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FULL PAPER

Synthesis and characterization of new (Bis) Schiff base derivatives based on adamantane and evaluation antioxidant activity

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In this study, we synthesized a series of new Schiff base derivatives containing adamantane moiety in the skeleton structure using adamantanol as the initial material, the adamantanol undergoes two reaction steps. In the first step, adamantanol reacts with acetanilide to produce 1,3-bis(4-acetamido-1-phenyl)adamantane as a salt. In the second step, the produced salt prepared in first step undergoes de-protection reaction by react with aqueous solution of sodium hydroxide to generate 1,3-bis (4-amino-phenyl)adamantane. This amine derivative reacts with different aromatic aldehydes to synthesis Schiff base derivatives of adamantane, as well as characterization of hybrid compounds by FT-IR, Mass spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and study of antioxidant activity. All synthesized derivatives have good scavenging ability against (2,2 diphenyl-1-picrylhydrazyl) free radical, at the range of 81.4-89.9% at high concentration of 1 mg/mL.

KEYWORDS

Adamantanol; cage compounds; Schiff base derivatives; antioxidant.

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Introduction

Adamantane ($C_{10}H_{16}$) are polycyclic hydrocarbon fused chair from cyclohexane rings, it is colorless crystalline compound with an odor like to camphor [1], it has unique chemical, and physical properties [2], such as high lipophilicity [3], rigid structure, and thermodynamically stable molecules [4]. These structural motifs need to demonstrate their value as effective pharmacophore additions as they are utilized rather infrequently in drug design [2]. It has (potential) applications in a number of domains, including chemical synthesis, molecular electronics, medical profession, and astrochemistry [5]. The synthesis and biological activities of adamantane derivatives, which developed into an attractive issue, were investigated by many researchers due to the benefit of the adamantyl group, which gives increased potency in medications in which it was present. As a result, several adamantane derivatives were found to have different biological functions [6], such as antiviral [7], especially influenza viruses [8], medicine catalysis [9], antibacterial, antifungal, anti-inflammatory [10], antidiabetic, carbonic anhydrase inhibitors, and anticancer effects [11].

Schiff base produce by condensation reaction of "ketones or aldehydes with primary amines" Schiff bases that prepared from aromatic amines and aromatic aldehydes are typically those that are stable[12]. Yet, due to steric and electronic factors, aldehydes react more quickly in condensation processes than ketones [13, 14]. These substances can be both found in nature and created in a lab. [15]. They have a wide range of biological functions [16], including antimalarial [17], antiprotozoal [18], antitumor [19], antifungal [20], antibacterial [21], analgesic, anti-inflammatory, antioxidant, cardiovascular, antitubercular, and used as local painkillers [17, 22], as well as they have extensive applications in organometallic chemistry [15, 23-25], catalysis[26], removal dyes[27], foodstuff industrial, diagnostic chemistry, an agricultural chemical such as an insecticide or an herbicide [28]. Due to their widespread applications and simplicity of manufacture, Schiff-based derivatives have drawn a lot of interest [29]. Imines are crucial starting materials and intermediates for numerous reactions, including the production of Mannich bases [30]. Typically, the Schiff bases with aromatic nuclei have strong bioactivities [31]. Several researchers were interested in the biological activities of adamantane derivatives of Schiff base such as Zhu *et al.* [32] created a series of Schiff base thiosemicarbazone derivatives with an adamantane moiety, that may contribute to the development of novel compounds with intriguing biological properties. Osman *et al.* [33] synthesize new Schiff bases by the condensation reaction of adamantane-1-carbohydrazide with a suitable isatin derivative. The resulting hybrid molecules should have improved brain penetration and the capacity to influence a variety of targets implicated in the epilepsy pathogenesis. Research on the creation of pharmaceuticals with unique architectures is crucial for therapeutic use [32]. The aim of the work is design hybridization molecules have adamantane moiety and bis azomethine group in the same structure, as well as identification of hybrid compound by FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, and evaluation antioxidant activity.

Materials and methods

All of the use's materials are commercially available and have relative purity about 95%-99%, the measuring devices used involve: Melting point Smp30 Stuart (UK). FT-IR spectrophotometer 8400s Shimadzu (Japan), ^{1}H-NMR, ^{13}C-NMR Bruker at (400 MHz) Switzerland with (DMSO) solvent, Mass spectroscopy Agilent Technology (HP), Model: 5973 Network Mass Selective Detector, at Isfahan University of Technology (IUT) with (DMSO), UV-Visible Spectrophotometry.

Preparation of adamantane salt [1,3 bis(4-acetamido-1-phenyl)adamantane] (A1)

1 eq. from adamantanol (15 g, 0.0985) was mixed with 2eq. of acetanilide (26.6 g, 0.197), 300 mL from H_2SO_4 as solvent, and oxidation agent was added with drop-wise under vigorously stirring for 24 hours at room temperature. After that, the produced mixture was poured into ice water with stirring for 30 minutes, and then the precipitate was washed for several times after filtration to remove the residue of the acid. Next, dries the product as a white powder with high yield 87%, as shown in Scheme 1. This method was according to Habib *et al.* [1].

Preparation of adamantane amine [1,3 bis(4-amino phenyl)adamantine] (A2)

1eq of adamantane salt of acetanilide was mixed with 2 eq of sodium hydroxide dissolved in less amount of water, and then added 250 mL of absolute ethanol the reaction occur under reflux conditions for 24

hours, after that the mixture poured into ice water with stirring for 30 minutes, and then the precipitate is washed carefully for several times after filtration to remove the residue of the base, the precipitate is dried as a light brown powder, melting point approximately (120 °C) with good yield 85%, as demonstrated in Scheme 1.

Synthesis of Bis Schiff's base derivatives

The diaminoadamantane derivative were treated with several aromatic aldehyde where, 1eq of prepared amine mixed with 2eq of aromatic aldehyde in 35 mL of absolute ethanol as a solvent and 0.5 mL of pyridine as catalyst, the reaction occurs under reflux condition for 5-6 hours, and then the mixture is filtered and recrystallization by absolute ethanol, general reaction of new Schiff base derivatives synthesized, as shown in Scheme 1.

Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-benzylideneaniline) (B1)

Off-white solid, Yield: 56%, M.P.: 155-156 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): 3061 (Ar-CH), 1627 (C=N), 1597 (C=C); ^{1}H-NMR (DMSO-d$_6$): δ 1.77-2.2 (m, 14H, C-H cycloaliphatic), 7.2-8.6 (m, 18H, Ar-H), 8-8.6 (s, 2H, N=C-H); ^{13}C-NMR (400 MHz, DMSO-d$_6$): δ 160 (C=N), 121-149 (C-Ar), 37-42 (C-Adamantane); m/z calculated 494.6 g/mol, m/z found 494.3 g/mol.

Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methylbenzylidene) aniline) (B2)

Off-white solid, Yield: 68%, M.P.: 142-144 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): 3045 (Ar-CH), 1626 (C=N), 1597 (C=C); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 1.75-2.2 (m, 14H, C-H cycloaliphatic); 2.2-2.3 (S, 6H, C-H aliphatic), 7.2-7.8 (m, 16H, Ar-H), 8.5 (s, 2H, N=C-H). ^{13}C-NMR (100 MHz, DMSO-d$_6$): 160 (C=N), 121-149 (C-Ar), 29-42 (C-Adamantane), 21.6 (CH$_3$); m/z calculated 522.7 g/mol, m/z found 522.4 g/mol.

Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(4-methoxybenzylidene)aniline) (B3)

Off-white solid, Yield: 72%, M.P.: 130-132 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): 3101 (Ar-CH), 1627 (C=N), 1577 (C=C). ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 1.75-2.2 (m, 14H, cycloaliphatic), 3.8 (s, 6H, C-H aliphatic), 7-7.9 (m, 16H, Ar-H), 8.54 (s, 2H, N=C-H). ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ 159.6 (C=N), 114-132 (C-Ar), 29-42 (C-Adamantane), 55.8 (C-O). The m/z calculated 554.7 g/mol, m/z found 554.4 g/mol.

Synthesis of 4,4'-(adamantane-1,3-diyl)bis(4,1-phenylene)bis(azanylylidene) bis(methanylylidene)bis(N,N-dimethylaniline) (B4)

Pale yellow solid, Yield: 67%, M.P.: 158-160 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): 3050 (Ar-CH), 1608 (C=N), 1599 (C=C), ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 1.76-2.27 (m, 14H, C-H cycloaliphatic), 3.02 (s, 12H, C-H aliphatic), 6.7-7.76 (m, 16H, Ar-H), 8.43 (s, 2H, N=C-H). ^{13}C-NMR (100 MHz, DMSO-d$_6$): 159.7 (C=N), 111-152 (C-Ar), 29-37 (C-Adamantane), 40-42 (C-N). Calculated 580.8 g/mol, m/z, found 580.4 g/mol.

Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(furan-2-ylmethylene) aniline) (B5)

Light brown solid, Yield: 43%, M.P.: 164-166 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): Above 3000 (Ar-CH), 1622 (C=N), 1516 (C=C). ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 1.7-2.9 (m, 14H, C-H cycloaliphatic), 6.3-7.1 (m, 8H, Ar-H), 7.1-7.9 (m, 6H, Ar-H heterocyclic), 8.4 (s, 2H, N=C-H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 152 (C=N), 112-126 (C-Ar), 146-149 (C-Aromatic heterocyclic), 29-42 (C-Adamantane); m/z calculated 474.59 g/mol, m/z found 474.3 g/mol.

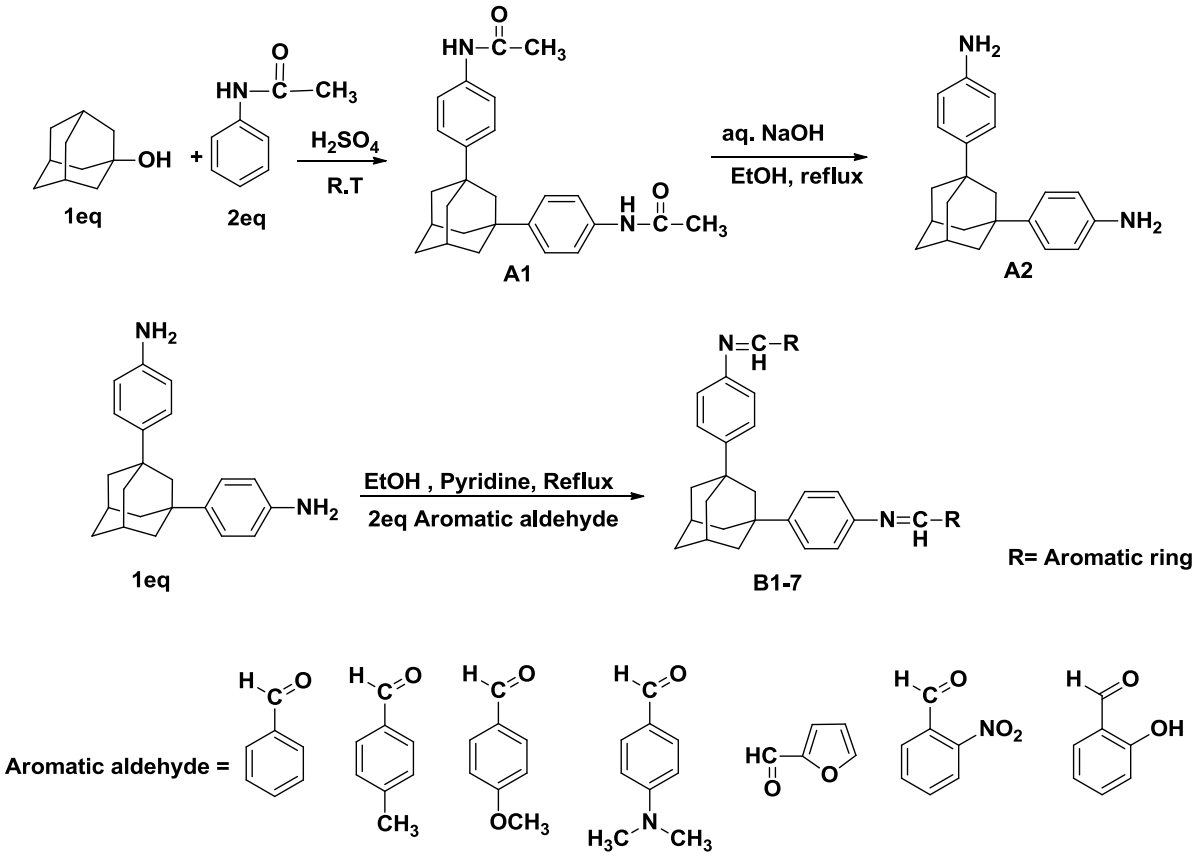
Synthesis of 4,4'-(adamantane-1,3-diyl)bis(N-(2-nitrobenzylidene)aniline) (B6)

Dark yellow solid, Yield: 54.5%, M.P.: 137-139 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): Above 3000 (Ar-CH), 1616 (C=N), 1570 (C=C), 1519 (NO_2). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.74-2.25 (m, 14H, C-H cycloaliphatic), 7.2-8.1 (m, 16H, Ar-H), 8.8 (s, 2H, N=C-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156 (C=N), 121-134 (C-Ar), 29-42 (C-Adamantane), 148-149 (C=C-NO_2). m/z calculated 584.66 g/mol, m/z found 584.4 g/mol.

Synthesis of 4,4'-(adamantane-1,3-diylbis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol (B7)

Light yellow solid, Yield: 58.7%, M.P.: 111-112 °C, FT-IR (KBr) (ν_{max}/cm^{-1}): Above 3000 (Ar-CH), 1618 (C=N), 1599 (C=C), 3400 (OH). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.76-2.2 (m, 14H, C-H cycloaliphatic), 7.6 (s, 2H, N=C-H), 4.8 (s, 2H, O-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160 (C=N), 117-133 (C-Ar), 29-42 (C-Adamantane), 149-145 (C=C-O); m/z calculated 526.6 g/mol, m/z found 526.3 g/mol.

Synthesis of 2,2'-(adamantane-1,3-diylbis(4,1-phenylene))bis



SCHEME 1 Steps of synthesized of adamantine's salt, diaminoadamantane, and schiff's bases

Antioxidant activity of Schiff base derivatives

Free radical highly reactive species are able to damage physiologically important components including DNA, carbohydrates, proteins, and lipids in the cell nucleus and cell membranes [34]. A number of illnesses and degenerative processes, including as inflammation, cancer, dementia, and physiological aging, have been linked to metabolic oxidative stress, either directly or indirectly, moreover, oxidative stress is a major factor in liver diseases [35]. As a result, antioxidants that can scavenge free radicals

are crucial for the treatment and prevention of various disorders [22]. The DPPH (2,2 diphenyl-1-picrylhydrazyl) radical is an extremely stable commercial nitrogen-centered free radical due to the steric hindrance and conjugation [36]. In this report, all the produced compounds were evaluated for their *in vitro* antioxidant activity by scavenging DPPH free radicals. 0.05 mg/ml prepared from DPPH in methanol and kept away from light as well as prepared different concentrations of 1 mg, 0.5 mg, 0.25 mg, and 0.125 mg from all compounds in methanol .0.1 ml of all concentrations of sample were mixed with 0.1 ml of DPPH solution, control solution was used from DPPH with methanol. All of the samples' absorbance were measured using a UV-Visible spectrophotometer at a maximum wavelength of 517 nm. The percentage inhibition of free radical was calculated by the following formula:

Percent inhibition % = $[(A^o - A)/A^o) \times 100]$
Where: A^o = Absorbance of solution control.

A = Absorbance of sample [37]

Results and discussion

The FT-IR spectrum(cm^{-1}): of Schiff bases derivatives shows a strong-moderate intensity absorption band at 1608-1627 cm^{-1} indicate to C=N stretching vibrations[38, 39]. Stretching vibrations of aromatic rings can be found in regions between 1410-1599 cm^{-1}. The absence of bands specific to the primary amine (N-H) and appearance (C=N) band indicates the formation of Schiff base derivatives. Other fundamental bands of Schiff base derivatives are listed in Table 1.

TABLE 1 Fundamental bands of Schiff base derivatives in FT-IR spectra

No. of compound	C-H Aromatic	C-H Aliphatic	C=N Schiff base	C=C Aromatic	Other band
B1	3061, 3030	2877, 2895	1627	1597, 1577, 1498 1450	
B2	3045, 3033	2847, 2897, 2900	1626	1597, 1570, 1512 1496	
B3	3030, 3062	2908, 2847	1624	1597, 1575, 1512 1446	
B4	3050, 3034	2847, 2897	1608	1599, 1554, 1525	
B5	Above 3000	2899, 2847	1622	1516, 1475, 1446	
B6	2943, 2897	3075, 3044	1616	1570, 1519, 1442	1519 (NO_2) 871 (C-N)
B7	2848, 2901	3055, 3031	1612	1599, 1573, 1491 1456	3400 (OH)

^{1}H-NMR spectrum (DMSO): For new Schiff base showed specific signals such as a singlet peak at the region of δ 8-8.6 ppm indicating to proton imine group [40, 41], multi- peaks at the region of δ 1.75-2.9 ppm indicate to protons of adamantane structure and multi-peaks at the region of δ 6.5-8 ppm refer to the aromatic ring. ^{13}C-NMR spectrum (DMSO): The presence of carbon of imine group (C=N) observed at the range of 152-160 ppm[42]. The chemical shift between 29 and 42 indicate to carbons of adamantane, while the chemical shift at the range of 110-150 indicated the aromatic carbons. Mass spectrometry: is based on a rather straightforward idea: A substance is ionized using the "ionization method," the ions are separated based on their mass/charge ratio using the "ion separation method," and the number of ions representing each

mass/charge unit is then recorded as a spectrum. The intensity of molecular ion peak depends on the stability of molecular ion[43]. All Schiff base derivatives (B1, B2, B3, B4, B5, B6, and B7), listed in Table 2, have parent ion and base peak in the same value except B5, which indicate the stability of these compound.

TABLE 2 Mass spectrum value of Schiff base derivatives

Compound	m/zCalculated	m/z Found	Base peak	Peak of first fragment	Peak of last fragment
B1	494.66	494.3	494.3	465.3	65.1
B2	522.7	522.4	522.4	494.3	65.1
B3	554.7	554.4	554.4	525.3	65
B4	580.8	580.4	580.4	565	55
B5	474.59	474.3	396.3	446.3	55.1
B6	584.66	584.3	584.3	565.3	55.1
B7	526.6	526.3	526.3	498.3	65.1

Antioxidant Activity: According to Table 3, Schiff base derivatives synthesized compounds (B1-B7) exhibited high inhibition percentage against DPPH free radical from less value of 81.4% in compound B4 to a higher value of 89.9% in compound B3 at a high concentration of 1 mg/mL, as well as the percent inhibition decreased with decreased concentration in all compounds. Figure 1 illustrated the change in color of all compounds in different concentrations. These changes prove the radical scavenging ability of all compounds. Likewise, the substituent on aromatic ring and their position make an influence on scavenging ability.

TABLE 3 Values of antioxidants activity of Schiff base derivatives by DPPH scavenging assay *: *P-value* = 0.033 **: *p-value* = 0.002 ***: *p-value* < 0.001.

Compound	1 mg/ml absorbance	% inhibition	0.5 mg/ml absorbance	% inhibition	0.25 mg/ml absorbance	% inhibition	0.125 mg/ml absorbance	% inhibition
B1	0.2854	87.8	0.3254	86.1	0.3952	83.1	0.425	81.8
B2	0.3254	86.1	0.3564	84.8	0.4952	78.8	0.5027	78.5
B3	0.2354	89.9	0.2465	89.4	0.2846	87.8	0.3685	84.2
B4	0.435	81.4	0.4578	80.4	0.4851	79.3	0.5022	78.5
B5	0.4354	81.4	0.4658	80.1	0.5624	76	0.6356	72.9
B6	0.4135	82.3	0.4754	79.7	0.5246	77.6	0.5486	76.6
B7	0.2745	88.3	0.3564	84.8	0.3812	83.7	0.4135	82.3

Absorbance of control solution (DPPH + methanol)= 2.3464

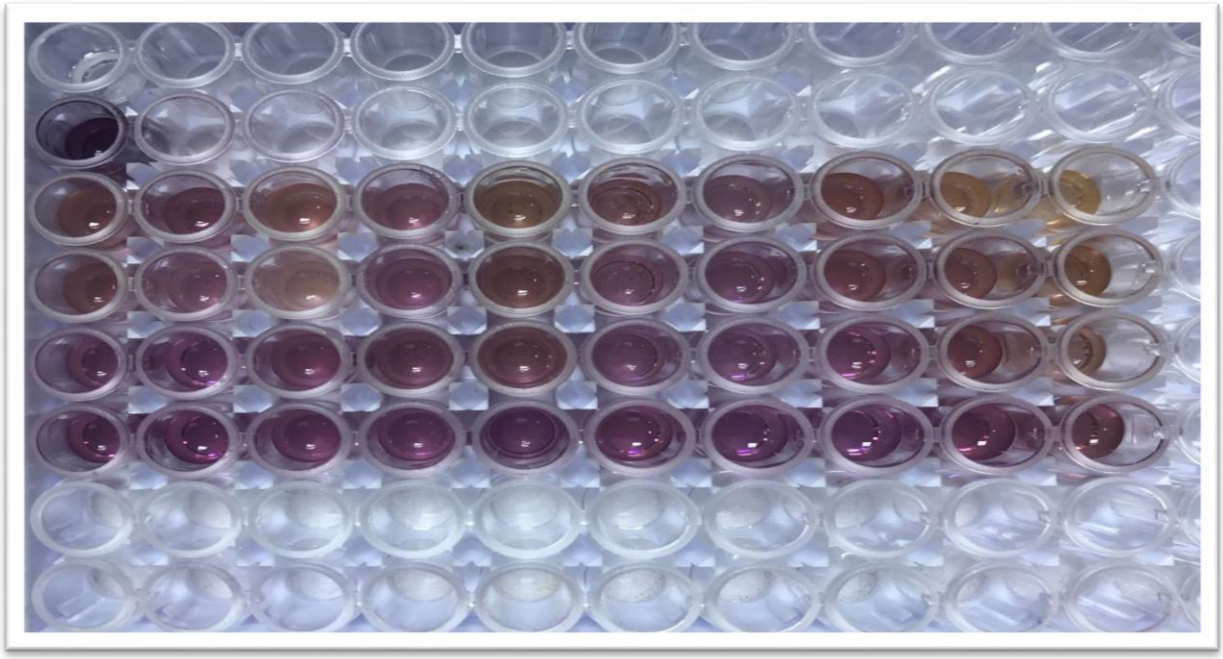


FIGURE 1 Change in color of DPPH at different concentrations of all Schiff base derivatives

Conclusion

In this report, a new series of Schiff base derivatives containing adamantane moiety in their structure have been successfully synthesized, as well as characterized by using FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, with yield percent from 43%-72%, and evaluation of the antioxidant activity of all synthesized compounds against DPPH free radical. All synthesized compounds have high scavenging ability against DPPH free radical, at a range from 81.4% to 89.9% at a high concentration of 1 mg/mL. The different substituent and their position on aromatic ring make an influence on the antioxidant activity. Further research is required to better understand the connection between structure and activity.

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Conflict of Interest

The authors declare that there is no conflict of interest

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