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Synthesis and Characterization of Some Chalcone Derivatives

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Abstract: Chalcones are the important constituent of many natural sources and have variety of biological activities. A series of chalcone derivatives were synthesized and their structure also confirmed. The compounds were synthesized by Claisen-Shimidt base catalyzed condensation of appropriate aromatic ketones or substituted aromatic ketones with benzaldehydes or substituted benzaldehydes. The structures of the synthesized compounds were confirmed by IR, mass spectroscopy and elemental analysis.

Key words: Chalcone, Claisen-Shimidit condensation, flavanone, benzaldehyde, acetophenone

INTRODUCTION

Chalcones or benzylideneacetophenone are the important constituents of natural sources. It was first isolated from Chinese liquorice (*Glycyrrhizae inflata*) (Yerra *et al*., 2004). It has 1,3-diaryl-1-ones skeletal system, which was recognized as the main pharmacophore for chalcones. From plants, stable chalcone moiety can't be isolated because the presence of enzyme chalcone synthetase (CSH) which immediately converts chalcone into flavanone (Fig. 1) (http//www.netsci.org/science/comchem/feature 12.html).

Chalcones and its derivatives are an important group of natural product and have been reported to possess varied biological and pharmacological activity. Yuh-Heei *et al*. (2002) synthesized different series of chalcone derivatives, which are having 90% inhibitory activity against *Mycobacterium tuberculosis*. They also performed pharmacophore mapping analysis on chalcone derivatives and concluded that ring A containing hydrophobic group and ring B containing hydrogen bonding substitutents are better for antitubercular activity (Yuh-Meei *et al*., 2002; Vishnu *et al*., 2000). Sylvie *et a l*. (1998) synthesized a series of chalcone derivatives and screened for cytotoxic activity against the K562 human leukemia cell line using the MTT assay method. But only one compound (E)-3-(3-hydroxy-4-methoxyphenyl)-2-methyl-1-(3',4',5'-trimethoxyphenyl)-prop-2-en-1-one showed maximum activity (Sylvie *et al*., 1998; Vibhute and Baseer, 2003; Anjaneyulu and Murthy, 1994). Fabiane *et al*. (2003) synthesized 10 compounds and tested for leishmanicidal and trypanocidal activity, among that 5 compounds showed distinct and potent inhibitory effect on the growth of *Tripanosoma cruzi* and only two compounds showed strong inhibitory activity on the

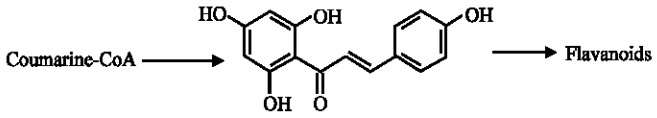

Fig. 1: Biochemical changes of chalcones

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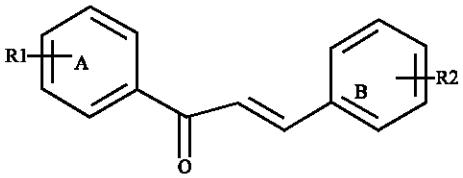


Fig. 2: Parent nucleus of chalcone derivatives

growth of *L. braziliensis* by *in vitro*. They also concluded that the position of the substitutent on chalcone derivatives plays an important role for their antiprotozoal activity. Fabio *et al*. (1998) synthesized a new series of chalcone derivatives and tested *in vitro* to inhibit aldose reductase enzyme (ALR2) and their specificity toward the target enzyme. All the compounds displayed affinity for ALR2. With the help of X-ray crystallography studies, they also proved that for an efficient inhibition of ALR2, the presence of hydroxyl group in the ring A or in case of their absence, the carboxylic moiety in the molecule is important for the interaction with ALR2. In the present investigation, we are attempted to synthesis some chalcone derivatives, which are biologically important.

Chemistry of Chalcones

In Claisen-Schmidt condensation reaction for synthesizing chalcones, aromatic aldehydes can be condensed with aliphatic or aromatic ketones in the presence of aqueous alkali to form α, β unsaturated ketones called chalcones. In this mechanism, the first step is condensation of the aldol type involving the nucleophilic addition of carbanion derived from the aryl ketones to carbonyl carbon of the aromatic aldehydes. Dehydration of the hydroxy ketones to form the conjugated α, β unsaturated ketones or chalcones (Fig. 2) (Yerra *et al*., 2004).

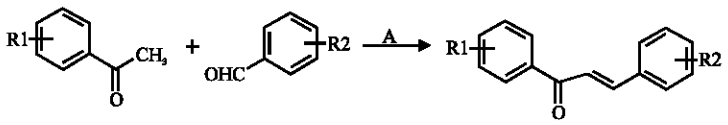
The structure of parent molecule of chalcones consist of two phenyl rings (A and B) and one α, β unsaturated double bond. The ring A must contain an electron deficient moiety like ethyl, methyl or alkyl groups for better activity. The ring B must contain the hydrophobic groups like halogens, nitro and cyano for better activity. The unsaturated double bond plays an important role for the activity but marginal modifications in this bond don't have much effect on the activity. Para position of the ring B is important for the activity. The ortho position of ring B also enhances the activity but in comparison with para position it is low. 3D QSAR and in house QSPR studies of chalcones have proved all these facts.

MATERIALS AND METHODS

All melting points (m.p.) were determined in open capillaries on Jindal melting point apparatus and were uncorrected. The purity of the compounds was routinely checked by thin layer Chromatography (TLC) using silica gel G (Merck). The instruments used for spectroscopic data are IR: Jasco FTIR-470 spectrophotometer (KBr) with diffuse reflectance method; MS-JEOL SX102 Mass spectroscopy by using Argon/Xenon (6Kv, 10mA) as the FAB gas and m-nitro benzyl alcohol (NBA) as the matrix.

Synthetic Scheme for Chalcone Derivatives

Chalcones were prepared by base catalyzed condensation of a mixture of the substituted acetophenones and substituted benzaldehydes in alcohol, 60% solution of potassium hydroxide (KOH) was added drop wise with stirring. The reaction mixture was kept at room temperature for 14-16 h, then diluted with water and acidified with 10% hydrochloric acid (Fig. 3). The progress of the reaction and purity of the synthesized compounds was monitored by TLC using silica gel-G as stationary



A = 60%KOH, Ethanol, Room temp

Fig. 3: Synthetic scheme for chalcone derivatives

Table 1: Detail of the substituents used for the synthesis of chalcones

R1	R2	Product
H	H	Chalcone
H	4'-$N(CH_3)_2$	4-Dimethyl amino Chalcone
2-OH	4'-$N(CH_3)_2$	2-Hydroxy 4-Dimethyl amino Chalcone
2-OH	H	2-Hydroxy Chalcone

phase, benzene: ethylacetoacetate (8:2) as mobile phase and iodine vapor was used as detecting agent. The entire compounds gave satisfactory Rf value. Detail of the synthesized compounds is given in Table 1 (Vogel, 1996).

Synthesis of Chalcone

To a solution of acetophenone (12 g, 0.1 mol) in ethanol (15 mL), benzeldehyde (10.6 g, 0.1 mol) was added. To this mixture aqueous potassium hydroxide (60%) was poured gradually with constant stirring and continues the stirring for 1.5 h. After adding, the mixture of potassium salt of chalcone was kept for 14-16 h at room temperature. The potassium salt of chalcone was separated by ice-cold hydrochloric acid (10%, 30 mL). The separated solid was filtered and washed with ice-cold water (2×50 mL) till the washing was neutral to litmus. Recrystallized the compound with ethanol and dried at room temperature.

Synthesis of 4-Dimethyl Amino Chalcone

Reaction with acetophenone (12 g, 0.1 mol) and p-dimethyl amino benzeldehyde (14.9 g, 0.1 mol), 4-dimethylamino chalcone was obtained by the above procedure.

2-Hydroxy 4-Dimethyl Amino Chalcone

A mixture of 2-hydroxy acetophenones (13.6 g, 0.1 mol), in ethanol (15 mL) and p-dimethyl amino benzeldehyde (14.4 g, 0.1 mol), 2-hydroxy 4-dimethyl amino chalcone was obtained by the above procedure.

2-Hydroxy Chalcone

2-hydroxy chalcone was obtained by the above procedure except that the starting material used was 2-hydroxy acetophenone (13.6 g, 0.1 mol) in ethanol (15 mL) and benzeldehyde (10.6 g, 0.1 mol).

RESULTS AND DISCUSSION

Synthesis of chalcone is a single step method. The synthesized chalcone derivatives were undergone physicochemical characterization and the obtained results are given in Table 2. The yields of the synthesized compounds were found to be significant.

The structure of the synthesized compounds was confirmed by IR, Mass and elemental analysis. Elemental analysis showed that the percentage of the nitrogen, hydrogen and carbon was found experimentally is equivalent to the calculated values in all compounds.

All the compounds give the characteristic IR peak that proved that the presence of particular functional groups (Table 3) and mass spectroscopy helps to find the molecular weight of the

Table 2: Physicochemical characterization data for synthesized compounds

Molecular Formula	Molecular weight	Yield (%)	MP (°C)	Elemental analysis (%) C Cal	C Fou	H Cal	H Fou	N Cal	N Fou
$C_{15}H_{12}O$	208	89	93	86.51	86.23	5.81	5.75	-----	----
$C_{17}H_{17}NO$	251	93	82	81.24	81.01	6.82	6.62	5.57	5.49
$C_{17}H_{17}NO_2$	267	90	95	76.38	76.15	6.41	6.26	5.24	5.15
$C_{15}H_{12}O_2$	224	79	79	80.34	80.12	5.39	5.02	----	----

Table 3: Interpreted IR spectra data of synthesized compound

Compound	IR Spectra
Chalcone	IR (KBr) ν cm^{-1} = 3051 (C-H aromatic), 3033 (C-H aromatic), 2800 (C-H), 1697 (C = O), 1448 (C-N), 751 (C-H bending).
4-Dimethyl amino chalcone	IR (Kbr) ν cm^{-1} = 3055 (C-H aromatic), 3040 (C-H aromatic), 2905-2800 (C-H stretching), 1697 (C=O), 1339 (C-N stretching tertiary amine), 751 (C-H bending)
2-Hydroxy 4-Dimethyl amino chalcone	IR (KBr) ν cm^{-1} = 3566 (O-H), 3086-3053 (C-H aromatic), 2989 (C-H), 1650 (C=O), 1437 (C-N), 1321 (C-N),722 (C-H bending).
2-Hydroxy chalcone	IR (KBr) ν cm^{-1} = 3051 (C-H aromatic), 3033 (C-H aromatic), 2905-2800 (C-H), 1697 (C=O), 1448 (C-N), 884 (C-H), 751 (C-H)

Table 4: Mass spectra data of synthesized compound

Compound	Molecular weight	Mass Spectra
Chalcone	207	MS: m/z, 207(M^+); m/z, 180(-OH); m/z, 77(-C = O)
4-Dimethyl amino chalcone	251	MS: m/z, 251(M^+); m/z, 77(-C = O)
2-Hydroxy 4-Dimethyl amino chalcone	267	MS: m/z, 267(M^+); m/z, 165 (H_2O+ alkene); m/z, 51(Alkyne)
2-Hydroxy chalcone	224	MS: m/z, 224(M^+); m/z, 207(M-18); m/z, 77(-C = O)

synthesized compounds (Table 4). The Chalcone derivatives showed that the molecular ion peak that equivalent to the molecular weight of proposed compound. Hence m/z value confirms the molecular weight of the respective synthesized compound.

- The Chalcone (first compound) have the molecular formula of $C_{15}H_{12}O$. The molecular ion peak at 207(M^+) showed that m/z that is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight of the compound. The IR peak at 1697 cm^{-1} suggesting the presence of C = O (Str) group. The IR peak at 3051cm^{-1} indicates that the presence of C-H (aromatic) streching. The IR peak at 2800 cm^{-1} indicates the presence of CH_2 streching. The IR peak at 751 cm^{-1} indicates the presence of aromatic bending. Melting point of the compound is 53°C, which is uncorrected.
- The molecular formula of 4-dimethyl amino chalcone is $C_{17}H_{17}NO$. The obtained molecular ion peak at 251(M^+); showed that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight of compound. The IR peak at 1695 cm^{-1} suggesting the presence of C = O (Str) group. The IR peak at 3055 cm^{-1} indicates the presence of C-H streching. The IR peak at 2905-2800 cm^{-1} indicates the presence of -CH_3CH_2 streching. The IR peak at 751 cm^{-1} indicates the presence of aromatic bending. The IR peak at 1339 cm^{-1} indicates the presence of C-N streching of tertiary amine. Melting point of the compound was 83°C and is uncorrected.
- 2-hydroxy 4-dimethyl amino chalcone have the molecular formula is $C_{17}H_{17}NO_2$ and the molecular weight of the compound is equivalent to the molecular ion peak at 267(M^+) of the compound. Hence m/z value confirms the molecular weight of compound. The IR peak at 3566 cm^{-1} suggesting the presence of -OH group The IR peak at 1647 cm^{-1} suggesting the presence of C = O (Str) group. The IR peak at 3086 cm^{-1} indicates the presence of C-H streching. The IR peak at 2989 cm^{-1} indicates the presence of -CH_3 streching. The IR peak at 722 cm^{-1} indicates the presence of aromatic bending. The IR peak at 1321 cm^{-1} indicates the presence of C-N streching 3° amine. Melting point of the compound was 95°C, is uncorrected.

- The obtained molecular ion peak of 2-hydroxy chalcone (molecular formula, $C_{15}H_{12}O_2$) at 224(M^+); is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight of compound. The IR peak at 1697 cm^{-1} suggesting the presence of C = O (Str) group. The IR peak at 3051 cm^{-1} indicates the presence of C-H streching. The IR peak at 2905-2800 cm^{-1} indicates the presence of -CH_3 streching. The IR peak at 751 cm^{-1} indicates the presence of aromatic bending. The IR peak at 884 cm^{-1} indicates the presence of C-N streching. Melting point of the compound was 79°C, is uncorrected.

CONCLUSIONS

The synthesized compounds were characterized by TLC, melting point, IR spectroscopy, elemental analysis and mass spectroscopy. The results obtained from this study confirmed that the product has formed. Henceforth viewing these characteristic properties more compounds can be synthesized and subjected to pharmacological evaluation. These Chalcone derivatives may have variety of biological activities *viz*., antitubercular, lishmanicidal, anticancer activity, etc. and may be a way for synthesis and characterization of some new chalcone derivatives.

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