

**MICROWAVE ASSISTED SYNTHESIS OF CHALCONES
DERIVATIVES**

A final report submitted to

**Lovely professional university, Punjab
of
Master of Science in Chemistry (Hons.)**

**By
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Under the guidance

Of

Dr. NAVEEN CHANDRA



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CERTIFICATE

This is to certify that this capstone project titled as 'MICROWAVE ASSISTED SYNTHESIS OF CHALCONES', submitted by Sukhraj Kaur to the Lovely Professional University, Punjab. India is a proof of bona fide research work carried out under my supervision and is worthy of consideration for the award of the degree of Master of Science in Chemistry of the University.

Supervisor
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(Assistant Professor)
Department of Chemistry
Lovely Professional University
Phagwara, Punjab

DATE:

DECLARATION

I here by declare that

The work contained in this thesis is original and has been carried by me under the guidance of my supervisor, Dr. Naveen Chandra Talniya

The work has not been submitted to any other Institute for any degree or diploma

\

I have followed the guidelines provided by the Institute in preparing the thesis

I have confirmed to the norms and guidelines by Institute

Date:

SUKHRAJ KAUR
(Registration No. 11502565)

ACKNOWLEDGEMENT

No word is sufficient to express my deepest gratitude and thanks to my supervisor, Dr. Naveen Chandra Talniya. He introduced me to the world of Chalcones. I am obliged to him for his crucial guidance, advice and encouragement in my project work, without which not even a single step was possible for me. His scientific knowledge makes a lifelong admiration and vivid impression about him to me. It is my great privilege to be an active part of his enthusiastic research group. I would like to thank all other faculty members, Praveen sir, Manish sir, Varun sir and Manoj sir for their support and time,

I want to give special thanks to my Head of school Dr. Ramesh Thakur. Without him every task was very difficult, due to his support and cares the completion of project took place. He is very polite to all the students and help us in any problem.

I want to acknowledge Department of Chemistry of Panjab University, Chandigarh for allowing us for NMR, MASS Spectroscopy, which is an important evidence for group attachment.

Finally no words can convey my sense of gratitude for my parents Mr. Sarvaprit Singh Sood and Mrs. Ravinder Kaur. It is due to their generous support and sacrifice that I am able to reach here. I am grateful to all of my family members for their continuous encouragement in my higher education.

Sukhraj Kaur

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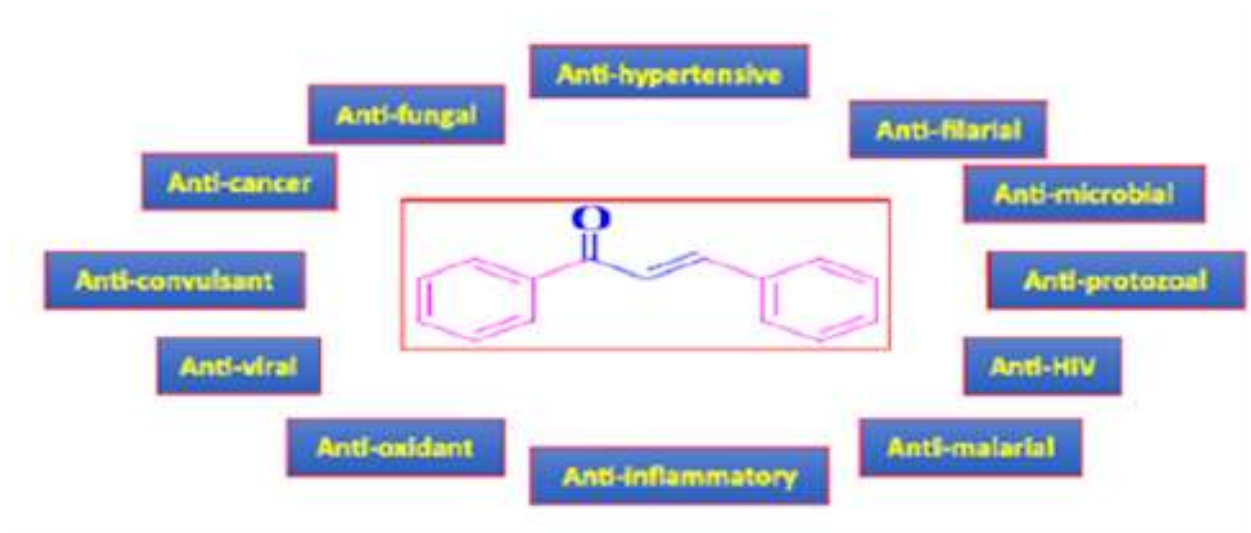
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INTRODUCTION

There are natural flavonoid class of molecules present in plants basically are plant chemicals are called chalcones. The general constitution of chalcones are 1,3-diphenyl-2-propen-1-one in which two aromatic rings are joined together by unsaturated ketonic compound.¹ The availability of chalcones is in abundance starting from bracken, lower plants to higher plants. Chalcones have unique property of different biological activities.² The basic skeleton of α - β unsaturated carbonyl group have been reported as main attraction for the scientific research as introduction of halogens to the benzenoid part of chalcones and derivatizing heterocyclic compounds of α - β unsaturated ketones enhance their biological activity as well.³ Chalcones give positive results in Wilson test i.e. it gives pink coloration with concentrated H_2SO_4 . On adding alcoholic $FeCl_3$ solution it gives purple colour which indicates the presence of phenolic hydroxyl group.⁴



(Figure 1)⁵

Classification of chalcones

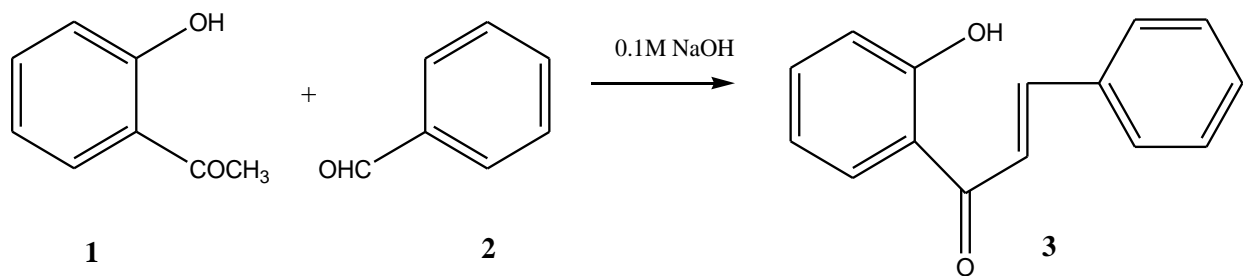
The chalcones are basically classified into 2 categories :-

(a) Natural chalcones: These are the class of chalcones which are available in nature directly. These are basically present in plants as flavonoids. Chalcones which are extracted from plants have many uses in medicines and so it has been studied and reported to have many biological effects including anti-inflammatory, anti-microbial, anti-fungal, anti-malarial, anti-oxidant, anti-viral, anti-protozoal(Figure1).

(b) Synthetic chalcones: These are the class of chalcones which are being synthesised in laboratory under various chemical reagents and conditions.

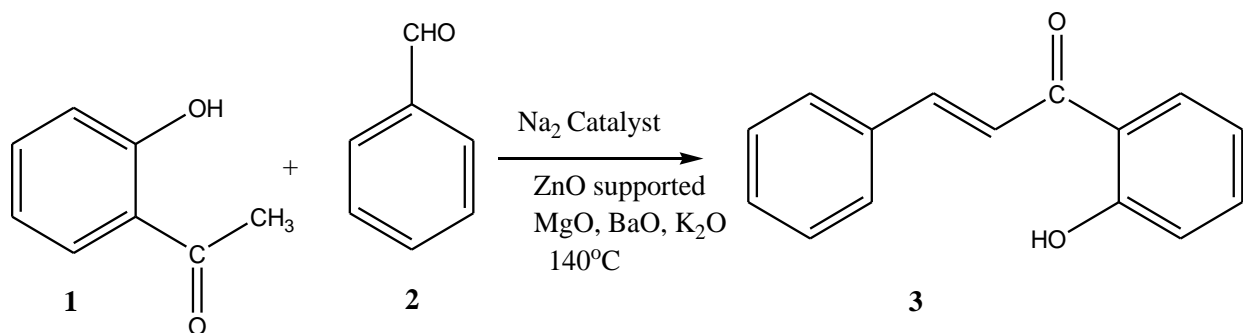
The basic schematic reaction for preparation of chalcones are claisen schmidt condensation.

- 2-hydroxyacetophenone **1** and benzaldehyde **2** are made to react for preparation of chalcones. This scheme is also known as aldol condensation and NaOH act as base catalyst in the reaction. **(Scheme 1).**⁶



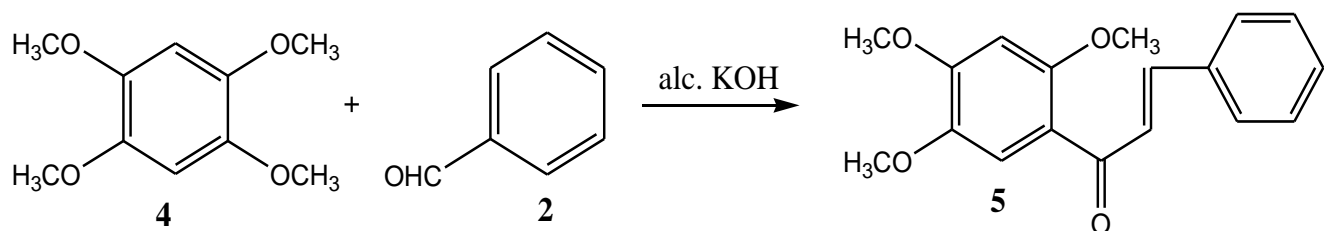
(Scheme 1)

- In this reaction, the reactants i.e 2-hydroxyacetophenone **1** and benzaldehyde **2** combines to give 2-hydroxy chalcones **3** so prepared under condition of ZnO supported over metal oxide with free solvent. **(Scheme 2).**⁷



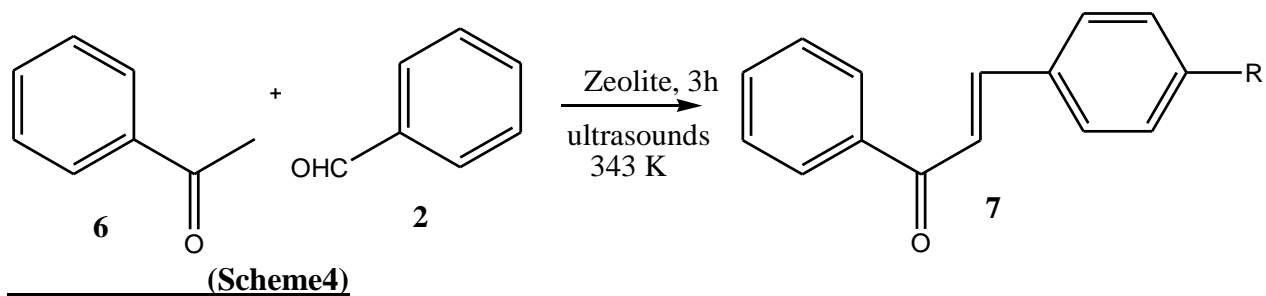
(Scheme2)

- In this reaction, chalcones are produced by reacting 2,4,5-trimethoxyacetophenone **4** with benzaldehyde **2** in the presence of alcoholic alkali. **(Scheme 3).**⁸

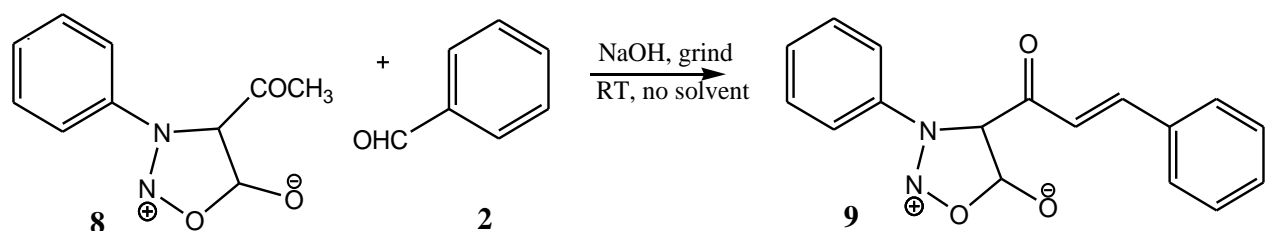


(Scheme3)

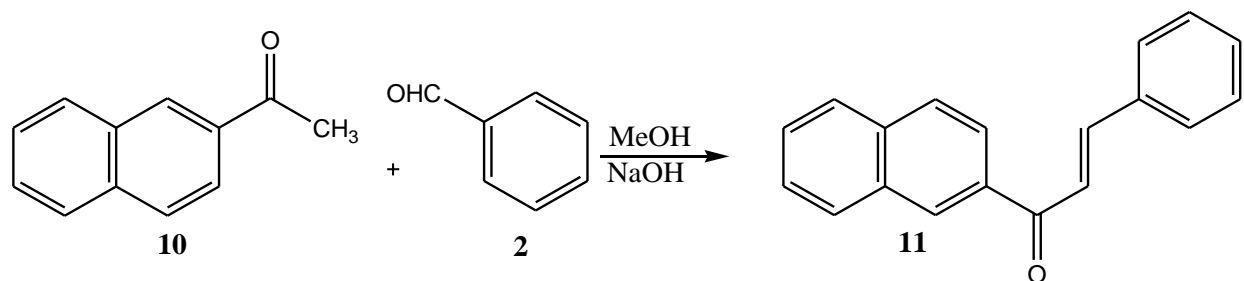
- In this reaction, zeolite is taken as catalyst under free solvent condition for the Claisen Schmidt condensation reaction between benzaldehyde **2** and acetophenone **6** by sonochemical and thermally activated reactions and thus produce chalcones **7**. **(Scheme4).**⁹



- In this reaction, 4-acetyl-3-aryl syndones **8** when made to condense with various aryl aldehydes **2**, it yields chalcones **9**, base is taken as catalyst without any solvent conditions. **(Scheme 5)**.¹⁰



- In this reaction, 2-naphthylmethyl ketones **10** is condensed with various aryl aldehydes **2** in the presence of NaOH and methanol act as solvent. These react to give corresponding chalcones **11**. **(Scheme 6)**.¹¹

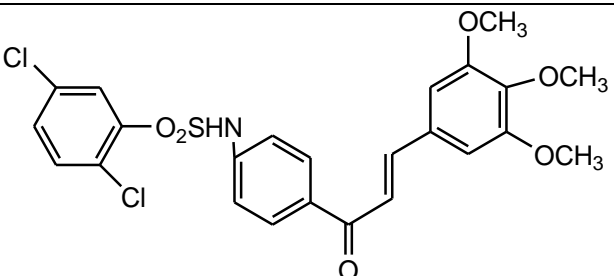
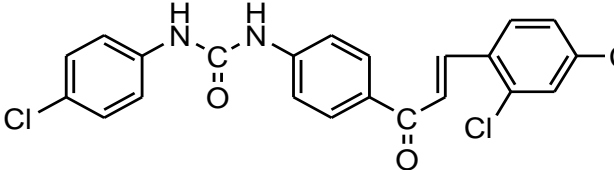


Review of literature

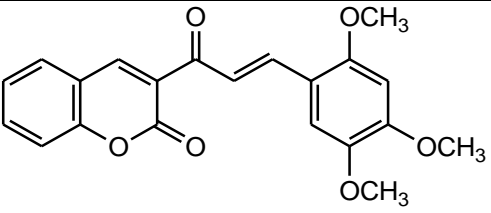
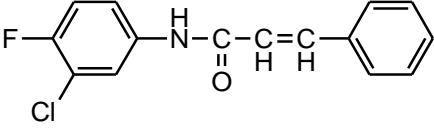
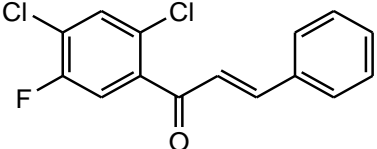
Chalcones are biologically active due to the presence of α - β unsaturated carbonyl moiety. Many derivatives have been synthesised and their activities are reported accordingly. Some are active for particular biological activity and some are inactive.¹² A number of synthetic routes have been designed for preparation of chalcones. As per base requirement in the reaction : barium hydroxide [Ba(OH)₂], Potassiumhydroxide [KOH], Sodium hydroxide [NaOH] .

Following tables gives us information about chalcones and their activities.

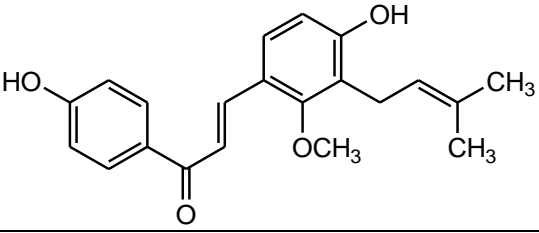
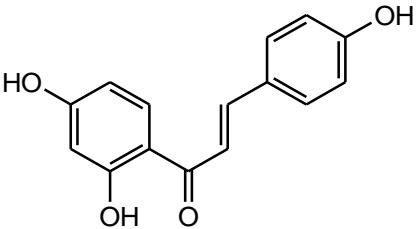
Antimalarial activity

Serial no.	Name	Structure	References
1.	Chalcones with sulphonamide moiety	 <p>The structure shows a chalcone core with a sulphonamide group (-SO₂NH-) attached to the benzene ring of the chalcone backbone. The other benzene ring is substituted with two chlorine atoms (Cl) at the 2 and 6 positions. The chalcone backbone also has a carbonyl group (C=O) and a double bond (C=C).</p>	14
2.	Phenylurenyl chalcones	 <p>The structure shows a chalcone core with a phenylurenyl group (-NH-C(=O)-NH-) attached to the benzene ring of the chalcone backbone. The other benzene ring is substituted with two chlorine atoms (Cl) at the 2 and 6 positions. The chalcone backbone also has a carbonyl group (C=O) and a double bond (C=C).</p>	15

Antimicrobial activity

Serial no.	Name	Structure	References
1.	3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-ones		16
2.	Chalcones with halogen substitution		17
3.	3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones		18

Antibacterial activity

Serial no.	Name	Structure	References
1.	Retrochalcone		19
2.	Isoliquiritigenine		20

Antifungal activity

Serial no.	Name	Structure	References
1.	Chalcone with naphthalene moiety and aryl moiety		21
2.	xanthoxylin-derived chalcones		22
3.	Isolated prenylated chalcones		23
4.	2', 4'-dihydroxy-3'-methoxychalcone		24

AntiHIV activity

Serial no.	Name	Structure	References
1.	Chalcones with substituents on aryl moiety		25
2.	Isolated butein		26

3.	Isolated a unique potent chalcone		27
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Antitumor activity

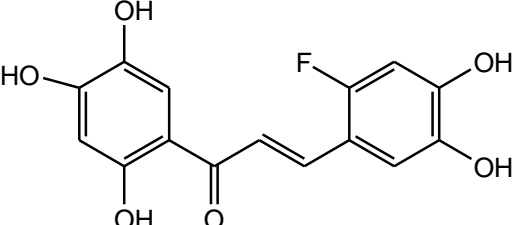
Serial No.	Name	Structure	References
1.	Methylene dioxy chalcone		28

Antileishmanial activity

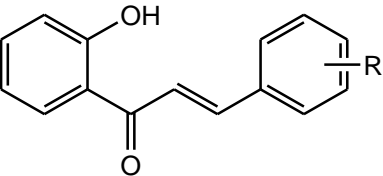
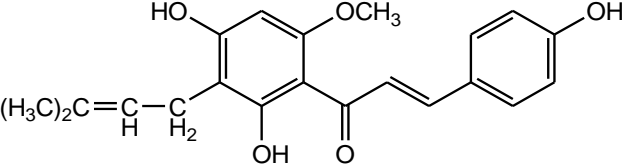
Serial no.	Name	Structure	References
1.	Dihydrochalcone		29
2.	2',6'-dihydroxy-4'-methoxy Chalcone		30

Anticancer activity

Serial No.	Name	Structure	References
1.	Furano Chalcones		31

2.	Fluorinated chalcones		32
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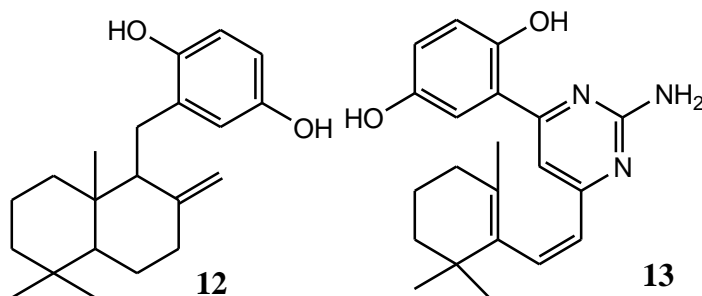
Antioxidant activity

Serial no.	Name	Structure	References
1.	2'-hydroxy Chalcones		33
2.	Prenylatedchalcone		34

OBJECTIVE OF THE PRESENT INVESTIGATION

The effort to prepare large number of novel, patentable, structures for lead discovery has historically relied on scaffolds and reagents that were commercially available.³⁵ The need to expand the scope of both the chemistries available to prepare libraries, created a new direction in the area of new sets of specialty materials that have been prepared from use as proprietary building blocks. This type of modular library design using sequential reactions in overlap on existing arrays allows for the very rapid generation of large number of compounds.

The objective of the present investigation is to successfully develop chemical libraries on a biologically active zonarol **12** and its analogs and to subject them towards various biological activities. Natural products having a decalin type core structure and a quinonoid or related aromatic chain often are characterized by pronounced biological properties. Several of these marine metabolites displayed interesting cytotoxic, anti-inflammatory, antifungal and anti-HIV activities. An especially notable terpene-hydroquinone/quinone family headed by zonarol **12** and its analog **13** isolated from the brown seaweed *Dictyopteris zonerioides* collected in the pacific ocean and in the gulf of California, displayed wide spectrum of biological activities. However, these natural products show pronounced toxic effects.



The chalcones play a vital role in anti parasitic diseases such as *leishmaniasis*. Leishmaniasis is an infectious disease caused by protozoa genus *leishmania*, it present several forms of diseases such as mucocutaneous(MCL), cutaneous(CL) and visceral leishmaniasis (VL) which can be fatal if it is left untreated. Leishmaniasis's chemotherapy which is currently available is not

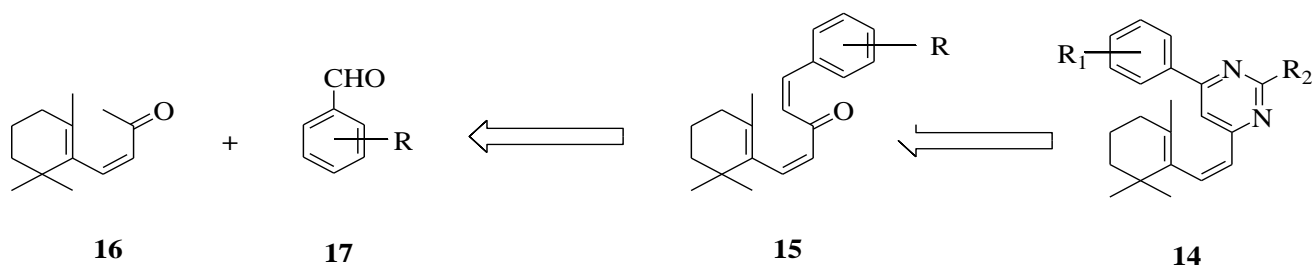
much satisfactory. The antileishmaniasis drugs, resistance to pentavalent antimonials³⁶, which are recommended for the treatment of both visceral(VL) and cutaneous leishmaniasis (CL) for >50 years is now widespread in India.³⁶ New drugs have become available for the treatment of diseases caused by leishmaniasis in recent years. Due to high toxicity of existing antileishmanial drug ,researches are going on for isolation of new molecules from natural resources which can act as lead in the chemotherapy of leishmania and in this endeavour, new lead molecules isolated so far are diaryl heptanoids, oxygenated abietanis, diterpene quinines.³⁷

In view of their biological potential, I proposed a **Scheme 7** to towards the synthesis of terpenyl pyrimidines **14** which belongs to the mimics of compound **13** as a drug candidate via the synthesis of chalcones**15**.

THE GENERAL REACTION SCHEME

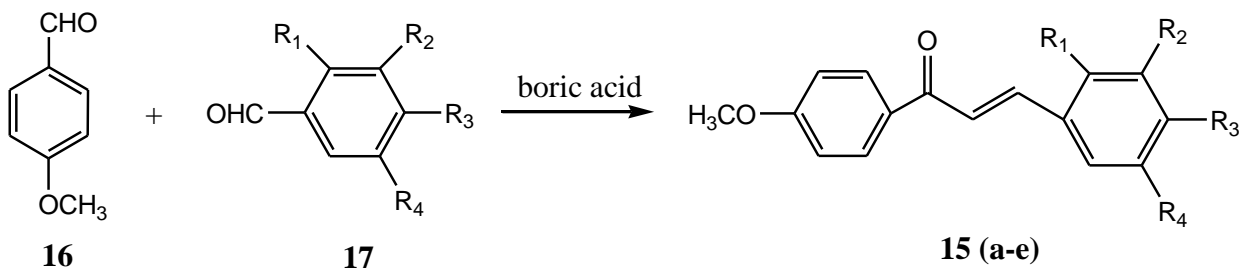
In proposed scheme terpenyl pyrimidine**14** could be obtained from the chalcones **15** on reaction with guanidine hydrochloride/isopropanol in good yields. The intermediate chalcone **15** can be easily prepared by reacting the starting material aromatic β - ionone **16** with aromatic aldehydes **17** under basic conditions.

❖ Retrosynthesis of proposed chalcones 15



(Scheme 8)

THE GENRAL SCHEME

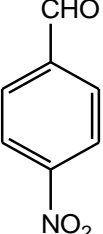
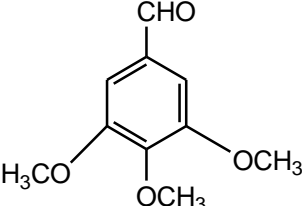
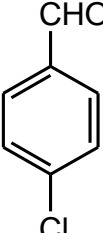


(Scheme 10)

Chalcone	R1	R2	R3	R4
15a	H	H	OCH ₃	H
15b	H	H	OH	H
15c	H	H	NO ₂	H
15d	H	OCH ₃	OCH ₃	OCH ₃
15e	H	H	Cl	H

❖ **The reacting aldehyde in my course work are following:**

1.	<p>OCH₃ Anisaldehyde</p>
2.	<p>OH 4-Hydroxal benzaldehyde</p>

3.	 <p style="text-align: center;">p- nitrobenzaldehyde</p>
4.	 <p style="text-align: center;">3,4,5-Trimethoxybenzaldehyde</p>
5.	 <p style="text-align: center;">p- chloroenzaldehyde</p>

METHODOLOGY

(A) MATERIALS :

A.1 Chemicals required: 4-methoxy acetophenone, 4-chlorobenzaldehyde, 3-nitrobenzaldehyde, Anisaldehyde, 4-hydroxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde Boric acid, hexane, ethylacetate were purchased from Blulux laboratories limited.

A.2 Apparatus and equipments required: Kitchen microwave, Iodine chamber, electronic balance, capillaries were purchased from JSGW.

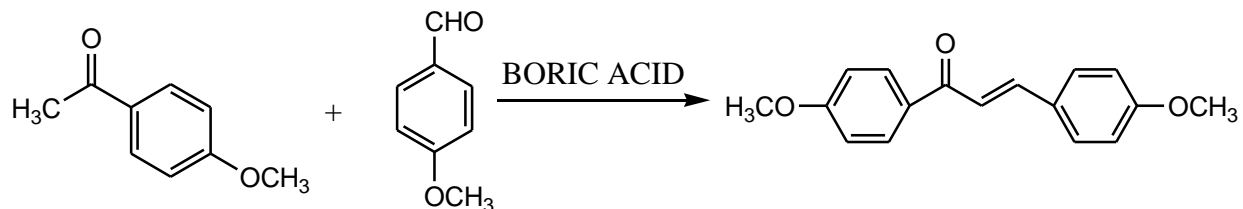
Melting point: The melting point was determined with a lab fit electrically heated apparatus.

Infrared spectroscopy: Infrared (IR) spectra were recorded using KBr pellets by SHIMADZU FTIR 8400S. (Fourier Transform Infrared spectrophotometer) by Department of Lovely Professional University.

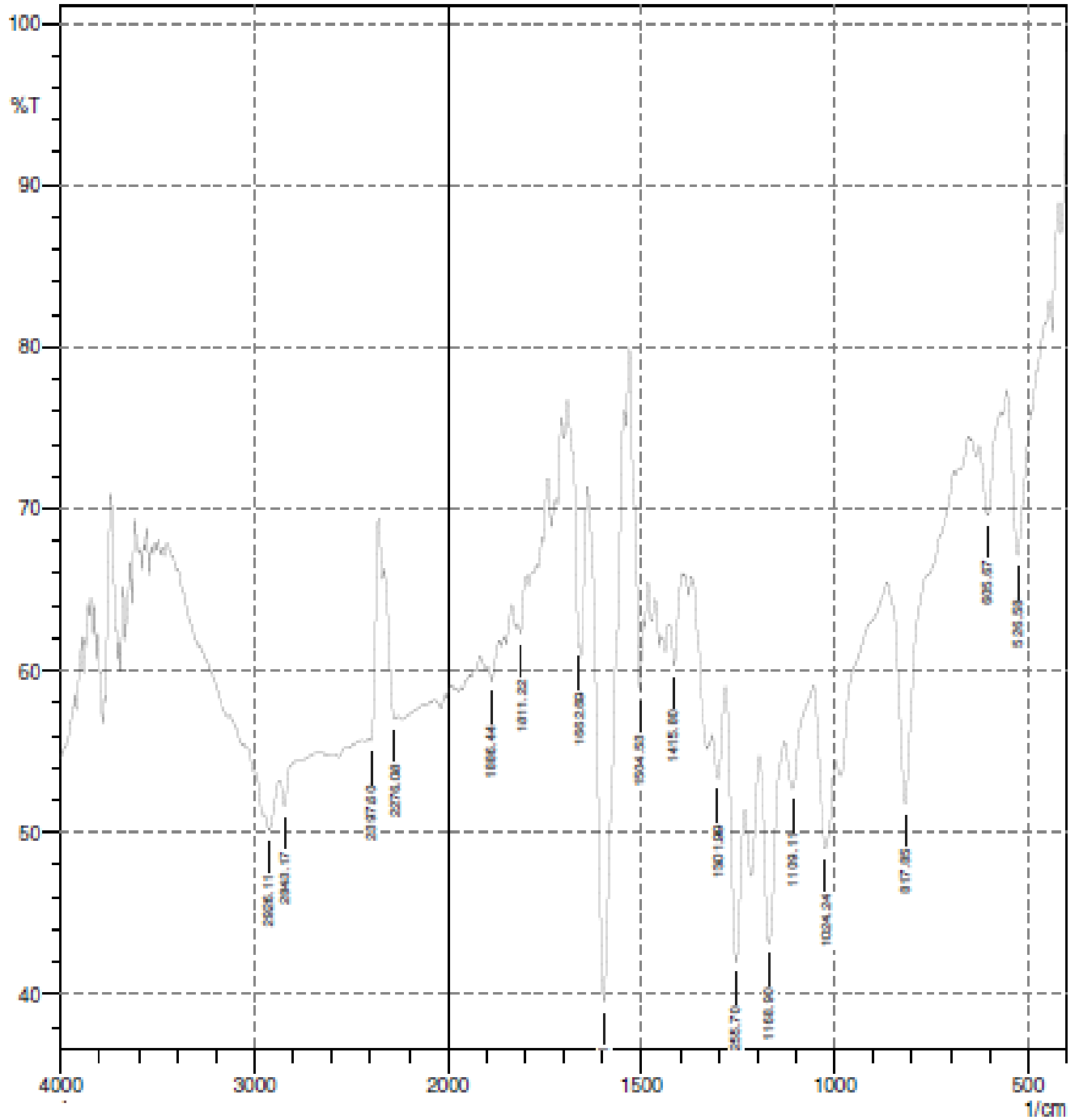
(B) EXPERIMENTAL :

(B.1) Synthesis of compound 1: Take a mixture of 4-methoxy Acetophenone (1.38 ml ,10 mmol) , Anisaldehyde (1.46 g ,10 mmol).Add boric acid (0.123g .10 mmol) in a 250 ml beaker. Mix it well with a glass rod initially. Place it in a kitchen microwave oven. Set the temperature around 100 °C and time for 20 minutes. At 10 minute , scratch it with a glass rod in order to avoid sticking and then keep it again for continue heating for rest minutes. Reaction is monitored with the help of TLC plate using Silica gel-G. After the crude chalcone is obtained, work up was done with separatory funnel. Add ethyl acetate to the product so the chalcone derivative get dissolved in it and filter the rest. Add water to it, there will be layer formation. The unused boric acid will go into the aqueous layer. Add NaHSO₄ to remove the traces of water. The product was obtained by evaporating solvent i.e Ethyl acetate with rotavapour instrument. The yield so obtained was 2.3 g .

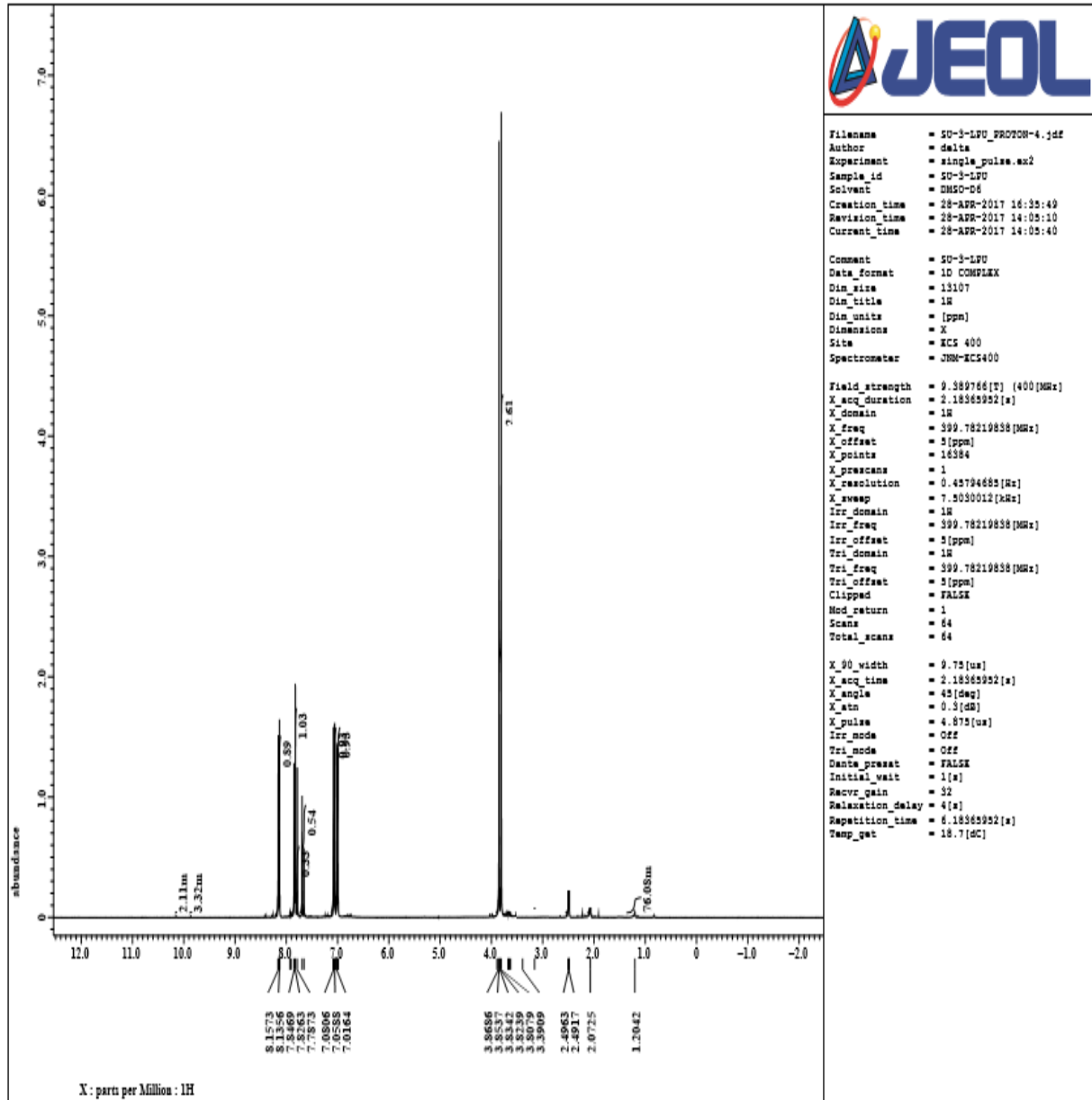
Reaction



IR SPECTRA : (KBr ,cm⁻¹) v 1662 (C=O in conjugation with C=C) , 1597 (C=C in conjugation with C=O) , 1168 (OCH₃ stretching) , 1415 (Ar-C=C) , 2843 (Ar-C-H).

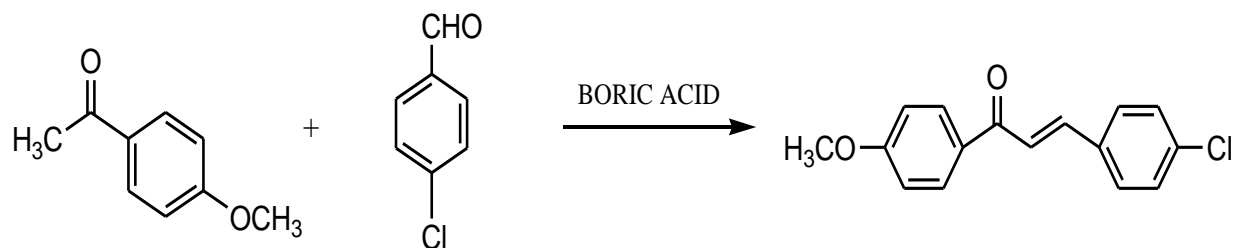


NMR SPECTRA of 15a: (DMSO, 400 MHz) δ ppm , 3.85 (s, 3H, OMe) , 7.01 (d, 2H, Ar), 7.08(d, 2H,Ar) , 7.82(d,2H,Ar) , 8.15(d,2H,Ar), 7.78(d,1H), 7.84(d,1H).

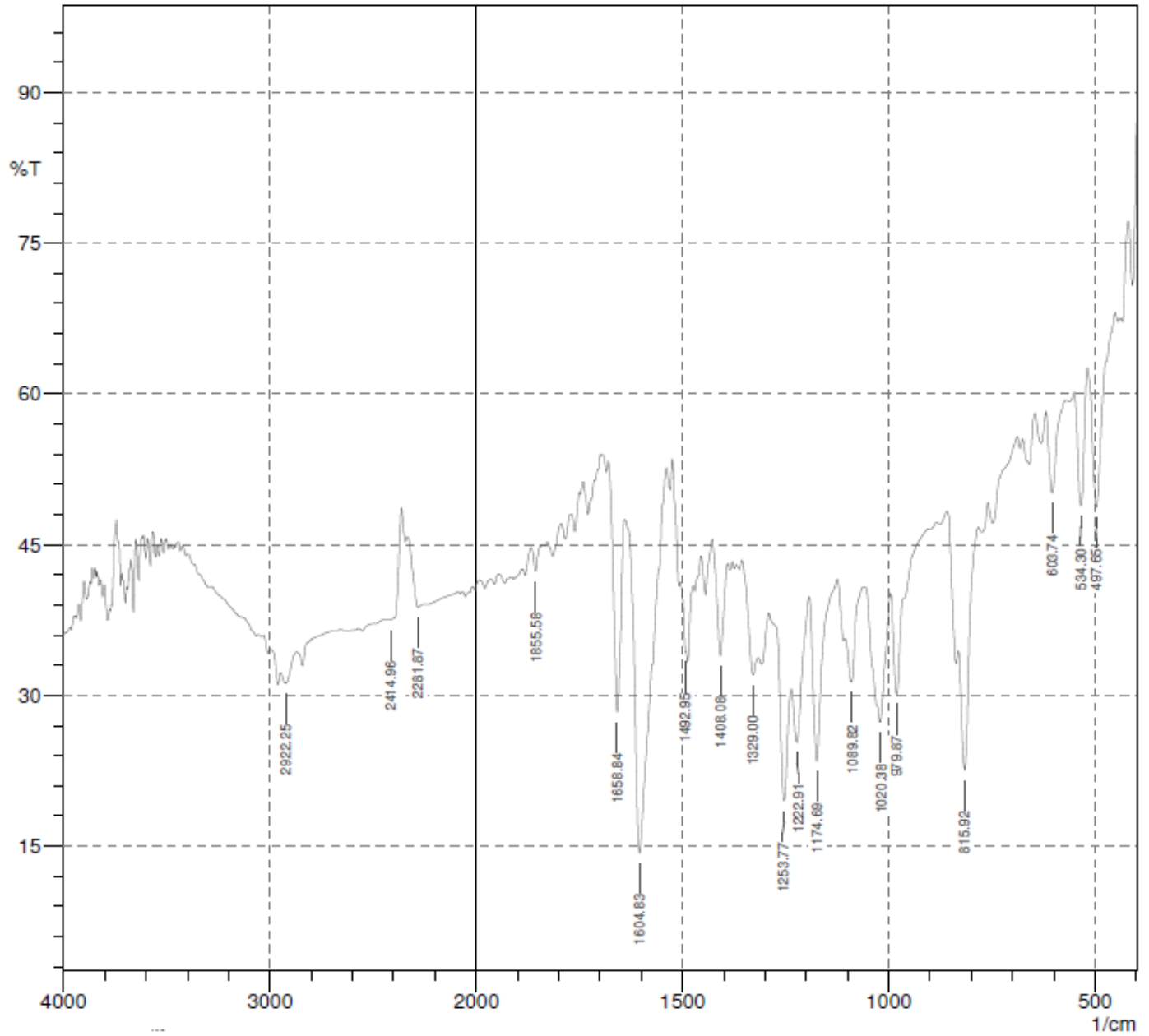


Synthesis of compound 2:: Take a mixture of 4-methoxy Acetophenone (1.38 ml, 10 mmol), 4-chlorobenzaldehyde (1.68g, 10 mmol). Add boric acid (0.123g, 10 mmol) in a 250 ml beaker. Mix it well with a glass rod initially. Place it in a kitchen microwave oven. Set the temperature around 100 °C and time for 20 minutes. At 10 minute, scratch it with a glass rod in order to avoid sticking and then keep it again for continue heating for rest minutes. Reaction is monitored with the help of TLC plate using Silica gel-G. After the crude chalcone is obtained, work up was done with separatory funnel. Add ethyl acetate to the product so the chalcone derivative get dissolved in it and filter the rest. Add water to it, there will be layer formation. The unused boric acid will go into the aqueous layer. Add NaHSO₄ to remove the traces of water. The product was obtained by evaporating solvent i.e Ethyl acetate with rotavapour instrument. The yield so obtained was 2 g. The melting point so obtained was 124 °C.

Reaction:

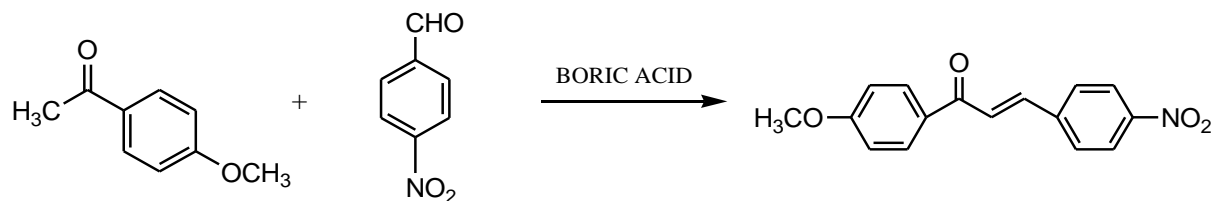


IR Spectra: (KBr ,cm⁻¹) v 1658 (C=O in conjugation with C=C) ,1174 (OCH₃ stretching) ,
1405 (Ar-C=C) , 2922 (Ar-C-H), 815 (Ar-Cl).

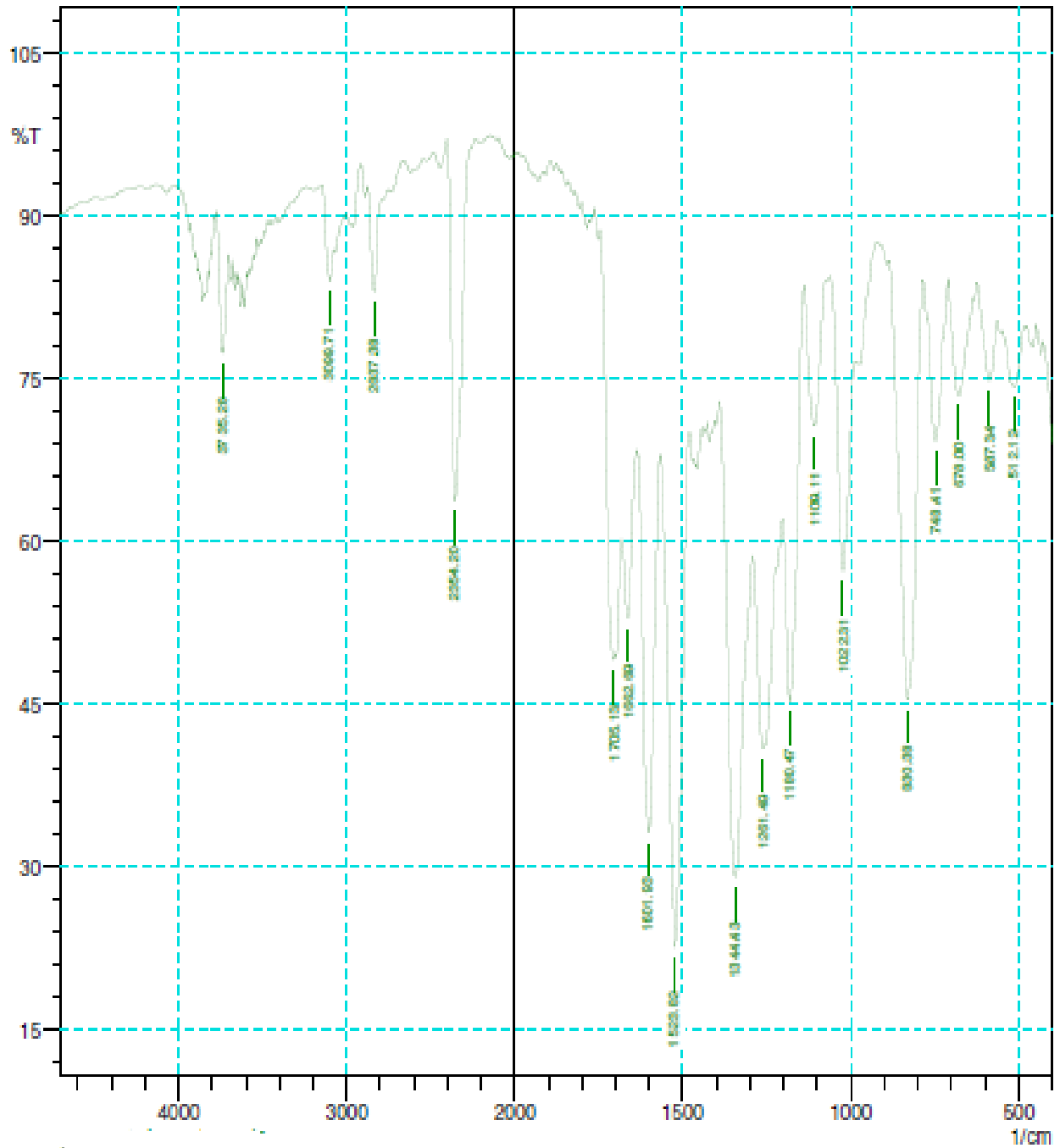


Synthesis of compound 3:: Take a mixture of 4-methoxy Acetophenone (1.38 ml ,10 mmol) , p-nitrobenzaldehyde (1.81 g ,10 mmol) .Add boric acid (0.123g ,10 mmol) in a 250 ml beaker. Mix it well with a glass rod initially. Place it in a kitchen microwave oven. Set the temperature around 100 °C and time for 20 minutes. At 10 minute , scratch it with a glass rod in order to avoid sticking and then keep it again for continue heating for rest minutes. Reaction is monitored with the help of TLC plate using Silica gel-G. After the crude chalcone is obtained, work up was done with separatory funnel. Add ethyl acetate to the product so the chalcone derivative get dissolved in it and filter the rest. Add water to it, there will be layer formation. The unused boric acid will go into the aqueous layer. Add NaHSO₄ to remove the traces of water. The product was obtained by evaporating solvent i.e Ethyl acetate with rotavapour instrument. The yield so obtained was 1.45 g .

Reaction:

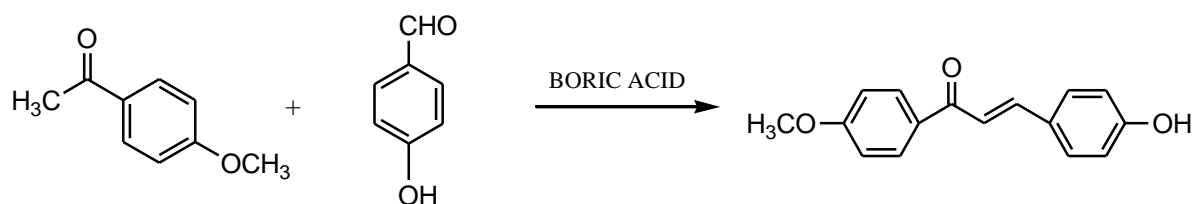


IR Spectra:(KBr , cm^{-1}) ν 1662 (C=O in conjugation with C=C),1523 (C=C in conjugation with C=O) 1180 (OCH₃ stretching) , 1405 (Ar-C=C) , 3099 (Ar-C-H), 1601 (Ar-NO₂)

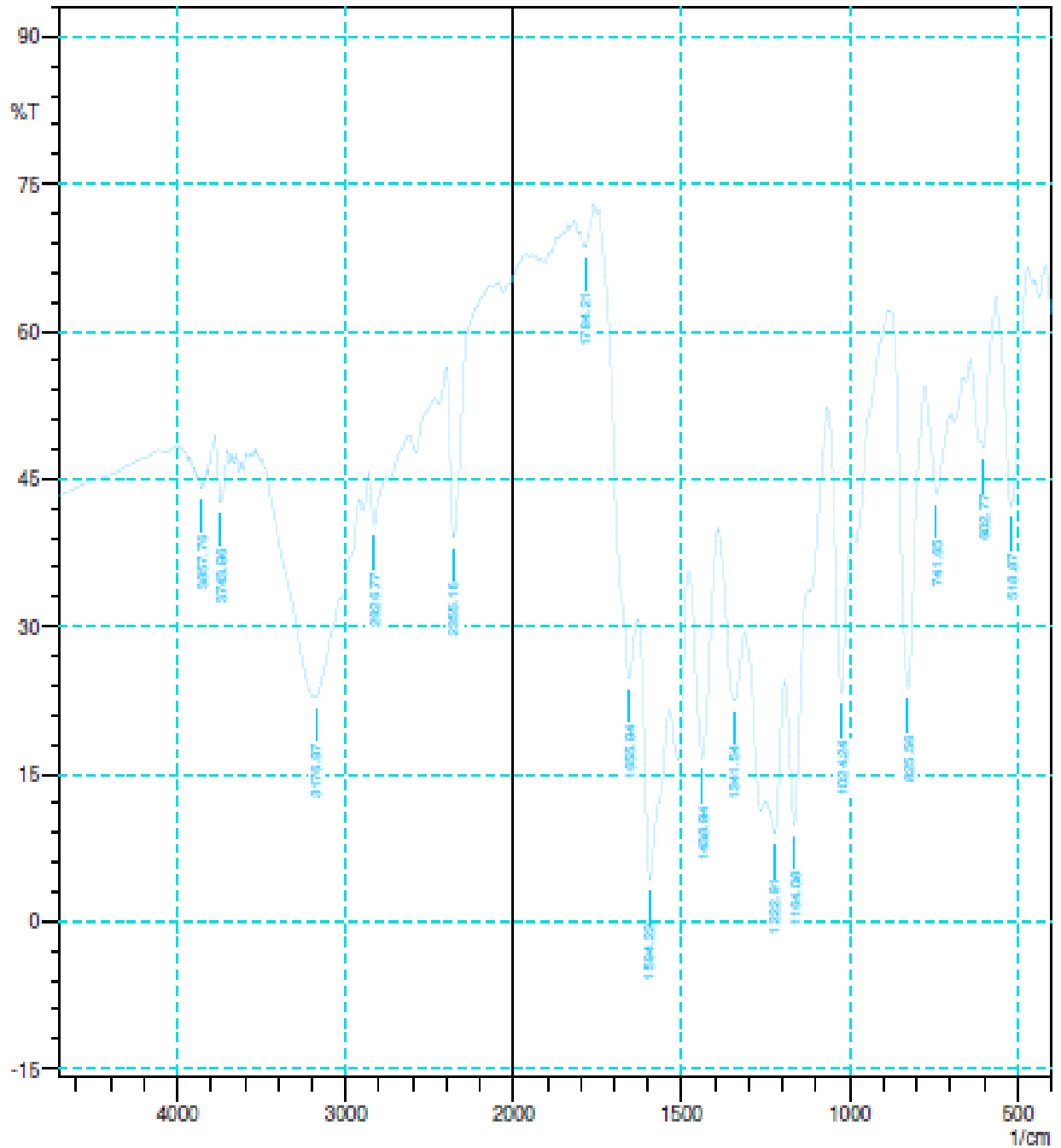


Synthesis of compound 4: Take a mixture of 4-methoxy Acetophenone (1.38 ml, 10 mmol), 4-Hydroxy benzaldehyde (1.81 g, 10 mmol). Add boric acid (0.123g, 10 mmol) in a 250 ml beaker. Mix it well with a glass rod initially. Place it in a kitchen microwave oven. Set the temperature around 100 °C and time for 20 minutes. At 10 minutes, scratch it with a glass rod in order to avoid sticking and then keep it again for continued heating for a few more minutes. Reaction is monitored with the help of TLC plate using Silica gel-G. After the crude chalcone is obtained, work up was done with a separatory funnel. Add ethyl acetate to the product so the chalcone derivative gets dissolved in it and filter the rest. Add water to it, there will be layer formation. The unused boric acid will go into the aqueous layer. Add NaHSO₄ to remove the traces of water. The product was obtained by evaporating solvent i.e. Ethyl acetate with a rotavapour instrument. The yield so obtained was 2.45 g.

Reaction:

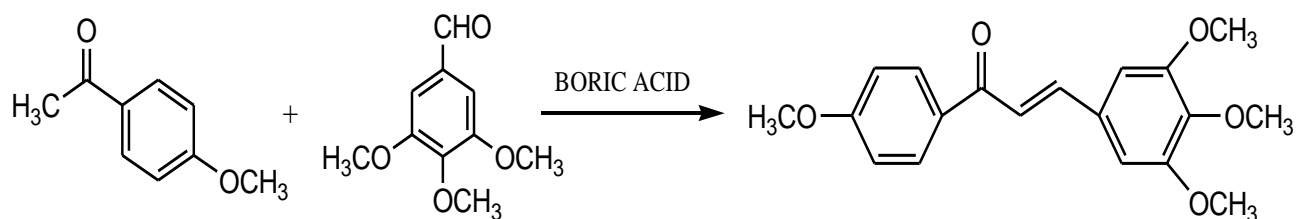


IR Spectra: : (KBr , cm^{-1}) v 1655 (C=O in conjugation with C=C),1594 (C=C in conjugation with C=O) 1164 (OCH₃ stretching) , 1438 (Ar-C=C) , 2826 (Ar-C-H), 3176 (Ar-OH).

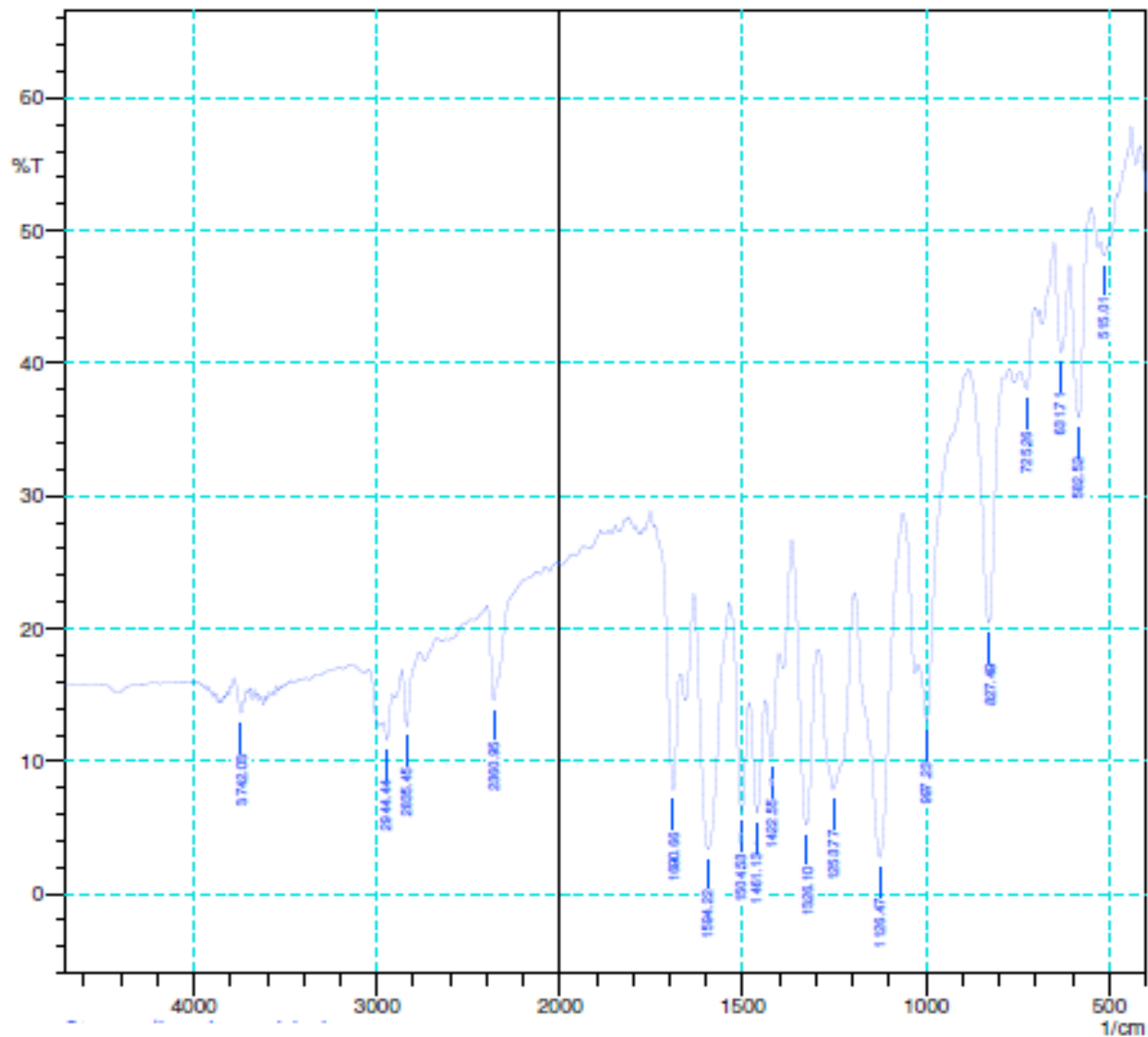


Synthesis of compound 5: Take a mixture of 4-methoxy Acetophenone (1.38 ml, 10 mmol), 3,4,5-trimethoxybenzaldehyde (2.35 g, 10 mmol). Add boric acid (0.123 g, 10 mmol) in a 250 ml beaker. Mix it well with a glass rod initially. Place it in a kitchen microwave oven. Set the temperature around 100 °C and time for 20 minutes. At 10 minutes, scratch it with a glass rod in order to avoid sticking and then keep it again for continue heating for rest minutes. Reaction is monitored with the help of TLC plate using Silica gel-G. After the crude chalcone is obtained, work up was done with separatory funnel. Add ethyl acetate to the product so the chalcone derivative gets dissolved in it and filter the rest. Add water to it, there will be layer formation. The unused boric acid will go into the aqueous layer. Add NaHSO₄ to remove the traces of water. The product was obtained by evaporating solvent i.e. Ethyl acetate with rotavapour instrument. The yield so obtained was 2.70 g.

Reaction:



IR Spectra:: (KBr ,cm⁻¹) ν 1690 (C=O in conjugation with C=C), 1594 (C=C in conjugation with C=O), 1126 (OCH₃ stretching) , 1461 (Ar-C=C) , 2835 (Ar-C-H).



Conclusions

From the present work we can conclude that amongst all the synthesized chalcone derivatives by Claisen–Schmidt condensation reaction. All the synthesized compounds were critically analyzed to ascertain the structure by melting point, IR spectra and ¹HNMR spectra which corresponds to our previous work reported 38 . Also all five compounds have been submitted for anti-bacterial activity. According to literature survey , these compounds would be a promising intermediate in drug synthesis.

