Synthesis and Antioxidant Properties of Novel 2-(2,4-Dioxothiazolidin-5-ylidene)-Acetamides Containing 1,3,4-Thia/Oxadiazole Moieties

Maryan Lelyukh 1*, Yuliia Matiichuk 2*, Vadym Flud 1*, Ihor Chaban 1*, Volodymyr Ogurtsov 2*

1 Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv, 79010, Ukraine; lelyukh.m@gmail.com (M.L.); chabanihor@ukr.net (I.C.);
2 Department of General, Bioinorganic, Physical and Colloidal Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv, 79010, Ukraine; yu_matiichuk@ukr.net (Y.M.); ogurtsov-v@ukr.net (V.O.);
3 Department of Obstetrics and Gynecology, Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv, 79010, Ukraine; nic2016@ukr.net (V.F.);
* Correspondence: lelyukh.m@gmail.com (M.L.);

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Abstract: A series of novel 1,3,4-thia(oxa)diazole substituted 2-(2,4-dioxothiazolidine-5-ylidene)-acetamides 3a-c, 4 and 5a-k have been synthesized following the acylation reaction of 2-amino-5-aryl-1,3,4-oxadiazoles, 5-amino-1,3,4-thiadiazole-2-thiol and it’s S-alkylated derivatives with 2-(2,4-dioxothiazolidine-5-ylidene)acetyl chloride in dioxane medium. The functionalization of compounds 3b, 3c, 5d and 5e was carried out on their N3 position under N-alkylation conditions with N-aryl-2-chloroacetamides in DMF/ethanol medium yielded the corresponding 2,4-dioxothiazolidine-3,5-diacetic acid diamides 6a-e and 7a-b. The structures of target compounds were confirmed by using 1H NMR spectroscopy and elemental analysis. The antioxidant activity evaluation in vitro of the synthesized compounds was performed by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. As a result, the highly active compound 4, namely 2-(2,4-dioxothiazolidin-5-ylidene)-N-(5-mercapto-[1,3,4]thiadiazol-2-yl)acetamide was found to be the most efficient candidate among all compounds with a radical scavenging ability of 88.9%, which was comparable that for ascorbic acid (92.7%). The experimentally calculated IC50 value of 43.1 µM for compound 4 was lower than for ascorbic acid (50.5 µM).

Keywords: organic synthesis; 2-(2,4-dioxothiazolidine-5-ylidene)acedamides; free radical scavenging; DPPH; antioxidant activity.

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1. Introduction

The 4-thiazolidinone core represents one of the privileged structure fragments widely used as a promising "building block" in modern medicinal chemistry for the rational drug-like molecules build-up [1-3]. 4-Thiazolidinone derivatives are characterized by different remarkable biological activities including anticancer [4-6], antibacterial [7, 8], antifungal [8, 9], antiviral [10, 11], anticonvulsant [12], trypanocidal [13, 14], analgesic [15], anti-inflammatory [15, 16], etc. Besides, 4-thiazolidinones have proven efficiency for the treatment of type 2 diabetes and its complications due to their affinity for PPARγ receptor [17] as well as α-glucosidase [18] and aldose reductase inhibitory action [19, 20].
Also, many works are devoted to highlighting the antioxidant potency of substituted 4-thiazolidinones and related heterocyclic systems [21-24]. This pharmacological action is of great interest because antioxidants are able to significantly delay or prevent oxidative processes by reducing the level of reactive oxygen species (ROS). It is known that ROS (e.g., superoxide radical, peroxynitryl, hydroxyl radical, and hydrogen peroxide) leads to oxidative stress in the human body, which is considered to be responsible for many pathological processes. For example, a series of 4-arylthiazole/benzothiazol substituted 2-(2,4-dioxothiazolidin-5-yl)acetamides I have exhibited good DPPH radical scavenging potential with EC$_{50}$ values ranging 20–60 µM as compared to ascorbic acid (40.28 µM) and luteolin (44.18 µM) as positive controls (Figure 1) [25]. A group of 2-arylthiazolidine-4-ones bearing coumarin fragment II showed 1.40-1.48 times better antioxidant activity than ascorbic acid by the phosphomolybdenum method [26]. Among indole-hydrazono thiazolidinones a highly active compound III was found, which showed to possess more potent antioxidant activity (85.9%) compared with other synthesized compounds and ascorbic acid as a standard antioxidant (82.3%) [27].

![Figure 1. Structures of antioxidant 4-thiazolidinone and 1,3,4-thia/oxadiazole derivatives as a background for design and synthesis of the target compounds.](https://biointerfaceresearch.com/)

1,3,4-Thia/oxadiazoles are another important class of heterocyclic compounds with diverse biological activities and a wide variety for chemical modification [28-32]. The antioxidant activity is also inherent for non-condensed heterocyclic systems containing 1,3,4-thia/oxadiazole moieties. Thus, among 5-naphthyloxymethylene-1,3,4-oxadiazoles IV (Figure 1), a highly active compound has been identified, which exhibited a noteworthy DPPH radical scavenging value almost comparable with the standard drug ascorbic acid [33]. A group of 2-(bis((5-aryl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-malononitriles V showed high antioxidant activity in both nitric oxide and DPPH methods at 100 µM concentration [34]. A series of 2-arylbenezimidazole and 2-methylamino-1,3,4-thiadiazole hybrids VI were synthesized and evaluated for their antioxidant properties by employing various in vitro systems [35]. The evaluation of antioxidant activity for 2-arylamino-1,3,4-thiadiazoles bearing butylated hydroxytoluene fragment VII using DPPH and lipid peroxidation assays led to the identification of the strongest free radical scavenging, reducing power and anti-lipid peroxidative agents [36].
Thus, the combination of pharmacologically significant templates – 4-thiazolidinone and 1,3,4-thia- or oxadiazole – has drawn common attention as a perspective approach for designing and synthesizing novel highly active molecules. They are especially considering that there are known thiazolidinone and 1,3,4-thia/ox diazole «double hybrids», which have shown synergistic effect and/or expansion of the pharmacological profile in many cases [37-42]. Considering the biological significance of thiazolidinones and 1,3,4-thia/oxadiazole derivatives, herein we designed and synthesized a series of novel 2-(2,4-dioxothiazolidine-5-ylidene)acetamides containing 1,3,4-thia(oxa)diazole moieties. Meanwhile, their in vitro antioxidant activity was evaluated based on the scavenging ability of a stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.

2. Materials and Methods

2.1. Materials.

All chemicals were of analytical grade and commercially available. The starting 2-amino-5-aryl-[1,3,4]oxadiazoles [43] 5-amino-1,3,4-thiadiazole-2-thiol [44] and (2,4-dioxothiazolidine-5-ylidene)-acetyl chloride [45] were obtained according to known methodologies. All reagents and solvents were used without further purification and drying. Ascorbic acid was purchased from a medical store. 2,2-Diphenyl-1-picrylhydrazyl was synthesized according to the procedure described by Goldschmidt and Renn (1922) [46].

2.2. Chemistry.

All melting points were determined by the open capillary method and are uncorrected. $^1$H NMR spectra were recorded on Varian Mercury 400 MHz (400 MHz for $^1$H) (USA) using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm units with the use of the δ scale. Mass spectra were recorded using Agilent 1100 series LC/MSD (USA) with an API–ES/APCI ionization mode. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer and were within ±0.4% of the theoretical values.

2.2.1. General procedure for synthesis of 2-(2,4-dioxothiazolidin-5-ylidene)-N-[5-aryl-[1,3,4]oxadiazol-2-yl]-acetamides (3a-c) and 2-(2,4-dioxothiazolidin-5-ylidene)-N-(5-mercapto-[1,3,4]thiadiazol-2-yl)-acetamide (4).

A solution of 3 mmol 2-(2,4-dioxothiazolidin-5-ylidene)-acetyl chloride in 5 ml of dioxane was added to a mixture of appropriate 2-amino-5-aryl-1,3,4-oxadiazole 1a-c or 5-amino-1,3,4-thiadiazole-2-thiol (3 mmol) and triethylamine (3 mmol) in 5 ml of dioxane and later was heated to 80-90°C during 20 min, cooled and poured water (50 ml). The obtained powder was filtered off, washed with water, dried, and recrystallized with DMF:AcOH (1:2) mixture.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-(4-chloro phenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (3a). Yield 84%; mp = 204-205°C. $^1$H NMR: δH = 12.84 (brs, 2H, NH-thiaz, CONH), 7.93 (d, J = 8.0 Hz, 2H, Ar), 7.66 (d, J = 8.0 Hz, 2H, Ar), 7.21 (s, 1H, =CHC(O)). ESI-MS: m/z 351 [M+H]$^+$. Anal. calcld. for C$_{13}$H$_7$ClN$_3$O$_4$S: C, 44.52; H, 2.01; N, 15.97. Found: C, 44.68; H, 2.14; N, 16.08.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (3b). Yield 81%; mp > 270°C. $^1$H NMR: δH = 12.73 (brs, 2H, NH-thiaz, CONH),
7.87 (d, J = 8.6 Hz, 2H, Ar), 7.22 (s, 1H, =CH(O)), 7.14 (d, J = 8.6 Hz, 2H, Ar), 3.83 (s, 3H, OCH₃). ESI-MS: m/z 347 [M+H]⁺. Anal. calcd. for C₁₆H₁₀N₄O₅S: C, 48.55; H, 2.91; N, 16.18. Found: C, 48.68; H, 3.02; N, 16.34.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-(3,4-dimethoxyphenyl)]-[1,3,4]oxadiazol-2-yl)-acetamide (3c). Yield 83%; mp = 232-233°C. ¹H NMR: δH = 12.74 (brs, 2H, NH-thiaz, CONH), 7.48 (d, J = 8.1 Hz, 1H, Ar), 7.41 (s, 1H, Ar), 7.19-7.13 (m, 2H, =CH(O), Ar), 3.86 (s, 6H, 2*OCH₃). ESI-MS: m/z 377 [M+H]⁺. Anal. calcd. for C₁₅H₁₂N₄O₆S: C, 47.87; H, 3.21; N, 14.89. Found: C, 47.74; H, 3.28; N, 15.02.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-(5-mercapto-[1,3,4]thiadiazol-2-yl)acetamide (4). Yield 88%; mp = 212-213°C. ¹H NMR: δH = 14.21 (brs, 1H, SH), 13.03 (brs, 1H, NH-thiaz). 7.14 (s, 1H, =CH(O)). ESI-MS: m/z 289 [M+H]⁺. Anal. calcd. for C₇H₄N₄O₃S₃: C, 29.16; H, 1.40; N, 19.43. Found: C, 29.31; H, 1.49; N, 19.57.

2.2.2. General procedure for synthesis of 2-(2,4-dioxothiazolidin-5-ylidene)-N-[5-(arylcarbamoyl)methylsulfanyl-[1,3,4]thiadiazol-2-yl]acetamides (5a-k).

A solution of 3 mmol 2-(2,4-dioxothiazolidin-5-ylidene)-acetyl chloride in 5 ml of dioxane was added to a mixture of appropriate 2-[5-amino-1,3,4-oxadiazol-2-yl]sulfanyl]-N-arylacetamide (2a-k) (3 mmol) and triethylamine (3 mmol) in 5 ml of dioxane and later was heated to 80-90°C during 20 min, cooled and poured water (50 ml). The obtained powder was filtered off, washed with water, dried, and recrystallized with DMF:AcOH (1:2) mixture.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-[2-methylphenylcarbamoyl]methylsulfanyl]-[1,3,4]thiadiazol-2-yl)-acetamide (5a). Yield 81%; mp = 246-247°C. ¹H NMR: δH = 13.49 (brs, 1H, CONH-thiazip), 13.02 (brs, 1H, NH-thiaz), 9.71 (s, 1H, CONH-Ar), 7.44 (d, J = 8.1 Hz, 1H, Ar), 7.25 (s, 1H, =CH(O)), 7.22-7.08 (m, 3H, Ar), 4.28 (s, 2H, SCH₂CO), 2.22 (s, 3H, CH₃). ESI-MS: m/z 436 [M+H]⁺. Anal. calcd. for C₁₆H₁₃N₅O₄S: C, 44.13; H, 3.01; N, 16.08. Found: C, 44.32; H, 3.14; N, 16.24.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-[2-methoxyphenylcarbamoyl]methylsulfanyl]-[1,3,4]thiadiazol-2-yl)-acetamide (5b). Yield 76%; mp = 252-253°C. ¹H NMR: δH = 13.43 (brs, 1H, CONH-thiazip), 12.83 (brs, 1H, NH-thiazip), 9.61 (s, 1H, CONH-Ar), 7.97 (d, J = 7.8 Hz, 1H, Ar), 7.23 (s, 1H, =CH(O)), 7.10-7.03 (m, 2H, Ar), 6.90 (t, J = 8.2 Hz, 1H, Ar), 4.29 (s, 2H, SCH₂CO), 3.83 (s, 3H, OCH₃). ESI-MS: m/z 452 [M+H]⁺. Anal. calcd. for C₁₆H₁₃N₅O₄S: C, 42.56; H, 2.90; N, 15.51. Found: C, 42.73; H, 3.02; N, 16.64.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-[2-trifluoromethylphenylcarbamoyl]methylsulfanyl]-[1,3,4]thiadiazol-2-yl)-acetamide (5c). Yield 90%; mp > 270°C. ¹H NMR: δH = 13.45 (s, 1H, CONH-thiazip), 12.84 (brs, 1H, NH-thiazip), 9.97 (s, 1H, CONH-Ar), 7.74 (d, J = 7.8 Hz, 1H, Ar), 7.69 (t, J = 7.7 Hz, 1H, Ar), 7.53 (d, J = 8.0 Hz, 1H, Ar), 7.47 (t, J = 7.7 Hz, 1H, Ar), 7.23 (s, 1H, =CH(O)), 4.26 (s, 2H, SCH₂CO). ESI-MS: m/z 490 [M+H]⁺. Anal. calcd. for C₁₆H₁₅F₃N₅O₄S: C, 39.26; H, 2.06; N, 14.31. Found: C, 39.43; H, 2.14; N, 14.47.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-[3-methylphenylcarbamoyl]methylsulfanyl]-[1,3,4]thiadiazol-2-yl)-acetamide (5d). Yield 88%; mp = 253-254°C. ¹H NMR: δH = 13.35 (brs, 1H, CONH-thiazip), 13.05 (brs, 1H, NH-thiazip), 10.28 (s, 1H, CONH-Ar), 7.43 (s, 1H, Ar), 7.36 (d, J = 8.1 Hz, 1H, Ar), 7.24 (s, 1H, =CH(O)), 7.20 (t, J = 8.0 Hz, 1H, Ar), 6.90 (d, J = 7.8 Hz, 1H, Ar), 4.24 (s, 2H, SCH₂CO), 2.28 (s, 3H, CH₃). ESI-MS: m/z 436 [M+H]⁺. Anal. calcd. for C₁₆H₁₃N₅O₄S: C, 44.13; H, 3.01; N, 16.08. Found: C, 43.92; H, 3.11; N, 16.27.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-[4-methylphenylcarbamoyl]methylsulfanyl]-[1,3,4]thiadiazol-2-yl)-acetamide (5e). Yield 93%; mp = 264-265°C. ¹H NMR: δH = 13.32 (brs,
2H, CONH-thiadiaz, NH-thiaz), 10.27 (s, 1H, CONH-Ar), 7.46 (d, J = 8.1 Hz, 2H, Ar), 7.22 (s, 1H, =CHC(O)), 7.11 (d, J = 8.1 Hz, 2H, Ar), 4.22 (s, 2H, SCH₂CO), 2.25 (s, 3H, CH₃). ESI-MS: m/z 436 [M+H]⁺. Anal. calcd. for C₁₆H₁₃N₃O₅S₃: C, 44.13; H, 3.01; N, 16.08. Found: C, 44.29; H, 2.89; N, 16.22.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-methoxyphenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5f). Yield 85%; mp > 270°C. ¹H NMR: δ_H = 13.42 (s, 1H, CONH-thiadiaz), 12.85 (brs, 1H, NH-thiaz), 10.21 (s, 1H, CONH-Ar), 7.48 (d, J = 9.0 Hz, 2H, Ar), 7.23 (s, 1H, =CHC(O)), 6.88 (d, J = 9.0 Hz, 2H, Ar), 4.20 (s, 2H, SCH₂CO), 3.71 (s, 3H, OCH₃). ESI-MS: m/z 452 [M+H]⁺. Anal. calcd. for C₁₆H₁₃N₃O₅S₃: C, 42.56; H, 2.90; N, 15.51. Found: C, 42.59; H, 3.02; N, 15.65.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-fluorophenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5g). Yield 82%; mp > 270°C. ¹H NMR: δ_H = 13.27 (brs, 1H, CONH-thiadiaz), 12.89 (brs, 1H, NH-thiaz), 10.29 (s, 1H, CONH-Ar), 7.59-7.56 (m, 2H, Ar), 7.26 (s, 1H, =CHC(O)), 7.14 (t, J = 8.7 Hz, 2H, Ar), 4.20 (s, 2H, SCH₂CO). ESI-MS: m/z 440 [M+H]⁺. Anal. calcd. for C₁₅H₁₀FNSO₅S: C, 41.00; H, 2.29; N, 15.94. Found: C, 41.21; H, 2.37; N, 16.07.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-chlorophenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5h). Yield 95%; mp = 256-257°C. ¹H NMR: δ_H = 13.42 (brs, 1H, CONH-thiadiaz), 12.94 (brs, 1H, NH-thiaz), 10.50 (s, 1H, CONH-Ar), 7.62 (d, J = 8.6 Hz, 2H, Ar), 7.38 (d, J = 8.5 Hz, 2H, Ar), 7.24 (s, 1H, =CHC(O)), 4.26 (s, 2H, SCH₂CO). ESI-MS: m/z 456 [M+H]⁺. Anal. calcd. for C₁₅H₁₀ClN₃O₅S: C, 39.53; H, 2.21; N, 15.36. Found: C, 39.69; H, 2.34; N, 15.52.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-bromophenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5i). Yield 85%; mp = 267-268°C. ¹H NMR: δ_H = 13.35 (brs, 1H, CONH-thiadiaz), 12.81 (brs, 1H, NH-thiaz), 10.42 (s, 1H, CONH-Ar), 7.54 (d, J = 9.0 Hz, 2H, Ar), 7.49 (d, J = 9.0 Hz, 2H, Ar), 7.24 (s, 1H, =CHC(O)), 4.23 (s, 2H, SCH₂CO). ESI-MS: m/z 501 [M+H]⁺. Anal. calcd. for C₁₅H₁₀BrN₃O₅S: C, 36.01; H, 2.01; N, 14.00. Found: C, 35.87; H, 2.14; N, 14.12.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-ethoxycarbonylphenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5j). Yield 85%; mp > 270°C. ¹H NMR: δ_H = 13.40 (brs, 1H, CONH-thiadiaz), 12.84 (brs, 1H, NH-thiaz), 10.69 (s, 1H, CONH-Ar), 7.92 (d, J = 8.7 Hz, 2H, Ar), 7.71 (d, J = 8.7 Hz, 2H, Ar), 7.22 (s, 1H, =CHC(O)), 4.30-4.25 (m, 4H, SCH₂CO, COOC₃H₇CH₃), 1.30 (t, J = 7.1 Hz, 3H, COOC₃H₇CH₃). ESI-MS: m/z 436 [M+H]⁺. Anal. calcd. for C₁₉H₁₅N₃O₅S₃: C, 43.81; H, 3.06; N, 14.19. Found: C, 43.94; H, 3.17; N, 14.33.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-{5-[(4-acetylaminophenylcarbamoyl)methylsulfanyl]-1,3,4]thiadiazol-2-yl}-acetamide (5k). Yield 73%; mp > 270°C. ¹H NMR: δ_H = 13.37 (brs, 1H, CONH-thiadiaz), 12.81 (brs, 1H, NH-thiaz), 10.23 (s, 1H, CONH-Ar), 9.85 (s, 1H, CH₃CONH), 7.49 (dd, J₁ = 9.1 Hz, J₂ = 6.0 Hz, 4H, Ar), 7.24 (s, 1H, =CHC(O)), 4.20 (s, 2H, SCH₂CO), 2.01 (s, 3H, CH₃CO). ESI-MS: m/z 479 [M+H]⁺. Anal. calcd. for C₁₇H₁₄N₆O₅S₃: C, 42.67; H, 2.95; N, 17.56. Found: C, 42.82; H, 3.08; N, 17.72.

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2.2.3. General procedure for synthesis of 2-[arylcarbamoyl]-methyl-2,4-dioxothiazolidin-5-ylidene)-N-[5-(aryl)-[1,3,4]oxadiazol-2-yl]acetamides (6a-e) and 2-[arylcarbamoyl]-methyl-2,4-dioxothiazolidin-5-ylidene)-N-[5-(arylcarbamoyl)methylsulfanyl-[1,3,4]thiadiazol-2-yl]acetamides (7a-b).

A suspension of compound 3b, 3c, 5d, or 5e (3 mmol) and potassium hydroxide (3 mmol) was heated in ethanol (5 ml) for 15 min. Then appropriate 2-chloro-N-arylacetamide (3.3 mmol) and DMF (5 ml) were added, and the mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature; the obtained precipitate was filtered off, washed with water and ethanol, dried, and recrystallized with DMF:EtOH (1:2) mixture.

2-[3-{2-Methylphenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]acetamide (6a). Yield 72%; mp = 235-236°C. 1H NMR: δH = 9.55 (s, 1H, CONH-Ar), 7.94 (d, J = 8.2 Hz, 2H, Ar), 7.42-7.39 (m, 2H, =CHC(O), Ar), 7.21-7.09 (m, 5H, Ar), 4.54 (s, 2H, N2-CH2CO), 3.90 (s, 3H, OCH3), 2.28 (s, 3H, CH3). ESI-MS: m/z 494 [M+H]+. Anal. calcd. for C23H19N6O6S: C, 55.98; H, 3.88; N, 14.19. Found: C, 56.15; H, 3.99; N, 14.32.

2-[3-{2-Methylphenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]acetamide (6b). Yield 77%; mp = 233-234°C. 1H NMR: δH = 9.62 (s, 1H, CONH-Ar), 7.96-7.90 (m, 3H, Ar), 7.38 (s, 1H, =CHC(O)), 7.11-7.00 (m, 4H, Ar), 6.87 (t, J = 7.6 Hz, 1H, Ar), 4.59 (s, 2H, N2-CH2CO), 3.87 (s, 6H, 2*OCH3). ESI-MS: m/z 510 [M+H]+. Anal. calcd. for C23H19N5O7S: C, 54.22; H, 3.76; N, 13.75. Found: C, 54.39; H, 3.91; N, 13.88.

2-[3-{4-Chlorophenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]acetamide (6c). Yield 76%; mp = 244-245°C. 1H NMR: δH = 10.53 (s, 1H, CONH-Ar), 7.89 (d, J = 8.4 Hz, 2H, Ar), 7.58 (d, J = 8.5 Hz, 2H, Ar), 7.39 (d, J = 8.6 Hz, 2H, Ar), 7.31 (s, 1H, =CHC(O)), 7.05 (d, J = 8.3 Hz, 2H, Ar), 4.50 (s, 2H, N2-CH2CO), 3.83 (s, 3H, OCH3). ESI-MS: m/z 514 [M+H]+. Anal. calcd. for C22H17ClN6O6S: C, 51.42; H, 3.14; N, 13.63. Found: C, 51.59; H, 3.27; N, 13.76.

2-[3-{4-Chlorophenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(3,4-dimethoxyphenyl)-[1,3,4]oxadiazol-2-yl]acetamide (6d). Yield 75%; mp = 223-224°C. 1H NMR: δH = 10.19 (s, 1H, CONH-Ar), 7.53-7.50 (m, 2H, Ar), 7.43 (s, 1H, Ar), 7.38 (s, 1H, =CHC(O)), 7.32 (d, J = 7.4 Hz, 1H, Ar), 7.14 (t, J = 7.7 Hz, 1H, Ar), 7.06 (d, J = 7.4 Hz, 1H, Ar), 6.85 (d, J = 7.6 Hz, 1H, Ar), 4.46 (s, 2H, N3-CH2CO), 3.88 (s, 6H, 2*OCH3), 2.31 (s, 3H, CH3). ESI-MS: m/z 524 [M+H]+. Anal. calcd. for C24H21ClN6O6S: C, 55.06; H, 4.04; N, 13.38. Found: C, 55.23; H, 3.94; N, 13.51.

2-[3-{4-Chlorophenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(3,4-dimethoxyphenyl)-[1,3,4]oxadiazol-2-yl]acetamide (6e). Yield 74%; mp = 229-230°C. 1H NMR: δH = 10.30 (s, 1H, CONH-Ar), 7.57-7.47 (m, 5H, =CHC(O), Ar), 7.28 (d, J = 7.9 Hz, 2H, Ar), 7.08 (d, J = 7.6 Hz, 1H, Ar), 4.50 (s, 2H, N2-CH2CO), 3.90 (s, 6H, 2*OCH3). ESI-MS: m/z 544 [M+H]+. Anal. calcd. for C23H18ClN6O6S: C, 50.79; H, 3.34; N, 12.88. Found: C, 50.96; H, 3.43; N, 13.07.

2-[3-{4-Chlorophenylcarbamoyl}-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-(3-methylphenylcarbamoyl)methylsulfanyl]-[1,3,4]thiadiazol-2-yl]acetamide (7a). Yield 71%; mp > 270°C. 1H NMR: δH = 13.47 (brs, 1H, CONH-thiadiaz), 10.53 (s, 1H, CONH-Ar), 10.27 (s, 1H, CONH-Ar), 7.57 (d, J = 8.7 Hz, 2H, Ar), 7.42-7.34 (m, 5H, =CHC(O), Ar), 7.21 (t, J = 7.6 Hz, 1H, Ar), 6.89 (d, J = 7.4 Hz, 1H, Ar), 4.52 (s, 2H, N2-CH2CO), 4.24 (s, 2H, SCH2CO), 3.87 (s, 3H, OCH3). ESI-MS: m/z 544 [M+H]+. Anal. calcd. for C23H18ClN6O6S: C, 50.79; H, 3.34; N, 12.88. Found: C, 50.96; H, 3.43; N, 13.07.
2.28 (s, 3H, CH₃). ESI-MS: m/z 603 [M+H]+. Anal. calcd. for C₂₅H₁₉ClN₂O₅S₃: C, 47.80; H, 3.18; N, 13.93. Found: C, 47.98; H, 3.31; N, 14.08.

2-{3-[(3-Methylphenylcarbamoyl)-methyl]-2,4-dioxothiazolidin-5-ylidene)-N-[5-{4-methylphenylcarbamoyl}-methylsulfanyl]-[1,3,4]thiadiazol-2-yl}acetamide (7b). Yield 68%; mp > 270°C. ¹H NMR: δH = 13.46 (brs, 1H, CONH-thiadiaz), 10.31 (s, 1H, CONH-Ar), 10.26 (s, 1H, CONH-Ar), 7.48-7.39 (m, 4H, =CHC(O), Ar), 7.33 (d, J = 8.0 Hz, 1H, Ar), 7.21 (t, J = 7.7 Hz, 1H, Ar), 7.13 (d, J = 7.6 Hz, 2H, Ar), 6.90 (d, J = 7.0 Hz, 1H, Ar), 4.50 (s, 2H, Nₛ-CΗ₂CO), 4.23 (s, 2H, SCH₂CO), 2.27 (s, 3H, CH₃), 2.25 (s, 3H, CH₃). ESI-MS: m/z 583 [M+H]+. Anal. calcd. for C₂₅H₂₂N₆O₅S₃: C, 51.53; H, 3.81; N, 14.42. Found: C, 51.67; H, 3.74; N, 14.53.

2.3. Free radical scavenging assays.

The evaluation of antioxidant activity was performed using a modified DPPH radical scavenging protocol reported by Blois [47, 48]. This effect of the studied compounds is based on the reduction of stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical with an odd electron which gives a maximum absorption at 517 nm. The test compound was initially dissolved in dimethyl sulfoxide (DMSO). The reaction mixture was prepared by mixing 4 mL of a 150 µM solution of DPPH in ethanol with 175 µL of the test compounds to reach a concentration of 100 µM. Simultaneously, to prepare the standard sample, an ethanolic solution of DPPH (4 mL) is mixed with an ascorbic acid solution in ethanol (0.2 mL). The reaction mixture was vortex mixed thoroughly and incubated at room temperature in the dark for 60 min. The absorbance of the reaction mixture was measured at 540 nm and compared to that for ascorbic acid as a standard. Also, the absorbance of DPPH solution as the control was measured. Percentage of free-radical-scavenging activity was expressed as percent inhibition, and it was calculated using the following formula:

\[%\text{Inhibition} = \frac{A_{DPPH} - A_c}{A_{DPPH}} \cdot 100\%
\]

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. The IC₅₀ is defined as the concentration of the test compound that causes 50% scavenging of DPPH radical and is calculated from the regression analysis obtained by plotting the scavenging effect of compounds at four different concentrations.

3. Results and Discussion

3.1. Chemistry.

The synthetic pathway for obtaining the target 1,3,4-thia/oxadiazole containing 2-(2,4-dioxothiazolidine-5-ylidene)acetedamides are depicted in Schemes 1 and 2.

The reaction of starting 2-amino-5-aryl-1,3,4-oxadiazoles 1a-c with 2-(2,4-dioxothiazolidine-5-ylidene)acetyl chloride in the presence of triethylamine in dioxane medium yielded the corresponding 2-(2,4-dioxothiazolidine-5-ylidene)-N-(5-aryl-1,3,4-oxadiazol-2-yl)acetamides 3a-c. Respectively, the use in similar transformations of 5-amino-1,3,4-thiadiazole-2-thiol and its S-alkylated derivatives 2a-k allowed obtaining 1,3,4-
thiadiazole substituted amide 4 and a group of novel analogs containing N-arylthioacetamide fragment 5a-k (Scheme 1).

Scheme 1. Synthesis of 1,3,4-thia(oxa)diazole substituted 2-(2,4-di)oxothiazolidine-5-ylidene)acetamides.
Reagents and conditions: a) (i) – KOH (1.0 equiv), EtOH, heating for 15 min; (ii) – appropriate N-aryl-2-chloroacetamide (1.1 equiv), reflux, 1 h; b) triethylamine (1.0 equiv), dioxane, heating at 90°C for 20-25 min.

The subsequent interaction of the obtained compounds 3b, 3c, 5d, and 5e with 2-chloro-N-aryl-acetamides in DMF/ethanol medium that included an intermediate stage of the synthesis of appropriate potassium salts led to the formation of the 1,3,4-thia(oxa)diazole substituted diamides of 2,4-dioxothiazolidine-3,5-diacetic acids 6a-e and 7a-b (Scheme 2).

Scheme 2. Synthesis of 1,3,4-thia(oxa)diazole substituted diamides of 2,4-dioxothiazolidine-3,5-diacetic acids.
Reagents and conditions: i) – KOH (1.0 equiv), EtOH, heating for 15 min; ii) – appropriate N-aryl-2-chloroacetamide (1.1 equiv), DMF, reflux, 5 h.

Structures of all synthesized compounds were confirmed by 1H NMR spectroscopy and elemental analysis. In 1H-NMR spectra, the signals for the protons of all the structural units were observed in their characteristic ranges.

In the 1H NMR spectra, the protons of the SCH2CO fragment for N-arylthioacetamide substituted derivatives 5a-k, and 7a-b appears as a singlet at δ ~ 4.20-4.29 ppm. For the protons of the N2-CH2CO group (compounds 6a-e and 7a-b) a singlet had been observed in the range of δ ~ 4.46-4.59 ppm. The signal of a 5-methylidene proton =CHC(O) for the target compounds 3a-c, 4, and 5a-k resonates as a singlet in the range of δ ~ 7.14-7.26 ppm, which indicates a Z-configuration of the exocyclic C=C bond at the 5-arylidene fragment. For the N3-alkylated
derivatives 6a-e and 7a-b, this signal is slightly shifted towards a weak magnetic field to $\delta \sim 7.31-7.42$ ppm.

The signal of arylamide CONH-Ar proton is observed as a singlet in the wide range of $\delta \sim 9.55-10.69$ ppm depending on the nature and location (ortho-, meta- or para-position) of the substituent at the aryl moiety.

The NH proton in position 3 of thiazolidine and CONH proton of heteryl substituted amide fragment for the compounds 4 and 5a-k (except 5e) appears as a broad singlet at the ranges of $\delta \sim 12.81-13.05$ ppm and $\delta \sim 13.27-13.49$ ppm, respectively. However, for the compounds 3a-c signals of this, both protons combine and resonate as a broad joint singlet at the range of $\delta \sim 12.73-12.84$ ppm. For the proton of the unsubstituted SH-group (compound 4) a singlet at $\delta \sim 14.21$ ppm has been observed. Instead, the signal of the CONH proton of thiadiazole substituted amide fragment for this compound does not appear, probably due to deutero-n exchange with the solvent.

3.2. Antioxidant activity evaluation in DPPH assay.

The antioxidant activity of the obtained compounds 3a-c, 4, and 5a-k was determined based on the free radical scavenging ability of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. The DPPH assay is well known as a simple, rapid, and convenient method for testing newly synthesized compounds to scavenge radicals and to find out promising antioxidant drug candidates. This simple test provides information on the ability of a compound to donate electrons during antioxidant action. Antioxidants tested on DPPH were also found extremely effective in cell systems. The radical scavenging mechanism is based on the transfer of acidic H-atom from the compound to DPPH radical to form DPPH-H.

DPPH radical has 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 517 nm. When antioxidants react with DPPH, giving DPPD-H, the absorbance decreases due to decolorization with respect to the number of electrons captured. The DPPH radical acts as a scavenger for other odd-electron species which afford para-substitution products at phenyl rings.

The free radical scavenging effect of the synthesized compound was assayed using a stable DPPH and was quantified by decolorization of the solution being mixed with DPPH at a wavelength of 517 nm. The absorbance of DPPH solution in ethanol (150 µ moles/L) was measured as 0.740.

| Compound | Absorbance of a sample, $A_s$ | % Inhibition | Compound | Absorbance of a sample, $A_s$ | % Inhibition |
|----------|-------------------------------|--------------|----------|-------------------------------|--------------|
| Control  | 0.740±0.025                   | –            | 5e       | 0.726±0.020                   | 1.89         |
| 3a       | 0.735±0.020                   | 0.67         | 5f       | 0.739±0.025                   | 0.14         |
| 3b       | 0.733±0.025                   | 0.95         | 5g       | 0.738±0.020                   | 0.27         |
| 3c       | 0.737±0.015                   | 0.40         | 5h       | 0.738±0.020                   | 0.27         |
| 4        | 0.082±0.020                   | 88.9         | 5i       | 0.739±0.025                   | 0.14         |
| 5a       | 0.730±0.025                   | 1.35         | 5j       | 0.736±0.025                   | 0.54         |
| 5b       | 0.728±0.020                   | 1.62         | 5k       | 0.738±0.020                   | 0.27         |
| 5c       | 0.729±0.020                   | 1.49         | Ascorbic acid | 0.053±0.015 | 92.7         |
| 5d       | 0.733±0.025                   | 0.95         |           |                               |              |
Initially, all compounds were tested at a single concentration of 100 µM. The absorbances and free radical scavenging activities % inhibitions of standard (ascorbic acid) and tested compound are shown in Table 1.

The antioxidant activity evaluation in vitro showed that most of the tested compounds (except compound 4) have a very weak effect on the release of free radicals in the range 0.14-1.89%. Also, the obtained data allowed the identification of one highly active compound, 4, whose free radical scavenging effect (88.9%) was significantly higher compared to other compounds and comparable that for ascorbic acid (92.7%).

The further study consisted of the experimental determining the radical scavenging effect of the tested compound 4 at different concentrations, calculating the IC50 value, and comparing it with ascorbic acid (Table 2, Figure 2a).

Table 2. Radical scavenging effect (%) on DPPH free radical of compound 4 and ascorbic acid at four concentrations.

| Radical scavenging activity | C, µΜ  |
|-----------------------------|--------|
|                             | 13.5   | 27    | 54    | 81    |
| Ascorbic acid               | 17.5%  | 33.0% | 51.8% | 74.2% |
| Compound 4                  | 15.3%  | 32.6% | 67.4% | 88.1% |

According to the obtained results, compound 4 exhibited a strong radical scavenging effect on the DPPH free radical with a respective IC50 value of 43.1 µM, which is lower than that of ascorbic acid (43.1 µM) (Figure 2b).

Figure 2. Graphical dependence of the free radical scavenging effect on concentration (a) and comparison of IC50 values (b) for the tested compound 4 and ascorbic acid.

Analysis of the following results revealed that the most significant influence on the manifestation of antioxidant activity has the presence of unsubstituted thiol SH-group. Due to the low activity values of most compounds, the available experimental data are insufficient to establish the impact of the substituents on the free-radical-scavenging activity level and to identify some patterns of correlation «structure – antioxidant action».

4. Conclusions

In the present paper, twenty-two novel 1,3,4-thia(oxa)diazole substituted 2-(2,4-dioxothiazolidine-5-ylidene)acetamides possessing antioxidant activity were described. We have shown that the proposed approaches and developed synthetic protocols provided the possibility to design 4-thiazolidine and 1,3,4-thia(oxa)diazole conjugates linked by ylidenacetamide fragment involving N-acylation and N-alkylation reactions. Fifteen synthesized compounds were evaluated for their antioxidant activity using DPPH method. According to the preliminary results, the most active compound – 2-(2,4-dioxothiazolidin-5-...
ylidene)-N-(5-mercapto-[1,3,4]thiadiazol-2-yl)acetamide (4) was identified, whose free radical scavenging ability at the level of 88.9% was comparable that for ascorbic acid. The experimental calculation of IC_{50} values for highly active compound 4 was performed using the regression analysis obtained by plotting the scavenging effect of compounds at different concentrations. The obtained value of 43.1 µM was lower than for ascorbic acid (50.5 µM), indicating that compound 4 has good radical scavenging activity. These results prove the necessity of further investigations to clarify the features underlying the antioxidant potential of non-condensed dual 4-thiazolidinone and 1,3,4-thia(oxa)diazole hybrid analogs.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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