# New Lewis Acid Catalysts For Biginelli Reaction of Benzaldehyde with Thiourea

***Project report submitted to***

***Mahatma Gandhi University, Kottayam***

***In partial fulfillment of the requirement for the award of the Bachelor's degree of***

**B.Sc. CHEMISTRY**

**BY**

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(Reg. no: **200021026015**)

Under the supervision of

Dr. Litty Sebastian

DEPARTMENT OF CHEMISTRY

BHARATA MATA COLLEGE, THRIKKAKARA

(Affiliated to Mahatma Gandhi University, Kottayam)

2020-2023

DEPARTMENT OF CHEMISTRY

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(Affiliated to Mahatma Gandhi University, Kottayam)

# CERTIFICATE

This is to certify that the project titled "**NEW LEWIS ACID CATALYSTS FOR BIGINELLI REACTION OF BENZALDEHYDE WITH THIOUREA**" is a bonafide work carried out by Aysha Beevi Marakkar, B.Sc Chemistry student, under my supervision and guidance and that no part of this has been presented earlier for the award of any other diploma or other similar titles of recognition.

Forwarded by

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**Place:**

**Date:**

# DECLARATION

I, Aysha Beevi Marakkar, declare that the project report entitled "**New Lewis Acid Catalysts For Biginelli Reaction of Benzaldehyde with Thiourea**", submitted to Mahatma Gandhi University, Kottayam, is an authentic record of original work done by me, under the supervision of Dr. Litty Sebastian, Department of Chemistry, Bharata Mata College, Thrikkakara and no part of this has been previously formed on the basis for the award of any assistantship of any other institution.

Place: Thrikkakara

Date:

# ACKNOWLEDGMENT

Praise and gratitude are first and foremost due to God, the Almighty, for his numerous blessings that made the project work possible.

Words are often inadequate to express my sincere gratitude to my guide, Dr. Litty Sebastian, for her frequent guidance and encouragement throughout the course of this project. Without her solicitude, I would not have been able to make such a study.

I want to take this opportunity to convey my heartfelt thanks to Dr. Amrutha U for her tremendous guidance and assistance in the completion of my project.

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**Aysha Beevi Marakkar**

# CONTENTS

# CHAPTER 1

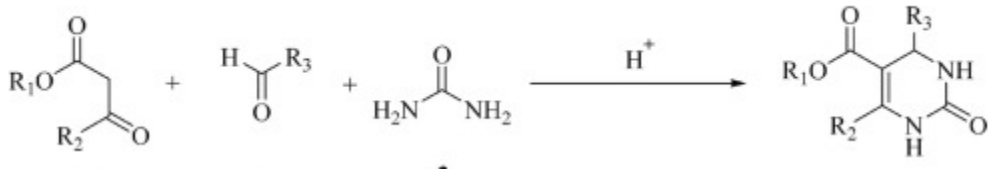
## 1.1 INTRODUCTION

The most significant heterocyclic ring systems that contribute significantly to the synthesis of DNA and RNA are dihydropyrimidines. They were produced artificially by means of multi-component reactions like the Biginelli reaction and Hantzsch dihydropyridine. These Biginelli type dihydropyrimidones have drawn a lot of attention in recent years because of the intriguing pharmacological characteristics connected to their heterocyclic structure.

## 1.2 BIGINELLI REACTION

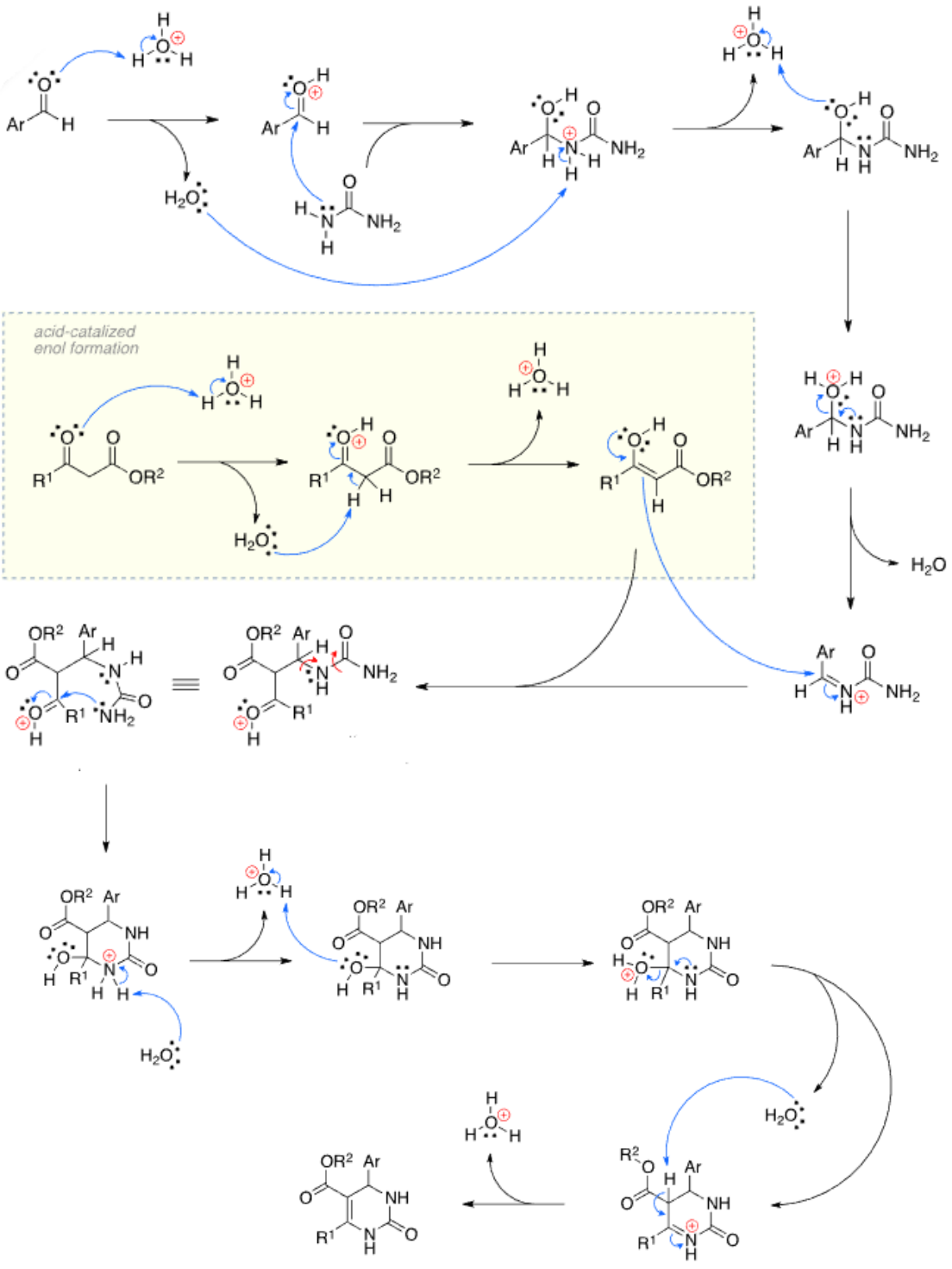
To produce dihydropyrimidones, a multicomponent chemical reaction known as the Biginelli reaction is used. An aldehyde, a ketoester, and urea/thiourea are involved in this reaction, which is facilitated by an acid. The reaction was discovered by Pietro Biginelli in 1891.

The Scheme of the reaction is given below:




## 1.3 MECHANISM

The aldehyde is first protonated by the acid, and then the amine from urea attacks it to complete the reaction. A protonated alcohol is produced as a result of the subsequent proton transfer steps, and it departs as water to create an intermediate N acyliminium ion. The enol form of the keto ester then engages in an attack on the intermediated. A cyclic intermediate is created when the carbonyl and the other amine group react. The final pyrimidone product is made up of proton transfer stages, water release, and deprotonation. Diagram of the mechanism is as follows:


acid-catalized
enol formation

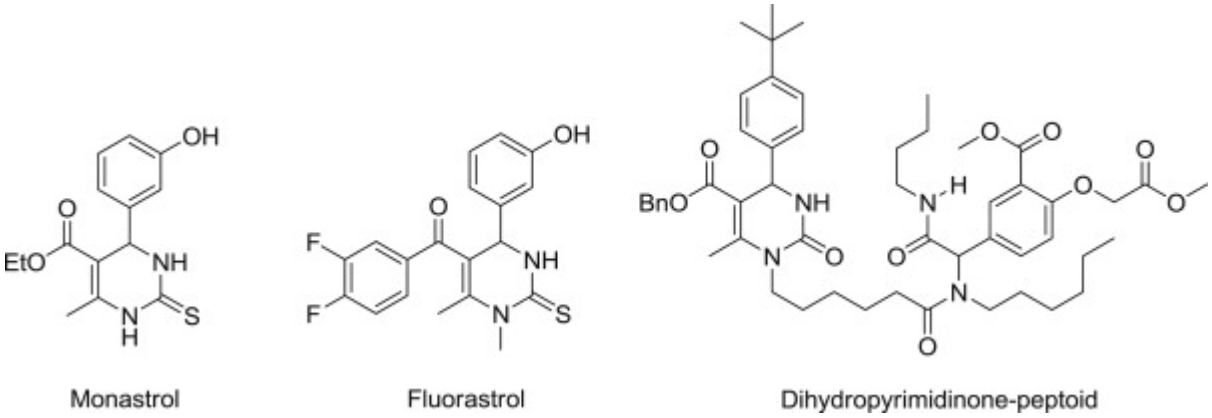
## 1.4 PHARMACEUTICAL ACTIVITY OF DIHYDROPYRAMIDINONES

### I. Anticancer activity

Monastrol has been the subject of the most research on biginelli adducts, which have the potential to treat malignancies. In 1999, a study was published that examined the impact of monastrolin on cancer cells for the first time. Monastrol was discovered to stop mitosis by preventing the kinesin Eg5 protein, which is essential for the development of spindle bipolarity, from moving. Since then, the development of fresh anticancer drugs has been motivated by monastrol.

Kinesin Eg5 is a motor enzyme that is responsible for the formation and maintenance of mitotic spindles. The inhibition of this enzyme activity by monastrol leads to the loss of chromosome alignments and bipolar spindle formation. The resulting "monastral phenotype" inspired scientists to name this specific Biginelli compound as monastrol. (*S*)-Monastrol was found to be more potent (15 times higher potency) inhibitor of Eg5 than the (*R*)-enantiomer.

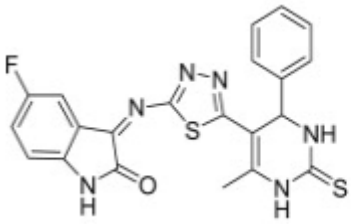
Fluorastrol, a monastrol-derived Eg5 inhibitor, showed to be more potent than monastrol as the former can interact with an allosteric site of this enzyme due to the presence of fluorine atoms.



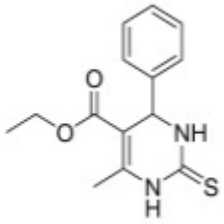

Biginelli compounds can also modulate the protein Hsp 70. DHPM-peptoid is one of the most active Biginelli adducts on Hsp 70. This protein, known to be overexpressed in some cancer cell lines, is responsible for many cellular processes, such as rearrangement and transport of protein complex

## II. Antifungal activity

In 2011, Akhaja and co-workers reported several Biginelli adducts with pronounced activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. The structure DHPM-1 exhibited good activity against all microbial strains tested. Singh and co-workers, reported the antifungal activity of Biginelli adducts against three species of fungi, among them are *Aspergillus niger* and *Trichoderma hammatum.* The DHPM-2 was one of the most potent synthesized molecules against *A. niger*, exhibiting an MIC value of 0.35 mg/mL.




DHPM -1

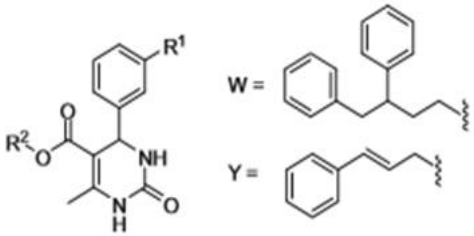



DHPM-2

## III. Antioxidant property

Oxygen and nitrogen reactive species (ROS and RNS, respectively) are ubiquitous in nature being a result of electron escape from electron transport chain (present in mitochondria and chloroplast). The overproduction of ROS and/or RNS can be deleterious to cells if the cellular antioxidant system is not able to efficiently restore the normal levels, which can ultimately cause pathologies.

The first report on the antioxidant properties of Biginelli adducts was published in 2006 in a study that investigated the potential of such molecules to prevent ROS formation and lipid peroxidation in male adult albino Wistar rats**.**



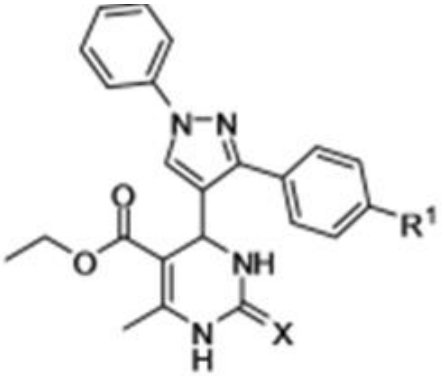

$R^1$ = H and $R^2$ = W DHPM-3
$R^1$ = $NO_2$ and $R^2$ = W DHPM-4

The Biginelli adducts DHPM-3 and DHPM-4 restored the lipid hydroperoxide to normal levels in liver cells when administered at 200 μM. These results indicate that the presence of a nitro group on aromatic ring is not mandatory for preventing lipid peroxidation.

## IV. Antibacterial Activity

Biginelli compounds bearing a 1,3-diarylpyrazole moiety (DHPM5-8) exhibited minimal inhibition concentration (MIC) of 20 ng $mL^{-1}$, 20 ng $mL^{-1}$, 250 ng $mL^{-1}$ and 125 ng $mL^{-1}$ against the *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB $H_{37}Rv$), respectively. The effect of these compounds on normal kidney-derived African green monkey cells (VERO line) was assessed, revealing that both Biginelli adducts are highly selective to MTB $H_{37}Rv$ (selectivity index >500).

Other 16 Biginelli adducts were found to be as potent as or more potent than the reference drugs ethambutol (MIC = 7.6 μM) and ciprofloxacin (MIC = 9.4 μM) against MTB $H_{37}Rv$. The MIC values for compounds ranged from 3.4 to 76.2 μM.

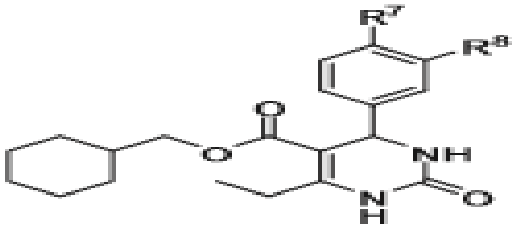



X = O and $R^1$ = F DHPM-5
X = O and $R^1$ = $NO_2$ DHPM-6
X = O and $R^1$ = Cl DHPM-7
X = S and $R^1$ = Cl DHPM-8

## V. Antiviral Activity

Kim and coworkers showed the potential of some Biginelli adducts as agents for preventing human immunodeficiency virus HIV-1 replication. Notably, compounds 77–82 compromised the HIV-1 replication in CEMx174- LTR-GFP cells (clone CG8) by 50% when employed at concentrations lower than 90 nM. At the same experimental conditions, the reference drug

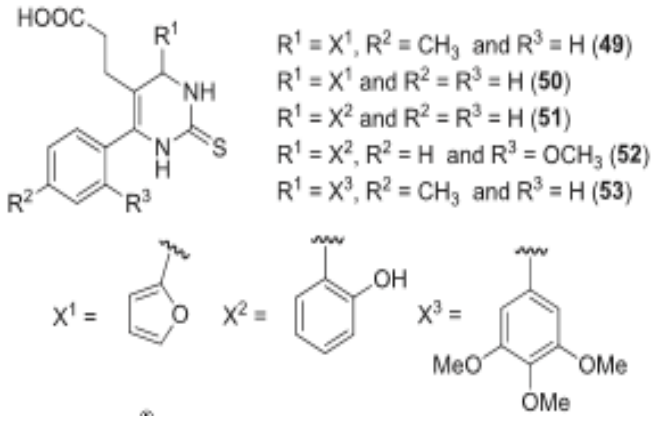
nevirapine exhibited an $EC_{50}$ value of 150 nM. The (*S*)-enantiomer was determined to be more potent than the corresponding (*R*)-enantiomer with respect to the antiviral activity. Indeed, it was shown that (*S*)-77 is at least 26-fold more potent than (*R*)-77.



$R^7 = H$ and $R^8 = OH$ (77)
$R^7 = OH$ and $R^8 = H$ (78)
$R^7 = NHAc$ and $R^8 = H$ (79)
$R^7 = CN$ and $R^8 = H$ (80)
$R^7 = F$ and $R^8 = H$ (81)
$R^7 = Cl$ and $R^8 = H$ (82)

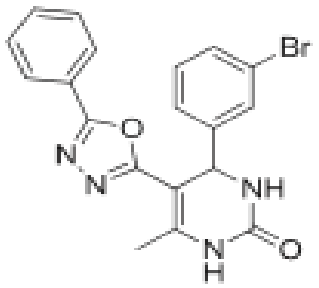
## VI. Anti InflammatoryActivty

Biginelli adducts have drawn a lot of interest because of their potential as anti-inflammatory drugs. When compared to diclofenac, a reference medicine, the propanoic acid derivatives thio adducts (49-53) were shown to be the most promising anti-inflammatory compounds based on the length of action and percentage of inflammation suppression on Albino rats paw edema.



$R^1 = X^1$, $R^2 = CH_3$ and $R^3 = H$ (**49**)
$R^1 = X^1$ and $R^2 = R^3 = H$ (**50**)
$R^1 = X^2$ and $R^2 = R^3 = H$ (**51**)
$R^1 = X^2$, $R^2 = H$ and $R^3 = OCH_3$ (**52**)
$R^1 = X^3$, $R^2 = CH_3$ and $R^3 = H$ (**53**)

By decreasing the carrageenan-induced rat paw edoema by 75% after 3 hours of therapy, the Biginelli derivative 54, which has a 1,3,4oxadiazol-2-yl moiety, inhibits the inflammatory process. This impact is comparable to that of diclofenac.



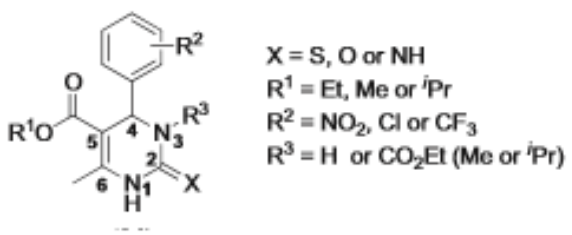

(54)

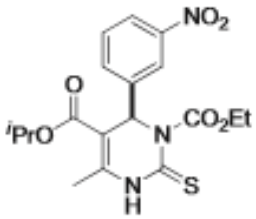
## VII. Calcium Channel Inhibitors

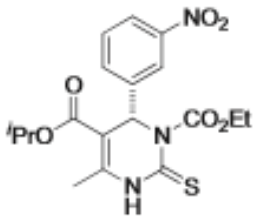
Due to their capacity to suppress calcium channel activity, dihydropyridines like nifedipine were first introduced to the market in 1975 for the treatment of cardiovascular disorders (hypertension, cardiac arrhythmias, and angina). Following the discovery of this medication, various Biginelli adducts were created to test its ability to inhibit calcium channels. In 1990, a study on the structure-activity relationship of Biginelli adducts with regard to calcium channel targeting was published. Determined that, when compared to and aza In vitro counterpart, thioIt was adducts were the most effective Biginelli compounds.

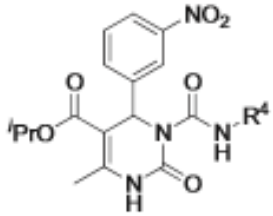
According to in vitro analogue studies, the adduct with a nitro group at the aromatic ring's orthoposition was a more potent antihypertensive molecule than the one with CF 3 or Cl as a substituent. Interestingly, compared to the effects of the Biginelli adducts having an ethyl ester or methyl ester group at the same carbon, respectively, the presence of an isopropyl ester group at C5 increased the potency by 10 and 60 times. Although substances with substituents at N3 are effective calcium channel blockers in vitro, metabolization causes these substances to lose their antihypertensive effects in in vivo tests.

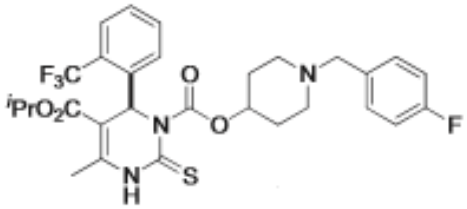
**Compounds showing calcium channel inhibition:**

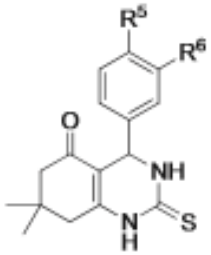


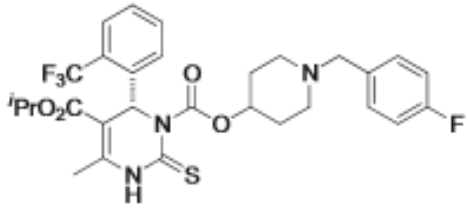



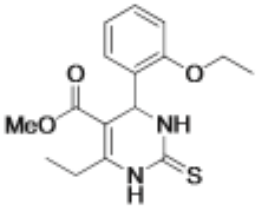


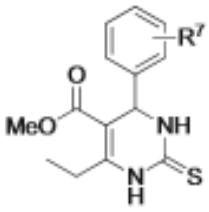


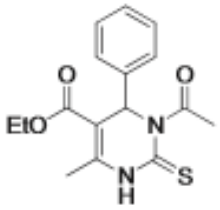







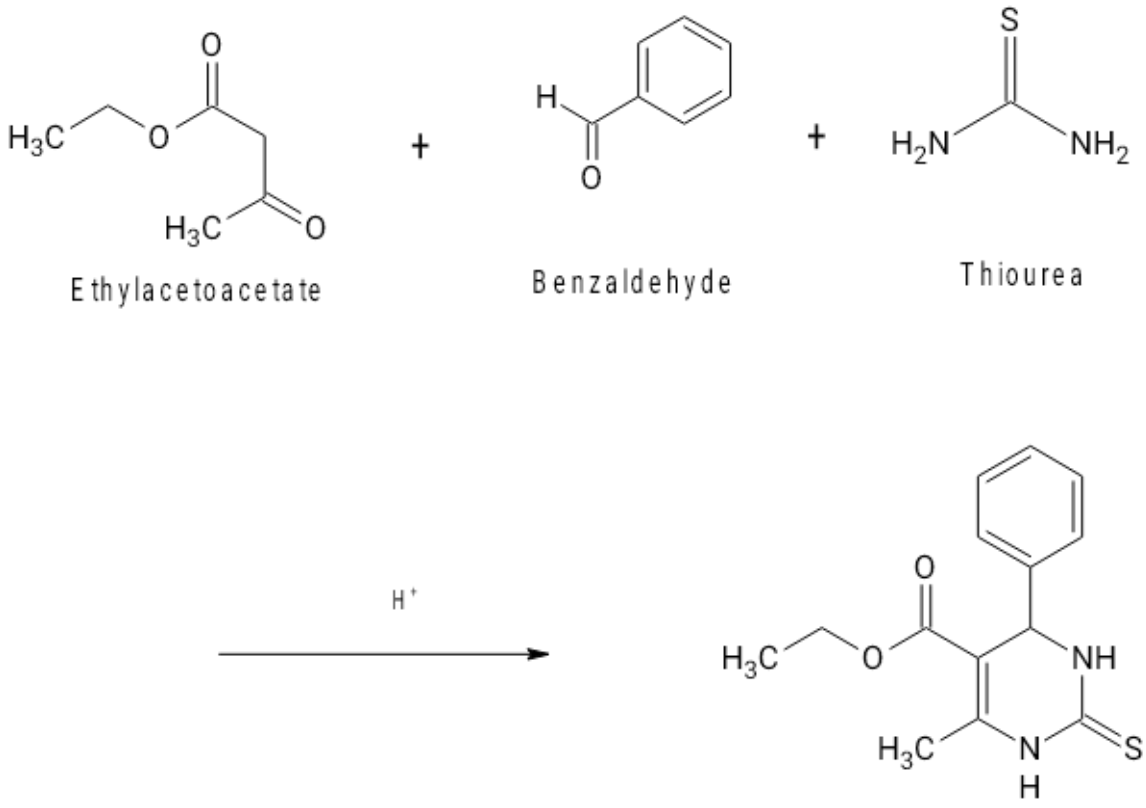


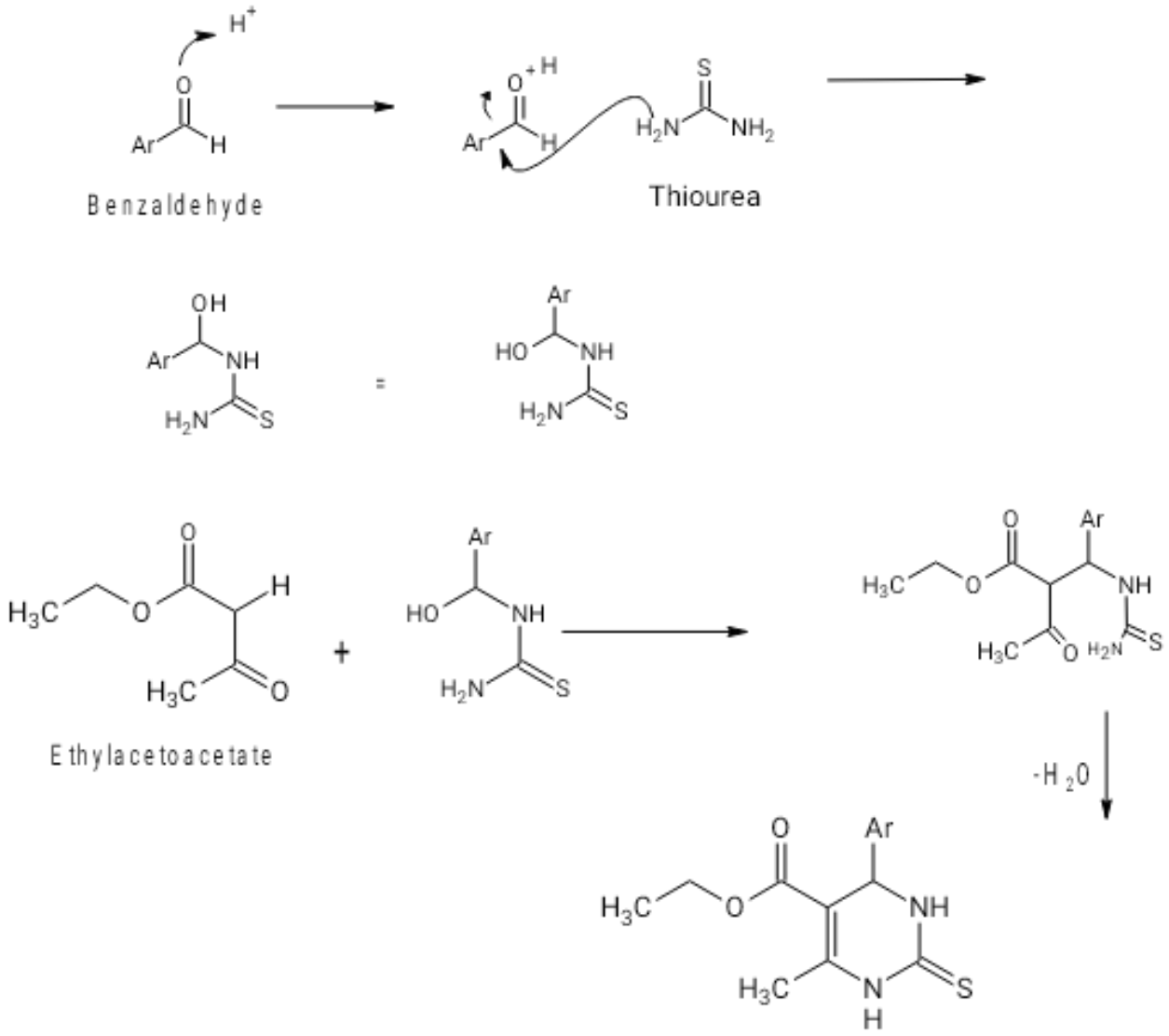
## 1.5 SCOPE AND OBJECTIVE OF THE PROJECT

Though, the synthesis of the Biginelli reaction using urea as a component has been well studied, the one using thiourea is not very well investigated. The aim of the present study was to investigate whether Lewis acid catalyst can be used for catalyzing the reaction. Five different Lewis acid catalysts were investigated for the purpose. They include $AlCl_3$ and $AlF_3$ and transition metal chlorides like $FeCl_3$ ,$MnCl_2$ and $ZnCl_2$.

**The scheme of the reaction is as follows:**



**Mechanism of the reaction is given below:**



# CHAPTER 2

## 2.1 MATERIALS AND METHODS

## 2.2 EXPERIMENT

### 2.2.1 Materials required

- 200 ML Erlenmeyer flask
- Condenser
- Bunsen burner
- Measuring jar
- Beaker
- Glass rod

### 2.2.2 Chemicals required

- Thiourea
- Benzaldehyde
- Ethyl acetoacetate
- Catalysts used were:
    - Hydrochloric Acid
    - Zinc Chloride
    - Aluminium Chloride
    - Aluminium Flouride
    - Ferric Chloride
    - Manganese Chloride

## 2.2.3 Procedure

**I. SYNTHESIS OF DIHYDROPYMIDNONES**.

In a 200 mL Erlenmeyer flask, 2.0mmol of benzaldehyde, 2.0 mmol of ethyl acetoacetate, and 3.00 mmol of thiourea are mixed. The catalysts are then added to the Erlenmeyer Flask (0.42 mmol). The mixture is warmed and mixed until solidification occurs in a water bath at 80 ° C. (time differ for different catalysts). The solid Bignelli product is processed by grinding it into a fine powder, collecting it under a vacuum, rinsing it with ethyl acetoacetate and drying it to generally produce an average yield of 65%, to 90%. The completion of the product formation was monitored by TLC and was characterized by NMR and IR. The amount of the reagent and the catalyst used is summarized in this table:

| Sl.no | Reagent & Catalyst | Amount |
|---|---|---|
| 1. | Benzaldehyde | 4ml |
| 2. | Thiourea | 4.56 g |
| 3. | Ethylacetoacetate | 5 ml |
| 4. | HCl | 0.01531 g |
| 5. | $ZnCl_2$ | 1.144 g |
| 6. | $AlF_3$ | 0.704 g |
| 7. | $AlCl_3$ | 1.12 g |
| 8. | $FeCl_3$ | 1.363 g |
| 9. | $MnCl_2$ | 1.662 9 |

## 2.2.4 Characterization Techniques

### I. THIN LAYER CHROMATOGRAPHY

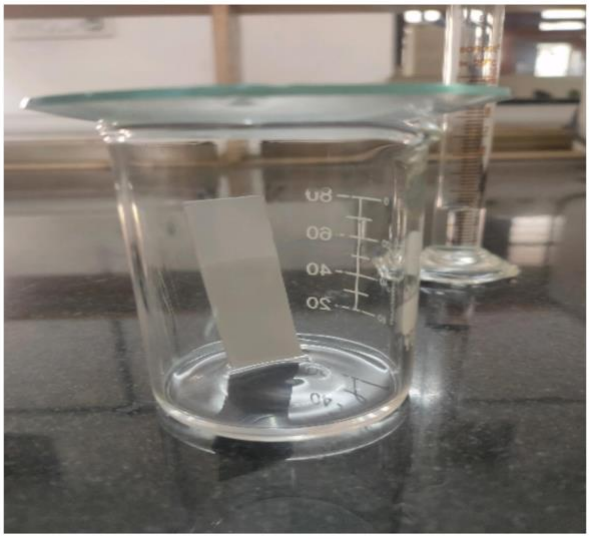
The analytical method of thin layer chromatography is used to recognise and separate the constituents of a mixture. The separation of two or more components from a mixture by passing a mobile phase through a stationary phase is the foundation of the TLC process. It is additionally used to ascertain a compound's purity in a combination. Additionally, the method is very discriminating. By comparing and aiding in the identification of chemicals by chromatography, the retention factor (Rf 13 In thinlayer) is used. The distance travelled by a compound divided by the distance travelled by the solvent front, both measured from the origin, gives the compound's Rf value. Rf value is unique to each component and can be used to determine.

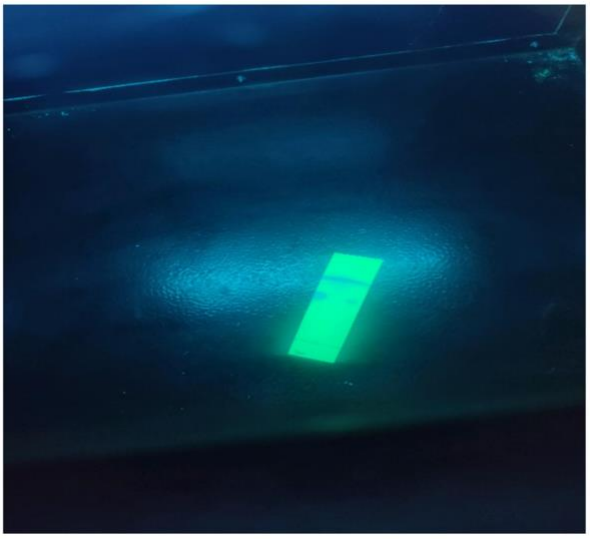
**PROCEDURE**

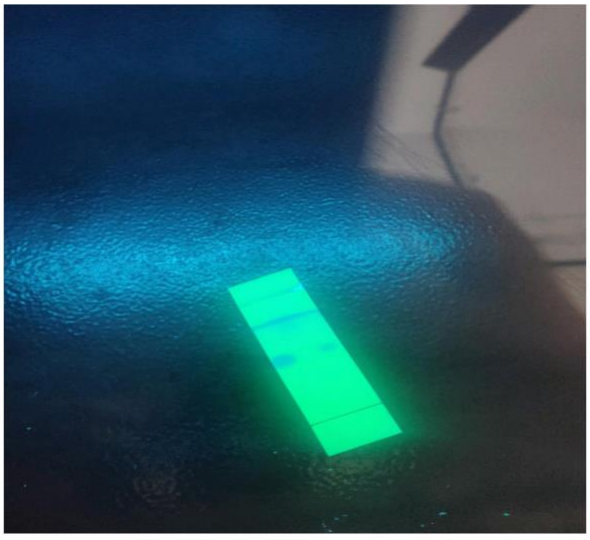
The TLC plate was cut to our convenience. A line was drawn near the bottom of TLC with a pencil. If one uses pen, there is a chance of ink smudge. The sample was dissolved in methanol.

The solvent used for TLC was a mixture of ethylacetate and hexane in the ratio 9:1. The solvent was added to into TLC chamber. The solvent here used is 4.5 ml ethyl acetate and 0.5 ml hexane(9:1 ratio).

Using a capillary tube, the prepared sample was spotted in in TLC plate and the TLC plate was placed in the chamber. The plate should be submerged to a depth where the sample spots are significantly higher than the mobile phase. The solvent will ascend through capillary action, sample will separate into fractions. After the development of spots the plates were taken out and spots was observed under UV light.








ENTIO METER

## II. INFRARED SPECTROSCOPY

Infrared Spectroscopy or IR Spectroscopy, as the name implies, deals with light particles. Infrared rays are at the far end of the spectrum of light because of their frequency, which is significantly lower than that of visible light. Understanding how one molecule interacts with infrared light or reacts under the influence of infrared light is the focus of infrared spectroscopy.

In order to see how molecules interact and what they really do, IR spectroscopy is frequently utilized in the domains of inorganic as well as organic chemistry. These particles, which are ordinarily invisible to the human eye, may be seen using infrared light.

An IR spectrum is a graph where the Y-axis represents the amount of absorbed infrared light and the X-axis represents the wavelength or frequency. If they indeed correlate to vibrations that are present in the bonds of that particular molecule, this is then employed in IR Spectroscopy to ascertain precisely how that molecule absorbs the infrared light.

Infrared light has a frequency that is identical to the bond frequency found inside these molecules. This also has a lot of highly useful uses in modern life and helps a lot of industrial operations.

Based on how they relate to the visible spectrum, the infrared spectrum may be roughly classified into three regions: near, mid, and distant. The 0.8-2.5 m wavelengths or 14000-4000 cm-1, in the high energy and near IR area can cause harmonic or overtone vibration. On the other hand, the mid-IR region, which has a wavelength of 2.5–25 m, or 400–400 cm-1, may be used to analyse basic vibrations as well as related rotational vibrational structure. The microwave zone is exactly close to the far IR region, which has wavelengths between 25 and 1000 m (or 400 and 10 cm-1). This is helpful for rotational spectroscopy since it is low energy.

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from 4000 $cm^{-1}$ to 1300 $cm^{-1}$ are useful for determining the functional group of a mystery molecule. And just like a fingerprint, the region between 1300 $cm^{-1}$ and 400 $cm^{-1}$—also known as the fingerprint region—contains bands that are exclusive to each molecule. These bands are helpful for comparing the spectra of various compounds with one another.

In the present study, the FTIR spectrum of the sample was taken using Thermo Scientific Nicolet iS 5 FTIR Spectrometer available in the Department of Chemistry, Bharata Mata College, Thrikkakara.

## III. NMR SPECTROSCOPY

Nuclear magnetic resonance (NMR) spectroscopy is a crucial analytical technique for organic chemists. The study being carried out in the organic lab has greatly benefited from the NMR. It can reveal details about the content and purity of the sample as well as the structure of the molecule. Proton (1H) NMR is one of the NMR techniques that organic chemists use the most frequently. By watching how a molecule's protons react to the surrounding chemical environment, one can infer the structure of the molecule.

It depends on evidence indicating that all nuclei have electric charges and that the majority of atoms' nuclei have spin. The base of NMR spectroscopy is the ability of electromagnetic radiation to absorb energy between the radiofrequency range of 3 kHz and 300 GHz. A magnetic field is formed by the electrical charge and spin of atom nuclei. When an external magnetic field is present, atomic nuclei will either align themselves in the direction of the external magnetic field or in the opposite path.

When there is an external magnetic field present, energy travels from the ground state to the excited state.

An electron generates a radio wave with the same frequency when it shifts from an excited state to the ground state since this shift happens at a wavelength that coincides with radio frequencies. This radio frequency allows entry to the NMR spectrum. The radiofrequency that is being radiated is directly associated with the magnitude of the applied external magnetic field.

The NMR of the sample was measured in NIT, Calicut using the machine Jeol 500 MHz.

# CHAPTER 3

## 3.1 RESULT AND DISCUSSION

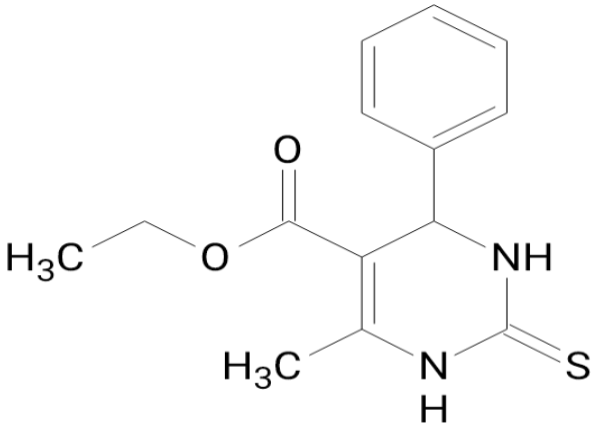
- In this study, the effect of five Lewis acids were used as a catalyst for the Biginelli reaction of Benzaldehyde, Ethylacetoacetate and thiourea.The list shows the quantity produced by each catalyst.

| S.No. | Catalyst Used | Time taken by the catalyst | % Yield of the complex |
|---|---|---|---|
| 1 | $ZnCl_2$ | 3hr 35 min | 54% |
| 2 | $MnCl_2$ | 4hr 5min | 56% |
| 3 | $AlCl_3$ | 45min | 55% |
| 4 | $AlF_3$ | 4hr 20min | 43% |
| 5 | $FeCl_3$ | 1hr 35min | 79% |
| 6 | HCl | 30 min | 58% |

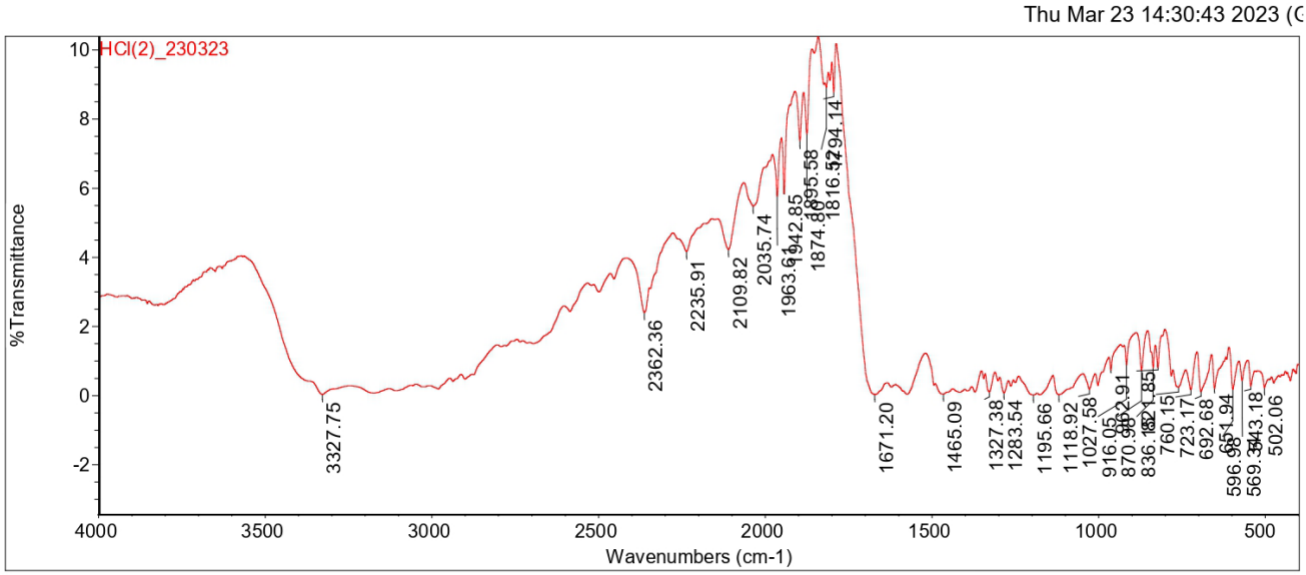
$AlCl_3$ found to be a good catalyst, almost at par with HCl. $AlF_3$ was not as efficient as $AlCl_3$. Of the three transition metal catalyst tried, $FeCl_3$ was found to be more efficient than $ZnCl_2$ and $MnCl_2$.

## IR SPECTRUM

The IR spectrum revealed the formation of the dihydropyramidine ring. The IR spectrum of the compounds are attached here. The compound show the characteristic two N-H stretching ar 3328 and 3176 $cm^{-1}$. The band appearing at 1670 $cm^{-1}$ is due to carbonyl stretching(C=O) of the ethylacetoacetate moiety. The peak ar 1620 $cm^{-1}$ could be N-H bending vibration. The peak at 1327 $cm^{-1}$ could be due to C=S stretching. The sharp bands in the 750~790 and 1520~1540 $cm^{-1}$ regions are due to aromatic C-H and C=C stretching, respectively. The band observed at 1165~1175 $cm^{-1}$ is due to C-N stretching.



- **HCl**

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Thu Mar 23 14:29:46 2023 (GMT+05:30)
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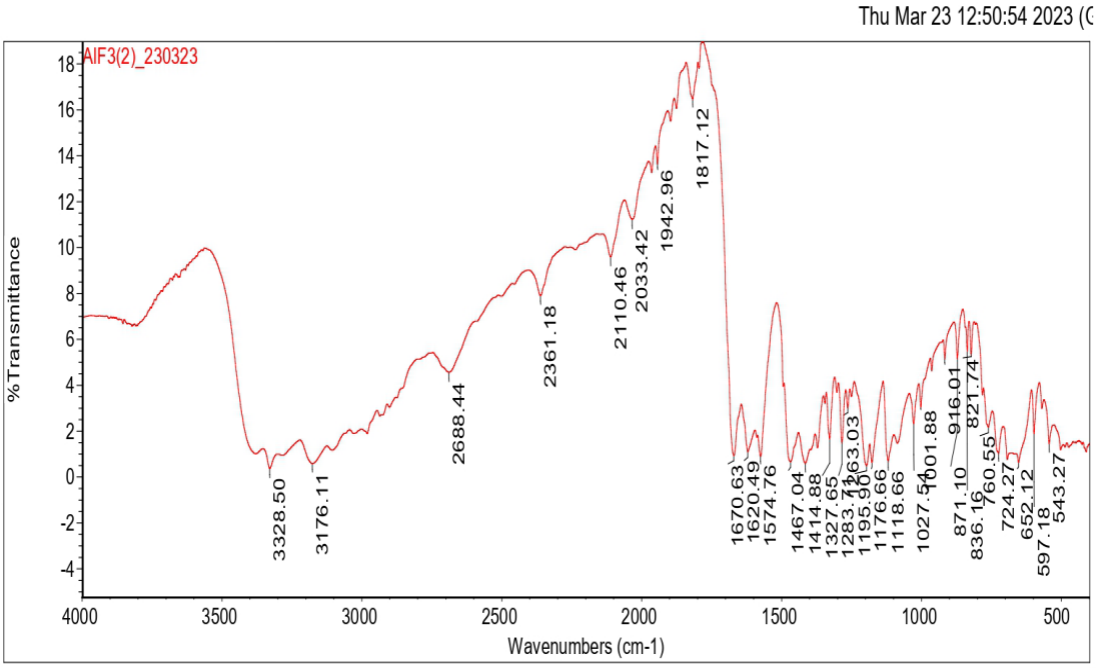
Spectrum: HCl(2)_230323
Region: 4000.00 400.00
Absolute threshold: 10.332
Sensitivity: 50
Peak list:

| | | | |
|---|---|---|---|
| Position: | 502.06 | Intensity: | 0.216 |
| Position: | 543.18 | Intensity: | 0.264 |
| Position: | 569.34 | Intensity: | 0.421 |
| Position: | 596.98 | Intensity: | 0.175 |
| Position: | 651.94 | Intensity: | 0.194 |
| Position: | 692.68 | Intensity: | 0.102 |
| Position: | 723.17 | Intensity: | 0.161 |
| Position: | 760.15 | Intensity: | 0.237 |
| Position: | 821.85 | Intensity: | 0.798 |
| Position: | 836.15 | Intensity: | 0.790 |
| Position: | 870.98 | Intensity: | 0.738 |
| Position: | 916.05 | Intensity: | 0.883 |
| Position: | 962.91 | Intensity: | 0.732 |
| Position: | 1027.58 | Intensity: | 0.178 |
| Position: | 1118.92 | Intensity: | 0.0156 |
| Position: | 1195.66 | Intensity: | 0.0091 |
| Position: | 1283.54 | Intensity: | 0.0723 |
| Position: | 1327.38 | Intensity: | 0.0971 |
| Position: | 1465.09 | Intensity: | 0.0374 |
| Position: | 1671.20 | Intensity: | 0.0248 |
| Position: | 1794.14 | Intensity: | 8.764 |
| Position: | 1816.52 | Intensity: | 8.908 |
| Position: | 1874.80 | Intensity: | 7.558 |
| Position: | 1895.58 | Intensity: | 7.366 |
| Position: | 1942.85 | Intensity: | 5.826 |
| Position: | 1963.61 | Intensity: | 5.764 |
| Position: | 2035.74 | Intensity: | 5.475 |
| Position: | 2109.82 | Intensity: | 4.222 |
| Position: | 2235.91 | Intensity: | 4.168 |
| Position: | 2362.36 | Intensity: | 2.396 |
| Position: | 3327.75 | Intensity: | 0.0288 |

- **$AlF_3$**

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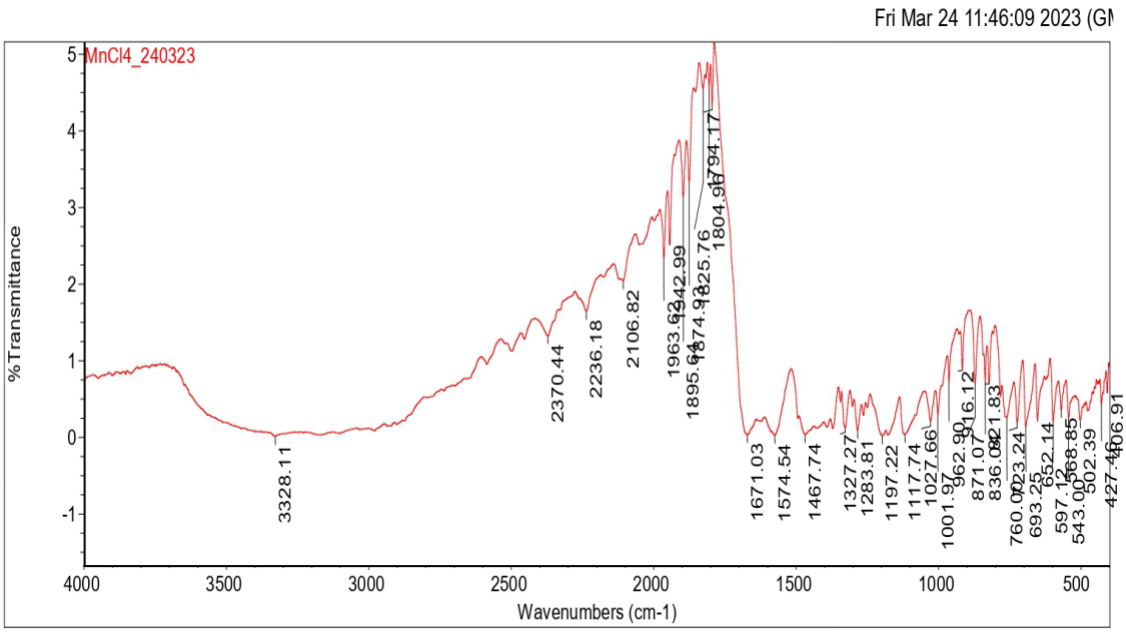
Thu Mar 23 12:50:37 2023 (GMT+05:30)
FIND PEAKS:
Spectrum: AlF3(2)_230323
Region: 4000.00 400.00
Absolute threshold: 16.865
Sensitivity: 50
Peak list:

| | | | |
|---|---|---|---|
| Position: | 543.27 | Intensity: | 1.434 |
| Position: | 597.18 | Intensity: | 1.871 |
| Position: | 652.12 | Intensity: | 0.615 |
| Position: | 724.27 | Intensity: | 1.019 |
| Position: | 760.55 | Intensity: | 2.165 |
| Position: | 821.74 | Intensity: | 5.316 |
| Position: | 836.16 | Intensity: | 5.454 |
| Position: | 871.10 | Intensity: | 5.150 |
| Position: | 916.01 | Intensity: | 5.131 |
| Position: | 1001.88 | Intensity: | 3.027 |
| Position: | 1027.54 | Intensity: | 2.307 |
| Position: | 1118.66 | Intensity: | 0.678 |
| Position: | 1176.66 | Intensity: | 0.615 |
| Position: | 1195.90 | Intensity: | 0.485 |
| Position: | 1263.03 | Intensity: | 2.999 |
| Position: | 1283.71 | Intensity: | 1.475 |
| Position: | 1327.65 | Intensity: | 1.657 |
| Position: | 1414.88 | Intensity: | 0.588 |
| Position: | 1467.04 | Intensity: | 0.654 |
| Position: | 1574.76 | Intensity: | 0.877 |
| Position: | 1620.49 | Intensity: | 1.097 |
| Position: | 1670.63 | Intensity: | 0.933 |
| Position: | 1817.12 | Intensity: | 16.483 |
| Position: | 1942.96 | Intensity: | 13.638 |
| Position: | 2033.42 | Intensity: | 11.219 |
| Position: | 2110.46 | Intensity: | 9.576 |
| Position: | 2361.18 | Intensity: | 7.897 |
| Position: | 2688.44 | Intensity: | 4.545 |
| Position: | 3176.11 | Intensity: | 0.570 |
| Position: | 3328.50 | Intensity: | 0.348 |

- **$MnCl_2$**

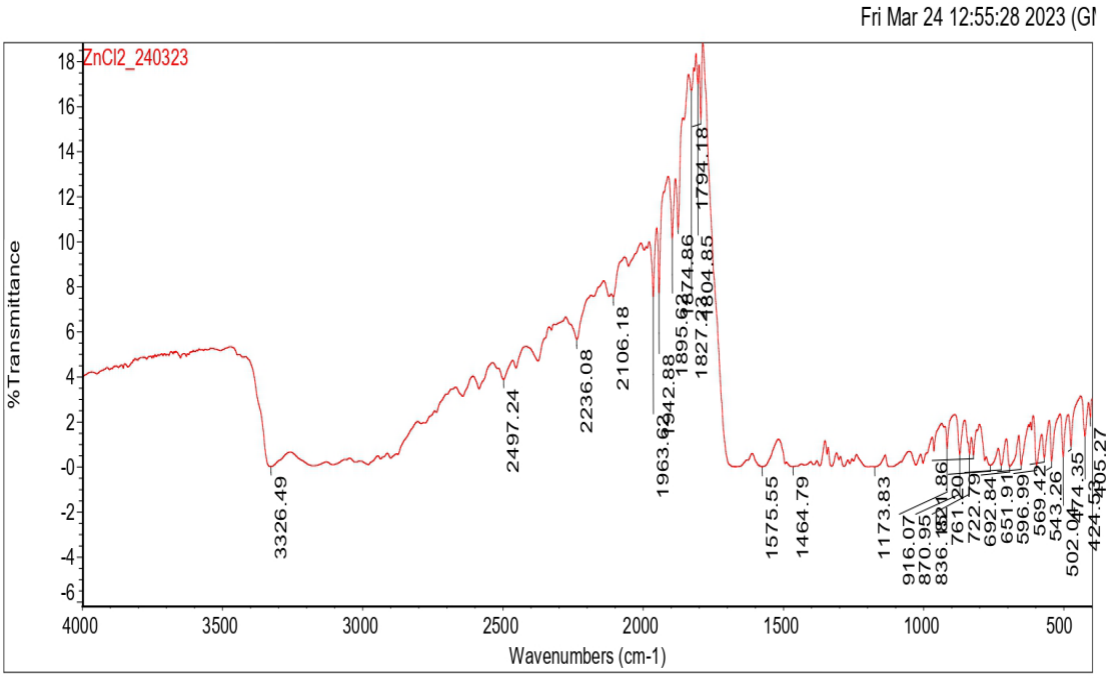



Collection time: Fri Mar 24 11:44:38 2023 (GMT+05:

Fri Mar 24 11:46:36 2023 (GMT+05:00)
FIND PEAKS:
Spectrum: MnCl4_240323
Region: 4000.00 400.00
Absolute threshold: 5.139
Sensitivity: 50
Peak list:

| | | | |
|---|---|---|---|
| Position: | 406.91 | Intensity: | 0.395 |
| Position: | 427.46 | Intensity: | 0.431 |
| Position: | 502.39 | Intensity: | 0.219 |
| Position: | 543.00 | Intensity: | 0.280 |
| Position: | 568.85 | Intensity: | 0.352 |
| Position: | 597.12 | Intensity: | 0.204 |
| Position: | 652.14 | Intensity: | 0.226 |
| Position: | 693.25 | Intensity: | 0.137 |
| Position: | 723.24 | Intensity: | 0.191 |
| Position: | 760.00 | Intensity: | 0.255 |
| Position: | 821.83 | Intensity: | 0.695 |
| Position: | 836.04 | Intensity: | 0.750 |
| Position: | 871.07 | Intensity: | 0.705 |
| Position: | 916.12 | Intensity: | 0.876 |
| Position: | 962.90 | Intensity: | 0.731 |
| Position: | 1001.97 | Intensity: | 0.303 |
| Position: | 1027.66 | Intensity: | 0.205 |
| Position: | 1117.74 | Intensity: | 0.0345 |
| Position: | 1197.22 | Intensity: | 0.0206 |
| Position: | 1283.81 | Intensity: | 0.0904 |
| Position: | 1327.27 | Intensity: | 0.115 |
| Position: | 1467.74 | Intensity: | 0.0345 |
| Position: | 1574.54 | Intensity: | 0.0240 |
| Position: | 1671.03 | Intensity: | 0.0302 |
| Position: | 1794.17 | Intensity: | 4.325 |
| Position: | 1804.96 | Intensity: | 4.996 |
| Position: | 1825.76 | Intensity: | 4.345 |
| Position: | 1874.93 | Intensity: | 3.331 |
| Position: | 1895.64 | Intensity: | 3.128 |
| Position: | 1942.99 | Intensity: | 2.310 |
| Position: | 1963.62 | Intensity: | 2.280 |
| Position: | 2106.82 | Intensity: | 2.036 |
| Position: | 2236.18 | Intensity: | 1.664 |
| Position: | 2370.44 | Intensity: | 1.323 |
| Position: | 3328.11 | Intensity: | 0.0106 |

- **$ZnCl_2$**

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Fri Mar 24 12:55:23 2023 (GMT+05:30)
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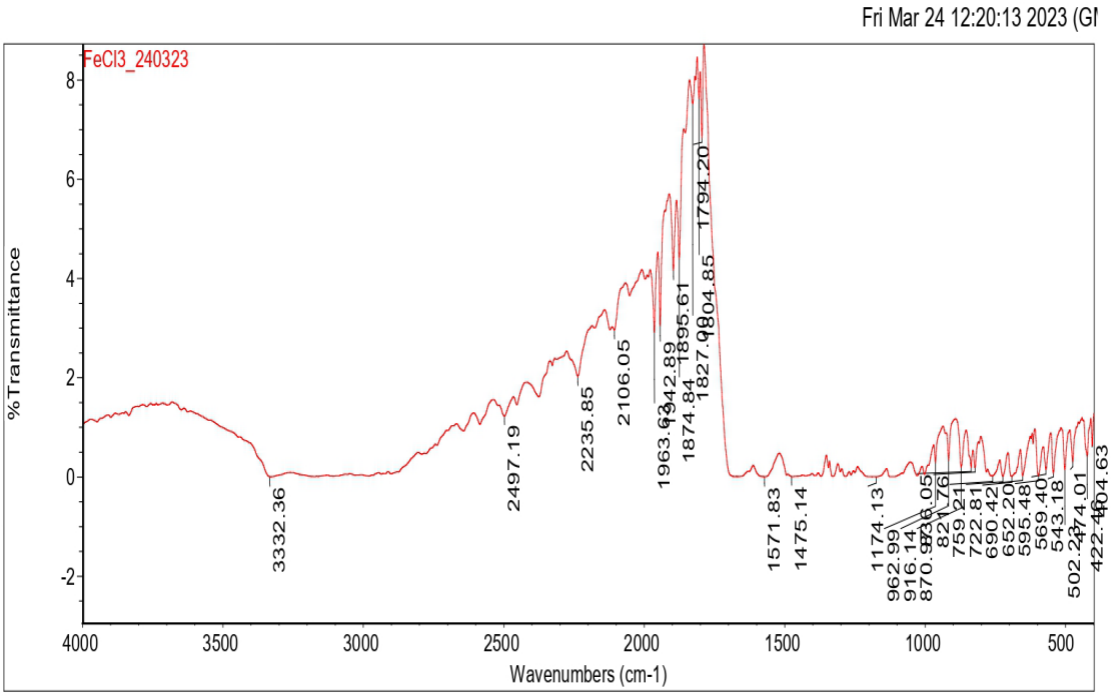
Spectrum: ZnCl2_240323
Region: 4000.00 400.00
Absolute threshold: 18.694
Sensitivity: 50
Peak list:

| | | | |
|---|---|---|---|
| Position: | 405.27 | Intensity: | 2.186 |
| Position: | 424.53 | Intensity: | 1.350 |
| Position: | 474.35 | Intensity: | 0.920 |
| Position: | 502.04 | Intensity: | 0.442 |
| Position: | 543.26 | Intensity: | 0.254 |
| Position: | 569.42 | Intensity: | 0.405 |
| Position: | 596.99 | Intensity: | 0.0826 |
| Position: | 651.91 | Intensity: | 0.0787 |
| Position: | 692.84 | Intensity: | 0.0209 |
| Position: | 722.79 | Intensity: | 0.0756 |
| Position: | 761.20 | Intensity: | 0.0673 |
| Position: | 821.86 | Intensity: | 0.513 |
| Position: | 836.15 | Intensity: | 0.549 |
| Position: | 870.95 | Intensity: | 0.547 |
| Position: | 916.07 | Intensity: | 0.817 |
| Position: | 1173.83 | Intensity: | -0.0068 |
| Position: | 1464.79 | Intensity: | 0.0028 |
| Position: | 1575.55 | Intensity: | -0.0047 |
| Position: | 1794.18 | Intensity: | 15.409 |
| Position: | 1804.85 | Intensity: | 16.996 |
| Position: | 1827.23 | Intensity: | 16.710 |
| Position: | 1874.86 | Intensity: | 10.571 |
| Position: | 1895.62 | Intensity: | 10.127 |
| Position: | 1942.88 | Intensity: | 7.713 |
| Position: | 1963.62 | Intensity: | 7.555 |
| Position: | 2106.18 | Intensity: | 7.544 |
| Position: | 2236.08 | Intensity: | 5.657 |
| Position: | 2497.24 | Intensity: | 3.872 |
| Position: | 3326.49 | Intensity: | 0.0088 |

- **$FeCl_3$**

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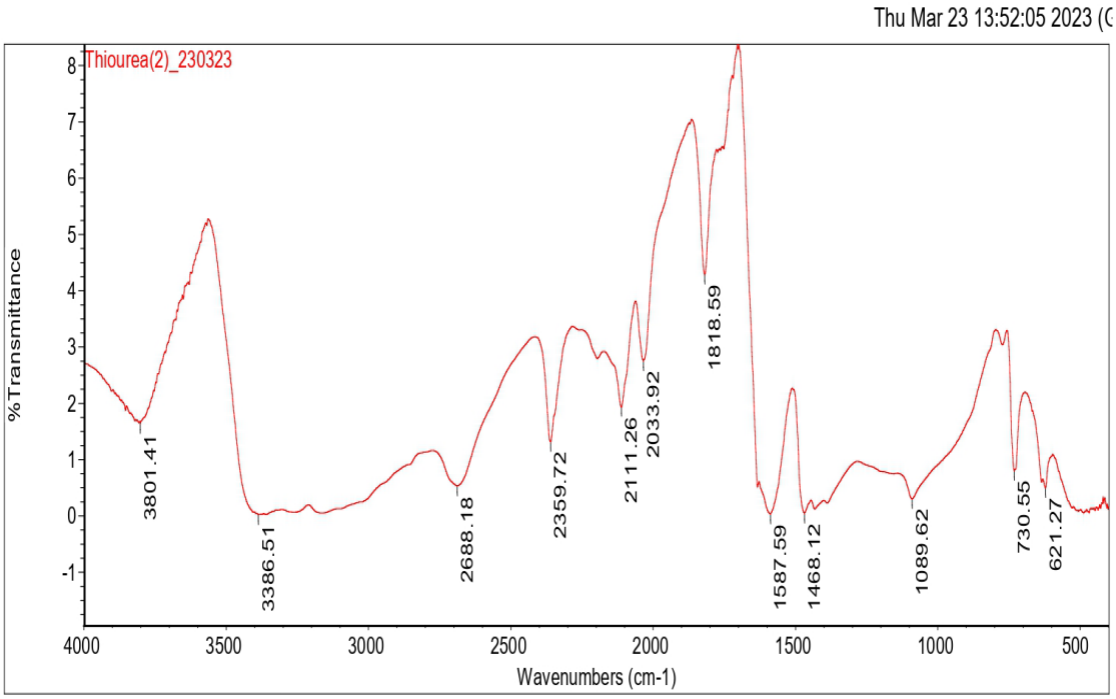
Spectrum: FeCl3_240323
Region: 4000.00 400.00
Absolute threshold: 8.694
Sensitivity: 50
Peak list:

| | | | |
|---|---|---|---|
| Position: | 404.63 | Intensity: | 0.826 |
| Position: | 422.46 | Intensity: | 0.417 |
| Position: | 474.01 | Intensity: | 0.299 |
| Position: | 502.23 | Intensity: | 0.137 |
| Position: | 543.18 | Intensity: | 0.0866 |
| Position: | 569.40 | Intensity: | 0.143 |
| Position: | 595.48 | Intensity: | 0.0312 |
| Position: | 652.20 | Intensity: | 0.0183 |
| Position: | 690.42 | Intensity: | 0.00092 |
| Position: | 722.81 | Intensity: | 0.0015 |
| Position: | 759.21 | Intensity: | 0.0125 |
| Position: | 821.76 | Intensity: | 0.174 |
| Position: | 836.05 | Intensity: | 0.187 |
| Position: | 870.97 | Intensity: | 0.191 |
| Position: | 916.14 | Intensity: | 0.330 |
| Position: | 962.99 | Intensity: | 0.282 |
| Position: | 1174.13 | Intensity: | -0.0082 |
| Position: | 1475.14 | Intensity: | -0.0013 |
| Position: | 1571.83 | Intensity: | -0.0056 |
| Position: | 1794.20 | Intensity: | 6.821 |
| Position: | 1804.85 | Intensity: | 7.629 |
| Position: | 1827.00 | Intensity: | 7.520 |
| Position: | 1874.84 | Intensity: | 4.388 |
| Position: | 1895.61 | Intensity: | 4.156 |
| Position: | 1942.89 | Intensity: | 3.045 |
| Position: | 1963.63 | Intensity: | 2.913 |
| Position: | 2106.05 | Intensity: | 2.956 |
| Position: | 2235.85 | Intensity: | 2.027 |
| Position: | 2497.19 | Intensity: | 1.217 |
| Position: | 3332.36 | Intensity: | -0.0061 |

- **Thiourea**

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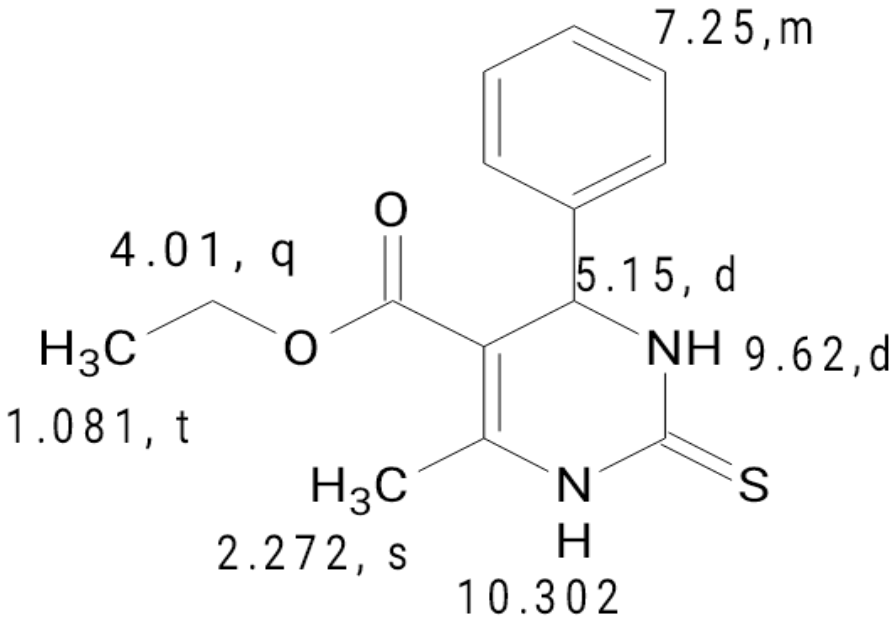
Thu Mar 23 13:51:20 2023 (GMT+05:30)
FIND PEAKS:
Spectrum: Thiourea(2)_230323
Region: 4000.00 400.00
Absolute threshold: 8.363
Sensitivity: 50
Peak list:

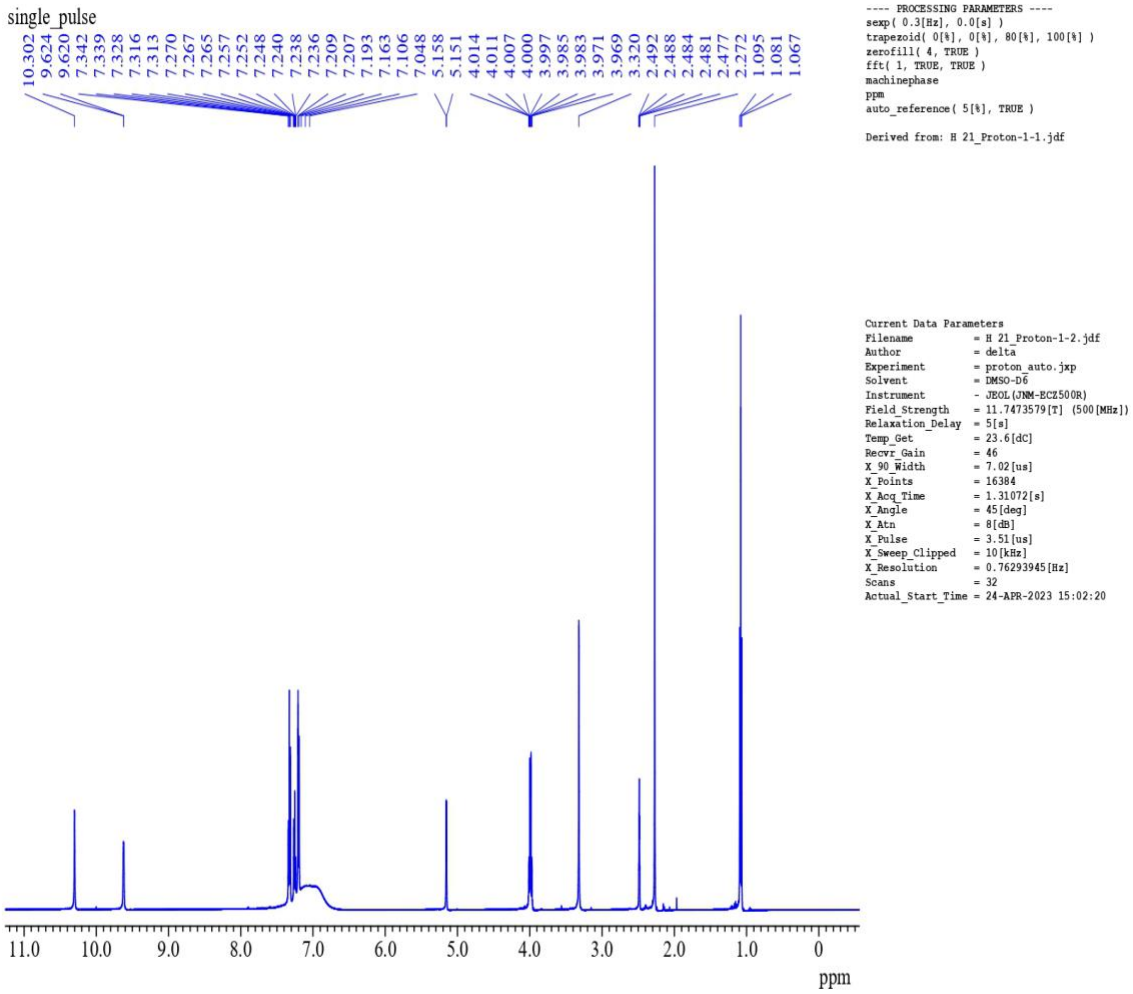
| | | | |
|---|---|---|---|
| Position: | 621.27 | Intensity: | 0.488 |
| Position: | 730.55 | Intensity: | 0.800 |
| Position: | 1089.62 | Intensity: | 0.296 |
| Position: | 1468.12 | Intensity: | 0.0450 |
| Position: | 1587.59 | Intensity: | 0.0306 |
| Position: | 1818.59 | Intensity: | 4.284 |
| Position: | 2033.92 | Intensity: | 2.757 |
| Position: | 2111.26 | Intensity: | 1.921 |
| Position: | 2359.72 | Intensity: | 1.307 |
| Position: | 2688.18 | Intensity: | 0.529 |
| Position: | 3386.51 | Intensity: | 0.0165 |
| Position: | 3801.41 | Intensity: | 1.644 |

## NMR SPECTRUM

The study's 1H-NMR spectrum, which was captured in DMSO at room temperature, supports the inferences made from the IR spectra. The NMR spectrum confirmed the presence of the formation of the compound. The peaks in the NMR are 1.081 (3H, t), 2.272 (s,3H), 2.484(5nos, 2H), 4.01(q, 2H), 5.158 and 5.151(doublet), 7.25(m,5H), 9.624 and 9.20 (d, 1H) and 10.302. The peaks were identified as:



- **HCl**


single_pulse
10.302
9.624
9.620
7.342
7.339
7.328
7.316
7.313
7.270
7.267
7.265
7.257
7.252
7.248
7.240
7.238
7.236
7.209
7.207
7.193
7.163
7.106
7.048
5.158
5.151
4.014
4.011
4.007
4.000
3.997
3.985
3.983
3.971
3.969
3.320
2.492
2.488
2.484
2.481
2.477
2.272
1.095
1.081
1.067
---- PROCESSING PARAMETERS ----
sexp( 0.3[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 4, TRUE )
fft( 1, TRUE, TRUE )
machinephase
ppm
auto_reference( 5[%], TRUE )
Derived from: H 21_Proton-1-1.jdf
Current Data Parameters
Filename = H 21_Proton-1-2.jdf
Author = delta
Experiment = proton_auto.jxp
Solvent = DMSO-D6
Instrument - JEOL(JNM-ECZ500R)
Field_Strength = 11.7473579[T] (500[MHz])
Relaxation_Delay = 5[s]
Temp_Get = 23.6[dC]
Recvr_Gain = 46
X_90_Width = 7.02[us]
X_Points = 16384
X_Acq_Time = 1.31072[s]
X_Angle = 45[deg]
X_Atn = 8[dB]
X_Pulse = 3.51[us]
X_Sweep_Clipped = 10[kHz]
X_Resolution = 0.76293945[Hz]
Scans = 32
Actual_Start_Time = 24-APR-2023 15:02:20
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

# CHAPTER 4

## 4.1 CONCLUSION

1. The Biginelli reaction between Benzaldehyde, ethylacetoacetate and thiourea was found to be catalysed by Lewis acids.
2. The reaction was done with five different Lewis acid catalysts.
3. Of all the catalysts, $AlCl_3$ was found to be the best.
4. Of the three transition metal catalyst tried, $FeCl_3$ was found to be more efficient than $ZnCl_2$ and $MnCl_2$.
5. The use of $FeCl_3$ as a catalyst gave the highest yield of the product.
6. IR and NMR data confirm the formation of Biginelli adduct.

# REFERENCE


1. Thorat, B. R., Gurav, A., Dalvi, B., Sawant, A., Lokhande, V., & Mali, S. N. (2020). Green Synthesis of Substituted Dihydropyrimidin-2 (1H)-one by Using Zinc Chloride/Acetic Acid Catalytic System. *Curr. Chinese Chem*, *1*(1), 30-46.
2. Wang, Y., Yang, H., Yu, J., Miao, Z., & Chen, R. (2009). Highly enantioselective Biginelli reaction promoted by chiral bifunctional primary amine-thiourea catalysts: asymmetric synthesis of dihydropyrimidines. *Advanced Synthesis & Catalysis*, *351*(18), 3057-3062.
3. Kappe, C. O. (1993). 100 years of the Biginelli dihydropyrimidine synthesis. *Tetrahedron*, *49*(32), 6937-6963.
4. O'reilly, B. C., & Atwal, K. S. (1987). Synthesis of substituted 1, 2, 3, 4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters: The Biginelli condensation revisited. *Heterocycles (Sendai)*, *26*(5), 1185-1188.
5. Pasha, M. A., Swamy, N. R., & Jayashankara, V. P. (2005). One pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones/-thiones catalysed by zinc chloride: An improved procedure for the Biginelli reaction using microwaves under solvent free condition.
6. Bahrami, K., Mehdi Khodaei, M., & Farrokhi, A. (2009). Highly efficient solvent-free synthesis of dihydropyrimidinones catalyzed by zinc oxide. *Synthetic Communications®*, *39*(10), 1801-1808.
7. Prasad, B. D., Sastry, V. G., Ramana, H., Devilal, J., & Rao, A. S. (2016). Multicomponent Biginelli's synthesis, antimycobacterial activity and molecular docking studies of dihydropyrimidine derivatives as thymidylate kinase protein targets. *Pharmacologia*, *7*(5), 256-263.