

# Ultrasound-assisted Synthesis of Some New Curcumin Analogs and Their Corresponding Pyrazoline Derivatives

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**Abstract**—In this work, a series of new curcumin mono-carbonyl analogs containing benzyloxy moieties and their pyrazoline derivatives were synthesized using a green method (ultrasound assisted technique) along with traditional method. The work also includes a comparison between the two methods together and with the reported results. Remarkable improvements were achieved by dropping down the reaction time from hours to minutes and obtaining higher yields of the products.

**Index Terms**—Curcumin, Mono carbonyl curcumins, Pyrazoline, Ultrasound.

## 1. INTRODUCTION

According to the high clash of the micro-organisms against typical antibiotics and low reactivity of communal antibiotics, there is an actual need for the innovation of new compounds and encourage chemists developing new biologically active compounds with higher antimicrobial activities and lower risks.

Scientific researches that exceed four decades have approved the diverse pharmacological influence of curcumin and established its ability to act as a chemopreventive agent as well as a potential therapeutic agent against several chronic diseases (Priyadarsini, 2014). Curcumin (bis- $\alpha$ ,  $\beta$ -unsaturated diketone) has an interesting structure with two phenolic groups and one active methylene function, which are potential sites for attaching biomolecules.

Curcumin is a natural yellow bioactive pigment which obtained from rhizomes of plant *Curcuma longa*, a member of the Zingiberaceae (ginger) family (Priyadarsini, 2014, and Shishodia, et al., 2005). Curcumin was first isolated from the plant *C. longa* in 1815 (Vogel and Pelletier, 1815), its structure as diferuloylmethane was determined in 1910

and first synthesis in 1937 started from the chloride of the carbomethoxyferulic acid was achieved by Paban, 1937. After the discovering, its potential anticancer effect of curcumin which was report by Singh and Aggarwal (1995), considerable attention has been focused to date on curcumin and its analogs including synthesis using different methods (Lei, et al., 2011; Li, et al., 2016), structure modification (Haneefa, et al., 2014; Wang, et al., 2016), biological and pharmacological effects such as: Anti-inflammatory (Zhao, et al., 2010), antioxidant (Bayomi, et al., 2013; Selvam, et al., 2005), antitumor anti-cancer (Pan, et al., 2016; Das and Chakraborty, 2016), antimalarial (Manohar, et al., 2013), antidiabetic activity (Konatham, et al., 2010), and highly potent antiparasitic activities (Din, et al., 2016). Curcumin is also used as flavor and food coloring-materials, used as environmental dye; it is known as Natural yellow 3 and is assigned E100 number (Gryniewicz and Slifirski, 2012). Mono carbonyl analogs of curcumin can be converted to heterocyclic compounds via cyclization of  $\alpha$ , $\beta$ -unsaturated carbonyl moieties with hydrazine hydrate and other cyclizing agents (Shim, et al., 2002).

Herein, we have described a green method (ultrasound technique) besides a traditional method to synthesize some new mono carbonyl curcumin analogues, and their cyclic products along with comparison between the two methods together and with previous reports.

## II. MATERIAL AND METHODS

### A. Experimental Notes

Melting Points were determined by a Stuart Scientific melting point apparatus (SMP3). IR-Spectra were recorded on a SHIMADZU, Fourier Transform-Infrared spectroscopy Mod IR Affinity-1 CE, in which solid materials were taken as a disc KBr special for spectroscopy. The  $^1\text{H}$ -nuclear magnetic resonance (NMR) and  $^{13}\text{C}$ -NMR were taken on a Bruker 400 MHz ultra-shield with TMS as internal references.

### B. Preparation of Benzyloxy-Benzaldehydes (1a-e)

Benzyloxy-benzaldehydes (1a-e) have been prepared according to reported procedure (Nagaini, et al., 2009).

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The ppt. was recrystallized from ethanol, the physical properties of the prepared substituted benzyloxy-benzaldehydes (1a-e) where outlined in Table I.

*C. Synthesis of 1, 5-bis (o,m, or p-(substitutedbenzyloxy) phenyl)penta-1,4-dien-3-one (2a-e)*

*Classical Method: 1,5-bis(4-(3-nitrobenzyloxy)phenyl)penta-1,4-dien-3-one (2a)*

Mono carbonyl analog of curcumin (2a) was synthesized by mixing acetone (0.14 g, 2.5 mmol), 4-(3-nitrobenzoxly) benzaldehyde (5 mmol) and sodium hydroxide (0.2 g, 5 mmol) in ethanol (20 mL). The mixture was refluxed for (3 h) until all starting materials had reacted, which was monitored by the formation of red color in testing with drops of  $H_2SO_4$ . The cooled mixture was solidified and filtered off, dried and recrystallized from ethanol to give pure yellow crystals of curcumin analog (2a), 0.63 g 84% (Shah, 2010).

*Ultrasound Assisted Synthesis Method (Chen, et al., 2004)*

A mixture of acetone (0.14 g, 2.5 mmol), sodium hydroxide (0.2 g, 5 mmol), and substituted benzaldehydes (5 mmol) in ethanol (20 mL) was irradiated in the water bath ultrasonic cleaner at room temperature for 5-10 min, until all starting materials had reacted, the reaction proceeded as in a. The results were tabulated in Table II.

*D. (o,m,p-(substitutedbenzyloxy)phenyl)-3-(o,m,p-(substitutedbenzyloxy) styryl)-2-pyrazoline (3a-e)*

*Classical Method (Hawaiz and Samad, 2012)*

A mixture of newly prepared curcumin analogues (2a-e) (1 mmol), hydrazine hydrate (2 mmoles) and sodium hydroxide (0.1 g, 2.5 mmol) in methanol (20 mL) was refluxed with stirring for (3-4 h) until complete the reaction which was monitored by change the color to green in testing with drops of  $H_2SO_4$ . The ppt. was isolated by suction filtration, washed with ethanol, dried and purified by recrystallization from xylene. The physical properties of the prepared pyrazolines (3a-e) are summarized in Table III.

*Ultrasound Assisted Synthesis Method (Trilleras, et al., 2013)*

A mixture of hydrazine hydrate (2 mmol), curcumin analogous (1 mmol), and sodium hydroxide (0.1 g, 5 mol) in methanol (20 mL) was irradiated for appropriate time at (25-40°C) in a water bath of an ultrasonic cleaner until the disappearance of curcumin analogs indicated by changing the color from yellow to white and monitoring by green color formation in testing with drops of  $H_2SO_4$ .

The desired products were separated by suction filtration and washed with water to neutralize and with ethanol, after which purified by recrystallization from xylene. The reaction time, m.p. and the percentage of yields are listed in Table III.

### III. RESULTS AND DISCUSSION

Some new curcumin analogs (2a-e) were synthesized and converted to pyrazolines (3a-e) using different methods and techniques such as traditional method and ultrasound irradiation technique to provide the products in high yields

TABLE I

SOME PHYSICAL PROPERTIES OF PREPARED BENZYLOXY BENZALDEHYDES (1A-E)

Comp.	R	Molecular formula	Yield%	M.P./C	Time hrs
1 <sub>a</sub>	4-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>15</sub> H <sub>13</sub> NO <sub>4</sub>	83	84-86°C	4
1 <sub>b</sub>	4-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>14</sub> O <sub>2</sub>	85	71-73°C	5
1 <sub>c</sub>	3-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>14</sub> O <sub>2</sub>	83	60-62°C	6
1 <sub>d</sub>	2-(4-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>15</sub> H <sub>13</sub> ClO <sub>2</sub>	85	82-83°C	5.5
1 <sub>e</sub>	2-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>15</sub> H <sub>13</sub> NO <sub>4</sub>	79	124-126°C	4

TABLE II

SOME PHYSICAL PROPERTIES OF PREPARED MONO-CARBONYL ANALOGUES OF CURCUMIN (2A-E)

Comp.	R	Molecular formula	Yield%	M.P./°C	Time min.
2 <sub>a</sub>	4-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub>	173-175°C	95 84 classic	5
2 <sub>b</sub>	4-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>31</sub> H <sub>26</sub> O <sub>3</sub>	179-180°C	90	10
2 <sub>c</sub>	3-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>31</sub> H <sub>26</sub> O <sub>3</sub>	98-99°C	86	10
2 <sub>d</sub>	2-(4-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>24</sub> Cl <sub>2</sub> O <sub>3</sub>	121-124°C	89	8
2 <sub>e</sub>	2-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub>	151-153°C	88	5

TABLE III

SOME PHYSICAL PROPERTIES OF THE PREPARED CYCLIZED CURCUMIN ANALOGUES (3A-E)

Comp.	R	Molecular formula	M.P./°C	Yield %		Time/ Hours
				Ultra 1	Ultra 1	
				2	Classic 2	
3 <sub>a</sub>	4-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	169-170°C	94	1	72 3
3 <sub>b</sub>	4-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>31</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	133-134°C	77	1	79 3
3 <sub>c</sub>	3-O-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	C <sub>31</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	232-234°C	80	1.25	54 3.5
3 <sub>d</sub>	2-(4-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	>300°C	90	1	80 3
3 <sub>e</sub>	2-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -O-)	C <sub>31</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	172-173°C	95	1.25	93 4

and short reaction times in three main steps as shown in the scheme of Fig. 1.

The exciting improvement was obtained in the formation of newly derivatives of curcumins (2a-e) in using ultrasonic technique by dropping down the reaction time from hours to minutes and increasing the percentages of the products as compared to the traditional methods and literatures (Handayani, et al., 2012).

The formation of the curcumine analogs (2a-e) was confirmed on the basis of their IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectral data. In the IR spectra Table IV, the shifting of the absorption band of carbonyl group of the two reactants benzyloxy benzaldehydes and acetone to lower wave numbers 1666-1647/cm is a strong evidence for the formation of conjugated dibenzalacetones (Hussein, et al., 2013).

The <sup>1</sup>H-NMR spectra of curcumin analogs (2b-d) (Fig. 2), Table V, show characteristic doublet signals for α, β- protons at (7-8) ppm, which overlapped with aromatic protons. Obviously, in all cases, the doublet for (H<sub>β</sub>) appear

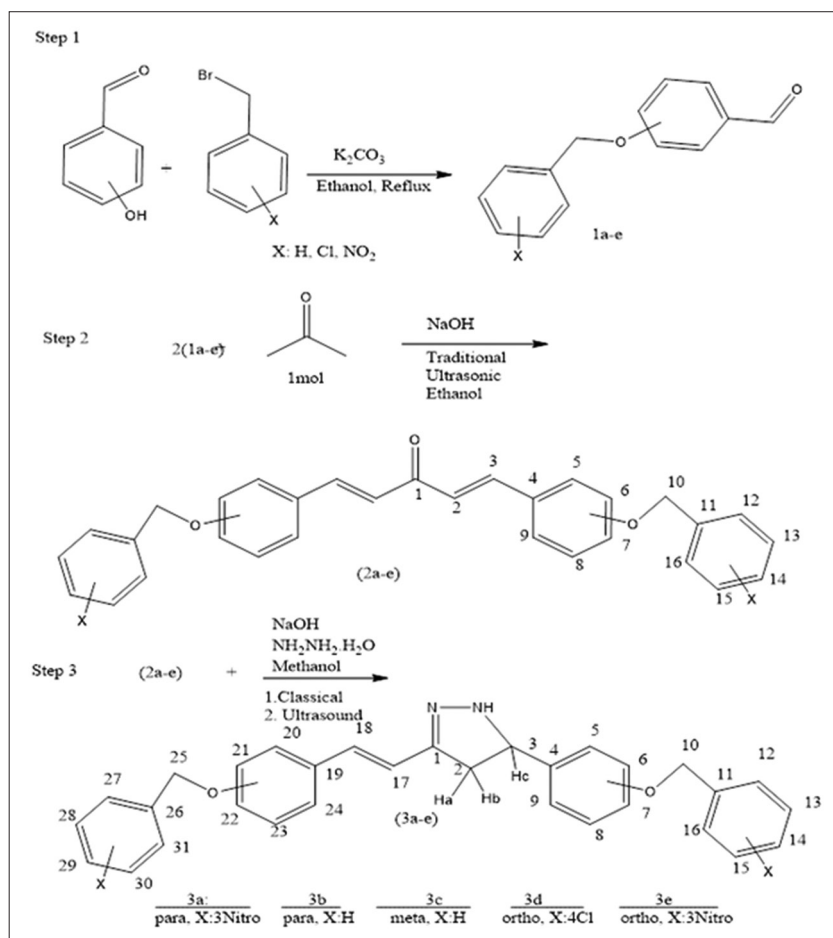


Fig. 1. Synthesis of curcumin mono-carbonyl compounds and their purazoline products.

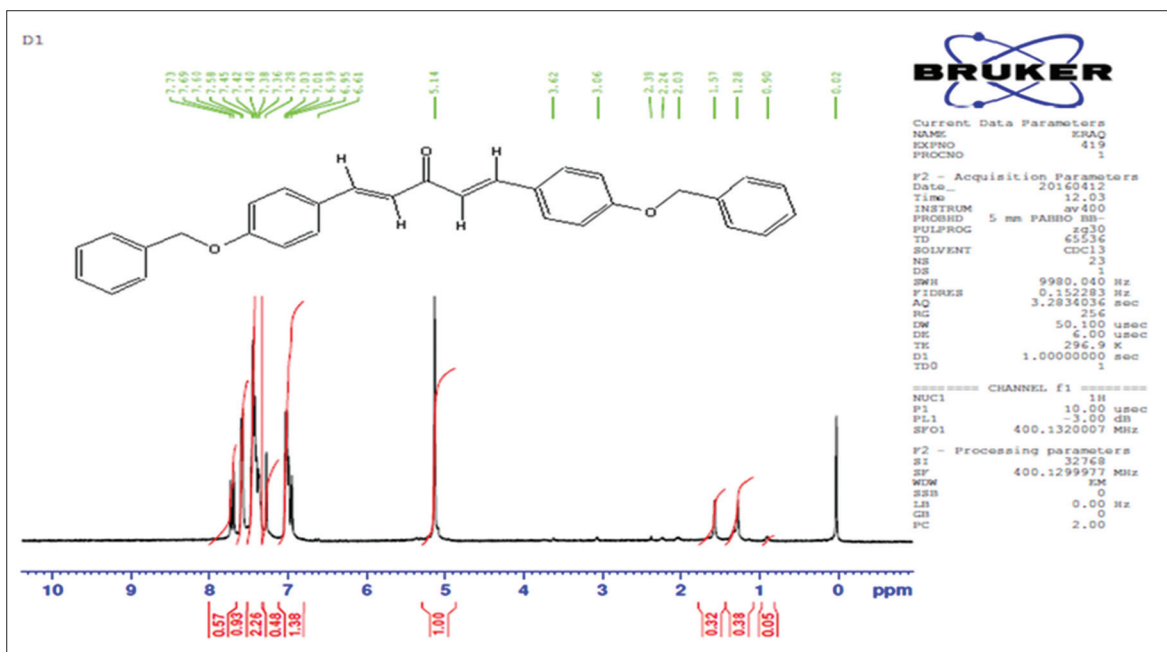


Fig. 2. The  $^1\text{H}$ -nuclear magnetic resonance spectrum of compound 2b.

at higher wave numbers than aromatic protons, while the ( $H_a$ ) completely mixed with aromatic protons; it is hard to distinguish it at a fixed number (Hussein, 2014). The

$^1\text{H}$ -NMR spectrum of all compounds showed a singlet signal at 5.1 ppm related to the two protons of  $-\text{O}-\text{CH}_2$  of benzyloxy group, and a doublet at 7.7 ppm corresponding to  $\text{CH}_\beta$  proton,

a multiplet at 6.9-7.5 ppm which contain  $H_\alpha$  and protons of two phenyl rings; this is a good confirmation for the expected products. Further support for structure elucidation is come from  $^{13}\text{C}$ -NMR spectra (Fig. 3) Table VI, assignment of

TABLE IV  
ASSIGNMENT OF CHARACTERISTIC FREQUENCIES ( $\text{cm}^{-1}$ ) OF IR SPECTRA FOR THE PREPARED COMPOUNDS (1A-E, 2A-E AND 3A-E)

Prod.	Benzyloxy-benzaldehyde (1a-e)		Curcumin analogs (2a-e)		Pyrazoline (3a-e)	
	C=Ostr.	C=Cstr.	C=Ostr.	C=Cstr.	N-Hstr.	C=C, C=N
a	1687	1601	1647	1618,1602	3340	1606
b	1683	1600	1653	1627, 1593	3327	1600
c	1680	1603	1653	1629,1595	3340	1598
d	1681	1600	1651	1616, 1593	3342	1600
e	1681	1598	1666	1612, 1596	3325	1598

TABLE V  
THE  $^1\text{H}$ -NMR DATA FOR THE PREPARED CURCUMIN ANALOGS (2 B, C, D) AND PYRAZOLINE (3B): SOLVENT  $\text{CDCl}_3$

Product	$\delta/\text{ppm}$	Multiplicity	Intensity	Assignment
2 b	5.14	s	2H	-O-CH <sub>2</sub> -H <sub>10</sub>
	6.95-7.6	m	10H	Ar-H-[H <sub>2</sub> , + 2Ar ring H]
	7.73	d	1H	H3- $\beta$ -proton
2 c	5.1	s	2H	-O-CH <sub>2</sub> -H <sub>10</sub>
	7.01-7.4	m	10H	Ar-H-[H <sub>2</sub> , + 2Ar ring H]
	7.7	d	1H	H3- $\beta$ -proton
2 d	5.1	s	2H	-O-CH <sub>2</sub> -H <sub>10</sub>
	6.93-7.50	m	10H	Ar-H-[H <sub>2</sub> , + 2Ar ring H]
	8.05	d	1H	H3- $\beta$ -proton
3 b	2.87	dd	1H	Ha
	3.27	dd	1H	Hb
	4.81	dd	1H	Hc
	5.07	s	2H	-O-CH <sub>2</sub> -H <sub>10,25</sub>
	5.86	d	1H	H <sub>17</sub>
	6.58	d	1H	H <sub>18</sub>
	6.98-7.4	m	18H	4Ar-H-ring proton

NMR: Nuclear magnetic resonance

TABLE VI  
THE  $^{13}\text{C}$ -NMR DATA FOR THE PREPARED CURCUMIN ANALOGS (2 B, C, D) AND PYRAZOLINE (3B): SOLVENT  $\text{CDCl}_3$

$^{13}\text{C}$ -NMR							
2 b		2 c		2 d		3 b	
$\delta/\text{ppm}$	Assign.	$\delta/\text{ppm}$	Assign.	$\delta/\text{ppm}$	Assign.	$\delta/\text{ppm}$	Assign.
70.29	C <sub>10</sub>	70.25	C <sub>10</sub>	69.81	C <sub>10</sub>	40.11	C <sub>2</sub>
115.47	C <sub>6,8</sub>	114.43	C <sub>5</sub>	112.9	C <sub>6</sub>	63.82	C <sub>3</sub>
123.79	C <sub>2</sub>	117.3	C <sub>7</sub>	121.52	C <sub>4</sub>	70.19	C <sub>10,25</sub>
127.61	C <sub>12,16</sub>	121.49	C <sub>9</sub>	124.5	C <sub>8</sub>	115.29	C <sub>6,8,21,23</sub>
128.05	C <sub>5,9</sub>	125.81	C <sub>2</sub>	126.66	C <sub>2</sub>	120.30	C <sub>17</sub>
128.31	C <sub>4</sub>	127.6	C <sub>12,16</sub>	128.68	C <sub>9</sub>	127.58	C <sub>12,16,27,31</sub>
128.83	C <sub>14</sub>	128.23	C <sub>14</sub>	129.02	C <sub>13,15</sub>	128.09	C <sub>14,19,29</sub>
130.23	C <sub>13,15</sub>	128.78	C <sub>13,15</sub>	131.65	C <sub>7</sub>	128.72	C <sub>20,24</sub>
136.62	C <sub>11</sub>	130.11	C <sub>8</sub>	133.97	C <sub>14</sub>	129.79	C <sub>5,9</sub>
142.76	C <sub>3</sub>	136.33	C <sub>4</sub>	135.23	C <sub>11</sub>	133.00	C <sub>13,15,28,30</sub>
160.88	C <sub>7</sub>	136.75	C <sub>11</sub>	138.22	C <sub>3</sub>	135.32	C <sub>4</sub>
189.6	C <sub>1</sub>	143.31	C <sub>3</sub>	157.50	C <sub>5</sub>	136.92	C <sub>18</sub>
		159.27	C <sub>6</sub>	190.14	C <sub>1</sub>	137.06	C <sub>11,26</sub>
		188.87	C <sub>1</sub>			152.93	C <sub>1</sub>
						158.53	C <sub>7</sub>
						159.04	C <sub>22</sub>

NMR: Nuclear magnetic resonance

carbon atoms presented in mono-carbonyl analogs, showed a characteristic peak related to the  $\beta$ -C atom approximately at (140) ppm which is more de-shielded than that of  $\alpha$ -C atom nearly around  $\delta$  (123) (Hawaiz, et al., 2012). The number of signals fitted with number carbon types of the expected desired products as shown in Table VI.

Pyrazolines (3a-e) have been synthesized on the basis of Claisen or Michael addition reactions of hydrazine hydrate on the prepared mono-carbonyl analogs (2a-e) by utilizing classical and ultrasound irradiation method in the presence of sodium hydroxide in methanol. Considerable improvement has been focused on the comparison of the results with the literature and the two efficient methods together. El-Rayyes and Al-Johary (1985) prepared similar pyrazolines in several hours, Pinto, et al., 2003, also prepared bis-pyrazoline in 24 h (Pinto, et al., 2003). While, in this work, products were obtained in good yields and shorter reaction times, about 60 min in ultrasound method. This demonstrates the notability of ultrasound over classical refluxing method.

The structures of the synthesized compounds (3a-e) were assigned on the basis of spectral data. In the IR spectra Table IV, the appearance of a sharp band at 3320/cm attributed to N-H stretching vibration, strong bands at 1600/cm for C=C and C=N stretching vibrations. On the other hand, the hiding of carbonyl band at 1666-1647/cm for enone system is a good exponent for the formation of C=N and the occurrence of cyclization reaction to give 2-pyrazolines (Samad, et al., 2015).

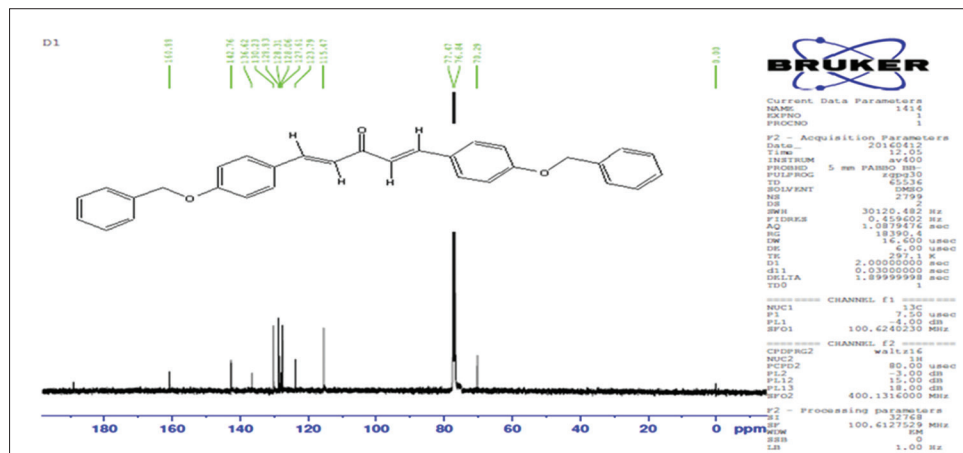
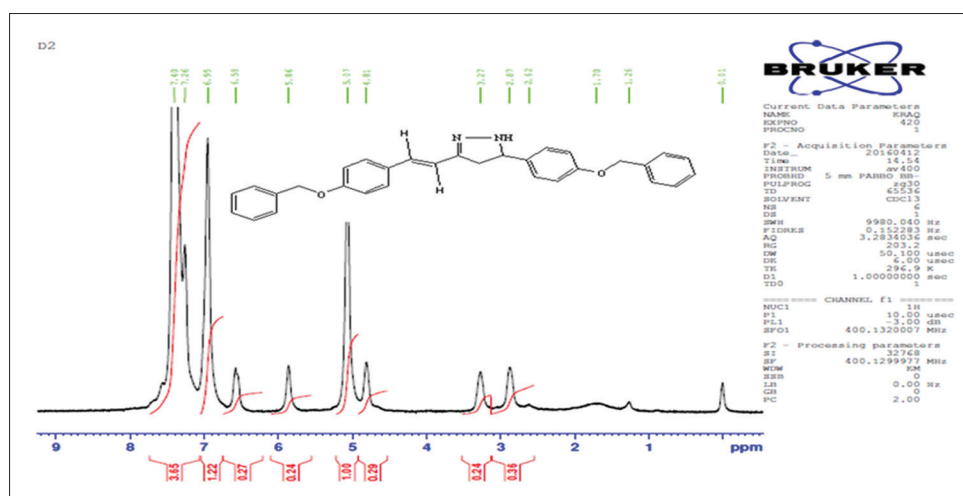
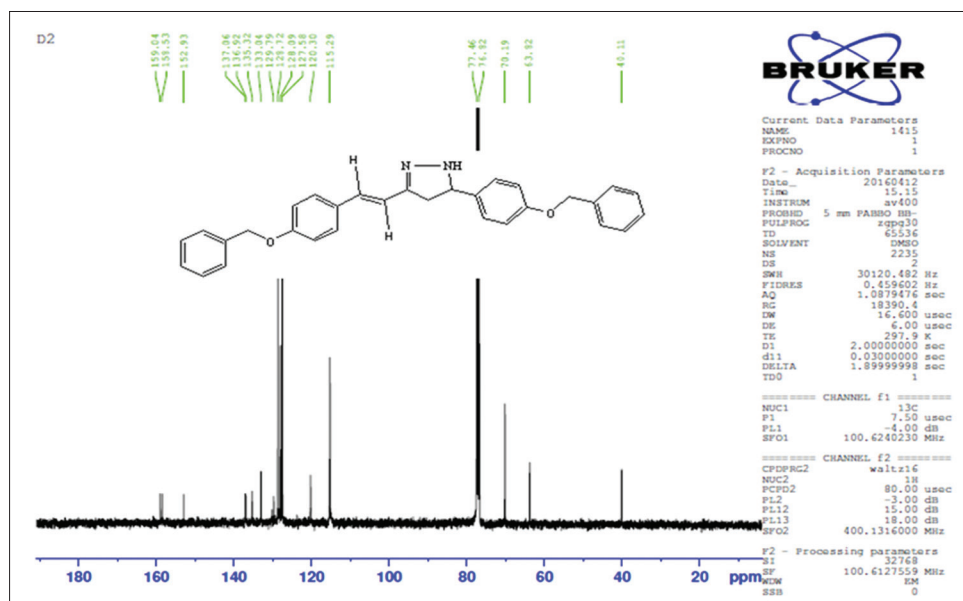
The  $^1\text{H}$ -NMR spectra of pyrazolines, Fig. 4, showed characteristic signals corresponding to protons of C<sub>2</sub> and C<sub>3</sub> of 2-pyrazoline ring; a distinct ABX system proving the nonequivalence of protons at C<sub>2</sub>. It causes to the appearance of three doublet to doublet (dd) signals at 2.87, 3.27, 4.81 ppm for H<sub>a</sub>, H<sub>b</sub> and H<sub>c</sub> respectively, with two doublets at 5.86 and 6.58 ppm due to the styryl double bond confirms expected structure. Table V shows the detail of the  $^1\text{H}$ -NMR data (Hussein, 2014).

The  $^{13}\text{C}$ -NMR spectra of pyrazolines, Fig. 5 showed three signals at 40.11, 63.82 and 70.19 ppm due to the presence of C<sub>2</sub>, C<sub>3</sub> of the pyrazoline ring and C<sub>10</sub> of the benzyloxy group, respectively, and the other 13 peaks between 115 and 159 ppm approximately attributed to 13 types of aromatic carbon atoms.

#### IV. CONCLUSIONS

The results presented in this work pretend that there is a substantial improvement effect in the yield and the rate of the aldol condensation between substituted benzaldehydes and acetone forming curcumin analogs and their corresponding pyrazolines using ultrasound irradiation technique. The formation of curcumin analogs under ultrasound technique found to be inexpensive, efficient, fast, with high yields. In some cases, no results were found when using a traditional method for preparation of curcumin analogs. The results showed that solid NaOH gives better yields than an appropriate solution of NaOH as a catalyst.



Fig. 3.  $^{13}\text{C}$ -nuclear magnetic resonance spectrum of compound 2b.Fig. 4.  $^1\text{H}$ -nuclear magnetic resonance spectrum of compound (3b).Fig. 5.  $^{13}\text{C}$ -nuclear magnetic resonance spectrum of compound (3b).

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