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Synthesis and Antioxidant Properties of Some [2-Methoxy-5-(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoates

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ABSTRACT

*In this paper, ten novel [2-Methoxy-5-(3-alkyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoates (**4**) were obtained with the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**) and 3-benzoxy-4-methoxbenzaldehyde (**3**), which has been synthesized by the reaction of 3-hydroxy-4-methoxybenzaldehyde with benzoyl chloride by using triethylamine. The novel synthesized compounds were identified by IR, ^{1}H NMR, ^{13}C NMR and UV spectral data. Besides, the newly synthesized compounds were analysed for their in vitro potential antioxidant capacities in three different techniques. Compounds **4e**, **4g** and **4i** demonstrated significant activity for metal chelating effect.*

Keywords: 4,5-dihydro-1*H*-1,2,4-triazol-5-one, Schiff base, syntheses, antioxidant capacity.

INTRODUCTION

In the last two decades there has been a growing attention in the role of reactive oxygen species (ROS) and nitrogen species (RNS) in food, drugs, and even living system. Therefore, scientists in diverse disciplines have become more curious about naturally-occurring antioxidant as well as in related synthetic derivatives that could supply active components which prohibit or decrease the effect of oxidative stress [1].

External chemicals and internal metabolic processes in the human body or in the food system may generate highly reactive free radicals. At high concentrations, they could be important mediators of damage among cell structures, including lipids and membranes, proteins, and nucleic acids [2]. In this regard, it is important to search for and synthesize new classes of compounds that have antioxidant properties.

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are recorded to own a wide variety of pharmacological activities like antibacterial [3], antioxidant [4], anti-inflammatory [5], antiparasitic [6], analgesic [7], antiviral [8], antitumor [9], anti-HIV [10], antihypertensive and diuretic [11] properties. Besides, a few articles declaring the synthesis of several *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been reported so far [3,4].

In the current paper, in order to determine their possible antioxidant activity, the newly synthesized 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were investigated by using different antioxidant assayss 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 taken using an Electrothermal Melting-point Apparatus in an open glass capillaries and were not corrected. The infrared spectra were recorded on a Perkin Elmer Instruments Spectrum One FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined in deuterated dimethyl sulfoxide with TMS as internal standard using a Bruker spectrophotometer at 200 MHz and 50 MHz, respectively. UV absorption spectra were evaluated in 10 mm quartz cells between 200 and 400 nm using a PG Instruments Ltd T80 UV/Vis spectrometer. Extinction coefficients (ε) are clarified in $L \cdot mol^{-1} \cdot cm^{-1}$.

Synthesis of [2-Methoxy-5-(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoates (4a-j)

3-Hydroxy-4-methoxybenzaldehyde (0.01 mol) dissolved in ethyl acetate (100 mL) was reacted with benzoyl chloride (0.01 mol), and to this solution was slowly mixed triethylamine (0.01 mol) by stirring at 0-5 °C. Stirring was continued for 2 h, and after that the mixture was refluxed for 3 hours and filtered. The filtrate was evaporated *in vacuo*, and the crude product was washed with water and recrystallized from ethanol to afford compound **3** [12]. mp 75-76 °C; IR (υ, cm^{-1}): 2844 and 2760 (CHO), 1731, 1679 (C=O), 1253 (COO), 770 and 698 (monosubstituted benzenoid ring). Then the corresponding compound **2** (0.01 mol) was dissolved in ethanoic acid (20 mL) and by treated 3-benzoxy-4-methoxybenzaldehyde **3** (0.01 mol). The mixture was refluxed for 1.5 hours and then evaporated at 50-55 °C *in vacuo*. A few recrystallizations of the residue from DMSO-H_2O (1:3) gave pure compounds **4a-j** as uncolored crystals.

[2-Methoxy-5-(3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4a)

Yield 94%, mp. 195-196 ºC. IR (KBr) cm^{-1}: 3179 (NH); 1732, 1708 (C=O); 1606 (C=N); 1268 (COO); 771 and 703 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.24 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 7.28 (1H, d, *J* = 8.48 Hz, Ar-H), 7.58-7.63 (2H, m, Ar-H), 7.72-7.76 (3H, m, Ar-H), 8.13 (2H, d, *J* = 7.67 Hz, Ar-H) 9.65 (1H, s, N=CH), 11.80 (1H, s, NH). ^{13}C NMR (50Mz, DMSO-d_6): δ 164.39 (COO), 153.21 (triazole C_5), 151.75 (N=CH), 144.73 (triazole C_3), [154.01, 140.25, 134.59, 130.33 (2C), 130.13, 129.46 (2C), 128.72, 126.93, 121.42, 113.20] (arom-C), 56.93 (OCH_3), 11.53 (CH_3). UV λ_{max} (ε): 304 (19745), 232 (22350), 214 (17236) nm.

[2-Methoxy-5-(3-ethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4b)

Yield 98%, mp. 203-205 ºC. IR (KBr) cm^{-1}: 3166 (NH); 1735, 1704 (C=O); 1607 (C=N); 1273 (COO); 771 and 706 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.18 (3H, t, *J* = 7.37 Hz, CH_3), 2.65 (2H, q, *J* = 7.39 Hz, CH_2), 3.83 (3H, s, OCH_3), 7.30 (1H, d, *J* = 8.19 Hz, Ar-H), 7.58-7.75 (5H, m, Ar-H), 8.14 (2H, d, *J* = 7.33 Hz, Ar-H), 9.65 (1H, s, N=CH), 11.82 (1H, s, NH). ^{13}C NMR (50Mz, DMSO-d_6): δ 164.38 (COO), 153.31 (triazole C_5), 151.88 (N=CH), 148.49 (triazole C_3), [154.01, 140.24, 134.62, 130.77 (2C), 130.34, 129.49 (2C), 128.69, 126.94, 121.41, 113.45] (arom-C), 56.64 (OCH_3), 18.92 ($\underline{CH_2}CH_3$), 10.43 ($CH_2\underline{CH_3}$). UV λ_{max} (ε): 306 (16986), 266 (14127), 234 (18437), 210 (12444) nm.

[2-Methoxy-5-(3-*n*-propyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4c)

Yield 92%, mp. 179-180 ºC. IR (KBr) cm^{-1}: 3173 (NH); 1734, 1703 (C=O); 1604, 1591 (C=N); 1279 (COO); 773 and 707 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.93 (3H, t, *J* = 7.43 Hz, CH_3), 1.66 (2H, sext, *J* = 7.38 Hz, $CH_2\underline{CH_2}CH_3$), 2.63 (2H, t, *J* = 7.32 Hz, $\underline{CH_2}CH_2CH_3$), 3.83 (3H, s, OCH_3), 7.30 (1H, d, *J* = 8.19 Hz, Ar-H), 7.58-7.75 (5H, m, Ar-H), 8.14 (2H, d, *J* = 7.33 Hz, Ar-H), 9.65 (1H, s, N=CH), 11.82 (1H, s, NH). ^{13}C NMR (50Mz, DMSO-d_6): δ 164.38 (COO), 153.50 (triazole C_5), 151.82 (N=CH), 147.34 (triazole C_3), [154.63, 140.25, 134.64, 130.15 (2C), 129.51 (2C), 128.90, 128.62, 126.93, 121.51, 113.53] (arom-C), 56.68 (OCH_3), 27.09 ($\underline{CH_2}$ CH_2CH_3), 19.27 ($CH_2\underline{CH_2}CH_3$), 13.91 ($CH_2CH_2\underline{CH_3}$). UV λ_{max} (ε): 304 (18164), 294 (18373), 268 (17538), 238 (18000), 226 (15900) nm.

[2-Methoxy-5-(3-benzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4d)

Yield 94%, mp. 211-213 ºC. IR (KBr) cm^{-1}: 3162 (NH); 1736, 1706 (C=O); 1603, 1592 (C=N); 1271 (COO); 773 and 703 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (3H, s, OCH_3), 4.05 (2H, s,

CH_2Ph), 7.17-7.33 (6H, m, Ar-H), 7.61-7.80 (5H, m, Ar-H), 8.16 (2H, d, *J* = 7.10 Hz, Ar-H), 9.60 (1H, s, N=CH), 11.95 (1H, s, NH). UV λ_{max} (ε): 308 (19485), 230 (23957), 214 (20319) nm.

[2-Methoxy-5-(3-*p*-methylbenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4e)
Yield 92%, mp. 230-232 ºC. IR (KBr) cm^{-1}: 3154 (NH); 1736, 1707 (C=O); 1615, 1603 (C=N); 1272 (COO); 832 (*p*-disubstituted benzene ring); 765 and 705 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.20 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 4.00 (2H, s, CH_2Ph), 7.06 (2H, d, *J* = 7.87 Hz, Ar-H), 7.18 (2H, d, *J* = 7.99 Hz, Ar-H), 7.30 (1H, d, *J* = 8.58 Hz, Ar-H), 7.62-7.81 (5H, m, Ar-H), 8.13-8.18 (2H, m, Ar-H), 8.13-8.18 (2H, m, Ar-H), 9.60 (1H, s, N=CH), 11.90 (1H, s, NH). UV λ_{max} (ε): 306 (23094), 234 (24208), 214 (19917) nm.

[2-Methoxy-5-(3-*p*-methoxybenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4f)
Yield 93%, mp. 197-198 ºC. IR (KBr) cm^{-1}: 3176 (NH); 1737, 1707 (C=O); 1613, 1589 (C=N); 1272 (COO); 810 (*p*-disubstituted benzene ring); 768 and 704 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.65 (3H, s, $PhOCH_3$), 3.85 (3H, s, OCH_3), 3.96 (2H, s, CH_2Ph), 6.82 (2H, d, *J* = 8.50 Hz, Ar-H), 7.21 (2H, d, *J* = 8.48 Hz, Ar-H), 7.30 (1H, d, *J* = 9.11 Hz, Ar-H), 7.60-7.79 (5H, m, Ar-H), 8.14-8.17 (2H, m, Ar-H), 9.60 (1H, s, N=CH), 11.90 (1H, s, NH). UV λ_{max} (ε): 308 (17698), 266 (15427), 232 (24885), 212 (18198) nm.

[2-Methoxy-5-(3-*p*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4g)
Yield 98%, mp. 217-219 ºC. IR (KBr) cm^{-1}: 3160 (NH); 1735, 1707 (C=O); 1615, 1602 (C=N); 1270 (COO); 814 (*p*-disubstituted benzene ring); 774 and 704 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (3H, s, OCH_3), 4.05 (2H, s, CH_2Ph), 7.27-7.32 (5H, m, Ar-H), 7.59-7.78 (5H, m, Ar-H), 8.13-8.16 (2H, m, Ar-H), 9.60 (1H, s, N=CH), 11.95 (1H, s, NH). ^{13}C NMR (50Mz, DMSO-d_6): δ 164.39 (COO), 153.04 (triazole C_5), 151.71 (N=CH), 146.36 (triazole C_3), [154.05, 140.21, 135.28, 134.65, 131.83, 131.24, 130.35 (2C), 129.52 (2C), 128.94, 128.93 (2C), 128.50 (2C), 126.87, 121.02, 113.49] (arom-C), 56.67 (OCH_3), 30.88 (CH_2Ph). UV λ_{max} (ε): 306 (28947), 234 (30336), 216 (25868) nm.

[2-Methoxy-5-(3-*m*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4h)
Yield 91%, mp. 240-241 ºC. IR (KBr) cm^{-1}: 3154 (NH); 1740, 1707 (C=O); 1614, 1603 (C=N); 1270 (COO); 799 and 702 (*m*-disubstituted benzene ring); 760 and 683 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (3H, s, OCH_3), 4.08 (2H, s, CH_2Ph), 7.24-7.34 (4H, m, Ar-H), 7.43 (1H, s, Ar-H), 7.61-7.80 (5H, m, Ar-H), 8.14-8.17 (2H, m, Ar-H), 9.63 (1H, s, N=CH), 11.98 (1H, s, NH). UV λ_{max} (ε): 308 (19306), 228 (25637), 214 (22500) nm.

[2-Methoxy-5-(3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4i)
Yield 85%, mp. 218-219 ºC. IR (KBr) cm^{-1}: 3169 (NH); 1740, 1707 (C=O); 1612, 1585 (C=N); 1272 (COO); 770 and 705 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (3H, s, OCH_3), 7.31 (1H, d, *J* = 8.56 Hz, Ar-H), 7.48-7.90 (10H, m, Ar-H), 8.12 (2H, d, *J* = 7.14 Hz, Ar-H), 9.60 (1H, s, N=CH), 12.35 (1H, s, NH). ^{13}C NMR (50Mz, DMSO-d_6): δ 164.35 (COO), 154.23 (triazole C_5), 151.86 (N=CH), 145.00 (triazole C_3), [156.63, 140.20, 134.59, 130.50 (2C), 129.46 (2C), 128.95, 128.88, 128.78, 128.40 (2C), 128.33 (2C), 127.16, 126.62, 122.24, 113.64] (arom-C), 56.68 (OCH_3). UV λ_{max} (ε): 306 (13975), 274 (16387), 232 (24368), 212 (17050) nm.

[2-Methoxy-5-(3-cyclopropyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoate (4j)
Yield 93%, mp. 206-208 ºC. IR (KBr) cm^{-1}: 3163 (NH); 1734, 1706 (C=O); 1608, 1591 (C=N); 1274 (COO); 765 and 707 (monosubstituted benzene ring). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.88 (3H, s, OCH_3), 7.34 (1H, d, *J* = 8.54 Hz, Ar-H), 7.63-7.68 (2H, m, Ar-H), 7.77-7.83 (3H, m, Ar-H), 8.16-8.19 (2H, m, Ar-H), 9.70 (1H, s, N=CH), 11.80 (1H, s, NH). UV λ_{max} (ε): 306 (18781), 276 (17382), 234 (22836), 212 (17098) nm.

Antioxidant Activity
Chemicals
Butylated hydroxytoluene (BHT), ferrous chloride, $DPPH^{\cdot}$, 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 **4a-j** was determined using the method of Oyaizu [13] as explained in [4].

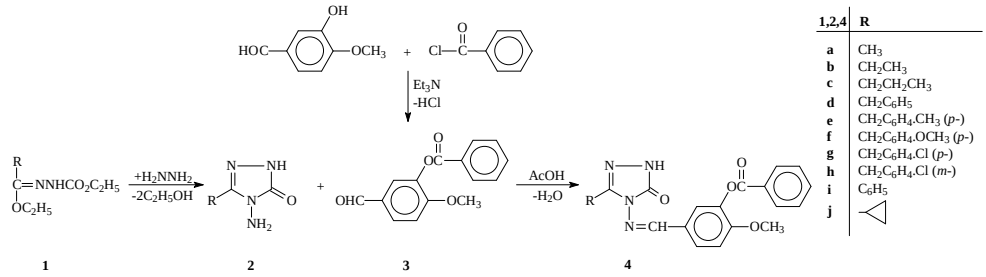
Free radical scavenging activity
Free radical scavenging effect of the compounds **4a-j** was estimated by $DPPH^{\cdot}$, by the method of Blois [14] as explained in [4].

Metal chelating activity
The chelating of ferrous ions by the compounds **4a-j** and references was measured according to the method of Dinis et al. [15] as explained in [4].

RESULTS AND DISCUSSION

In the current paper, [2-methoxy-5-(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoates (**4a-j**) were prepared. The starting compounds **2a-j** were prepared as explained in the literature [16,17]. Compounds **4a-j** were obtained from the reactions of compounds **2a-j** with 3-benzoxy-4-methoxy benzaldehyde **3** [12], which were obtained through the reactions of 3-hydroxy-4-methoxybenzaldehyde including benzoyl chloride with triethylamine (**Scheme 1**).

Ten novel [2-methoxy-5-(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinphenyl benzoates (**4a-j**) were characterized with IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data.



Scheme 1 Synthetic route of compounds 4

Antioxidant activity
The antioxidant capacities of ten newly synthesized compounds **4a-j** were determined. Different processes have been used to identify antioxidant capacities. The processes used in the paper are clarified below:

Reducing power
The compounds **4a-j** were screened for their in-vitro reducing activities by Fe^{3+}-Fe^{2+} transformation in the presence compounds samples. The reducing ability of a compound may serve as a significant indicator of its potential antioxidant capacity. The presence of reductants like antioxidants substances in the antioxidant examples causes the reduction of the Fe^{3+} / ferricyanide complex to the ferrous form. Therefore, the Fe^{2+} may be monitored by measuring the formation of Perl's Prussian blue at 700 nm [18]. 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 [19]. In the paper, all of the concentrations of the compounds showed lower absorbance then reference antioxidants. Hereby, any reductive activities were not observed.

$DPPH^{\cdot}$ radical scavenging activity
The scavenging of stable $DPPH^{\cdot}$ model is an extensively used technique to measure antioxidant activities in a relatively short time comparatively to other techniques. The effect of antioxidants on $DPPH^{\cdot}$ scavenging was thought to be due to their hydrogen donating ability [20]. DPPH is a stable free radical and accepts an electron or hydrogen radical to become a stable diamagnetic molecule [21]. The reduction capacity of DPPH radicals was defined of a decrease in the absorbance at 517 nm induced by antioxidants, resulting a color change from purple to yellow. In the

study, antiradical capacities of compounds **4a-j** and reference antioxidants for instance α-tocopherol BHA and BHT were detected by using DPPH· method. The newly synthesized compounds did not show any ability like a radical scavenger.

Iron binding capacity

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 [22). 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 [23]. The production of these radicals can lead to protein modification, lipid peroxidation and DNA damage. Chelating agents are effective as secondary antioxidants as a result of their potentially inhibition the metal-dependent processes thereby stabilizing the oxidized form of the metal ion [24].

Iron binding activities of the compounds **4**, α-tocopherol, BHT and BHA are shown in Figure **1**. In the current paper, high iron binding capacity of synthesized compounds would be beneficial in retarding metal-chelating oxidation. The data acquired from Figure **1** disclose that the metal chelating effects of the compounds **4e**, **4g** and **4i** were concentration-dependent, the other compounds were not. Thus, the compounds **4e**, **4g** and **4i** demonstrate a marked capacity for iron binding. The metal chelating effect of the compounds and references decreased in order of **4g** > **4e** > BHA > α-tocopherol > **4i** > BHT.

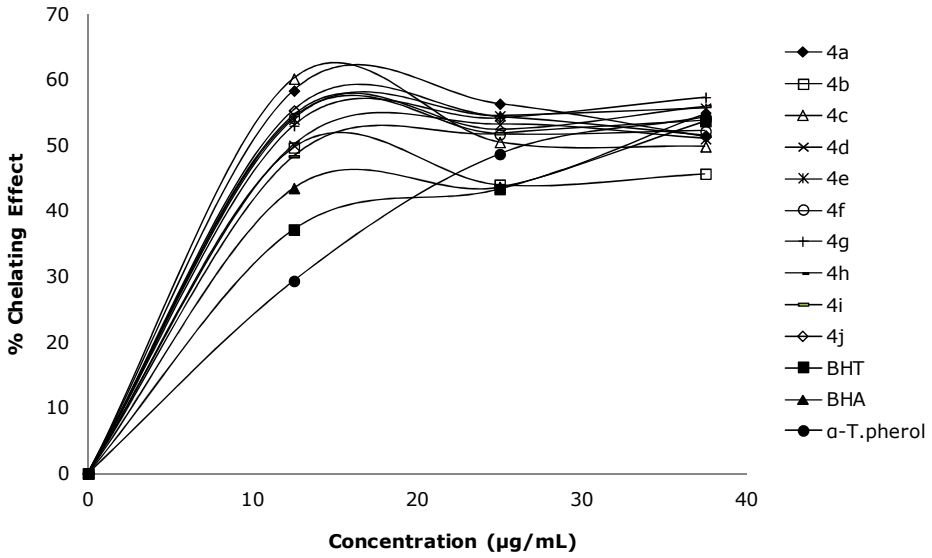


Figure 1. Iron binding effect of diverse amount of the compounds 4a-j, and reference antioxidants

CONCLUSION

New 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were obtained and evaluated for their *in-vitro* antioxidant capacity. Compounds **4e**, **4g** and **4i** 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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