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ORIGINAL ARTICLE / ÖZGÜN MAKALE

MICROWAVE SYNTHESIS OF 3- AND 4-SUBSTITUTED-5-((3-PHENYLPROPYL)THIO)-4H-1,2,4-TRIAZOLES

3- VE 4-SÜBSTİTÜE-5-((3-FENİLPROPİL)TİYO)-4H-1,2,4-TRİAZOLLERİN MİKRODALGA SENTEZİ

Andrii A. SAFONOV[1,*], Alina V. NEVMYVAKA[1], Olexandr I. PANASENKO[1], Yevgeniy G. KNYSH[2]

[1]Zaporizhzhya State Medical University, Department of Natural Sciences for Foreign Students and Toxicological Chemistry, 69035, Zaporizhzhya, Ukraine.

[2]Zaporizhzhya State Medical University, Department of Management and Economics of Pharmacy, 69035, Zaporizhzhya, Ukraine.

ABSTRACT

Objective: *The purpose of this work was to synthesize 3- and 4-substituted-5-((3-phenylpropyl)thio) 4H-1,2,4-triazoles by the Milestone Flexi Wave microwave synthesis system and choose the best method of synthesis.*

Material and Method: *The initial compounds 4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiol (1) and 5-(2-bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3) were synthesized at the Department of Natural Sciences for Foreign Students and Toxicological Chemistry of the Zaporizhzhya State Medical University (Ukraine). Milestone Flexi Wave microwave synthesis system was used to synthesize 3- and 4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles. The elemental analysis of synthesized compounds was established by the universal analyzer Elementar Vario L cube (CHNS). The 1H spectra (at 400 MHz) were recorded in DMSO-d_6 on a Varian MR-400 spectrometer and analyzed with ADVASP™ Analyzer program. The gas chromatograph Agilent 7890B with a 5977B mass spectrometry detector (US) was used to define the completeness of the reactions and the individuality of the resulting compounds.*

Result and Discussion: *The reaction was carried out in i-propanol medium and an equivalent amount of sodium hydroxide. (3-Bromopropyl)benzene was added to starting substances 1 and 3. To study the completeness of the reaction, different reaction times were used. Conditions such as temperature, microwave radiation, pressure were unchanged. The temperature of the reaction mixture was kept at 1650C, pressure 12.2 bar, MW ≈ 540 W. The reaction time was set at 15 minutes, 30 minutes, and 45 minutes. The most effective reaction time for obtaining 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (2) is*

* **Corresponding Author / Sorumlu Yazar:** Andrii Safonov
e-mail / e-posta: 8safonov@gmail.com, **Phone / Tel.:** +38 066-177-71-06

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45 minutes. The most energy efficient reaction time for 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (4) is 30 minutes heating. The signals of ^{1}H NMR for compounds 2 and 4 are consented with the proposed structure. The elemental analysis (CHNS) was accomplished for synthesized compounds to confirm their basic chemical structures and revealed acceptable agreement with the calculated percentages.

Keywords: *Gas chromatography, heterocyclic compounds, ^{1}H NMR, synthesis, 1,2,4-triazole products*

ÖZ

Amaç: *Bu çalışmanın amacı, Milestone Flexi Wave mikrodalga sentez sistemi ile 3- ve 4-sübstitüe-5-((3-fenilpropil)tiyo)-4H-1,2,4-triazolleri sentezlemek ve sentez için en iyi yöntemi belirlemektir.*

Gereç ve Yöntem: *Başlangıç bileşikleri olan 4-amino-5-(tiyofen-2-il-metil)-4H-1,2,4-triazol-3-tiyol (1) ve 5-(2-bromofenil)-4-fenil-4H-1,2,4-triazol-3-tiyol (3), Zaporizhzhya Devlet Tıp Üniversitesi (Ukrayna) Yabancı Öğrenciler için Doğa Bilimleri ve Toksikolojik Kimya Bölümü'nde sentezlendi. 3- ve 4-Sübstitüe-5-((3-fenilpropil)tiyo)-4H-1,2,4-triazolleri sentezlemek için Milestone Flexi Wave mikrodalga sentez sistemi kullanıldı. Sentezlenen bileşiklerin elementel analizi, Elementar Vario L cube (CHNS) evrensel analiz cihazı ile gerçekleştirildi. 1H-NMR spektrumları (400 MHz), DMSO-d_6 içerisinde Varian MR-400 spektrometresi ile çekildi ve ADVASP™ Analiz programı ile analiz edildi. Reaksiyonların tamamlanıp tamamlanmadığı ve elde edilen bileşiklerin tayini, 5977B kütle spektrometre detektörü içeren Agilent 7890B gaz kromatografisi ile gerçekleştirildi.*

Sonuç ve Tartışma: *Reaksiyon, i-propanol içerisinde ve eşdeğer miktarda sodyum hidroksit varlığında gerçekleştirildi. Başlangıç maddeleri 1 ve 3'e (3-bromopropil)benzen eklendi. Reaksiyonun tam olarak sonlanmasının takibi için farklı reaksiyon süreleri kullanıldı. Sıcaklık, mikrodalga radyasyonu, basınç gibi koşullar değiştirilmedi. Reaksiyon ortamının sıcaklığı 1650C'de, basınç 12.2 bar'da, MW ≈ 540 W'da tutuldu. Reaksiyon süresi 15 dakika, 30 dakika ve 45 dakikaya ayarlandı. 3-(Tiyofen-2-il-metil)-4-amino-5-((3-fenilpropil)tiyo)-4H-1,2,4-triazol (2) elde etmek için en uygun reaksiyon süresi 45 dakikadır. 3-(2-Bromofenil)-4-fenil-5-((3-fenilpropil)tiyo)-4H-1,2,4-triazol (4) için en uygun reaksiyon süresi 30 dakika ısıtma olarak bulundu. Bileşik 2 ve 4 için ^{1}H NMR sinyalleri, önerilen yapı ile uyumludur. Sentezlenen bileşiklerin kimyasal yapılarını doğrulamak için elementel analiz (CHNS) yapıldı ve hesaplanan yüzdeler kabul edilebilir aralıkta bulundu.*

Anahtar Kelimeler: *Gaz kromatografisi, heterosiklik bileşikler, ^{1}H NMR, sentez, 1,2,4-triazol*

INTRODUCTION

The search for a new substance that would have a biological and pharmacological effect [1-4] can be equated to finding a needle in a haystack. If there is no appropriate strategy and plan, this conception is desperate.

Most scientists are trying to find just that substance based on heterocyclic compounds. A rather interesting heterocyclic compound, on the basis of which a huge number of new biologically active substances has already been synthesized, is the nucleus of 1,2,4-triazole [5-8]. The new compounds 1,2,4-triazole derivatives have a variety of designs and structures.

Quite interesting methods for obtaining 1,2,4-triazole derivatives using various reagents and reaction conditions are described [9, 10]. Many hours of reactions are mainly used to obtain these substances.

A somewhat new aspect in the synthesis of 1,2,4-triazole derivatives is the use of the microwave synthesis system [11-13]. The authors claim that these systems can speed up the reaction several times and increase the quantitative yields.

To confirm this theory, we also chose the microwave synthesis system, that's why the aim of the work was to synthesize 3- and 4-substituded-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles by the Milestone Flexi Wave microwave synthesis system and choose the best method of synthesis.

MATERIAL AND METHOD

Chemicals

The initial compounds 4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiol (1) and 5-(2-bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3) were synthesized at the Department of natural sciences for foreign students and toxicological chemistry of the Zaporizhzhya State Medical University (Ukraine) and purified by recrystallization with content of the main component ≥ 95% [14]. The sodium hydroxide (98%), 1-propanol (anhydrous, 99,7%) and (3-bromopropyl)benzene (98%) were obtained from SIGMA-ALDRICH (Germany).

Equipment

It was used as equipment the following devices. Milestone Flexi Wave microwave synthesis system (technical specifications: rotor SK-15, maximum volume - 100 ml, minimum volume - 10 ml, maximum working pressure - 100 bar, maximum temperature - 300°C, maximum shutter speed 220°C - 30 min). To determine the melting point was used 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 Varian MR-400 spectrometer and ADVASP™ Analyzer program (Umatek International Inc.) were used for recording the 1H spectra (at 400 MHz and 100 MHz) (DMSO-d6 , δ = 2.49 ppm as internal standard). The gas chromatograph Agilent 7890B with a 5977B mass spectrometry detector (US) was used to define the completeness of the reactions and the individuality of the 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (2) and 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (4). The column is DB-5ms 30 m x 250 μm x 0.25 μm with length. The gas-carrier speed (helium) is 2.0 ml/min. Injection volume - 0.5 μl. Separation of the flow is 1:25. The temperature of the sampling unit is 300°C → 10°C / s → 310°C. Thermostat temperature: programmable, initial temperature 90°C (1 minute delay) → 40°C/min → 240°C) → 10°C/min → 280°C) → 2°C/min → 300°C (delay 31,25 min.). The total time of examination is 50 min. Temperature of interface GS/MS - 280°C; ion sources - 230°C; quadrupole mass analyzer - 150°C. Type of ionization: EI with electron energy of 70 eV. The range of mass numbers that was scanned: 50-500 m /z.

Characterization of 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (2)

Bright brown powder; yield 76.8%; m.p. 174-1760C; 1HNMR (400 MHz, DMSO-d6, δ=ppm): 7.50 (2H, m, Ar-H); 7.37 (1H, d, thiophen-H); 7.26(3H, m, Ar-H); 6.81 (1H, t, thiophen-H); 6.64 (1H, d, thiophen-H); 5,86 (2H, s, NH2); 3.88 (2H, s, CH2); 3.11 (2H, t, CH2); 2.66 (2H, t, CH2); 2.04 (2H, m, CH2); CHNS elemental analysis Calcd. for (C16H18N4S2) : found C% 57.98, H% 5.47, N% 16.99, S% 19.48; calculated C% 58.15, H% 5.49, N% 16.95, S% 19.48 MH 330.

Characterization of 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (4)

Yellow powder; yield 81.6%; m.p. 149-1510C; 1HNMR (400 MHz, DMSO-d6, δ=ppm): 7.67 (2H, m, Ar-H); 7.53 (6H, m, Ar-H); 7.39 (2H, m, Ar-H); 7.26 (4H, m, Ar-H); 3.15 (2H, t, CH2); 2.64 (2H, t, CH2); 2.01 (2H, m, CH2); CHNS elemental analysis Calcd. for (C23H20BrN3S) : found C% 61.53, H% 4.49, N% 9.38, S% 7.15; calculated C% 61.33, H% 4.48, N% 9.33, S% 7.12. MH 450.

RESULT AND DISCUSSION

As starting materials were used 4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiol (1) and 5-(2-bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3) which were synthesized and described by us earlier [14]. 3- and 4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles were obtained by adding (3-bromopropyl)benzene to starting substances 1 and 3. The synthesis was performed in i-propanol medium and an equivalent amount of sodium hydroxide.

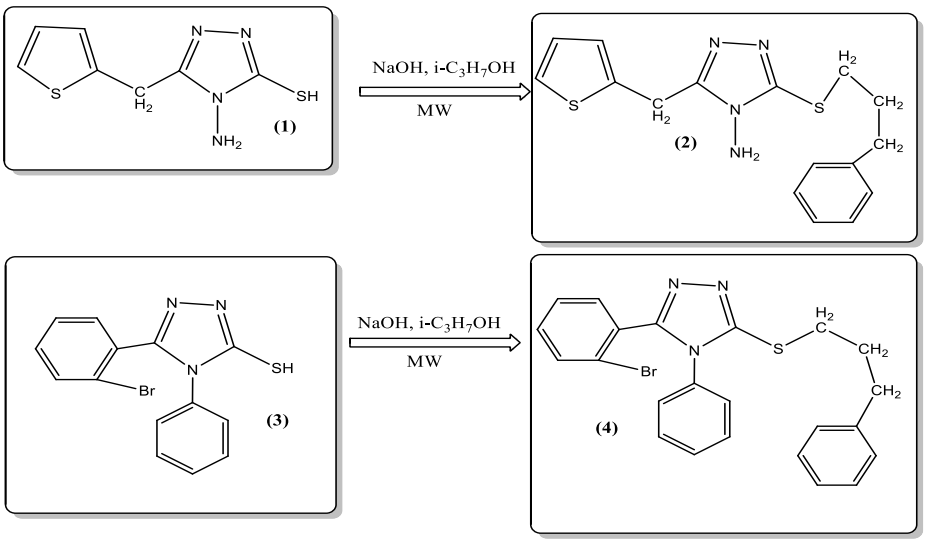

Figure 1. Synthesis of 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole (**2**) and 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole (**4**)

Different reaction times were used to study the completeness of the reaction. Conditions (temperature, microwave radiation, pressure) were unchanged. The temperature of the reaction mixture was kept at 1650C, pressure 12.2 bar, MW ≈ 540 W (Fig. 2).

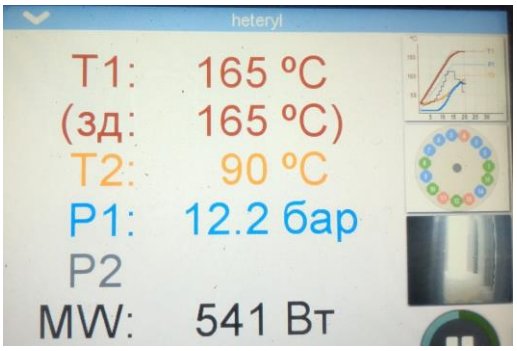

Figure 2. Conditions of microwave synthesis of 3- and 4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles

For synthesis 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (2) (Fig. 3) and 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (4) (Fig. 9) the reaction time was set at 15 minutes, 30 minutes, and 45 minutes. The completeness of the reaction was determined using a gas chromatograph Agilent 7890B with a mass spectrometric detector 5977B.

The most effective method for obtaining 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole: the temperature of the reaction mixture is 165^0C, pressure is 12.2 bar, MW ≈ 540 W, reaction time is 45 minutes.

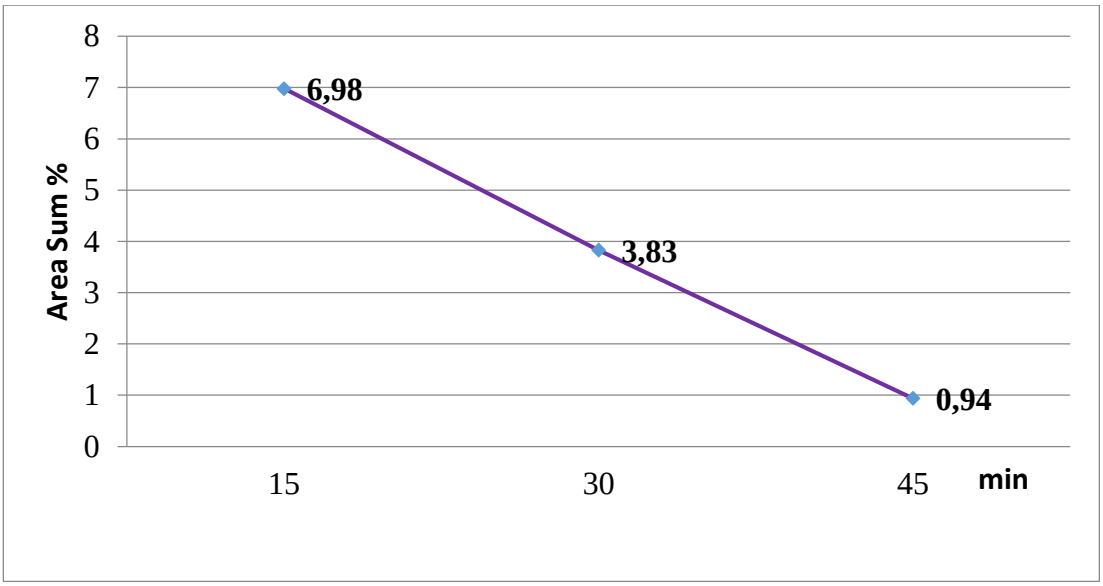

Figure 3. Concentration change of (3-bromopropyl)benzene

As can be seen from Fig. 4 the concentration of (3-bromopropyl)benzene decreases over time and the most effective is 45 minutes heating.

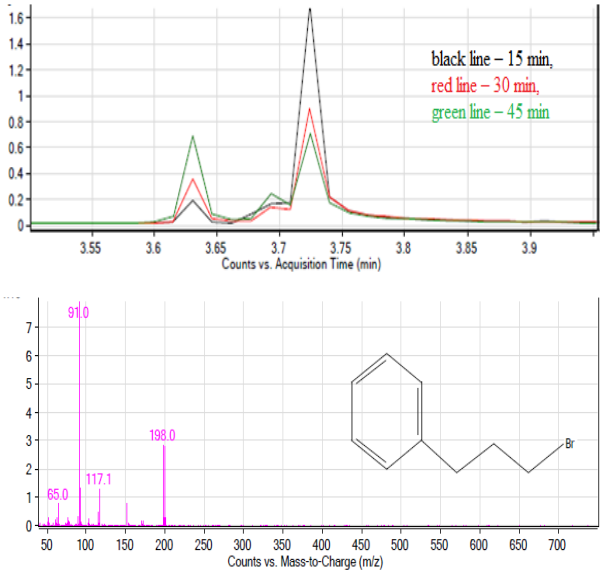

Figure 4. Common chromatogram of the reaction mixture and mass spectrum of (3-bromopropyl)benzene

Over time, the concentration of 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole also increases accordingly and after 45 minutes of heating the maximum concentration occurs (Fig. 5).

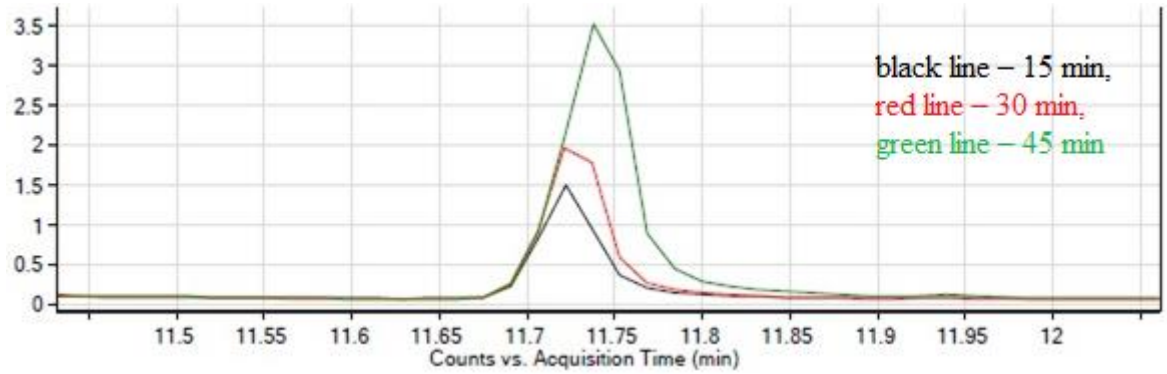

Figure 5. Common chromatogram of the reaction mixture of 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole

A molecular peak with a value of 330,1 (m/z) corresponds to 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole and match the calculated theoretical value (Fig. 6).

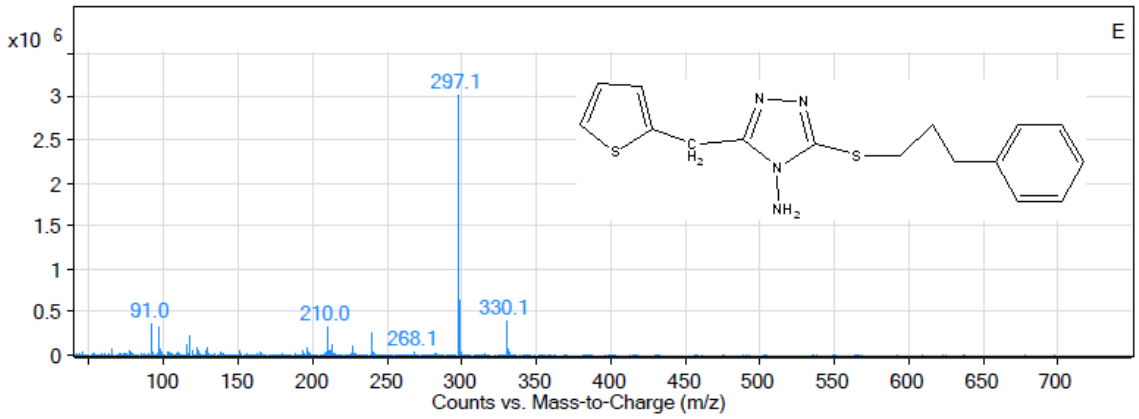

Figure 6. Mass spectrum of 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole

A slightly different situation is observed for microwave synthesis of 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (Fig. 7).

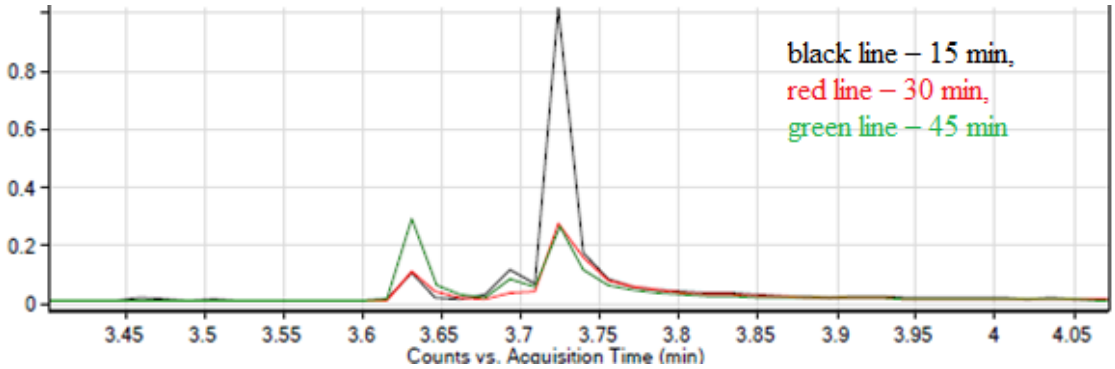

Figure 7. Common chromatogram of the reaction mixture of (3-bromopropyl)benzene

After 45 minutes heating, there is almost no change in concentration of 3-bromopropyl)benzene. The most energy efficient method is 30 minutes heating. Studying the chromatogram of compound 4 we can say the same (Fig. 8).

Analyzing the GS/MS chromatogram in the MS spectrum there is a molecular peak with a value of 451.1 (m/z), which corresponds to the calculated theoretical value of 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (Fig. 9).

In conclusion, 3-(thiophen-2-ylmethyl)-4-amino-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (2) and 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole (4) (Fig. 2) were synthesized and characterized. The structure of synthesized compounds is confirmed using Elemental analysis (CHNS), 1HNMR and Chromatographic mass spectral analysis. When the temperature of the reaction mixture was kept at 1650C, pressure 12.2 bar and MW ≈ 540 W, the most effective reaction

time is 45 minutes for compound 2 and the most energy efficient method for compound 4 is 30 minutes heating.

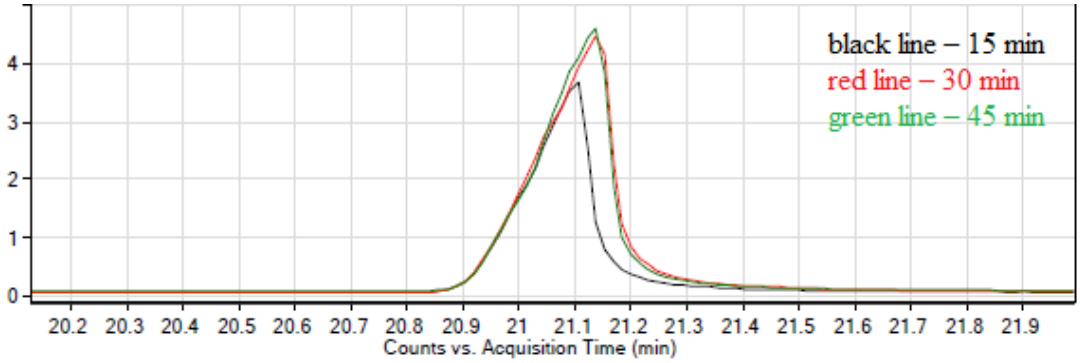

Figure 8. Common chromatogram of the reaction mixture of 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole

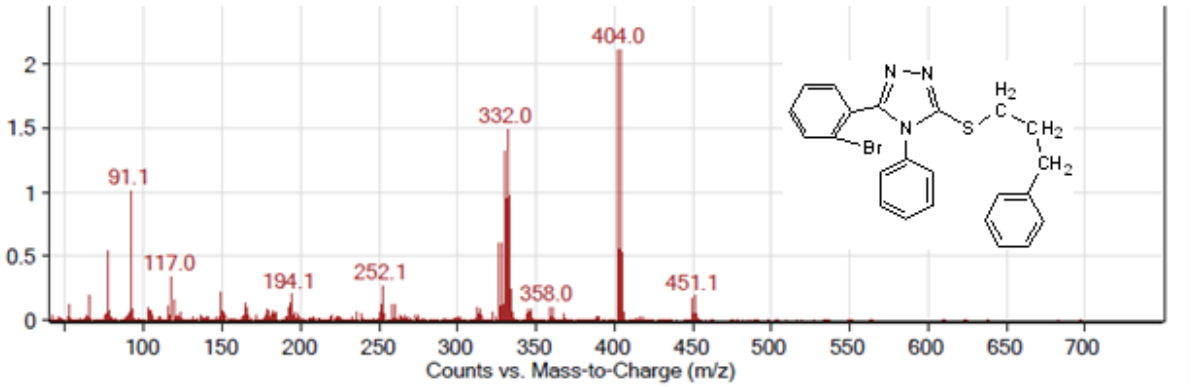

Figure 9. Mass spectrum of 3-(2-bromophenyl)-4-phenyl-5-((3-phenylpropyl)thio)-4*H*-1,2,4-triazole

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AUTHOR CONTRIBUTIONS

Conception: *A.A.S.*, *A.V.N.*, *O.S.P.*; Design: *Y.G.K.*, *A.A.S.*, *A.V.N.*; Supervision: *O.I.P.*, *Y.G.K.*; Resources: *A.A.S.*, *A.V.N.*; Materials: *O.I.P.*, *Y.G.K.*; Data collection and/or processing: *A.A.S.*, *O.I.P.*, *A.V.N.*, *Y.G.K.*; Analysis and/or interpretation: *A.A.S.*; Literature search: *A.V.N.*; Writing manuscript: *A.A.S.*, *A.V.N.*, *O.I.P.*, *Y.G.K.*; Critical review: *A.A.S.*, *A.V.N.*, *O.I.P.*, *Y.G.K.*; Other: -

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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