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Synthesis, Characterization, and Antioxidant Activities of Novel 1-(Morpholine-4-yl-Methyl)-3-Alkyl(Aryl)-4-[4-(Dimethylamino)-Benzylidenamino]-4,5-Dihydro-1H-1,2,4-Triazol-5-Ones

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Abstract: In this paper, eight novel 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**) were obtained by the reactions of 3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**1**) with formaldehyde and morpholine. The novel synthesized compounds were identified by FT-IR, ^{1}H NMR, and ^{13}C NMR spectral data. Besides, the newly synthesized compounds were analyzed for their *in vitro* potential antioxidant capacities in three different assays. All of the compounds demonstrated significant activity for metal chelating effect.

Keywords: 4,5-Dihydro-1*H*-1,2,4-triazol-5-one; synthesis; mannich base; antioxidant capacity.

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INTRODUCTION

Mannich bases have applications the field medicinal chemistry, the product synthetic polymers, the petroleum industry, as products used in water treatment, cosmetics, the dyes industry, *etc.* (1). Moreover, Mannich bases have some biological activities such as anticancer (2,3), antibacterial (4,5), antimycobacterial (6), anti-HIV (7), anti-inflammatory (8,9), analgesic (10,11), antifungal (12,13), antitumor (14,15), antiviral (16), antidepressant (17), antiulcer (18), anticonvulsant (19), antimalaria (20), and antioxidant activities (21).

Antioxidants are extensively studied for their capacity to protect organisms and cells from damage that is induced by the oxidative stress. A great deal of research has been devoted to the study of different types of natural and synthetic antioxidant. A large number of heterocyclic compounds, containing the 1,2,4-triazole ring, are associated with diverse biological properties such as antioxidant, anti-inflammatory, antimicrobial, and antiviral activity. External chemicals and internal metabolic processes in human body or in food system might produce highly reactive free radicals, especially oxygen-derived radicals, which are capable of oxidizing biomolecules by resulting in cell death and tissue damage. Oxidative damages play a significantly pathological role in human diseases. Cancer, emphysema, cirrhosis, atherosclerosis, and arthritis have all been correlated with oxidative damage. Also, excessive generation of reactive oxygen species (ROS) induced by various stimuli and which exceeds the antioxidant ability of the organism leads to variety of pathophysiological processes like inflammation, diabetes, genotoxicity and cancer (22).

Triazoles are heterocyclic compounds that contain three nitrogen atoms. 1,2,4-Triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives are reported to possess a broad spectrum of biological activities such as analgesic, antibacterial, antioxidant, and antiparasitic properties (23–26). Considering about the development of new hetero moieties by combining potential biological active scaffolds, an attempt was made here to obtain 1,2,4-triazoles bearing morpholine ring and to evaluate their antioxidant activity.

In this regard, eight new 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**) were synthesized and investigated by using different antioxidant methodologies like reducing

power, 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging activity, and iron binding effect.

MATERIALS AND METHODS

Chemicals and Apparatus

Chemical reagents used in this paper were bought from Merck AG, Aldrich, and Fluka. Melting points were recorded in open glass capillaries using an Electrothermal melting point apparatus and were not corrected. The infrared spectra were recorded on an Alpha-P Bruker FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were determined in deuteriated dimethyl sulfoxide with TMS as internal standard using a Bruker Ultrashield spectrometer at 400 MHz and 100 MHz, respectively.

Synthesis of Compounds 2: General Procedure

3-Alkyl(Aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**1**) were obtained according to the literature (27). To the solution of this compound (**1**) (5 mmol) in absolute ethanol was added formaldehyde (% 37, 10 mmol) and morpholine (6 mmol). The reaction mixture was refluxed for 4 hours. The mixture was left at room temperature overnight. After cooling the mixture in the refrigerator, the solid formed was obtained by filtration, washed with cold ethanol, and recrystallized from ethanol.

Physical data of the new compounds are presented in Table 1. IR, ^{1}H-NMR and ^{13}C-NMR spectral data are given in Tables 2, 3, and 4, respectively.

ANTIOXIDANT ACTIVITY

Chemicals

Butylated hydroxytoluene (BHT), iron(II) chloride, DPPH·, α-tocopherol, 3-butylated hydroxyanisole (BHA), (2-pyridyl)-5,6-bis(phenylsulfonic acid)-1,2,4-triazine (ferrozine), and trichloroacetic acid (TCA) were obtained from E. Merck or Sigma.

Reducing power

The reducing power of the compounds **2a-h** was determined using the method of Oyaizu (28). Different concentrations of the samples (50-250 µg/mL) in DMSO (1 mL) were mixed with phosphate buffer (2.5 mL, 0.2 M, pH = 6.6) and potassium ferricyanide (2.5 mL, 1%). The mixture was incubated at 50 °C for 20 min. after which a portion (2.5 mL) of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged for 10 min at 1000 x g. The upper layer of solution (2.5 mL) was mixed with distilled water (2.5 mL) and $FeCl_3$ (0.5 mL, 0.1%), and then the absorbance at 700 nm was measured in a spectrophometer. Higher absorbance of the reaction mixture indicated greater reducing power.

Free radical scavenging activity

Free radical scavenging effect of the compounds **2a-h** was estimated by DPPH·, by the method of Blois (29). Briefly, 0.1 mM solution of DPPH. in ethanol was prepared, and this solution (1 mL) was added to sample solutions in DMSO (3 mL) at different concentrations (50-250 µg/mL). The mixture was shaken vigorously and allowed to stand at room temperature for 30 min. Then the absorbance was measured at 517 nm in a spectrophometer. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The DPPH. concentration (mM) in the reaction medium was calculated from the following calibration curve and determined by linear regression (R: 0.997):

$$\text{Absorbance} = 0.0003 \times \text{DPPH.} - 0.0174$$

The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH. scavenging effect (\%)} = (A_0 - A_1/A_0) \times 100$$

where A_0 is the absorbance of the control reaction and A_1 is the absorbance in the presence of the samples or standards.

Table 1. Physical data of the compounds **2a-h.**

Compound No	R	Yield (%)	m.p. (°C) (Crystallized from)
2a	CH_3	67	135 (Ethanol)
2b	CH_2CH_3	66	108 (Ethanol)
2c	$CH_2C_6H_5$	64	148 (Ethanol)
2d	$CH_2C_6H_4.CH_3$ (*p*-)	70	152 (Ethanol)
2e	$CH_2C_6H_4.OCH_3$ (*p*-)	95	194 (Ethanol)
2f	$CH_2C_6H_4.Cl$ (*p*-)	66	148 (Ethanol)
2g	$CH_2C_6H_4.Cl$ (*m*-)	66	184 (Ethanol)
2h	C_6H_5	75	155 (Ethanol)

Table 2. FTIR data of the compounds **2** (cm^{-1})

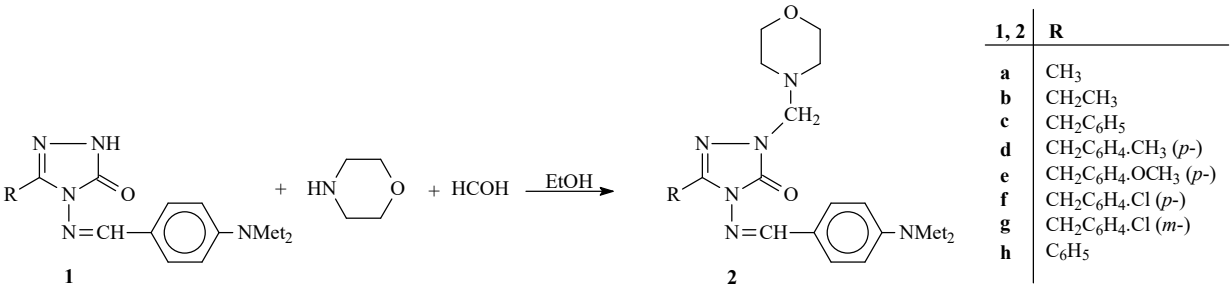
Compound No	$\nu_{C=O}$	$\nu_{C=N}$	$\nu_{1,4\text{-disubstituted benzenoid ring}}$	$\nu_{monosubstituted benzenoid ring}$
2a	1682	1596	857	-
2b	1702	1610, 1589	814	-
2c	1692	1592	816	775 and 693
2d	1702	1590	**813**	-
2e	1705	1608, 1587	816	-
2f	1707	1609, 1584	811	-
2g	1701	1588	811	-
2h	1696	1613, 1586	814	777 and 692

Metal chelating activity

The chelating of ferrous ions by the compounds **2a-h** and references was measured according to the method of Dinis *et al.* (30). Briefly, the synthesized compounds (30–60 μg/mL) were added to a 2 mM solution of $FeCl_2 \cdot 4H_2O$ (0.05 mL). The reaction was initiated by the addition of 5 mM ferrozine (0.2 mL), and then the mixture was shaken vigorously and left to stand at room temperature for 10 min. After the mixture had reached equilibrium, the absorbance of the solution was measured at 562 nm in a spectrophotometer. All tests and analyses were run in triplicate and averaged. The percentage of inhibition of ferrozine–Fe^{2+} complex formation was given by the formula: % inhibition = $(A_0 - A_1 / A_0) \times 100$, where A_0 is the absorbance of the control, and A_1 is the absorbance in the presence of the samples or standards. The control did not contain compound or standard.

RESULTS and DISCUSSION

In the current paper, eight new 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2a-h**) were synthesized. The starting compounds **1a-h** were prepared as explained in the literature (27). Compounds **2a-h** were obtained by the reactions of 3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (1) with formaldehyde and morpholine (**Scheme 1**). The novel 3-alkyl(aryl)-4-(3-benzoxy-4-methoxy-benzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2a-h**) were characterized with FT-IR, ^{1}H NMR and ^{13}C NMR and spectral data.



1, 2	R
a	CH_3
b	CH_2CH_3
c	$CH_2C_6H_5$
d	$CH_2C_6H_4.CH_3$ (*p*-)
e	$CH_2C_6H_4.OCH_3$ (*p*-)
f	$CH_2C_6H_4.Cl$ (*p*-)
g	$CH_2C_6H_4.Cl$ (*m*-)
h	C_6H_5

Scheme 1 Synthetic pathway of compounds **2**.

Table 3. ^{1}H-NMR data of the compounds **2** (DMSO-d_6, δ/ppm)

Comp.No	CH_3	CH_2NCH_2	CH_2	$2CH_3$	CH_2OCH_2	OCH_3	CH_2Ph	NCH_2	Aromatic H	N=CH
2a	2.27 (s)	2.56-2.59 (m)	-	2.99 (s)	3.54-3.57 (m)	-	-	4,51 (s)	6.77 (d,2H,*J*=8.8 Hz); 7.64 (d,2H,*J*=8.8 Hz	9.41 (s)
2b	1.21 (t, *J*=7.60Hz)	2.56-2.58 (m)	2.68 (q, *J*=7.60Hz)	2.99 (s)	3.55-3.57 (m)	-	-	4.52 (s)	6.78 (d,2H,*J*=8.8 Hz); 7.63 (d,2H,*J*=8.8 Hz	9.40 (s)
2c	-	2.57-2.59 (m)	-	3.00 (s)	3.56-3.57 (m)	-	4.05 (s)	4.55 (s)	6.76 (d,2H,*J*=8.8Hz); 7.22-7.24 (m,1H); 7.31-732 (m,4H); 7.60 (d,2H,*J*=8.8 Hz)	9.37 (s)
2d	2.24 (s)	2.57-2.58 (m)	-	3.00 (s)	3.56-3.57 (m)	-	3.99 (s)	4.55(s)	6.77 (d,2H,*J*=8.8 Hz); 7.11 (d,2H,*J*=7.6 Hz); 7.20 (d,2H,*J*=8.8 Hz); 7.61 (d,2H,*J*=8.8 Hz)	9.36 (s)
2e	-	2.54-2.57 (m)	-	3.00 (s)	3.56 (m)	3.65 (s)	3.97 (s)	4.54 (s)	6.77 (d,2H,*J*=8.8 Hz); 6.87 (d,2H,*J*=8.4 Hz); 7.23 (d,2H,*J*=8.4 Hz); 7.61 (d,2H,*J*=8.8 Hz)	9.37 (s)
2f	-	2.56-2.58 (m)	-	3.00 (s)	3.55-3.57 (m)	-	4.06 (s)	4.54 (s)	6.77 (d,2H,*J*=8.4 Hz); 7.33-7.39 (m,4H); 7.6 (d,2H,*J*=9.2 Hz)	9.38 (s)
2g	-	2.57 (m)	-	3.00 (s)	3.56 (m)	-	4.08 (s)	4.55 (s)	6.76 (d,2H,*J*=8.4 Hz); 7.29-7.37 (m,3H); 7.42 (s,1H); 7.60 (d,2H,*J*=8.0 Hz)	9.38 (s)

Table 4. ^{13}C-NMR data of the compounds **2** (DMSO-d_6, δ/ppm)

Comp.No	Triazole C_5	N=CH	Triazole C_3	Aromatic C	Aliphatic C
2a	152.49	150.50	142.92	156.02; 132.23(2C); 120.13; 111.06(2C)	66.04(CH_2OCH_2); 65.85(NCH_2N); 50.00(CH_2NCH_2); 38.95($2CH_3$); 11.03(CH_3)
2b	152.50	150.63	146.70	156.03; 129.29(2C); 120.16; 111.65(2C)	66.04(CH_2OCH_2); 65.88(NCH_2N); 50.01(CH_2NCH_2); 38.94($2CH_3$); 18.50($\underline{CH_2}CH_3$); 10.06($CH_2\underline{CH_3}$)
2c	152.50	150.51	144.81	155.66; 135.79; 129.32 (2C); 128.70 (2C); 128.45 (2C); 126.72; 120.10; 111.65 (2C)	66.04(CH_2OCH_2); 65.97(NCH_2N); 50.02(CH_2NCH_2); 38.95($2CH_3$); 30.99(CH_2Ph)
2d	152.49	150.51	144.97	155.62; 135.79; 132.66; 129.31 (2C); 129.01 (2C); 128.59 (2C); 120.13; 111.66 (2C)	66.04(CH_2OCH_2); 65.95(NCH_2N); 50.02(CH_2NCH_2); 38.96($2CH_3$); 30.58(CH_2Ph); 20.37($PhCH_3$)
2e	152.49	150.51	145.12	158.09; 155.62; 129.77 (2C); 129.33 (2C); 127.54; 120.13; 113.89 (2C); 111.63 (2C)	66.03(CH_2OCH_2); 65.95(NCH_2N); 55.01(OCH_3); 50.02(CH_2NCH_2); 38.94($2CH_3$); 30.13(CH_2Ph)
2f	152.51	150.50	144.49	155.74; 134.76; 131.43; 130.65 (2C); 129.35 (2C); 128.39 (2C); 120.04; 111.66 (2C)	66.04(CH_2OCH_2 + NCH_2N); 50.00(CH_2NCH_2); 38.95($2CH_3$); 30.34(CH_2Ph)
2g	152.53	150.49	144.31	155.75; 138.21; 132.96; 130.28; 129.36 (2C); 128.85; 127.51; 126.77; 120.04; 111.64 (2C)	66.04(CH_2OCH_2 + NCH_2N); 50.02(CH_2NCH_2); 38.96($2CH_3$); 30.58(CH_2Ph)

Antioxidant activity

The antioxidant capacities of ten newly synthesized compounds **2a-h** were determined. Different processes have been used to identify the antioxidant capacities. The processes used in the paper are clarified below:

Reducing power

The reducing power of the compounds **2** was determined. The reducing capacity of a compound may serve as a significant indicator of its potential antioxidant activity. The presence of reductants such as antioxidant substances in the samples causes the reduction of the Fe^{3+} / ferricyanide complex to the ferrous form. Therefore, the Fe^{2+} can be monitored by measuring the formation of Perl's Prussian blue at 700 nm (31). The antioxidant activity of putative antioxidant has been attributed to various mechanisms such as prevention chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging (32). In the paper, all of the concentrations of the compounds showed lower absorbance than reference antioxidants as seen in Figure **1**. Hereby, any reductive activities were not observed.

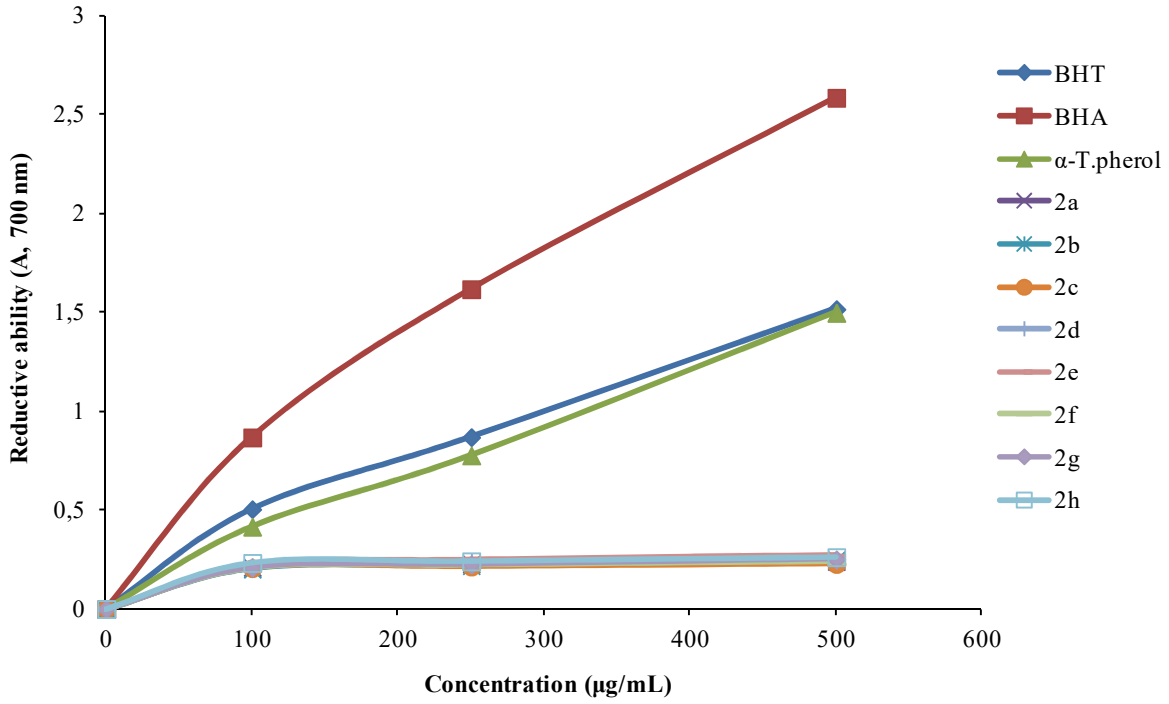
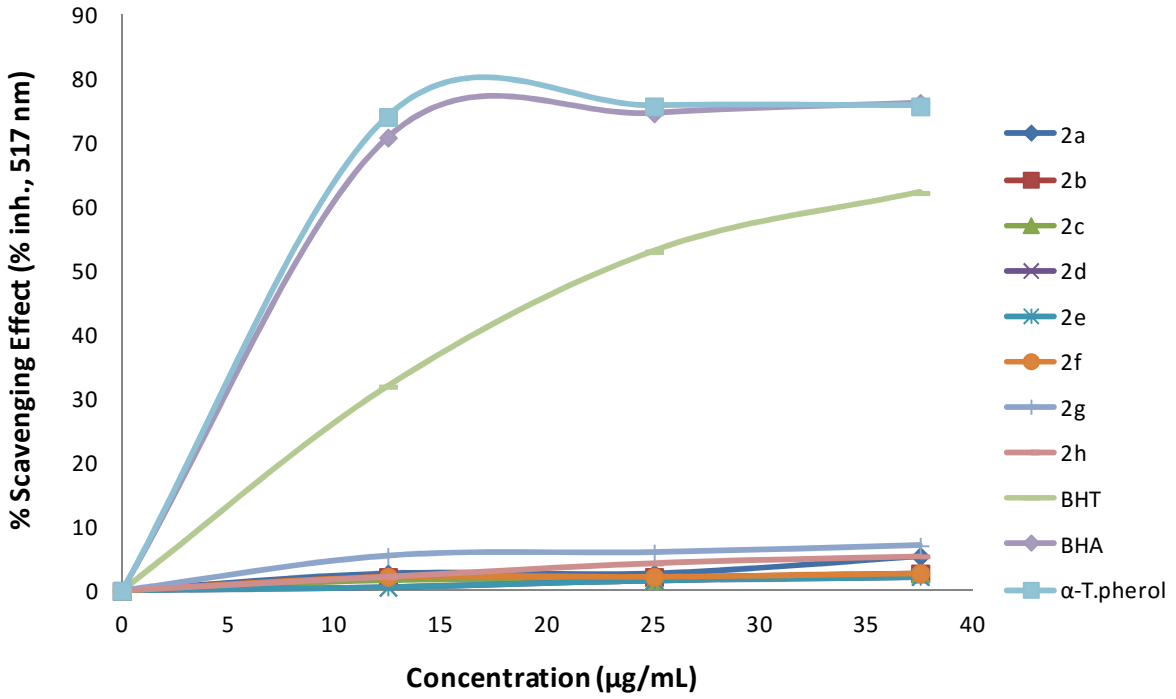


Figure 1. Total reductive potential of different concentrations of compound **2a-h**, BHT, BHA and α-tocopherol.

DPPH radical scavenging activity

Free radical scavenging effect of the compounds **2** was estimated by DPPH radical model. The effect of antioxidants on DPPH radical scavenging was thought to be due to their hydrogen donating ability (33). DPPH is a stable free radical and accepts an electron or hydrogen radical to become a stable diamagnetic molecule (34). The reduction capability of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants. In the study, antiradical capacities of the compounds **2a-h** and reference antioxidants for instance α-tocopherol, BHA and BHT were detected by using DPPH· method. Scavenging effect values of compounds **2** with BHT, BHA and α-tocopherol at different concentrations are given in Figure 2. All of the compounds tested with this method exhibited very low DPPH free radical scavenging activity in a concentration-dependent manner. In other words the newly synthesized compounds did not show any ability like a radical scavenger.



Iron binding capacity

The chelating of ferrous ions by the compounds **2** and references was measured. Ferrozine can quantitatively form complexes with Fe^{2+}. In the presence of chelating agents, the complex formation is disrupted with the result that the red color of the complex is decreased. Measurement of color reduction therefore allows estimation of the chelating activity of the coexisting chelator (35). The transition metals ions play an important role as catalysts of oxidative process, leading to formation of hydroxyl radicals and hydroperoxide decomposition reaction via Fenton chemistry (36). The production of

these radicals may lead to lipid peroxidation, protein modification, and DNA damage. Chelating agents are effective as secondary antioxidants because they potentially inhibit the metal-dependent processes thereby stabilizing the oxidized form of the metal ion (37). Iron binding activities of the compounds **2**, α-tocopherol and EDTA are shown in Figure 3. In the current paper, high iron binding capacity of synthesized compounds would be beneficial in retarding metal-chelating oxidation. The data acquired from Figure 3 discloses that the metal chelating effects of the compounds **2** were significant and concentration-dependent. The metal chelating effect of the compounds and references decreased in order of EDTA > **2g** ≈ **2b** > **2a** ≈ **2h** > **2c** ≈ **2d** > **2f** ≈ **2e** > α-tocopherol, which were 85.4, 84.5, 84.0, 82.5, 82.0, 60.3 (%), at the highest concentration, respectively.

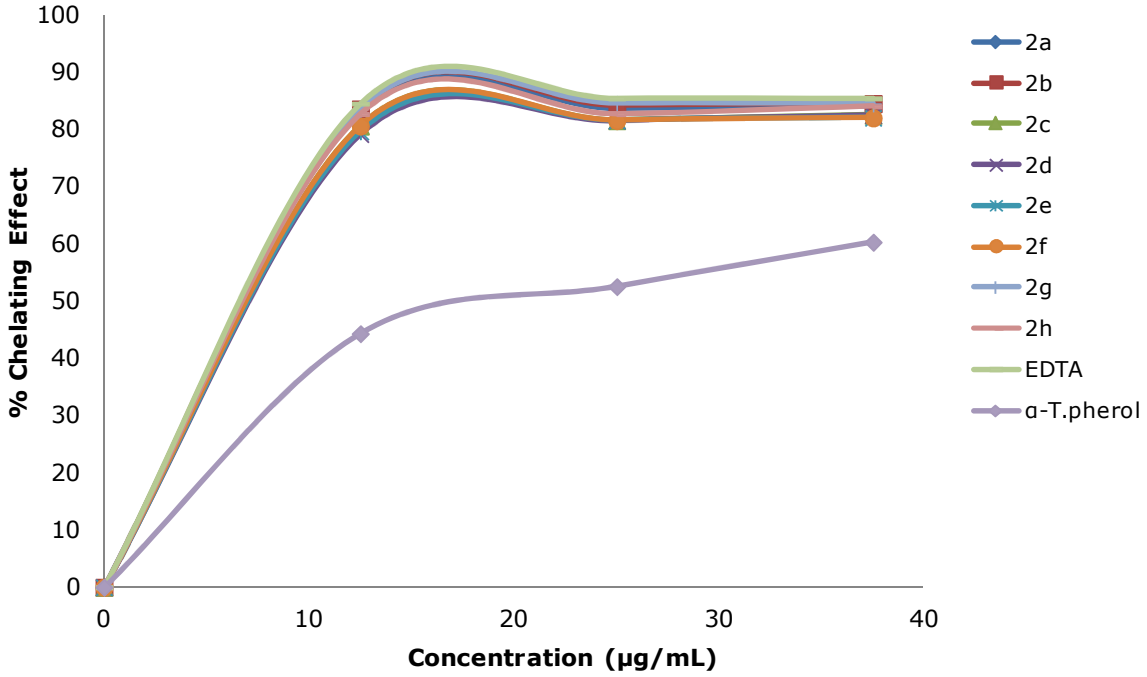


Figure 3. Iron binding effect of diverse amount of the compounds **2a-h**, and reference antioxidants.

CONCLUSION

New 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were obtained and evaluated for their *in-vitro* antioxidant capacity. All of the compounds demonstrate a marked ability for metal chelating activity. The data reported with regard to the observed metal chelating activities of the studied compounds could prevent redox cycling. The results may also give several advices for the improvement of new triazole-based therapeutic target.

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Türkçe Öz ve Anahtar Kelimeler

Yeni 1-(Morfolin-4-il-Metil)-3-Alkil(Aril)-4-[4-(Dimetilamino)-Benzilidenamino]4,5-dihidro-1H-1,2,4-Triazol-5-On'ların Sentezi, Karakterizasyonu ve Antioksidan Aktiviteleri

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Öz: Bu yayında sekiz adet yeni 1-(morfolin-4-il-metil)-3-alkil(aril)-4-[4-(dimetilamino)-benzilidenamino]-4,5-dihidro-1H-1,2,4-triazol-5-on'lar (**2**), 3-alkil(aril)-4-[4-(dimetilamino)-benzilidenamino]-4,5-dihidro-1H-1,2,4-triazol-5-on'ların (**1**) formaldehit ve morfolin ile tepkimesinden elde edildi. Yeni sentezlenen bileşikler IR, ^{1}H HMR ve ^{13}C NMR spektral verileri ile tanımlandı. Bunun yanında, yeni bileşikler üç farklı ölçüm türüyle *in vitro* potansiyel antioksidan kapasiteleri açısından analiz edildi. Bütün bileşiklerin metal kelatlama etkisi olarak belirgin aktiviteye sahip olduğu görüldü.

Anahtar kelimeler: 4,5-Dihidro-1*H*-1,2,4-triazol-5-on, Sentez, Mannich bazı, Antioksidan kapasitesi.

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