LOVELY PROFESSIONAL UNIVERSITY

(May- 2017)

DISSERTATION-II FINAL REPORT

For the Partial Fulfilment of the Degree of Masters of Sciences (Chemistry)

On the project entitled as

Green multi component condensation of thiourea in eco-friendly and biodegradable reaction medium

Submitted by

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(Registration number - 11502165)

Under the guidance of

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TOPIC APPROVAL PERFORMA

School of Chemical Engineering and Physical Sciences

Program : P266-H: M.Sc. (Hons.) Chemistry

COURSE CODE : CHE645 **REGULAR/BACKLOG :** Regular **GROUP NUMBER :** SCRGD0005

Supervisor Name: Dr. Tanay Pramanik **UID :** 16842 **Designation :** Assistant Professor

Qualification : _____ **Research Experience :** _____

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SPECIALIZATION AREA : Organic Chemistry **Supervisor Signature:** _____

PROPOSED TOPIC : Green multi component condensation of thiourea in eco-friendly and biodegradable reaction medium.

Qualitative Assessment of Proposed Topic by PAC		
Sr.No.	**Parameter**	**Rating (out of 10)**
1	Project Novelty: Potential of the project to create new knowledge	7.25

2	Project Feasibility: Project can be timely carried out in-house with low-cost and available resources in the University by the students.	7.00
3	Project Academic Inputs: Project topic is relevant and makes extensive use of academic inputs in UG program and serves as a culminating effort for core study area of the degree program.	7.50
4	Project Supervision: Project supervisor's is technically competent to guide students, resolve any issues, and impart necessary skills.	7.50
5	Social Applicability: Project work intends to solve a practical problem.	7.25
6	Future Scope: Project has potential to become basis of future research work, publication or patent.	6.75

PAC Committee Members		
PAC Member 1 Name: Dr. Gurpinder Singh	UID: 13608	Recommended (Y/N): Yes
PAC Member 2 Name: Dr. Ashish Kumar	UID: 16464	Recommended (Y/N): Yes
PAC Member 3 Name: Dr. Rekha	UID: 14537	Recommended (Y/N): NA
DRD Nominee Name: Dr. Runjhun Tandon	UID: 19532	Recommended (Y/N): Yes
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Final Topic Approved by PAC: **Green multi component condensation of thiourea in eco-friendly and biodegradable reaction medium.**

Overall Remarks: Approved

PAC CHAIRPERSON Name: 11800::Dr. Ramesh Chand Thakur **Approval Date:** 13 Oct 2016

CERTIFICATION

This is to certify that this research was carried out by GURINDERPAL SINGH under the supervision of Dr. Tanay Parmanik at the Department of Chemistry, Lovely Professional University, for the award of M.Sc. (Hon's) chemistry.

Date:

(Signature of supervisor)

Dr. Tanay parmanik

(Assistant Professor)

Department of chemistry,

Lovely Professional university.

DECLARATION

I here declare that the dissertation entitled "**Green multi component condensation of thiourea in eco-friendly and biodegradable reaction medium**" submitted for M.Sc. (hons.) chemistry degree to Department of Chemistry, Lovely Professional University is entirely original work and all ideas and references have been duly acknowledged. The dissertation has not formed the basis for the award of any other degree.

DATE:

GURINDERPAL SINGH

11502165

ACKNOWLEDGEMENT

First of all I would like to thank the Almighty without whose blessings this would not have completed. I thank God for being there always with me through every thick and thin phase of time.

Secondly, I would like to express my deepest gratitude to my mentor, **Dr. Tanay Parmanik**, for introducing me to this subject of "**Green multi component condensation of thiourea in eco - friendly and biodegradable reaction medium**". His erudite guidance, undying patience and trust in me has made me able to complete this dissertation. It is my privilege to have worked under his guidance. Words are not enough to describe the emotions and feeling of gratitude.

I would like to thanks **Dr. Ramesh Thakur** (HOS) of school of chemical engineering and physical sciences, who has encouraged and supported me at each and every stage, listened to our problems and provided an adequate solution to them. Without his experience, motivation and direction, this project would not have been reached to its completion.

Last but not at the least important, I owe more than thanks to my family, for their support and unconditional love and care that they have always showered upon me. I owe my each and every success to them.

GURINDERPAL SINGH

LOVELY PROFESSIONAL UNIVERSITY

PUNJAB

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List of tables and spectra's

List of Abbreviations

SNo.	Code	Name
1.	GCL	Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
2.	GNO	Ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
3.	GBR	Ethyl 4-(4-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
4.	GCN	Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
5.	DHPM's	Dihydropyrimidinones
6.	MW	Microwave
7.	IR	Infrared
8.	NMR	Nuclear Magnetic Resonance
9.	MORE	Microwave Induced Organic Reaction Enhancement
10.	DNA	Deoxyribonucleic acid
11.	RNA	Ribonucleic acid
12.	TLC	Thin Layer Chromatography
13.	DMSO-d^6	Dimethyl Sulfoxide

ABSTRACT

A large number of multi component condensation reactions of thiourea are reported in literature for synthesis of hetero cyclic compounds of great pharmaceutical importance. However most of those reactions were reported by making use of toxic solvents and non-eco-friendly catalysts. Although the biodegradability and eco-friendly nature of glucose, vinegar and water have made them potentiality useful green reaction medium for organic reactions, unfortunately they have not been well explored in literature as eco-friendly reaction medium for performing multi component condensation reactions. In this project a series of multi component condensation reactions of thiourea will be carried out by making use of glucose, vinegar and water as eco- friendly and green reaction medium for the first time ever.

INTRODUCTION

Green chemistry

Green chemistry is the branch of chemistry in which the reaction pathways are design to reduce the wastage and formation of hazardous substances after the completion of reaction and chemical products are formed with the maximum use of reactant.

Principles of green chemistry

1. Prevention: - The chemical synthesis should be designed in such a way that there is no wastage left to clean up or treat.

2. Economy of Atom: - The product formed should have the maximum proportion of the starting material. There is not any wastage of atom in the synthesis.

3. Less Hazardous Chemical Syntheses: - The product formed should be less or not toxic to the human, environment.

4. Design of safe chemicals: - The products formed are effective with less or no toxicity.

5. Use of safer reaction condition and solvents: - Avoid the use of solvents and separation agents. Instead of this use green solvents.

6. Energy efficiency: - Wherever possible done reaction under room temperature of pressure.

7. Use of renewable feedstock's: - Instead of using depletable starting materials, use renewable one. The raw starting material can be agricultural products or other processes waste etc.

8. Reduce chemical derivative: - Derivatization (use of blocking or protecting groups) in chemical processes use additional reagents and generate waste. It is better to avoid this wherever possible.

9. Use of catalysts: - It is better to use catalysts rather than using stoichiometric reagents.

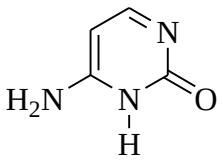
10. Degradation after use: - The products and chemicals are designed in such a way that they can degrade after use and not harm the environment.

11. To prevent pollution do real time analysis: - the reaction pathways are designed for real time and in process monitoring, control of reaction so to avoid the formation of hazardous byproducts.

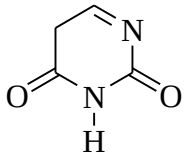
12. Safer chemistry to avoid accident: - The chemicals and other material are used which are not potentially harmful to cause explosion, fires and releases to the environment.

IMPORTANCE OF DHPM

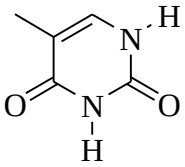
The dihydropyrimidinones i.e. 3, 4-Dihydropyrimidin-2(1H)-one (DHPMs) that can be synthesized under acidic condition by the condensation of urea, Keto-ester and an aldehyde. These are heterocyclic compounds having immense applications in pharmacology. The derivatives of pyrimidine compound are also present in DNA and RNA in the form of Cytosine, Thymine and Uracil. Hence these compounds gets immense attention and importance in organic chemistry.



Cytosine



Uracil



Thymine

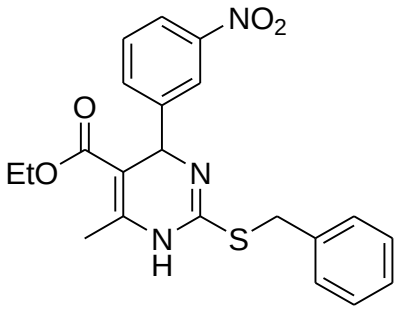
Nucleic acids

Fig 1.1.1

DHPMs have various therapeutic, multifaceted and remarkable biological activities, such as antitumor, antiviral, antiflammatory, antibacterial, antihypertensive agents, anticancer medications, anti-epileptics, anti-malarial, anti-microbial, anti-tubercular, anti-oxidants, calcium channel modulating activity and many more. Due to these activities these compounds have significant industrial scope. [1-6]

Examples of DHPM's with different activities:

Anti-Hypertensive agents[7]



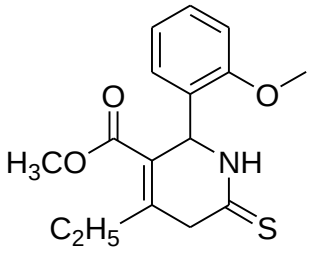


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Fig 1.1.2

Potassium Channel Antagonists[8]

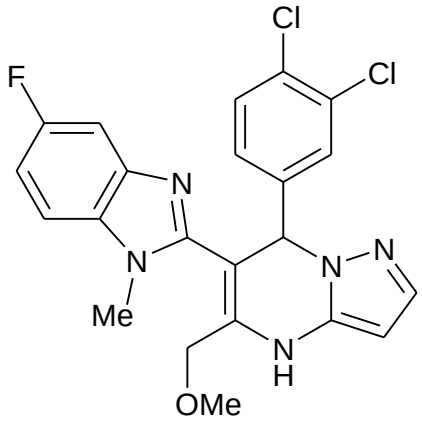
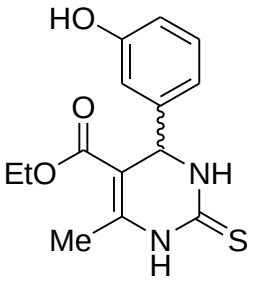


Fig 1.1.3

Anti-Tumor Activity[9]



(S)-MONASTROL

a

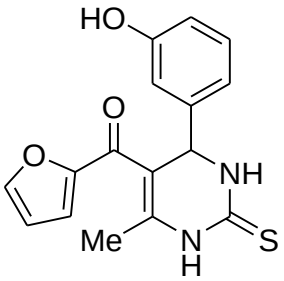


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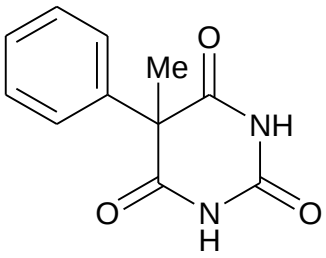
Fig 1.1.4

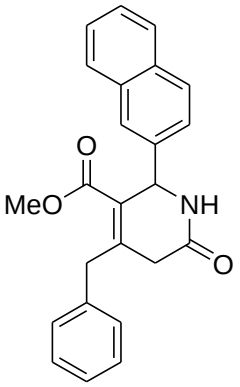
Anti-Epileptics[10]



Phenobarbital

Fig 1.1.5

Anti-Malarial[11]



J AB 75

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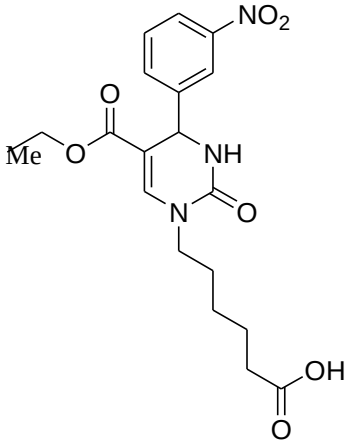

MAL 2-29

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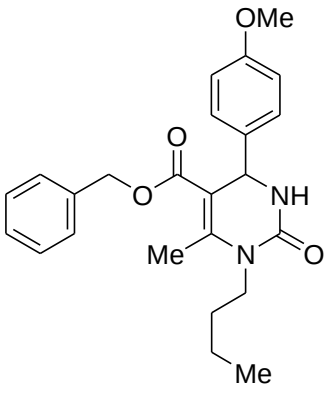


MAL 2-39

c

Fig 1.1.6

Anti-Microbial[12]

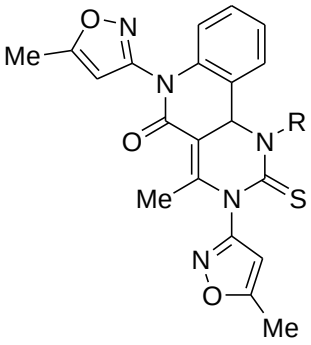


Fig 1.1.7

Anti-inflammatory[13]

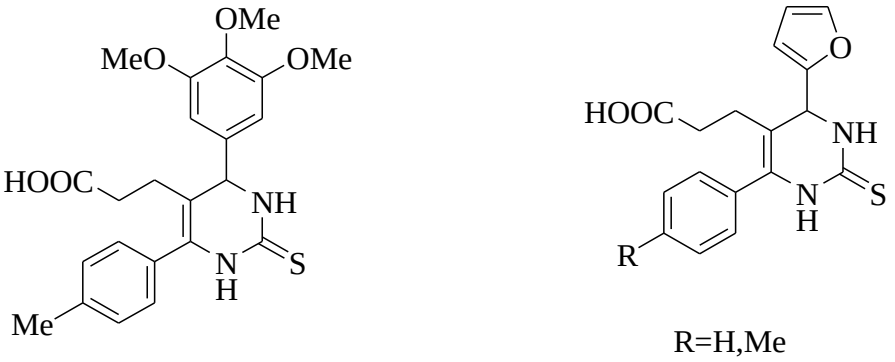


Fig 1.1.8

Anti-Tubercular activity[14]

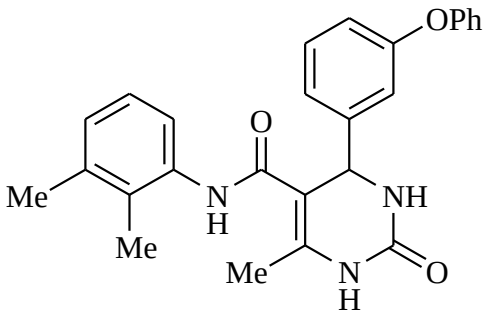
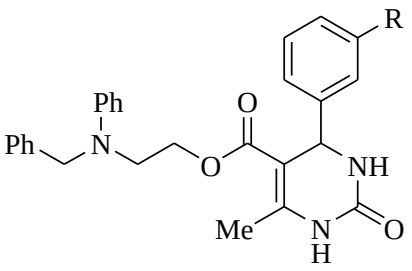
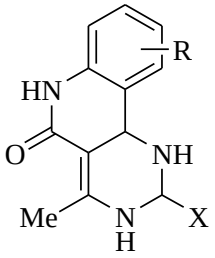


Fig 1.1.9

Miscellaneous[15]



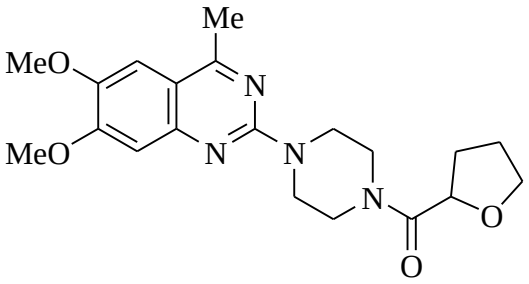
R=H,NO_2



X=O,S

Fig 1.1.10

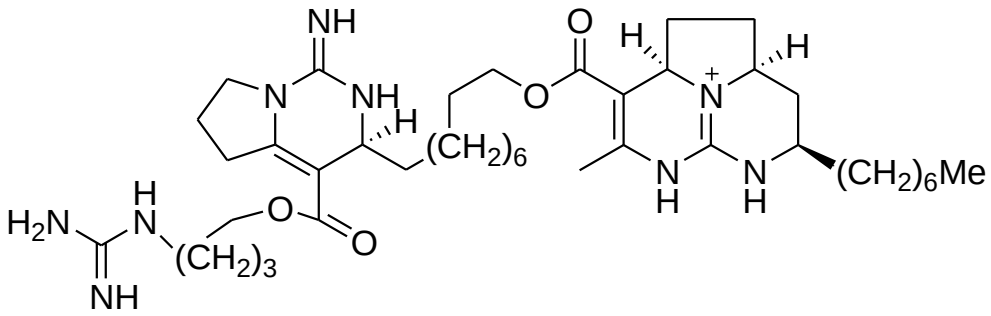
Anti-oxidants[16]



Tetrazosin

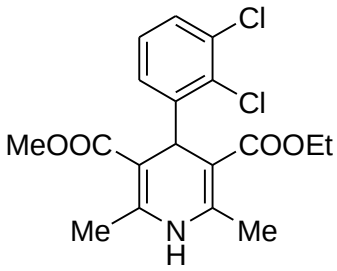
Fig 1.1.11

In many marine alkaloids these pyrimidinone derivatives are found to be as core units and these are found to be potent to HIV-gp-120 CD4 inhbitors, e,g. batzelladine and carambine.



Batzelladine

Fig 1.1.12



Felodipine

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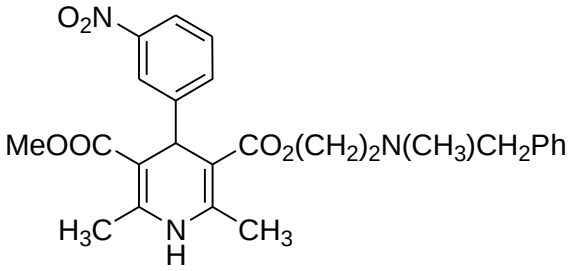
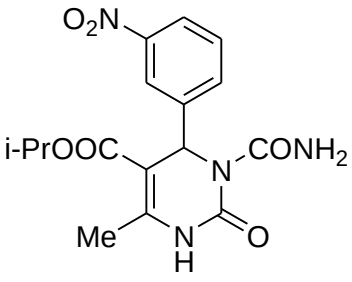


Nicardipine

b

Fig 1.1.13



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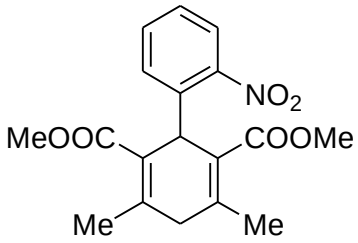


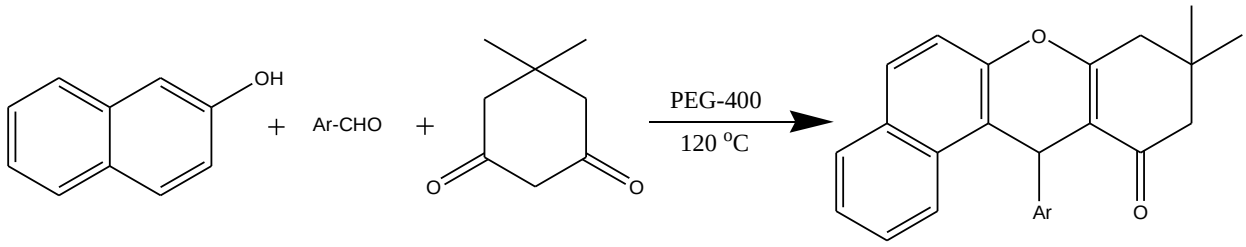
Nifedipine

b

Fig 1.1.14

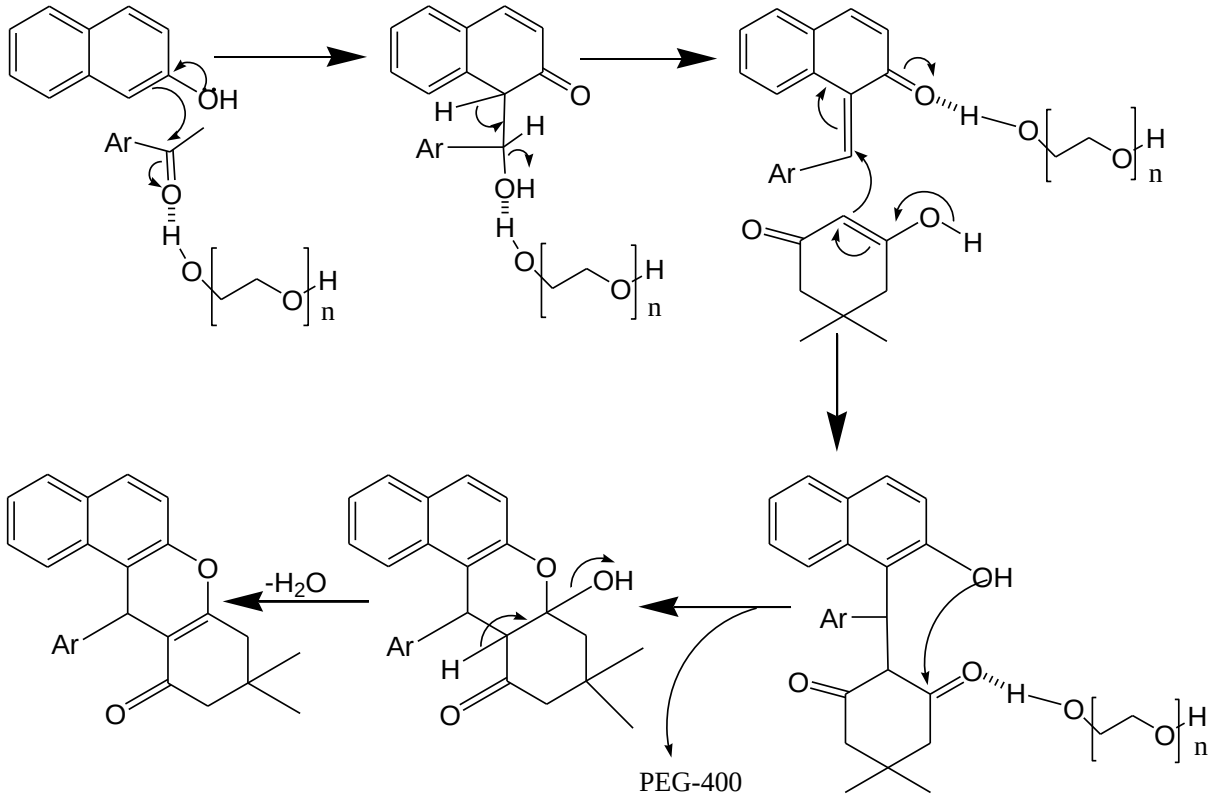
Multicomponent condensation reactions

A multicomponent condensations reaction are single vessel reactions in which three or more compounds are combined to give useful product and the product obtained has characteristic of all the compounds. As these reactions occur in single vessel so they are easier to perform than the other multistep reactions. These reactions proceeds by the creation of many sigma bonds in a single step and provide the remarkable advantages like convergence, simplicity in operations, simplistic automation, workup reduction, extraction and purification processes, and hence decreasing the waste production, leads to the green transformations. In comparison to multistep reactions these reactions provide high chemical yield in shorter period of time. Now the scientists are taking more interest in carrying out these reactions in environmental friendly conditions by taking the measure of green chemistry.[17] Glucose and glycerol both are green solvents and they are never been used as solvent in any reaction before. In this reaction they are working as solvent as well as catalyst to increase the rate of reaction. There was not any mechanism known in literature for Biginelli reaction using glucose and glycerol as reaction media. There has been a reaction known for the synthesis of Tetrahydrobenzo[α]-xanthen-11-one, which is acid catalyze reaction. But in this reaction instead of acid they have used PEG-400 which results to be efficient reaction media and catalyze a reaction through hydrogen bonding between carbonyl oxygen of aldehyde and OH of PEG-400. This hydrogen bonding helps in increasing the polarity of carbonyl bond and increase the reaction rate. Reaction scheme and reaction mechanism was as shown below:-



Scheme A: - synthesis of tetrahydrobenzo[α]-xanthen-11-one by using PEG-400 as a greener solvent.

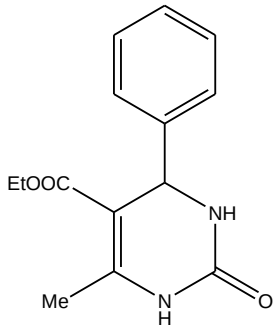
Mechanism:-



In this reaction the PEG-400 has been catalyzing the reaction efficiently by participating in every step of the reaction. Our reaction is also an acid catalyze reaction. Considering the above mechanism we used glucose as a reaction medium because it also have some hydroxyl functional groups in its structures which can do hydrogen bonding with aldehyde and catalyze the reaction as shown above.[2]

BIGINELLI REACTION

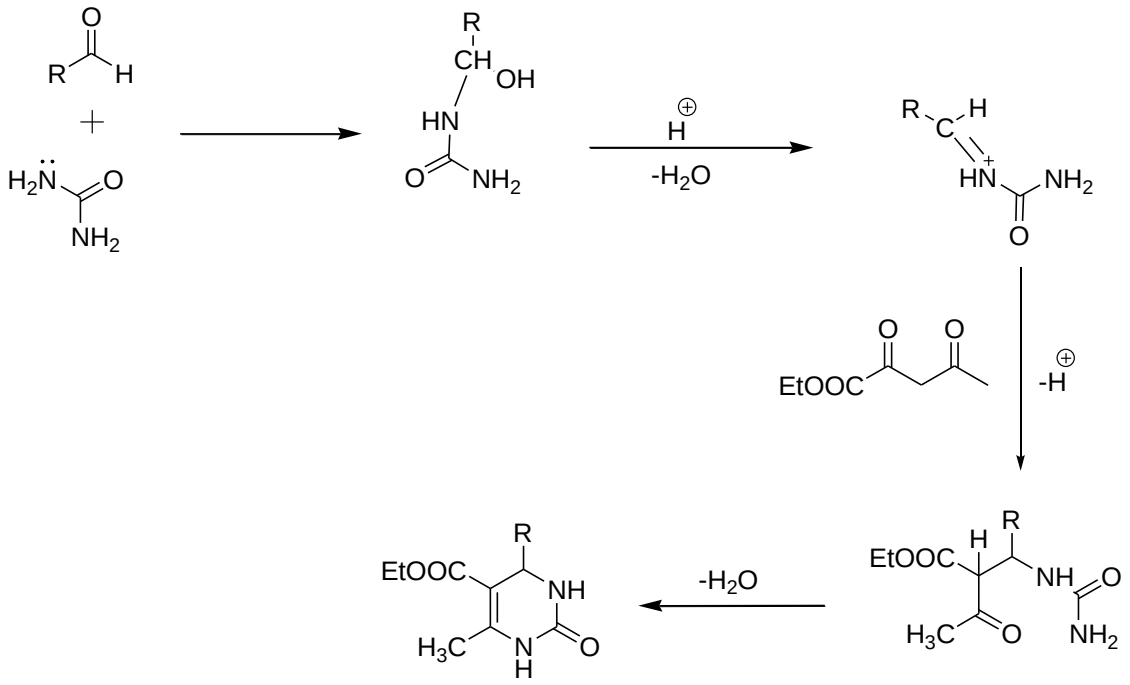
Biginelli reaction is the condensation reaction of urea, ethyl acetoacetate and aldehyde in the alcoholic acidic reaction condition. The product of this reaction is the well-known compound 3, 4-Dihydropyrimidin-2(1H)-ones.[1]



Biginelli Compound

MECHANISM

As the compound formed by biginelli reaction is very useful industrially as well as pharmaceutically, many chemists done different studies to find the pathway by which the reaction may proceed. As this reaction proceeds with the condensation 1, 3-carbonyl compound, aldehydes and urea or thiourea in stepwise manner. The possible mechanism for the reaction keeping the reactivity of these compounds in mind is given below:-



Scheme B: - Mechanism of biginelli reaction.

MICROWAVE DIELECTRIC HEATING MECHANISM

The increase in the efficiency and the rate of organic reactions by using microwave irradiations have been recognized widely in the chemistry world. The reduced reaction time and increased reaction selectivity are the main reason for this. Those reactions can also be done by this method which don't occur by conventional heating method. Because of the less reaction time, higher yields and milder reaction conditions this method gives energy efficient reactions.

This method comes under the application of microwave technology for microwave induced organic reaction enhancement chemistry (MORE). The processes are considered highly green which occurs in microwave irradiations. In between the radio wave region and infrared region there is microwave region in the electromagnetic spectra. 12.2cm to 33.3cm is the working range of industrial and domestic microwaves.

Electromagnetic energy transforms into heat by microwave heating, in comparison to conventional heating. The heating and the absorption of the radiation may be performed selectively and the heating magnitude depends on molecule's dielectric properties. The simultaneous heating of whole reaction occurs because of the rapid nature of these radiations.

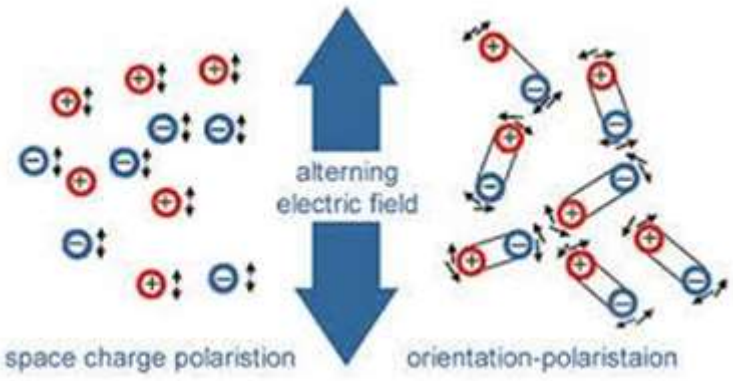


Fig 1.2.1 Heating under microwave irradiations

[www.pueschner.com]

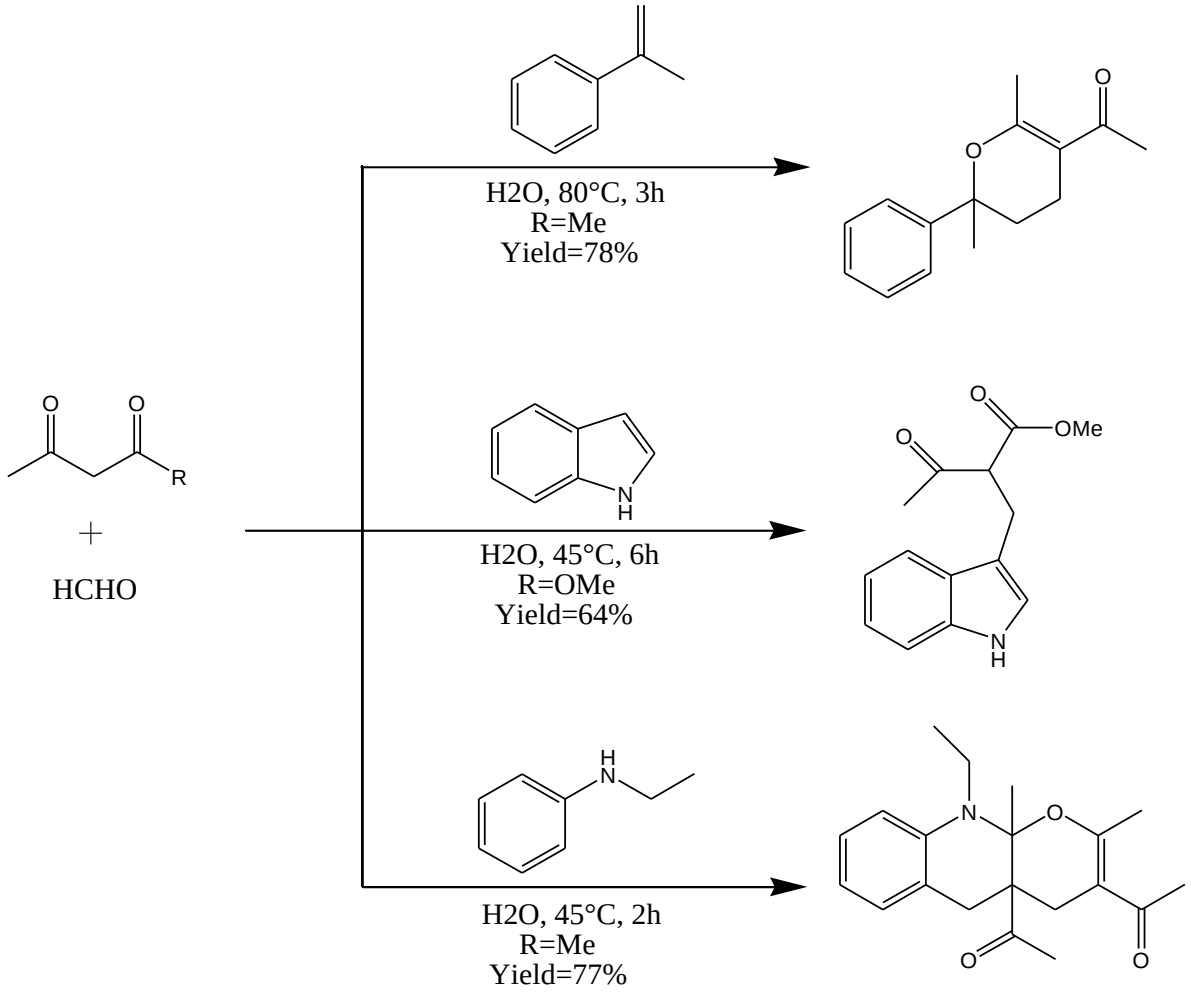
GREEN SYNTHESIS UNDER VISIBLE LIGHT RADIATION

Light is always a good source of energy for performing many of the chemical reaction. There are certain research papers were also there, in which there was a use of light as an energy source or reagent for chemical reaction has been reported. Electronically excited state of the molecule is reached when it absorbs light radiation. Significant difference is there in the energy between the two electronic states. This energy gap cause changes in the reactivity and chemical properties of the molecule. These changes helps chemists to synthesize variety of new compounds. There is no use of any additional reagent for the reaction is required in many of the photochemical reaction so there is very less formation of by-products. According to green chemistry, these reactions are very good and efficient. Even in the presence visible light and sunlight some reactions proceeds very easily. Those reactions can also be done by this method which don't occur by conventional heating method. The transformation inside the supramolecular structures or crystals can also be assist by light. The stereo selective control of the photochemical reactions by light is also reported in some research papers.[19-21]

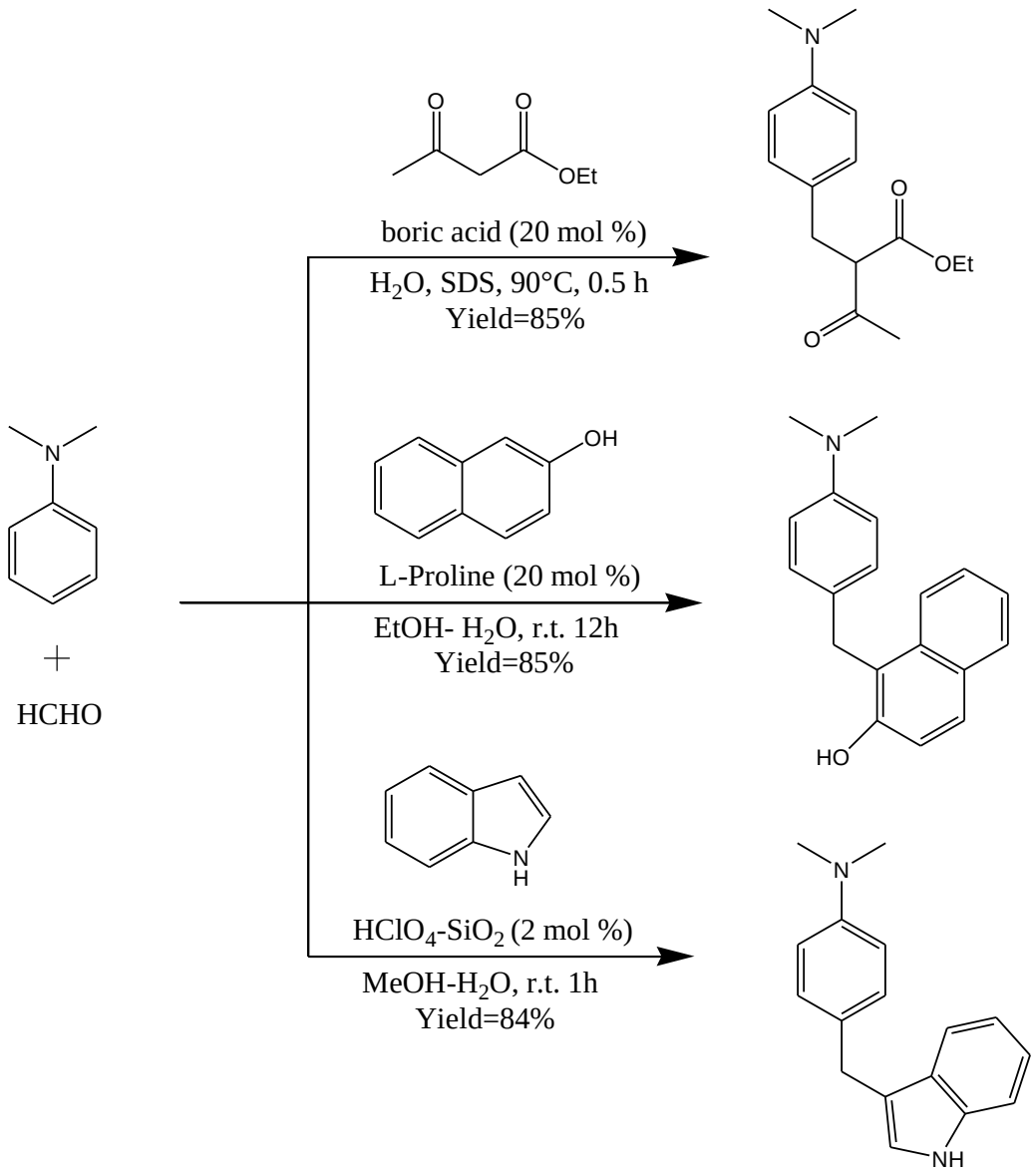
LITERATUE REVIEW

MULTICOMPONENT CONDENSATION REACTIONS

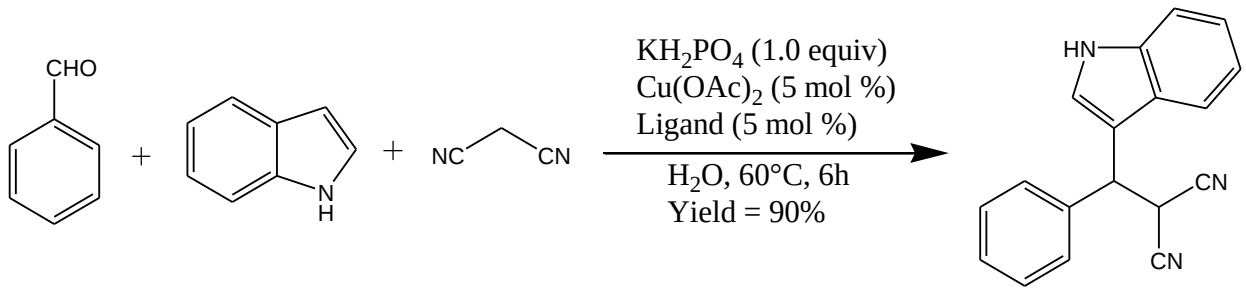
MCR's in water based on Knoevenagel condensation:-Knoevenagel reations are base catalyzed reactions in which aldehydes and 1,3 dicarbonyl reacts to give polyfunctional organic compounds, that can be converted easily into more complex molecule by using suitable reagents.

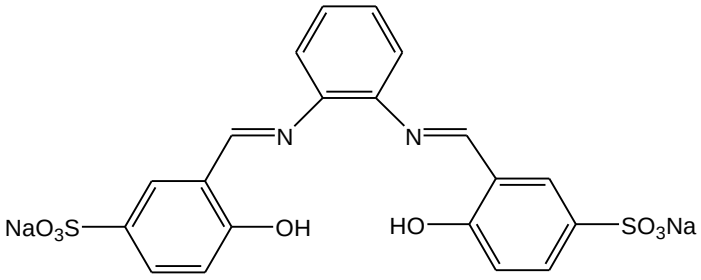


Scheme 1: -MCRs of formaldehyde with β-dicarbonyl compound in water.[22]



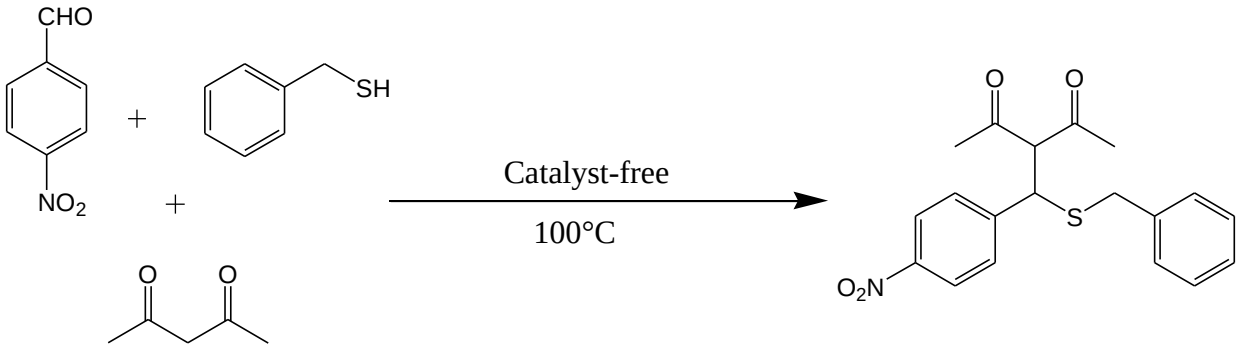
Scheme 2:- MCRs of formaldehyde with N, N-dimethyl aniline in water.[23]





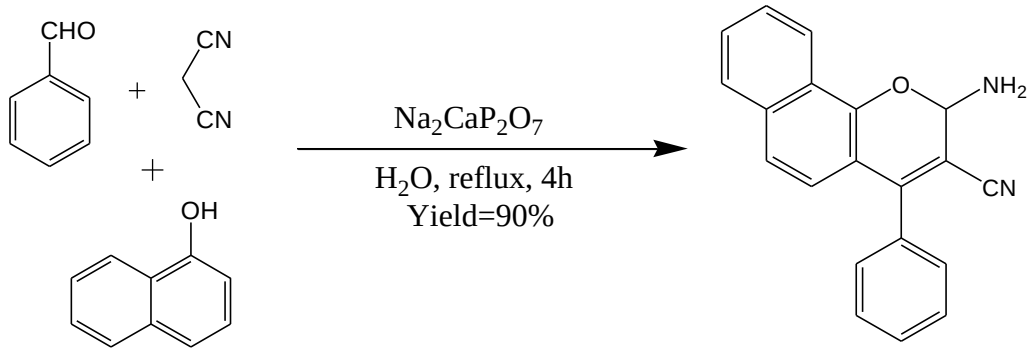
Ligand

Scheme 3:- MCRs of indole, aldehyde, and malononitrile in water.[24]

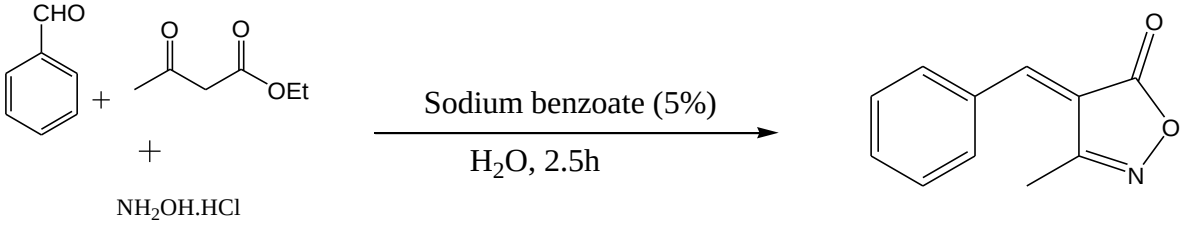


Solvent	Time (h)	Yield(%)
H_2O	12	92
toluene	24	trace
DMSO	24	33
DMF	24	22

Scheme 4:-MCRs of 4-nitrobenzaldehyde, benzyl mercaptan and acetylacetone in water.[25]

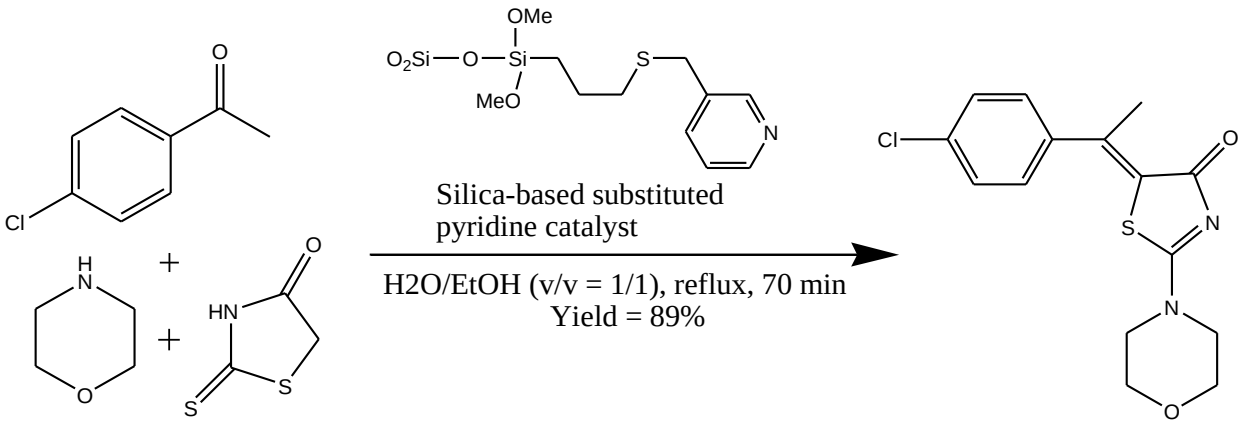


Scheme 5:- MCRs of benzaldehyde, malononitrile and 1-naphthol in water.[26]

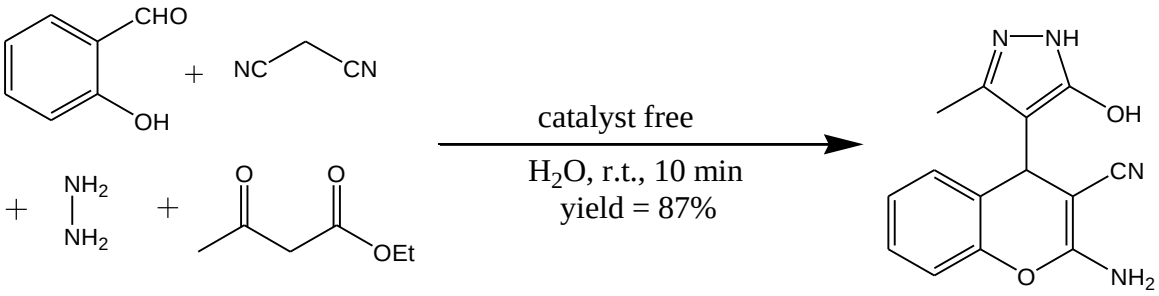


Solvent	Yield (%)
H_2O	84
EtOH	60
Cyclohexane	58
1,4 dioxane	28
Acetone	trace
Solvent-free	51

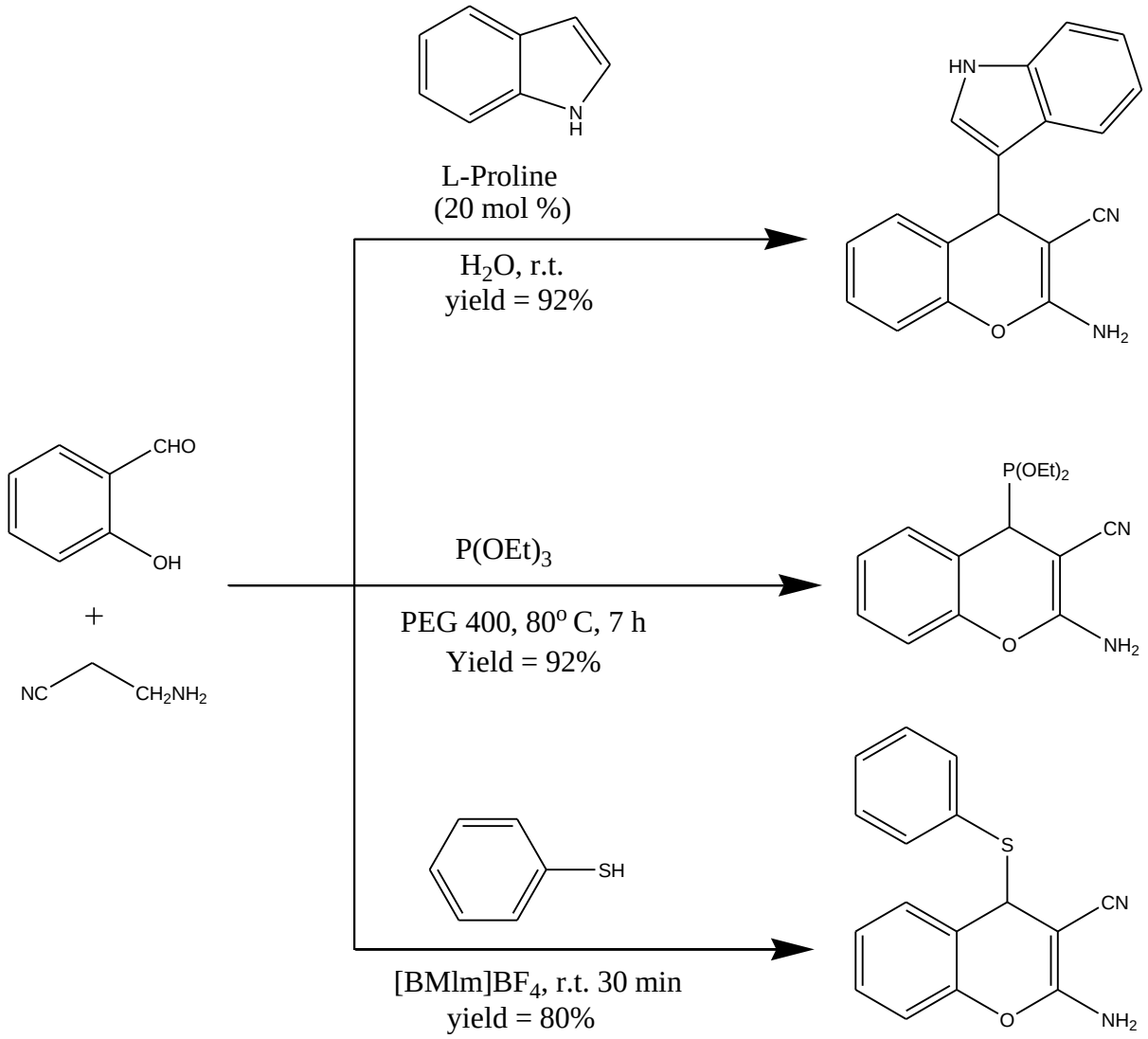
Scheme 6:- MCRs of benzaldehyde, ethyl acetoacetate and hydroxylamine hydrochloride in water.[27]



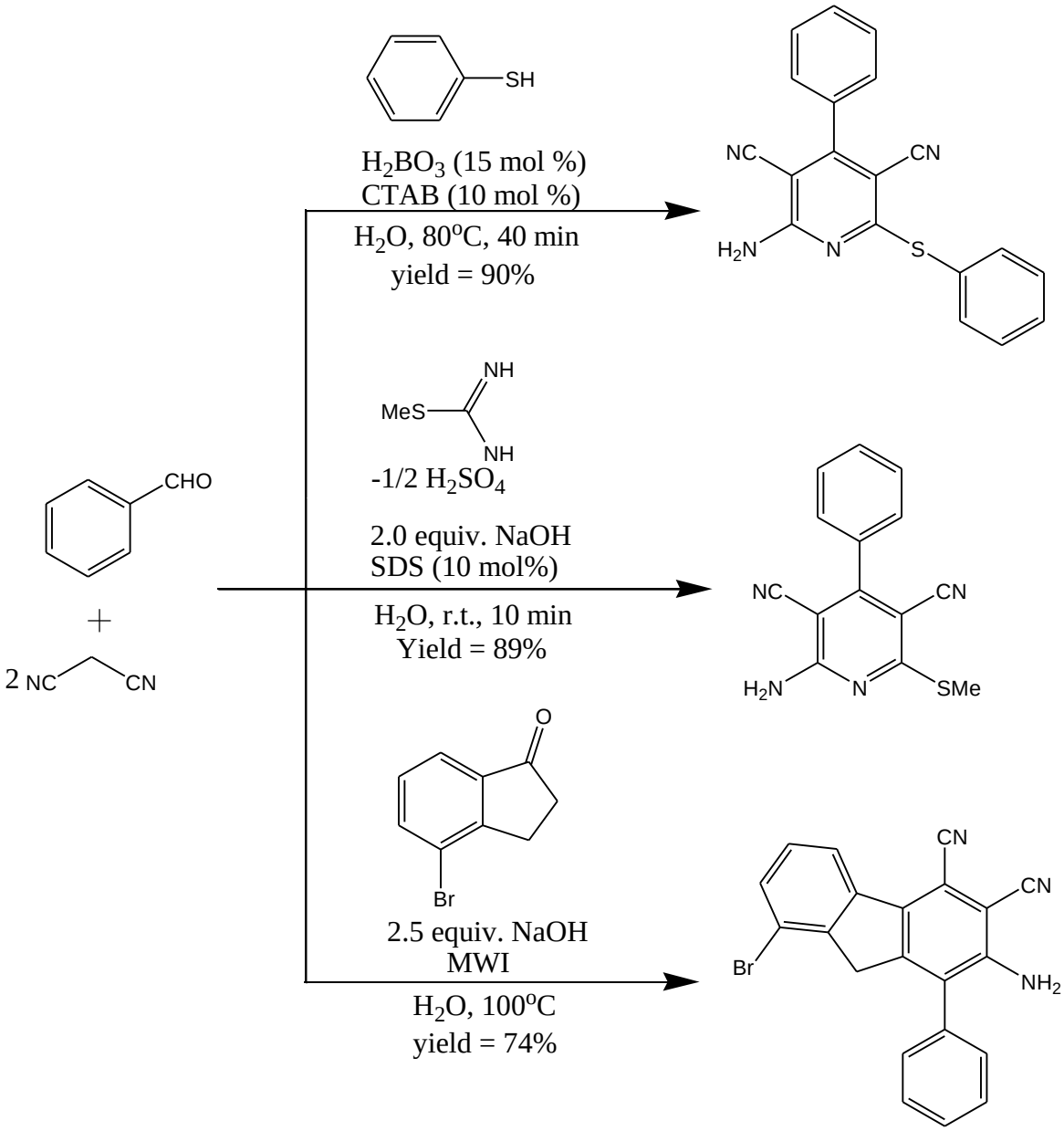
Scheme 7:- MCRs of rhodanine, amines and methyl ketone in aqueous media.[28]



Scheme 8:- MCRs of hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehyde and malononitrile in water.[29]

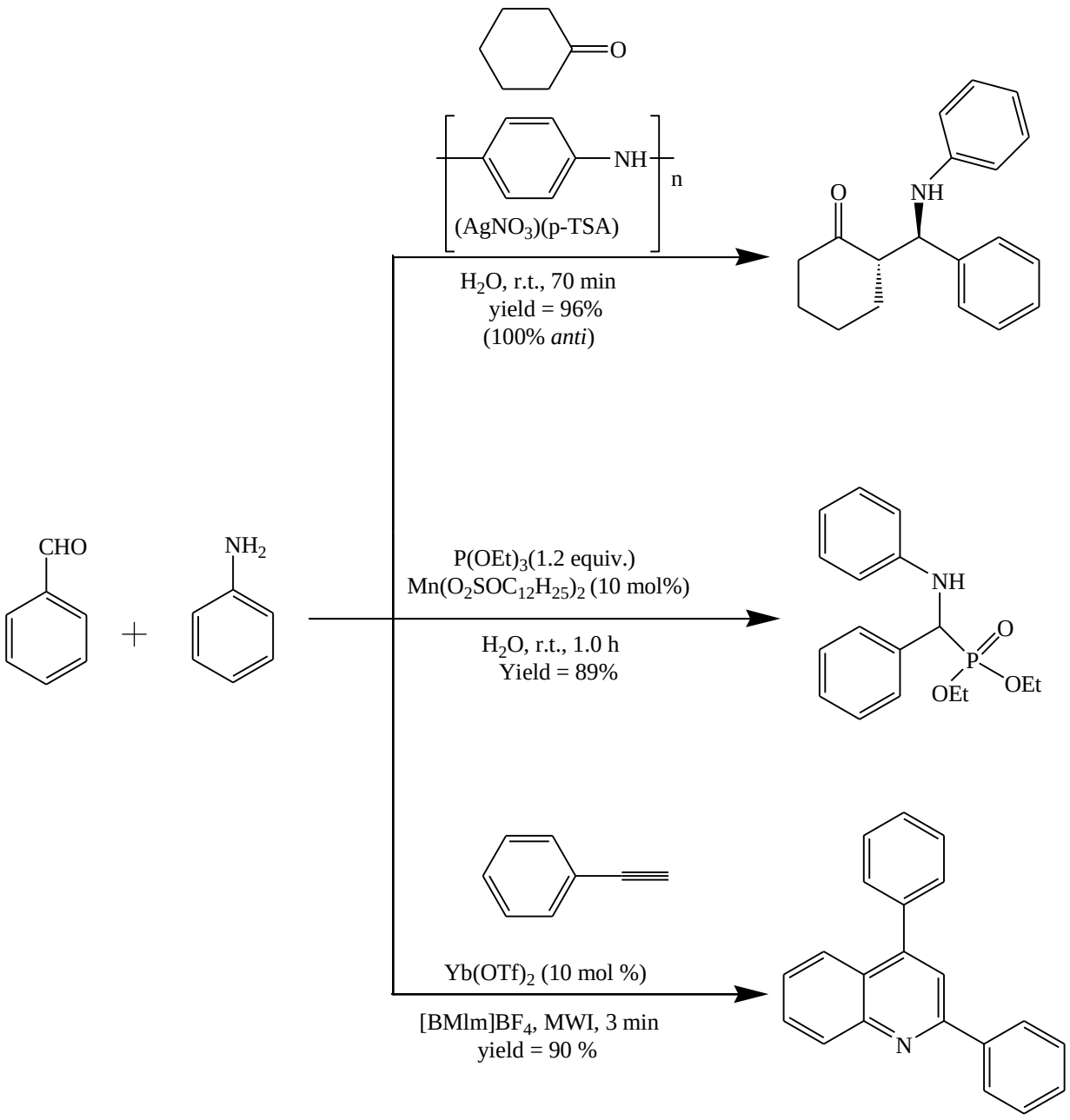


Scheme 9:-MCRs of salicylaldehyde and malononitrile.[30]

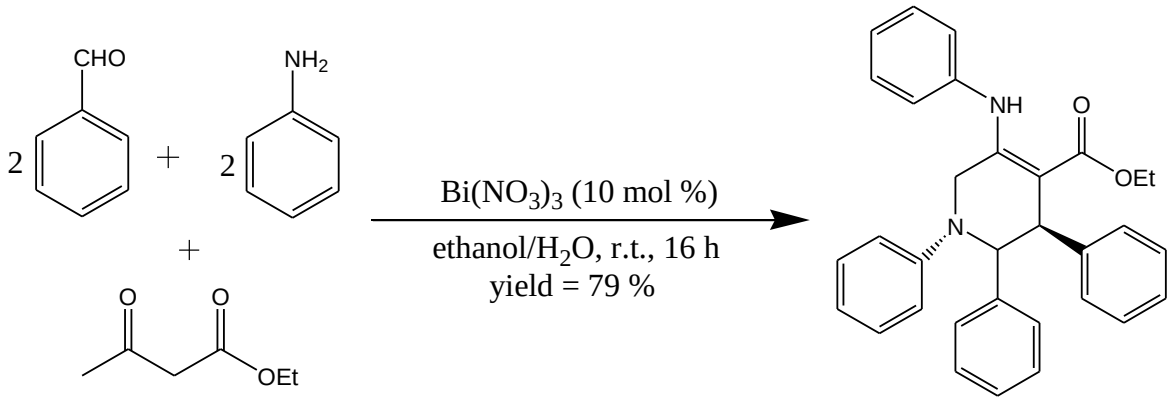


Scheme 10:- Pseudo-four-component reactions of benzaldehyde and malononitrile in water.[31]

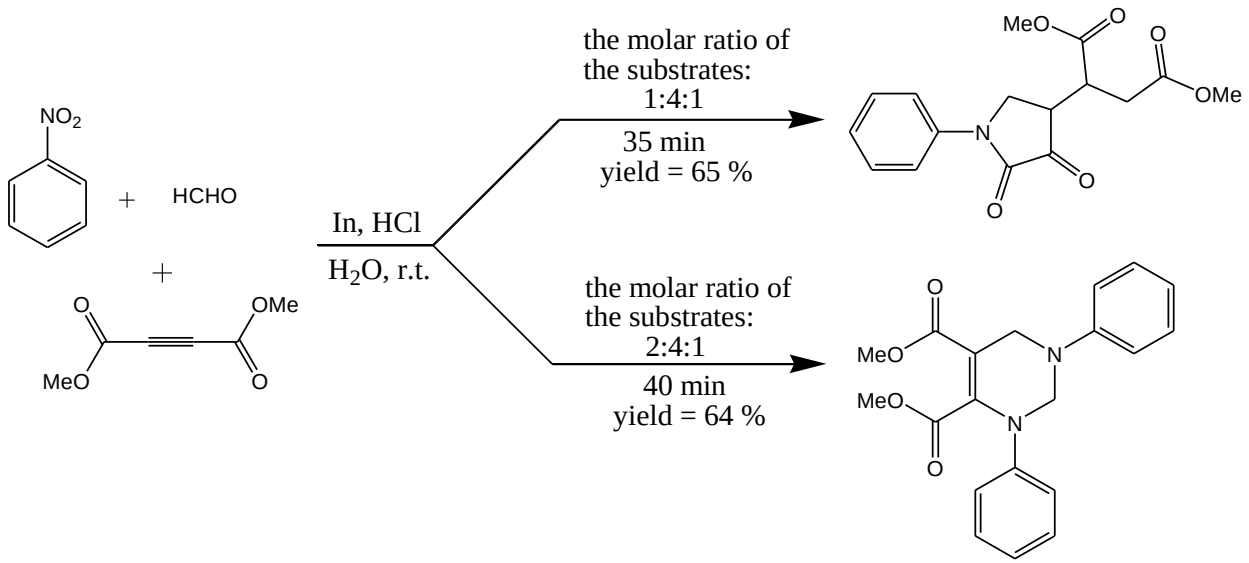
2. MCRs in water based on imine formation: - This MCR is a Mannich type of reaction in which aldehyde and aniline in water combine to give imine. Many reaction under this fact are investigated using aldehydes, aniline and ketones in water.



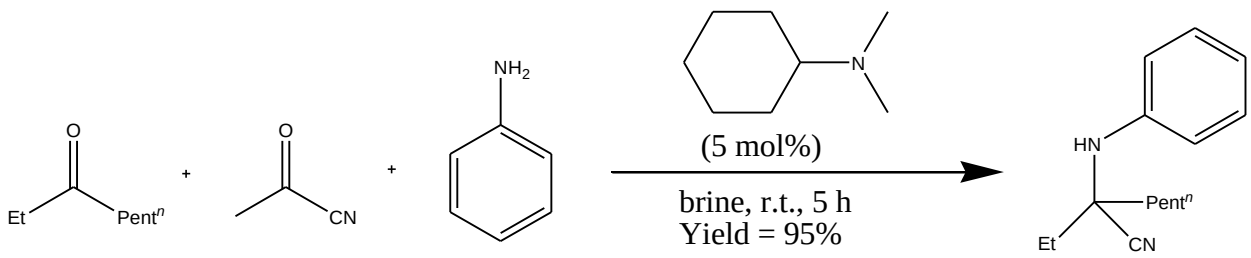
Scheme 11: - MCRs of benzaldehyde and aniline in water or ionic liquid.[32]



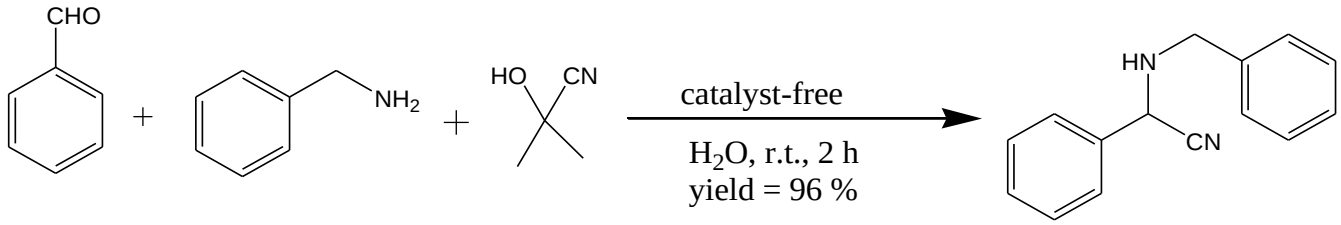
Scheme 12: - Pseudo-five-component reaction of β-ketonester, benzalaldehyde and aniline in water.[33]



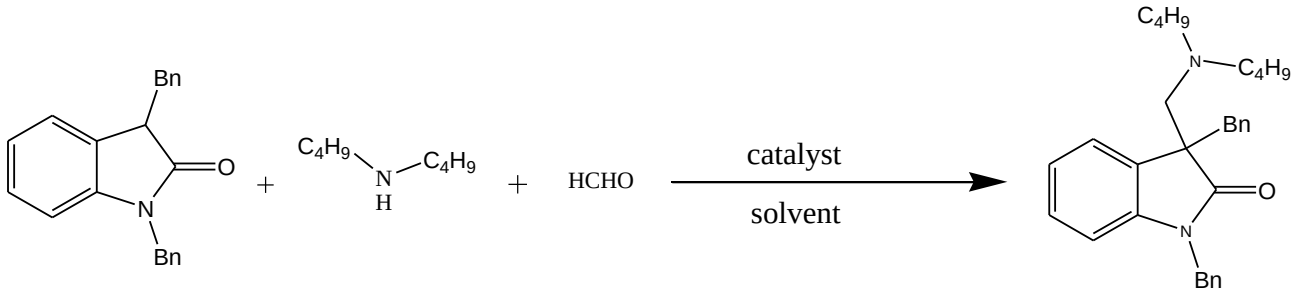
Scheme 13: - Three-component reactions of nitroarenes, formaldehyde, and dialkyl acetylene dicarboxylate in water.[34]



Scheme 14: -Strecker reaction of ketones and aniline using acetyl cyanide in water.[35]

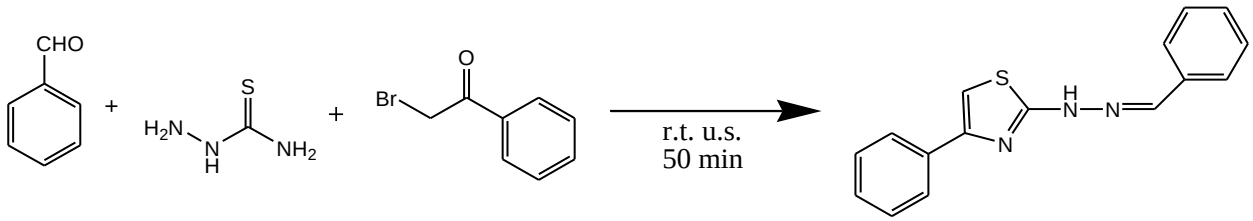


Scheme 15:-Strecker reaction of benzaldehyde, benzylamine, and acetone cyanohydrin in water.[36]



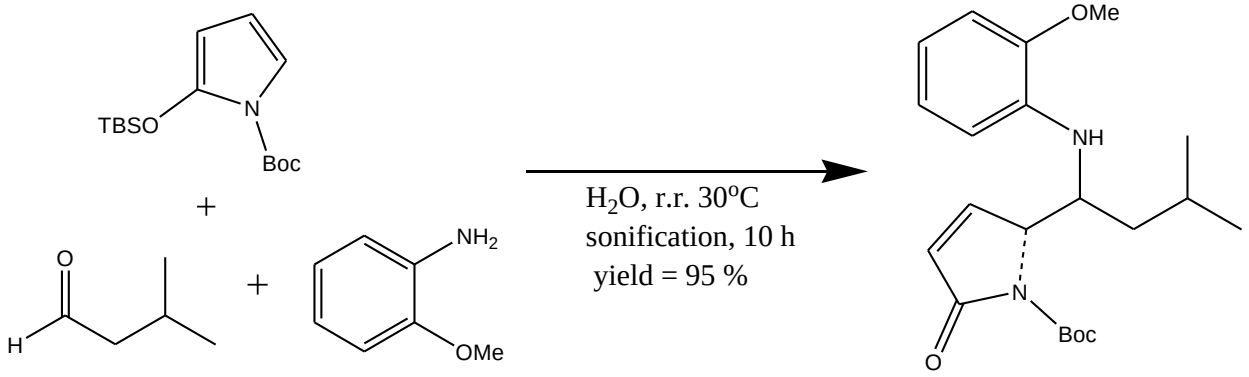
Solvent	Formaldehyde source	catalyst	Time (h)	Temp. (°C)	Yield (%)
Ethyl acetate	$(HCHO)_n$	-	24	35	90
H_2O	HCHO *aqu.*	SDS (10 mol %)	3	90	85

Scheme 16:- Mannich reaction of 3-substituted oxindoles, formalin, andvarious secondary amines.[37]



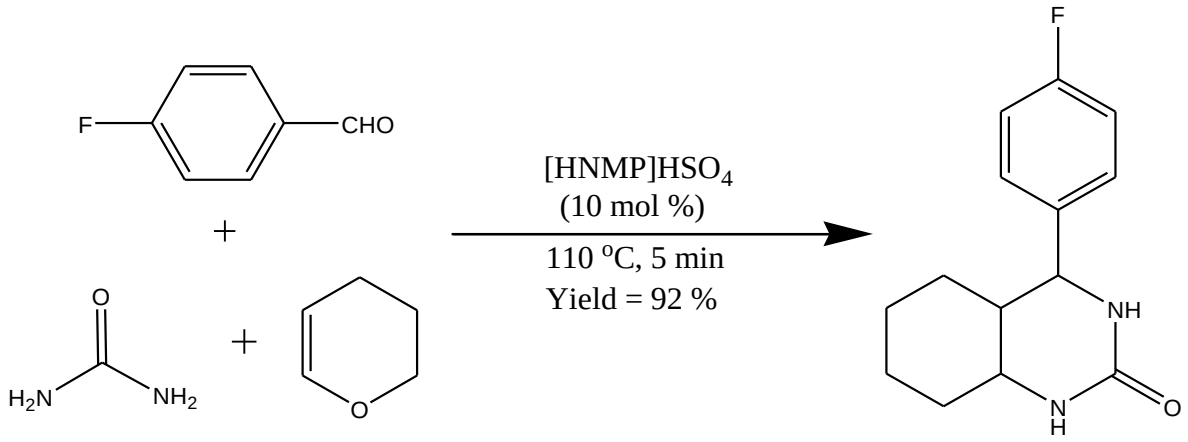
Solvent	Yield (%)
H_2O	90
EtOH	63
2-propanol	65
CH_3CN	45
CH_2Cl_2	56

Scheme 17:- Three-component reaction of aromatic aldehyde, thiosemicarbazide and phenacyl bromide in different solvents.[38]



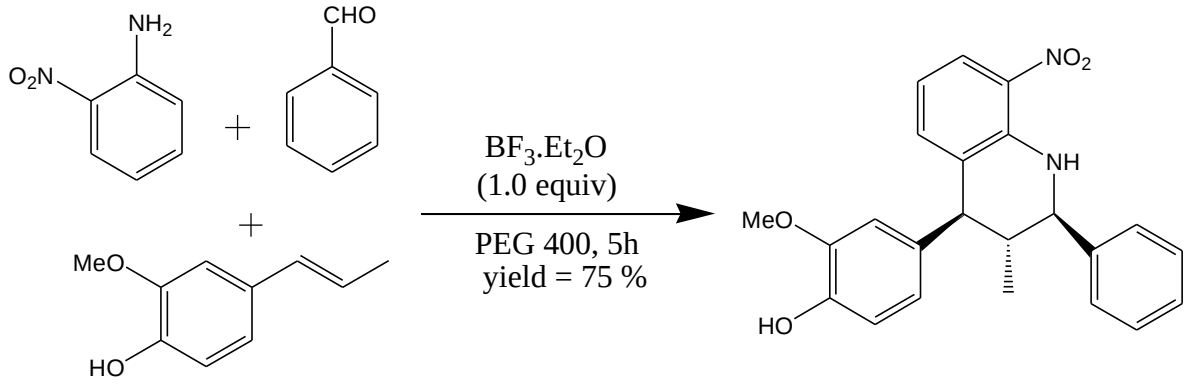
Scheme 18:- Three-component vinylogous Mukaiyama–Mannich reaction of pyrrole ketene silyl-N, O-acetal, aniline, and aldehydes in water.[39]

3. MCRs in ionic liquids:-The attractiveness of ionic liquids as reaction media is attributedto their unusual physicochemical properties, such as negligible vapor pressure, low volatility, tunable polarity and miscibility with organic or inorganic compounds.

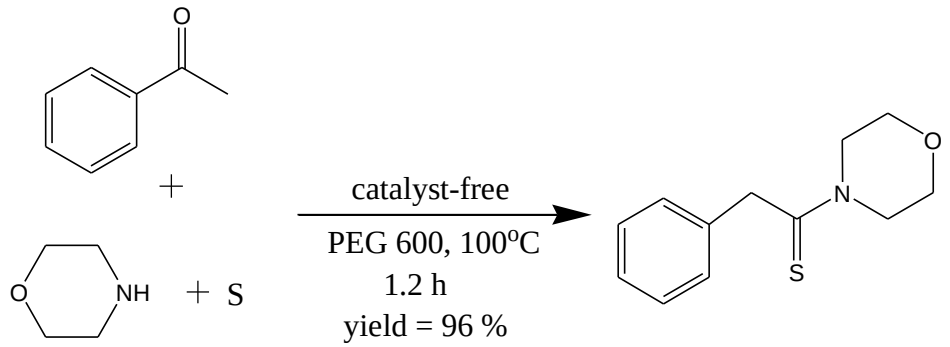


Scheme 20: - Three-component reaction of aromatic aldehydes, urea or thiourea, and 3, 4-dihydro-2H-pyran in ionic liquid.[40]

4. MCRs in PEGs: - PEG (polyethylene Glycol) is a polymers and an environmental friendly reaction media.



Scheme 21: -Povarov reaction in PEG-400.[41]



Scheme 22:- Willgerodt-Kindler reaction in PEG 600.[41]

MULTICOMPONENT CONDENSATION REACTIONS WITH THIOUREA

BIGINELLI REACTIONS USING THIOUREA: -

J. P. Wan and Y. J. Pan have reported the Chemo-/regioselective synthesis of 6-unsubstituted dihydropyrimidinones, 1, 3-thiazines and chromones via novel variants of Biginelli reaction.[43]

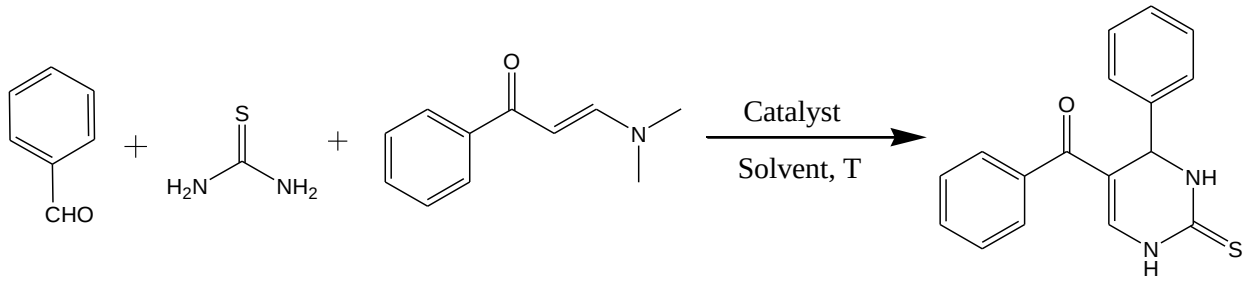


Table 2 Different conditions for the synthesis of DHPMs[a]

Entry	Catalyst	Solvent	T/°C	Yield(%)[b]
1.	TFA (0.5)	DMF	85	80
2.	AcOH(0.5)	DMF	85	Trace
3.	TMSCL(0.5)	DMF	85	86
4.	TMSCL(1.0)	DMF	85	91

5.	TMSCL(1.5)	DMF	85	95[c]
6.	TMSCL(2.0)	DMF	85	93
7.	TMSCL(1.5)	DMF	100	95
8.	TMSCL(1.5)	DMF	70	Mixture
9.	TMSCL(1.5)	Toluene	85	Paste

[a]Reaction condition: 0.3 mmol 1a, 0.35 mmol 2a and 0.3 mmol 3astirred for 10 h. [b] Isolated yield based on aldehyde. [c]Average yield of two identical run.

DMF:- Dimethyl formamide , TFA:- Trifluoroacetic acid, TMSCl:- TrimethylSilyl chloride

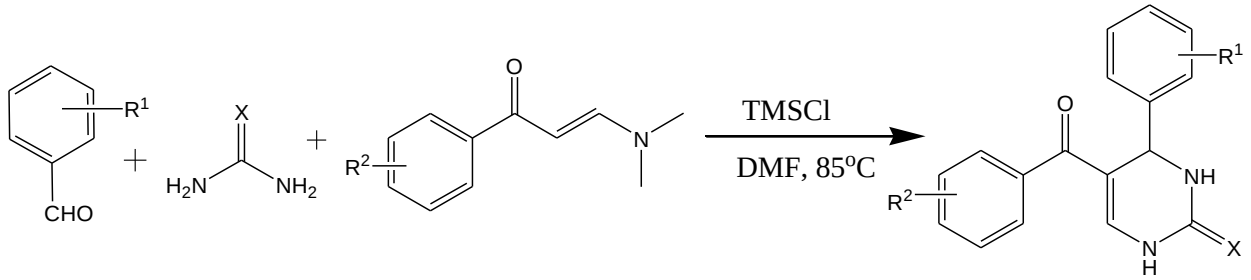


Table 3 Synthesis of 6-unsubstituted DHPMs from various aromatic substrates.

Entry	R^1	R^2	X	Yield (%)
1.	H	H	S	95
2.	4-Me	H	S	91
3.	4-OMe	H	S	86
4.	4-Cl	H	S	95
5.	4-Br	H	S	89
6.	4-CF_3	H	S	96
7.	4-OH	H	S	82
8.	4NO_2	H	S	93
9.	4-NMe_2	H	S	79
10.	2-OMe	H	S	80
11.	2-F	H	S	77
12.	3,4-$(OMe)_2$	H	S	61
13.	4-Cl	4-Me	S	90

14.	4-Me	4-Me	S	92
15.	4-Me	4-NO_2	S	87
16.	3-NO_2	4-NO_2	S	90
17.	H	H	O	89
18.	4-Me	H	O	86
19.	4-OMe	H	O	85
20.	4-F	H	O	86
21.	4-NO_2	H	O	92
22.	3-NO_2	H	O	82
23.	H	4-Me	O	93
24.	4-OMe	4-OMe	O	90
25.	4-Cl	4-OMe	O	96

[a] Reaction conditions: 0.3 mmol 1, 0.35 mmol 2 and 0.3 mol 3 mixedin 2 mL DMF, 1.5 eq. mol TMSCl, stirred at 85 1C for 10 h. [b]Isolatedyield based on aldehyde.

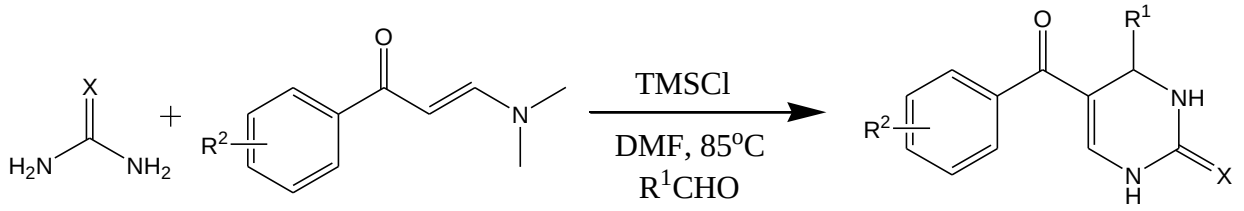


Table 4 Synthesis of 6-unsubstituted DHPMs from aliphaticaldehydes

Entry	R^1	R^2	X	Yield (%)
1.	CH_2CH_3	H	S	72
2.	$CH_3(CH_2)_2$	H	S	69
3.	$CH_3(CH_2)_5$	H	S	74
4.	$(CH_3)_2CHCH_2$	H	S	70
5.	CH_2CH_3	4-OMe	O	65
6.	$CH_3(CH_2)_2$	4-OMe	O	62

[a] Identical conditions as Table 2. [b] Isolated yield based on aldehyde

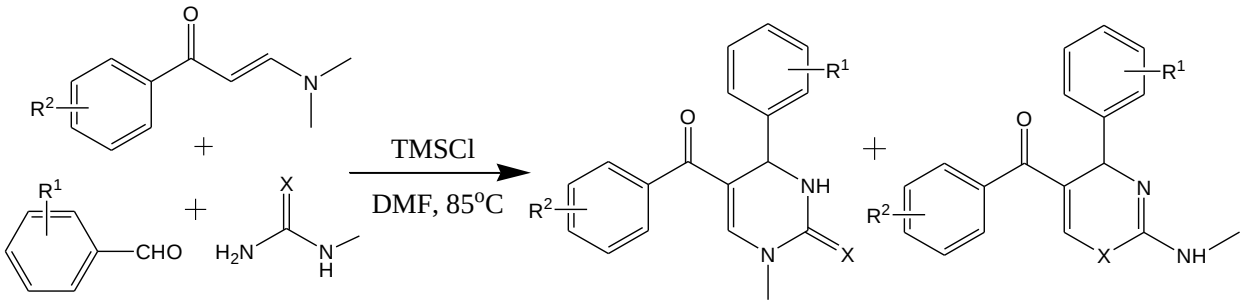


Table 5 Regioselective formation of DHPMs and 1, 3-thiazines.

Entry	R^1	R^2	X	Yield (7/8%)
1.	4-NO_2	4-OMe	O	62
2.	4-CH_3	H	O	66
3.	H	4-OMe	S	19/60
4.	4-NO_2	H	S	20/60
5.	4-CH_3	H	S	71

[a]Identical conditions as Table 2. [b]Isolated yield based on aldehyde.

A.K. Bose et al. have reported a simplified green chemistry approach to the Biginelli reaction using "Grindstone Chemistry".[44]

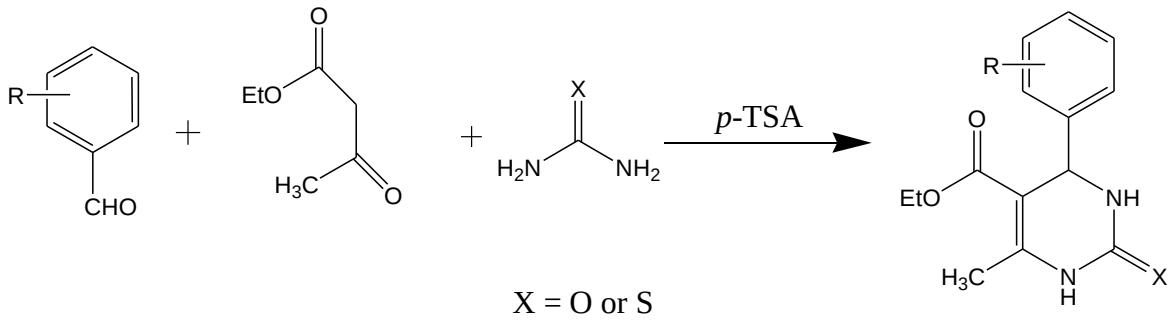


Table 6. Synthesis of tetrahydropyrimidinone derivatives (4) using Grindstone Chemistry.

ENTRY	R	X	Yield(%)	Mp(°C)
1.	H	O	93	208-210
2.	4-OH	O	95	236-238
3.	4-OMe	O	96	208-209
4.	4-NO_2	O	94	207-208

5.	4-Cl	O	83	210-211
6.	H	S	71	205-206

R. Wang and Z.Q. Liu have reported Solvent-Free and Catalyst-Free Biginelli Reaction To Synthesize Ferrocenoyl Dihydropyrimidine and Kinetic Method To ExpressRadical-Scavenging Ability.[45]

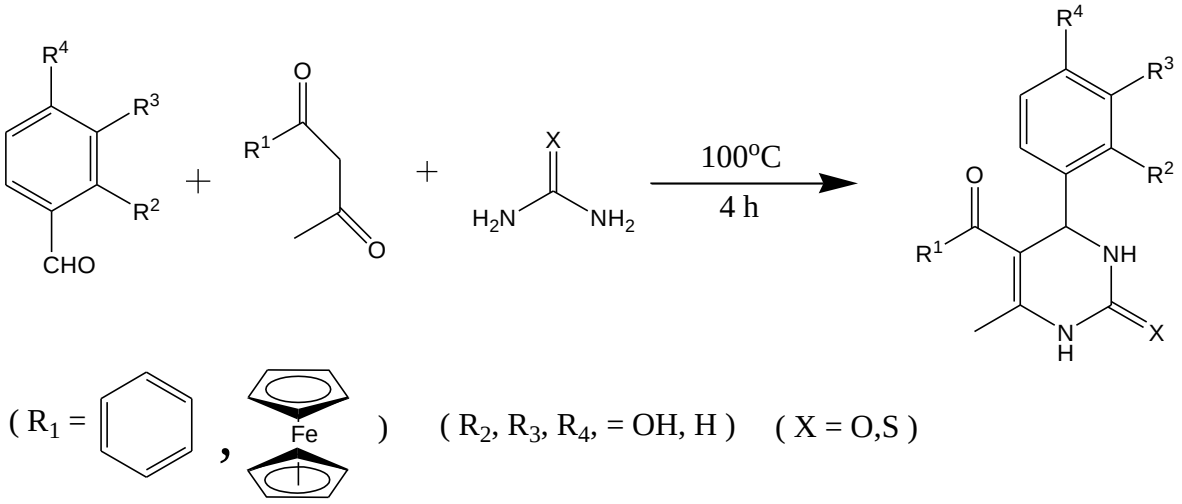


Table 7. Synthesis and Structures of DHPMs Employed Herein

Compound	R_2	R_2	R_3	R_4	X	Yield (%)
1.	Ph	H	H	H	O	77
2.	Ph	H	H	H	S	61
3.	Ph	H	H	OH	O	60
4.	Ph	H	H	OH	S	55
5.	Ph	H	OH	OH	O	34
6.	Ph	H	OH	OH	S	31
7.	Fc	H	H	H	O	50
8.	Fc	H	H	H	S	43
9.	Fc	H	H	OH	O	41
10.	Fc	H	H	OH	S	37
11.	Fc	O-	H	H	O	25

Structure of compound 11 was :-

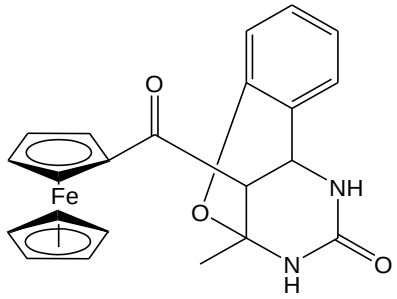
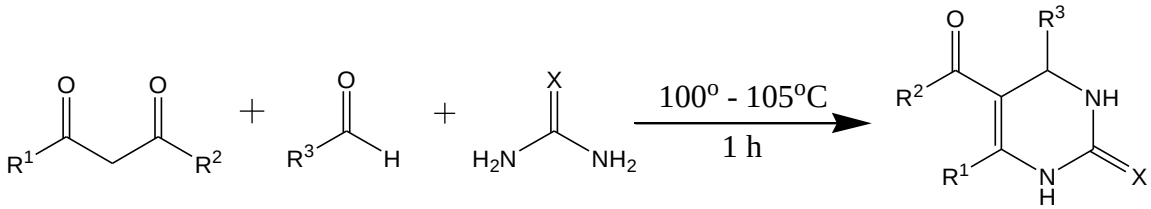


FIG 1.3.1

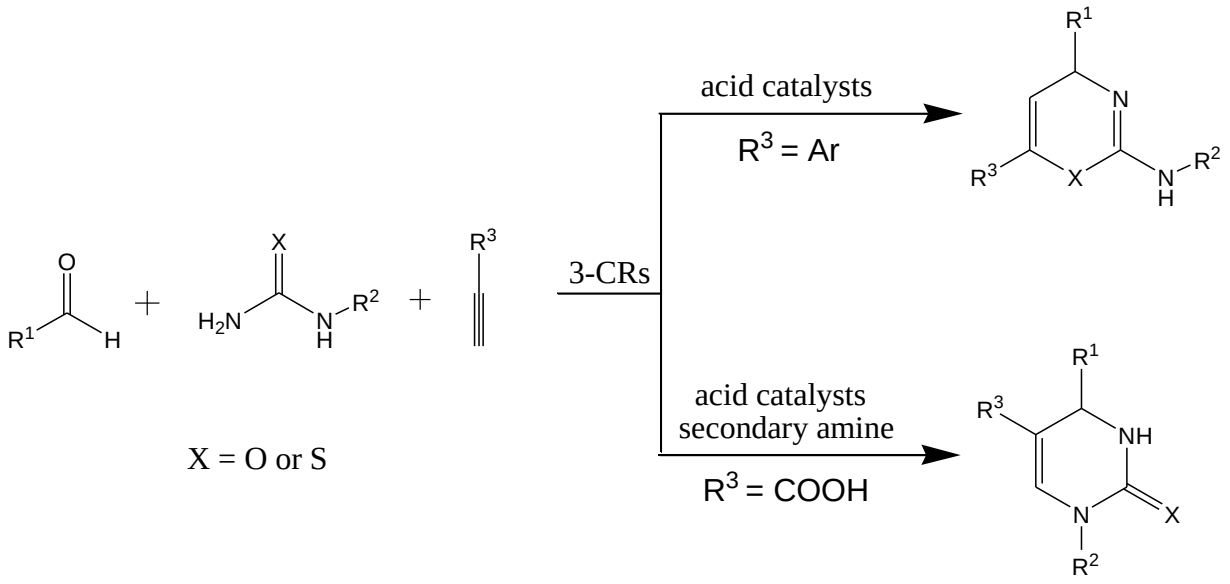
M. M . Kirrchhoff have reported the bignelli reaction in catalyst and solvent free condition.[46]



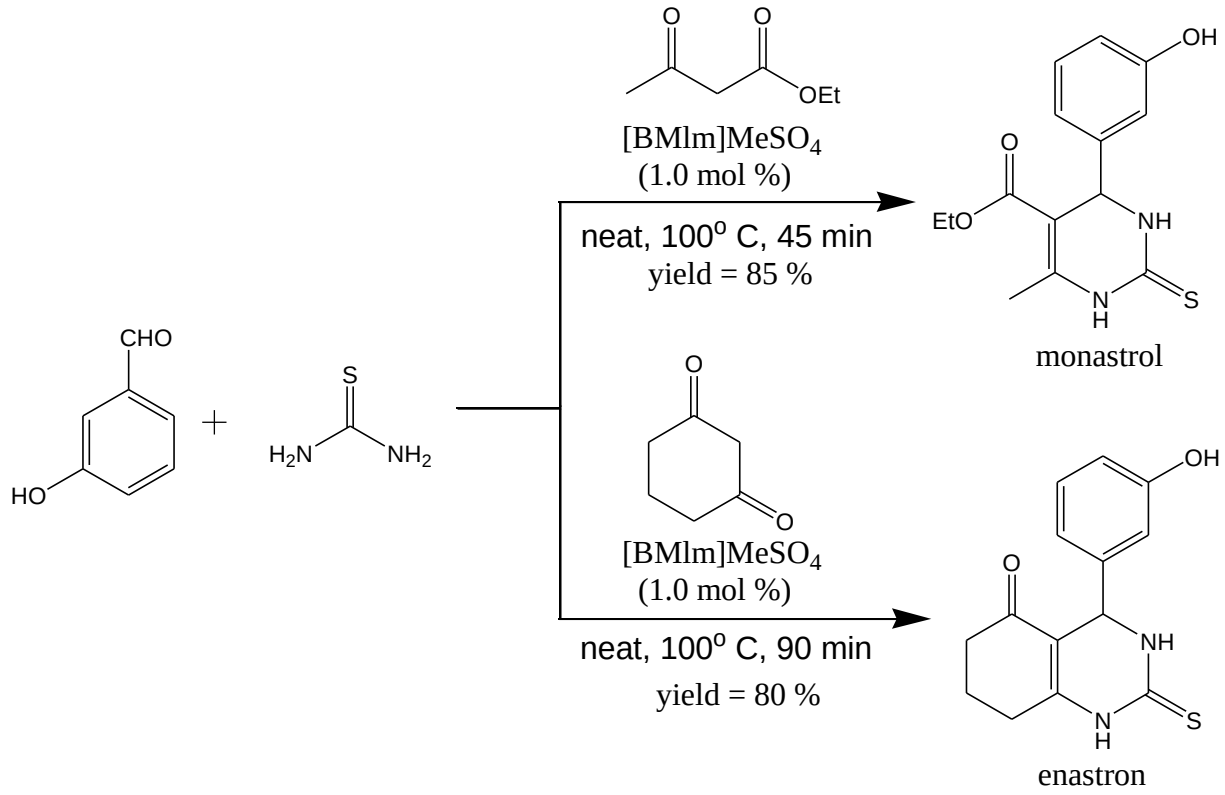
X = O, S

Scheme 1. Solvent- and catalyst-free synthesis of dihydropyrimidinones.

Jie-Ping Wan et al. have studied multicomponent synthesis of 3, 4-dihydropyrimidinones and thiones involving aldehydes, alkynes and thiourea/urea initiated by secondary amines.[47]



Scheme 2:- Regioselective 1,3 thiazines and DHPMs via aldehydes alkynes and thiourea/urea.[48]



Scheme 3 :- Synthesis of monastrol and enastron in ionic liquid [BMlm]MesSO4.[49]

RESEARCH GAP

Pietro Biginelli in 1891 discovered the multicomponent condensation reaction named bignelli reaction that was the condensation of urea, ethyl acetoacetate and aldehyde using ethanol and sulphuric acid as solvent and catalyst respectively. This reaction got immense attention because the product formed by this reaction i.e. DHPMs have large number of applications in pharmacology. Bacause of harmful nature of ethanol and sulphuric acid towards the environment, many research group started working on finding the different reaction conditions, solvents and catalysts for this reaction to enhance the reaction rate and productivity of the reaction. The catalysts and solvents which they have tried, unfortunately were non eco-friendly. Many different attempts were made to develop green methodologies for this reaction. The reaction needs higher temperature when done under solvent and catalyst free condtions and the reaction time increases when it was done at room temperature. Than the reactions were done using different aromatic aldehydes subsituted with different electron releasing and electron withdrawing groups and dependent on the properties of the aldehydes variations in the reaction time was observed. There are large number of green solvents and catalysts that can be used for these reactions such as glucose, polyvinyl alcohol, vinger, water etc.. Our research group has used them as reaction medium. As the polarity of aldehydes affects the reaction rate, taking the idea from “scheme A” , given above aquos solution of glucose is taken as reaction solvent and catalyst. Vineger which is slightly acidic in nature is also used as reaction medium which fulfill both conditions of solvent and catalyst for the reaction. The reaction is also done without catalyst in water as solvent. Aquos solution of glucose, vineger and water all three are green solvents. The reaction rate is enhanced by doing these reaction in microwave. The reaction time is reduced significant by microwave assistance. This can be taken as greener approach as time reqiured for the reaction is lesser. For these reactions visible light is also used as green source of energy. They provide the milder condtions for the reactions to happen and also reduce the time of the reaction. As the reactions conditions used for the reactions are eco- friendly so our work is probably the novel and green approach for the biginelli reaction.

It was found out that biginelli reaction in aqous solution of glucose, vineger and water induced by microwave and visible light are not well explored in literature.

OBJECTIVE

As mention in research gap we observed that new optimized methods are needed for the synthesis of dihydroprimidinones which are greener, cleaner, much efficient and faster. This leads us to an objective to use microwave and visible light for the synthesis of DHPMs. In this project a series of Biginelli reaction have been done using thiourea as reactant in water, Vineger and Aquos Solution of Glucose as green reaction medium. TLC's and melting point are used as priliminary tests for the detection of suitable compound. The infrared spectroscopy and proton NMR is used to confirm the identity of compound.

WORK DONE

GENERAL PROCEDURE FOR SYNTHESIS OF DHPM IN MICROWAVE HEATING

The aldehydes, Thiourea and acetyl acetoacetate have been taken in equimoler quantity (1 equivalent) i.e. 0.03 moles of each. The different solvents used for the reaction are 10 ml glucose (1 molar solution in water), vinger and water. After weighing all the components accurately, they were added to 100 ml borosilicate conical flask. The reaction is done for the definite time in 180W microwave irradiation. After the regular interval of 1 minute the conical flask is taken out of microwave and proper stirring and cooling of the reaction mixture is done. To check the completion of reaction thin layer chromatography is used. The solvent system used for TLC was DCM, hexane in different ratios and was observed in UV chamber. The crude solid product from the reaction mixture was precipitated out and collected after cooling it down to the room

temperature when the reaction was completed. Recrystallization of the crude product is done by dissolving it in minimum quantity of hot ethanol and the pure white/yellowish DHPM is obtained. The melting point, IR and ^{1}H NMR spectroscopy are different techniques used for the characterization of these DHPMs. The different aldehydes used were p-chloro benzaldehyde, p-bromo benzaldehyde, p-nitro benzaldehyde and p-cyno benzaldehyde.

Table 1. Microwave irradiated biginelli reaction in aqous solution of glucose with different aldehydes.

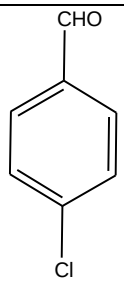
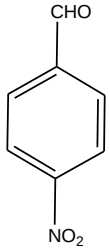
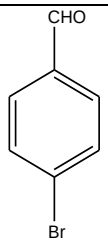
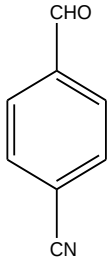
Entry	Aldehyde	DHPM	Time	Melting point	%Yield
1.		GCL	10 min	180-182^{o}C	80%
2.		GNO	8 min	108-110 ^{o}C	86%
3.		GBR	18 min	43-45 ^{o}C	76%
4.		GCN	9.30 min	62-64 ^{o}C	71%

Table 2. Microwave irradiated biginelli reaction in vineger with different aldehydes.

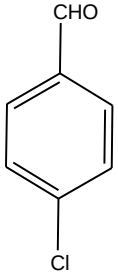
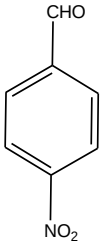
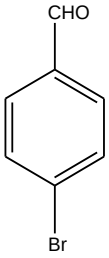
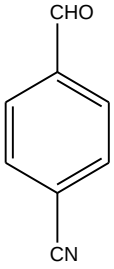
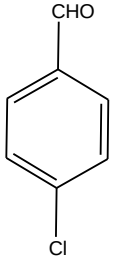
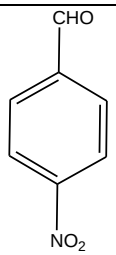
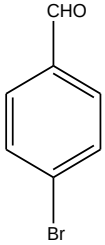
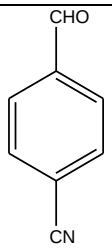
Entry	Aldehyde	DHPM	Time	Melting point	%Yield
1.		GCL	10.30 min	179-181^{o}C	78%
2.		GNO	9.30 min	108-110 ^{o}C	82%
3.		GBR	15 min	43-45 ^{o}C	75%
4.		GCN	16 min	62-64 ^{o}C	69%

Table 3. Microwave irradiated biginelli reaction in water with different aldehydes.

Entry	Aldehyde	DHPM	Time	Melting point	%Yield
1.		GCL	11 min	179-181^{o}C	76%
2.		GNO	15 min	108-110 ^{o}C	78%
3.		GBR	19 min	43-45 ^{o}C	70%
4.		GCN	18 min	62-64 ^{o}C	65%

DISCUSSION ON MICROWAVE IRRADIATED REACTIONS:-

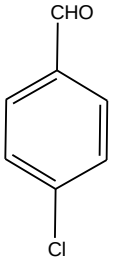
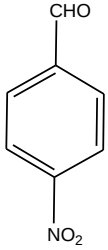
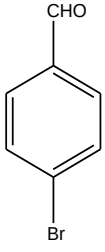
Thiourea, ethyl acetoacetate and aldehydes (which contain electron withdrawing subsitutents) were employed for the synthesis of series of DHPMs. Aquos solution of glucose, vineger and water were the three reaction conditions used to perform the reaction. The reactions takes very less time when performed in microwave 10-20 minutes as compare to the reaction performed at room temperature which takes hours for the completion. The aldehyde containing electron withdrawing subsitution takes less time for the completion of reaction as compare to the normal aldehyde. The time taken by the reaction depends on type of subsituent present on the aldehyde. The presence of electronegative subsituent increases the electrophillicity of the carbonyl carbon of aldehyde and the nucleophile attacks easily on the carbonyl carbon which makes the reaction much facile. The nitro derivative of aldehyde takes less time and give maximum yield in all of the three solvents because of the high electronegative effect of the nitro functional group. The cyano derivative takes more time and gave less yield as compare to all other aldehyde in all of the three reaction conditions because of the less electronegative effect of cyano functional group. The chloro derivative takes more time than nitro derivative and give good yield. The bromo derivatives takes more time than chloro and nitro derivative and gave good yield. The aqous solution of glucose was the best working solvent for all the four aldehydes derivative takes less time and give good yield. The glucose works as catalyst shows hydrogen bonding with the carbonyl oxygen of the aldehyde and makes carbonyl carbon more electron deficient and increases the rate of reaction. Vineger being slightly acidic in nature completes the reaction in less time as compare to water (catalyst free condition) but both takes more time than glucose.

GENERAL PROCEDURE FOR SYNTHESIS OF DHPM IN VISIBLE LIGHT MEDIUM

The aldehydes, Thiourea and acetyl acetoacetate have been taken in equimoler quantity (1 equivalent) i.e. 0.01 moles of each. The solvent used for the reaction is 10 ml water. After weighing all the components accurately, they were added to 10 ml borosilicate round bottom flask. The

reaction is done for the definite time in 100W halogen bulb irradiation. The continues strring of the reaction is done using magnetic stirrer. To check the completion of reaction thin layer chromatography was used. The solvent system used for TLC was DCM, hexane in different ratios and was observed in UV chamber. The crude solid product from the reaction mixture was precipitated out and collected after cooling it down to the room temperature when the reaction was completed. Recrystallization of the crude product is done by dissolving it in minimum quantity of hot ethanol and the pure white/yellowish DHPM is obtained. The melting point, IR and ^{1}H NMR are different techniques used for the characterization of these DHPMs. The different aldehydes used were p-chloro benzaldehyde, p-bromo benzaldehyde and p-nitro benzaldehyde.

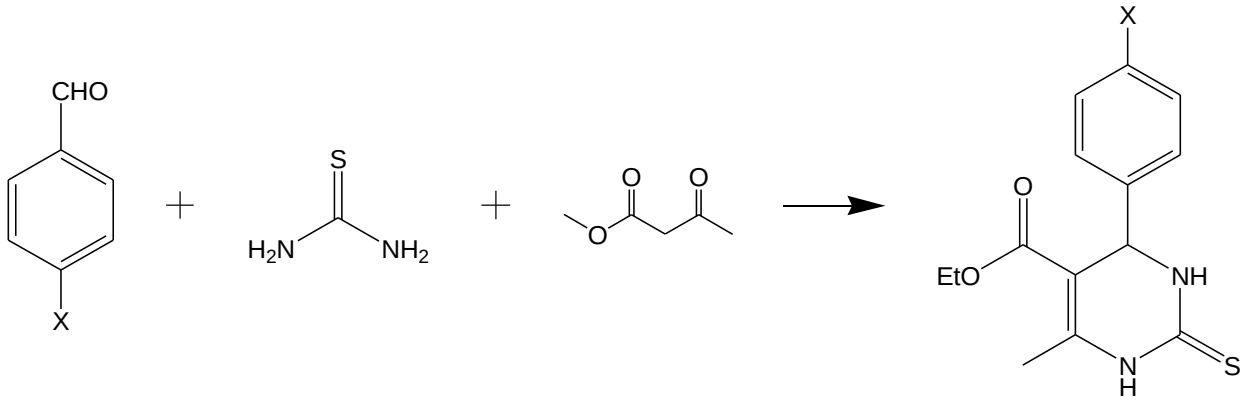
Table 4. Visible light irradiated biginelli reaction in water with different aldehydes.

Entry	Aldehyde	DHPM	Time	Melting point	%Yield
1.		GCL	3 hour 15 min	179-181^{o}C	80%
2.		GNO	2 hour 45 min	108-110 ^{o}C	84%
3.		GBR	3 hour 45 min	43-45 ^{o}C	75%

DISCUSSION ON VISIBLE LIGHT IRRADIATED REACTIONS:-

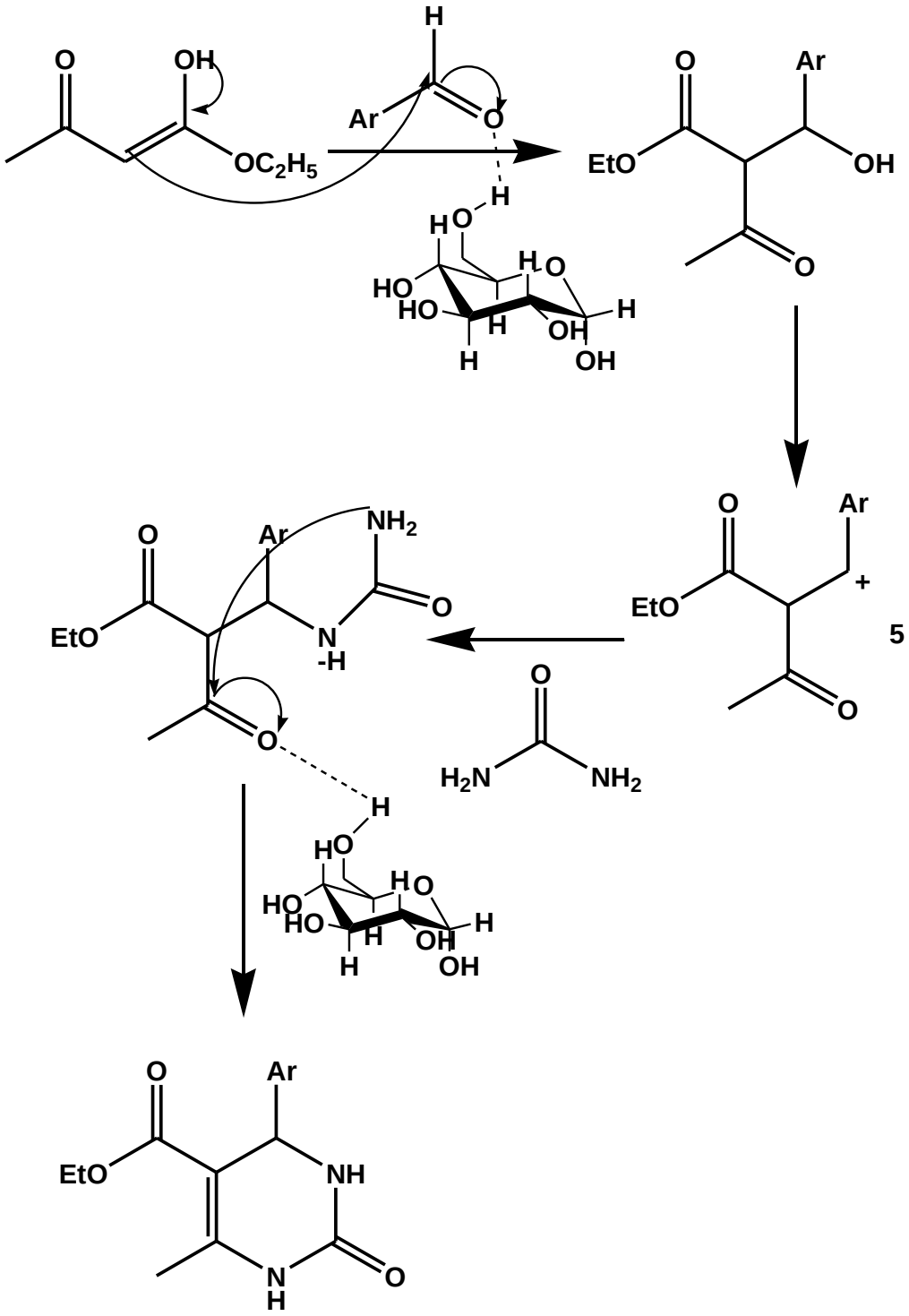
Thiourea, ethyl acetoacetate and aldehydes (which contain electron withdrawing subsitutents) were employed for the synthesis of series of DHPMs. Water was used as solvent to perform the reaction. Because in literature search there was no reaction done in water under visible light irradiation. The reaction takes 2-4 hours for completion in visible light which is very less and efficient than the reactions done by conventional heating method. The aldehyde containing electron withdrawing subsitution takes less time for the completion of reaction as compare to the normal aldehyde. The time taken by the reaction depends on type of subsituent present on the aldehyde. The presence of electronegative subsituent increases the electrophillicity of the carbonyl carbon of aldehyde and the nucleophile attacks easily on the carbonyl carbon which makes the reaction much facile. The nitro derivative of aldehyde takes less time and give maximum yield in all of the three solvents because of the high electronegative affect of the nitro functional group. The chloro derivative takes more time time then nitro derivative and give good yield. The bromo derivatives takes more time then chloro and nitro derivative and gave good yield. The reactions proceeds very slow in visible light irradiation as compare to microwave irradiation.

REACTIONS SCHEME FOR DERIVATIVES



X= Cl, Br, NO_2 , CN.

Mechanism of the reaction using aqous solution glucose as reaction medium :-



CHARACTERIZATIONS

1. **Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:-**

(Compound GCL) White crystalline powder,

Melting point : - 180-182º C,

IR spectra data analysis (KBr)

3277.17 cm^{-1} – N-H stretch

3176.87 cm^{-1} – sp^2 stretch

2683.07 cm^{-1} – sp^3 stretch

1411.94 cm^{-1} – C=S (thiamide)

1616.82 cm^{-1} – C=O (ester)

1469.81 cm^{-1} – C=C (aromatic)

729.12 cm^{-1} – C-Cl stretching

^{1}H-NMR (400 MHz, DMSO-d^6): δ 1.03 (t, 3H), 2.30 (s, 3H), 4.35 (q, 2H), 5.28 (d, 1H), 6.90–7.19 (m, 5H), 9.97 (s, 1H).

2. Ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

(Compound GNO) Brownish yellow powder

Melting point : - 108-110 º C

IR spectra data analysis

3379.4 cm^{-1} – N-H stretch

3105.53 cm^{-1} – sp^2 stretch

2847.03 cm^{-1} – sp^3 stretch

1708.02 cm^{-1} – C=O (ester)

1606.76 cm^{-1} – C=C (aromatic)

1470.77 cm^{-1} – C=C (aliphatic)

1349.25 cm^{-1} – C=S (thiamide)

1530.57 cm^{-1} – NO_2 stretch

^{1}H-NMR (400 MHz, DMSO-d^6): δ 1.06 (t, 3H), 2.33 (s, 3H), 4.38 (q, 2H), 5.31 (d, 1H), 8.15–8.43 (m, 5H), 10.16 (s, 1H).

3. Ethyl 4-(4-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

(Compound GBR) yellow crystalline powder

Melting point : - 43-45 ^{o} C

IR spectra data analysis

3356.25 cm^{-1} – N-H stretch

3174.94 cm^{-1} – sp^2 stretch

2855.71 cm^{-1} – sp^3 stretch

1698.38 cm^{-1} – C=O (ester)

1580.72 cm^{-1} – C=C (aromatic)

1383.01 cm^{-1} – C=S (thiamide)

682.82 cm^{-1} – C-Br stretching

^{1}H-NMR (400 MHz, DMSO-d^6): δ 1.23 (t, 3H), 2.42 (s, 3H), 4.25 (q, 2H), 5.36 (d, 1H), 7.80–7.84 (m, 5H), 9.97 (s, 1H).

4. Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound GCN) orange crystalline powder

Melting point : - 62-64 ^{o} C

IR spectra data analysis

3091.99 cm^{-1} – N-H stretch

2819.06 cm^{-1} – sp^2 stretch

2349.03 cm^{-1} – sp^3 stretch

1702.24 cm^{-1} – C=O (ester)

1517.06 cm^{-1} – C=C (aromatic)

1386.86 cm^{-1} – C=S (thiamide)

2226.89 cm^{-1} – $C{\equiv}N$ stretch

^{1}H-NMR (400 MHz, DMSO-d^{6}): δ 1.16 (t, 3H), 2.21 (s, 3H), 4.25 (q, 2H), 5.16 (d, 1H), 7.57–7.67 (m, 5H), 10.08 (s, 1H).

CONCLUSION

This project work is based on the green synthesis of DHPM's by using various eco-friendly solvents like aquos solution of glucose, vineger and water. A series of DHPM's were synthesized using aldehydes with different electron withdrawing functional groups. The reaction were done under microwave and visible light radiation. The reaction that were carried out in microwave irradiation are faster and took very less time as compare to the reactions that were carried out in visible light radiation.

The reactions that were done using aqous solution of glucose as reaction medium shows good results as compare to vineger and water. Glucose shows hydrogen bonding with the reactants and catalyse the reaction by increasing there reactivity. Vineger being slightly acidic in nature helps the reaction to proceed faster as compare to water (catalyst free) as reaction medium.

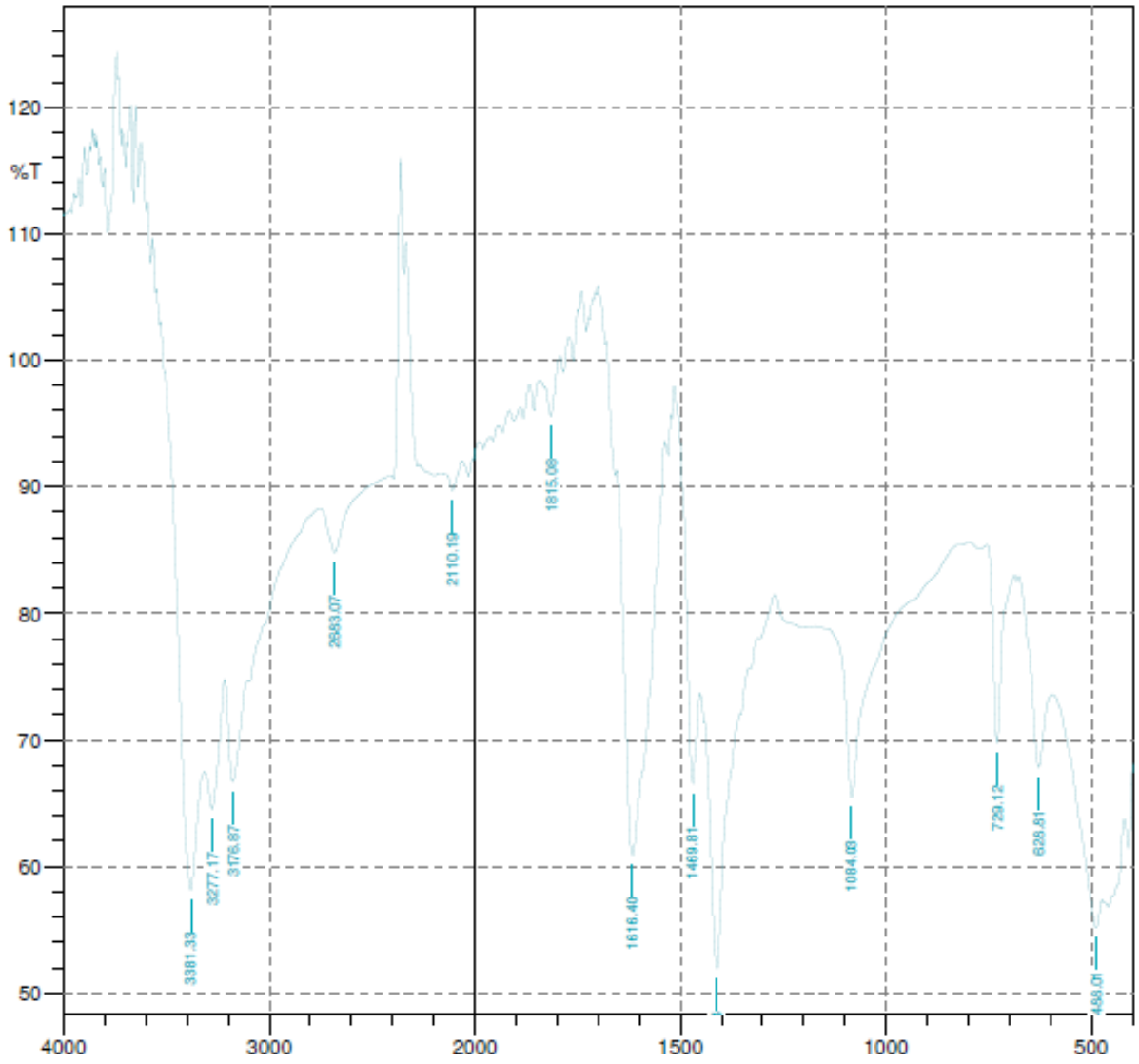
Out of all four derivatives of benzaldehyde, 4-Nitrobenzaldehyde shows better results (less time, higher yield) beacause of its high electronegativity affect, which increases the electrophillicity of the carbonyl carbon and makes the nucleophllic attack easier. The reaction time and the product yield using different aldehyde follows the order as 4-nitrobenzaldehyde < 4- chlorobenzaldehyde < 4-bromo benzaldehyde < 4-cyno benzaldehyde. This was because of the electronegativity difference in electron withdrawing groups. The electronegativity order NO_2 > Cl > Br > CN.

As the methods used in this project are green according to green chemistry, this work motivates the chemists to explore more of the green solvents rather than using hazardous and toxic solvents and catalysts for various chemical reactions.

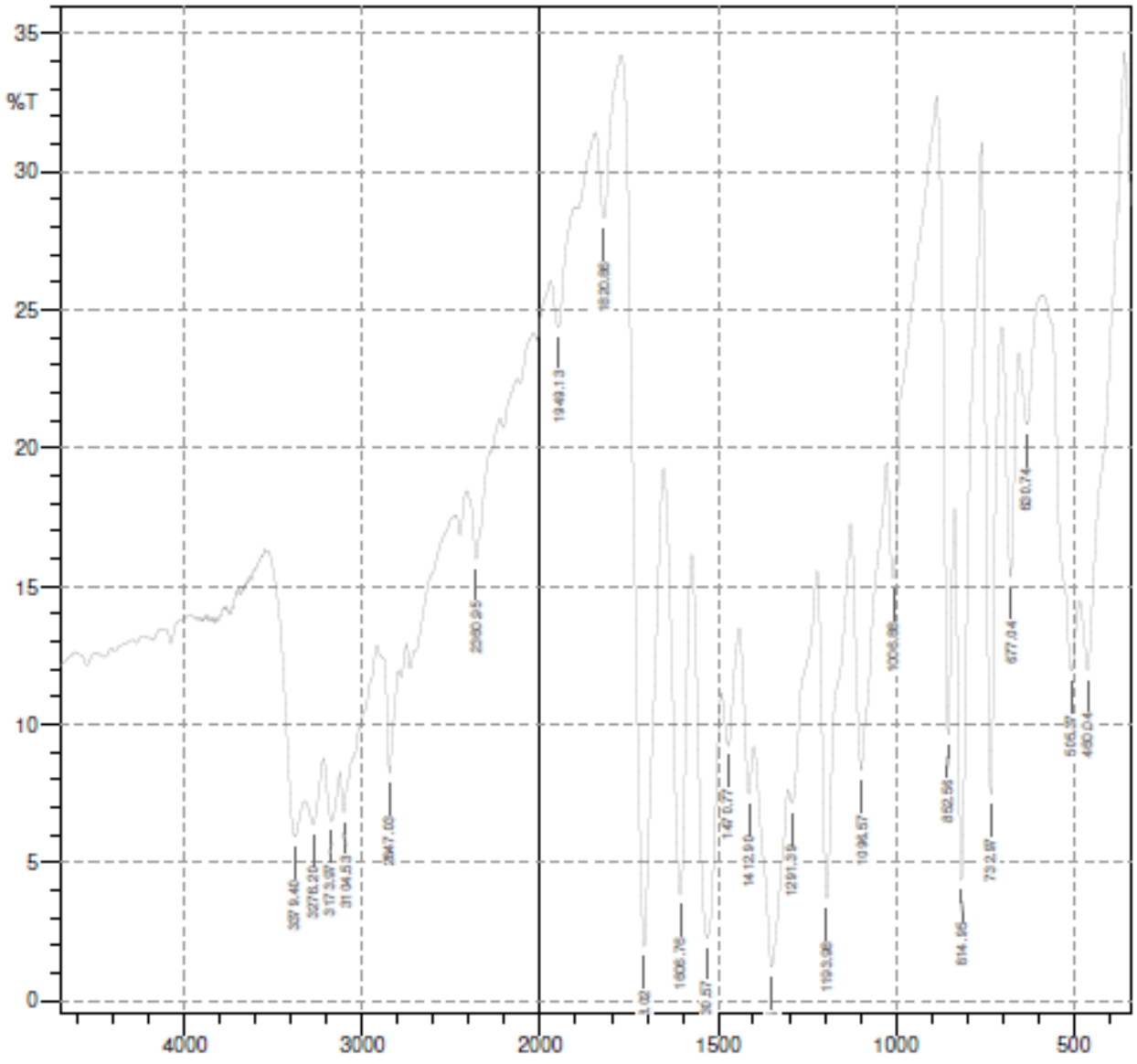
APPENDIX

IR SPECTRA OF COMPOUNDS

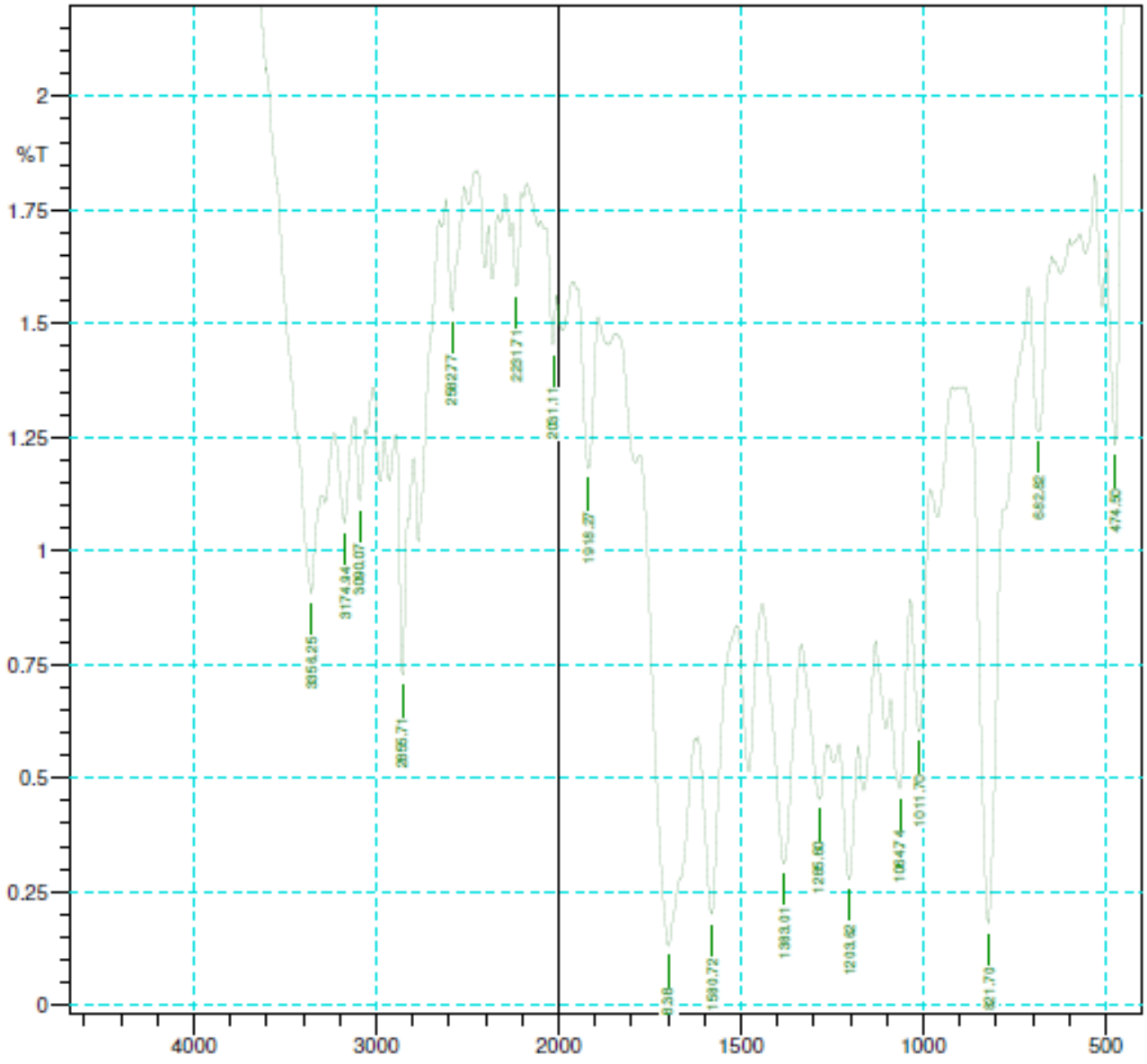
GCL



GNO



GBR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2
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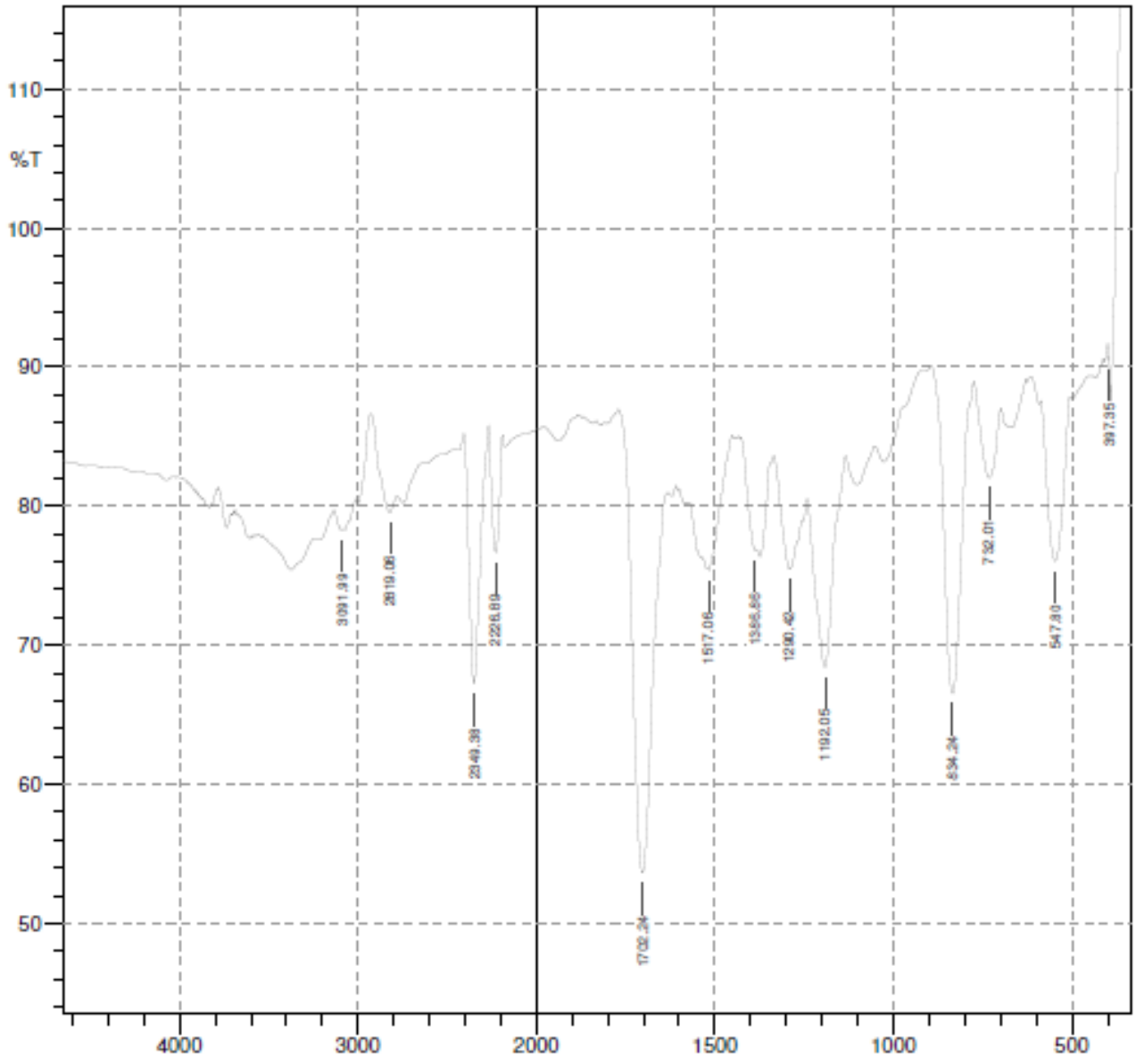
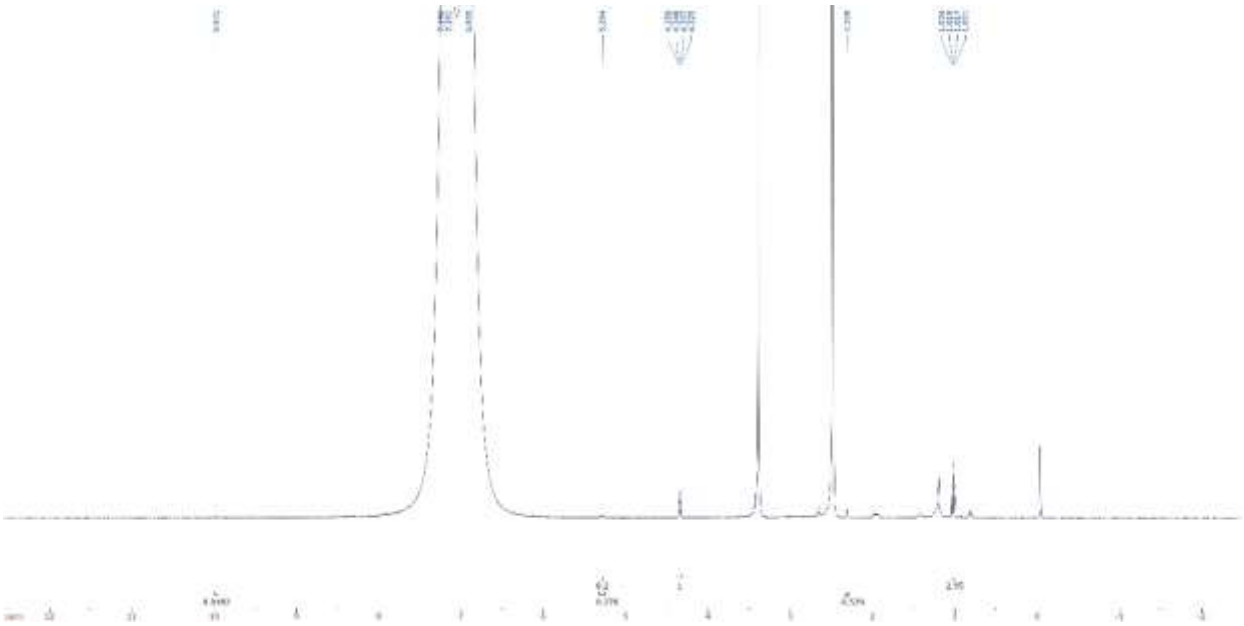
1.5
1.25
1
0.75
0.5
0.25
0
4000
3000
2000
1500
1000
500
3354.25
3174.94
3090.07
2895.71
2592.77
2251.71
2051.11
1918.27
1593.01
1285.62
1203.62
1064.74
1011.70
652.82
474.50

GCN

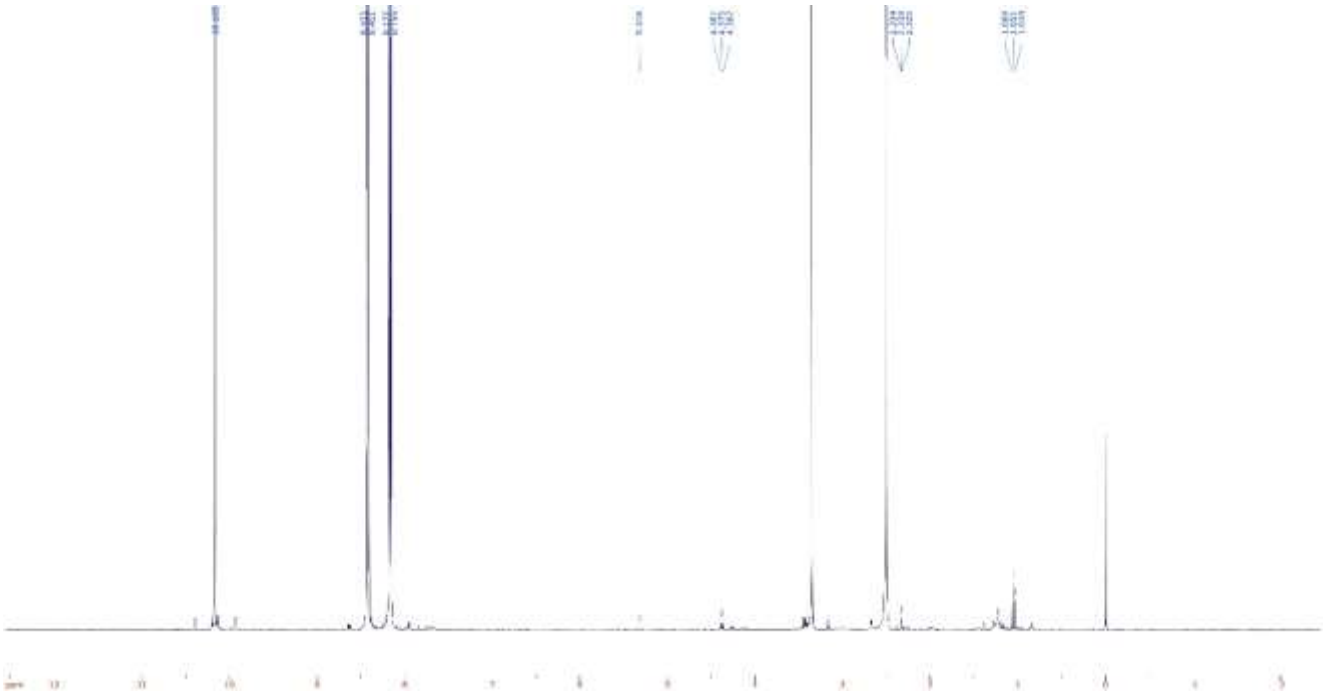

%T
110
100
90
80
70
60
50
4000
3000
2000
1500
1000
500
3091.99
2919.06
2349.38
2226.89
1732.24
1517.06
1356.66
1240.42
1192.05
834.24
732.01
547.90
397.35

NMR DATA OF COMPOUNDS

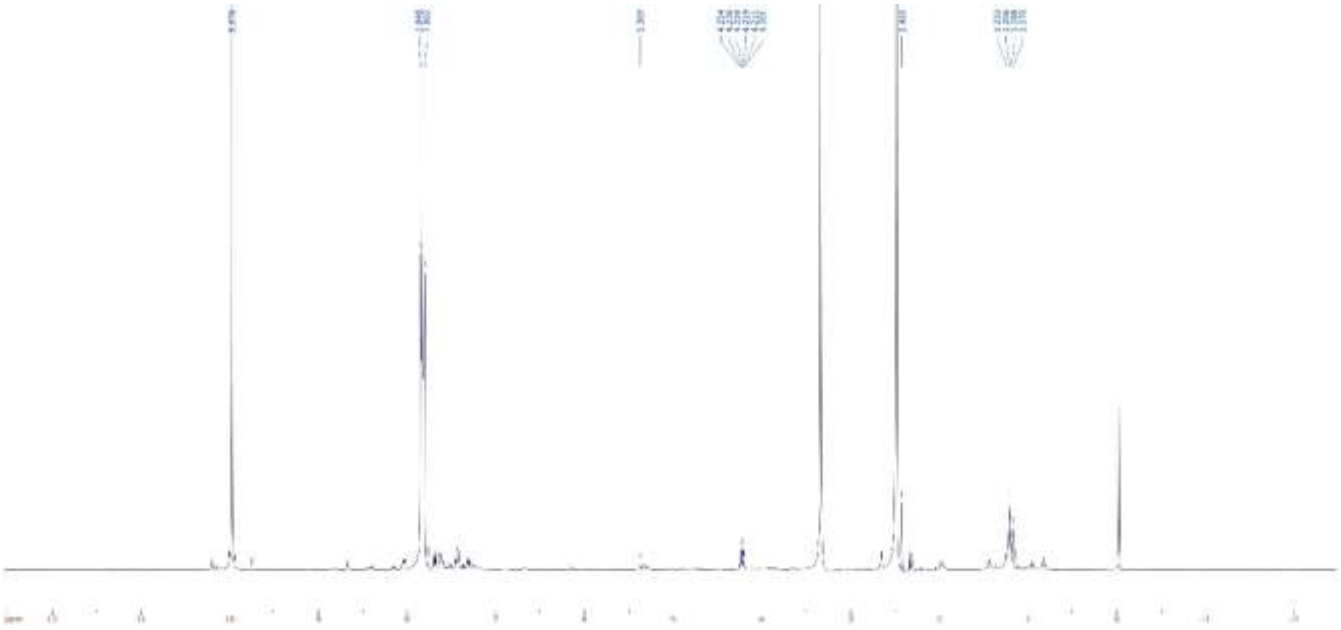
GCL



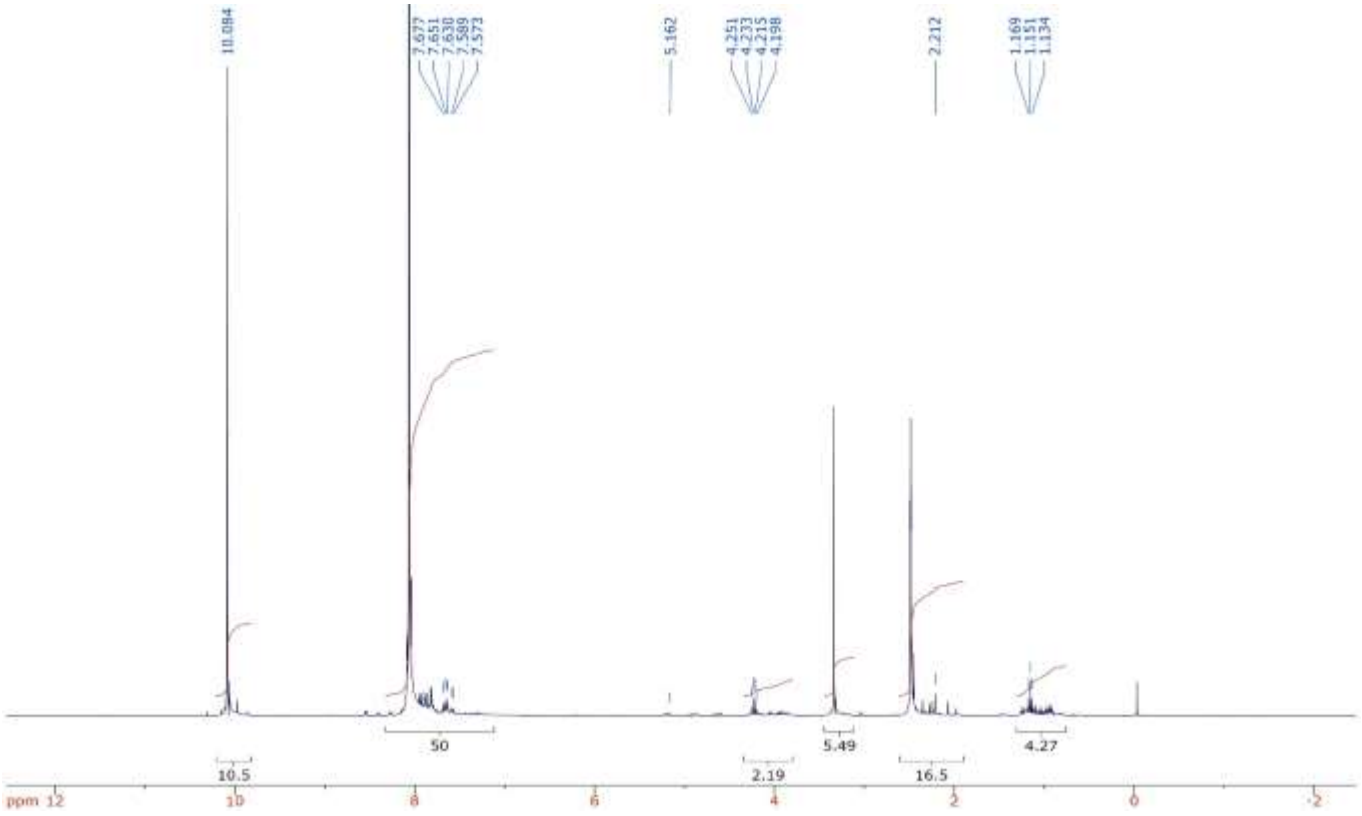
GNO



GBR



GCN


10.084
7.677
7.651
7.630
7.589
7.573
5.162
4.251
4.233
4.215
4.198
2.212
1.169
1.151
1.134
10.5
50
2.19
5.49
16.5
4.27
ppm 12
10
8
6
4
2
0
-2

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