GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Synthesis, *In-vitro* antibacterial and antioxidant activity of chalcone derivatives

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GSC Biological and Pharmaceutical Sciences, 2022, 21(03), 021–030

Publication history: Received on 10 October 2022; revised on 29 November 2022; accepted on 02 December 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.21.3.0413

Abstract

In the face of the emergence of bacteria resistant to common antibacterials and excessive accumulation of free radicals that can cause several diseases, it is important to look for new antibacterials and antioxidants. The goal of this work was to synthesize three chalcones derivatives by the Claisen-Schmidt condensation and then evaluate their antibacterial and antioxidant activities. The structure of these 3 compounds has been determined by NMR (^{1}H and ^{13}C) spectroscopy. The in vitro antibacterial activity assessed by Microdilution methods, was tested against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) at different concentrations ranging from 7.82 to 1000 µg/mL. All three synthesized chalcones showed good antibacterial activity against gram positive and negative bacteria used with a range of MIC ranging from 62.50 to 1000 µg/mL. However, the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one showed excellent activity against *Bacillus subtilis* with Minimum Inhibitory Concentration (MIC) of 62.5 µg/mL which is similar to that of the standard (Ampicillin) against the same bacterial strain. Antioxidant activity evaluated using 2,2-diphenyl2-picryl- hydrazyle (DPPH) revealed that all the synthesized chalcones showed an antioxidant activity with IC_{50} values of 8.22; 6.89 and 3.39 µg/mL for (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one, respectively. These values are closer to that of ascorbic acid used as a standard. The results suggest that the synthesized chalcones, especially the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one could be used, after in vivo and clinical tests, like antibacterial and antioxidant supplement or even replace current drug therapies.

Keywords: Chalcones; Claisen-Schmidt condensation; Antioxidant; Antibacterial; NMR

1. Introduction

Faced to the increased resistance of certain microorganisms to existing antibacterial agents and the need to combat oxidative stress, which is implicated in several diseases, much scientific research is directed towards the discovery of new antibacterials with other mechanisms of action against microorganisms and new antioxidants [1]. The increase of certain oxidants such as superoxide anions, hydrogen peroxide, hydroxyl, nitric oxide and peroxynitrite in human cells leads to the destruction of these latter and subsequently is the basis of various diseases such as diabetes, atherosclerosis, myocardial infarction, damage may result into many diseases including diabetes mellitus, atherosclerosis, myocardial infarction, arthritis, anemia, asthma, and inflammation [1,2,3].

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Natural medical compounds have always been considered as an inspiration for the development of new anti-bacterial, antifungal, antiviral, antoxidants, anti-inflammatory drugs [4-7]. Among these natural medical compounds with many biological activities, there is also the class of Chalcones, which are known as 1,3-diphenylprop-2-en-1-one, are the aromatic ketones and the enones that form a variety of biological agents and they considered the main precursors for flavonoids and isoflavonoids biosynthesis in plants [8-10]. They are widely distributed in nature (in plants, bacteries, fungi, etc.) and are generally synthesized in the Laboratory from aromatic aldehydes and aliphatic aldehydes or ketones via the condensation reaction Claisen-Schmidt in the presence of base or acid catalysts [11–13]. Chalcones have several biological activities such as antibacterial, antioxidant, anti-inflammatory, antiviral, antifungal, anti-ulceral, antimalarial, antileishmanial, anticancer, antitubercular, antihyperglycemic, anti-HIV, carboxygenase inhibitor, insecticidal, ect. And according to the literature these activities are due to the presence of the reactive function α,β-unsaturated keto present in the molecule [14-22]. The goal of this work is to synthesize (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one and then evaluate their antibacterial and antioxidant activities.

2. Material and methods

2.1. Chemical materials

All the starting materials, reagents and solvents were commercially obtained (Merck). Thin-layer chromatography was carried out on silica gel plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). The melting points are determined using a Büchi M-565 melting point apparatus (Büchi Labortechnick AG). NMR spectra were obtained using a Jeol ECA 400 (400 MHz) and Lambda 400 NMR spectrometers. All chemical shifts are reported in ppm.

General Procedure for the Synthesis of (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one.

These three substituted chalcones have been synthesized by Claisen-Schmidt reaction using Sodium hydroxide (NaOH) as catalyst in anhydrous ethanol according to the literature [21,23,24].

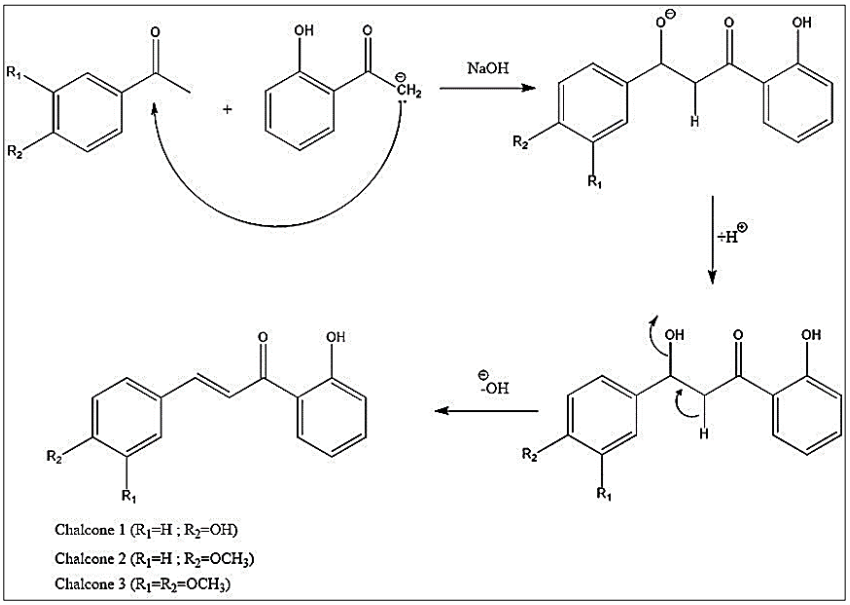


Figure 1 General mechanism of the Claisen-Schmidt reaction using Sodium hydroxide (NaOH) as catalyst

To a solution of 2-hydroxyacetophenones (1 eq) in Ethanol (2.5mL/mmol), Sodium hydroxide (3 eq) was added. After10 min, appropriated benzaldehydes (Para-hydroxybenzaldehyde or Para-methoxybenzaldehyde or 3,4-Dimethoxybenzaldehyde) (1.2eq) was added and the mixture was stirred for 30 min at room temperature, then left to stand for 24 h. After cooling the reaction mixtures with ice, the mixture was neutralized carefully using 1N hydrochloric acid. The crude mixture was extracted with ethyl acetate, washed with water and brine afforded chalcones, which were purified by column chromatography using hexane: ethyl acetate as eluent to give three pure chalcones (E)-1-(2-

hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one. The purity of these 3 synthesized chalcones was evaluated by using high performance liquid chromatography (HPLC) and thin layer chromatography (TLC) methods and these compounds have been characterized by nuclear magnetic resonance (NMR).

2.2. Determination of antibacterial activity

Standard bacterial cultures of *Staphylococcus aureus* (ATCC 25923, gram positive), *Bacillus subtilis* (NRRL B-543, gram positive), *Escherichia coli* (ATCC 25922, gram negative), and *Pseudomonas aeruginosa* (ATCC 27853, gram negative) were used. The bacterial stock cultures were maintained on Muller Hinton Agar, which were stocked at 4°C. Three to five similar colonies were selected from the stock and transferred using loop into 8 mL of sterile TSB (Trypton Soja Broth) and incubated for 24 hours at 37°C. The antibacterial assays were carried out by the microdilution method according to literature [1,3].

2.2.1. Microdilution Method

The MICs (concentration which completely inhibit bacterial) of the (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one against the test bacteria were determined using the modified microdilution technique as described by Mulula et al.[1,3].

Under aseptic conditions, 96 wells microplates were used. All the wells of microplate were filled with 50µl of nutrient broth (Trypton Soja Broth). Test solutions (3.75mg/mL) of the chalcones were prepared in sterile dimethyl sulphoxide (DMSO) and 50 µL of this test solution were serially diluted to 0.029 mg/mL in the microplate's wells. Finally, 10 µL (10^6 cfu/mL) of the inoculums were added to each well of the microplates. The covered microplates were incubated at 37°C for 24h. To indicate growth, 5 µL of resazurin dissolved in water was added to the microplate's wells and incubated at 37°C for 30min. All experiments were performed in triplicates. The minimum bactericidal concentrations (MBCs) were determined by subcultivation. Ten microliter (10 µL) of well's contents were placed in petri dish which restrained 100 µL of Typic Soja Agar (TSA) and incubated for 18-24h at 37°C. The lowest concentration with no visible growth was defined as MBC, indicating = 99.9% killing of the original inoculum.

2.3. Determination of antioxidant activity

The *in-vitro* antioxidant activity of these three synthetized chalcones was determined using the 1,1- diphenyl-2-picryl-hydrazyl (DPPH) method as described by Mulula et al.[1,3]. The synthesized chalcones were prepared in methanol to obtain concentrations of 2, 4, 6, 8 and 10 µg/mL that will be used as test solutions for the determination of antioxidant activity. The DPPH solution (30 mg/mL) was prepared in methanol and 1 mL of this solution was added to 9 mL of various concentrations of synthetized chalcones test solutions and ascorbic acid as reference compound at 2, 4, 6, 8 and 10 µg/mL. After 30 min in the dark, absorbance was measured at 517 nm by UV spectrophotometer. An equal amount of DPPH and methanol served as blank solution control. All the tests were performed in triplicate and the graph was plotted with the mean value. The percentage of inhibition was calculated by comparing the absorbance values of control blank solution to that of test solutions. The percentage scavenging activity was calculated using the following formula:

$$\text{Inhibition (\%)} = \frac{(Ao - As)/Ao}{Ao} \times 100$$

Where **Ao** is the absorbance of the blank and **As** the absorbance of synthetized chalcones test solutions or ascorbic acid.

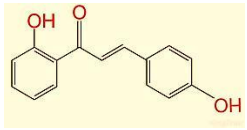
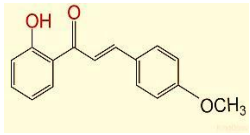
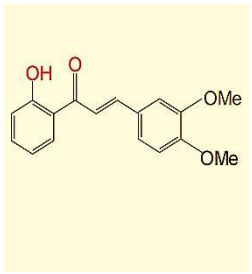
3. Results and discussion

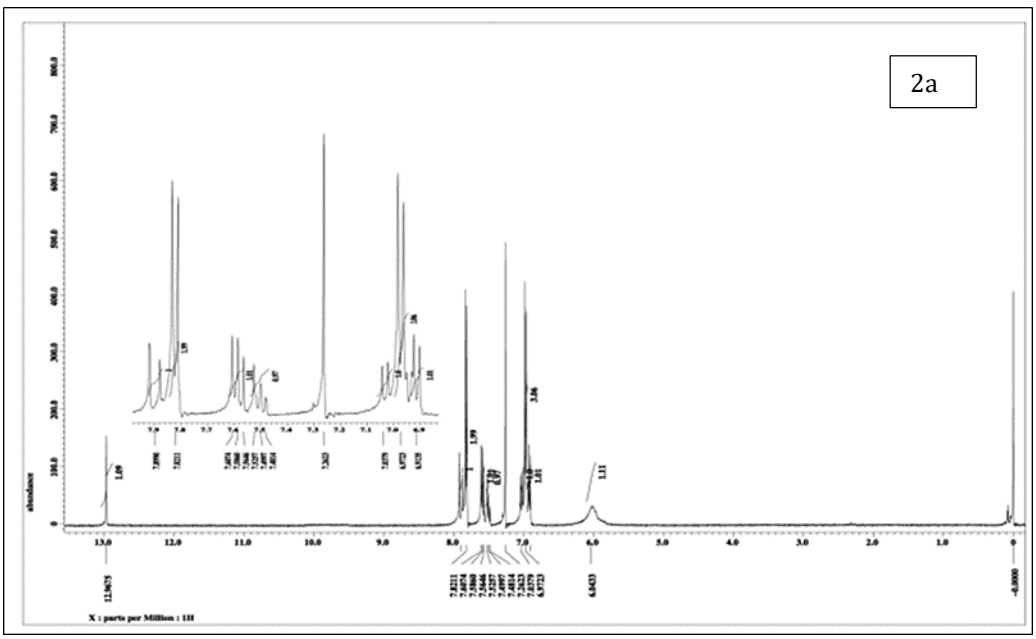
3.1. Chalcones synthesis

The characteristics, yield, physicochemical properties and NMR spectral data of 3 synthesized chalcones [(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one] are represented in Table 1.

The melting temperature and yield of these 3 synthesized chalcones were (138 ºC; 67%), (93ºC; 88%), and (113ºC; 91%) for (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one, respectively. The ^{1}H-NMR and ^{13}C-NMR spectra of these synthesized chalcones are represented in the figures 2 and 3.

Table 1 Characteristics of synthesized chalcones

Compounds (IUPAC name)	Formula/Colour	Yield (%)	Melting Point (ºC)	NMR Spectra data
(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one	 Yellow solid	67	138	^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.96 (s, OH), 7.82(d, J=15.57 HZ, 1H), 7.82 (d, J= 8.38HZ, 2H), 7.58 (t, J= 8.68HZ, 1H), 7.49 (t, J= 9.27HZ, 1H), 7.03 (d, J= 8.08HZ, 1H), 6.97 (d, J= 8.98HZ, 3H), 6.91 (d, J=8.86HZ, 1H), 6.04 (bs, OH); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 191.32, 161.65, 158.45, 145.53, 136.34, 132.61, 130.91, 129.93,129.67, 120.17, 118.93, 117.53, 116.14
(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one	 Yellow solid	88	93	^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.94 (s, OH), 7.88-7.94(m, 2H), 7.63 (d, J= 8.04HZ, 2H), 7.54 (d, J= 16.11HZ, 1H), 7.48 (t, J= 8.05HZ, 1H), 7.02 (d, J= 8.05HZ, 1H), 6.95 (d, J= 8.63HZ, 3H), 3.86 (s, 3H, OCH_3); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 193.76, 163.64, 162.11, 145.45, 136.25, 130.66, 129.64, 127.40, 120.20, 118.86, 118.67, 117.63, 114.61, 55.54.
(E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one	 Yellow solid	91	113	^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.99 (s, OH), 7.91(d, J= 8.71 HZ, 1H), 7.84 (d, J= 15.75HZ, 1H), 7.42-7.52 (m, 2H), 7.22 (d, J= 7.71HZ, 1H), 7.15 (s, 1H), 7.00 (d, J= 8.38HZ, 1H), 6.85-6.93 (m, 2H), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH3); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 193.65, 163.64, 151.89, 149.38, 145.75, 136.27, 129.63, 127.66, 123.71, 120.17, 118.83, 118.68, 117.83, 111.23, 110.33, 56.12, 56.09.



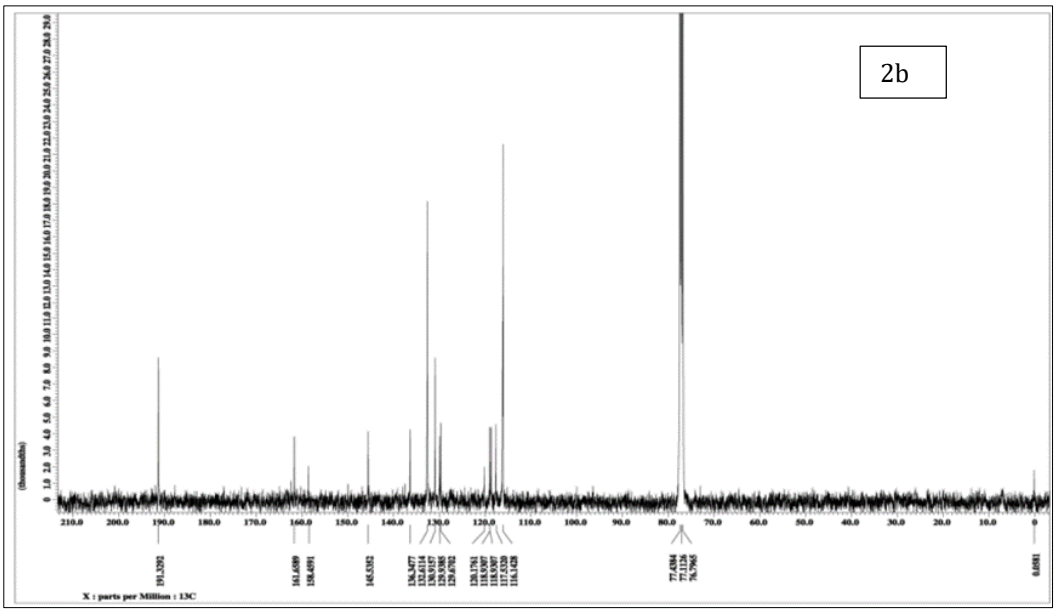
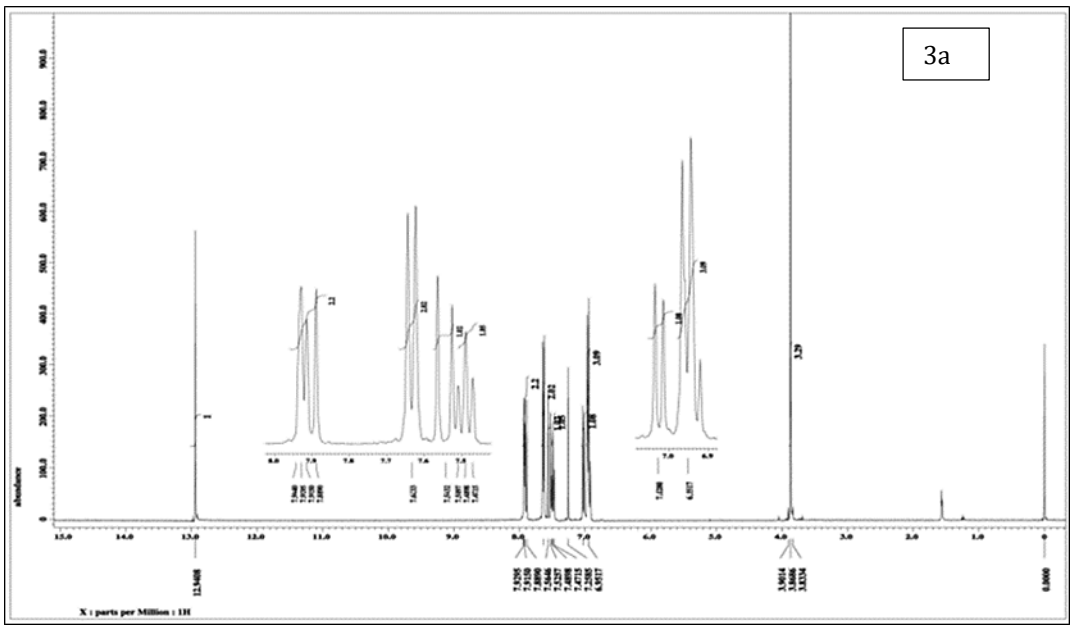


Figure 2 (a) ^{1}H NMR and (b) ^{13}C NMR of (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one

^{1}H-NMR spectrum of these three synthesized chalcones (1,2, and 3) each revealed the singlet at δ 12.96; 12.94 and 12.99 ppm, respectively. This corresponds to the proton of the hydroxyl group close to the carbonyl group which is shielded and this difference could be due to the presence of the OH group in the other benzene cycle of the first synthetic chalcone, either the methoxy group OCH_3 in the second chalcone or the two methoxy (OCH_3) groups in the other benzene of the third synthesized chalcone. Whereas the proton of the hydroxyl group of the first synthetic chalcone, which is in the other benzenic nucleus and therefore far from the carbonyl group, has a chemical shift (δ) of 6.03 ppm.

In addition, the ^{1}H-NMR spectrum of (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one is distinguished from that of (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one by the presence of two intense sets of singlet at δ 3.91 ppm and δ 3.91 ppm while the three protons less shielded of the methoxy group present in the second synthesized chalcone [(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one] resonate as a singlet at δ 3.86 ppm.



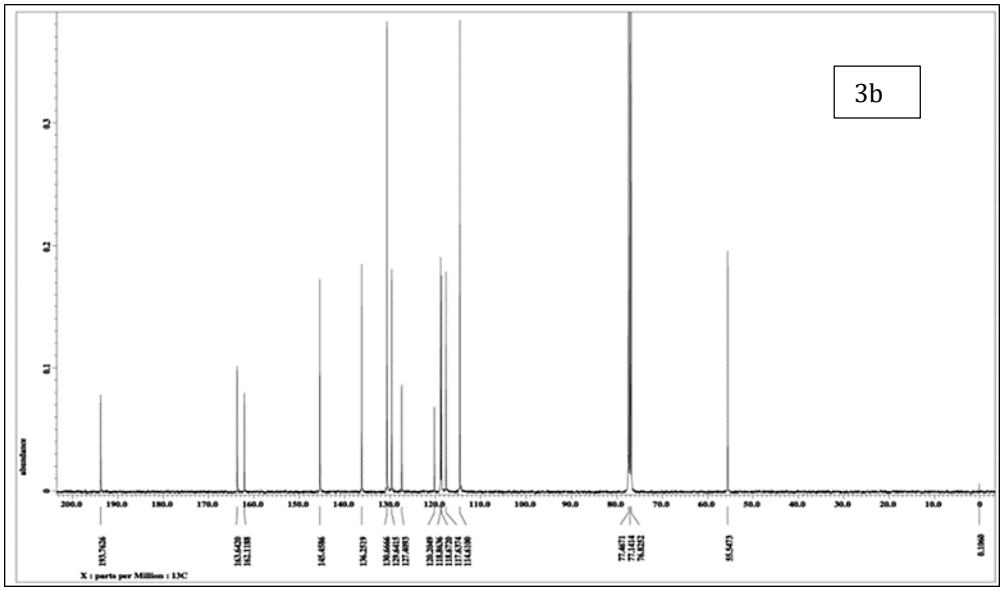


Figure 3 (a) ^{1}H NMR and (b) ^{13}C NMR of (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one

3.2. Antibacterial activity

Table 2 MIC, MBC and MBC/MIC of synthesized chalcones against the pathogenic bacteria by Microdilution assay

Sample/ Standard	Bacterial strains	Concentrations (µg/mL)								MIC (µg/mL)	MBC (µg/mL)	MBC/MIC
		1000	500	250	125	62.50	31.25	15.63	7.82			
(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one	*S. aureus*	-	-	+	+	+	+	+	+	250	500	2
	B. subtilis	-	-	-	+	+	+	+	+	250	1000	4
	E. coli	-	-	+	+	+	+	+	+	500	1000	2
	P. aeruginosa	-	-	+	+	+	+	+	+	500	1000	2
(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one	*S. aureus*	-	-	-	+	+	+	+	+	250	500	2
	B. subtilis	-	-	-	-	+	+	+	+	125	500	4
	E. coli	-	-	+	+	+	+	+	+	500	1000	2
	P. aeruginosa	-	-	-	+	+	+	+	+	250	500	2
(E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one	*S. aureus*	-	-	-	-	+	+	+	+	125	500	4
	B. subtilis	-	-	-	-	-	+	+	+	62.5	250	4
	E. coli	-	-	-	+	+	+	+	+	250	500	2
	P. aeruginosa	-	-	-	-	+	+	+	+	125	500	4
Ampicillin	*S. aureus*	-	-	-	-	-	+	+	+	62.5	62.5	1
	B. subtilis	-	-	-	-	-	+	+	+	62.5	125	2
	E. coli	-	-	-	+	+	+	+	+	250	250	1
	P. aeruginosa	-	-	-	-	+	+	+	+	125	250	2

(+) indicates microbial growth; (-) indicates no microbial growth

Antibacterial activity of three synthesized chalcones against *Staphylococcus aureus* (ATCC 25923, gram positive), *Bacillus subtilis* (NRRL B-543, gram positive), *Escherichia coli* (ATCC 25922, gram negative), and *Pseudomonas aeruginosa* (ATCC 27853, gram negative) was determined using the modified Microdilution method. Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (MBC) and the ration MBC/MIC values are reported in Table 2.

The minimum inhibitory concentration (MIC) is the lowest concentration of the extract at which no microbial survive. All three synthesized chalcones showed good antibacterial activity against gram positive and negative bacteria used with a range of MIC ranging from 62.50 to 1000 µg/mL. However, the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3) showed excellent activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa* with Minimum Inhibitory Concentration (MIC) of 125; 62.5; 250 and 125 µg/mL, respectively. Against *Bacillus subtilis*, the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3) presented the same minimum inhibitory concentration MIC value as ampicillin which is used as the standard antibacterial. This could well be explained by the structure of this chalcone according to the literature [25,26].

Minimum bactericidal concentration (MBC) of a test solution is the lowest dilution level needed to completely inhibit bacterial growth and it depends on the solvent and the bacteria. All of these 3 synthesized chalcones [(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one] showed moderate bactericidal activity with bactericidal concentrations (MBC) ranging from 250 to 1000 µg/mL and their ratios of MBC/MIC are below to 4. This is a clear indication of their large bactericidal activity.

3.3. Antioxidant activity

The increase of certain oxidants such as superoxide anions, hydrogen peroxide, hydroxyl, nitric oxide and peroxynitrite in human cells leads to the destruction of these latter [2]. The free radical scavenging activity of (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one called chalcones 1, 2 and 3, respectively, was studied by its ability to reduce the 2,2-diphenyl-1-picrylhydrazyl (DPPH), a stable free radical. Ascorbic acid used as standard. DPPH is a free radical and it gives a strong absorption band at 517nm in the visible region of the electromagnetic radiation [1,2,25,26]. The results of the antioxidant activity of 3 synthesized chalcones and the standard are shown in the table 3 and figure 4. All synthesized chalcones have very good antioxidant activity with IC_{50} values of 8.22; 6.89 and 3.39 µg/mL for (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1), (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2) and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3), respectively. Whereas that of ascorbic acid was 2.17 µg/mL**.** These results are almost identical to those described in the literature [25-29].

Table 3 IC_{50} (µg/mL) of Synthetized chalcones and Ascorbic acid

Compounds/Standard	**IC50 (µg/mL)**
(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1)	8.22
(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2)	6.89
(E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3)	3.56
Ascorbic acid	2.17

At a concentration of 10 µg/mL, the inhibition percentage of the third chalcone was 87.71%. This is almost similar to ascorbic acid used as antioxidant standard (See Figure 4). This could be explained by the presence of two methoxy groups in this third chalcone that can bind to the DPPH radical. This is contrary to the first two chalcones. Indeed, the methyl group (having an electrodonor effect) present in methoxy could also have a stabilizing effect of the chalcone-DPPH complex [27-29].

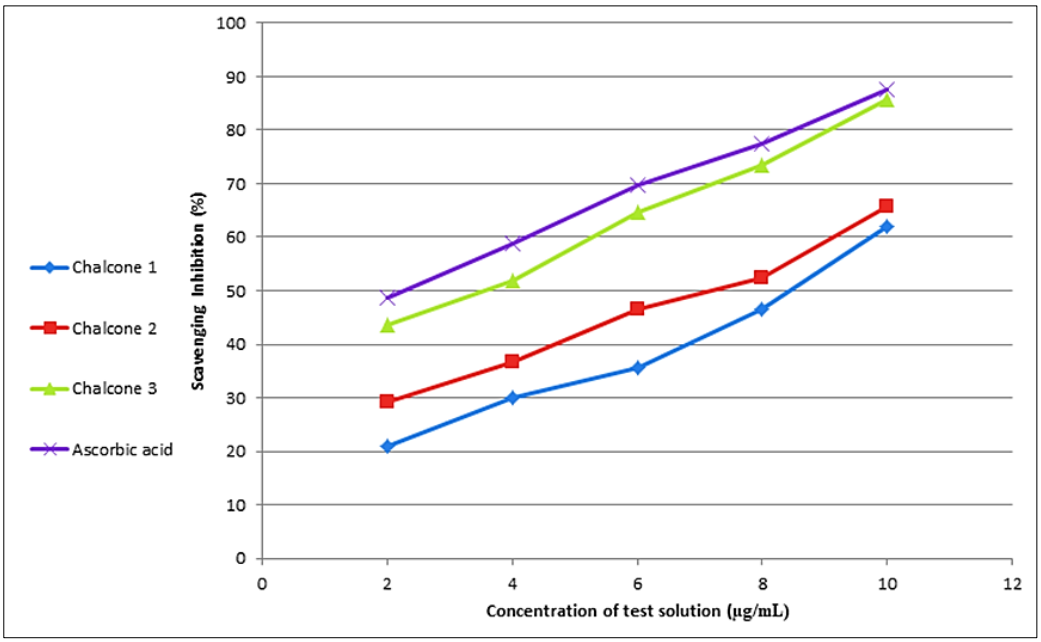


Figure 4 Scavenging inhibition of synthetized chalcones and Ascorbic acid

4. Conclusion

In this study, we synthetized three chalcones derivative [(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one] and was identified by NMR (^{1}H and ^{13}C) spectroscopy. These synthetized chalcones are screened for antibacterial and antioxidant activity. All three synthesized chalcones showed good antibacterial activity against gram positive and negative bacteria used with a range of MIC ranging from 62.50 to 1000 µg/mL. However, the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3) showed excellent activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa* with Minimum Inhibitory Concentration (MIC) of 125; 62.5; 250 and 125 µg/mL, respectively. Regarding antioxidant activity, all the synthesized chalcones showed an antioxidant activity with IC_{50} values of 8.22; 6.89 and 3.39 µg/mL for (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1), (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2) and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3), respectively. The results suggest that the synthesized chalcones, especially the (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one could be used, after in vivo and clinical tests, like antibacterial and antioxidant supplement or even replace current drug therapies.

Compliance with ethical standards

Acknowledgments

We are grateful to the Laboratory of Bacteriology (National Research Center) for biological analysis.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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