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Pharmaceutical Chemistry

Synthesis and Antibacterial Activity of 4-Methoxy Phenyl Propenone Chalcones

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Abstract: Chalcones belongs to a class of naturally occurring compounds called flavonoids which are found in plants and they are known to possess variety of biological activities. They are very useful and good lead compounds in drug research and are continuously been tested for activity against various infectious diseases. Series of 4-methoxy phenyl propenone chalcone moieties were synthesized by modified Aldol condensation reaction involving aromatic aldehydes and acetophenones at low temperature and the progress monitored by TLC. The various 4-methoxy phenyl propenones did not show any antibacterial activity, therefore may substantiate that most chalcones are made active by the enzyme chalcone synthetase.

Keywords: Chalcones, 4-methoxy phenyl propenone, Biological activity.

INTRODUCTION

Chalcone moieties are natural or synthetic compounds belonging to the flavonoids. They have evoked a great deal of interest owing to their diver's biological activities and characteristic conjugated molecular framework. Chalcones have been considered as derivatives of 1,3 –diaryl-2-propene-1-one. The Parent compound is composed of the phenolic rings referred to as A and B rings.

Many of them possess important pharmacological activities such as antibacterial, antipyretic, antiviral etc. [1-3]. Due to the presence of chromophore, they are coloured in nature ranging from yellow, orange to reddish brown.

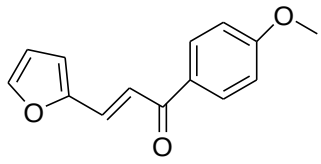
Many literatures have nearly confirmed that almost all chalcones have biological activity' ranging from antibacterial to antiviral.

The pharmacological properties of chalcones are believed to be due to the presence of both α, β unsaturation [4] and the aromatic ring [5]. In this study 4-methoxy phenyl propenone chalcones were synthesized using modified Claisen Schmidt condensation reaction and screened for antibacterial activity.

MATERIALS AND METHODS

Evaluation of Compounds: Structures and purity of compounds were confirmed by ^{1}H-NMR using JOEL Lambda 400 spectrometer, an internal standard of TMS was used. Thin layer chromatography (TLC) (E. Merck Kieselgel 60 F254) was used to check purity of compounds. Melting point (uncorrected) was determined using Gallenkamp melting point machine.

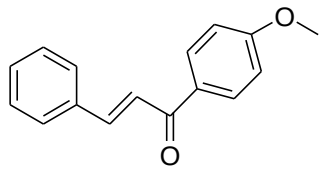
General synthesis of 4-methoxy phenyl propanone chalcones were carried out using modified Claisen-Schmidt condensation reaction.



3-Furan-2-yl-1-(4-methoxy-phenyl)-propenone (**A**)

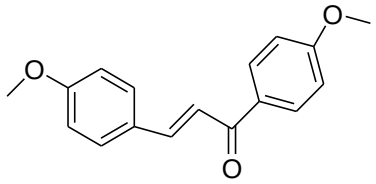
(A).was synthesized by mixing furfural (5.0 g, 0.05 mol) and p-methoxy acetophenone (7.8 g, 0.05 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours. The temperature was monitored such that the reaction flask remained below 10 ^{o}C. Ice cold 10 % Potassium hydroxide (20 ml) was added and stirred for a further 2 hours. The reaction mixture was then

allowed to stand on the reaction bench at room temperature for 72 hours. To the resultant mixture was added cold distilled water (50 ml) and then 10 % acetic acid (30 ml) to acidify using litmus paper to determine the acidity. The resultant crude precipitate was collected by filtration washed with cold water and dried. It was then recrystallized from ethanol, collected by filtration and dried *in vacuo* over silica to yield the compound **A**. Yield: 4.47 g, 37.6 %; mp 68 – 70 °C; Colour: Yellow; UV: λ_{max} 260, 500, 640 nm; IR: 2922.59, 1956.71, 1607.88, 1168.99 V cm-1; ^{1}H-NMR: [400 MHz, $CDCl_3$], δ_H: 3.86 (3H, d, J = 2.8 Hz),



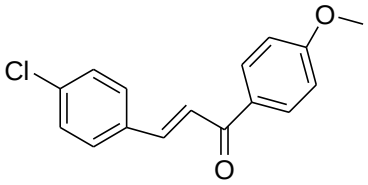
1-(4-Methoxy-phenyl)-3-phenyl-propenone (**B**)

(B) was synthesized by mixing p-anisaldehyde (5.0 g, 0.04 mol) and acetophenone (4.41 g, 0.04 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours. It was treated as the reaction above. Yield: 7.93 g, 90.6 %; mp 56 – 59 °C; Colour: Pale Yellow; UV: λ_{max} 480, 580, 640, 780 nm; IR: 3734.82, 3648.69, 2923.10, 1653.21, 1601.38 V cm-1; ^{1}H-NMR: [400 MHz, $CDCl_3$], δ_H: ^{13}C-NMR,



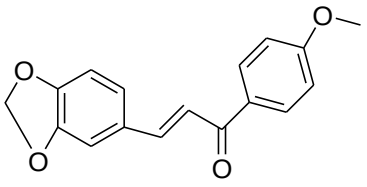
1,3-Bis-(4-methoxy-phenyl)-propenone (**C**)

(C) was synthesized by mixing p-anisaldehyde (5.0 g, 0.04 mol) and p-methoxy acetophenone (5.51 g, 0.04 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours. Treated as in A above. Yield: 4.47 g, 37.6 %; mp 68 – 70 °C; Colour: Yellow; (Found C, 76.01; H, 6.01 %; $C_{17}H_{16}O_3$ requires C, 76.10; H, 6.01 %); UV: λ_{max} 260, 500, 640 nm; IR: 2922.59, 1956.71, 1607.88, 1168.99 V cm-1; ^{1}H-NMR: [400 MHz, $CDCl_3$], δ(ppm): 3.75 (3H, S, O-CH_3), 3.84 (3H, S, O-CH_3), 6.77 -7.05 (2X 2Ar-H, dd), 7.66 -7.68 (2Ar-H, d), 7.57(1H, d, =CH), 7.71 (1H, d, =CH), 7.75-7.93 (2Xar-H, d); ^{13}C-NMR [100 MHz, MeOD] δ_C 47.8, 48.0, 54.6, 113.6, 114.1, 119.1, 127.7,130.1, 130.6, 130.9, 144.1, 162.0, 163.9, 189.6; m/z 268.15 (M^+, 100 %)



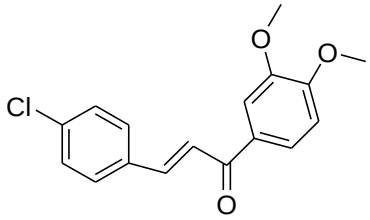
3-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-propenone (**D**)

(D) was synthesized by mixing p-chlorobenzaldehyde (5.0 g, 0.04 mol) and p-methoxy acetophenone (5.33 g, 0.04 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours. It was then allowed to stand at room temperature and treated as in A above. Yield: 9.42 g, 97.1 %; mp 113-115 °C; Colour: Cream; (Found C70.56, H 5.02, Cl 13.00, O 11.42; $C_{16}H_{13}ClO_2$ requires C 70.46, H 4.80, Cl 13.00, O 11.73) UV: λ_{max} 380, 500, 640 nm; IR: 2922.46, 2359.77, 1654.73, 1602.89, 1178.64V cm-1;



3-Benzo[1,3]dioxol-5-yl-1-(4-methoxy-phenyl)-propenone (E)

(E) was synthesized by mixing piperonal (5.0 g, 0.03 mol) and p-methoxy acetophenone (5.0 g, 0.03 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours and was treated as A above Yield: 9.25 g, 98.4 %; mp 117-120 °C; Colour: Pale-Yellow; (Found C, 72.3; H 5.02 %; $C_{17}H_{14}O_4$ requires C, 72.33; H 5.00 %), UV: λ_{max} 400, 500, 640,780 nm; IR: 2922.59, 1956.71, 1607.88, 1168.99 V cm-1; GC-MS (m/z) 282.11 (M^+, 100 %), 267.09 (14 %), 135.04 (40 %), 77 (25 %); ^{1}H-NMR: [400 MHz, MeOD], δ(ppm): 3.02 (3H, S O-CH_3), 6.76 (1H, d, J = 19.6 Hz, =CH), 7.6-7.09 (m-H, J= 3.0, 15.5 Hz, 7 X Ar-H), 8.02 (1H, d, J = 19.6 Hz, =CH); 13C-NMR [MeOD, 100 MHz] δc 38.8, 44.9, 46.9, 47.3, 47.6, 48.2, 110.8, 111.7, 115.9, 122.4, 127.9, 128.3, 130.4,



3-(4-Chloro-phenyl)-1-(3,4-dimethoxy-phenyl)-propenone (**F**)

(F) was synthesized by mixing p-chlorobenzaldehyde (5.0 g, 0.04 mol) and dimethoxy acetophenone (6.37 g, 0.04 mol) in ice cold ethanol (20 ml) in a round bottom flask equipped with magnetic stirrer for 2 hours and then treated as sample A above. Yield: 10.21 g, 95.2 %; mp 109 -111 °C; Colour: Cream; UV: λ_{max} 500, 580 640 nm; IR: 2923.48, 1668.59, 1576.67 V cm^{-1}; m/z 302.07 (M+, 5 %), 180 (43 %), 165 (100 %).

Antibacterial Activity

Test Organisms

The test organisms were clinical isolates obtained from the Department of Medical Microbiology, College of Health Sciences, Niger Delta University. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia Coli* and B. subtilis species were used. These isolates were already resistant to commonly used antibiotics (Ampicillin, Oxacillin, Erythromycin and Amoxicillin-clavulanic acid and Ciprofloxacin).

Bacterial Susceptibility Testing (Agar Diffusion Test)

Sterilized Mueller Hinton agar medium was prepared by autoclaving after following manufacturer's instructions in media preparation. Standardized 24 hour old cultures of the test bacterial organisms were inoculated into the molten agar medium (at 45 ^{o} C) aseptically using a Bunsen burner flame sterilised wire loop. A sterilized corn borer of 5 mm diameter was used to make seven ditches on each agar plate and 0.1 ml of the sample of various concentrations (1 mg/ml and 5 mg/ml) were dropped into each labelled ditch. Standard antibiotic discs were used as positive control, while distilled water was used as negative control. The solvent (methanol) was also used separately from the plant extracts to its effect compared with the samples. The inoculated plates were then left on the table for 1 hour to allow the sample to diffuse into the agar. The Mueller Hinton plates were incubated aerobically at 37 ^{o}C for 18 – 24 hours. Zones of inhibition produced after incubation were then measured in millimeters.

RESULTS AND DISCUSSIONS

The synthesis of the six (A – F) Chalcone derivatives as shown above followed the modified Claisen Schmidt condensation reaction using benzaldehyde derivatives and various acetophenone moieties in cold alkaline (potassium hydroxide) conditions and stirred at room temperature for over 2 hours and allowed to stand overnight for 24 hours in appreciable good yields of nearly over 90 %. In 78-98%. All the synthesized 4-methoxy phenyl propenone chalcone derivatives were characterized by either ^{1} H NMR, IR and Mass spectral data. In general, the IR spectral data of the chalcone derivatives obtained indicated the presence of distinctive functional groups such as –OH, –C=O, -CH=CH stretch in the range 3445-3290, 1700-1640 and 1644-1618, 1610-1590 cm^{-1}

Table-1: Result of antibacterial screening of compounds against S. aureus, B subtilis, E.coli and P. aeruginosa

Compound	Zone of Inhibition			
	S. aureus	E. coli	B. subtilis	P.aeruginosa
A	-	-	-	-
B	-	-	-	-
C	-	-	-	-
D	-	-	-	-
E	-	-	-	-
F	-	-	-	-

KEY: - NO ACTIVITY

CONCENTRATION USED: 1 mg/ml and 5 mg/ml for each sample.

The mass spectra of compounds obtained showed (M^*) peaks, is in agreement with their molecular formula. As a representative example, the ^1H NMR spectrum of compound E indicated the following signals: singlet at 3.02 corresponding to O-CH_3 and doublet at, 6.76 with a J value of 19.6 Hz corresponding to a methane group =CH and another doublet at 8.02 with a corresponding coupling constant of 19.6 Hz indicating =CH that is highly deshielded. Aromatic peaks at 7.6-7.09 (m-H, J= 3.0, 15.5 Hz, 7 X Ar-H), were observed at expected regions.

Antimicrobial activities

Antibacterial evaluation data (Zone of inhibition) of the synthesized chalcone derivatives (A-F) is presented in Table 1 It is observed that none of the 4-methoxy phenyl propenone chalcone derivatives (A-F) showed antibacterial activity.

CONCLUSION

From our studies, it shows that not all chalcones exhibit antibacterial activity as earlier made believe by several other researchers.

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