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#### Organic Synthesis of Some New Compounds Derived from Furfural and Their Evaluation as Antioxidants

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#### ARTICLE INFO

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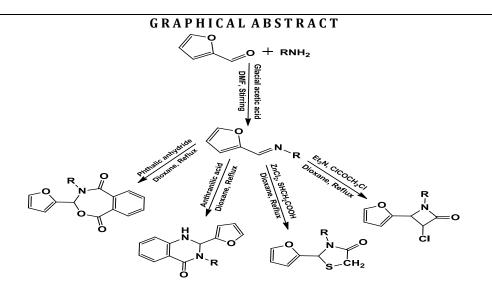
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#### A B S T R A C T

Heterogeneous organic compounds play an important role in our daily life as they contribute in many medical and industrial fields and are in continuous development as a result of the preparation of new derivatives with different properties. From this premise, the goal of this work appears, which is preparation of (four, five, six, and seven) membered ring systems derived from furfural, by its reaction with different aromatic aldehydes, and record their antioxidant activity by using free radical scavenging method of DPPH radicals. The new ring systems are synthesized by reacting the prepared Schiff-bases with different ring closure agents (chloroacetyl chloride, mercaptoaceticacid, anthranilic acid, and phthalic anhydride), the prepared compounds were characterized by measuring their melting points and recording their infrared spectra in addition to the NMR spectra for some of them, the recorded results for some derivatives were higher when comparing them with ascorbic acid as a drug because these compounds have electrons that are able to terminate the free radicals that cause the oxidation process.



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#### Introduction

Some oxidation processes lead to the formation of free radicals, which can be reduced or eliminated by molecules with the ability to neutralize free radicals, and these molecules are called anti-oxidants [1]. This activity can occur inside living bodies. Therefore, the importance of these molecules appears to protect cells in which oxidation processes occur. These molecules act as drugs that prevent cell damage by free radicals [2]. The DPPH (2,2-Diphenyl-1-picrylhydrazyl) is the most common method among many methods available to measure antioxidants [3], the DPPH solution has a deep purple color absorbed at the wavelength of 517 nm. It is characterized by having free radicals that can be scavenged by antioxidants either by adding an electron or hydrogen atom [4] to turn the color of the solution to yellow, the antioxidants' effectiveness can be determined by measuring the difference in absorbance resulting from the difference in color at the same wavelength. The importance of furfural in comes from being the primary component for any compound that contain a furyl, furfuryl, furoyl, or furfurylidene radical in their structure, furfural as an aldehyde participates in many reactions as acetalization, acylation, aldol and knoevenagel condensations, reduction to alcohols, reductive amination to amines, decarbonylation, oxidation to carboxylic acids, and grignard reactions. Moreover, the effect of withdrawing of electrons in carbonyl group enables furan ring to undergo alkylation, hydrogenation, oxidation, halogenation, and nitration reactions [5, 6]. It can be found in nature in fruit, tea, coffee, cocoa, alcoholic beverages, wood wastes, and whole grain bread. It is considered as artificially flavoring substance and it is dangerous in the case of contact with the skin. Moreover, it is toxic when entering the mouth, irritating to eyes and respiratory system [5]. The use of heterogeneous catalysts in furfural preparation has received the widespread attention in the recent years due to its ability to accelerate the reaction and its selectivity in addition to being environmentally friendly. All these reasons make it the most desirable for practical uses [7]. The purpose of this study is to

prepare new derivatives of furfural and evaluate them as antioxidants.

#### **Martials and Methods**

All chemicals and solvents which are used in this work were locally purchased from Fluke and BDH and were used directly without any further purification. Melting point were recorded by Gallenkamp capillary melting point using and where uncorrected, apparatus FT-IR spectrum was recorded with Perkin Elmer spectrophotometer by using KBr disk the frequencies were estimated in cm<sup>-1</sup>, the NMR spectra were recorded on Bruker Avance 600 spectrometer by using DMSO- $d_6$  as a solvent. The chemical shifts of compounds are expressed by  $\delta$ (ppm). The reaction time was recorded by using TLC silica gel, solvent used was ethyl acetate: petroleum ether (2:1) and spots were shown by placing the TLC paper in contact with iodine vapor. The antioxidant activity was measured by using spectrophotometer at the wavelength of 517 nm.

#### Synthesis of furan-2-ylmethylene derivatives (C<sub>1</sub>-C<sub>3</sub>) [8, 9]

Furfural (0.3 mmol, 0.3 mL) was placed in a round flask and mixed with glacial acetic acid (0.3 mmol, 0.25 mL). The mixture was let to stir for 10 minutes at room temperature followed by adding the amine (0.3 mmol) dissolved in DMF (10 mL). The mixture was stirred for 3-5 hours monitored by TLC ethyl acetate: petroleum ether (2:1), the products were cooled filtered, washed with water, and re-crystallized with ethanol. Physical properties of compounds ( $C_1$ - $C_3$ ) are listed in Table 1.

# Synthesis of 3-chloro-4-(furan-2-yl) azetidin-2-one derivatives (C<sub>4</sub>-C<sub>6</sub>) [10]

Imine group derivatives (0.9 mmol) were mixed with chloroacetyle chloride (0.9 mmol,0.075 mL) with triethylamine (0.9 mmol, 0.13 mL) and all were dissolved in 10 mL dioxane. The mixture was gently heated for 14-19 hours monitored by TLC ethyl acetate: petroleum ether (2:1), and then the products were cooled, filtered, and

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recrystallized with ether. The physical properties of compounds (C<sub>4</sub>-C<sub>6</sub>) are summarized in Table 2.

Synthesis of 2-(furan-2-yl) thiazolidin-4-on derivatives (C7-C9) [11, 12]

Imine group derivatives (0.9 mmol) were mixed with thioacetic acid (0.9 mmol, 0.065 mL) with

zinc chloride (0.9 mmol, 0.126 g) all dissolved in 10 mL dioxane. The mixture was refluxed for 17-23 hours monitored by TLC ethyl acetate: petroleum ether (2:1), and then the products were cooled, filtered, and re-crystallized with ether. The physical properties of compounds ( $C_{7}$ - $C_{9}$ ) are presented in Table 3.

Table 1. Physical properties of compounds (CI-C3)									
Compounds	Chemical formula	M.Wt. (g/mol)	M.P(°C)	Time (hrs.)	Color	Yield (%)			
<b>C</b> <sub>1</sub>	$C_{11}H_8N_2O$	184	160-162	3	Dark-brown	93			
C2	C <sub>12</sub> H <sub>7</sub> N <sub>2</sub> SOBr	307	204-206	5	Pale-yellow	76			
C <sub>3</sub>	$C_{12}H_{10}NO_3$	216	182-184	4	White-yellow	61			

Table 1: Phy	vsical pro	perties of	compounds	$(C_1 - C_3)$

<b>Table 2:</b> Physical properties of compounds (C4-C6)								
Compounds	Chemical formula M.Wt. (g/mol)		M.P. (°C)	Time (h)	Color	Yield (%)		
C4	$C_{13}H_9N_2O_2Cl$	260.6	>360	19	Dark-brown	72		
C <sub>5</sub>	$C_{14}H_8N_2SO_2BrCl$	383.6	144-146	19	Light-gray	66		
C <sub>6</sub>	$C_{14}H_{11}NO_4Cl$	292.7	>360	14	Black	67		

Table 3: Physical properties of compounds (C7-C9)

Compounds	Chemical formula	M.Wt. (g/mol) M.P. (°C) Time (h) Color		Yield (%)		
C7	$C_{13}H_{10}N_2O_2S$	258.3	>360	19	Black	65
C <sub>8</sub>	$C_{14}H_9N_2S_2O_2Br$	381.2	155-160	23	Light-gray	97
<b>C</b> 9	$C_{14}H_{12}NO_4S$	290.3	182-184	17	Dark-brown	73

#### Synthesis of 2-(furan-2-yl)-2,3-dihydroquinazolin-4(1H)-one derivatives (C<sub>10</sub>-C<sub>12</sub>) [13]

Imine group derivatives (0.9 mmol) were mixed with anthranilic acid (0.9 mmol, 0.12 g) dissolved in 10 mL dioxane. The mixture was refluxed for 16-30 hours monitored by TLC ethyl acetate: petroleum ether (2:1), and then the products were cooled, filtered, and re-crystallized by ether. The physical properties of compounds ( $C_{10}$ - $C_{12}$ ) are listed in Table 4.

#### Synthesis of 3-(furan-2-yl)-3,4dihydrobenzo[e][1,3]oxazepine-1,5-dione derivatives (C<sub>13</sub>-C<sub>15</sub>) [14]

Imine group derivatives (2.6 mmol) were mixed with phthalic anhydride (2.6 mmol, 0.4 g) dissolved in 10 mL dioxane. The mixture was refluxed for 8-17 hours, monitored by TLC ethyl acetate: petroleum ether (2:1), the products were cooled, filtered, and re-crystallized with ether. The physical properties of compounds  $(C_{13}-C_{15})$  are presented in Table 5.

#### Antioxidant assay

Antioxidant activity was measured by using the free radical scavenging method of DPPH by dissolving 1 mg of each sample in 10 mL of DMSO to prepare a concentration of 100 ppm. Then, by taking 1 mL of the solution and dissolving it in 1 mL of DMSO to prepare the concentration of 50 ppm, and finally it was taken from the stock solution of 0.5 mL and dissolved in 1.5 mL of DMSO to prepare the concentration of 25 ppm. Thus, three concentrations were prepared from each sample, the efficacy was measured by taking 1 mL of each concentration and adding it to 1 mL of a 50 ppm DPPH solution in a test tube and leaving the samples in incubator for half an hour in the absence of light, and then it was measured

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by using spectrophotometer at the wavelength of 517 nm and compared with the standard ascorbic acid solution. The blank solution was prepared by mixing 1 mL of methanol to 1 mL of DPPH solution 50 ppm dissolved in DMSO [15], IC<sub>50</sub> for

samples was calculated and the results were displayed in Figure 1. The mechanism of free radical scavenging by using (DPPH) is described in Scheme 1.

-											
Compounds	Chemical formula	M.Wt. (g/mol) M.P (°C)		Time (h)	Color	Yield (%)					
C10	$C_{18}H_{13}N_4O_2$	317.3	>360	16	Dark-brown	53					
C11	$C_{19}H_{12}N_4SO_2Br$	440.3	3 205-206		Gray	90					
C12	C <sub>12</sub> C <sub>19</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub>		178-180	30	Brown	65					

#### **Table 4:** Physical properties of compounds C<sub>10</sub>-C<sub>12</sub>

 <b>Table 5:</b> Physical properties of compounds $C_{13}$ - $C_{15}$									
Compounds	Chemical formula	M.Wt. (g/mol)	M.P(°C)	Time (h)	Color	Yield (%)			
C13	$C_{19}H_{12}N_2O_3$	316.3	>360	17	Black	98			
C14	C20H9N2SO3Br	437.2	oily	17	Brown	74			
C15	$C_{20}H_{14}NO_6$	364.3	210(d)	8	Black	63			

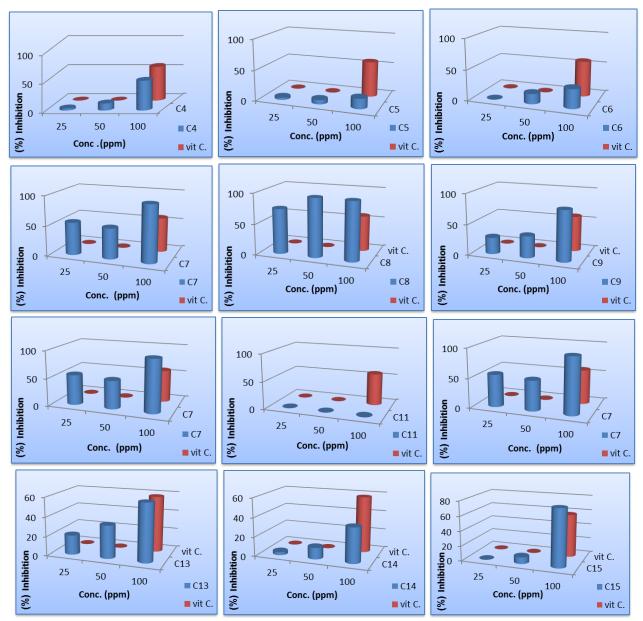
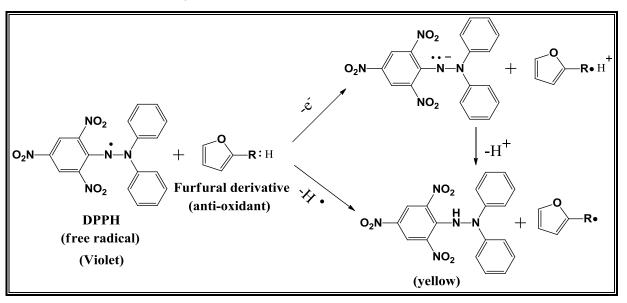


Figure 1: A comparison between the tested compounds and ascorbic acid in (%I) by using different concentrations

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Scheme 1: Mechanism of free radical scavenging

#### **Results and Discussion**

Furfural derivatives were synthesized by his reaction with different aromatic amines followed by cyclization reaction to form different ring closure derivatives, as displayed in Scheme 2. Compounds  $(C_1-C_3)$  were synthesized by a nucliuphilic addition of different substituted amines to furfural carbonyl group in the presence of glacialacetic acid. The spectral results of the compounds (C1-C3) showed clear differences indicating the occurrence of the Schiff base reaction, as the FT-IR spectrum demonstrates the main difference in the groups in terms of the absence of the carbonyl band and the presence of other bands indicating the presence of imine group [8] v(C=N) at 1662-1614 cm<sup>-1</sup>, as listed in Table 6. <sup>1</sup>H-NMR indicates the appearance signal of imine group C=N at  $\delta$  8.51 (1H, s, CH=N) for compound C<sub>1</sub>, at  $\delta$  8.08 (1H, s, CH=N) for compound C<sub>2</sub>, at  $\delta$  8.37 (1H, s, CH=N) for compound C<sub>3</sub>, in addition to other characteristic groups as the amino group in compound  $C_1$  at  $\delta$ 6.61 (2H, s,  $NH_2$ ), and the hydroxyl group of compound C<sub>3</sub> at  $\delta$  12.79 (1H, s, OH). <sup>13</sup>C-NMR also depicts the presence of imine group (CH=N) at the following chemical shifts at  $\delta$  152.52 for compound  $C_1$  and  $C_2$ , at  $\delta$  150.09 for compound C<sub>3</sub>.

Azetidine-2-one rings were prepared by a nucleophilic addition reaction of chloro acetyle chloride to the imine compound in the presence

of trimethylamine. These rings illustrate a significant FT-IR absorption bands indicating the appearance of carbonyl group at 1699-1683 cm<sup>-1</sup> and v(C-N) at 1292-1230 cm<sup>-1</sup> resulting from the nucleophilic attack on the double bond of imine group. <sup>1</sup>H-NMR for compound C<sub>5</sub> indicates the presence of significant chemical shift at  $\delta$  4.29-4.23 (1H, d, CH-N), as in <sup>13</sup>C-NMR for compound C<sub>5</sub> shows a chemical shift at  $\delta$  42.98 (CH-N), at  $\delta$  167.72 (C=O).

Thiazolin-4-one rings undergoes addition mechanism also including steps two of nucleophilic attack of thio acetic acid in the presence of zinc chloride, in this type of fivemembered ring systems appears as similar the ones to those of the aforementioned ring systems, new bands are observed in the FT-IR spectrum, such as v(C=O) at 1701-1685 cm<sup>-1</sup> and v(C-N) at 1394-1215 cm<sup>-1</sup>, as well as  $v(CH_2)$  aliphatic at 3137-3004 cm<sup>-1</sup> and v(C-S) at 686-648 cm<sup>-1</sup>. <sup>1</sup>H-NMR for compound C<sub>8</sub> illustrates a characteristic chemical shift at  $\delta$  3.68 (1H, s, CH), as the <sup>13</sup>C-NMR spectrum for compound  $C_8$  at  $\delta$  66.83 for CH-N group.

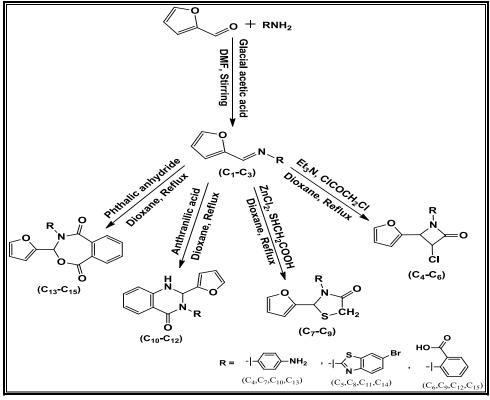
Quinazolin-4-one rings were prepared by reaction of Schiff base derivatives with anthranilic acid, the absorption bands of FT-IR shows distinct peaks in the six-membered rings formed as the carbonyl group at 1681-1631 cm<sup>-1</sup> as well as v(N-H) at 3317-3083 cm<sup>-1</sup>. <sup>1</sup>H-NMR spectrum for compound  $C_{12}$  shows the

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appearance of significant chemical shifts at  $\delta$  4.56-4.53 (1H, d, NH) and  $\delta$  4.96 (1H, d, CH), as in <sup>13</sup>C-NMR for compound C<sub>12</sub> at  $\delta$  65.29 for CH-N group.

phthalic anhydride, FT-IR spectra indicates the appearance of carbonyl groups at 1731-1699 cm<sup>-1</sup> and ester group at 1373-1139 cm<sup>-1</sup>. All data are listed in Tables 7, 8, and 9.

1,3-Oxazepane compounds were prepared from the addition reaction of imine compounds to



Scheme 2: Preparation of furfural derivatives

Symbol of		FT-IR spectral data				
Compund	Structure	V(C=N)	V(C=C) aromatic	Others		
C1		1614	1510	v(NH2) 3521-3433		
C2	CH S Br	1631	1527	v(C-S) 651		
C3		1602	1577	v(O-H) acidic 3074-2565, v(C=O) 1731		

Table 6: FT-IR spectral data of compounds (C1-C3)

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Table 7: FT-IR spectral data of compounds (C4-C15)								
Course had a f	X	FT-IR spectral data						
Symbol of Compound	Structure	V(C=0)	V(C-H) aliphatic	Others				
C4	CH-N HC-C CI O	1683	2887, 2950	v(NH2) 3452-3421				
C5	CI-CCNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	1699	2947, 2991	v(C-S) 682				
C6		1699	2848, 2918	v(0-H) acidic 3444-3425, v(C=0) 1699				
C7		1701	2823, 2893	v(NH2) 3564-3477, v(CH2) aliphatic 2893-2823				
C <sub>8</sub>	$ \begin{array}{c}                                     $	1699	2918, 2975	v(C-S) 688, v(CH <sub>2</sub> ) aliphatic 2975-2850				
C9		1685	2910, 2950	v(O-H) acidic 3481-3386, v(C=O) 1768 v(CH <sub>2</sub> ) aliphatic 2910-2794				
C10	H <sub>2</sub> N O C H H	1681	2848, 2904	v(NH2) 3456-3427, v(NH) 3126				
C11	Br N O CH H H	1701	2852, 2918	v(C-S) 694, v(NH) 3083				
C <sub>12</sub>		1664	2893, 2950	v(O-H) acidic 3074-2854, v(C=O) 1730, v(NH) 3317				

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C13		1714	2884, 2920	v(NH2) 3444-3421
C14	Br N O CH O O	1731	2923, 2956	v(C-S) 719
C <sub>15</sub>		1699	2893, 2947	v(O-H) acidic 3438-3429, v(C=O) 1787

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Table 8: <sup>1</sup>H-NMR spectral data for some prepared compounds C<sub>1</sub>-C<sub>15</sub>

Symbol of Compound	Structures	<sup>1</sup> H-NMR spectral data (δ ppm)
C1		6.61 (2H, s, NH <sub>2</sub> ), 7.97-6.66 (7H, m, H aromatic), 8.51 (1H, s, CH)
C2	CH S Br	7.88-7.25 (6H, m, H aromatic), 8.08 (1H, s, CH)
C3		8.35-6.50 (7H, m, H aromatic), 8.37 (1H, s, CH), 12.79 (1H, s, OH)
C5	$CI \rightarrow CH \\ CI \rightarrow CH \\ N \\ $	4.29-4.23 (1H, d, CH-N), 4.49 (1H, d, CH- Cl), 8.36-7.25 (6H, m, H aromatic)
C8	$ \begin{array}{c}                                     $	3.68 (2H, s, CH <sub>2</sub> ), 7.25 (1H, s, CH), 7.90-7.28 (6H, m, H aromatic)
C12		4.56-4.53 (1H, d, NH), 4.96 (1H, d, CH), 8.38-6.49 (11H, m, H aromatic), 12.79 (1H, s, OH)

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Symbol of Compound	Structures	<sup>13</sup> C-NMR spectral data
C1	$\begin{array}{c} 6 \\ 0 \\ 9 \\ 1 \\ 3 \\ 4 \end{array} \begin{array}{c} 4 \\ 2 \\ 4 \\ 4 \end{array} \begin{array}{c} 2 \\ 7 \\ 1 \\ 4 \\ 2 \end{array} \right)$	112.73(C1),113.05-114.72(C2),117.45(C3),122.50,122.84(C4),142.91,1146.89(C5),148.15,148.53(C6),149.51,149.68(C7),152.52(C8),153.22(C9)
C2	$ \begin{array}{c} 8 \\ 1 \\ 3 \\ 3 \\ 0 \\ 1 \\ 3 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0$	112.60 (C1),112.56 (C2),123.72 (C3), 125.30 (C4),125.72 (C5),128.76(C6), 130.87 (C7),133.59 (C8),152.52 (C9), 152.11 (C10),167.67 (C11), 169.27 (C12)
C3	$ \begin{array}{c} 0 \\ 8 \\ 0 \\ 1 \\ 3 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	111.34, 111.43 (C1), 112.55, 112.82 (C2), 115.81, 115.97 (C3), 132.14 (C4), 132.30 (C5), 132.85 (C6), 134.65 (C7), 134.98 (C8), 150.09 (C9), 150.68 (C10), 161.21 (C11), 170.34, 170.46 (C12)
C5	$\begin{array}{c} 4 & 10 \\ 3 & 0 \\ 2 & 11 \\ H & CH \\ CI - C \\ 1 \\ CI \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	41.97 (C1), 42.98 (C2), 112.70 (C3), 119.34 (C4), 122.82 (C5), 123.83 (C6), 124.86 (C7), 128.84 (C8), 133.30 (C9), 148.09 (C10), 151.97 (C11), 158.88 (C12), 167.72 (C13), 169.09 (C14)
C8	$ \begin{array}{c} 3 \\ 4 \\ 0 \\ 2 \\ 11 \\ 0 \\ 3 \\ CH \\ 11 \\ N \\ 12 \\ 6 \\ 0 \\ 6 \\ 7 \\ Br \\ Br \\ 6 \\ 8 \\ 0 \\ 6 \\ 8 \\ 0 \\ 6 \\ 8 \\ 0 \\ 6 \\ 8 \\ 0 \\ 6 \\ 8 \\ 0 \\ 6 \\ 8 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	41.07 (C1), 66.83 (C2), 112.67 (C3, C4), 119.47 (C5, C6), 123.80 (C7), 128.82 (C8), 133.37 (C9, C10), 152.13 (C11, C12), 167.70 (C13), 170.99 (C14)
C <sub>12</sub>	$\begin{array}{c} OH \\ 9 \\ 13 \\ 7 \\ 14 \\ 15 \\ 3 \\ 2 \\ \end{array} \begin{array}{c} OH \\ 19 \\ 0 \\ 0 \\ 0 \\ 11 \\ 10 \\ 10 \\ 10 \\ $	65.29 (C1), 111.36 (C2), 111.45 (C3), 112.55 (C4), 115.82 (C5, C6), 115.98 (C7, C8), 132.15 (C9), 132.32 (C10), 132.85 (C11), 134.56 (C12, 13), 134.97 (C14), 150.09 (C15), 150.68 (C16), 161.17 (C17), 170.35 (C18), 170.74 (C19)

**Table 9:** <sup>13</sup>C-NMR spectral data (δ ppm) for some of the prepared compounds (C<sub>1</sub>-C<sub>15</sub>)

#### Antioxidant activity

The effectiveness of some of the prepareded derivatives  $(C_1-C_{15})$  as antioxidants was measured by free radicals scavenging [9] by using DPPH method [10]. Several concentrations of the derivatives were prepared and the strength in

inhibiting free radicals of DPPH was tested by coupling with their own free radicals, ascorbic acid was used as a standard when measuring the absorption for its high effectiveness as an antioxidant due to its possession of a number of hydroxyl groups that can be stable free radicals capable of capturing free radicals of DPPH. The 1073 | Page

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compounds absorbance after mixing them with DPPH was measured by using spectral methods at wavelength 517 nm, taking into account the provision of a dark environment during work because the DPPH are affected by light, which may cause the radicals to duplicate.

The percentage of inhibition (%I) was measured according to Equation (1).

$$\%I \frac{\text{blank abs.} - \text{sample abs.}}{\text{blank abs.}} \times 100$$

It denotes the amount of substance required to inhibit 50% of the DPPH radicals with  $IC_{50}$ , where the greater the strength of the substance inhibition of free radicals the less  $IC_{50}$ . All the results are summarized in Table 10.

Symbol of compound	Concentration (ppm)	% I	IC <sub>50</sub>	Symbol of compound	Concentration (ppm)	% I	IC <sub>50</sub>
	25	3.669725			25	0	
C4	50	12.15596	112.6	C11	50	0	29.4
	100	51.31086			100	0.229358	
	25	3.669725			25	60	
C5	50	7.110092	312.7	C12	50	100	39.8
	100	16.51376			100	100	
	25	0			25	20.18349	
C6	50	16.51376	166.3	C <sub>13</sub>	50	33.94495	80.6
	100	31.19266			100	59.40367	
	25	54.68164	49	C14	25	3.211009	153.6
C7	50	50.94007			50	11.92661	
	100	94.75655			100	36.23853	
	25	73.78277			25	0	
C <sub>8</sub>	50	95.50562	40.7	C <sub>15</sub>	50	8.988764	80.7
	10	95			100	76.77903	
	25	27.34082			25	0	
<b>C</b> 9	50	35.58052	61.5	Vit c	50	0	113.3
	100	82.02247			100	57.94506	
	25	44.19476					
C10	50	68.53933	57.9				
	100	68.04869					

Table 10: Inhibition percentage and IC<sub>50</sub> of some prepared compounds C<sub>1</sub>-C<sub>15</sub>

#### Conclusion

In general, the activity of the measured compounds increased with the substance concentration as a result of increasing the percentage of free radicals captured by DPPH, the effectiveness is weak in the four memberd ring derivatives (C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub>) due to the absence of groups that have the ability to form free radicals, while, in five membered rings derivatives (C<sub>7</sub>, C<sub>8</sub>, and C<sub>9</sub>), the activity is higher due to the presence of the sulfur atom that can be stable free radicals, and also shows the good activity in the sixmembered rings derivatives ( $C_{10}$ ,  $C_{11}$ , and  $C_{12}$ ) because they have two groups of carbonyls, as is the case in the seven-membered rings derivatives ( $C_{13}$ ,  $C_{14}$ , and  $C_{15}$ ). On the other hand, all the derivatives prepared from 1,4-phenylenediamine  $(C_4, C_7, C_{10}, and C_{13})$  have good efficacy due to the presence of the terminal amine group. In contrast, it is noted that the effectiveness of the from 6-bromo-2prepared derivatives aminobenzothiazole (C<sub>5</sub>, C<sub>8</sub>, C<sub>11</sub>, and C<sub>14</sub>) is low because the nitrogen atom is bounded by three bonds and it is not able to form free radicals, as for the prepared derivatives from anthranilic acid have a good efficacy due to the presence of the alcohol group. From these conclusions and from the results summerized in the Table (1.10), the compounds (C<sub>4</sub>, C<sub>14</sub>, C<sub>6</sub>, and C<sub>5</sub>) appear in sequence weak activity. As for the compounds (C<sub>9</sub>,  $C_{13}$ , and  $C_{15}$ ), respectively, shows the medium-strength activity, and the compounds (C<sub>8</sub>, C<sub>7</sub>, and C<sub>10</sub>) in sequence show a high activity, were the highest activity compound is  $(C_{12})$  due

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to its containment of many heterogeneous atoms that are capable of formation of free radicals, the compound  $(C_{11})$  indicated the least activity among all the compounds.

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#### **Authors' contributions**

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

#### **Conflict of Interest**

We have no conflicts of interest to disclose.

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