J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 43(3): 220-229, 2019
Doi: 10.33483/jfpau.533166

ORIGINAL ARTICLE / ÖZGÜN MAKALE

MICROWAVE-ASSISTED SYNTHESIS OF SOME NEW DERIVATIVES OF 4-SUBSTITUTED-3-(MORPHOLINOMETHYL)-4*H*-1,2,4-TRIAZOLE-5-THIOLES

BAZI YENİ 4-SÜBSTİTÜE-3-(MORFOLİNOMETİL)-4H-1,2,4-TRİAZOL-5-TİYOL TÜREVLERİNİN MİKRODALGA YARDIMIYLA SENTEZİ

Roman SHCHERBYNA*

Zaporizhzhya State Medical University, Faculty of Pharmacy, Department of Toxicological and Inorganic Chemistry, Zaporizhzhya, Ukraine

ABSTRACT

Objective: *The purpose of this work is to synthesize new series of 4-((5-((cyclohexylmethyl)thio)-4-R_1-4H-1,2,4-triazol-3-yl)methyl)morpholines and 4-((4-R_1-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholines using a microwave synthesis system.*

Material and Method: *As starting compounds are used 4-R_1-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thioles (where, R_1=H, methyl, ethyl, phenyl, amino). Synthesis was carried out using a microwave synthesis system Milestone Flexi Wave. The structure of synthesized compounds is confirmed by the use of modern methods of analysis ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis and gas chromatography–mass spectrometry (GS/MS).*

Result and Discussion: *As a result of the conducted experiment, the synthesis method is optimized for 4-((5-((cyclohexylmethyl)thio)-4-R_1-4H-1,2,4-triazol-3-yl)methyl)morpholines and 4-((4-R_1-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholines by microwave irradiation. It was established that the reactions proceed to the end in all described conditions, but the reaction with the parameters t=10 min, T=160 ^{o}C is the most technologically optimal. This approach has allowed reducing energy costs and increasing the yield of target compounds. As a result, a class of new derivatives of 1,2,4-triazole has been obtained, which can be used in further pharmacological studies as valuable biological agents.*

Keywords: *1,2,4-triazole; microwave-assisted synthesis; heterocyclic*

* **Corresponding Author / Sorumlu Yazar:** Roman Shcherbyna
e-mail: rscherbyna@gmail.com

Submitted/Gönderilme: 27.02.2019 **Accepted/Kabul:** 01.07.2019

ÖZ

Amaç: *Bu çalışmanın amacı, mikrodalga sentez sistemi kullanarak 4-((5-((siklohekzilmetil)tiyo)-4-R_1-4H-1,2,4-triazol-3-il)metil)morfolinler ile 4-((4-R_1-5-(piridin-2-iltiyo)-4H-1,2,4-triazol-3-il)metil)morfolinlerin yeni serisini sentezlemektir.*

Gereç ve Yöntem: *Başlangıç bileşikleri olarak 4-R_1-3-(morfolinometil)-4H-1,2,4-triazol-5-tiyoller (burada, R=H, methyl, ethyl, phenyl, amino) kullanılır. Sentez, bir mikrodalga sentez sistemi Milestone Flexi Wave kullanılarak gerçekleştirildi. Sentezlenen bileşiklerin yapısı modern analiz yöntemleri olan ^{1}H NMR, ^{13}C NMR-spektroskopisi, element analizi ve gaz kromatografisi-kütle spektrometresi (GS/MS) kullanılarak doğrulandı.*

Sonuç ve Tartışma: *Yapılan deney sonucunda sentez yöntemi mikrodalga ışınımıyla 4-((5-((siklohekzilmetil)tiyo)-4-R_1-4H-1,2,4-triazol-3-il)metil)morfolinler and 4-((4-R_1-5-(piridin-2-iltiyo)-4H-1,2,4-triazol-3-il)metil)morfolinler için optimize edilmiştir Tanımlanan tüm koşullar altında reaksiyonların sonuna kadar geldiği ancak reaksiyonun t = 10 min, T = 160 °C parametreleri ile teknolojik olarak en uygun olduğu tespit edilmiştir. Bu yaklaşım enerji maliyetlerini düşürmeyi ve hedef bileşiklerin verimini arttırmayı sağlamıştır. Sonuç olarak, ileri farmakolojik çalışmalarda biyolojik bileşikler olarak kullanılabilecek bir yeni 1,2,4-triazol türevi sınıfı elde edilmiştir.*

Anahtar Kelimeler: *1,2,4-triazol; mikrodalga sentezi; heterosiklik*

INTRODUCTION

Synthetic organic chemistry has made significant progress in recent times [1, 2]. Thus, the synthetic strategy actively examines modern approaches to optimizing the process of creating new molecules [3, 4]. One of the options for this optimization is the use of microwave synthesis systems, which allow not only to increase the final output of reaction products but also to significantly accelerate its yield [5-7].

Derivatives of 1,2,4-triazole are widely used not only in medicine and pharmacy [8, 9] but also in agriculture [10]. Thus, **Tryfuzol®** (piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate) provides high immunomodulatory, antioxidant and hepatoprotective properties [8]. New compound 4-((5-(decylthio)-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)morpholine shows high antifungal and antimicrobial activities [9]. In our previous studies, the ability of 2-((5-R_1-4-R_2-4*H*-1,2,4-triazole-3-yl)thio)acetic acid salts to influence the growth of blackberries propagules is shown [10].

The derivatives of 1,2,4-triazole are pharmacologically valuable molecules which are also essential syntones in organic synthesis. It is noted that derivatives of 4-R-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thioles are able to exhibiting anti-TB activity and affecting the cultures of *M. bovis* [11]. Further, the S-derivatives of 1,2,4-triazole-5-thioles exhibit diuretic and antipyretic activity [12-15].

The analysis of scientific literature data indicates that the creation of new drugs of synthetic origin is based on the chemical substance hetero- and alkyl- cyclic characters. Therefore, the introduction into the structure of 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol these radicals as substitutes is relevant, has got practical significance and requires further study [16].

Known reactions of arylation of derivatives of 5-R_1-4-R_2-1,2,4-triazol-3-thioles with 2-chloropyridine, 5-chloro-1-methyl-4-nitro-1*H*-imidazole, 9-chloro-2-ethoxy-6-nitroacridine in alkaline

environment. However, the lack of classical methods for conducting the reaction is long enough boiling (more than 30 hours) and in some cases low practical yields (less than 70%) of reaction products [17].

Therefore, the purpose of this work was to conduct a reaction of the interaction of derivatives of 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol with (bromomethyl)cyclohexane and 2-chloropyridine using the Milestone Flexi Wave microwave synthesis system.

MATERIAL AND METHOD

Chemicals

The initial compounds 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thioles **(1-5)** were synthesized at the Department of Toxicological and Inorganic Chemistry of the Zaporizhzhya State Medical University (Ukraine) and purified by recrystallization with content of the main component ≥ 98% [18]. The (bromomethyl)cyclohexane (assay-99%), 2-chloropyridine (assay-99%), sodium hydroxide (reagent grade, 97%, flakes), 1-propanol (anhydrous, 99,7%) and 2-propanol (99,5%) were obtained from SIGMA-ALDRICH (Germany).

Equipment

To achieve the purpose, the following devices were used. Milestone Flexi Wave microwave synthesis system (technical specifications: rotor SK-15, minimum volume - 10 ml, maximum volume - 100 ml, maximum temperature - 300 ° C, maximum working pressure - 100 bar, maximum shutter speed 220 °C - 30 min).

The melting point is defined by the open capillary method on the OptiMelt MPA100 device with platinum RTD sensor and temperature measurements to 400°C with 0.1°C resolution.

The elemental analysis of synthesized compounds was established by the universal analyzer Elementar Vario L cube (CHNS) (standard - sulfanilamide).

The ^{1}H and ^{13}C NMR spectra (at 400 MHz and 100 MHz) were recorded in DMSO-$_{d6}$ on a Varian MR-400 spectrometer and analysed with ADVASP™ Analyzer program (Umatek International Inc.); chemical shifts are reported in ppm (δ scale) down field with residual protons of the solvent (DMSO-d_6 , δ = 2.49 ppm) as internal standard.

The completeness of the reactions and the individuality of the resulting compounds were controlled by the gas chromatograph Agilent 7890B with a 5977B mass spectrometry detector. The column is DB-5ms 30 m x 250 μm x 0.25 μm with length. The gas-carrier speed (helium) is 1.6 ml / min. Injection volume - 0.5 μl. Separation of the flow is 1:50. The temperature of the sampling unit is 230° C → 12° C / s → 275° C. Thermostat temperature: programmable, 240° C (1 minute delay) → 5° C / min → 280° C. (delay 1 min.). The total time of examination is 10 min. Temperature of interface

GS/MS - 280ºC; ion sources - 230ºC; quadrupole mass analyzer - 150ºC. Type of ionization: EI with an electron energy of 70 eV. The range of mass numbers that was scanned: 30-500 m /z.

RESULT AND DISCUSSION

To achieve the goal, as starting materials were used 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thioles (**1-5**) which were synthesized and described by us earlier [18]. Synthesis 4-((5-((cyclohexylmethyl)thio)-4-R_1-4*H*-1,2,4-triazol-3-yl)methyl)morpholine (**6-10**) was realized due to the interaction of initial thiols **1-5** with (bromomethyl)cyclohexane with adding the equivalent of sodium hydroxide in 1-propanol **(Fig. 1)**. Synthesis 4-((4-R_1-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholine **(11-15)** carried out by the interaction of the above-mentioned 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thioles **(1-5)** with 2-chloropyridine in the presence of an equivalent amount of sodium hydroxide in 1-propanol **(Fig. 1).**

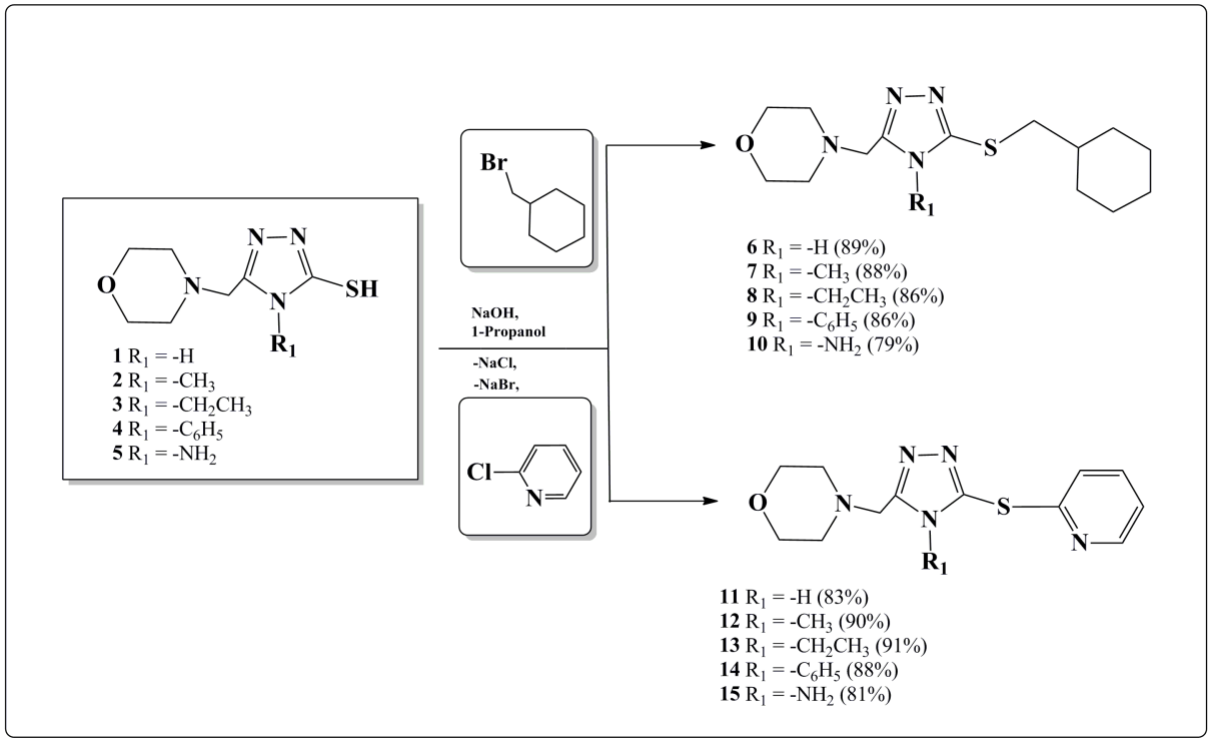

Figure 1. Synthesis of 4-((5-((cyclohexylmethyl)thio)-4-R_1-4*H*-1,2,4-triazol-3-yl)methyl)-morpholines **(6-10)** and 4-((4-R_1-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholines **(11-15).**

In both cases, the reactions were carried out in the Milestone Flexi Wave microwave system. There were three series of experiments, which differed in reaction time, temperature and radiation power. Thus, in the first series, the reaction was carried out for 40 minutes (the radiation power of 600 W, the temperature of the reaction mixture was 140 ° C), the second series of 20 minutes (radiation power 700 W, temperature of the reaction mixture of 150 ° C), the third series of 10 minutes (radiation

power 800 W, temperature of the reaction mixture 160 °C). The reaction was monitored by gas chromatography.

The structure of the synthesized compounds was determined by ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis and gas chromatography-mass spectrometry (GS/MS).

It is noted that in all cases the reactions run to the end and leads to the formation of the corresponding target compounds. By analyzing the GS / MS chromatogram of the solution the reaction mixture of the compound 4-((4-methyl-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholine (**12**) the individual peak at 13.580 min is identified which corresponds to a marked compound with an area of 98.17%.

Thus, it was found that the reactions run to the end in all conditions, but the reaction with the parameters t = 10 min, T = 160 °C and radiation power 800 W is the most technologically optimal.

Analyzing the GS/MS chromatogram 4-((5-((cyclohexylmethyl)thio)-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)morpholine **(7**), an individual compound with a retention time 6.806 min was fixed. In the MS spectrum there is a molecular peak with a value of 310.2 (m/z), which corresponds to the calculated theoretical value of 4-((5-((cyclohexylmethyl)thio)-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)morpholine compound (**7**) **(Fig. 2).**

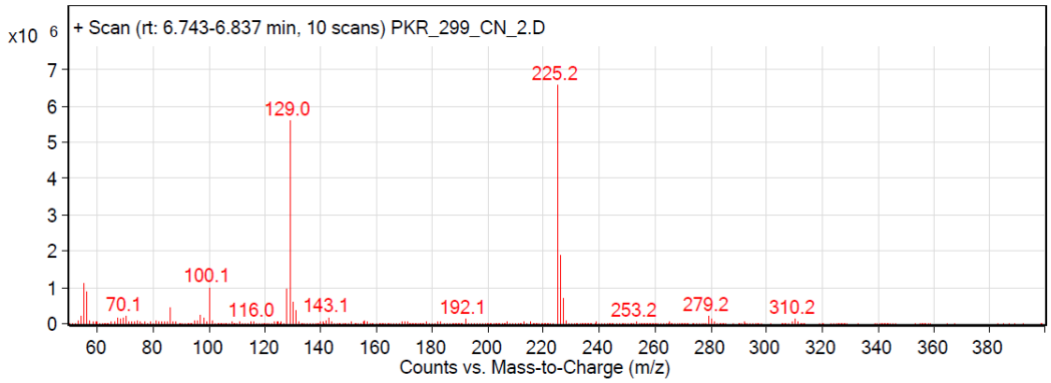

Figure 2. Mass spectrum of 4-((5-((cyclohexylmethyl)thio)-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)morpholine **(7).**

^{1}H NMR spectra of compounds **6-10** indicate the presence of protons of the cyclohexane fragment, which are slightly shielded and manifest in a strong field in the form of a widespread multiplet in the range δ 1.24-1.55 ppm. Additionally, in the spectra of these compounds there are characteristic doublets of methyl groups (-CH_2-) which bind the cyclohexane moiety with the sulfur atom of the 1,2,4-triazole nucleus in the range of δ 4.12-4.19 ppm. The ^{1}H NMR spectras of the substances **11-15** are characterized by the corresponding signals of the 2-pyridine radical which resonate by peaks with characteristic multiplicity in the range of 7.13-8.44 ppm. In the ^{13}C NMR spectral data of the compound **6**, the most characteristic signal of δ 25.3-41.0 ppm indicates the availability of the cyclohexyl radical.

In the spectrum of compound **15**, there are carbon atomic signals of about δ 120.5-149.6 ppm which indicate the presence of the 2-pyridine nucleus. The obtained elemental analysis values are in good agreement with theoretical data. Furthermore, the molecular weight and individuality of all compounds (**6-15**) were confirmed by GS/MS. In substances chromatograms, there are individual peaks of the synthesized compounds, and the mass spectra of these compounds showed a molecular peak corresponding to the exact theoretical mass.

General produce of the 4-((5-((cyclohexylmethyl)thio)-4-R_1-4*H*-1,2,4-triazol-3-yl)methyl)morpholines (6-10).

In a 50 ml thermostable flask to 0.01 mol of the corresponding initial thiols (3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(1),** 4-methyl-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiol **(2),** 4-ethyl-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(3),** 4-phenyl-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(4),** 4-amino-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol (**5**)) in 30 ml of 1-propanol, add 0.01 mol of sodium hydroxide (pre-dissolved in a minimum amount of distilled water) and heat in a water bath until it is completely dissolved. Transfer the reaction mixture to the reaction flask for microwave synthesis and add 0.01 mol (bromomethyl)cyclohexane. In the reaction flask place a magnetic stirrer, set in the microwave system to conduct the reaction. After passing the reaction time (40 min, 20 min, 10 min) check the pH of the reaction mixture which should be at pH = 7 (according to the universal indicator). The reaction mixture is filtered, the filtrate is evaporated. The obtained substances for analysis are recrystallized from 2-propanol.

General produce of the 4-((4-R_1-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholines (11-15).

In a 50 ml thermostable flask to 0.01 mol of the corresponding initial thiols (3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(1),** 4-methyl-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiol **(2),** 4-ethyl-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(3),** 4-phenyl-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol **(4),** 4-amino-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thiol (**5**)) in 30 ml. 1-propanol, add 0.01 mol of sodium hydroxide (pre-dissolved in a minimum amount of distilled water) and heat in a water bath until it is completely dissolved. Transfer the reaction mixture in the reaction flask to microwave synthesis and add 0.01 mol of 2-chloropyridine. In the reaction flask place a magnetic stirrer, set in the microwave system to conduct the reaction. After passing the reaction time (40 min, 20 min, 10 min) check the pH of the reaction mixture which should be at pH = 7 (according to the universal indicator). The reaction mixture is filtered, the filtrate is evaporated. The obtained substances for analysis are recrystallized from 2-propanol.

4-((5-((cyclohexylmethyl)thio)-4H-1,2,4-triazol-3-yl)methyl)morpholine **(6).** White solid with 89% yield, m.p. 118–120 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.24-1.53 (10H, m, cyclohexyl), 1.64 (1H, m, cyclohexyl), 2.52 (4H, t, morpholine), 3.54-3.66 (4H, t, morpholine), 4.12 (2H, d, *J* = 6.3Hz, -

CH_2-), 4.33 (2H, s, -CH_2-); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 157.3, 152.8, 66.3, 53.7, 53.3, 40.9, 32.5, 32.1, 26.3, 25.3.; GS/MS: 296 (m/z); Anal. Calcd. for $C_{14}H_{24}N_4OS$: C, 56.72; H, 8.16; N, 18.90; S, 10.82. Found: C, 56.99; H, 8.14; N, 18.93; S, 10.87.

4-((5-((cyclohexylmethyl)thio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)morpholine **(7).** White solid with 88% yield, m.p. 155–157 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.25-1.55 (10H, m, cyclohexyl), 1.67 (1H, m, cyclohexyl), 2.52 (4H, t, morpholine), 3.60 (4H, t, morpholine), 3.72 (3H, s, -CH_3), 3.89 (2H, s, -CH_2-), 4. 12 (2H, d, *J* = 5.73Hz, -CH_2-);^{13}C-NMR (100 MHz, DMSO-d_6): δ 153.8, 144.0, 66.3, 53.7, 40.9, 37.7, 32.5, 32.1, 26.3, 25.3; GS/MS: 310 (m/z); Anal. Calcd. for $C_{15}H_{26}N_4OS$: C, 58.03; H, 8.44; N, 18.05; S, 10.33. Found: C, 58.19; H, 8.46; N, 18.07; S, 10.35.

4-((5-((cyclohexylmethyl)thio)-4-ethyl-4H-1,2,4-triazol-3-yl)methyl)morpholine **(8).** Yellow solid with 86% yield, m.p. 66–68 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, -CH_3), 1.40-1.55 (10H, m, cyclohexyl), 1.69 (1H, m, cyclohexyl), 2.55 (4H, t, morpholine), 3.66 (4H, t, morpholine), 3.89 (2H, m, -CH_2-), 3.97 (2H, s, -CH_2-), 4.17 (2H, d, *J* = 5.83Hz, -CH_2-); GS/MS: 324 (m/z); Anal. Calcd. for $C_{16}H_{28}N_4OS$: C, 59.22; H, 8.70; N, 17.27; S, 9.88. Found: C, 59.29; H, 8.72; N, 17.23; S, 9.85.

4-((5-((cyclohexylmethyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)morpholine **(9).** Yellow solid with 86% yield, m.p. 84–86 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.35-1.51 (10H, m, cyclohexyl), 1.65 (1H, m, cyclohexyl), 2.57 (4H, t, morpholine), 3.62 (4H, t, morpholine), 3.79 (2H, d, *J* = 7.34Hz, -CH_2-), 4.13 (2H, s, -CH_2-), 7.19 (1H, t, -Ar), 7.42 (2H, dddd, *J* = 8.0, 7.4, 1.3, 0.5 Hz, -Ar), 7.66 (2H, dddd, *J* = 8.0, 1.4, 1.2, 0.5 Hz -Ar); GS/MS: 372 (m/z); Anal. Calcd. for $C_{20}H_{28}N_4OS$: C, 64.48; H, 7.58; N, 15.04; S, 8.61. Found: C, 64.69; H, 7.56; N, 15.06; S, 8.64.

3-((cyclohexylmethyl)thio)-5-(morpholinomethyl)-4H-1,2,4-triazol-4-amine **(10).** White solid with 79% yield, m.p. 199–201 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.33-1.50 (10H, m, cyclohexyl), 1.63 (1H, m, cyclohexyl), 2.55 (4H, t, morpholine), 3.66 (4H, t, morpholine), 3.82 79 (2H, d, *J* = 7.29Hz, -CH_2-), 4.19 (2H, s, -CH_2-), 5.79 (2H, s, -NH_2-); GS/MS: 311 (m/z); Anal. Calcd. for $C_{14}H_{25}N_5OS$: C, 53.99; H, 8.09; N, 22.49; S, 10.30. Found: C, 54.09; H, 8.06; N, 22.53; S, 10.27.

4-((5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholine **(11).** Yellow solid with 83% yield, m.p. 92–94 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.52 (4H, t, morpholine), 3.60 (4H, t, morpholine), 4.14 (2H, s, -CH_2-), 7.15-7.27 (2H, m, Pyridin), 7.75 (1H, t, Pyridin), 8.44 (1H, ddd, *J* = 7.8, 1.4, 0.5 Hz, Pyridin); ^{13}C-NMR (100 MHz, DMSO-d_6): δ159.9, 157.3, 152.8, 149.5, 136.1, 122.3, 120.4, 66.3, 53.7, 53.3. GS/MS: 277 (m/z); Anal. Calcd. for $C_{12}H_{15}N_5OS$: C, 51.97; H, 5.45; N, 25.25; S, 11.56. Found: C, 52.09; H, 5.47; N, 25.21; S, 11.53.

4-((4-methyl-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholine **(12).** Yellow solid with 90% yield, m.p. 118-120 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.50 (4H, t, morpholine), 3.21 (3H, s, -CH_3), 3.63 (4H, t, morpholine), 4.19 (2H, s, -CH_2-), 7.13-7.24 (2H, m, Pyridin), 7.70 (1H, t, Pyridin), 8.41 (1H, ddd, *J* = 7.8, 1.4, 0.5 Hz, Pyridin); GS/MS: 291 (m/z); Anal. Calcd. for $C_{13}H_{17}N_5OS$:

C, 53.59; H, 5.88; N, 24.04; S, 11.00. Found: C, 53.67; H, 5.90; N, 24.06; S, 11.02.

4-((4-ethyl-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholine **(13).** Yellow solid with 91% yield, m.p. 151-153 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.41 (3H, t, -CH_3), 2.52 (4H, t, morpholine), 3.64 (4H, t, morpholine), 3.99 (2H, q, -CH_2-), 4.20 (2H, s, -CH_2-), 7.18 (1H, t, Pyridin), 7.33 (1H, m, Pyridin), 7.83 (1H, t, Pyridin), 8.44 (1H, ddd, J = 7.8, 1.4, 0.5 Hz, Pyridin).GS/MS: 305 (m/z); Anal. Calcd. for $C_{14}H_{19}N_5OS$: C, 55.06; H, 6.27; N, 22.93; S, 10.50. Found: C, 55.12; H, 6.28; N, 22.95; S, 10.53.

4-((4-phenyl-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholine **(14).** Yellow solid with 88% yield, m.p. 179-181 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.56 (4H, t, morpholine), 3.69 (4H, t, morpholine), 4.21 (2H, s, -CH_2-), 7.11-7.14 (1H, m, -Ar), 7.21-7.27 (1H, m, Pyridin), 7.37 (1H, d, Pyridin), 7.53 (2H, t, -Ar), 7.70 (2H, dddd, *J* = 8.1, 1.4, 1.2, 0.5 Hz, -Ar), 7.89 (1H, t, Pyridin), 8.44 (1H, ddd, *J* = 7.8, 1.4, 0.5 Hz, Pyridin).GS/MS: 353 (m/z); Anal. Calcd. for $C_{18}H_{19}N_5OS$: C, 61.17; H, 5.42; N, 19.81; S, 9.07. Found: C, 61.23; H, 5.44; N, 19.85; S, 9.05.

3-(morpholinomethyl)-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-4-amine **(15).** Yellow solid with 81% yield, m.p. 143-145 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.51 (4H, t, morpholine), 3.66 (4H, t, morpholine), 4.17 (2H, s, -CH_2-), 5.69 (2H, s, -NH_2-), 7.13-7.25 (2H, m, Pyridin), 7.73 (1H, t, Pyridin), 8.40 (1H, *J* = 7.8, 1.4, 0.5 Hz, Pyridin); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.3, 159.9, 152.8, 149.5, 136.1, 122.3, 120.4, 66.3, 53.7, 53.3; GS/MS: 292 (m/z); Anal. Calcd. for $C_{12}H_{16}N_6OS$: C, 49.30; H, 5.52; N, 28.75; S, 10.97. Found: C, 49.54; H, 5.54; N, 28.79; S, 10.94.

As a result of the study, a new class of 1,2,4-triazole derivatives was obtained by using the microwave synthesis system. The use of modern optimized approaches, in particular, the microwave synthesis system, has made it possible to optimize the method of obtaining data for derivatives of 4-R_1-3-(morpholinomethyl)-4*H*-1,2,4-triazole-5-thioles. The structure of the synthesized compounds is confirmed by the complex use of modern methods of analysis: ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis and GS/MS. The resulting compounds can be used as objects of further biological research.

REFERENCES

1. Arnold, F.H. (2018). Directed Evolution: Bringing New Chemistry to Life. *Angewandte Chemie International Edition*, 57(16), 4143-4148.

2. Gerry, C.J., Schreiber, S.L. (2018). Chemical Probes and Drug Leads from Advances In Synthetic Planning And Methodology. *Nature Reviews Drug Discovery*, 17(5), 333.

3. Minozzi, C., Caron, A., Grenier-Petel, J.C., Santandrea, J., Collins, S.K. (2018). Heteroleptic Copper (I)-Based Complexes for Photocatalysis: Combinatorial Assembly, Discovery, and Optimization. *Angewandte Chemie International Edition*, *57*(19), 5477-5481.

4. Bédard, A.C., Adamo, A., Aroh, K.C., Russell, M.G., Bedermann, A.A., Torosian, J., Jamison, T.F. (2018). Reconfigurable System For Automated Optimization Of Diverse Chemical Reactions. *Science*, *361*(6408), 1220-1225.

5. Mermer, A., Demirbaş, N., Şirin, Y., Uslu, H., Özdemir, Z., Demirbaş, A. (2018). Conventional And Microwave Prompted Synthesis, Antioxidant, Anticholinesterase Activity Screening And Molecular Docking Studies Of New Quinolone-Triazole Hybrids. *Bioorganic chemistry*, *78*, 236-248.

6. Basoglu Ozdemir, S., Demirbas, N., Demirbas, A., Ayaz, F. A., Çolak, N. (2018). Microwave-Assisted Synthesis, Antioxidant, and Antimicrobial Evaluation of Piperazine-Azole-Fluoroquinolone Based 1,2,4-Triazole Derivatives. *Journal of Heterocyclic Chemistry*, *55*(12), 2744-2759.

7. Aljohani, G., Said, M.A., Lentz, D., Basar, N., Albar, A., Alraqa, S.Y., Ali, A.A.S. (2019). Microwave-Assisted Synthesis of Mono-and Disubstituted 4-Hydroxyacetophenone Derivatives via Mannich Reaction: Synthesis, XRD and HS-Analysis. *Molecules*, 24(3), 590-604.

8. Bushueva, I., Parchenko, V., Shcherbyna, R., Safonov, A., Kaplaushenko, A., Gutyj, B., Hariv, I. (2017). Tryfuzol-New Original Veterinary Drug. *J. Fac. Pharm. Ankara/Ankara Ecz. Fak. Derg*, 41(1), 42-49.

9. Shcherbyna, R., Parchenko, V., Martynyshyn, V., Hunchak, V. (2018). Evaluation Of Acute And Subacute Toxicity Of Oil Liniment Based On 4-((5-(Decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)morpholine. *J. Fac. Pharm. Ankara/Ankara Ecz. Fak. Derg*, 42 (1), 43-52. Retrieved from http://dergipark.gov.tr/jfpanu/issue/42653/514314.

10. Shcherbyna, R.O., Danilchenko, D.M., Parchenko, V.V., Panasenko, O.I., Knysh, E.H., Hromyh, N.A., Lyholat, Y.V. (2017). Studying Of 2-((5-R-4-R-1-4H-1,2,4-triazole-3-yl)thio)acetic Acid Salts Influence On Growth And Progress Of Blackberries (KIOWA Variety) Propagules. *Research Journal of Pharmaceutical Biological and Chemical Sciences*, *8*(3), 975-979.

11. Shcherbyna, R.O., Parchenko, V.V., Safonov, A.A., Bushueva, I.V., Zazharskiy, V.V., Davydenko, P.O., Borovic, I.V. (2018). Synthesis and Research Of The Impact Of New Derivatives Of 4-R-3-(Morpholinomethyl)-4H-1,2,4-Triazole-5-thiol On Cultural Attributes Of Pathogenic M. Bovis. *Research Journal of Pharmaceutical Biological and Chemical Sciences*, *9*(2), 70-79.

12. Samelyuk, Y. G., Kaplaushenko, A. G. (2014). Synthesis of 3-Alkylthio(sulfo)-1,2,4-triazoles, Containing Methoxyphenyl Substituents at C5atoms, Their Antipyretic Activity, Propensity To Adsorption And Acute Toxicity. *Journal of Chemical and Pharmaceutical Research*, *6*(5), 1117-1121.

13. Rud, A.M., Kaplaushenko, A.G., Pruglo, Y.S., Frolova, Y.S. (2018). Establishment Of Diuretic Activity Indicators For (3-Thio-4-R-4-H-1,2,4-triazole-5-yl)(phenyl)methanols And Their Derivatives. *Aktual'nì Pitannâ Farmacevtičnoï ì Medičnoï Nauki ta Praktiki*, *2018*(2), 215-219.

14. Hulina, Y.S., Kaplaushenko, A.G. (2018). Synthesis, Physicochemical Properties And Further Transformations In The Series 5-((1H-tetrazol-1-yl)methyl)-4-R-4H-1,2,4-triazol-3-thiols. *Biopharmaceutical Journal*, 10 (1), 26-30.

15. Ignatova, T.V., Kaplaushenko, A.H., Frolova, Y.S. (2018). The Synthesis, Study Of 6-((5-Phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridyn-3-yl)-(alkyl, heteryl)methanimines And Their Derivatives. *Žurnal organìčnoï ta farmacevtičnoï hìmìï*, 16(4 (64)), 34-39.

16. Shcherbyna, R.O. (2014). Pharmacological Activity Analysis Of The 1,2,4-Triazole Derivatives. *Pharmaceutical Journal*, (4), 145-150.

17. Kaplaushenko A. Synthesis, Structure And Biological Activity Of 4-Mono And 4,5-Di-Substituted 1,2,4-Triazoles-3-thione.(Doctoral dissertation, AG Kaplaushenko- Zaporizhzhya, 2012.-387p).

18. Shcherbyna, R.A., Panasenko, A.I., Knysh, E.G., Varinsky, B.A. (2014). Synthesis And Physicochemical Properties Of 2-((4-R-3-(morpholinomethylene)-4H-1,2,4-triazol-5-yl)thio)acetic Acids. *Aktual'nì Pitannâ Farmacevtičnoï ì Medičnoï Nauki ta Praktiki*, 3 (16), 18-21.