Synthesis and Antimicrobial Activity of Novel Hydrazone and 1,2,4-Triazole-3-thione Derivatives

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Abstract—Novel hydrazone and 1,2,4-triazole-3-thione derivatives were obtained via the reaction of $N^1,N^3,2$-triaryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides with acid hydrazides and thiosemicarbazide, respectively. Structure of the products was proved using IR and $^1$H NMR spectroscopy methods. Some of the synthesized compounds were tested for antimicrobial activity

Keywords: acid hydrazides, thiosemicarbazide, hydrazones, 1,2,4-triazole-3-thiones, antimicrobial activity

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The synthesis and determination of the practical value of hydrazones are relevant, since a hydrazone fragment is present in the molecules of a number of biologically active compounds [1], which have antimicrobial [2–5], anti-inflammatory [6], analgesic [7], antipROTOzoal [8], antituberculous [9], antiCONVULSANT [10], and cardioprotective activity [11]. The combination of different functional groups in hydrazones results in a large number of compounds with unique physical and chemical properties. Some of them can be used in the treatment of diseases of the central nervous system [12], as well as in molecular targeted therapy of drug treatment of cancer [13, 14]. Structural analogs of hydrazones have shown good results in their study as growth promoters in plants of \textit{Nicotiana tabacum L.} and \textit{Arabidopsis thaliana} species [15].

The 1,2,4-triazole-3-thione fragment occurs in the structure of many natural and biologically active compounds [16, 17], for example, in bicyclic anxiolytic drugs, estazolam, alprazolam (Scheme 1), in the triptan 5-HT\textsubscript{1} agonist (rizatriptan) and in antimicrobial agents based on spiropropiridinyl-1,2,4-triazolidine-3-thione [18–22]. For the synthesis of heterocyclic compounds with antimicrobial activity with a 1,2,4-triazole-3-thione moiety, the reaction of ketones with thiosemicarbazide is used [23–27].

In this regard, the synthesis of compounds with hydrazone and 1,2,4-triazole-3-thione fragments is promising for the preparation of biologically active compounds and for the creation of new drugs based on them.

Scheme 1 shows examples of biologically active hydrazones and 1,2,4-triazole-3-thione derivatives, which have antimicrobial (1) [4], antipROTOzoal (2) [8], antimicrobial (3) [21], and anti-inflammatory activity (4) [6]. Hydrazone 5 inhibits the phosphodiesterase 10A enzyme responsible for neurological and psychological disorders (schizophrenia) [14].

Previously, we have obtained new oxocyclohexane-1,3-dicarboxamide derivatives by the condensation of acetooacetic acid amides with aromatic aldehydes in the presence of a basic piperidine catalyst in ethanol at room temperature [28–31]. The reactions of the obtained compounds with $N$-nucleophiles [29] and Baeyer–Villiger oxidation [33] have been studied.

In continuation of studying the reactivity of cyclohexanone derivatives [28–34] and in order to obtain new compounds with potential biological activity, herein we reported the reactions of $N^1,N^3,2$-triaryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides with acid hydrazides and thiosemicarbazide. New derivatives

In this regard, the synthesis of compounds with hydrazone and 1,2,4-triazole-3-thione fragments is promising for the preparation of biologically active compounds and for the creation of new drugs based on them.
of hydrazones and 1,2,4-triazole-3-thione were obtained, respectively. The reaction of equimolar amounts of 4-oxocyclohexane-1,3-dicarboxamides 6a–6l with hydrazides of salicylic, isonicotinic, and p-toluenesulfonic acids upon boiling in ethanol proceeds at the carbonyl group of the alicycle to form the corresponding hydrazones 7a–7d, 8a, 8b, 9a–9f (Scheme 2).

The hydrazone form of compounds 7–9 is confirmed by the presence in the NMR spectra of the spin-spin coupling between the protons at the C3 (3.65–4.42 ppm) C2 atoms of the ring (3.12–4.04 ppm). The proton signal of the NH group not linked to the benzene ring also proves the proposed structure. The chemical shifts of the proton singlets of the two NH groups of the arylamide substituents are shifted to a stronger field compared to the chemical shifts of the starting compounds 6a–6o [28–30].

Existence of compounds 7–9 in the hydrazone form can be explained by its stabilization due to intermolecular hydrogen bonds. Heterocyclization apparently does not proceed due to the low nucleophilicity of nitrogen atoms in acid hydrazides.

The reaction of cyclohexanone derivatives 6d, 6m–6o with thiosemicarbazide in an equimolar ratio under similar conditions gave N6,N8,7-triaryl-9-hydroxy-9-methyl-3-thioxo-1,2,4-triazaspiro[4.5]decane-6,8-dicarboxamides 10a–10d.

In the IR spectra of compounds 10a–10d there are no stretching vibrations of the conjugated CO group of the alicycle and C=C bonds. The presence of stretching vibration bands of the N(C=S)N fragment at 1336–1360 cm⁻¹ and the C=S moiety at 1592–1600 cm⁻¹, as well as the presence of proton signals of the NH groups at the C1 and C2 atoms (8.05–8.54 ppm), C4 (10.33–10.46 ppm) and C6 atoms (3.54–4.46 ppm) resonating with a proton at the C7 atom (3.67–4.00 ppm) in the ¹H NMR spectra confirm the proposed structure of spiro compounds 10a–10d and excludes possible alternative enamine and imine structures. When comparing the spectral characteristics of spiro compounds 10a–10d with the starting cyclohexanones 6d, 6m–6o, it was found that the chemical shift of the proton doublet at the C8 atom of the ring in the spectra of compounds 10a–10d is shifted to upfield region (2.78–3.12 ppm, J 11.4–12.0 Hz) [29, 30].

Compounds 7b, 8b, 9c, 10a, and 10c were studied for antimicrobial activity against strains of gram-negative (Escherichia coli ATCC 25922) and gram-positive
1,3-dicarboxamides with acid hydrazides and thiosemicarbazide.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument from KBr pellets. 1H NMR spectra were registered on a Bruker DRX 500 (500 MHz) and Bruker AVANCE III HD 400 (400 MHz) spectrometers in DMSO-d6,
tetramethylsilane was used as the internal standard. Mass spectra were taken on an ultra-HPLC-MS spectrometer (Waters Acuity UPLC BEH C18 column 1.7 μm, mobile phases were acetonitrile and water, flow rate was 0.6 mL/min, ESI detector MS Xevo TQD). Elemental analysis was performed on an elemental analyzer Euro EA3028-NT for simultaneous determination of C, H, N. Melting points were determined on a Melting Point M-565.

**Table 1. Antimicrobial activity of compounds 7b, 8b, 9c, 10a, 10c**

| Compound               | **Escherichia coli ATCC 6538-P** | **Staphylococcus aureus ATCC 25922** | **Candida albicans NCTC 885-653** |
|------------------------|---------------------------------|-------------------------------------|----------------------------------|
| 7b                     | 1000                            | 1000                                | 1000                             |
| 8b                     | 1000                            | 1000                                | 1000                             |
| 9c                     | >1000                           | >1000                               | 1000                             |
| 10a                    | 500                             | 500                                 | 1000                             |
| 10c                    | 500                             | 125                                 | –                                |
| Furacilin              | 250                             | 3.9–6.25                            | –                                |
| Dioxide                | 62.5–1000                       | –                                   | 8–31                             |
| Fluconazole            | –                               | –                                   | –                                |

6-Hydroxy-4-[2-(2-hydroxyphenyl)hydrazinylidene]-6-methyl-N,3-di(2-methylphenyl)-2-(4-chlorophenyl)cyclohexane-1,3-dicarboxamide (7b). Yield 32%, mp 245–247°C. 1H NMR spectrum (500 MHz, DMSO-d6), δ, ppm: 1.40 s (3H, CH3), 1.80 s (6H, 2-MeC6H4O2), 2.05 d (1H, CH3H3B, J 14.0 Hz), 2.48 d (1H, CH3H3B, J 14.0 Hz), 3.10 d (1H, C1H, J 12.0 Hz), 3.70 t (1H, C2H, J 12.0 Hz), 3.90 d (1H, C3H, J 12.0 Hz), 5.10 s (1H, OH), 6.88–7.30 m (16H, 4C6H4), 7.86 s (1H, C1CONH), 9.18 s (1H, C3CONH), 11.15 s (1H, C4=NHCO), 11.70 s (1H, 2-CONH3). Found, %: C 67.62; H 5.50; N 8.75. C34H35N5O4. Calculated, %: C 67.65; H 5.52; N 8.77.

6-Hydroxy-4-[2-(2-hydroxyphenyl)hydrazinylidene]-6-methyl-N3-di(2-methylphenyl)-2-(pyridin-3-yl)cyclohexane-1,3-dicarboxamide (7c). Yield 51%, mp 234–235°C. 1H NMR spectrum (400 MHz, DMSO-d6), δ, ppm: 1.41 s (3H, Me), 1.81 s (3H, 2-MeC6H4), 1.82 s (3H, 2-MeC6H4), 2.36 d (1H, CH3H3B, J 14.0 Hz), 2.99 d (1H, CH3H3B, J 14.0 Hz), 3.18 d (1H, C1H, J 12.0 Hz), 3.90 d (1H, C3H, J 12.0 Hz), 3.95 t (1H, C4H, J 12.0 Hz), 5.11 s (1H, OH), 6.76–8.43 m (16H, 3C6H4, Py), 9.06 s (1H, C1CONH), 9.23 s (1H, C3CONH), 11.12 s (1H, C4=NHCO), 11.60 br. s (1H, 2-CONH3). Found, %: C 70.86; H 5.50; N 12.24. C36H35ClN4O5. Calculated, %: C 70.69; H 5.50; N 12.24.
12.0 Hz), 3.85 t (1H, C²H, J 12.0 Hz), 4.09 d (1H, C¹H, J 12.0 Hz), 5.49 s (1H, OH), 6.46–7.87 m (16H, 4-C₆H₄), 9.39 s (1H, C³HCONH), 9.41 s (1H, C⁴HCONH), 11.21 br. s (2H, 2-OH(C₆H₄)₂SO₂). Found: %: C 63.87; H 5.41; N 10.43. C₃₅H₃₅N₅O₄. Calculated, %: C 63.64; H 5.34; N 10.60.

6-Hydroxy-4-(2-isonicotinoylhydrazinylidene)-6-methyl-2-(3,4-dimethoxyphenyl)-N¹,N³-diphenylcyclohexane-1,3-dicarboxamide (9a). Yield 30%, mp 231–232°C. ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm: 1.30 s (3H, Me), 2.48 d (1H, C³H²H²B, J 14.0 Hz), 2.93 d (1H, C²H²H²B, J 14.0 Hz), 3.10 d (1H, C¹H, J 12.0 Hz), 3.58 s (3H, 2-MeOC₆H₄), 3.60 s (3H, 2-MeOC₆H₄), 3.90 t (1H, C²H, J 12.0 Hz), 4.42 d (1H, C¹H, J 12.0 Hz), 4.88 br. s (1H, OH), 6.70–7.50 m (17H, 2C₆H₅, C₆H₃, Py), 9.48 s (1H, C¹HCONH), 9.67 s (1H, C³HCONH), 10.80 s (1H, NH). Found: %: C 67.60; H 5.66; N 11.23. C₃₅H₃₅N₅O₄. Calculated, %: C 67.62; H 5.67; N 11.27.

6-Hydroxy-4-(2-isonicotinoylhydrazinylidene)-6-methyl-2-(4-methylphenyl)-N¹,N³-di(2-methoxyphenyl)cyclohexane-1,3-dicarboxamide (8b). Yield 30%, mp 231–232°C. ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm: 1.31 s (3H, Me), 2.13 s (3H, 4-MeC₆H₄), 2.35 d (1H, C²H²H²B, J 14.0 Hz), 2.84 d (1H, C³H²H²B, J 14.0 Hz), 3.12 d (1H, C¹H, J 12.0 Hz), 3.69 s (3H, 2-MeOC₆H₄), 3.75 s (3H, 2-MeOC₆H₄), 4.00 t (1H, C²H, J 12.0 Hz), 4.31 d (1H, C¹H, J 12.0 Hz), 5.51 br. s (1H, OH), 6.70–7.11 m (16H, 3C₆H₃, Py), 8.73 s (1H, C¹HCONH), 9.12 s (1H, C³HCONH), 10.78 s (1H, NH). Found: %: C 68.00; H 5.85; N 11.00. C₃₅H₃₅N₅O₄. Calculated, %: C 68.02; H 5.87; N 11.02.

6-Hydroxy-6-methyl-4-(2-tosylhydrazinylidene)-N¹,N³-diphenylcyclohexane-1,3-dicarboxamide (9a). Yield 60%, mp 235–236°C. IR spectrum (KBr), ν, cm⁻¹: 3450 (OH), 3342 (CONHAr), 3240 (NH), 1672 (CONHAr), 1552 (NH, C=O), 1380, 1168 (SO₂), 912 (S–N). ¹H NMR spectrum (400 MHz, DMSO-d₆), δ, ppm: 1.28 s (3H, Me), 2.19 s (3H, 4-MeC₆H₄SO₂), 2.47 d (1H, C³H²H²B, J 14.0 Hz), 2.85 d (1H, C²H²H²B, J 14.0 Hz), 3.12 d (1H, C¹H, J 12.0 Hz), 3.67 s (3H, 2-MeOC₆H₄), 3.77 s (3H, 2-MeOC₆H₄), 3.86 d (1H, C¹H, J 12.0 Hz), 4.04 t (1H, C²H, J 12.0 Hz), 5.32 s (1H, OH), 6.59–8.25 m (17H, 3C₆H₅, C₆H₃), 8.46 s (1H, C¹HCONH), 9.12 s (1H, C³HCONH), 9.99 s (1H, C⁴H₃N₅O₄). Found, %: C 64.69; H 5.62; N 8.24. C₃₆H₃₄N₅O₄. Calculated, %: C 64.46; H 5.71; N 8.35.
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6-Hydroxy-6-methyl-2-(4-dimethylaminophenyl)-N,3-di(2-methoxyphenyl)-4-(2-thiosalicylic acid)-cyclohexane-1,3-dicarboxamide (9f). Yield 48%, mp 241–242°C. IR spectrum (KBr), ν, cm⁻¹: 3460 (OH), 3360 (CONHAr), 3254 (NH), 1660 (CONHAr), 1555 (NH, C=N), 1330, 1168 (SO₂), 910 (S–N). Predicted, %: C 60.40; H 5.88; N 12.39. C₂₉H₃₆N₅O₄S. Calculated, %: C 60.38; H 5.81; N 12.36.

9-Hydroxy-9-methyl-6,8-diacetoxy-7-(pyridin-3-yl)-3-thioxo-1,2,4-triazaspiro[4.5]decane-6,8-dicarboxamide (10c). Yield 81%, mp 188–189°C. IR spectrum (KBr), ν, cm⁻¹: 3480 (OH), 3380 (CONHAr), 3288, 3240, 3120, 3000 (NH), 1648 (CONHPy), 1592 (C=S), 1336 (N–CS–N). ν, cm⁻¹: 3380 (OH), 3288, 3240, 3120, 3000 (NH), 1648 (CONHAr), 1592 (C=S), 1336 (N–CS–N). IR spectrum (400 MHz, DMSO-d₆), δ, ppm: 1.25 s (3H, Me), 2.17 s (3H, 4-MeOC₂H₄), 2.41 d (1H, C₈H, J 14.0 Hz), 2.73 s (6H, 2-MeOC₂H₆), 2.84 d (1H, C₈H, J 14.0 Hz), 3.27 d (1H, C₈H, J 12.0 Hz), 3.78 s (3H, 2-MeOC₂H₄), 3.94 s (3H, 2-MeOC₂H₄), 3.95 d (1H, C₈H, J 12.0 Hz), 4.00 t (1H, C₈H, J 12.0 Hz), 5.32 s (1H, OH), 6.35–8.28 m (16H, 4C₈H), 8.40 s (1H, C₈CONH), 9.07 s (1H, C₈CONH), 9.97 c (1H, C₈NNHSO₂). Found, %: C 63.73; H 6.14; N 9.92. C₂₉H₃₆N₅O₄S. Calculated, %: C 63.74; H 6.07; N 9.81.

9-Hydroxy-9-methyl-3-thioxo-N₆,8-diphenyl-7-(4-ethoxyphenyl)-1,2,4-triazaspiro[4.5]decane-6,8-dicarboxamide (10a). Yield 79%, mp 180–181°C. IR spectrum (KBr), ν, cm⁻¹: 3460 (OH), 3360, 3240, 3200, 3080 (NH), 1664 (CONHPy), 1600 (C=S), 1376 (N–CS–N). 1H NMR spectrum (400 MHz, DMSO-d₆), δ, ppm: 1.19 t (3H, 4-MeCH₂OC₂H₄, J 7.0 Hz), 1.28 s (3H, CH₃), 2.14 d (1H, C₈H, J 14.6 Hz), 2.89 d (1H, C₈H, J 12.0 Hz), 3.28 d (1H, C₈H, J 14.6 Hz), 3.55 d (1H, C₈H, J 12.0 Hz), 3.89 q (2H, 4-MeCH₂OC₂H₄, J 7.0 Hz), 3.91 t (1H, C₈H, J 12.0 Hz), 4.87 s (1H, OH), 6.59–7.34 m (14H, 2C₈H, 2C₄H), 8.05 c (1H, N=H), 8.52 s (1H, N=H), 9.42 s (1H, C₈CONH), 9.62 s (1H, C₈CONH), 10.46 br. s. (1H, N=H). Mass spectrum, m/z: 559 [M + H]⁺. Found, %: C 64.56; H 5.88; N 12.39. C₃₉H₃₆N₅O₄S. Calculated, %: C 64.38; H 5.94; N 12.51. M 558.

9-Hydroxy-9-methyl-N₆,8-di(2-methoxyphenyl)-7-(thien-2-yl)-3-thioxo-1,2,4-triazaspiro[4.5]decane-6,8-dicarboxamide (10b). Yield 74%, mp 163–164°C. IR spectrum (KBr), ν, cm⁻¹: 3460 (OH), 3390, 3280, 3180, 3010 (NH), 1676 (CONHPy), 1604 (C=S), 1360 (N–CS–N). 1H NMR spectrum (400 MHz, DMSO-d₆), δ, ppm: 1.33 s (3H, Me), 2.14 d (1H, C₈H, J 14.8 Hz), 2.78 d (1H, C₈H, J 11.4 Hz), 3.23 d (1H, C₈H, J 14.8 Hz), 3.54 d (1H, C₈H, J 11.4 Hz), 3.90 s (3H, 2-MeOC₂H₆), 3.93 s (3H, 2-MeOC₂H₆), 4.00 t (1H, C₈H, J 11.4 Hz), 5.40 s (1H, OH), 6.71–7.76 m (13H, 2C₈H₄, thienyl), 8.20 s (1H, N=H), 8.54 s (1H, N=H), 9.67 s (1H, C₈CONH), 9.71 s (1H, C₈CONH), 10.33 br. s (1H, N=H). Mass spectrum, m/z: 581 [M + H]⁺. Found, %: C 57.99; H 5.45; N 11.90. C₂₉H₃₆N₅O₄S. Calculated, %: C 57.81; H 5.37; N 12.04. M 580.

Antimicrobial activity of compounds 7b, 8b, 9c, 10a, and 10c against Escherichia coli ATCC 6538-P, Staphylococcus aureus ATCC 25922, and Candida
albicans NCTC 885-653 strains was determined by successive dilutions of a solution of the test substances in meat-peptone broth at a bacterial load of 250 000 microbial units per 1 mL of the solution. The minimum inhibitory concentration of the compound, i.e., the maximum dilution leading to complete suppression of the test microbes growth, was taken as the effective dose. As reference drugs, furacilin and dioxidine were used for Escherichia coli ATCC 25922 and Staphylococcus aureus ATCC 6538-P, fluconazole for Candida albicans NCTC 885-653.

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CONFICT OF INTEREST

No conflict of interest was declared by the authors.

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