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3-Alkil(Aril)-4-(4-metiltiyo-benzilidenamino)-4,5-dihidro-1H-1,2,4-triazol-5-on Türevlerinin Sentezi ve Biyolojik Değerlendirmesi

Synthesis and Biological Evaluation of 3-Alkyl(Aryl)-4-(4-methylthio-benzylideneamino)-4,5-dihidro-1H-1,2,4-triazol-5-one Derivatives

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Makale Bilgileri
Geliş Tarihi
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Anahtar Kelimeler
1,2,4-triazol,
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Antimikrobiyal aktivite

Öz

Bu çalışmada, 3-alkil(aril)-4-amino-4,5-dihidro-1*H*-1,2,4-triazol-5-on'lar (3c, f, h), 4-metiltiyobenzaldehit ile reaksiyona sokularak 3-alkil(aril)-4-(4-metiltiyobenziliden-amino)-4,5-dihidro-1*H*-1,2,4-triazol-5-on (4c, f, h) bileşikleri elde edildi. Üç yeni bileşiğin yapıları elementel analiz, IR, ^{1}H NMR ve ^{13}C NMR spektral verileri kullanılarak belirlendi. Yeni sentezlenen üç adet ve yakın zamanda sentezlenen altı adet olmak üzere toplam dokuz adet 3-alkil(aril)-4-(4-metiltiyobenzilidenamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-on türevlerinin antioksidan aktiviteleri, üç yöntem kullanılarak analiz edildi. 4a Bileşiği metal şelatlama etkisi açısından en iyi aktiviteyi gösterdi. Ayrıca bu bileşiklerin antimikrobiyal aktiviteleri de incelendi.

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Abstract

In the present study, 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3c**, **f, h**) reacted with 4-methylthiobenzaldehyde to afford 3-alkyl(aryl)-4-(4-methylthio-benzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-ones (**4c**, **f**, **h**). The structures of three new compounds were established from the elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectral data. Three methods were used to analyze the antioxidant activities of nine 3-alkyl(aryl)-4-(4-methylthiobenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, three newly synthesized and six recently synthesized. Compound **4a** showed the best activity for the metal chelating effect. Furthermore, the compounds' antimicrobial activity was screened.

1. INTRODUCTION

The quest for new antioxidant and antimicrobial agents is a matter of utmost scientific urgency. Antioxidants, with their cell and tissue-protective properties, are pivotal for

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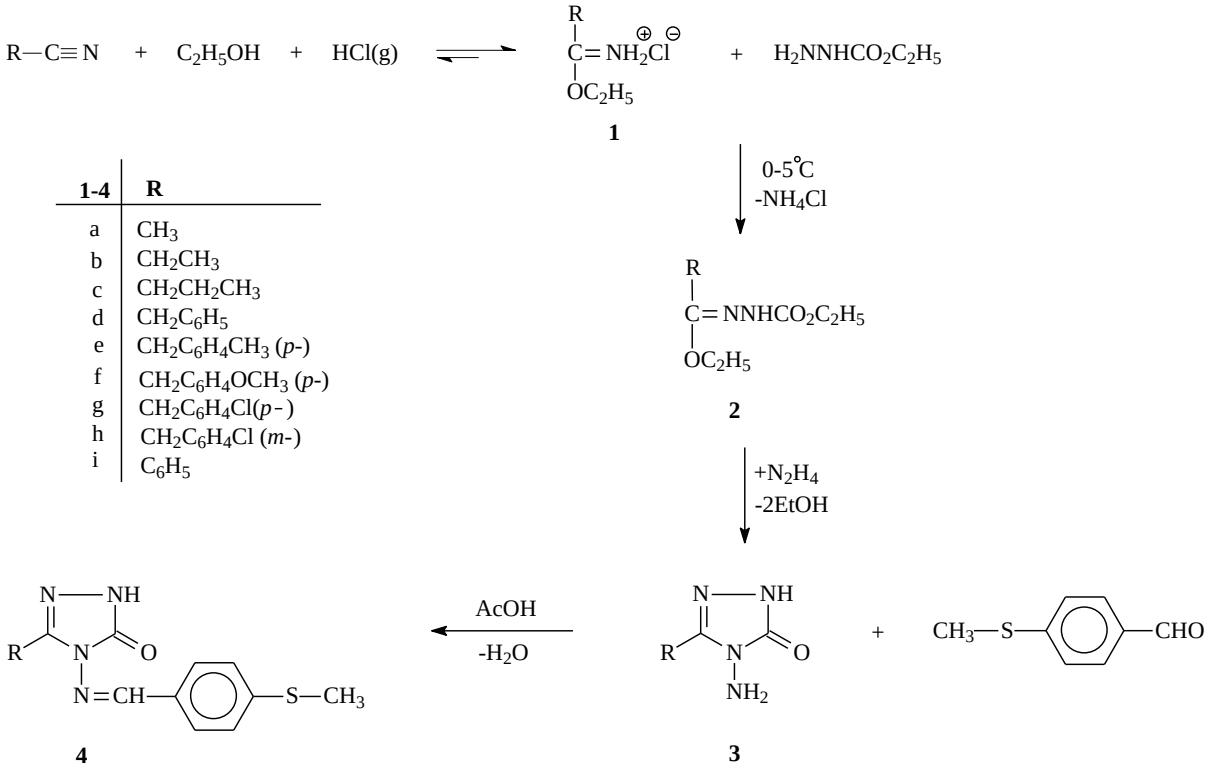
maintaining bodily functions. In recent times, the therapeutic potential of antioxidants in treating a range of diseases, from atherosclerosis and stroke to diabetes, Alzheimer's disease, certain cancers, has garnered significant attention (Bajpai et al., 2016; Gupta & Sharma, 2006; Rathore et al., 2011). Equally pressing is the global burden of bacterial infections, with over one-third of the world's population at risk and two million deaths annually, necessitating the development of effective antimicrobial agents (Monaghan & Barrett, 2006).

Heterocyclic compounds are versatile players in medicinal chemistry. Among the compounds, many 1,2,4-triazoles and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives have been synthesized and evaluated for antioxidant and antimicrobial effects between many biological properties (Aktas-Yokus et al., 2017; Manap et al., 2020; Medetalibeyoğlu et al., 2023; Yüksek et al., 2013). But their potential doesn't stop there- they also show promise in anti-inflammatory, antifungal, hypolipidemic, hypoglycemic, antiproliferative, analgesic, anti-HIV, anticonvulsant, antiviral, and anticancer applications (Abbas et al., 2017; Aboeldahab et al., 2018; Abuelhassan et al., 2018; Iqbal et al., 2012; Li et al., 2013).

In the paper, we present the synthesis of 3-*n*-propyl-4-(4-methylthio-benzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one (**4c**), 3-*p*-methoxybenzyl-4-(4-methylthiobenzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one (**4f**) and 3-*m*-chlorobenzyl-4-(4-methylthiobenzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one (**4h**) (Scheme 1). The starting compounds (**3**) were prepared as described in the literature (Ikizler & Un, 1979; Ikizler & Yüksek, 1993), and their reaction with 4-methylthiobenzaldehyde enabled us to obtain these compounds. Our study on the antimicrobial activities of 3 newly synthesized (**4c, 4f, 4h**) and 6 recently synthesized (**4a, 4b, 4d, 4e, 4g, 4i**) (Yüksek & Kardaş, 2022) 3-alkyl(aryl)-4-(4-methylthiobenzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one derivatives was conducted thoroughly. We employed a variety of antioxidant methodologies, including 1,1-diphenyl-2-picryl-hydrazyl (DPPH$^{\cdot}$) free radical scavenging, reducing power, and metal chelating activities, to ensure a comprehensive investigation of the compounds' properties.



Scheme 1. Synthetic route of the titled compound

2. MATERIALS AND METHODS

Materials and Measurements

Merck, Fluka, and Aldrich provided the chemicals used in the study. Melting points of the compounds synthesized within the scope of the study were determined on the Stuart melting point SMP30 apparatus. IR spectra used in structure illumination were taken on the ALPHA-P BRUKER FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker spectrometer at 400 and 100MHz. Microanalysis of three compounds synthesized in the study was performed on a LECO, CHNS-932 elemental analyzer.

Synthesis

The preparation of compound **4c** was as follows: The compound **3c** (0.01 mol) was dissolved in acetic acid (20 mL) and treated with 4-methylthiobenzaldehyde (0.01 mol). The mixture was refluxed for an hour and evaporated at 50-55 °C in vacuo. Several recrystallizations of the residue from ethanol gave pure compound 3-n-propyl-4-(4-methylthiobenzylideneamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one (**4c**) as colorless crystals; mp. 142 °C, yield 2.71 g (98%). Two other compounds (**4f** and **4h**) were obtained similarly;

their melting points and yields were mp. 189 °C; yield 3.48 g (98%) and 198 °C; yield 3.55 g (99%), respectively.

Characterization of 4c, 4f and 4h

For compound **4c**: "IR (KBr, υ, cm^{-1}): 3168 (N-H), 1693 (C=O), 1588 (C=N), 806 (1,4-disubstitued aromatic ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (t, 3H, $CH_2CH_2\underline{CH_3}$; *J*=7.20Hz), 1.68 (sext, 2H, $CH_2\underline{CH_2}CH_3$; *J*=7.20Hz), 2.53 (s, 3H, SCH_3), 2.63 (t, 2H, $\underline{CH_2}CH_2CH_3$; *J*=7.20Hz), 7.36 (d, 2H, ArH, *J*=8.40 Hz), 7.75 (d, 2H, ArH, *J*=8.40 Hz), 9.65 (s, 1H, N=CH), 11.82 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.46 ($CH_2CH_2\underline{CH_3}$), 14.16 (SCH_3), 18.60 ($CH_2\underline{CH_2}CH_3$), 26.74 ($\underline{CH_2}CH_2CH_3$), [125.62 (2CH), 127.99 (2CH), 129.86 (C), 142.89 (C)] (arom-C), 146.88 (triazol C_3), 151.36 (triazol C_5), 153.46 (N=CH). Anal. Calcd. for $C_{13}H_{16}N_4OS$ (276.36): C, 56.50; H, 5.84; N, 20.27; S, 11.60. Found: C, 55.46; H, 6.13; N, 20.11; S, 10.99."

For compound **4f**: "IR (KBr, υ, cm^{-1}): 3163 (N-H), 1692 (C=O), 1589 (C=N), 805 (1,4-disubstitued aromatic ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, SCH_3), 3.70 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2Ph), 6.86 (d, 2H, ArH, *J*=8.80 Hz), 7.23 (d, 2H, ArH, *J*=8.40 Hz), 7.36 (d, 2H, ArH, *J*=8.40 Hz), 7.73 (d, 2H, ArH, *J*=8.40 Hz), 9.61 (s, 1H, N=CH), 11.92 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.14 (SCH_3), 30.28 (CH_2Ph), 55.02 (OCH_3), [113.87 (2CH), 125.59 (2CH), 127.58 (2C), 128.04 (2CH), 129.83 (2CH), 142.83 (C), 158.09 (C)] (arom-C), 146.49 (triazol C_3), 151.28 (triazol C_5), 153.21 (N=CH). Anal. Calcd. for $C_{18}H_{18}N_4O_2S$ (354.43): C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.12; H, 5.32; N, 15.78; S, 8.68."

For compound **4h**: "IR (KBr, υ, cm^{-1}): 3156 (N-H), 1694 (C=O), 1588 (C=N), 814 (1,4-disubstitued aromatic ring).^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, SCH_3), 4.08 (s, 2H, CH_2Ph), 7.27-7.42 (m, 6H, ArH), 7.72 (d, 2H, ArH, *J*=8.40 Hz), 9.62 (s, 1H, N=CH), 11.98 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.13 (SCH_3), 30.69 (CH_2Ph), [125.56 (2CH), 126.74 (CH), 127.59 (CH), 128.07 (2CH), 128.89 (CH), 129.74 (C), 130.25 (CH), 132.93 (C), 138.19 (C), 143.02 (C)] (arom-C), 145.67 (triazol C_3), 151.23 (triazol C_5), 153.33 (N=CH). Anal. Calcd. for $C_{17}H_{15}ClN_4OS$ (358.85): C, 56.90; H, 4.21; N, 15.61; S, 8.94. Found: C, 55.55; H, 4.71; N, 15.24; S, 8.33.

Biological Activity

In the study, bacterial and yeast strains were purchased from the company of Microbiological Environmental Protection Laboratories (France): "Bacillus substilis (ATCC

11774), Bacillus cereus (ATCC 11778), Pseudomonas aeruginosa (ATCC 27853), Klebsiella pneumonia (ATCC 4352), Staphylococcus aureus (ATCC 6538), Escherichia coli (ATCC 25922)." Simple susceptibility screening test using an agar well diffusion technique was used (Ahmad et al., 1998; Perez et al., 1990). All new compounds were measured and dissolved in DMSO to obtain 1 mg/ml of extract stock solution.

The antioxidant effects of new compounds and standard antioxidant compounds, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), α-tocopherol and ethylenediaminetetraacetic acid (EDTA) were determined by several antioxidant tests, such as reducing power, free radical scavenging activity and metal chelating activity. The reducing power of the compounds and standard antioxidants was determined according to the procedure (Oyaizu, 1986). Free radical scavenging activity of the synthesized compounds and standards was evaluated via DPPH· (2,2-diphenyl-1-picrylhydrazyl) by the procedure (Blois, 1958). The chelation of ferrous ions by the compounds and standards was estimated by the method (Dinis et al., 1994).

All the methods for the biological part have been extensively investigated in the literature (Aktas-Yokus et al., 2017).

3. RESULTS AND DISCUSSION

Chemistry

In the study, three new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives (**4c, 4f, 4h**) synthesized as shown in Scheme 1. The structures of three new Schiff bases were characterized by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR data.

Biological Evaluation

In the present work, three new compounds (**4c**, **4f**, **4h**) and recently synthesized six compounds (**4a**, **4b**, **4d**, **4e**, **4g**, **4i**) were screened for their antimicrobial activity (Table 1). The compounds **4a-d**, **4h**, and **4i** did not display any antimicrobial activity against all tested microorganisms. Also, none of the compounds showed any activity against *P. aeruginosa* and *K. pneumoniae*. However, **4f** and **4g** observed low activity against *B. subtilis*. Besides, they showed moderate activity against *B. cereus* at a similar level with Streptomycin. Also, compounds **4e**, **4f**, and **4g** showed activity against S. aureus; **4e** and **4g** are similar to Neomycin, but **4f** is low.

Table 1. Screening results for antimicrobial activity of the compounds **4**

Compounds	Microorganisms and inhibition zone (mm)					
	Bs	Bc	Pa	Kp	Sa	Ec
4a	-	-	-	-	-	-
4b	-	-	-	-	-	-
4c	-	-	-	-	-	-
4d	-	-	-	-	-	-
4e	-	-	-	-	12	-
4f	9	12	-	-	9	-
4g	8	11	-	-	13	-
4h	-	-	-	-	-	-
4i	-	-	-	-	-	-
Amp.	33	36	36	35	37	34
Neo.	17	17	17	16	13	16
Str.	12	12	12	11	21	10

"Bs: Bacillus subtilis (ATCC-11774), Bc: Bacillus cereus (ATCC-11778), Pa: Pseudomonas aeruginosa (ATCC-27853), Kp: Klebsiella pneumoniae (ATCC-4352) Sa: Staphylococcus aureus (ATCC-6538), Ec: Escherichia coli (ATCC-25922), Amp.: Ampicillin (3261), Neo.: Neomycin (3360), Str.: Streptomycin (3385)."

According to the antioxidant evaluation, the new compounds (**4c**, **4f**, **4h**) and recently synthesized compounds (**4a**, **4b**, **4d**, **4e**, **4g**, **4i**) exhibited neither reductive activity nor a scavenging effect. Figure 1 shows the chelating activity of the compounds **4**, α-tocopherol, and EDTA. The data from the figure express that the compounds show a remarkable effect on iron binding, but this effect does not increase depending on concentration, except for compound **4a.**

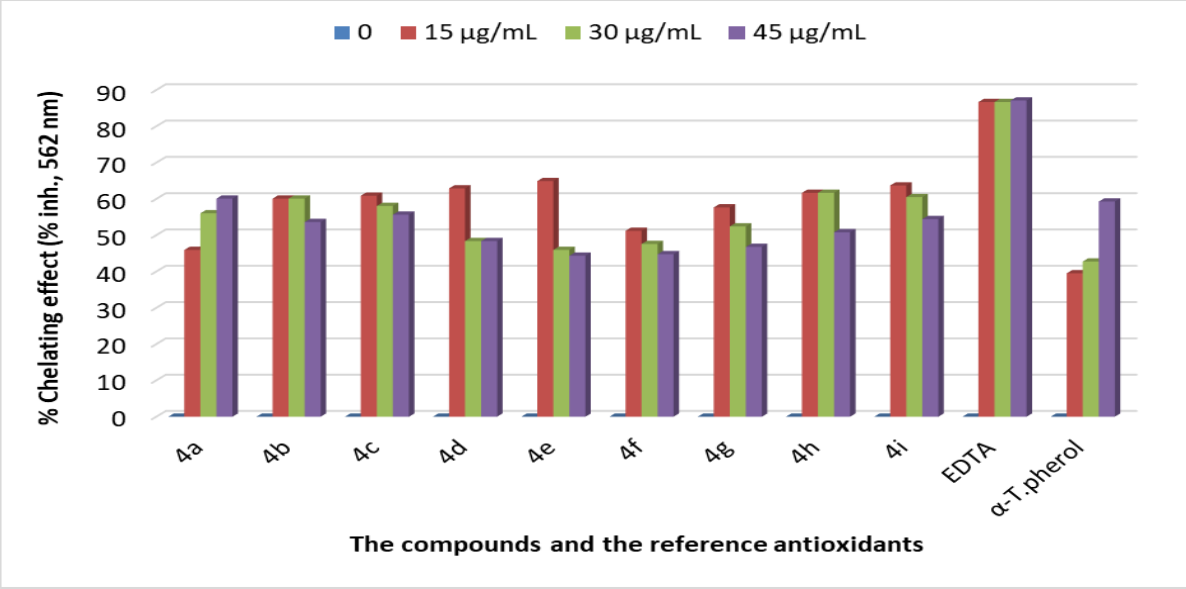


Figure 1. Metal chelating effect of different amount of the compounds **4**, EDTA and α-tocopherol on ferrous ions

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Conflict of Interest

There is no conflict of interest among the article authors.

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