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ORIGINAL PAPER

Synthesis and in vitro antioxidant and antimicrobial activities of novel 3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones, and their *N*-acetyl, *N*-Mannich base derivatives

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Abstract

The reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with 3-methoxy-4-(2-furylcarbonyloxy)-benzaldehyde (**2**) formed 3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**). Moreover, their five *N*-acetyl derivatives were synthesized. Besides, 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **(5)**/1-(4-methylpiperazin-1-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **(6)**/1-(piperidine-4-carboxyamide-1-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **(7)**/*N,N′*-bis-{3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-on-1-yl-methyl}-piperazines **(8)** were obtained by Mannich reaction between compounds **3** and morpholine/N-methylpiperazine/piperidine-4-carboxyamide/piperazine in the presence of formaldehyde. The newly obtained thirty-four compounds were characterized from IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data. Also, these compounds were evaluated for their in vitro antioxidant activity. Furthermore, in vitro antibacterial activity of the compounds was screened against six bacteria.

Keywords Mannich base · Schiff base · 4,5-Dihydro-1*H*-1,2,4-triazole · Antioxidant activity · Antibacterial activity

Introduction

Emerging antibiotic resistance is realized as one of the most important common health issues in the last few decades. The emergence and prevalence of antibiotic-resistant pathogens require an important attempt to define, improve and create novel antibiotics [1]. From another point of view, nanoparticles are progressively being used to target bacteria as an alternative to antibiotics. Nanotechnology may be favorable in treating bacterial infections [2]. Nanoparticles have indicated antibacterial activities against both Gram (−) and Gram (+) bacteria [3, 4].

Moreover, the balance between pro-oxidants and antioxidants reflects the morphological consequences. Oxidative stress can occur with an imbalance in favor of pro-oxidants and/or against antioxidants. This situation may cause cellular dysfunction or death [5]. Many scientists have become more concerned with natural antioxidants and the related synthetic derivative ones that could supply active components to prevent or reduce the effects of oxidative stress [6]. Besides, the synthesis of new heterocyclic molecules has an important role because of their importance in medicinal chemistry.

Heterocyclic compounds with nitrogen and oxygen have been accepted with prominent interest owing to a broad spectrum of their biological activities [7]. Triazole is a five-membered heterocyclic ring with three nitrogen atoms. Various modern drugs that contain a triazole ring are estazolam, triazolam, alprazolam, trazodone, trapidil, rilmazafone, terconazole, hexaconazole, etizolam, and rizatriptan [8]. 1,2,4-Triazoles and their derivatives of

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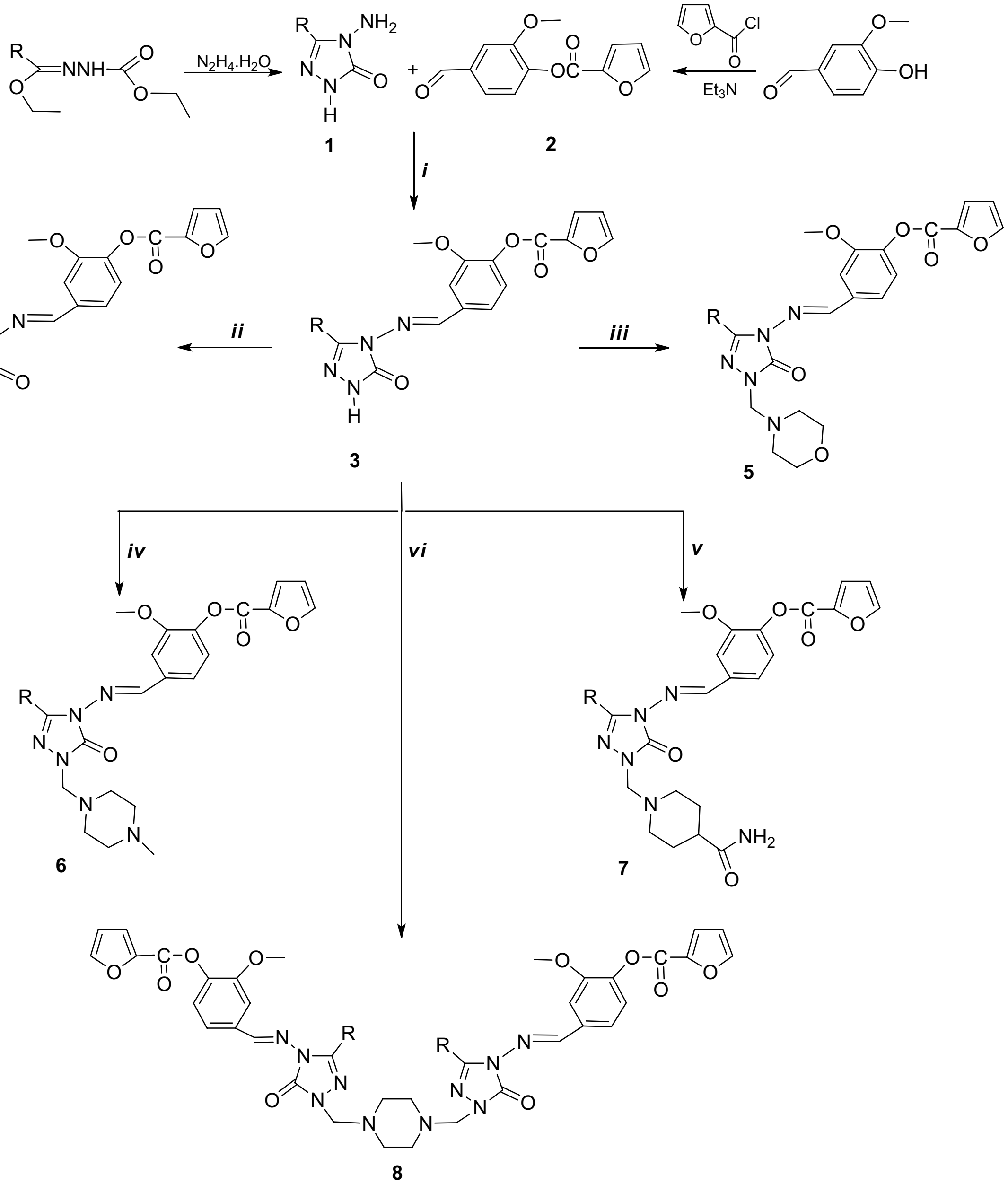
4,5-dihydro-1*H*-1,2,4-triazol-5-ones have a wide range of pharmacological properties [9–14]. Besides, the synthesis of substituted furans is an imperative structural unit in various biologically active and natural products [15, 16]. Furans are found as synthons in both natural product synthesis, medicinal chemistry, and diversity-oriented synthesis [17, 18]. Also, the furan ring has shown better antimicrobial activity compared to other substituents [16, 19].

The three-component condensation reaction between substrates with an active hydrogen atom at least, an amine reagent, and an aldehyde component, leads to the Mannich bases [20]. Two diverse molecules are connected in just one step in this reaction mechanism [21]. Mannich bases acquired from the derivatives of 1,2,4-triazoles have been declared to possess biological properties such as anti-lipase, antioxidant, antifungal, and antibacterial properties [22–24].



a) R = CH_3, b) R = CH_2CH_3, c) R = $CH_2CH_2CH_3$, d) R = $CH_2C_6H_5$, e) R = $CH_2C_6H_4CH_3$ (*p*-),
f) R = $CH_2C_6H_4OCH_3$ (*p*-), g) R = $CH_2C_6H_4Cl$ (*p*-), h) R = $CH_2C_6H_4Cl$ (*m*-), i) R = C_6H_5

i) AcOH, reflux; ***ii***) Ac_2O, reflux; ***iii***) CH_2O, morpholine, reflux; ***iv***) CH_2O, N-methyl-piperazine, reflux; ***v***) CH_2O, pyridine-4-carboxamide, reflux; ***vi***) CH_2O, piperazine, reflux

Scheme 1 The synthesis of compounds **1**–**8**

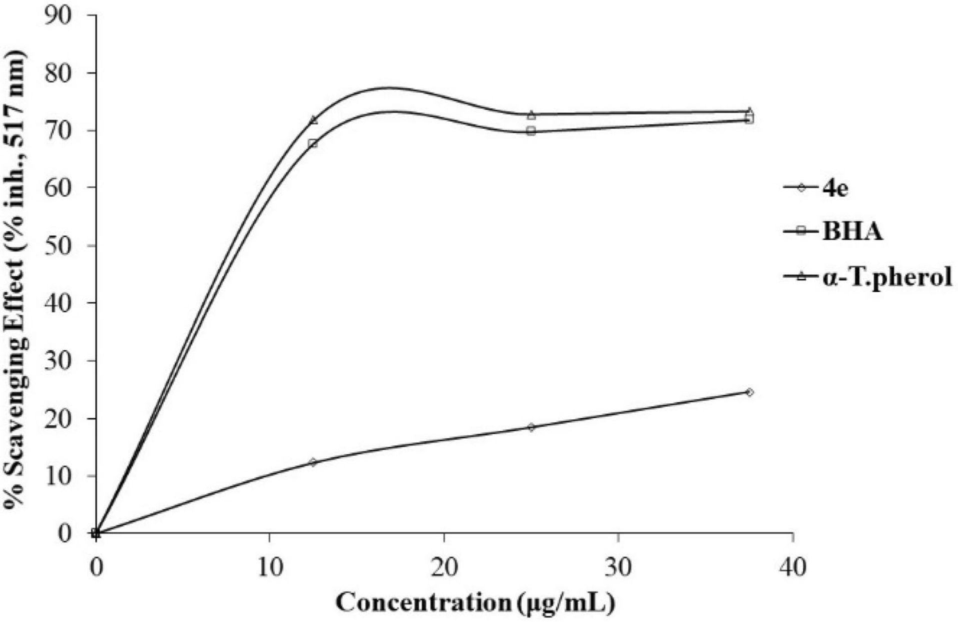


Fig. 1 Scavenging activity of compounds **4**, α-tocopherol and BHA at different concentrations

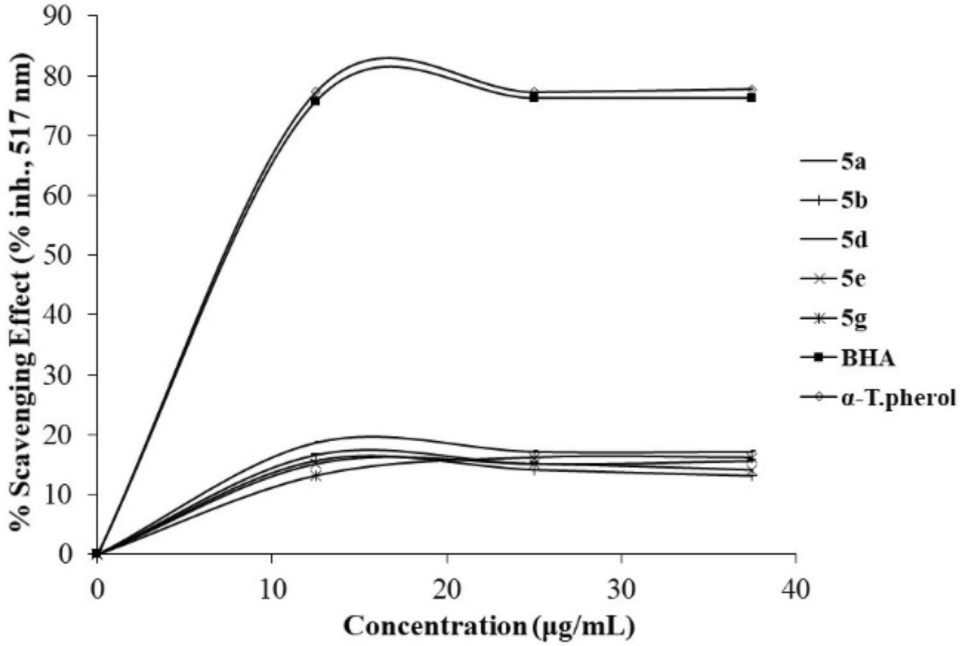


Fig. 2 Scavenging activity of compounds **5**, α-tocopherol and BHA at different concentrations

Results and discussion

Chemistry

In the paper, the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with 3-methoxy-4-(2-furylcarbonyloxy)-benzaldehyde (**2**), that was acquired by the reaction of 3-methoxy-4-hydroxybenzaldehyde and 2-furoyl chloride with triethylamine were given 9 new 3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**). After that, **3a, 3b, 3d, 3e, 3g** compounds treated with acetic anhydride and compounds **4** were obtained. Finally, **3a, 3b, 3d, 3e, 3g** compounds were treated

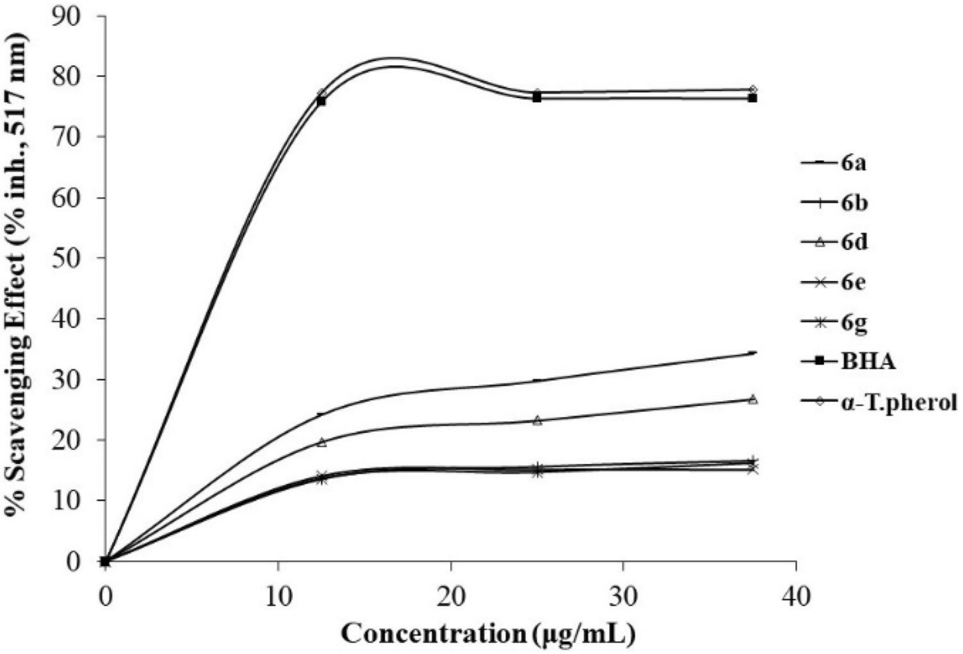


Fig. 3 Scavenging activity of compounds **6**, α-tocopherol and BHA at different concentrations

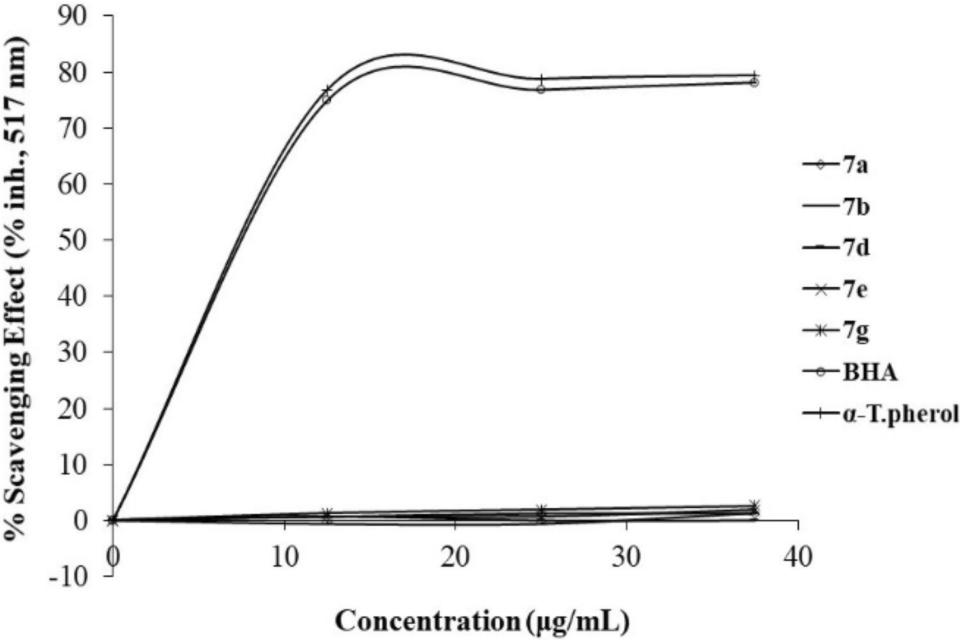


Fig. 4 Scavenging activity of compounds **7**, α-tocopherol and BHA at different concentrations

morpholine/N-methylpiperazine/piperidine-4-carboxyamide/piperazine by Mannich reaction, and compounds **5a**, **5b**, **5d**, **5e**, **5g**/compounds **6a**, **6b**, **6d**, **6e**, **6g** compounds **7a**, **7b**, **7d**, **7e**, **7g** compounds **8a**, **8b**, **8d**, **8e**, **8g** obtained respectively, in the presence of formaldehyde (Scheme 1).

3-Alkyl(Aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **(1a–i)** were formed by the reactions of the corresponding ester ethoxycarbonylhydrazones with an aqueous solution of hydrazine hydrate as represented [25, 26].

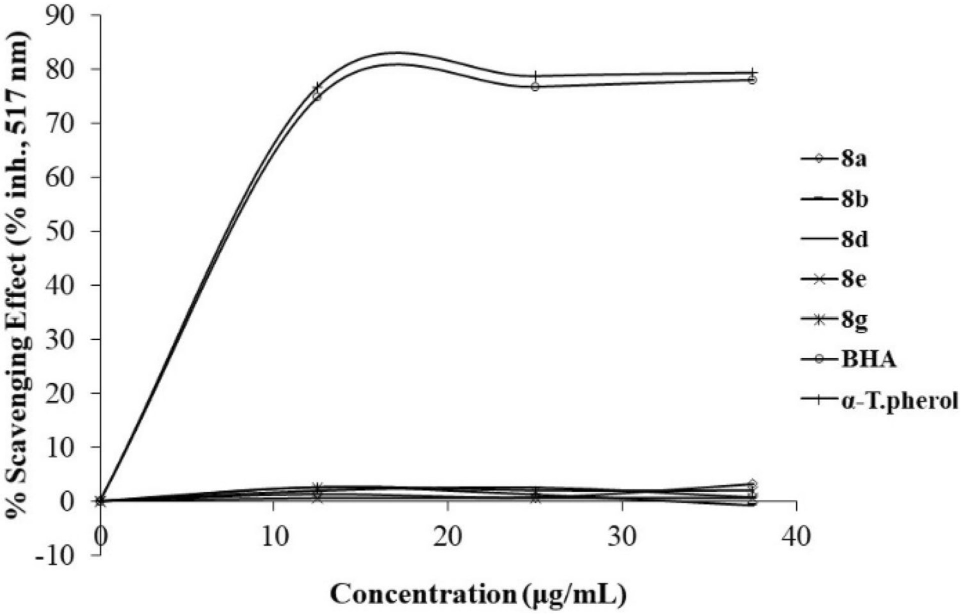


Fig. 5 Scavenging activity of compounds **8**, α-tocopherol and BHA at different concentrations

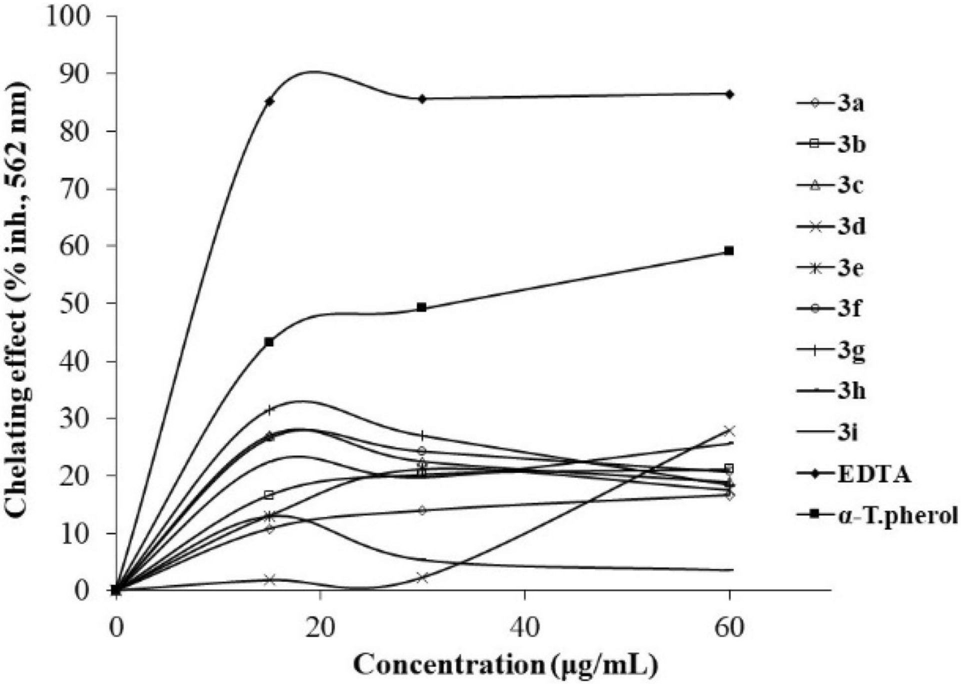


Fig. 6 The chelation activity of the compounds **3**, α-tocopherol and EDTA

Newly synthesized nine Schiff base compounds (**3**), five *N*-acetyl derivative compounds (**4**), twenty *N*-Mannich base derivatives (**5**, **6**, **7,** and **8**) of **3** type compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and also MS data.

Antioxidant activity

Thirty-four newly synthesized compounds **3a–i**, **4a**, **4b**, **4d**, **4e**, **4g**, **5a**, **5b**, **5d**, **5e**, **5g**, **6a**, **6b**, **6d**, **6e**, **6g**, **7a**, **7b**, **7d**, **7e**, **7g**, **8a**, **8b**, **8d**, **8e**, and **8g** were investigated for their

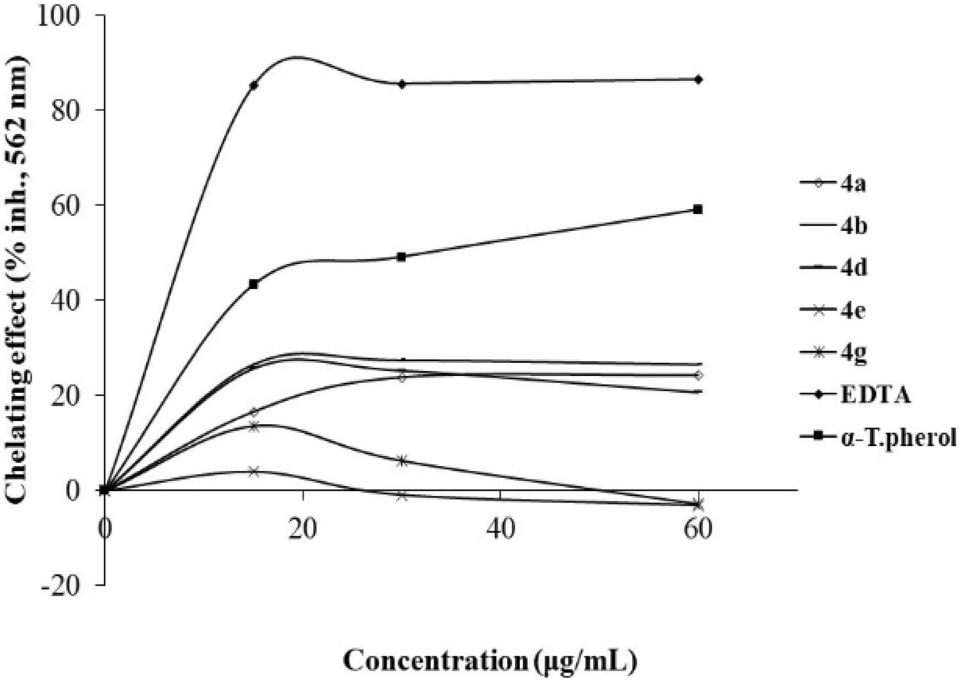


Fig. 7 The chelation activity of the compounds **4**, α-tocopherol and EDTA

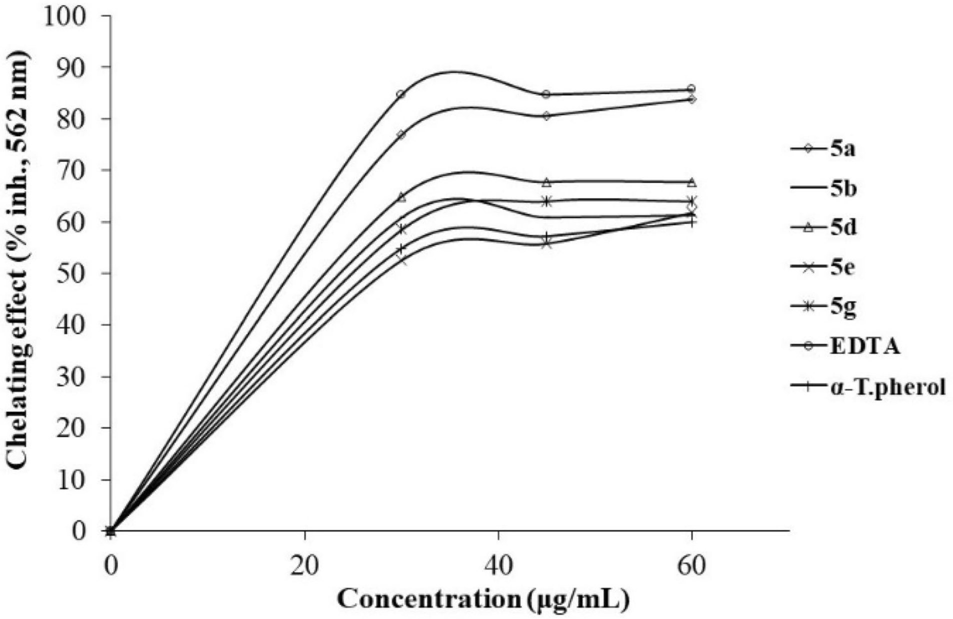


Fig. 8 The chelation activity of the compounds **5**, α-tocopherol and EDTA

antioxidant properties by three methods. First, the reductive abilities of the obtained compounds were determined by the extent of conversion of the ferricyanide complex (Fe^{3+}) to ferrous form (Fe^{2+}). The new compounds were examined for their reducing power at different concentrations, and the results were compared with α-tocopherol and butylated hydroxytoluene (BHT). The reductive ability of one compound may serve as an important indicator of its potential antioxidant effect [27]. Hereby, all the amounts of the

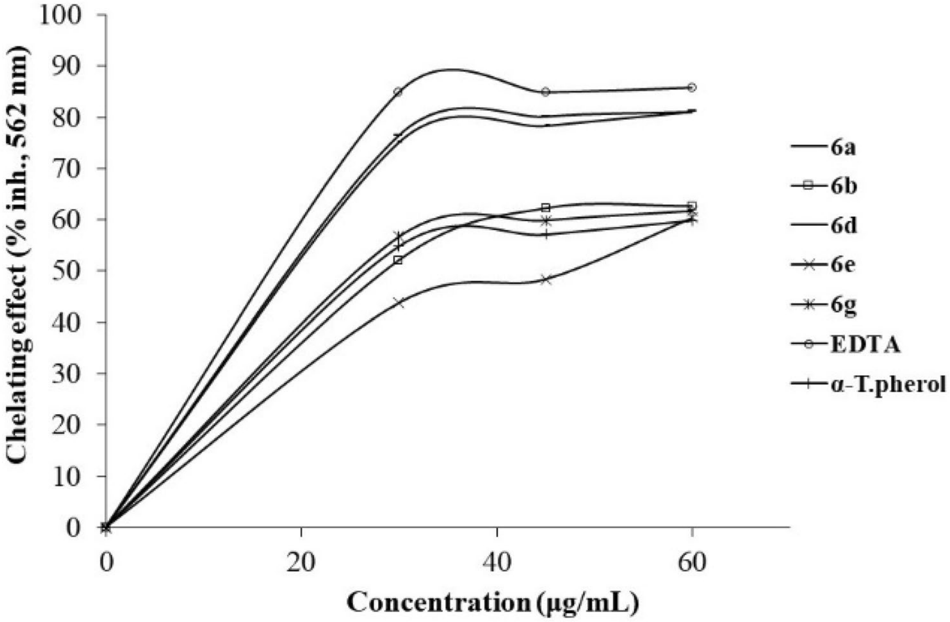


Fig. 9 The chelation activity of the compounds **6**, α-tocopherol and EDTA

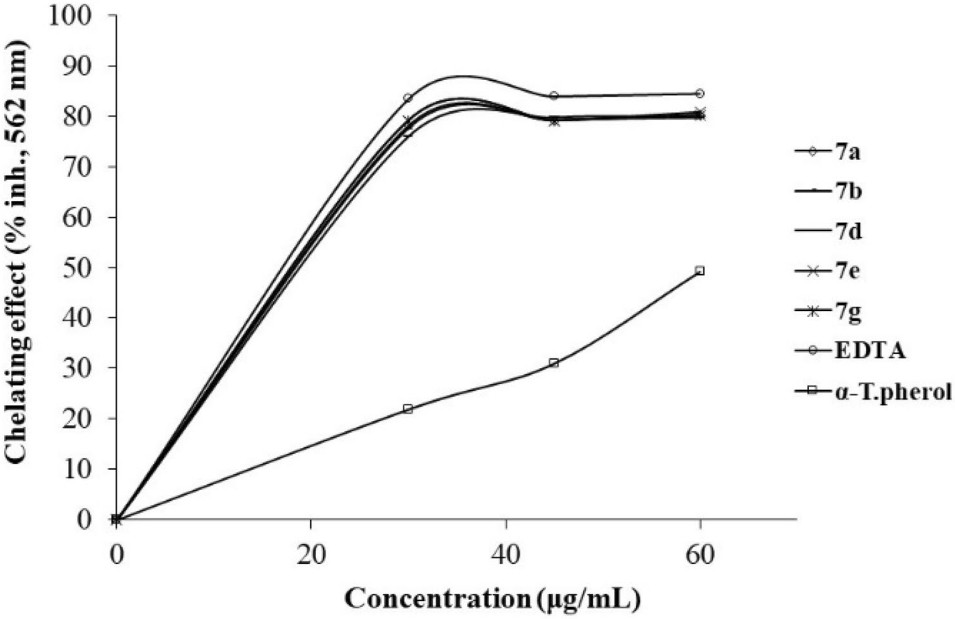


Fig. 10 The chelation activity of the compounds **7**, α-tocopherol and EDTA

compounds indicated lower absorbance than α-tocopherol and BHT. Therefore, no reducing power was observed.

Secondly, the activity of antioxidant molecules on 1,1-diphenyl-2-picryl-hydrazyl (DPPH) scavenging was evaluated. It was regarding the ability of their hydrogen donating [28]. DPPH is described as a stable nitrogen-centered free radical and becomes a stable, diamagnetic molecule while accepts a hydrogen radical or an electron. [29]. The reductive ability of DPPH radical was characterized by a decrease in its absorbance induction of antioxidants. The

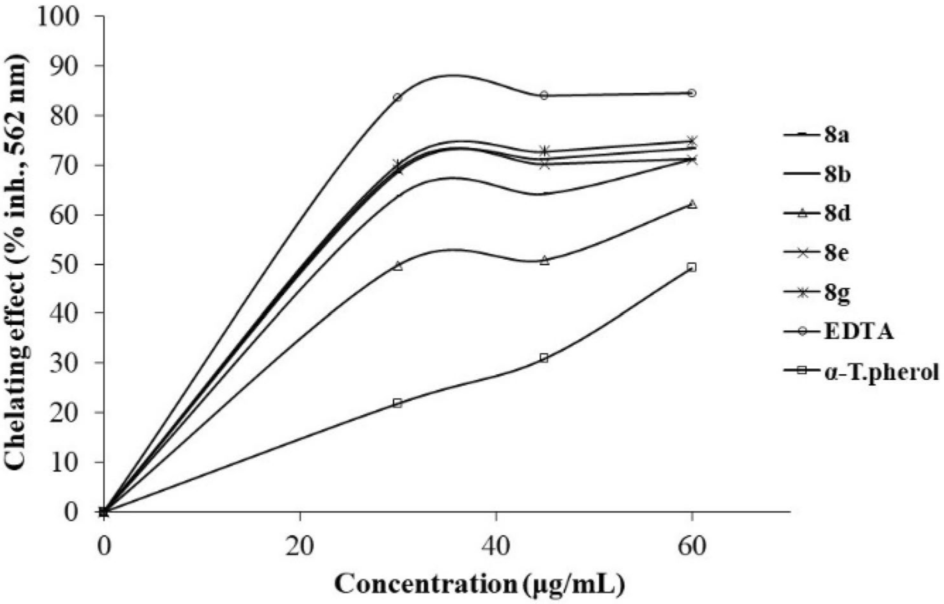


Fig. 11 The chelation activity of the compounds **8**, α-tocopherol and EDTA

absorption maximum of the stable DPPH in ethanol was at 517 nm. It is noticeable as the color changes from purple to yellow. Therefore, the stable radical serves as a substrate to determine the antioxidative effect of antioxidant molecules [30]. The activities of the novel compounds, α-tocopherol and butylated hydroxyanisole (BHA) were evaluated and the scavenging effect of the compounds (**4–8**), and references are shown in Figs. 1, 2, 3, 4 and 5. The newly synthesized compounds (**3**, **4**, **7**, **8**), except compound **4e**, did not show any activity as radical scavengers. The other ones (**4e**, **5**, **6**) showed low activity.

Finally, the chelation activity against ferrous ions by the new compounds and the standard antioxidants was evaluated. Ferrozine can establish complexes with Fe^{2+}. The complex production is interrupted with the result that the red color of the complex is decreased in the presence of the chelating agents. Hence, measuring the color reduction permits the evaluation of the chelation effect of the coexisting chelator [31]. Transition metals have an important part in the formation of oxygen-free radicals in alive organisms. Fe^{3+} is the relatively biologically inactive form of iron. Nevertheless, it can be reduced to the active one, Fe^{2+}, depending on the conditions, particularly pH [32] and oxidized back through the Haber–Weiss reactions with superoxide anions or the Fenton-type reactions with the production of hydroxyl radical. The formation of the radical molecules may cause serious health problems. The chelating agents may not initialize the metal ions and hinder the metal-dependent processes potentially [33].

The compounds with two or more functional groups, including -SH, -OH, -COOH, $–PO_3H_2$, C=O, –O–, –S–, $–NR_{2,}$ in a favorable function-structure configuration may demonstrate a chelating effect [34–36]. In this regard, L-carnitine may have the chelating effect with carboxylate and hydroxyl functional groups [36]. In the study, chelation activity of the new compounds (**3–8**), α-tocopherol and ethylenediaminetetraacetic acid (EDTA) are given in Figs. 6, 7, 8, 9, 10 and 11, respectively. The data released from the figures show that the metal chelation effects of the compounds **3a**, **3b**, **3d**, **4a**, **5–8** were concentration-dependent. Finally, the Mannich bases have a significant capacity for iron-binding at all.

Antimicrobial activity

The results are shown in Table 1. When the antibacterial effects of Schiff and Mannich Bases synthesized in the study are examined, it is seen that the antibacterial effects obtained from Schiff Bases are lower. Microbiology results are not promising for Schiff bases (**3**, **4**),

Table 1 Antimicrobial effect of the new compounds (**3**–**8**)

	Microorganisms, inhibition zone (mm) and effect value											
	B. subtilis		*B. cereus*		*P. aeruginosa*		*K. pneumoniae*		*S. aureus*		*E. coli*	
Compound	Zone	Effect	Zone	Effect	Zone	Effect	Zone	Effect	Zone	Effect	Zone	Effect
Schiff Bases												
3a	−	−	−	−	11	+	8	+	−	−	−	−
3b	−	−	−	−	14	++	11	++	−	−	10	+
3c	−	−	−	−	−	−	13	++	−	−	−	−
3d	−	−	−	−	11	++	8	+	−	−	−	−
3e	−	−	−	−	−	−	12	++	−	−	−	−
3f	−	−	−	−	13	++	10	+	−	−	8	+
3g	−	−	−	−	−	−	10	+	−	−	−	−
3h	−	−	−	−	−	−	−	−	−	−	−	−
3i	−	−	−	−	13	++	8	+	−	−	−	−
4a	9	+	−	−	11	++	−	−	−	−	9	+
4b	12	++	−	−	−	−	−	−	−	−	8	+
4d	10	−	−	−	−	−	−	−	−	−	−	−
4e	11	++	−	−	12	++	8	+	−	−	11	++
4g	12	++	−	−	10	−	−	−	−	−	9	−
Mannich Bases												
5a	***19***	**+++**	***17***	**+++**	13	++	16	++	***21***	**+++**	14	++
5b	***21***	**+++**	***19***	**+++**	14	++	***19***	**+++**	***18***	**+++**	15	++
5d	***17***	**+++**	15	++	11	++	15	++	***20***	**+++**	11	++
5e	13	++	12	++	11	++	9	+	−	−	11	++
5g	14	++	14	++	−	−	−	−	13	++	9	+
6a	***21***	**+++**	***19***	**+++**	−	−	***21***	**+++**	***24***	**+++**	14	++
6b	***23***	**+++**	14	++	16	++	***20***	**+++**	***23***	**+++**	10	+
6d	***20***	**+++**	15	++	13	++	***19***	**+++**	***21***	**+++**	11	++
6e	***20***	**+++**	11	++	−	−	***18***	**+++**	***19***	**+++**	−	−
6g	***23***	**+++**	9	+	−	−	***17***	**+++**	***17***	**+++**	16	++
7a	***23***	**+++**	16	++	***19***	**+++**	***18***	**+++**	***19***	**+++**	***17***	**+++**
7b	***22***	**+++**	***19***	**+++**	15	++	***19***	**+++**	***22***	**+++**	***19***	**+++**
7d	***18***	**+++**	***17***	**+++**	***17***	**+++**	15	++	***17***	**+++**	14	++
7e	***19***	**+++**	15	++	13	++	14	++	13	++	13	++
7g	***24***	**+++**	13	++	12	++	16	++	14	++	14	++
8a	8	+	11	++	13	++	−	−	−	−	12	++
8b	11	++	11	++	11	++	14	++	8	+	12	++
8d	8	+	10	+	15	++	−	−	−	−	13	++
8e	10	+	11	++	11	++	12	++	8	+	12	++
8g	8	+	11	++	11	++	12	++	8	+	−	−
Amp	33	+++	36	+++	36	+++	35	+++	37	+++	34	+++
Neo	17	+++	17	+++	17	+++	16	++	13	++	16	++
Str	12	++	12	++	12	++	11	++	21	+++	10	+

Scale of effect values according to zone diameter: (−): < 5.5 mm; (+): 5.5–10 mm; (++): 11–16 mm; (+++): ≥ 17 mm [37]

Table 2 Experimental and MS data of compounds **3**

No	Yield (%)	M.p. (°C)	MS
3a	99	210	*m/z:* [M^{+} + 1] 343.00
3b	98	188	*m/z:* [M^{+} + 1] 357.03
3c	95	203	*m/z:* [M^{+} + 1] 371.08
3d	98	224	*m/z:* [M^{+} + 1] 419.06
3e	97	225	*m/z:* [M^{+} + 1] 433.04
3f	97	195	*m/z:* [M^{+} + 1] 449.08
3g	97	209	*m/z:* [M^{+}] 453.00
3h	95	207	*m/z:* [M^{+}] 452.97
3i	95	242	*m/z:* [M^{+} + 1] 405.08

especially against *Bacillus cereus* and *Staphylococcus aureus*. The data also reveals that the results are better for Mannich bases (**5**–**8**), especially compounds (**5**–**7**). The active ones are emphasized with italic bold characters in Table 1. The effect value of Ampicillin on the bacteria used is 33 mm and above. This value could not be obtained in any of the synthesized Schiff and Mannich Bases. However, values close to or higher than the effect obtained were found especially for neomycin and streptomycin. These results were frequently obtained, especially in Mannich Bases. The zone diameter values of the **6** and **7** type compounds against *B. subtilis*, *K. pneumonia* and *S. aureus* bacteria seem to dominate the values obtained from neomycin and streptomycin. When the evaluation is made in general, it is concluded that Mannich Bases are in the group of compounds that show antibacterial effects. While no effect was obtained for *B. cereus* and *S. aureus* in Schiff Bases, a significant increase in effect in Mannich Bases supports this result.

Experimental

Chemistry

Chemicals used in the paper were acquired from Aldrich, Merck AG, Fluka. The melting point data were determined in open capillary tubes by an Electrothermal Melting-point Apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer Instruments Spectrum One FT-IR spectrophotometer. ^{1}H/^{13}C NMR spectra were performed in deuterated dimethyl sulfoxide (DMSO-d$_{6}$) with tetramethylsilane (TMS) at 400 MHz/100 MHz using a Bruker Ultrashield spectrophotometer. Electrospray ionization mass spectrometry (ESI–MS) was recorded on a TSQ Quantum Access Max Triple Stage Quadrupole Mass Spectrometer.

General method for the synthesis of 3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3) 0.01 mol 3-Methoxy-4-hydroxybenzaldehyde dissolved in 30 mL ethyl acetate was reacted with 0.01 mol 2-furoyl chloride. Then 0.01 mol triethylamine in 10 mL ethyl acetate was added by stirring slowly to the solution at 0–5 °C. It proceeded for 2 h; after that, the mixture was refluxed for 3 h, then filtered. Afterward, the filtrate was evaporated, the crude product was washed with water, then recrystallized by ethyl alcohol to acquire compound **2** [38]. Yield: 94%; m.p. 104–105 °C, (lit. 25: m.p. 103–104 °C): White solid; IR (cm^{-1}): 1268 (COO), 1682, 1737 (C=O), 2745 and 2863 (CHO); ^{1}H NMR (400 MHz), DMSO-d_{6}, δ (ppm): 10.02 (s, 1H, CHO), 8.14 (m, 1H), 7.68 (d, $J = 1.60$ Hz, 1H), 7.66 (d, $J = 1.60$ Hz, 1H), 7.64–7.62 (m, 1H), 7.53 (d, $J = 8.00$ Hz, 1H), 6.83

Table 3 IR spectrum data (cm^{-1}) of compounds **3**

No	ν_{NH}	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{\text{1,4-disubstitue benzene ring}}$	$\nu_{\text{1,3-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
3a	3174	1699, 1740	1608	1262	–	–	–
3b	3273	1748, 1691	1583, 1601	1263	–	–	–
3c	3155	1699, 1738	1577	1267	–	–	–
3d	3138	1699, 1731	1597	1262	–	–	702 and 767
3e	3156	1701, 1731	1596	1268	827	–	–
3f	3165	1703, 1729	1608	1247	836	–	–
3g	3186	1707, 1735	1599	1263	832	–	–
3h	3138	1702, 1730	1596	1267	–	789 and 883	–
3i	3151	1697, 1742	1583, 1609	1258	–	–	691 and 766

Table 4 ^{1}H-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **3**

No	CH$_3$	OCH$_3$	CH$_2$	CH$_2$	CH$_2$Ph	Aromatic H	N=CH	NH
3a	2.31(s)	3.86(s)	–	–	–	6.83–6.82 (m, 1H), 7.39 (d, $J=8.08$ Hz, 1H), 7.51 (d, $J=8.20$ Hz, 1H), 7.61 (m, 1H), 7.64 (m, 1H), 8.13(s, 1H)	9.76(s)	11.86(s)
3b	1.23(t, $J=7.20$ Hz)	3.85(s)	2.72(q, $J=7.20$ Hz)	–	–	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.38 (d, 1H, $J=8.00$ Hz), 7.51 (dd, 1H, $J=8.00$, 1.60 Hz), 7.61 (dd, 1H, $J=3.60$, 0.80 Hz), 7.63 (d, 1H, $J=2.00$ Hz), 8.12 (dd, 1H, $J=2.00$, 0.80 Hz)	9.75(s)	11.88(s)
3c	0.97(t, $J=7.20$ Hz)	3.86(s)	1.71(sext, $J=7.20$ Hz)	2.67(t, $J=7.20$ Hz)	–	6.82 (dd, 1H, $J=3.60$, 2.00 Hz), 7.39 (d, 1H, $J=8.40$ Hz), 7.51 (dd, 1H, $J=8.40$, 2.00 Hz), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 7.63 (d, 1H, $J=2.00$ Hz), 8.12 (dd, 1H, $J=2.00$, 0.80 Hz)	9.75(s)	11.89(s)
3d	–	3.85(s)	–	–	4.09(s)	6.81 (dd, 1H, $J=3.60$, 1.60 Hz), 7.21–7.25 (m, 1H), 7.30–7.38 (m, 5H), 7.44 (dd, 1H, $J=8.00$, 1.60 Hz), 7.55 (d, 1H, $J=2.00$ Hz), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 8.12 (dd, 1H, $J=2.00$, 0.80 Hz)	9.71(s)	12.03(s)
3e	2.25(s)	3.85(s)	–	–	4.03(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.12 (d, 2H, $J=8.00$ Hz), 7.23 (d, 2H, $J=8.00$ Hz), 7.37 (d, 1H, $J=8.40$ Hz), 7.44 (dd, 1H, $J=8.40$, 2.00 Hz), 7.55 (d, 1H, $J=1.60$ Hz), 7.60 (dd, 1H, $J=2.00$, 0.80 Hz), 8.13 (dd, 1H, $J=1.60$, 0.80 Hz)	9.70(s)	12.00(s)
3f	3.71(s)	3.86(s)	–	–	4.01(s)	6.82 (dd, 1H, $J=3.60$, 2.00 Hz), 6.88 (d, 2H, $J=8.80$ Hz), 7.27 (d, 2H, $J=8.80$ Hz), 7.38 (d, 1H, $J=8.00$ Hz), 7.46 (dd, 1H, $J=8.40$, 1.60 Hz), 7.58 (d, 1H, $J=1.60$ Hz), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 8.13 (dd, 1H, $J=2.00$, 0.80 Hz)	9.71(s)	11.99(s)
3g	–	3.85(s)	–	–	4.10(s)	6.81 (dd, 1H, $J=3.60$, 2.00 Hz), 7.36–7.38 (m, 5H), 7.44 (dd, 1H, $J=8.40$, 2.00 Hz), 7.54 (d, 1H, $J=1.60$ Hz), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 8.12 (dd, 1H, $J=2.00$, 0.80 Hz)	9.71(s)	12.04(s)
3h	–	3.86(s)	–	–	4.11(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.30–7.34 (m, 4H), 7.37 (d, 1H, $J=8.00$ Hz), 7.44 (dd, 1H, $J=8.40$, 1.60 Hz), 7.57 (d, 1H, $J=1.60$ Hz), 7.60 (dd, 1H, $J=3.60$, 1.60 Hz), 8.12 (dd, 1H, $J=1.60$, 0.80 Hz)	9.71 s)	12.05(s)
3i	–	3.83(s)	–	–	–	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.40 (d, 1H, $J=8.40$ Hz), 7.49 (dd, 1H, $J=8.40$, 2.00 Hz), 7.53–7.57 (m, 3H), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 7.92–7.95 (m, 2H), 8.13 (dd, 1H, $J=2.00$, 0.80 Hz)	9.71(s)	12.40(s)

(dd, $J=3.60$, 1.60 Hz, 1H), 3.90 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz), DMSO-d_6, δ (ppm): 191.90 (CHO), 155.24 (COO), [151.61 (C), 148.09 (CH), 143.73 (C), 142.39 (C), 135.57 (C), 123.86 (CH), 123.58 (CH), 120.71 (CH), 112.02 (CH), 111.99 (CH)] (Ar–C), 56.06 (OCH$_3$). To obtain compounds **3a**–**i**; 0.01 mol corresponding compound **1**, was dissolved in 20 mL ethanoic acid then treated with 0.01 mol 3-methoxy-4-(2-furylcarbonyloxy)-benzaldehyde (**2**). After

Table 5 ^{13}C-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **3**

No	COO	N=CH	Triazole C$_5$	Triazole C$_3$	Aromatic C	C-3 Aromatic C	Aliphatic C
3a	155.97	151.78	149.30	144.79	111.99, 113.30, 120.95, 121.01, 124.09, 133.32, 141.30, 143.02, 151.68, 153.21	–	11.57(CH_3), 56.46(OCH_3)
3b	155.49	152.80	151.32	148.07	111.60, 112.82, 120.36, 120.52, 123.64, 132.88, 140.83, 142.54, 148.81, 151.34	–	9.99($CH_2\underline{CH_3}$), 18.49($\underline{CH_2}CH_3$), 55.99(OCH_3)
3c	155.49	152.73	151.27	146.95	111.63, 112.80, 120.28, 120.51, 123.65, 132.89, 140.83, 142.54, 148.80, 151.31	–	13.49 ($CH_2CH_2\underline{CH_3}$), 18.96 ($CH_2\underline{CH_2}CH_3$), 26.69 ($\underline{CH_2}CH_2CH_3$), 55.96(OCH_3)
3d	155.48	152.22	151.20	146.22	110.77, 112.82, 120.53, 121.04, 123.60, 132.82, 140.88, 142.54, 148.81, 152.29	126.71, 128.48 (2C), 128.70 (2C), 135.88	31.20(CH_2Ph), 55.97(OCH_3)
3e	155.41	152.07	151.12	146.29	110.67, 112.74, 120.45, 120.97, 123.52, 132.76, 140.79, 142.46, 148.74, 151.21	128.49 (2C), 128.94 (2C), 132.67, 135.70	20.50($PhCH_3$), 30.74(CH_2Ph), 55.87(OCH_3)
3f	155.50	152.22	151.22	146.53	110.85, 112.82, 120.53, 121.00, 123.61, 132.85, 140.88, 142.54, 148.81, 151.30	113.86 (2C), 127.61, 129.77 (2C), 158.06	30.33(CH_2Ph), 54.98($PhCH_3$-*p*), 55.98(OCH_3)
3g	155.48	152.38	151.18	145.89	110.84, 112.83, 120.54, 121.04, 123.62, 132.77, 140.91, 142.53, 148.82, 151.30	128.40 (2C), 130.64 (2C), 131.40, 134.87	30.49(CH_2Ph), 55.99(OCH_3)
3h	155.39	152.28	151.07	145.63	110.65, 112.74, 120.45, 121.05, 123.52, 132.86, 140.85, 142.44, 148.74, 151.23	128.68, 127.40, 128.68, 130.21, 132.67, 138.22	30.64(CH_2Ph), 55.90(OCH_3)
3i	155.48	155.17	151,31	144.57	111.42, 112.83, 120.56, 120.86, 123.75, 132.71, 141.03, 142.51, 148.83, 151.34	126.56, 128.01 (2C), 128.50 (2C), 130.15	55.90(OCH_3)

Table 6 Experimental and MS data of compounds **4**

No	Yield (%)	M.p. (°C)	MS
4a	75	214	*m/z:* [M$^+$ +1] 384.98
4b	94	192	*m/z:* [M$^+$ +1] 399.05
4d	76	171	*m/z:* M$^+$ +1] 461.13
4e	90	194	*m/z:* [M$^+$ +1] 475.09
4g	90	196	*m/z:* [M$^+$] 494.96

that, the mixture was refluxed for 1.5 h and evaporated in vacuo at 50–55 °C. Various recrystallizations of the residue from ethanol formed the compounds as uncolored crystals. Experimental and MS data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **3** are presented in Tables 2, 3, 4 and 5, respectively.

Table 7 IR Spectrum data (cm^{-1}) of compounds **4**

No	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{\text{1,4-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
4a	1735, 1722	1618	1251	–	–
4b	1742, 1697	1609, 1583	1258	–	–
4d	1737, 1699	1613	1230	–	745 and 703
4e	1736, 1697	1609	1230	806	–
4g	1736, 1697	1609	1230	806	–

Table 8 ^{1}H-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **4**

No	CH_3	OCH_3	CH_2	$COCH_3$	CH_2Ph	Aromatik H	N=CH
4a	2.38(s)	3.86(s)	–	2.51(s)	–	6.80–6.83 (m, 1H), 7.41 (d, 1H, *J* = 8.00 Hz), 7.55 (dd, 1H, *J* = 8.00, 1.60 Hz), 7.60 (m, 1H), 7.68 (d, 1H, *J* = 1.60 Hz), 8.12 (dd, 1H, *J* = 3.60, 1.20 Hz)	9.62(s)
4b	1.26(t, *J* = 7.20 Hz)	3.86(s)	2.79(q, *J* = 7.20 Hz)	2.50(s)	–	6.82 (dd, 1H, *J* = 3.60, 1.60 Hz), 7.41 (d, 1H, *J* = 8.00 Hz), 7.54 (dd, 1H, *J* = 8.40, 1.60 Hz), 7.60 (dd, 1H, *J* = 3.60, 0.80 Hz), 7.67 (d, 1H, *J* = 1.60 Hz), 8.12 (dd, 1H, *J* = 2.00, 0.80 Hz)	9.62(s)
4d	–	3.85(s)	–	2.52(s)	4.18(s)	6.82 (dd, 1H, *J* = 3.60, 1.60 Hz), 7.23–7.27 (m, 1H), 7.32–7.35 (m, 3H), 7.38–7.41 (m, 2H), 7.47 (dd, 1H, *J* = 8.00, 1.60 Hz), 7.57 (d, 1H, *J* = 2.00 Hz), 7.60 (dd, 1H, *J* = 3.60, 0.80 Hz), 8.13 (dd, 1H, *J* = 1.60, 0.80 Hz)	9.59(s)
4e	2.25(s)	3.85(s)	–	2.52(s)	4.12(s)	6.82 (dd, 1H, *J* = 3.60, 1.60 Hz), 7.13 (d, 2H, *J* = 7.60 Hz), 7.27 (d, 2H, *J* = 8.00 Hz), 7.39 (d, 1H, *J* = 8.00 Hz), 7.48 (dd, 1H, *J* = 8.40, 1.60 Hz), 7.57 (d, 1H, *J* = 1.60 Hz), 7.60 (dd, 1H, *J* = 3.60, 0.40 Hz), 8.13 (dd, 1H, *J* = 1.60, 0.80 Hz)	9.58(s)
4g	–	3.84(s)	–	2.51(s)	4.19(s)	6.82 (dd, 1H, *J* = 3.60, 1.60 Hz), 7.38–7.44 (m, 5H), 7.48 (dd, 1H, *J* = 8.40, 2.00 Hz), 7.56 (d, 1H, *J* = 1.60 Hz), 7.60 (dd, 1H, *J* = 3.60, 0.80 Hz), 8.13 (dd, 1H, *J* = 1.60, 0.80 Hz)	9.59 (s)

Table 9 ^{13}C-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **4**

No	$\underline{C}OCH_3$	COO	N=CH	Triazole C_5	Triazole C_3	Aromatic C	C-3 Aromatic C	$CO\underline{C}H_3$	Aliphatic C
4a	168.66	155.63	154.96	151.01	146.73	111.70, 112.84, 120.58, 121.03, 123.73, 132.31, 141.27, 142.50, 147.87, 151.39	–	23.45	11.22 (CH_3), 56.02 (OCH_3)
4b	165.99	154.44	152.80	150.22	148.10	111.75, 112.84, 120.59, 120.91, 123.76, 132.34, 141.26, 142.49, 148.87, 151.39	–	23.48	9.44 ($CH_2\underline{CH_3}$), 18.58 ($\underline{CH_2}CH_3$), 56.05 (OCH_3)
4d	165.99	155.44	154.20	148.87	148.03	110.90, 112.85, 120.60, 121.58, 123.71, 132.31, 141.28, 142.48, 148.25, 151.35	126.96, 128.53 (2C), 128.90 (2C), 134.78	23.55	31.14 (CH_2Ph), 56.03 (OCH_3)
4e	165.99	155.44	154.15	148.87	148.02	110.88, 112.85, 120.59, 121.60, 123.71, 132.33, 141.27, 142.49, 148.39, 151.35	128.78 (2C), 129.09 (2C), 131.68, 136.06	23.54	20.60 ($PhCH_3$), 30.77 (CH_2Ph), 56.01 (OCH_3)
4g	165.96	155.43	154.27	148.87	147.95	110.94, 112.85, 120.60, 121.57, 123.72, 132.27, 141.30, 142.48, 148.02, 151.36	128.45 (2C), 130.84 (2C), 131.66, 133.81	23.53	30.44 (CH_2Ph), 56.04 (OCH_3)

Table 10 Experimental and MS data of compounds **5**

No	Yield (%)	M.p. (°C)	MS
5a	70	170	*m/z:* [M^+ +1] 442.10
5b	72	138	*m/z:* [M^+ +1] 456.14
5d	80	127	*m/z:* [M^+ +1] 518.13
5e	93	169	*m/z:* [M^+] 532.17
5g	91	157	*m/z:* [M^+] 552.11

General method for the synthesis of 1-acetyl-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4) 0.01 mol Compound **3**, was refluxed with 15 mL acetic anhydride for half an hour. The addition of 50 mL absolute ethyl alcohol, then the mixture was refluxed for an hour. After that, the process of evaporating the solution in vacuo at 40–45 °C and various crystallization of the residue, formed compounds **4**. Experimental and MS data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **4** are presented in Tables 6, 7, 8 and 9, respectively.

General method for the synthesis of 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (5) Compound **3** (5 mmol) was dissolved in absolute ethyl alcohol, then formaldehyde (10 mmol, 37%) and morpholine (6 mmol) was added to the solution. After that, the mixture was refluxed for 4 h and left at RT overnight. Then cooling the mixture, the solid was acquired by filtration and washed with cold ethyl alcohol. Recrystallization from ethyl alcohol yielded colorless crystals, compounds **5**. Experimental and MS data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **5** are presented in Tables 10, 11, 12 and 13, respectively.

General method for the synthesis of 1-(4-methylpiperazin-1-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (6) 5 mmol Compound **3** was dissolved in 100 mL ethyl alcohol, then N-methylpiperazine (0.015 mol) and formaldehyde (10 mmol, 37%) was added. The mixture was then refluxed for 3 h and left overnight at RT. The solid was then filtered, crystallized from ethyl alcohol. Recrystallization and purification in vacuo by drying yielded uncolored crystals, compounds **6**. Experimental and MS data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **6** are presented in Tables 14, 15, 16 and 17, respectively.

General method for the synthesis of 1-(piperidine-4-carboxyamide-1-yl-methyl)-3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (7) 5 mmol Compound **3** was dissolved in

Table 11 IR Spectrum data (cm^{-1}) of compounds **5**

No	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{1,4\text{-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
5a	1734, 1702	1602	1265	–	–
5b	1730, 1694	1612	1293	–	–
5d	1728, 1705	1577	1273	–	748 and 696
5e	1744, 1697	1611	1269	816	–
5g	1745, 1697	1611	1271	823	–

Table 12 ^{1}H-NMR Spectrum data (DMSO-d_6, δ/ppm) of Compounds **5**

No	CH_3	CH_2NCH_2	CH_2OCH_2	OCH_3	NCH_2N	CH_2	CH_2Ph	Aromatic H	N=CH
5a	2.34(s)	2.59(t, $J=4.40$ Hz)	3.57(t, $J=4.40$ Hz)	3.85(s)	4.55(s)	–	–	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.38 (dd, 1H, $J=8.00$, 3.60 Hz), 7.50–7.53 (m, 1H), 7.60 (d, 1H, $J=3.60$ Hz), 7.64 (dd, 1H, $J=6.00$, 1.60 Hz), 8.12 (d, 1H, $J=0.80$ Hz)	9.73(s)
5b	1.24(t, $J=7.20$ Hz)	2.59(t, $J=4.40$ Hz)	3.57(t, $J=4.40$ Hz)	3.85(s)	4.56(s)	2.76(q, $J=7.20$ Hz)	–	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.40 (d, 1H, $J=8.40$ Hz), 7.52 (dd, 1H, $J=8.40$, 1.60 Hz), 7.60 (d, 1H, $J=4.00$ Hz), 7.65 (d, 1H, $J=1.60$ Hz), 8.13 (d, 1H, $J=1.60$ Hz)	9.73(s)
5d	–	2.61(t, $J=4.40$ Hz)	3.58(t, $J=4.40$ Hz)	3.85(s)	4.60(s)	–	4.13(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.24–7.25 (m, 1H), 7.31–7.38 (m, 5H), 7.44 (dd, 1H, $J=8.40$, 1.60 Hz), 7.55 (d, 1H, $J=1.60$ Hz), 7.60 (d, 1H, $J=3.60$ Hz), 8.13 (d, 1H, $J=1.60$ Hz)	9.68(s)
5e	2.25(s)	2.60(t, $J=4.40$ Hz)	3.57(t, $J=4.40$ Hz)	3.85(s)	4.59(s)	–	4.07(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.13 (d, 2H, $J=8.00$ Hz), 7.24 (d, 2H, $J=8.00$ Hz), 7.38 (d, 1H, $J=8.00$ Hz), 7.45 (d, 1H, $J=8.40$ Hz), 7.56 (d, 1H, $J=1.60$ Hz), 7.60 (dd, 1H, $J=3.60$, 0.40 Hz), 8.12 (d, 1H, $J=1.60$ Hz)	9.67(s)
5g	–	2.60(t, $J=4.40$ Hz)	3.57(t, $J=4.40$ Hz)	3.85(s)	4.59(s)	–	4.14(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.37–7.40 (m, 5H), 7.44–7.46 (m, 1H), 7.55 (d, 1H, $J=1.60$ Hz), 7.60 (d, 1H, $J=3.60$ Hz), 8.13 (d, 1H, $J=0.80$ Hz)	9.69 (s)

Table 13 ^{13}C-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **5**

No	COO	N=CH	Triazole C$_5$	Triazole C$_3$	Aromatic C	C-3 Aromatic C	NCH$_2$N	CH$_2$OCH$_2$	CH$_2$NCH$_2$	Aliphatic C
5a	155.46	153.58	150.22	143.14	111.62, 112.80, 120.50, 120.72, 123.65, 132.65, 140.90, 142.56, 148.79, 151.21	–	66.03	65.93	49.97	10.95 (CH$_3$), 56.05 (OCH$_3$)
5b	155.46	153.57	150.35	146.85	111.67, 112.80, 120.50, 120.59, 123.67, 132.68, 141.02, 142.56, 148.79, 151.38	–	66.03	65.97	49.98	9.88 (CH$_2\underline{CH_3}$), 18.39 ($\underline{CH_2}$CH$_3$), 56.03 (OCH$_3$)
5d	155.45	152.96	150.24	144.93	110.85, 112.80, 120.51, 121.25, 123.63, 132.62, 141.06, 142.56, 148.79, 151.33	126.79, 128.52 (2C), 128.64 (2C), 135.71	66.04	66.04	50.00	31.04 (CH$_2$Ph), 56.01 (OCH$_3$)
5e	155.46	152.91	150.23	145.08	110.54, 112.80, 120.51, 121.16, 123.63, 132.63, 141.06, 142.55, 148.60, 151.83	128.52 (2C), 129.09 (2C), 132.57, 135.69	66.04	66.04	50.00	20.57 (PhCH$_3$), 30.64 (CH$_2$Ph), 55.99 (OCH$_3$)
5g	155.45	153.11	150.22	144.61	110.90, 112.81, 120.52, 121.24, 123.65, 132.56, 141.08, 142.54, 148.81, 151.54	128.47 (2C), 130.59 (2C), 131.50, 134.71	66.09	66.03	49.97	30.34 (CH$_2$Ph), 56.02 (OCH$_3$)

Table 14 Experimental and MS data of compounds **6**

No	Yield (%)	M.p. (°C)	MS
6a	91	Oil	*m/z:* [M$^+$ +1] 455.11
6b	71	75	*m/z:* [M$^+$ +1] 469.15
6d	71	Oil	*m/z:* [M$^+$ +1] 531.17
6e	73	94	*m/z:* [M$^+$] 545.16
6g	71	103	*m/z:* [M$^+$] 565.12

100 mL ethyl alcohol, then piperidine-4-carboxyamide (0.05 mol) and formaldehyde (10 mmol, 37%) was added. The mixture was then refluxed for 3 h and left overnight at RT. The solid was then filtered and crystallized from ethyl alcohol. Recrystallization and purification *in vacuo* by drying yielded uncolored crystals, compounds **7**. Experimental data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **7** are presented in Tables 18, 19, 20 and 21, respectively.

General method for the synthesis of *N,N′*-bis-{3-alkyl(aryl)-4-[3-methoxy-4-(2-furylcarbonyloxy)-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-on-1-yl-methyl}-piperazines (8) 10 mmol Compound **3** was dissolved in 100 mL ethyl alcohol, then piperazine (5 mmol) and formaldehyde (15 mmol, 37%) was added. The mixture was then refluxed for 3 h, left overnight at RT. The solid was then filtered, crystallized using ethyl alcohol. Recrystallization and purification in vacuo by drying yielded uncolored crystals, compounds **8**. Experimental data, IR, ^{1}H NMR, ^{13}C NMR spectral data of the compounds **8** are presented in Tables 22, 23, 24 and 25, respectively.

Antioxidant activity

BHT was purchased from E. Merck. α-Tocopherol, ferrous chloride, DPPH radical, BHA, 3-(2-pyridyl)-5,6-bis(phenylsulfonic acid)-1,2,4-triazine (ferrozine), EDTA, and trichloroacetic acid (TCA) were purchased from Sigma-Aldrich.

The reducing effect of the new compounds was evaluated using the Oyaizu method [39]. Radical scavenging effect of the new compounds was evaluated by Blois [40]. The chelation effect of new compounds was determined by Dinis et al. [41]. The methodology used in the study was explained in the literature [23].

Antimicrobial activity

All yeast and bacterial strains [*Bacillus Substilis* (ATCC 11774)*, Staphylococcus aureus* (ATCC 6538), *Bacillus Cereus* (ATCC 11778)*, Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 4352), *Pseudomonas aeruginosa* (ATCC 27853)] were purchased from the company

Table 15 IR Spectrum data (cm^{-1}) of compounds **6**

No	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{\text{1,4-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
6a	1725, 1704	1598	1288	–	–
6b	1730, 1703	1577	1233	–	–
6d	1738, 1703	1577	1286	–	749 and 704
6e	1727, 1698	1574	1286	815	–
6g	1740, 1696	1575	1267	820	–

Table 16 ^{1}H-NMR Spectrum data (DMSO-d_6, δ/ppm) of compounds **6**

No	NCH_3	CH_3	$2CH_2$	OCH_3	NCH_2N	CH_2	CH_2Ph	Aromatic H	N=CH
6a	2.16(s)	2.34(s)	2.31(m) 2.60(m)	3.86(s)	4.55(s)	–	–	6.82 (dd, 1H, $J=3.60$, 2.00 Hz), 7.39 (d, 1H, $J=8.40$ Hz), 7.52 (d, 1H, $J=8.40$ Hz), 7.61 (dd, 1H, $J=3.60$, 0.80 Hz), 7.65 (d, 1H, $J=2.00$ Hz), 8.13 (d, 1H, $J=1.60$ Hz)	9.74(s)
6b	2.13(s)	1.24(t, $J=7.20$ Hz)	2.31(m) 2.60(m)	3.85(s)	4.56(s)	2.75(q, $J=7.20$ Hz)	–	6.81–6.83 (m, 1H), 7.39 (d, 1H, $J=8.00$ Hz), 7.52 (d, 1H, $J=8.40$ Hz), 7.60–7.61 (m, 1H), 7.65 (m, 1H), 8.12–8.13 (m, 1H)	9.73(s)
6d	2.15(s)	–	2.32(m) 2.63(m)	3.85(s)	4.60(s)	–	4.12(s)	6.81–6.83 (m, 1H), 7.31–7.43 (m, 7H), 7.55–7.56 (m, 1H), 7.60 (m, 1H), 8.13 (s, 1H)	9.68(s)
6e	2.14(s)	2.25(s)	2.30(m) 2.61(m)	3.85(s)	4.59(s)	–	4.06(s)	6.81–6.83 (m, 1H), 7.13 (d, 2H, $J=8.00$ Hz), 7.23 (d, 2H, $J=8.00$ Hz), 7.37 (d, 1H, $J=8.40$ Hz), 7.45 (d, 1H, $J=8.40$ Hz), 7.56 (m, 1H), 7.59–7.60 (m, 1H), 8.12–8.13 (m, 1H)	9.67(s)
6g	2.15(s)	–	2.32(m) 2.61(m)	3.85(s)	4.59(s)	–	4.14(s)	6.81–6.83 (m, 1H), 7.37–7.41 (m, 5H), 7.55 (d, 1H, $J=8.00$ Hz), 7.54–7.55 (m, 1H), 7.60 (d, 1H, $J=3.60$ Hz), 8.12–8.13 (m, 1H)	9.70 (s)

Table 17 ^{13}C-NMR Spectrum data (DMSO-d_6, δ/ppm) of compounds **6**

No	COO	N=CH	Triazole C_5	Triazole C_3	Aromatic C	C-3 Aromatic C	NCH_2N	$2CH_2$	NCH_3	Aliphatic C
6a	155.44	153.37	150.33	144.53	111.58, 112.75, 120.43, 120.66, 123.66, 132.65, 141.02, 142.59, 148.73, 151.82	–	65.73	49.34 54.54	45.61	10.89 (CH_3), 56.00 (OCH_3)
6b	155.46	153.49	150.31	146.71	111.68, 112.78, 120.48, 120.57, 123.65, 132.69, 141.01, 142.57, 148.77, 151.36	–	65.77	49.41 54.50	45.70	10.01 ($CH_2\underline{CH_3}$), 18.38 ($\underline{CH_2}CH_3$), 56.02 (OCH_3)
6d	155.45	152.83	150.20	144.78	111.20, 112.76, 120.46, 121.22, 123.59, 132.63, 141.06, 142.57, 148.75, 151.33	126.76, 128.50 (2C), 128.60 (2C), 135.72	65.88	49.38 54.46	45.62	31.04 (CH_2Ph), 55.98 (OCH_3)
6e	155.46	152.84	150.19	144.94	110.85, 112.80, 120.51, 121.24, 123.62, 132.65, 141.04, 142.55, 148.79, 151.33	128.50 (2C), 129.08 (2C), 132.60, 135.88	65.88	49.44 54.52	45.72	20.56 ($PhCH_3$), 30.64 (CH_2Ph), 55.99 (OCH_3)
6g	155.45	153.06	150.18	144.47	110.93, 112.80, 120.51, 121.23, 123.63, 132.57, 141.09, 142.55, 148.79, 151.34	128.47 (2C), 130.56 (2C), 131.49, 134.72	65.92	49.38 54.47	45.66	30.34 (CH_2Ph), 56.02 (OCH_3)

of Microbiological Environmental Protection Laboratories (France). The method used in the paper was a simple susceptibility screening test using the agar well diffusion method [37, 42]. The methodology used in the study was explained in the literature [23]. Antibacterial activity was determined by the measurement of the inhibition zone against the test organism. Neomycin (Neo., X3360), Ampicillin (Amp., X3261), and Streptomycin (Str., X3385) standard antibiotic

Table 18 Experimental data of compounds **7**

No	Yield (%)	M.p. (°C)
7a	73	194
7b	74	192
7d	82	201
7e	84	210
7g	89	214

Table 19 IR Spectrum data (cm^{-1}) of compounds **7**

No	ν_{NH2}	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{1,4\text{-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
7a	3365 and 3184	1742, 1701, 1646	1605	1268	–	–
7b	3413 and 3202	1733, 1692, 1648	1615	1273	–	–
7d	3335 and 3185	1735, 1713, 1648	1602	1269	–	763 and 705
7e	3396 and 3194	1740, 1696, 1643	1618	1236	838	–
7g	3398 and 3194	1741, 1696, 1641	1616	1236	825	–

Table 20 ^{1}H-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **7**

No	CH_3	Piperidine H	OCH_3	NCH_2N	CH_2	CH_2Ph	NH_2	Aromatic H	N=CH
7a	2.33(s)	1.49–1.56 (m, 2H), 1.66–1.69 (m, 2H), 1.94–1.98 (m, 1H), 2.26–2.30 (m, 2H), 2.90–2.93 (m, 2H)	3.85(s)	4.54(s)	–	–	6.72(s) 7.16(s)	6.81 (dd, 1H, $J=3.60$, 2.00 Hz), 7.39 (d, 1H, $J=8.00$ Hz), 7.52 (dd, 1H, $J=8.00$, 1.60 Hz), 7.60 (d, 1H, $J=3.20$ Hz), 7.65 (d, 1H, $J=1.60$ Hz), 8.12 (d, 1H, $J=0.80$ Hz)	9.73(s)
7b	1.24(t, $J=7.20$ Hz)	1.50–1.55 (m, 2H), 1.66 (m, 2H), 1.93 (m, 1H), 2.28 (m, 2H), 2.91–2.94 (m, 2H)	3.85(s)	4.55(s)	2.75 (q, $J=7.20$ Hz)	–	6.71(s) 7.16(s)	6.81 (dd, 1H, $J=3.60$, 1.60 Hz), 7.39 (d, 1H, $J=8.40$ Hz), 7.52 (dd, 1H, $J=8.40$, 1.60 Hz), 7.60 (dd, 1H, $J=3.60$, 0.80 Hz), 7.65 (d, 1H, $J=2.00$ Hz), 8.12 (dd, 1H, $J=1.60$, 0.80 Hz)	9.73(s)
7d	–	1.53 (m, 2H), 1.67 (m, 2H), 1.98 (m, 1H), 2.30 (m, 2H), 2.93–2.96 (m, 2H)	3.84(s)	4.59(s)	–	4.12(s)	6.72(s) 7.17(s)	6.82 (dd, 1H, $J=3.60$, 2.00 Hz), 7.24 (m, 1H), 7.31–7.38 (m, 5H), 7.44 (dd, 1H, $J=8.40$, 1.60 Hz), 7.55 (d, 1H, $J=1.60$ Hz), 7.59 (dd, 1H, $J=3.60$, 0.40 Hz), 8.12 (dd, 1H, $J=2.00$, 0.80 Hz)	9.68(s)
7e	2.25(s)	1.50 (m, 2H), 1.67 (m, 2H), 1.98 (m, 1H), 2.27–2.30 (m, 2H), 2.92–2.95 (m, 2H)	3.85(s)	4.59(s)	–	4.06(s)	6.72(s) 7.13(s)	6.82 (dd, 1H, $J=3.60$, 1.60 Hz), 7.13 (d, 2H, $J=8.00$ Hz), 7.23 (d, 2H, $J=8.40$ Hz), 7.37 (d, 1H, $J=8.40$ Hz), 7.44 (dd, 1H, $J=8.00$, 1.60 Hz), 7.56 (d, 1H, $J=2.00$ Hz), 7.59 (dd, 1H,; $J=3.60$, 0.80 Hz), 8.12 (dd, 1H, $J=1.60$, 0.80 Hz)	9.67(s)
7g	–	1.53–1.54 (m, 2H), 1.67 (m, 2H), 1.95 (m, 1H), 2.29–2.30 (m, 2H), 2.92–2.94 (m, 2H)	3.84(s)	4.58(s)	–	4.14(s)	6.73(s) 7.17(s)	6.81 (dd, 1H, $J=3.60$, 1.60 Hz), 7.36–7.42 (m, 5H), 7.44 (dd, 1H, $J=8.00$, 1.60 Hz), 7.54 (d, 1H, $J=1.60$ Hz), 7.59 (dd, 1H, $J=3.60$, 0.80 Hz), 8.12 (dd, 1H, $J=1.60$, 0.80 Hz)	9.69 (s)

Table 21 ^{13}C-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **7**

No	CONH$_2$	COO	N=CH	Triazole C$_5$	Triazole C$_3$	Aromatic C	C-3 Aromatic C	NCH$_2$N	Piperidine C	Aliphatic C
7a	176.39	155.46	153.46	150.20	142.93	111.67 (CH), 112.79 (CH), 120.48 (CH), 120.67 (CH), 123.63 (CH), 132.67 (C), 141.03 (C), 142.57 (C), 148.78 (CH), 151.36 (C)	–	66.35	28.41 (2CH$_2$), 41.09 (CH), 49.73 (2CH$_2$)	10.94 (CH$_3$), 56.05 (OCH$_3$)
7b	176.41	155.47	153.50	150.34	146.67	111.73 (CH), 112.80 (CH), 120.49 (CH), 120.56 (CH), 123.67 (CH), 132.71 (C), 141.02 (C), 142.57 (C), 148.78 (CH), 151.37 (C)	–	66.38	28.41 (2CH$_2$), 41.09 (CH), 49.74 (2CH$_2$)	10.03(CH$_2\underline{CH_3}$), 18.38($\underline{CH_2}$CH$_3$), 56.04 (OCH$_3$)
7d	176.37	155.46	152.85	150.23	144.73	110.88 (CH), 112.80 (CH), 120.50 (CH), 121.22 (CH), 123.62 (CH), 132.64 (C), 141.05 (C), 142.56 (C), 148.79 (CH), 151.33 (C)	126.77 (CH), 128.53 (2CH), 128.61 (2CH), 135.76 (C)	66.48	28.42 (2CH$_2$), 41.09 (CH), 49.75 (2CH$_2$)	31.04 (CH$_2$Ph), 56.02 (OCH$_3$)
7e	176.37	155.46	152.79	150.23	144.88	110.87 (CH), 112.80 (CH), 120.50 (CH), 121.22 (CH), 123.63 (CH), 132.66 (C), 141.04 (C), 142.56 (C), 148.79 (CH), 151.33 (C)	128.49 (2CH), 129.09 (2CH), 132.62 (C), 135.87 (C)	66.45	28.42 (2CH$_2$), 41.09 (CH), 49.75 (2CH$_2$)	20.57(PhCH$_3$), 30.64(CH$_2$Ph), 56.00 (OCH$_3$)
7g	176.35	155.46	153.01	150.21	144.40	110.96 (CH), 112.80 (CH), 120.51 (CH), 121.21 (CH), 123.64 (CH), 132.59 (C), 141.09 (C), 142.56 (C), 148.79 (CH), 151.34 (C)	128.48 (2CH), 130.54 (2CH), 131.49 (C), 134.77 (C)	66.50	28.41 (2CH$_2$), 41.05 (CH), 49.72 (2CH$_2$),	30.34(CH$_2$Ph), 56.03 (OCH$_3$)

Table 22 Experimental data of compounds **8**

No	Yield (%)	M.p. (°C)
8a	81	242
8b	76	249
8d	71	202
8e	91	235
8g	86	227

discs were used to compare the antibacterial effects of Schiff and Mannich Bases synthesized in the study. Ampicillin is an antibiotic chosen as a penicillin derivative. Neomycin and streptomycin are aminoglycoside group antibiotics. DMSO was used as a solved control.

Antibacterial effect levels of the synthesized compounds were made according to the scale developed by the literature [37]. The low effect represents the 5.5–10 mm zone diameter, the moderate effect represents the 11–16 mm zone diameter, and the 17 mm and above zone diameter represents the high level of effect.

Conclusion

In this paper, new 1,2,4-triazole derivatives (**3**–**8**) were obtained. Their structures were characterized using IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data. The synthesized molecules were screened for antibacterial and antioxidant effects. The promising in vitro metal-chelating effect and antimicrobial activity of some of the Mannich bases has encouraged us to further study novel agents. It is known that compounds acting on bacteria achieve their effects by disrupting the outer wall or membrane of bacteria, by preventing the production of proteins and enzymes that provide resistance, or by destroying the DNA and RNA of the bacteria's chromosomes [43–46]. The study is an in vitro study performed in a laboratory environment. In vivo studies and microscopic examinations are required to examine how the effect of Mannich Bases takes place. Examination of the effect that occurs in bacteria will be considered as a different study topic.

Table 23 IR Spectrum data (cm^{-1}) of compounds **8**

No	$\nu_{C=O}$	$\nu_{C=N}$	ν_{COO}	$\nu_{\text{1,4-disubstitue benzene ring}}$	$\nu_{\text{monosubstitue benzene ring}}$
8a	1734, 1702	1602	1269	–	–
8b	1744, 1699	1610	1265	–	–
8d	1740, 1701	1609	1242	–	749 and 701
8e	1738, 1700	1598	1272	791	–
8g	1739, 1701	1597	1242	796	–

Table 24 ^{1}H-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **8**

No	2CH$_3$	4CH$_2$	2OCH$_3$	2NCH$_2$N	2CH$_2$	2CH$_2$Ph	Aromatic H	2N=CH
8a	2.33(s)	2.62 (s)	3.85(s)	4.53(s)	–	–	6.80 (dd, 2H, $J=3.60$, 1.60 Hz), 7.37 (d, 2H, $J=8.40$ Hz), 7.50 (dd, 2H, $J=8.40$, 1.60 Hz), 7.58 (m, 2H), 7.64 (d, 2H, $J=1.60$ Hz), 8.10 (s, 2H)	9.72(s)
8b	1.24(t, $J=7.20$ Hz)	2.62 (s)	3.85(s)	4.55(s)	2.73(q, $J=7.20$ Hz)	–	6.81 (dd, 2H, $J=3.60$, 1.60 Hz), 7.39 (d, 2H, $J=8.00$ Hz), 7.52 (dd, 2H, $J=8.00$, 1.60 Hz), 7.59 (dd, 2H, $J=3.60$, 0.40 Hz), 7.64 (d, 2H, $J=1.60$ Hz), 8.12 (dd, 2H, $J=1.60$, 0.80 Hz)	9.72(s)
8d	–	2.64 (s)	3.84(s)	4.59(s)	–	4.12(s)	6.81 (dd, 2H, $J=3.60$, 1.60 Hz), 7.21–7.25 (m, 2H), 7.30–7.38 (m, 10H), 7.44 (dd, 2H, $J=8.40$, 1.60 Hz), 7.55 (d, 2H, $J=1.60$ Hz), 7.59 (dd, 2H, $J=3.60$, 0.60 Hz), 8.12 (dd, 2H, $J=1.60$, 0.80 Hz)	9.68(s)
8e	2.24(s)	2.64 (s)	3.85(s)	4.58(s)	–	4.06(s)	6.81 (dd, 2H, $J=3.60$, 1.60 Hz), 7.12 (d, 4H, $J=8.00$ Hz), 7.23 (d, 4H, $J=8.00$ Hz), 7.37 (d, 2H, $J=8.00$ Hz), 7.43 (d, 2H, $J=8.40$ Hz), 7.55 (d, 2H, $J=1.60$ Hz), 7.59 (d, 2H, $J=3.60$ Hz), 8.11 (s, 2H)	9.68(s)
8g	–	2.63 (s)	3.84(s)	4.58(s)	–	4.13(s)	6.81–6.82 (m, 2H), 7.36–7.46 (m, 12H), 7.54 (m, 2H), 7.60 (d, 2H, $J=2.80$ Hz), 8.12 (s, 2H)	9.69 (s)

Table 25 ^{13}C-NMR Spectrum data (DMSO-d$_6$, δ/ppm) of compounds **8**

No	2COO	2N=CH	2Triazole C_5	2Triazole C_3	Aromatic C	C-3 Aromatic C	NCH_2N	$4CH_2$	Aliphatic C
8a	155.46	153.52	150.16	143.00	111.64 (2CH), 112.79 (2CH), 120.49 (2CH), 120.69 (2CH), 123.64 (2CH), 132.65 (2C), 141.03 (2C), 142.58 (2C), 148.79 (2CH), 151.37 (2C)	–	65.77	49.40	10.93 ($2CH_3$), 56.05($2OCH_3$)
8b	155.47	153.50	150.30	143.00	111.72 (2CH), 112.80 (2CH), 120.49 (2CH), 120.59 (2CH), 123.68 (2CH), 132.69 (2C), 141.00 (2C), 142.57 (2C), 148.80 (2CH), 151.47 (2C)	–	65.80	49.41	10.02($CH_2\underline{CH_3}$), 18.38($\underline{CH_2}CH_3$), 56.04($2OCH_3$)
8d	155.46	152.92	150.20	144.83	110.87 (2CH), 112.79 (2CH), 120.50 (2CH), 121.24 (2CH), 123.63 (2CH), 132.62 (2C), 141.07 (2C), 142.56 (2C), 148.79 (2CH), 151.34 (2C)	126.78 (2CH), 128.52 (4CH), 128.63 (4CH), 135.74 (2C)	65.95	49.45	31.04 (CH_2Ph), 56.02($2OCH_3$)
8e	155.46	152.85	150.20	144.97	110.86 (2CH), 112.79 (2CH), 120.50 (2CH), 121.24 (2CH), 123.63 (2CH), 132.60 (2C), 141.06 (2C), 142.57 (2C), 148.79 (2CH), 151.34 (2C)	128.51 (4CH), 129.09 (4CH), 132.65 (2C), 135.88 (2C)	65.93	49.45	20.56($PhCH_3$), 30.65(CH_2Ph), 55.99($2OCH_3$)
8g	155.45	153.08	150.19	144.51	110.94 (2CH), 112.80 (2CH), 120.51 (2CH), 121.23 (2CH), 123.65(2CH), 132.58 (2C), 141.10 (2C), 142.56 (2C), 148.80 (2CH), 151.15 (2C)	128.47 (4CH), 130.57 (4CH), 131.50 (2C), 134.73 (2C)	65.90	49.42	30.35(CH_2Ph), 56.03($2OCH_3$)

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