SYNTHESIS OF QUINAZOLINE DERIVATIVES BY USING BIGINELLI TYPE REACTION UNDER MICROWAVE IRRADIATION

BY

M. A. A SHOFI UDDIN SARKAR

A
DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF
MASTER OF PHYLOSOPHY (M. Phil.)
IN
CHEMISTRY

ORGANIC SYNTHESIS AND CATALYSIS LABORATORY
DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET)
DHAKA-1000
MARCH, 2019.

DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY
BUET
DHAKA-1000

THESIS ACCEPTANCE LETTER

The thesis titled **"Synthesis of Quinazoline Derivatives by Using Biginelli Type Reaction Under Microwave Irradiation"** submitted by M.A.A Shofi Uddin Sarkar, Roll No.: 0413033109F, Registration No.: 0413033109, Session: April-2013 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Philosophy (M.Phil.) in Chemistry on March 24, 2019.

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Assistant Professor
Department of Chemistry
BUET, Dhaka
(Supervisor)

24.03.19
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4. Dr. Kawsari Akhter
Professor
Department of Chemistry
University of Dhaka, Dhaka

Member (External)

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Chapter 3 : Results and Discussions

Chapter 4 : Conclusions

CANDIDATE'S DECLARATION

It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

Signature of the candidate

M.A.A SHOFI UDDIN SARKAR
Name of the Candidate

Dedicated
To
My Family

ACKNOWLEDGEMENT

All praise and admiration for almighty Allah, the most kind and merciful who has enabled me in carrying out the research work presented in this dissertation.

I am extremely delighted to express my deepest gratitude and sincere thanks to my respected teacher and supervisor, Dr. Md. Ayub Ali, Assistant Professor, Department of Chemistry, BUET, Dhaka, for his helpful advices, patience, motivation, keen interest, worthy suggestions and encouragement throughout the progress of my research work.

I am grateful to all my respected teachers of this department for their helpful suggestions at different stages of studies in Chemistry.

I owe my deepest gratitude to the Bangladesh University of Engineering and Technology (BUET), Dhaka, Bangladesh for giving me the financial support to carry out my research work and I am also grateful to the Department of Chemistry to give me opportunity to do M. Phil. Program. I thank all staffs in the Department of Chemistry, BUET for their kind co-operations.

I would like to extend my thanks to Mr. Shadhon Kumar das, Sakila Yasmin, M. Jannat, Limon, Mr. Ashutosh Nath and Komol kanti for their co-operation in the laboratory and special thanks to Md. Moniruzzaman for his co-operation in taking IR spectra for my research work.

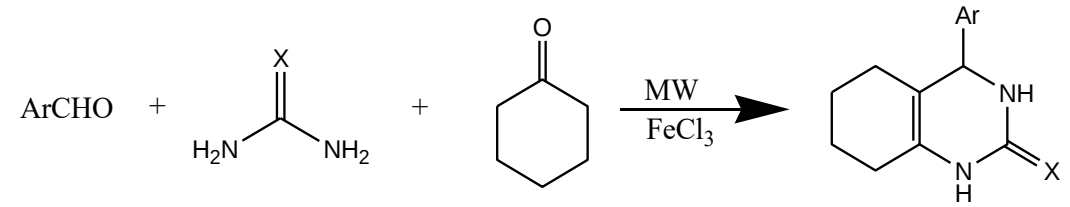
Finally, I must express my very profound gratitude to my parents for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

M. A. A SHOFI UDDIN SARKAR

Author

Abstract

Microwave irradiation has become a very convenient tool in organic synthesis. Microwave technology in organic chemistry has been explored extensively within the last decade. A Biginelli one-pot three-component reaction involving cyclohexanone, aromatic/or heterocyclic aldehyde, and urea or thiourea was applied in this work to prepare quinazoline-2(1H) one derivatives under solvent free and microwave irradiation assistance method.



Ar = C_6H_4Cl X= O or S
$C_6H_4NO_2$
$C_6H_4OCH_3$
C_6H_4OH

Scheme 1

It significantly shortens the reaction time and is best suited for the chemical reactions carried out on solid supports as well. Microwave-assisted reactions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling. Thereby this method plays an important role in the development of Green Chemistry. All the synthesized compounds was subjected to both physical and chemical methods of analysis, especially spectroscopic method (UV, IR, ^{1}H NMR, ^{13}C NMR and Mass spectra) for assuring the molecular structure of the synthesized compounds.

In conclusion, we have evolved a much improved modification of Biginelli reaction exploiting $FeCl_3$ as a catalyst without using any organic solvent with increased yield, while the reaction time shortened from 4-5 h to a few minutes under microwave irradiation.

List of Figures and Tables

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List of Abbreviations

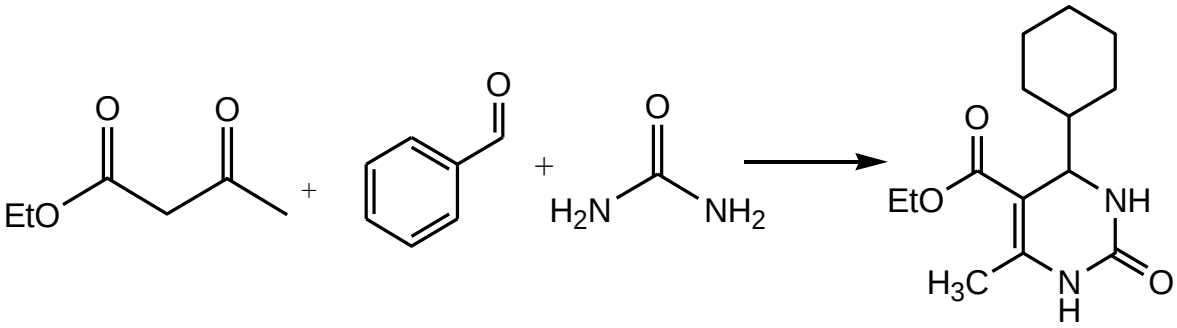
Elaborations	Abbreviations
Mega Hertz	MHz
Hertz	Hz
Singlet	s
Doublet	d
Triplet	t
Quartz	q
Multiplet	m
Melting point	m.p.
Ultra Violet-Visible	UV-Vis
Infrared Spectroscopy	IR
Nuclear Magnetic Resonance	NMR
Mass Spectroscopy	MS
Thin Layer Chromatography	TLC
Gas Chromatography-Mass Spectroscopy	GC-MS
Proton NMR	^{1}H-NMR
Carbon-13 NMR	^{13}CNMR
Tetramethylsilane	TMS
Deuterated chloroform	$CDCl_3$

Chapter 1

Introduction

1.1. Biginelli reaction

The Biginelli reaction is a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1H)-ones from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde), and urea [1,2] which are interesting compounds with a potential for pharmaceutical application. It is named for the Italian chemist Pietro Biginelli [3, 4].



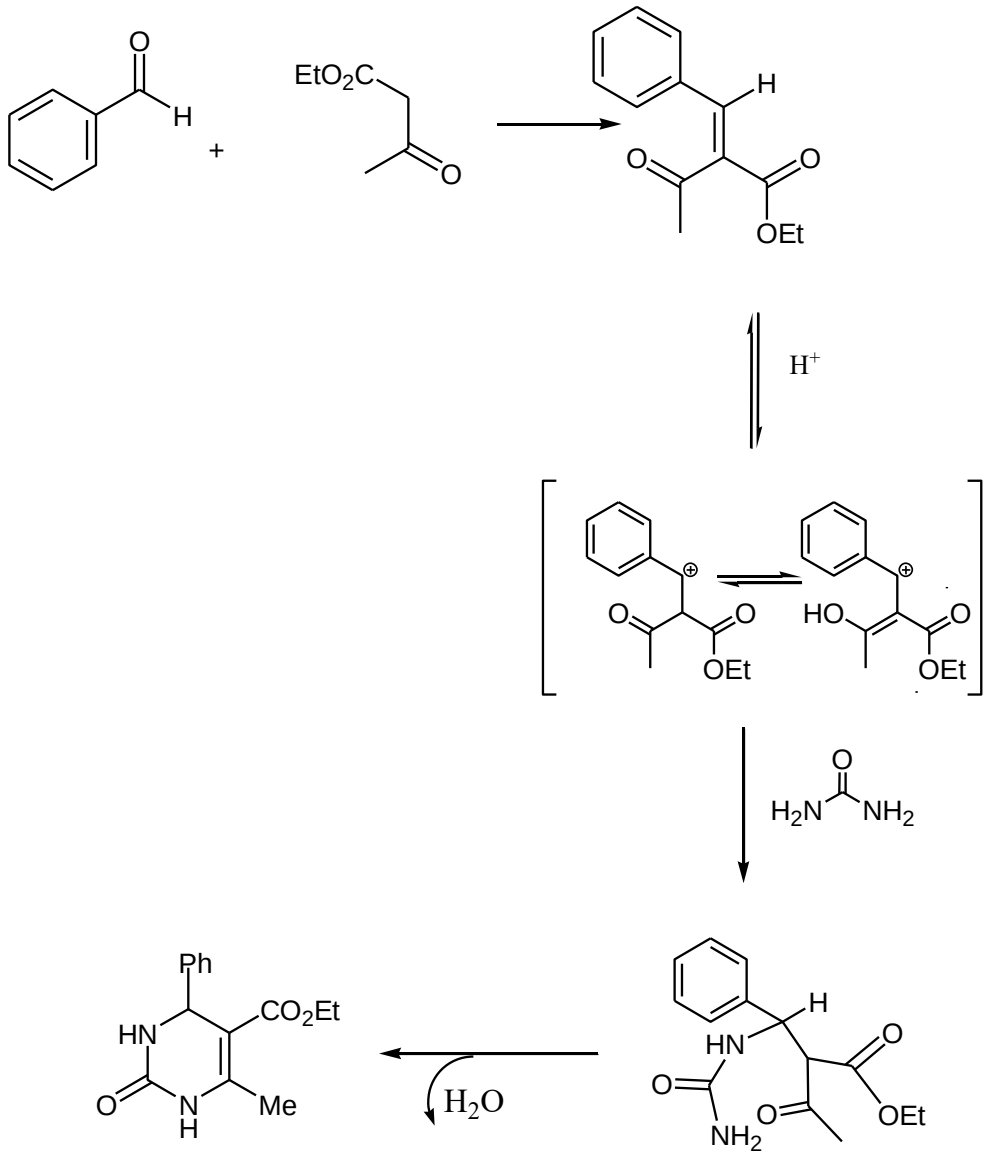
Scheme 2

This reaction was developed by Pietro Biginelli in 1891. The reaction can be catalyzed by Brønsted acids and/or by Lewis acids such as boron trifluoride [5]. Several solid-phase protocols utilizing different linker combinations have been published [6]. Dihydropyrimidinones, the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers [7], antihypertensive agents, and alpha-1- a-antagonists. In view of the ease with which the Biginelli reaction is conducted, many exciting prospects await for its utilization in various fields.

Reaction mechanism

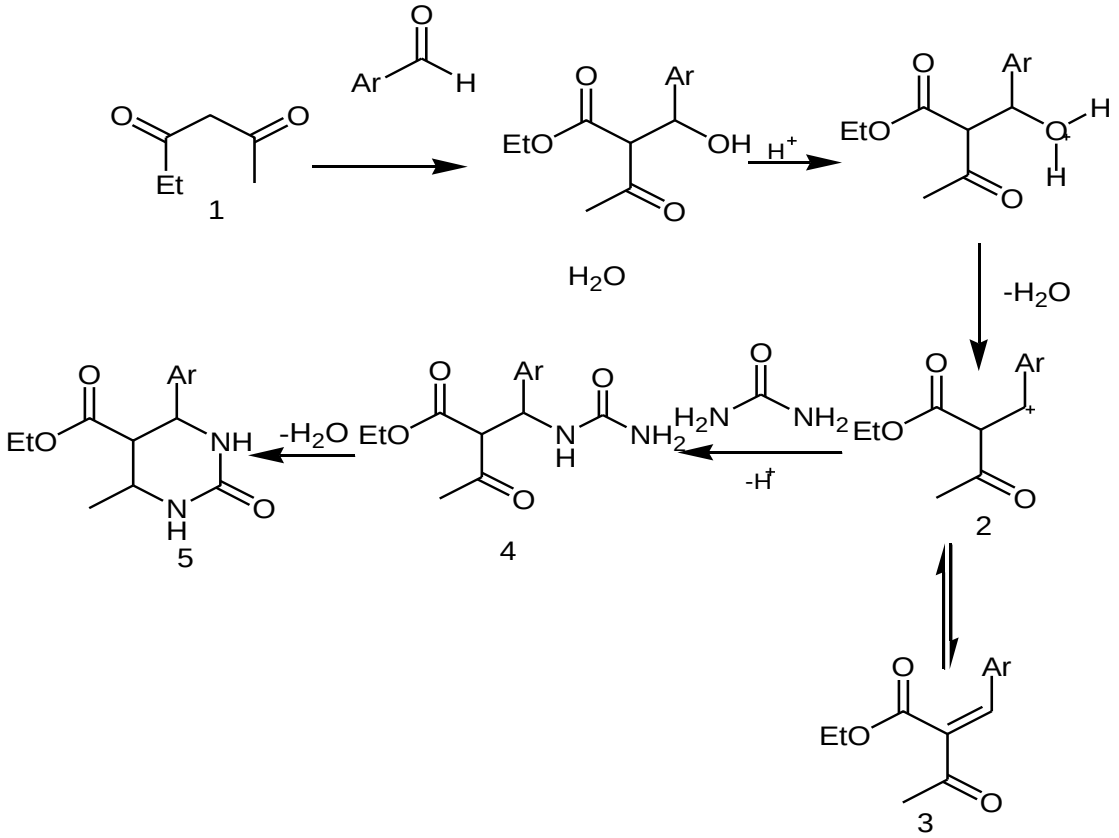
The reaction mechanism of the Biginelli reaction is a series of bimolecular reactions leading to the desired dihydropyrimidinone [8].

First reaction mechanism was proposed in 1933 by Folkers

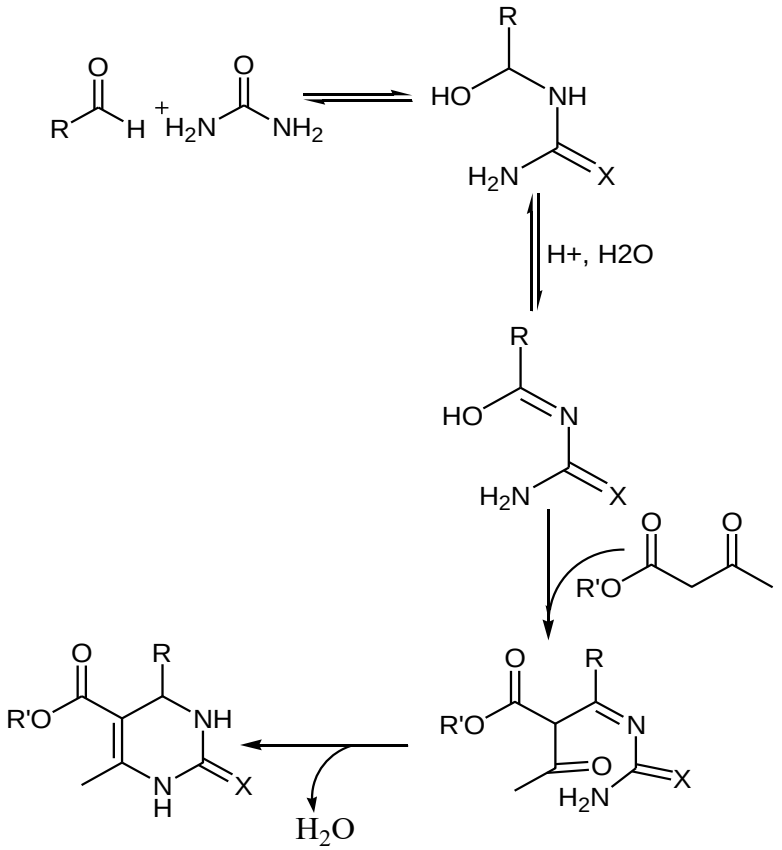


Scheme 3

According to a mechanism proposed by Sweet in 1973 the aldol condensation of ethylacetoacetate **1** and the aryl aldehyde is the rate-limiting step leading to the carbenium ion **2**. The nucleophilic addition of urea gives the intermediate **4**, which quickly dehydrates to give the desired product **5**.



This mechanism is superseded by one by Kappe in 1997:



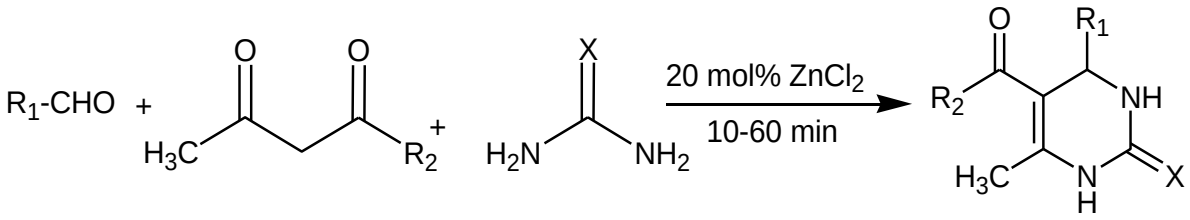
Scheme 4

This scheme performs with rate determining nucleophilic addition by the urea to the

aldehyde [9]. The ensuing condensation step is catalyzed by the addition of acid, resulting in the imine nitrogen. The β-ketoester then adds to the imine bond and consequently the ring is closed by the nucleophilic attack by the amine on to the carbonyl group. This final step ensues a second condensation and results in the Biginelli compound.

1.2. Review

Biginelli reaction is a three component reaction which incorporates an aldehyde, a urea or thiourea and an open chain β-dicarbonyl compound under acidic conditions in ethanol. The classical Biginelli reaction of an aldehyde, β-keto ester and urea or thiourea involves strongly acidic conditions. Usually only low to moderate yields are acquired, in particular when substituted aromatic or aldehyde are obtained.



R_1 = C_6H_6, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$0HC_6H_4$
R_2 = C_2H_5O, CH_3
X = S,O

Scheme 5

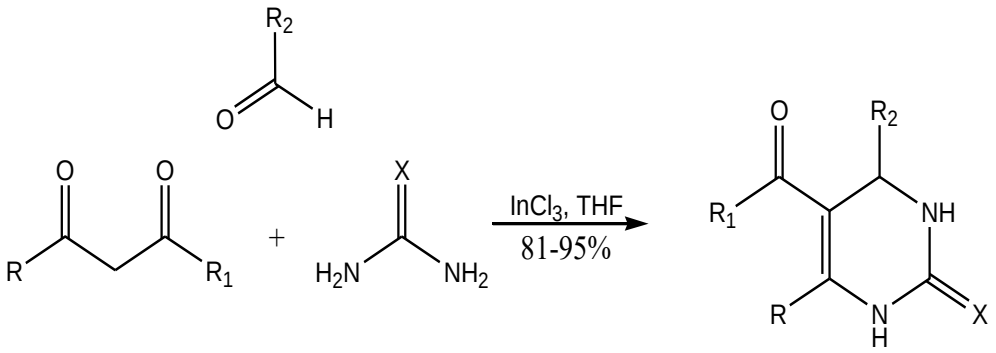
Very recently, for novel Biginelli-like scaffold synthesis, the use of common open chain β-dicarbonyl compounds has been extended to cyclic β-diketones, β- ketolactones. These reactions suffer from limitations such as low yields, very long reaction times, harsh reaction conditions and unrecoverable strong acids.

1.2.1. Catalysts used in Biginelli Reaction

In order to enhance the efficiency of Biginelli reaction, many catalysts have been developed, such as

-Lewis acids, namely, Yb $(OTf)_3$ [10], $InCl_3$ [11], $VC1_3$ [12], $CuCl_2$. $2H_20$ [13], LiBr [14],

-Indium(III)Chloride mediated Biginelli reactions [15]



Scheme 6

Brônsted acids such as p-toluenesulfonic acid [16], silica sulphuric acid [17].

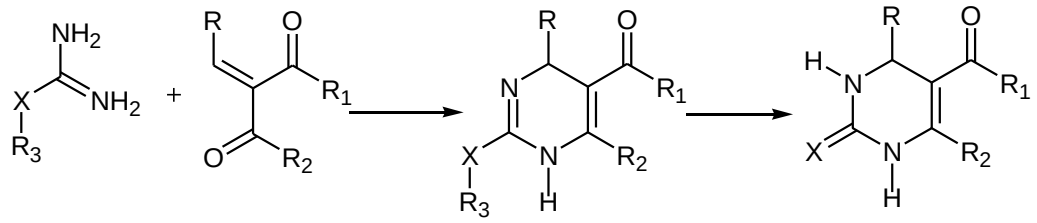
Even baker's yeast has been used as an efficient catalyst in Biginelli reaction [18]. Moreover, asymmetric syntheses of DHPMs using $CeCl_3/InCl_3$ or $Yb(OTf)_3$ as catalysts in the presence of chiral ligands have been reported [19].

These reactions can be carried out in ionic liquids, under solid or fluorous phase [20], under microwave with polyphosphate ester [21] or ultrasound irradiations in the presence of NH_2SO_3H [22] or $Mg(ClO_4)_2$ [23].

Some of them are really very fascinating from a synthetic chemist's point. Despite their tremendous success, however, some drawbacks still remain. Some of them catalysts are expensive, complex or unavailable and organic solvents are used.

Very attractive approach to the synthesis of Biginelli compounds was developed by Atwal and co-workers [24]. This approach is based on the reaction of α-arylidene-β-oxoesters with S-(4-methoxybenzyl)isothiourea or O-methylisourea in the presence of sodium bicarbonate followed by transformation of the obtained 2-(4-methoxybenzylthio)-

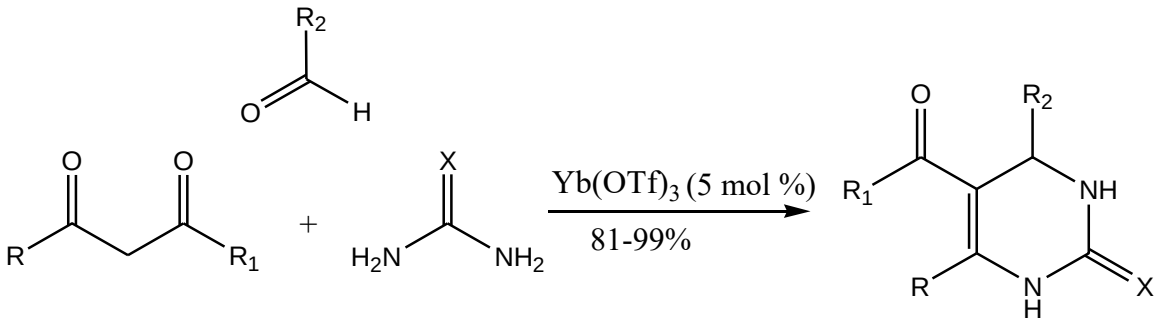
or 2-methoxy-1,4-dihydropyrimidine-5-carboxylates into 2-thioxo- or 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates.



R_3X = 4-$MeOC_6H_4CH_2S$, MeO

Scheme 7

Lanthanides triflates are unique Lewis acids that are currently of great research interest. They are unlike common Lewis acids, which are trapped nitrogen atoms of imines or tertiary amines that decompose readily in the presence of water so that more than stoichiometric amounts are required to complete the reaction.



Scheme 8

Conversely, Lanthanidetriflates are quite stable to water reusable as well as highly effective for the activation of imines. Therefore lanthanide trifaltes are unique catalysts compared to traditional Lewis acids in several important carbon-carbon bond forming reaction [25].

Yun Ma and his co-workers [26] disclosed a novel lanthanide triflates catalyzed Biginelli reaction applied to one-pot synthesis of dihydropyrimedinones under solvent free conditions, which not only is very simple and high-yielding (81-99%) but also greatly

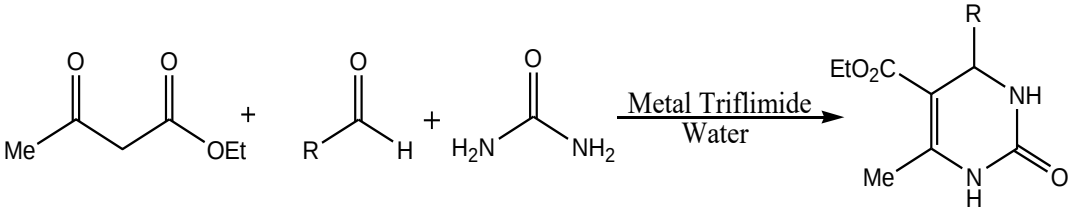
decreases environmental pollution.

A model reaction employing benzaldehyde, ethyl acetoacetate and urea in the presence of three types of Envirocats, namely EPZ 10 (clay-supported $ZnCl_2$), EPZG (clay-supported $FeCl_3$) and EPIC (clay-supported poly phosphoric acid) that was studied by Key-Young Lee and Kwang-Youn Ko [27].

All Envirocats catalysts were activated via azeotropic drying with toluene to remove loosely bound water in clay support [28]. In refluxing toluene, EPZ10 was found to be the most reactive among three catalysts, giving the product in 84% isolated yield within 6 h. Li contrast, the classical Biginelli condition (cat. HC1 in EtOH, reflux, 18 h) gave 80% yield. The solvent effect was studied in the case of EPZ10 catalyzed reaction. Clearly, toluene was a much better solvent than other solvents tested in terms of yields. Lower boiling solvent (dichloromethane), protic solvent (EtOH) and Lewis basic solvents (THF, CH_3CN) retarded the reaction. Also, the solvent-free reaction condition gave a good yield of product.

The same reaction was carried out by F.S Canto and his co-workers [29] using $SnCl_2.6H_2O$ catalyst in acetonitrile or ethanol as a solvent in neutral media and represents an Improvement of the classical Biginelli protocol and an advantage in comparison with $FeCl_2.6H_20$, $NiCl_2.6H_2O$ and $CoCl_2.6H_2O$ which were used with HC1 as co-catalyst. The synthesis of dihydropyrimedinones was achieved in good to excellent yields.

In 2007 Ichiro Suzuki and his co-workers have first demonstrated that metal triflimide [30] salts can work as a Lewis acids in pure water and these Lewis acids such as $Ni(NTf_2)_2$, $Cu(NTf_2)_2$, and $Yb(NTf_2)_3$, catalyze the Biginelli reaction more efficiently in pure water under mild conditions than do conventional metal triflates in pure water [31]. The addition of a Bronsted acid considerably improved the yields of the reaction.

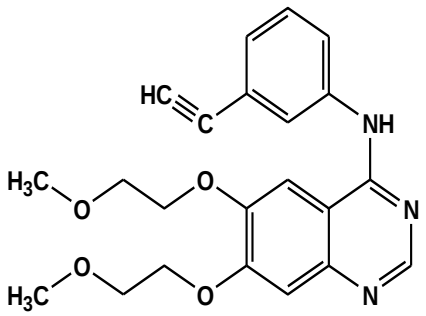


Scheme 9

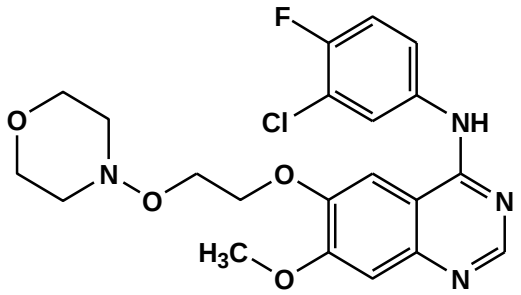
In 2008 M.A. Zolfigol and his co-workers [32] have described a simple and efficient method for the synthesis of dihydropyrimidinones using a reusable $Fe(HSO_4)_3$ both in solution and under solvent free conditions. The method offers several advantages including simple, easy and clean work up procedure, relatively short reaction times and goods to yields of the products, which make it a useful addition to the present methodologies for the synthesis of dihydropyrimidinones.

1.2.2. Pharmacological importance of heterocyclic compounds

Heterocyclic moiety is an important astructure in many bioactive natural products and therapeutic compounds. In view of the increasing interest for the preparation of large heterocyclic compounds libraries and beside the usual multi-step syntheses, multicomponent reactions (MCRs) are becoming increasingly prevalent due to their improved efficiency, simple procedure, one-pot character, quantitative yields of the target molecules and the high and ever increasing number of accessible backbones. Quinazoline, a heterocyclic compound, has been extensively studied and used in certain specific biological activities



(a)



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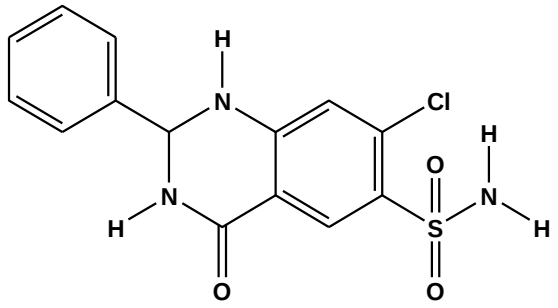

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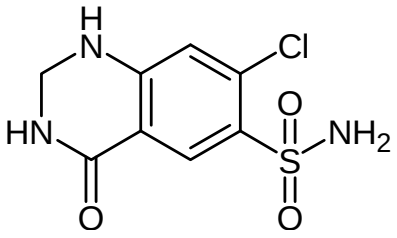


(d)

Fig 1: Quanazoline Drugs as Anti-cancer (a, b) and Anti-diuretic (c, d)

1.3. Microwave Chemistry For Synthesis

Microwave chemistry involves the use of microwave radiation to conduct chemical reactions, and essentially pertains to chemical analysis and chemical synthesis. Microwave radiation has been successfully applied to numerous industrial applications (drying, heating, sintering, etc.) too.

This section provides a basic overview of microwave chemistry. It starts with an insight into the scientific principle governing the function of microwave radiation and its use in chemical analysis and synthesis. It also discusses the mechanism of microwave heating and provides a background to the evolution of microwave chemistry, enumerating its benefits and limitations, while briefly delving into the controversy pertaining to the 'microwave effect'.

Microwaves lie in the electromagnetic spectrum between infrared waves and radio waves. They have wavelengths between 0.01 and 1metre, and operate in a frequency range between 0.3 and 30 GHz. However, for their use in laboratory reactions, a frequency of 2.45 GHz is preferred, since this frequency has the right penetration depth for laboratory reaction conditions. Beyond 30 GHz, the microwave frequency range overlaps with the radio frequency range.

1.3.1. Fundamentals of Microwave Technology

The fundamental mechanism of microwave heating involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. However, the motion of these particles is restricted by resisting forces (inter-particle interaction and electric resistance), which restrict the motion of particles and generate random motion, producing heat.

Since the response of various materials to microwave radiation is diverse, not all materials are amenable to microwave heating. Based on their response to microwaves, materials can be broadly classified as follows:

- Materials that are transparent to microwaves, e.g., sulphur
- Materials that reflect microwaves, e.g., copper
- Materials that absorb microwaves, e.g., water

Only materials that absorb microwave radiation are relevant to microwave chemistry. These materials can be categorized according to the three main mechanisms of heating namely:

1) Dipolar polarization
2) Conduction mechanism
3) Interfacial polarization

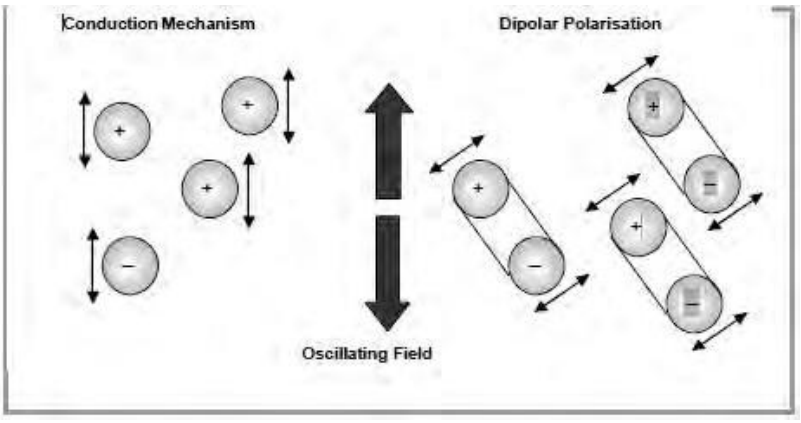


Fig 2: Methods of heating by Microwave radiation

1.3.2. Dipolar Polarization

Dipolar polarization is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, and this random interaction generates heat. Dipolar polarization can generate heat by either one or both the following mechanisms:

- Interaction between polar solvent molecules such as water, methanol and ethanol
- Interaction between polar solute molecules such as ammonia and formic acid

The key requirement for dipolar polarization is that the frequency range of the oscillating field should be appropriate to enable adequate inter-particle interaction. If the frequency range is very high, inter-molecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction.

On the other hand, if the frequency range is low, the polar molecule gets sufficient time to align itself in phase with the field. Hence, no random interaction takes place between the adjoining particles. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions.

In addition, the energy in a microwave photon (0.037 kcal/mol) is very low, relative to The typical energy required to break a molecular bond (80-120 kcal/mol). Therefore, microwave excitation of molecules does not affect the structure of an organic molecule, and the interaction is purely kinetic.

1.3.3. Conduction Mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor.

The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them.

1.3.4. Interfacial Polarization

The interfacial polarization method can be considered as a combination of the conduction and dipolar polarization mechanisms. It is important for heating systems that comprise a conducting material dispersed in a non-conducting material. For example, consider the dispersion of metal particles in sulphur. Sulphur does not respond to microwaves, and metals reflect most of the microwave energy they are exposed to, but combining the two makes them a good microwave-absorbing material. However, for this to take place, metals have to be used in powder form. This is because, unlike a metal surface, metal powder is a good absorber of microwave radiation. It absorbs radiation and is heated by a mechanism that is similar to dipolar polarization. The environment of the metal powder acts as a solvent for polar molecules and restricts the motion of ions by forces that are equivalent to inter-particle interactions in polar solvents. These restricting forces, under the effect of an oscillating field, induce a phase lag in the motion of ions. The phase lag generates a random motion of ions and results in the heating of the system.

1.3.5. Evolution of Microwave Chemistry

The use of microwave radiation as a method of heating is over five decades old. Microwave technology developed in 1946, when Dr. Percy Le Baron Spencer, while conducting laboratory tests for a new vacuum tube called a magnetron, accidentally

Discovered that a candy bar in his pocket melted on exposure to microwave radiation. Dr. Spencer developed the idea further and established that microwaves could be used as a method of heating. Subsequently, he designed the first microwave oven for domestic use in 19476. Since then, the development of microwave radiation as a source of heating has been very gradual (Table 1)

Table 1: Evolution of Microwave Chemistry

1946	Microwave radiation was discovered as a method of heating
1947	First commercial domestic microwave oven was introduced
1978	First microwave laboratory instrument was developed by CEM Corporation to analyse moisture in solids
1980-82	Microwave radiation was developed to dry organic materials
1983-85	Microwave radiation was used for chemical analysis processes such as ashing, digestion and extraction
1986	Robert Gedye, Laurentian University, Canada; George Majetich, University of Georgia, USA; and Raymond Giguere of Mercer University, USA, published papers relating to microwave radiation in chemical synthesis
1990s	Microwave chemistry emerged and developed as a field of study for its applications in chemical reactions
1990	Milestone s.r.l. generated the first high pressure vessel (HPV 80) for performing complete digestion of difficult to digest materials like oxides, oils and pharmaceutical compounds
1992-1996	CEM developed a batch system (MDS 200) reactor, and a single mode cavity system (Star 2) that were used for performing chemical synthesis
1997	Milestone s.r.l and Prof. H.M (Skip) Kingston of Duquesne University culminated a reference book titled "Microwave-Enhanced Chemistry – Fundamentals, Sample Preparation, and Applications", and edited by H. M. Kingston and S. J. Haswell
2000	First commercial microwave synthesizer was introduced to conduct chemical synthesis

1.3.6. Microwave Chemistry Apparatus

Most pioneering experiments in chemical synthesis using microwaves were carried out in domestic microwave ovens. However, developments in microwave equipment technology have enabled researchers to use dedicated apparatus for organic reactions. The following are the two categories into which microwave chemistry apparatus are classified:

- Single-mode apparatus
- Multi-mode apparatus

1.3.7. Uniform Heating

Microwave radiation, unlike conventional heating methods, provides uniform heating throughout a reaction mixture (Figure 5).

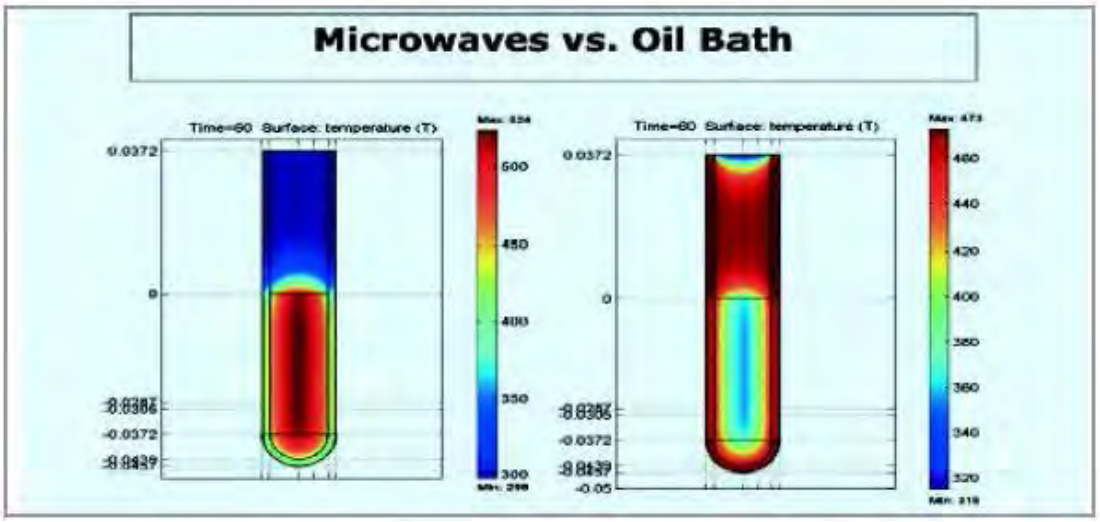


Figure 3: Uniform Heating through Microwave Irradiation

In conventional heating, the walls of the oil bath get heated first, and then the solvent. As a result of this distributed heating in an oil bath, there is always a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent. This feature allows the chemist to place reaction vessels at any location in the cavity of a microwave oven. It also proves vital in processing multiple reactions simultaneously, or in scaling up reactions that require identical heating conditions.

1.3.8. Environmentally-friendly Chemistry

Reactions conducted through microwaves are cleaner and more environmentally friendly than conventional heating methods. Microwaves heat the compounds directly; therefore, usage of solvents in the chemical reaction can be reduced or eliminated, for example, Hamelin developed an approach to carry out a solvent-free chemical reaction on a sponge- like material with the help of microwave heating. The reaction is conducted by heating a spongy material such as alumina. The chemical reactants are adsorbed to alumina, and on exposure to microwaves, react at a faster rate than conventional heating. The use of microwaves has also reduced the amount of purification required for the end products of chemical reactions involving toxic reagents.

1.3.9. Change in the Kinetics of the Reaction

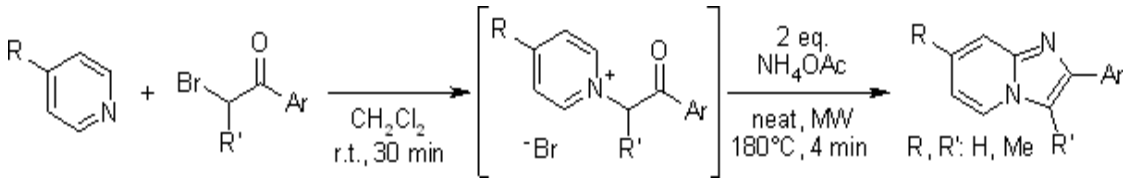
One of the most important aspects of microwave energy is the rate at which it heats. Microwaves will transfer energy in 10-9 seconds with each cycle of electromagnetic energy. The kinetic molecular relaxation from this energy is approximately 10-5 seconds. This means that energy transfers at a faster rate than the molecules can relax, which results in non- equilibrium conditions and high instantaneous temperatures that affect the kinetics of the system. This leads to enhancement in reaction rates and product yields. In the Arrhenius reaction rate equation (k=Ae-Ea/RT), the reaction rate constant is dependent on two factors: the frequency of collisions between molecules that have the correct geometry for a reaction to occur (A), and the fraction of those molecules with the minimum energy required to overcome the activation energy barrier (e-a/RT). It would be worthwhile to note that microwaves neither influence the orientation of collisions nor the activation energy – activation energy remains constant for each particular reaction. However, microwave energy affects the temperature parameter in this equation. An increase in temperature causes greater movement of molecules, which leads to a greater number of energetic collisions. This occurs much faster with microwave energy due to high instantaneous heating of the substance(s) above the normal bulk temperature, and is the primary factor for observed rate enhancements. Microwave heating is extremely useful in slower reactions where high activation energy is required.

Stuerga discovered that when the reaction involving the addition of the sulphonic acid group to naphthalene was exposed to microwaves, the selectivity of the reaction for 1-

naphthalene sulphonic acid (1- NSA) or 2- naphthalene sulphonic acid (2- NSA) could be controlled. It was observed that the rate at which the sample was heated determined the concentration of the products. An interesting fact that emerged from this reaction was that the effect of conventional heating and microwave radiation on the concentration of end products was identical. Therefore, it was concluded that microwave heating does not change the kinetics of the reaction

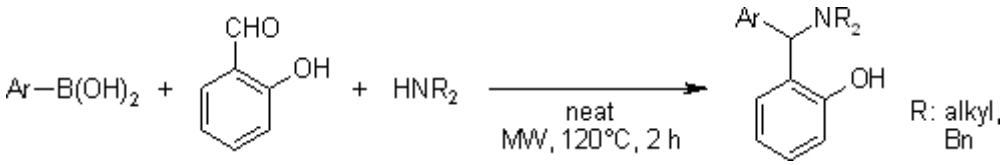
1.4. Reviews on Microwave Synthesis

N-Phenacylpyridinium bromides [34], which were prepared in situ from the addition of pyridines to α-bromoketones, undergo nucleophilic addition of ammonium acetate under microwave irradiation and solvent-free conditions to afford the corresponding imidazo[1,2- *a*]pyridines in excellent yields.



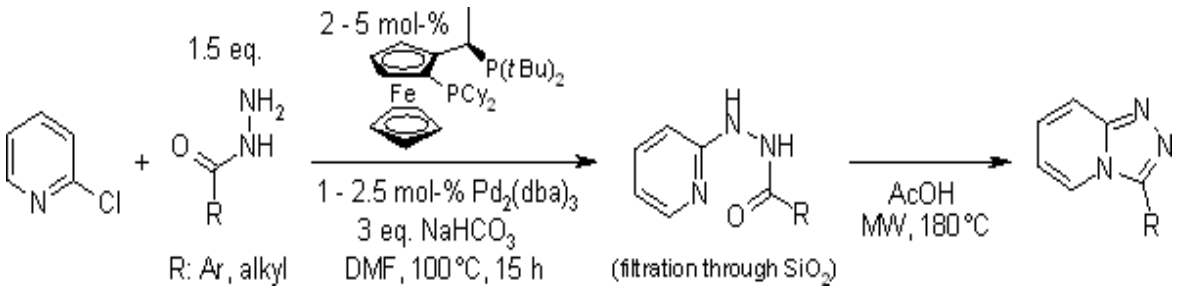
Scheme 10

Borono-Mannich reactions [35] can be performed in solvent-free conditions under microwave irradition with short reaction time. Full conversion of the starting materials towards the expected product was achieved, starting from stoichiometric quantities of reactants, avoiding column chromatography. No purification step other than an aqueous washing was required.



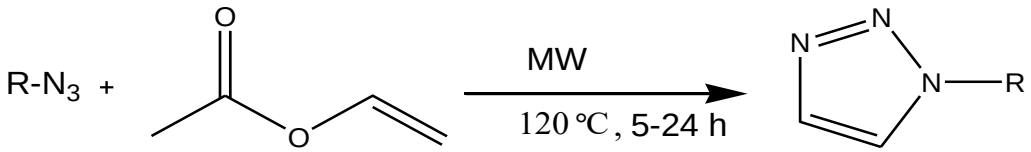
Scheme 11

An efficient and convenient synthesis of 1,2,4-triazolo [4,3-*a*]pyridines [36] involves a palladium-catalyzed addition of hydrazides to 2-chloropyridine, which occurs chemoselectively at the terminal nitrogen atom of the hydrazide, followed by dehydration in acetic acid under microwave irradiation.



Scheme 12

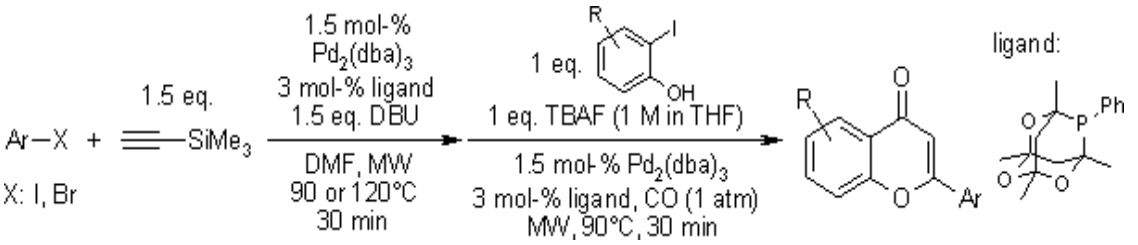
1-Monosubstituted 1,2,3-triazoles [37] have been prepared by a reaction of azides with vinyl acetate under microwave irradiation. Additionally, a microwave-assisted, two-step, one-pot procedure from halides involving azide substitution using $TBAN_3$ in diethyl ether, followed by reaction with vinyl acetate, has effectively been employed.



R: benzyl, alkyl

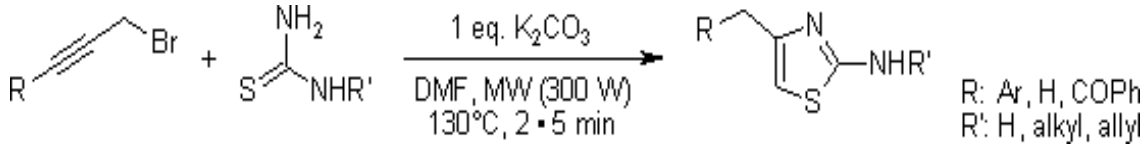
Scheme 13

A palladium complex of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane [38] is an effective catalyst for a sequential microwave-assisted Sonogashira and carbonylative annulation reaction to give substituted flavones.



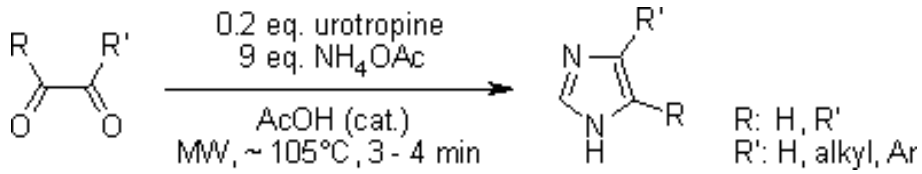
Scheme 14

A domino alkylation-cyclization [39] reaction of propargyl bromides with thioureas and thio- pyrimidinones allows the synthesis of 2-aminothiazoles and 5*H*-thiazolo[3,2-*a*]pyrimidin-5- ones, respectively. Domino reactions were performed under microwave irradiation leading to desired compounds in a few minutes and high yields.



Scheme 15

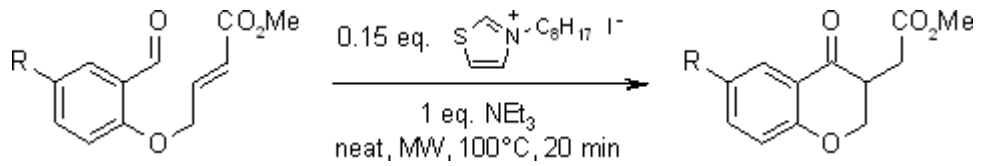
Starting from 1,2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solventless microwave-assisted [41] enabled the synthesis of 4,5-disubstituted imidazoles.



Scheme 17

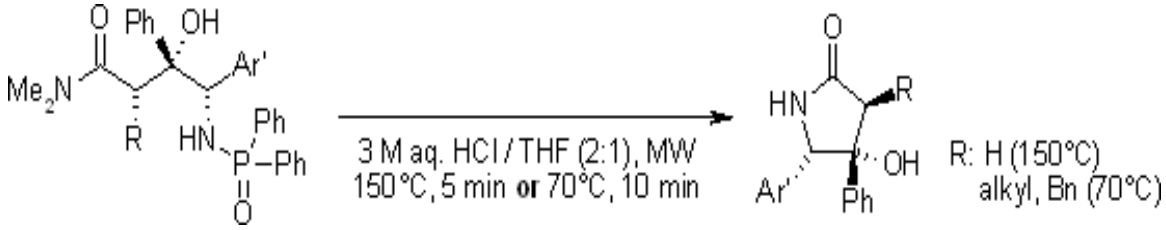
Alkylthiazolium-based ionic liquids, which can be synthesized under green conditions [42] and triethylamine have been found to catalyze efficiently the intramolecular Stetter reaction, giving excellent yields within very short reaction times using solvent-free

microwave activation conditions.



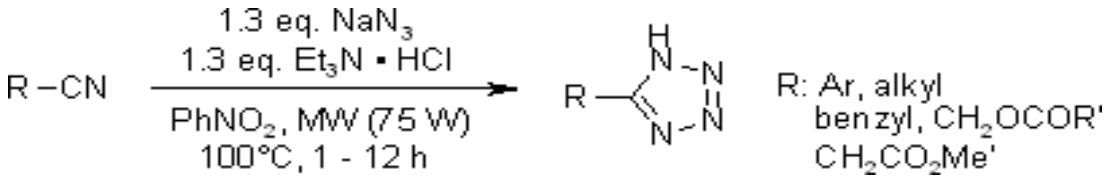
Scheme 18

Addition of amide enolates to acylsilanes generates β-silyloxy homoenolates [43] by undergoing a 1,2-Brook rearrangement. These unique nucleophiles formed in situ can then undergo addition to alkyl halides, aldehydes, ketones, and imines. γ-Amino-β-hydroxy amide products derived from a diastereoselective addition to *N*-diphenylphosphinyl imines can be efficiently converted to γ-lactams.



Scheme 19

5-Substituted tetrazoles [44] were prepared in very good yields and short reaction times by treatment of nitriles with sodium azide and triethylammonium chloride in nitrobenzene in a microwave reactor. Even sterically hindered tetrazoles, as well as those deactivated by electron-donating groups, can be prepared.



Scheme 20

1.5. Benefits of MW-assisted Synthesis

- Higher temperatures (superheating / sealed vessels)
- Faster reactions, lesser by products, pure compounds
- Selective heating *I* activation of catalysts
- Energy efficient, rapid energy transfer
- Easy access to high pressure performance
- Rapid synthesis results in lesser evaporation of solvents

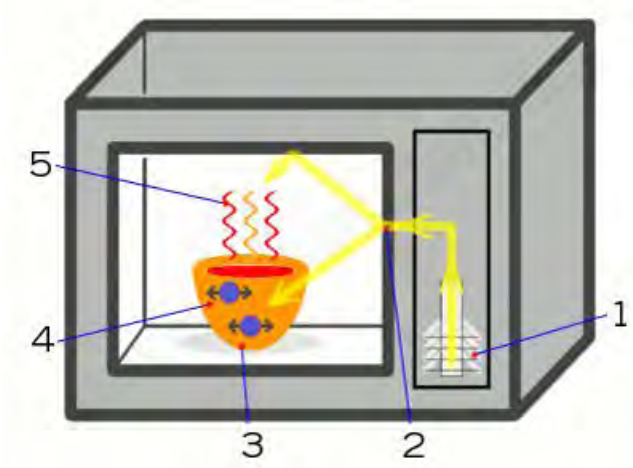


Fig 4: Microwave Oven

1.6. Objective Of the research work

Literature view shows heterocyclic compounds cover a broader area of chemotherapeutic. Heterocyclic compounds have always been on the forefront of attention because of their numerous uses in pharmaceutical applications [45,46]. Among them, nitrogen-containing heterocyclic compounds have maintained the interest of researchers and their unique structures have led to several applications in different areas. Quinazolinones are important heterocycles with wider range of microbial activities such as anti-malarial, anti-cancer, anti-inflammatory, anti-hypertensive, anti-convulsant, anti-HIV, etc. These compounds have been synthesized from various precursors by adopting different methods. Many of the existing methods involve expensive reagents stoichiometric amount of catalyst, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation and environmental pollution. Therefore, there is a need for versatile, simple and environmentally friendly processes for the synthesis of quinazoline derivatives. The development of alternative methods would extend the scope of the useful Biginelli reaction. One of such methods is microwave irradiation technology which is eco-friendly and environment friendly.

However, these conventional and microwave methodologies are associated with various drawbacks, like the reaction conditions, availability of reagents and chemical hazards. The synthesis of highly bioactive quinazoline compounds from simple and easily available reagents under microwave irradiations has been adopted in present synthesis. Except production of water vapour, the reaction is hundred percent atoms economic and therefore green in nature.

With this background we carried out the reactions of aldehydes, cyclohexanone and urea/thio-urea, catalyzed by iron chloride in the laboratory under microwave irradiation under solvent free conditions.

The aim and objective of the present work are:

- To find out synthetic process which is simple, economic, fast and environmentally friendly.

- To carry out the reactions under microwave irradiation using a low cost domestic microwave oven (a common household appliance of today)
- To use mild Lewis acid like iron chloride as catalyst which is inexpensive and easily available.
- To compare the synthesis of Quinazolines qualitatively and quantitatively under conventional condition and Microwave Condition.
- To identify the mode of purification, identification and characterization of the synthesized Quinazolines.

Chapter 2
Experimental

2.1. Materials and instruments

2.1.1. Chemicals and reagents

The chemicals and reagents used in this research were analytical grade and commercial grade.

The chemicals and reagents which were used in this research are given below:

1. Ethanol
2. Acetone
3. n-hexane
4. Methyl cyclohexanone
5. 4-Hydroxy benzaldehyde
6. 4-Chloro benzaldehyde
7. O-tolualdehyde
8. P-Anisaldehyde
9. Chloroform
10. TLC plate

2.1.2. Instruments

The synthesized diamides and catalysed were analysed using the following instruments:

- UV-visible Spectrophotometer (Shimadzu-1800)
- Fourier Transform Infrared Spectrophotometer (SHIMADZU FTIR-8400)
- Nuclear Magnetic Resonance Spectrometer (Bruker BPX- 400)
- Gas Chromatography Mass Spectrometer (SHIMADZU GCMS)
- Centrifuge machine (Model-800)
- Digital Balance (Precision electrical balance)
- Oven
- Rotatory evaporator
- UV-light

2.1.3. Purification technique

- Recrystallisation technique

Solid organic compounds when isolated from organic reactions are seldom pure; they are usually contaminated with small amounts of other compounds which are produced along with the desired product. The purification of impure crystalline compounds is effected by crystallization from a suitable solvent or mixture of solvents.

The purification of solid by crystallization is based upon differences in their solubility in a given solvent or mixture of solvents. In its simplest form, the crystallization process consists of; (1) dissolving the impure substance in some suitable solvent at or near the boiling point; (2) filtering the hot solution from particles of insoluble material and dust; 3) allowing the hot s solution to cool thus causing the dissolved substance to crystallize out (4) separating the crystals from the supernatant solution (or mother liquer).

The resulting solid after drying is tested for purity (usually by a melting temperature determination or by thin layer chromatography).

The theory underlying the removal of impurities by crystallization may be from the following considerations. It is assumed that the impurities are present in comparatively all proportion - usually less than 5 percent of the whole. Let the pure sulbstance be denoted by A and the impurities by B, and let the portion of the later be 5 percent. In most instances the solubilities of A (S_A) and of B(S_B) are different in a particular solvent : the influence of each compound upon he solubility of other will be neglected. Two cases will be arise for any particular solvent: (i) the impurity is more soluble than the compound which is being purified ($S_B > S_A$) and, (ii) the impurity is less than the compound ($S_B < S_A$). It is evident that in case (i) several recrystallisation will give pure sample of A, and B will remain in the mother-liquor. Case (ii) can be more clearly illustrated by a specific example.

- Preparatory HPLC

HPLC is used to separate and refine high-purity target compounds from a mixed solution after a synthesis reaction. An HPLC preparative system must offer different capabilities from a normal analysis system. It is used to fraction high-purity (and in some cases large quantities of) compounds required for subsequent evaluation, analysis, and processes in the shortest possible time. A semi- or large-scale preparative system

uses a lot of solvent, so that measures must be taken to cope with liquid leaks. For example, position a tray below the plunger head to cope with liquid leaks from the pump plunger seal. Take special care if using a flammable solvent. Recommended measures include not positioning equipment that is a potential ignition source nearby and grounding the drain tank to prevent ignition due to static electricity.

2.2. General Experimental

Melting points were determined in open capillary tubes in melting point apparatus.IR spectra were recorded on a Shimadzu FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrophotometer (400MHz) using tetramethylsilane as internal reference. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60F-254(E. Merck), and the spots were visualized with UV light.

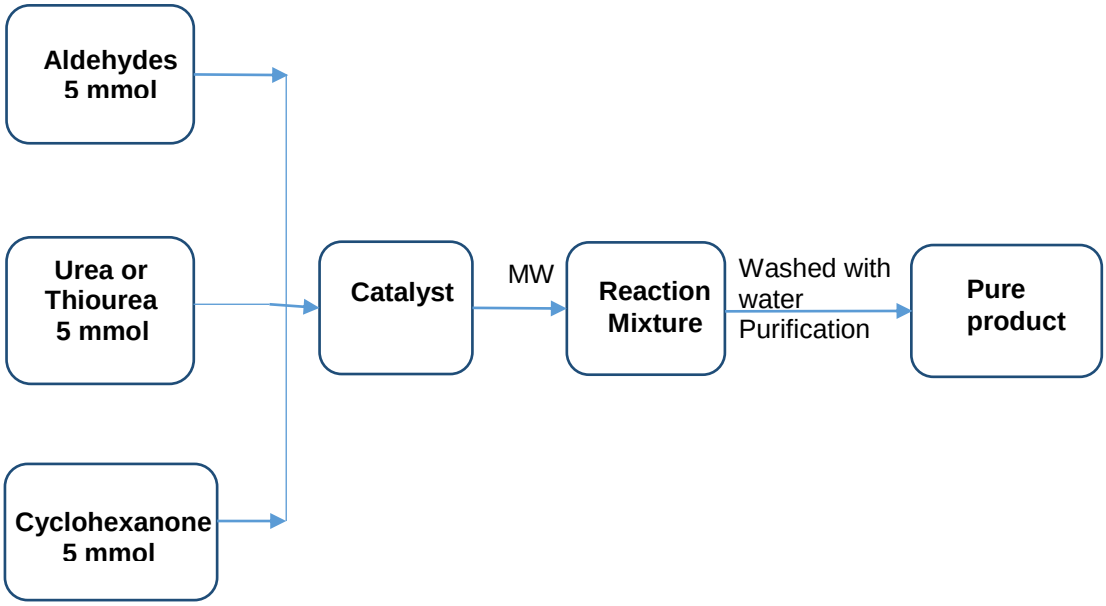


Fig 5: Quinazoline synthesis

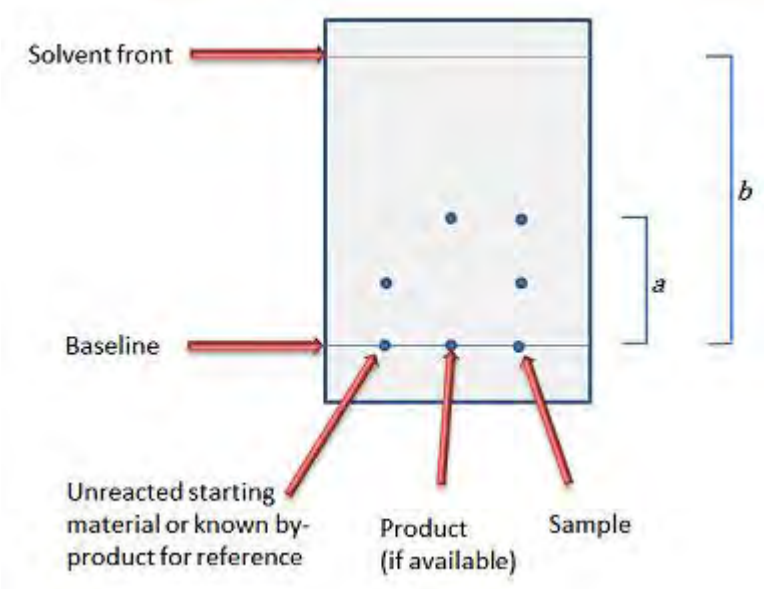
Fig 6: Reactor

Fig 7: Domestic Microwave oven

Chromatographic techniques

Thin layer chromatography (TLC) is a chromatographic technique used to separate the components of a mixture. In planar chromatography in particular, the retardation factor R_f is defined as the ratio of the distance traveled by the center of a spot to the distance traveled by the solvent front.

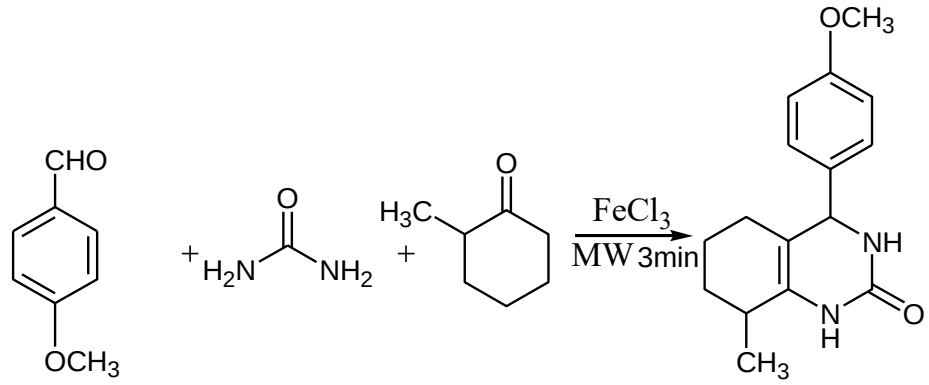
$$R_f = \frac{Distance\ traveled\ by\ the\ solute}{Distance\ traveled\ by\ the\ solvent}$$



$$R_f = \frac{a}{b}$$

2.2.1. Synthesis of 4-(4-Methoxy-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro 1H-quinazolin-2-one

A mixture of 4-Methoxybenzaldehyde (5mmol), 2-Methylcyclohexanone(5mmol), Urea(5mmol) and $FeCl_3$ (2mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600watt for 3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [solvent: hexane: chloroform (1:1)]. After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re-crystallization (ethyl acetate: hexane) to give pure compound (1).



Scheme 21: Synthesis of 4-(4-Methoxy-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro 1H-quinazolin-2-one

Table 2: Optimization of reaction condition

Condition	MW (watt)	Time (min)	Yield(%)
1	400	3.00	65
2	600	3.00	80
3	800	3.00	70

Physical state : White crystalline solid.

Yeild : 80 %

Molecular Formula : $C_{16}H_{20}N_2O_2$

Molecular Weight : 272.15

Melting Point : 273-275 ^oC

Purification :

- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

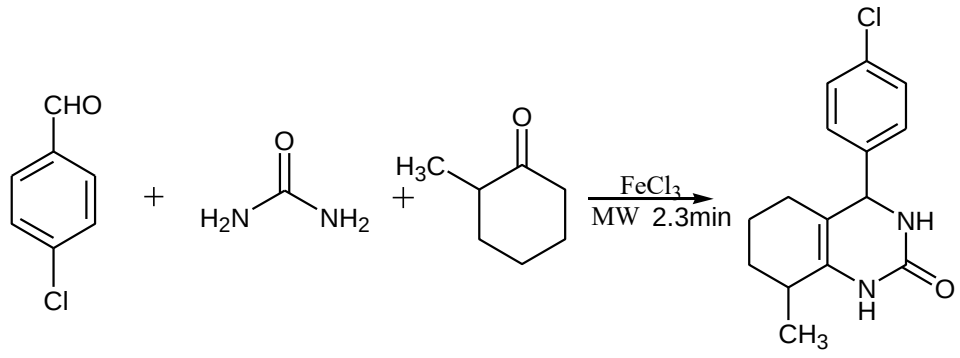
IR (KBr) : v max 3250, 2927, 1667, 1608, 1176

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06-6.99 (m, 4H, Ar), δ 6.89 (s, 1H, NH), 6.87(s, 1H, -NH), 3.89 (s, 3H, -OCH3) 3.81 (s, 1H, CH),2.39 (1H, -CH), 1.28 (s, 3H, -CH3)

^{13}CNMR (100 MHz, $CDCl_3$): δc 159 (C-9), 154 (C-17), 131 (C-7), 130 (C-15), 127 (C-12), 127 (C-13), 114 (C-6), 113 (C-16), 55 (C-18), 30 (C-11), 28 C-2), 27 (C-3), 22 (C-4), 17 (C-1)

2.2.2. Synthesis of 4-(4-Chloro-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

A mixture of 4-Chlorobenzaldehyde (5 mmol), 2-Methylcyclohexanone (5 mmol) urea (5 mmol) and $FeCl_3$ (2 mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600 watt for 2.3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [solvent ; hexane : chloroform (1:1)]. After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re-crystallization (ethyl acetate : hexane) to give pure compound (2).



Scheme 22 : Synthesis of 4-(4-Chloro-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

Table 3: Optimization of reaction condition

Condition	MW (watt)	Time (min)	Yield(%)
1	400	2.30	70
2	600	2.30	83
3	800	2.30	75

Physical state : White crystalline solid.

Yeild : 83 %

Molecular Formula : $C_{15}H_{17}ClN_2O$

Molecular Weight : 276.10

Melting Point : 272-275 ^oC

Purification :

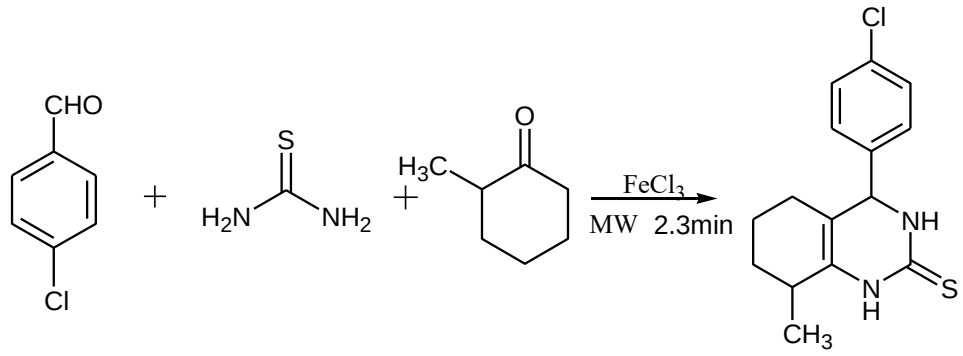
- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

IR(KBr) : ν_{max} 3210, 2962, 1712, 1682, 1376,1201

Mass spectroscopic data (ESI^+ m/z): 276.1(M^+), 262.1, 246.1, 221.2

2.2.3. Synthesis of 4-(4-Chloro-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-thione

A mixture of 4-Chlorobenzaldehyde (5mmol), 2-Methylcyclohexanone (5mmol), thiourea (5mmol) and $FeCl_3$ (2mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600 watt for 2.3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [solvent: hexane : chloroform (1:1)].After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re- crystallization (ethyl acetate : hexane) to give pure compound (3).



Scheme 23 : Synthesis of 4-(4-Chloro-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-thione

Table 4: Optimization of reaction condition

Condition	MW (watt)	Time (min)	Yield (%)
1	400	2.30	70
2	600	2.30	83
3	800	2.30	75

Physical state : White crystalline solid.

Yeild : 78 %

Molecular Formula : $C_{15}H_{17}ClN_2S$

Molecular Weight : 292.08

Melting Point : 271-273 ^oC

Purification :

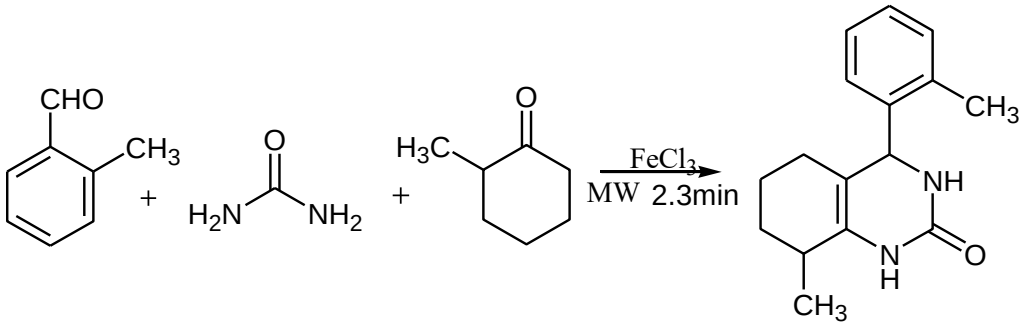
- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

IR(KBr) : ν_{max} 3308, 2929, 1654, 1607,1302 cm^{-1}

Mass spectroscopic data (ESI^+ m/z): 291(M^+), 279, 207, 147

2.2.4. Synthesis of 4-(2-Methyl-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

A mixture of o-Tolualdehyde (5mmol), 2-Methylcyclohexanone (5mmol), Urea (5mmol) and $FeCl_3$ (2mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600 watt for 2.3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [stationary phase: silica gel, solvent: hexane : chloroform (1:1)]. After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re- crystallization (ethyl acetate : hexane) to give pure compound (4).



Scheme 24: Synthesis of 4-(2-Methyl-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

Table 5: Optimization of reaction condition

Condition	MW (watt)	Time (min)	Yield (%)
1	400	2.30	70
2	600	2.30	83
3	800	2.30	75

Physical state : White crystalline solid.

Yeild : 83 %

Molecular Formula : $C_{16}H_{20}N_2O$

Molecular Weight : 256.16

Melting Point : 273-275 ^oC

Purification :

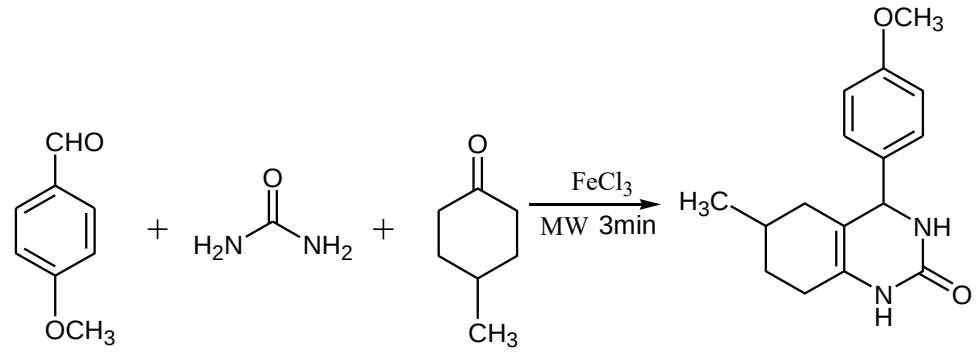
- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

IR(KBr) : ν_{max} 3325, 2929, 1703, 1607, 1251cm^{-1}

Mass spectroscopic data (ESI^+ m/z): 256.1(M^+), 226.1 (M^+-30), 170.1 (M^+-86)

2.2.5. Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

A mixture of 4-Methoxybenzaldehyde (5mmol), 4-Methylcyclohexanone (5mmol), Urea (5mmol) and $FeCl_3$ (2mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600 watt for 2.3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [stationary phase: silica gel, solvent: hexane : chloroform (1:1)]. After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re- crystallization (ethyl acetate : hexane) to give pure compound (5).



Scheme 25: Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3,4,5,6,7,8-hexahydro-1H-Quinazolin-2-one

Table 6: Optimization of reaction condition

Condition	MW(watt)	Time(min)	Yield(%)
1	400	2.30	70
2	600	2.30	82
3	800	2.30	75

Physical state : White crystalline solid.

Yeild : 82 %

Molecular Formula : $C_{16}H_{20}N_2O$

Molecular Weight : 272.15

Melting Point : 272-274 ^oC

Purification :

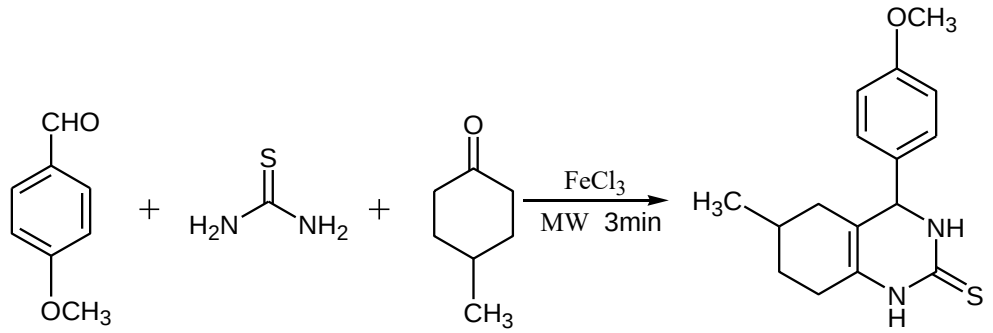
- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

IR(KBr) : ν_{max} 3325, 2929, 1703, 1607, 1251cm^{-1}

Mass spectroscopic data (ESI^+ m/z) : 271.1(M^+), 257.1, 230.1, 195.1

2.2.6. Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione

A mixture of 4-Methoxybenzaldehyde (5mmol), 4-Methylcyclohexanone (5mmol), Thiourea (5mmol) and $FeCl_3$ (2mmol) was put on the microwave oven in the flask along with a beaker of ice, and the mixture was irradiated at 600 watt for 2.3 min. The reaction was carried out in a special microwave resistant glass ware. The progress of the reaction was followed by TLC [stationary phase: silica gel, solvent: hexane: chloroform (1:1)]. After completion of the reaction, the reaction mixture was poured into water. The precipitate was filtered under suction on a Buchner funnel and successively washed with water to remove completely any remaining starting compound. The crude product was then purified by re- crystallization (ethyl acetate: hexane) to give pure compound (6).



Scheme 26: Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione

Table 7: Optimization of reaction condition

Condition	MW (watt)	Time (min)	Yield (%)
1	400	3.00	65
2	600	3.00	80
3	800	3.00	70

Physical state : White crystalline solid.

Yeild : 80 %

Molecular Formula : $C_{16}H_{20}N_2OS$

Molecular Weight : 288.13

Melting Point : 275-257 ^oC

Purification :

- Re- crystallization (ethyl acetate: hexane) to give pure Compound
- Preparatory HPLC also used to give highly pure compound where HPLC grade ethanol act as a mobile phase.

IR (KBr) : ν_{max} 3201, 2942, 1662, 1605, 1245, 1021cm^{-1}

Mass spectroscopic data (ESI^+ m/z): 288.1 (M^+), 260.1, 246.1

2.3. Characterization of synthesized product

2.3.1. UV-Visible spectrophotometer

The UV-Visible spectral analysis was performed with a double beam UV-Visible spectrophotometer. The analyses were involved within 200-800 nm range [47, 48]. For, UV-Vis spectral analyses, purified and dried quinazoline derivatives were dissolved in chloroform solvent. The dissolved sample was placed in the sample cuvette while the reference cuvette was filled with the corresponding solvents. All the analyses were performed at room temperature 30 °C (±2 °C).

2.3.2. Fourier transform infrared (FTIR) analysis

The infrared spectra of the synthesized diamides were recorded on an FT-IR spectrometer in the region of 4000-500 cm-1. All the samples had dried. A small portion of samples were taken and mixed with KBr [47, 48]. The powder mixtures were then compressed in a metal holder under pressure to make pellets. The pellets were then placed in the path of IR beam for measurements.

2.3.3. Nuclear magnetic resonance (NMR) analysis

^{1}H and ^{13}C-NMR spectra were recorded by Bruker BPX- 400 spectrometer operating at 400 MHz and 100 MHz respectively and $CDCl_3$ used as solvent, tetramethylsilane (TMS) as an internal standard. All chemical shifts (δ) were reported in ppm and coupling constants (J) in Hz. Chemical shifts were performed relative to tetramethylsilane (TMS) and d-solvent peaks (7.28 ppm in ^{1}H and 77.00 ppm in ^{13}C, chloroform), respectively[47, 48].

2.3.4. Gas chromatography mass spectrum (GC-MS) analysis

Retention time and mass spectrum for quinazoline derivatives was recorded using column: Rxi-5ms, 30m, 0.25mm ID, 0.25µ df by Shimadzu GC-MS. To determine mass spectrum the molecule bombarded with high electron beam then form molecular ion again fragmentation of molecular ion occurs form many fragment ions.

2.3.5. Melting Point

Melting points of quinazoline derivatives were determined in open capillary tubes in melting point apparatus.

2.3.6. Solubility

All the quinazoline derivatives were soluble in chloroform.

2.4. Determination of antimicrobial activity

The antibacterial activity of the synthesized quinazoline compound were determined by discs diffusion method by measuring the diameter of the inhibitory zone in millimeter by a transparent scale. The tested compound solution were prepared in chloroform and evaluated them for their in vitro antibacterial and antifungal activity against Staphylococcus aureus, Escherichia coli, respectively. 0.1 ml culture of microbial culture was taken and spread plate technique on nutrient agar plate was applied. Spread the culture by using glass rod. Flame the glass rod before spreading the culture. After spreading the culture, 16 mm diameter disk placed on the plate which is soaked with intended compound with different concentration (1 ppm, 5 ppm, 10 ppm). Incubate the plate at 37 ^{o}C for 24 hours than investigate the plate for inhibition zone and measure the diameter of inhibition zone.

Fig 8: Nutrient agar media

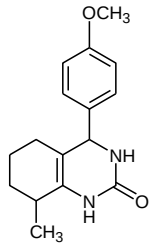
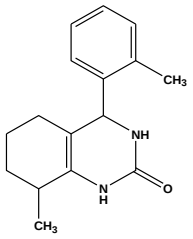
Fig 9: Zone of Inhibition exhibited by 4-(4-Methoxy-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro 1H-quinazolin-2-one(5ppm) against *Escherichia coli* .

Fig 10: Zone of Inhibition exhibited by 4-(4-Methoxy-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro 1H-quinazolin-2-one(10 ppm) against *Escherichia coli* .

Fig 11: Zone of Inhibition exhibited by 4-(4-Methoxy-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro 1H-quinazolin-2-one(5 ppm) against *Staphylococcus aureus* .

Fig 12: Zone of Inhibition exhibited by 4-(4-Methoxy-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro 1H-quinazolin-2-one(10 ppm) against *Staphylococcus aureus* .

Table 8: In Vitro antimicrobial activity of Quinazoline derivatives:

Compound	E-coli	S-Aureus
	+	++
	+	++

*Effectively was classified in to three zones on the bases of the diameter of zone of inhibition

++ : Moderate effective

+ : Slightly effective

Chapter 3

Result and Discussion

3.1. Result and Discussion

3.1.1. Characterization of 4-(4-Methoxy-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro 1H-quinazolin-2-one

i) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3250 (N-H Stretching),
- 2927 (C-H, Stretching
- 1667 (C=C, Stretching)
- 1608 (C=O, Stretching)
- 1176 (C-N, Stretching)

ii) ^{1}H-NMR spectroscopy:

The 1H-NMR spectrums (Fig.3., Page no. 68) of the diamide-4 exhibited signals (in δ ppm) which were assigned as follows:

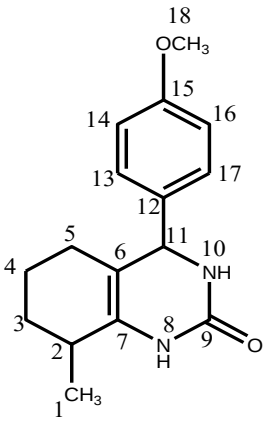
- δ 7.06-6.99 (m, 4H, Ar)
- δ 6.89 (s, 1H, NH)
- δ 6.87 (s,1H, NH)
- δ 3.89 (s, 3H, -OCH3)
- δ 3.81 (s, 1H, CH)
- δ 2.39 (1H, -CH)
- δ 1.28 (s, 3H ,-CH3)

iii) ^{1}H-NMR spectroscopy:

In the ^{13}CNMR spectrum (Fig. 4) the compound showed the chemical shift at

- δ 159 (C-9)
- δ 154 (C-17)
- δ 131 (C-7)
- δ 130 (C-15)
- δ 127 (C-12)
- δ 127 (C-13)
- δ 114 (C-6)
- δ 113 (C-16)
- δ 55 (C-18)
- δ 30 (C-11)
- δ 28 (C-2)
- δ 27 (C-3)
- δ 22 (C-4)
- δ 17 (C-1)

On the basis of the UV, IR, ^{1}H NMR, ^{13}CNMR and Mass spectrum data, the structure of this compound was assigned as



3.1.2. Characterization of 4-(4-Chloro-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro-1H-quinazolin-2-one

i) FT-infrared spectroscopy:

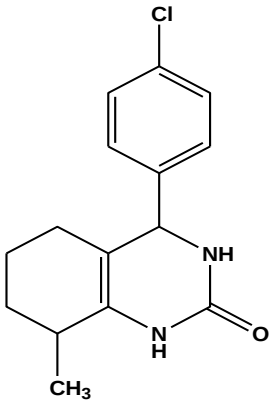
The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3210 (N-H Stretching)
- 2962 (C-H, Aromatic)
- 1712 (C=O, Stretching)
- 1682 (C=C, Stretching)
- 754 (C-Cl, Stretching)

ii) Mass spectrometry:

Mass spectroscopic data (ESI^+ m/z): 276.1(M^+), 275, 262.1, 246.1, 221.1

On the basis of the UV IR, and Mass spectrum data, the structure of this compound was assigned as



3.1.3 Characterization of 4-(4-Chloro-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro-1H-quinazolin-2-thione

i) FT-infrared spectroscopy:

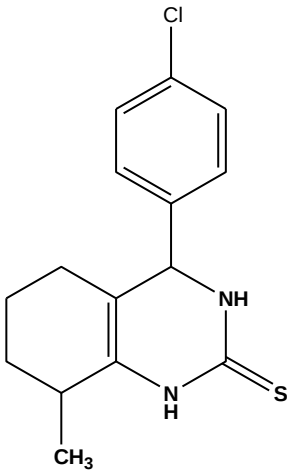
The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3308 (N-H Stretching)
- 2929 (C-H, Aromatic)
- 1654 (C=C, Stretching)
- 1251 (C=S, Stretching)
- 838 (C-Cl, Stretching)

ii) Mass spectrometry:

Mass spectroscopic data (ESI^+ m/z): 291(M^+), 279, 183, 147, 126

On the basis of the UV, IR and Mass spectrum data, the structure of this compound was assigned as



3.1.4 Characterization of 4-(2-Methyl-phenyl)-8-methyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-one

i) FT-infrared spectroscopy:

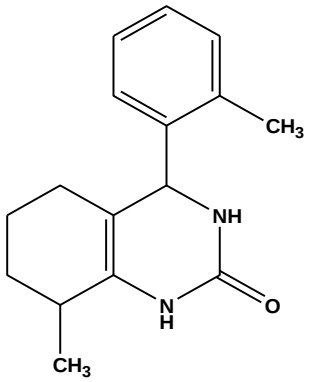
The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3325 (N-H Stretching)
- 2929 (C-H, Stretching)
- 1703 (C=O, Stretching)
- 1607 (C=C, Stretching)

ii) Mass spectrometry:

Mass spectroscopic data (ESI^+ m/z): 255.1(M^+), 241.1, 212.1, 184.1

On the basis of the UV, IR and Mass spectrum data, the structure of this compound was assigned as



3.1.5. Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3, 4, 5, 6, 7, 8-hexahydro-1H-quinazolin-2-one

i) FT-infrared spectroscopy:

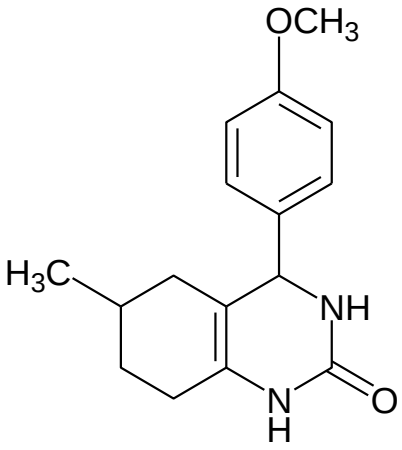
The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3210 (N-H, Stretching)
- 2907 (C-H, Stretching)
- 1707 (C=O, Stretching)
- 1607 (C=C, Stretching)

ii) Mass spectrometry:

Mass spectroscopic data (ESI^+ m/z): 272.1(M^+), 257.1, 230.1

On the basis of the UV, IR and Mass spectrum data, the structure of this compound was assigned as



3.1.6. Synthesis of 4-(4-Methoxy-phenyl)-6-methyl-3, 4, 5, 6, 7, 8-hexahydro-1H-quinazolin-2-thione

i) FT-infrared spectroscopy:

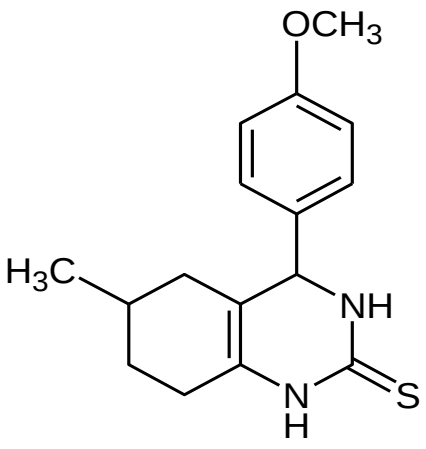
The FT-IR (KBr) spectrum (Fig. , Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- 3201 (N-H, Stretching)
- 2942 (C-H, Stretching)
- 1662 (C=C, Stretching)
- 1245 (C=S, Stretching)

ii) Mass spectrometry:

Mass spectroscopic data (ESI^+ m/z): 288.1(M^+), 246.1, 230.1

On the basis of the UV, IR and Mass spectrum data, the structure of this compound was assigned as



3.2. Antibacterial Activity of quinazoline derivatives

Table 9: Zone of inhibition exhibited by 4-(4-Methoxy-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro 1H-quinazolin-2-one:

Sl No	Bacterial Species	Zone of Inhibition (mm)		
		1 ppm	5 ppm	10 ppm
1	*Escherichia coli*	7	9	12
2	*Staphylococcus aureus*	9	10	14

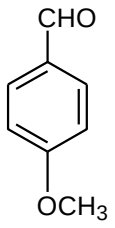
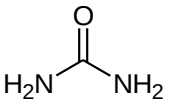
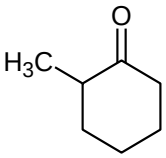
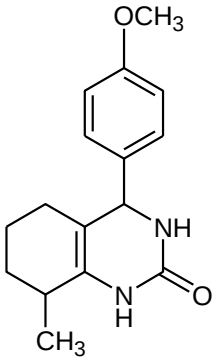
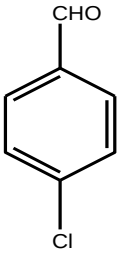
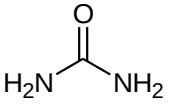
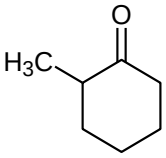
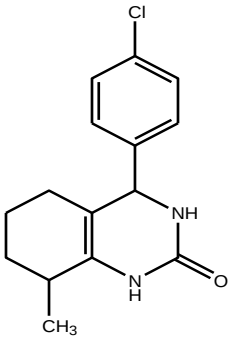
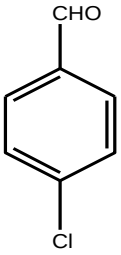
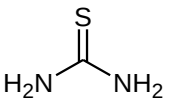
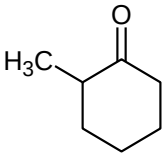
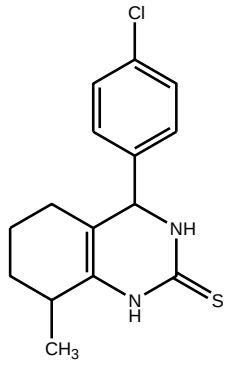
Table 10: Zone of inhibition exhibited by 4-(2-Methyl-phenyl)-8-methyl-3, 4, 5, 6, 7, 8-hexahydro-1H-quinazolin-2-one:

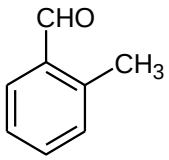
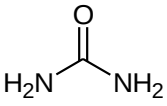
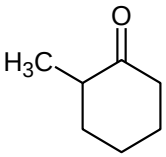
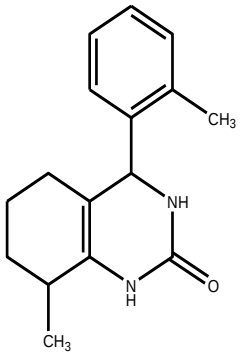
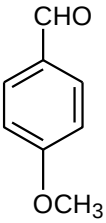
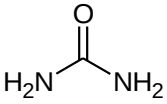
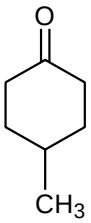
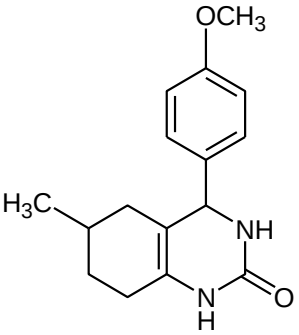
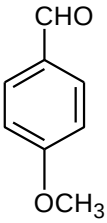
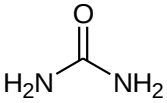
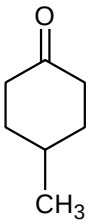
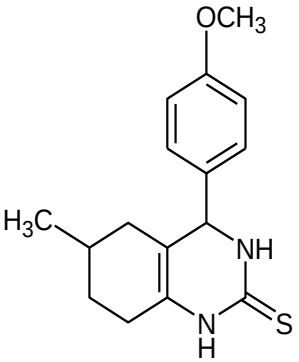
Sl No	Bacterial Species	Zone of Inhibition (mm)		
		1 ppm	5 ppm	10 ppm
1	*Escherichia coli*	8	10	13
2	*Staphylococcus aureus*	9	11	15

The entire synthesized compounds were tested for in vitro antimicrobial activity by the disk diffusion technique. The results are summarized in Table 2 that includes the activity of reference compound Ampicillin. The tested compound exhibited mild to moderate antibacterial activity against this two bacteria.

3.3. Summary

Table-11: The Synthesized 3, 4-dihydropyrimidin-2(1H)-ones/-thiones compounds are summarized below:

Entry	A	B	C	Product
a				
b				
c				

d				
e				
f				

Spectra

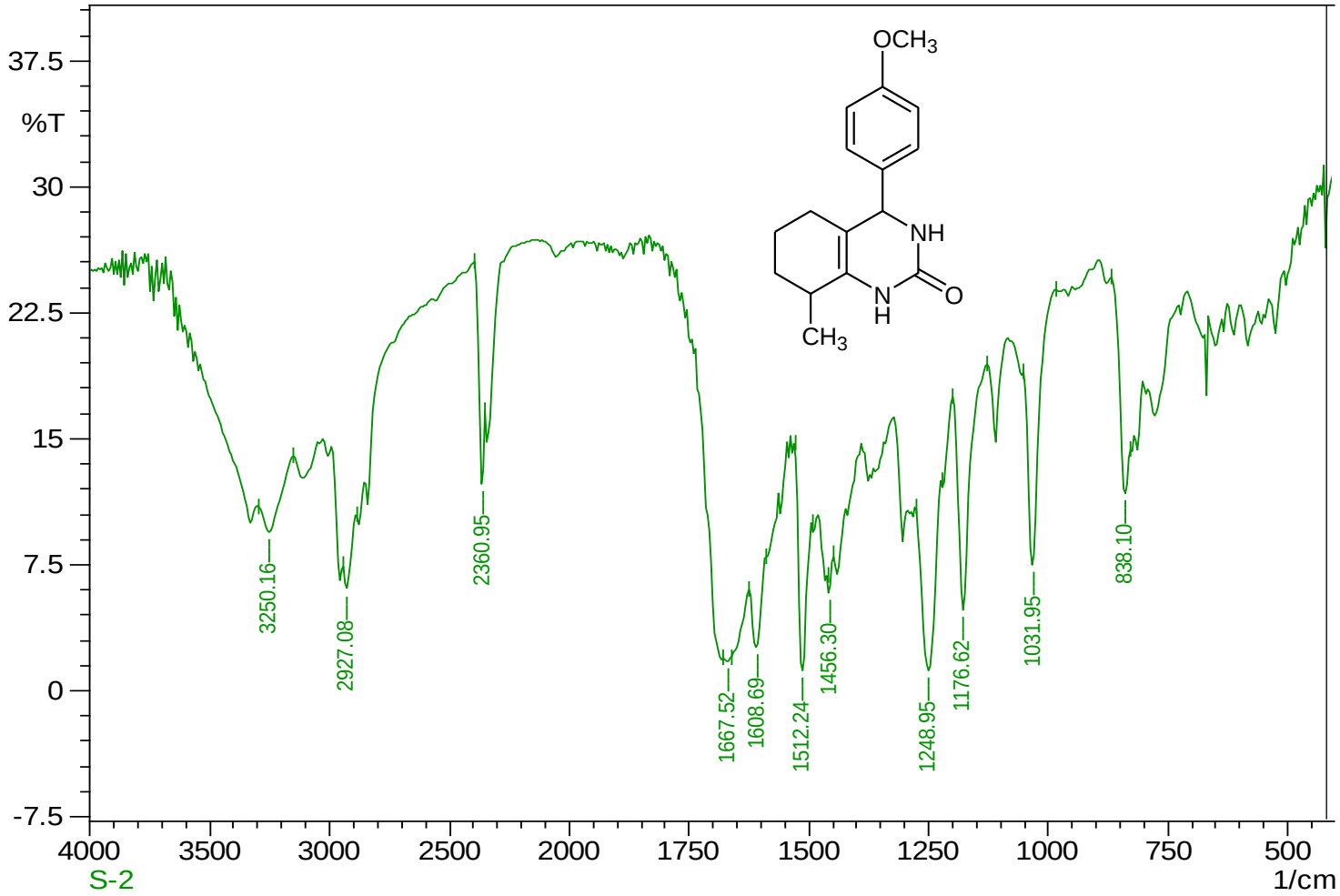


Fig 13: IR spectrum of compound (1)

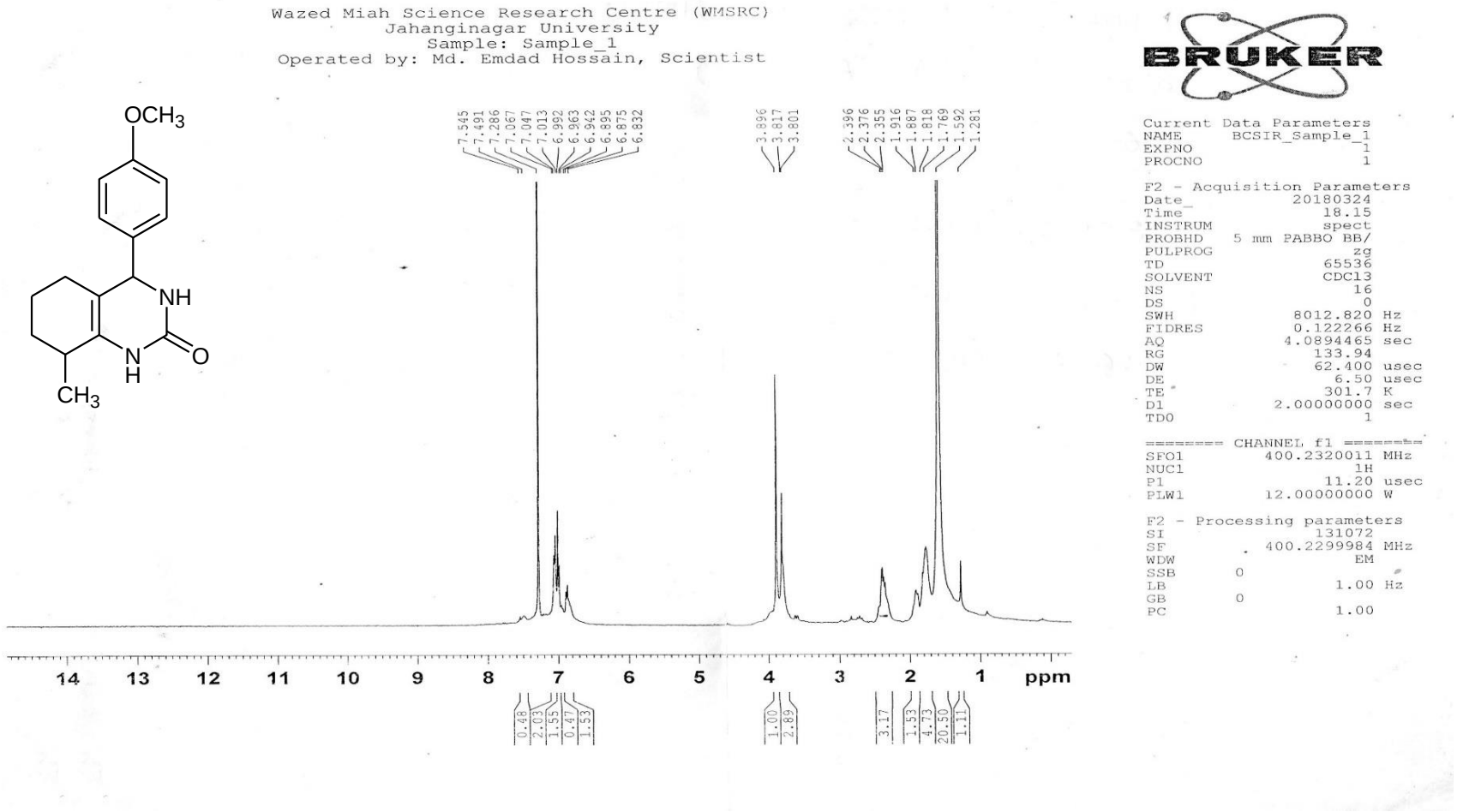


Fig 14 : ^{1}H-NMR Spectrum for Compound (1)

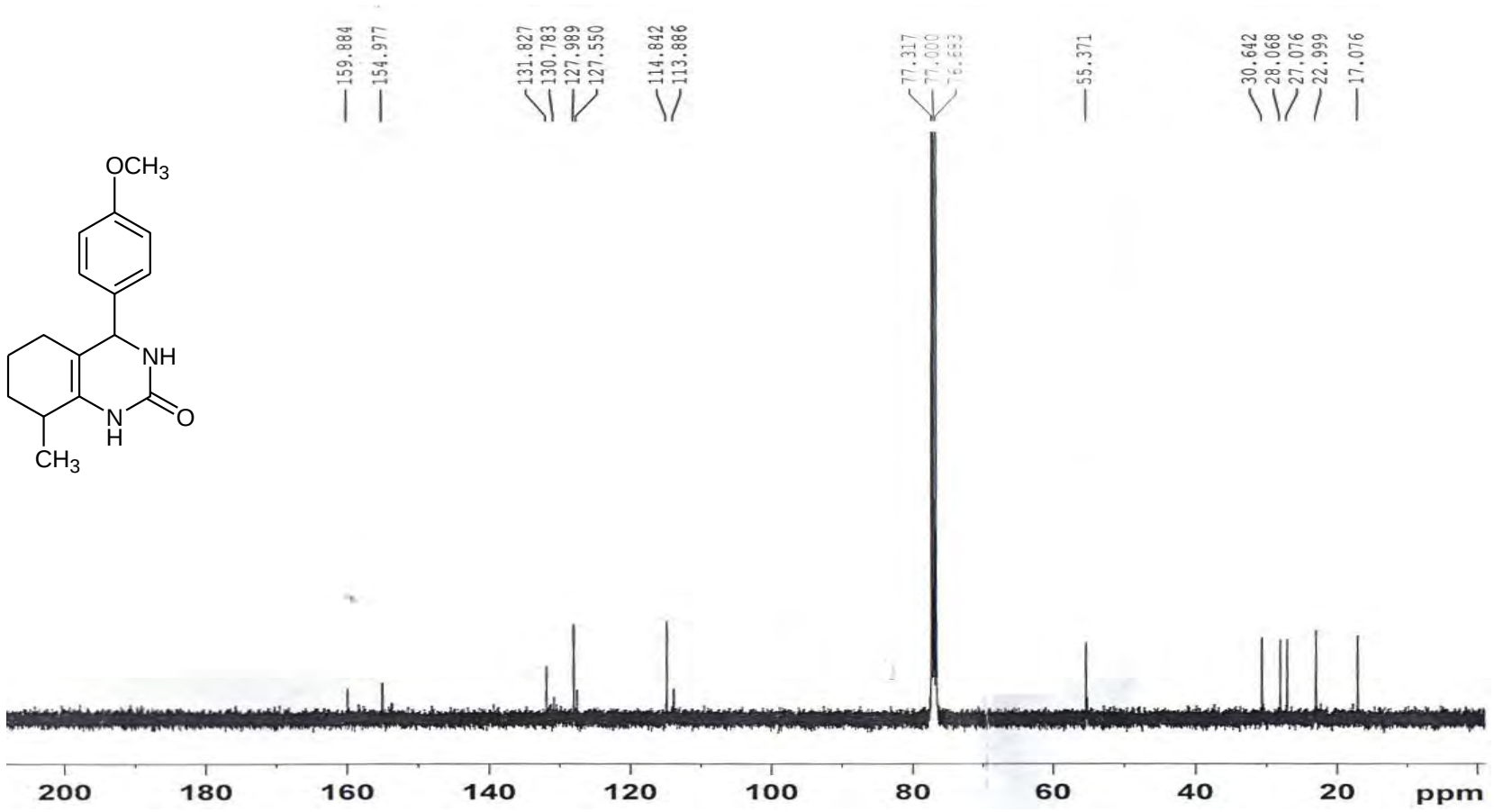


Fig 15 : ^{13}C-NMR Spectrum for Compound (1)

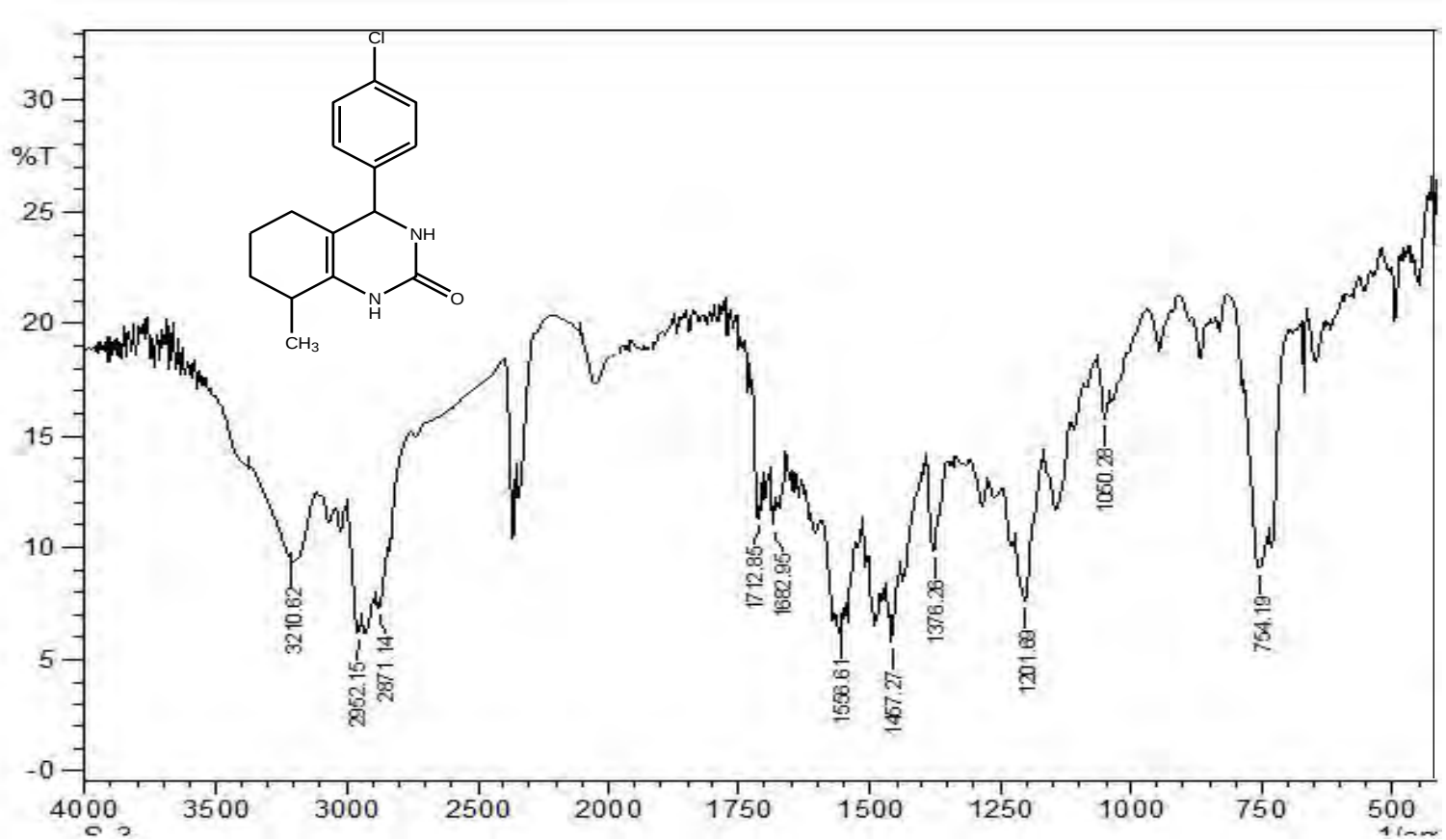


Fig 16: IR spectrum of compound (2)

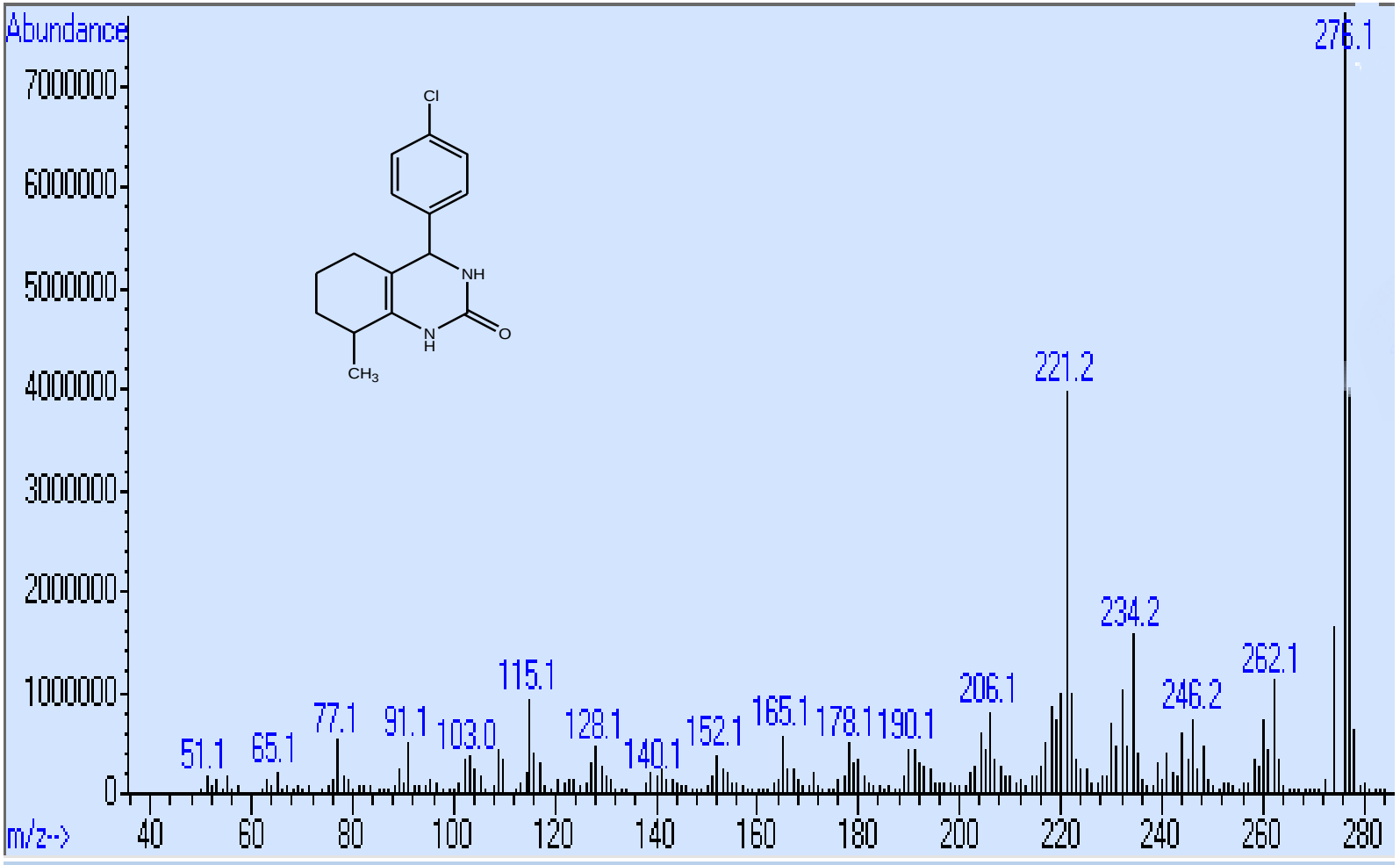


Fig 17: Mass spectrum for Compound(2)

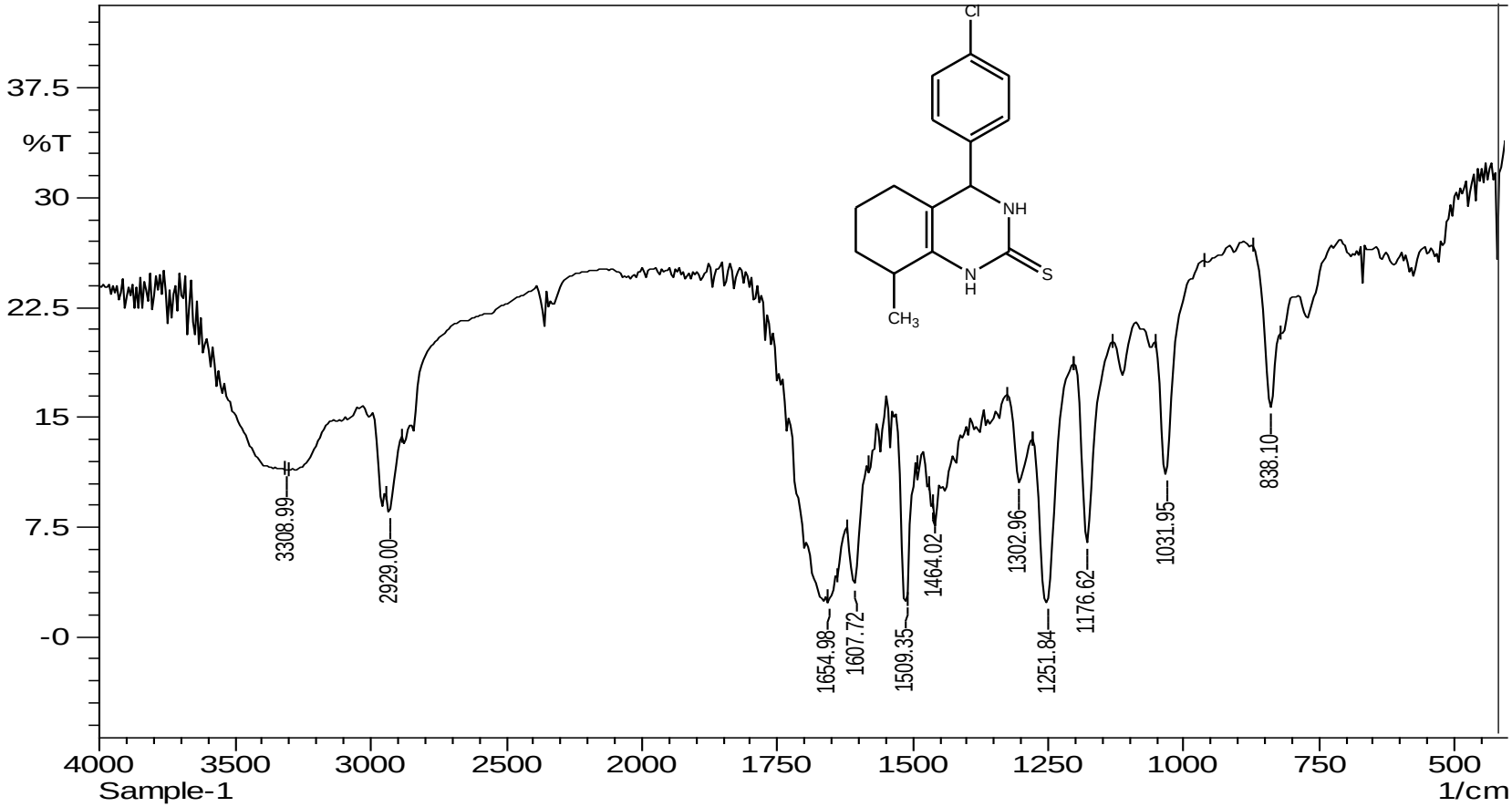


Fig 18: IR spectrum of compound (3)

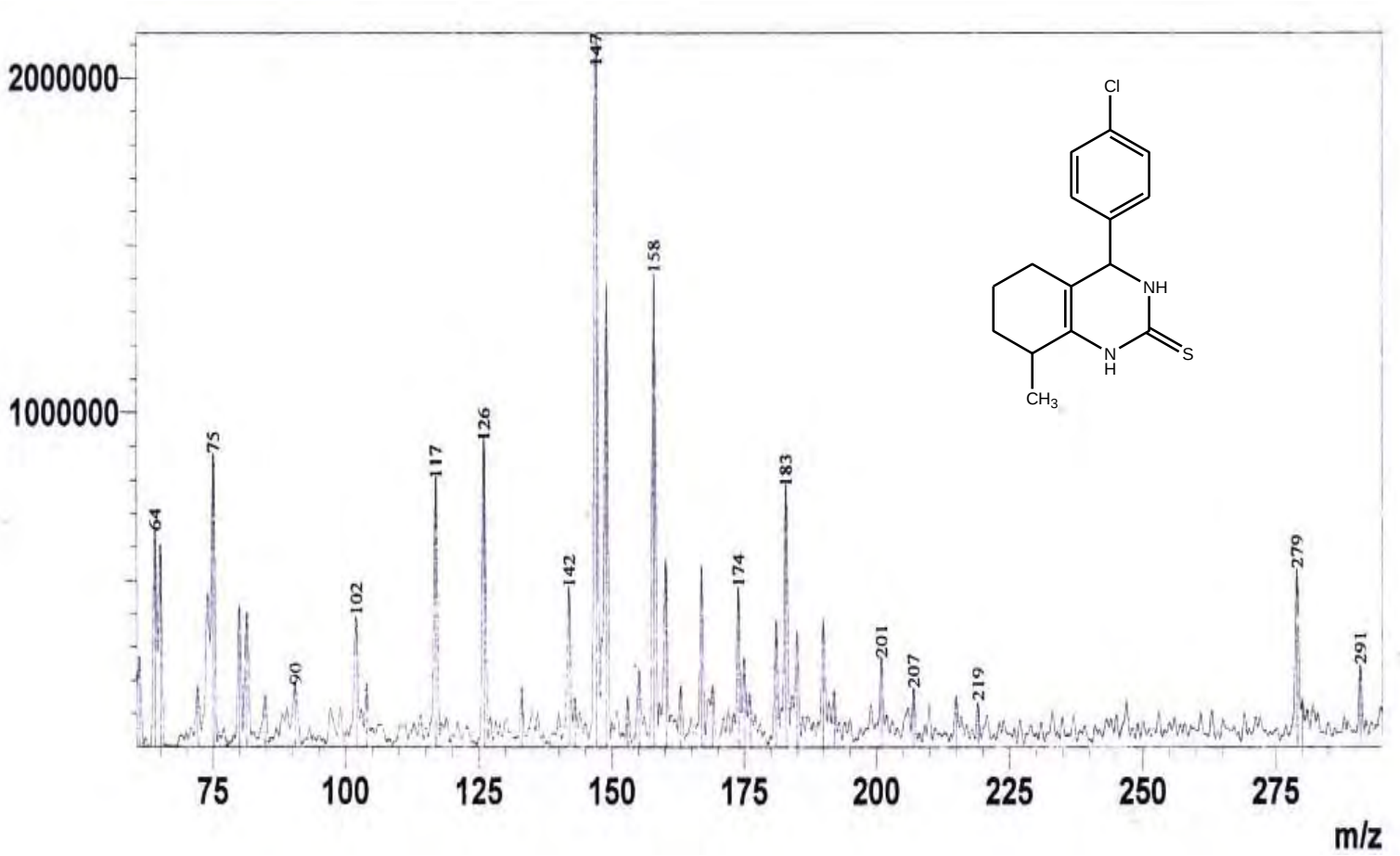


Fig 19: Mass spectrum for Compound (3)

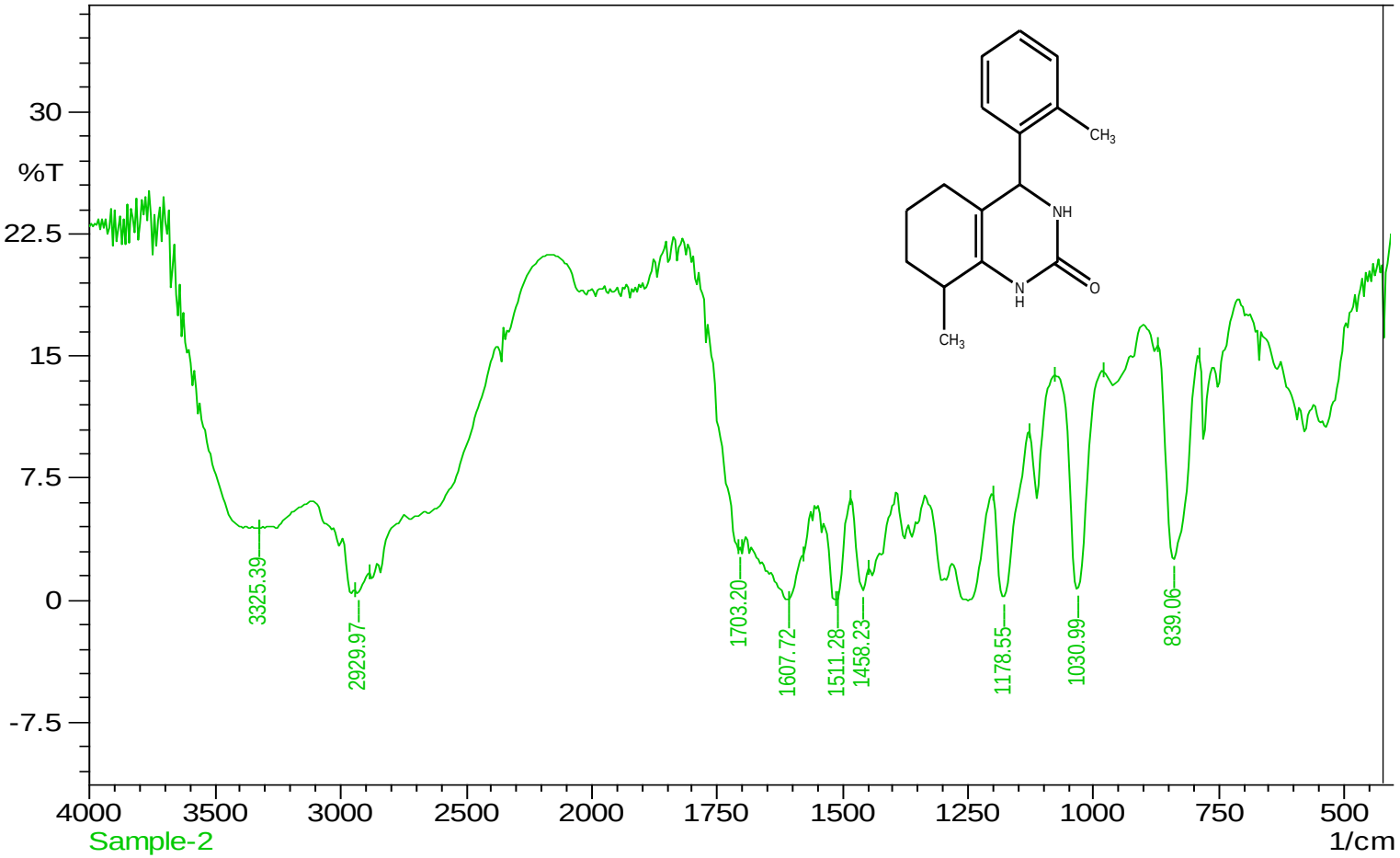


Fig 20: IR spectrum of compound (4)

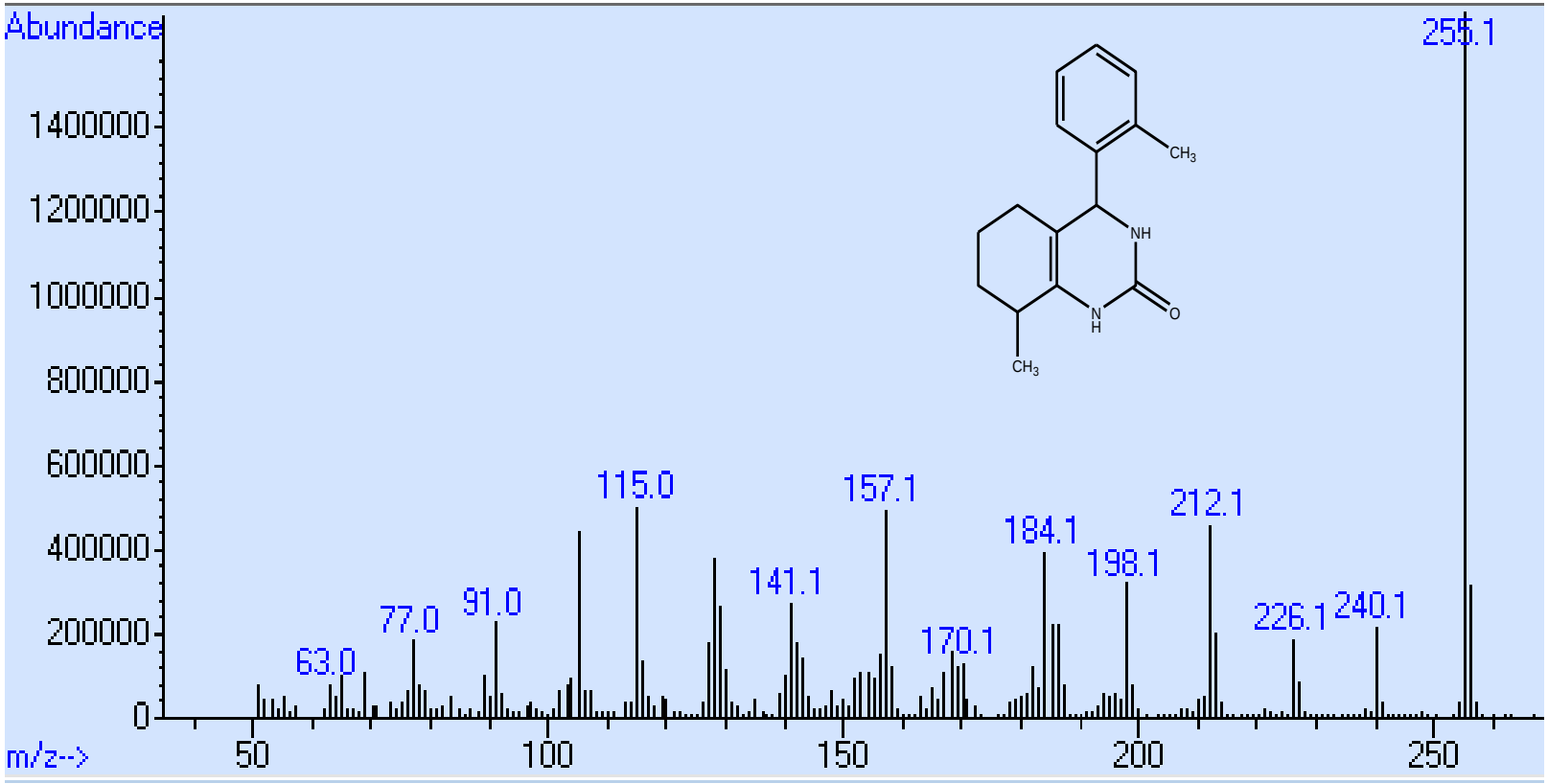


Fig 21: Mass spectrum for Compound (4)

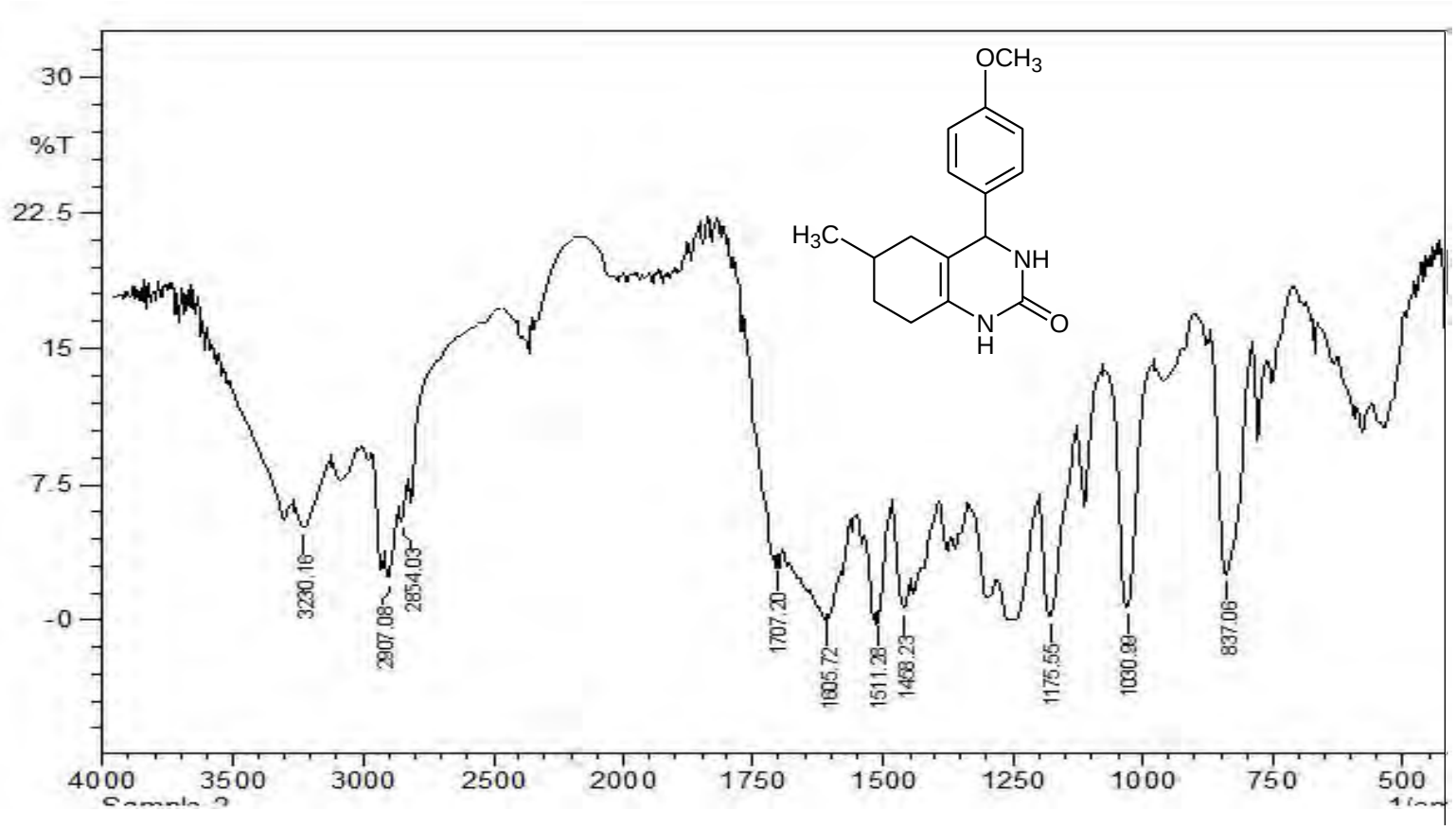


Fig 22: IR spectrum of compound (5)

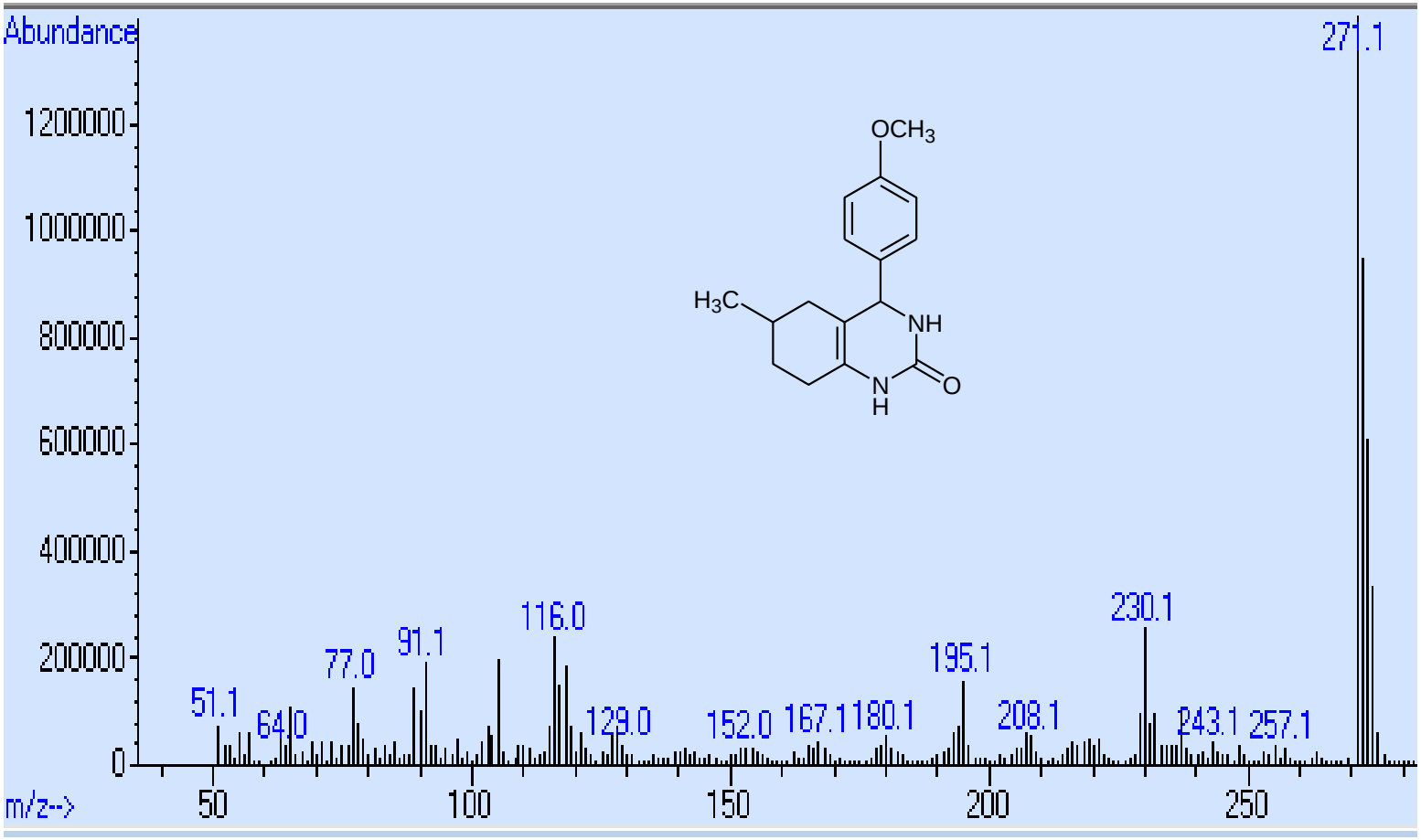


Fig 23: Mass spectrum for Compound-5

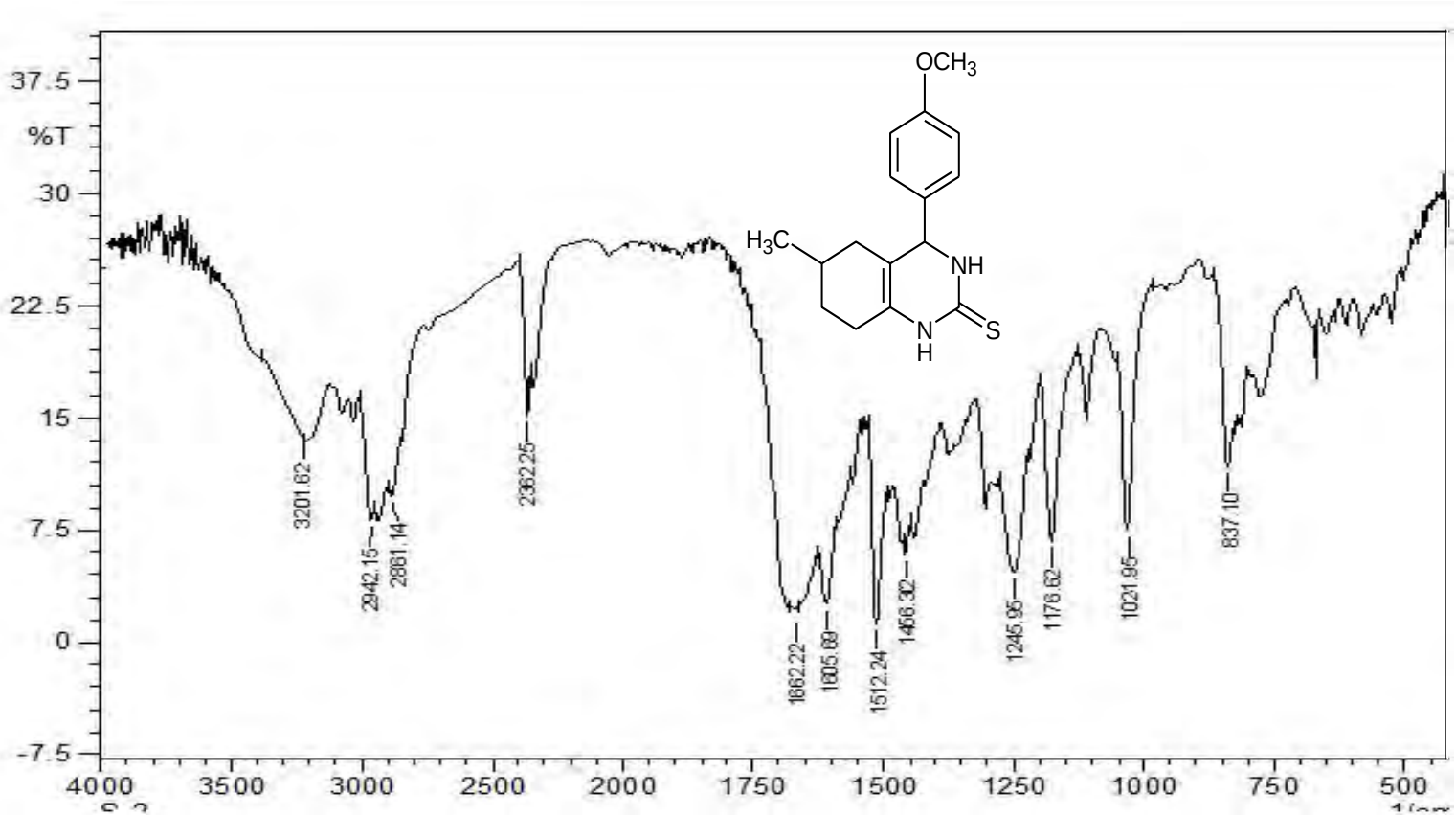


Fig 24: IR spectrum of compound (6)

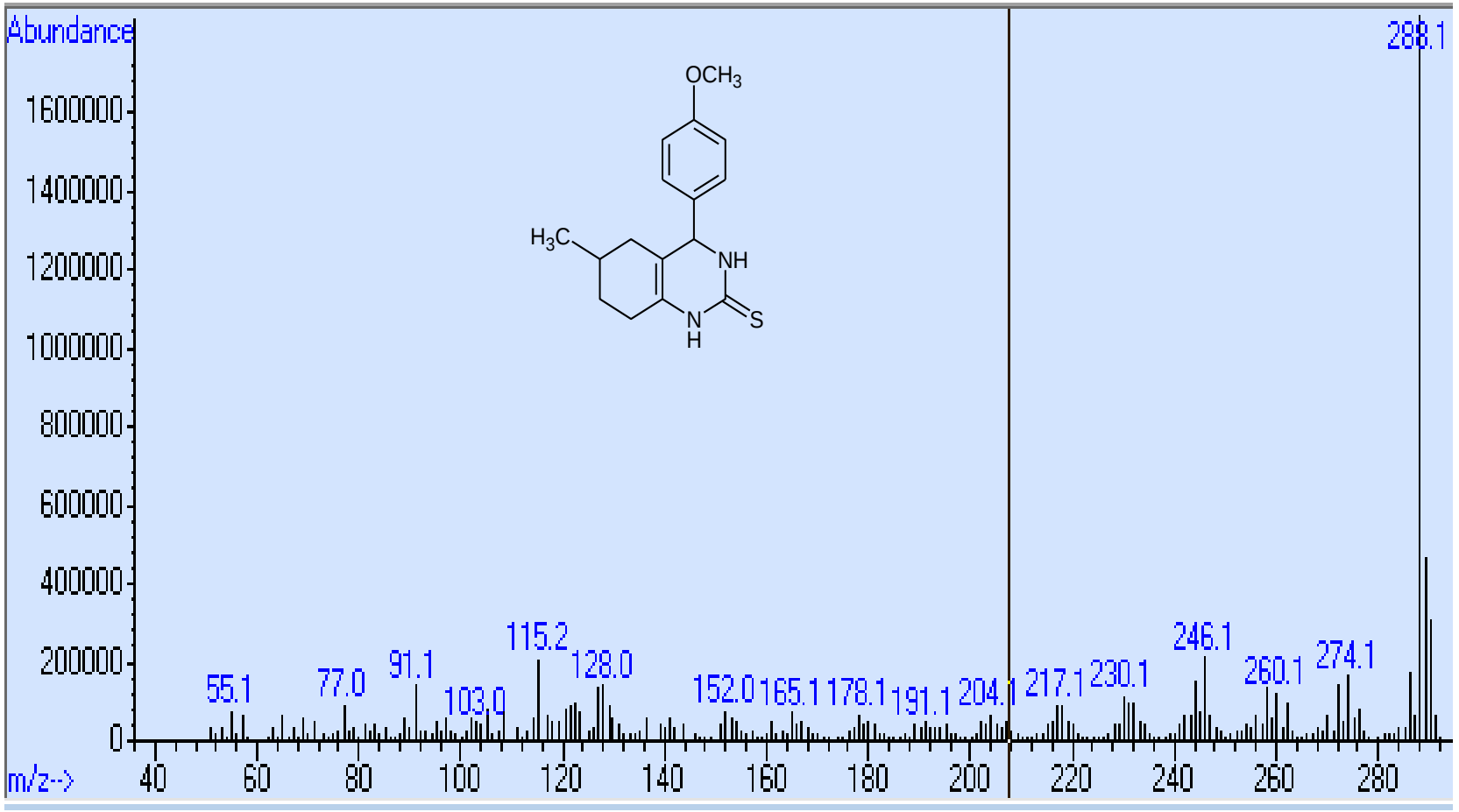


Fig 25: Mass spectrum for Compound (6)

Chapter 4
Conclusions

4.1. Conclusions

Many of the existing methods in carrying out Biginelli reaction involve expensive reagents, stoichiometric amount of catalyst, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation and environmental pollution. Some of the above mentioned hurdles were minimized in the thesis work under discussion.

- In this experiment $FeCl_3$ is used under microwave irradiation which is inexpensive and easily available
- All reactions were carried out in a domestic microwave oven [a common household appliance these days] with special fabricated glassware and optimum reaction conditions were determined.
- These synthesis apart from reducing the use of organic solvents from work up step, also gave improved yield as compared to the conventional heating with reaction time reduced from hours to minutes.
- Low amount of chemicals were used making the method of synthesis environmental friendly. In other words this modest thesis work was a part of 'Green chemistry' too.
- All the product shows antimicrobial activity.

In conclusion, we have developed a much improved modification of Biginelli reaction exploiting $FeCl_3$ as a catalyst without using any protic acid and organic solvent with increased yield, while the reaction time shortened from 4-5 h to a few minutes under microwave irradiation.

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