MICROWAVE-INDUCED, EFFICIENT, CONVENIENT AND RAPID SYNTHESIS OF BENZYLOXYCHALCONES AS POTENT GROWTH INHIBITOR

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Keywords: Chalcones, Claisen-Schmidt condensation; microwave irradiation; antibacterial activity; antifungal activity.

A novel series of substituted chalcones containing benzyloxy moiety (3a-3h) was synthesized by microwave induced Claisen-Schmidt condensation of 2-acetyl-1-naphthol and its halo derivatives with different substituted aromatic aldehydes. All the synthesized chalcones were characterized by spectral analysis and screened for their antibacterial and antifungal effectiveness by using standard methods. It is found that the microwave irradiation technique is superior in terms of considerable increase in the reaction rate, yields and shortening the reaction time. The investigation of antimicrobial screening revealed that compounds (3a-3d) containing benzyloxy group at para position of aldehyde ring of chalcones possessing more potent antimicrobial activity.

INTRODUCTION

Chalcone is a generic term given to compounds bearing 1,3-diphenyl-2-propen-1-one framework.1 Chalcones and their derivatives are polyphenolic compounds of flavonoids family. They have been found in many plants as metabolic precursors of other flavonoids and isoflavonoids.2 It is noteworthy to mention that the presence of chalcones have been reported in plants traditionally employed for therapeutical purposes.3 Chemist have been attracted towards the nucleus of chalcones due to their relatively simple structures and wide variety of pharmacological activities.4-7 Chalcone based compounds have been reported to exhibit anticancer,8,9 anti-inflammatory activity,10,11 anti-ulcerative,12 analgesic,13 anti-viral,14 anti-fungal,15 antimarial16 and anti-bacterial activity17 etc. which may be altered depending on the type of substituents on aromatic rings. Chalcones are synthesized by Claisen Schmidt condensation, which involve cross aldol condensation of suitable benzaldehyde derivatives and acetophenone derivatives by base catalysed or acid catalysed reactions followed by removal of water molecule. Synthetic and naturally occurring chalcones have been extensively studied and developed as one of the pharmaceutically important molecules. Therefore, in the present investigation it has been considered worthwhile to synthesize some new chalcone derivatives that may be of value in development of new, potent, selective and less toxic antimicrobial agent by conventional and microwave irradiation methods. Microwave induced enhancement of organic reaction is gaining popularity as a non-conventional technique for rapid synthesis.18 The important features of this technique are easy access to high temperature, safe and environmentally benign techniques with shorter reaction time.

The synthesized compounds were purified by recrystallization and chromatography. The compounds were assigned on the basis of 1H NMR, IR and GC-MS analysis. The compounds were tested for their anti-bacterial and anti-fungal activities by standard methods.

EXPERIMENTAL

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. 1H NMR spectra were recorded on a Gemini 300-MHz instrument in CDCl3 as solvent and TMS as an internal standard. The mass spectra were recorded on EISHIMADZU-GC-MS spectrometer. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. Synthon-3000, Anton Paar reaction system was used for microwave synthesis. The purity of products was checked by Thin Layer Chromatography (TLC) on silica gel. All solvents and chemicals were purchased from Alfa chemicals and used without further purification.

General procedure for synthesis of chalcones (3a-3h)

Equimolar quantities (0.001 mol) of 2-acetyl-1-naphthol or its halo derivative and respective aromatic aldehydes (0.001 mol) were mixed and dissolved in minimum amount (5 mL) of ethanol. To this, catalytic quantity of aqueous KOH solution was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 2-5 min at 180 W. The reactions were monitored through TLC using solvent system benzene:ethyl acetate (8:2), when the reaction was complete the reaction mixture was cooled in an ice bath and product thus formed was filtered, washed with distilled water and recrystallized from ethanol.

![Scheme 1. Synthesis of Chalcones under Microwave condition](image)
A comparison (Table 1) of the results obtained from the two synthetic approaches indicate that the effect of microwave irradiation is not purely thermal, besides giving decreased reaction times and improved yield.

| No. | X   | R           | R1          | Time, min | M.P. a  | Yield b |
|-----|-----|-------------|-------------|-----------|---------|---------|
| 3a  | H   | OMe        | OMe         | 3         | 150±2   | 90      |
| 3b  | Br  | OMe        | OMe         | 4         | 155±2   | 92      |
| 3c  | I   | OMe        | OMe         | 5         | 160±2   | 88      |
| 3d  | Cl  | OMe        | OMe         | 5         | 152±2   | 90      |
| 3e  | H   | OMe        | OMe         | 3.5       | 148±2   | 85      |
| 3f  | Br  | OMe        | OMe         | 4         | 150±2   | 88      |
| 3g  | I   | OMe        | OMe         | 5         | 158±2   | 92      |
| 3h  | Cl  | OMe        | OMe         | 5         | 152±2   | 85      |

(a) M.P. refers to solvent-free and other technique. b Yield of the isolated product in % term.

(Hydroxynaphthalen-2-yl-1-one (3a))

Yellow solid. El-MS m/2 (rel. int. %): 410 (90) [M+1]+. IR (KBr): 3402 (OH), 3059 (C-H), 1680 (C=O), 1570 (C=C) cm⁻¹. ¹H NMR (400MHz, CDCl₃) δ = 14.0 (s, OH), 8.20 (d, C=CH, J = 15.6Hz), 7.30 (d, CO=CH, J = 15.6Hz), 7.25-6.60 (m, Ar-H), 5.16 (s, CH₃), 3.96 (s, CH₃). ¹³C NMR (CDCl₃) δ = 192, 164, 149, 145, 134, 135, 134, 132, 131, 130, 129, 127, 126, 125, 118, 114, 111, 71. 56. Anal. Calcd. for C₂₂H₁₄O₂Cl: C, 66.70; H, 3.88; Cl, 23.69. Found: C, 66.62; H, 4.29; Br, 16.15. 2(E)-3-(4-Benzoyl-4-iodonaphthalen-2-yl)-1-(1-chloro-4-hydroxynaphthalen-3-yl)prop-2-enone (3b)

Brown solid. El-MS m/2 (rel. int. %): 536 (75) [M+2]+. IR (KBr): 3420 (OH), 3030 (C-H), 1675 (C=O), 1560 (C=C) cm⁻¹. ¹H NMR (400MHz, CDCl₃) δ = 13.96 (s, OH), 8.43 (d, C=CH, J = 15.6Hz), 7.89 (d, CO=CH, J = 16.7Hz), 7.80-7.25 (m, Ar-H), 5.19 (s, CH₃), 3.96 (s, CH₃). ¹³C NMR (CDCl₃) δ = 192, 164, 149, 145, 144, 138, 137, 136, 135, 134, 132, 131, 130, 129, 128, 127, 125, 118, 114, 111, 95, 71, 56. Anal. Calcd. for C₂₂H₁₄O₂Cl: C, 60.44; H, 3.91; I, 23.69. Found: C, 66.42; H, 3.88; I, 23.65. 2(E)-3-(4-Benzoyl-4-methoxyphenyl)-1-(1-chloro-4-hydroxynaphthalen-3-yl)prop-2-enone (3b)

Brown solid. El-MS m/2 (rel. int. %): 445 (60) [M+2]+. IR (KBr): 3360 (OH), 3010 (C-H), 1670 (C=O), 1560 (C=C) cm⁻¹. ¹H NMR (400MHz, CDCl₃) δ = 13.80 (s, OH), 8.20 (d,
C=CH, J= 15.6Hz), 7.90 (d, CO=CH, J= 16.2Hz), 7.73-7.49 (m, Ar-H), 4.98 (s, CH2), 3.83 (s, CH3) \(^{13}\)C NMR (CDCl3) \(\delta = 192, 164, 149, 145, 144, 138, 137, 136, 135, 134, 132, 131, 130, 129, 128, 127, 126, 125, 120, 118, 114, 112, 111, 71, 56; Anal. Calcd. for C27H21O4Cl: C, 72.80; H, 4.71; Cl, 131, 56-60; Found: C, 72.77; H, 4.68; Cl, 8.05.

**Biological Activity**

The newly synthesized compounds were screened for their antibacterial activity against Gram +ve bacterial strain of *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginasa* (ATCC-27853) and Gram-ve bacterial strain of *Klebsiella Pneumoniae* (ATCC-700603) and *Escherichia coli* (ATCC-25922) by disk diffusion method. \(^{19,20}\) The sterile disks, previously soaked in a known concentration of the test compounds (50 mg ml\(^{-1}\)), were placed in nutrient agar medium. Solvent and growth controls were kept. Ofloxacin was used as positive control while the disk poured in DMSO was used as negative control. The plate was incubated for 24 h at 37\(^{\circ}\)C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram +ve and Gram -ve bacteria. Inhibition zone were measured and compare with controls.

Antifungal activity was performed by plate poison method.\(^{21}\) The medium used was potato dextrose agar (Himedia). The medium was prepared and sterilized at 10 psi in autoclave for 15 min. The compounds to be tested were added to the sterile medium in aseptic condition so as to get final concentration of 1 %. A plate with DMSO was prepared as negative control, similarly a plate with 1 % Gresiofulvin was prepared as standard reference plate i.e. positive control. *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium monoliforme* and *Aspergillus flavus* were selected as test fungal cultures. They were allowed to grow on slant for 48 h so as to get profuse sporulation. 5 mL of 1:100 aqueous solution of Tween 80 was added to get the slant and spores were scraped with the help of nicrome wire loop to form suspension. The fungal suspension was spot inoculated on the plates prepared using compound with the help of nicrome wire loop. The plates were incubated at room temperature for 48 h, after the incubation plates were observed for the growth of inoculated fungi.

The minimum inhibitory concentration of compounds was obtained by Broth dilution method. In this the concentration of synthesized compounds were maintained at 8 mg mL\(^{-1}\) in the first tube containing 1 mL of broth. The tubes were vortexed to make the initial standard concentration. This were serially dilute in other tubes and finally 1 mL was discarded from the last tube to make the dilution of 1, 0.5, 0.25 mg mL\(^{-1}\), respectively. To all these tubes, 0.1 mL of the long phase culture of target microorganism was added separately and incubated at 37 \(^{\circ}\)C for 24-48 h for microbial growth.\(^{22-23}\)

**RESULTS AND DISCUSSION**

**Synthesis**

In view of applications of chalcones and in continuation of our previous works reported on green synthetic protocol towards synthesis of bioactive compounds,\(^{24-27}\) we synthesized new class of benzyloxy chalcone derivatives (3a-3h) under the condition of microwave assisted Claisen-Schmidt condensation of substituted aromatic aldehydes with 2-acetyl-1-naphthol/halosubstituted 2-acetyl-1-naphthol in presence of KOH in good yield.\(^{28}\) We found that microwave technique has several advantages including clean and easy work-up procedure, short reaction time, high yield and eco-friendliness.

The structure of chalcone derivatives were characterized by recording their IR, \(^1\)HNMR and GC-MS spectra. All the chalcones showed absorption band in region 1680-1640 cm\(^{-1}\) due to C=O stretching vibration. \(^1\)HNMR spectra is best analyzing tool for the structural elucidation it showed two doublet in the region of \(\delta = 8.10-8.40\) ppm due to olefinic protons (CH=CH-) and also showed a singlet in the range of 13.80-14.00 ppm due to hydroxyl group. \(^{13}\)C NMR spectra of chalcones were recorded in CDCl\(_3\) and are in good agreement with theoretical \(^{13}\)C NMR spectra proposed for all compounds.

**Antimicrobial activity**

The investigation of antibacterial screening data revealed that all tested compounds (3a-3h) showed good to moderate bacterial inhibition against *S. aureus*, *P. aeruginasa*, *K. pneumoniae* and *E. coli* species. The good activity is attributed to the presence of pharmacologically active electron releasing methoxy and benzyloxy groups attached to aldehyde ring of chalcones. A comparative study also revealed that the compounds (3a-3d) containing benzyloxy group at para and methoxy group at meta position of aldehyde ring of chalcones showed more potent inhibitory activities against Gram +ve and Gram –ve bacteria than the compounds (3e-3h) having position of both groups interchanged. From this comparative study it is concluded that by changing the position of substituents of chalcones the microbial inhibition activities are altered. The bacterial zone of inhibition value are given in (Table 2).

Antifungal screening data of all compounds (3a-3h) revealed good to moderate antifungal activity against all tested organisms. In term of structure activity relationship the compounds that contain benzoyl group at para position of aldehyde ring of chalcones showed significant antifungal activities. Results were recorded as growth of fungi in percentage of zone of inhibition in (Table 2).

**Table 2. Antimicrobial data of synthesized chalcones.**

| Compound | Antimicrobial activity | A | B | C | D | E | F | G | H |
|----------|------------------------|---|---|---|---|---|---|---|---|
| 3a       |                        | 23 | 21 | 24 | 24 | 82 | 86 | 85 | 87 |
| 3b       |                        | 25 | 22 | 23 | 26 | 80 | 85 | 83 | 85 |
| 3c       |                        | 26 | 24 | 22 | 28 | 83 | 88 | 80 | 85 |
| 3d       |                        | 24 | 23 | 26 | 27 | 90 | 80 | 80 | 78 |
| 3e       |                        | 19 | 15 | 20 | 22 | 61 | 60 | 62 | 59 |
| 3f       |                        | 19 | 14 | 16 | 22 | 60 | 70 | 60 | 62 |
| 3g       |                        | 18 | 19 | 20 | 16 | 61 | 65 | 65 | 58 |
| 3h       |                        | 17 | 17 | 16 | 18 | 59 | 60 | 61 | 60 |
| Ofloxacin|                        | 26 | 25 | 28 | 30 | 99 | 99 | 100 | 99 |

\(^{A}:\) P. aeruginosa, \(^{B}:\) S. aureus, \(^{C}:\) K. pneumoniae, \(^{D}:\) E. coli, Ofloxacin, \(^{E}:\) P. chrysogenum, \(^{F}:\) F. moniliforme, \(^{G}:\) A. flavus, \(^{H}:\) A. niger, Griseofulvin
Minimum inhibitory concentration (MIC)

The minimum inhibitory concentration of the synthesized compounds was evaluated at different concentration i.e. 1.0, 0.5, 0.25 mg mL⁻¹. The result of MIC are given in table 3, it is clear that the chalcones (3a-3d) shows more promising inhibition than chalcones (3e-3h) at minimum concentration (0.25 mg mL⁻¹) against all tested bacterial and fungal strains. The chalcones (3g, 3h) shows good inhibition against P. aeruginosa, S. aureus (Gram+ve) and K. pneumoniae, E. coli (Gram –ve) strains, at minimum concentration 0.5 mg mL⁻¹. The chalcones 3e, 3f showed moderate inhibition against all bacterial strains at minimum concentration 1.0 mg mL⁻¹. The chalcones 3g and 3h showed effective inhibitory potential against all fungal strains at minimum concentration 0.5 mg mL⁻¹. The P. chrysogenum, F. moniliforme, A. flavus, A. niger are prominently affected by chalcones 3e, 3f at minimum concentration 1.0 mg mL⁻¹. The comparative analysis also revealed that the chalcones having electron releasing benzyloxy group at para position of ring B had more potent inhibition against all bacterial and fungal strains at minimum concentration 0.25 mg mL⁻¹.

CONCLUSION

In conclusion, salient feature of our approach is coupling microwave with keeping modernization and simplification over classical procedure for avoiding the generation of valuable toxic organic solvents, which are corrosive, and an efficient and cheap technology to synthesize chalcone derivatives. The evaluation of antimicrobial activities of chalcones carrying benzyloxy and methoxy group were reported. The activity results showed that compounds (3a-3d) possessing benzyloxy group at para position of aldehyde ring of chalcones are most active against all bacterial and fungal strains tested than the compounds (3e-3h) having position of benzyloxy group was changed from para to meta. This electronic effect played very important role in activity, as can be seen for the compounds having electron donor groups such as benzyloxy, methoxy. Thus in future this class of benzyloxy substituted chalcones may be used for the generation of better lead molecules to fight against bacterial and fungal strains.

Table 3. Minimum inhibitory concentration of synthesized chalcones.

A. Bacterial strains

| Compound, mg mL⁻¹ | P. aeruginosa | S. aureus | K. pneumonia | E. coli |
|-------------------|---------------|-----------|--------------|---------|
|                   | 1.0           | 0.5       | 0.25         | 1.0     | 0.5 | 0.25 | 1.0 | 0.5 | 0.25 |
| 3a                | -             | -         | -            | -       | -   | -    | -   | -   | -    |
| 3b                | -             | -         | -            | -       | -   | -    | -   | -   | -    |
| 3c                | -             | -         | -            | -       | -   | -    | -   | -   | -    |
| 3d                | -             | -         | -            | -       | -   | -    | -   | -   | -    |
| 3e                | -             | +         | +            | -       | +   | +    | -   | +   | +    |
| 3f                | -             | +         | +            | -       | +   | +    | -   | +   | +    |
| 3g                | -             | -         | +            | -       | -   | -    | -   | -   | -    |
| 3h                | -             | -         | +            | -       | -   | -    | -   | -   | -    |

B. Fungal strains

| Compound, mg mL⁻¹ | P. chrysogenum | F. moniliforme | A. flavus | A. niger |
|-------------------|----------------|----------------|-----------|----------|
|                   | 1.0 | 0.5 | 0.25 | 1.0 | 0.5 | 0.25 | 1.0 | 0.5 | 0.25 |
| 3a                | -   | -   | -    | -   | -   | -    | -   | -   | -    |
| 3b                | -   | -   | -    | -   | -   | -    | -   | -   | -    |
| 3c                | -   | -   | -    | -   | -   | -    | -   | -   | -    |
| 3d                | -   | -   | -    | -   | -   | -    | -   | -   | -    |
| 3e                | -   | +   | -    | +   | +   | +    | -   | +   | +    |
| 3f                | -   | +   | -    | +   | +   | +    | -   | +   | +    |
| 3g                | -   | -   | +    | -   | -   | -    | -   | -   | -    |
| 3h                | -   | -   | +    | -   | -   | -    | -   | -   | -    |

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