# SYNTHESIS OF CHROMENE-2-ONE BY PECHMANN CONDENSATION REACTION AND ITS ZONE OF INHIBITION ON GRAM NEGATIVE BACTERIA

**Submitted in partial fulfilment of the requirements for the award of Master of Science Degree in Chemistry**
**By:**


**C. MERLIN SHEEBA**

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**DEPARTMENT OF CHEMISTRY**

**SCHOOL OF SCIENCE & HUMANITIES**

**SATHYABAMA INSTITUTE OF SCIENCE AND TECHNOLOGY**
**(DEEMED TO BE UNIVERSITY)**
**Accredited with Grade "A" by NAAC I 12B Status by UGC I Approved by AICTE**

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**March – 2021**

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## DEPARTMENT OF CHEMISTRY

## BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of **C. MERLIN SHEEBA (39910012)** who carried out the project entitled "**SYNTHESIS OF CHROMENE-2-ONE BY PECHMANN CONDENSATION REACTION AND ITS ZONE OF INHIBITION ON GRAM NEGATIVE BACTERIA**" under my supervision from December 2020 to March 2021.

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## DECLARATION

**I, C. MERLIN SHEEBA,** hereby declare that the Project Report entitled "**SYNTHESIS OF CHROMENE-2-ONE BY PECHMANN CONDENSATION REACTION AND ITS ZONE OF INHIBITION ON GRAM NEGATIVE BACTERIA" done** by me under the guidance of **Dr. T. Krithiga M.Sc., M. Phil, Ph.D.,** Associate Professor, Department of Chemistry, Sathyabama Institute of Science and Technology is submitted in partial fulfilment of the requirements for the award of Master of Science degree in Chemistry.

**DATE:**

**PLACE:**

**C. MERLIN SHEEBA**

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**C. MERLIN SHEEBA**

# ABSTRACT

The key goal of this project is to use oxalic acid as a catalyst to make 6-keto -8-methoxy -4-methyl -2-H-Chromen-2-one from Vanillin and Ethyl acetoacetate by Pechmann Condensation. It also aims to find antibacterial activity of same product by zone of inhibition method. The collected product's biological activity is investigated by evaluating its antibacterial activity. Substituted coumarin derivative was synthesized by the reaction of Vanillin and Ethyl acetoacetate using oxalic acid as a catalyst in Ethanol under reflux conditions. The obtained product was characterized by FTIR and NMR spectroscopic Techniques. The structure and the functional group present in the obtained product were found from spectral studies. The synthesized coumarin derivatives are tested for their antibacterial activity against a gram negative bacterium and found to have a good antibacterial activity against Escherichia Coli.

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| | | |
|---|---|---|
| MCR | - | Multicomponent Reactions |
| I-DOPA | - | l-3,4-dihydroxyphenylalanine |
| CGA | - | Chlorogenic acid |
| FTIR | - | Fourier Transform Infrared |
| NMR | - | Nuclear Magnetic Resonance |
| E. Coli | - | Escherichia Coli |

# CHAPTER 1

# INTRODUCTION

## 1.1 MULTICOMPONENT REACTION

An optimal chemical reaction should be easy to carry out, produce high yields, and use readily available starting materials. It must also be environmentally susceptible. Multicomponent reactions are the best tools for this. Multicomponent reactions are those in which two or more than two reactants are made to react in a single reactor to give a single product fusing all or most of the atoms from the starting material. In comparison with normal multi-step reactions, MCRs are substantially convergent reactions with high atom power, strong bond formation capability and higher yields [Brauch. S et al,. 2021].

A substance is formed in an MCR using a sequence of elementary chemical reactions. As a result, there's a chain of reaction equilibria that eventually flow through an irreversible phase that yields the substance. The goal is to carry out an MCR in such a way that the network of pre-equilibrated reactions channels into the main product while eliminating side products. The reaction conditions, like solvent, concentration, temperature, catalyst, and functional groups, all have an impact on the outcome. Such factors are particularly significant in discovery and design of novel MCRs [Majid. H et al,. 2020]. These reactions have a big future in the quest for new drugs in pharmaceutical chemistry because their products may have a lot of structural complexity. The conditions for successful synthesis of compounds in a cost-effective and time-effective manner are thus approached by multicomponent reactions [ Ian. B.C et al,. 2018].

Since MCRs come under the category of One -Pot Synthesis, they are much simpler to carry out. Among the tens of thousands of organic reactions known, hundreds of organic reactions have achieved certain recognition that they have been named after their discoverers or founders. For over 150 years, multicomponent reactions have been documented [Weigang. F et al,. 2020]. The

Strecker synthesis of alpha-amino cyanides was the first documented multicomponent reaction in 1850. Several well-known MCRs have been documented since then, including the Hantzsch dihydropyridine synthesis (1881), the Biginelli reaction (1891) [Felicia. P.L.L et al,. 2021] , the Mannich reaction (1912) [Etienne. L et al,. 2018], the Passerini reaction (1921) [Banty. K et al,. 2021], and the Ugi reaction (1959) [Siamak.J et al,. 2020].

## 1.2 VANILLIN

Vanillin comes under the Benzaldehyde family, which has methoxy and hydroxy substituents at positions 3 and4, respectively. It acts as a flavoring agent, antioxidant, and anticonvulsant in addition to being a plant metabolite. It is a phenol, as well as a monomethoxybenzene and a benzaldehyde [Labuda.I et al,. 2009]. Vanillin occurs as needles that are white or partially yellow. Vanillin is a well-known nutritional and cosmetic additive with antimutagenic and antioxidant effects. It's also been proposed that it has antifungal action against some of the more common human pathogenic fungi, but it's not very successful.

Vanillin is a widely used industrial chemical for flavoring desserts, drinks, fruits, and animal feeds. It's also used in cosmetics as fragrance and flavor, and also in pharmaceuticals and other chemicals. Vanillin is also used in galvanotechnical procedures as a brightener. It's a significant intermediate in the manufacture of pharmaceuticals like l-3,4-dihydroxyphenylalanine (l-DOPA) and methyldopa [Jenkins. A et al,. 2014].

Vanillin is also used to avoid foaming of lubricating oils, as a brightener in zinc coating baths, as a riboflavin solubilizing agent, as activator in zinc electroplating, as a support to the linseed oil oxidation, as an insecticide attractant, as an agent to avoid mouth roughness caused by chewing tobacco and in the preparation of syntans for tanning and as a polymerization catalyst for methyl methacrylate.

## 1.3 PERKIN REACTION

The Perkin reaction produces unsaturated carboxylic acids by condensation of a carboxylic acid anhydride and an aldehyde in presence of weak base, usually the K(anPotassium) or Na(Sodium) salt of acid or triethylamine. Perkin identified the primary example of this reaction in1868, involving the synthesis of coumarin from heating the sodium salt of salicylaldehyde alongside anhydride. The reaction is only applicable to aromatic aldehydes and is especially useful for preparing substituted cinnamic acids [Terry. R et al,. 1991].

The Perkin conversion does not work for simple aliphatic or aromatic ketones as substrates. Aliphatic aldehydes are also not commonly suitable components for this reaction. Crawford and Little investigated this long-known restriction. They did demonstrate, however, that many short chain aldehydes, including trans-citral, undergo Perkin condensation with p-nitrophenylacetic anhydride; the anhydride is activated by the p-nitrophenyl substituent, and the reactions take place at 35-55 °C [Sandler. S.R et al,. 1983].

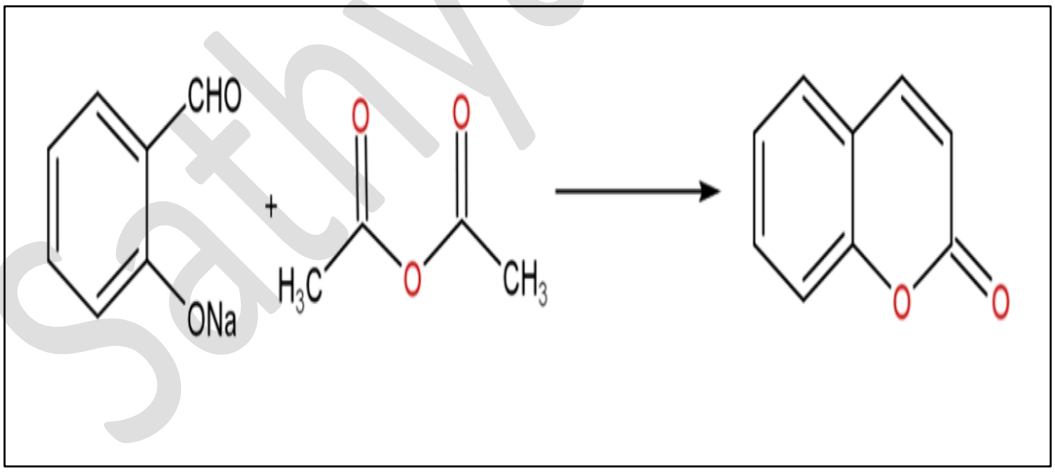



***Fig. 1.1 Perkin reaction of Coumarin synthesis***

## 1.4 PECHMANN CONDENSATION

In1883, Duisberg and Hans von Pechmann announced the synthesis of coumarin derivatives from phenols and -ketoesters or -keto carboxylic acids under acidic conditions. Because of the readily available reactants, the Pechmann reaction is still the most commonly used synthetic technique for the preparation of coumarins. To generate coumarins and harmless by-products, this condensation reaction involves transesterification or esterification, accompanied by cyclization and then dehydration reaction.

Because of the utility and reliability of the Pechmann reaction in the production of basic to complicated coumarins, a growing number of experiments have been performed to enhance the reaction conditions of this reaction, including the use of various acidic catalysts like lewis acids , supported catalysts, resins and methods that use microwaves and ultrasound irradiation to speed up the process [Marlyn. C.O.V et al,. 2018].

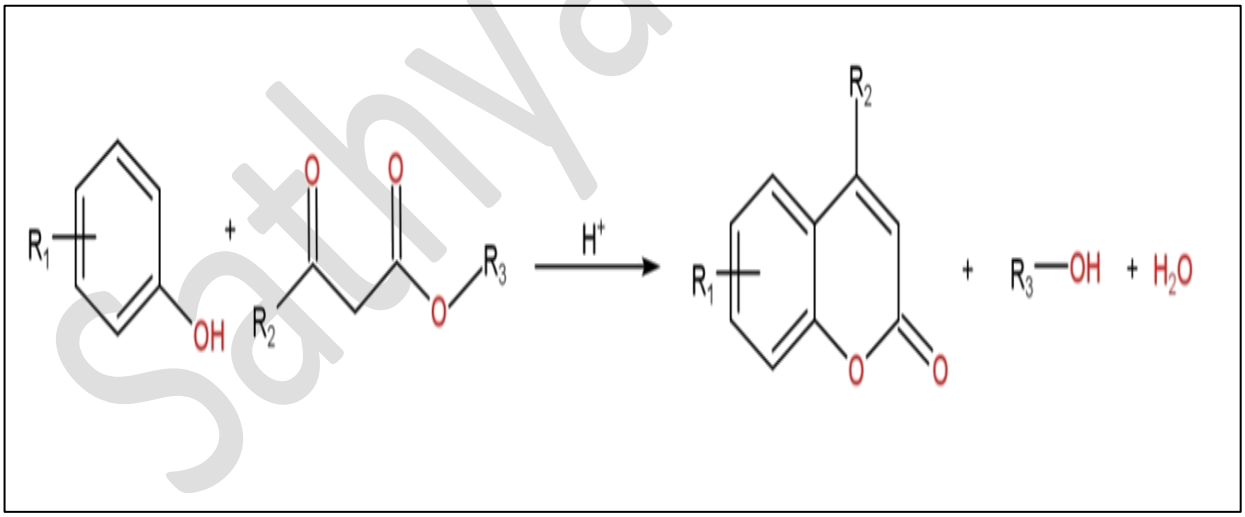



***Fig. 1.2 Pechmann condensation reaction***

## 1.5 ANTIBACTERIAL ACTIVITY

Antibacterial activity of a molecule is entirely associated with compounds that exclusively eliminate bacteria or delay their rate of growth without causing extensive tissue damage. The most recently found antimicrobial agents are natural compounds that have been chemically engineered, such as cephalosporins, β-lactams (penicillin) or carbapenems. Pure natural antibiotics, like aminoglycosides, and synthetic antibiotics, such as sulfonamides, are also often used. Antibacterial agents can be categorised into Bactericidal (killing bacteria) or Bacteriostatic (slowing the growth of bacteria) categories.

Antibacterial agents are essential in fighting against communicable diseases. However, as a result of their frequent usage and violence, bacterial resistance to antibacterial agents has arisen as a significant concern for today's pharmaceutical industry. The rising tolerance of microorganisms to antibacterial agents has resulted in severe health problems in recent years. The majority of infectious bacteria are immune to at least one of the antibiotics which are used to treat infections. This dilemma necessitates the development of novel agents capable of effectively inhibiting the growth of microorganisms [Kushagiri. S et al,. 2019]

CGA (chlorogenic acid) has broad-spectrum antibacterial activity, with inhibitory activity against Escherichia coli, yeast, Staphylococcus aureus, Bacillus subtilis, and Aspergillus niger, and strong resistance activity against Escherichia coli and Staphylococcus aureus. It is used to treat acute bacterial infections in the clinic. CGA has been shown in studies to damage the biofilm of Aspergillus fumigatus and Pseudomonas aeruginosa, as well as affect their normal development, resulting in a bacteriostatic effect [Mingsan. M et al,. 2020]

# CHAPTER 2

# LITERATURE SURVEY

Multicomponent condensation reactions involving three or more reactants in one pot have recently been discovered to produce a structurally complex biologically active heterocyclic compound. It is seen as a method for increasing the efficiency of a chemical process in which a reactant is exposed to several chemical reactions in a single reactor rather than having to go through a lengthy isolation and purification procedure. The synthetic schemes are built with the least amount of pollution to the atmosphere in mind. Some of such reactions which were previously reported are given below,

Ajay. K.D et al used Sulfated Titania ($TiO_2$-$SO_4^{2-}$) as a heterogeneous solid acid catalyst in multicomponent reactions in water to produce benzylamino coumarin derivatives by microwave irradiation (100°C) [Ajay. K.D et al,. 1998]. Elemental analysis, Melting points, IR, 1H, and 2D NMR and 13C NMR, spectral data were used to validate the structure of those benzylamino coumarin derivatives.

Mohammed Arifuddin et al engineered a series of novel 4, 7-disubstituted coumarin hybrids and tested their inhibitory action against the mammalian carbonic anhydrase isoforms CA I, CA II, CA IX, and CA XII with the aim of developing novel potential anti-cancer agents [Chandra. K.M et al,. 2021]

Irina Kosenko et al synthesized and characterized Novel coumarins containing carborane units.They stated that when cyclic oxonium derivatives of cobalt bis (1, 2-dicarbollide) and closo-dodecaborate anions were broken down with a sequence of 7-hydroxy-3-substituted coumarins, conjugates were formed at the C-7 position of the coumarin unit [Tiziana. P et al,. 2017].

Meng-qiu Song et al synthesized twelve carbazole-coumarin hybrids and tested them as acetylcholinesterase inhibitors with dual binding sites. IR, NMR, HRMS, and single-crystal X-ray diffraction experiments confirmed the structures of the carbazole-coumarin hybrids [Wangze. S et al,. 2016].

Srikanth Mamidala developed a sequence of new coumarin-based thiazoles by microwave irradiation of aldehydes, thiocarbohydrazide, and 3-(2-bromoacetyl) coumarins. Spectral (FTIR, Mass,$^{1}$H NMR and $^{13}$C NMR) and analytical data verified the structures of all synthesized compounds [Mamidala. S et al,. 2021].

Dusica Simijonovic et al studied the reaction of phthalhydrazide with corresponding bromopropoxycoumarin derivatives to obtain a sequence of new phthalhydrazide-coumarin hybrids. They studied these reactions in the presence of $Cs_2CO_3$, in the presence of acetonitrile as a solvent, and at reflux for 5 hours. Experimental and theoretical evidence were used to deduce the properties of these compounds (IR, 1H NMR, and 13C NMR). They found the experimental and theoretical spectra to agree very well [Dusica. S et al,. 2021].

The majority of studies stated that one-pot synthesis of coumarin derivatives is a simple experimental method that produces the desired product in a short amount of time with high yield. This substance was mostly used as an antibiotic.

# CHAPTER 3

# AIM AND SCOPE

## 3.1 AIM

The main aim of this project is to synthesize 6-keto -8-methoxy -4-methyl -2-H-Chromen-2-one from Vanillin and Ethyl acetoacetate using oxalic acid as catalyst. Spectral analysis of the product is determined by studying FTIR and NMR Spectroscopy. The biological activity of the obtained product is studied by determining its antibacterial activity.

## 3.2 SCOPE

- Preparation of Coumarin derivative from vanillin and ethyl acetoacetate by Pechmann reaction
- Confirmation of product by characterization studies (FTIR and $^{1}$H-NMR).
- Testing for antibacterial activity of the obtained product with Escherichia coli.

# CHAPTER 4

# MATERIALS AND METHODS

## 4.1 MATERIALS

Materials used in this reaction are Vanillin, Ethyl acetoacetate, Oxalic acid and ethanol which are bought from Merck chemicals and is used as it is.

## 4.2 CHARACTERIZATION TECHNIQUES

### 4.2.1 *Fourier Transform Infrared Spectroscopy (FTIR)*

The analysis tool (Fourier transform) is used in Fourier transform infrared spectroscopy (FTIR) to convert the raw data (interferogram) into the real spectrum. The infrared spectrum of transmission or absorption of a substance is achieved using the FTIR process. The identity of organic and inorganic compounds in a sample can be determined using FTIR [Mohammad Shameer. P et al,. 2019]. The precise molecular groups present in the sample can be determined using spectrum data in advanced automated spectroscopy software based on the infrared absorption frequency range 900 to 3600 cm−1 [Chevali. V et al,. 2016]. A shift in the material structure is clearly illustrated by changes in the absorption band pattern. FTIR can be used to classify and characterize unfamiliar materials, detect toxins in a sample, identify additives, and detect decomposition and oxidation.

A source, detector, sample cell, A/D converter, amplifier, and device are all part of a standard FTIR spectrometer. After going through the interferometer, radiation from the sources enters the detector. The amplifier and A/D convertor amplifies and transforms the signal to a digital signal, which is then passed to the computer, where the Fourier transform is done. A schematic representation of FTIR spectrometer is given in the figure 4.1 [Deena. T et al,.2019] .

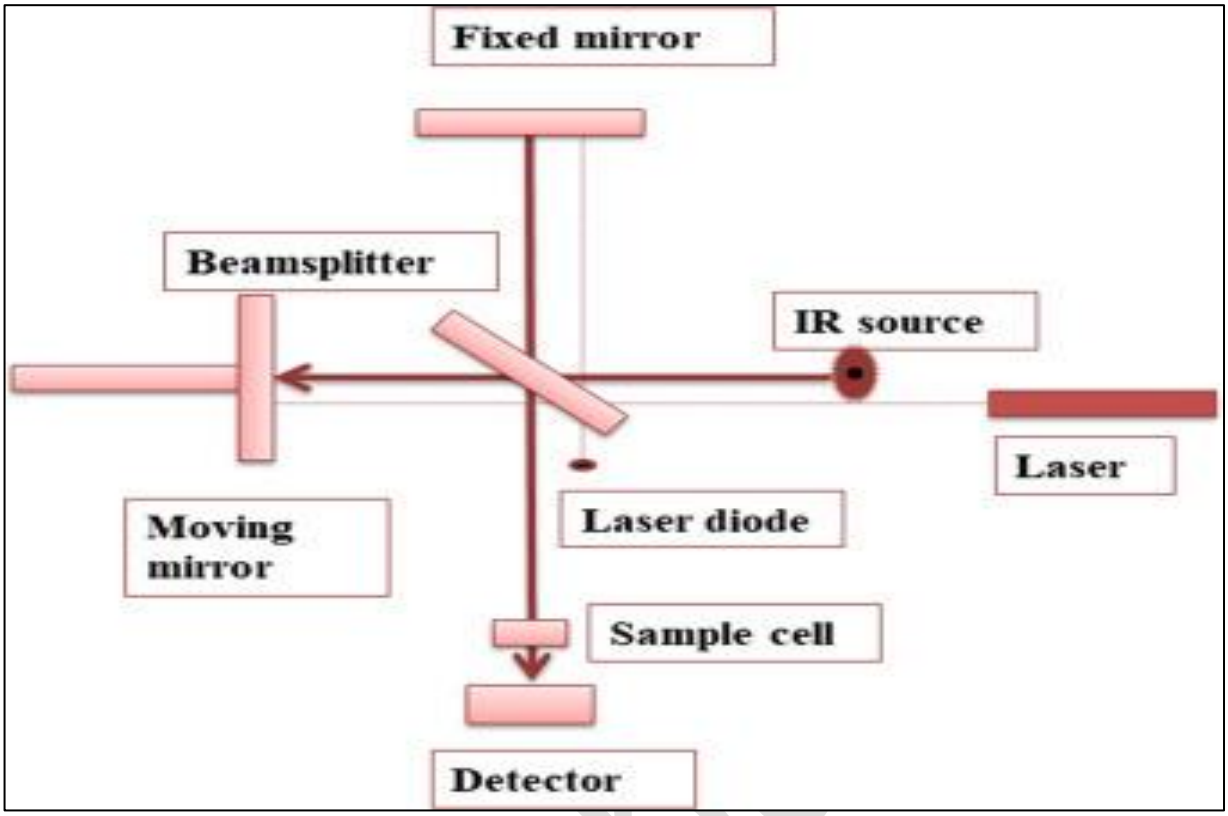



***Fig. 4.1 Schematic representation of FTIR Spectrometer***

### *4.2.2 Nulear Magnetic Resonance Spectroscopy (NMR*

High-resolution liquid and solid-state NMR spectroscopy, magnetic resonance imaging (MRI), diffusometry, and relaxometry are all areas of expertise for nuclear magnetic resonance (NMR). While these approaches tend to vary in several ways, such as instrumentation, sample processing, data interpretation, and so on, they both work on the same theory of magnetic resonance: a set of atom nuclei with magnetic properties are dispersed into various energy levels determined by the direction of their magnetic moments with respect to an external magnetic field [Jennifer .J et al,. 2020]. Based on the NMR approach, this region may be homogeneous or inhomogeneous. A second feeble radiofrequency field is used to irradiate nuclei after they have reached so-called thermal equilibrium. Excited nuclei expel their surplus energy and return to low energy levels by one of two relaxation processes: contact with the atmosphere or energy sharing with neighboring nuclei at lower energy levels. The relaxation time scale of the nuclei is

highly dependent on the molecular weight of the molecule, the chemical atmosphere of the nuclei, and the physical state (liquid or solid) of the sample; thus, it is important for each NMR application.

NMR spectroscopy has a lot of potential for analyzing multicomponent structures. The growing number of NMR applications by food scientists in academic institutions, government food labs, and the food industry reflects this. The sensitivity of solid-state and liquid NMR experiments has improved dramatically as a result of recent technical developments in NMR instrumentation, such as high magnetic fields created by superconducting solenoids and the invention of cryogenic probes. The stereochemical analysis, residual dipolar couplings, and other appropriate techniques have already begun to develop in the next stage of NMR technology [Ziaulla. H.P et al,. 2015]


***Fig. 4.2 Nuclear Magnetic Resonance Spectrometer***

### *4.2.3 Mass Spectroscopy*

Mass spectroscopy is an analytical chemistry tool that uses the mass-to-charge ratio and concentration of gas-phase ions to determine the volume and form of chemicals found in a sample. The sample is converted to quickly flowing positive ions by electron bombing, and charged particles are isolated according to their masses in this instrumental technique. A mass spectrum is a graph between relative abundance and mass to charge ratio. These spectra are used to figure out a sample's isotopic or elemental signature, molecular and particle weights and the structural compositions of molecules and other chemical compounds .

Forensic toxicology, metabolomics, proteomics, pharma/biopharma, and clinical science are all areas where mass spectrometry can be used. Drug monitoring and exploration, pesticide residue analysis , food toxicity tracking, protein recognition, isotope ratio determination, and carbon dating are all examples of mass spectrometry applications [Uttam.G et al,.]. Mass spectroscopy may also be used to characterize proteins and protein complexes, as well as to sequence peptides and recognize posttranslational modifications [Bruno. D et al,. 2006].

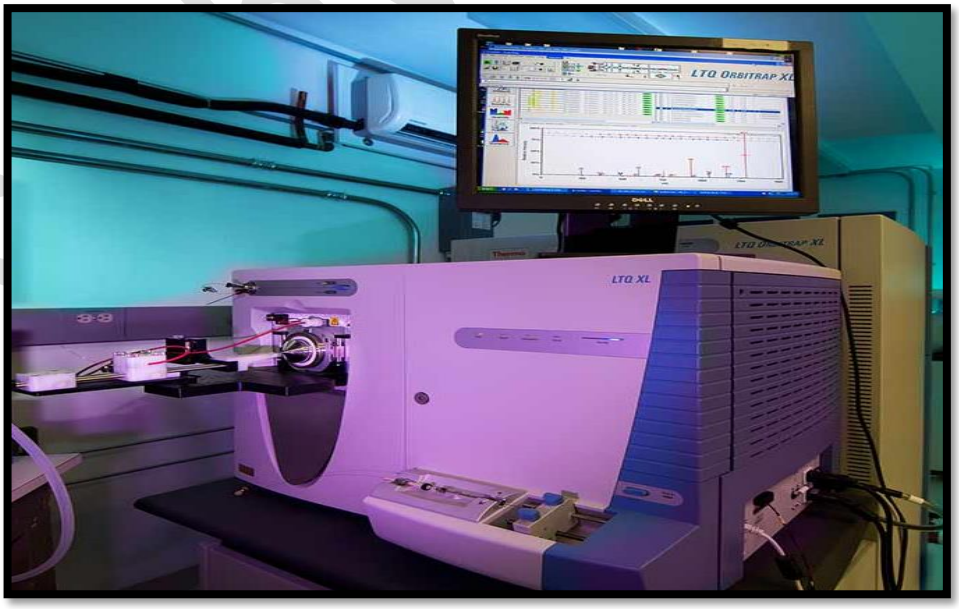
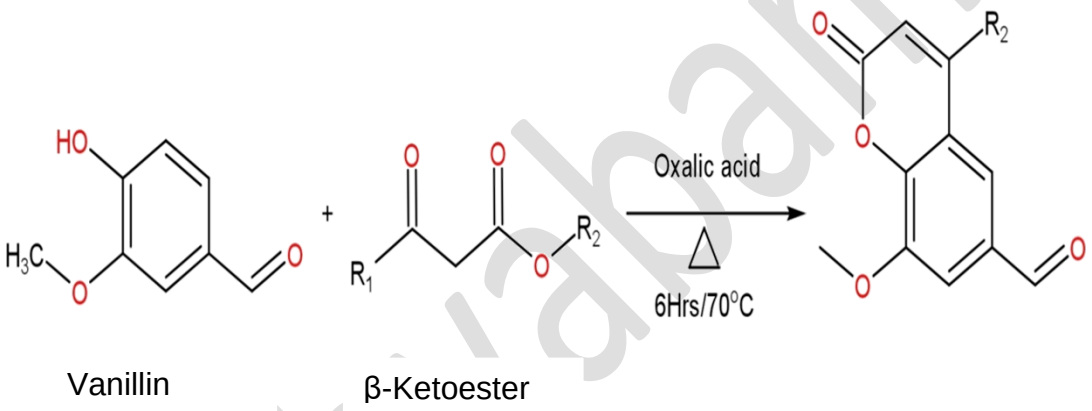



***Fig. 4.3 Mass spectrometer***

## 4.3 ONE POT SYNTHESIS

### *4.3.1 Synthesis of substituted chromene derivative*

A mixture of Vanillin (10 mmol) , Ethyl acetoacetate (10 mmol) and Oxalic acid (1 gram) (Catalyst) were taken in a round bottom flask and refluxed at 70°C for about 6 hours using Ethanol (10 mL) as a solvent. After the reaction gets finished , the solvent was left to evaporate in room temperature and the crude product was obtained. The pure product was obtained by recrystallization of the crude product with hot ethanol.




Vanillin β-Ketoester

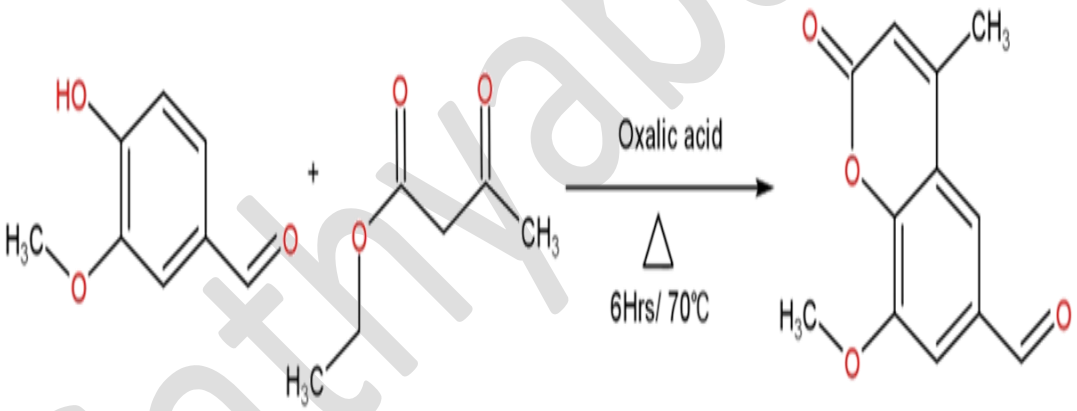
***Fig. 4.4 Reaction scheme of formation of substituted chromene derivative***

# CHAPTER 5

# RESULT AND DISCUSSION

## 5.1 SYNTHESIS OF 6 – KETO - 8 – METHOXY - 4 – METHYL -2H CHROMEN-2-ONE

The simple Pechmann condensation reaction is carried out by reacting Vanillin and Ethyl acetoacetate in 1:1 ratio using oxalic acid as a catalyst. Ethanol is used as a solvent and the reaction is carried out for about 6 hours. The obtained product is subjected to spectral studies ( FTIR , NMR Spectroscopy ) to find the functional group and structural formula.




Vanillin Ethyl acetoacetate

6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2-one

***Fig. 5.1 Reaction scheme of formation of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2-one***

### *5.1.1 Spectral data of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2-one*

**FTIR Data:** The FTIR Spectral data of the obtained product is shown in the below given Fig. 5.2. The obtained product peaks are 3114 $cm^{-1}$ , 1313 $cm^{-1}$ and 1096 $cm^{-1}$ which corresponds to $sp^3$ -CH , C-O Stretch and C=O stretch.

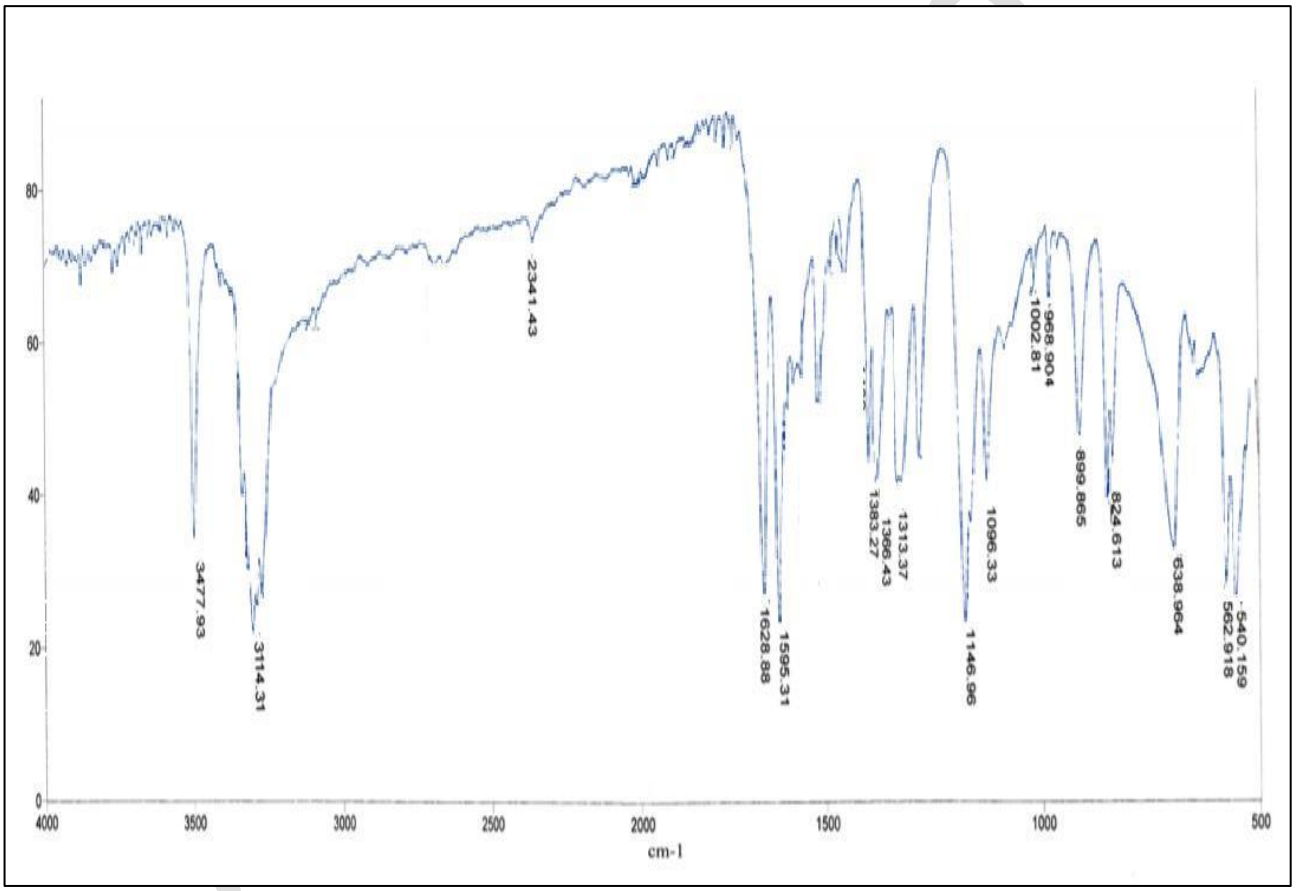



***Fig. 5.2 FTIR Spectra of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2- one***

***Table 5.1 FTIR Vibrational frequencies of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2- one by FTIR spectra***

| Vibrational Frequency | Functional group identification |
|---|---|
| 3114 | C-H Stretching ($Sp^3$) |
| 1383 | C-H Bending ($Sp^3$) |
| 1313 | C-O Stretching |
| 1096 | C=O Stretching |
| 824 | C-H Bending ($Sp^2$) |

**NMR Data:** The $^1$H NMR spectra of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2-one are given in the figure 5.3 which will confirm its structure. The chemical shift of structural units from $^1$H NMR Spectrum in 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2-one are shown in table 5.2.

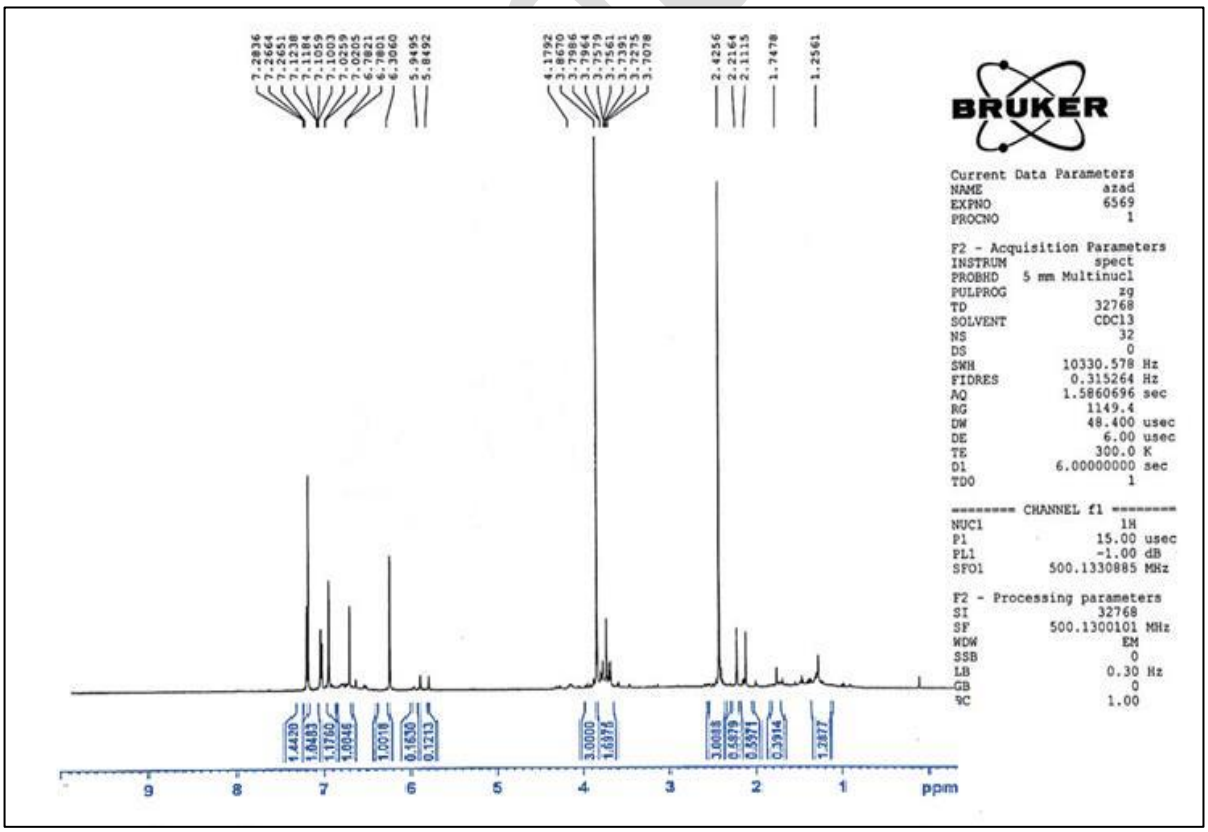



***Fig. 5.3 NMR Spectra of 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2- one***

***Table 5.2 Chemical shift of structural units in from 6 – keto - 8 – methoxy – 4 – methyl -2H Chromen-2- one from $^{1}H$ NMR Spectrum***

| Chemical shift(δ) | Structural unit |
|---|---|
| 2.4 | Ar-$CH_3$ |
| 3.7 | RO-$CH_3$ |
| 5.9 | Vinylic Proton |
| 6.3 | Vinylic Proton |
| 6.7 – 7.2 | Aromatic Proton |

## 5.2 MECHANISM OF FORMATION OF 6 – KETO - 8 – METHOXY – 4 – METHYL -2H CHROMEN-2- ONE

A solid Bronsted acid, such as oxalic acid is used in this reaction. Transesterification reaction and keto-enol tautomerization reaction are all catalyzed by the acid.In the next step Coumarin skeleton is formed ,when it undergoes a Michael Addition. Following this stage, rearomatization occurs. The compound is then formed by the acid-induced removal of water.

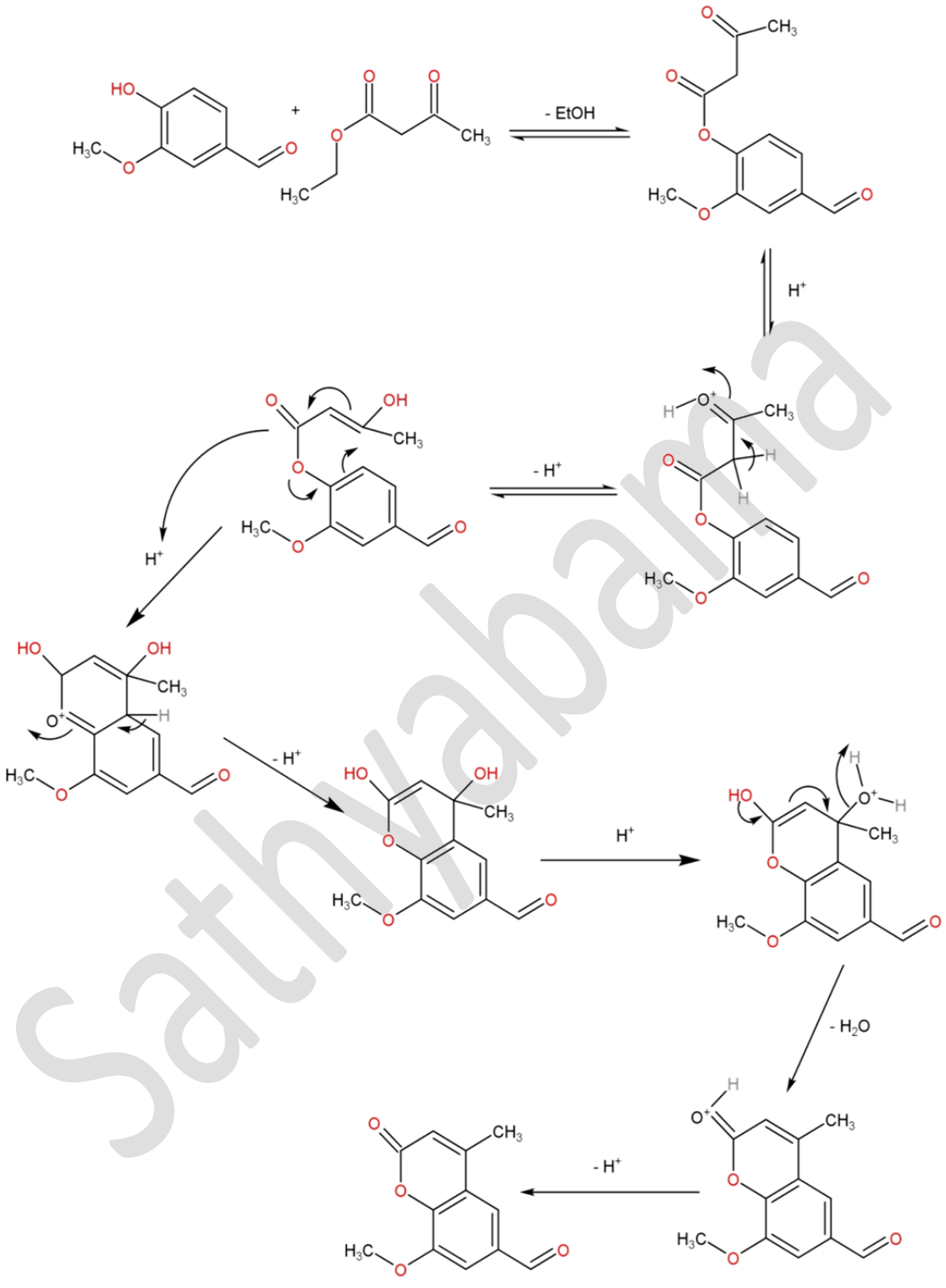





***fig. 5.4 Mechanism of formation of 6 – keto - 8 – methoxy – 4 – methyl -2h chromen-2- one***

## 5.3 ANTIBACTERIAL STUDIES

- Agar diffusion methods could be used to measure antibacterial activity.
- The whole agar plate surface is injected by distributing a volume of bacterial culture over it.
- A cavity of 3 to 4 mm in radius is drilled aseptically with a clean cork borer and the extract solution or antimicrobial agent is injected into the well at the desired concentration.
- Based on the test microorganism, agar plates are incubated at appropriate conditions.
- The zone of inhibition is the region around the disks that would be visible against a thick growth of the bacteria around it.
- The diameter of zone of inhibition is measured to find the antibacterial activity.
- Antibacterial activity was found against E. Coli bacterium.
- RESULT : It shows good antibacterial activity.

***Table 5.3 zone of inhibition***

| MICRO-ORGANISM | ZONE OF INHIBITION IN mm |
|---|---|
| Escherichia Coli | 12 |

### *5.3.1 Antibacterial Activity Result*


**Escherichia coli**

***FIG. 5.5 Zone of Inhibition***

# CHAPTER 6

# CONCLUSION

An easy, reliable, environmental friendly chromene-2-one derivative have been synthesized. The reaction between vanillin and ethyl acetoacetate by Pechmann condensation reaction using oxalic acid as a catalyst gives an excellent yield of product. The benefits of this approach include a straightforward experimental technique, fast reaction times, excellent product yields, mild reaction conditions, quick purification, inexpensive catalyst supply, and an environmental standard. The Structural formula and functional group analysis were done by Spectrscopic studies (FTIR,NMR and Mass spectroscopy). The obtained product was tested for their antimicrobial activity against a gram negative bacterium and was found to have a good antibacterial activity.

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