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Synthesis and In vitro Biological Activity Evaluation of Substituted Chalcones

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ABSTRACT

Chalcones and its derivatives are gaining a great deal of attention due to their biological and molecular activities in humans with an ever increasing investigation by in vitro or preclinical studies. In this study, four substituted chalcone derivatives (**I-IV**) were successfully synthesized using the conventional Claisen-Schmidt condensation between various substituted aromatic ketones and aromatic aldehydes in the presence of aqueous sodium hydroxide. The synthesized compounds gave good yields between 72.5 – 81.8 % . In vitro Anti-inflammatory, antimicrobial and antioxidant activities were conducted to evaluate compounds' pharmacological efficacy. In the anti-inflammatory test, compound **1** was most active which exhibits 20.9 % Membrane Stabilization Effect at 50 mg/mL which is lower than Diclofenac used as the standard. At the concentration of 3.91 µg/mL, compounds **III** and **IV** were found to neutralize 50 % of the DPPH free radicals, while the lowest activity was found in compound **II** at the concentration of 68.7 µg/mL. All the synthesized compounds were found to possess moderate activity against the test organisms when compared to the standards. Chalcones should be explored more as scaffold pharmacophore agents.

Keywords: Chalcones; Claisen-Schmidt Condensation; In vitro Biological Activity.

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INTRODUCTION

Chalcone also known as 1, 3-diphenyl-2-propen-1-one is a secondary metabolite which is a prominent member of the flavonoid family. They are also α, β-unsaturated ketones due to their functionality. Chemically, they consisted of open chain flavonoid linked by a three carbon, α, β -unsaturated carbonyl system (Jayapal and Sreedhar, 2011). However, chalcones are considered as the main precursors in the biosynthesis of flavonoids and isoflavonoids that are abundant in edible plants and are widely spread in nature such as fruits, vegetables, spices, tea and soy based foodstuff (Albuquerque et al., 2014). They possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions (Rahman et al.,2007).Chalcones also occur naturally but can be equally synthesized and derivatized in order to increase its potency as therapeutic agents. Chalcones can be called different names ranging from benzalacetophenone or benzylideneacetophenone due to their reactive ketoethylenic group present in their makeup (Chahar et al., 2011). Chalcones have several pharmacological importance such as: potential cytotoxic agents with antiangiogenic activity, antimalarial, anti-tumour, antiviral, anaesthetics', mydriatics, antileishmanial, anti-inflammatory, antifedent, antimitoitic, anticancer, antimicrobial (antifungal and antibacterial), anti-allergic, antiulcerative, immunomodulatory, antihyperglycemic, anticonvulsant, antiplatelet, antitubercular, antihyperlipidemic, and antiprotozoal, antihistaminic, antipyretic properties and inhibitor of topoisomerase I, amidst other medicinal properties (Vibhute and Basser, 2003; Ni et al., 2004; Liu and Go, 2006 and Modzelewska et al., 2006). They are also metal chelators and free radical scavengers since

they are polyphenolic plant secondary metabolites (Middleton et al., 2000).
The synthesis of chalcones is a single step method involving the condensation of aromatic aldehydes with aromatic ketones in order to get α, β -unsaturated ketone (Mandge et al., 2007). There are various methods of synthesizing these chalcones among which are: Aldol condensation (Jayapal et al., 2010), Suzuki Reaction (Eddarir et al., 2003), Microwave assisted method (Bora et al., 2005), Ultrasound irradiation method (Wei et al., 2005) and Claisen Schmidt Condensation Method. However, the main method of chalcone synthesis is still the conventional Claisen Schmidt Condensation reaction this is because of its fast reaction time and eco-friendly conditions (Aastha et al., 2013).

Experimental

Physical Characterization of the Synthesized Chalcones

The Infrared spectra of the synthesized compounds were recorded using Shimadzu Spectrum 100 FT-IR spectrophotometer using KBr pellets with universal attenuated total reflectance (ATM) sampling accessory. The UV-Visible spectra of the synthesized compounds were obtained on Beckman Coulter DU 730 UV-Visible Spectrophotometer. The electronic spectra of the synthesized compounds were run in the range 200-800 nm. ^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded at 295K with 5.0-10.0 mg of the samples dissolved in 0.75 ml $CDCl_3$ in 5.0 mm NMR tube using 500.13 MHz for ^{1}H NMR and 125.77 MHz for ^{13}C NMR 9.4T Bruker, Germany NMR Spectrophotometer. Chemical shifts (δ) were reported in ppm. The ^{1}H NMR chemical shifts of the deuterated solvent ($CDCl_3$) was at 7.26 ppm while for ^{13}C NMR, chemical shift was at 77.16 ppm with reference to the internal standard Tetramethylsilane (TMS).

General Procedure for the Synthesis of Chalcones

An equimolar mixture of aromatic aldehyde and aromatic ketone were dissolved in 10 mL 95 % ethanol in a 100 ml round-bottomed flask equipped with a magnetic stirring bar placed in an ice bath. Then 10 ml NaOH solution (1 g in 10 ml H_2O) was added in drop-wise to the reaction mixture on vigorous stirring for 30 minutes till the solution becomes turbid.The reaction temperature was maintained between 20-25 ºC using a cold water bath on the magnetic stirrer. After vigorous stirring for 4-5 hours, the reaction mixture was neutralized by 0.1 - 0.2 N HCl whereby precipitation occurred. On filtering off, the crude chalcones was air-dried and recrystallization was carried out by the addition of ethanol. The residue was purified on column chromatography (glass column packed with silica gel, elute with 10 % ethyl acetate in n-hexane) in order to get pure chalcones (Choudhary and Juyal, 2011).

Antimicrobial Screening

The synthesized compounds were screened for antibacterial activity against fresh isolates of six pathogenic organisms: Staphylococcus gallinarum, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi and Escherichia coli, while the fungi used for antifungal assay were four: Candida albicans, Aspergillus nigar, Rhizopus stolonifer and Penicillium notatum. The pour plate and surface plate method (Collins and Lyne, 1970) were used for antibacterial and antifungal activities respectively. Dimethylsufoxide (DMSO) was used as the solvent of extraction for the tested compounds to get a solution of 1 mg/ml. The inhibition zones were measured in 8 mm diameter at the end of an incubation period of 18-24 hrs at 37 ºC for bacterial and 48 hrs at 26-28 ºC for fungi.Sterile Nutrient Agar and Sabouraud Dextrose Agar were used as basal media to test the bacteria and fungi respectively. Gentamycine and Tioconazole were used as positive control for bacteria and fungi, respectively under similar conditions for comparison.

Spectra Data

3-(2, 4-dimethoxyphenyl)-1-phenylprop-2-en-1-one (I): yellow crystals, UV (λ_{max}) nm: 360, 279. IR (KBr) υ_{max} cm^{-1}: 1651 (C=O), 1582 (Ar C=C), 1346 (C-O). ^{1}H NMR (500MHz, $CDCl_3$) δ_H : 3.86 (s, 3H, OCH_3), δ_H 3.88 (s, 3H, OCH_3), δ_H 7.47 (d, 1H, H-α), δ_H 8.07 (d, 1H, H-β) δ_H 6.45 – 7.82 (m, 8H, Ar - H), ^{13}C NMR (125MHz, $CDCl_3$) δ_C : 55.3 (-OCH_3), δ_C 98.7–164.4 (Ar-C), δ_C 192.6 (C=O), δ_C 121.1 (C-α), δ_C 140.2 (C-β).

3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (II): white crystals, UV (λ_{max}) nm: 337, 270. IR (KBr) υ_{max} cm^{-1}: 1661 (C=O), 1589 (Ar C=C), 1017 (C-F). ^{1}H NMR (500MHz, $CDCl_3$) δ_H 7.61 (d, 1H, H-α), δ_H 8.01 (d, 1H, H-β), δ_H 7.12 – 7.80 (m, 9H, Ar-H) ^{13}C NMR (125MHz, $CDCl_3$) δ_C 115. 7 – 162.9 (Ar-C), δ_C 165.2 (C-F), 190.1 (C=O), δ_C 121.9 (C-α), δ_C 162.9 (C-β).

3-(2,4-dichlorophenyl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-one (III): yellow crystals, UV (λ_{max}) nm: 355, 283. IR (KBr) υ_{max} cm^{-1}: 3449 (O-H), 1641 (C=O), 1578 (Ar C=C), 1298 (C-O), 1157 (C-F), 797 (C-Cl). ^{1}H NMR (500MHz, $CDCl_3$) δ_H 7.65 (d, 1H, H-α), δ_H 8.18 (d, 1H, H-β), δ_H 6.64 – 7.88 (m, 6H, Ar-H), δ_H 13.0 (s, 1H, Ar-OH), ^{13}C NMR (125MHz, $CDCl_3$) δ_C : 105.4–166.2 (Ar-C), 192.1 (C=O), 166.2 (C-OH), 168.9 (C-F), 122.8 (C-α), 140.2 (C-β), 132.1 – 137. 0 (Ar–C-Cl).

3-(2,4-dimethoxyphenyl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-one (IV): yellow crystals, UV (λ_{max}) nm: 370, 284. IR (KBr) υ_{max} cm^{-1}: 3442 (O-H), 1634 (C=O), 1559 (Ar C=C), 1286 (C-O), 1025 (C-F). ^{1}H NMR (500MHz, $CDCl_3$) δ_H: 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 7.57 (d, 1H, H-α), 8.16 (d, 1H, H-β), 6.52 – 7.88 (m, 6H, Ar-H), 13.5 (s, 1H, Ar-OH), ^{13}C NMR (125MHz, $CDCl_3$) δ_C: 55.6 (-OCH_3), 98.5–131.9 (Ar-C), 193.1 (C=O), 166.0 (C-OH), 168.4 (C-F), 117.4 (C-α), 141.6 (C-β), 160.8 – 163. 6 (Ar–C-O).

Antioxidant Screening

The ability of the synthesized compounds to scavenge DPPH (2, 2-dyphenyl-1-picrylhydrazyl) free radicals was assessed by the standard method (Tekao et al., 1994), adopted with suitable modifications (Kumarasamy et al., 2007). The stock solution of the extracts was prepared in methanol to achieve the concentration of 1 mg/1ml. Serial dilutions were made to obtain various concentrations. 2 ml each of diluted solutions was mixed with 2 ml of methanolic solution of DPPH in concentration of 1 mg/ml and after 45 minutes of incubation in darkness at room temperature (23 ºC), the absorbance was recorded at 517 nm. The control sample contained all the reagents except the synthesized compounds. Percentage inhibition was calculated using the equation below, whilst IC_{50} values were estimated from the % inhibition versus concentration plot, using a non-linear regression algorithm. The data was presented as mean values ± standard deviation (n=3, where n= absorbance).

$$\% \text{ Scavenging} = \frac{A_0 \text{ (Control)} - A_1 \text{ (Sample)} \times 100}{A_0 \text{ (Control)}}$$

Anti-inflammatory Screening

All the newly synthesized compounds were tested for their anti-inflammatory activity by in-vitro (HRBC) Human Red Blood Cell Membrane Stabilization using the method as prescribed by Gopalakrishnan et al., 2009 and Sakat et al., 2010 with some modifications. The blood was collected from animals who had not taken any NSAIDS for 2 weeks prior to the experiment and mixed with equal volume of Alsever solution (2 % dextrose, 0.8 % sodium citrate, 0.5 % citric acid and 0.42 % NaCl) and centrifuged at 3,000 rpm. The packed cells were washed with isosaline and a 10 % suspension was made. Various concentrations of extracts were prepared (100 and 120 mg/ml) using distilled water and to each concentrations, 1 ml of phosphate buffer, 2 ml hyposaline and 0.5 ml of HRBC suspension was added. It was then incubated at 37 ºC for 30 minutes and centrifuged at 3,000 rpm for 20 minutes and the haemoglobin content of the supernatant solution was estimated by spectrophotometer at 560 nm.

Diclofenac (50 mg/ml) was used as reference standard and a control was prepared by omitting the extracts. The experiments were performed in triplicates and mean values of the three were considered. The percentage (%) of HRBC membrane stabilization or protection was calculated using the following formula:

$$\% \text{ Stabilization} = \left\{ \frac{100 - \text{O. D. of drug sample}}{\text{O. D. of control}} \right\} \times 100$$

Results and Discussion

Four different derivatives of chalcones were successfully synthesized using Claisen-Schmidt condensation method of aromatic ketones with appropriate aromatic aldehydes as shown in Scheme 1. All the synthesized compounds result in good yield between 72.5 – 81.8 % (Table 3). The structures of the products were deduced from their UV, IR, ^{1}H NMR, and ^{13}C NMR. All the synthesized compounds have two absorption bands characteristics in the UV-Visible spectra which showed major transitions of n-π^* for the longer wavelengths in the range 337-370 nm and π- π^* for the shorter wavelengths in the range 270-284 nm. The presence of non-bonding electrons, π bonds (α, β-unsaturated carbonyl system) and aromatic rings were responsible for the observed transitions. For the IR spectra, the characteristics (C=O) stretching band was observed in all the synthesized compounds in the range of 1660 to 1633 cm^{-1} which showed an indication of a conjugated unsaturated

ketone system. However, the difference in this wave number (υ) arises due to the presence of other substituents on both rings (A and B). The characteristic broad peaks with small intensities in the range of 3448 to 3442 cm^{-1} which is typical for the presence of free hydroxyl groups was observed for compounds III and IV. This confirms hydroxyl group (-OH) and it little/disappearance in both compounds I and II confirmed its absence. Also, the observation of a band at 796 cm^{-1} indicates the presence of (C-Cl) in compound III while its disappearance confirmed the absence of chlorine in the other three compounds.

The proton nuclear magnetic resonance spectra of all the synthesized compounds showed characteristics Hα signal in the range 7.47 - 7.65 ppm as a doublet, the Hβ signal in the range 8.01 - 8.18 ppm as a doublet. This confirms the vinylic proton while the aromatic carbon proton signal appeared in the range 6.45 – 7.82 ppm as a multiplet consisting of 8 protons for compound I, 7.12 – 7.80 ppm as a multiplet consisting of 9 protons for compound II, 6.64 – 7.88 ppm as a multiplet consisting of 6 protons for compound III and 6.52 – 7.88 ppm also as a multiplet consisting of 6 protons for compound IV. For compounds III and IV, a singlet peak in the range of 13.0 – 13.5 was observed. This signifies the presence of OH in these compounds. The ^{13}C NMR data of all the synthesized compounds showed characteristics (C=O) signal (δc) in the range 190.1-193.1 ppm which occurred more downfield than the other aromatic carbons. The Cα signal was observed in the range 121.1-141.6 ppm while the Cβ signal was observed in the range 140.2-162.9 ppm for all the synthesized compounds. The presence of a signal observed in the range 55.3-55.6 ppm for compounds I and IV, is as a result of the shielding effect caused by the methoxy atoms ($-OCH_3$), thereby making the signal move more upfield than other signals. However, the signal 168.4 – 168.9 ppm was observed for compounds III and IV. This is due to the presence of fluorine in the compounds. This further confirmed the formation of chalcone derivatives.

The four synthesized compounds were tested for antimicrobial activity as shown in Table 1, compounds III and IV were found to be active and exhibit significant antimicrobial activity in comparisons to compounds I and II. Comparatively, among the bacteria cultures tested, Staphylococcus aureus was found to be highly susceptible to all the four synthesized compounds. Moreover, among the fungi culture tested, Candida albicans showed significant susceptibility for all the synthesized compounds in comparison to the other three fungi. From Table 1 below, it can be concluded that all the four synthesized compounds are appreciably sensitive to the various test organisms thereby making them good candidate for the treatment of infections.

For the Antioxidant properties, the highest capacity to neutralize DPPH radicals was found in compounds III and IV which neutralized 50 % of free radicals at the concentration of 3.91 µg/mL while the lowest activity was found in compounds II at the concentration of 68.7 µg/mL (Fig 1). This low IC_{50} value which indicates high antioxidant activity of compounds III and IV can be attributed to the presence of hydroxyl group in position II of their ring B. It was also observed that at higher concentrations for all the compounds, the percentage inhibition is higher especially when compared to the lower concentrations.However, the anti-inflammatory activity carried out on the synthesized compounds revealed that out of all of them, compound I & II showed the highest % inhibition (40.9 & 37.7) in comparison to the standard control (Diclofenac) percentage inhibition which is 42.47 %, compound I showed the slightly closer percentage inhibition amidst other compounds at the same concentration. However, at similar concentrations of compounds III and IV displayed no inhibitory Membrane Stabilization Effect, nevertheless all the synthesized compounds exhibit anti-inflammatory activity.

Conclusion

All compounds were successfully synthesized using the conventional Claisen-Schmidt condensation reaction method. The base-catalyzed (NaOH/EtOH) reaction between various substituted acetophonone and benzaldehydes led to the formation of these chalcone derivatives. The yields of the synthesized compounds were reported in the range of 72.5 - 81.8 % which is relatively high and shortest reaction time (5 hours). This method did not involve harmful or hazardous substances but it is eco-friendly and they were all characterized by ^{1}H and ^{13}C NMR, IR, and UV spectroscopic techniques. In vitro biological activity (antimicrobial, anti-inflammatory and antioxidant activities) carried out on synthesized compounds showed that all the synthesized chalcone derivatives have good to moderate considerable biological activity.

Conflict of Interest

There is no conflict of interest as regards this manuscript. All articles cited in the text were referenced in order to acknowledge all the contributory authors.

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Table 1: Antimicrobial Assay Results of the Synthesized Compounds

Compound No.	Zone of Inhibition (mm) on the Test Organism									
	S. gallinarum	E. coli	B. subtilis	P. aeruginosa	S. aureus	S. typhi	C. albicans	A. niger	P. notatum	R. stolonifer
I	18	14	18	18	22	18	18	16	14	14
II	18	18	18	18	24	18	18	14	16	14
III	26	24	24	20	28	18	20	18	18	18
IV	24	22	24	20	26	20	20	18	16	18
Standard	36	38	36	36	44	36	26	26	26	28

Table 2: Anti-inflammatory Activity Results of the Synthesized Compounds

Compound No.	% Membrane Stabilization Effect
I	40.9
II	37.7
III	0
IV	0
Diclofenac	42.47

Table 3: Physical Constants of Synthesized Compounds

Compound Code	Molecular formular	Molecular Weight	Yield %	Melting Point (ºC)	Elemental Analysis (Calcd. & Found)
I	$C_{17}H_{16}O_3$	268.3185	77.8	87-89	C, 76.10; H, 6.01; O, 17.89 C, 76.23; H, 5.96; O, 17.81
II	$C_{15}H_{11}FO$	226.0842	72.5	95-97	C, 79.63; H, 4.90; F, 8.40; O, 7.10 C, 79.58; H, 3.88; F, 8.47; O, 8.07
III	$C_{15}H_9Cl_2FO_2$	311.2412	80.7	167-169	C, 57.91; H, 2.92; Cl, 22.79; F, 6.11; O, 10.28 C, 57.85; H, 2.86; Cl, 22.80; F, 5.96; O, 10.53
IV	$C_{17}H_{15}FO_4$	302.3021	82.5	134-136	C, 67.54; H, 5.00; F, 6.28; O, 21.17 C, 67.47; H, 4.83; F, 6.02; O, 21.68

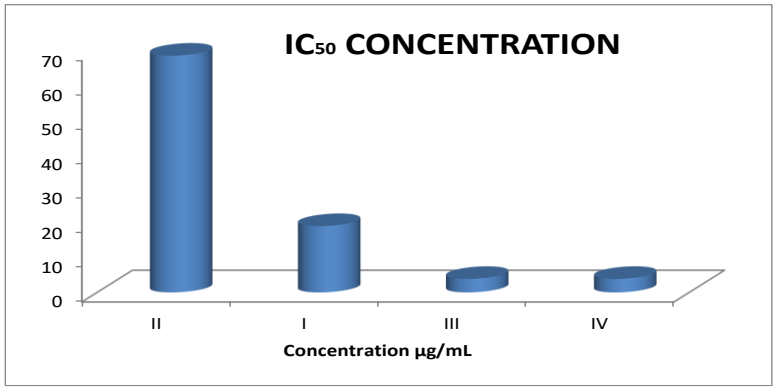
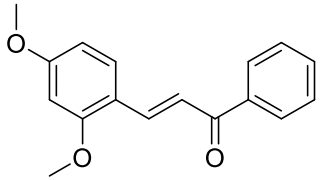
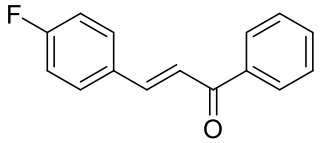


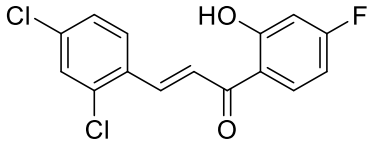
Figure 1: IC_{50} Concentration of Scavenging Effect of the Synthesized Chalcones



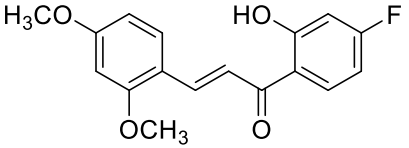
3-(2,4- dimethoxylphenyl)-1-phenylprop-2-en-1-one
Compound I



3-(4- fluorophenyl) -1-phenylprop-2-en-1-one
Compound II

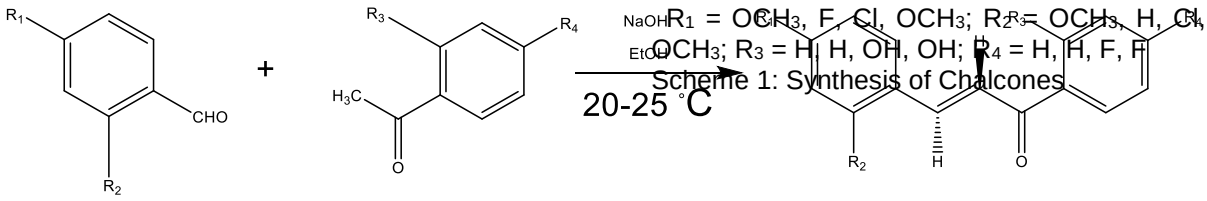


3-(2,4- dichlorophenyl)-1-(-4-fluoro-2-hydroxyphenyl) prop-2-en-1-one
Compound III



3-(2,4- dimethoxylphenyl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-one
Compound IV

Figure 2: Structure of the Synthesis Compounds (I – IV)



Scheme 1: Synthesis of Chalcones

R_1 = OCH_3, F, Cl, OCH_3; R_2 = OCH_3, H, Cl, OCH_3; R_3 = H, H, OH, OH; R_4 = H, H, F, F

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