting point (m.p.) = 277–278°C (ethanol).

^{1}H NMR, δ, ppm: 2.27 s (3H, CH_3), 2.40 s (3H, CH_3), 6.91 s (1H, Py), 12.44 s (1H, NH). ^{13}C NMR, δ, ppm: 19.3, 23.3, 118.7, 127.4, 137.4, 139.3 141.4, 168.6. Found%: C, 53.31; H, 4.47; N, 15.54. Calculated for $C_8H_8N_2OS$%: C, 53.02; H, 4.49; N, 15.44.

3-(5,7-Dimethyl-2-Oxo-Thiazolo[4,5-b]Pyridin-3-yl)-Propionitryl (2). A mixture of pyridine (50 mL) and water (10 mL) with acrylonitrile (3 mL) was added to the compound **1** (10 mmol). The reaction mixture was refluxed 5 h. On cooling the precipitation was achieved with petroleum ether–water mixture (3:1). The precipitate was recrystallized from ethanol, filtered off, and dried. This compound was isolated as a white crystalline powdered solid, well soluble in ethanol, chloroform, dioxane, DMF, and acetic acid.

Yield 67%, m.p. = 99–100°C.

^{1}H NMR, δ, ppm: 2.33 s (3H, CH_3), 2.48 s (3H, CH_3), 3.06 t (2H, CH_2), 4.23 t (2H, CH_2), 7.04 s (1H, Py). Found%: C, 56.02; H, 4.89; N, 18.24. Calculated for $C_{11}H_{11}N_3OS$%: C, 56.63; H, 4.75; N, 18.01.

3-(5,7-Dimethyl-2-Oxo-Thiazolo[4,5-b]Pyridin-3-yl)-Propionic Acid (3). The mixture of the compound **2** (10 mmol), acetic acid (30 mL), and hydrochloric acid (15 mL) were placed into the round-bottomed flask. The reaction mixture was refluxed for 3 h and the product was precipitated with water. The mixture was left standing for 24 h at ambient temperature, and next, the precipitate was filtered off and treated with toluene. The precipitate was recrystallized from ethanol, filtered off, and dried. This compound was isolated as a white crystalline powdered solid, well soluble in ethanol, chloroform, dioxane, DMF, and acetic acid.

Yield 60%, m.p. = 103–104°C. ^{1}H NMR, δ, ppm: 2.31 s (3H, CH_3), 2.47 s (3H, CH_3), 2.69 t (2H, CH_2), 4.17 t (2H, CH_2), 7.01 s (1H, Py), 12.47 s (1H, COOH). Found%: C, 52.02; H, 4.69; N, 11.35. Calculated for $C_{11}H_{12}N_2O_3S$%: C, 52.37; H, 4.79; N, 11.10.

5,7-Dimethyl-6-Phenylazo-3*H*-Thiazolo[4,5-b]Pyridin-2-One (4). Metallic sodium (0.2 mol) was dissolved in anhydrous methanol (100 mL), and to the solution obtained 4-iminothiazolidin-2-one (50 mmol) and α-phenylazoacetylacetone (50 mmol) were added at 20°C. The mixture was left standing for 7 days with the intermittent stirring, then it was acidified with acetic acid to pH ~5, five-fold diluted with water. The precipitate was filtered off, washed with water, and dried at 100–110°C. The precipitate next was recrystallized from toluene. Compound **4** was obtained as a brick-red crystalline powdered solid, well soluble in DMF, DMSO, alkalis, and mineral acids solutions, feebly soluble in benzene, toluene, alcohols, and almost insoluble in water.

Yield 86%, m.p. = 258–259°C (decomp., toluene).

^{1}H NMR, δ, ppm: 2.42 s (3H, CH_3), 2.61 s (3H, CH_3), 2.69 t (2H, CH_2), 7.59–7.61 m (3H, C_6H_5), 7.80 d (2H, J = 8.0 Hz, C_6H_5), 12.78 s (1H, NH). Found%: C, 58.81; H, 4.32; N, 19.79. Calculated for $C_{14}H_{12}N_4OS$%: C, 59.14; H, 4.25; N, 19.70.

6-Amino-5,7-Dimethyl-3*H*-Thiazolo[4,5-b]Pyridin-2-One (5). To a solution of pyridine (20 mL) and acetic acid (15 mL) compound **2** (1.42 g, 5 mmol) was added. The mixture was heated to boiling, compound **2** completely dissolved. To the solution obtained activated zinc powder (2.3 g, 35 mmol) was added at heating in several portions within 1 h, the solution decolorized. Next, it was filtered; the filtrate, cooled to room temperature, was diluted with 50 mL of water and left standing for 4 h. The separated precipitate was filtered off, washed with water, and dried. The precipitate was recrystallized from acetic acid. This compound was isolated as a white crystalline powdered solid, well soluble in DMF, DMSO, alkalis, and mineral acids solutions, and insoluble in water.

Yield 62%, m.p. = 280–281°C (decomp.).

^{1}H NMR, δ, ppm: 2.11 s (3H, CH_3), 2.83 s (3H, CH_3), 4.67 s (2H, NH_2), 11.89 s (1H, NH). ^{13}C NMR, δ, ppm: 16.2, 20.8, 117.0, 124.5, 137.1, 139.0, 140.0, 168.6. Found%: C, 49.25; H, 4.65; N, 21.52. Calculated for $C_8H_9N_3OS$%: C, 49.21; H, 4.65; N, 21.52.

General Procedure for the Synthesis of 6-Arylidenamino-5,7-Dimethyl-3*H*-Thiazolo[4,5-b]Pyridin-2-Ones (6 a–d). The mixture of the compound **5** (5 mmol) and the appropriate aromatic aldehyde (5 mmol) was added to acetic acid (15 mL). The reaction mixture was refluxed 30 min. On cooling the crystalline precipitate was filtered off, washed with acetic acid, and dried. The obtained compounds were recrystallized from acetic acid.

*6-[(2-thienylmethylene)amino]-5,7-dimethyl-3H-thiazolo[4,5-b]pyridin-2-one **(6a)**.* Yield 72%, m.p. = 275–276°C (decomp.).

^{1}H NMR, δ, ppm: 2.13 s (3H, CH_3), 2.29 s (3H, CH_3), 7.24 s (1H, thiophene), 7.67 s (1H, thiophene), 7.98 d (2H, J = 4.4 Hz, thiophene), 8.54 s (1H, CH), 12.09 s (1H, NH). ^{13}C NMR, δ, ppm: 16.2, 20.8, 117.0, 124.5, 125.0, 131.0, 134.8, 137.2, 139.0, 165.7, 168.6.

Found%: C, 53.75; H, 3.73; N, 14.65. Calculated for $C_{13}H_{11}N_3OS_2$%: C, 53.96; H, 3.83; N, 14.52.

*6-[(4-chlorobenzylidene)amino]-5,7-dimethyl-3H- thiazolo[4,5-b]pyridin-2-one **(6b)**.* Yield 68%, m.p. = 290–291°C (decomp.).

^{1}H NMR, δ, ppm: 2.12 s (3H, CH_3), 2.28 s (3H, CH_3), 7.61 d (2H, J = 6.5 Hz, aryl), 7.98 d (2H, J = 6.5 Hz, aryl), 8.46 s (1H, CH), 12.40 s (1H, NH). ^{13}C NMR, δ, ppm: 16.7, 21.1, 129.6, 130.7, 131.4, 134.9, 137.1, 164.9, 168.9. Found%: C, 56.75; H, 3.73; N, 13.40. Calculated for $C_{15}H_{12}ClN_3OS$%: C, 56.69; H, 3.81; N, 13.22.

6-[(4-bromobenzylidene)amino]-5,7-dimethyl-3H- thiazolo[4,5-b]pyridin -2-one ***(6c).*** Yield 55%, m.p. = 270–271°C (decomp.). ^{1}H NMR, δ, ppm: 2.13 s (3H, CH_3), 2.19 s (3H, CH_3), 7.77 d (2H, J = 8.2 Hz, aryl), 7.91 d (2H, J = 8.3 Hz, aryl), 8.45 s (1H, CH), 12.38 s (1H, NH). Found%: C, 49.55; H, 3.30; N, 11.40. Calculated for $C_{15}H_{12}BrN_3OS$%: C, 49.74; H, 3.34; N, 11.60.

6-[(2-hydroxybenzylidene)amino]-5,7-dimethyl-3H-thiazolo[4,5-b]pyrid in-2-one ***(6d).*** Yield 68%, m.p. = 252–253°C.

^{1}H NMR, δ, ppm: 2.18 s (3H, CH_3), 2.35 s (3H, CH_3), 7.01–7.03 t (2H, aryl), 7.47 t (1H, J = 8.2 Hz, aryl), 7.66 d (1H, J = 7.8 Hz, aryl), 8.69 s (1H, CH), 12.47 s (1H, OH), 12.58 s (1H, NH). ^{13}C NMR, δ, ppm: 17.1, 21.3, 117.2, 118.4, 119.6, 119.7, 131.9, 132.7, 134.1, 139.5, 145.1, 160.6, 168.9, 169.6. Found%: C, 59.75; H, 4.52; N, 14.24. Calculated for $C_{15}H_{13}N_3O_2S$%: C, 60.19; H, 4.38; N, 14.04.

General Procedure for the Synthesis of 6-Acylamino-5,7-Dimethyl-3*H*-Thiazolo[4,5-b]Pyridin-2-Ones (7a,b). The compound **5** (5 mmol), an appropriate aliphatic chloroanhydride (5 mmol), and triethylamine (5 mmol) were added to dioxane (20 mL). The reaction mixture was refluxed 15 min. On cooling the crystalline precipitate was filtered off, washed with methanol and dried. The obtained compounds were recrystallized from methanol.

N-(5,7-dimethyl-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-b]pyridin-6-yl)aceta mide ***(7a).*** Yield 60%, m.p. = 150–151°C.

^{1}H NMR, δ, ppm: 2.07 s (3H, $COCH_3$), 2.14 s (3H, CH_3), 2.32 s (3H, CH_3), 9.46 s (1H, NH), 12.41 s (1H, NH). ^{13}C NMR, δ, ppm: 16.5, 20.9, 40.3, 117.3, 130.8, 129.6, 143.0, 143.1, 166.6. Found%: C, 50.35; H, 4.72; N, 17.85. Calculated for $C_{10}H_{11}N_3O_2S$%: C, 50.62; H, 4.67; N, 17.71.

2-chloro-N-(5,7-dimethyl-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-b]pyridin-6-yl) acetamide ***(7b).*** Yield 65%, m.p. = 135–136°C. ^{1}H NMR, δ, ppm: 2.15 s (3H, CH_3), 2.33 s (3H, CH_3), 4.32 s (2H, CH_2), 9.86 s (1H, NH), 12.43 s (1H, NH). ^{13}C NMR, δ, ppm: 16.8, 21.0, 66.8, 116.6, 126.2, 139.7, 147.5, 152.7, 166.0, 169.0. Found%: C, 44.70; H, 3.80; N, 15.70. Calculated for $C_{10}H_{10}ClN_3O_2S$%: C, 44.20; H, 3.71; N, 15.46.

General Procedure for the Synthesis of 6-Sulfanylacetamido-5,7-Dimethyl-3*H*-Thiazolo[4,5-b]Pyridine-2-Ones (8a–d). The compound **7b** (5 mmol) and the appropriate thiol (5 mmol) were added to anhydrous methanol (20 mL). The reaction mixture was refluxed 1 h. On cooling the crystalline precipitate was filtered off, washed with methanol, and dried. The obtained compounds were recrystallized from methanol.

2-{[4-amino-5-(4-methyl-4,5-dihydrofuran-3-yl)-1,2,4-triazolidin-3-yl]th io}-N-(5,7-dimethyl-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-b]pyridin-6-yl) acetam ide ***(8a).*** Yield 70%, m.p. = 150–151°C.

^{1}H NMR, δ, ppm: 2.13 s (3H, CH_3), 2.29 s (3H, CH_3), 2.51 s (3H, CH_3), 4.17 s (2H, CH_2), 6.09 s (2H, NH_2), 7.05 s (1H, aryl), 7.68 s (1H, aryl), 9.87 s (1H, NH), 12.51 s (1H, NH). ^{13}C NMR, δ, ppm: 11.2, 16.9, 21.0, 35.0, 114.8, 116.5, 123.0, 126.7, 137.8, 139.8, 144.3, 147.9, 148.5, 152.8, 167.2, 169.1. Found%: C, 47.41; H, 3.85; N, 22.60. Calculated for $C_{17}H_{17}N_7O_3S_2$%: C, 47.32; H, 3.97; N, 22.72.

2-(2,3-Dihydro-1,3-benzothiazol-2-yl thio)–N-(5,7-dimethyl-2-oxo-2,3-dih ydro [1,3] thiazolo[4,5-b pyridin-6-yl) acetamide ***(8b).*** Yield 66%, m.p. = 172–173°C. ^{1}H NMR, δ, ppm: 2.16 s (3H, CH_3), 2.33 s (3H, CH_3), 4.42 s (2H, CH_2), 7.39 t (1H, aryl), 7.50 t (1H, aryl), 7.84 d (1H, aryl), 8.04 d (1H, aryl), 9.95 s (1H, NH), 12.45 s

(1H, NH). ^{13}C NMR, δ, ppm: 16.9, 21.1, 36.9, 119.3, 121.5, 122.4, 125.1, 126.7, 126.9, 135.3, 139.8, 153.0, 166.4, 166.4, 169.1. Found%: C, 50.71; H, 3.88; N, 13.70. Calculated for $C_{17}H_{16}N_4O_2S_3$%: C, 50.48; H, 3.99; N, 13.85.

*N-(5,7-Dimethyl-2-oxo-2,3-dihydro-thiazolo[4,5-b]pyridin-6-yl)-2-(5-phenyl-[1,3,4] oxadiazol-2-ylsulfanyl) acetamide (**8c**).* Yield 80%, m.p. = 184–185°C. ^{1}H NMR, δ, ppm: 2.23 s (3H, CH_3), 2.37 s (3H, CH_3), 4.48 s (2H, CH_2), 7.49 s (2H, aryl), 7.55 s (1H, aryl), 7.83 s (2H, aryl), 10.89 s (1H, NH), 12.70 s (1H, NH). ^{13}C NMR, δ, ppm: 16.8, 21.0, 43.1, 123.0, 126.6, 130.0, 132.8, 139.7, 162.0, 166.0, 169.1, 177.9. Found%: C, 52.40; H, 3.73; N, 16.68. Calculated for $C_{18}H_{15}N_5O_3S_2$%: C, 52.29; H, 3.66; N, 16.94.

*N-(5,7-Dimethyl-2-oxo-2,3-dihydro-thiazolo[4,5-b]pyridin-6-yl)-2-[1-(4-methyl-1-vinyl-penta-1,3-dienyl)-1H-tetrazol-5-ylsulfanyl]-acetamide (**8d**).* Yield 75%, m.p. = 179–180°C. ^{1}H NMR, δ, ppm: 2.06 s (3H, aryl-CH_3), 2.40 s (3H, CH_3), 2.48 s (3H, CH_3), 3.39 s (2H, CH_2), 7.52 d (2H, J = 8.8 Hz, aryl), 7.65 d (2H, J = 8.8 Hz, aryl), 10.04 s (1H, NH), 14.29 s (1H, NH). ^{13}C NMR, δ, ppm: 16.9, 21.0, 21.2, 36.8, 107.4, 121.9, 125.2, 126.5, 130.4, 131.8, 133.5, 139.7, 140.5, 148.0, 154.4, 165.9, 169.0. Found%: C, 50.60; H, 4.08; N, 22.73. Calculated for $C_{18}H_{17}N_7O_2S_2$%: C, 50.57; H, 4.01; N, 22.93.

Free Radical Scavenging Assays

The antioxidant activity was determined on basis of free-radical-scavenging activity of stable DPPH. The effect of the studied compounds on DPPH radicals were estimated according to the method of Blois[21,22] 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 been 250 μmoles/L (0.2 mL). The reaction mixture was vortex mixed thoroughly and incubated at room temperature in the dark for 60 min. Simultaneously a control was prepared as ascorbic acid solution in ethanol (0.2 mL) mixed with DPPH solution in ethanol (4 mL) without sample fraction. Reduction in the absorbance of the mixture was measured at 540 nm using ethanol as blank. Ascorbic acid was used as a standard. Also the absorbance of DPPH solution was measured. Percentage of free-radical-scavenging activity was expressed as percent inhibition and it was calculated using the following formula:

$$\%\,\text{Inhibition} = \frac{A_{\text{DPPH}} - A_{\text{C}}}{A_{\text{DPPH}}} \times 100\,\%$$

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.

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