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Synthesis and Antioxidant Activities of Some Novel 1-(Morpholine-4-il-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones

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Abstract: In this study, 3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-ones (1) were treated with morpholine in the presence of formaldehyde according to the Mannich reaction to synthesize five novel 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2). In addition, the antioxidant properties of compounds 2 were analyzed and evaluated using three antioxidant assays, including reducing power, free radical scavenging and metal chelating activity. For the measurement of the reductive ability, Fe^{3+}-Fe^{2+} transformation was investigated in the presence of compound using by the method of Oyaizu (1986). The hydrogen atoms or electrons donation ability of the synthesized compound was measured by $DPPH^{\cdot}$ using the method of Blois (1958). The chelating effect of ferrous ions by the compound was determined according to the method of Dinis, Madeira & Almeida (1994). BHT, BHA, EDTA and α-tocopherol were used as reference antioxidant compounds.

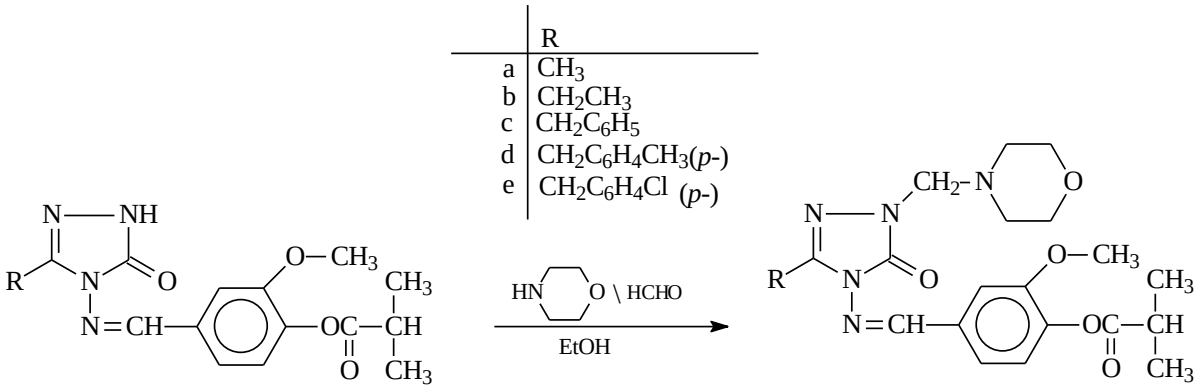
Keywords: 1,2,4-Triazol-5-one, Mannich base, Antioxidant activity

Introduction

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to possess a broad spectrum of biological activities such as antitumor (Chen et al., 2016), antibacterial (Zhang et al., 2014), antioxidant (Chidananda et al., 2012), anti-inflammatory (El-Serwy, Mohamed, Abbas, & Abdel-Rahman, 2013), analgesic (Uzgören-Baran et al., 2012), antihypertensive and diuretic (Ali, Ragab, Farghaly, & Abdalla, 2011) properties.

Antioxidants are extensively studied for their capacity to protect organism and cell 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 (McClements & Decker, 2000).

In the present paper, the antioxidant activities of five new 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**), which were obtained by the reactions of 3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with morpholine in the presence of formaldehyde (Scheme 1).



1 **2**

Scheme 1 Synthesized of compounds 2

Method

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 a Stuart SMP30 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 deuterated dimethyl sulfoxide with TMS as internal standard using a Bruker Avance III spectrophotometer at 400 MHz and 100 MHz, respectively.

Synthesis of Compounds 4: The General Procedure

1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) were synthesized by the reactions of 3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (1) with morpholine in the presence of formaldehyde. The corresponding compound **1** (0.01 mol) was dissolved in 100 mL of ethanol followed by addition of morpholine (0.015 mol) and formaldehyde (0.02 mol). The reaction mixture was refluxed for 3 hours. After standing at room temperature overnight, the solid was filtered and crystallized from ethanol. The solid was recrystallized from the same solvent and purified by drying *in vacuo* to obtain pure compounds **2** as colourless crystals.

*1-(Morpholine-4-yl-methyl)-3-methyl-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one (**2a**)*

Yield: 76.9%, m.p. 136 °C. IR: 3067 (C=CH), 1762, 1691 (C=O), 1601, 1577 (C=N), 1237 (COO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.24 (d, 6H, 2CH_3; *J*=7.20 Hz), 2.32 (s, 3H, CH_3), 2.58 (t, 4H, CH_2NCH_2; *J*=4.40 Hz), 2.84 (hept, 1H, CH; *J*=7.20 Hz), 3.56 (t, 4H, CH_2OCH_2; *J*=4.40 Hz), 3.84 (s, 3H, OCH_3), 4.54 (s, 2H, NCH_2), 7.23 (d, 1H, ArH; *J*=8.40 Hz), 7.46 (dd, 1H, ArH; *J*=8.40 Hz, 2.00 Hz), 7.59 (d, 1H, ArH; *J*=1.60 Hz), 9.69 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 10.95 (CH_3), 18.73 (2CH_3), 33.18 (CH), 49.97 (CH_2NCH_2), 56.06 (OCH_3), 65.92 (NCH_2), 66.05 (CH_2OCH_2), [111.50; 120.69; 123.40; 132.13; 142.08; 151.32] (ArC), 143.12 (Triazole C_3), 150.23 (N=CH), 153.79 (Triazole C_5), 174.20 (COO). MS (70 eV): *m/z (%):* 118.11 (24), 129.09 (24), 132.13 (38), 418.13 (M+1, 100), 459.13 (6).

*1-(Morpholine-4-yl-methyl)-3-ethyl-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one (**2b**)*

Yield: 77.4%, m.p. 154 °C. IR: 3077 (C=CH), 1763, 1692 (C=O), 1611, 1578 (C=N), 1235 (COO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.23 (d, 6H, $2CH_3$; *J*=7.20 Hz), 1.24 (t, 3H, CH_2CH_3; *J*=6.80 Hz), 2.59 (t, 4H, CH_2NCH_2; *J*=4.40 Hz), 2.74 (q, 2H, CH_2CH_3; *J*=7.60 Hz), 2.84 (hept, 1H, CH; *J*=7.20 Hz), 3.56 (t, 4H, CH_2OCH_2; *J*=4.40 Hz), 3.84 (s, 3H, OCH_3), 4.55 (s, 2H, NCH_2), 7.23 (d, 1H, ArH; *J*=8.00 Hz), 7.46 (dd, 1H, ArH; *J*=8.00 Hz, 1.60 Hz), 7.58 (d, 1H, ArH; *J*=1.60 Hz), 9.69 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 9.96 ($CH_2\underline{C}H_3$), 18.38 ($\underline{C}H_2CH_3$), 18.72 ($2CH_3$), 33.18 (CH), 49.98 (CH_2NCH_2), 56.03 (OCH_3), 65.96 (NCH_2), 66.03 (CH_2OCH_2), [111.52; 120.56; 123.40; 132.17; 142.07; 151.32] (ArC), 146.83 (Triazole C_3), 150.35 (N=CH), 153.75 (Triazole C_5), 174.19 (COO). MS (70 eV): *m/z (%):* 118.11 (12), 129.10 (44), 132.13 (28), 432.15 (M+1, 100).

*1-(Morpholine-4-yl-methyl)-3-benzyl-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one (**2c**)*

Yield: 72.6%, m.p. 131 °C. IR: 3068 (C=CH), 1758, 1696 (C=O), 1596, 1578 (C=N), 1246 (COO), 747 and 697 (monosubstituted benzenoid ring) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.24 (d, 6H, $2CH_3$; *J*=7.20 Hz), 2.60 (t, 4H, CH_2NCH_2; *J*=4.40 Hz), 2.84 (hept, 1H, CH; *J*=7.20 Hz), 3.57 (t, 4H, CH_2OCH_2; *J*=4.40 Hz), 3.83 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2Ph), 4.59 (s, 2H, NCH_2), 7.21 (d, 1H, ArH; *J*=8.00 Hz), 7.23-7.25 (m, 1H, ArH), 7.31-7.36 (m, 4H, ArH), 7.38 (dd, 1H, ArH; *J*=8.00 Hz, 1.60 Hz), 7.49 (d, 1H, ArH; *J*=1.60 Hz), 9.64 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 18.72 ($2CH_3$), 31.05 (CH_2Ph), 33.17 (CH), 50.00 (CH_2NCH_2), 56.00 (OCH_3), 66.04 (NCH_2+CH_2OCH_2), [110.68; 121.22; 123.34; 132.11; 142.10; 151.29] (ArC), [126.77; 128.50(2C); 128,63(2C); 135.70] (ArC linked C-3), 144.91 (Triazole C_3), 150.24 (N=CH), 153.07 (Triazole C_5), 174.18 (COO). MS (70 eV): *m/z (%):* 118.11 (40), 129.10 (64), 132.13 (60), 494.20 (M+1, 100).

*1-(Morpholine-4-yl-methyl)-3-p-methylbenzyl-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one (**2d**)*

Yield: 72.8 %, m.p. 122 °C. IR: 3072 (C=CH), 1756, 1695 (C=O), 1613, 1579 (C=N), 1243 (COO), 860 (1,4-disubstituted benzenoid ring) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.24 (d, 6H, $2CH_3$; *J*=6.80 Hz), 2.24 (s, 3H, $PhCH_3$), 2.59 (t, 4H, CH_2NCH_2; *J*=4.40 Hz), 2.84 (hept, 1H, CH; *J*=6.80 Hz), 3.57 (t, 4H, CH_2OCH_2; *J*=4.40 Hz), 3.84 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2Ph), 4.58 (s, 2H, NCH_2),7.12 (d, 2H, ArH; *J*=8.00 Hz), 7.21 (d, 1H, ArH; *J*=8.00 Hz), 7.23 (d, 2H, ArH; *J*=8.00 Hz), 7.39 (dd, 1H, ArH; *J*=8.40 Hz, 1.60 Hz), 7.50 (d, 1H, ArH; *J*=1.60 Hz), 9.64 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 18.72 ($2CH_3$), 20.56 ($PhCH_3$), 30.65 (CH_2Ph), 33.17 (CH), 49.99 (CH_2NCH_2), 55.98 (OCH_3), 66.03 (NCH_2+CH_2OCH_2), [110.67; 121.23; 123.36; 132.13; 142.08; 151.28] (ArC), [128.52(2C); 129.07(2C); 132.57; 135.88] (ArC linked C-3), 145.06 (Triazole C_3), 150.24 (N=CH), 153.01 (Triazole C_5), 174.20 (COO). MS (70 eV): *m/z (%):* 118.11 (36), 129.10 (56), 132.13 (36), 508.21 (M+1, 100).

*1-(Morpholine-4-yl-methyl)-3-p-chlorobenzyl-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one (**2e**)*

Yield: 73.8 %, m.p. 125 °C. IR: 3062 (C=CH), 1763, 1697 (C=O), 1594, 1576 (C=N), 1245 (COO), 860 (1,4-disubstituted benzenoid ring) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.24 (d, 6H, $2CH_3$; *J*= 7.20 Hz), 2.59 (t, 4H, CH_2NCH_2; *J*=4.40 Hz), 2.84 (hept, 1H, CH; *J*= 6.80 Hz), 3.57 (t, 4H, CH_2OCH_2; *J*= 4.40 Hz), 3.83 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2Ph), 4.58 (s, 2H, NCH_2), 7.21 (d, 1H, ArH; *J*= 8.00 Hz), 7.36-7.42 (m, 5H, ArH), 7.49 (d, 1H, ArH; *J*=2.00 Hz), 9.65 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 18.72 ($2CH_3$), 30.51 (CH_2Ph), 33.17 (CH), 49.97 (CH_2NCH_2), 56.01 (OCH_3), 66.03 (NCH_2), 66.09 (CH_2OCH_2), [110.77; 121.21; 123.37; 132.06; 142.13; 151.30] (ArC), [128.45 (2C); 130.58 (2C); 131.49; 134.70] (ArC linked C-3), 144.59 (Triazole C_3), 150.33 (N=CH), 153.24 (Triazole C_5), 174.19 (COO). MS (70 eV): *m/z (%):* 118.11 (48), 129.10 (84), 132.10 (48), 528.18 (M+1, 100).

Antioxidant Activity

Chemicals

Butylated hydroxytoluene (BHT), ferrous 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-e** was determined using the method of Oyaizu (1986). 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-e** was estimated by $DPPH^{\cdot}$, by the method of Blois (1958). Briefly, 0.1 mM solution of $DPPH^{\cdot}$ 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 $DPPH^{\cdot}$ concentration (mM) in the reaction medium was calculated from the following calibration curve and determined by linear regression (R: 0.997):

Absorbance = 0.0003 x $DPPH^{\cdot}$ – 0.0174

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

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.

Metal chelating activity

The chelating of ferrous ions by the compounds **2a-e** and references was measured according to the method of Dinis et al., (1994). Briefly, the synthesized compounds (30–60 µg/mL) were added to a 2 mM solution of $FeCl_2$ (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 standing 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

Synthesis

In this study, the structures of five new 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy)benzylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) were identified by using IR, ^{1}H NMR, ^{13}C NMR, and MS data.

Antioxidant Activity

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

Total reductive capability using the potassium ferricyanide reduction method
The reducing power of the compounds **2** was determined. The reductive capabilities of compounds are assessed by the extent of conversion of the Fe^{3+}/ferricyanide complex to the Fe^{2+}/ferrous form. The reducing powers of

the compounds were observed at different concentrations, and results were compared with BHA, BHT and α-tocopherol. The reducing capacity of a compound may serve as a significant indicator for its potential antioxidant activity (Meir, Kanner, Akiri, & Philosoph-Hadas, 1995). The antioxidant activity of a putative antioxidant has been attributed to various mechanisms, among which are prevention chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging (Yildirim, Mavi, & Kara, 2001). In this study, all of the amounts of the compounds showed lower absorbance than blank. Hence, no activities were observed to reduce metal ions complexes to their lower oxidation state or to take part in any electron transfer reaction.

DPPH Radical Scavenging Activity

The model of scavenging the stable DPPH radical model is a widely used method to evaluate antioxidant activities in a relatively short time compared with other methods. The effect of antioxidants on DPPH radical scavenging was thought to be due to their hydrogen donating ability (Baumann J, Wurn G & Bruchlausen V, 1979). DPPH is a stable free radical and accepts an electron or hydrogen radical to become a stable diamagnetic molecule (Soares J R, Dinis T C P, Cunha A P & Almeida L M,1997). The reduction capability of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants. The absorption maximum of a stable DPPH radical in ethanol was at 517 nm. The decrease in absorbance of DPPH radical was caused by antioxidants because of reaction between antioxidant molecules and radical, progresses, which resulted in the scavenging of the radical by hydrogen donation. It is visually noticeable as a discoloration from purple to yellow. Hence, $DPPH^{\cdot}$ is usually used as a substrate to evaluate antioxidative activity of antioxidants (Duh P D, Tu Y Y & Yen G C, 1999). Antiradical activities of compounds and standard antioxidants such as BHT, BHA and α-tocopherol were determined by using $DPPH^{\cdot}$ method. Scavenging effect values of the compounds with BHT, BHA and α-tocopherol at different concentrations are respectively given Figures **1**. The newly synthesized compounds which demonstrate increasing scavenging effect with growing concentration were plotted on the graphs.
The metal chelating effect of these compounds and references decreased in order of α-tocopherol > BHA > BHT > 4b, which were 74.9, 74.3, 65.8, 9.6 (%), at the highest concentration, respectively.

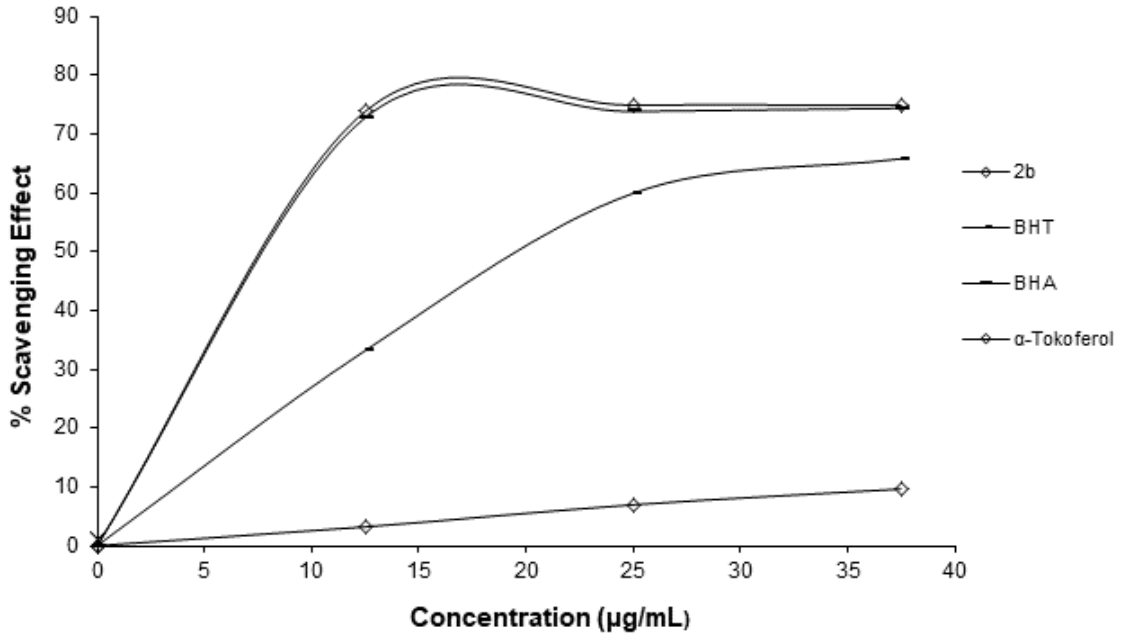


Figure 1. Scavenging effect of compounds 2b, BHT, BHA and α-tocopherol at different concentrations

Ferrous ion chelating activity

The chelating effect towards ferrous ions by the compounds and standards was determined. 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 colour of the complex is decreased. Measurement of colour reduction therefore allows estimation of the chelating activity of the coexisting chelator (Yamaguchi F, Ariga T, Yoshimura Y &

Nakazawa H, 2000). Transition metals have pivotal role in the generation oxygen free radicals in living organism. The ferric iron (Fe^{3+}) is the relatively biologically inactive form of iron. However, it can be reduced to the active Fe^{2+}, depending on condition, particularly pH (Strlic M, Radovic T, Kolar J & Pihlar B, 2002) and oxidized back through Fenton type reactions with the production of hydroxyl radical or Haber-Weiss reactions with superoxide anions. The production of these radicals may lead to lipid peroxidation, protein modification and DNA damage. Chelating agents may not activate metal ions and potentially inhibit the metal-dependent processes (Finefrock, A. E., Bush, A. I., & Doraiswamy, P. M, 2003). Also, the production of highly active ROS such as $O_2^{\cdot-}$, H_2O_2 and OH is also catalyzed by free iron though Haber-Weiss reactions:

$$O^{\cdot}_2 + H_2O_2 \rightarrow O_2 + OH^- + OH^{\cdot}$$

Among the transition metals, iron is known as the most important lipid oxidation pro-oxidant due to its high reactivity. The ferrous state of iron accelerates lipid oxidation by breaking down the hydrogen and lipid peroxides to reactive free radicals via the Fenton reactions:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\cdot}$$

Fe^{3+} ion also produces radicals from peroxides, even though the rate is tenfold less than that of Fe^{2+} ion, which is the most powerful pro-oxidant among the various types of metal ions (Calis I, Hosny M, Khalifa T & Nishibe S,1993). Ferrous ion chelating activities of the compounds **2**, EDTA and α-tocopherol are respectively shown in Figures **2**

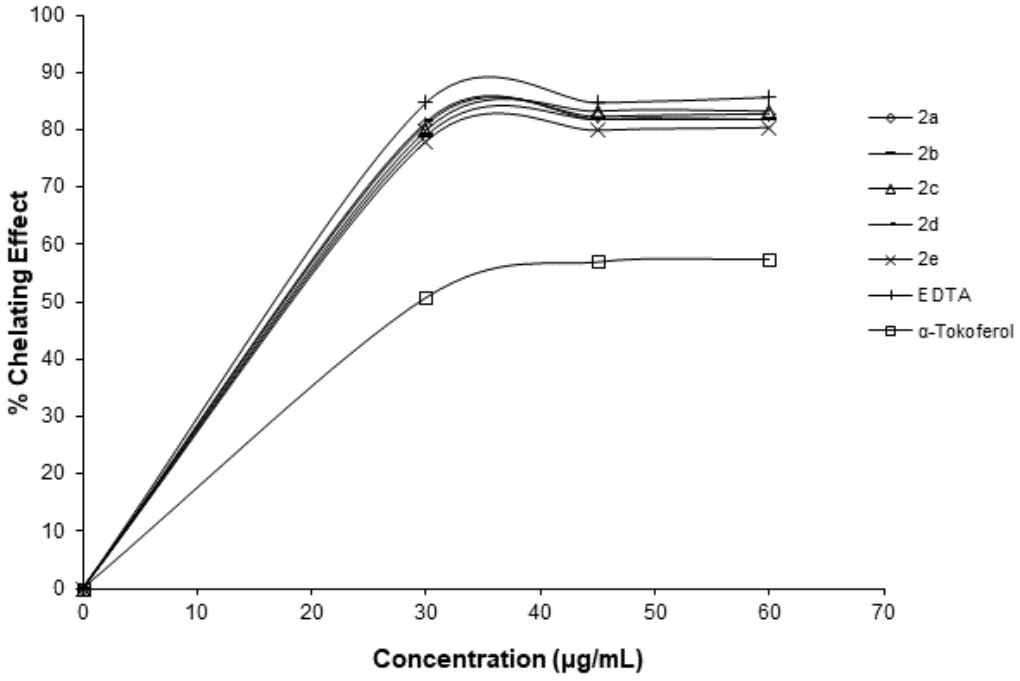


Figure 2. Metal chelating effect of the compounds 2a-e, EDTA and α-tocopherol on ferrous ions

In this study, metal chelating capacity was significant since it reduced the concentrations of the catalyzing transition metal. It was reported that chelating agents that form σ-bonds with a metal are effective as secondary antioxidants because they reduce the redox potential thereby stabilizing the oxidized form of metal ion (Gordon, M., H, 1990). The data obtained from Figures **2** reveal that the compounds demonstrate a marked capacity for iron binding, suggesting that their action as peroxidation protectors may be related to their iron binding capacity.

Conclusion

In this study, the structures of five new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives synthesized from the reactions of 1 type compounds with a benzaldehyde derivative were identified by using IR, ^{1}H NMR, ^{13}C NMR, and MS data. The newly synthesized compounds were screened for their antioxidant activities.

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