Synthesis, Characterization and Antimicrobial Activity of Novel Chalcones Analogue

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Abstract: A new series of chalcones (3a-j) have been prepared by Claisen-Schmidt condensation between substituted acetophenone and substituted aldehyde. All these compounds were characterized by physical and spectral methods such as melting point, IR, 1H NMR and Mass analysis. All the synthesized compounds have been screened for their antimicrobial activity.

Keywords: Chalcones, Spectral analysis, Anti microbial Activity

Introduction

Chalcones are a major class of natural products belonging to the flavonoid family. They are considered as the precursors of flavonoids and isoflavonoids. They are also the precursors of a number of biologically important heterocycles such as benzothiazepines, pyrazolines and flavones.

Chalcones (trans-1, 3-diaryl-2propen-1-ones) are α, β-unsaturated ketones consisting of two aromatic rings having diverse array of substituents. Rings are interconnected by a highly electronegative three carbon α, β-unsaturated carbonyl system that assumes linear or nearly planar structure. They contain the electron ketoethylenic group (–CO– CH=CH–). Chalcones possess conjugated double bonds and a completely delocalized π- system on both benzene rings. Chalcones have been used as intermediate for the preparation of compounds having therapeutic value. Chalcones and their derivatives, whether synthetic or naturally occurring are an interesting and significant group of molecules as they possess a wide range of pharmacological activities such as anti-inflammatory, antimicrobial, antifungal, antibacterial, antioxidant, cytotoxic antitumor, anticancer, antimitotic, antileishmanial, antimalarial, antitubercular, antiviral and so on.
Claisen-Schmidt condensation

Synthetic method of preparing chalcones

The most convenient method is the Claisen Schimdt condensation of equimolar quantities of aryl methyl ketone with aryl aldehyde in the presence of alcoholic alkali. The reaction scheme is as follows:

\[
\text{aryl methyl ketone} + R\text{CHO} \xrightarrow{\text{aq. KOH, alcohol}} \text{arylated ketone}
\]

Reagents: (a) aq. KOH, alcohol

Scheme 1

The synthesis of chalcone compounds incorporating with hetero cycles became great importance in medicinal chemistry. The hetero atoms in ther structure such as (S, N, O) explain variety applications in the biological engineering and in other field of their specific structures.

Experimental

Melting points of the compounds were determined in open capillary tubes and are uncorrected, IR Spectra were recorded on Shimadzu FT-IR Spectrometer using potassium bromide pellets, \(^1\)H NMR was determined on a Bruker Avance II 400 Spectrometer against TMS as internal standard. Mass spectra were recorded on waters Micromass Q-T of Micro spectrometry.

General method for the synthesis of chalcones

A mixture of substituted acetophenone (1 mmol), substituted aldehyde (1 mmol) and KOH (2 mmol, in minium H\(_2\)O) were taken in ethanol and stirred at 50-60 °C temperature for one hour. The completion of reaction was monitored by TLC. The products were isolated by acidification of the cool diluted acid solution and obtained solid product was filtered and washed with water and recrystallize by ethanol to get pure product.

![Scheme 1. Synthesis of chalcones](image)

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>Product</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>R(_3)</th>
<th>R(_4)</th>
<th>Ar(^*)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>I</td>
<td>OH</td>
<td>I</td>
<td>Ar(_1)</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>OH</td>
<td>I</td>
<td>H</td>
<td>I</td>
<td>Ar(_1)</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>OH</td>
<td>I</td>
<td>H</td>
<td>Cl</td>
<td>Ar(_1)</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>OH</td>
<td>I</td>
<td>H</td>
<td>CH(_3)</td>
<td>Ar(_1)</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>H</td>
<td>I</td>
<td>OH</td>
<td>I</td>
<td>Ar(_2)</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>OH</td>
<td>I</td>
<td>H</td>
<td>I</td>
<td>Ar(_2)</td>
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<tr>
<td>7</td>
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<td>OH</td>
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<td>Cl</td>
<td>Ar(_2)</td>
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<td>8</td>
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<td>OH</td>
<td>I</td>
<td>H</td>
<td>CH(_3)</td>
<td>Ar(_2)</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>H</td>
<td>I</td>
<td>OH</td>
<td>I</td>
<td>Ar(_3)</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>OH</td>
<td>Br</td>
<td>H</td>
<td>Cl</td>
<td>Ar(_4)</td>
</tr>
</tbody>
</table>
Results and Discussion

A variety of novel chalcones were synthesized via Claisen-Schmidt condensation of substituted acetophenones and aromatic benzaldehyde (Table 1). The reaction proceeded at room temperature. Work up procedure is simple and yield of the product is excellent.

All the newly synthesized chalcones were characterized by their chemical, physical and spectral analysis data (Table 2) and are further subjected to antimicrobial studies which exhibit moderate to good activity.

Table 2. Physical data of synthesized chalcones

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Product</th>
<th>Mol. Formula</th>
<th>Yield %</th>
<th>M.P., °C</th>
<th>Solubility</th>
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<tr>
<td>1</td>
<td>3a</td>
<td>C_{13}H_{21}O_{2}I_2BrS</td>
<td>90</td>
<td>176-178</td>
<td>DMF</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>C_{13}H_{21}O_{2}I_2BrS</td>
<td>92</td>
<td>162</td>
<td>DMF</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>C_{13}H_{21}O_{2}I_2BrS</td>
<td>80</td>
<td>178</td>
<td>DMF</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>C_{14}H_{19}O_{2}I_2BrS</td>
<td>92</td>
<td>142</td>
<td>DMF</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>C_{17}H_{17}O_{4}I_2BrS</td>
<td>86</td>
<td>162-164</td>
<td>DMF</td>
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<tr>
<td>6</td>
<td>3f</td>
<td>C_{17}H_{17}O_{4}I_2BrS</td>
<td>88</td>
<td>174-176</td>
<td>DMF</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>C_{15}H_{15}I_2O_{4}I_2BrS</td>
<td>80</td>
<td>178</td>
<td>DMF</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>C_{15}H_{15}I_2O_{4}I_2BrS</td>
<td>90</td>
<td>159</td>
<td>DMF</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>C_{17}H_{17}I_2O_{4}I_2BrS</td>
<td>88</td>
<td>150</td>
<td>DMF</td>
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<tr>
<td>10</td>
<td>3j</td>
<td>C_{15}H_{15}BrClO_{3}I_2BrS</td>
<td>85</td>
<td>108-110</td>
<td>DMF</td>
</tr>
</tbody>
</table>

Spectral analysis of the compounds

The structure of the compounds were done by spectral analysis (IR, ¹H NMR, Mass) and the results are shown below

**Compound 3a**

(E)-3-(5-Bromothiophen-2-yl)-1-(4-hydroxy-3,5-diiodophenyl)prop-2-en-1-one

FTIR (KBr, cm⁻¹): 3224(OH), 1646(C=O), 1576(C=C), 1465(C-C Aromatic str), 683(C-Br).

¹H NMR: 7.24(d, 1H, H₁), 7.48(d,1H,H₂), 7.49(d, 1H, Hα, J=15Hz), 7.58(d, 1H, Hβ, J=15Hz), 7.48(s1H,H₃), 7.53(s,1H, H₄), 8.43(s, 1H, OH).
M.S. (m/z): (M)= 560(m), 561(m+1), 558(m-2).

**Compound 3b**

(E)-3-(5-Bromothiophen-2-yl)-1-(2-hydroxy-3,5-diiodophenyl)prop-2-en-1-one
FTIR (KBr, cm⁻¹): 3425(OH), 1623(C=O), 1546(C=C), 1419(C=C Aromatic str), 621(C-Br). ¹H NMR: 7.33(d, 1H,H₃), 7.48(d,1H,H₄), 7.73(d, 1H, Ha, J=15Hz), 7.97(d, 1H, H β, J=15Hz), 8.27(s, 1H,H₃), 8.55(s,1H,H₆), 13.7(s, 1H, OH). M.S. (m/z): (M) = 558(m-2).

**Compound 3c**

(E)-3-(5-Bromo thiophen-2-yl)-1-(5-hydroxy-3-iodophenyl)prop-2-en-1-one

FTIR (KBr, cm⁻¹): 3436(OH), 1635(C=O), 1526(C=C), 1419(C=C Aromatic str), 621(C-Br), 802(C-Cl), 675(C-Br). ¹H NMR: 7.12(d, 1H,H₃), 7.21(d,1H,H₄), 7.27(d, 1H, Ha, J=15Hz), 7.97(d, 1H, H β, J=15Hz), 8.23(s, 1H,H₃), 8.47(s,1H,H₆), 13.46(s, 1H, OH). M.S. (m/z): 468(m).

**Compound 3d**

(E)-3-(5-Bromo thiophen-2-yl)-1-(2-hydroxy-3-iodophenyl)prop-2-en-1-one

FTIR (KBr, cm⁻¹): 3425(OH), 1639(C=O), 1569(C=C), 1415(C=C Aromatic str), 675(C-Br), 802(C-Cl), 675(C-Br). ¹H NMR: 2.32(s,3H,CH₃), 7.27(d, 1H,H₃), 7.52(d,1H,H₄), 7.65(d, 1H, Ha, J=15Hz), 7.95(d, 1H, H β, J=15Hz), 7.85(s, 1H,H₃), 8.04(s,1H,H₆), 13.46(s,1H, OH). M.S. (m/z): 450(m+1),448(m-1),447(m-2).

**Compound 3e**

(E)-3-(2,5-Dimethoxyphenyl)-1-(4-hydroxy-3,5-diiodophenyl)prop-2-en-1-one

FTIR (KBr, cm⁻¹): 3382(OH), 1658(C=O), 1589(C=C), 1492(C=C Aromatic str). ¹HNMR: 3.81(s,3H,OMe), 3.85(s,3H,OMe), 7.00(S,1H₃)7.01(d,1H₄)7.57(d,1H₆), 7.80(d, 1H, Ha, J=15Hz), 8.00(d, 1H, H β, J=15Hz), 8.45-8.50(s,2H,H₆,H₇), 10.28(s, 1H, OH). M.S. (m/z): 536(m), 535(m-1),534(m-2).

**Compound 3f**

(E)-3-(2,5-Dimethoxyphenyl)-1-(2-hydroxy-3,5-diiodophenyl)prop-2-en-1-one
FTIR (KBr, cm\(^{-1}\)): 3433(OH), 1635(C=O), 1558(C=C), 1431(C-C Aromatic str). \(^1\)H NMR: 3.82(s,3H,OMe), 3.86(s,3H, Ome), 7.02(S,1H)7.07(d,1H)7.46(d,1H)8.00(d, 1H, H\(_a\), J=15Hz), 8.22(d, 1H, H \(\beta\))J=15Hz), 8.23(s,1H,H\(_b\)), 8.57(s,1H\(_\gamma\)), 13.84(s,1H, OH). M.S. (m/z): 535(m-1), 534(m-2).

**Compound 3g**

\((E)-1-(5-chloro-5-hydroxy-3-iodophenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one\)

FTIR (KBr, cm\(^{-1}\)): 3425(OH), 1667(C=O), 1550(C=C), 1496(C-C Aromatic str), 785(C-Cl). \(^1\)H NMR: 3.80(s,3H,Ome), 3.85(s,3H,Ome), 7.03(S,1H)7.22(d,1H)7.50(d,1H)8.04(d, 1H, H\(_a\), J=15Hz), 8.12(d, 1H, H \(\beta\))J=15Hz), 8.16(s,1H,H\(_b\)), 8.26(s,1H\(_\gamma\)), 13.51(s,1H, OH). M.S. (m/z): 443(m-1),445(m+1).

**Compound 3h**

\((E)-3-(2,5-dimethoxyphenyl)-1-(2-hydroxy-3-ido-5-methylphenyl)prop-2-en-1-one\)

FTIR (KBr, cm\(^{-1}\)): 3440(OH), 1631(C=O), 1562(C=C), 1430(C-C Aromatic str). \(^1\)H NMR: 3.80(s,3H,Ome),3.85(s,3H,Ome), 7.03(S,1H)7.22(d,1H)7.50(d,1H)8.04(d, 1H, H\(_a\), J=15Hz), 8.12(d, 1H, H \(\beta\))J=15Hz), 8.16(s,1H,H\(_b\)), 8.26(s,1H\(_\gamma\)), 13.51(s,1H, OH). M.S. (m/z): 423 (m-1).

**Compound 3i**

\((E)-1-(4-Hydroxy-3,5-diiodophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one\)

FTIR (KBr, cm\(^{-1}\)): 1663(C=O), 1570(C=C), 1461(C-C Aromatic str). \(^1\)H NMR: 7.18((d, 1H, H\(_a\),J=15Hz), 7.26(d, 1H, H \(\beta\))J=15Hz), 8.05(s,1H,H\(_a\)), 8.12(s,1H,H\(_b\)),8.14(S,1H,H\(_b\)),8-8.45(m,4H,Ar-H) .9. 95(s,1H, OH), 11.99(s,1H,NH) .M.S. (m/z): 423 (m-1).

**Compound 3j**

\((E)-1-(3-Bromo-5-chloro-2-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one\)
FTIR (KBr, cm⁻¹): 1641(C=O), 1563(C=C), 1422(C-C Aromatic str). ¹H NMR: 7.40((d, 1H, Hα, J=15Hz), 8.51(d, 1H, Hβ,J=15Hz), 7.44-7.77(m,4H,Ar-H), 9.95(s,1H, OH), 7.61(s,1H,H₃,Ar),7.72(s,1H,H₄), 11.99(s,1H,NH), 8.24(s,1H,OH). M.S. (m/z): 353 (M), 355(m+2), 351(m-2).

Antimicrobial activity

Antimicrobial screening was done using disc diffusion method at a concentration of 500 µg/mL.

Procedure

The test was performed according to the disk diffusion method adopted with some modification for the prepared compound using Penciline and streptomycin as references. The prepared compounds were tested against one strain of Gram +ve bacteria, Gram –ve bacteria, fungi. Whatman filter paper disk of 5 mm diameter were sterilized by autoclaving for 15 min at 121 °C. The sterile disk were impregnated with different compounds (600 g/disk). Agar plates were surface inoculated uniformly from the both culture of the tested microorganism. The disk were placed on the medium suitably spaced apart on the plate were incubated at 50 °C for 1 h to permit good diffusion and then transferred to an incubator at 37 °C for 24 h for bacteria and 28 °C for 72 h for fungi.

The compounds were evaluated for antibacterial activity against Staphylococcus aureus gr +ve, Escherichia coli gr –ve Bacillus subtilis gr +ve, Pseudomonas aeruginosa gr –ve, and antifungal activity against Aspergillus oryze, Aspergillus niger. DMSO was used as solvent control. The results of antimicrobial data are summarized in Table 3. All compounds show the moderate to good activity against bacteria, but for all compounds did not stop the growth of Aspergillus oryze fungus and all compounds were not effective towards Aspergillus niger fungus.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
<th>Fungus</th>
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<tbody>
<tr>
<td></td>
<td>Staph aureus</td>
<td>Bacillus subtilis</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>3a</td>
<td>++</td>
<td>++</td>
<td>-ve</td>
</tr>
<tr>
<td>3b</td>
<td>-</td>
<td>-</td>
<td>-ve</td>
</tr>
<tr>
<td>3c</td>
<td>-</td>
<td>-</td>
<td>-ve</td>
</tr>
<tr>
<td>3d</td>
<td>-</td>
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</tr>
<tr>
<td>3e</td>
<td>++</td>
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<tr>
<td>3h</td>
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</tr>
<tr>
<td>3i</td>
<td>++</td>
<td>++</td>
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</tr>
<tr>
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<td>+</td>
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<tr>
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<td>+</td>
<td>+</td>
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<tr>
<td>Streptomycin 2</td>
<td>++</td>
<td>++</td>
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</tr>
</tbody>
</table>

++ = Clear Zone of Inhibition + = Minimum Zone of Inhibition -ve = Growth (Antibacteria and Antifungal Activities Observed) - = No Effect X = Not applicable, Standard 1 Penciline +, Standard 2 Streptomycin++
Conclusion

We have reported some novel chalcones using substituted acetophenone with substituted aldehyde with high yield. The newly synthesized chalcones were confirmed by spectral analysis and further evaluated for their antimicrobial activity. The antibacterial activity revealed that of the compounds showed moderate to good activity against the pathogens used, the result was negative on fungus.

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References

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