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SYNTHESIS OF AMIDES OF 5-ARYLIDENE-2,4-DIOXOTHIAZOLIDINE-3-ACETIC ACID WITH 1,2,4-TRIAZOLE SYSTEM

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Abstract: In the reaction of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid chloride with 1,2,4-triazole, 1,2,4-triazoline-5-one and 1,2,4-triazoline-5-thione, the new corresponding 5-arylidene-2,4-dioxothiazolidine-3-acetic acid amides **(5-16)** were obtained. Compounds **6**, **14** i **15** were investigated *in vitro* for their antioxidant activity.

Keywords: 5-Arylidene-2,4-dioxothiazolidine-3-acetic acid amides, 1,2,4-triazole derivatives, antioxidant activity.

2,4-Dioxothiazolidine derivatives can have implementations in medicine in view of their anti-cancer, antidiabetic activity and application in liver disease (1-3).

Widening the possibility of the medical implementation of 2,4-dioxothiazolidine derivatives can be performed by connecting them with another heterocyclic system e.g. 1,2,4-triazole derivatives which showed broad spectrum of pharmacological activity.

Depending of the nature of substituents, the 1,2,4-triazole derivatives can show various pharmacological activity, such as sedative action on the central nervous system (4-6) and analgesic (7-11), anticonvulsive (12,13) and hypotensive (14), anti-inflammatory (15-19) and anti-cancer (20-24), antibacterial, bacteriostatic and virusostatic action (25-29), as well as they are used as herbicides and fungicides (30-32).

The broad spectrum of biological activity of these compounds were inspiration for synthesis of new derivatives having both 2,4-dioxothiazolidine and 1,2,4-triazole systems. These compounds were obtained from such starting materials like new derivatives of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid.

From the literature data it is known that 5-phenylpropenilidene-2,4-dioxothiazolidine-acetic acid show high antioxidant activity in autooxidation of lipids initiated by Fe^{2+} (33). Hence, the purpose of the present work was the comparative study of *in vitro* antioxidant activity (AA) of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid derivatives with 1,2,4-triazole system in position 3.

Scheme 1 presents the reactions carried out in this work.

EXPERIMENTAL

Chemistry

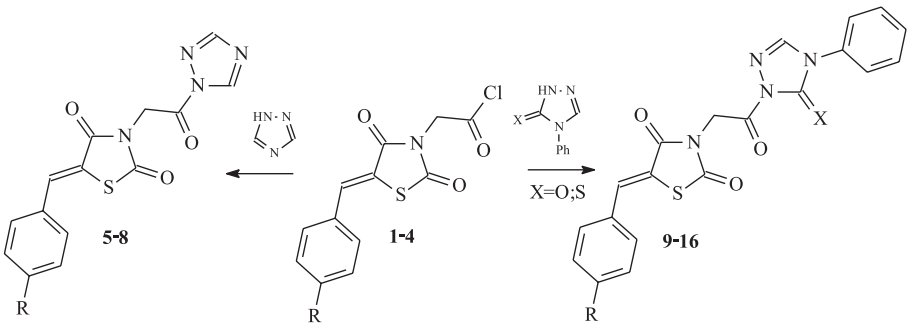
Melting points were determined in Fischer-Johns blocks (Sanyo, Japan) and are presented without corrections. The IR spectra were recorded in KBr using a Specord IR-75 spectrophotometer (Perkin Elmer, UK). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 apparatus (Bruker, Germany) in DMSO-d_6 with TMS as internal standard. The mass spectra were recorded on ThermoFinnigan Trace TSQGC MS apparatus.
Purity of all compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck), in a $CHCl_3/C_2H_5OH$ (10:2, v/v) solvent system with UV visualizaton (λ=254 nm).

The results of elemental micro analysis for C, H, N were performed in the Department of Organic Chemistry, Lublin Medical University and were within ±0,5% of the theoretical values.

Synthesis of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid amides **(5-16)**

General procedure

To the solution of 0.01 mole of 1,2,4-triazole, 4-phenyl-1,2,4-triazoline-5-one or 4-phenyl-1,2,4-



Scheme 1.

triazoline-5-thione and 1.00 g (0.01 mole) of triethylamine in 5 cm^3 of anhydrous dioxane, 0.01 mole of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid chloride in 5 cm^3 of anhydrous dioxane were added. After 15 min water was added to the reaction mixture. The precipitate was filtered off and then recrystallized from acetic acid, n-propanol or n-butanol.

1-[(5-Benzylidene-2,4-dioxothiazolidin-3-yl)acetyl]-1,2,4-triazole **(5)**

Yield 2.20 g (70%), m.p. 175-176°C. IR (KBr, cm^{-1}): 3042 ($CH_{ar.}$); 2952, 1421 ($CH_{al.}$); 1734, 1682 (C=O); 1611 (C=N); 1499 (C-N); 681 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.26 (s, 2H, CH_2); 7.46-7.62 (m, 5H, Ph); 7.80 (s, 1H, =CH); 8.43, 9.42 (2s, 2H, 1,2,4-triazole).

1-{[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-1,2,4-triazole **(6)**

Yield 2.92 g (85%), m.p. 176-178°C. IR (KBr, cm^{-1}): 3065 ($CH_{ar.}$); 2959, 1421 ($CH_{al.}$); 2840 (OCH_3); 1739, 1689 (C=O); 1595 (C=N); 1512 (C-N); 828 (*p*-substituted benzene); 686 (C-S-C). ^{1}H NMR (DMSO-d_6) ä (ppm): 3.85 (s, 3H, OCH_3); 5.29 (s, 2H, CH_2); 7.15 (d, 2H, 4-MeO-$C_6\underline{H}_4$, *J*=8.7 Hz); 7.66 (d, 2H, 4-MeO-$C_6\underline{H}_4$, *J*=8.7 Hz); 8.00 (s, 1H, =CH); 8.44, 9.45 (2s, 2H, 1,2,4-triazole).

1-{[5-(4-Methylbenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-1,2,4-triazole **(7)**

Yield 2.13 g (65%), m.p. 218-220°C. IR (KBr, cm^{-1}): 3128 ($CH_{ar.}$); 2959, 1405 ($CH_{al.}$); 1735, 1685 (C=O); 1599 (C=N); 1514 (C-N); 810 (*p*-substituted benzene); 685 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.37 (s, 3H, CH_3); 5.30 (s, 2H, CH_2); 7.38 (d, 2H, 4-Me-$C_6\underline{H}_4$, *J*=8.1 Hz); 7.56 (d, 2H, 4-Me-$C_6\underline{H}_4$, *J*=8.1 Hz); 7.97 (s, 1H, =CH); 8.44, 9.46 (2s, 2H, 1,2,4-triazole).

1-{[5-(4-Bromobenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-1,2,4-triazole **(8)**

Yield 3.34 g (85%), m.p. ~250°C. IR (KBr, cm^{-1}): 3126 ($CH_{ar.}$); 2959, 1405 ($CH_{al.}$); 1737, 1686 (C=O); 1600 (C=N); 1514 (C-N); 811 (*p*-substituted benzene); 685 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.29 (s, 2H, CH_2); 7.63 (d, 2H, 4-Br-C_6H_4, *J*=8.4 Hz); 7.77 (d, 2H, 4-Br-C_6H_4, *J*=8.7 Hz); 7.97 (s, 1H, =CH); 8.43, 9.42 (2s, 2H, 1,2,4-triazole). ^{13}C NMR: 45.37 (CH_2); 121.56; 123.86; 131.72; 132.37 (6$C_{ar.}$, 4-Br-C_6H_4); 124.67 (=$\underline{C}$(S-)C(O)); 130.28; 132.57 (2C, triazole); 132.24 (CH=); 164.95 (C-$\underline{C}$(O)-N); 166.64 ($CH_2\underline{C}$=O); 167.75 (N-C(O)-S).

1-[(5-Benzylidene-2,4-dioxothiazolidin-3-yl)--acetyl]-4-phenyl-5-oxo-4,5-dihydro-1,2,4-triazole **(9)**

Yield 2.64 g (65%), m.p. 235-237°C. IR (KBr, cm^{-1}): 3060 ($CH_{ar.}$); 2953, 1448 ($CH_{al.}$); 1740, 1692 (C=O); 1610 (C=N); 1495 (C-N); 688 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.19 (s, 2H, CH_2); 6.91-7.69 (m, 10H, 2Ph); 7.97 (s, 1H, =CH); 8.62 (s, 1H, 1,2,4-triazole). ^{13}C NMR: 44.36 (CH_2); 120.60 (=$\underline{C}$(S-)C(O)); 122.85; 127.72; 130.32; 133.31 (6$C_{ar.}$, C_6H_5-N); 128.05; 129.40; 129.57; 132.72 (6$C_{ar.}$, $\underline{C}_6H_5$-CH=); 130.91 (CH=); 134.19 (N=CH); 150.22 (N-C(O)-N); 162.56 ($CH_2\underline{C}$=O); 164.96 (C-$\underline{C}$(O)-N); 166.74 (N-C(O)-S). MS m/z (%): 406 (M, 9); 288 (3); 246 (67); 218 (83); 190 (5); 161 (38); 147 (30); 134 (100); 129 (8); 91 (10); 77 (17).

1-{[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-4-phenyl-5-oxo-4,5-dihydro-1,2,4-triazole **(10)**

Yield 2.92 g (67%), m.p. 243-245°C. IR (KBr, cm^{-1}): 3071 ($CH_{ar.}$); 2953, 1441 ($CH_{al.}$); 2839 (OCH_3); 1736, 1688 (C=O); 1595 (C=N); 1511 (C-N); 829 (*p*-substituted benzene); 691 (C-S-C). ^{1}H

NMR (DMSO-d_6) δ (ppm): 3.84 (s, 3H, OCH_3); 5.19 (s, 2H, CH_2); 7.13 (d, 2H, 4-MeO-$C_6\underline{H}_4$, *J*=9.0 Hz); 7.51-7.69 (m, 5H, Ph and 2H, 4-MeO-$C_6\underline{H}_4$); 7.99 (s, 1H, =CH); 8.64 (s, 1H, 1,2,4-triazole). ^{13}C NMR: 42.38 (CH_2); 55.51 (OCH_3); 114.99; 125.19; 133.96; 168.01 ($6C_{ar.}$, 4-MeO-C_6H_4); 117.24 (=$\underline{C}$(S-)C(O)); 122.83; 127.38; 129.57; 133.33 ($6C_{ar.}$, C_6H_5-N); 132.39 (CH=); 134.20 (N=CH); 150.23 (N-C(O)-N); 161.41 ($CH_2\underline{C}$=O); 164.94 (C-$\underline{C}$(O)-N); 166.81 (N-C(O)-S). MS m/z (%): 436 (M, 16); 318 (4); 293 (2); 248 (65); 235 (1); 192 (4); 177 (18); 164 (100); 149 (62); 121 (20); 77 (19).

1-{[5-(4-Methylbenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-4-phenyl-5-oxo-4,5-dihydro-1,2,4-triazole **(11)**

Yield 2.98 g (71%), m.p. 249-252°C. IR (KBr, cm^{-1}): 3066 ($CH_{ar.}$); 2947, 1435 ($CH_{al.}$); 1738, 1684 (C=O); 1598 (C=N); 1507 (C-N); 825 (*p*-substituted benzene); 689 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.37 (s, 3H, CH_3); 5.19 (s, 2H, CH_2); 7.40 (d, 2H, 4-Me-$C_6\underline{H}_4$, *J*=8.1 Hz), 7.50-7.68 (m, 5H, Ph and 2H, 4-Me-$C_6\underline{H}_4$); 7.99 (s, 1H, =CH); 8.65 (s, 1H, 1,2,4-triazole).

1-{[5-(4-Bromobenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-4-phenyl-5-oxo-4,5-dihydro-1,2,4-triazole **(12)**

Yield 3.30 g (68%), m.p. 256-258°C. IR (KBr, cm^{-1}): 3071 ($CH_{ar.}$); 2942, 1424 ($CH_{al.}$); 1741, 1689 (C=O); 1603 (C=N); 1506 (C-N); 817 (*p*-substituted benzene); 688 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.20 (s, 2H, CH_2); 7.51-7.68 (m, 5H, Ph and 2H, 4-Br-C_6H_4); 7.77 (d, 2H, 4-Br-C_6H_4, *J*=8.4 Hz); 7.98 (s, 1H, =CH); 8.64 (s, 1H, 1,2,4-triazole). ^{13}C NMR: 44.41 (CH_2); 121.41; 124.45; 131.98; 132.72 ($6C_{ar.}$, 4-Br-C_6H_4); 121.55 (=$\underline{C}$(S-)C(O)); 122.84; 127.73; 129.57; 133.29 ($6C_{ar.}$, C_6H_5-N); 131.91 (CH=); 132.99 (N=CH); 150.23 (N-C(O)-N); 162.51 ($CH_2\underline{C}$=O); 164.92 (C-$\underline{C}$(O)-N); 166.61 (N-C(O)-S). MS m/z (%): 486 (M+1, 16); 366 (3); 326 (46); 298 (67); 242 (4); 214 (69); 182 (13); 161 (100); 156 (5); 77 (25).

1-[(5-Benzylidene-2,4-dioxothiazolidin-3-yl)acetyl]-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazole **(13)**

Yield 2.57 g (61%), m.p. 244-246°C. IR (KBr, cm^{-1}): 3063 ($CH_{ar.}$); 2950, 1432 ($CH_{al.}$); 1741, 1694 (C=O); 1606 (C=N); 1497 (C-N); 1381 (C=S); 685 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.21 (s, 2H, CH_2); 6.92-7.68 (m, 10H, 2Ph); 7.99 (s, 1H, =CH); 9.01 (s, 1H, 1,2,4-triazole).

1-{[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazole **(14)**

Yield 3.16 g (70%), m.p. 230-232°C. IR (KBr, cm^{-1}): 3054 ($CH_{ar.}$); 2977, 1404 ($CH_{al.}$); 2839 (OCH_3); 1734, 1686 (C=O); 1593 (C=N); 1511 (C-N); 1382 (C=S); 864, 827 (*p*-substituted benzene, phenyl); 682 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 3.84 (s, 3H, OCH_3); 5.20 (s, 2H, CH_2); 7.15 (d, 2H, 4-MeO-$C_6\underline{H}_4$, *J*=8.7 Hz); 7.52-7.68 (m, 5H, Ph and 2H, 4-MeO-$C_6\underline{H}_4$); 8.01 (s, 1H, =CH); 9.02 (s, 1H, triazole). ^{13}C NMR: 44.86 (CH_2); 55.54 (OCH_3); 115.05; 125.19; 134.26; 168.03 ($6C_{ar.}$, 4-MeO-C_6H_4); 117.16 (=$\underline{C}$(S-)C(O)); 126.80; 129.32; 132.50; 133.41 ($6C_{ar.}$, C_6H_5-N); 133.69 (CH=); 143.25 (N=CH); 161.44 ($CH_2\underline{C}$=O); 163.63 (N-C(O)-N); 165.05 (C-$\underline{C}$(O)-N); 166.97 (N-C(O)-S). MS m/z (%): 452 (M, 2); 293 (8); 276 (17); 248 (16); 193 (2); 176 (66); 164 (100); 149 (66); 135 (6); 121 (23); 77 (28).

1-{[5-(4-Methylbenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazole **(15)**

Yield 3.00 g (69%), m.p. 240-241°C. IR (KBr, cm^{-1}): 3062 ($CH_{ar.}$); 2960, 1417 ($CH_{al.}$); 1747, 1693 (C=O); 1597 (C=N); 1509 (C-N); 1377 (C=S); 822 (*p*-substituted benzene); 681 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.39 (s, 3H, CH_3); 5.20 (s, 2H, CH_2); 7.40 (d, 2H, 4-Me-$C_6\underline{H}_4$, *J*=8.1 Hz); 7.52-7.62 (m, 5H, Ph and 2H, 4-Me-$C_6\underline{H}_4$); 8.00 (s, 1H, =CH); 8.98 (s, 1H, 1,2,4-triazole).

1-{[5-(4-Bromobenzylidene)-2,4-dioxotiazolidin-3-yl]acetyl}-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazole **(16)**

Yield 3.45 g (69%), m.p. 252-253°C. IR (KBr, cm^{-1}): 3052 ($CH_{ar.}$); 2943, 1399 ($CH_{al.}$); 1755, 1720 (C=O); 1610 (C=N); 1486 (C-N); 1378 (C=S); 817 (*p*-substituted benzene); 697 (C-S-C). ^{1}H NMR (DMSO-d_6) δ (ppm): 5.20 (s, 2H, CH_2); 7.50-7.64 (m, 5H, Ph and 2H, 4-Br-C_6H_4,); 7.76 (d, 2H, 4-Br-C_6H_4, *J*=8.4 Hz); 8.00 (s, 1H, =CH); 9.02 (s, 1H, 1,2,4-triazole).

Pharmacology

The investigations were carried out in the laboratory of the Department of Pharmacology of Lugansk State Medical University, certified by the State Pharmacological Center of Ministry of Health of Ukraine (certificate No. 7 of 29.09.2005).

Antioxidant activity (AA) in modelling system was determined under conditions of non-enzymatic initiation of lipid peroxidation by Fe^{2+} ions (34). The

suspension of egg lipoproteids (SEL) was used as a substrate. A water soluble antioxidant – ascorbic acid was used as a standard (35). SEL was prepared by homogenization of an egg yolk with full volume of the phosphate buffer pH 7.4. The investigated substances (10^{-3} mole/dm^3) were added to the suspension. The free-radical reaction was induced by addition of 1.0 cm^3 of 0.7% solution of $FeSO_4 \cdot 7H_2O$. Three samples were investigated: the experimental (containing the investigated compounds and iron (II) sulfate), the control (containing iron (II) sulfate) and the blind test (without Fe^{2+} ions and the investigated compounds).

AA of 2,4-dioxothiazolidine derivatives were investigated in dynamics after 15, 30 and 60 min. from the moment of the LPO induction. The reaction was stopped by entering of 1.0 cm^3 of 25% trichloroacetic acid (containing 2.5 mg EDTA in 100 cm^3 of solution for linkage of Fe^{2+} and stop of free-radical oxidation) into modelling system.

AA of the investigated compounds was calculated according to the formula:

$$AA = \frac{C_c - C_i}{C_c} \cdot 100\%$$

AA – antioxidant activity

C_c – concentration of TBA-reactants in control sample

C_i – concentration of TBA-reactants in the investigated sample

The obtained results were evaluated statistically with the Student's *t*-criteria.

RESULTS AND DISCUSSION

Chemistry

As the starting materials were used 5-arylidene-2,4-dioxothiazolidine-3-acetic acid chlorides (**1-4**) which by the reaction of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid with thionyl chloride were obtained by the method described earlier (36,37). These chlorides were applied to obtain new derivatives of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid connected with 1,2,4-triazole ring by reaction with 1,2,4-triazole, 4-phenyl-1,2,4-triazoline-5-one and 4-phenyl-1,2,4-triazoline-5-thione. These reactions were carried out in anhydrous 1,4-dioxane with the presence of triethylamine and led to derivatives substituted in position 1 of 1,2,4-triazole system. Such substitution in position 1 was confirmed by investigation of nucleophilic substitution of derivatives with 1,2,4-triazole ring (38). 1,2,4-Triazole was obtained by the reaction by triformylaminomethane with hydrazine sulfate (39), whereas 4-phenyl-1,2,4-triazoline-5-one and 4-phenyl-1,2,4-triazoline-5-thione were obtained by the cyclization in alkaline media from 4-phenyl-1-formylsemicarbazide and 4-phenyl-1-formylthiosemicarbazide, respectively, by the method described earlier (40-43).

The structure of newly synthesized amides (**5-16**) was confirmed by elemental analysis and IR, ^{1}H NMR spectra and for some derivatives by ^{13}C NMR and MS.

In the IR spectra of derivatives (**5-16**) with 1,2,4-triazole ring the following characteristic absorption bands were observed: 1695-1750 cm^{-1} corresponding to C=O group and to C=S group near 1382 cm^{-1}. The absorption bands of C=N and C-N groups were observed at 1590-1620 cm^{-1} and 1485-1514 cm^{-1}, respectively. For the C-S-C group characteristic bands were observed at 687 cm^{-1}.

In the ^{1}H NMR spectra, all 5-arylidene derivatives show proton signal typical of the Ar<u>CH</u>= group in the δ=7.93-8.01 ppm range. All 4-substituted derivatives with benzene ring show characteristic dublets of aromatic proton in the δ=7.14-7.78 ppm range, *J*=8.1-9.0 Hz. All compounds with 1,2,4-triazole, 1,2,4-triazoline-5-one and 1,2,4-triazoline-5-thione system (**5-16**) show proton signal of the CH group in the δ=8.44-9.46 ppm range.

The results of ^{13}C NMR and MS are presented in the experimental part.

Pharmacology

The results of determination of AA of 2,4-dioxothiazolidine derivatives under conditions of Fe^{2+}-induced LPO obtained in *in vitro* experiment are presented in Figure 1.

It was found that under conditions of entering of the investigated compounds **6** and **15** into modelling system the level of TBA-active products practically did not differ from the parameters registered for control sample by 15th minute of identification ($p>0.05$). Under the action of compound **14** the content of LPO products increased 1.5 times, that indicates the prooxidant effect of this compound at that time.

After 30 min the quantity of LPO products, determined in incubation mixture with compounds **6** and **15** increases and is equal to a level identified in a control series. It is important to emphasize that at 30 min after incubation of probes with substance **14** the intensity of LPO processes decreased ($p<0.01$), demonstrating AA, which exceeds the results of standart preparation – ascorbic acid.

Later on, by screening investigations it was shown, that at 60 min of incubation compounds **14** and **15** showed the strongest antioxidant properties in experimental model used (Figure 1). So, the quantity of TBA-reactants at this time of observation decreases by 25-29% in comparison with the control ($p<0.01$). It is also necessary to note, that the analyzed parameter does not differ from that for the ascorbic acid, that testifies the antioxidant efficiency of the investigated compounds.

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