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ORIGINAL ARTICLE / ÖZGÜN MAKALE

MICROWAVE SYNTHESIS OF NEW 3-(ALKYLTHIO)-5-(THIOPHEN-2-YLMETHYL)-1,2,4-TRIAZOL-4-AMINES

YENİ 3-(ALKİLTİYO)-5-(TİYOFEN-2-İLMETİL)-1,2,4-TRİAZOL-4-AMİNLERİN MİKRODALGA SENTEZİ

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ABSTRACT

Objective: *The aim of this work is to synthesize 3-(alkylthio)-5-(thiophen-2-ylmethyl)-1,2,4-triazol-4-amines by the Milestone Flexi Wave microwave synthesis system and to prove structure synthesized compounds.*

Material and Method*: The initial compounds 3-(thiophen-2-ylmethyl)-4H-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). Milestone Flexi Wave microwave synthesis system was used to synthesize 3-(alkylthio)-5-(thiophen-2-ylmethyl)-1,2,4-triazol-4-amines. The elemental analysis of synthesized compounds was established by the universal analyzer Elementar Vario L cube (CHNS). The ^{1}H spectra (at 400 MHz and 100 MHz) were recorded in DMSO-d_6 on a Varian MR-400 spectrometer and analysed with ADVASP™ Analyzer program. 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.*

Result and Discussion: *The reaction was carried out in an alcoholic medium by adding a catalytic amount of HCl to 5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiols. Methyl and i-propyl alcohols were used as alcohols. The mixture was heated for 45 minutes at a temperature of 150°C, a pressure 14.4 bar, ΔMW = 200 W.*

The signals of ^{1}H NMR for (4a-b, 6a-j) 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: *1,2,4-triazole, synthesis, ^{1}H-NMR, gas chromatography, heterocyclic compounds.*

ÖZ

Amaç: *Bu çalışmanın amacı, Milestone Flexi Wave mikrodalga sentez sistemi ile 3-(alkiltiyo)-5-(tiyofen-2-ilmetil)-1,2,4-triazol-4-aminlerin sentezlenmesi ve sentezlenen bileşiklerin yapısının onaylanmasıdır.*

Gereç ve Yöntem: *İlk bileşikler 3-(tiyofen-2-ilmetil)-4H-1,2,4-triazol-5-tiyoller (1-5) Zaporizhzhya State Medical Üniversite Toksikolojik ve İnorganik Kimya Anabilim Dalı'nda sentezlendi (Ukrayna). 3-(alkiltiyo)-5-*

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(tiyofen-2-ilmetil)-1,2,4-triazol-4-aminlerin sentezlenmesi için Milestone Flexi Wave mikrodalga sentez sistemi kullanıldı. Sentezlenen bileşiklerin element analizi evrensel analiz Elementar Vario L küpü (CHNS) tarafından yapıldı. ^{1}H spektrumları (400 MHz ve 100 MHz'de), DMSO-d_6'da bir Varian MR-400 spektrometresi üzerinde kaydedildi ve ADVASP ™ Analyzer programı ile analiz edildi. Reaksiyonlar ve elde edilen bileşikler, bir 5977B kütle spektrometre detektörü ile Agilent 7890B gaz kromatografisinde kontrol edildi.

Sonuç ve Tartışma: *Reaksiyon, 5-(tiyofen-2-ilmetil)-4H-1,2,4-triazol-3-tiyollere katalitik miktarda HCI ilave edilerek alkollü bir ortamda gerçekleştirildi. Alkol olarak metil ve i-propil alkoller kullanıldı.*

Karışım, 45 dakika boyunca 150°C sıcaklıkta, 14.4 bar basınçta, ΔMW = 200 W sıcaklıkta ısıtıldı.

Çözücü olarak asetik asit kullanıldı. (4a-b, 6a-j) için önerilen yapı, ^{1}H NMR sinyalleri ile doğrulandı. Temel kimyasal yapılarını doğrulamak için sentezlenen bileşikler üzerinde element analizi (CHNS) yapıldı ve hesaplanan yüzdelerle kabul edilebilir bir uyum sağladığını gösterdi.

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

INTRODUCTION

Heterocyclic compounds have become the most attractive class of organic compounds as a result of the intensive development of science. Studies of the synthetic capabilities of heterocyclic compounds have increased tenfold over the past ten years [1-3]. This tendency has a reasoned explanation due to the many special properties of these substances and the progressive development of organic synthetic chemistry.

1,2,4-Triazoles occupy a worthy place among heterocyclic compounds due to a number of unique properties [4-6]. High reactivity, low toxicity and certainly high biological activity make this class of heterocyclic compounds and its derivatives very attractive for comprehensive study.

The search for biologically active compounds among 1,2,4-triazole derivatives is being carried out by teams of scientists from many countries of the world [7-14]. An interesting fact remains the attempt of many scientists to combine 1,2,4-triazole with various functional substitutes, which in the "complex" may be promising for the detection of new types of pharmacological activity. We have attempted to attach to the 1,2,4-triazole "nuclei" of thiophene, aliphatic and aromatic substituents, each of which is separately a fragment of molecules of biologically active compounds or drugs. Therefore, in our opinion, derivatives of 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazoles may be interesting and promising in the process of creating new "libraries" of biologically active compounds.

The aim of the work was to synthesize 3-(alkylthio)-5-(thiophen-2-ylmethyl)-1,2,4-triazol-4-amines by the Milestone Flexi Wave microwave synthesis system and to prove structure synthesized compounds.

MATERIAL AND METHOD

Chemicals

The initial compounds 3-(thiophen-2-ylmethyl)-4H-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% [15]. The chloride acid (35%), 1-propanol (anhydrous, 99,7%) and methanol (99,5%) were obtained from SIGMA-ALDRICH (Germany).

Equipment

To achieve the purpose, the following devices were used. Milestone Flexi Wave microwave synthesis system (Milestone Srl, Italy) (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 (US production).

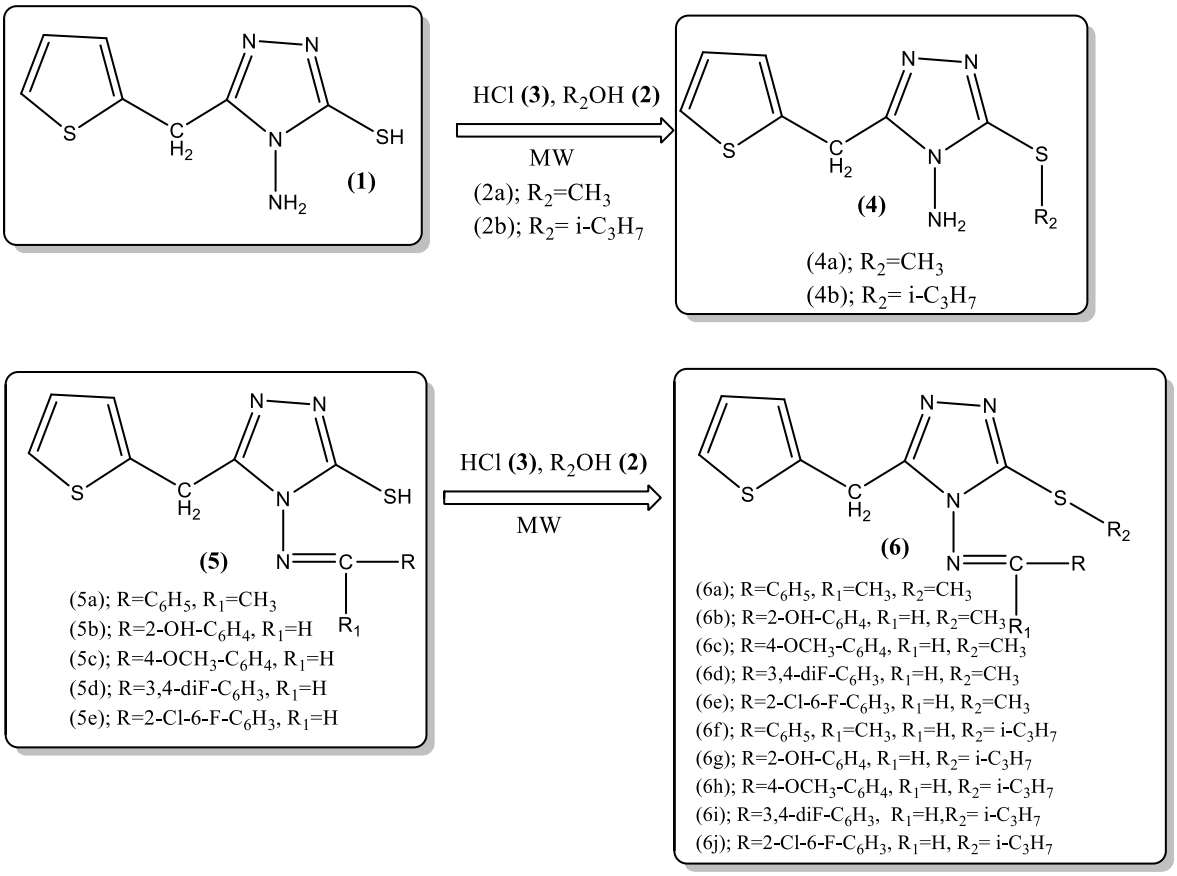
The elemental analysis of synthesized compounds was established by the universal analyzer Elementar Vario L cube (CHNS) (standard - sulfanilamide) (Analysensysteme GmbH, Germany).

The ^{1}H 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 (US production). 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 - 280 ºC; ion sources - 230 ºC; quadrupole mass analyzer - 150 ºC. 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

As starting materials were used 4-R-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-3-thiols (**1, 5**) which were synthesized and described by us earlier [15]. The reaction was carried out in an alcoholic medium by adding a catalytic amount of HCl to 4-R-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-3-thiols. Methyl and i-propyl alcohols were used as alcohols.



Scheme 1: Synthesis of 3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines (4a-4b) and N-(2-methoxybenzylidene)-3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines (6a-6j)

To achieve better results, a change in temperature and reaction time was used. The reaction was carried out for 60 minutes (the temperature of the reaction mixture was 110° C), the second series of 50 minutes (temperature of the reaction mixture of 130° C), the third series of 45 minutes (temperature of the reaction mixture 150 ° C). The most technologically optimal method was chosen whereby quantitative outputs were highest.

The mixture was heated for 45 minutes at a temperature of 150 ° C, a pressure 14.4 bar, ΔMW = 200 W (Figure 1).

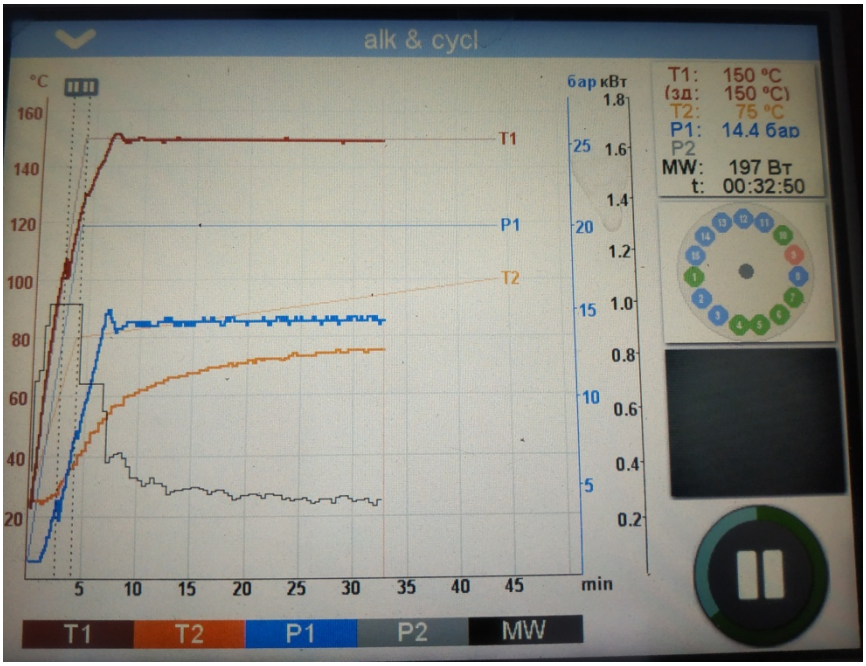


Figure 1. Microwave synthesis of N-R-3-(alkylthio)-5-(thiophen-2-ylmethyl)-1,2,4-triazol-4-amines

The completeness of the reaction was determined using a gas chromatograph Agilent 7890B with a mass spectrometric detector 5977B.

Analyzing the GS/MS chromatogram in the MS spectrum there is a molecular peak with a value of 226.0 (m/z), which corresponds to the calculated theoretical value of 3-(methylthio)-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-4-amine (4a) (Figure 2)

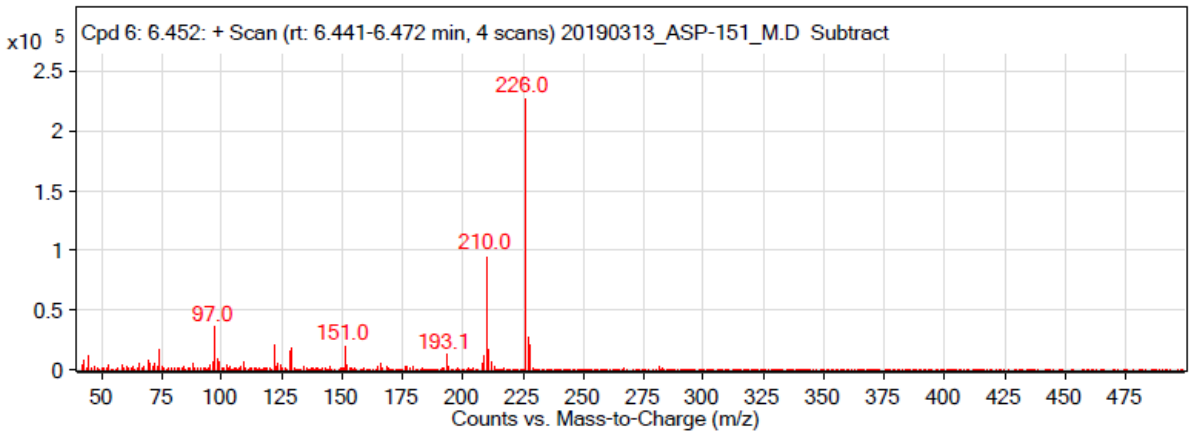


Figure 2. Mass spectrum of 3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (4a)

In the MS spectrum (Figure 3) there is a molecular peak with a value of 330.1 (m/z), which corresponds to the calculated theoretical value of 2-(((3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-yl)imino)methyl)phenol (6b).

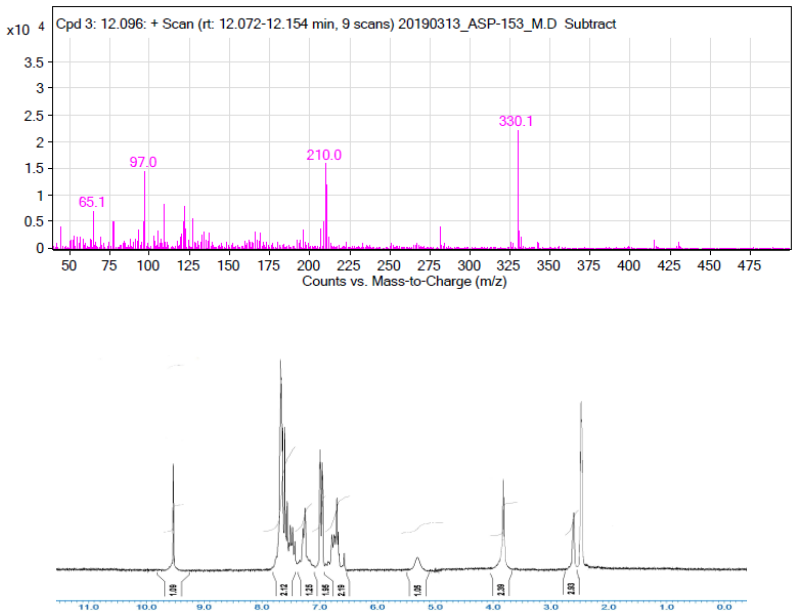


Figure 3. Mass spectrum (left) and ^{1}HNMR spectrum (right) of 2-(((3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-yl)imino)methyl)phenol (6b)

3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (4a)

Bright brown powder; yield 89.9%; m.p. 132-134^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 7.32 (1H, d, thiophen-H); 6.86 (1H, t, thiophen-H); 6.68 (1H, d, thiophen-H); 5,82 (2H, S, NH_2); 3.79 (2H, s, CH_2); 2.51 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_8H_{10}N_4S_2$) : found C% 43.60, H% 4.41, N% 24.68, S% 28.36; calculated C% 43.46, H% 4.45, N% 24.76, S% 28.34. MS (EI) *m/z* (rel. intensity): 226 (M^+, 100).

3-(isopropylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (4b)

Bright yellow powder; yield 87.8%; m.p. 130-132^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 7.38 (1H, d, thiophen-H); 6.81 (1H, t, thiophen-H); 6.69 (1H, d, thiophen-H); 5,80 (2H, S, NH_2); 3.82 (2H, s, CH_2); 2.90 (1H, m, CH); 1.23 (6H, d, $2CH_3$); CHNS elemental analysis Calcd. for ($C_{10}H_{14}N_4S_2$) : found C% 47.40, H% 5.54, N% 22.07, S% 25.24; calculated C% 47.22, H% 5.55, N% 22.03, S% 25.21. MS (EI) *m/z* (rel. intensity): 254 (M^+, 100).

3-(methylthio)-N-(1-phenylethylidene)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6a)

Yellow powder; yield 86.7%; m.p. 118-120^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 7.98(2H, d, Ar-H); 7.61(3H, m, Ar-H); 7.42 (1H, d, thiophen-H); 6.76 (1H, t, thiophen-H); 6.68 (1H, d, thiophen-H); 3.80 (2H, s, CH_2); 2.51 (3H, s, CH_3); 1.64 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_{16}H_{16}N_4S_2$) : found C% 58.49, H% 4.93, N% 17.10, S% 19.48; calculated C% 58.51, H% 4.91, N% 17.06, S% 19.52. MS (EI) *m/z* (rel. intensity): 328 (M^+, 100).

2-(((3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-yl)imino)methyl)phenol (6b)

Bright orange powder; yield 86.5%; m.p. 200-202^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.56 (1H, s, CH); 7.64 (1H, d, Ar-H); 7.49 (1H, t, Ar-H); 7.38 (1H, d, thiophen-H); 7.02 (2H, d, Ar-H); 6.76 (1H, t, thiophen-H); 6.68 (1H, d, thiophen-H); 5.31(1H, s, OH); 3.82 (2H, s, CH_2); 2.54 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_{15}H_{14}N_4OS_2$) : found C% 54.41, H% 4.29, N% 16.99, S% 19.42; calculated C% 54.52, H% 4.27, N% 16.96, S% 19.41. MS (EI) *m/z* (rel. intensity): 330 (M^+, 100).

N-(4-methoxybenzylidene)-3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6c)

Yellow powder; yield 89.1%; m.p. 180-182^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.96 (1H, s, CH); 7.86 (2H, d, Ar-H); 7.39 (1H, d, thiophen-H); 7.08 (2H, d, Ar-H); 6.79 (1H, t, thiophen-H); 6.65 (1H, d, thiophen-H); 3.96 (3H, s, CH_3); 3.81 (2H, s, CH_2); 2.55 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_{16}H_{16}N_4OS_2$) : found C% 55.86, H% 4.70, N% 16.29, S% 18.58; calculated C% 55.79, H% 4.68, N% 16.27, S% 18.62. MS (EI) *m/z* (rel. intensity): 344 (M^+, 100).

N-(3,4-difluorobenzylidene)-3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6d)

Bright yellow powder; yield 90.4%; m.p. 168-170^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.98 (1H, s, CH); 7.82 (1H, m, Ar-H); 7.54 (1H, m, Ar-H); 7.39 (1H, d, thiophen-H); 7.30 (1H, m, Ar-H); 6.79 (1H, t, thiophen-H); 6.64 (1H, d, thiophen-H); 3.80 (2H, s, CH_2); 2.51 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_{15}H_{12}F_2N_4S_2$) : found C% 51.23, H% 3.44, N% 15.96, S% 18.32; calculated C% 51.41, H% 3.45, N% 15.99, S% 18.30. MS (EI) *m/z* (rel. intensity): 350 (M^+, 100).

N-(2-chloro-6-fluorobenzylidene)-3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6e)

Brown powder; yield 86.7%; m.p. 149-151^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.54 (1H, s, CH); 7.48 (1H, m, Ar-H); 7.39 (1H, d, thiophen-H); 7.24 (2H, m, Ar-H); 6.76 (1H, t, thiophen-H); 6.64 (1H, d, thiophen-H); 3.78 (2H, s, CH_2); 2.57 (3H, s, CH_3); CHNS elemental analysis Calcd. for ($C_{15}H_{12}ClFN_4S_2$) : found C% 49.02, H% 3.32, N% 15.28, S% 17.44; calculated C% 49.11, H% 3.30, N% 15.27, S% 17.48. MS (EI) *m/z* (rel. intensity): 366 (M^+, 100).

3-(isopropylthio)-N-(1-phenylethylidene)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6f)

Bright yellow powder; yield 91.3%; m.p. 126-128^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 7.91(2H, d, Ar-H); 7.56(3H, m, Ar-H); 7.40 (1H, d, thiophen-H); 6.78 (1H, t, thiophen-H); 6.64 (1H, d, thiophen-H); 3.80 (2H, s, CH_2); 2.89 (1H, m, CH); 1.84 (3H, s, CH_3); 1.24 (6H, d, CH_3); CHNS elemental analysis Calcd. for ($C_{18}H_{20}N_4S_2$) : found C% 49.02, H% 3.32, N% 15.28, S% 17.44; calculated C% 49.11, H% 3.30, N% 15.27, S% 17.48. MS (EI) *m/z* (rel. intensity): 356 (M^+, 100).

2-(((3-(isopropylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-yl)imino)methyl)phenol (6g)

Bright brown powder; yield 88.9%; m.p. 154-156^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.54 (1H, s, CH); 7.61 (1H, d, Ar-H); 7.50 (1H, t, Ar-H); 7.39 (1H, d, thiophen-H); 7.04 (2H, d, Ar-H);

6.74 (1H, t, thiophen-H); 6.63 (1H, d, thiophen-H); 5.30(1H, s, OH); 3.84 (2H, s, CH_2); 2.88 (1H, m, CH); 1.24 (6H, d, CH_3); CHNS elemental analysis Calcd. for ($C_{17}H_{18}N_4OS_2$) : found C% 56.91, H% 5.07, N% 15.65, S% 17.92; calculated C% 56.96, H% 5.06, N% 15.63, S% 17.89. MS (EI) *m/z* (rel. intensity): 358 (M^+, 100).

3-(isopropylthio)-N-(4-methoxybenzylidene)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6h)

Yellow powder; yield 89.9%; m.p. 183-185^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.97 (1H, s, CH); 7.85 (2H, d, Ar-H); 7.39 (1H, d, thiophen-H); 7.04 (2H, d, Ar-H); 6.78 (1H, t, thiophen-H); 6.69 (1H, d, thiophen-H); 3.84 (3H, s, CH_3); 3.81 (2H, s, CH_2); 2.88 (1H, m, CH); 1.24 (6H, d, CH_3); CHNS elemental analysis Calcd. for ($C_{18}H_{20}N_4OS_2$) : found C% 57.14, H% 5.44, N% 15.08, S% 17.24; calculated C% 57.08, H% 5.41, N% 15.04, S% 17.22. MS (EI) *m/z* (rel. intensity): 358 (M^+, 100).

N-(3,4-difluorobenzylidene)-3-(isopropylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6i)

Bright yellow powder; yield 93.5%; m.p. 205-207^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 10.01 (1H, s, CH); 7.81 (1H, m, Ar-H); 7.50 (1H, m, Ar-H); 7.36 (1H, d, thiophen-H); 7.30 (1H, m, Ar-H); 6.74 (1H, t, thiophen-H); 6.63 (1H, d, thiophen-H); 3.82 (2H, s, CH_2); 2.89 (1H, m, CH); 1.24 (6H, d, CH_3); CHNS elemental analysis Calcd. for ($C_{17}H_{16}F_2N_4S_2$) : found C% 53.86, H% 4.27, N% 14.81, S% 16.95; calculated C% 53.95, H% 4.26, N% 14.80, S% 16.94. MS (EI) *m/z* (rel. intensity): 378 (M^+, 100).

N-(2-chloro-6-fluorobenzylidene)-3-(isopropylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine (6j)

Orange powder; yield 91.2%; m.p. 217-219^{0}C ; ^{1}HNMR (400 MHz, DMSO-d6, δ=ppm): 9.55 (1H, s, CH); 7.49 (1H, m, Ar-H); 7.36 (1H, d, thiophen-H); 7.21 (2H, m, Ar-H); 6.75 (1H, t, thiophen-H); 6.64 (1H, d, thiophen-H); 3.79 (2H, s, CH_2); 2.88 (1H, m, CH); 1.22 (6H, d, CH_3); CHNS elemental analysis Calcd. for ($C_{17}H_{16}ClFN_4S_2$) : found C% 51.61, H% 4.09, N% 14.20, S% 16.27; calculated C% 51.70, H% 4.08, N% 14.19, S% 16.24. MS (EI) *m/z* (rel. intensity): 394 (M^+, 100).

In conclusion, the novel 3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines (4a-4b) and N-(2-methoxybenzylidene)-3-(methylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines (6a-6j) were synthesized and characterized. The structure of synthesized compounds is confirmed using Elemental analysis (CHNS), ^{1}HNMR and Chromatographic mass spectral analysis.

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