



# SYNTHESIS OF 6-CHLOROFLAVONE FROM 4-CHLOROPHENOL AND THEIR BIOCIDAL ACTIVITY

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## ABSTRACT

Flavones are the organic compounds essential for human body found naturally in cereals and herbs. Usually, flavones have been prepared by Baker-Venkataraman rearrangement, which involves the conversion of 2-hydroxyacetophenones into benzoyl esters followed by rearrangement in base to give 1, 3-diketone as a reaction intermediate, which upon cyclization under acidic conditions to afford respective flavones. The present work deals with the synthesis of 6-chloroflavone from 4-chlorophenol and its characterization on the basis of UV-Vis, IR and <sup>1</sup>H-NMR spectral data. Also the biocidal activity of synthesized compound have been evaluated against the growth of microorganisms using paper disc method and compared with streptomycin as a standard.

**Key words:** 4-Chlorophenol, 6-Chloroflavone, Synthesis, Biocidal activity.

## INTRODUCTION

Flavones are important naturally occurring organic compounds possessing broad range of bio-medicinal properties and also for the treatment of various diseases. Numbers of methods are reported for the synthesis of flavones and its derivatives but the most important is Baker-Venkataraman rearrangement, which gives 1, 3-diketone in high yield of 68 to 72% and it is an important synthetic intermediate for the synthesis of flavones, flavanones, xanthenes, chromones, coumarins, benzopyrans and anthracyclins<sup>1</sup>. Synthesis of flavones is an important platform for the preparation of pharmaceutical agents, which are active against the gram positive and negative bacteria as well as different fungi also. Both natural and laboratory prepared derivatives are responsible to show anti-tumour, anti-viral, anti-oxidant<sup>2</sup>, anti-cancer<sup>3</sup>, anti-diabetic<sup>4</sup>, anti-inflammatory<sup>5</sup> properties as well as show more anti-oxidants properties with presence of hydroxyl group<sup>6</sup>. The daily intake of 20-25 mg/day flavones is essential for human body<sup>7</sup>. In the present work, we have synthesized a 6-chloroflavone in an

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excellent yield, recrystallised and characterized by UV-Vis, IR and <sup>1</sup>H-NMR spectral data. The anti-bacterial and anti-fungal activity of a synthesized compound was done by agar well diffusion method.

## EXPERIMENTAL

### Material and methods

In the present work, the chemicals and reagents of analytical grade of Sigma-Aldrich Corporation, Richman Chemical Inc., Merck and Alfa Aesar Company Ltd. were used. The synthesized substituted 6-chloroflavone was characterized by UV-Vis spectrum recorded from Lab India 3000+ spectrophotometer. IR spectra was recorded on Cary 60-FTIR (Agilent Technologies) and <sup>1</sup>H-NMR spectrum on Bruker Avance II 400 MHz NMR spectrometer using CDCl<sub>3</sub> as a solvent and TMS as an internal standard. The purity of the compounds was checked by thin layer chromatography and was recrystallised from hot ethanol. The melting point was measured by open capillary method and is uncorrected.

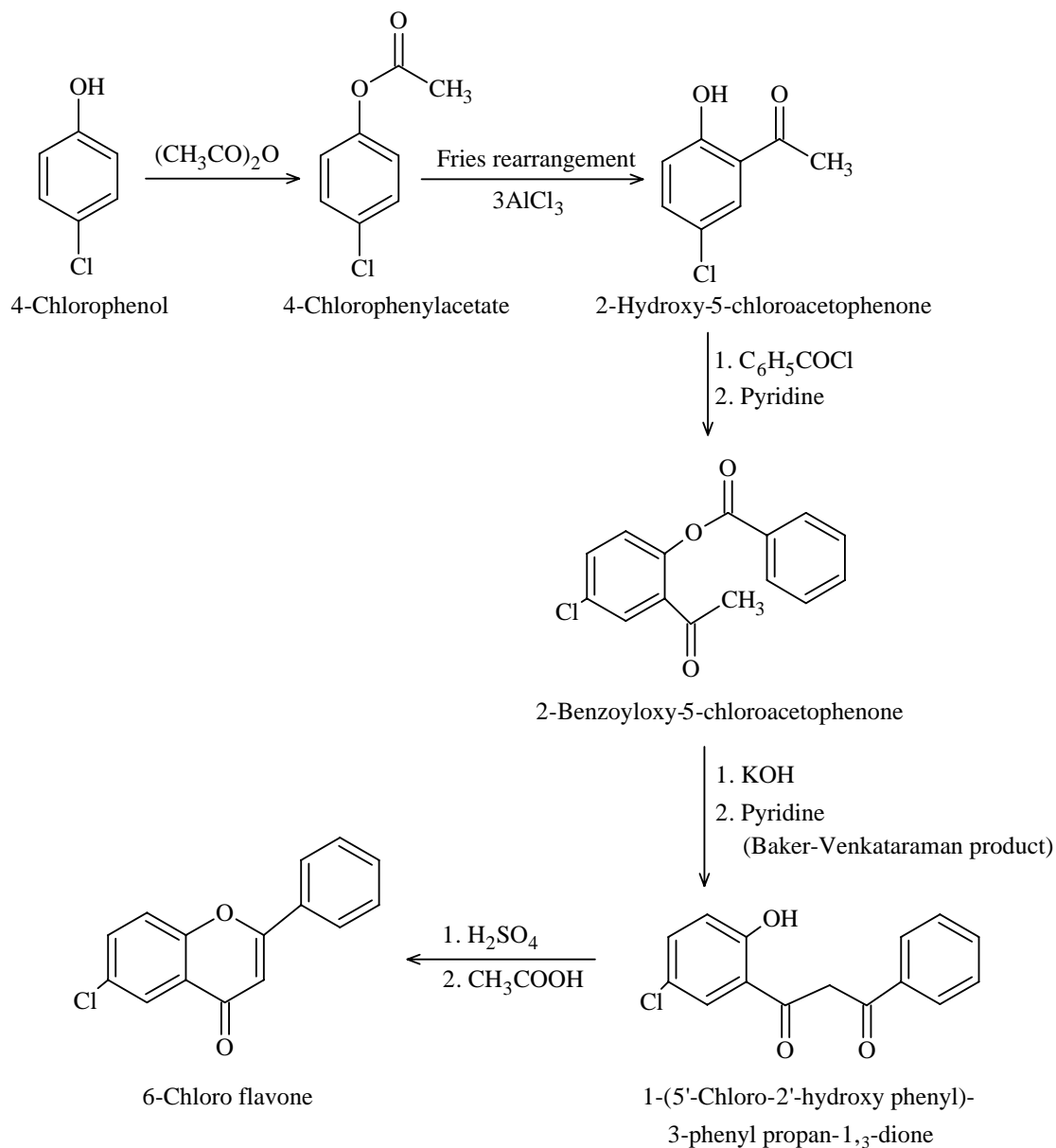
### Procedure for the synthesis of substituted 6-chloro flavone

4-Chlorophenol was refluxed with acetic anhydride in presence of dry anhydrous sodium acetate for one and half hours, cooled and decomposed in water. The two layers are formed, out of which lower organic layer was separated by means of separating funnel and then purified by distillation. The resultant product undergoes Fries rearrangement with anhydrous AlCl<sub>3</sub> and then decomposed by 10% ice cold HCl, filtered and crystallised using glacial acetic acid. The prepared substituted acetophenone is shaken with benzoyl chloride and dry pyridine for 18-20 min. The reaction mixture becomes warm and it is poured over crushed ice with HCl (1M). The separated product is filtered, washed with ice-cold methanol and then water. The resultant product is 2-benzoyloxy-5-chloroacetophenone, which was heated with KOH (powder form) and pyridine at 50<sup>0</sup>C for 15 min and acidified with 10% glacial acetic acid giving diketone namely 1-(5'-chloro-2'-hydroxyphenyl)3-phenyl propan-1,3-dione as product by Baker-Venkataraman rearrangement<sup>8,9</sup>. Conc. H<sub>2</sub>SO<sub>4</sub> was added with continuous stirring in glacial acetic acid. The reaction mixture was heated in a water bath for 1 hour with occasional stirring and poured over crushed ice. The separated flavone was washed with water and stirred at 50<sup>0</sup>C and crystallized from petroleum ether. The reaction scheme for synthesis of substituted flavone is shown in Fig. 1.

### Biocidal activity

The synthesized substituted 6-chloroflavone compound was tested for their biocidal

activities on the basis of their potential to inhibit the growth of bacteria like *Escherichia coli*, *Staphylococcus aureus* and fungus like *Aspergillus niger*, *Fusarium oxysporum* by using paper disc method from Microbial Section, Food Testing Laboratory, Krishi Vigyan Kendra, Durgapur (Badnera), Dist. Amravati.



**Fig. 1: The reaction scheme for synthesis of substituted flavone from 4-chlorophenol**

## RESULTS AND DISCUSSION

The compound name, molecular formula, molecular weight and melting point of 6-chloroflavone are given in Table 1. UV-Vis, FT-IR and  $^1\text{H-NMR}$  spectroscopic data are illustrated in Table 2, 3 and 4, respectively. The data on biocidal activity of synthesized compound over different pathogens at 25 mcg/disc and 500 mcg/disc are illustrated in Table 5, 6, 7 and 8 and shown in Figs. 2, 3, 4 and 5, respectively.

**Table 1: Compound name, molecular formula, molecular weight and melting point of synthesized substituted flavone**

Name of compound	Molecular formula	Molecular weight	Melting point
6-Chloroflavone	$\text{C}_{15}\text{H}_9\text{O}_2\text{Cl}$	256.5 g/mol	$98^\circ\text{C}$

**Table 2: UV-Vis interpretation of synthesized compound**

Calculated Lambda max value (Via woodward-fisher rule)	354 nm
Observed Lambda max value (Via UV-Vis spectrophotometer)	367 nm

**Table 3: The IR spectrum of synthesized compound with important peaks**

Literature value ( $\text{cm}^{-1}$ )	Absorption observed ( $\text{cm}^{-1}$ )	Assignment
785-540	769.96	C-Cl stretching
1300-1000	1164.59	C-O linkage
1600-1475	1565.03	C=C Aromatic
1725-1705	1685.66	C=O stretching
3100-3000	3081.05	C-H Alkene stretching
3150-3050	3081.05	C-H Aromatic stretching

**Table 4: The  $^1\text{H-NMR}$  spectrum of synthesized compound with important shifts**

Peak observed ( $\delta$ value in ppm)	Multiplicity	No of protons	Assignment
6.89	s	1H	Ar-H
7.26	s	5H	Ar-H
7.3-7.4	m	1H	Ar-Ph
7.9-8.2	s	2H	Ar-H

**Table 5: Anti-bacterial activities at 25 mcg/disc**

Name of bacteria	Standard streptomycin	Substituted flavone
<i>E.coli</i>	20 mm	9 mm
<i>S.aureus</i>	26 mm	9 mm

**Table 6: Anti-bacterial activities at 500 mcg/disc**

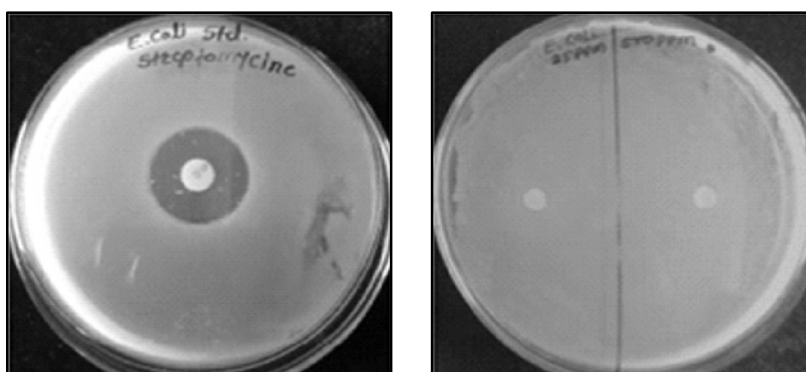
Name of bacteria	Std. Streptomycin	Substituted Flavone
<i>E.coli</i>	20 mm	12 mm
<i>S.aureus</i>	26 mm	11 mm

**Table 7: Anti-fungal activities at 25 mcg/disc**

Name of Fungus	Std. Streptomycin	Substituted flavone
<i>A.niger</i>	No effect	No effect
<i>F.oxysporum</i>	Minimum growth	Minimum growth

**Table 8: Anti-fungal activities 500 mcg/disc**

Name of Fungus	Std. Streptomycin	Substituted Flavone
<i>A.niger</i>	No Effect	No Effect
<i>F.oxysporum</i>	Minimum growth	Minimum growth

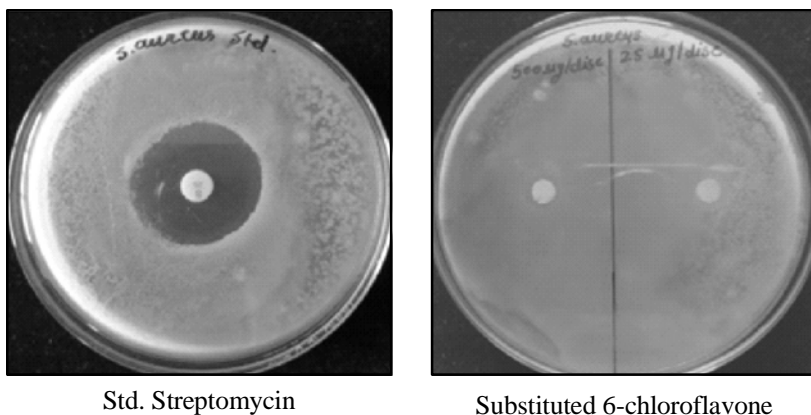


Std. Streptomycin

Substituted 6-chloroflavone

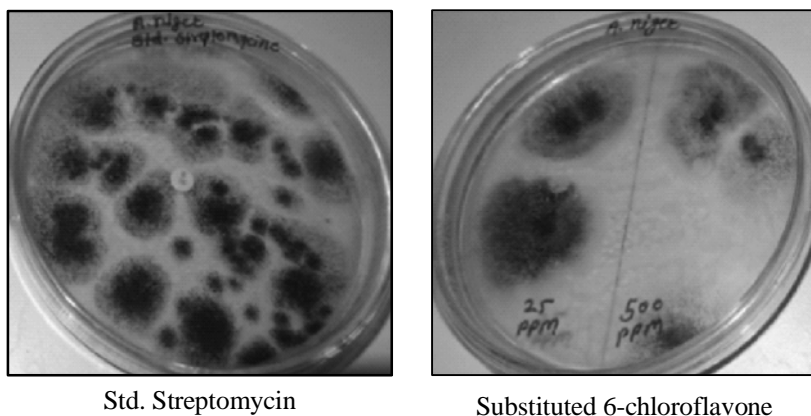
**Fig. 2: Effect of 6-chloroflavone and standard streptomycin on *E.coli* cell**

Standard streptomycin on *E.coli* shows zone of inhibition 20 mm at 25 mcg/disc and 500 mcg/disc and synthesized flavone shows 9 mm and 12 mm at 25 mcg/disc and 500 mcg/disc, respectively.



**Fig. 3: Effect of 6-chloroflavone and standard streptomycin on *S. aureus* cell**

Standard streptomycin on *S. aureus* shows zone of inhibition 26 mm at 25 mcg/disc and 500 mcg/disc and synthesized flavone shows 9 mm and 11 mm at 25 mcg/disc and 500 mcg/disc, respectively.



**Fig. 4: Effect of 6-chloroflavone and standard streptomycin on *A. niger* cell**

Standard streptomycin on *A.niger* does not show zone of inhibition at 25 mcg/disc and 500 mcg/disc and synthesized flavone also does not show any effect.

Standard streptomycin on *F.oxysporum* shows reduced growth at 25 mcg/disc and 500 mcg/disc and synthesized flavone also shows reduced growth at 25 mcg/disc and 500 mcg/disc.

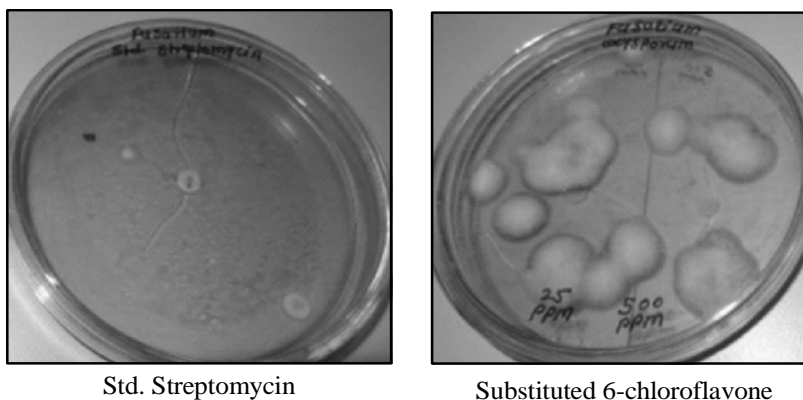


Fig. 5: Effect of 6-chloroflavone and standard streptomycin on *F.oxyspoum* cell

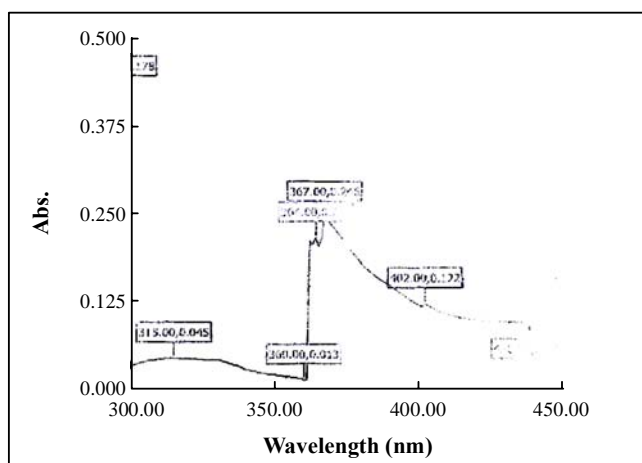


Fig. 6: UV Spectrum of synthesized substituted flavone

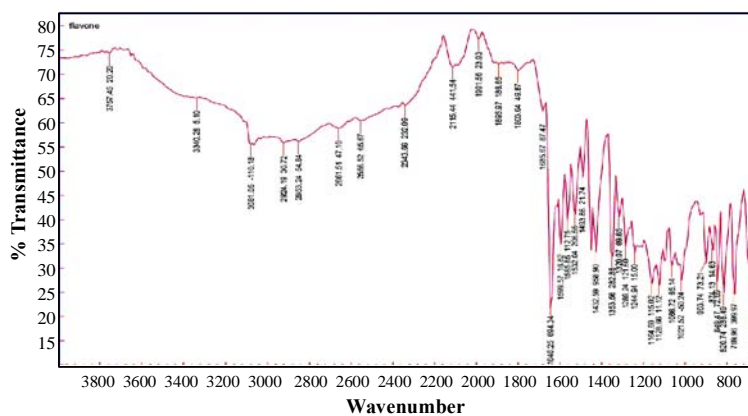


Fig. 7: IR Spectrum of synthesized substituted flavone





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