




# Synthesis and antioxidant evaluation for monocarbonyl curcuminoids and their derivatives

Síntesis y evaluación antioxidante para monocarbonyl curcuminoides y sus derivados

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## ARTÍCULO DE INVESTIGACIÓN CIENTÍFICA Y TECNOLÓGICA

### How to cite this paper:

Agel, K N, Abood, E, Alsalmim, T., Synthesis and antioxidant evaluation for monocarbonyl curcuminoids and their derivatives, Basrah, Iraq. Innovaciencia Facultad de Ciencias Exactas, Naturales y Agropecuarias. 2018; 6(1) S1: 1-13.

### Reception date:

Received: 15 August 2018

Accepted: 25 November 2018

Published Online: 28 December 2018

### DOI:

<http://dx.doi.org/10.15649/2346075X.481>

### Keywords:

Cucumine; Monocarbonylcurcuminoids; Antioxidant; DPPH; Pepronal; 4-thiomethoxy benzaldehyde

## ABSTRACT

**Introduction:** Curcumin is a yellow pigment extracted from the *Curcuma longa* L, which have a several biological activities and pharmacological properties. Curcuminoids have a wide range as antioxidant not only in a food system, but also for biological systems. **Materials and Methods:** Acetone, 4-thiomethoxy benzaldehy, pepronal, thiosemicarbazide, 4-phenylthiosemicarbazide and chloroethylacetate. The two Analogous of monocarbonyl curcuminoids (MCCs) have been synthesized by claisen –Schmidt condensation from the reaction between one mole of acetone with two moles of appropriate aromatic aldehydes (4-thiomethoxy benzaldehyde and pepronal) then synthesized their hetero derivatives. The pyrazols derived from the reaction MCCs with hydrazine or one of their derivative (thiosemicarbazide, 4-phenylhydrazine). **Results and Discussion:** All synthesized compounds were characterized by various spectroscopic techniques such as FTIR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, Mass spectroscopies and CHN analysis. The antioxidant activity of synthesized MCCs, 1, 2, 1a, 2a, 3, were determined by the ability to scavenge the stable 1,1-diphenyl-2-picryl hydrazyl (DPPH) free radical according to Blois method. The DPPH inhibition activity was measured by spectrophotometric method. The polyhydroxy curcuminoid has showed a high activity for scavenging of DPPH radicals, the reason is the hydroxyl phenolic group OH give the compound high activity of scavenging the radical by donating hydrogen atom to the DPPH radicals and inhibition the radical activity by hydrogen atom transfer (HAT). Therefore the scavenge of radical activity will be in the order: 3>2a>1a>2>1 and the half maximal inhibitory concentration (IC<sub>50</sub>) between (17.35-135.2) μmol/L. **Conclusions:** The proposed structure of the synthesized compounds were confirmed by used a spectroscopic technique such as, FTIR, Mass spectra (EI), <sup>1</sup>H and <sup>13</sup>C NMR, The antioxidant activity of curcuminoids were studied by using DPPH as a source of radicals. The higher activity of compounds can be attributed to present the phenolic OH group.

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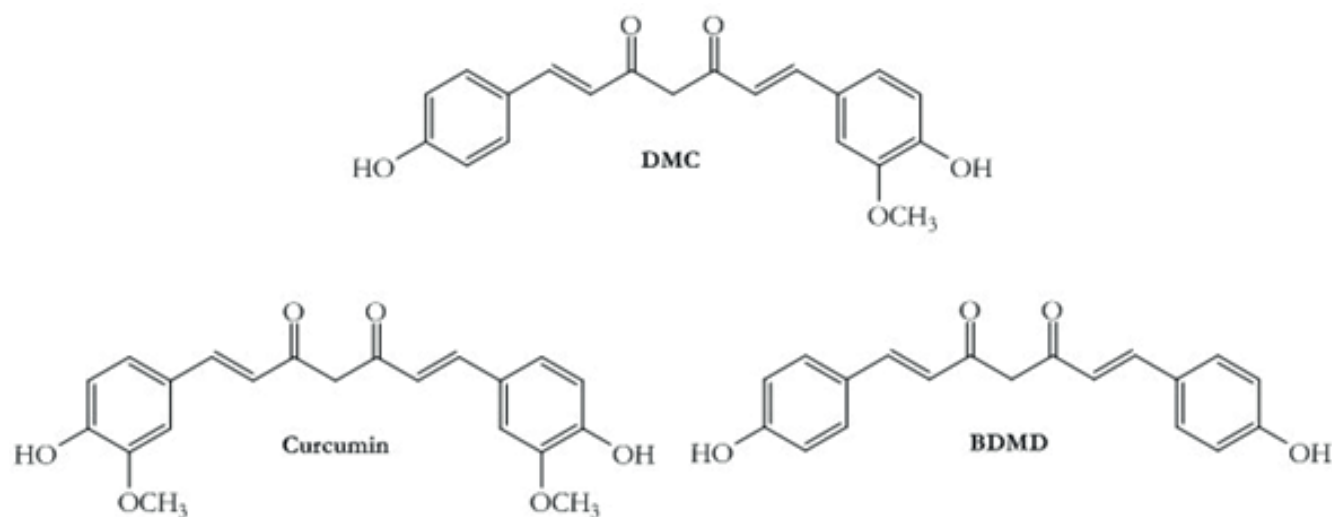
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## INTRODUCTION

Curcumin is a natural extract from rhizome of *curcuma longa* (Turmeric)<sup>(4)</sup> The pigment yellow color of extracted contained three isomers of curcuminoids (curcumin, demethoxy curcumin and bis demethoxy curcumin)<sup>(2)</sup>. This natural compound has been used as food pigment and in food industries<sup>(3)</sup>.

Figure 1 Some examples of Curcumins



In the last decades the pharmacological activity of curcumin has many applications *in-vivo* and *-vitro* as antioxidant<sup>(4)</sup>, anticancer<sup>(5)</sup>, antifungal<sup>(6)</sup>, anti-inflammatory<sup>(7)</sup>, antibacterial<sup>(8)</sup>, and antiviral<sup>(9)</sup>. Because of the curcumin poor solubility in aqueous media<sup>(10)</sup>, which is the most curcumin problems of this material leads to poor bioavailability and absorption then cause a rapid metabolism. Therefore, this material attracted a lot of attention in past decades, especially by modifying their structure and preparing new analogues to increase their bioactivity as anticancer and antioxidant<sup>(11)</sup>. In this study, two monocarbonyl curcumin analogues (MCCs) and their derivatives have been designed, and their activity as an antioxidant agents for scavenging of DPPH radicals have been investigated.

## MATERIALS AND METHOD

### Materials and Reagents

All the chemicals and solvents were used with analytical grade (AR) and highest purity which included piperonal and thiomethoxybenzaldehyde (Aldrich), thiosemicarbazide, pyrogallol and chloroacetylchloride (Merck). All the solvents were used equipped by (BDH) company.

### Instrumentation

FTIR spectra of all compounds were recorded on shimadzu FTIR model Affinity spectrophotometer using KBr pellets in the range (4000-400)  $\text{cm}^{-1}$ . The Mass spectra were scanned by the EI technique 70eV with an Agilent Technologies 5975 spectrometer. The experimental values of  $^1\text{H}$  and  $^{13}\text{C}$ NMR spectra for the studied compounds were scanned on a

Bruker 400MHz spectrometer with a field gradient to operate at 400 MHz for proton observation and 100 MHz for carbon observation using DMSO-d<sub>6</sub> as solvent and TMS as internal standard. Elemental analysis (CHNS) were measured by using elemental Vario MICRO. UV-VISIBLE spectra were measured using a PG-instrument T80<sup>+</sup> spectrophotometer.

## Synthesis

### Preparation of monocarbonyl curcuminoids (MCCs) (1, and 2):

The monocarbonyl curcuminoids 1, and 2 were synthesized by Claisen–Schmidt condensation between acetone (16.65 mmol) with appropriate aromatic aldehydes (33.7 mmol) in (50 mL) ethanol, and (34 mmol) of sodium hydroxide solution as a catalyst. The reaction mixture was stirred for further 10 hours at room temperature. The solid product was collected by filtration, and then washed by water several times, dried then recrystallized from the appropriate solvent (scheme 1).

#### (1E,4E)-1,5-bis(benzo[d][1,3]dioxol-5-yl) penta-1,4-dien-3-one (1):

Color: yellow powder, recrystallized from ethyl acetate, yield: 84%, M.P.: 186-188°C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ ppm): 6.1 (s, 4H, -OCH<sub>2</sub>O-), 7.00 (d, 2H, J=5 Hz, CH=C), 7.19 (d, 2H, J=5 Hz, aromatic), 7.26 (d, 2H, J=10 Hz, aromatic), 7.45 (s, 2H, aromatic), 7.71 (d, 2H, J=5 Hz, CH=C). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ ppm): 102.1, 107, 109, 124.3, 125.7, 129.7, 142.8, 148.2, 149.8, 189.1. MS (70 eV, m/z): 322[M], 279, 189, 175, 135. FTIR (KBr disk, ν, cm<sup>-1</sup>): 3014, 2912, 1643, 1598, 1490, 1190, 1118. Anal. calc. for C<sub>19</sub>H<sub>14</sub>O<sub>5</sub>: C, 70.80; H, 4.38; found: C, 69.47; H, 4.24.

#### (1E,4E)-1,5-bis(4-(methylthio) phenyl) penta-1,4-dien-3-one (2):

Color: yellow powder, recrystallized from ethanol,

yield: 80%, M.P.: 158-159°C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ ppm): 2.52 (s, 6H, -SCH<sub>3</sub>), 7.33 (d, 2H, J=5 Hz, CH=C), 7.27 (d, 4H, J=10 Hz, aromatic), 7.72 (d, 4H, J=10 Hz, aromatic), 7.75 (d, 2H, J=5 Hz, CH=C). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ ppm): 14.7, 125.3, 126.1, 129.4, 131.6, 142.2, 142.5, 186.6. MS (70 eV, m/z): 226.2[M], 311.2, 279.1, 204.2, 177.1, 134.1, 102.1, 89.1, 77.1, 48.1. FTIR (KBr disk, ν, cm<sup>-1</sup>): 3016, 2919, 1643, 1589, 1489, 1337. Anal. calc. for C<sub>19</sub>H<sub>18</sub>OS<sub>2</sub>: C, 69.90; H, 5.56; S, 19.64, found: C, 68.59; H, 5.48; S, 19.47.

### General procedure for the synthesis pyrazoles(1a-c) &(2a-b)

MACs (3.11 mmol) dissolved in (50 mL) of ethanol, and (3.13 mmol) of appropriate hydrazine was added or one of their derivatives (hydrazine monohydrate, thiosemicarbazide, and 4-phenyl hydrazine), then (0.6 g) sodium hydroxide was added to the mixture. The reaction mixture was heated under reflux for 16 hours, then cooled down and poured into iced water, then neutralized by the addition 0.1N HCl. The product was collected by filtration, and then dried and recrystallized from a suitable solvent (scheme 2).

#### (E)-5-(benzo[d][1,3]dioxol-5-yl)-3-(2-(benzo[d][1,3]dioxol-5-yl) vinyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (1a):

Color: yellow powder, recrystallized from benzene: petroleum ether, yield: 55.9%, M.P.: 208-210 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ ppm): 2.97 (dd, H, J=5 Hz, CH<sub>2</sub>-C pyrazole ring), 3.68 (dd, H, J=10 Hz, CH<sub>2</sub>-C pyrazole ring), 5.81 (dd, H, J=5 Hz, CH-N pyrazole ring), 5.97 (s, 2H, -OCH<sub>2</sub>O-), 6.05 (s, 2H, -OCH<sub>2</sub>O-), 6.58 (d, 1H, J=10 Hz, CH=C), 6.62 (s, 1H, Ar), 7.04 (d, 1H, J=5 Hz, CH=H), 6.83-7.28 (d, 4H, J=10 Hz, aromatic), 7.48 (s, 1H, aromatic), 8 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ ppm): 41.9, 62.7, 101.3, 101.8, 106.2, 108.7, 108.9, 116.4, 118.7, 123.7, 130.5, 137.8, 139.2, 146.5, 147.7, 148.4, 148.7, 157.1, 176, 187.6. MS (70 eV, m/z): 395[M], 153, 125, 79, 51. FTIR (KBr disk, ν, cm<sup>-1</sup>): 3458, 3336, 3066, 2891,

1625, 1583, 1489, 1359, 1253, 1193, 1039. Anal. calc. for  $C_{20}H_{17}N_3O_4S$ : C, 60.75; H, 4.33; N, 10.63; S, 8.11, found: C, 60.14; H, 4.08; N, 10.21; S, 7.88.

**(E)-5-(benzo[d][1,3]dioxol-5-yl)-3-(2-(benzo[d][1,3]dioxol-5-yl) vinyl)-N-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1b):**

Color: yellow powder, recrystallized from benzene: petroleum ether, yield: 49%, M.P.: 198-200°C,  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $\delta$  ppm): 3.00 (dd, H,  $J=15\text{ Hz}$ ,  $\text{CH}_2\text{-C}$  pyrazole ring), 3.68 (dd, H,  $J=10\text{ Hz}$ ,  $\text{CH}_2\text{-C}$  pyrazole ring), 5.43 (dd, H,  $J=10\text{ Hz}$ , CH-N pyrazole ring), 5.98 and 6.06 (s, 4H,  $-\text{OCH}_2\text{O}-$ ), 6.71 (d, 1H,  $J=10\text{ Hz}$ ,  $\text{CH}=\text{C}$ ), 6.74-7.36 (m, 11H, aromatic), 7.58 (d, 1H,  $J=8\text{ Hz}$ ,  $\text{CH}=\text{C}$ ), 8.93 (s, 1H, N-H),  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-d}_6$ ,  $\delta$  ppm): 41.7, 59.9, 106.4, 108.7, 109, 110, 118.6, 119.1, 120.5, 128.7, 128.9, 130.8, 139.7, 146.7, 147.9, 148.4, 151.4, 153.8. FTIR (KBr disk,  $\nu$ ,  $\text{cm}^{-1}$ ) 3383, 3037, 2893, 1685, 1654, 1595, 1489, 1244, 1122, 1039. Anal. calc. for  $C_{26}H_{21}N_3O_4S$ : C, 66.23; H, 4.49; N, 8.91; S, 6.80, found: C, 65.82; H, 4.31; N, 7.82; S, 6.44.

**(E)-5-(benzo[d][1,3]dioxol-5-yl)-3-(2-(benzo[d][1,3]dioxol-5-yl) vinyl)-4,5-dihydro-1H-pyrazole (1c):**

Color: yellow powder, recrystallized from methanol, yield: 50%, M.P.: 208-210°C,  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $\delta$  ppm): 3.65 (dd, H,  $\text{CH}_2\text{-C}$  pyrazole ring), 4.1 (dd, H,  $\text{CH}_2\text{-C}$  pyrazole ring), 5.05 ppm (dd, H, CH-N pyrazole ring), 5.96 (s, 2H,  $-\text{OCH}_2\text{O}-$ ), 6.08 (s, 2H,  $-\text{OCH}_2\text{O}-$ ), 6.7 (s, H, -NH), 6.81 (d, 1H,  $\text{CH}=\text{C}$ ), 6.85-7.37 (m, 6H, aromatic), 7.43 (d, 1H,  $J=5\text{ Hz}$ ,  $\text{CH}=\text{C}$ ). MS (70 eV, m/z): 336.3 [M], 309, 135, 123, 71. FTIR (KBr disk,  $\nu$ ,  $\text{cm}^{-1}$ ) 3116, 2924, 1627, 1604, 1489, 1242, 1111, 1033. Anal. calc. for  $C_{19}H_{14}N_2O_4$ : C, 68.26; H, 4.22; N, 8.38, found: C, 67.85; H, 4.24; N, 8.09.

**(E)-5-(4-(methylthio) phenyl)-3-(4-(methylthio) styryl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (2a):**

Color: yellow powder, recrystallized from ethanol, yield: 53.3%, M.P.: 138-140°C,  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $\delta$  ppm): 2.44 (s, 3H,  $-\text{SCH}_3$ ), 2.49 (s, 3H,  $-\text{SCH}_3$ ), 2.98 (dd, H,  $J=15\text{ Hz}$ ,  $\text{CH}_2\text{-C}$  pyrazole ring), 3.7 (dd, H,  $J=10\text{ Hz}$ ,  $\text{CH}_2\text{-C}$  pyrazole ring), 5.85 (dd, H,  $J=5\text{ Hz}$ , CH-N pyrazole ring), 7.04-8.08 (m, 10H, aromatic &  $\text{CH}=\text{C}$ ), 8.4 (s, 2H, NH), MS (70 eV, m/z): 499.3 [M], 339, 352, 276, 248, 191, 150, 60. FTIR (KBr disk,  $\nu$ ,  $\text{cm}^{-1}$ ) 3417, 3248, 3039, 2916, 1620, 1589, 1489, 1342, 1265, 1188, 1087. Anal. calc. for  $C_{19}H_{20}N_2S_2$ : C, 67.02; H, 5.92; N, 8.23; S, 18.83, found: C, 66.83; H, 5.88; N, 8.01; S, 17.90.

**(E)-5-(4-(methylthio) phenyl)-3-(4-(methylthio) styryl)-4,5-dihydro-1H-pyrazole (2b):**

Color: yellow powder, recrystallized from ethanol: n-hexane, yield: 50.4%, M.P.: 169-171°C,  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $\delta$  ppm): 2.44 (s, 3H,  $-\text{SCH}_3$ ), 2.49 (s, 3H,  $-\text{SCH}_3$ ), 2.9 (dd, H,  $J=5\text{ Hz}$ ,  $\text{CH}_2\text{-C}$  pyrazole ring), 3.8 (dd, H,  $\text{CH}_2\text{-C}$  pyrazole ring), 5.2 (dd, H, CH-N pyrazole ring), 6.47 (s, H, -NH), 7.17-7.56 (m, 10H, aromatic &  $\text{CH}=\text{C}$ ). MS (70 eV, m/z): 340.2 [M], 307, 277, 137, 103, 91, 78. FTIR (KBr disk,  $\nu$ ,  $\text{cm}^{-1}$ ): 3224, 3016, 1581, 1481, 1489, 1388, 1157, 1065. Anal. calc.  $C_{20}H_{21}N_3S_3$ : C, 60.12; H, 5.30; N, 10.52; S, 24.07, found: C, 59.79; H, 5.11; N, 10.26; S, 23.87.

**Procedure for the synthesis of 2 - chloro -1-(2,3,4-trihydroxyphenyl) ethan-1- one:**

To a cooled solution of stirred of aluminum chloride (24g) dissolved in DCM at 10-15°C, (8g) of pyrogallol in (50mL) DCM was added drop-wisely within 20 min. (5mL) of chloroacetyl chloride was added to the reaction mixture which is still at the same temperature. The temperature of reaction mixture raised up to room temperature and further stirring for

another 20 hours. After that time the reaction was poured onto (100 mL) of dilute hydrochloric acid with stirring for 2 hours at room temperature. The solid material was collected by filtration and washed with water, then the solid suspended in dilute acetic acid solution and heated to 85°C. The mixture was cooled down to room temperature. The product was filtered, washed with water and dried, then recrystallized from benzene (scheme 3).

Color: white powder, recrystallized from benzene, white powder, recrystallized from benzene, yield: 85%, M.P.: 169-170 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ ppm): 5.03 (s, 2H, -CH<sub>2</sub>-), 6.44 (d, H, J=5 Hz, aromatic), 7.3 (d, H, J=5 Hz, aromatic), 8.77, 10.28, 11.63 (s, 3H, -OH), <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ ppm): 47.3, 109, 112, 123, 133, 152.2, 153.4, 195.2. MS (70 eV, m/z): 202.1 [M], 153, 125, 79, 51. FTIR (KBr disk, ν, cm<sup>-1</sup>), 3498, 3390, 3095, 2989, 1637, 1523.

**Procedure for the synthesis of (E)-4-(2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(2 (benzo[d][1,3]dioxol-5-yl) vinyl)-4,5-dihydro-1H-pyrazol-1-yl) thiazol-4-yl) benzene-1,2,3-triol (3):**

In the reaction vessel (0.9g, 2.36 mmol) of compound (1a), and (0.48g, 2.36 mmol) of compound 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one dissolved in (20 mL) of dimethyl formamide. The reaction mixture was heated under reflux for 6 hours. The solid product was collected by filtration, dried then recrystallized from ethylacetate (scheme 4).

Color: light brown powder, recrystallized from ethanol, yield: 56%, M.P.: 260-261 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ ppm): 3.12 (dd, H, J= 10 Hz, pyrazole ring), 3.84 (dd, H, J=10 Hz, pyrazole ring), 5.58 (dd, H, J=5 Hz, pyrazole ring), 5.98, and 6.05 (s, 4H, -OCH<sub>2</sub>O-), 6.28 (d, 1H, J=10 Hz, CH=C), 6.93 (s, 1H, H of thiazole), 6.79-7.17 (m, 8H, aromatic), 7.38 (d, 1H, J=5 Hz, CH=C) 8.06 (s, H, -OH), 8.98 (s, 1H, -OH), 10.64 (s, H, -OH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ ppm): 43.1, 64, 101.7, 106.2, 106.3, 107.7, 108.9, 109, 111.1, 116.9, 118.4, 119.7, 123.6, 130.9, 133.3, 135.6, 137.5, 145.5, 146.6, 147.2, 148.2, 148.4, 148.5, 149.5, 155.5, 164. MS (70 eV, m/z): 543.3 [M], 394, 336, 147, 89, 43. FTIR (KBr disk, ν, cm<sup>-1</sup>), 3537, 3429, 3032, 2908, 1604, 1489, 1242, 1087, 1037. Anal. calc. C<sub>28</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>S: C, 61.87; H, 3.89; N, 7.73; S, 5.90, found: C, 61.61; H, 3.67; N, 7.57; S, 5.73.

**DPPH Radical Scavenging Assay**

The antioxidant activity of synthesized curcuminoids (1, 1a, 2, 2a, and 3) were determined by measuring the ability of scavenging the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals according to Blois method<sup>(12,13)</sup>. The DPPH inhibition activity was measured by spectrophotometric method, by mixing (1 mL, 200 μmol/L) of ethanolic solution of DPPH with (1 mL) of different concentrations (50, 100, and 200) μmol/L of ethanolic solution of synthesized curcuminoids. The absorbance was read at 517 nm as functional of different times by using uv-visible spectrophotometer. In addition, there was a notable change DPPH color graduate from violet to yellow or colorless. The percentage of inhibition was calculated by the following equation<sup>(14,15)</sup>.

$$\% \text{inhibition percentage} = \frac{A_c - A_s}{A_c} \times 100$$

*A<sub>c</sub>*: control absorbance, the absorbance of pure DPPH

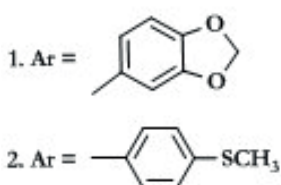
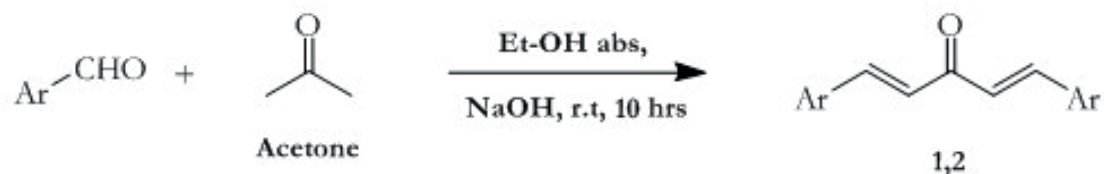
*A<sub>s</sub>*: sample absorbance, the absorbance of DPPH mixed with sample

The liner curve was obtained by plotting inhibitor percentage of radical versus concentrations of compounds.

## RESULTS AND DISCUSSION

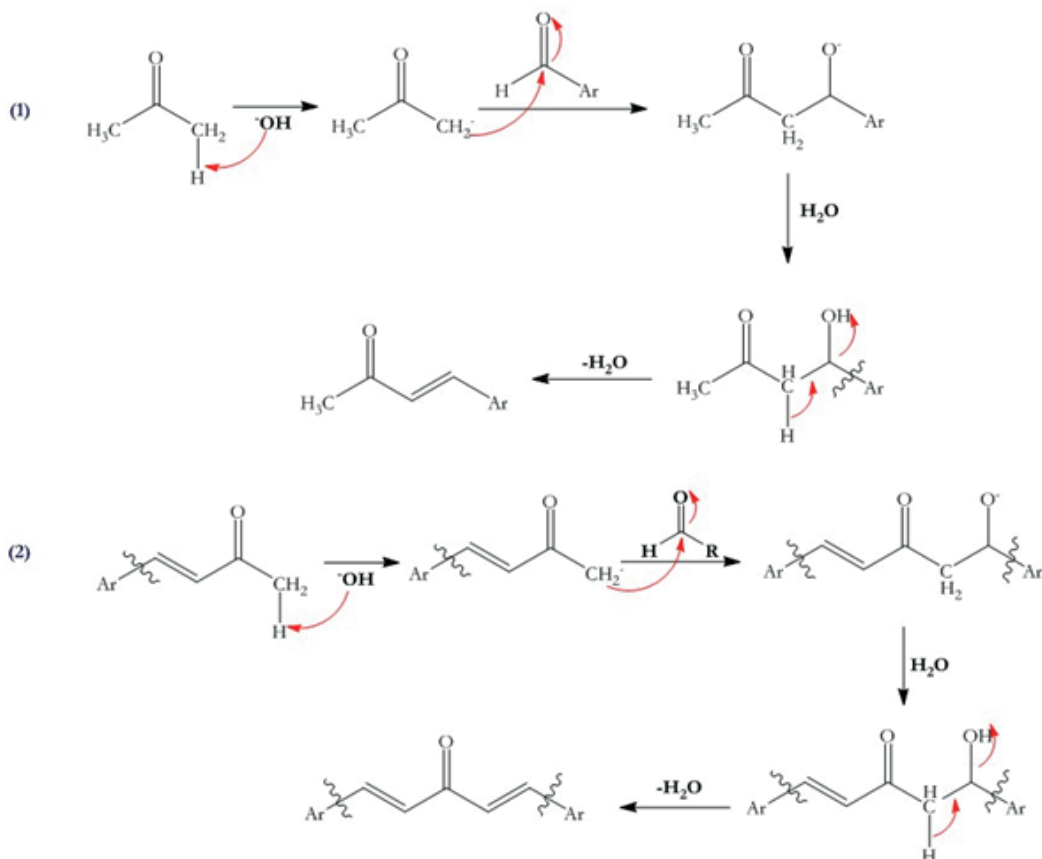
### Spectroscopy identification:

The monocarbonyl curcuminoids (MCCs) (**1**, and **2**) prepared according to (Scheme1). The proposed structure has confirmed by using spectroscopic techniques such as FTIR, Mass spectrometry,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy as well as the elemental analysis.



### Scheme 1 Preparation compound (MCCs).

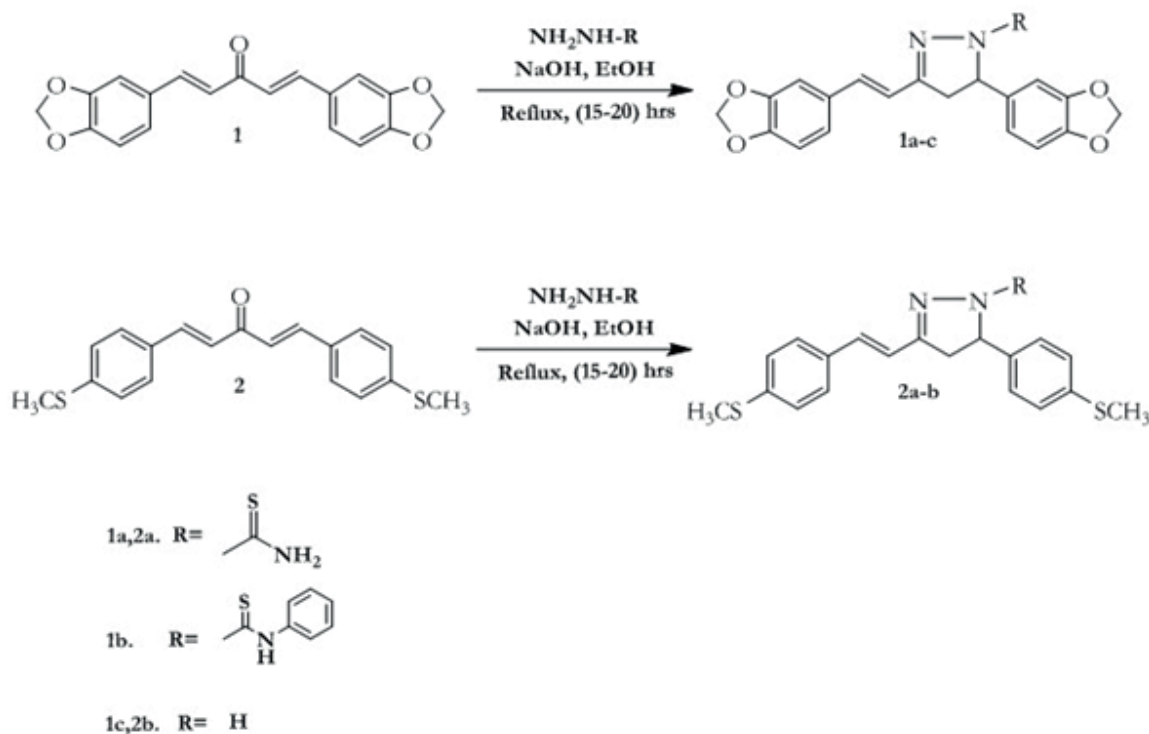
The (MCCs) prepared according to Claisen–Schmidt condensation reaction between acetone and, aromatic aldehyde, (scheme 2) represents the suggested proposed reaction mechanism.



### Scheme 2 Reaction mechanism of (MCCs).

The IR spectra of the prepared compounds exhibit all bands of functional groups. The spectra of compound (**1**, and **2**) have shown stretching vibration bands at  $\nu$  (3014, 3016)  $\text{cm}^{-1}$ , and  $\nu$  (2912, 2916)  $\text{cm}^{-1}$  attributed to C-H aliphatic, and C-H aromatic, respectively. The stretching vibration band appeared at  $\nu$  (1643, 1643.35)  $\text{cm}^{-1}$  attributed to ketone group as well as band of C=C group at  $\nu$  (1598, 1603)  $\text{cm}^{-1}$ . The  $^1\text{H}$ NMR spectra analysis for (MCCs) at room temperature in  $\text{DMSO-d}_6$  confirmed the proposed

structure. The spectrum of compound (**1**) has shown singlet signal for  $\text{CH}_2\text{-O}$  at  $\delta$  (6.10) ppm, doublet signals of vinylic proton at  $\delta$  (7.0, and 7.71) ppm and signals at  $\delta$  (7.19, 7.26, and 7.45) ppm which attributed to CH-C aromatic. The  $^{13}\text{C}$ NMR spectra showed signal at  $\delta$  (102) ppm, and  $\delta$  (188) ppm assigned to  $\text{CH}_2\text{-O}$  and ketone groups, respectively. The pyrazole derivatives of (MCCs) was synthesized from the reaction curcuminoids with hydrazine and their derivatives according to (scheme 3).



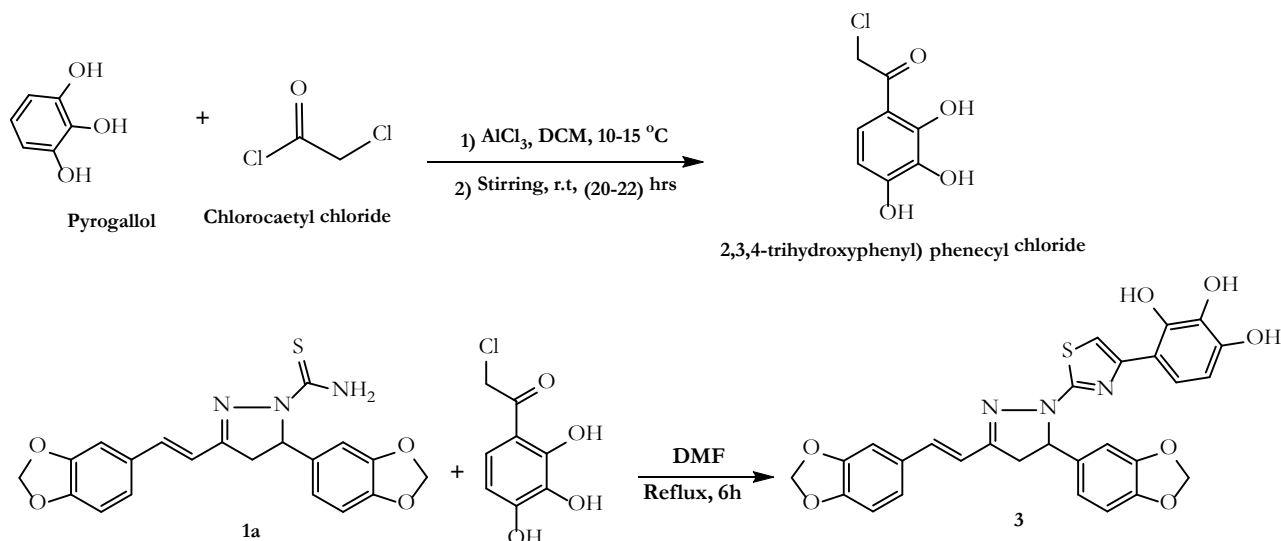
**Scheme 3** Preparation pyrazols of (MCCs).

The IR spectra of pyrazole compounds show a new band at  $\nu$  1620-1627 ( $\text{cm}^{-1}$ ) attributed to the C=N in pyrazol ring<sup>(16)</sup>, the bands at  $\nu$  (3066-3014)  $\text{cm}^{-1}$  related to C-H aromatic and at  $\nu$  (1604-1598)  $\text{cm}^{-1}$  assigned of stretching vibration of C=C group. In addition, the band of carbonyl group disappeared in spectra of curcuminoids derivatives (pyrazoles). The  $^1\text{H}$ NMR spectra analysis for pyrazoles show new signals due to the interaction between neighbor protons in pyrazole ring, two doublet of doublet signals at  $\delta$  (2.49- 2.97) ppm, and  $\delta$  (3.68- 4.0) ppm attribut-

ed to C- $\text{CH}_2$ -C of pyrazol ring as well as doublet of doublet signal at  $\delta$  (5.05-5.85) ppm assigned of CH=N of pyrazol ring<sup>(17)</sup>. In addition exhibited signals attributed to the aliphatic, aromatic, and vinylic protons. The  $^{13}\text{C}$ NMR spectra of pyrazoles display signals of the carbon skeleton for pyrazoles. The spectra characterized signals attributed to aliphatic carbon, vinylic carbon, aromatic carbon, and C=N of pyrazol ring. Mass spectra (EI) results show the proposed formula. The elemental analysis was used to determine the molecular formula of the prepared

compounds. In all cases, the differences in values of elemental percentage between measured and calculated formula are within acceptable values. The com-

ound (**3**) was prepared from the reaction of compound (**1a**) with 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one, according to (scheme 4).



**Scheme 4** preparation thiazolo thiazole of (MCCs).

The compound 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one was prepared according to Friedel-Crafts reaction. The proposed structure was confirmed by using spectroscopic techniques. The IR spectrum shows strong band at  $\nu(3390) \text{ cm}^{-1}$  and band at  $\nu(1637) \text{ cm}^{-1}$  attributed to hydroxyl group, and carbonyl group, respectively. The  $^1\text{H}$ NMR spectrum shows signal at  $\delta(5.03) \text{ ppm}$ , doublet signals at  $\delta(6.44, \text{ and } 7.3) \text{ ppm}$  attributed to aromatic proton as well as three singlet signals at  $\delta(8.77, 10.28, \text{ and } 11.63)$  assigned to phenolic proton. The  $^{13}\text{C}$ NMR spectrum shows eight signals one of them at  $\delta(196) \text{ ppm}$  attributed to carbonyl carbon. The Mass spectrum results improved the proposed formula. The pyrazolo thiazol derivatives characterized by spectroscopic techniques, the IR spectrum shows bands at  $\nu(3527) \text{ cm}^{-1}$ ,  $\nu(3032) \text{ cm}^{-1}$ ,  $\nu(2908) \text{ cm}^{-1}$ ,  $\nu(1621) \text{ cm}^{-1}$ ,  $\nu(1604) \text{ cm}^{-1}$  and  $\nu(1087, 1037) \text{ cm}^{-1}$  attributed to C-OH, C-H aromatic, C-H aliphatic, C=N, C=C, and O-CH<sub>2</sub>-O groups. The  $^1\text{H}$ NMR spectrum shows signals at  $\delta(10.46, 8.98, \text{ and } 8.06) \text{ ppm}$  attributed to phenolic proton, signals at  $\delta(6.23-7.38) \text{ ppm}$  attributed to olefinic and aromatic protons, as well as

signal at  $\delta(6.28) \text{ ppm}$  assigned to O-CH<sub>2</sub>-O proton and three doublet of doublet signals at  $\delta(3.12, 3.84, \text{ and } 5.58) \text{ ppm}$  attributed to protons of pyrazol ring. The elemental analysis was used to determine the molecular formula of prepared compounds. In all cases, the differences in values of elemental percentage between measured and calculated formula are within the acceptable values.

#### Antioxidant activity assay

The *in-vitro* free radical inhibition activity of (MCCs) and some derivatives were analyzed by the DPPH method, the percentage of inhibition activity and the result of IC<sub>50</sub> are gathered in (Table1), and (figure 7). The inhibition percentage activity of synthesized compounds (**1, 1a, 2, 2a, and 3**) concentration (50-200)  $\mu\text{mol/L}$  are measured by the decreasing of DPPH absorbance at 517 nm with time (figures 1-6). The compounds showed lower in scavenging activity in comparison with ascorbic acid, expect the compound (**3**) which showed higher inhibition activity of 66.8% at 50  $\mu\text{mol/L}$ , 78.57% at 100  $\mu\text{mol/L}$ , and 95% at 200  $\mu\text{mol/L}$ . The other compounds (**1, 1a,**



2, and 2a) showed lower inhibition at 200  $\mu\text{mol/L}$ . Therefore the compound 3 showed a high inhibition activity due to the phenolic OH groups<sup>(18)</sup> that able to scavenge the radicals. The scavenge of radicals ac-

tivity of compounds (1, 1a, 2, 2a, and 3) will be in the order of: 3 > 2a > 1a > 2 > 1. As well as half maximal inhibitory concentration ( $\text{IC}_{50}$ ) between (17.35-135.2)  $\mu\text{mol/L}$ .

Figure 2: DPPH free radical scavenging activity of compounds (1) at 50-200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

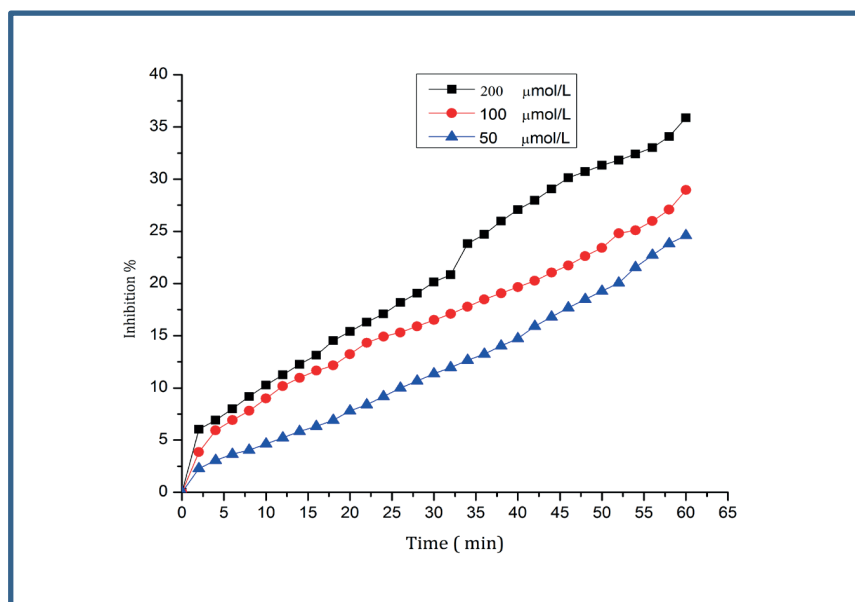


Figure 3: DPPH free radical scavenging activity of compounds (1a) at 50-200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

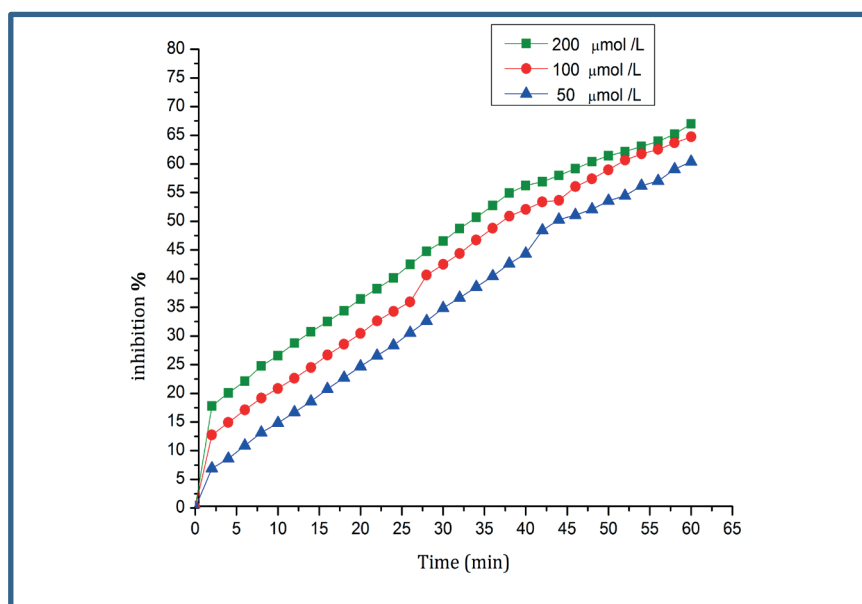


Figure 4: DPPH free radical scavenging activity of compounds (2) at 50-200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

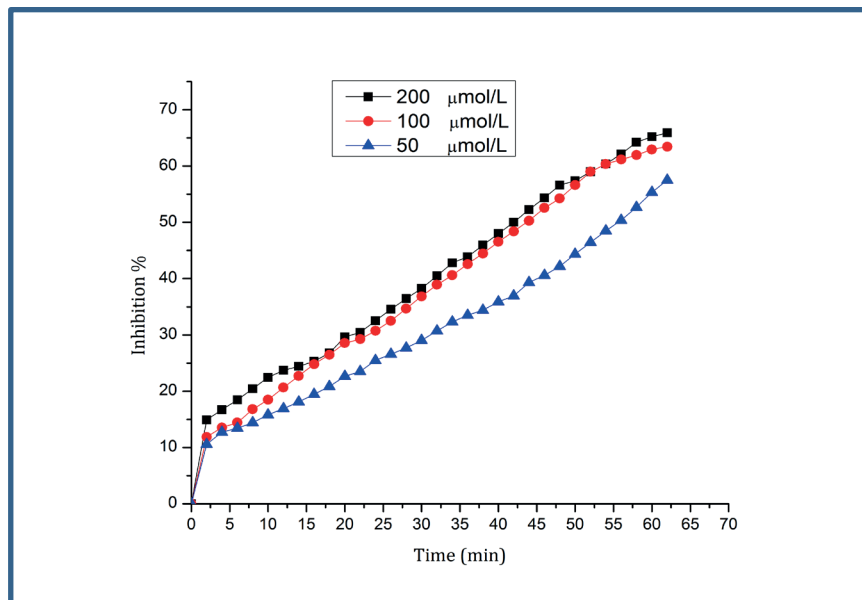


Figure 5: DPPH free radical scavenging activity of compounds (2a) at 50-200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

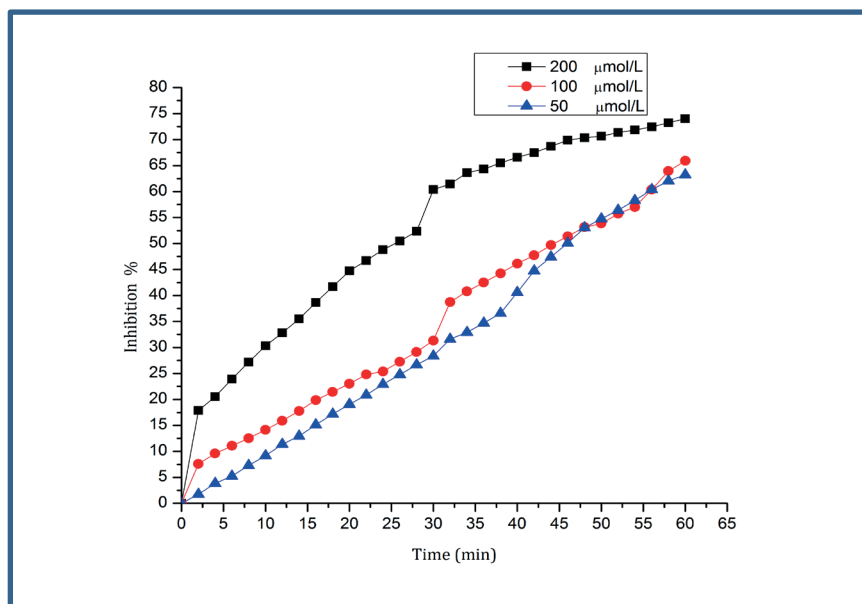


Figure 6: DPPH free radical scavenging activity of compounds (3) at 50-200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

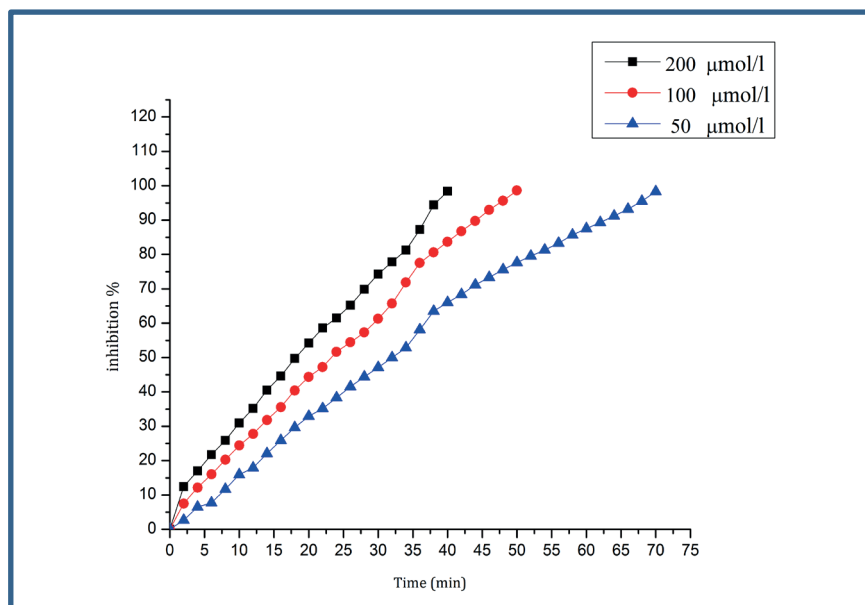


Figure 7: DPPH free radical scavenging activity of ascorbic acid at 200  $\mu\text{mol/L}$  concentrations showing percentage inhibition.

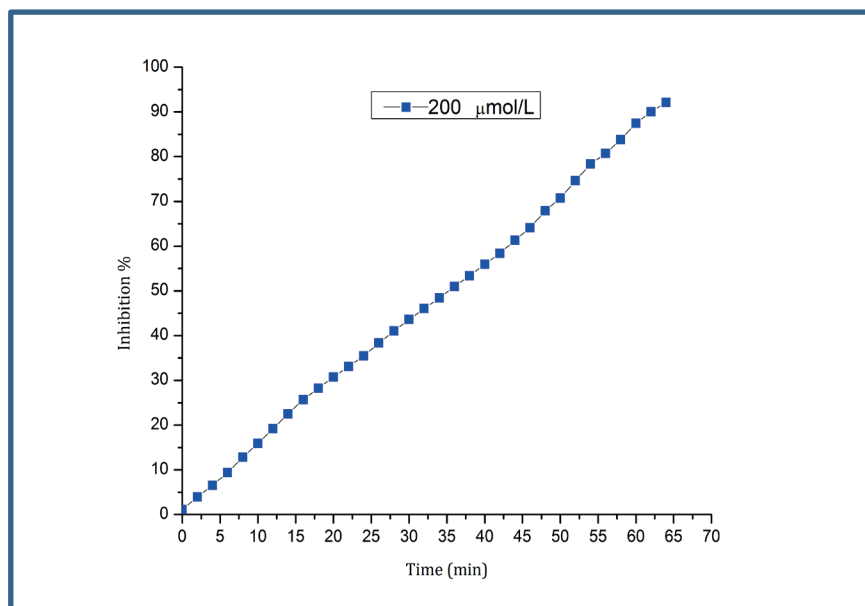


Figure 8: The percentage inhibition of DPPH free radical scavenging activity of compounds (1, 1a, 2, 2a, 3, and Vit.C) at 50-200  $\mu\text{mol/L}$  concentrations.

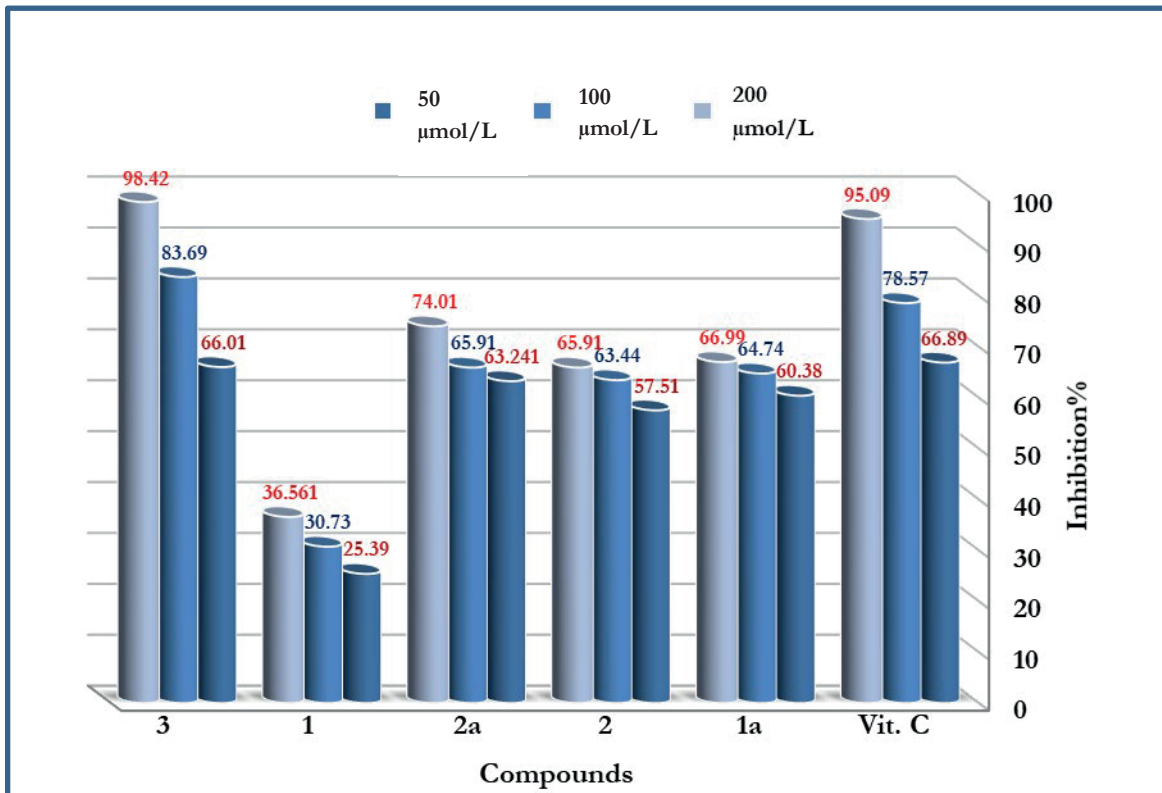


Table 1: *In-vitro* antioxidant activities of compounds (1, 1a, 2, 2a, and 3).

Compounds	Percentage of Inhibition			IC <sub>50</sub> $\mu\text{mol/L}$
	50 $\mu\text{mol/L}$	100 $\mu\text{mol/L}$	200 $\mu\text{mol/L}$	
Ascorbic acid	66.89	78.57	95.09	18.74
1a	60.38	64.74	66.99	60.12
2	57.51	63.44	65.91	20.97
2a	63.241	65.91	74.01	31.59
1	25.39	30.73	36.561	135.2
3	66.01	83.69	98.42	17.35

## CONCLUSIONS

In this study, the monocarbonyl curcuminoids (MCCs) was synthesized according to Claisen–Schmidt condensation reaction between acetone and aromatic aldehydes, followed by synthesis of their derivatives. The IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, and Mass

spectra as well as elemental analysis of the studied-compounds are considered as the essential identification. The antioxidant activity of curcuminoids were studied by using DPPH as a source of radicals. The higher activity of compounds can be attributed to present the phenolic OH group. IC<sub>50</sub> value between (17.35-135.2)  $\mu\text{mol/L}$ .

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