Chemical transformation of carbocyclic compounds and development of novel reaction protocols

A Thesis submitted to the University of North Bengal

For the Award of

Doctor of Philosophy (Ph.D.) in Chemistry

By

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February-2021

Dedicated

To

My Beloved Parents

&

Family Members

DECLARATION

I hereby declare that the thesis entitled **"Chemical transformation of Carbocyclic Compounds and Development of Novel Reaction Protocols"** has been prepared by myself under the guidance of Prof. Pranab Ghosh, Department of Chemistry, University of North Bengal, Darjeeling - 734013. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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CERTIFICATE

I certify that **Mr. Rabindranath Singha** has prepared the thesis entitled **"Chemical transformation of Carbocyclic Compounds and Development of Novel Reaction Protocols"**, for the award of Ph.D. Degree of the University of North Bengal, under my guidance. He has carried out the research work at the Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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Dept. of Chemistry, NBU where I have done my research work and my Laptop where I have made the draft of my thesis.

I am also thankful to UGC, New Delhi, for awarding me Junior Research Fellowship and Senior Research Fellowship and University of North Bengal for providing the infrastructural facilities.

Finally, this work would not have been possible without the blessings of my beloved parents Shri Suresh Chandra Singha and Smt. Anjali Singha and the support of my brother Janak Singha and sister Jayanti Singha who always stood by my side.

I would also take this opportunity to express my sincere apologies for any mistake on my part or any word or behaviour of mine that may have hurt anyone working with me.

Finally despite best of my efforts and sincerity I might have committed some unintentional errors and mistakes in my thesis. Suggestions and criticisms from learned professors will be thankfully accepted.

Thank you.

Rabindranath Singha
18.02.2021

Rabindranath Singha

ABSTRACT

The thesis entitled "Chemical transformation of Carbocyclic Compounds and Development of Novel Reaction Protocols" comprises six chapters and a brief of their contents are as follows:

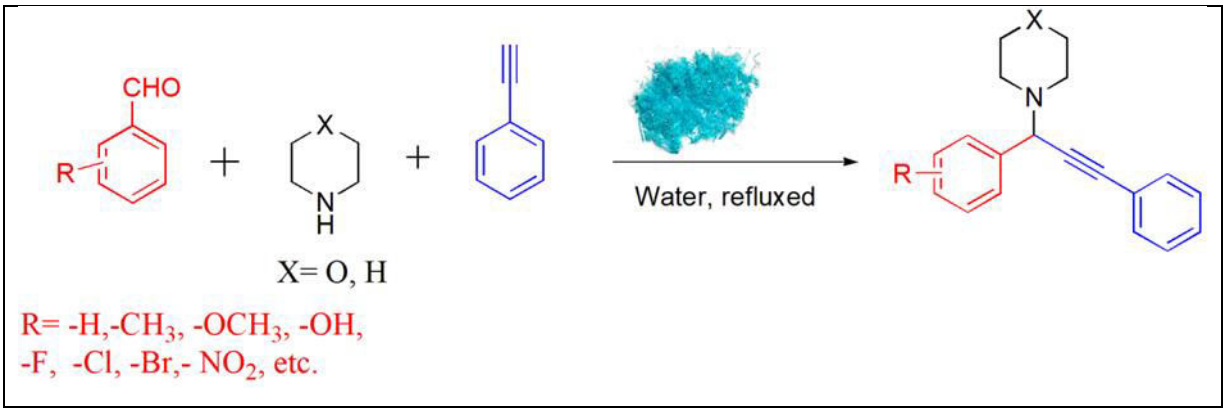
CHAPTER I

A brief review on the "Chemical transformation of Carbocyclic Compounds and Development of Novel Reaction Protocols". The work is mainly focused on the carbocyclic compounds and development of novel reaction protocols for the transformative reaction on carbocyclic compounds.

CHAPTER II

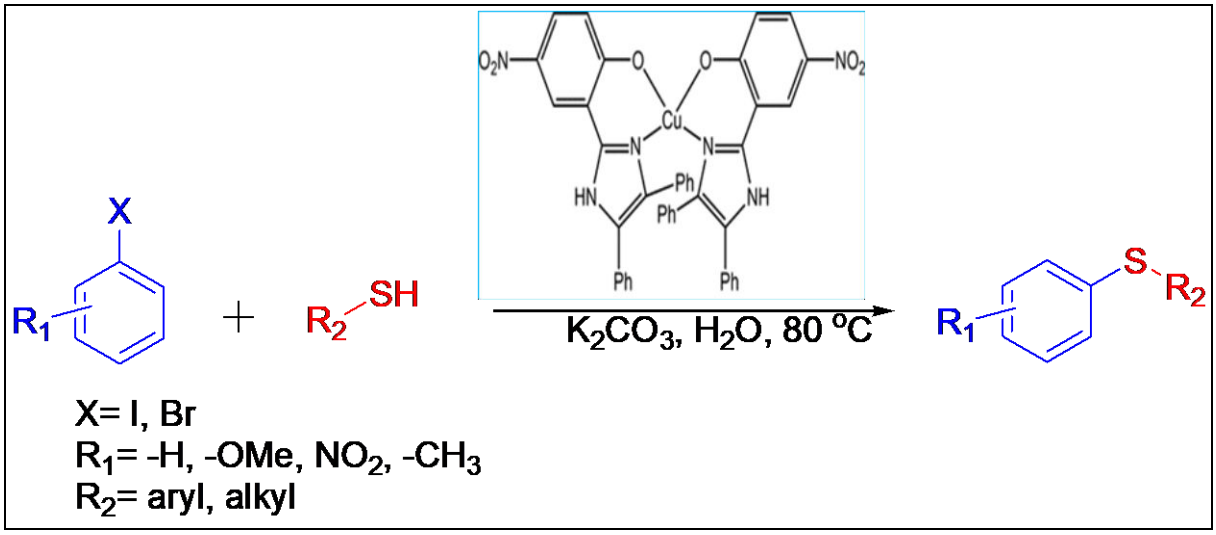
A greener and sustainable approach towards the synthesis of propargylamine using multicomponent A^3-coupling reaction

The abundance of toxic contaminated effluents from the pharmaceutical industries and the serious risk of contamination of the aquatic systems combine to provide strong motivating factors to tackle this environmental problem. Use of non-hazardous chemicals, reaction in aqueous medium is an interesting ecological alternative for the bulk production of important drugs and fine chemicals. Taking advantage of the remarkable ability of the selected catalytic systems, alternative sustainable methods have been exploited for the decontamination of industrial effluents and exhausts. Here we developed a new metal-organic complex [Bis(picolinate-$\kappa^2N:O$) Cu(II)] catalysed water mediated greener A^3-coupling reaction for the synthesis of propargylamine. Low toxicity, easy access to active sites, high surface area, high thermal stability, recyclability of the catalyst and easy way to separate the catalyst from the reaction mixture are the added advantage of this developed greener and sustainable protocol.



CHAPTER III

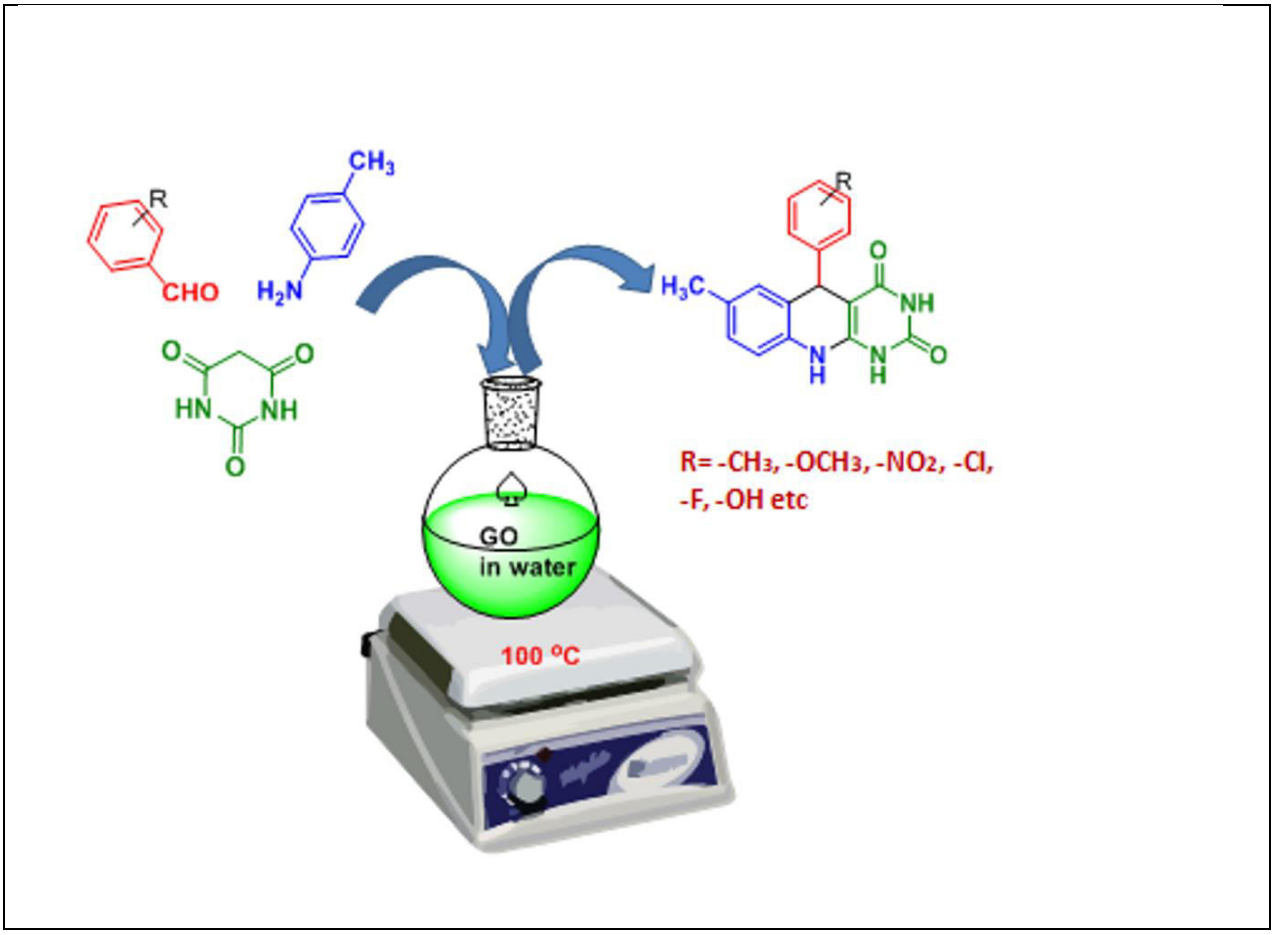
Environmentally begin approach towards C-S cross-coupling reaction by organo-copper(II) complex, C-S cross coupling reaction in water giving excellent yield of the desired C-S coupled product using a newly developed Bis[2-(4,5-diphenyl-1*H*-imidazol-2-yl)-4-nitrophenolato]copper(II) dehydrate complex as catalyst. The catalyst has low toxicity, easy access to the active sites, high surface area, high thermal stability, easy to separate from the reaction mixture and yielded the best result of the developed greener reaction protocol for the synthesis of C-S coupled product. Although it was the first report of the synthesis of such a novel organo-copper complex from our laboratory, its potential catalytic application was not tested so far. Keeping this in mind and based on our anticipation, recently we developed a greener route for the C-S coupling reaction. The result is very interesting and comprises the subject matter of this report.



CHAPTER IV

Graphene oxide catalysed one pot synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones and their biological evaluation.

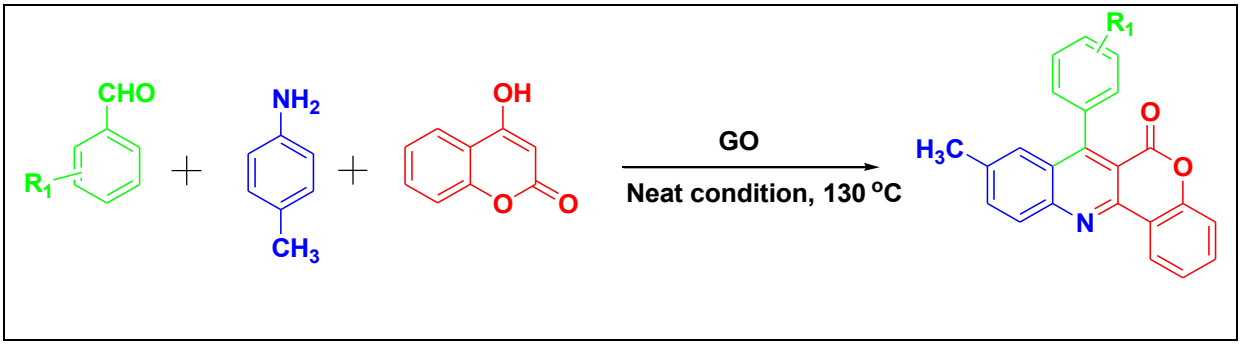
A simple and highly efficient method for the synthesis of 5-aryl-pyrimido quinoline 2,4-diones has been demonstrated. Graphene oxide (GO) has proved to be a new class of carbocatalyst for the synthesis of Pyrimido[4,5,*b*]quinolinone-2,4-diones through one pot three component reaction using aromatic amines, aldehydes and barbituric acid. The effects of reaction temperature, catalyst amount, reaction time, molar ratio of reactants were investigated. The GO could easily be recovered and reused upto 5th run.



CHAPTER V

One-pot three-component tandem annulation of 4-hydroxycoumarine with aldehyde and aromatic amines using Graphene oxide as an efficient catalyst.

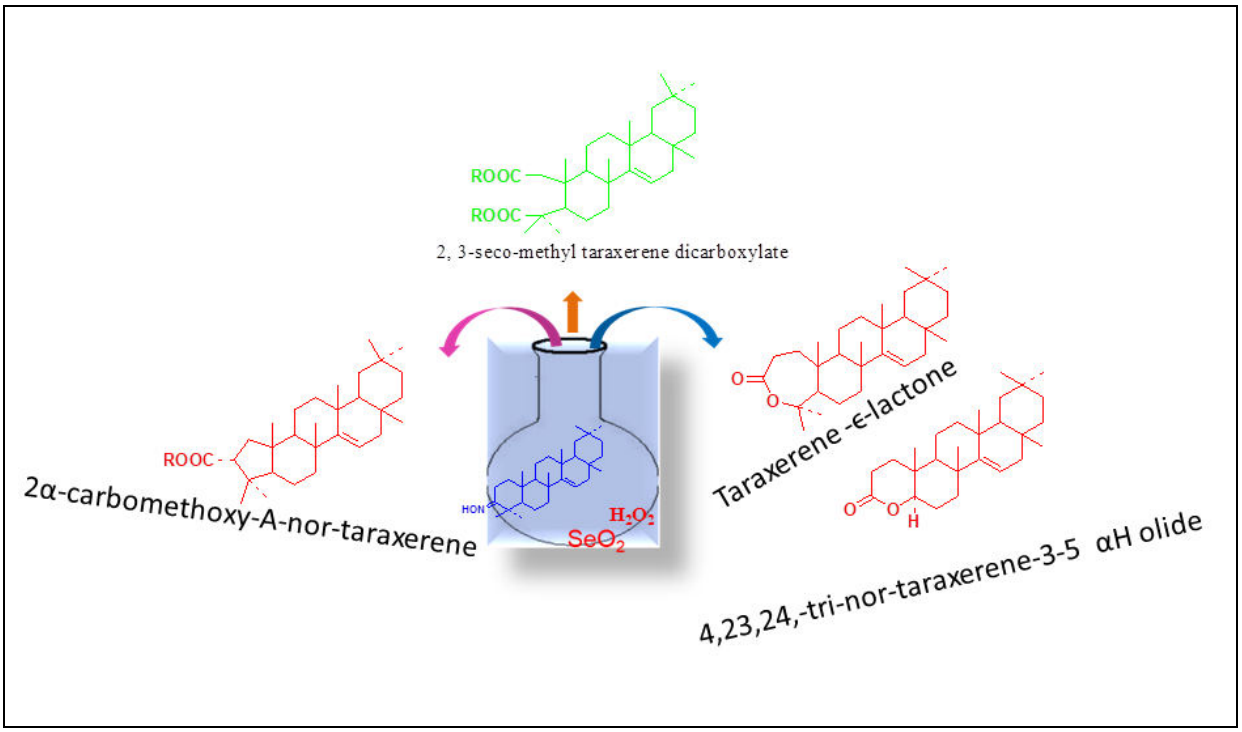
We demonstrate a facile, efficient and environmentally begin graphene oxide one-pot multi-component reaction method for the synthesis of a variety of chromeno[4,3-*b*]quinolin-6-ones derivative from aromatic amines, aldehydes and 4-hydroxycumarine under solvent free condition. This heterogeneous solid Carbocatalyst GO was found to be highly efficient for furnishing the corresponding products good to excellent yield. GO was cheap and easy recoverable catalyst and its catalytic activity sustained up to fifth run.



CHAPTER VI

Transformative reaction on triterpenoids: Action of hydrogen peroxide in presence of selenium dioxide on the oxime derivative of taraxerone and antimicrobial activity of the isolated compounds

Although studies on oxidation of triterpenoid ketones with hydrogen peroxide and selenium dioxide have been reported but literature reports on the effect of the above oxidizing agent on the oxime derivative of triterpenoid ketones are scanty. Thus in continuation of our studies on the transformative reactions on pentacyclic triterpenoids of lupane and friedelin skeleton and in order to examine the nature of the products formed on the oxidation of oxime derivatives of 3-keto-triterpenoids having gem dimethyl group at C4 and a double bond at ring D (between C14-C15), the oxidation of keto-oximes of taraxerone with hydrogen peroxide and selenium dioxide has been taken up and characterisation of the products (A -D) along with the evaluation of their preliminary biological activity are presented in this paper. The oxime derivative of taraxerone in tertiary butanol was refluxed with selenium dioxide and hydrogen peroxide. The residue obtained after recovery of solvent by distillation was extracted with ether and separated into neutral and acid parts by usual method.



PREFACE

The thesis is the compilation of the research work carried out by the author under the supervision of Professor Pranab Ghosh in the Department of Chemistry, University of North Bengal during the period 2015 to 2020. It comprises a number of transformative reactions on different carbocyclic compounds. And as the author had privilege to work in the natural products laboratory, the carbocyclic compounds chosen as the starting substrates. Because of the presence of large extent catenation capability of carbone, it can produced wide range of molecules solely made by them, it implies that nature provide wide number of carbocyclic compounds. Carbocyclic compounds are produce by joining of two or more carbocycles together in a number of different fashions. This carbocycles are most common in all kinds of natural products.

Thus Carbocycles are another class of fundamental molecular skeletons in various types of organic compounds, pharmaceuticals, natural products, agrichemicals, and bioactive molecules.

The thesis starts with **Chapter I,** where a brief review on the carbocyclic compounds and the transformative reactions of carbocyclic compounds transformation reactions is described. **Chapter II** deals with the A greener and sustainable approach towards the synthesis of propargylamine using multicomponent A^3-coupling reaction. **Chapter III** represents Environmentally begin approach towards c-s cross coupling reaction by organo-copper(II) complex. **Chapter IV** describes Graphene Oxide catalysed one pot synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones and their biological evaluation. **Chapter V** describes One-pot three-component tandem annulation of 4-hydroxycumarine with aldehyde and aromatic amines using Graphene oxide as an efficient catalyst. And the last but not the least **Chapter VI** represents Transformative reaction on triterpenoids: Action of hydrogen peroxide in presence of selenium dioxide on the oxime derivative of taraxerone and antimicrobial activity of the isolated compounds.

TABLE OF CONTENTS

Chapter I

A brief review on the carbocyclic compounds and the transformative reactions of carbocyclic compounds

Chapter II

A greener and sustainable approach towards the synthesis of propargylamine using multi-component A^3-coupling reaction

Chapter III

Environmentally begin approach towards C-S cross coupling reaction by organo - copper(II) complex

Chapter IV

Graphene oxide catalysed one pot synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones and their biological evaluation

Chapter V

One-pot three-component tandem annulation of 4-hydroxycumarine with aldehyde and aromatic amines using Graphene oxide as an efficient catalyst

Chapter VI

Transformative reaction on triterpenoids: Action of hydrogen peroxide in presence of selenium dioxide on the oxime derivative of taraxerone and antimicrobial activity of the isolated compounds

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF APPENDICES

APPENDIX A

List of Research Publications

1. Graphene Oxide Catalyzed One-pot Synthesis of Pyrimido [4,5-b]quinolinone-2,4-diones and their Biological Evaluation, **Rabindranath Singha**, Puja Basak, Malay Bhattacharya, and Pranab Ghosh, *ChemistrySelect.*, **2020**, *5*, 6514 –6525.
2. A greener and sustainable approach towards the synthesis of propargylamine using multicomponent A^3-coupling reaction, **Rabindranath Singha**, Dhiraj Brahman, Biswajit Sinha, Pranab Ghosh, *Asian Journal of Green Chemistry*, **2021**, *5*, 91-110.
3. Transformative reaction on triterpenoids: action of hydrogen peroxide in presence of selenium dioxide on oxime derivative of taraxerone and antimicrobial activity of isolated compounds, **Rabindranath Singha**, Pranab Ghosh, *Journal of Medicinal and Chemical Sciences*, **2020**, *3*, 95-102.
4. Isolation of olean-12(13), 15 (16)-diene, olean-12(13), 15(16)-dien-3β-oland olean-15(16)-en-11α-ol from the pet-benzene extract of Psidiumguajava and their biocidal activity, **Rabindranath Singha**, Md. Golam Rasul, Pranab Ghosh, *Journal of Medicinal and Chemical Sciences*, **2020**, *3*, 118-137.
5. Phytochemical Investigation of Sapium baccatum: Identification of 3α-hydroxy-1α, 2α-epoxy lupan, **Rabindranath Singha**, Pranab Ghosh, *The Pharmaceutical and Chemical Journal*, **2018**, *5*, 9-15.
6. p-TsOH mediated solvent and metal catalyst free synthesis of nitriles from aldehydes via Schmidt reaction, Bijeta Mitra, Gyan Chandra Pariyar, **Rabindranath Singha**, Pranab Ghosh, *Tetrahedron Letters*, **2017**, *58*, 2298–2301.
7. Silica gel an Efficient Catalyst for One-pot Synthesis of Pyrazines from Ethylenediamine and 1, 2-Diketones and their Analogs, Rakesh Ranjan Chakraborty, **Rabindranath Singha**, Pranab Ghosh, Indian Journal of Heterocyclic Chemistry, **2018,** *28, 373-381.*
8. Environmentally benign approach towards C–S cross-coupling reaction by organo-copper(II) complex, **Rabindranath Singha, S**ailesh Chettri, Dhiraj Brahman, Biswajit Sinha, Pranab Ghosh, *Molecular Diversity*, **2021**, https://doi.org/10.1007/s11030-020-10180-5.

APPENDIX B

Oral Presentations

1. Transformative reaction on triterpenoids: action of hydrogen peroxide in presence of selenium dioxide on oxime derivative of taraxerone and antimicrobial activity of isolated compounds, **Rabindranath Singha**, Pranab Ghosh, National seminar on "Frontiers in Chemistry" 14th September 2017, organized by Department of chemistry, University of North Bengal.

Poster Presentations

1. Graphene Oxide Catalyzed One-pot Synthesis of Pyrimido [4,5-b]quinolinone-2,4-diones and their Biological Evaluation, **Rabindranath Singha** and Pranab Ghosh, "International seminar on "Frontiers in Chemistry 2018", organized by Department of chemistry, University of North Bengal and CRSI North Bengal Local Chapter on 27th August, 2018.
2. Isolation of olean-12(13), 15 (16)-diene, olean-12(13), 15(16)-dien-3β-oland olean-15(16)-en-11α-ol from the pet-benzene extract of Psidiumguajava and their biocidal activity, **Rabindranath Singha**, Md. Golam Rasul, Pranab Ghosh, "International seminar on RECENT TRENDS IN CHEMISTRY, Organized by Department of Chemistry, P.D, Women's College, Jalpaiguri, 3rd January, 2019.
3. Environmentally benign approach towards C–S cross-coupling reaction by organo-copper(II) complex, **Rabindranath Singha** and Pranab Ghosh, National seminar on "Frontiers in Chemistry" 5th March 2020, organized by Department of chemistry, University of North Bengal.

ABBREVIATION

Å	Angstrom
Acac	Acetylacetonate
AcOH	Acetic acid
br	Broad
cm	Centimeter
Cy	Cyclohexyl
$CDCl_3$	Deuterated chloroform
d	Doublet
DMF	N, N–Dimethylformamide
DMSO	Dimethyl sulfoxide
DABCO	(1,4-diazabicyclo[2.2. 2]octane)
DMEDA	1,2-Dimethylethylenediamine
EQUIV	Equivalent
EtOH	Ethanol
FT-IR	Fourier-transform infrared spectroscopy
g	gram/grams
GO	Graphene oxide
h	hour/hours
HIV	Human immunodeficiency virus
HRMS	High-resolution mass spectroscopy
m	Multiplet
MHz	Mega hertz
min	minute/minutes
mL	millilitre
mmol	millimole
mol%	mole percent
MS	Molecular sieve
MNPs	magnetic nanoparticles
MW	microwave
MCM	mesoporous material
MCPBA	meta-chloroperoxybenzoic acid
nm	Nanometer

NMR	Nuclear magnetic resonance
NPS	Nanoparticles
^{o}C	Degree Celsius
Phen	Phenyl
RT	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TON	turnover number
TMS	tetramethylsilane
TOF	turnover frequency
TFA	Trifluoroacetic acid
UV	Ultraviolet

Chapter I

A brief review on the carbocyclic compounds and the transformative reactions of carbocyclic compounds

I.A. Introduction to carbocyclic compounds

Carbocyclic compounds are those which contain a group of organic chemical compounds in which all the atoms composing the ring are carbon atom. In its wide range of periphery, the unlimited molecules are formed with their novel interactions. Organic compounds based on their structural aspect, can broadly be classify in to two ways- acyclic and cyclic. The cyclic molecules also represent those which are literally formed by the combination of both cyclic and acyclic molecules. For example, hexyl cyclohexane (1) is a cyclic compound (Figure I.1). A huge number of cyclic entities thus present in nature.

In addition of this, cyclic molecules are also classified into homocyclic and heterocyclic. Homocyclic compounds are those in which all the ring members are constituted by the same element. For example benzene (2), cyclopropane (3), friedelane (4), pentazole (5) etc. Heterocyclic compounds are those in which the rings are formed by one or more different elements. For example morpholine (6), thiophene (7), benzimidazole (8), pyridine (9) etc. (Figure I.1)

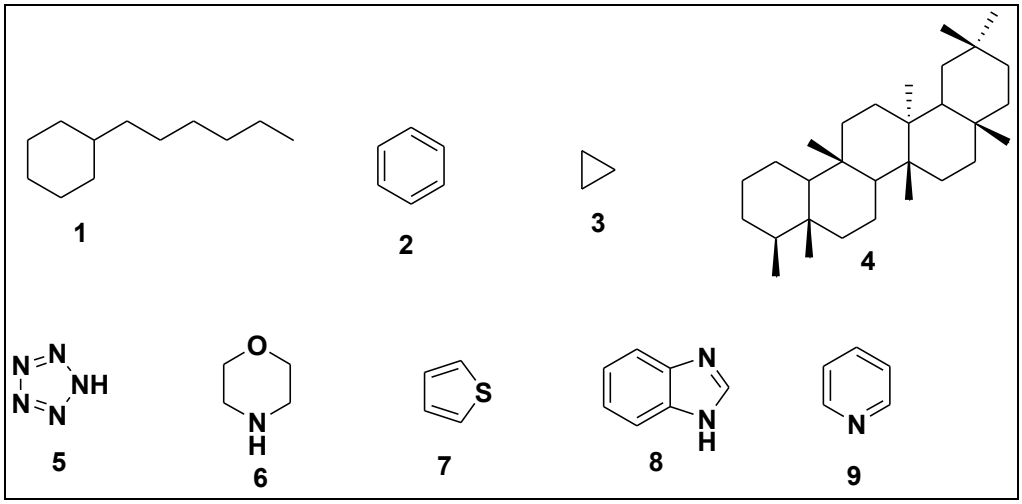


Figure I.1. Some cyclic organic compounds (1-4: carbocyclic compounds, 5: nitrogen-based homocyclic, 6-9: heterocyclic)

I.A.1. Carbocyclic compounds and natural products

Through the ages of all human beings we are all together very closely bound with the nature and we always fulfil our basic need from nature weather it is food purpose or medicinal purpose for good health. Nature always helps us by providing the raw material to fight against the wide range of diseases; especially the plant kingdom produces the basis of traditional medicinal systems. The term natural product means any substance or chemical compounds produced by the living organism which are found in nature.[1,2] A wide range of commercially available substance or materials are obtained from natural resources that are

used in our daily life without any artificial additives e.g foods, some kind of medicines, cosmetics etc.[3] Consequently, many of the natural products have been synthesized in the laboratory by the chemical process to supply the required amount natural compounds.

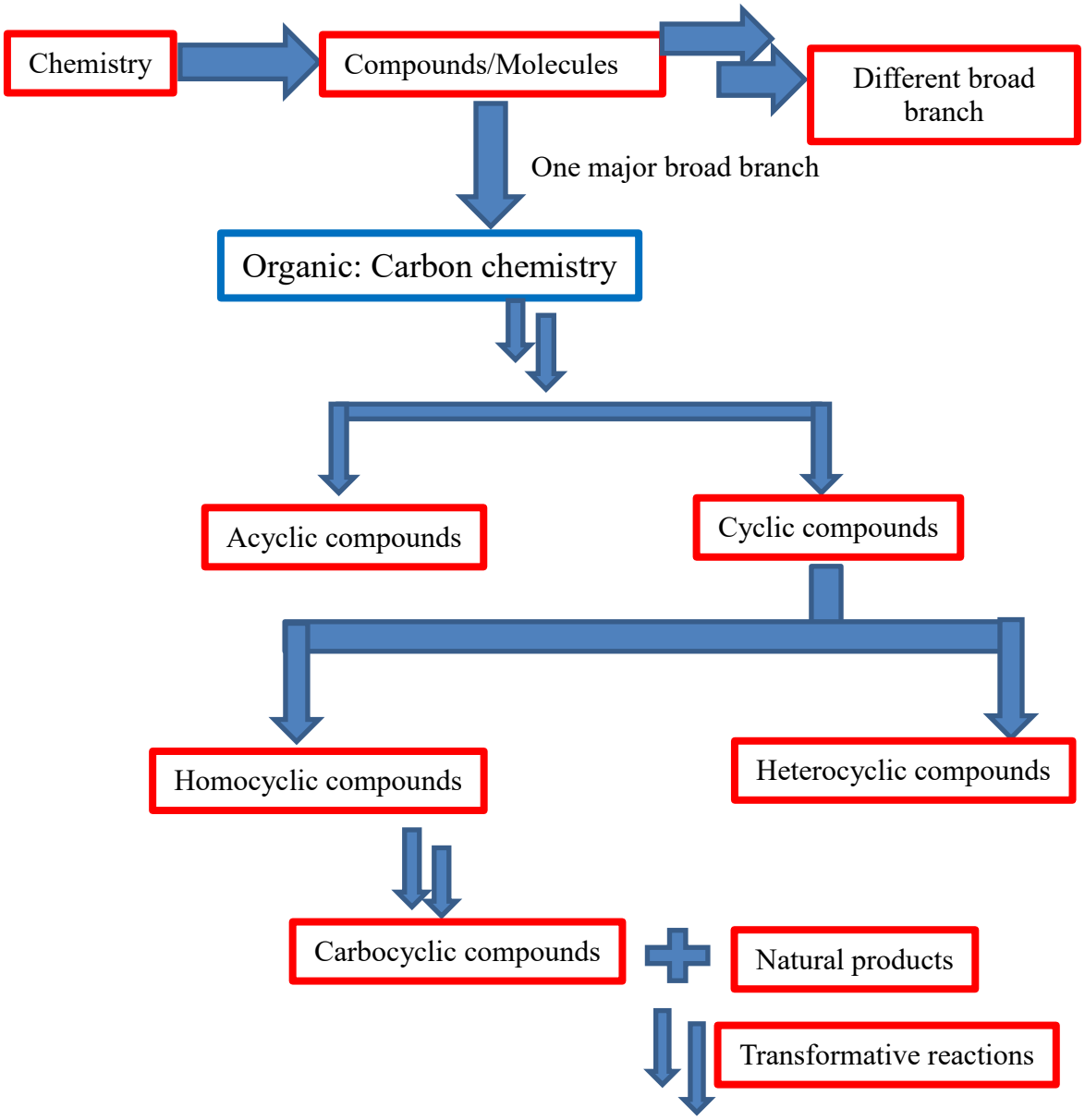


Figure I.2. Schematically representation for the development of transformative reaction

Because of the presence of large extent catenation capability of carbon, it can produce wide range of molecules solely made by it. It implies that nature provides wide number of carbocyclic compounds. Carbocyclic compounds are produced by joining of two or more carbocycles together in a number of different fashions. This carbocycles are most common in all kinds of natural products.

Thus carbocycles are another class of fundamental molecular skeletons in various types of organic compounds, pharmaceuticals, natural products, agrichemicals and bioactive molecules.[4-12]

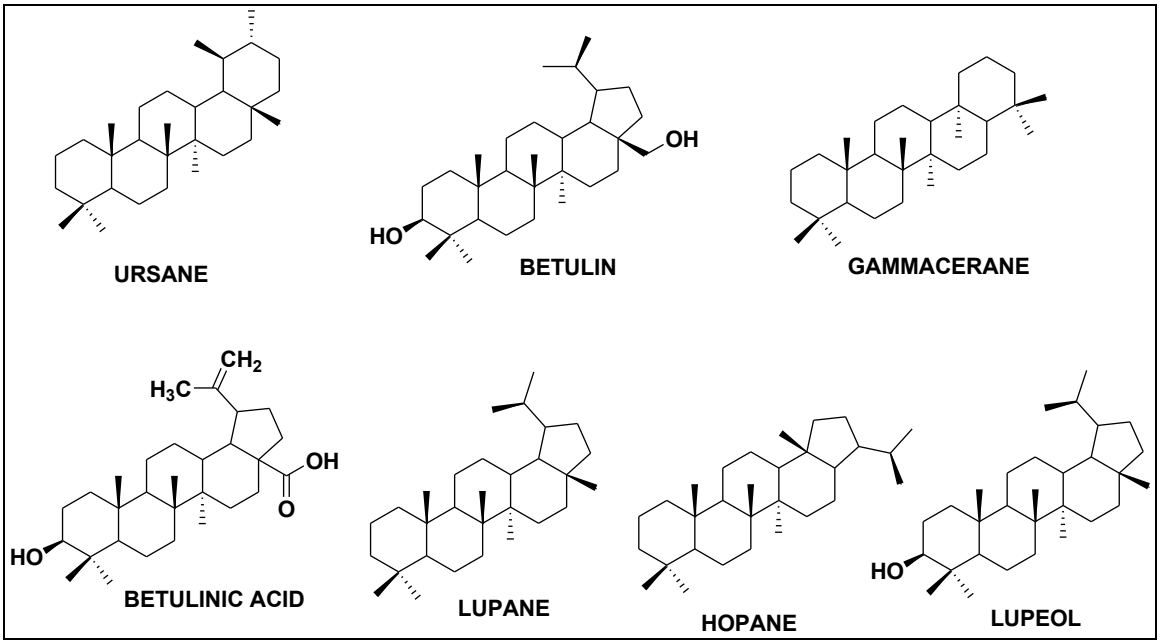


Figure I.3. Some biologically active pentacyclic triterpenes

Considering the great significances of the carbocyclic ring skeletons in the synthetic chemistry, pharmaceutical chemistry as well as in the synthesis of a variety of natural products, bioactive molecules and agrichemicals, the author is interested to work on carbocyclic compounds. The author carried out some chemical transformative reaction of carbocyclic compound. The author also carried out the transformative reaction of pentacyclic carbocyclic compound.

I.B. Transformation reactions of carbocyclic compounds

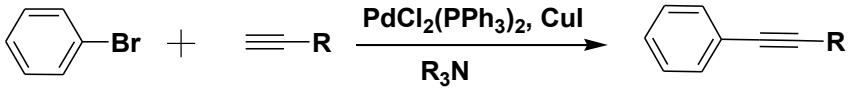
A number of methodologies have been reported in literature for transformation reactions of carbocyclic compounds. A brief review has been discussed in this section.

I.B.1. Carbon-Carbon bond transformation reactions

Carbon-Carbon bond formation reaction plays major role in the organic synthesis for the construction of variety structurally diverse organic molecules. A number of methodologies have been reported in literature for reactions involving carbon-carbon bond formation. A brief review has been discussed in this section.

I.B.2. Sonogashira coupling reaction

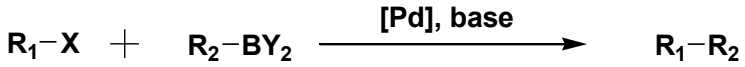
Sonogashira in 1975 provided a powerful tool for the C-C bond forming reaction. The reaction was carried out between the terminal alkynes with aryl or vinyl halides by using a palladium catalyst, a copper (I) co-catalyst, and an amine base.[13,14] This reaction has been widely applied to diverse areas such as natural products synthesis, heterocyclic synthesis and material science.[15] Copper salts were the most common co-catalyst (Scheme I.1).



Scheme I.1. Sonogashira Coupling reaction

I.B.3. Suzuki coupling reaction

A. Suzuki *et al.*[16] have reported the cross-coupling reaction of organic halides with organoboron compounds by using phosphine-based palladium catalysts. It is versatile and an important method for the generation of unsymmetrical biaryls from arylboronic acids and aryl halides in a single step. It is important for the synthesis of natural products as well as pharmaceuticals, herbicides, conducting polymers (Scheme I.2).[17]

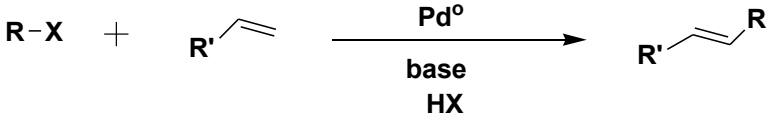


BY_2 = $B(OH)_2$, $B(OR)_2$, 9-BBN, $BF_3^-K^+$, $B(CHCH_3CHCH_3)_2$
X= I, Br, Cl, OSO_2
R_1 = aryl, alkenyl, alkynyl, benzyl, allyl
[Pd] = $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $PdCl_2(dppf)$
base = Na_2CO_3, NaOEt, NEt_3, TlOH, K_3PO_4

Scheme I.2. Suzuki Coupling reaction

I.B.4. Heck coupling reaction

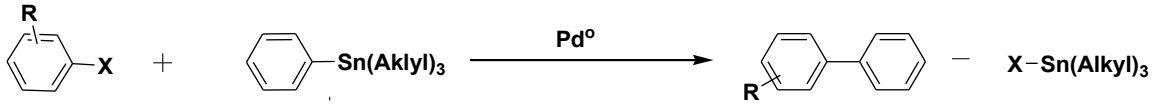
Heck coupling reaction is a C-C coupling reaction between the alkene and unsaturated halide (or triflate) by using the palladium catalyst (or palladium nanomaterial-based catalyst) in the presence of a base to form a substituted alkene (Scheme I.3).[18]



Scheme I.3. Heck coupling reaction

I.B.5. Stille coupling reaction

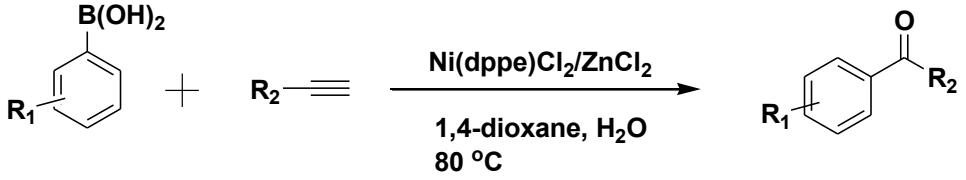
Stille coupling reaction provided a method by which the C-C bond formation occurred through the coupling of alkenyl and aryl halides with organostannanes with the help of palladium catalyst (Scheme I.4).[19]



Scheme I.4. Stille coupling reaction

I.B.6. Direct synthesis of arylketones

C. Chien-Hong *et al.* recently reported an efficient and convenient nickel-catalysed addition reaction of the arylboronic acids and nitriles for the synthesis of aryl ketones. By this reaction various aryl ketone derivatives have been synthesized (Scheme I.5).[20]



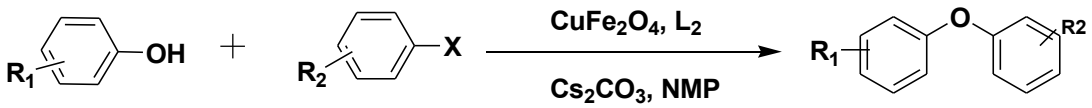
Scheme I.5. Direct synthesis of aryl ketones

I.C. Carbon-hetero bond transformation reactions

A wide number of methodologies have been reported for the transformative reaction of carbocyclic compounds which involved the formation of carbon–hetero bond formation. A very short review has been discussed below.

I.C.1. C-O bond formation reaction

W. Yang *et al.*[21] reported the air stable copper ferrite ($CuFeO_4$) nanoparticle catalysed Ullmann C-O coupling reaction of phenols and aryl halides. The reaction was reported to furnish good yield of the products and the catalyst was easily recovered by using the external magnetic field (Scheme I.6).

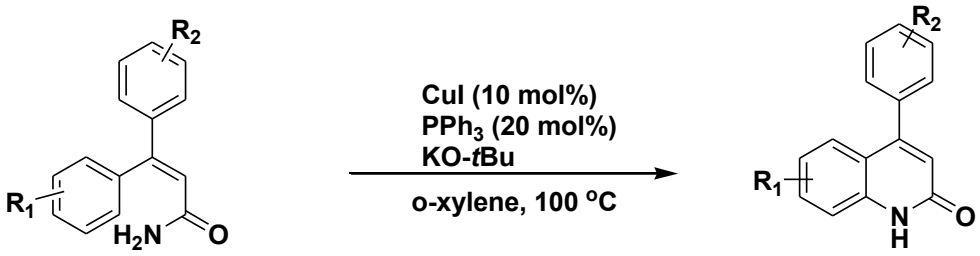


Scheme I.6. Copper ferrite ($CuFeO_4$) nanoparticle catalysed Ullmann C-O coupling reaction of phenols and aryl halides

I.C.2. C-N bond formation reaction

Cacchi *et al.* developed new Cu-catalysed approach for the construction of 2-quinolones. The process was the basis of intra-molecular C–H functionalization/C–N bond formation. The reaction was carried out by the CuI (10 mol%) catalyst with PPh_3 (20 mol%) and KO-*t*Bu in

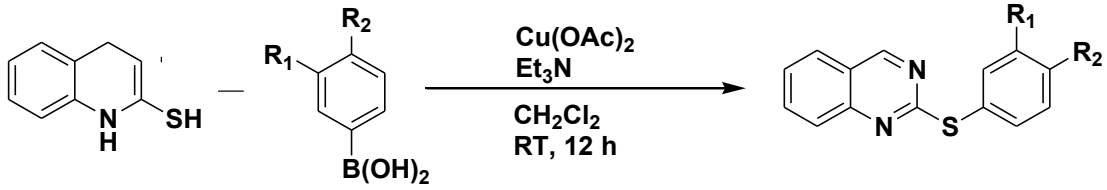
ortho-xylene at 100 ^{o}C for 5 to 24 h under aerobic conditions (Scheme I.7).[22]



Scheme I.7. Intra-molecular C–H functionalization/C–N bond formation in the synthesis of quinolones

I.C.3. C-S bond formation reaction

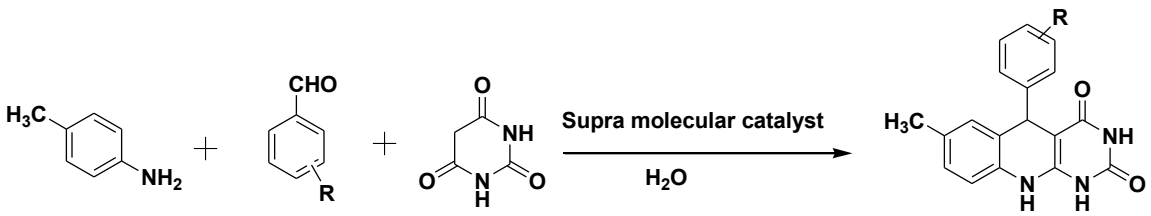
N. K. Katari *et al.*[23] developed a Chan-Lam coupling reaction for the synthesis of S-aryl/heteroaryl-quinazoline. In this reaction, 1,4-dihydroquinazoline was treated with a variety of aryl and hetero-arylboronic acids by using $Cu(OAc)_2$ as a catalyst in CH_2Cl_2 solvent (Scheme I.8).



Scheme I.8. $Cu(OAc)_2$ catalysed the synthesis of S-aryl/heteroaryl-quinazoline

I.C.4. Water mediated β-cyclodextrin catalysed three-component reaction for the synthesis of pyrimido[4,5-*b*]quinoline-diones

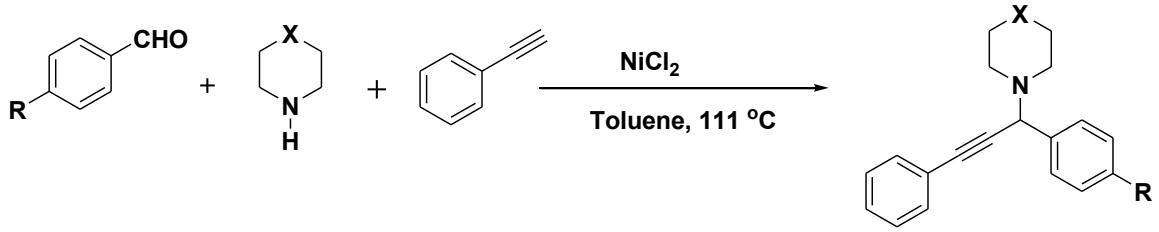
P. V. G. Reddy have reported a method for the synthesis of pyrimido[4, 5-*b*]quinoline-diones by the condensation of aldehyde, aniline and barbituric acid by using the β-cyclodextrin as a catalyst in water solvent. The method was efficient and environmentally benign and useful for the construction of a series of pyrimido[4,5-*b*]quinoline-diones derivatives (Scheme I.9).[24]



Scheme I.9. Synthesis of pyrimido[4,5-*b*]quinoline-diones

I.C.5. One-pot synthesis of propargylamines by three-component A^3-coupling of aldehydes, amines and alkynes

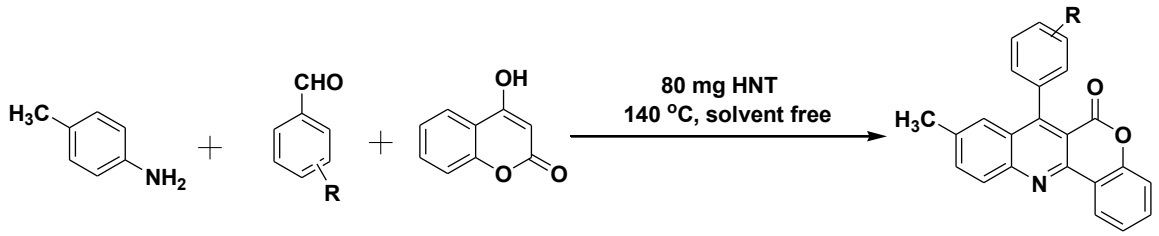
Recently, in the year of 2010, M. S. Singh *et al.*[25] have synthesized propargylamines by the coupling of aldehydes, amines, and alkynes using $NiCl_2$ as a catalyst in toluene solvent. Here vast array of aldehydes including aliphatic, aromatic hetero aldehydes are smoothly converted to the corresponding product (Scheme I.10).



Scheme I.10. Synthesis of propargylamines

I.C.6. Synthesis of chromeno[4,3-*b*]quinolin-6-one derivatives

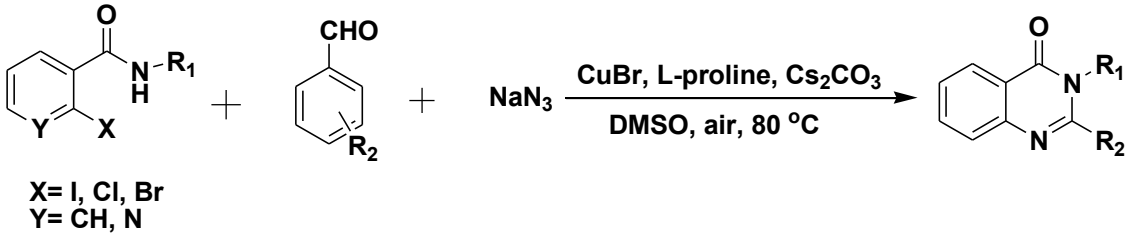
I. Mohammadpoor-Baltork recently in the year of 2019, reported a straightforward solvent free multi-component reaction for the synthesis of chromeno[4,3-*b*]quinolin-6-ones. The reaction was carried out between aldehydes, 4-hydroxycoumarin and aryl amines and halloysitenanoclay was used as eco-friendly and green heterogeneous catalyst (Scheme I.11).[26]



Scheme I.11. Synthesis of chromeno[4,3-*b*]quinolin-6-one

I.C.7. Synthesis of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones

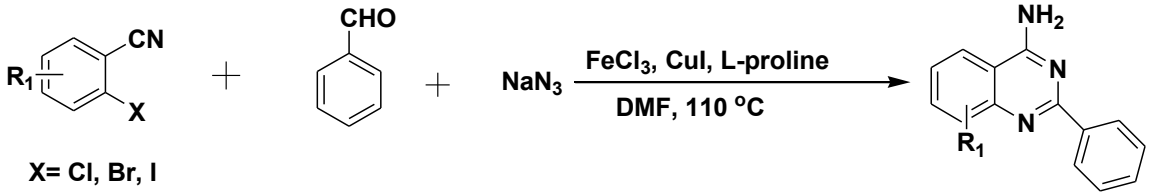
D. Chen *et al.*[27] have developed a consecutive method for the synthesis for quinazolin 4(3*H*) ones and pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones from 2-halobenzamides (or -halo-nicotinamides), aldehydes and sodium azide by using CuBr in DMSO solvent. The method was reported to be highly reliable and provided high scope with respect to the reactants and provided a novel synthetic strategy for bioactive molecules containing quinazolinone skeletons (Scheme I.12).



Scheme I.12. Synthesis of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones

I.C.8. Synthesis of 2-phenylquinazolin-4-amines

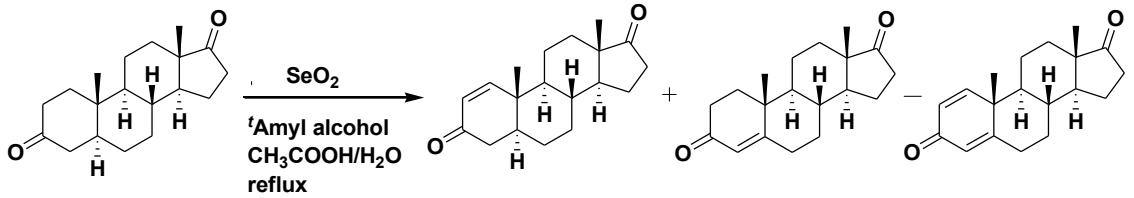
In the year of 2015, W. An-Xin *et al.* have reported reaction protocol for the synthesis of 2-phenylquinazolin-4-amines by the treatment of easily available *ortho*-halogenated benzonitriles, aldehydes and sodium azide with Fe/Cu relay-Catalyst. 2-phenylquinazolin-4-amines derivatives are the privileged core structure of some drugs and bioactive molecules (Scheme I.13).[28]



Scheme I.13. Synthesis of 2-phenylquinazolin-4-amines by the treatment of easily available ortho-halogenated benzonitriles, aldehydes and sodium azide with Fe/Cu relay-Catalyst

I.C.9. Carbocyclic transformative reaction of 5α- androstane-3,17-dione

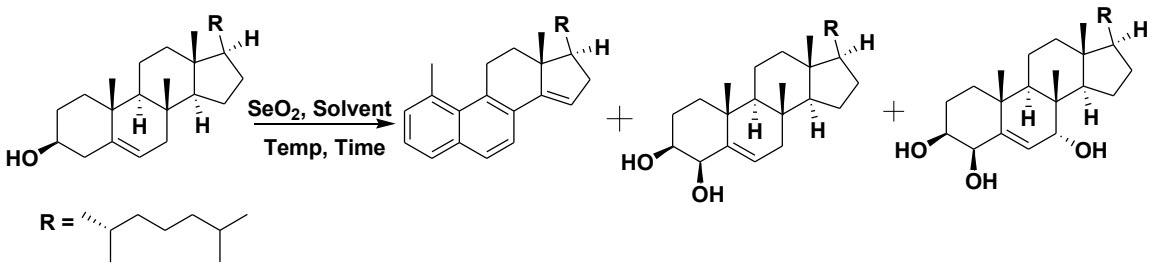
When 5α-androstane-3,17-dione was treated with selenium dioxide in *t*-amyl alcohol, acetic acid and water under refluxed condition where 5α-androst-l-ene-3,17-dione, androst-4-ene-3,17-dione and androsta-l, 4-dien-3,l7-dione were obtained as product (Scheme I.14).[29]



Scheme I.14. Transformative reaction of 5α- androstane-3,17-dione

I.C.10. Carbocyclic transformative reaction of cholesterol

J. Das *et al.* firstly reported the solvent-selective transformative reaction of cholesterol with SeO_2. The reaction was carried out by the treatment of cholesterol with SeO_2 in various solvent and naphthalene analogue obtained as a product along with 4β-hydroxy and 4β,7α-dihydroxy compound (Scheme I.15).[30]



Scheme I.15. Transformative reaction of cholesterol with SeO_2

I.D. Conclusion

In conclusion, we can say that various synthetic methods have been developed for the transformative reaction of carbocyclic compounds involving the carbon-carbon bond transformation and carbon-hetero bond formation reactions. We also showed the transformative reaction on big carbocyclic compounds. But most of them suffer some limitation due to use of expensive catalyst, harsh reaction condition, long reaction time, low yield of desired products etc. From this drawback it is clear that some improvement is needed in such transformative reaction of carbocyclic compounds.

I.E. References

References are given in BIBLIOGRAPHY under Chapter I.

Chapter II

A greener and sustainable approach towards the synthesis of propargylamine using multi-component A^3-coupling reaction

II.A. Introduction

Propargylamines are the versatile building blocks for the synthesis of variety of nitrogen-containing heterocyclic compound[1-7] and these nitrogen-containing heterocyclic compounds are used as an important intermediate for the preparation of biologically active molecules and natural products.[7-14] Some of the propargylamine derivatives clinically have been used for the treatment Parkinson's diseases,[15] Alzheimer's diseases.[16,17] Besides, they also act as antitumor,[18] herbicides,[19] enzyme inhibitors,[20] antibiotics,[21] and pharmaceutical agents.[22] They are also useful as intermediate such as oxotremorine analogues, peptide isosters, therapeutic drug molecules, β-lactams, natural products and polyfunctional amino derivatives in organic synthesis as well as some drug molecules.[23,24]

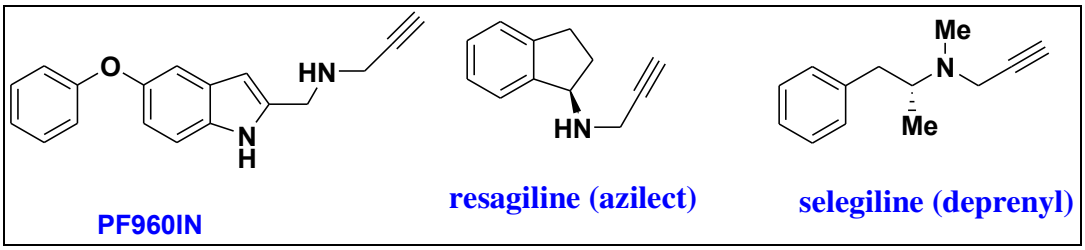
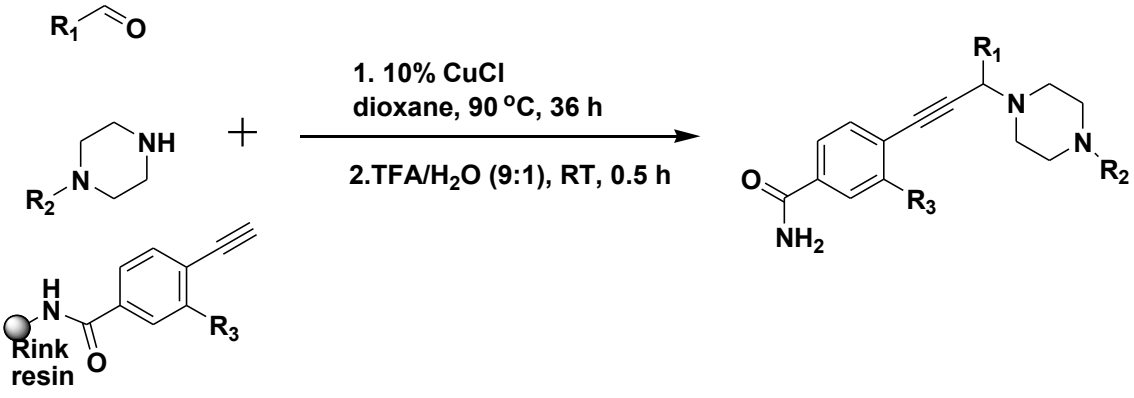


Figure II.1. Bioactive compounds bearing a propargylamine moiety

II.B. Backgrounds and Objectives

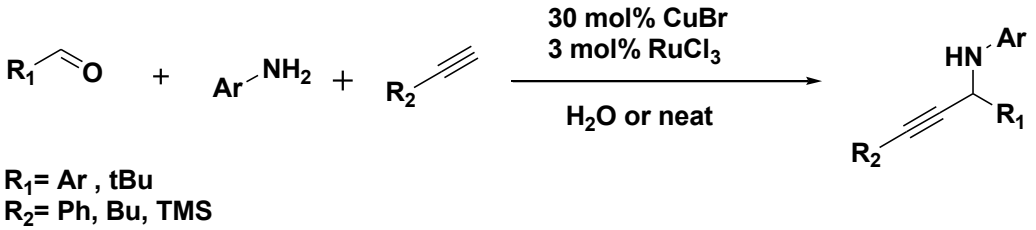
II.B.1. Classical method for synthesis of propargylamines

The story of A^3-coupling reaction starts in 1998 when Dax *et al.* reported the solid-phase three-component reaction for the synthesis of propargylamine by the coupling of aldehyde, alkyne and secondary amine with the implement of 2 equiv. of CuCl.[25] But interestingly, when they were utilized a stoichiometric amount of CuCl catalyst in the solid-phase methodology then they observed that the criteria for the A^3- coupling reaction does not completely meet. Later on, in the same year Dyatkin *et al.* developed a complementary protocol by the implication of polymer-supported aryl alkynes and different substituted aldehydes and secondary amines for the synthesis of propargylamines in the presence of catalytic amount (10 mol%) of CuCl (Scheme II.1). This was the first general and solid-phase modified A^3-coupling reaction protocol.[26]



Scheme II.1. Synthesis of propargylamines

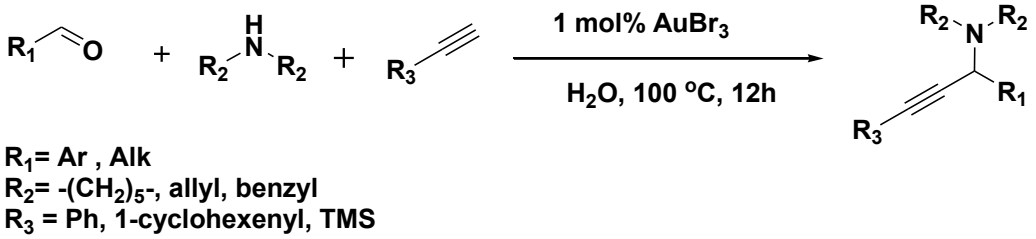
On further developing reaction, a great contributions have been made by the group of Prof. Chao-Jun Li of McGill University and was first termed ''A^3-coupling''.[27] In 2002, Li and Wei reported the application of CuBr-$RuCl_3$ catalytic system for the synthesis of *N*-arylpropargylamines in water medium as well as solvent free medium *via* the A^3- coupling reaction (Scheme II.2).



Scheme II.2. CuBr–$RuCl_3$ co-catalyzed A^3-coupling reaction.

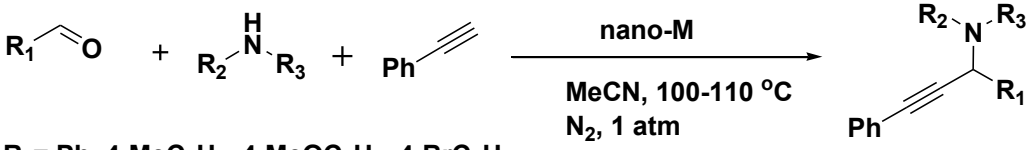
II.B.2. Modern methods for the synthesis of propargylamines

A number of methods have been reported for the synthesis of propargylamines. In the year 2003, same authors developed the gold catalysed A^3- coupling reaction for the synthesis of tertiary propargylamines from aldehydes, secondary amines and alkynes (Scheme II.3).[28]



Scheme II.3. $AuBr_3$-catalyzed A^3-coupling for the synthesis of tertiary propargylamines

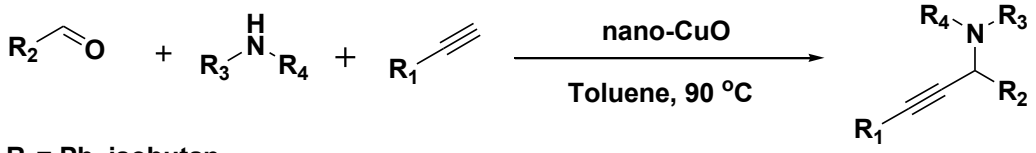
Recently, in the year 2007 Kidwai *et al.*[29] successfully synthesized the propargylamine by using the metal nanocatalysts (Au, Ag, Ni and Cu). This was the firstly reported nano-catalysed A^3-coupling reaction by aromatic aldehydes, secondary amines and phenylacetylene in MeCN solvent under nitrogen atmosphere (Scheme II.4).



R_1= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-furfuryl, *c*-Hex
R_2R_3NH = Morpholine, piperidine and pyrrolidine

Scheme II.4. Nano-metal as catalysed A^3-coupling reaction.

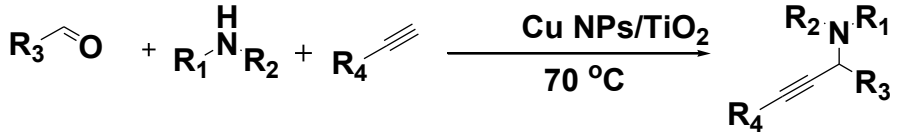
In 2008, Kantam *et al.*[30] reported the nanocrystalline copper (II) oxide catalysed A^3-coupling reaction for the synthesis of various propargylamines by using the aliphatic as well as aromatic aldehydes, amines and alkynes in toluene as a solvent (Scheme II.5).



R_1= Ph, isobutan
R_2= Cyclohexyl, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$
R_3R_4NH = Morpholine, piperidine, pyrrolidine, dibutylamine, dibenzylamine, N-benzylaniline

Scheme II.5. Synthesis of propargylamines catalysed by nano CuO

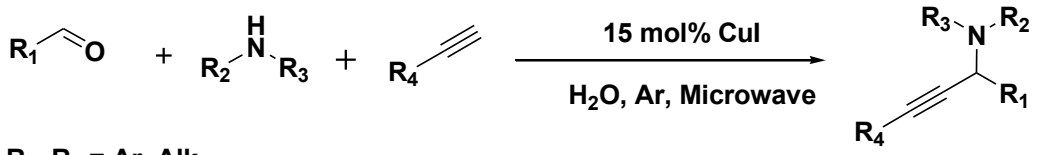
Alonso and colleagues in 2012 reported a simple method for the synthesis of propargylamines from aldehydes or ketone, amines, and alkynes by using their synthesized copper NPs (mainly as Cu_2O) on titania (Cu NPs/TiO_2) at 70 °C under solvent-free conditions (Scheme II.6).[31]



R_1R_2NH = Morpholine, piperidine, 4-methylpiperidine, 2-methylpiperidine, *N*-methylaniline, *N*-methylbenzylamine, *N*-methyl-*N*-phenylamine,diethylamine
R_3= H, Ph, 4-$MeOC_6H_4$,2-IC_6H_4, 3-$NO_2C_6H_4$, 1-naphthyl, 2-benzafuryl, -$(CH_2)_8Me$, C_6H_{11}, 2 -benzofuryl, (*S*)-2,6-dimethylhept-5-enal
R_4= Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, C_6H_{11}, -$(CH_2)Me$

Scheme II.6. Cu NPs/TiO_2 catalysed three-component A^3-coupling reaction

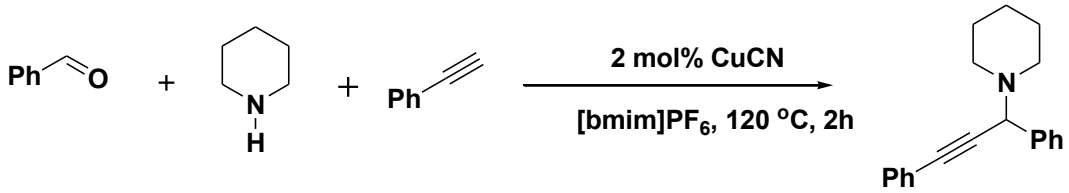
Though Li provide collectively a direct and environmentally benign reaction protocols to access a wide range of propargylamines derivatives, but all of them contained few drawback such as long reaction time and small substrate scope. Tu *et al.*[32] in the year 2004 identified this problem and reported a universal microwave-assisted CuI-catalysed (15 mol% CuI) A^3-coupling reaction for the synthesis of propargylamines in water medium. This reaction protocol was applicable for the aliphatic and aromatic aldehydes and alkynes as well as secondary amines, *t*-butyl amine and aniline (Scheme II.7). But the problem in this reaction was to recycle the catalyst after completion of the reaction.



R_1, R_4 = Ar, Alk
R_2, R_3= Alk or
R_2 = H; R_3 = Ph, *t*Bu

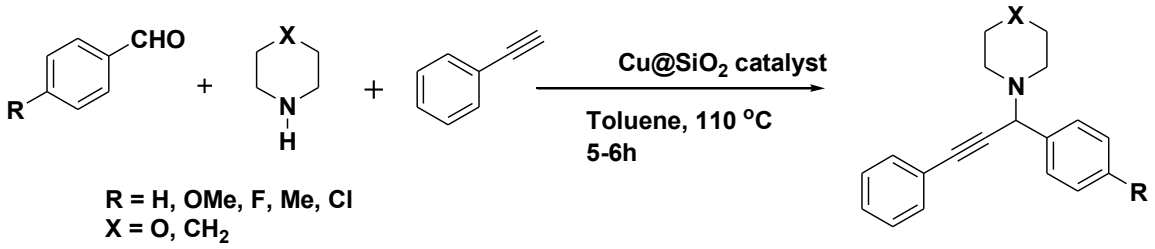
Scheme II.7. Universal microwave-assisted CuI catalysed A^3-coupling reaction.

In 2005, Park *et al.* firstly reported Cu(I) salt catalysed A^3-coupling reaction protocol in ionic liquid. The reaction were carried out in [bmim]PF_6 by using 2 mol% CuCN catalyst at 120 ^oC for 2 h and after completion of the reaction the catalyst was recovered (Scheme II.8).[33]



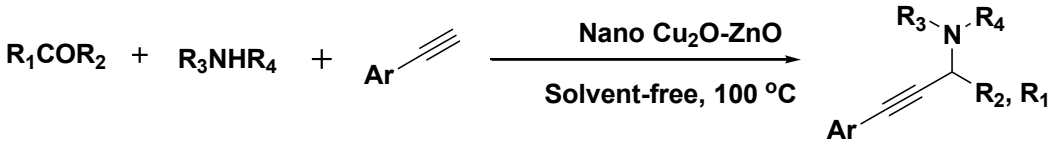
Scheme II.8. CuCN catalysed A^3-coupling reaction

Peng *et al.*[34] in 2013 developed a Cu@SiO_2 nano-catalyst for the synthesis of propargylamine through A^3-coupling reaction in toluene medium (Scheme II.9).



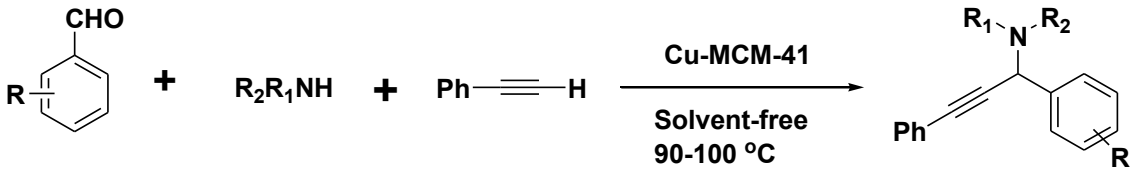
Scheme II.9. SiO_2@Cu catalysed synthesis of propargylamine through A^3- coupling reactions

Hosseini-Sarvari *et al.*[35] reported a nano-copper (I) oxide-zinc oxide (nano Cu_2O-ZnO) efficient and greener method for the synthesis of propargylamine through the C-H bond activation. The protocol was developed for the synthesis of tertiary or quaternary carbon-containing propargylic amines by the one-pot three-component coupling reaction of the terminal alkynes, aldehydes or ketones and secondary amines under neat conditions at 100 ^oC temperature (Scheme II.10).



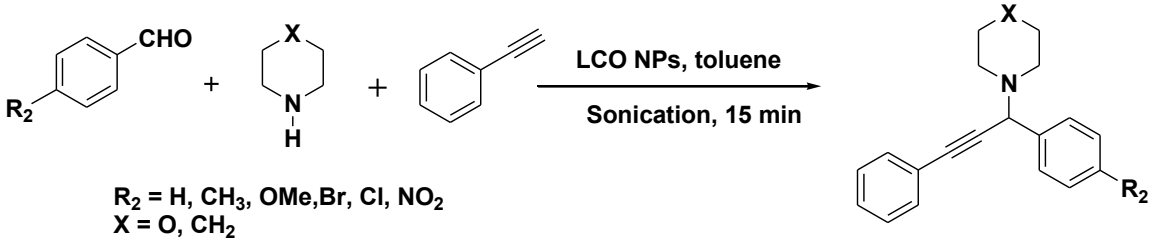
Scheme II.10. Synthesis of propargylamines catalysed by Cu_2O-ZnO nanoparticles under solvent-free conditions

Abdollahi-Alibeik developed a three-component A^3-coupling reaction of aldehydes, amines and phenylacetylene which was an efficient, environmentally benign economical beneficial reaction procedure for the synthesis of propargylamine by using their own synthesised Cu-MCM-41 NPs as catalyst under solvent free conditions (Scheme II.11).[36]



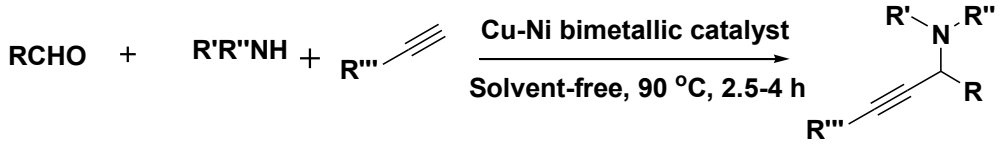
Scheme II. 11. Cu–MCM-41 catalysed synthesis of propargylamines

Karthikeyan in 2015 successfully reported the lathanum loaded CuO NPs (LCO NPs) for A^3-coupling reaction of wide variety of aldehydes, alkynes and amines for the synthesis of a variety of propargylamines derivatives under ultrasonic irradiation (Scheme II.12).[37]



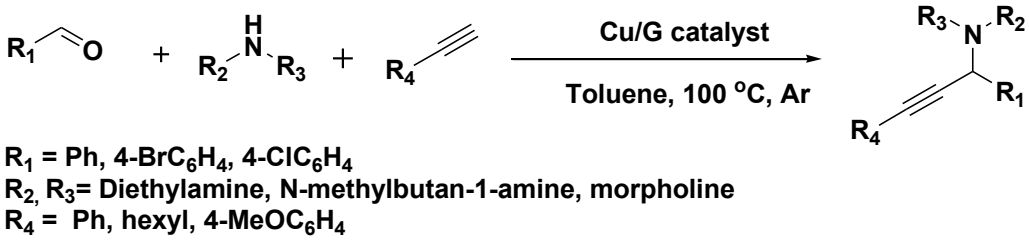
Scheme II.12. Lanthanum loaded CuO NPs catalysed A^3-coupling reaction

Jayaram *et al.* in 2014 reported a magnetically separated Cu-Ni bimetallic catalysed multi-component A^3-coupling reaction for the synthesis of propargylamine from aldehydes, secondary amines and alkynes via the C-H bond activation under the neat condition (Scheme II.13).[38]



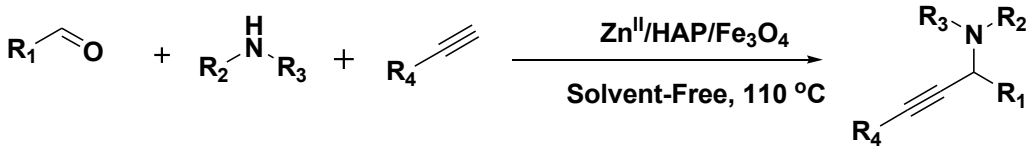
Scheme II. 13. Synthesis of propargylamines by using Cu-Ni bimetallic catalyst

In the year 2016, Garcia *et al.* proposed a more efficient and inexpensive Cu/graphene catalysed A^3-coupling reaction in toluene medium at 100 °C (Scheme II.14).[39]



Scheme II.14. A^3-coupling of terminal alkynes, aldehydes and amines using Cu/G catalyst

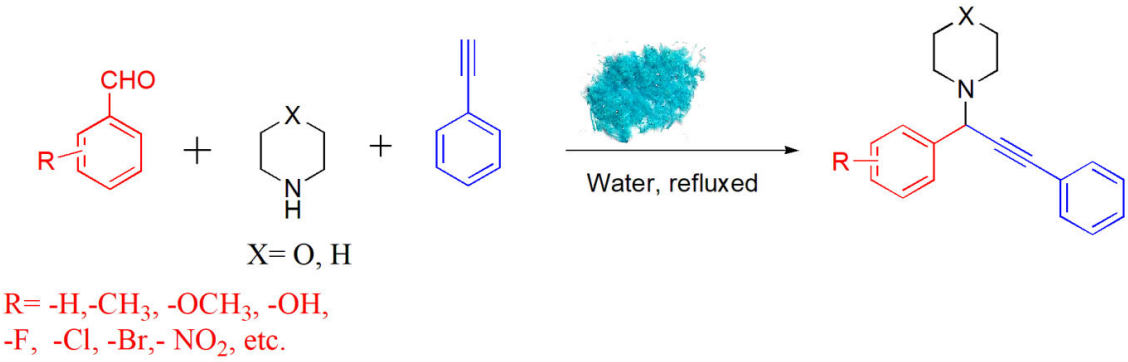
In the same year (2016) Akhlaghinia *et al.*[40] reported solvent free Zn(II)/HAP/Fe_3O_4 catalysed one-pot three-component A^3-coupling reaction. The reaction protocol was simple, efficient and environmentally benign and the catalyst after the reaction was easily recovered by applying magnetic field and reused for several times (Scheme II.15).



Scheme II.15. Zn(II)/HAP/Fe_3O_4 catalysed synthesis of propargylamines

II.C. Present work

In order to investigate the catalytic activity of our synthesized catalyst, here we established an excellent greener protocol to yield propargylamine through the A^3-coupling reaction in water medium by using our synthesized catalyst metal-organic complex [Bis(picolinate-κ^2N:O) Cu(II)] catalyst. Low toxicity, easy access to active sites, high surface area, high thermal stability, recyclability of the catalyst and easy way to separate the catalyst from the reaction mixture are the added advantage of this developed greener and sustainable protocol.



Scheme II.16. Metal-organic complex [Bis(picolinate-κ^2N:O) Cu(II)] catalysed A^3-coupling reaction

II.C.1. Result and discussion

In order to explore the catalytic activity of the newly synthesized catalyst, we carried out A^3-coupling reaction with benzaldehyde (1 mmol), phenylacetylene (1 mmol) and morpholine (1 mmol) under reflux condition using water as solvent. We found that the reaction was completed in 8 h with a 95 % yield of the desired product (Table II.1, entry 6). However, when the same reaction was attempted under similar condition in the absence of catalyst we did not get the desired product. Therefore, we conclude that the reaction did not occur in absence of catalyst (Table II.1, entry 1). Hence to optimize the protocol, the model reaction was repeated with varying amount of the synthesized copper catalyst (Table II.1) and out of all attempts we established that 10 mg of the catalyst (per mmol of the reactants) yielded the

best result. We also tried various solvents, such as DCM, DMF, toluene, DMSO (Table II.I, entry 13, 14, 15, 16) but could not able to beat the superiority of water as solvent. Thus fortunately water was established as the optimal medium of the reaction. The reaction was also carried out in solvent free condition which also afforded the corresponding product but with only moderate yield (Table II.1, entry 3). Further, in order to optimize the temperature the model reaction was carried out at 50, 60, 70, 80 and 90 ^{o}C. Among them best yield was obtained at 80 ^{o}C (Table II.1, entry 6). The yield of product gradually increases with increasing temperature and the best result is obtained at 80 ^{o}C (Table II.I). At a temperature beyond 80 ^{o}C the increase of yield was not considerable and as a result, 80^{o}C was taken as an optimal temperature. The reaction was also tried at room temperature and even after 24 h of reaction we failed to isolate minimum yield of the product (Table II.1, entry 17). With this optimized condition we also carried out the same reaction by using the various amount of catalyst viz. 2, 4, 6, 8, 10, 12 and 14 mg. We found that 10 mg catalyst (per mmol of the reactants) was sufficient for the complete conversion of the reaction. Further increase in the amount of catalyst did not increase the yield of the product considerably. With this optimized condition we performed the reaction with various substituents (Table II.2).

Table II.1. Optimization of reaction parameters for the synthesis of propargylamine derivatives[a]

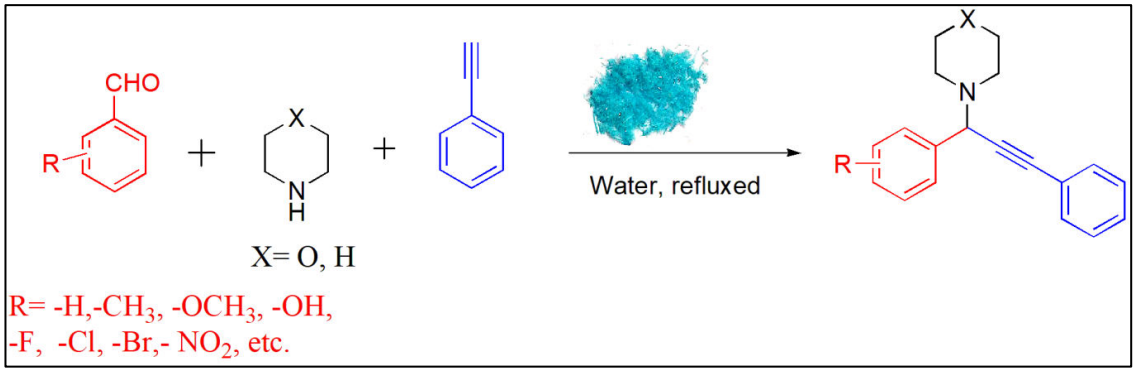
Entry	Catalyst (mg)	Time (h)	Temperature (^{o}C)	Solvent (5 mL)	Yield[b] (%)
1	-	24	80	Water	NR
2	2	12	80	Water	30
3	4	12	80	Neat	50
4	6	8	80	Water	80
5	8	8	50	Water	73
6	**10**	**8**	**80**	**Water**	**95**
7	10	12	80	Water	96
8	12	8	80	Water	95
9	14	8	80	Water	93
10	10	8	60	Water	75
11	10	8	70	Water	80
12	10	8	90	Water	90
13	10	8	80	Toluene	60
14	10	8	80	DMSO	59
15	10	8	80	DMF	86

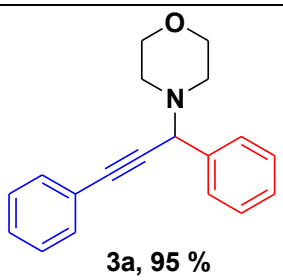
16	10	8	80	Ethanol	87
17	10	24	RT[c]	Water	NR

[a]Reaction conditions: Benzaldehyde (1 mmol), phenylacetylene (1 mmol), morpholine (1 mmol), Copper catalyst (10 mg) at different temperatures and solvent. [b]Isolated yields, [c]room temperature reaction, NR = No reaction.

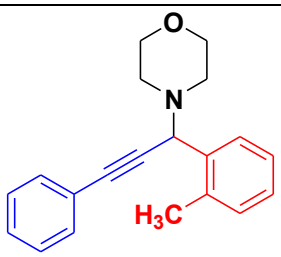
To investigate the generality and scope of the catalytic activity of the synthesized catalyst in A^3-coupling reaction, we carried out the reaction with a variety of aldehydes and terminal alkynes with different secondary amines. Both the electron donating/electron withdrawing groups were employed with secondary amine. Aldehyde with electron donating groups afforded the desired product with high yield which may be due to the increased electron density in the aldehyde nucleus and thereby facilitating reaction faster (Table II.2, entries 3a-3v). Bromo, chloro and fluorobenzaldehydes were also tried and afforded excellent yields and the order of reactivity of aromatic halo aldehyde was –Br > -Cl > -F (Table II.2, entry 3e, 3i, 3m, 3v). Aldehyde with electron withdrawing group such as $–NO_2$ was needed more time to complete and afforded low yield of the product (Table II.2, entry 3j). However, hetero aldehyde provided with good yield of the product (Table II.2, entry 3h). The above protocol was also examined with aliphatic aldehydes (Table II.2, entries 3t, 3u), which yielded the corresponding product in good yield. Naphthaldehydes were tried to determine the substrate scope of this reaction and the results afforded the desired product in good yield (Table II.2, entry 3f, 3g). From these results listed in Table II.2, it is obvious that the newly developed greener catalyst may direct the A^3-coupling reaction for a wide range of substrate applicability for the synthesis of propargylamine derivatives.

Table II.2. Substrate scope of amines and aldehydes for the synthesis of propargylamine[a]

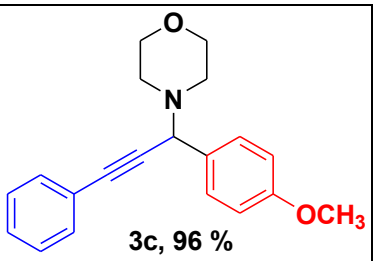




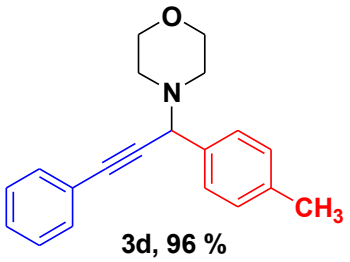
3a, 95 %



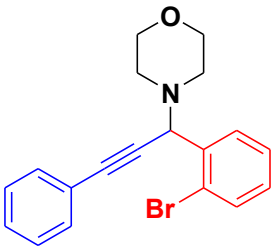
3b, 96 %



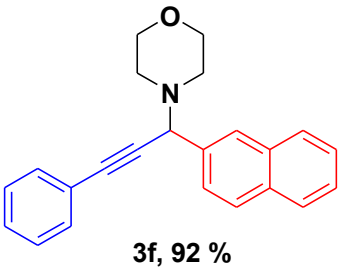
3c, 96 %



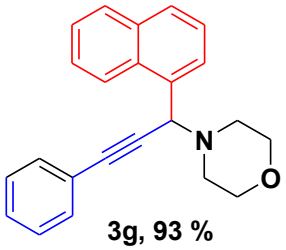
3d, 96 %



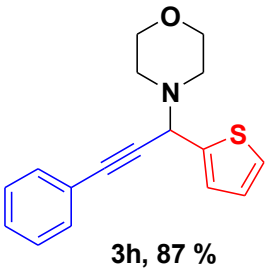
3e, 90 %



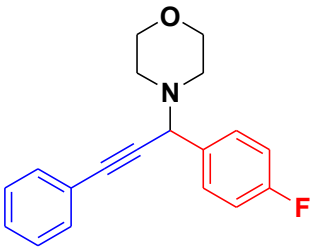
3f, 92 %



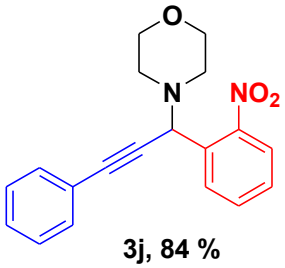
3g, 93 %



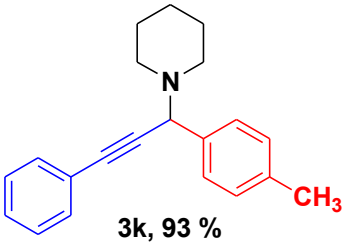
3h, 87 %



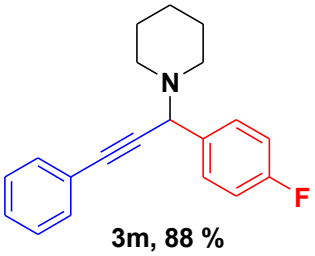
3i, 85 %



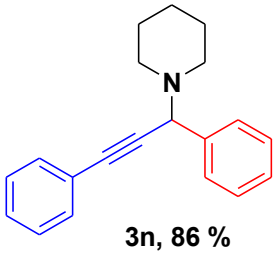
3j, 84 %



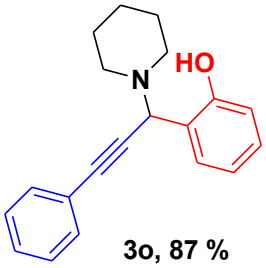
3k, 93 %



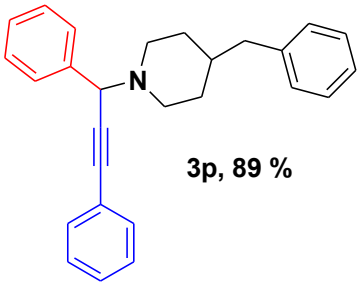
3m, 88 %



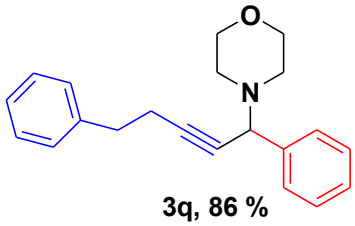
3n, 86 %



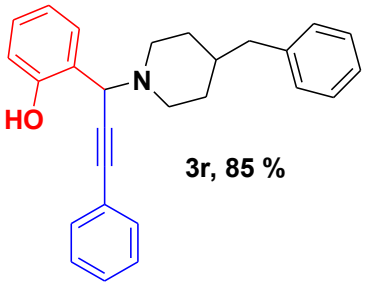
3o, 87 %



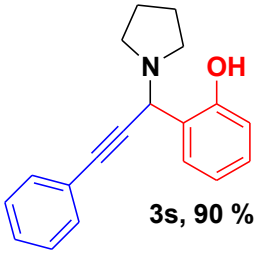
3p, 89 %



3q, 86 %



3r, 85 %

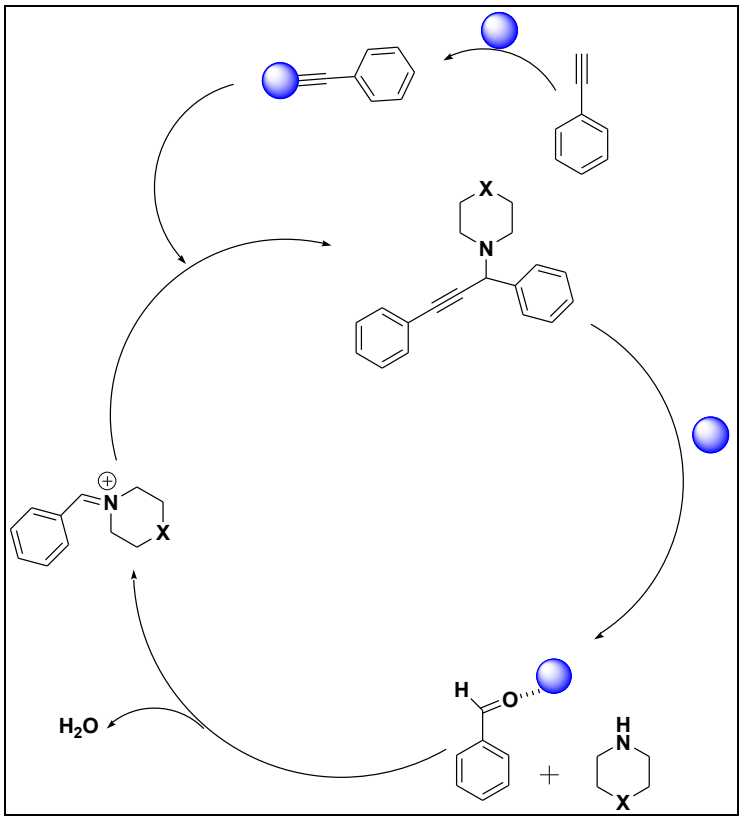


3s, 90 %

[a]Reaction conditions: Benzaldehyde (1 mmol), phenylacetylene (1 mmol), morpholine (1 mmol), Copper catalyst (10 mg) at 80 ^{o}C temperatures and water solvent. [b]Isolated yields.

III.C.2. Mechanism

From the earlier reports[41,42] a plausible mechanism to access propargylamine involving aldehyde, phenylacetylene and morpholine in the presence of the synthesized catalyst depicted in Scheme II.17 below. It is assumed that, the reaction initiated by the nucleophilic attack of the amine to the activated electrophilic carbon of the aldehydic group, followed by the removal of H_2O molecule to yield the iminium ion. Simultaneously, the catalytically activated C-H bond of the phenylacetylene formed the active acetylidine complex. Finally the activated acetylidine complex was added with the iminium ion to yield the corresponding propargylamine.



Scheme II.17. Proposed mechanism of the A^3- coupling reaction

II.D. Conclusion

In conclusion, synthesized copper catalyst was applied in a greener and sustainable version of multi-component A^3-coupling reaction of aldehyde, amine and terminal alkynes in water to obtain the desired product in good yield with excellent TOF, TON and atom economy. The recyclability of the synthesized catalyst was found capable up to fifth run without any aggregation and significant metal leaching. The catalyst was recovered easily after the completion of the reaction.

II.E. Experimental

II.E.1. Material Apparatus

All reagents were purchased from Sigma–Aldrich, TCI, Alfa Aesar and used directly without further purification. The solvents were purchased from the commercial suppliers and used after distillation. All the synthesized products were purified by column chromatography on 60-120 mesh silica gel (SRL, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^1H NMR and ^{13}C NMR were recorded on 400 MHz and 300 MHz Bruker Avance NMR Spectrometer using TMS as internal standard.

II.E.2. Preparation and characterization of catalyst

Synthesis of the Copper complex: The Copper (II) complex has been synthesized by following our earlier report.[29] In a typical hydrothermal reaction, 1 mmol (0.123 gm) pyridine-2-carboxylic acid, 1 mmol (0.21 gm) trimesic acid and 1 mmol (0.242 gm) Copper nitrate tri-hydrate was grind in agate motor and pastel. The blue colored mass was then carefully transferred in a 10 mL Teflon lined stainless steel autoclave and 5 mL of distilled water was added. The reaction mixture was stirred for 30 minutes with the help of magnetic stirrer to get a suspension. The reaction mixture was then heated in an automated hot air oven at a temperature of 150 ^oC for 48 h. After 48 h, the autoclave was cooled to room temperature and the product obtained was filtered, washed with ethanol and finally with water to remove the impurities if any present in the compound. The compound was then dried over the vacuum pump.

Characterization of the copper (II) complex: The copper (II) complex has been characterized by various analytical techniques (Single crystal X-ray analysis, FE-SEM, FT-IR). The synthesized blue colored Copper (II) complex was air stable and has melting point above 300 ^oC. Single crystal X-ray analysis of the complex revealed that the complex crystallizes in monoclinic crystal system with space group P *121*/c*1* and the description of the structure is reported earlier.[29] The crystal structure along with packing of the complex is given below:

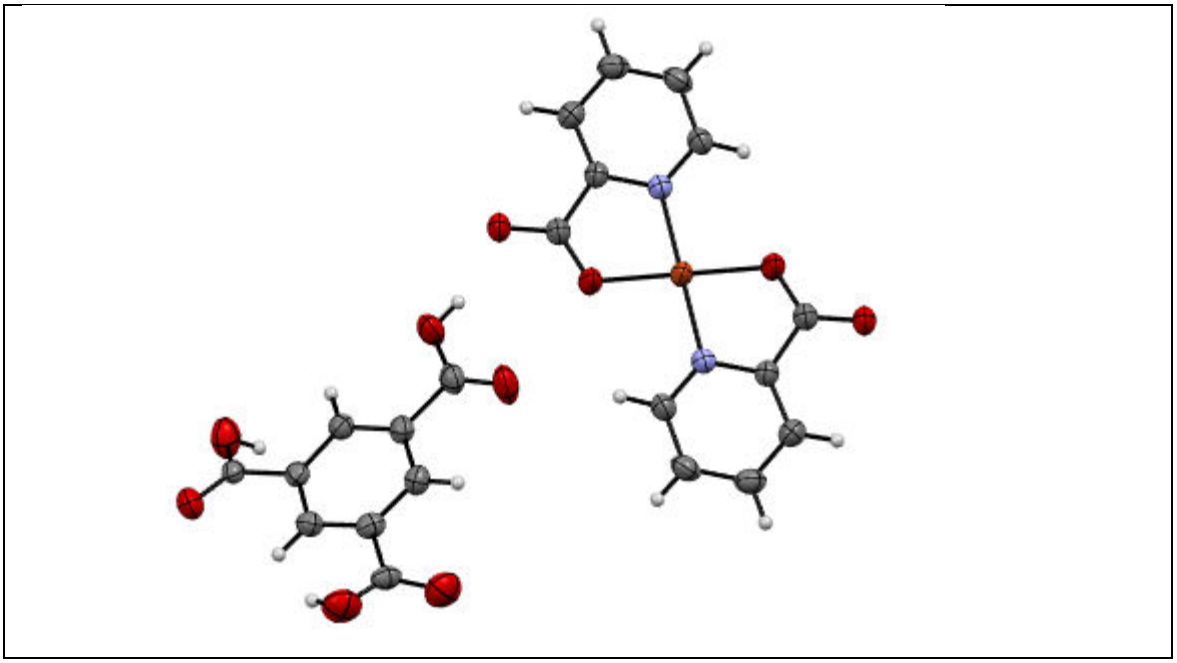


Figure II.2. Single crystal X-ray analysis

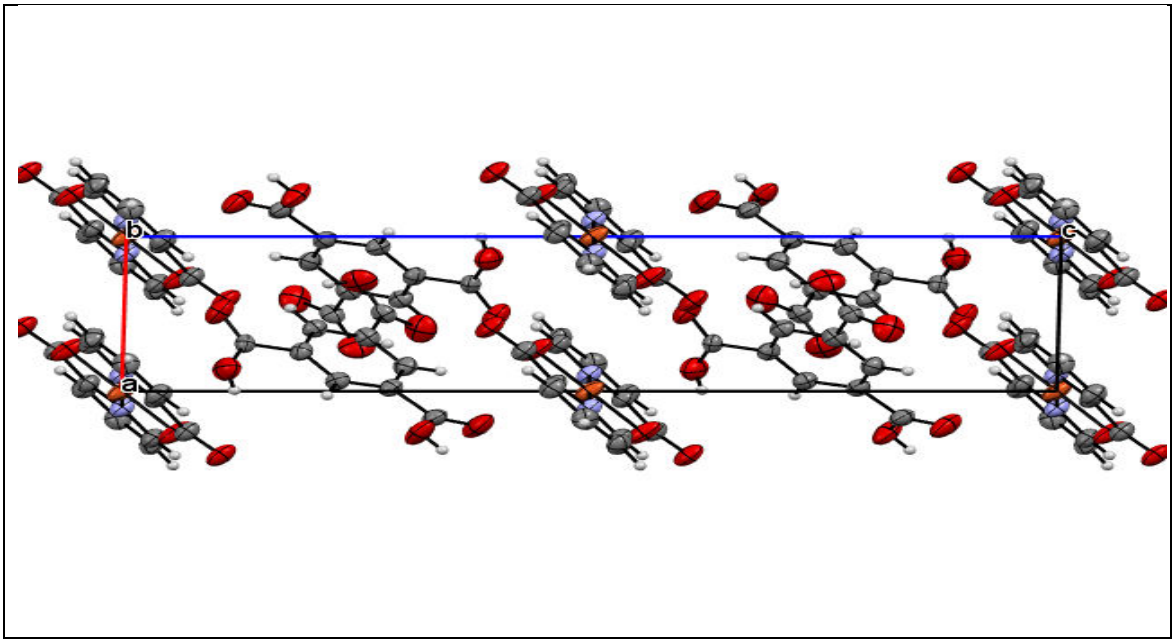


Figure II.3. Packing diaram of the synthsized catalyst

FE-SEM Analysis: The Field emission Scanning Electron Microscopy analysis (INSPECT F-50, FEI, The Netherland) was carried out to analyze the morphology of the symthesized copper(II) complex. From the electron micrograph of the complex, it is clear that the crystals have rod like morphology having several millimeters in length and thickness of 0.6-1 µm. Some of the Scanning Electron Micrograph of the copper(II) complex is shown in the figure II.4. From the Electron Micrograph, it is evident that the complex has same merphology

throughout and it appears that the bulk of the crystal has rectangular morphology or squared cross section. Also it is evident from the ruptured crystal that the single crystals are composed of long filamentous grains running along the length of the crystals.

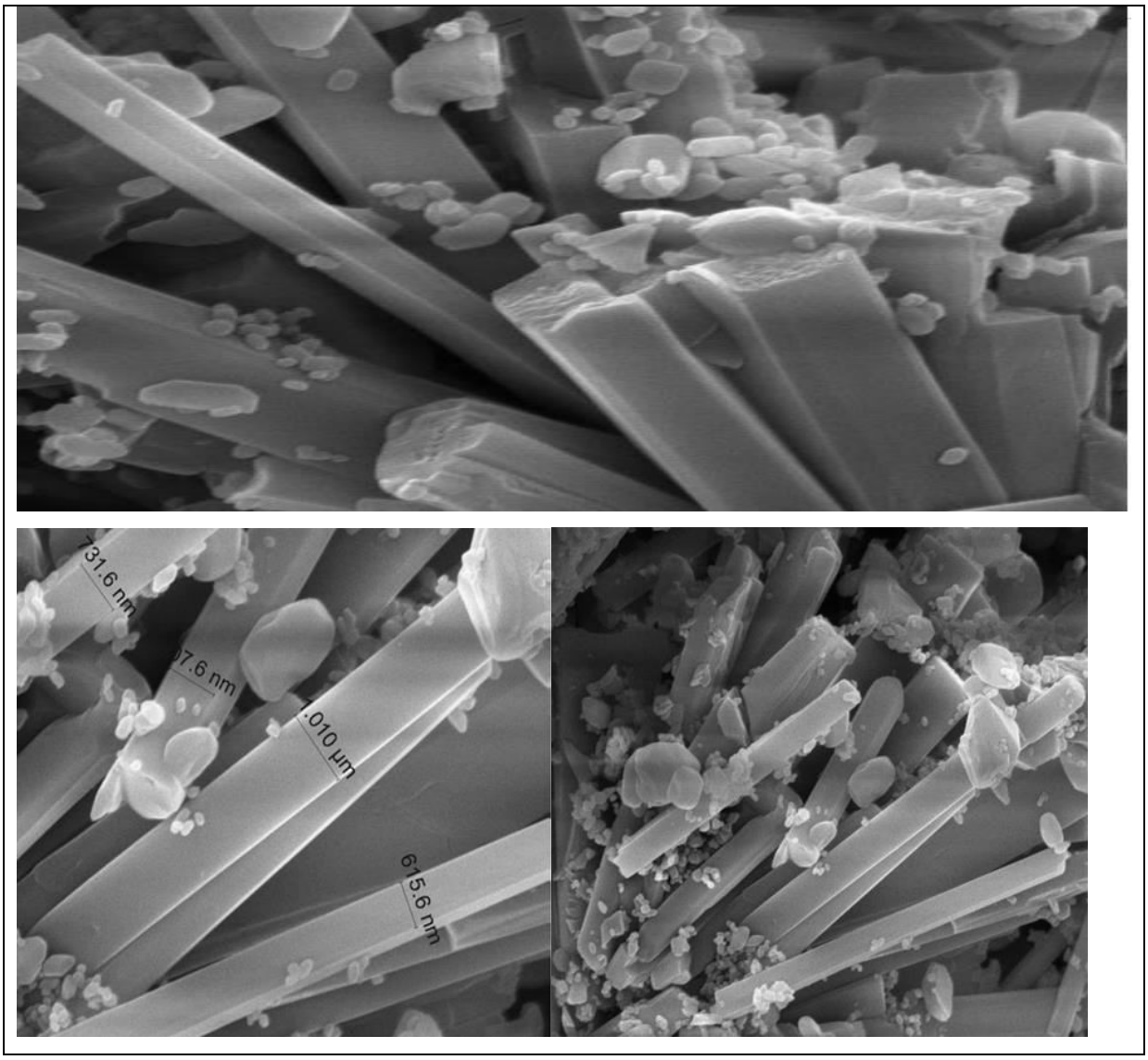


Figure II.4. SEM image of the synthesized catalyst

The FT-IR spectra of the synthesized copper(II) complex has been compared with the FT-IR spectrum of the earlier reported complex and all the vibration reported earlier for the complex is exactly matches for the synthesized complex. IR (ν/cm^{-1}): 3091 (m), 1718 (s), 1599 (s), 1320 (s), 471 (w), 423 (w).

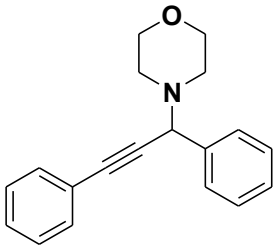
II.E.3. General procedure for the synthesis of propargylamines

A 25 mL round-bottom flask was charged with benzaldehyde (1 mmol), phenylacetylene (1 mmol) and morpholine (1 mmol) after that the reaction mixture was reflux using water as solvent. This was taken as model reaction. The reaction mixture was stirred under reflux

condition until consumption of the reactants indicated by TLC. After completion of the reaction the reaction mixture was partitioned between ethyl acetate and water and the catalyst was separated by simple filtration. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under water bath. After that the products were purified by column chromatography on 60-120 mesh silica gel.

II.E.4. Physical properties and spectroscopy data of synthesized propargylamines derivatives

4-(1,3-Diphenylprop-2-ynyl)morpholine (3a)

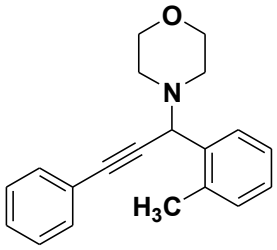


Brown oil

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.53 (s, 4H), 3.62 (s, 4H), 4.68 (s, 1H), 7.20-7.28 (m, 6H), 7.39-7.43 (m, 2H), 7.53 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.47, 49.46, 61.60, 66.70, 84.66, 88.07, 117.66, 122.56, 127.31, 127.77, 127.85, 128.12, 131.35, 137.41.

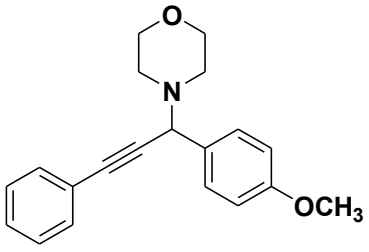
4-(3-Phenyl-1-o-tolylprop-2-ynyl)morpholine (3b)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.37 (s, 3H), 2.52 (s, Hz, 4H), 3.56-3.60 (t, *J* = 9.3 Hz, 4H), 7.09-7.11 (m, 3H), 7.20-7.22 (m, 3H), 7.40-7.43 (m, 2H), 7.58-7.60 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 18.62, 49.30, 59.39, 66.78, 84.61, 88.14, 122.64, 124.91, 127.38, 127.73, 127.86, 128.57, 130.26, 131.33, 135.34, 137.05.

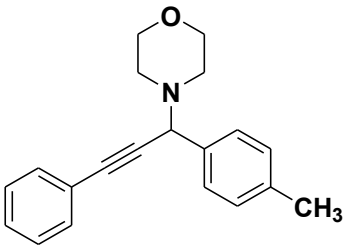
4-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl)morpholine (3c)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.62 (s, 4H), 3.73 (s, 3H), 3.80 (s, 4H), 4.73 (s, 1H), 6.89 (d, *J* = 9 Hz, 2H), 7.31-7.33 (m, 3H), 7.49-7.55 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.33, 54.80, 60.96, 66.65, 84.88, 87.77, 113.07, 122.51, 127.75, 127.82, 129.27, 131.30, 158.71, 161.83.

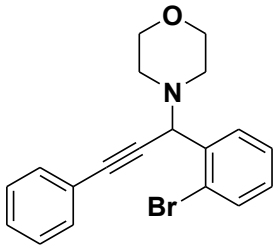
4-(3-Phenyl-1-p-tolylprop-2-ynyl)morpholine (3d)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.40 (s, 3H), 2.66-2.67 (m, 4H), 3.77 (s, 4H), 4.79 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.35-7.37 (m, 3H), 7.54-7.56 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 20.06, 48.82, 60.73, 66.09, 84.30, 87.20, 122.00, 127.13, 127.23, 127.45, 127.85, 130.73, 133.76, 136.38, 161.83.

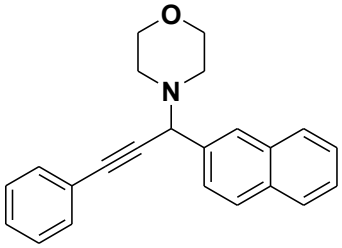
4-(1-(2-Bromophenyl)-3-phenylprop-2-ynyl)morpholine (3e)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.66 (s, 4H), 3.68 (s, 4H), 5.06 (s, 1H), 7.12-7.17 (m, 1H), 7.22-7.31 (m, 4H), 7.48-7.59 (m, 3H), 7.73-7.75 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.76, 61.35, 67.14, 84.66, 88.69, 122.84, 125.28, 126.96, 128.37, 129.39, 130.68, 131.84, 133.31, 137.23.

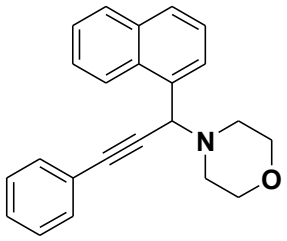
4-(1-(Naphthalen-3-yl)-3-phenylprop-2-ynyl)morpholine (3f)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.66 (s, 4H), 3.74 (s, 4H), 4.92 (s, 1H), 7.33-7.35 (m, 3H), 7.46-7.49 (m, 2H), 7.54-7.57 (m, 2H), 7.72-7.75 (m, 1H), 7.82-7.85 (m, 3H), 8.08 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.54, 61.74, 66.70, 84.57, 88.33, 122.54, 125.62, 126.03, 127.03, 127.13, 127.54, 127.64, 127.88, 131.39, 132.62, 134.94.

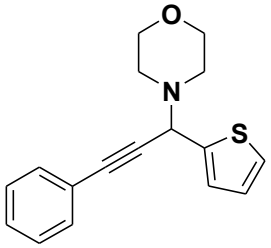
4-(1-(Naphthalen-8-yl)-3-phenylprop-2-ynyl)morpholine (3g)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.68 (s, 4H), 3.65 (s, 4H), 5.40 (s, 1H), 7.29 (m, 3H), 7.39-7.52 (m, 5H), 7.77-7.92 (m, 3H), 8.35 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.97, 60.28, 67.28, 85.13, 89.16, 123.16, 124.89, 125.79, 126.00, 127.20, 128.34, 128.43, 128.61, 129.00, 131.78, 131.92, 133.29, 134.16.

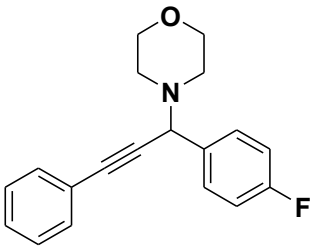
4-(3-Phenyl-1-(thiophen-2-yl)prop-2-ynyl)morpholine (3h)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.68 (s, 4H), 3.76 (s, 4H), 6.97-6.98 (m, 1H), 4.99 (s, 1H), 7.24-7.34 (m, 5H), 7.51 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.69, 57.83, 67.13, 84.29, 87.59, 122.69, 125.79, 126.32, 126.39, 128.34, 128.43, 131.86, 142.80.

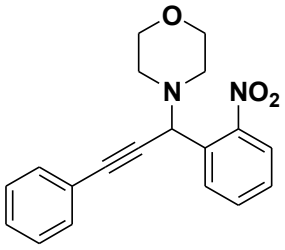
4-(1-(4-Fluorophenyl)-3-phenylprop-2-ynyl)morpholine (3i)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.60-2.62 (m, 4H), 3.71-3.73 (m, 4H), 4.75 (s, 1H), 7.01-7.07 (m, 2H), 7.31-7.33 (m, 3H), 7.49-752 (m, 2H), 7.58-7.59 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.00, 57.33, 66.36, 81.45, 90.18, 121.94, 123.87, 127.91, 128.13, 128.34, 129.60, 130.99, 131.36, 131.64, 149.41.

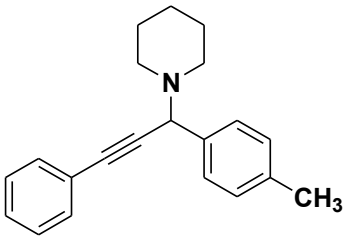
4-(1-(2-Nitrophenyl)-3-phenylprop-2-ynyl)morpholine (3j)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.43 (s, 2H), 2.62 (s, 2H), 3.63 (s, 4H), 5.65 (s, 1H), 7.26-7.56 (m, 7H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 49.00, 57.33, 66.36, 81.45, 90.18, 121.94, 123.87, 127.91, 128.13, 128.34, 129.60, 130.99, 131.36, 131.64, 149.41.

1**-(3-Phenyl-1-p-tolylprop-2-ynyl)piperidine (3k)**

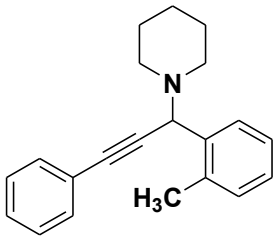


Pale yellow oil

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 7.19-7.20 (m, 2H), 7.40-7.42 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 20.65, 24.05, 25.77, 50.24, 61.71, 85.97, 87.20, 123.02, 127.51, 127.79, 128.00, 128.30, 131.35, 135.21, 136.58.

1-(3-Phenyl-1-o-tolylprop-2-ynyl)piperidine (3l)

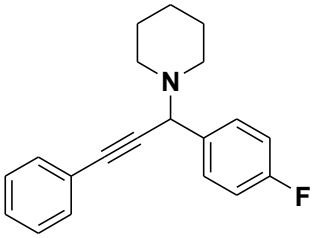


Pale yellow oil

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.19-7.20 (m, 3H), 7.40-7.42 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 20.07, 25.18, 28.68, 49.66, 61.12, 85.37, 86.59, 122.42, 126.92, 127.20, 127.41, 127.71, 130.75, 134.61, 135.99.

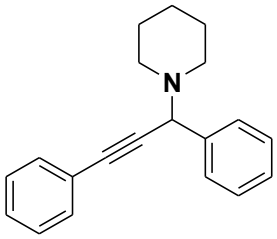
1-(1-(4-Fluorophenyl)-3-phenylprop-2-ynyl)piperidine (3m)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.43-1.59 (m, 6H), 2.53 (s, 4H), 4.76 (s, 1H), 7.00-7.05 (m, 2H), 7.31-7.32 (m, 3H), 7.49-7.51 (m, 2H), 7.57-7.61 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 23.32, 25.66, 49.52, 60.55, 84.60, 87.00, 113.54, 113.82, 127.01, 127.17, 127.87, 130.67, 133.39.

1-(1,3-Diphenylprop-2-ynyl)piperidine (3n)

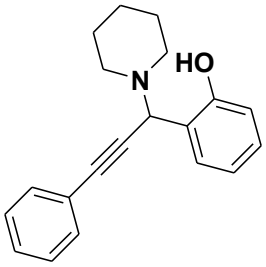


Pale yellow oil

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32-1.64 (m, 8H), 2.60-2.62 (m, 4H), 4.85 (s, 1H), 7.29-7.47 (m, 7H), 7.56-7.71 (m, 3H), 7.85-7.91 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.73, 29.17, 50.25, 61.92, 85.67, 87.39, 121.76, 122.95, 128.47, 130.00, 131.32, 132.22, 138.26, 144.32.

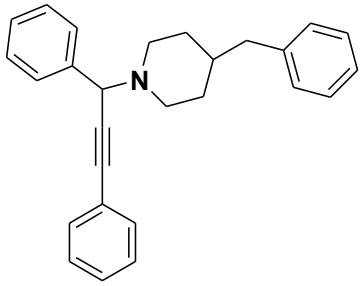
2-(3-Phenyl-1-(piperidin-1-yl)prop-2-ynyl)phenol (3o)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.51 (s, 2H), 1.67 (s, 4H), 2.70-2.73 (m, 4H), 5.08 (s, 1H), 6.83-6.87 (m, 2H), 7.18-7.25 (m, 1H), 7.34-7.38 (m, 3H), 7.51-7.57 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.01, 26.02, 50.03, 61.09, 82.36, 89.84, 116.36, 119.03, 121.32, 122.64, 128.42, 128.45, 128.58, 129.37, 131.90, 157.66.

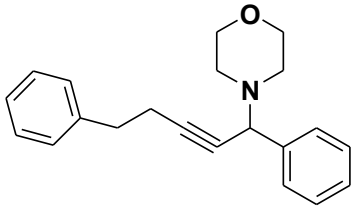
4-Benzyl-1-(1,3-diphenylprop-2-ynyl)piperidine (3p)



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.43-1.47 (m, 1H), 1.50-153 (m, 1H), 1.59-1.67 (m, 2H), 1.75-1.78 (m, 1H), 2.21-2.27 (m, 1H), 2.53-2.61 (m, 3H), 2.72-2.75 (m, 1H), 3.02-3.05 (m, 1H), 4.89 (m, 1H), 7.19-27 (m, 3H), 7.31-7.44 (m, 8H), 7.56-7.58 (m, 2H), 7.69-7.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 32.18, 37.57, 42.85, 46.96, 52.24, 61.61, 85.53, 87.55, 122.88, 125.34, 127.10, 127.69, 127.74, 127.88, 128.11, 128.73, 131.40, 138.16, 140.40.

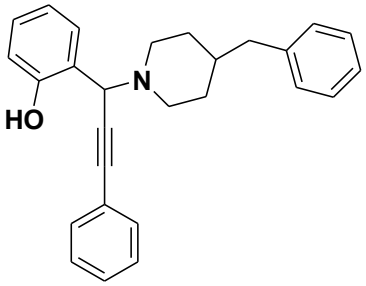
4-(1,5-Diphenylpent-2-ynyl)morpholine (3q)



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.35-2.46 (m, 4H), 2.58-2.62 (m, 2H), 2.84-2.88 (m, 2H), 3.61-3.68 (m, 4H), 4.45 (s, 1H), 7.03-7.30 (m, 8H), 7.37-7.45 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.50, 29.34, 34.88, 49.32, 61.24, 66.72, 87.36, 125.90, 127.16, 127.68, 127.82, 128.01, 128.19, 128.46, 137.82, 140.22.

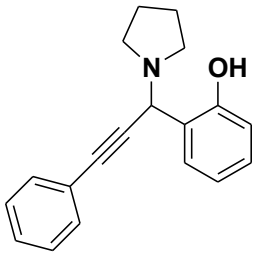
2-(1-(4-Benzylpiperidin-1-yl)-3-phenylprop-2-ynyl)phenol (3r)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.26-1.48 (m, 2H), 1.56-1.81 (m, 3H), 2.33-2.40 (m, 1H), 2.52-2.54 (m, 2H), 2.65-2.74 (m, 2H), 3.00-3.04 (m, 1H), 5.10 (s, 1H), 6.82-6.86 (m, 2H), 7.10-7.34 (m, 9H), 7.49-7.55 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 31.90, 32.56, 37.74, 42.96, 46.40, 52.04, 60.70, 89.93, 116.40, 119.10, 121.30, 122.57, 125.98, 128.29, 128.46, 128.63, 129.10, 129.44, 131.91, 140.34, 157.62.

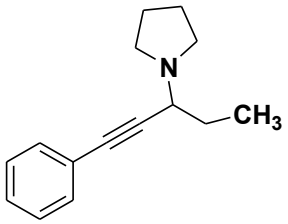
2-(3-Phenyl-1-(pyrrolidin-1-yl)prop-2-ynyl)phenol (3s)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.87-1.89 (m, 4H), 2.78-2.88 (m, 4H), 5.29 (s, 1H), 6.82-6.87 (m, 2H), 7.19-7.27 (m, 1H), 7.34-7.37 (m, 3H), 7.51-7.54 (m, 3).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 23.87, 48.97, 57.10, 83.05, 89.06, 116.26, 118.96, 122.20, 122.62, 127.84, 128.40, 128.56, 128.82, 129.96, 131.90, 157.62.

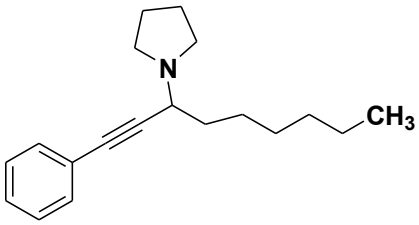
1-(1-Phenylpent-1-yn-3-yl)pyrrolidine (3t)



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.06-1.10 (m, 3H), 1.69-1.80 (m, 5H), 2.69-2.78 (m, 5H), 3.61 (s, 1H), 7.25-7.29 (m, 3H), 7.41-7.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 10.06, 23.05, 27.72, 49.40, 56.47, 84.93, 87.58, 122.98, 127.85, 129.06, 131.27.

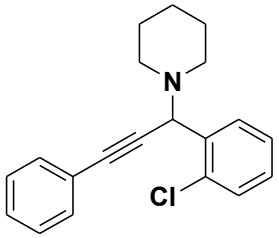
1-(1-phenylnon-1-yn-3-yl)pyrrolidine(3u)



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30-1.37 (m, 3H), 1.44-1.49 (m, 5H), 1.53-1.59 (m, 2H), 1.68-1.69 (m, 2H), 1.71-1.75 (m, 4H), 1.99 (s, 1H), 2.68-2.77 (m, 4H), 3.67-3.69 (m, 1H), 7.41-7.42 (m, 2H), 7.25-7.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.63, 22.18, 23.04, 26.25, 28.66, 31.30, 34.61, 49.28, 54.70, 84.83, 87.81, 123.03, 127.35, 127.75, 131.27.

1-(1-(2-Chlorophenyl)-3-phenylprop-2-ynyl)piperidine (3v)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.52-1.54 (m, 2H), 1.66-1.68 (m, 4H), 2.73 (s, 4H), 5.22 (s, 1H), 7.14-7.60 (m, 6H), 7.67-7.76 (m, 2H), 7.86-8.01 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.78, 29.28, 50.37, 58.92, 85.42, 87.37, 122.83, 125.74, 126.79, 127.84, 128.94, 129.36, 130.12, 131.36, 134.30, 136.12.

II.E.4. Scanned copy of ^{1}H and ^{13}C NMR spectra of various propargylamines derivatives

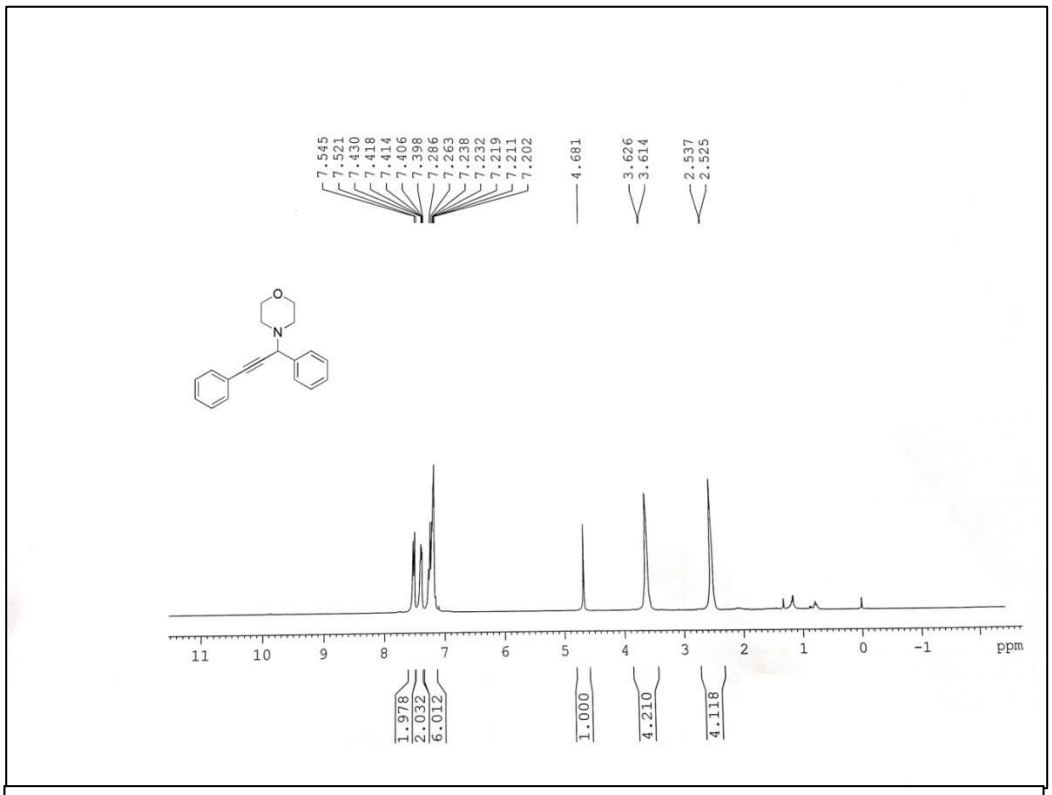


Figure II.5. ^{1}H NMR scanned copy of 4-(1,3-diphenylprop-2-ynyl)morpholine

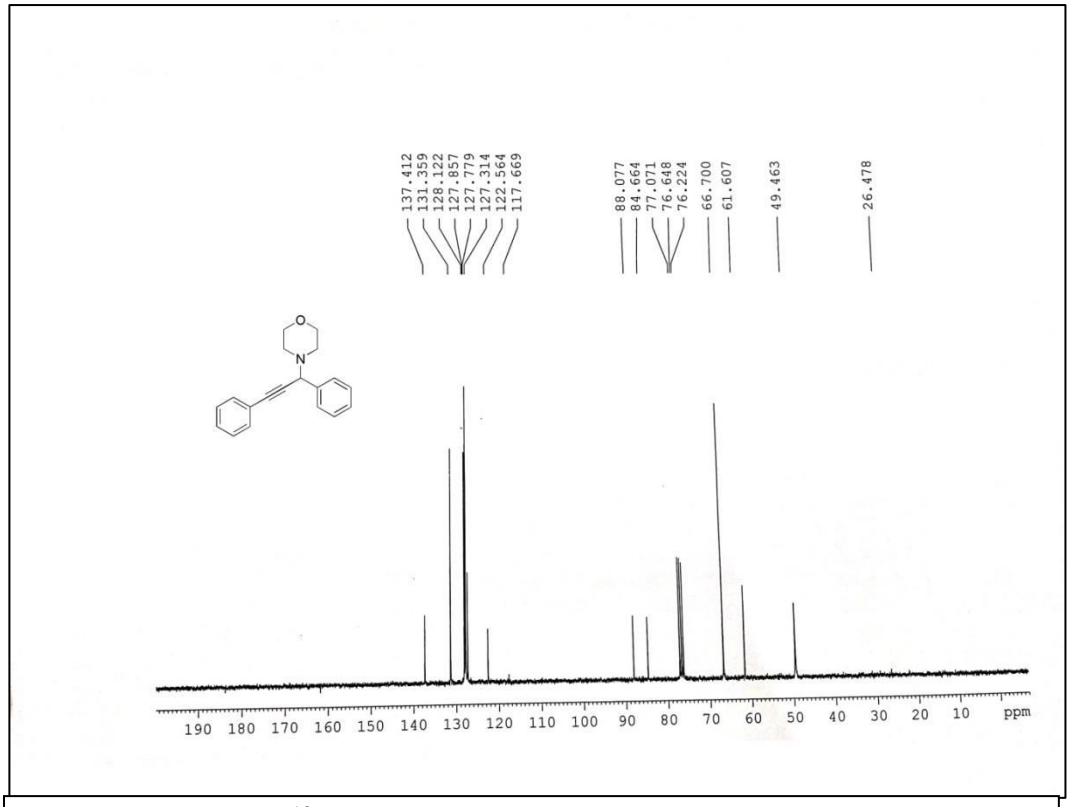


Figure II.6. ^{13}C NMR scanned copy of 4-(1,3-diphenylprop-2-ynyl)morpholine

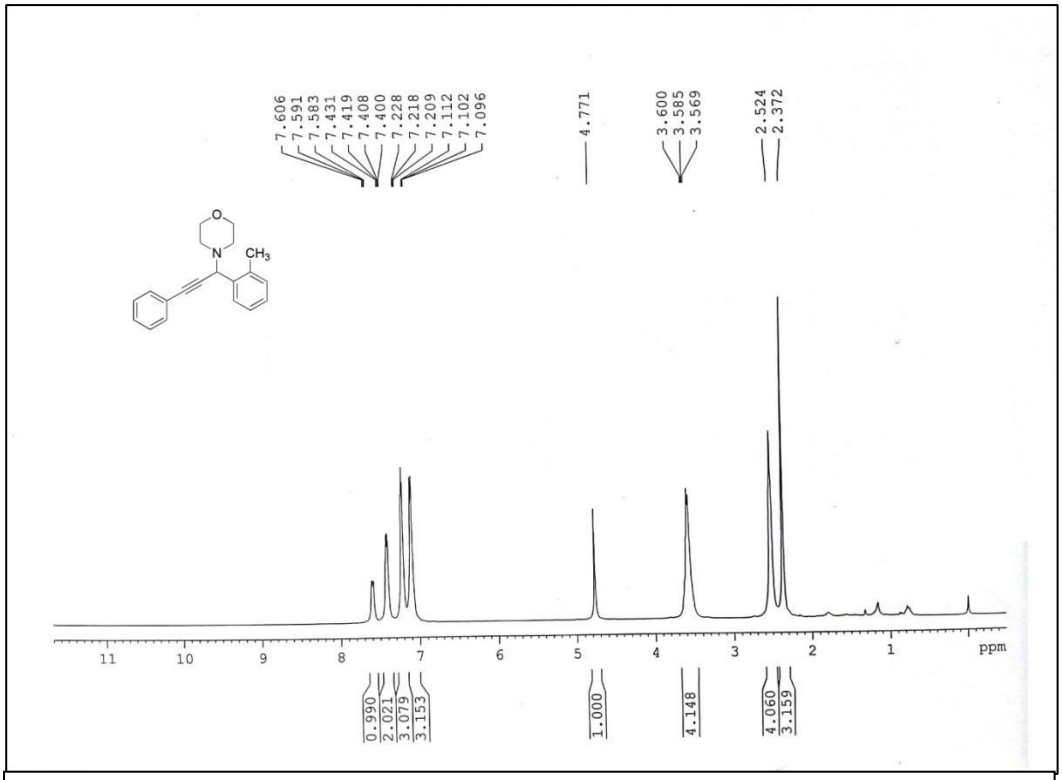


Figure II.7. ^{1}H NMR scanned copy of 4-(3-phenyl-1-o-tolylprop-2-ynyl)morpholine

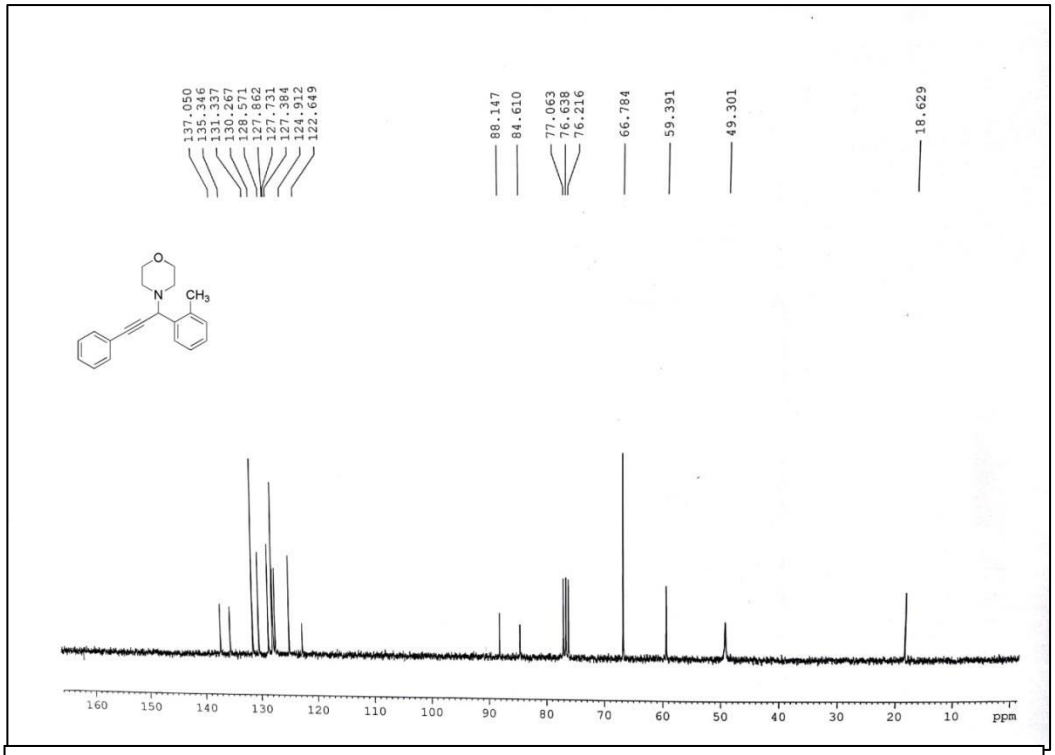


Figure II.8. ^{13}C NMR scanned copy of 4-(3-phenyl-1-o-tolylprop-2-ynyl)morpholine

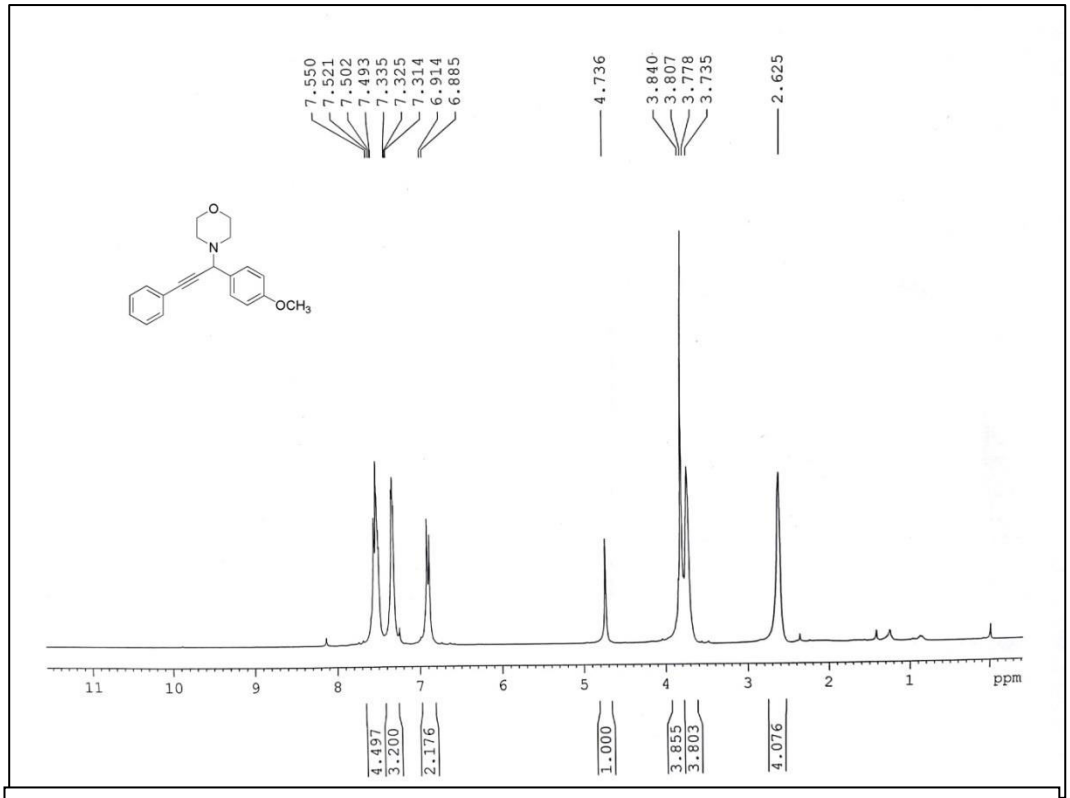


Figure II.9. ^{1}H NMR scanned copy of 4-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)morpholine

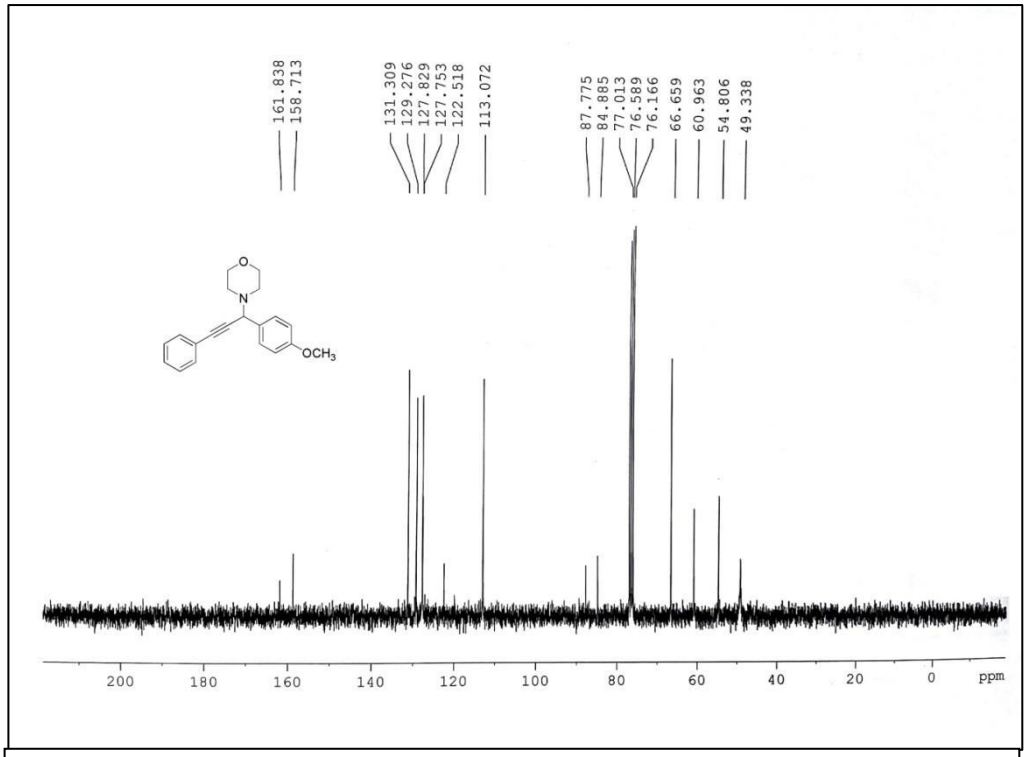


Figure II.10. ^{13}C NMR scanned copy of 4-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)morpholine

II.F. References

References are given in BIBLIOGRAPHY under Chapter II.

Chapter III

Environmentally benign approach towards C-S cross coupling reaction by organo-copper(II) complex

III.A. Introduction

Now a day, carbon-hetero bond is the most important in organic synthesis. It has widely used as a precursor or as an intermediate in the formation of basis or vital infrastructure in the organic synthesis.[1] Carbon-sulphur bond is one of them. Over the last decades, organosulfur or sulphur containing compounds draws significant attention towards the extraordinary applications in the frontiers of modern organic synthetic chemistry like material science and biochemistry and it also widely used in the field of medicine and modern chemical.[2,3] C-S cross coupling reaction is one of fascinating approach for the synthesis of pharmaceutically as well as industrially important compounds.[4-7] Furthermore, aryl-sulfide functional group containing derivatives have been widely used in a number of drugs such as Parkinson's, diabetes, Alzheimer's, cancer, HIV diseases, Leprosy, Tuberculosis.[8-10]

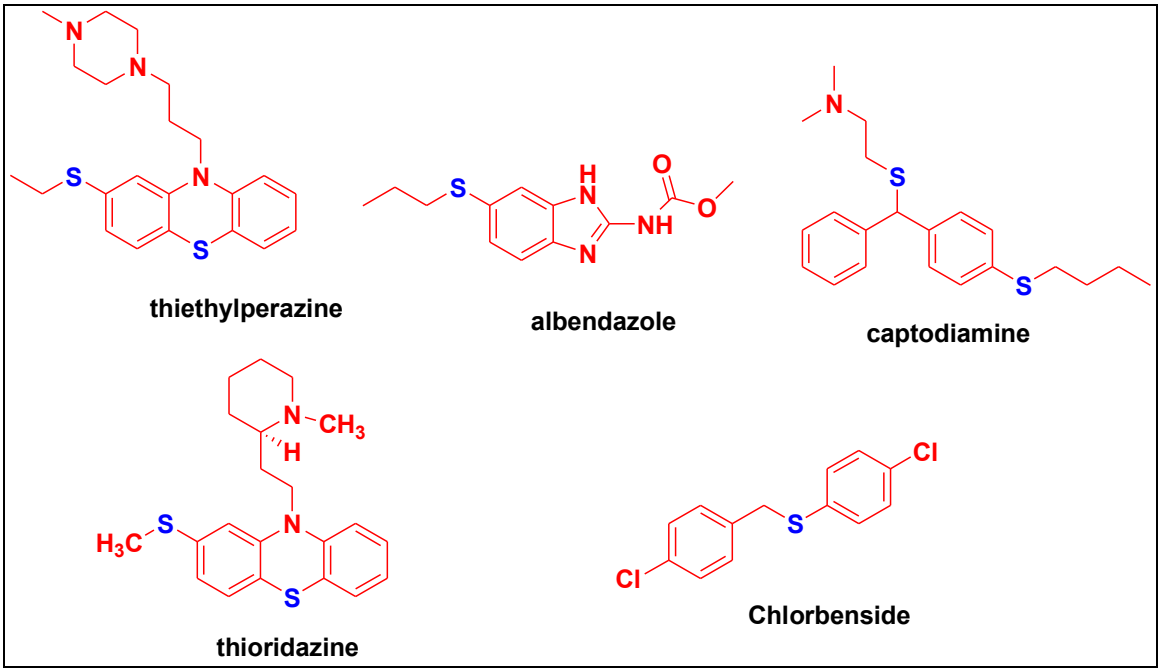
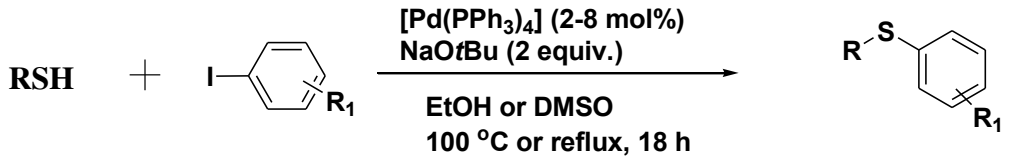


Figure III.1. Some important examples of pharmaceutically and biologically active molecules with aryl alkyl and diaryl sulphide skeleton

III.B. Backgrounds and Objectives

III.B.1. Modern methods for the C-S cross coupling

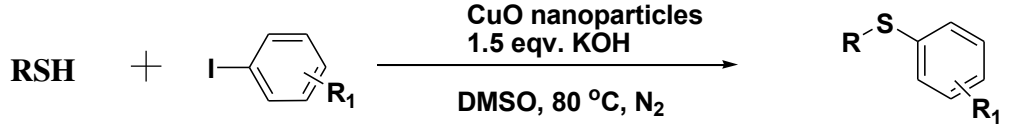
C-S cross-coupling was first reported by Migita *et al.*[11] in 1980, which was involving cross coupling between aryl halides and thiols by using the $Pd(PPh_3)_4$. They investigated various transition metal catalytic systems (Scheme III.1).[12-16]



Scheme III.1. T. Migita proposed first palladium-catalysed C-S coupling reaction

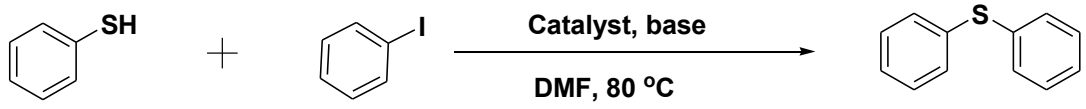
But this protocol has several limitations like use of cost material, long reaction time, use of toxic substances and low turnover numbers. Despite of the several drawbacks mentioned, there is required an alternative simple and efficient synthetic strategies for the formation of carbone-sulphur bond through the C-S cross coupling reaction. A number of methods have been proposed for the C-S coupling reaction.

In the year of 2007, Punniyamurthy *et al.* reported the first time C-S cross coupling reaction of aromatic and aliphatic thiols with iodobenzene by using the easy recyclable CuO nanoparticle as a catalyst with KOH base in DMSO solvent at 80 ^{o}C. This protocol was efficient to give good yield of the desired product (Scheme III.2).[17]



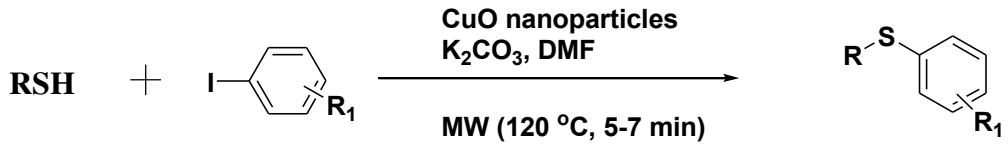
Scheme III.2. CuO nanoparticles catalysed C–S cross-coupling

R. Gupta *et al.*[18] in 2012 published a nickel-based coordination polymers based on metalloligands catalysed C-S cross coupling reaction with the substituted aromatic halides to that of thiophenol as well as cyclohexane thiol and ethane thiol (Scheme III.3).



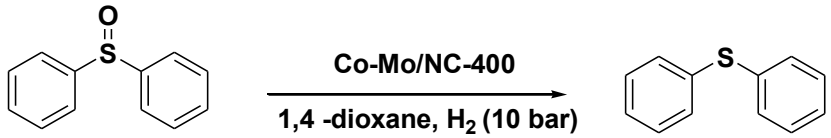
Scheme III.3. Nickel-based coordination polymers based on metalloligands catalysed synthesis of diaryl sulfide

In 2007, Ranu *et al.*[19] have been proposed ligand free microwave irradiation copper nanoparticles catalysed C-S cross coupling reaction of aryl iodides with a series of thiophenols and alkanethiols by using K_2CO_3 as base in DMF solvent at 120 ^{o}C temperature (Scheme III.4).



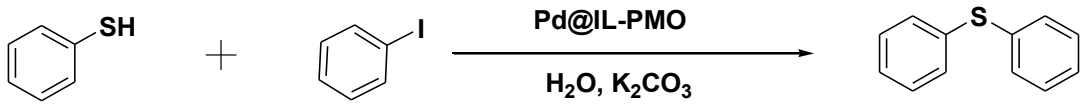
Scheme III.4. Cu-nanoparticles catalysed cross-coupling reaction

K. Yao *et al.* successfully reported an efficient nitrogen-doped carbon-supported heterogeneous cobalt–molybdenum catalysed hydrodeoxygenation of sulfoxides into sulfides under mild conditions at 25-80 ^{o}C (Scheme III.4).[20]



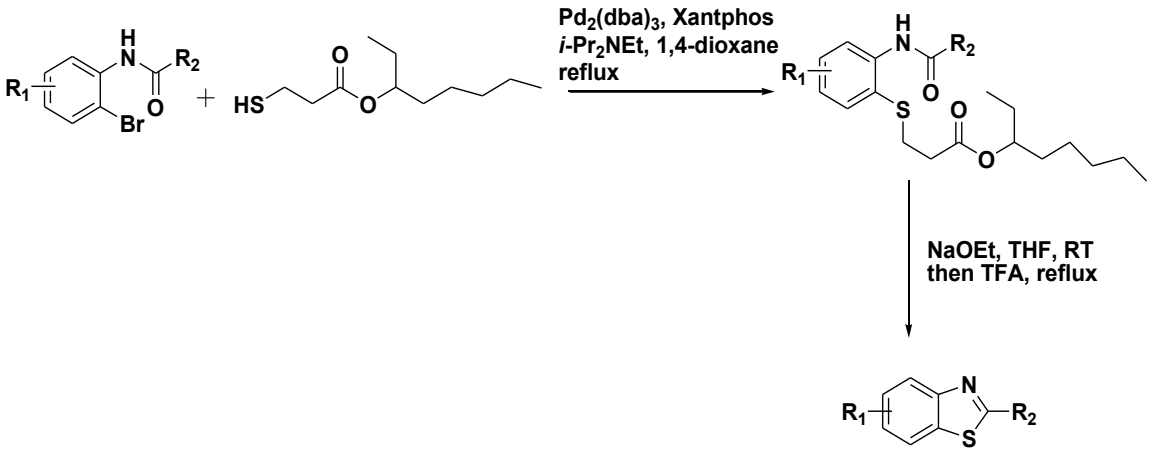
Scheme III.5. Cobalt–molybdenum bimetallic catalysed hydrodeoxygenation of sulfoxides into sulfides

S. Rostamnia *et al.* in 2016, were able to developed an efficient and green method for the C-S coupling by using their synthesised palladium ions supported inside periodic mesoporous organosilica with ionic liquid framework as a catalyst (Pd@IL-PMO) with K_2CO_3 base in water medium (Scheme III.6).[21]



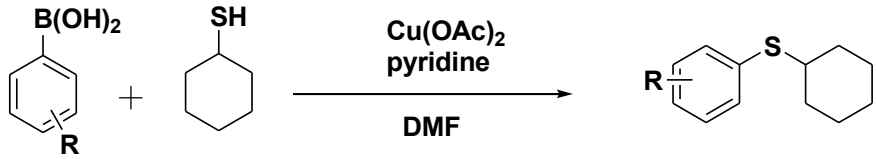
Scheme III.6. Pd@IL-PMO catalysed C-S coupling reaction

In 2007, T. Itoh *et al.* reported the Pd catalysed synthesis of substituted benzothiazoles through the intermolecular C-S bond formation. They carried out the reaction between 2-bromoanilides and 2-ethylhexyl 3-mercaptopropionate with Pd catalyst in 1,4-dioxane and then afforded the corresponding benzothiazoles (Scheme III.7).[22]



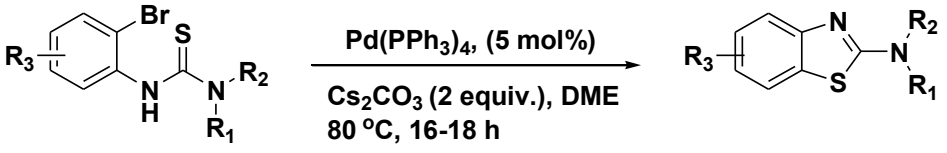
Scheme III.7. Synthesis of substituted benzothiazoles via the C-S bond formation

R. K. Guy *et al.*[23] in the year of 2000, developed a copper(II) acetate catalysed cross-coupling reaction of aryl boronic acids and alkane thiols, mediated by pyridine in anhydrous dimethylformamide affords the corresponding aryl alkyl sulfides in good yield. This protocol covers a wide variety of substituted aryl boronic acids and by this method they were also able to synthesis of aryl sulfides of cysteine (Scheme III.8).



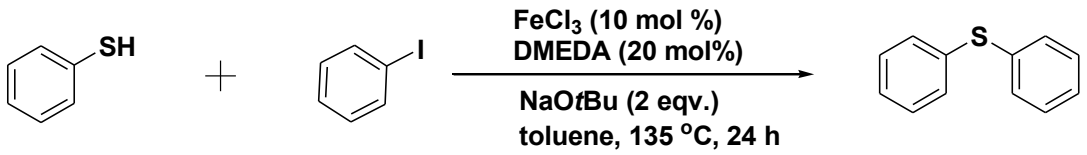
Scheme III.8. Copper-mediated cross-coupling of aryl boronic acids and alkyl thiols

In 2004, R. A. Batey *et al.*[24] developed an interesting copper or palladium-catalysed intramolecular C-S coupling reaction protocol for the synthesis of 2-aminobenzothiazoles from aryl halide and a thiourea derivative. They were found that the catalysis of copper was superior over palladium-catalyst (Scheme III.9).



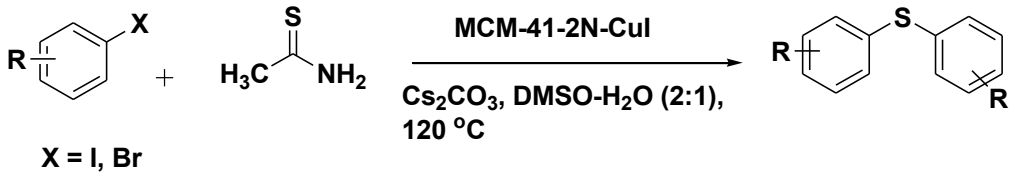
Scheme III.9. Copper or palladium-catalysed synthesis of 2-aminobenzothiazoles through the C-S bond formation

C. Bolm *et al.* in 2008, have successfully reported the first iron-catalysed C-S cross-coupling reaction of aryl iodides with aryl thiols by using the *N,N*-dimethylethylenediamine (DMEDA) (Scheme III.10).[25]



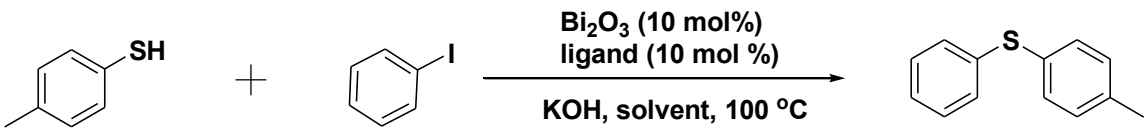
Scheme III.10. Iron-catalysed C-S cross-coupling reaction

In 2014, H. Zhao *et al.* published a simple and efficient heterogeneous catalysed carbon-sulphur coupling reaction of aryl halides with thioacetamide. They carried out the reaction by the treatment of heterogeneous MCM-41-immobilized bidentate nitrogen copper(I) complex [MCM-41-2N-CuI] as catalyst with aryl halides with thioacetamide and yielded the diaryl sulfides product moderate to high (Scheme III.11).[26]



Scheme III.11. MCM-41-2N-CuI catalysed C-S coupling reaction of aryl halides with thioacetamide

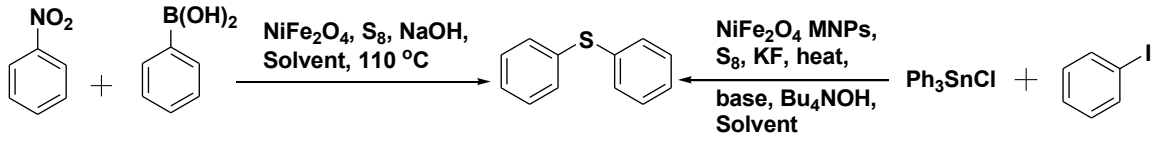
D. Chakraborty *et al.*[27] proposed a simple, efficient and multi-functional groups tolerance Bi_2O_3 catalysed synthetic route for the coupling of aryl halides with thiophenols in water medium and yielded the product moderate to high (Scheme III.12).



Scheme III.12. Bi_2O_3 catalysed C-S coupling reaction

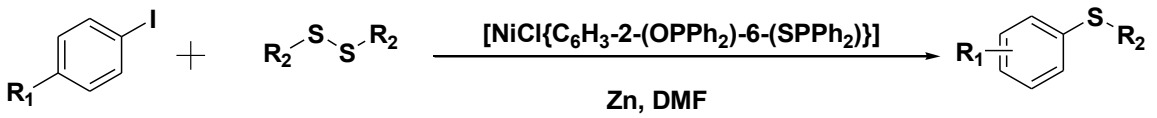
In 2017, S. Farzin *et al.*[28] have been reported an efficient one-pot methodologies for the synthesis of unsymmetrical diaryl sulfides by using of arylboronic acid/S_8 or triphenyltin chloride/S_8 as a thiolating agents with aryl halides or nitroarenes. The reaction was carried

out by $NiFe_2O_4$ magnetic nanoparticles (MNPs) in the presence of K_2CO_3 or NaOH in water at 80-110 ^oC. The reaction method was green and eco-friendly (Scheme III.13).



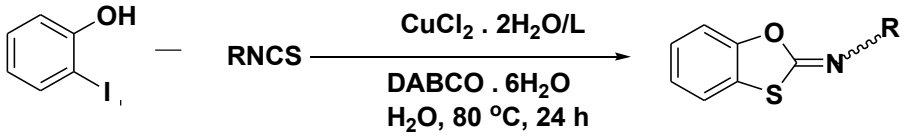
Scheme III.13. $NiFe_2O_4$ magnetic nanoparticles (MNPs) catalysed C-S coupling reaction

D. Morales-Morales *et al.*[29] reported the C-S cross-coupling reaction of disulfides with iodobenzenes by using their own synthesised non-symmetric phosphinito-thiophosphinito PSCOP-Ni(II) pincer complex as a catalyst in DMF solvent at 130 ^oC (Scheme III.14).



Scheme III.14. Nickel catalysed C-S coupling of disulfides with iodobenzenes

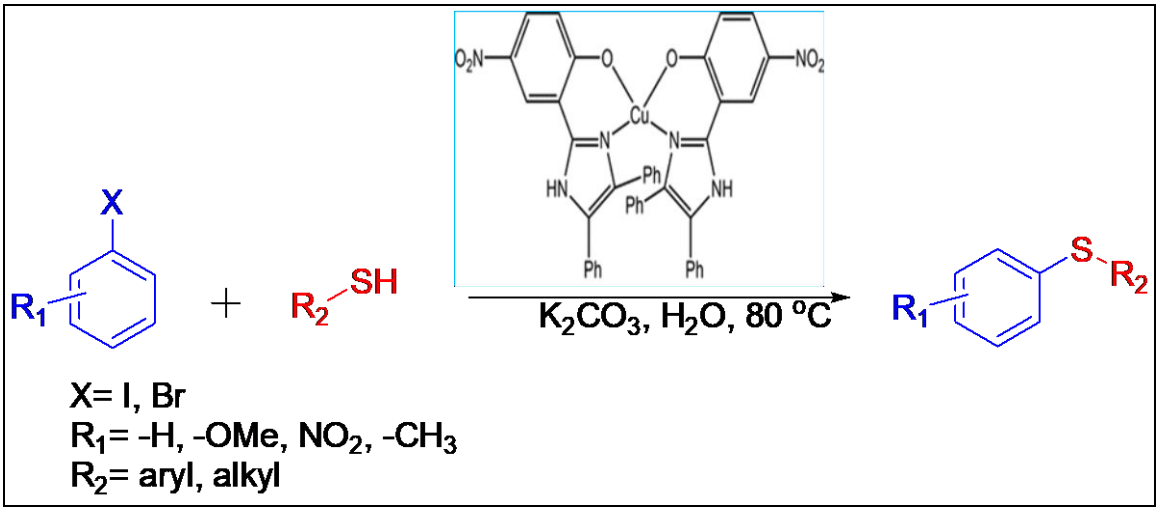
In 2011, Q. Ding *et al.*[30] published a water mediated environmentally benign $CuCl_2.H_2O$ catalysed tandem C-S cross-coupling reaction of 2-iodophenol with isothiocyanate (Scheme III.15).



Scheme III.15. $CuCl_2.H_2O$ catalysed tandem C-S cross-coupling reaction of 2-iodophenol with isothiocyanate

III.C. Present Work

Here we report the water mediated C-S cross coupling reaction by using newly developed bis[2-(4,5-diphenyl-1*H*-imidazol-2-yl)-4-nitrophenolato]copper(II)-dehydrate complex as catalyst. In this method the desired product was obtained in good yields.



Scheme III.16. C-S cross coupling reaction

III.C.1. Result and discussion

In order to explore the catalytic activity of the newly synthesize copper catalyst, we begun C-S cross-coupling as a model reaction by the conventional method. The results of the optimization studies are summarized in table III.1.

Table III.1. Optimization of reaction parameters for the C-S coupling reaction[a]

Entry[a]	Catalyst (mg)	Time (h)	Solvent	Base	Temperature (^oC)	Yield[b] (%)
1	12	10	DMF	K_2CO_3	80	90
2	12	10	DMSO	K_2CO_3	80	87
3	12	10	CH_3CN	K_2CO_3	80	90
4	12	10	Toluene	K_2CO_3	80	92
5	12	10	Ethanol	K_2CO_3	80	91
6	**12**	**10**	**Water**	**K_2CO_3**	**80**	**96**
7	12	10	Water	K_2CO_3	100	97
8	12	10	water	K_2CO_3	60	40
9	12	10	Water	K_2CO_3	RT	Nil
10	Nil	24	Water	K_2CO_3	80	Nil
11	12	10	Water	Cs_2CO_3	80	97
12	12	10	Water	KO^tBu	80	60
13	12	10	Water	Et_3N	80	62
14	12	10	Water	KOH	80	70

[a]Reactions carried out with 10 mg synthesised copper catalyst, 4-iodo anisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol), [b] Yield based on column chromatography, [c]Reaction carried out without catalyst

Initially, a mixture of 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol) and 12 mg of synthesised catalyst were taken in water as solvent and heated in a round bottom flask under reflux condition for 10 h. We observed that the reaction was completed with a 96 % yield of the desired C-S coupled product (Table III.1, entry 6). However, the same reaction when carried out under similar condition but in the absence of catalyst we did not get the desired product. Therefore, we concluded that the reaction does not proceed in the absence of catalyst (Table III.1, entry 10). Hence, to explore the role of catalyst we repeated the model reaction with varying amount of catalyst (Table III.2) and out of all attempt we established that 12 mg of the synthesised catalyst yielded the best result (Table III.2, Entry 5). Further increase in the amount of catalyst the yield of the product did not increase considerably. We also examined the protocol using various solvents, such as DMF, DMSO, CH_3CN, toluene, ethanol, but none of them could able to beat the efficiency of water as a solvent. Keeping this observation in mind water was chosen as the optimal medium of the reaction. Further, in order to optimize the reaction temperature, the model reaction was carried out at 60, 80 and 100 ^oC. Among them 80 ^oC was found to yield the best result (Table III.1, entry 6). We also studied the reaction by using various bases (Table III.1) and among them K_2CO_3 and Cs_2CO_3 were found to produce the best yield of the desired product. However, considering the cost of Cs_2CO_3 and as the product yield is not considerably greater than K_2CO_3, the latter was chosen as the optimized base of the reaction. With this optimized greener reaction condition we performed the reaction with various substituents (Table III.3).

Table III.2. Optimization of catalyst loading

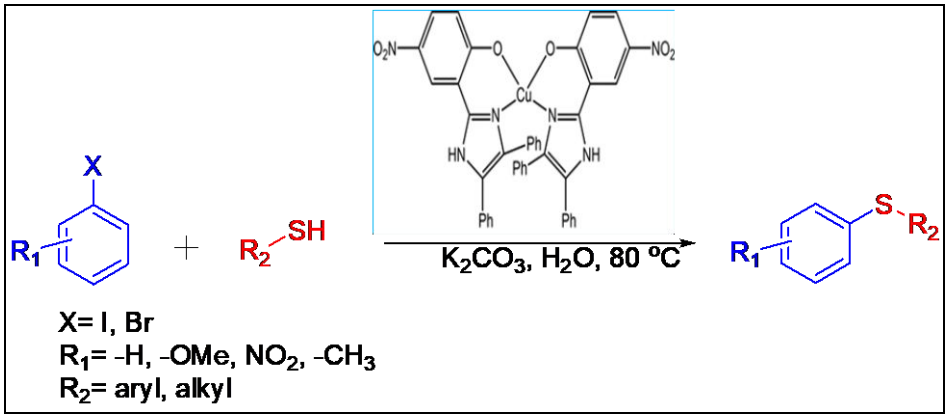
Entry	Catalyst (mg)	Yield (%)
1	4	30
2	6	45
3	8	72
4	10	85
5	**12**	**96**
6	14	97

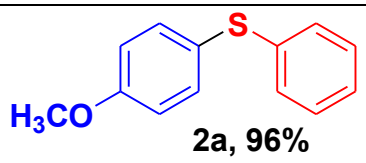
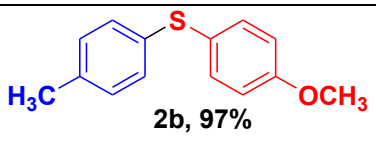
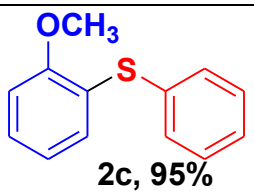
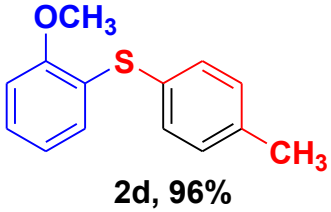
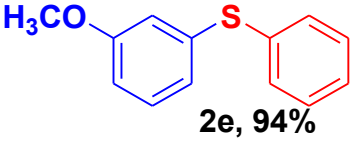
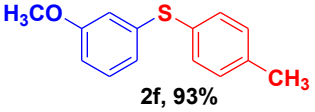
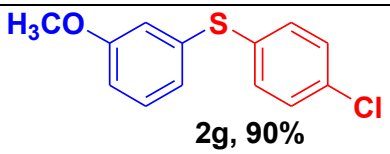
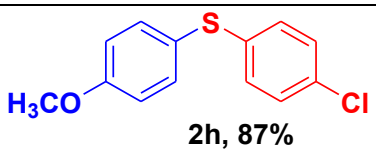
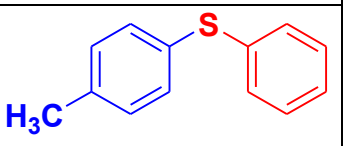
Reaction conditions: 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol), water solvent and 12 mg catalyst at 80 ^oC.

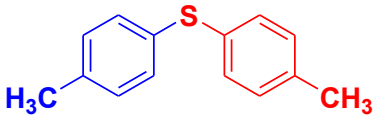
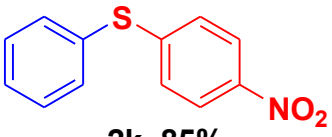
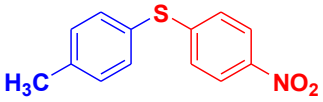
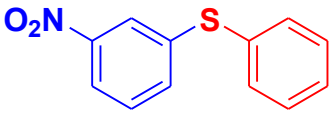
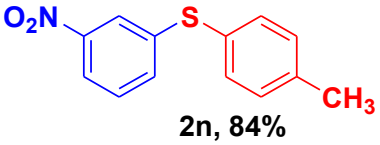
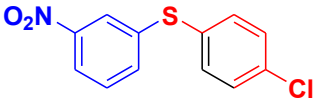
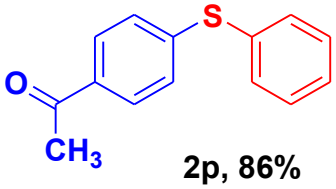
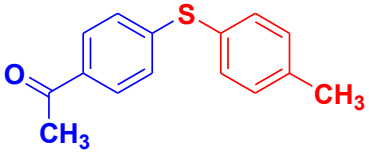
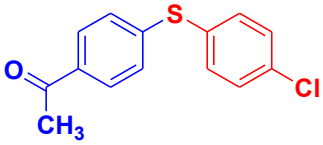
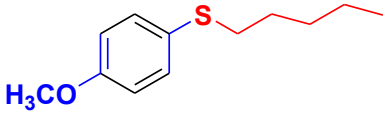
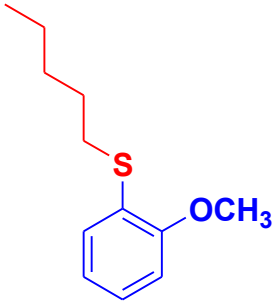
To investigate the catalytic activity of the synthesized catalyst and to cheek the generality of the C-S coupling reaction, we carried out the reaction with a variety of halo arenes and aliphatic as well as aromatic thiols. Both the electron donating/electron withdrawing groups

of the haloarenes were employed with the thiols. Haloarenes with electron donating groups afforded the desired product with good yields which might be due to the increase the electron density towards the nucleus of the haloarenes and thereby facilitating the reaction faster (Table III.3). Bromo and iodobenzene were tried which afforded the product with excellent yields and the order of reactivity of the haloarenes are I>Br (Table III.3). Haloarenes with electron withdrawing group such as -NO_2 needed more time for completion but gave good yield (Table III.3, entry 2k, 2l, 2m, 2n, 2o) of the product. On the other hand, aromatic thiols with electron donating group also produce better result (Table III.3). The reaction was also examined with the aliphatic thiol which also gave the corresponding product and in good yield (Table III.3, 2s, 2t). Thus, it appeared that the newly developed catalyst might direct the C-S coupling reaction with a wide range of substrates(Table III.3).

Table III.3. Synthesized copper catalysed C-S cross-coupling of aryl halides and aryl thiols[a]



 2a, 96%	 2b, 97%	 2c, 95%
 2d, 96%	 2e, 94%	 2f, 93%
 2g, 90%	 2h, 87%	 2i, 90%

 2j, 95%	 2k, 85%	 2l, 86%
 2m, 93%	 2n, 84%	 2o, 80%
 2p, 86%	 2q, 87%	 2r, 84%
 2s, 80%	 2t, 79%	

[a] Reactions carried out with 10 mg synthesised copper catalyst, 4-iodo anisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol) in water medium at 80 ^oC, [b] Yield based on column chromatography

III.D. Conclusion

We investigate the catalytic activity of our synthesized copper(II) catalyst in the C-S cross coupling reaction of haloarene and thiols in water medium and obtained the expected product in good yield. The recyclability of the synthesized catalyst was found to be capable up to fifth run without significant loss of the yield of the product. The catalyst was also easily recovered after completion of the reaction.

III.E. Experimental

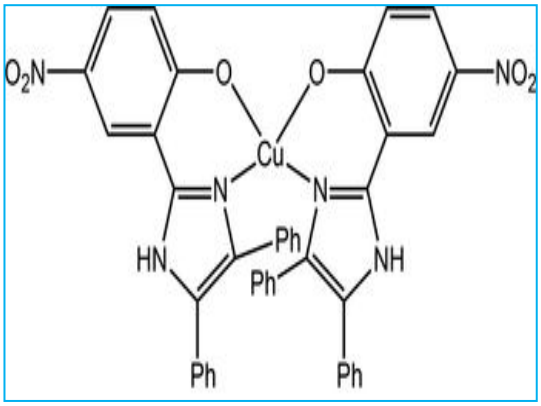
III.E.1. Material Apparatus

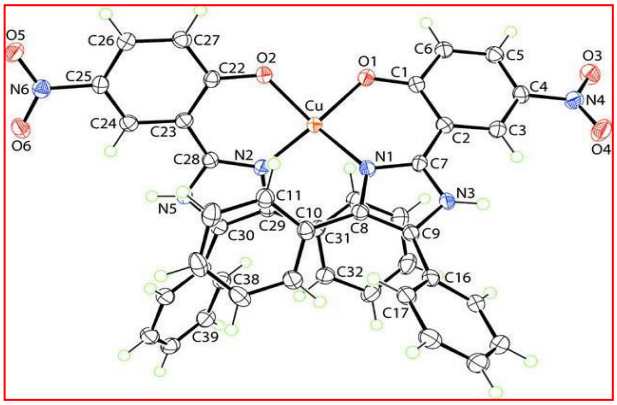
All the synthesized products were purified by column chromatography on 60-120 mesh silica gel (SRL, India). For TLC, Merck plates coated with silica gel 60, F254 were used. IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 400 MHz and 300 MHz Bruker Avance NMR Spectrometer using TMS as internal standard.

III.E.2. Preparation and characterization of catalyst

The Cu (II) catalyst has been prepared by the reported procedure. [31] In a multi-component template synthesis of tri-aryl imidazole, the titled copper complex was obtained when 2-hydroxy 5-nitro benzaldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2.5 mmol) was allowed to react in the presence of CuB_4O_7 (1 mmol) at a temperature 130 ºC in the presence of silica gel as a solid support. After completion of the reaction, blue coloured crystal was obtained and the product was washed with methanol followed by diethyl ether to afford the pure complex. Melting point >300 ºC, IR (KBr, cm^{-1}): 3430 (O-H stretching of H_2O), 3065 (N-H Stretching), 2926 (Aromatic C-H Stretching), 1578 (C=N Stretching), 1487, 1135 (C-H stretching), 466 (Cu-N stretching).

The molecular structure and the packing of the crystal are given below:





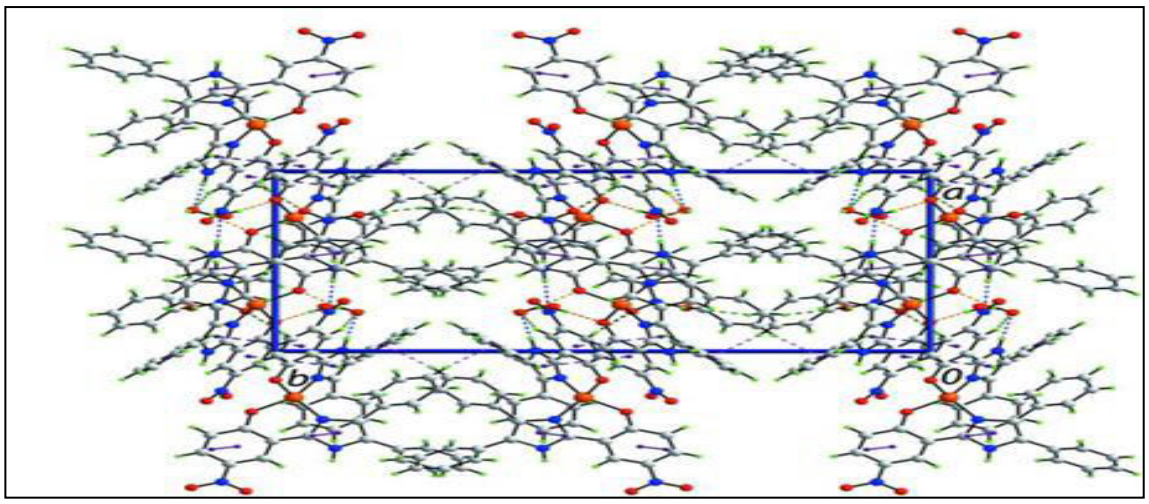


Figure III.2. The molecular packing of the crystal

The molecular packing in the crystal of Cu (II) complex, isolated as $[Cu(C_{21}H_{14}N_3O_3)_2]\cdot 2H_2O$

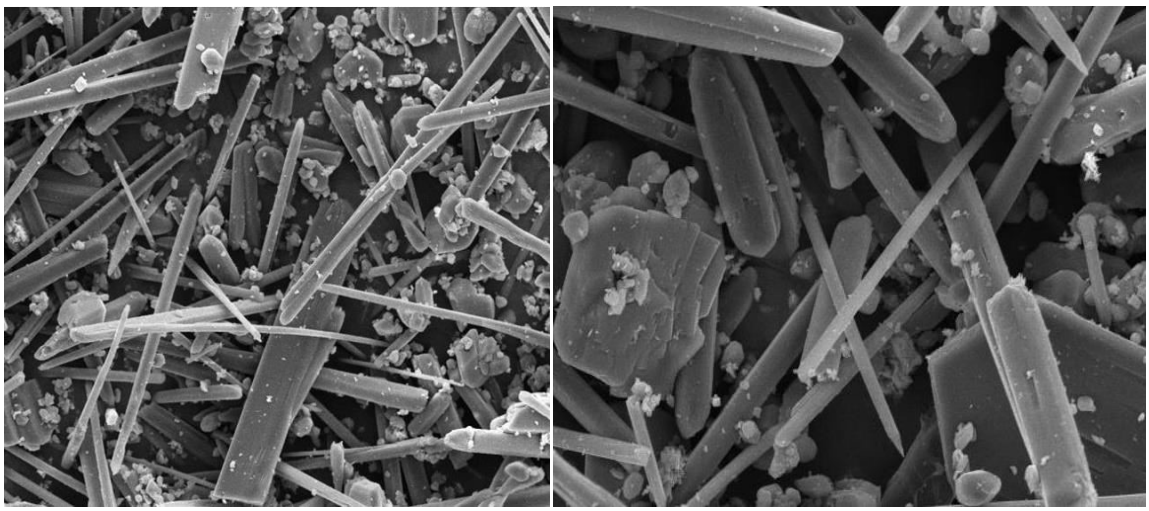


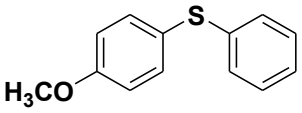
Figure III.3. SEM image of the synthesized catalyst

III.E.3. General procedure for the synthesis of the C-S cross-coupled compounds

A 25 mL round-bottom flask was charged with a mixture of 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol) and 12 mg of synthesised catalyst were taken in water, as the solvent and heated under reflux condition. The reaction mixture was stirred under reflux condition until consumption of the reactants indicated by TLC. After completion of the reaction the reaction mixture was partitioned between ethyl acetate and water. And the catalyst was separated by simple filtration. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under water bath. After that the products were purified by column chromatography on 60-120 mesh silica gel.

III.E.4. Physical properties and spectroscopy data of synthesized C-S coupled compounds

(4-Methoxyphenyl)(phenyl)sulfane (2a)



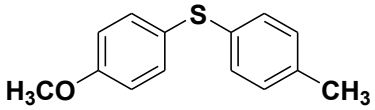
Slightly yellow liquid

IR (neat, $\nu_{máx}$, cm^{-1}): 690, 2802, 2919, 2942, 3042, 3085.

^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 3.80 (s, 3H), 6.87-6.90 (m, 2H), 7.09-7.25 (m, 4H), 7.39-7.43 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 55.38, 115.02, 124.30, 125.78, 128.21, 128.96, 135.41, 138.64, 159.85.

(4-Methoxyphenyl)(*p*-tolyl)sulfane (2b)



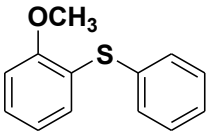
White solid, m.p. 46 °C.

IR (KBr, $\nu_{máx}$, cm^{-1}): 635, 822, 2846, 2925.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H), 3.73 (s, 3H), 6.77-6.81(m, 2H), 6.97-7.06 (m, 4H), 7.27-7.30 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 20.99, 55.36, 114.85, 125.59, 129.34, 129.77, 134.37, 136.12, 159.44.

(2-Methoxyphenyl)(phenyl)sulfane (2c)



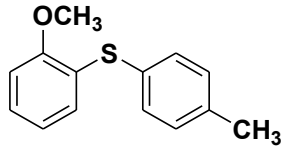
Colourless oil

IR (neat, $\nu_{max,}$ cm^{-1}): 690, 753, 2837, 2974.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.72 (s, 3H), 6.74-6.78 (m, 2H), 6.96-6.99 (m, 1H), 7.11-7.25 (m, 6 H).

^{13}C N MR (75 MHz, $CDCl_3$) δ ppm: 54.75, 109.73, 120.14, 122.89, 125.98, 127.26, 128.06, 130.34, 130.48, 133.35, 156.16.

(2-Methoxyphenyl)(*p*-tolyl)sulfan (2d)



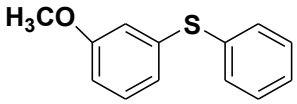
Colourless liquid

IR (neat, $\nu_{max,}$ cm^{-1}): 681, 743, 1272, 1473, 1576, 2835, 2934, 3005.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.34 (s, 3H), 3.87 (s, 3H), 6.79-6.94 (m, 3H), 7.12-7.23 (m, 3H), 7.30-7.32 (d, *J* = 6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.23, 55.89, 110.59, 121.23, 125.72, 127.44, 129.73, 129.83, 130.15, 133.04, 137.80, 156.48.

(3-Methoxyphenyl)(phenyl)sulfane (2e)



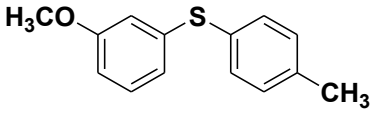
Slightly yellow liquid

IR (neat, $\nu_{max,}$ cm^{-1}): 691, 2806, 2932, 2954, 3026, 3078.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.73 (s, 3H), 6.74-6.77 (m, 1H), 6.86-6.91 (m, 2H), 7.16-7.37 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 55.30, 112.81, 115.93, 122.98, 127.30, 129.27, 130.00, 131.46, 135.29, 137.26, 160.07.

(3-Methoxyphenyl)(*p*-tolyl)sulfane (2f)



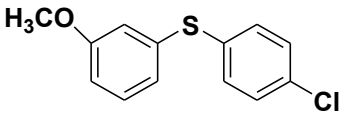
Yellow oil

IR (neat, $\nu_{max,}$ cm^{-1}): 692, 1247, 1478, 1574,1591.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.31 (d, *J* = 8.1, 2H), 7.12-7.19 (m, 3H), 6.78-6.83 (m, 2H), 6.70-6.73 (m, 1H), 3.72 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.19, 55.26, 112.05, 114.77, 121.73, 130.12, 130.72, 132.66, 137.86, 138.64, 159.98, 162.33.

(4-Chlorophenyl)(3-methoxyphenyl)sulfane (2g)



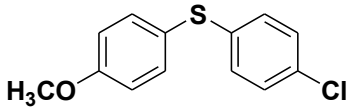
Yellow oil

IR (neat, $\nu_{máx,}$ cm^{-1}): 680, 741, 1272, 1475, 1576, 2930, 2957.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.15 (s, 3H), 6.26 (d, *J* = 7.5 Hz, 3H), 6.65-6.69 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 54.71, 112.50, 115.63, 122.60, 128.73, 129.49, 131.75, 132.61, 133.55, 135.88, 159.50.

(4-Chlorophenyl)(4-methoxyphenyl)sulfane (2h)



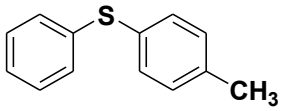
Colourless oil

IR (neat, $\nu_{máx,}$ cm^{-1}): 685, 741, 1276, 1470, 1578, 2935, 2960.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.82 (s, 3H), 6.89-6.92 (m, 2H), 7.04-7.08 (m, 2H), 7.17-7.25 (m, 2H), 7.38-7.44 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 55.40, 115.12, 129.01, 129.26, 131.55, 132.19, 135.54, 135.93, 137.37.

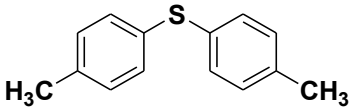
Phenyl(*p*-tolyl)sulfane (2i)



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.33 (s, 3H), 7.11-7.21 (m, 2H), 7.25-7.41 (m, 6H), 7.45-7.50 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.17, 126.42, 127.49, 129.07, 130.10, 131.25, 132.32, 137.14, 137.64.

Di-*p*-tolylsulfane (2j)



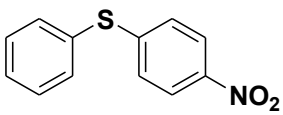
Slightly yellow oil

IR (neat, $\nu_{max,}$ cm^{-1}): 690, 743, 810, 1020, 1093, 1442, 1482, 1490, 1591, 2930, 3051.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.31 (s, 6H), 6.97-7.10 (m, 4H), 7.21-7.23 (m, 3H), 7.36-7.39 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.13, 128.55, 129.96, 131.09, 132.67, 136.94.

(4-Nitrophenyl)(phenyl)sulfane (2k)



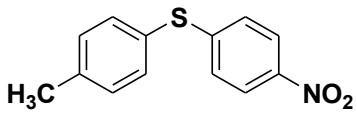
Yellow solid m.p.: 54 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 514, 691, 741, 851, 1082, 1430, 1475, 1515, 1577, 3065.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.15-7.17 (m, 2H), 7.44-7.52 (m, 5H) , 8.04 (d, *J* = 6.6, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 124.05, 126.71, 129.70, 130.07, 130.48, 134.77, 145.38, 148.53.

(4-Nitrophenyl)(*p*-tolyl)sulfane (2l)



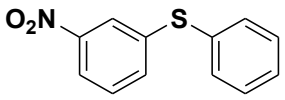
Yellow solid, m.p.: 87 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 686, 1338, 1506, 1570.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.40 (s, 3H), 7.12 (d, *J* = 7. 5, 2H), 7.42 (d, *J* = 6.9, 2H), 8.02 (d, *J* = 7.2, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.36, 123.98, 124.54, 126.14, 126.51, 130.88, 135.09, 140.25, 145.15, 149.36.

(3-Nitrophenyl)(phenyl)sulfane (2m)



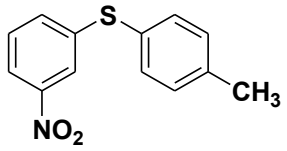
Yellow oil

IR (neat, $\nu_{máx,}$ cm^{-1}): 656, 782, 998, 1056, 1453, 1472, 1565, 3098.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.94-8.00 (m, 2H), 7.36-7.72 (m, 3H), 7.09-7.26 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 120.93, 123.10, 128.99, 129.76, 129.91, 132.14, 133.45, 134.27, 140.58, 148.67.

(3-Nitrophenyl)(*p*-tolyl)sulfane (2n)



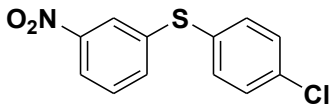
Yellow solid, m.p.: 61 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 680, 1573, 1338, 1507.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.39 (m, 3H), 7.22-7.26 (m, 2H), 7.35-7.45 (m, 4H), 7.95-7.96 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 120.44, 122.19, 127.82, 129.54, 130.73, 133.32, 134.20, 139.60, 141.65, 148.67.

(4-Chlorophenyl)(3-nitrophenyl)sulfane (2o)



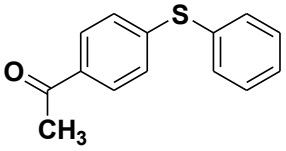
Yellow solid, m.p. 58 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 688, 1338, 1506, 1572.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.37-7.50 (m, 6H), 8.03 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 121.34, 123.47, 129.90, 130.06, 130.95, 134.45, 134.57, 135.17, 139.76, 148.72.

1-(4-(Phenylthio)phenyl)ethanone (2p)



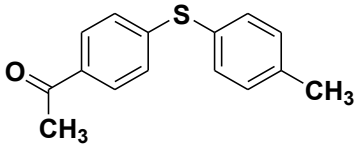
White solid. m.p.: 67 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 680, 1680, 2821, 2942, 2910, 3012, 3060.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47 (s, 3H), 7.19-7.26 (m, 1H), 7.39-7.50 (m, 6H), 7.81 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.50, 127.45, 128.82, 128.91, 129.70, 132.07, 133.90, 134.46, 144.96, 197.19,

1-(4-(*p*-Tolylthio)phenyl)ethanone (2q)



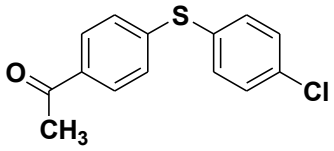
White solid, m.p.: 92 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 680, 1685, 2821, 2915, 2943, 3009, 3059.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.39 (s, 3H), 2.54 (s, 3H), 7.15 (d , *J* = 8.4, 2H), 7.21-7.26 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.78-7.81 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.30, 26.47, 126.63, 127.86, 128.84, 130.55, 134.10, 134.52, 139.37, 145.98, 197.22.

1-(4-(4-Chlorophenylthio)phenyl)ethanone (2r)



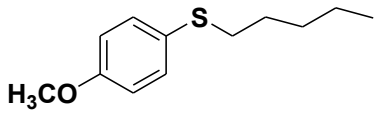
White solid, m.p.: 42 °C.

IR (KBr, $\nu_{máx,}$ cm^{-1}): 685, 1687, 2822, 2916, 2943, 3010, 3060.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.55 (s, 3H), 7.21 (d, *J* = 6.6 Hz, 2H), 7.38 (d, *J* = 6 Hz, 4H), 7.83 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.37, 29.63, 126.16, 127.84, 128.94, 129.81, 130.97, 134.75, 143.90, 196.95.

(4-Methoxyphenyl)(pentyl)sulfane (2s)



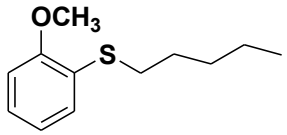
Colourless oil

IR (neat, $\nu_{máx,}$ cm^{-1}): 683, 1024, 1270, 1470, 1577, 2929, 2959.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.81(t, *J* = 6.9 Hz, 3H), 1.01-134 (m, 4H), 1.45-1.53 (m, 2H), 2.71-2.75 (m, 2H), 3.71 (s, 3H), 6.75-6.776 (m, 2H), 7.18-7.34 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.00, 22.27, 29.04, 30.90, 35.80, 55.33, 114.47, 126.92, 132.90, 158.69.

(2-Methoxyphenyl)(pentyl)sulfane(2t)



Colourless oil

IR (neat, $\nu_{máx,}$ cm^{-1}): 683, 741, 1270, 1475, 1576, 2928, 2954.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.91 (t, 3H), 1.29-1.45 (m, 4H), 1.59-1.68 (m, 2H), 2.85-2.90 (m, 2H), 3.88 (s, 3H), 6.82-6.94 (m, 2H), 7.13-7.25 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 13.99, 22.30, 28.60, 31.15, 31.80, 56.76, 110.29, 121.02, 125.26, 126.56, 128.53, 156.97.

III.E.5. Scanned copies of ^{1}H and ^{13}C NMR spectra of various synthesized C-S coupled compounds

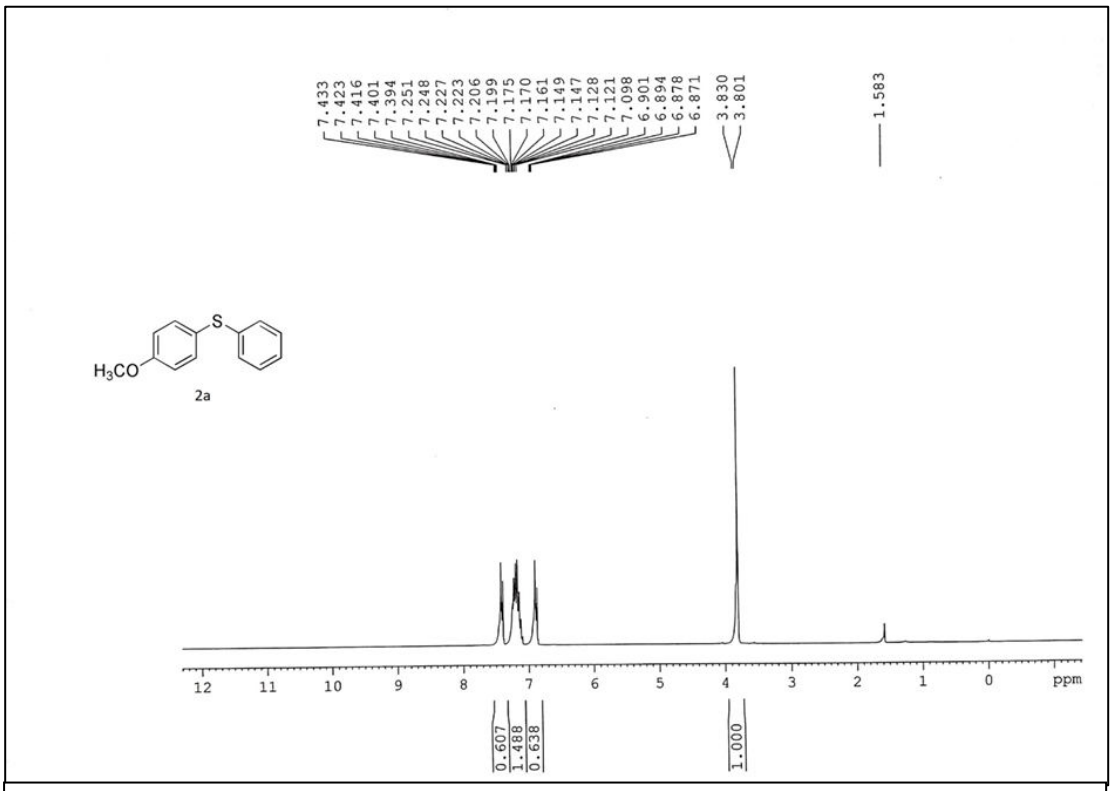


Figure III.4. ^{1}H NMR scanned copy of (4-methoxyphenyl)(phenyl)sulfane (2a)

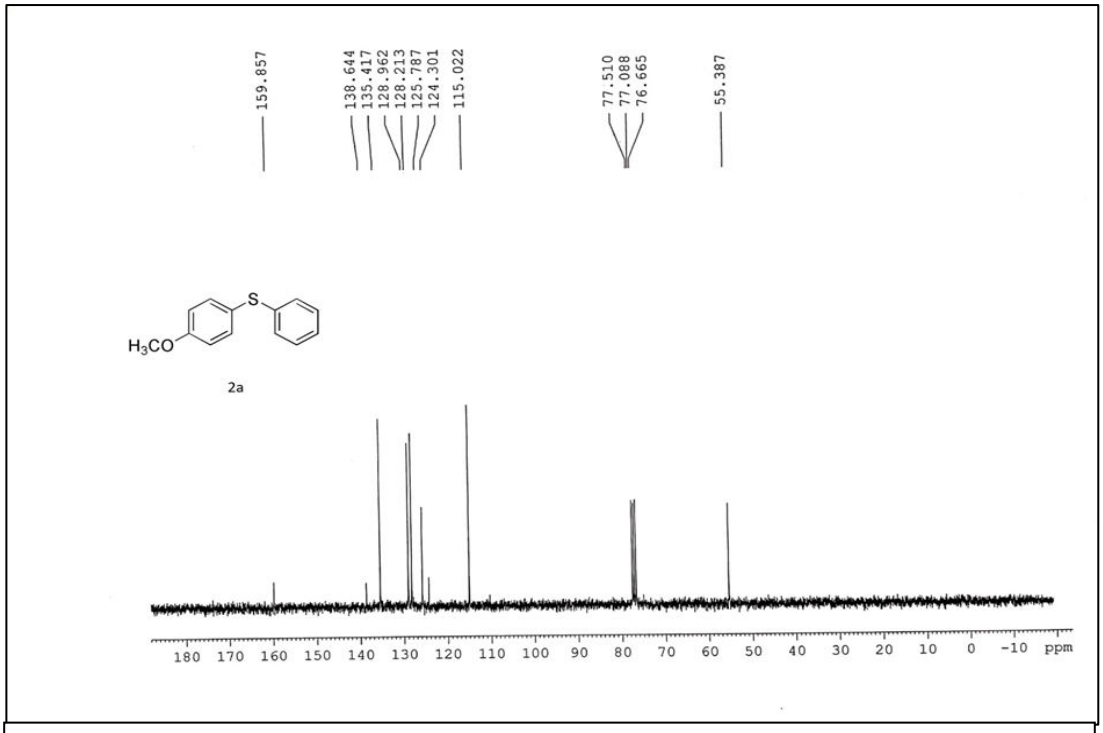


Figure III.5. ^{13}C NMR scanned copy of (4-methoxyphenyl)(phenyl)sulfane (2a)

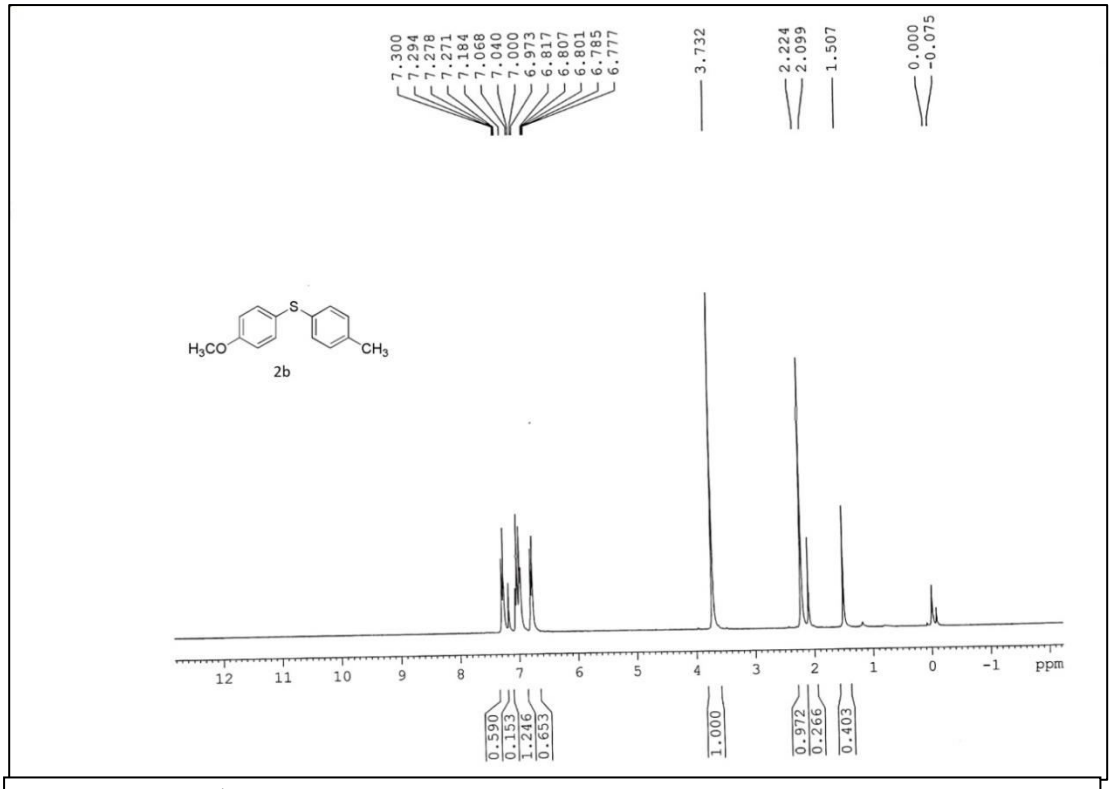


Figure III.6. ^{1}H NMR scanned copy of (4-methoxyphenyl)(*p*-tolyl)sulfane (2b)

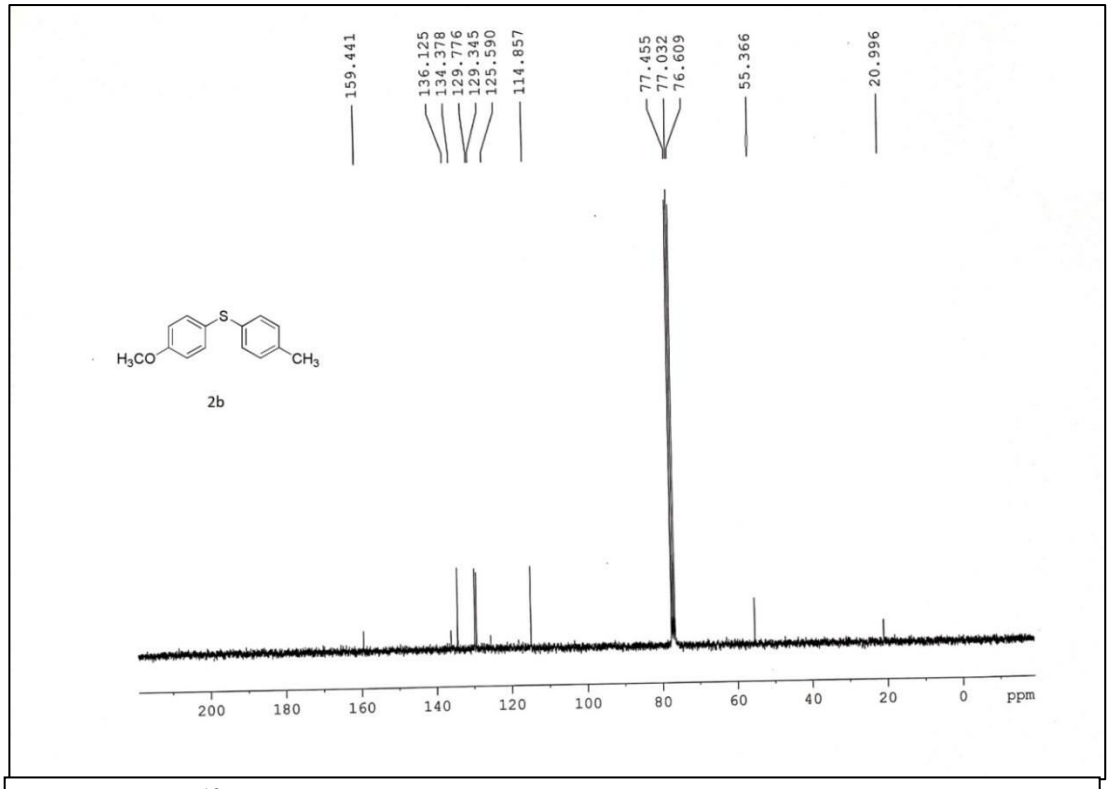


Figure III.7. ^{13}C NMR scanned copy of (4-methoxyphenyl)(*p*-tolyl)sulfane (2b)

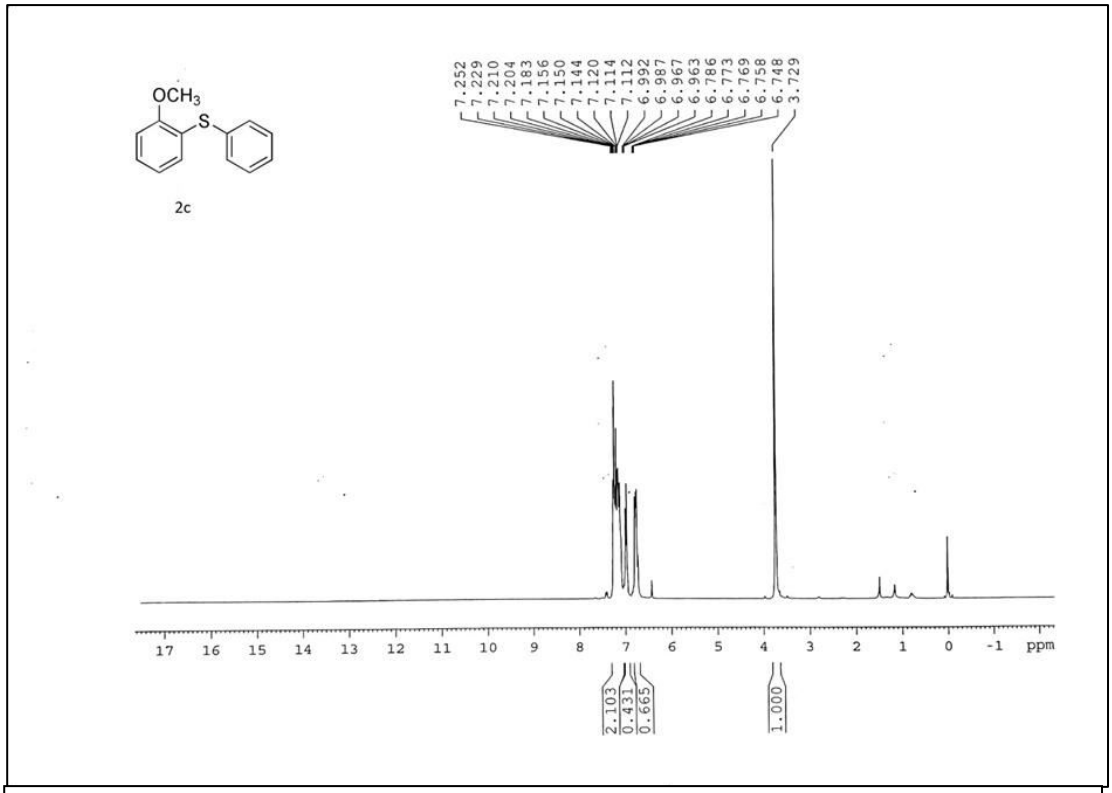


Figure III.8. ^{1}H NMR scanned copy of (2-methoxyphenyl)(phenyl)sulfane (2c)

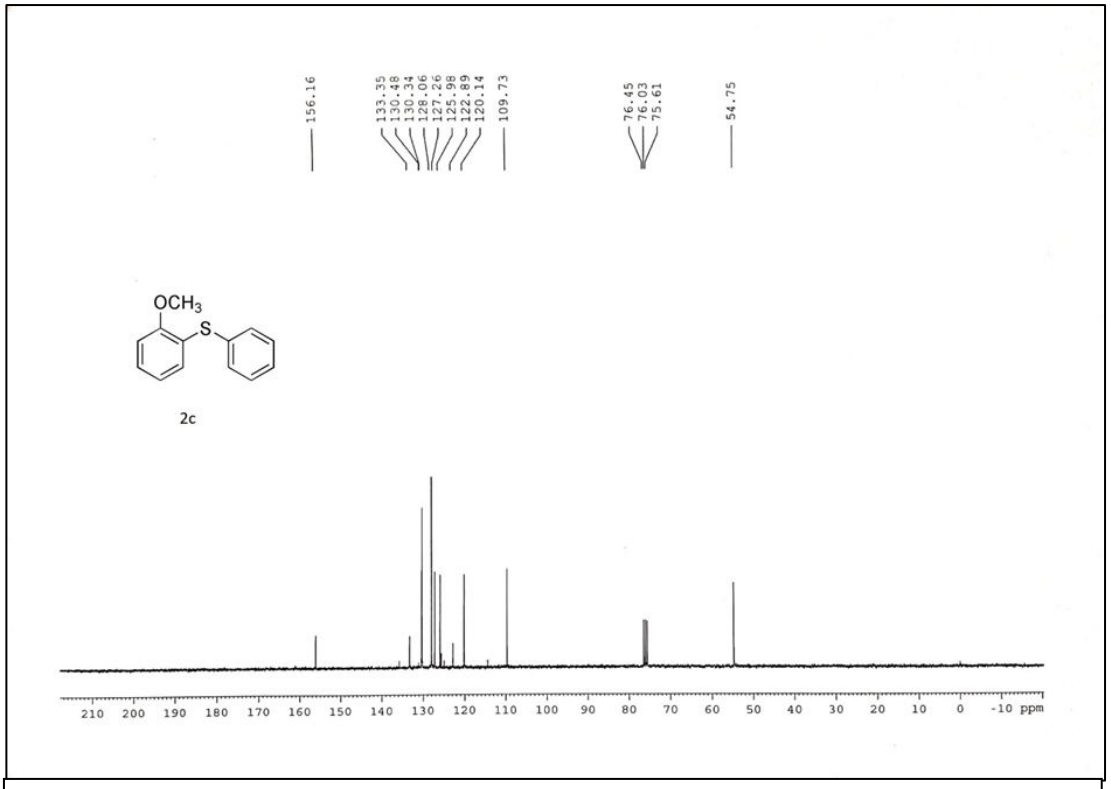


Figure III.9. ^{13}C NMR scanned copy of (2-methoxyphenyl)(phenyl)sulfane (2c)

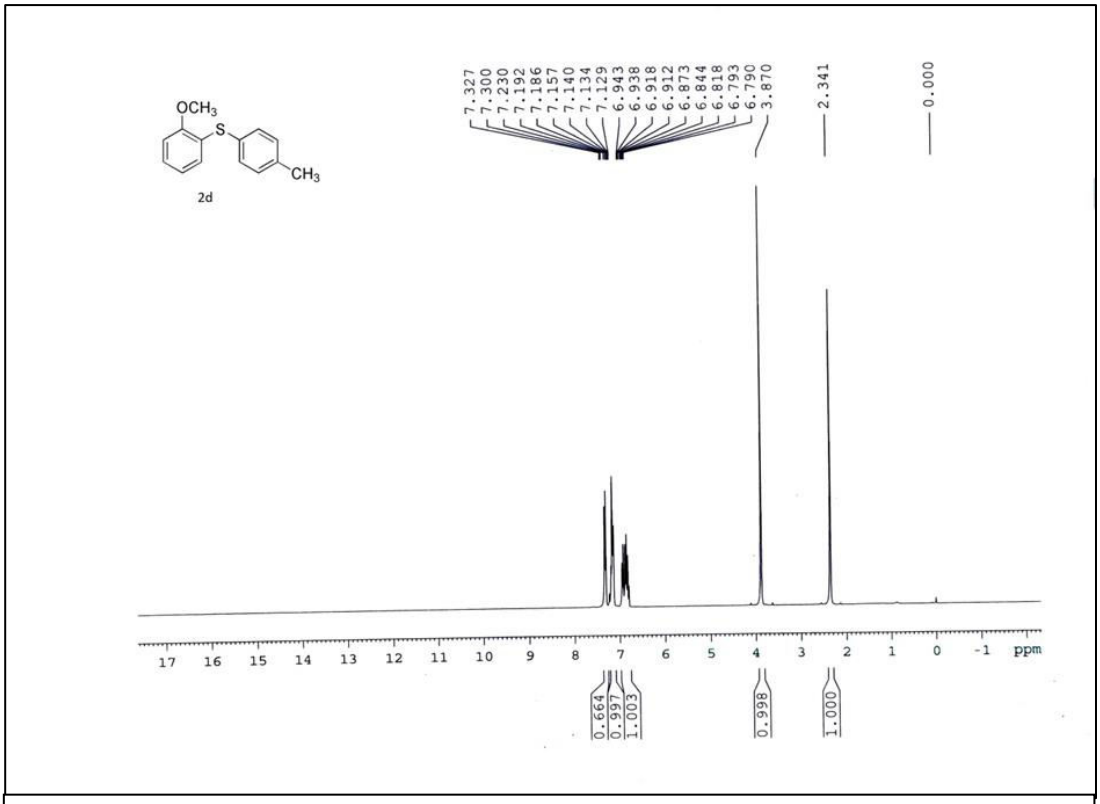


Figure III.10. ^{1}H NMR scanned copy of (2-methoxyphenyl)(*p*-tolyl)sulfan (2d)

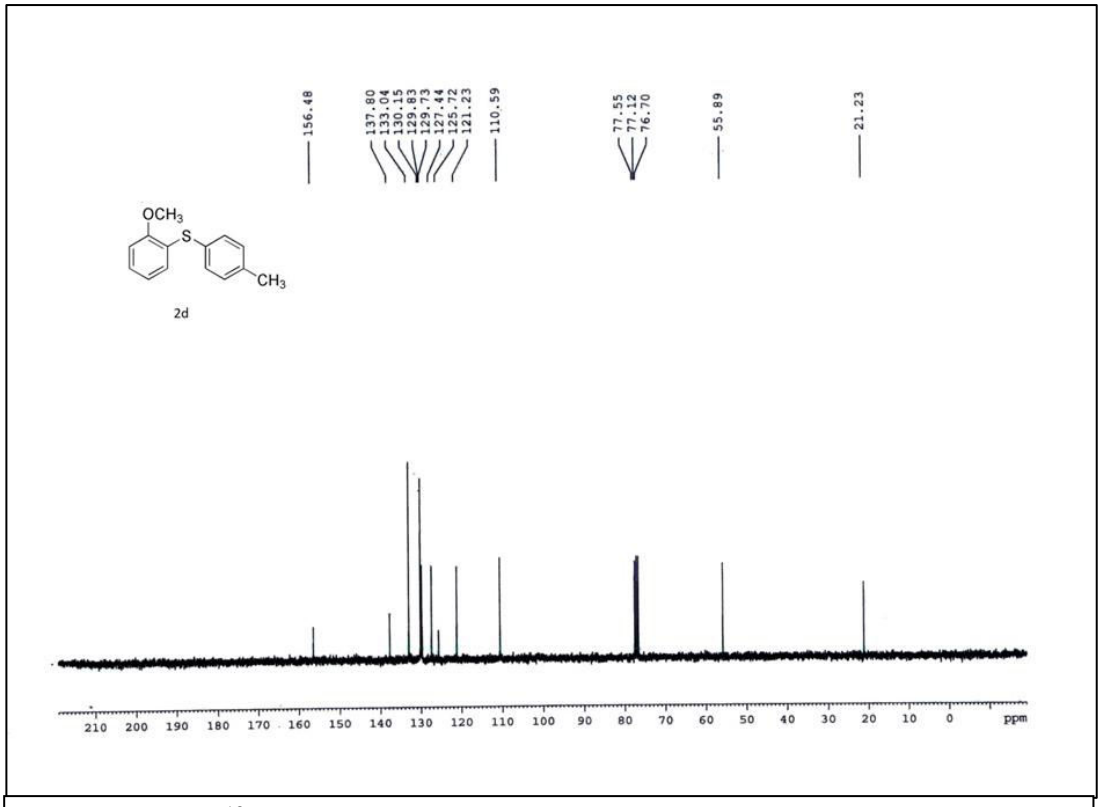


Figure III.11. ^{13}C NMR scanned copy of (2-methoxyphenyl)(*p*-tolyl)sulfan (2d)

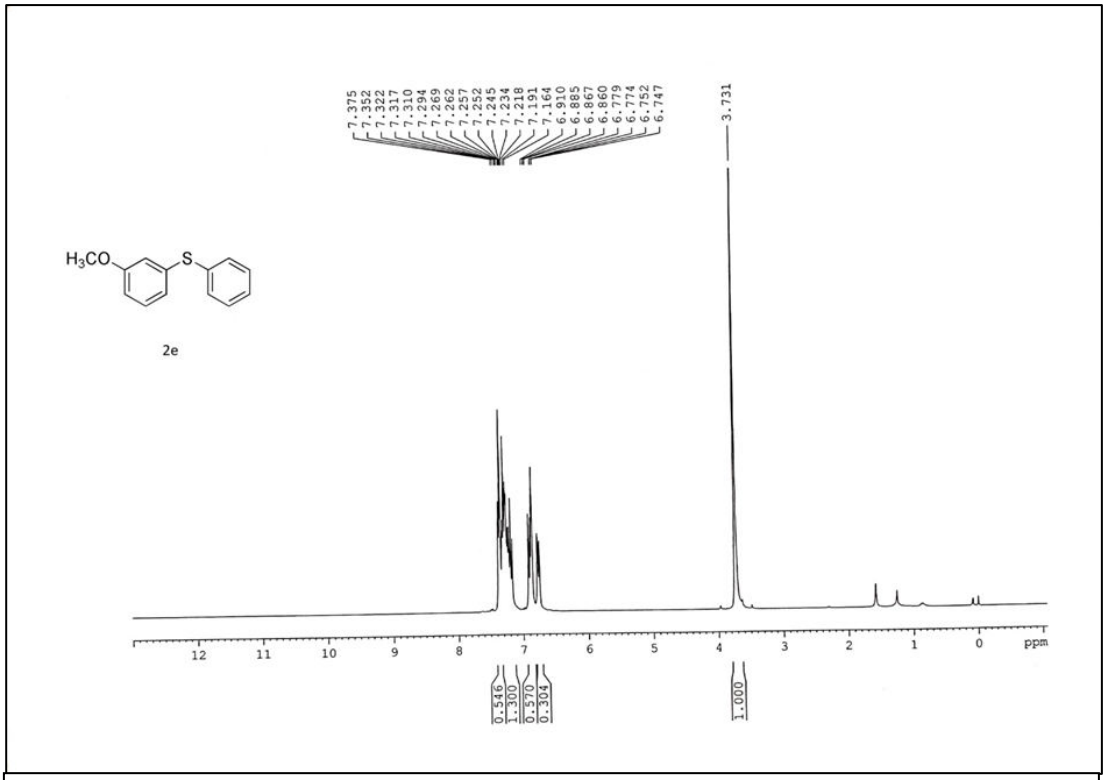


Figure III.12. ^{1}H NMR scanned copy of (3-methoxyphenyl)(phenyl)sulfane (2e)

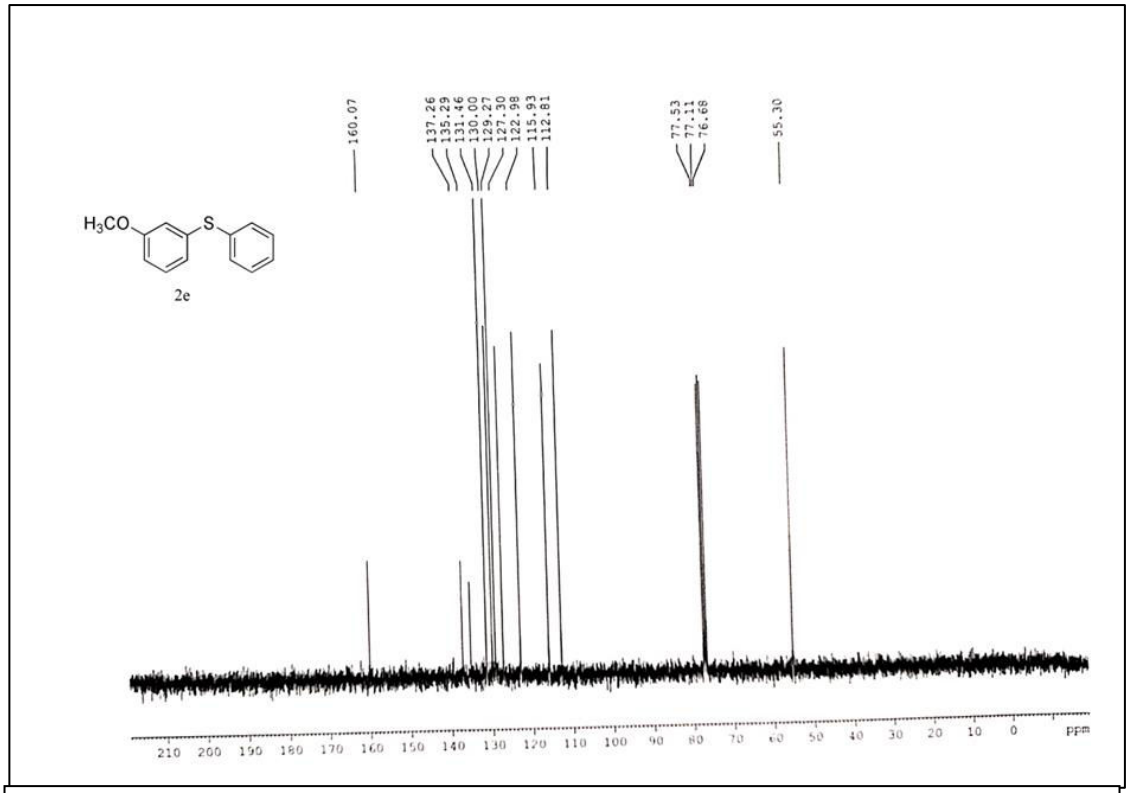


Figure III.13. ^{13}C NMR scanned copy of (3-methoxyphenyl)(phenyl)sulfane (2e)

III.F. References

References are given in BIBLIOGRAPHY under Chapter III.

Chapter IV

Graphene oxide catalysed one pot synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones and their biological evaluation

IV.A. Introduction

Cyclic organic compounds containing hetero-atom is known as heterocyclic compounds. W. Ramsey in 1877 was able to synthesize the first heterocyclic compound known as pyridine. Various synthetic approaches were reported so far for the synthesis of heterocyclic compounds. Heterocyclic compounds shows biological activities such antidepressant, antihistamine, antitumor, anti-HIV, analgesic and numerous others.[1]

In particular pyrimido[4,5-*b*]quinolinone-2,4-diones are an important class of heterocyclic compounds (Figure IV.1) that contained promising biological activities[2-7] such as anti-bacterial, anti-malarial, anti-tumor, analgesic, antifolate, inhibitory activity of lytic KSHV DNA synthesis.[8] Due to their high fluorescence activity, they have also found applications in the synthesis of electroluminescent materials.[9-12] Due to their synthetic and effective biological importance, chemist received an attention for this type of fused heterocyclic compound in the last few decades.[13]

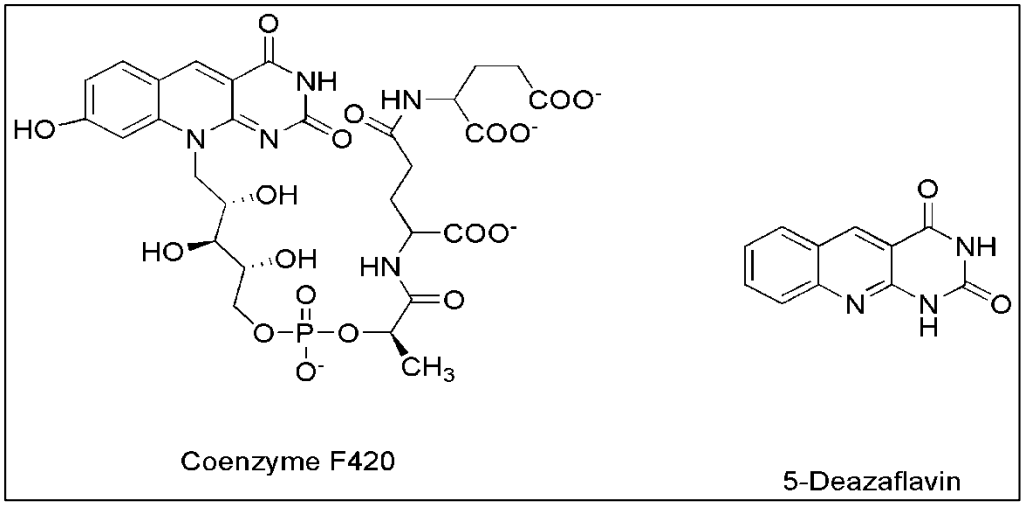
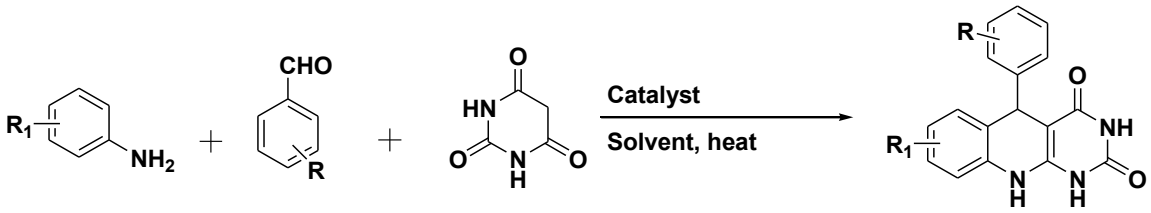


Figure IV.1. Some biologically important pyrimido[4,5-*b*]quinolone-2,4-diones

IV.B. Background and Objectives

IV.B.1. Conventional procedure for synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones

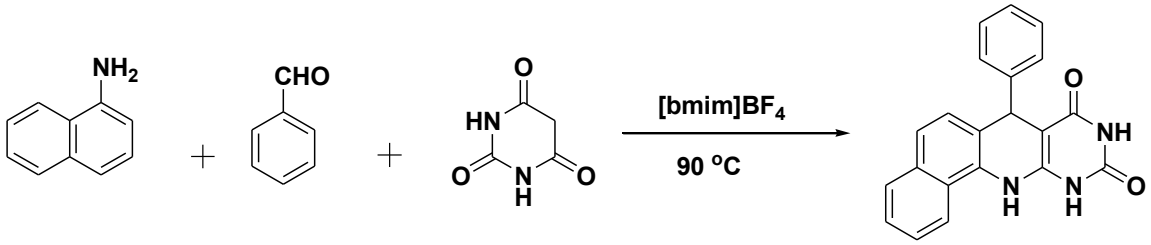
There are several number methods have been developed in the synthetic area of pyrimido[4,5-*b*]quinolinone-2,4-diones in the past decade but most of conventional procedure occurred through the adduct formation of aldehyde and barbituric acid with aniline followed by the cyclisation and with the elimination of water (Scheme IV.1). A number of catalytic and solvent system has been used to developed the reaction condition and yield of the pyrimido[4,5-*b*]quinolinone-2,4-dione derivative (Scheme IV.1).



Scheme IV.1. Conventional procedure for the synthesis of pyrimido[4,5,-*b*]quinolinone-2,4-dione derivative

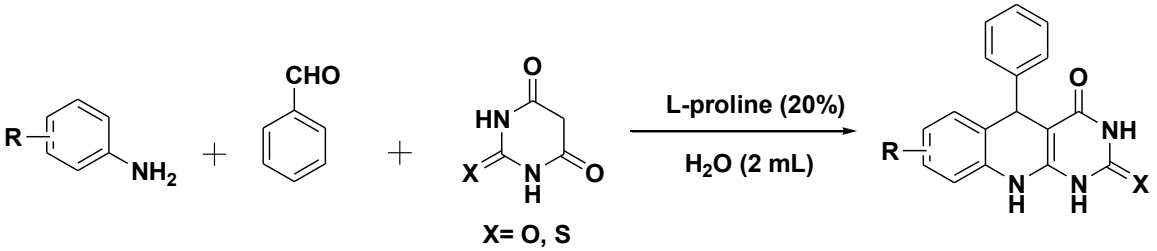
IV.B.2. Modern methods for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones

A number of method have been reported for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones which most commonly involved in the formation of adduct with aldehyde and barbituric acid followed by the cyclisation with aniline and with the elimination of water molecule. A number of catalytic system and reaction conditions have been applied to increase the impact of the reaction. In the year of 2010 H. Y. Guo *et al.*[14] reported the one-pot three-component reaction for the synthesis of 7-aryl-11,12-dihydrobenzo[*h*]pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*) diones in ionic liquid. By this method a series of 7-aryl-11,12-dihydrobenzo[*h*]pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*) diones have been synthesized from aldehydes, 1-naphthylamine and barbituric acid in ionic liquid (Scheme IV.2).



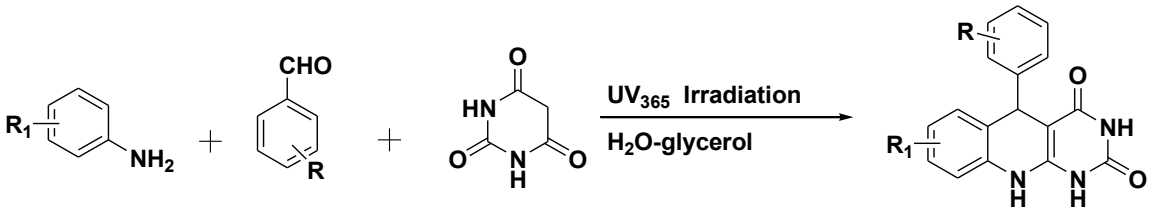
Scheme IV.2. One-pot three-component reaction for the synthesis of 7-aryl 11, 12-dihydrobenzo[*h*]pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*)-diones

In 2012, A. K. Nezhad *et al.*[15] reported *L*-proline-promoted a green and efficient one-pot process to achieve three-component reaction for the synthesis of regioselective 5-arylpyrimido-[4,5-*b*]quinoline-diones and 2-amino-4-arylquinoline-3-carbonitriles from anilines, aldehydes and barbituric acids/malononitrile in water (Scheme IV.3).



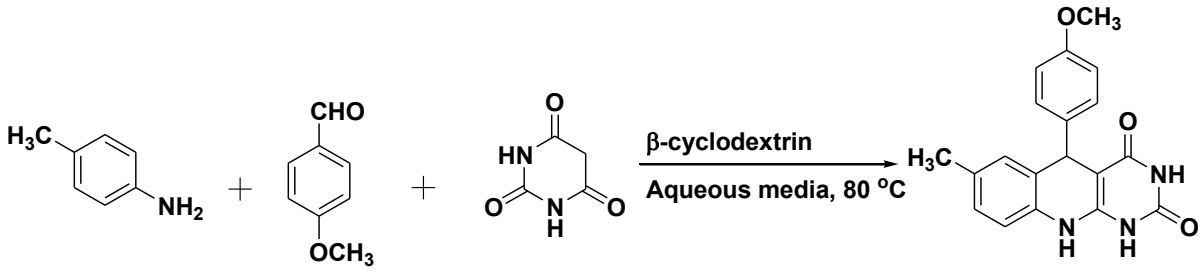
Scheme IV.3. *L*-proline catalysed reactions of anilines, aldehydes and barbituric acids in water

R. Nongkhlaw *et al.*[16] in 2016 reported an environmentally benign and highly efficient multi-component reaction protocol for the synthesis of biologically important pyrimido[4,5-*b*]quinolinone-2,4-diones from aromatic amines, barbituric acid and aryl aldehyde by using direct irradiation from a UV_{365} light source. The reaction protocol was very clean, environmentally green. This reaction protocol was applicable for the synthesis of large scale of pyrimido[4,5-*b*]quinolinone-2,4-diones (Scheme IV.4).



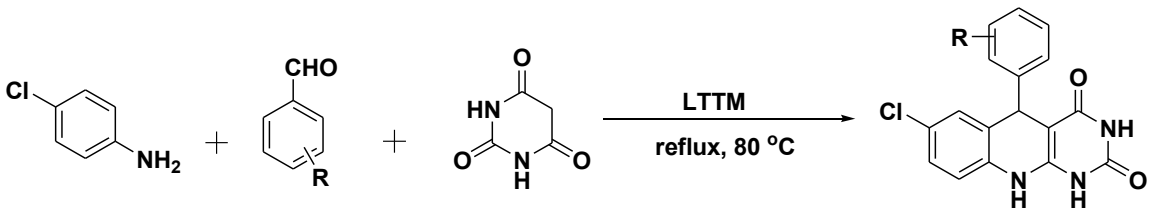
Scheme IV.4. Synthesis of pyrimido[4,5-*b*]quinoline-2,4-dione derivatives under UV_{365} irradiation.

In the year of 2018, P. V. G. Reddy *et al.*[17] developed a supramolecular catalyst *β*-cyclodextrin catalysed condensation reaction of aldehyde, aniline and barbituric acid for the synthesis of pyrimido[4,5-*b*]quinoline-diones in aqueous media. The protocols was efficient and straight forward, environmentally safer towards the synthesis of a series of pyrimido[4, 5-*b*]quinoline-diones derivatives (Scheme IV.5).



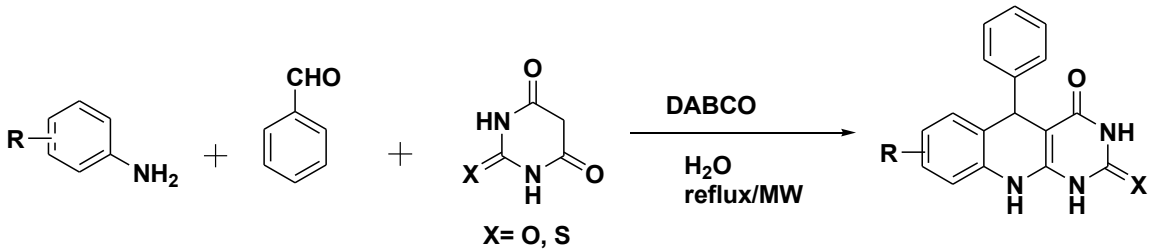
Scheme IV.5. Supramolecular catalyst β-cyclodextrin catalysed synthesis of pyrimido[4, 5 *b]*quinoline-diones in aqueous media.

Low transition temperature mixtures prompted one-pot multi-component, an efficient green reaction protocol was developed by P. P. Mohire *et al.*[18] for the synthesis of 5, 10 dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione derivatives. In this method no chromatographic purification required to get the pure product (Scheme IV.6).



Scheme IV.6. One-pot multi-component reaction for the synthesis of 5,10 dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione

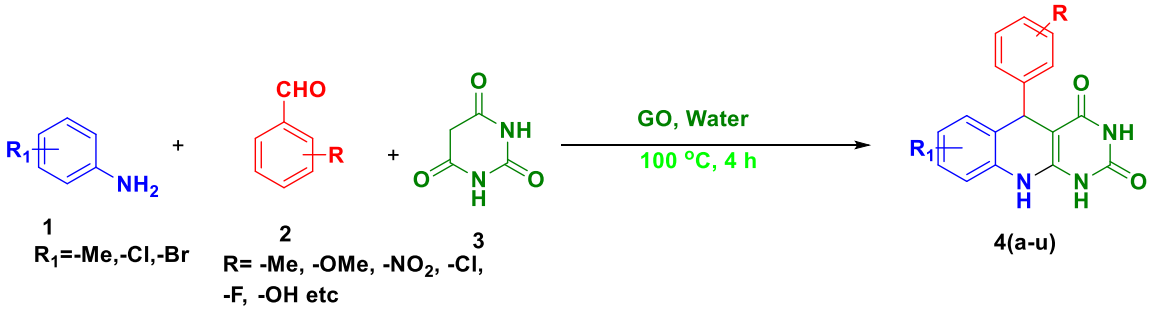
In 2014, M. H. Mosslemin *et al.*[19] reported a green efficient microwave irradiation multi-component reactions for the synthesis of 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-*b*]quinoline-2,4-diones from aldehydes, anilines and barbituric acids by using 1,4-diazabicyclo[2.2.2]octane as a catalyst in water media. The multi-component reaction was carried out under reflux condition (Scheme IV.7).



Scheme IV.7. DABCO catalysed microwave irradiation multi-component reactions for the synthesis of 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-*b*]quinoline-2,4-diones

IV.C. Present work

Here we developed a very simple, environmentally benign, efficient reaction protocol for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones by the reaction of barbituric acid with various aldehydes and aromatic amines (Scheme IV.8).



Scheme IV.8. Synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones

IV.C.1. Result and Discussion

We start our explorative work by taking 4-methyl aniline (1 mmol), 4-methoxy benzaldehyde (1 mmol) and barbituric acid (1 mmol) as a model reaction using water as environmentally benign solvent medium at 100 ^{o}C for 4 h. When the reaction carried out in absence of catalyst even after 24 h the reaction did not occur. So we repeated our model reaction with the varying amount of graphene oxide catalyst (Table IV.1). We get the best result when 20 mg of graphene oxide catalyst was used out of the 16 attempts. We used various solvent such as DMF, toluene, DMSO, CH_3CN and get the expected product but no superiority over the water as a solvent (Table IV.1). We also used ethanol as a solvent get the expected product in good yield (Table IV.1, entry 15). Keeping environmentally benign medium in mind we chosen water as the optimal medium of the reaction. The reaction also carried out under neat condition which gave the expected product with moderate yield (Table IV.1, entry 3). Further, we examine the effect of temperature to reduce the reaction time and to enhance the yield of the corresponding product. Variation in yield was observed at different temperatures. The yield was found to increase with gradual increase in temperature. Best yield of the product obtained under reflux condition. The reaction also carried out at room temperature for 24 h then only trace amount of the product obtained.

Table IV.1. Screening of the reaction conditions[a]

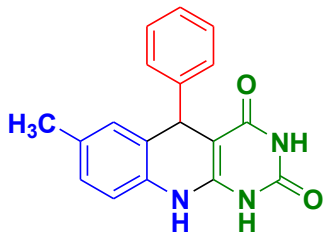
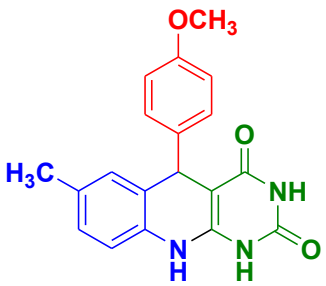
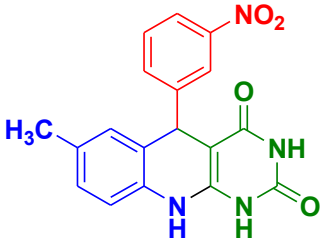
Entry	Catalyst (mg)	Time (h)	Temperature	Solvent	Yield (%)[b]
1	-	24	100	Water	NR
2	10	12	100	Water	78
3	10	12	100	Neat	65
4	15	6	100	Water	80
5	20	6	80	Water	83
6	**20**	**4**	**100**	**Water**	**89**
7	20	6	80	Water	76
8	25	4	100	Water	85
9	50	12	100	Water	83
10	15	24	100	Water	91
11	15	4	100	DMF	72

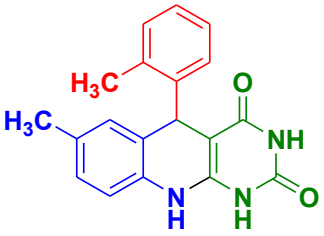
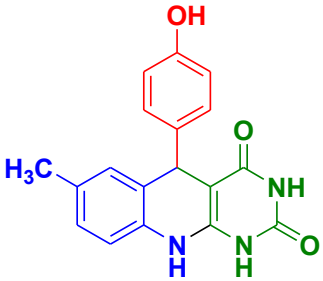
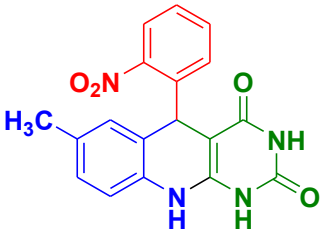
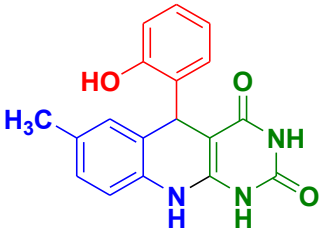
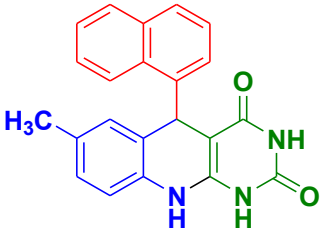
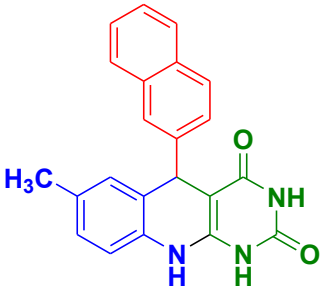
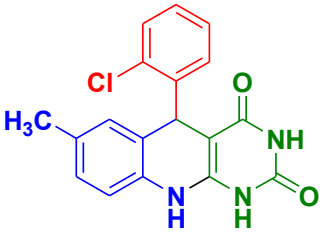
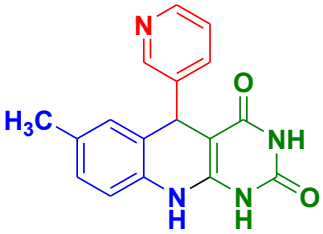
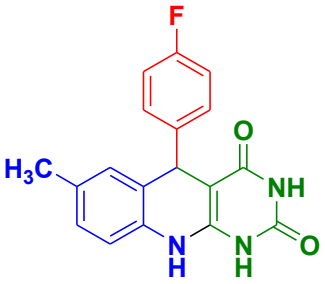
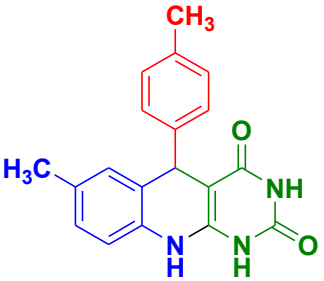
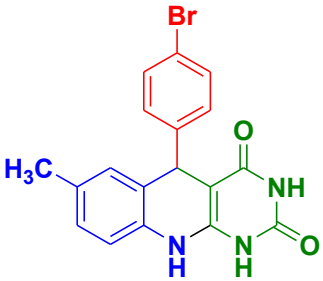
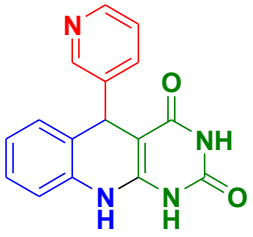
12	15	4	100	Toluene	40
13	15	4	150	DMSO	59
14	15	4	80	CH_3CN	47
15	15	4	80	Ethanol	86
16	15	4	RT[c]	Water	NR

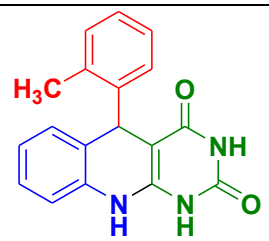
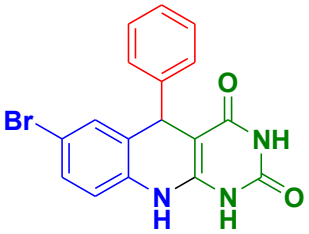
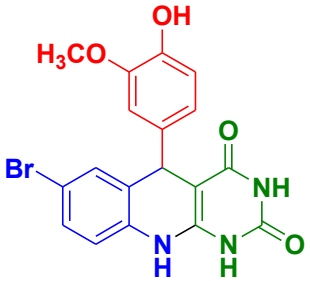
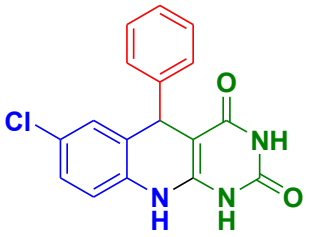
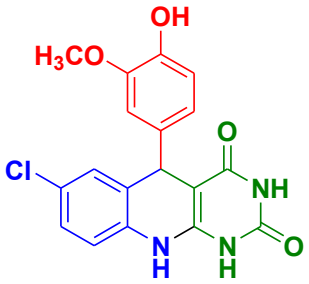
The bold significance represents the optimized protocol/conditions, [a]Reaction conditions: 4-methyl aniline (1 mmol), 4-methoxy benzaldehyde (1 mmol), barbituric acid (1 mmol), GO (20 mg) at different temperatures and solvent. [b]Isolated yields, [c]room temperature reaction, NR= no reaction

Inspiring from the above results, we carried out the reaction with a variety of aldehydes and anilines containing with electron withdrawing as well as electron donating group with barbituric acid. Aniline containing electron donating group gave the desired with good yield which may be due to enhance of the electron density towards the aniline nucleus and thereby coursing the ortho attack (Table IV.2). Similarly, aromatic aldehyde with different group gave the corresponding product with good yields. We also carried out the reaction with aliphatic aldehyde but it failed to gave the desired product with good yields. Further, when reaction was carried with napthaldehydes and heterocyclic aldehydes good yield of the corresponding product was observed. The above results are tabulated below (Table IV.2).

Table IV.2. Substrate scope of anilines and aldehydes for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones[a]

 **4a, 80%**	 **4b, 89%**	 **4c, 70%**

 4d, 87%	 4e, 79%	 4f, 76%
 4g, 78%	 4h, 80%	 4i, 76%
 4j, 78%	 4k,70%	 4l, 70%
 4m, 88%	 4n, 70%	 4o, 72%

 4p, 75%	 4q, 80%	 4r, 70%
 4s, 75%	 4t, 74%	

[a]Reaction conditions: anilines (1 mmol), aldehydes (1 mmol), barbituric acid (1 mmol), GO 20 mg, water 5 mL at 100 ^{o}C

We explored the catalytic activity of graphene oxide (GO) by using as an acid promoted three-component condensation reaction of aromatic amines, aldehydes and barbituric acid. We synthesized graphene oxide by modified Hummer's method and graphene oxide surface consists functional groups such as epoxide, carbonyl, hydroxyl, carboxyl moieties. Synthesized GO showed the stretching frequencies at 3400-3600 cm^{-1}, 1720-1755 cm^{-1}, 1605-1620 cm^{-1}, 1230 cm^{-1} etc. in FT-IR spectra. This was supported the presence of such oxygenated functional groups. The formation of layered structure of graphene oxide was confirmed by HR-TEM and SEM images of GO during its preparation. Agglomeration and disintegration of GO into small layers after successive runs strongly support the fact that the surface acidic functionalities of GO have taken part in the reaction and this is distinctly predictable from Figure IV.1 and Figure IV.2.

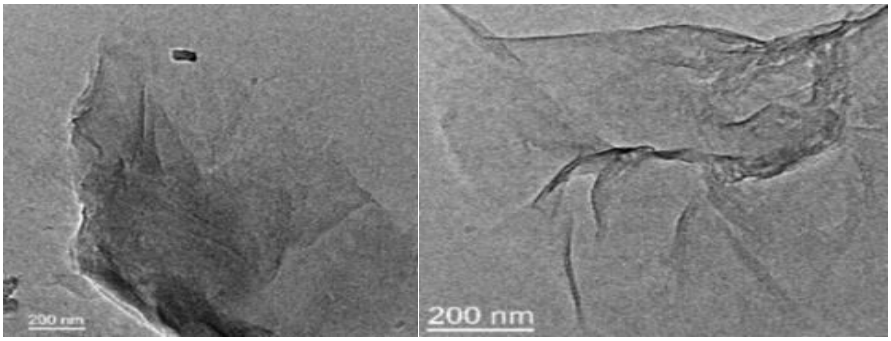


Figure IV.2. HR-TEM images of GO and GO after 4th run

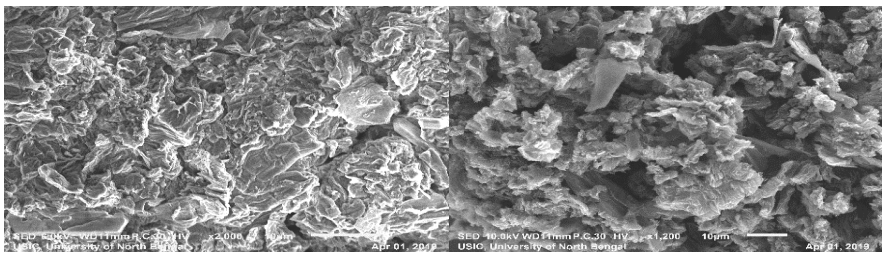


Figure IV.3. SEM images of GO and GO after 4th run

The participation of acidic groups of GO during the catalysis were explained by comparing the FT-IR spectra of the fresh GO and recovered GO after 2nd and 4th run. The band intensity of –OH group and –COOH group appeared at 3400-3600 cm^{-1} and 1720-1755 cm^{-1} respectively (Figure IV.4). This significant reduction of the band intensity clearly indicates the participation of these functional groups during the reaction (Figure IV.4). The catalytic activity of GO gradually decreases after 5th run (Figure IV.5) and may be due to participation of oxygen containing acidic groups in the reaction.

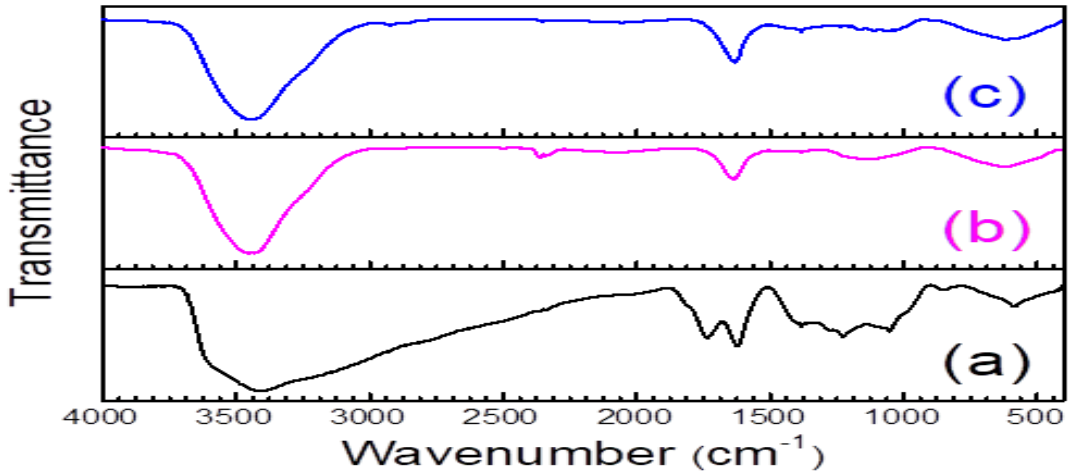


Figure IV.4. FT-IR spectra of (a) GO (b) after 2nd run and (c) after 4th run

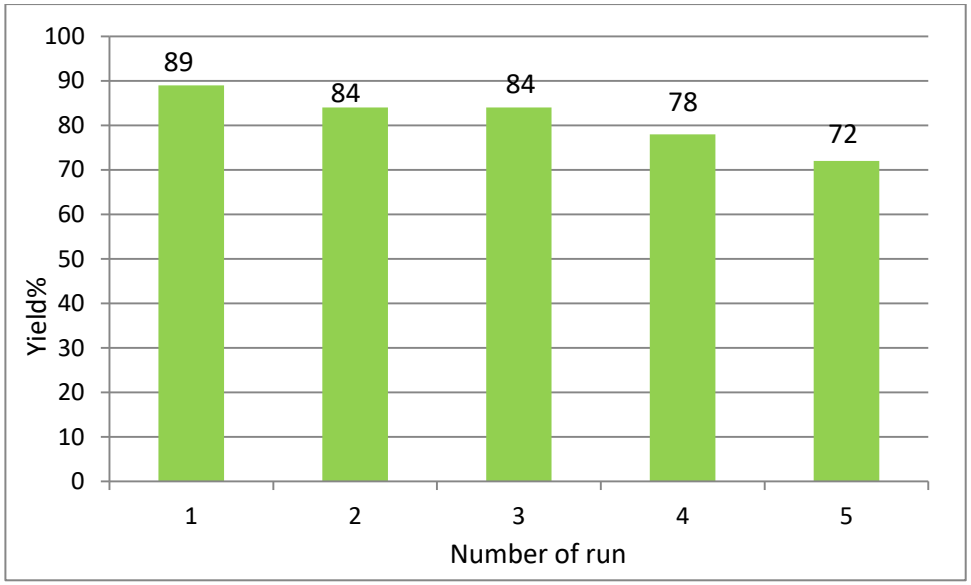


Figure IV.5. Recyclability test of Graphene Oxide (GO)

IV.C.2. Mechanism

From earlier reports[20,21] we suggested a plausible mechanism to access pyrimido[4,5-*b*]quinoline-dione involving aniline, aldehyde and barbituric acid in presence of graphene oxide. As shown in the figure IV.6 in the first step protonation of the aldehydic oxygen atom thereby encouraging the attack by barbituric acid to result enone. In the 2nd step this enone react with aniline via the Michael addition reaction followed by the cyclisation with the elimination of water molecule and affording the corresponding product.

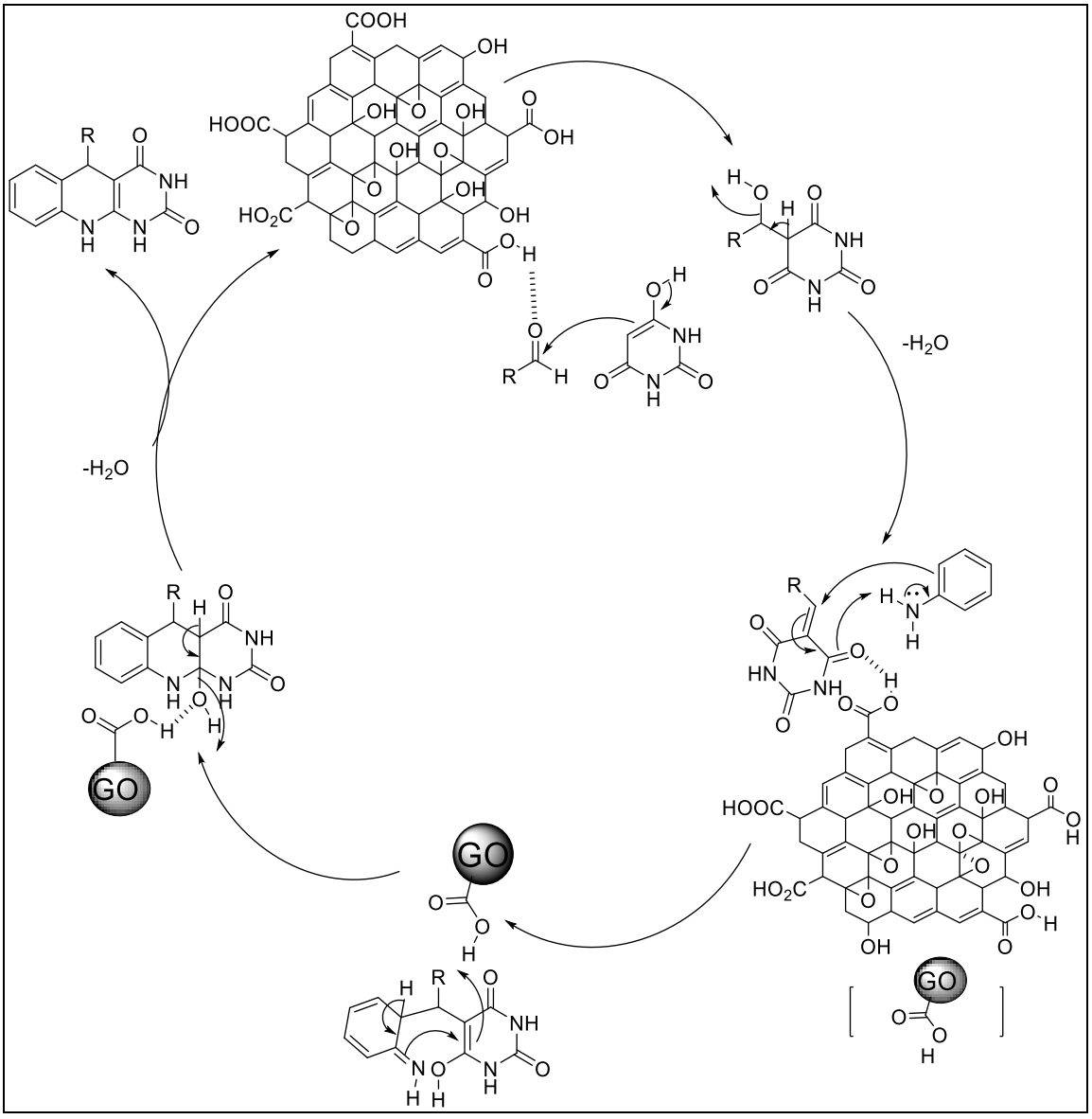


Figure IV.6. Plausible mechanism for the formation of pyrimido[4,5-*b*]quinolinone-2,4-diones

IV.C.3. Antimicrobial activity analysis of some synthesized compounds

The vast range of biological activity of 5-aryl-pyrimido quinoline 2,4-diones prompted us to investigate antimicrobial activity with some of the synthesized compounds.

IV.C.4. Materials and methods

Overnight grown broth culture of two gram positive (*Staphylococcus aureus* and *Bacillus cereus*) and two gram negative (*Escherichia coli* and *Klebsiella pneumonia*) were used for the present study to assess the antimicrobial activities of synthesized samples. Mueller-Hinton (MH) agar media (Himedia) was used for susceptibility tests. 38.0 grams of MH media was added in 1000 mL of double distilled water and heated to dissolve completely.

The media was sterilized by autoclaving at 20 lbs pressure at 121 ºC for 20 minutes. The media was cooled down to room temperature and poured in sterile petriplates at sterile condition of laminar air flow cabinet 100 µL of bacterial strains were added separately to each petriplates containing media and agitated for mixing.

The synthesized compounds (4l, 4h, 4c, 4k, 4d, 4t, 4r) were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 100 mg/mL. Paper disc diffusion method was applied. Circular paper discs (6 mm diameter) were cut from Whatman 42 filter papers and were dipped in the sample solutions for one hour. The paper discs dipped in sample solutions were placed on the media containing bacterial culture and incubated overnight at 37 ºC.

IV.C.5. Result and discussion

Efficacy of synthesized compounds in inhibiting bacterial growth can be ascertained by susceptibility tests. These synthesized compounds showed high variability (Figure IV.7 and Table IV.3). Samples 1 (4l), 2 (4h), 3 (4c), 4 (4k), 5 (4d), 6 (4t) and 7 (4r) have inhibitory function against both gram positive and gram negative bacteria. Compounds 4l (with $-CH_3$ group in the aniline part and fluorine group in the aldehydic part) showed the inhibitory function against both gram positive and gram negative bacteria. So presences of $-CH_3$ or halide are inevitable for these compounds for antibacterial activity. Compound 2 and 3 are with one $-CH_3$ groups is present in the aniline part and aldehydic part contained naphthalene moiety in compound 2 and nitro group in compound 3. Both the compound has inhibitory function against both gram positive and gram negative bacteria. Specially compound 3 shows good antimicrobial activity due to the presence of nitro group. Compound 4k fails to inhibit antimicrobial activity. Sample number 5 with $-CH_3$ groups in both the aniline (*para*-toluidine) part and aldehydic (*ortho*-tolualdehyde) part is found to be active against only gram positive bacteria. Compounds 6 and 7 are with chlorine atom while compound 7 is with bromine atom in the aniline part, they are effective against both gram positive and gram negative bacteria, but with less intensity. Maximum inhibition zone was produced by sample 3. So, nitro group may have some additional effect in inhibiting both gram positive and gram negative bacterial growth.

From the above observation we conclude that the presence of substituent in the aniline part is important for antimicrobial activity.

Table IV.3. Antimicrobial activity analysis of some synthesized compounds

Code	Compound	Gram negative		Gram positive	
		Escherichia coli	***Klebsiella pneumonia***	***Bacillus cereus***	***Staphylococcus aureus***
1	4l	9	7	8	10
2	4h	12	8	8	9
3	4c	13	11	10	15
4	4k	---	---	---	---
5	4d	---	---	7	7
6	4t	8	9	7	8
7	4r	8	8	10	7

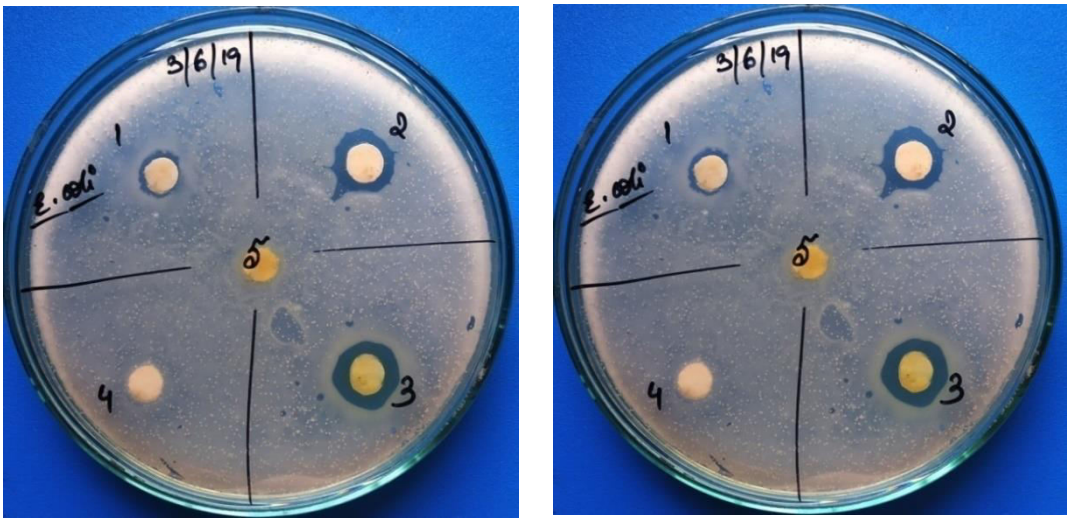


Figure IV.7. Plates showing variable inhibition activities of samples

To the best of our knowledge, the antibacterial properties of these synthesized compounds are reported for the first time in our work. It is the preliminary work towards vast range of antimicrobial activity and the positive response of these compounds will drive us to carry out further explorative work on this biologically important molecule.

IV.C.6. Conclusion

Herein, we have developed a greener, simple and efficient protocol for the three-component synthesis of pyrimido[4,5-*b*]quinoline-diones from aromatic amines, aldehydes and barbituric acid. GO was found to be highly efficient, cheap and recoverable heterogeneous solid acid catalyst in furnishing the corresponding products from high to excellent yield. The fused ring structure of pyrimido[4,5-*b*]quinoline-diones is highly promising regarding pharmaceutical aspects. The antimicrobial activity of some compounds showed promising results which will encourage us to carry out further work on it.

IV.D. Experimental section

IV.D.1. General Information

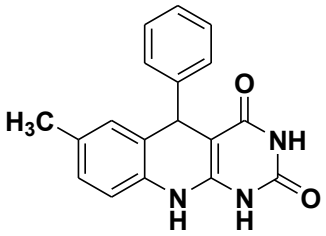
Aldehydes, aniline and barbituric acid were purchase from Sigma-Aldrich. Graphite, H_2SO_4, $KMnO_4$, H_2O_2 were purchase from Sigma-Aldrich and Alfa aeser respectively. All the synthesized compounds were purified by the column chromatography through 60-120 mesh silica gel (SRL, India). Merck plates coated with silica gel 60 have been used for TLC. KBr pellets were used in IR spectra for the record the spectra of the solid compounds in the range 4000-400 cm^{-1} on shimadzu FT-IR 8300 Spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 400 MHz on Bruker Advance. In DMSO-d_6, the splitting patterns of protons were denoted as s (singlet), d (doublet), t (triplet) and m (multiplet).

IV.D.2. General procedure for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones

A mixture of aniline (1 mmol), benzaldehyde (1 mmol) and barbituric acid (1 mmol) in water (5 mL) was stirred at 100 ^{o}C and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cool to room temperature, then the mixture was poured into 100 mL water and extract with ethyl acetate and washed it for the several times with water. After that the combined organic mixture were dried over anhydrous Na_2SO_4, concentrated it and the residue was purified by the column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate (75:25) as an eluent to get the pure solid product. All the compounds were analysed by melting point, IR, ^{1}H and ^{13}C NMR techniques.

IV.D.3. Physical properties and spectral data of the synthesized pyrimido[4,5-*b*] quinoline-diones derivatives

7-Methyl-5-phenylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4a)



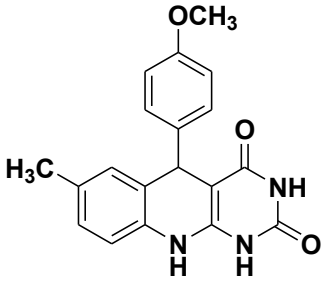
Colourless solid; m.p.: 200-202 °C.

IR (KBr, ν_{max}, cm^{-1}): 580, 780, 1160, 1230, 1560, 1620, 1660, 2950, 3110, 3330, 3440.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.50 (s, 3H), 4.44 (s, 1H), 6.98 (s, 1H), 7.23 (s, 2H), 7.48 (s, 3H), 7.67 (s, 1H), 7.77 (d, J = 8.1 Hz, 2H), 11.14 (s, 1H), 11.61 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.90, 44.70, 115.72, 125.98, 127.83, 128.53, 128.72, 128.95, 129.18, 131.96, 135.08, 140.02, 153.81, 166.73, 170.68.

5-(4-Methoxyphenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione(Table IV.2, Entry 4b)



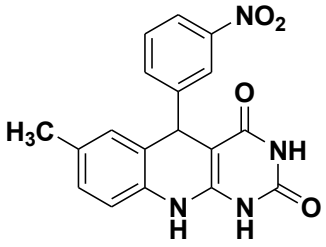
Colourless solid; m.p.: 200-202 °C.

IR (KBr, ν_{max}, cm^{-1}): 591, 779, 1130, 1233, 1560, 1630, 1640, 2930, 3150, 3310, 3430.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.09 (s, 3H), 3.74 (s, 3H), 4.44 (s, 1H), 6.35 (s, 1H), 6.82-6.95 (m, 3H), 7.13-7.22 (m, 3H), 10.33 (s, 1H), 10.55 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.42, 43.45, 54.96, 114.04, 115.17, 125.93, 128.00, 128.13, 129.53, 131.21, 131.41, 134.55, 153.32, 158.29, 166.30, 170.28.

7-Methyl-5-(3-nitrophenyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4c)



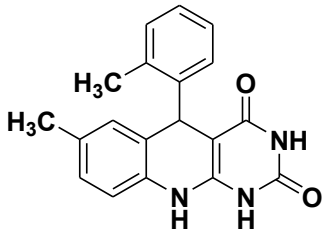
Yellow solid; m.p.: 235-236 °C.

IR (KBr, ν_{max}, cm^{-1}): 560, 3460, 780, 1150, 1223, 1550, 1630, 1640, 2930, 3110, 3330.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 0.92 (s, 3H), 5.27 (s, 1H, NH), 5.86 (d, J = 8.1 Hz, 1H), 6.08 (s, 1H), 6.29 (s, 1H), 6.49 (d, J = 8.7 Hz, 2H), 6.99 (s, 2H), 9.30 (s, 1H), 9.48 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.83, 44.30, 115.97, 123.04, 123.70, 124.54, 129.23, 128.61, 132.36, 135.24, 130.84, 135.57, 142.56, 148.47, 153.71, 162.34, 166.10, 170.23.

7-Methyl-5-o-tolylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4d)



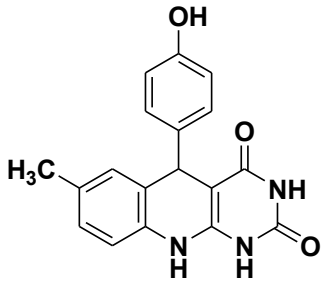
Colourless solid; m.p.: 238-239 °C.

IR (KBr, ν_{max}, cm^{-1}): 589, 787, 1177, 1237, 1555, 1625, 1660, 2950, 3130, 3340, 3470.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.04 (s, 3H), 2.29 (s, 3H), 4.78 (s, 1H), 6.08 (s, 1H), 6.86-7.51 (m, 7H), 10.32 (s, 1H), 10.65 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 19.24, 20.48, 54.96, 115.25, 125.60, 126.58, 127.20, 128.13, 130.51, 131.57, 134.58, 136.98, 137.29, 153.23, 166.74, 170.31.

5-(4-Hydroxyphenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4e)



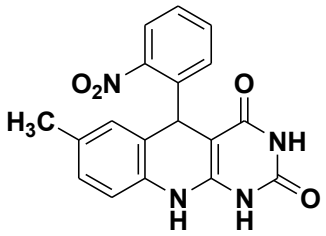
Yellow solid; m.p.: 210-212 °C.

IR (KBr, ν_{max}, cm^{-1}): 562, 723, 1160, 1243, 1552, 1630, 1657, 2943, 3120, 3329, 3458.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.50 (s, 3H), 4.14 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 7.14 (s, 1H), 7.66 (s, 1H), 7.75(d, J = 8.4 Hz, 1H), 9.60 (s, 1H), 11.09 (s, 1H), 11.55 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 21.17, 44.30, 107.98, 114.60, 125.44, 126.58, 126.74, 129.55, 170.31, 161.37, 156.90, 153.26, 150.23, 147.12, 134.71, 134.26,

7-Methyl-5-(2-nitrophenyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4f)



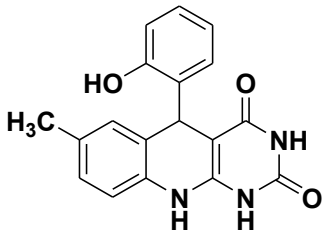
Colourless solid; m.p.: 237-239 °C.

IR (KBr, ν_{max}, cm^{-1}): 548, 753, 1140, 1243, 1557, 1630, 1650, 2950, 3150, 3370, 3490.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.10 (s, 3H), 4.99 (s, 1H), 6.33 (s, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.25 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.58-7.63 (m, 1H), 7.76-7.79 (m, 1H), 8.00 (d, *J* = 7.8 Hz, 1 H), 10.28 (s, 1H), 10.72 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.91, 54.33, 115.91, 124.93, 125.09, 128.28, 129.09, 129.51, 130.15, 132.33, 133.95, 134.22, 135.06, 151.11, 153.44, 166.15, 170.28.

5-(2-Hydroxyphenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4g)



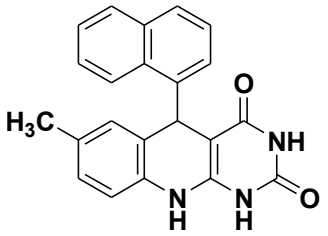
Yellow solid; m.p.: 220-221 °C.

IR (KBr, ν_{max}, cm^{-1}): 533, 758, 1159, 1236, 1557, 1624, 1658, 2940, 3123, 3320, 3458.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.32 (s, 3H), 4.01 (s, 1H), 6.90-6.99 (m, 4H), 7.08 (s, 1H), 7.27-7.31 (m, 1H), 7.65-7.67 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 9.23 (s, 1H), 11.11 (s, 1H), 11.58 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 21.68, 109.12, 115.69, 119.08, 124.00, 125.52, 126.33, 127.25, 129.49, 129.71, 134.72, 135.28, 147.75, 150.30, 150.73, 151.14, 154.32, 161.66.

Methyl-5-(naphthalen-1-yl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4h)



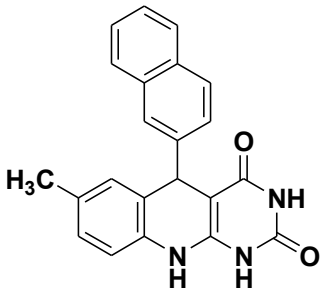
Yellow solid; m.p.: 228-229 °C.

IR (KBr, ν_{max}, cm^{-1}): 1150, 1320, 1502, 1650, 1680, 2930, 3110, 3350, 34200.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.90 (s, 3H), 5.99 (s, 1H), 6.88-6.98 (m, 2H), 7.17 (s, 1H), 7.38-7.41 (m, 2H), 7.52-7.57 (m, 3H), 7.89-8.07 (m, 3H), 10.36 (s, 1H), 10.72 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.88, 53.91, 115.79, 124.21, 126.16, 126.41, 126.96, 128.20, 128.44, 128.59, 129.32, 131.92, 132.31, 133.98, 134.95, 135.82, 153.69, 167.29, 170.70.

7-Methyl-5-(naphthalen-7-yl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4i)



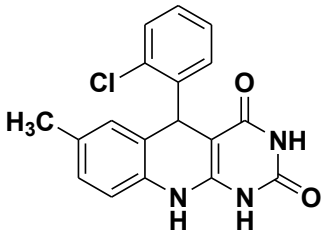
Colourless solid; m.p.: 238-239 °C.

IR (KBr, ν_{max}, cm^{-1}): 1170, 1380, 1502, 1664, 1686, 2940, 3120, 3320, 3450.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H), 4.73 (s, 1H), 6.32 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.22 (s, 1H), 7.39-7.53 (m, 4H), 7.76 (s, 1H), 7.88-7.96 (m, 3H), 10.41 (s, 1H), 10.66 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.86, 44.85, 54.70, 115.78, 125.91, 126.68, 126.88, 128.12, 128.58, 128.90, 132.03, 132.72, 133.40, 135.12, 137.36, 153.75, 166.71, 170.68.

5-(2-Chlorophenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4j)



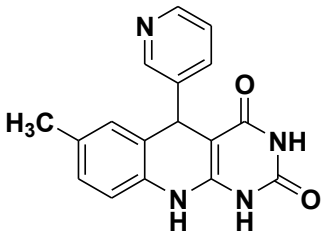
Yellow solid; m.p.: 187-188 °C.

IR (KBr, ν_{max}, cm^{-1}): 497, 782, 1150, 1235, 1555, 1623, 1652, 2942, 3125, 3325, 3450.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.06 (s, 3H), 4.99 (s, 1H), 7.00 (d, J = 6.3 Hz, 1H), 6.99-7.01 (m, 1H), 7.29-7.56 (m, 6H), 10.35 (s, 1H), 10.69 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.96, 53.10, 115.92, 124.88, 127.46, 128.45, 128.87, 129.42, 129.73, 130.30, 132.20, 134.70, 134.85, 136.80, 153.63, 166.84, 170.28.

7-Methyl-5-(pyridin-3-yl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4k)



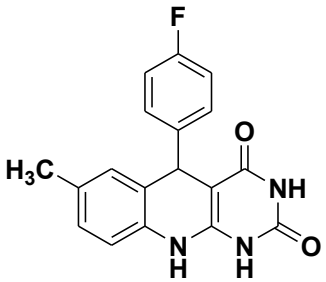
Colourless solid; m.p.: 199-200 °C.

IR (KBr, ν_{max}, cm^{-1}): 545, 728, 1150, 1243, 1557, 1630, 1660, 2949, 3130, 3320, 3445.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.97 (s, 3H), 4.63 (s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.25 (s, 1H), 7.35-7.49 (m, 2H), 7.61 (d, J = 7.5 Hz, 1H), 8.51 (m, 2H), 10.38 (s, 1H), 10.64 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.84, 42.38, 54.60, 115.93, 124.27, 125.04, 128.39, 129.01, 132.21, 135.21, 135.74, 136.34, 149.20, 150.43, 153.67, 166.27, 170.36.

5-(4-Fluorophenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4l)



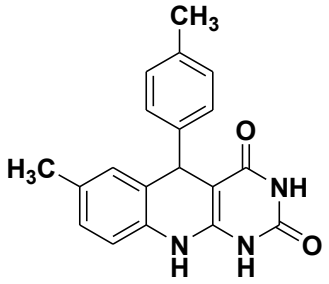
Colourless solid; m.p.: 202-204 °C.

IR (KBr, ν_{max}, cm^{-1}): 529, 789, 1150, 1230, 1555, 1623, 1656, 2945, 3120, 3220, 3350.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.09 (s, 3H), 4.57 (s, 1H), 6.37 (s, 1H), 6.85 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.18-7.27 (m, 5H), 10.37 (s, 1H), 10.58 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.87, 44.05, 54.99, 115.84, 116.12, 125.77, 128.82, 130.94, 132.06, 135.11, 136.25, 153.77, 160.15, 163.38, 166.53, 170.57.

7-Methyl-5-*p*-tolylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (TableIV.2, Entry 4m)



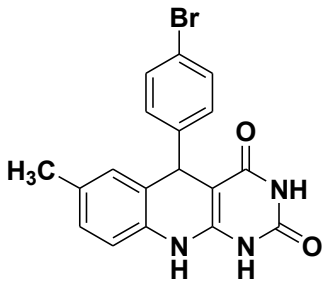
Colourless solid; m.p.: 239-240 °C.

IR (KBr, ν_{max}, cm^{-1}): 549, 783, 1160, 1230, 1570, 1660, 3465, 1689, 2940, 3167, 3335.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.28 (s, 3H), 1.51 (s, 3H), 3.67 (s, 1H), 5.52 (s, 1H), 6.05-6.18 (m, 2H), 6.34-6.38 (m, 5H), 9.58 (s, 1H), 9.80 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.12, 43.69, 54.32, 114.85, 125.21, 126.42, 127.82, 128.76, 130.99, 134.32, 135.90, 136.46, 152.82, 165.69, 169.76.

5-(4-Bromophenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4n)



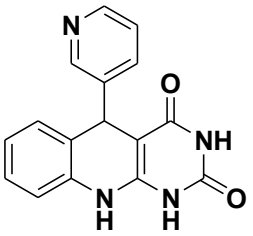
Colourless solid; m.p.: 250-251 °C.

IR (KBr, ν_{max}, cm^{-1}): 560, 780, 1190, 1234, 1554, 1630, 1660, 2947, 3125, 3338, 3437.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.10 (s, 3H), 4.52 (s, 1H), 6.34 (s, 1H), 6.83 (s, 1H), 7.00 (s, 1H), 7.18 (s, 1H), 7.47-7.76 (m, 4H), 10.36 (s, 1H), 10.59 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 20.32, 43.91, 54.52, 115.36, 124.70, 126.85, 128.06, 128.35, 130.57, 131.58, 134.74, 149.76, 153.12, 165.74, 169.88.

5-(Pyridin-3-yl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4o)



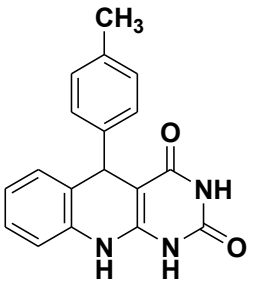
Pink solid; m.p.: 149-150 °C.

IR (KBr, ν_{max}, cm^{-1}): 548, 788, 1109, 1233, 1559, 1622, 1680, 2950, 3125, 3327, 3455.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.07 (s, 1H), 6.30 (d, J = 8 Hz, 1H), 6.86-7.32 (m, 2H), 7.36-7.57 (m, 6H), 10.39 (s, 1H), 10.78 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6): δ ppm: 52.99, 115.94, 123.28, 124.93, 127.10, 128.41, 129.42, 129.72, 130.29, 134.73, 135.58, 136.76, 137.21, 153.60, 166.96, 170.21.

5-*P*-tolylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4p)



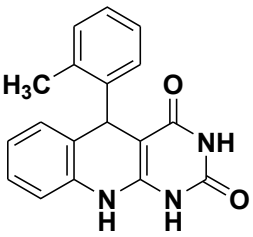
Colourless solid; m.p.: 179-181 °C.

IR (KBr, ν_{max}, cm^{-1}): 546, 759, 1099, 1233, 1552, 1625, 1657, 2950, 3120, 3220, 3340.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.67 (s, 1H), 11.18 (s, 1H), 7.81-7.87 (m, 2H), 7.38-7.42 (m, 1H), 7.26-7.31 (m, 3H), 7.13 (d, J = 8 Hz, 2H), 6.71 (s, 1H), 2.51 (s, 3H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 21.36, 50.04, 108.46, 125.51, 125.79, 127.39, 128.61, 129.20, 129.75, 133.03, 133.88, 137.23, 149.15, 150.89, 154.19, 161.67.

5-*O*-tolylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4q)



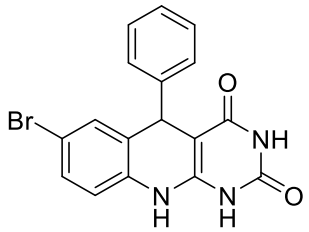
Yellow solid; m.p.: 190-192 °C.

IR (KBr, ν_{max}, cm^{-1}): 550, 770, 1140, 1233, 1470, 1620, 1665, 2940, 3120, 3319, 3350.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.80 (s, 3H), 5.15 (s, 1H), 6.30-6.64 (m, 1H), 6.79-7.00 (m, 3H), 7.10-7.44 (m, 3H), 7.61-7.71 (m, 2H), 11.04 (s, 1H), 11.54 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 19.73, 51.05, 108.68, 115.10, 125.05, 125.84, 127.34, 127.53, 128.20, 129.82, 130.06, 133.29, 134.96, 136.72, 149.22, 150.98, 153.49, 161.71.

7-Bromo-5-phenylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4r)



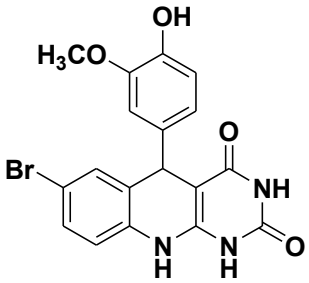
Colourless solid; m.p.: 235-236 °C.

IR (KBr, ν_{max}, cm^{-1}): 542, 789, 1105, 1235, 1550, 1625, 1670, 2946, 3130, 3350, 3470.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.90 (s, 1H), 6.74 (d, J = 8.4 Hz), 6.97 (s, 1H), 7.10-7.13 (m, 1H), 7.23-7.26 (m, 2H), 7.29-7.36 (m, 3H), 11.07 (s, 1H), 11.13 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 50.92, 63.38, 106.69, 116.25, 124.37, 128.10, 128.61, 129.01-129.88 (Ar-*C*), 136.71, 137.87, 144.50, 149.19, 167.09, 171.44.

7-Bromo-5-(4-hydroxy-3-methoxyphenyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4s)



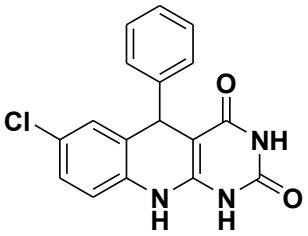
Colourless solid; m.p.: 228-229 °C.

IR (KBr, ν_{max}, cm^{-1}): 569, 759, 1160, 1283, 1552, 1628, 1659, 2930, 3123, 3327, 3450.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.68 (s, 3H), 4.47 (s, 1H), 6.54-6.91 (m, 5H), 7.25-7.51 (m, 2H), 9.08 (s, 1H), 10.39 (s, 1H), 10.74 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 44.23, 54.67, 56.53, 113.54, 114.59, 116.35, 117.76, 121.32, 129.22, 130.09, 130.67, 130.89, 136.99, 146.57, 148.42, 153.71, 166.71, 170.43.

7-Chloro-5-phenylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4t)



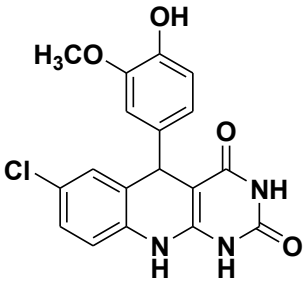
Colourless solid; m.p.: Above 250 °C (Lit. m.p. 274-276 °C).

IR (KBr, ν_{max}, cm^{-1}): 487, 728, 1100, 1239, 1540, 1630, 1680, 2945, 3150, 3320, 3450.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.04 (s, 1H), 6.41 (s, 1H), 6.71-6.83 (m, 1H), 7.02-7.22 (m, 2H), 7.27-7.64 (m, 5H), 11.12 (s, 1H), 11.18 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 51.21, 63.64, 115.96, 119.56, 123.95, 126.67, 127.16, 128.51, 129.46, 136.87, 137.94, 144.17, 149.05, 167.01, 171.46.

7-Chloro-5-(4-hydroxy-3-methoxyphenyl)pyrimido[4,5-*b*]quinoline 2,4(1*H*,3*H*,5*H*,10*H*)-dione (Table IV.2, Entry 4u)



Colourless solid; m.p.: > 250 °C.

IR (KBr, ν_{max}, cm^{-1}): 547, 786, 1100, 1233, 1550, 1620, 1650, 2940, 3120, 3320, 3450.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.71 (s, 3H), 4.47 (s, 1H), 6.51-6.54 (m, 1H), 6.69-6.74 (m, 2H), 6.83-6.87 (m, 2H), 7.22 (s, 1H), 7.34-7.37 (m, 1H), 9.06 (s, 1H), 10.37 (s, 1H), 10.72 (s, 1H),

^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 44.23, 54.67, 56.50, 113.55, 114.59, 116.35, 117.76, 121.32, 129.22, 130.10, 130.68, 130.89, 136.98, 146.43, 148.42, 153.71, 166.61, 170.57.

IV.E. Scanned copies of ^{1}H NMR and ^{13}C NMR of the synthesized compounds

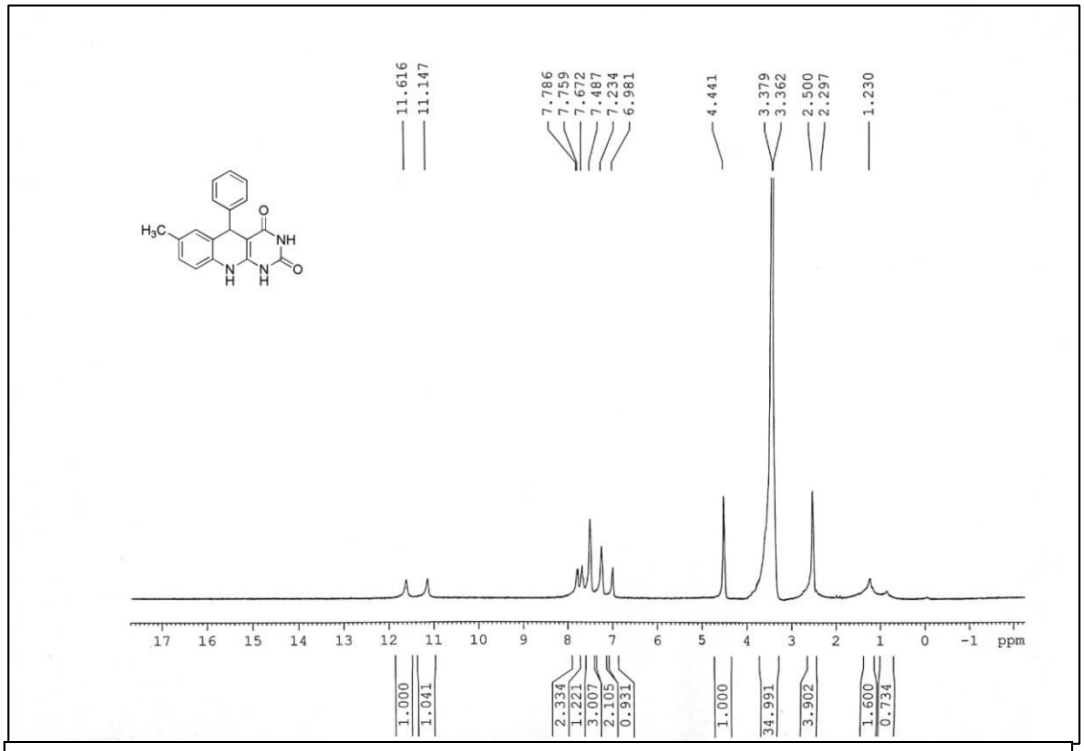


Figure IV.8. ^{1}H NMR scanned copy of 7-methyl-5-phenylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione

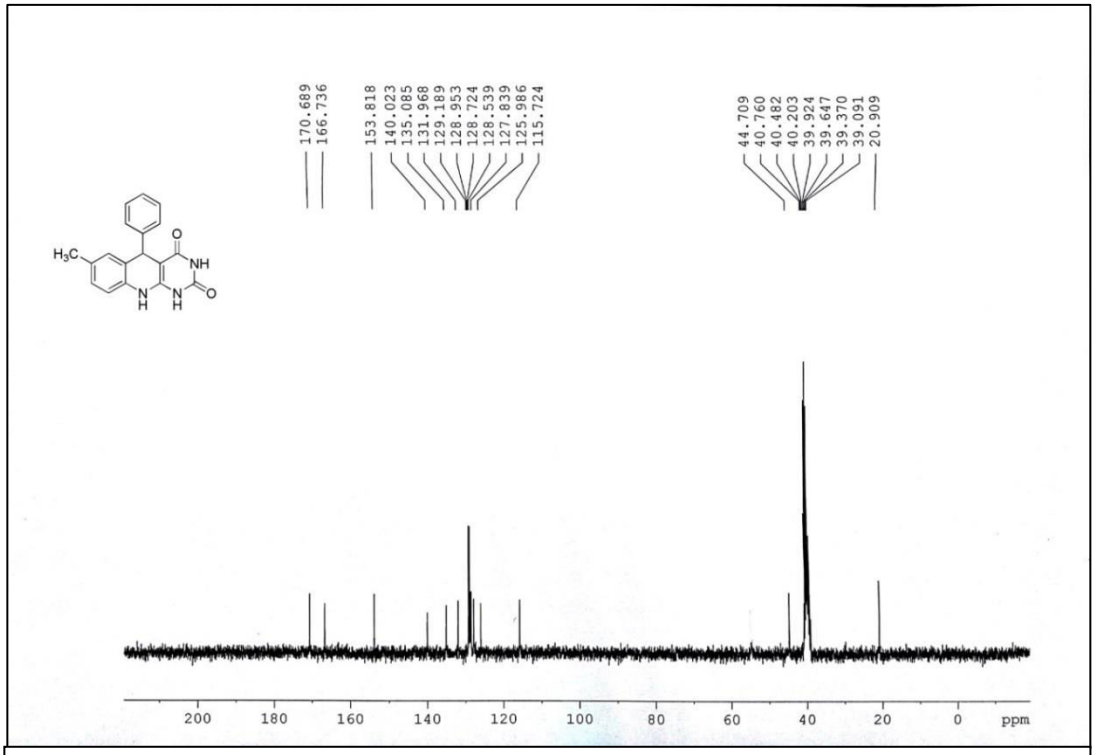


Figure IV.9. ^{13}C NMR scanned copy of 7-methyl-5-phenylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione

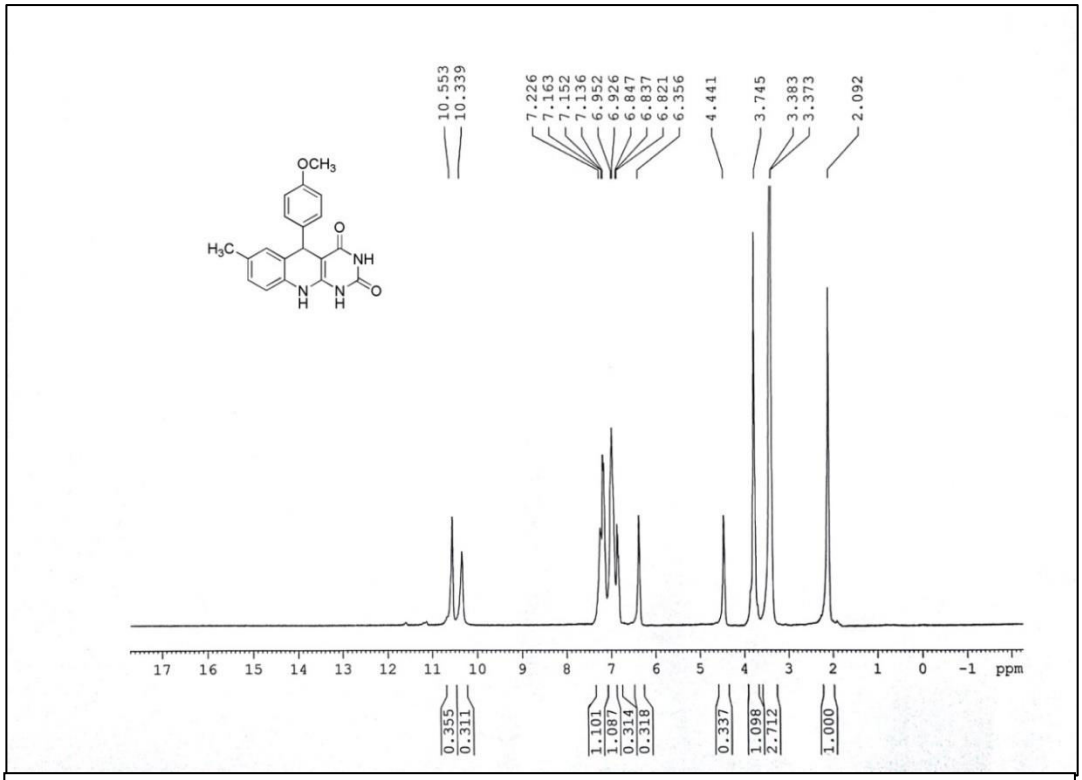


Figure IV.10. ^{1}H NMR scanned copy of 5-(4-methoxyphenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione

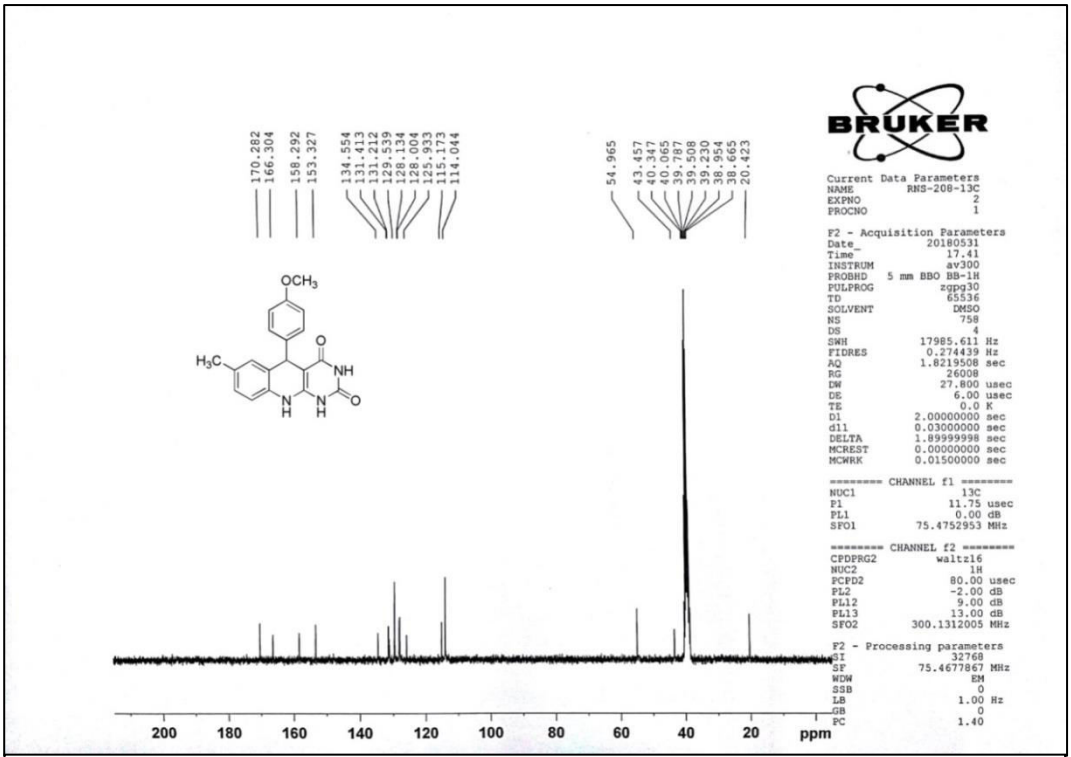


Figure IV.11. ^{13}C NMR scanned copy of 5-(4-methoxyphenyl)-7-methylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione

IV. F. References

References are given in BIBLIOGRAPHY under Chapter IV.

Chapter V

One-pot three-component tandem annulation of 4-hydroxycoumarine with aldehyde and aromatic amines using Graphene oxide as an efficient catalyst

V.A. Introduction

The quinoline moiety is the most common moiety in a variety of biologically active compounds as well as in natural products.[1,2] The quinolone derivatives are widely useful in several biological activities and pharmacological purpose including anticancer activities,[3] antimalarial,[4] antimicrobial,[5] antidepressant.[6] In chromeno-quinoline derivatives, 2*H*-chromen-2-one ring and a 2*H*-chromene ring fused to quinoline ring. These chromeno-quinoline derivatives possess some considerable properties such as fluorescent pH sensors and estrogen receptor β-selective ligands functions.[7,8] These chromeno-quinoline derivatives also shows anticancer,[9] anti-inflammatory,[10] bacteriostatic activities.[11]

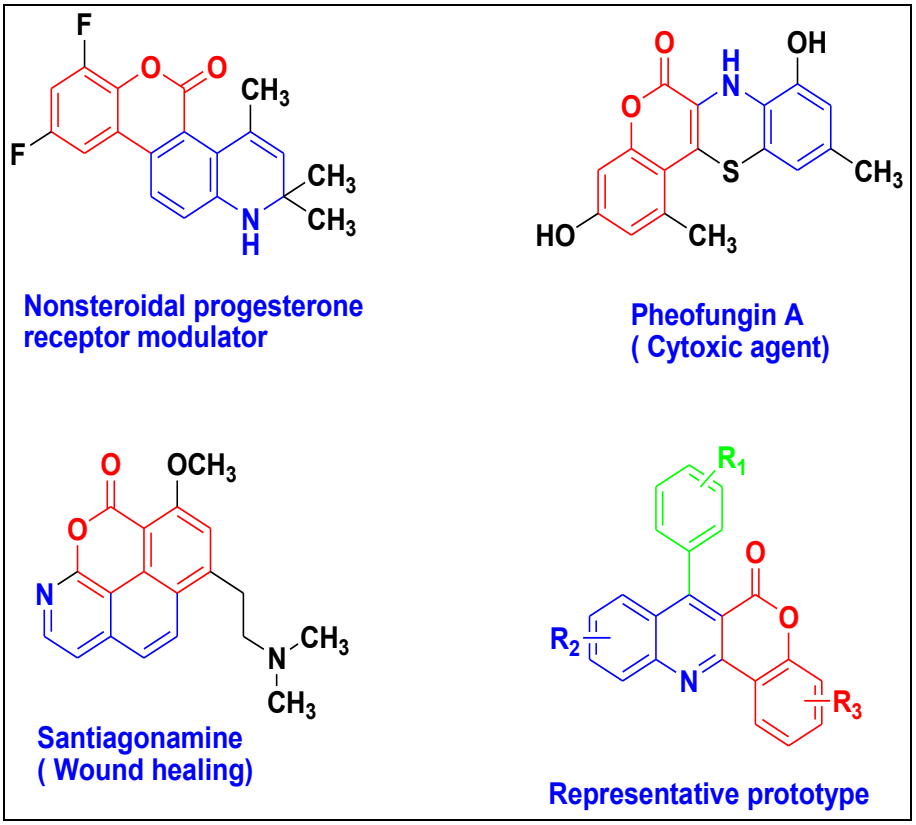


Figure V.1. Some examples of biologically active coumarin–quinoline hybrids and synthesized prototype

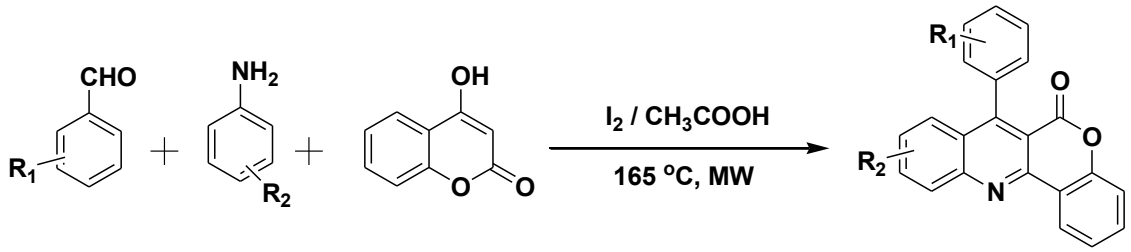
V.B. Backgrounds and Objectives

V.B.1. Modern methods of synthesis of chromeno[4,3-*b*]quinolin-6-ones

Tabakovic *et al.*[12] in the year of 1987, reported the general strategies for the synthesis of 6*H*-chromeno[4,3-*b*]quinolin-6-ones. They treated 4-arylaminocoumarins with the Vilsmeier reagent ($POCl_3$/DMF) which was used as a the formylating reagents and 6*H* chromeno[4,3-

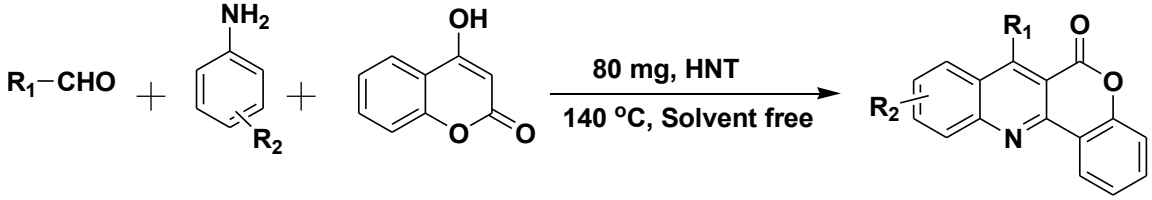
b]quinolin-6-ones obtained as a product. But this has several limitations such as use of the toxic reagent, long reaction time, low yield of the product. Thus there needed modification on this method. Wu *et al.*[13] have been carried out the reaction between 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde and aryl isocyanides for the synthesis of 6*H*-chromeno[4,3-*b*]quinolin-6-ones. But this method also has limitation in the view point of narrow substrate scope.

Recently, K. V. Sashidhara *et al.* in the year of 2015, develop a novel, efficient, and environment-friendly method for the successful synthesis of 6*H*-chromeno[4,3-*b*]quinolin-6-ones. They carried out one-pot tandem reaction of 4-hydroxycoumarin, aromatic aldehydes and aromatic amine by using the molecular iodine as catalyst under MW irradiation (Scheme IV.I).[14]



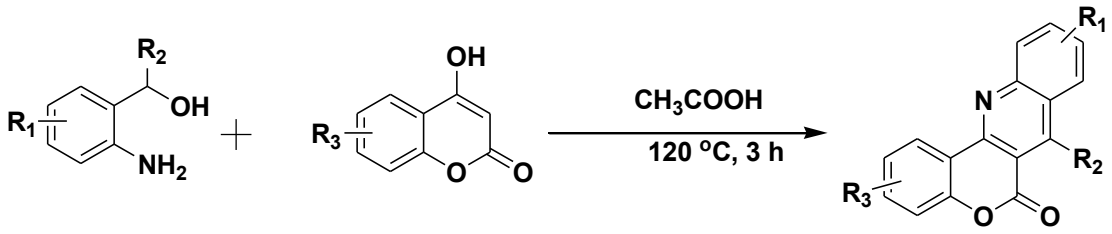
Scheme V.1. Synthesis of chromeno[4,3-*b*]quinolin-6-one

In 2019, I. Mohammadpoor-Baltork *et al.* reported a straightforward green and efficient one-pot three component reaction protocol for the synthesis of chromeno[4,3-*b*]quinolin-6-ones from easily available 4-hydroxycoumarin, aldehydes and aryl amines by using the eco-friendly, inexpensive and green heterogeneous halloysite nanoclay as a catalyst (Scheme V.2).[15]



Scheme V.2. Green heterogeneous halloysite nanoclay synthesis of chromeno[4,3-*b*]quinolin-6-ones

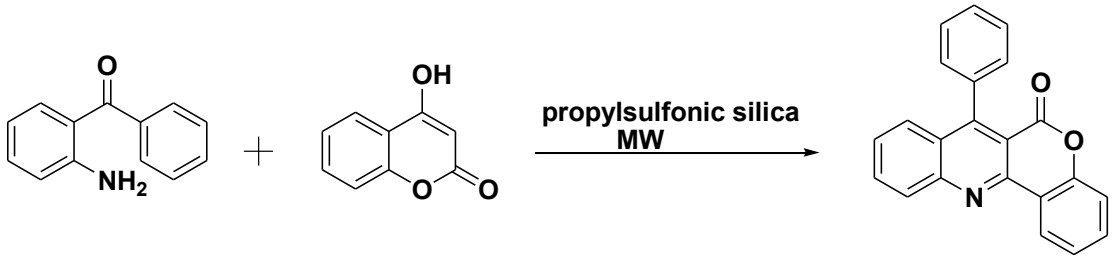
T. T. Nguyen *et al.* published an aerobic, transition-meta free coupling reaction of 4-hydrocoumarins and 2-aminobenzyl alcohols in acetic acid solvent and with the use of oxygen as oxidant for the synthesis of 6*H*-chromeno[4,3-*b*]quinolin-6-ones. This reaction protocol provided good yields and multifunctional group tolerance (Scheme V.3).[16]



Scheme V.3. Transition-meta free synthesis of chromeno[4,3-*b*]quinolin-6-ones

V.B.2. Friedlander annulation type synthesis of chromeno[4,3-*b*]quinolin-6-ones

D. Garella *et al.* together reported a Friedlander annulation type solvent free microwave-promoted silica-propylsulfonic acid catalysed reaction protocols for the synthesis of chromeno[4,3-*b*]quinolin-6-ones. The reaction was found to obtain the desired product in good yield (Scheme V.4).[17]



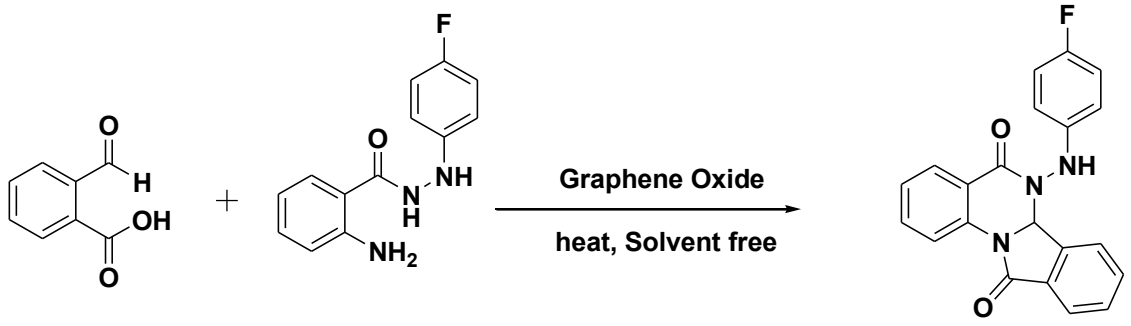
Scheme V.4. Solvent free microwave-promoted silica-propylsulfonic acid catalysed synthesis of chromeno[4,3-*b*]quinolin-6-ones

V.C. Graphene oxide catalysed organic synthesis

In recent years, there has been tremendous attention toward developing greener synthetic methods for industrial production of fine and commodity chemicals. A number of factors responsible for spreading the toxic chemical during the reaction. A huge number of graphene oxide catalysed organic synthesis reaction have reported. Very few of them are discussed here.

V.C.1. Graphene oxide catalysed synthesis of isoindolo[2,1-*a*]quinazoline-5,11-diones

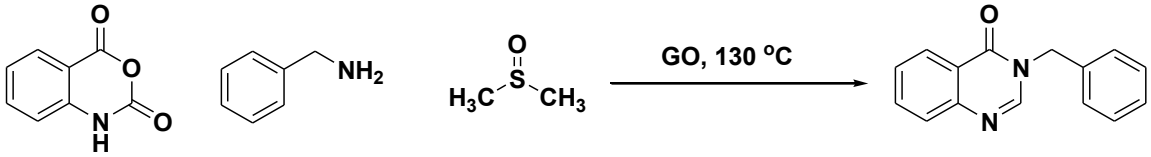
In 2018, A. Pramanik *et al.* reported a solvent free, an efficient and environmentally benign graphene oxide catalysed reaction for the synthesis of isoindolo[2, 1-*a*]quinazoline-5,11-diones from 2-carboxybenzaldehyde and 2-aminobenzohydrazides/2-aminobenzamides (Scheme V.5).[17]



Scheme V.5. Graphene oxide catalysed synthesis of isoindolo[2, 1-*a*]quinazoline-5,11-diones

V.C.2. Graphene oxide catalysed synthesis of 3-substituted quinazolinones

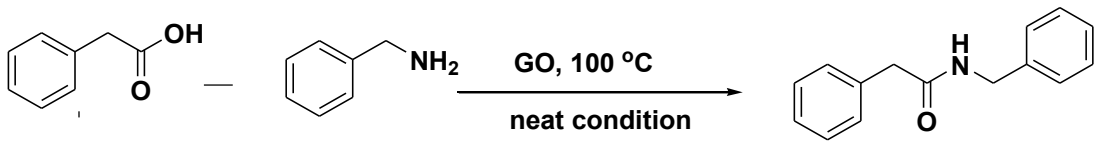
N. Kumari *et al.*[19] have been reported a metal-free graphene oxide catalysed multi-component reaction for the synthesis of 3-substituted quinazolinones by the reaction of isatoic anhydride, benzylamines and dimethyl sulfoxide at 130 ^{o}C (Scheme V.6).



Scheme V.6. Graphene oxide catalysed synthesis of 3-substituted quinazolinones

V.C.3. Graphene oxide as a metal-free carbocatalyst for direct synthesis of amide

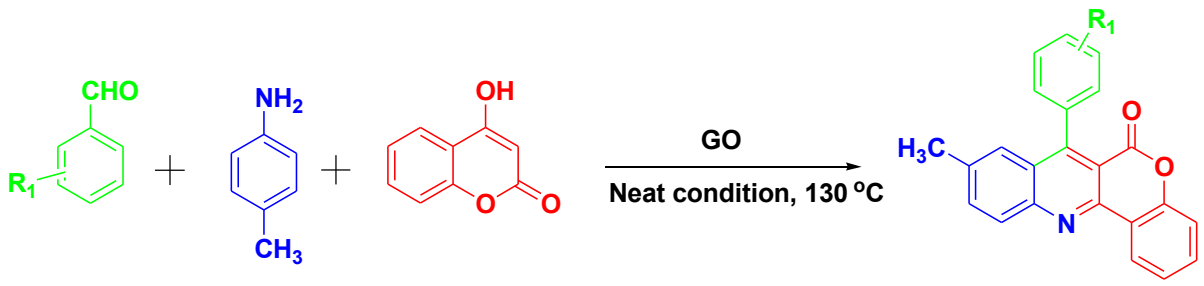
In the year of 2020, G. S. Shankarling *et al.* published a highly efficient, graphene oxide carbocatalyst direct synthesis of amides through the amidation of carboxylic acids with amines under the neat condition (Scheme V.7).[20] The reaction was afforded good yield of the desired product.



Scheme V.7. Carbocatalyst direct synthesis of amides through the amidation of carboxylic acids with amines

V.D. Present Work

Here we report graphene oxide catalysed synthesis of chromeno[4,3-*b*]quinolin-6-ones under solvent free condition at 130 ^{o}C. The heterogeneous solid acid catalyst GO was found to be highly efficient for furnishing the corresponding products good to excellent yield.



Scheme V.8. Graphene oxide catalysed synthesis of chromeno[4,3-b]quinolin-6-ones

V.D.1. Result and discussion

To start with the explorative work, 4-hydroxycoumarine (1 mmol), 4-methoxy benzaldehyde (1a, 1 mmol) and 4-methyl aniline (2a, 1 mmol), were taken as the model reaction at 130 ^{o}C under neat condition for the reaction and this was selected as optimized condition of the model reaction. Initially, the model reaction was carried out in absence of the catalyst at 130 ^{o}C under neat condition for 24 h and we did not get the expected product 3a (Table V.1, entry 1). Hence, the model reaction was repeated with varying amount of graphene oxide catalyst (Table V.1) and out of 15 attempts we get 20 mg of GO exerted the best result. The model reaction was also carried out in different solvent in order to check the yield of the product such as EtOH, Water gave low yield viz., 40%, 50%, (Table V.1, entry 3, 4). As a consequence greener solvent-free condition was chosen as the optimal medium of the reaction. The reaction was also carried out at room temperature under solvent free condition for 12 h which did not afforded the corresponding product (Table V.1, entry 13). In further attempts, the effect of temperature was tested to reduce the reaction time and to increase the yield of the product. The model reaction was carried out at different temperatures for the production of the desired product with variety of yield. As can be seen from Table V.1, yields are gradually increases with increasing temperature and the best result is obtained at 130 ^{o}C. However, the yield of the desired product considerable decrease beyond the temperature 130 ^{o}C, hence, it was chosen as acceptable temperature to produce the product with high yield.

Table V.1 Optimization of reaction parameters for the synthesis of chromeno[4,3-*b*]quinolin-6-ones in the protocol[a]

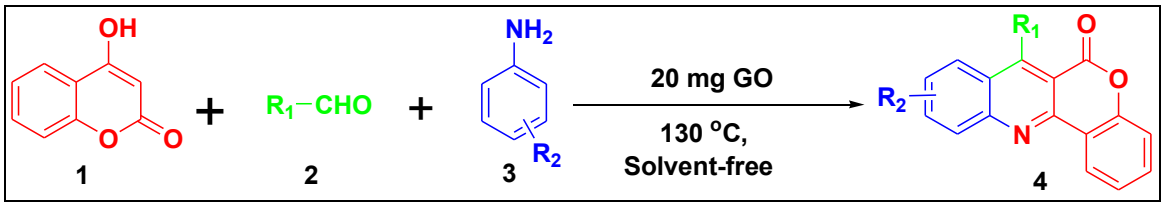
Entry	Catalyst (mg)	Solvent (10 mL)	Temperature (^{o}C)	Time (h)	Yield (%)[d] 3a
1	-[b]	-[c]	130	24	NR
2	20	-	130	10	95

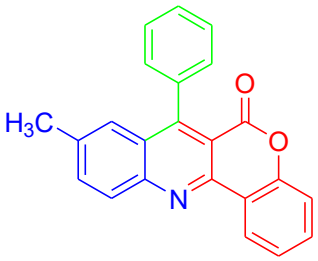
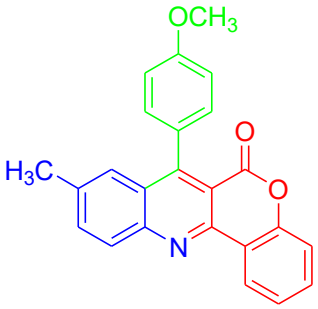
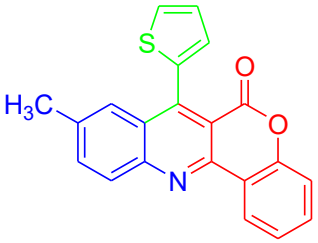
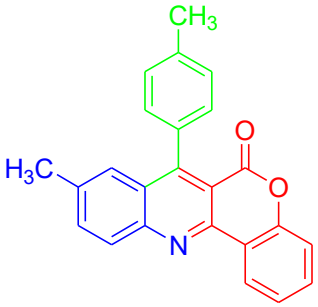
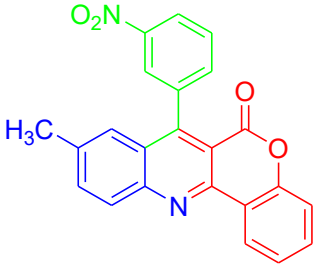
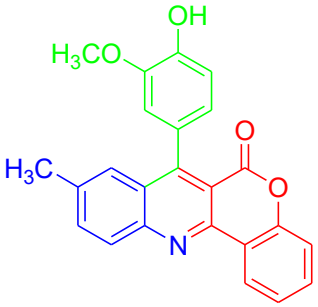
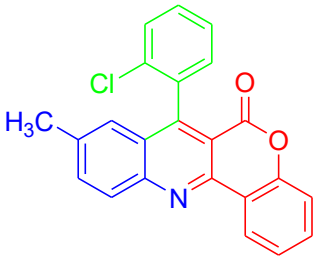
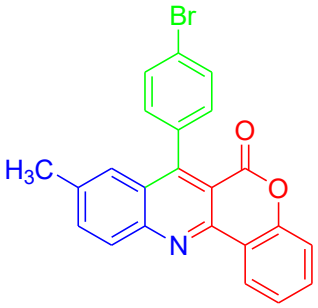
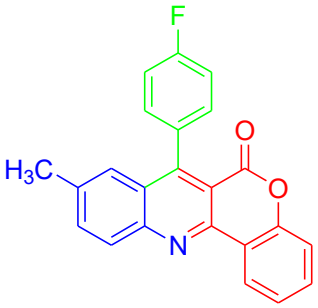
3	20	H_2O	reflux	10	40
4	20	EtOH	reflux	10	50
5	20	-	130	7	83
6	20	-	140	10	96
7	30	-	130	10	96
8	35	-	130	10	97
9	20	-	60	10	NR
10	20	-	80	10	NR
11	20	-	100	10	20
12	20	-	120	10	70
13	20	-	RT[e]	12	NR
14	15	-	130	10	60
15	10	-	130	10	40

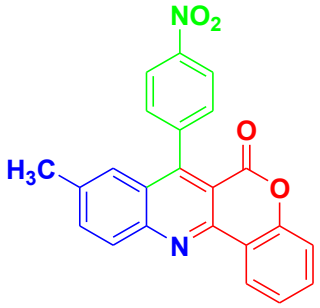
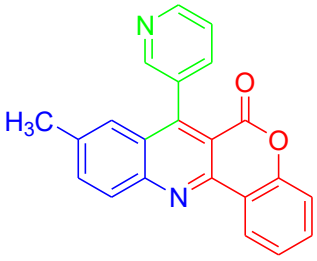
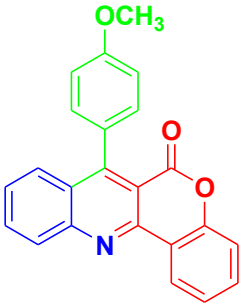
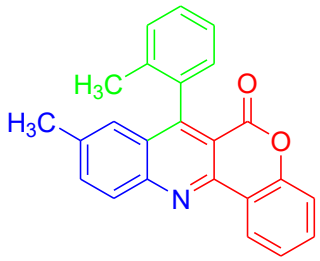
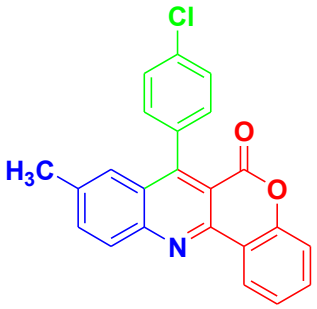
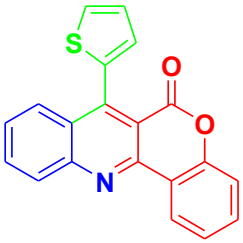
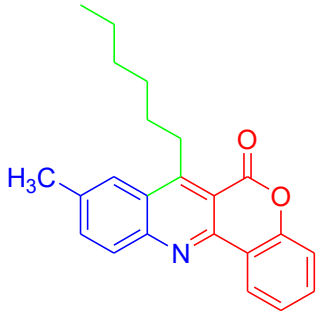
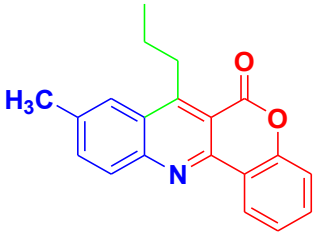
[a] Reaction conditions: 4-hydroxycoumarine (1, 1 mmol), 4-methoxy benzaldehyde (2a, 1 mmol), *p*-toludine (3a, 1 mmol), GO (20 mg) at different temperatures, [b]In absence of catalyst, [c] Under solvent-free condition, [d]Isolated yields, [e] room temperature reaction, NR= no reaction.

To examine the applicability and generality of the reaction, a variety of anilines and aldehydes with different electron donating/electron withdrawing groups were employed with 4-hydroxycoumarine. Anilines with electron donating groups afforded the desired product with high yield which might be due to the increased electron density in the aniline nucleus and hence facilitating the ortho attack (Table V.2, entries 4a-4k, 4m, 4n, 4p, 4q). On the other hand, aromatic aldehydes with a variety of groups furnished the corresponding product in good yields without any significant deviation. The above protocol was also examined in case of aliphatic aldehydes, we get the desired product but the yield was comparatively low (Table V.2, entries 4p, 4q). Heterocyclic aldehydes were also tried to determine the substrate scope of this reaction and the results afforded the desired product in good yield (Table V.2, entries 4k, 4o). From these results listed in Table V.2, it is obvious that different type of aldehydes and anilines can be successfully used in this protocol and it has wide range of substrate applicability.

Table V.2. Substrate scope of anilines and aldehydes for the synthesis of chromeno[4,3-*b*]quinolin-6-ones in the protocol[a]



 $R_1 = C_6H_5$, $R_2 = CH_3$, 4a(10 h, 85%)	 $R_1 = 4\text{-}MeOC_6H_4$, $R_2 = CH_3$ 4b(10 h, 94%)	 R_1 = Thiophene-2-yl $R_2 = CH_3$ 4c(9 h, 85%)
 $R_1 = 4\text{-}MeC_6H_4$, $R_2 = CH_3$ 4d (10 h, 90%)	 $R_1 = 3\text{-}NO_2C_6H_4$, $R_2 = CH_3$ 4e (11 h, 80%)	 $R_1 = 4\text{-}(OH)\text{-}3\text{-}(MeO)C_6H_3$ $R_2 = CH_3$, 4f (10 h, 83%)
 $R_1 = 2\text{-}ClC_6H_4$, $R_2 = CH_3$ 4g (10 h, 80%)	 $R_1 = 4\text{-}BrC_6H_4$, $R_2 = CH_3$ 4h (10 h, 85%)	 $R_1 = 4\text{-}FC_6H_4$, $R_2 = CH_3$ 4i (10 h, 70%)

 R_1 = 4-$NO_2C_6H_4$, R_2= CH_3 4j(11h, 80%)	 R_1 = Pridine- 2-yl, R_2= CH_3 4k(9 h, 85%)	 R_1 = 4-$MeOC_6H_4$, R_2= H 4l(10 h, 90%)
 R_1 = 4-MeC_6H_4, R_2= CH_3 4m(10 h, 95%)	 R_1 = 4-ClC_6H_4, R_2= CH_3 4n(10 h, 75%)	 R_1 = Thiophene-2-yl, R_2= H 4o(9 h, 75%)
 R_1 = Heptyl , R_2= CH_3 4p(12 h, 50%)	 R_1 = Butyl, R_2= CH_3 4q(12 h, 52%)	

We explored the catalytic activity of graphene oxide (GO) in the three-component condensation reaction between aldehydes, amines and 4-hydroxycoumarine as an acid promoted catalyst. The synthesis and the characterization of graphene oxide were already discussed in the chapter IV.

V.D.2. Mechanism

We were highly encourage to draw the possible mechanism of the reaction catalysed by GO from the supportive instrumental results as well as from the earlier report [21]. We assumed that, in the first step of the reaction is the condensation of aldehyde and 4-hydroxycoumarine.

The nucleophilic attack of para toluidine on the unstable adduct A (Figure V.2). Then the adduct undergo rearrangement through the transition intermediate and subsequently undergo oxidation in the presence of GO and finally furnished the desired product B.

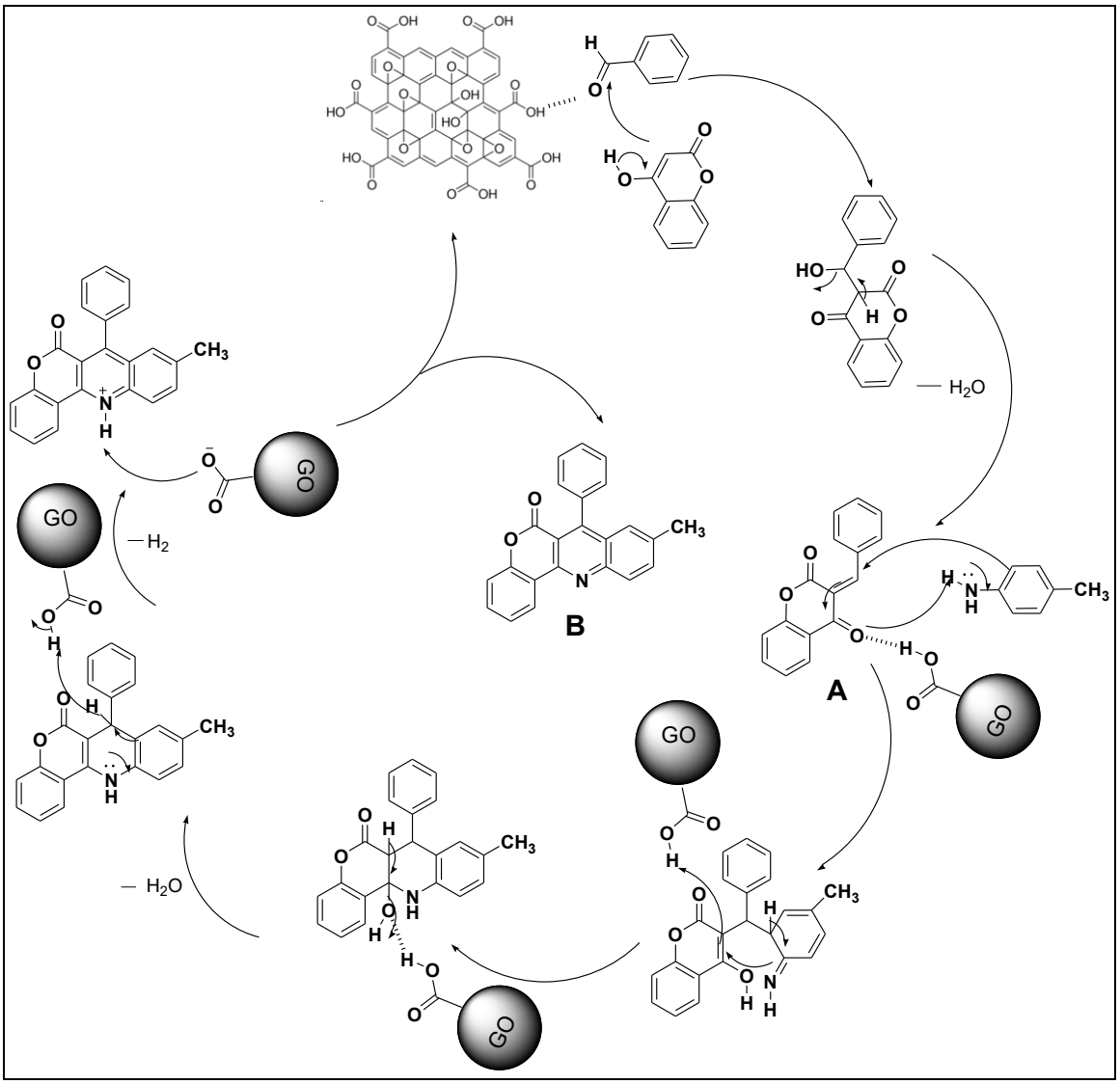


Figure V.2. Plausible mechanism of the reaction

V.D.3. Conclusion

We demonstrate a facile, efficient and environmentally benign graphene oxide one-pot multi-component reaction method for the synthesis of a variety of chromeno[4,3-*b*]quinolin-6-ones derivative from aromatic amines, aldehydes and 4-hydroxycoumarine under solvent free condition. This heterogeneous solid carbocatalyst GO was found to be highly efficient for furnishing the corresponding products good to excellent yield. GO was cheap and easy recoverable catalyst and its catalytic activity sustained up to fifth run.

V.E. Experimental

V.E.1. General Information

All reagents were purchased from Sigma–Aldrich, TCI, Alfa-Aesar and used directly without further purification. The solvents were purchased from the commercial suppliers and used after distillation. All the synthesized products were purified by column chromatography on 60-120 mesh silica gel (SRL, India). For TLC, Merck plates coated with silica gel 60, F254 were used. IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 400 MHz and 300 MHz Bruker Avance NMR Spectrometer using TMS as internal standard.

V.E.2. General procedure for the preparation of GO by modified Hummer's method

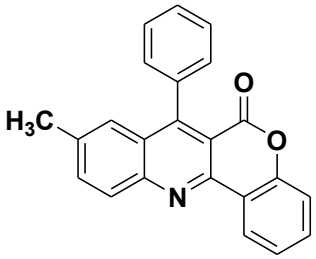
Graphene oxide (GO) was produced by modified hummers method from graphite powder. In this method, 180 mL of sulphuric acid (H_2SO_4) and 20 mL of phosphoric acid (H_3PO_4) with a volume ratio 9:1 were mixed and then 1.5 g of graphite powder was added to the solution in stirring condition. The temperature of the solution was kept below 20 ^{o}C and 9 g of potassium permanganate ($KMnO_4$) was then added slowly into it. This mixture was stirred for 12 h and small amount of hydrogen peroxide (H_2O_2) was added drop wise to eliminate excess $KMnO_4$. 30 mL of 30 % hydrochloric acid (HCl) and 200 mL of deionized water was added and centrifuged at 5000 rpm for 20 minutes. Then, the supernatant was decanted away and the residual was dried at 90 ^{o}C to get dry GO.

V.E.3. General procedure for the synthesis of chromeno[4,3-*b*]quinolin-6-ones

A 25 mL round-bottom flask was charged with aldehyde (1 mmol), aniline (1 mmol), 4-hydroxycoumarine (1 mmol) and water (5 mL) and then added graphene oxide (20 mg). The reaction mixture was stirred at 130 ^{o}C until consumption of the reactants indicated by TLC. After completion of the reaction the reaction mixture was partitioned between ethyl acetate and water and the catalyst was separated by simple filtration. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under water bath. After that the products were purified by column chromatography on 60-120 mesh silica gel.

V.E.4. Physical properties and spectroscopy data of synthesized chromeno[4,3-*b*]quinolin-6-ones

9-Methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



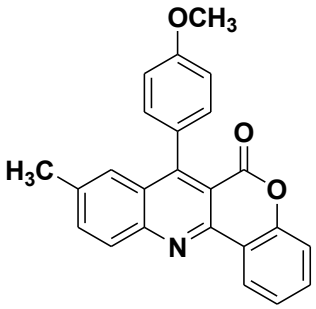
White solid, m.p: 272-273 °C.

IR (KBr, ν_{max}, cm^{-1}): 750, 830, 999, 1631, 1194, 1722, 2945, 3019.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H), 7.26-7.29 (m, 4H), 7.59 (s, 4H), 7.68-7.73 (m, 2H), 8.00-8.02 (m, 1H), 8.12 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.87, 113.42, 117.94, 121.95, 124.18, 126.75, 127.05, 127.21, 127.82, 128.00, 128.13, 128.37, 135.69, 135.76, 136.25, 137.30, 147.32, 154.72, 155.44, 157.51, 178.28.

7-(4-Methoxyphenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



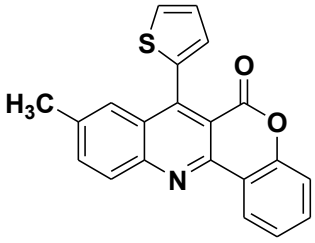
Yellow solid. m.p: 246-248 °C.

IR (KBr, ν_{max}, cm^{-1}): 750, 827, 990, 1179, 1243, 1454, 1553, 1602, 1745, 2923, 3050.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.41 (s, 41), 3.95 (s, 3H), 7.09-7.12 (m, 2H), 7.30 (d, J = 8.4 2H), 7.21-7.24 (m, 2H), 7.37-7.41 (m, 1H), 7.52-7.56 (m, 1H), 7.66 (dd, ^1J = 8.4 Hz, ^2J = 1.8 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.80 (dd, ^1J = 8 Hz, ^2J = 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.98, 55.40, 113.41, 113.88, 116.93, 120.05, 124.56, 126.86, 125.58, 128.40, 129.20, 129.29, 129.49, 132.02, 135.24, 137.28, 149.04, 149.30, 152.59, 154.76, 159.50, 159.72.

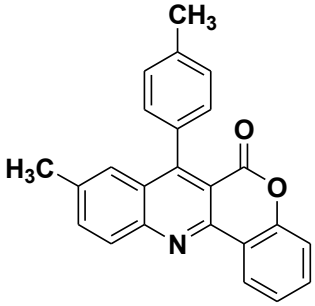
9-Methyl-7-(thiophen-2-yl)-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47 (s, 3H), 7.07-7.08 (m, 1H), 7.26-7.33 (m, 2H), 7.38-7.42 (m, 1H), 7.48 (s, 1H), 7.53-7.58 (m, 1H), 7.63-7.64 (m, 1H), 7.71 (dd, ^{1}J = 8.6 Hz, ^{2}J = 1.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.81 (dd, ^{1}J = 8 Hz, ^{2}J = 1.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.06, 114.67, 116.97, 119.87, 124.66, 125.59, 126.38, 127.04, 127.24, 127.59, 129.00, 129.29, 132.19, 135.60, 136.55, 137.87, 147.49, 149.03, 149.28, 152.55, 159.11.

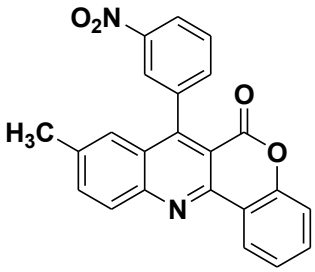
9-Methyl-7-p-tolyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 2.52 (s, 3H), 7.17 (d, J = 8 Hz, 2H), 7.26-7.33 (m, 1H), 7.37-7.42 (m, 3H), 7.53-7.57 (m, 1H), 7.69 (dd, ^{1}J = 8.8 Hz, ^{2}J = 1.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.33 (dd, ^{1}J = 8 Hz, ^{2}J = 1.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.65, 21.97, 113.34, 116.97, 120.08, 124.57, 125.59, 126.87, 127.98, 128.24, 129.12, 129.30, 129.30, 132.05, 134.16, 135.30, 137.28, 137.81, 149.10, 149.35, 152.64, 155.08, 159.66.

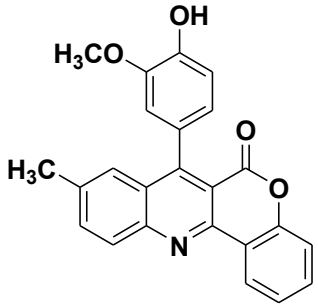
9-Methyl-7-(3-nitrophenyl)-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 7.06 (d, J = 7.2 Hz, 1H), 7.15-7.26 (m, 1H), 7.32-7.48 (m, 5H), 7.54-7.59 (m, 1H), 7.72 (dd, ^{1}J = 8.8 Hz, ^{2}J = 1.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.86 (dd, ^{1}J = 8 Hz, ^{2}J = 1.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.00, 113.55, 117.04, 120.08, 124.64, 125.55, 125.91, 126.27, 127.53, 127.70, 128.31, 129.46, 130.04, 132.13, 135.02, 135.52, 136.91, 137.61, 149.28, 149.48, 152.67, 154.65, 159.43.

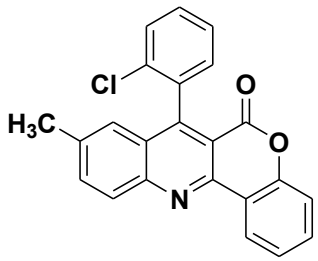
7-(4-Hydroxy-3-methoxyphenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.45 (s, 3H), 3.88 (s, 3H), 5.83 (s, 1H), 6.77-6.80 (m, 2H), 7.12 (d, J = 8 Hz, 1H), 7.26-7.33 (m, 1H), 7.37-7.43 (m, 2H), 7.53-7.58 (m, 1H), 7.70 (dd, ^{1}J = 8.6 Hz, ^{2}J = 1.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.83 (dd, ^{1}J = 7.8 Hz, ^{2}J = 1.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.01, 56.13, 111.11, 113.41, 114.50, 116.94, 120.05, 121.33, 124.60, 125.61, 126.92, 128.45, 128.90, 129.30, 132.08, 135.33, 137.37, 145.62, 146.68, 149.14, 149.36, 152.61, 154.75, 159.57.

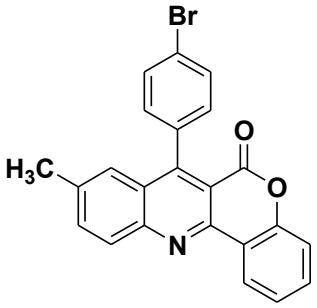
7-(2-Chlorophenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.44 (s, 3H), 7.16-7.37 (m, 3H), 7.40-7.63 (m, 5H), 7.71-7.73 (m, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.84 -8.86 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.05, 113.67, 117.07, 119.98, 124.71, 125.54, 125.88, 126.95, 127.30, 129.41, 129.55, 129.67, 129.71, 130.46, 131.64, 132.19, 132.37, 135.63, 136.31, 137.88, 149.45, 149.35, 151.31, 152.60, 159.44.

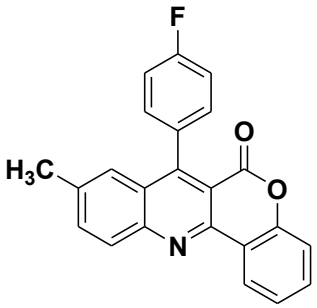
7-(4-bromophenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.44 (s, 3H), 7.16-7.21 (m, 3H), 7.32 (d, J = 8 Hz, 1H), 7.40-7.43 (m, 1H), 7.54-7.58 (m, 1H), 7.69-7.2 (m, 3H), 8.15 (d, J = 8.4 Hz, 1H), 8.82 (dd, ^{1}J = 7.8 Hz, ^{2}J = 1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.67, 153.23, 152.57, 149.31, 149.17, 137.74, 136.16, 135.53, 132.22, 131.67, 129.79, 129.45, 127.73, 126.39, 125.59, 124.72, 122.42, 119.90, 117.02, 113.15, 21.99.

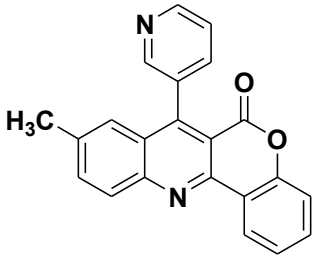
7-(4-Fluorophenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.44 (s, 3H), 7.23-7.27 (m, 5H), 7.31-7.33 (m, 1H), 7.41-7.43 (m, 1H), 7.56-7.57 (m, 1H), 7.21 (dd, ^{1}J = 8.6 Hz, ^{2}J = 2 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.83 (dd, ^{1}J = 7.6 Hz, ^{2}J = 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.95, 161.49, 159.72, 153.66, 152.58, 149.34, 149.16, 137.62, 135.47, 132.99, 132.95, 132.19, 129.90, 129.81, 129.42, 128.09, 126.50, 125.60, 124.70, 119.95, 117.00, 115.72, 115.51, 113.37, 22.00.

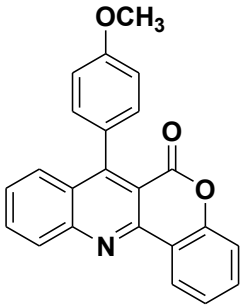
9-Methyl-7-(pyridin-3-yl)-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 7.19 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.42-7.44 (m, 1H), 7.52-7.57 (m , 2H), 7.66-7.67 (m, 1H), 7.73 (dd, ^{1}J = 8.6 Hz, ^{2}J = 1.4 Hz, 1H), 8.80-8.85 (m, 2H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.54-8.55 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.85, 152.53, 150.52, 149.38, 149.34, 149.25, 148.30, 138.06, 135.92, 135.72, 133.33, 132.34, 129.59, 127.82, 126.09, 125.61, 124.83, 123.21, 119.72, 117.05, 113.51, 22.00.

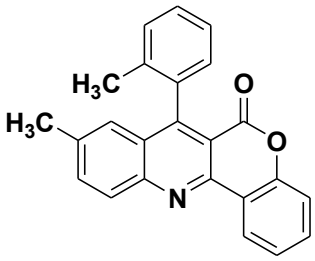
7-(4-Methoxyphenyl)-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.93 (s, 3H), 7.10 (s, 2H), 7.22 (s, 2H), 7.33 (s, 1H), 7.41-7.49 (m, 2H), 7.50-7.61(m, 2H), 7.86-7.87 (m, 1H), 8.24(s, 1H), 8.85 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.63, 159.59, 155.80, 152.78, 150.41, 150.18, 132.80, 132.32, 129.60, 129.51, 129.00, 128.48, 128.41, 127.07, 125.78, 124.63, 119.98, 117.00, 113.90, 113.46, 55.40.

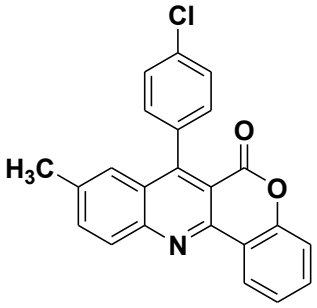
9-Methyl-7-o-tolyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.96 (s, 3H), 2.43 (s, 3H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.15-7.26 (m, 1H), 7.32-7.48 (m, 5H), 7.54-7.58 (m, 1H), 7.70-7.72 (m, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.85 (dd, ^{1}J = 7.6 Hz, ^{2}J = 1.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.44, 154.65, 152.66, 149.48, 149.28, 137.62, 136.92, 135.53, 135.02, 132.13, 130.04, 129.45, 128.32, 127.70, 127.53, 126.27, 125.92, 126.55, 124.64, 120.08, 117.04, 113.55, 22.00, 19.88.

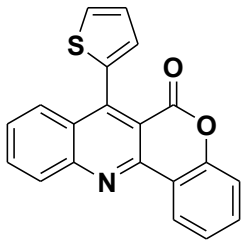
7-(4-Chlorophenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 7.16-7.26 (m, 3H), 7.31-7.33 (m, 1H), 7.40-7.43 (m, 1H), 7.54-7.59 (m, 1H), 7.70 (dd, ^{1}J= 8.6 Hz, ^{2}J = 1.6 Hz, 3H), 8.15 (d, J = 8.8 Hz, 1H), 8.82 (dd, ^{1}J = 7.8 Hz, ^{2}J = 1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 59.68, 153.23, 152.58, 149.32, 149.18, 137.74, 136.16, 135.53, 132.22, 131.68, 129.79, 129.45, 127.73, 126.39, 125.53, 124.73, 122.42, 119.90, 117.02, 113.15, 21.99.

7-(Thiophen-2-yl)-6*H*-chromeno[4,3-*b*]quinolin-6-one



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.07-7.08 (m, 1H), 7.25-7.28 (m, 1H), 7.33-7.35 (m, 1H), 7.40-7.44 (m, 1H), 7.54-7.58 (m, 2H), 7.62-7.64(m, 1H), 7.77(d, J= 8.4 Hz, 1H), 7.87-7.90 (m, 1H), 8.25 (d, J = 8.4Hz, 1H), 8.85 (dd, ^{1}J= 7.6 Hz, ^{2}J = 1.6 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.95, 152.74, 150.34, 150.13, 148.58, 136.32, 133.07, 132.47, 129.58, 129.04, 127.96, 127.75, 127.55, 127.21, 127.15, 125.79, 124.71, 119.80, 117.02, 114.73.

V.F. Scanned copies of ^{1}H NMR and ^{13}C NMR of the synthesized compounds

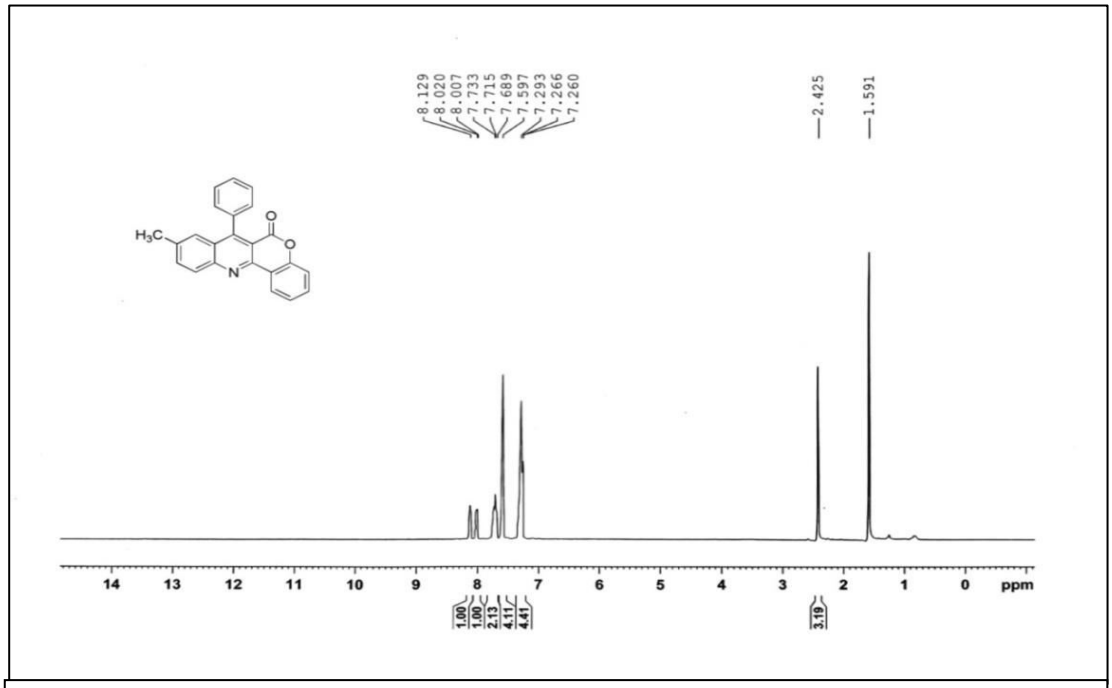


Figure V.6. ^{1}H NMR scanned copy of 9-methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

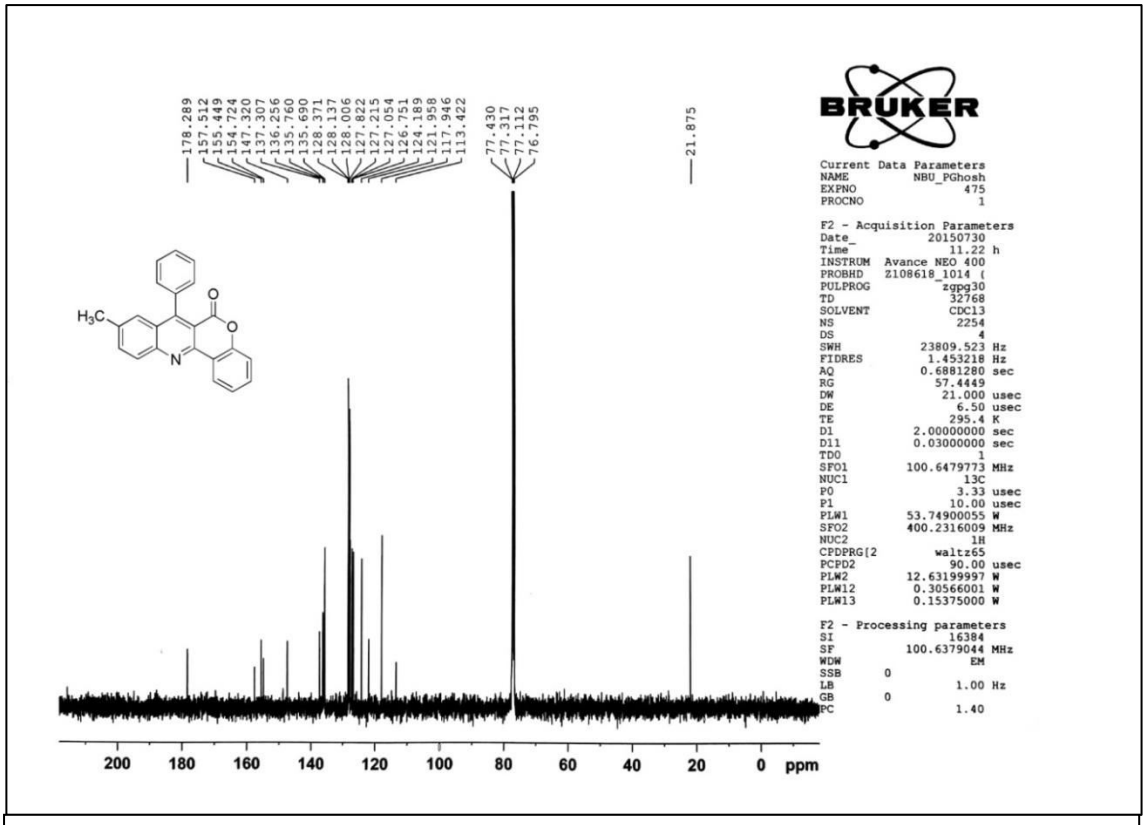


Figure V.7. ^{13}C NMR scanned copy of 9-methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

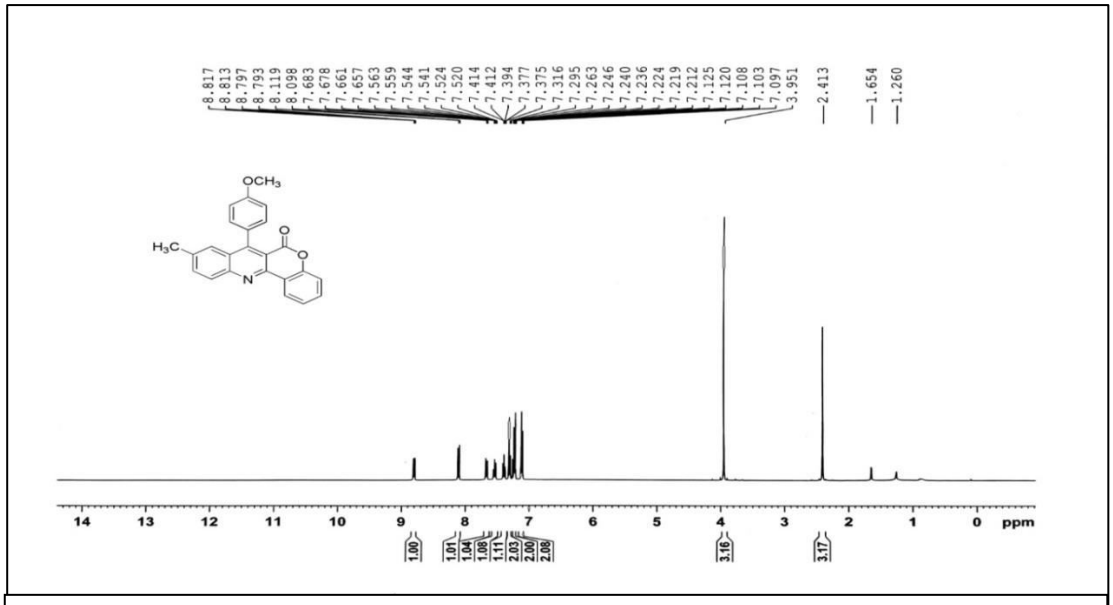


Figure V.8. ^{1}H NMR scanned copy of 7-(4-methoxyphenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

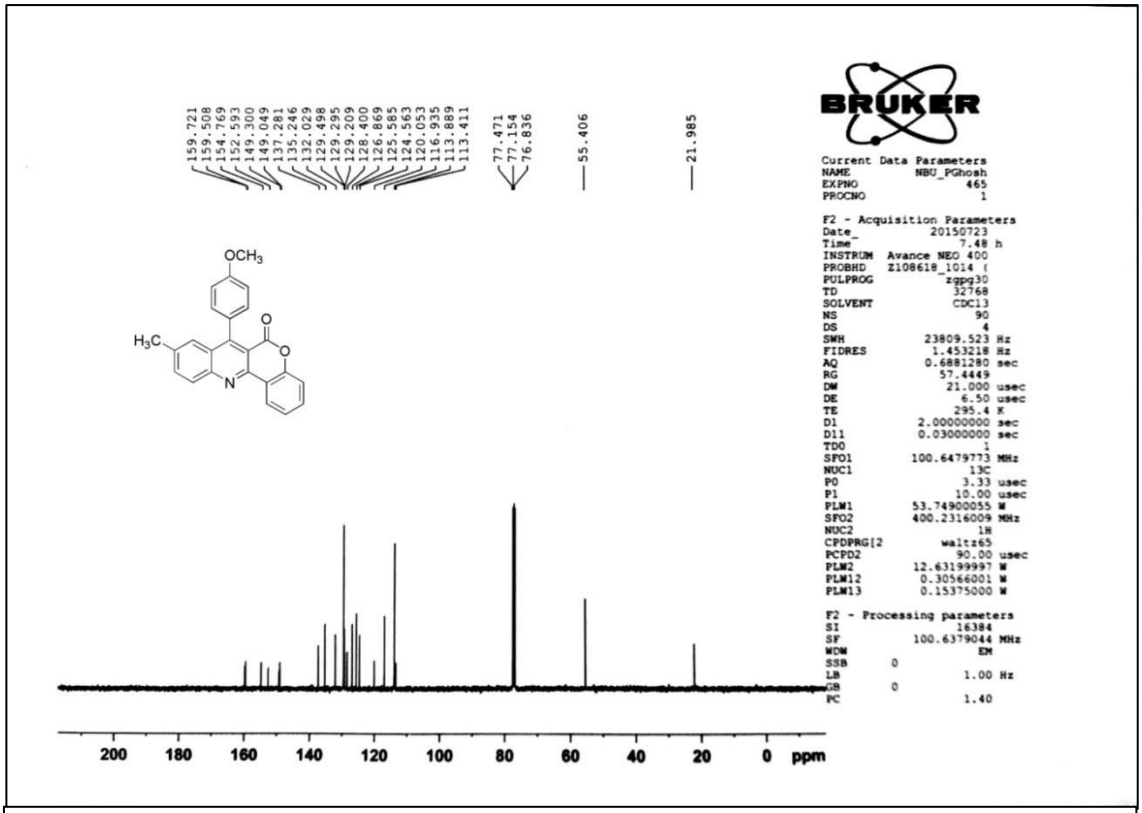


Figure V.9. ^{13}C NMR scanned copy of 7-(4-methoxyphenyl)-9-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

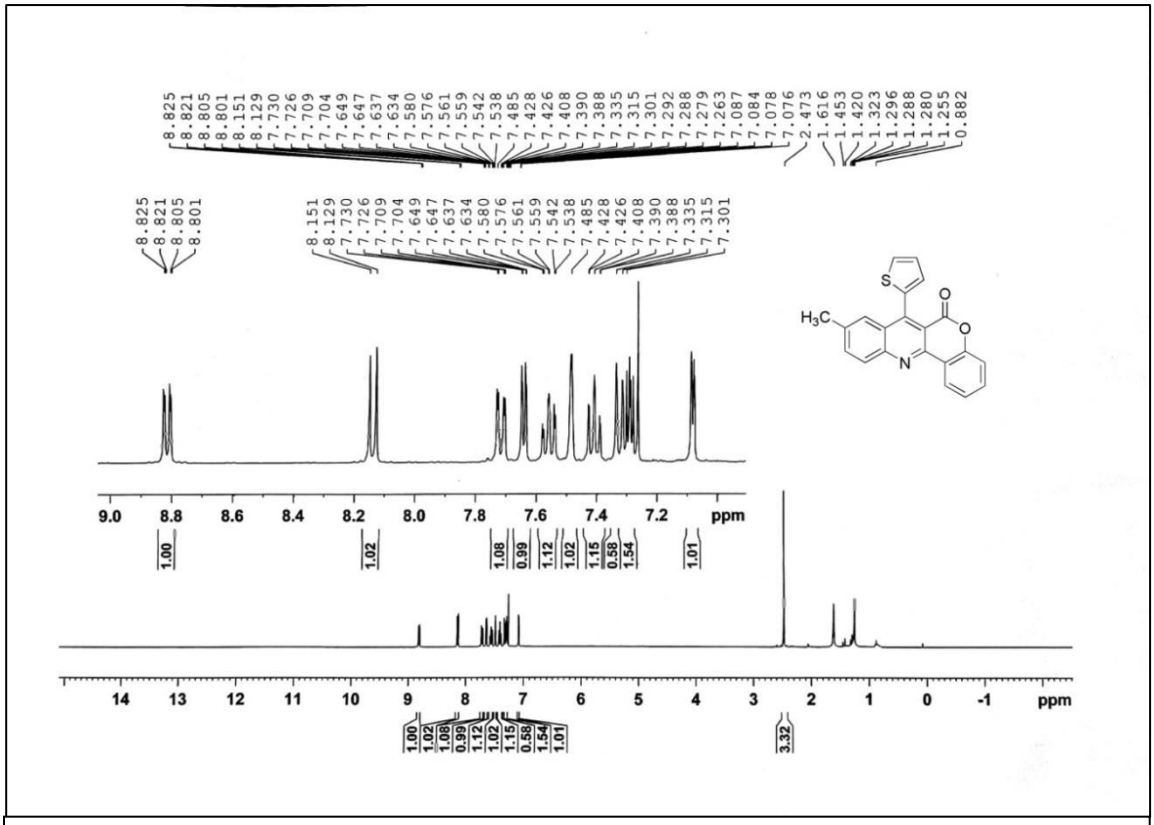


Figure V.10. ^{1}H NMR scanned copy of 9-methyl-7-(thiophen-2-yl)-6*H*-chromeno[4,3-*b*]quinolin-6-one

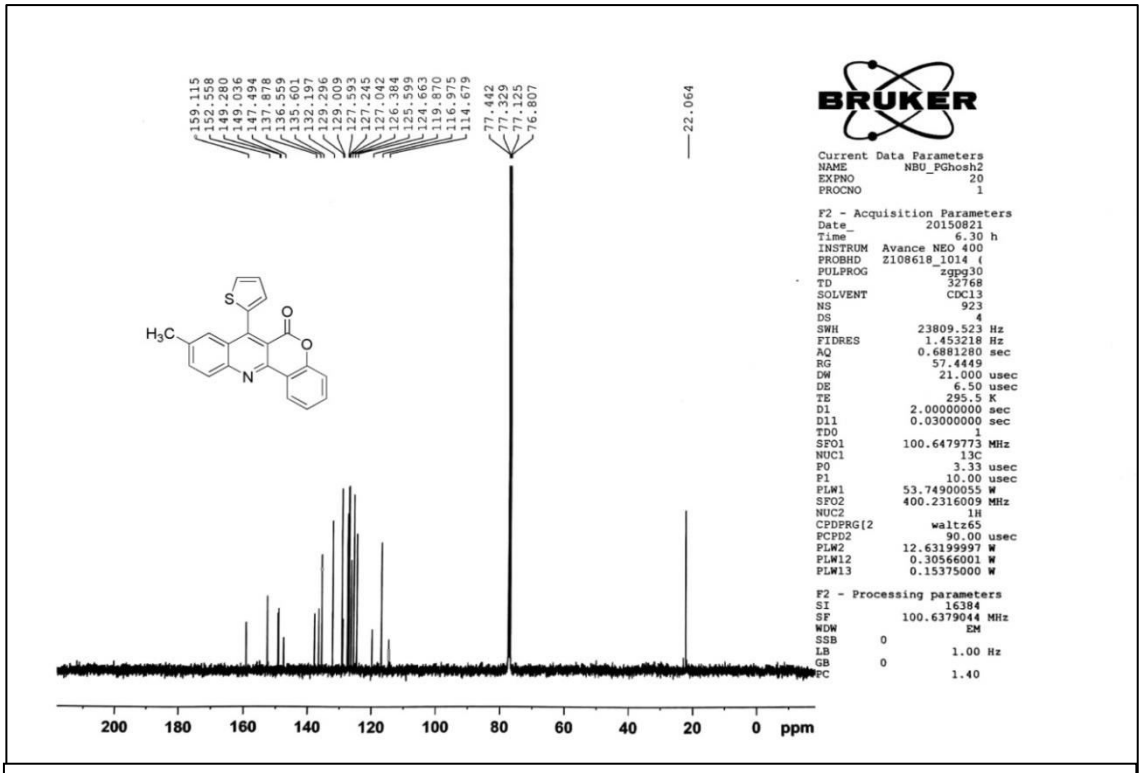


Figure V.11. ^{13}C NMR scanned copy of 9-methyl-7-(thiophen-2-yl)-6*H*-chromeno[4,3-*b*]quinolin-6-one

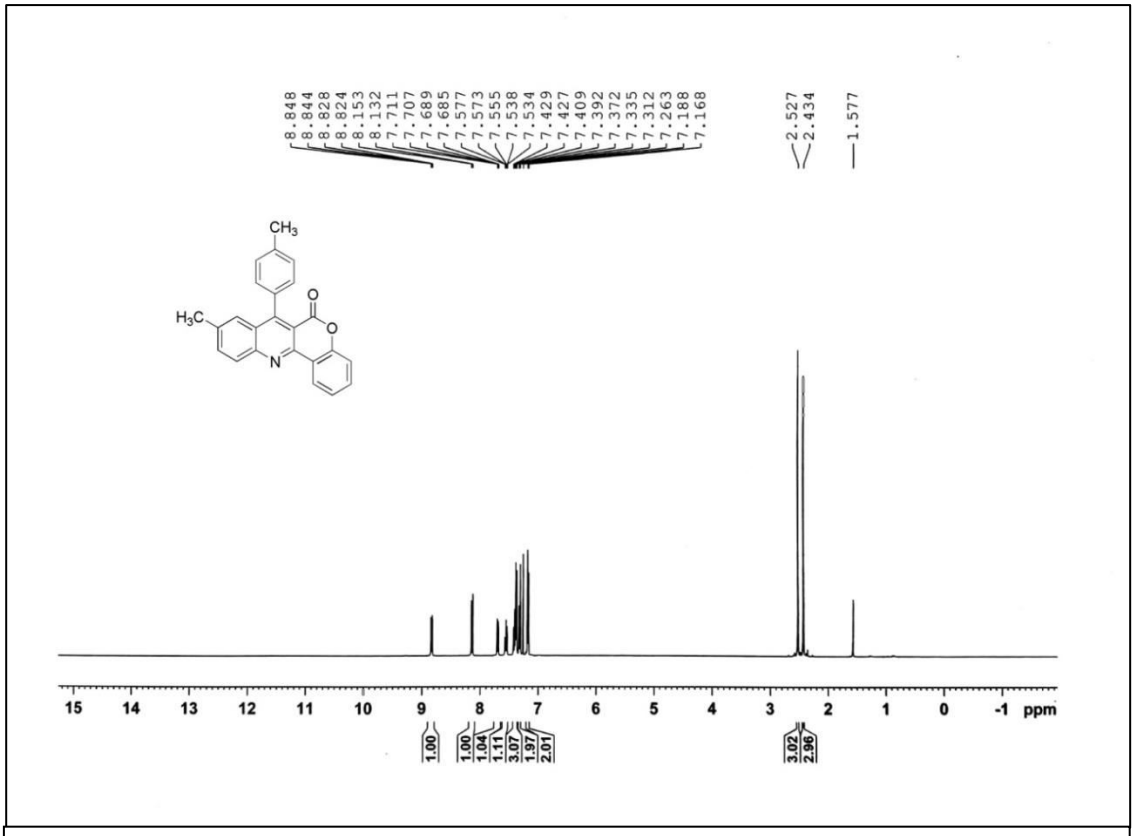


Figure V.12. [1]H NMR scanned copy of 9-methyl-7-p-tolyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

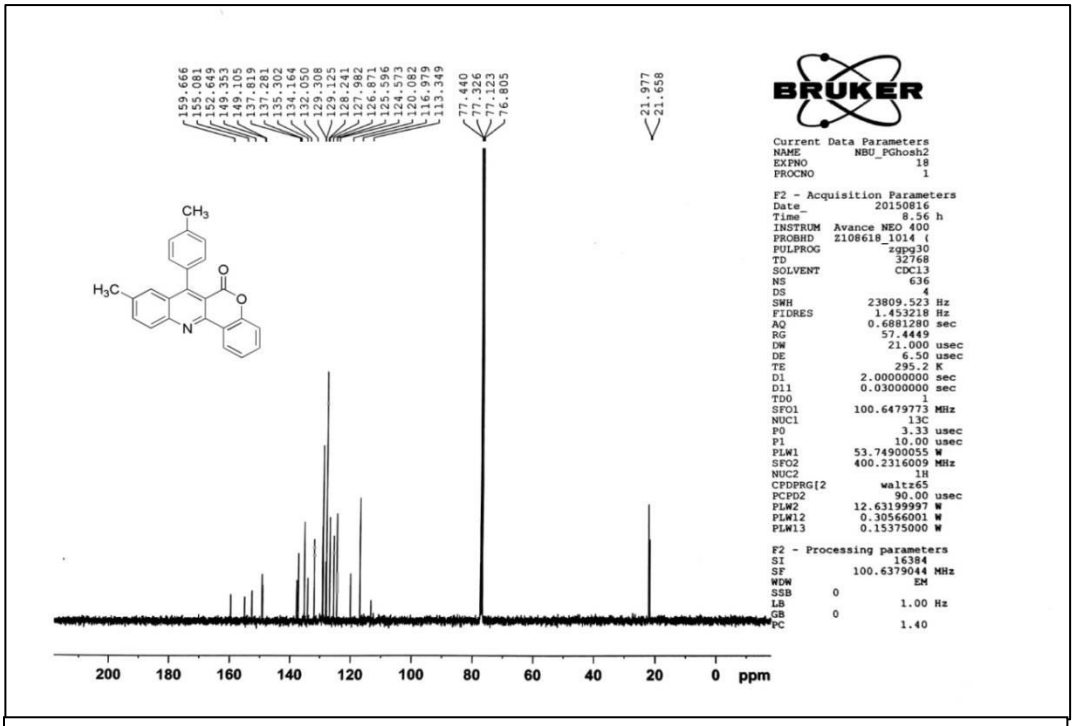


Figure V.13. ^{13}C NMR scanned copy of 9-methyl-7-p-tolyl-6*H*-chromeno[4,3-*b*]quinolin-6-one

V.G. References

References are given in BIBLIOGRAPHY under Chapter V.

Chapter VI

Transformative reaction on triterpenoids: Action of hydrogen peroxide in presence of selenium dioxide on the oxime derivative of taraxerone and antimicrobial activity of the isolated compounds

VI.A. Introduction

Taraxerone is a pentacyclic triterpenoid compound in which structure was composed of five six membered ring. It is the naturally occurring pentacyclic triterpenoid compound which naturally exists in wide range of higher plant.

Throughout history, humankind has always been wondered and interested about the naturally occurring wide range of compounds from animals, plants, microbial and prebiotic sources. Plants extracts from the different parts of plants have been widely used as a folk medicines and subsequently also been used as food flavour, perfumes, preservatives and are more commonly utilized in chronic diseases like asthma, cancer, diabetes.[1,2] Pentacyclic triterpenoids are the secondary metabolites which are widely distributed in plants and are traditionally used as chemical defense against bacteria, fungi, harmful insects and vertebrate herbivores.[3] Nowadays, this wide range of compounds draws more attention in the pharmaceutical industry because of their having wide range of medicinal properties such as antifungal, antibacterial, anticancer and anti HIV activities.[4,5] They also show the potential biological activities which including, antimicrobial, antioxidant, antiviral, antiallergic, antiangiogenic, antipruritic and spasmolytic activity.[6,7]

VI.B. Backgrounds and Objectives

VI.B.1. Pentacyclic triterpenoids

Pentacyclic triterpenoid (PT) compounds are the type of carbocyclic compounds where the five carbocyclic rings composed one-by-one along with some –Me groups and have altogether 30 carbon atom which obey the isoprene rule.[8] Pentacyclic triterpenoid are the secondary metabolites which are widely distributed in the plants. They are widely used as the traditional medicines.[9] Pentacyclic triterpenoid possesses a number of important pharmacological activities including antiviral, antimicrobial, anti-inflammatory, antitumor, antidiabetic, antiparasitic, analgesic, wound-healing effects, gastro-protective, cardio-hepato and gastro-protective activity. Nowadays a number of PTs are marketed as the therapeutic agents and consequently some of these are under clinical trials.[10]

VI.B.2. Different groups of pentacyclic triterpenoids

Depending on their basic structural skeletons, pentacyclic triterpenoids are broadly classify as 1) friedelane, 2) lupane, 3) ursane, 4) oleanane, 5) serratane, 6) Ψ-taraxastane (Figure VI.1**).**

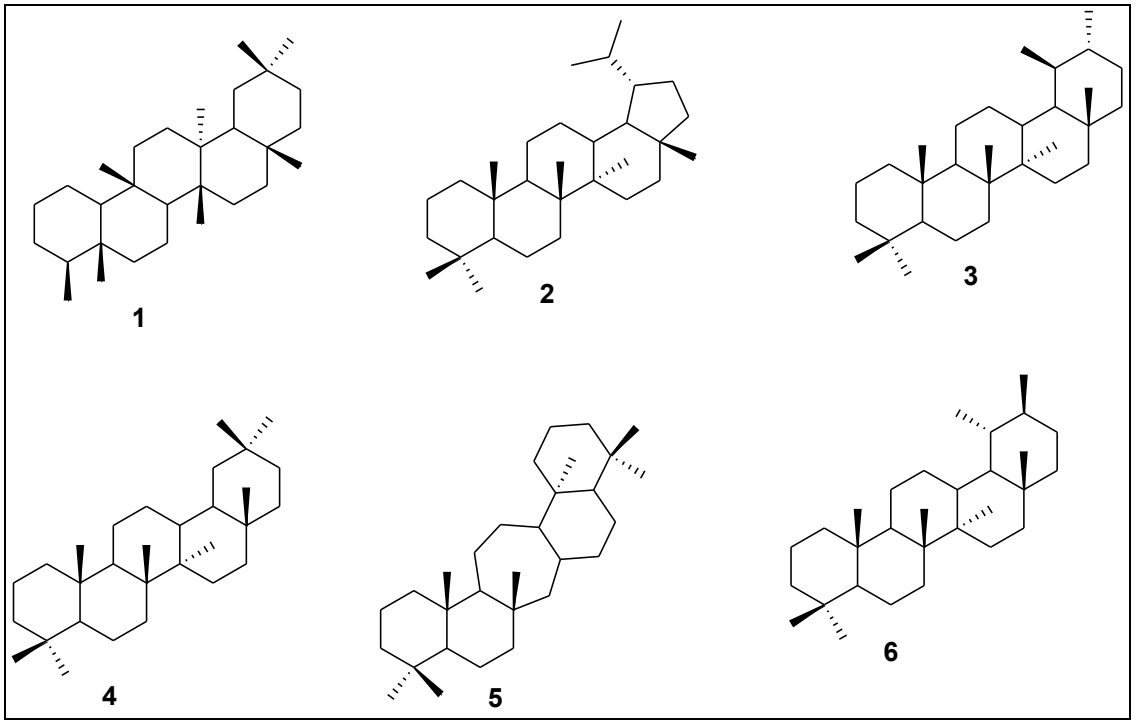
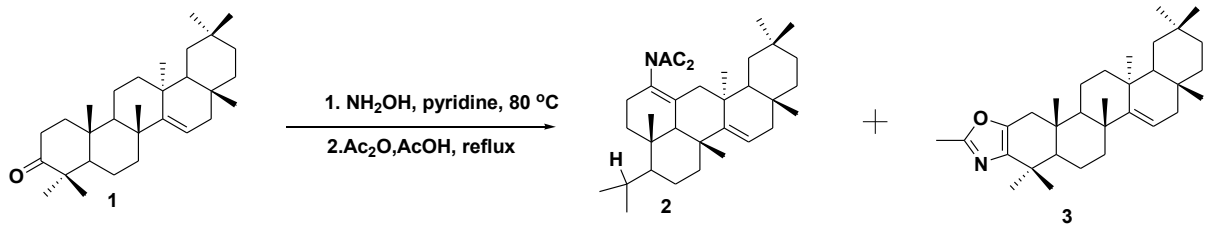


Figure VI.1. Structural skeletons of various pentacyclic triterpenoids

VI.B.3. Modern transformative reactions on pentacyclic triterpenoids

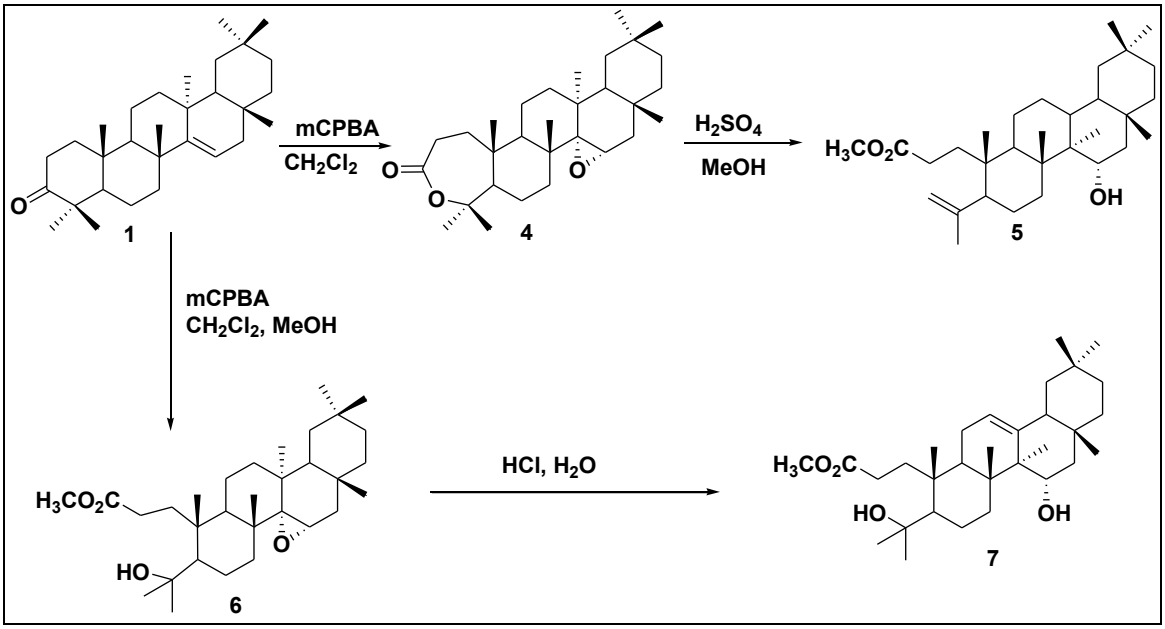
Since the transformative reactions on pentacyclic triterpenoids is very broad and elaborate subject, so here we discussed very briefly about the different transformative scopes on some major and selective pentacyclic triterpenoids. The transformative process may consist of a number of steps as well as may involve different transformative protocols.

In the year of 2014, P. M. Gianga *et al.*[11] reported unexpected course of Beckmann rearrangement of taraxerone oxime with Ac_2O/AcOH. The reaction was carried out in two steps (Scheme VI.1). They were firstly prepared the taraxerone oxime from taraxerone (1) by the treatment with hydroxylamine hydrochloride in pyridine at 80 °C. Then they were performed the Beckmann rearrangement on the taraxerone oxime with acetic anhydride and acetic acid under refluxing condition and finally they got product 2 and 3 (Scheme VI.1).



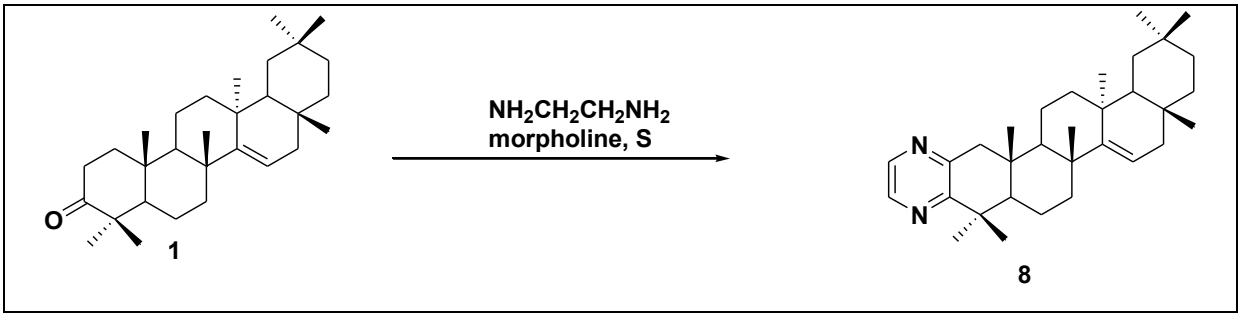
Scheme VI.1. Unexpected course of Beckmann rearrangement of taraxerone oxime with Ac_2O/AcOH

Next year P. M. Giang *et al.*[12] also reported application of the taraxerane–oleanane rearrangement to the synthesis of seco-oleanane triterpenoids from taraxerone. They carried out reaction of taraxerone (1) with *m*-chloroperoxybenzoic acid (mCPBA) in CH_2Cl_2 solution at room temperature led to the epoxidation of C-14/C-15 double bond and Baeyer–Villiger oxidation of C-3 ketonic group (4) (Scheme VI.2)**.** Further treatment of lactone ring of 4 with a catalytic amount of H_2SO_4 in MeOH yielded product 5. On the other hand, treatment of 1 with mCPBA in a mixture of CH_2Cl_2 and CH_3OH. It could be formed 14,15-epoxy-3,4-seco-taraxerane (6) followed by the treatment KOH in MeOH and then quick acidification of the hydrolysis product with 10% aqueous HCl afforded 15-hydroxyolean-12-ene (7).



Scheme VI.2. Taraxerane–oleanane rearrangement to the synthesis of seco-oleanane triterpenoids from taraxerone

R. E. Trifonov *et al.*[13] in 2017, propose a synthetic method for the synthesis of new semisynthetic taraxerone derivative fused to a pyrazine ring through the C_2–C_3 bond (Scheme VI.3).

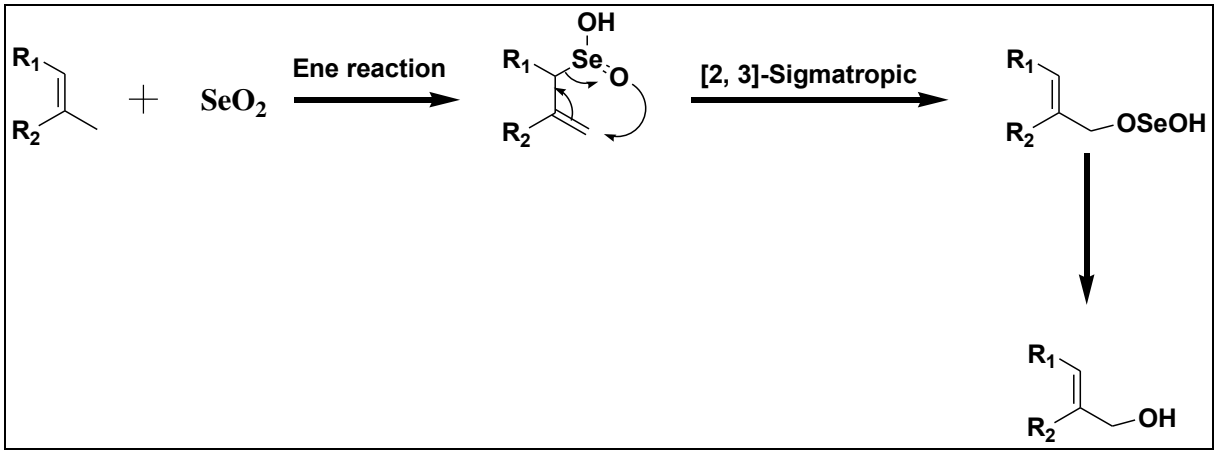


Scheme VI.3. Synthesis of pyrazine ring fused taraxerone derivative from taraxerone

VI.B.4. A short review on the action of selenium dioxide as a reagent for organic syntheses and some of it application

In the year of 1930-1932, H. L. Riley *et al.* was first reported the specific oxidizing action nature of selenium dioxide on organic compounds. By using this reagent they were able to isolate the 1,2-diketones and 1,2-ketoaldehydes from the ketones and aldehydes respectively.[14,15] A. Newman *et al.* proposed that when ethanol was heated at 230 ^{o}C with selenium dioxide then glyoxal was obtained as product but n-propyl and n-butyl alcohols on heating with selenium dioxide gave the complex product along with the alkyl selenites.[16] Aldehydes, ketones and olefins are most commonly oxidised by the reagent. Methyl or methylene groups which are adjacent to benzene ring are easily converted to aldehydes, ketones or carboxylic acids by using the selenium dioxide (SeO_2).[17,18]

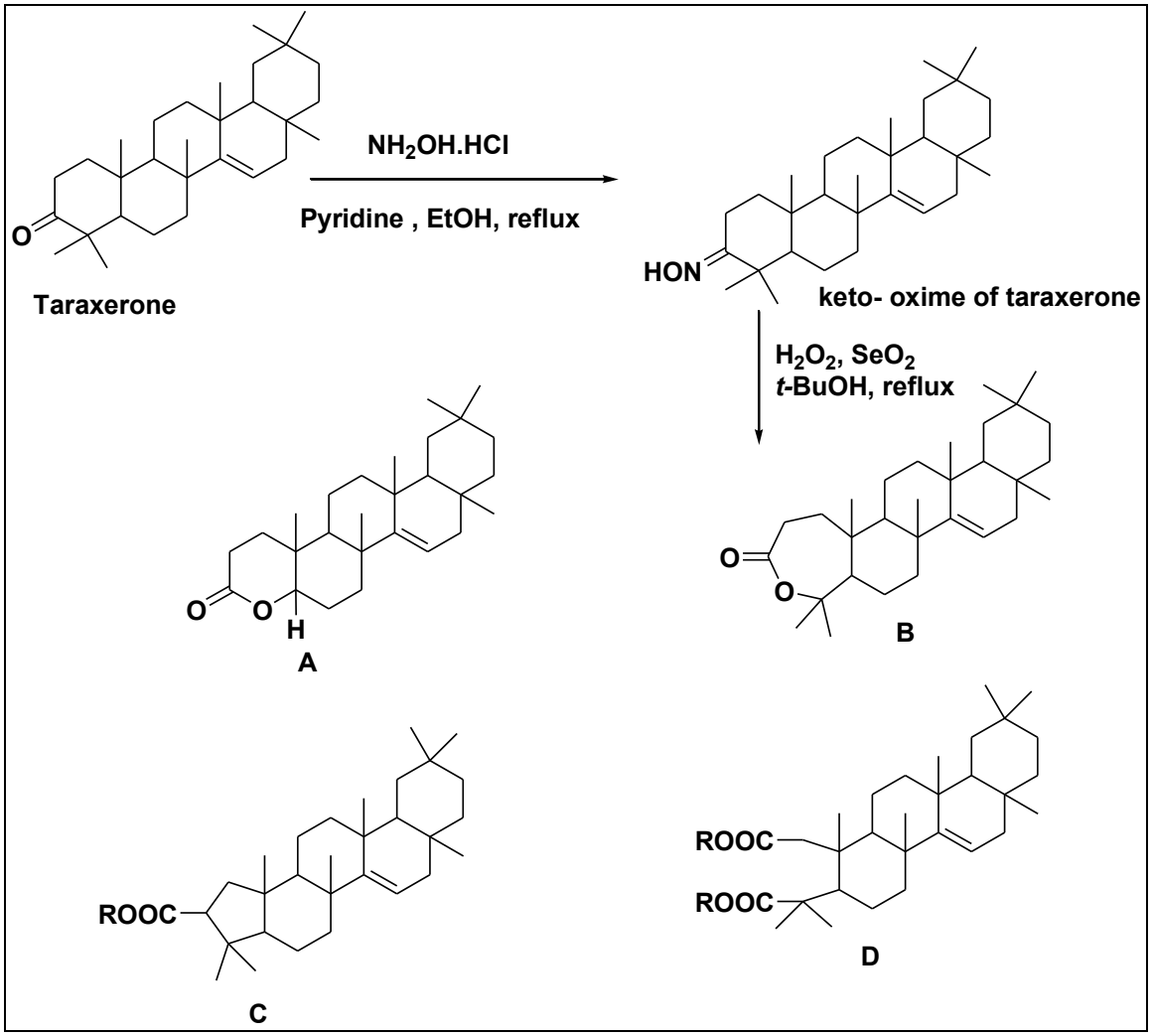
The most reliable and predictable method in the utilization of selenium dioxide was allylic hydroxylation besides the other transformative utilization.[19-25] A well-established mechanism was proposed by Sharpless which involved pericyclic reaction followed by 2, 3- sigmatropic rearrangement (Scheme VI.4).[26, 27]



Scheme VI.4. General mechanism of allylic hydroxylation with SeO_2

VI.C. Present work

Here we carried out the oxidation of keto-oximes of taraxerone with hydrogen peroxide and selenium dioxide in tertiary butanol medium. We also had done the characterisation of the products (A-D) along with the evaluation of their preliminary biological activity.



Scheme VI.5. Transformative reaction of the keto-oxime derivative of taraxerone

VI.C.1. Materials and methods:

Plants of Sapium baccatum ROXB used in this experiment were collected from North Bengal, India in May, 2016. The present author has submitted specimens of Sapium baccatum with the tag numbers to Taxonomy and Environmental Biology Laboratory, Department of Botany, University of North Bengal, Darjeeling, India. After collection, all the plants were washed thoroughly by plenty of water and stem bark were separated by simple cutting through a knife in wet condition and separated these from the rest parts. The plant's materials were shade dried and were cut into small pieces. It was then grinded in small lots to powdered form in a mechanical grinder and used for the extraction process. IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 400 and 300 MHz Bruker Avance NMR Spectrometer using TMS as internal standard.

VI.C.2. Isolation of taraxerone from sapium baccatum ROXB

Dried and powdered stem bark of Sapium baccatum ROXB (2 kgs) was extracted with toluene in a soxhlet apparatus for 20 h. On cooling the toluene extract, a yellow insoluble compound separated out, this was collected by filtration and was kept aside. This was identified as 3, 3/-di-o-methyl ellagic acid. From the clear filtrate, toluene was distilled off and the residual gummy solid (30 gms) was taken up in ether (2 ltrs). A cloudy precipitate which remained in the ether extract was separated by filtration. The clear ether solution was washed with 10% aqueous sodium hydroxide solution for three to four times and then washed with cold water till washings were neutral and dried over anhydrous Na_2SO_4.

The solvent was evaporated when the neutral material (11 gms) was obtained as a yellow gummy solid, which after chromatography and crystallisation from chloroform-methanol mixture gave shining crystals (1.3 gm), m.p 238-240 ^oC, IR spectrum appeared at 2933, 2866, 1745, 1459, 1383 cm^{-1} which was identical with the authentic sample of taraxerone. It was also identical with respect to mixed melting point, Co-TLC etc. Other compounds isolated were 1-hexacosanol, taraxerol and baccatin.

VI.C.3. Preparation of oxime derivative of taraxerone

To a solution of taraxerone (3 g) dissolved in pyridine (30 mL) was added hydroxylamine hydrochloride (3 g) and ethanol (150 mL).The mixture was then refluxed on water bath for 4 h. It was then cooled and poured over ice-cold water when white solid separated out. It was washed with water filtered through suction and dried. The dried mass was crystallised several times with chloroform-methanol mixture when taraxerone oxime m.p. 250 ^oC was obtained. The oxime derivative was further confirmed by ^1H and ^{13}C NMR data. In ^1H NMR the peak appeared at 8.40 ppm which indicate the presence of oxime -OH proton, peak appeared at 5.29 ppm indicate the presence of trisubstituted double bond proton of olefinic proton and other were appeared in the range of 0.83 to 2.45 ppm.

Then taraxerone oxime prepared from taraxerone was subjected to oxidation with molar proportion of hydrogen peroxide and catalytic amount of selenium-dioxide in tertiary butanol by refluxing over water-bath for 20 h (Scheme VI.5). The completion of the reaction was indicated by the precipitation of black selenium metal. After recovery of solvent by distillation, the residue was extracted with ether and separated into neutral and acid parts by the usual method.

The neutral part was chromatographed over silica-gel, the column on elution with petroleum ether:ethylacetate (2:3) mixture afforded a solid which on fractional crystallisation from

chloroform-methanol afforded two solid compound A and B. Compound A was analysed for $C_{27}H_{42}O_2$ and compound B was analysed for $C_{30}H_{48}O_2$.

VI.C.4. Structure elucidation of compound A

Compound A was recrystallized from chloroform-methanol mixture m.p. 228-30 ^oC. It was analysed for $C_{27}H_{42}O_2$. Its IR-spectroscopy showed sharp absorption peak at 1750 cm^{-1} indicating the presence of a lactone carbonyl group and the other at 810 cm^{-1} indicating the presence of trisubstituted double bond that was supported by TNM test. Elemental analysis showed the molecular formula of compound A found to be $C_{27}H_{42}O_2$ which is in agreement with its mass-spectrum. It showed molecular ion peak at m/z 398 (M+) with the other fragment of prominence appeared at m/z 383, 274, 259, 204. The PMR spectrum of compound A showed the presence of a lactonic proton (-CO-O-CH-CH_2-) at 3.56 as a quartet (q, *Jae* = 5 Hz, *Jaa* = 12 Hz) the appearance of multiplet at 2.10 due to presence of methylene proton adjacent (alpha) to the carbonyl group (m, 2H,-O-CO-CH_2-CH_2-), the multiplet centered at 5.66 was due to the presence of trisubstituted double bond proton of olefinic proton (m, 1H) and six tertiary methyls as singlet from 0.83 to 1.11 (6s, 18H, 6xt-CH_3). The high *J*-value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. Thus, from the study of IR, mass-spectrum and PMR spectrum the structure of the compound A has been assigned as 4, 23, 24-tri-nor-taraxerene-3-5α *H* olide (A). Elem. Anal.: C. 81.35; H. 10.62; O. 8.03; Found: C. 81.32; H. 10.60; O. 8.01.

VI.C.5. Structure elucidation of compound B

Compound B was recrystallized from chloroform-methanol mixture m.p. 218 ^oC. It was analysed for $C_{30}H_{28}O_2$. Its IR-spectroscopy showed sharp peak at 1730 cm^{-1} indicating the presence of a ϵ-lactone carbonyl group and the other at 857 cm^{-1} indicating the presence of trisubstituted double bond. The presence of the olefinic double bond is confirmed by the generation of yellow colour in TNM test. Elemental analysis showed the molecular formula of the compound B is $C_{30}H_{48}O_2$ which is in agreement with its mass-spectrum. It showed molecular ion peak at m/z 440 (M+) and the other fragments of prominence at m/z 425, 316, 301, 205, 204 and 189. Thus, from the study of IR spectrum and mass spectral analysis, the structure of the compound B has been assigned as taraxerene-ϵ-lactone.

The genesis of the ion fragment m/z 316, 301, 204 and 189 of the compound B is explained in the (Figure VI.2) shown below which stands as support for the structure (B). Elem. Anal.: C. 81.76; H. 10.98; O. 7.26; Found: C. 81.75; H. 10.97; O. 7.27.

The acid part showed two spots on chromoplate. The gummy mass was esterified with diazomethane and the products were separated by column chromatography on a deactivated

alumina column. Elution with pet.ether (b.p. 60-80 ^{o}C) furnished compound C which was crystallised from chloroform-methanol mixture and analysed for $C_{31}H_{50}O_2$ m.p. 161-163 ^{o}C. Further elution of the column with pet.ether:ethylacetate (1:1) gave a white solid compound D which was crystallised from chloroform-methanol mixture and analysed for $C_{32}H_{52}O_4$, m.p. 151 ^{o}C.

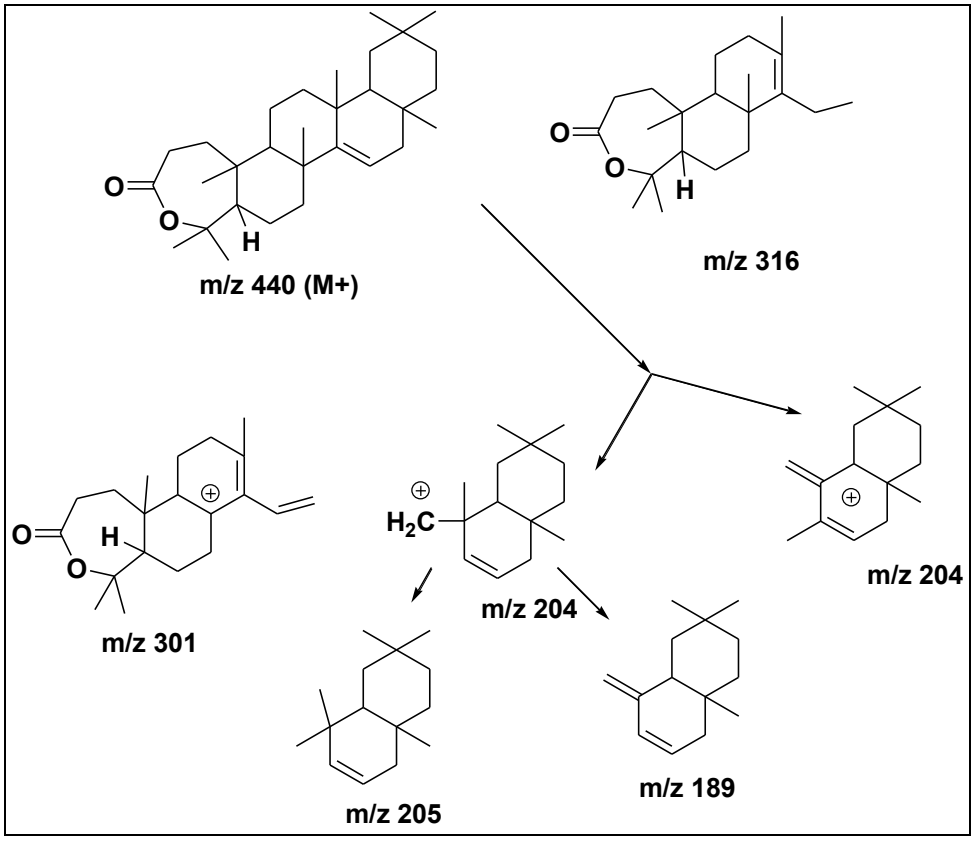


Figure VI.2. The genesis of the ion fragment of the compound B

VI.C.6. Structure elucidation of Compound C

Compound C was recrystallized from chloroform-methanol mixture m.p. 161-163 ^{o}C. It was analysed for $C_{31}H_{50}O_2$. Its IR-spectroscopy showed peak at 1730 cm^{-1} indicating the presence of carbomethoxy group, at 1144 cm^{-1} for –C-O stretching vibration of the ester group and at 814 cm^{-1} indicating the presence of trisubstituted double bond. Elemental analysis showed the molecular formula of compound C is $C_{31}H_{50}O_2$ which in agreement with its mass-spectrum. It showed molecular ion peak at 454 (M+) and the other fragments at 439, 330, 315, 287, 204. Elem. Anal.: C. 81.88; H. 11.08; O. 7.04; Found: C. 81.87; H. 11.07; O. 7.03.

The ^{1}H NMR spectrum of compound C showed the presence of eight tertiary methyl-group which resonated at (ppm) 0.82 to 1.16 (8s, 24H, 8xt-CH_3). A three proton singlet at 3.69 ppm shows the presence of carbomethoxy group in the compound (s, 3H, -$COOCH_3$). A quartet centered at 2.27 ppm integrable for one proton may be assigned to the hydrogen atom

germinal to the carbomethoxy group (q, 1H, *Jae* = 5 Hz, *Jaa* = 11 Hz, -CH_2-C-CO-O). The *J* value also indicate that the proton is axially oriented with one axial and one equatorial neighbours. The multiplet at 5.71 ppm integral for one proton indicate the presence of trisubstituted olefinic proton (m, 1H, –C=CH). Thus, on the basis of spectral data the structure of compound has been assigned as 2α-carbomethoxy-A-nor-taraxerene (C).

VI.C.7. Structure elucidation of Compound D

Compound D was recrystallized from chloroform-methanol mixture m.p. 151 ^oC. It was analysed for $C_{32}H_{52}O_4$. Its IR-spectroscopy showed absorption peaks at 1730 cm^{-1} indicating the presence of two carbomethoxy group. Stretching frequency at 813 cm^{-1} indicates the presence of trisubstituted double bond. The absorption at 1445 cm^{-1} and 1144 cm^{-1} are due to –CH_3 vibration of ester group and –C-O stretching vibration of the ester group respectively.

The ^1H NMR spectrum of the compound D showed eight singlet tertiary-methyl groups which resonated in the range 0.81-1.25 ppm (8s, 24H, 8x t-CH_3). Six protons at 3.69 ppm indicate the presence of two carbomethoxy group in the compound. The two proton multiplet centred at 2.27 ppm is attributed to a methylene group alpha to a carbomethoxy group. The multiplet centred at 5.74 ppm is due to the presence of trisubstituted double bond. The mass spectrum of the compound D showed molecular ion peak at m/z 500 (M+), 485, 470, 468, 440, 399, 376, 361, 344, 316, 287, 204. Elem. Anal.: C. 76.75; H. 10.47; O. 12.78; Found: C. 76.74; H. 10.46; O. 12.46.

All these spectral data analysis of the compound D assigned the structure as 2, 3-seco-methyl taraxerene dicarboxylate (D).

VI.D. Biocidal activity of the isolated compounds

In this present work the in vitro antifungal, antibacterial activities and the phytotoxicity of isolated taraxerone, 4,23,24-tri-nor-taraxerene-3-5α *H* olide (A), taraxerene-ϵ-lactone (B), 2α-carbomethoxy-A-nor-taraxerene (C), 2,3-seco-methyl taraxerene dicarboxylate (D), have been studied. Five different fungal pathogens namely, Colletrichum gloeosporioides, Fusarium equisitae, Curvularia eragrostidies, Alterneria alternata and Colletotrichum camelliae were used for the antifungal study. For antibacterial study Escherichia Coli, Bacillus subtilis, Staphylococcus aureus, Enterobactor were used as bacterial pathogens. Suitable strains of these organisms were procured from the microbiology laboratory of our institute (for details see experimental). MICs (minimum inhibitory concentrations) of the triterpenoids against bacterial pathogens are presented in Table 1 and 2.

Table VI.1. MICs of oxime derivative to D against different bacteria

Compounds	MIC in µg/mL against different bacterial strains			
	EC	**BS**	**SA**	**EB**
Oxime derivative	100	100	98	96
A	130	<150	100	100
B	150	100	200	100
C	200	170	130	200
D	150	150	<150	100
Ampicillin	128	64	64	128

EC- Escherichia coli, BS- Bacillus subtilis, SA- Staphylococcus aureus, EB-Enterobactor, MIC- Minimum inhibitory concentration

Table VI.2. MICs of oxime derivative to D against different fungi

Compounds	MIC in µg/mL against different fungal strains				
	CG	**FE**	**CE**	**AA**	**CC**
Oxime derivative	<5.0	20.0	40.0	10.0	<5.0
A	5.00	20.0	35.0	20.0	39.0
B	4.50	19.0	35.0	20.0	40.0
C	4.00	15.0	32.5	15.5	35.0
D	3.70	10.5	30.5	15.0	32.5
Bavistin	3.50	3.50	3.70	4.00	4.20

CG- Colletotrichum gloeosporioides, FE- Fusarium equisiti, CE- Curvularia eragrostidis, AA- Alternaria alternata, CC- Colletotrichum camelliae

VI.E. Conclusion

Taraxerone was isolated from the toluene extract of stem bark of *Sapium baccatum*. Oxidation of its keto-oxime derivative with SeO_2-H_2O_2 in tert-butanol yielded two lactones, a nor acid and a seco dicarboxylic acid. It is very interesting that the oxidation was limited within ring A of the pentacyclic triterpenoid of friedelin skeleton. Biological activity of the compounds has encouraged us to carry out explorative studies with them and also with similar naturally available compounds as well as on their prepared derivatives.

VI.F. Scanned copies of ^{1}H NMR and ^{13}C NMR of the synthesized compounds

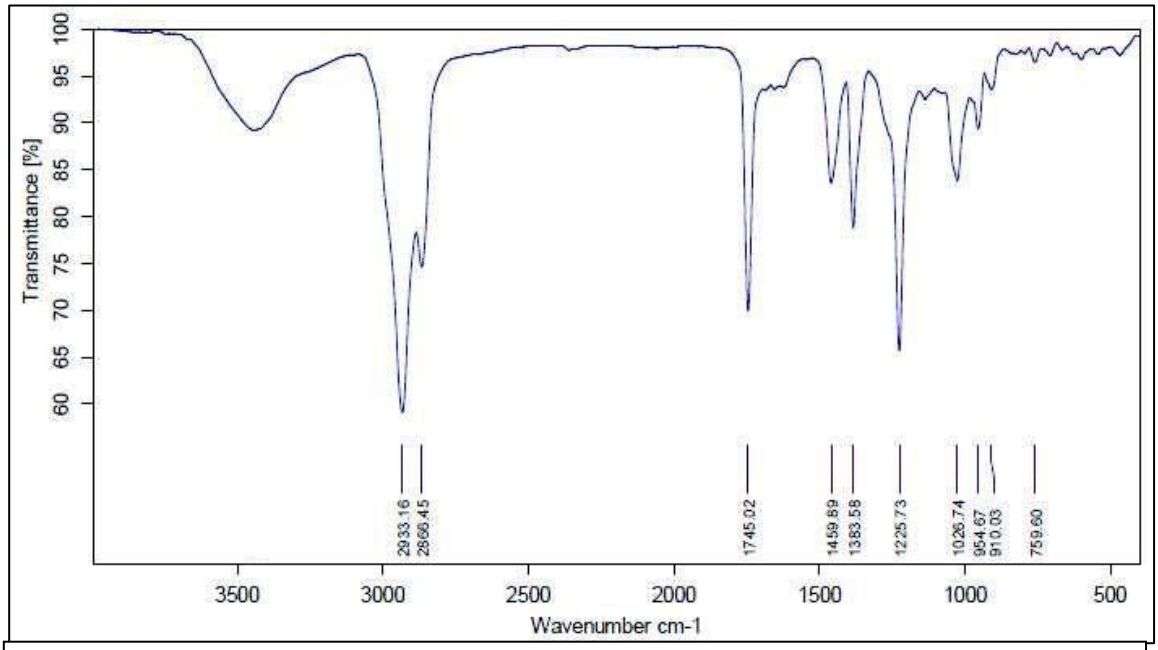


Figure VI.3. IR scanned copy of taraxerone

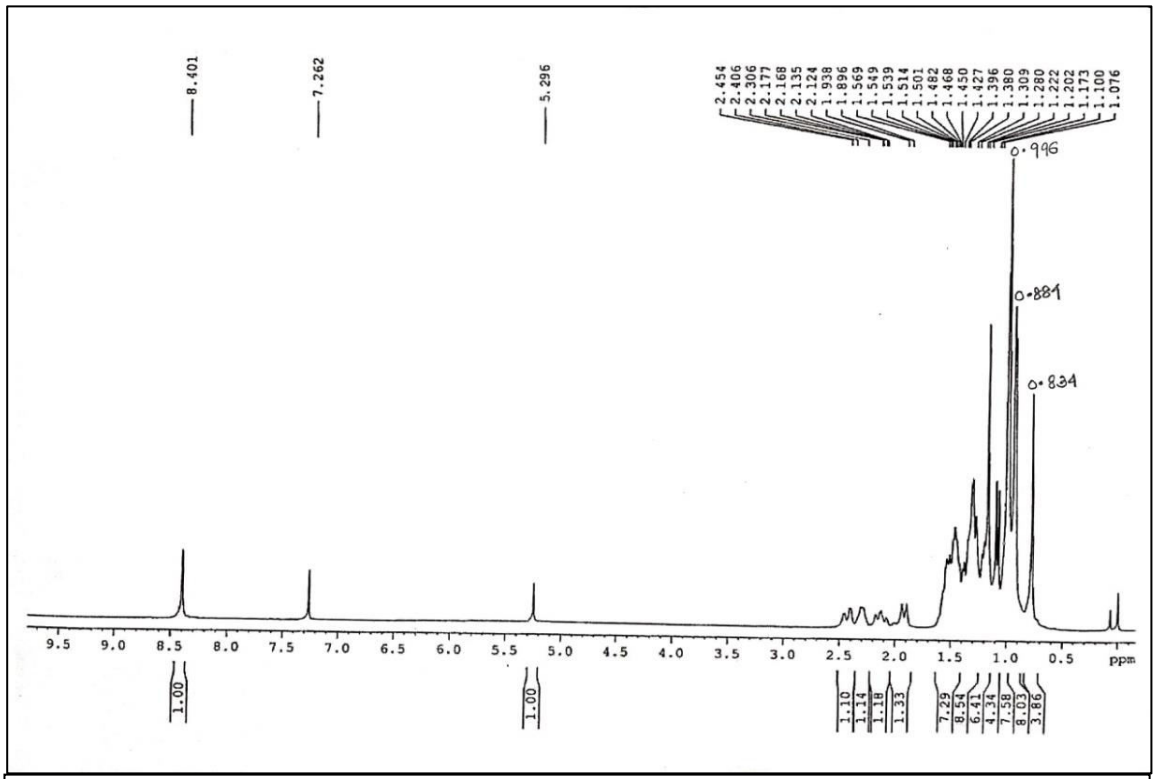


Figure VI.4. ^{1}H NMR scanned copy of taraxerone oxime

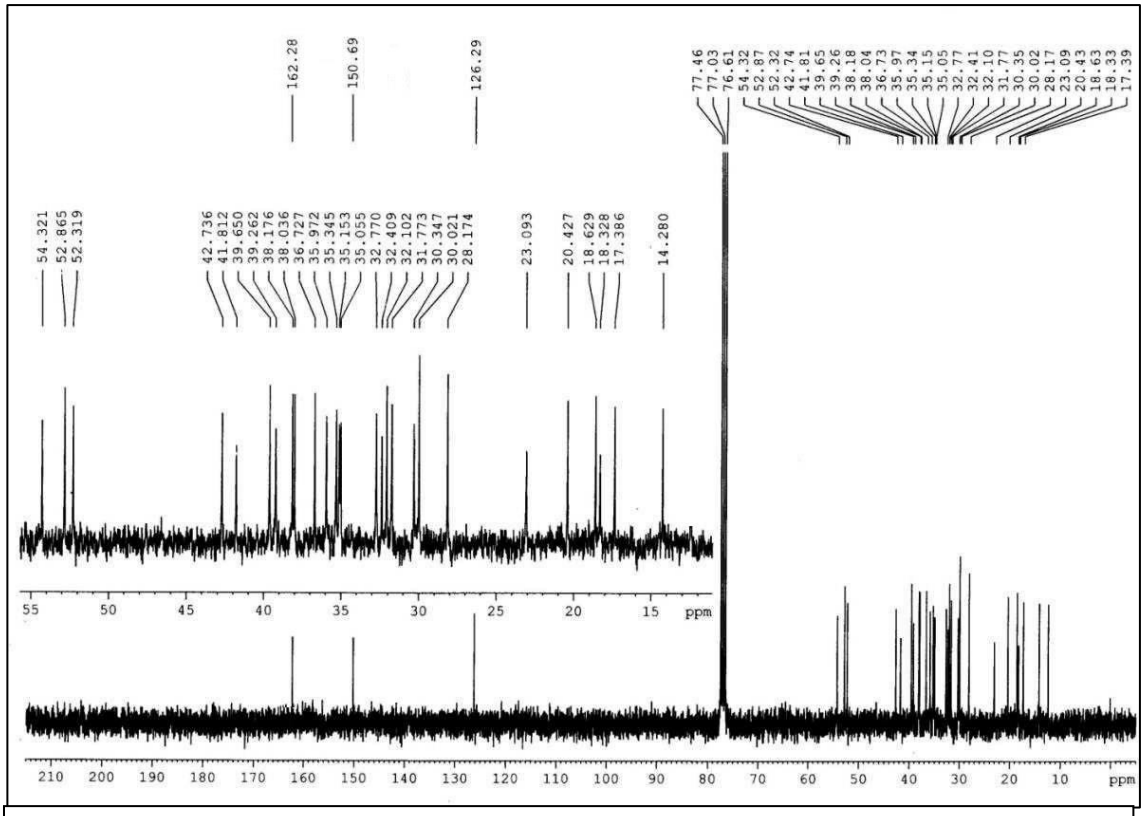


Figure VI.5. ^{13}C NMR scanned copy of taraxerone oxime

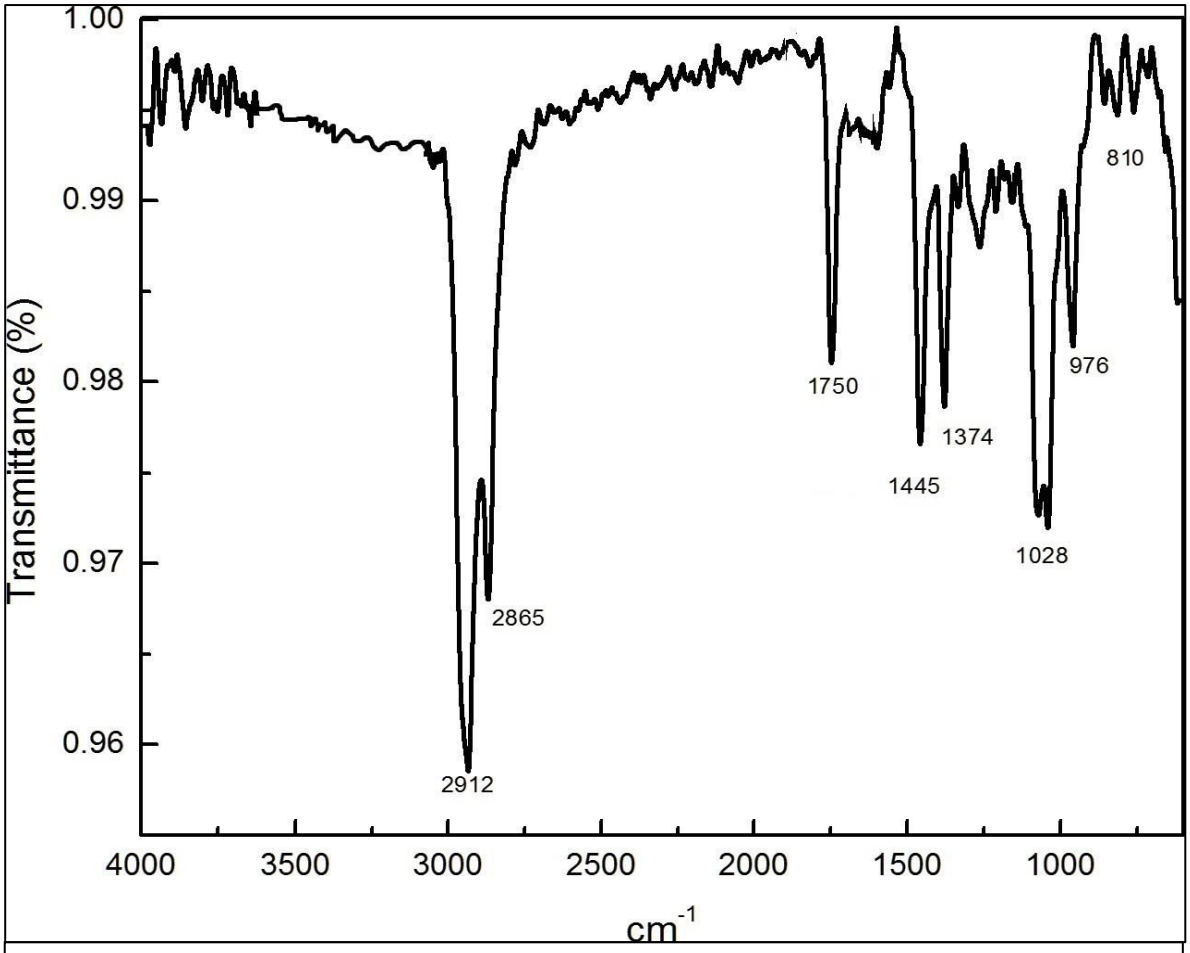


Figure VI.6. IR scanned copy of 4, 23, 24-tri-nor-taraxerene-3-5α *H* olide (A)

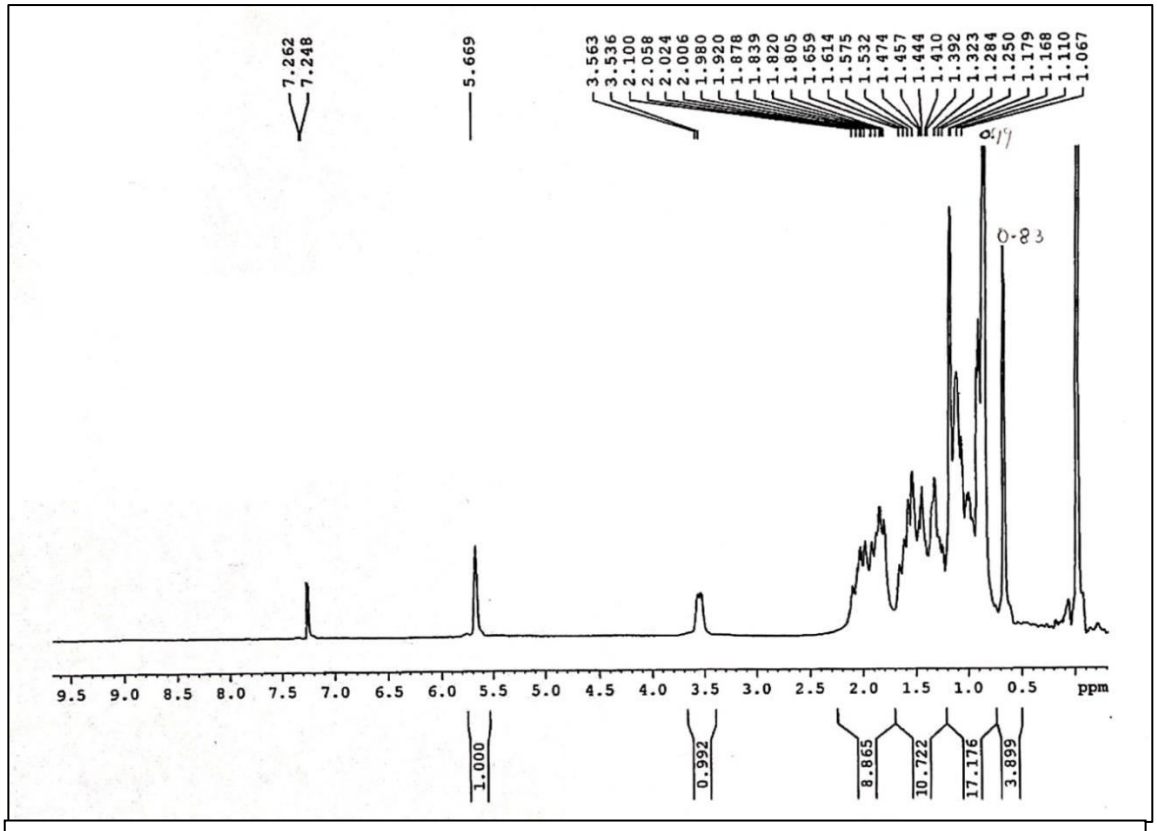


Figure VI.7. ^{1}H NMR scanned copy of 4, 23, 24-tri-nor-taraxerene-3-5α *H* olide (A)

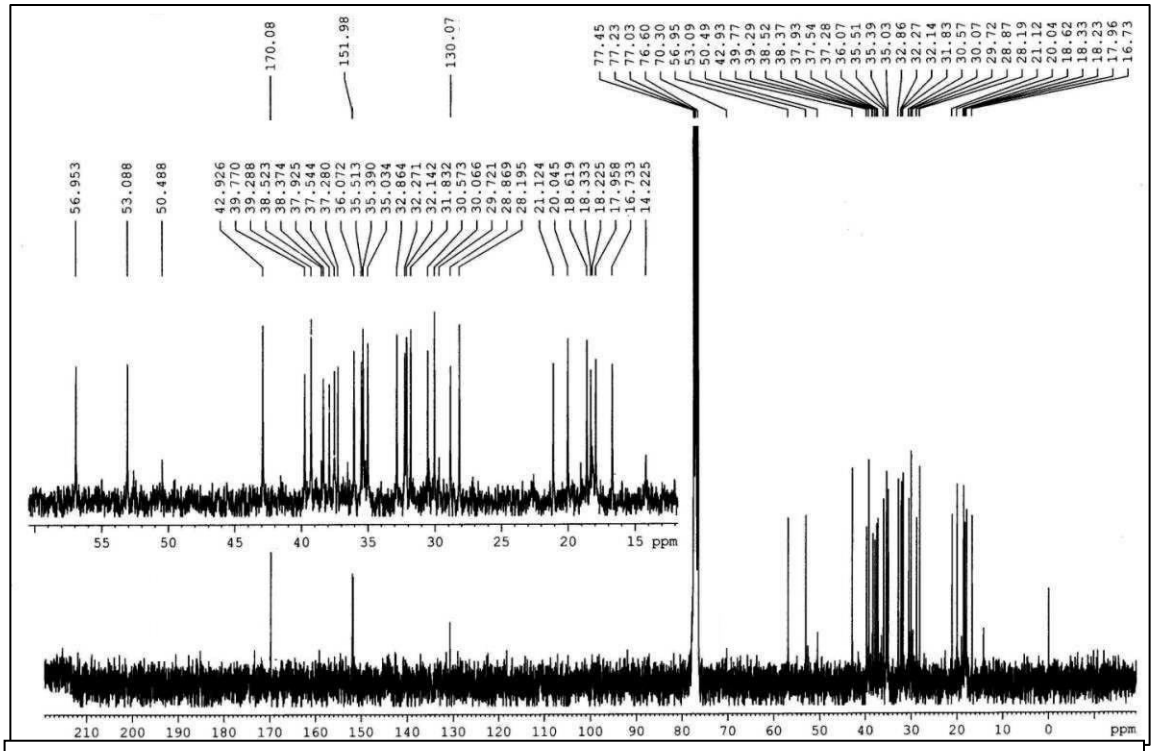


Figure VI.8. ^{13}C NMR scanned copy of 4, 23, 24-tri-nor-taraxerene-3-5α *H* olide (A)

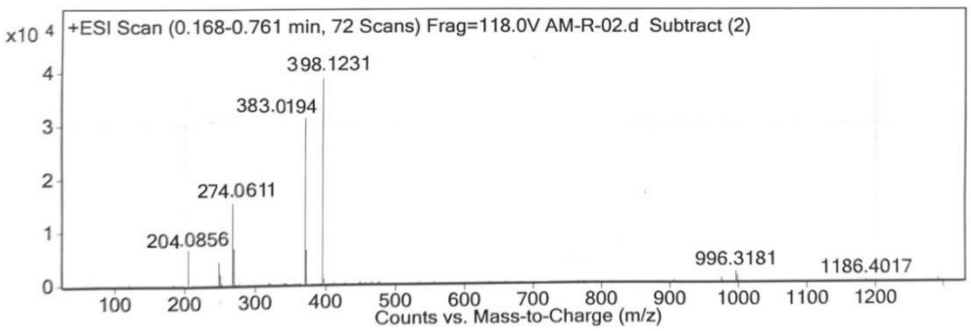


Figure VI.8. Mass scanned copy of 4, 23, 24-tri-nor-taraxerene-3-5α *H* olide (A)

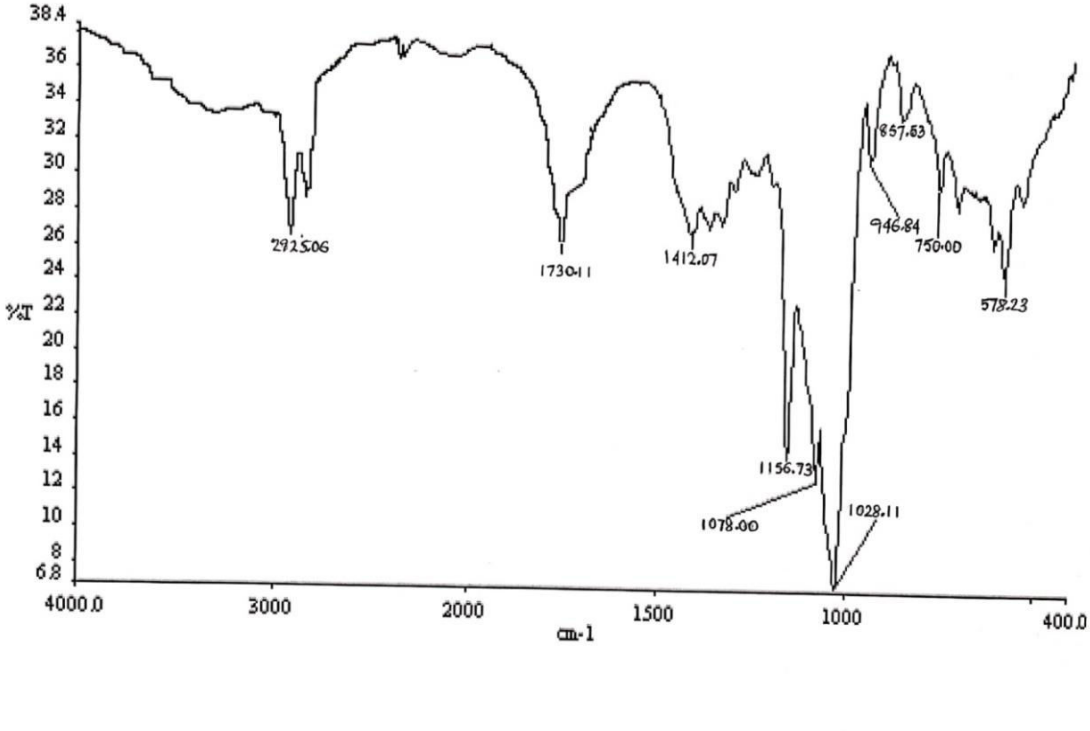


Figure VI.9. IR scanned copy of taraxerene-ϵ-lactone (B)

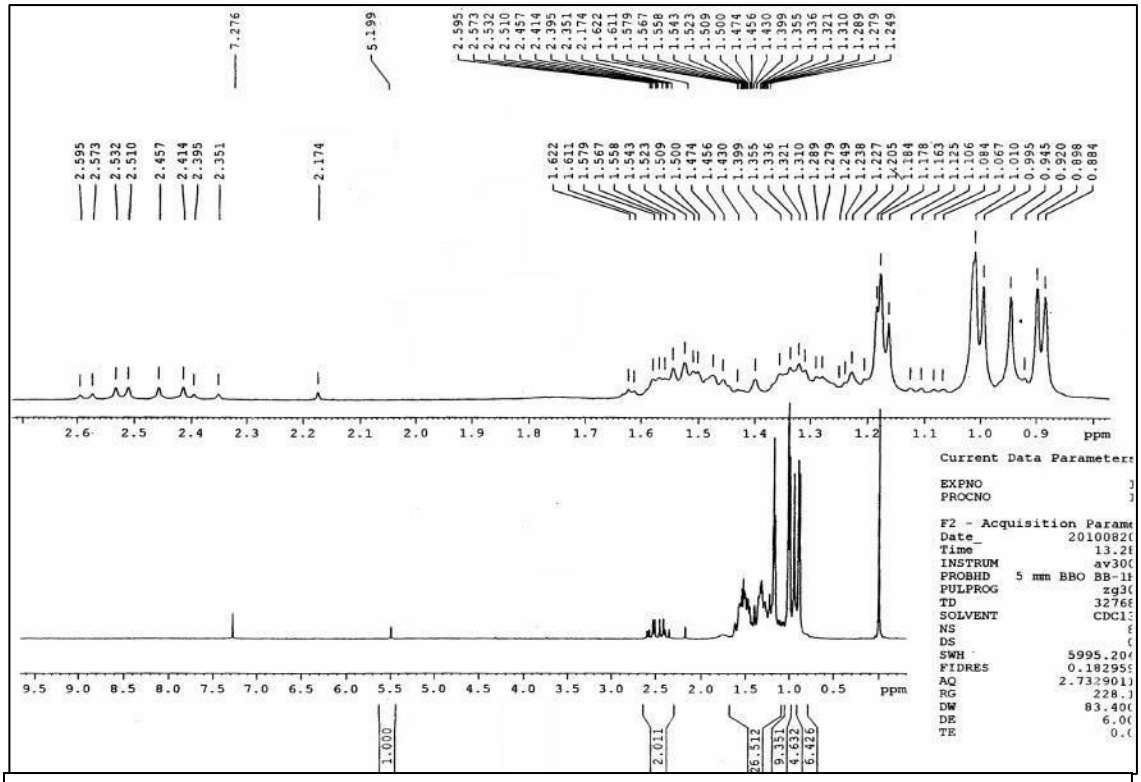


Figure VI.10. ^{1}H NMR scanned copy of taraxerene-ϵ-lactone (B)

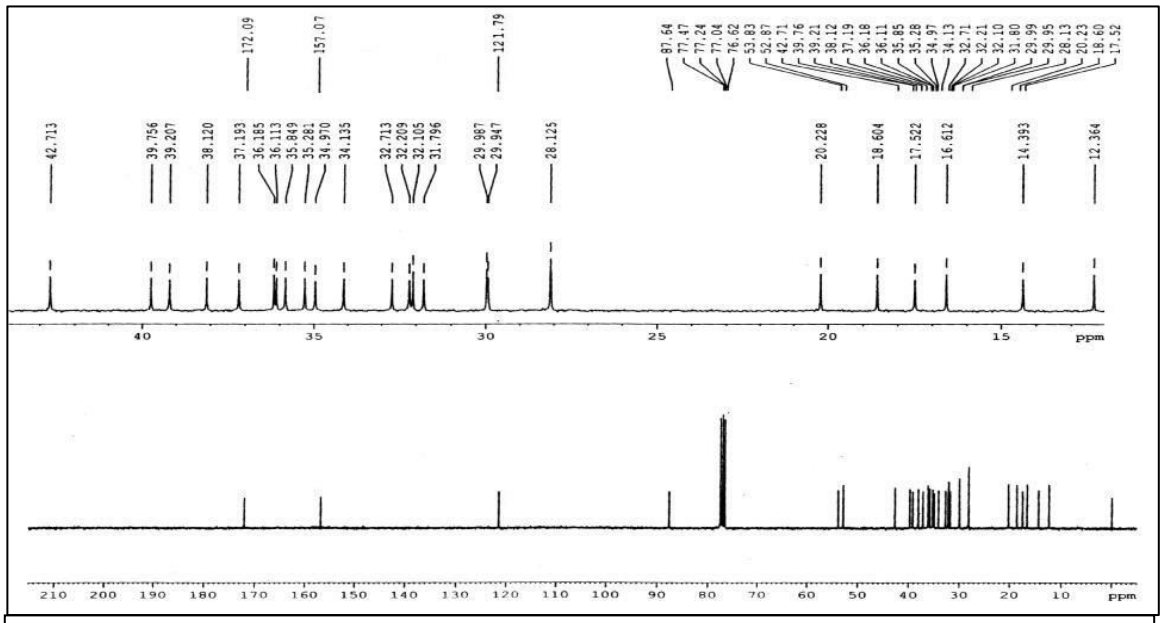


Figure VI.11. ^{13}C scanned copy of taraxerene-ϵ-lactone (B)

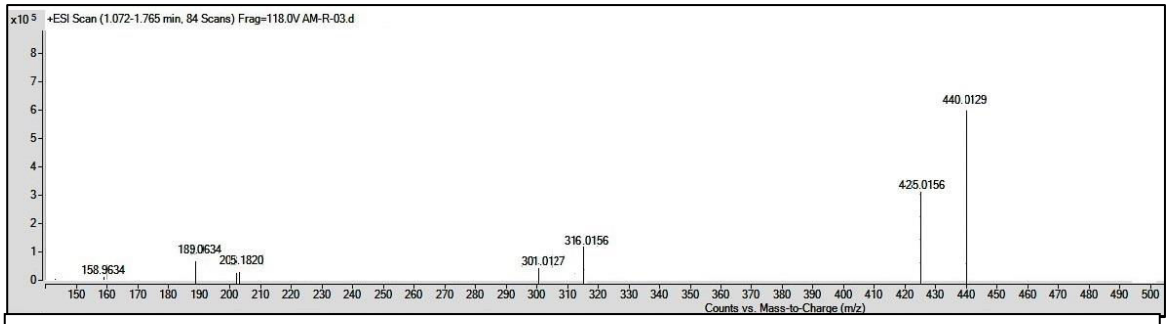


Figure VI.12. Mass scanned copy of taraxerene-ϵ-lactone (B)

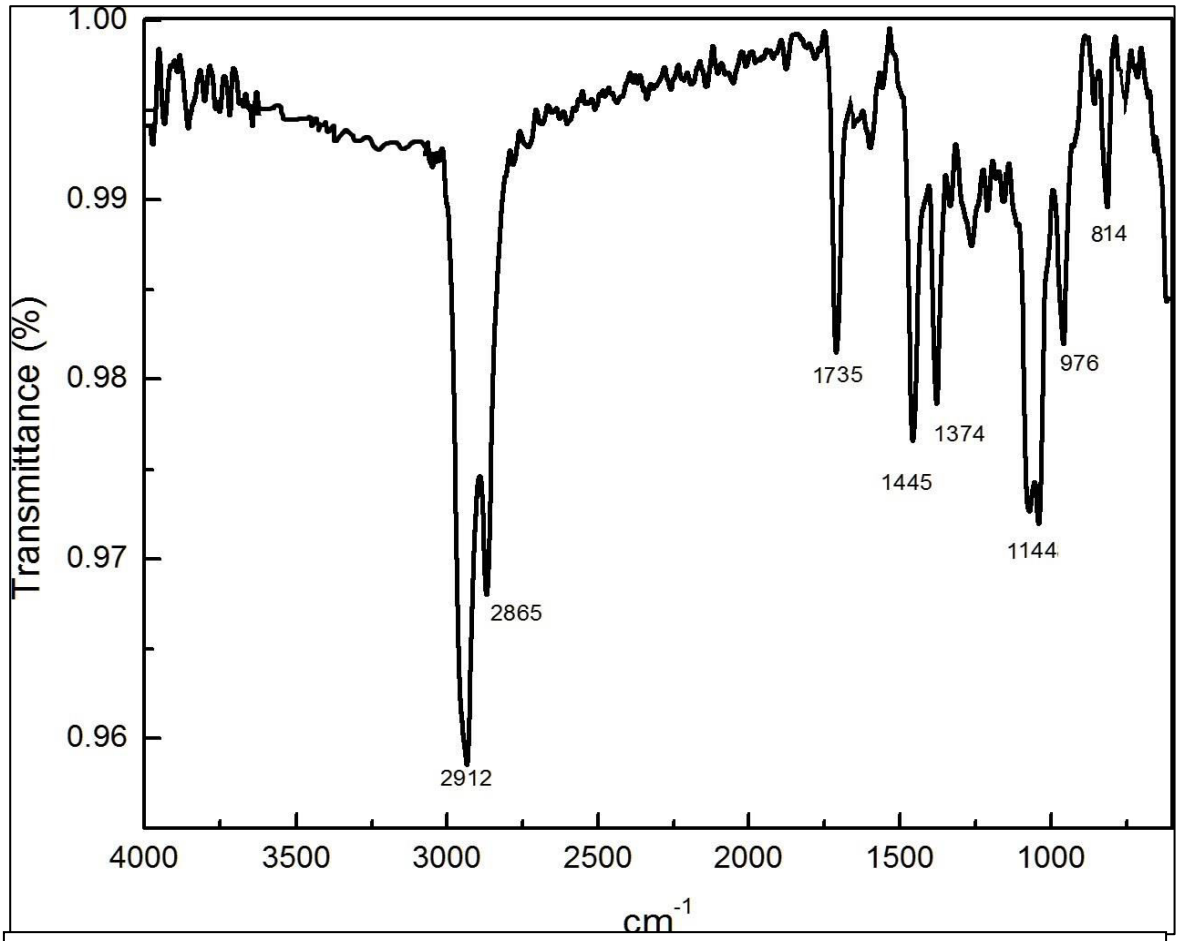


Figure VI.13. IR scanned copy of 2α-carbomethoxy-A-nor-taraxerene (C)

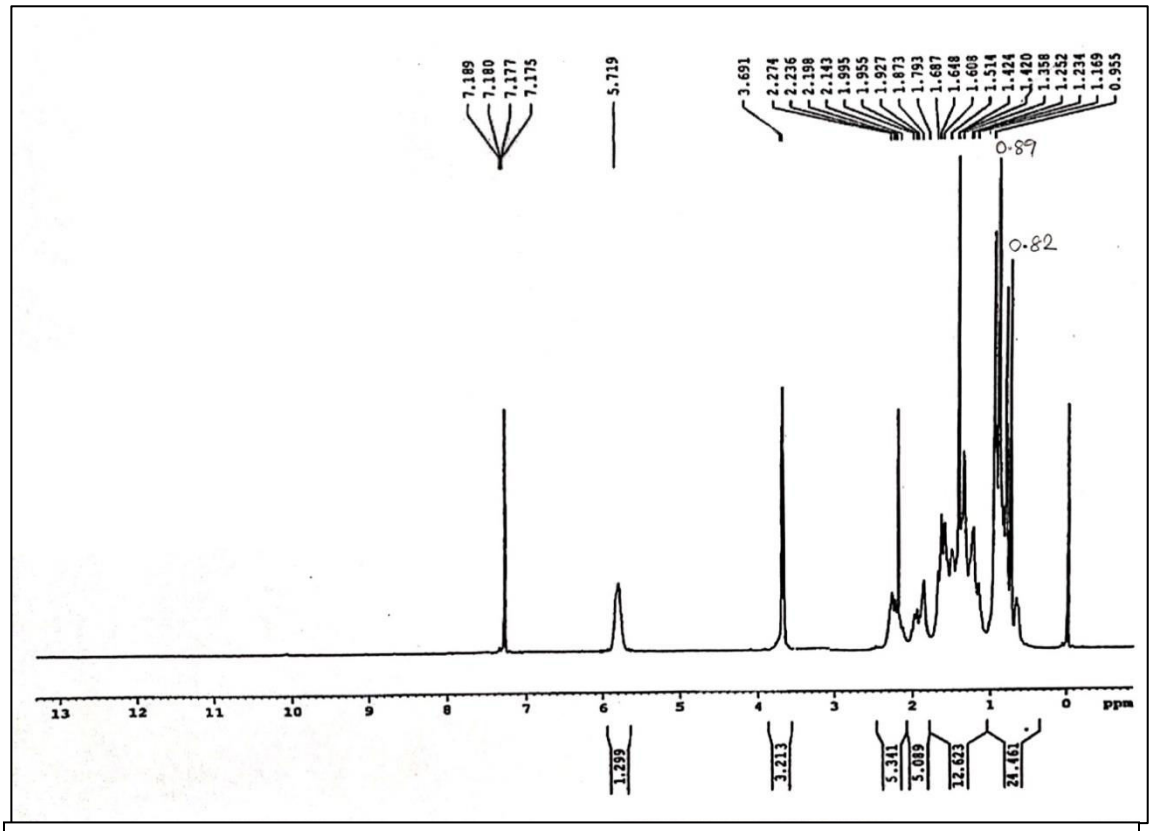


Figure VI.14. ^{1}H NMR scanned copy of 2α-carbomethoxy-A-nor-taraxerene (C)

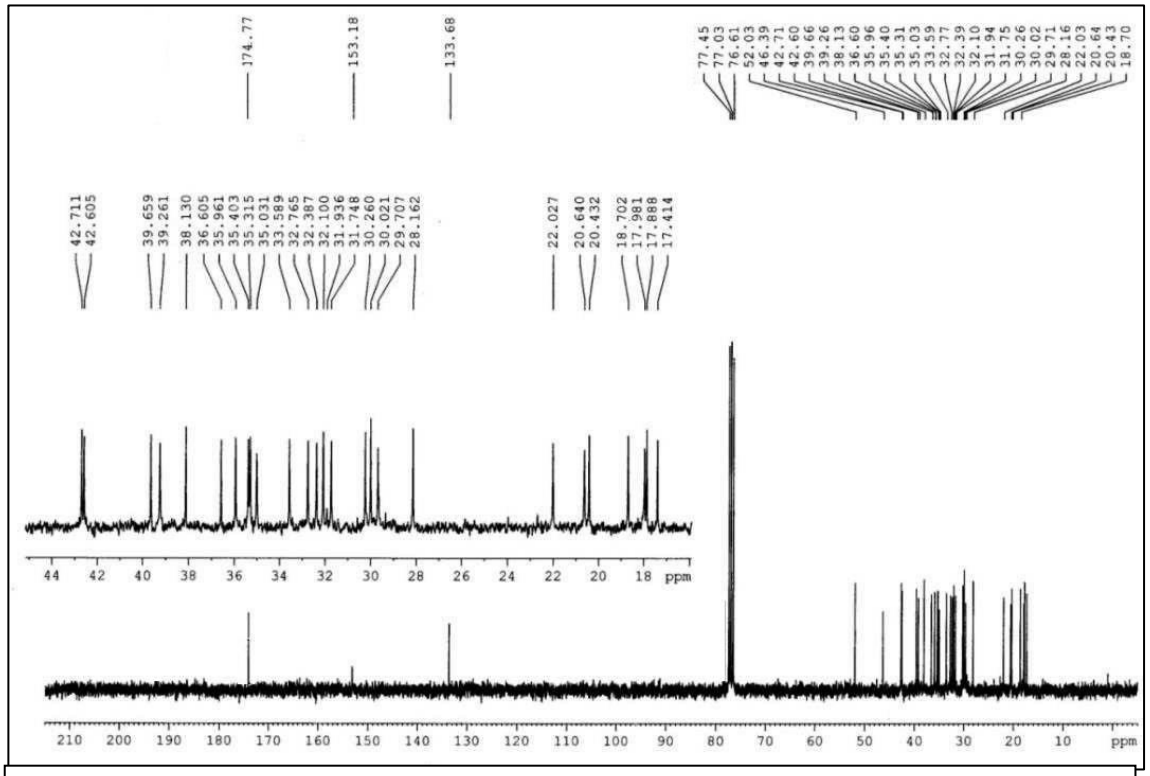


Figure VI.15. ^{13}C scanned copy of 2α-carbomethoxy-A-nor-taraxerene (C)

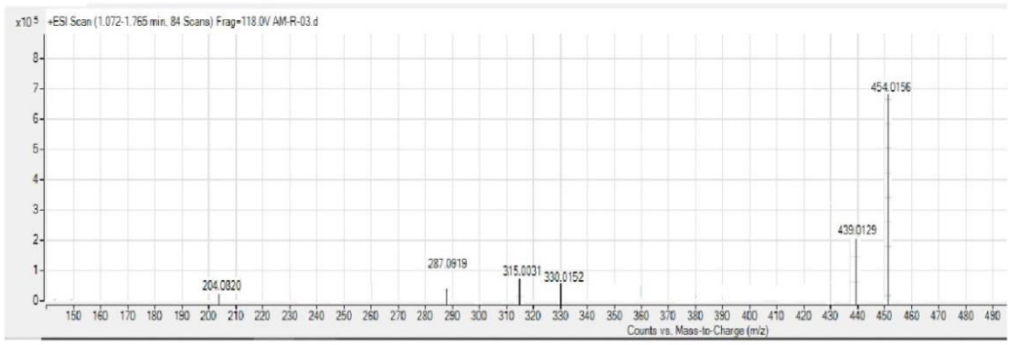


Figure VI.16. Mass scanned copy of 2α-carbomethoxy-A-nor-taraxerene (C)

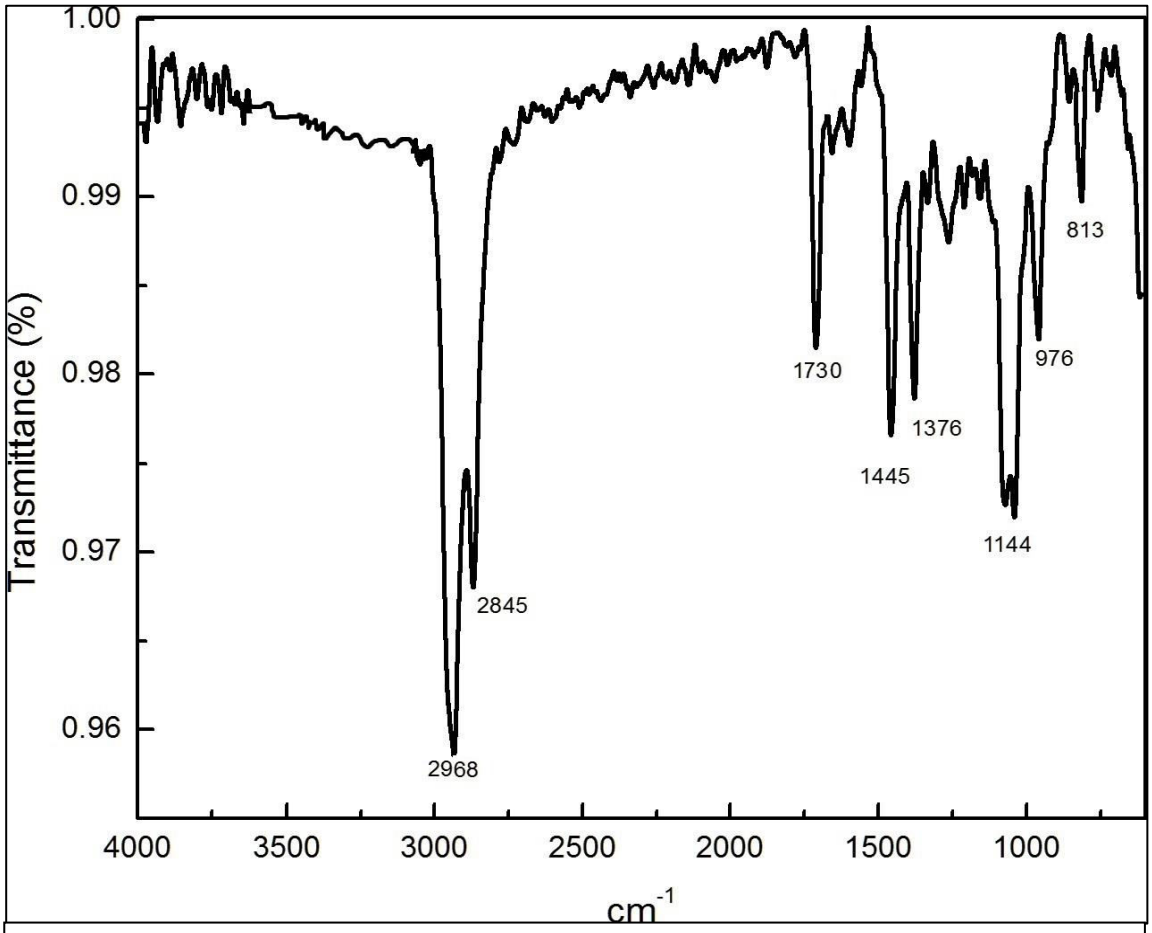


Figure VI.17. IR scanned copy of 2, 3-seco-methyl taraxerene dicarboxylate (D)

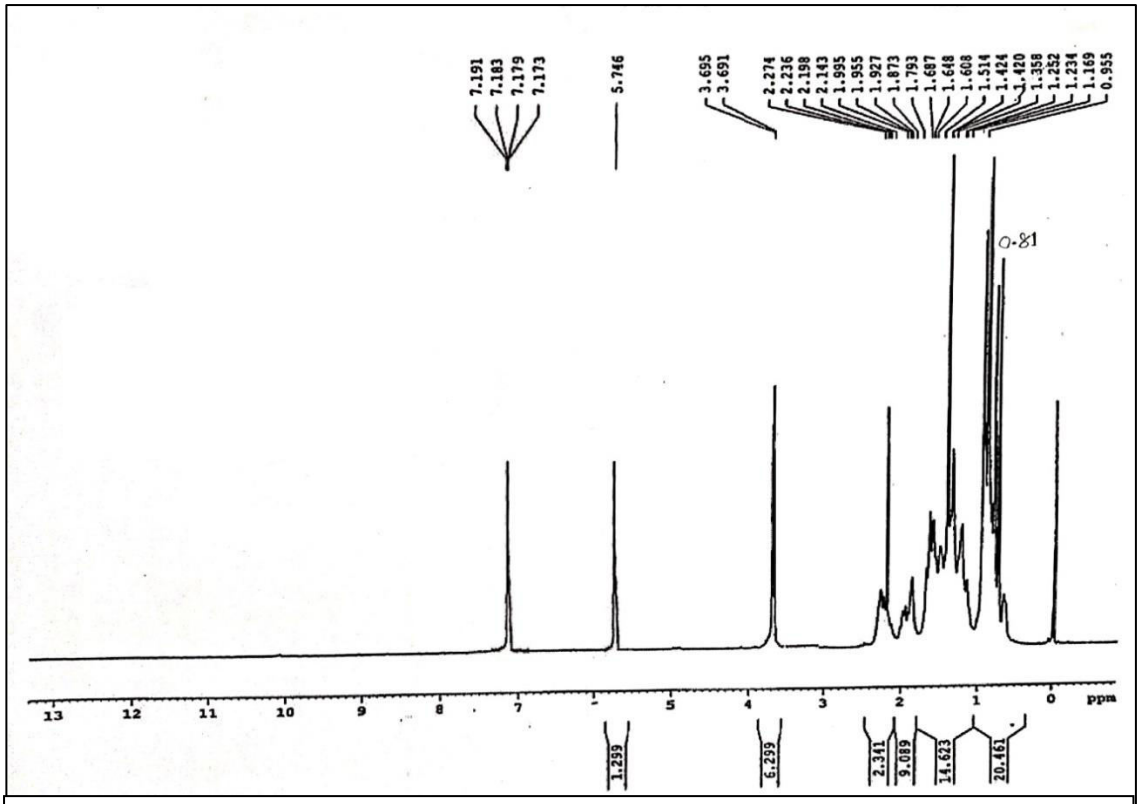


Figure VI.15. [1]H NMR scanned copy of 2, 3-seco-methyl taraxerene dicarboxylate (D)

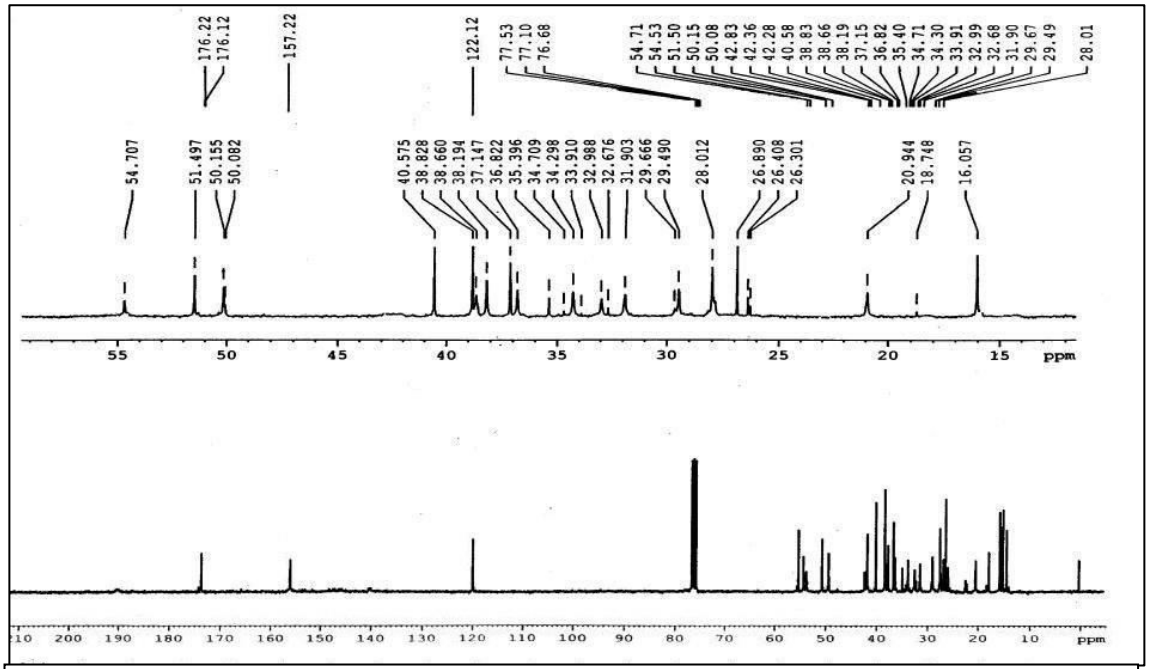


Figure VI.15. [13]C NMRscanned copy of 2, 3-seco-methyl taraxerene dicarboxylate (D)

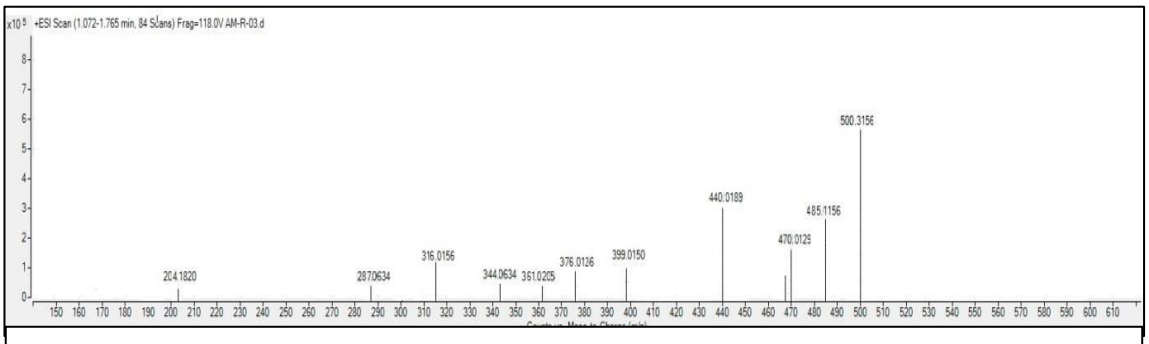


Figure VI.16. Mass scanned copy of 2, 3-seco-methyl taraxerene dicarboxylate (D)

VI.G. References

References are given in BIBLIOGRAPHY under Chapter VI.

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Index

REPRINT OF PAPERS

Catalysis

Graphene Oxide Catalyzed One-pot Synthesis of Pyrimido [4,5-b]quinolinone-2,4-diones and their Biological Evaluation

Rabindranath Singha,[a] Puja Basak,[a] Malay Bhattacharya,[b] and Pranab Ghosh*[a]

A simple and highly efficient method for the synthesis of 5-aryl-pyrimido quinoline 2,4-diones has been demonstrated. Graphene oxide (GO) has proved to be a new class of carbocatalyst for the synthesis of pyrimido[4,5-b]quinolinone-2,4-diones through one-pot three component reaction using aromatic amines, aldehydes, and barbituric acid. The antimicrobial activity of the synthesized compounds was examined for the first time. The effects e.g. reaction temperature, catalyst amount, reaction time, the molar ratio of reactants were investigated. The GO could easily be recovered and reused upto 5th run without loss of its catalytic activity.

Introduction

The multicomponent reactions (MCR) are emerging as environmentally benign synthetic methods for building up of polyfunctionalized heterocyclic compounds.[1] A high level of structural diversity and bond forming efficiency can be achieved with MCR.[2-7] Quinoline derivatives have attracted much attention because of its various biological activities such as antitumor, antibacterial, antimalarial, antiplatelet etc.[8] Also, many antibiotics and UT antiinfectives are based on the quinoline scaffold, like norfloxacin, levofloxacin and others. In a similar fashion, one more important heterocyclic compound pyrimidine and their derivatives are widely used as chemotherapeutic agents, anticancer 5-fluorouracil, antiviral zidovudine, antifungal flucytosine and as a variety of antimicrobial agent.[9,10] Pyrimidoquinolines are an important class of fused heterocyclic compounds, contains both pyrimidine and quinoline nucleus which has been used as a potent drug in recent years. Compounds with pyrimido[4,5-b]quinolinone-2,4-diones possess profound biological activity such as antimalarial, anti-bacterial, analgesic, anti-tumour etc[11] and inhibitory activity to lytic KSHV DNA synthesis.[12–16]

Despite of its broad application, only a few congeners have been reported till now. Previous reports reveal that pyrimidoquinoline derivatives are extensively prepared from pyrimidine as starting material.[17–23] Several works have also been reported to synthesize pyrimidoquinoline using aniline, aldehyde and tetronic acid as the starting material.[24–26] Sequentially, Akin et al. synthesized pyrimidoquinolinone using barbituric acid instead of tetronic acid.[27] Previous protocols on the synthesis of pyrimidoquinoline involve photocatalytic condition (UV_{365} radiation),[28] use of iodine in aqueous medium,[29] β-cyclodextrin,[30] ionic liquid,[31] microwave irradiation,[32] use of benzyltriethylammonium chloride (TEBAC) in presence of water at 90 °C[33] and the use of DABCO[34] as well as L-proline in water at refluxed condition.[35] Nevertheless, these reported methods have some limitations regarding the usage of toxic reagents, prolonged reaction time, low product yield. Most of these reported methods have used homogeneous catalyst which cannot be recovered from the reaction mixture. Although very few works have been reported on its synthesis, it is necessary to find out an alternative simple pathway that eliminates all the drawbacks of the previous protocols.

Graphene oxide (GO), a two dimensional thin layer nanostructure has attracted much consideration in recent years due to its unique chemical properties, high mechanical and thermal resistance. One of the most widely used methods for the synthesis of GO is modified Hummers method, which involves the vigorous oxidation of graphite powder in the presence of H_2SO_4, H_3PO_4, $KMnO_4$, and hydrogen peroxide. Hence, GO contains different kinds of oxygen containing functional groups like epoxide, carbonyl, hydroxyl, carboxyl during its preparation under harsh condition.[36] Due to the presence of these different oxygenated groups in GO, it has been reported as an oxidant and moderate acidic catalyst in several reactions.[36–40] As a consequence, it is envisioned that GO may be a facile and potential heterogeneous acid catalyst for the synthesis of pyrimidoquinoline using aniline, aldehyde and barbituric acid. However, no reports on their preparation using graphene oxide (GO) have been conducted till now. The mild reaction condition, an aqueous medium of the reaction, short reaction time, usage of less hazardous substances, reusable and low cost catalyst are the main advantages of our reported protocol.

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GO is used as solid acid catalyst and it can be reused upto 5th cycle without loss of its catalytic activity. Synthesized GO was characterized by HR-TEM, SEM, FT-IR analysis and the effects of catalyst amount, solvent, reaction temperature were investigated systematically.

Result and Discussion

To start with the explorative work, 4-methyl aniline (1 mmol), 4-methoxy benzaldehyde (1 mmol) and barbituric acid (1 mmol) were taken as model substrates for the reaction. The optimum condition was achieved using water as a solvent and the reaction mixture was stirred for 24 hrs at 100 °C temperature. In contrast, the reaction did not occur in absence of the catalyst even after 24 hr exertion of the reaction (Table 1, entry 1). Hence, the model reaction was repeated with a varying amount of graphene oxide catalyst (Table1) and out of 16 attempts we get 20 mg of GO exerted the best result. Due to the increasing acceptability of green chemistry, other solvents were also used to check the yield of the product. DMF, toluene, DMSO, CH_3CN displayed no superiority to water as solvent, showed the desired product with low yield viz., 72%, 40%, 59%, and 47% respectively (Table 1). Apart from water, ethanol also gave the product with high yield (Table 1, entry 15) and as a consequence greener solvent water was chosen as the optimal medium of the reaction. The reaction was also carried out in solvent free condition which afforded the corresponding product with moderate yield (Table 1,entry 3). In further attempts, the effect of temperature was tested to reduce the reaction time and to increase the yield of the product. The model reaction was carried out at different temperatures for the production of the desired product with variety of yield. As can be seen from Table 1, yields gradually increase with increasing temperature and the best results were obtained under refluxing condition. However, the reaction does not exert considerable yield beyond 100 °C temperature, hence, it was chosen as acceptable temperature to produce the product with high yield. The reaction was also tried at room temperature for 24 hr to examine the effect of temperature which afforded only traces of the desired product (Table 1, entry 17).

Table 1. Optimization of reaction parameters for the synthesis of pyrimido [4,5-b]quinolinone-2,4-diones in the protocol[a]

Entry	Catalyst(mg)	Time(h)	Temperature	Solvent	Yield(%)[b]
1	-	24	100	Water	NR
2	10	12	100	Water	78
3	10	12	100	Neat	65
4	15	6	100	Water	80
5	20	6	80	Water	83
6	**20**	**4**	**100**	**Water**	**89**
7	20	6	80	Water	76
8	25	4	100	Water	85
9	50	12	100	Water	83
10	15	24	100	Water	91
11	15	4	100	DMF	72
12	15	4	100	Toluene	40
13	15	4	150	DMSO	59
14	15	4	80	CH_3CN	47
15	15	4	80	Ethanol	86
16	15	4	RT[c]	Water	NR

[a] Reaction conditions: 4-methyl aniline (1 mmol), 4-methoxy benzaldehyde (1 mmol), barbituric acid (1 mmol), GO (20 mg) at different temperatures and solvent. [b] Isolated yields, [c] room temperature reaction.

To examine the applicability and generality of the reaction, a variety of anilines and aldehydes with different electron donating/electron withdrawing groups were employed with barbituric acid. Anilines with electron donating groups afforded the desired product with high yield which may be due to the increased electron density in the aniline nucleus and thereby facilitating the ortho attack (Table 2 entries 1–14). Contrarily, aromatic aldehydes with a variety of groups furnished the corresponding product in good yields without any significant deviation. The applicability of this protocol was also examined with aliphatic aldehydes (entries 21–24), however the corresponding products were obtained in low yield. Heterocyclic aldehydes and napthaldehydes were tried to determine the substrate scope of this reaction and the results afforded the desired product in good yield (Table 2. entries 8–9, 11, 15). From these results listed in Table 2, it is obvious that different types of aldehydes and anilines can be successfully used in this protocol and it has wide range of substrate applicability.

We have evaluated the catalytic activity of Graphene oxide (GO) as an acid promoted three component condensation reaction between aldehydes, aromatic amines, and barbituric acid. GO was synthesized by modified Hummer's method and its surface consists of different oxygen containing functionalities namely epoxide, hydroxyl, carbonyl, carboxyl moieties. FT-IR spectra of the synthesized GO showed the stretching frequencies at 3400–3600 cm^{-1}, 1720–1755 cm^{-1}, 1605–1620 cm^{-1}, 1230 cm^{-1} etc. which further supported the existence of these oxygenated functionalities. These results prompted us to use GO as viable solid acid catalyst for this reaction. HR-TEM and SEM images of GO show the formation of layered structure of graphene oxide (GO) during its preparation. Agglomeration and disintegration of GO into small layers after successive runs strongly support the fact that the surface acidic functionalities of GO have taken part in the reaction and this is distinctly predictable from Figure 1 and Figure 2.

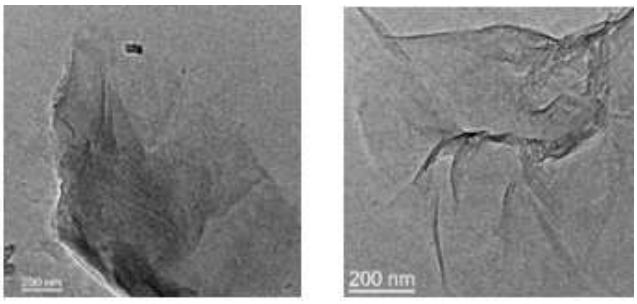

Figure 1. HR-TEM images of GO and GO after 4th run

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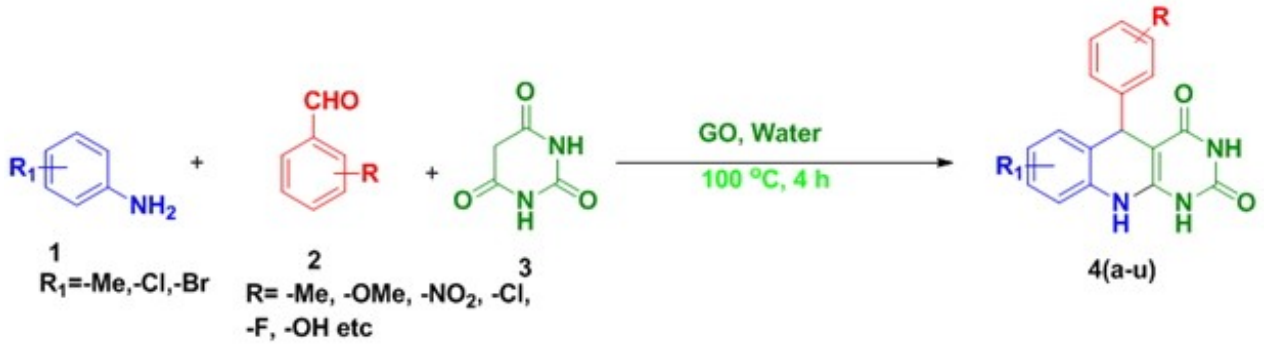
Table 2. Substrate scope of anilines and aldehydes for the synthesis of pyrimido[4,5-b]quinolinone-2,4-diones.[a]



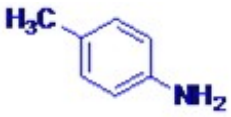
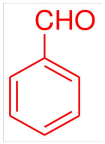
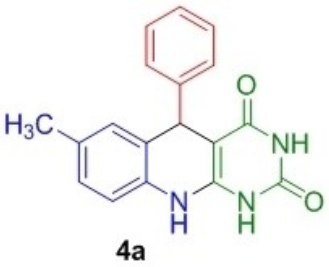
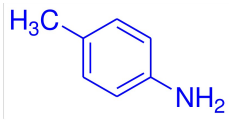
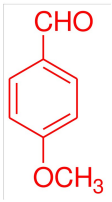
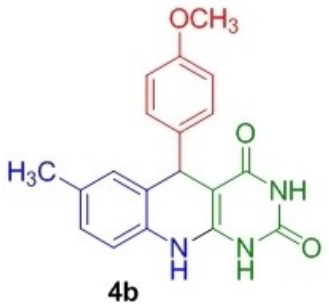
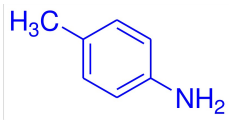
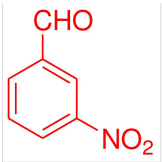
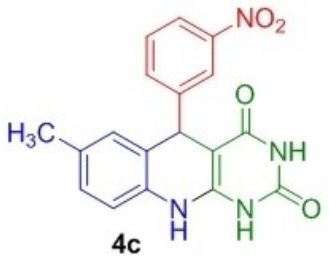
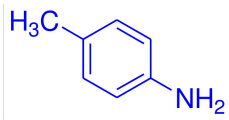
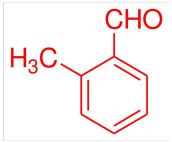
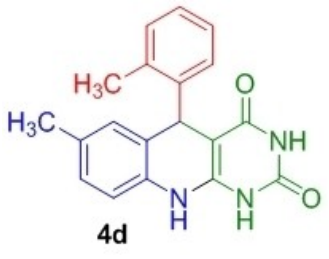
Entry	Anilines	Aldehydes	Product	Yield[b] (%)
1			 4a	80
2			 4b	89
3			 4c	70
4			 4d	87

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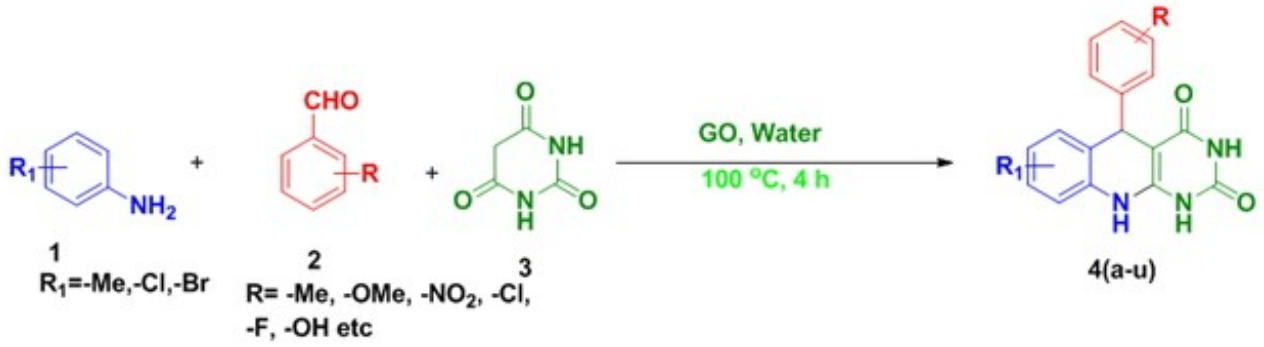
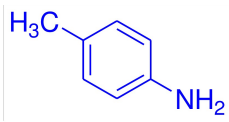
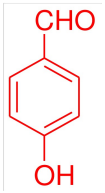
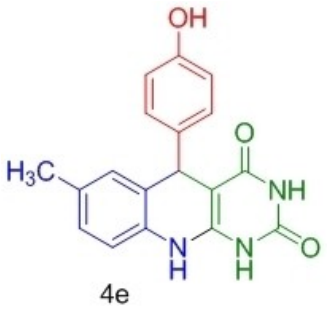
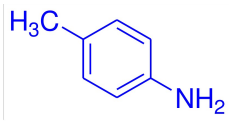
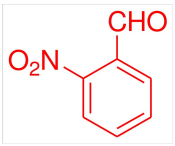
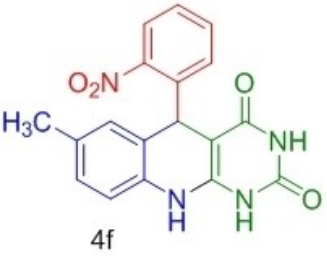
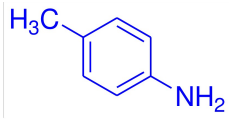
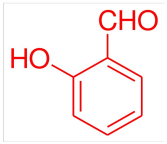
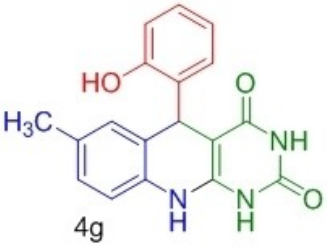
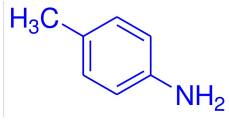
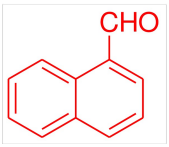
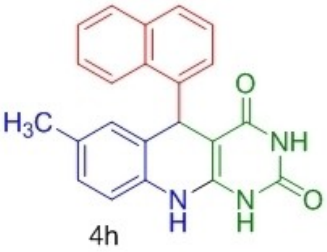
Table 2. continued



Entry	Anilines	Aldehydes	Product	Yield[b] (%)
5			 4e	79
6			 4f	76
7			 4g	78
8			 4h	80

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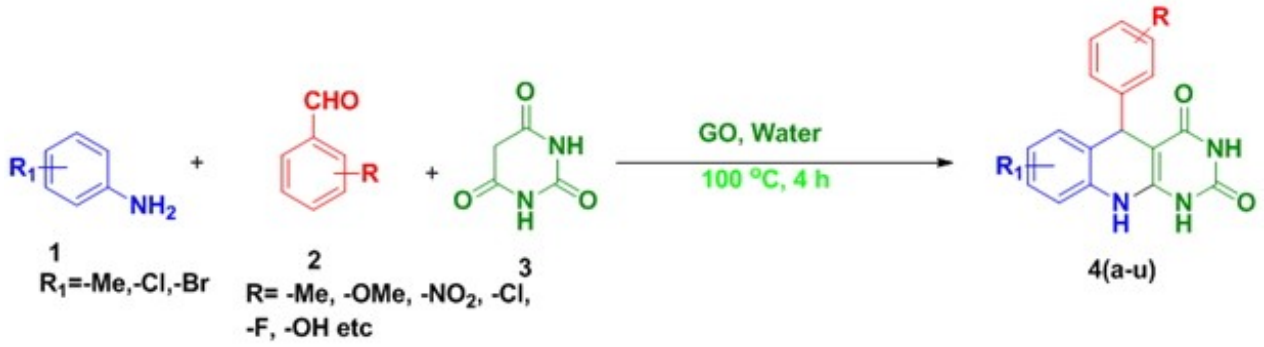


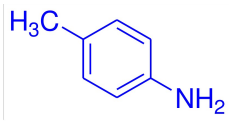
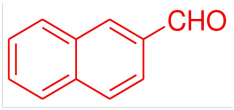
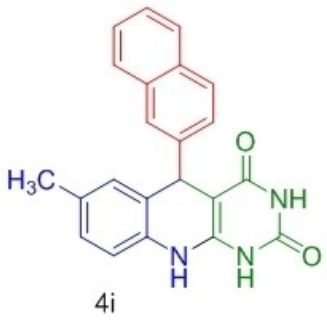
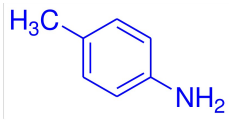
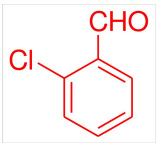
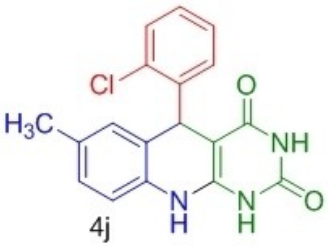
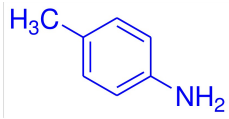
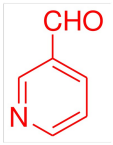
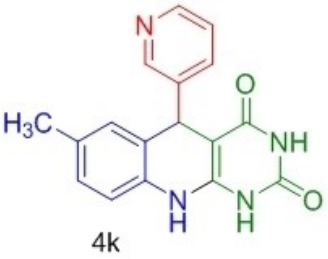
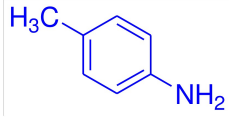
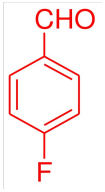
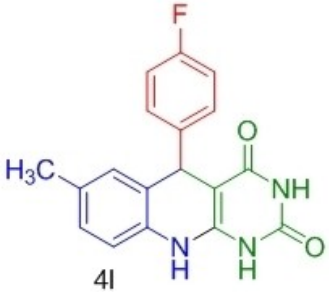
Entry	Anilines	Aldehydes	Product	Yield[b](%)
9			 4i	76
10			 4j	78
11			 4k	70
12			 4l	70

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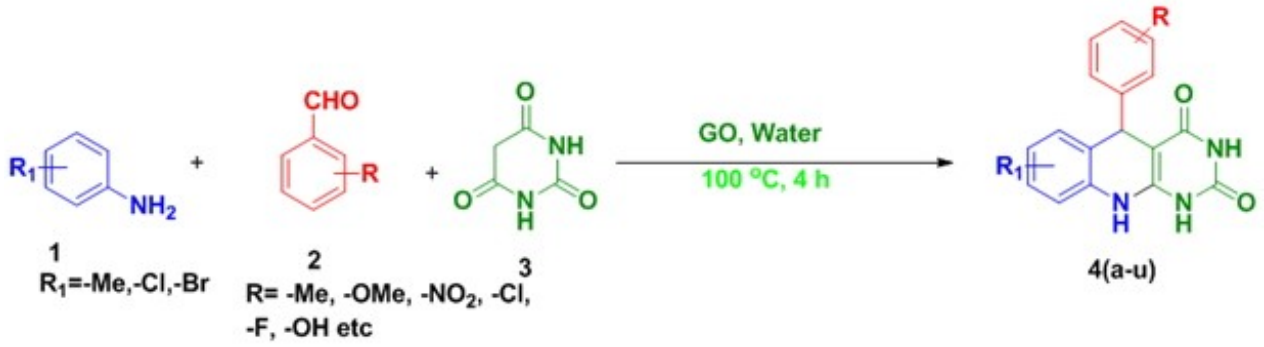
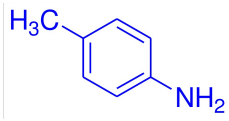
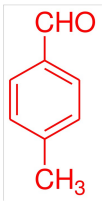
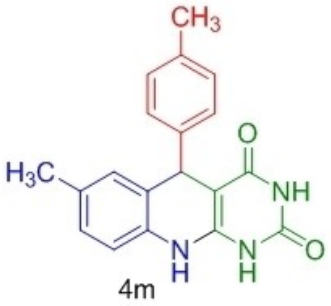
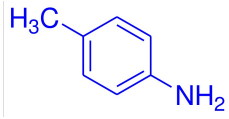
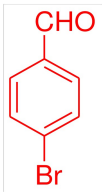
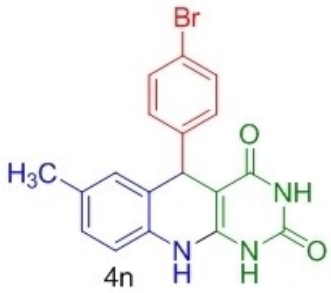
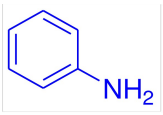
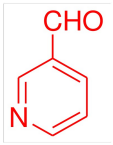
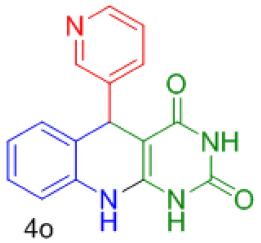
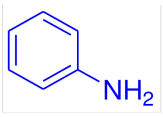
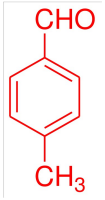
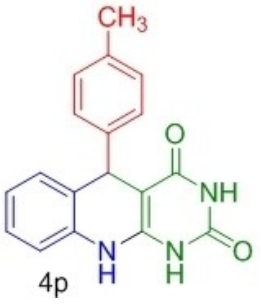
Table 2. continued



Entry	Anilines	Aldehydes	Product	Yield[b](%)
13			 4m	88
14			 4n	70
15			 4o	72
16			 4p	75

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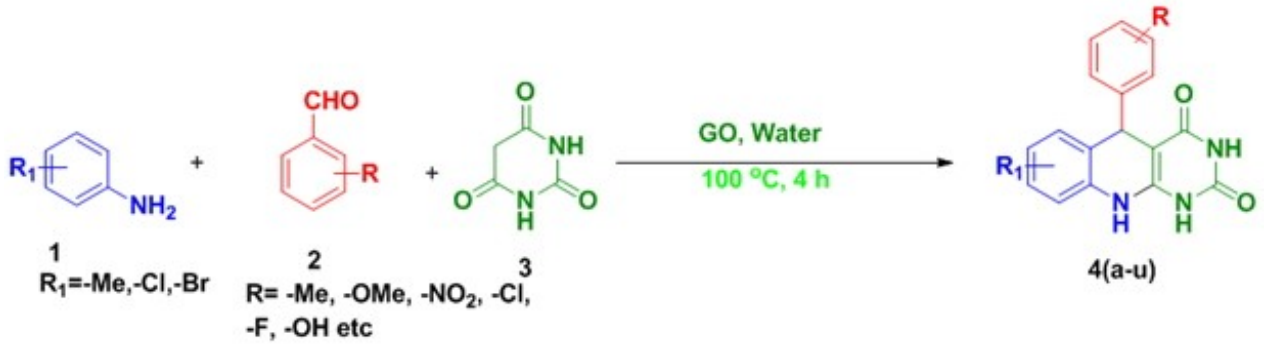


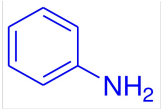
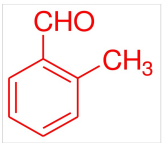
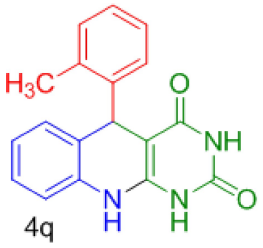
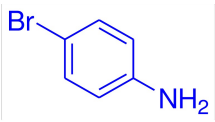
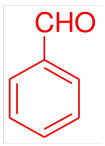
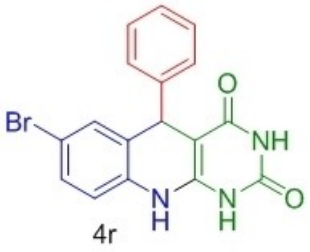
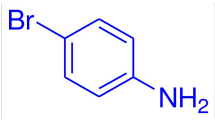
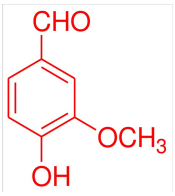
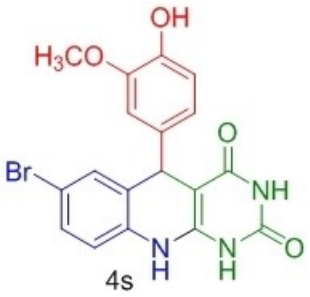
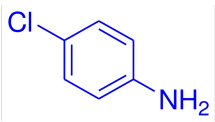
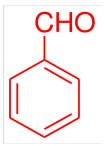
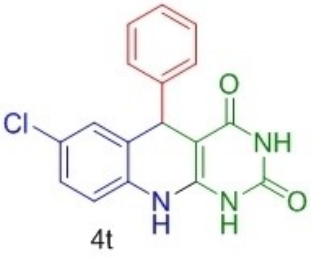
Entry	Anilines	Aldehydes	Product	Yield[b] (%)
17				80
18				70
19				75
20				74

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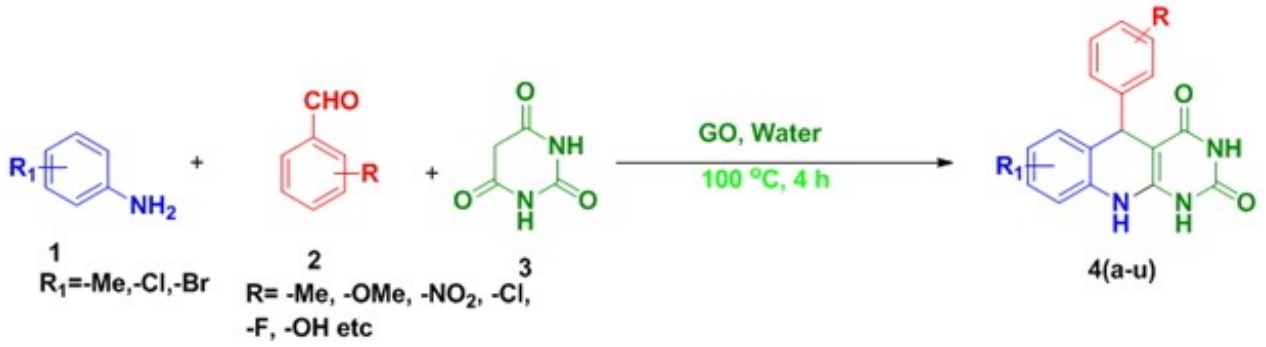
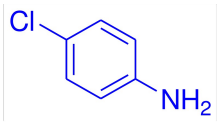
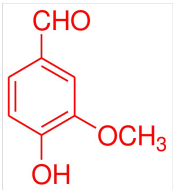
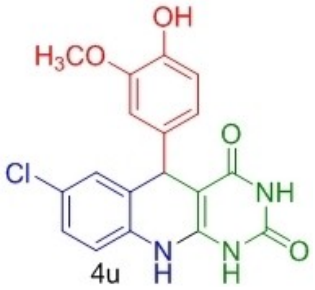
Table 2. continued



Entry	Anilines	Aldehydes	Product	Yield[b](%)
21				75

[a] Reaction conditions: anilines (1 mmol), aldehydes (1 mmol), barbituric acid (1 mmol), GO 20 mg, water 5 mL at 100 °C. [b] Isolated yields.

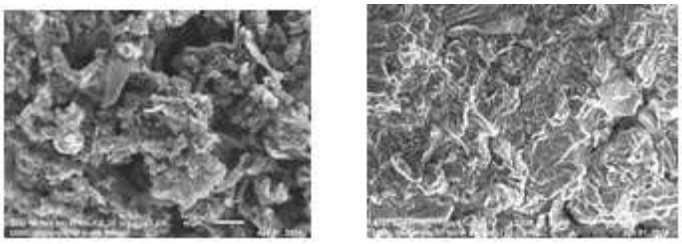


Figure 2. SEM images of GO and GO after 4th run

FT-IR spectra of fresh GO and GO recovered after 2nd and 4th run were compared to explain the participation of acidic groups during the catalysis. The reduction of the band intensity of –OH at 3400–3600 cm^{-1} and –COOH at 1720–1755 cm^{-1} significantly indicates the participation of these functional groups in reaction, the intensities of the bands gradually decreases. (Figure 3) The catalytic activity of GO is reduced after 5th run (Figure 4.) and the reason may be due to the participation of oxygen containing acidic groups in the reaction.

The supportive instrumental results encouraged us to draw a possible mechanism of the reaction catalyzed by GO. It is assumed that, very first step of the reaction involves protonation on aldehydic oxygen atom which intensifies electrophilic charge on carbonyl carbon thereby facilitating the attack by barbituric acid. In the 2nd step aniline is getting attached with the adduct of aldehyde and barbituric acid. The 3rd step of the reaction involves acid catalyzed cyclization followed by simultaneous elimination of water molecule and exerts the corresponding product.

Antimicrobial activity analysis of some synthesized compounds;

The vast range of biological activity of 5-aryl-pyrimido quinoline 2,4-diones prompted us to investigate antimicrobial activity with some of the synthesized compounds.

Materials and methods

Overnight grown broth culture of two gram positive (*Staphylococcus aureus* and *Bacillus cereus*) and two gram negative (*Escherichia coli* and *Klebsiella pneumonia*) were used for the present study to assess the antimicrobial activities of synthesized samples. Mueller-Hinton (MH) agar media (Himedia) wasused for susceptibility tests. 38.0 grams of MH media was added in 1000 mL of double distilled water and heated to dissolve completely. The media was sterilized by autoclaving at 20 lbs pressure at 121 °C for 20 minutes. The media was cooled down to room temperature and poured in sterile petriplates at sterile condition of laminar air flow cabinet. 100 µl of bacterial strains were added separately to each petriplates containing media and agitated for mixing.

The synthesized compounds (4 l, 4 h, 4c, 4k, 4d, 4 t, 4r) were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 100 mg/mL. Paper disc diffusion method was applied (Su et al., 2015). Circular paper discs (6 mm diameter) were cut

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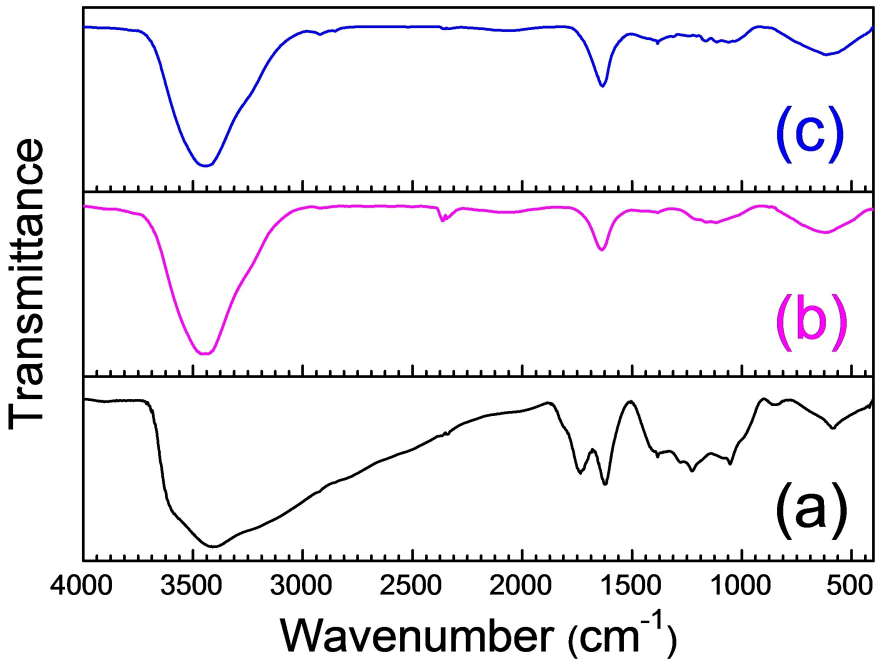

Figure 3. FT-IR spectra of (a) GO (b) after 2nd run and (c) after 4th run

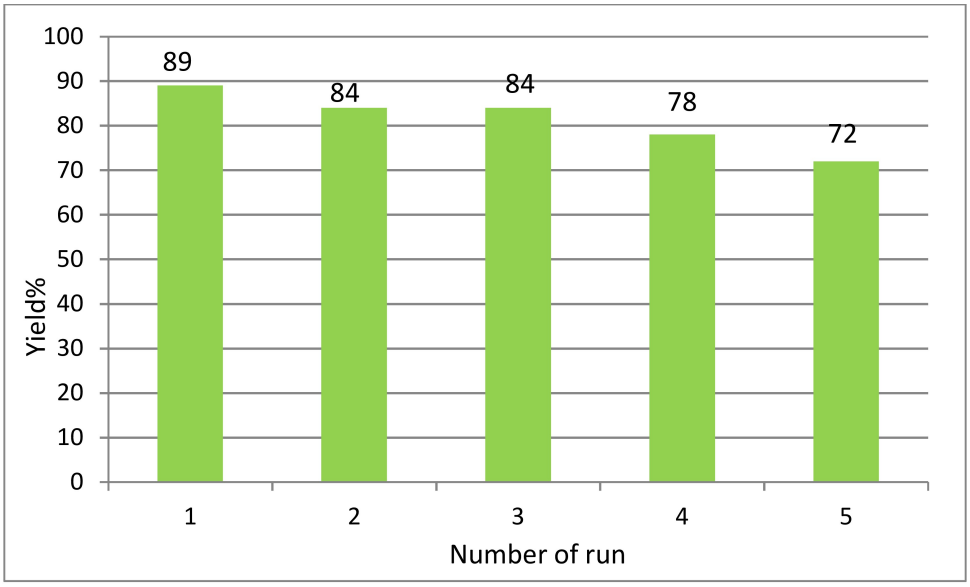

Figure 4. Recyclability test of Graphene Oxide (GO)

from Whatman 42 filter papers and were dipped in the sample solutions for one hour. The paper discs dipped in sample solutions were placed on the media containing bacterial culture and incubated overnight at 37 °C.

Result and discussion

Efficacyof synthesized compounds in inhibiting bacterial growth can be ascertained by susceptibility tests. These synthesized compounds showed high variability (Figure 5 and Table 3). Samples 1(4 l), 2(4 h), 3(4c),4(4k), 5(4d), 6(4 t) and 7(4r) have inhibitory function against both gram positive and gram negative bacteria. Compounds 4 l (with -CH_3 group in the aniline part and Fluorine group in the aldehydic part) showed the inhibitory function against both gram positive and gram negative bacteria. So presences of -CH_3 or halide are inevitable for these compounds for antibacterial activity. Compound 2 and 3 are with one -CH_3 groups is present in the aniline part and aldehydic part contained naphthalene moiety in compound 2 and nitro group in compound 3. Both the compound

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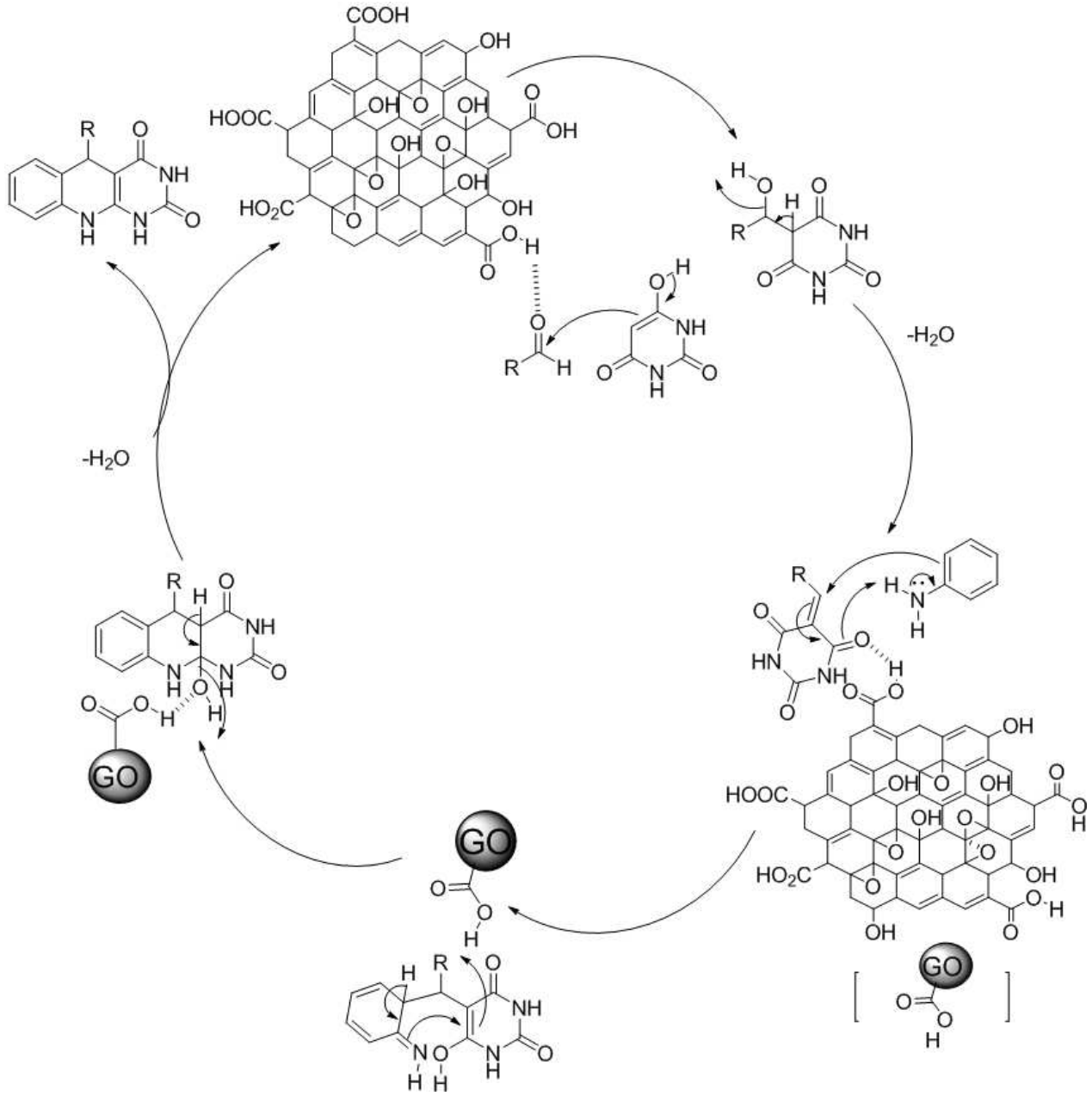

Figure 5. Possible mechanism for the synthesis of pyrimido[4,5-b]quinolinone-2,4-dione

Table 3. Antimicrobial activity analysis of some synthesized compounds

Code	Compound	Gram negative *Escherichiacoli*	*Klebsiellapneumonia*	Gram positive *Bacillus cereus*	*Staphylococcus aureus*
1	4 l	9	7	8	10
2	4 h	12	8	8	9
3	4c	13	11	10	15
4	4k	–	–	–	–
5	4d	–	–	7	7
6	4 t	8	9	7	8
7	4r	8	8	10	7

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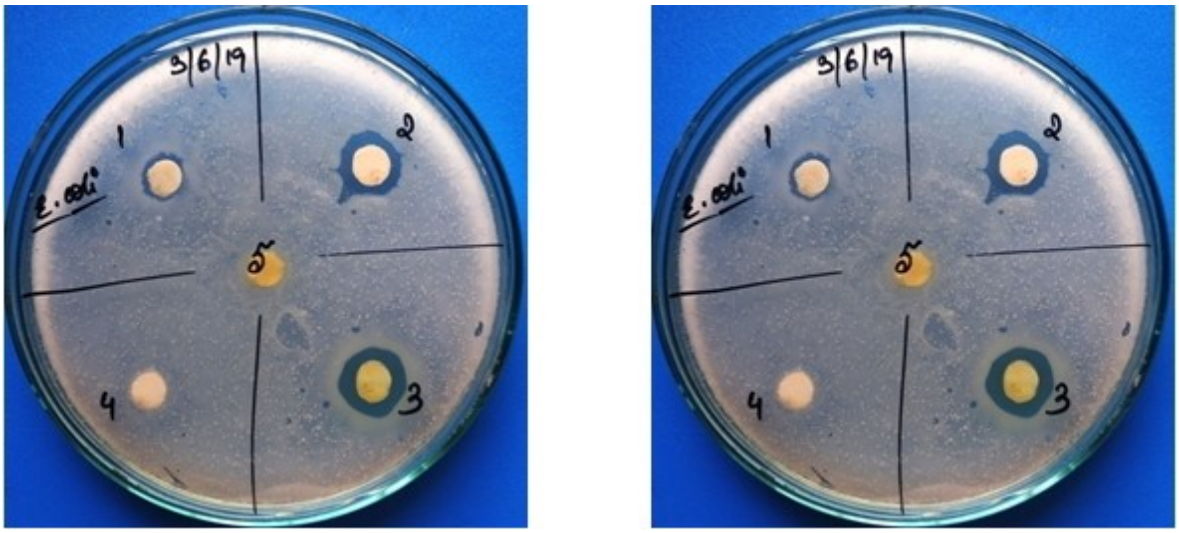

Figure 6. Plates showing variable inhibition activities of samples

has inhibitory function against both gram positive and gram negative bacteria. Specially compound 3 shows good Antimicrobial activity due to the presence of nitro group. Compound 4k fails to inhibit Antimicrobial activity. Sample number 5 with -CH_3 groups in both the aniline (Para toluidine) part and aldehydic (ortho-tolualdehyde part) is found to be active against only gram positive bacteria. Compounds 6 and 7 are with Chlorine atom while compound 7 is with Bromine atom in the aniline part,they are effective against both gram positive and gram negative bacteria, but with less intensity. Maximum inhibition zone was produced by sample 3. So, nitro group may have some additional effect in inhibiting both gram positive and gram negative bacterial growth.

From the above observation we conclude that the presence of substituent in the aniline part is important for antimicrobial activity.

To the best of our knowledge, the antibacterial properties of these synthesized compounds are reported for the first time in our work. It is the preliminary work towards vast range of antimicrobial activity and the positive response of these compounds will drive us to carry out further explorative work on this biologically important molecule.

Conclusion

Herein, we have developed a greener, simple and efficient protocol for the three component synthesis of pyrimido[4,5-b] quinolinone-2,4-diones from aromatic amines, aldehydes, and barbituric acid. GO was found to be highly efficient, cheap and recoverable heterogeneous solid acid catalyst in furnishing the corresponding products from high to excellent yield. The fused ring structure of pyrimido[4,5-b]quinoline-diones is highly promising regarding pharmaceutical aspects. The antimicrobial activity of some compounds showed promising results which will encourage us to carry out further work on it.

Supporting Information Summary

Supplementary data provide general procedure for the catalyst preparation and synthesis of pyrimido[4,5-b]quinolinone-2,4-diones. ^{1}H NMR, ^{13}C NMR spectra and IR data of all the synthesized compounds (4a-4u) have been included in this section.

Acknowledgement

One of us (RS) is thankful to UGC, New Delhi, India for financial support (RGN fellowship).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Antibacterial activity · Carbocatalyst · Graphene oxide · Pyrimido[4 · 5-b]quinolinone-2 · 4-diones.

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SHORT COMMUNICATION

Environmentally benign approach towards C–S cross-coupling reaction by organo-copper(II) complex

Rabindranath Singha[1] · Sailesh Chettri[1] · Dhiraj Brahman[1] · Biswajit Sinha[1] · Pranab Ghosh[1]

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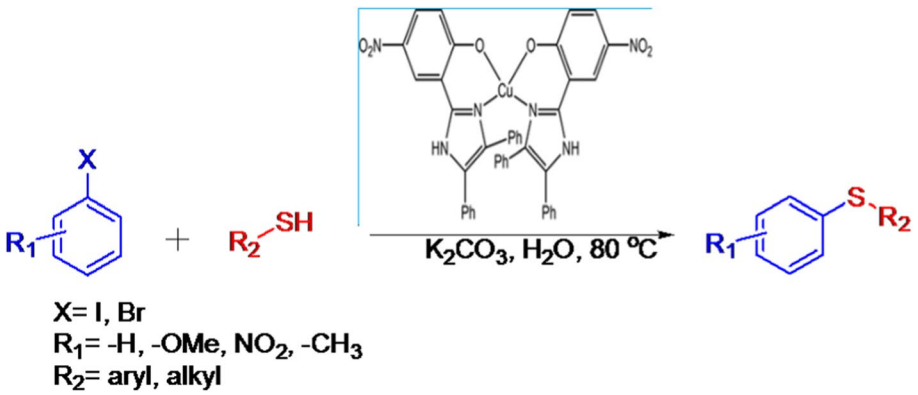
Abstract

C–S cross-coupling reaction in water giving an excellent yield of the desired C–S coupled product by using a newly developed Bis[2-(4,5-diphenyl-1*H*-imidazol-2-yl)-4-nitrophenolato] copper(II) dehydrate complex as catalyst. Although it was the first report of the synthesis of such a novel organo-copper complex from our laboratory, its potential catalytic application was not tested so far. Keeping this in mind and based on our anticipation, we developed a greener route for the C–S coupling reaction. The result is very interesting and comprises the subject matter of this report.

Graphic abstract



Keywords C–S coupling reaction · Greener protocol · Metal–organic complex

Introduction

Nowadays, the development of multicomponent reaction for the synthesis of fine chemicals and biologically active compounds through the greener approach draws much more attention [1]. C–S cross-coupling reaction is one of the fascinating approaches for the synthesis of pharmaceutically as well as industrially important compounds [2–6]. Aryl sulphide functional group containing derivatives have been used in a number of drugs such as Parkinson's, diabetes, Alzheimer's, cancer, HIV diseases [7]. A variety of the transitional metal-catalysed synthetic methods have been reported so far for the formation of C–S bond, but most of them require drastic reaction condition such as high temperature and long reaction time, and associated with low yield of the desired product [8–10]. On the other hand, modern transition metals such as palladium [11–21], nickel [22–25], copper [4, 26–41], cobalt [42], iron [43, 44] and indium [45] are used in combination with appropriate ligands for catalysing properly in the C–S cross-coupling reaction of

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aryl halides with thiols for the synthesis of aryl sulphides in good yields under milder reaction conditions. However, the high cost and air sensitivity of Pd catalyst limit the large-scale processes. Keeping this observation in mind, water was chosen as the optimal medium of the reaction. With these views in mind, we applied our laboratory-reported synthesized organo-copper complex in an attempt to establish a greener C–S coupling reaction.

Low toxicity, easy access to active sites, high surface area, high thermal stability and easy way to separate the catalyst from the reaction mixture yielded the best result of the desired protocol [46].

Result and discussion

In order to explore the catalytic activity of the newly synthesized copper catalyst, we begun C–S cross-coupling as a model reaction by the conventional method. The results of the optimization studies are summarized in Table 1.

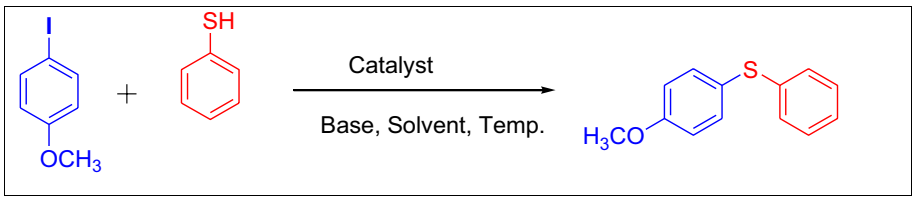
Initially, a mixture of 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol) and 10 mg of synthesized catalyst were taken in water, as the solvent heated in a round-bottom flask under the reflux condition. We observed that the reaction was completed with a 96% yield of the desired C–S coupled product (Table 1, entry 6 showed with bold letters). However, when the same reaction was carried out under the similar condition, but in the absence of catalyst, we did not get the desired product. Therefore, we concluded that the reaction does not proceed in the absence of catalyst (Table 1, entry 10). Hence, to explore the role of catalyst we repeated the model reaction with varying amounts of catalyst (Table 2), and out of all attempts we established that 10 mg of the synthesized catalyst yielded the best result

Table 2 Optimization of catalyst loading

Entry	Catalyst (mg)	Yield (%)
1	2	60
2	4	65
3	6	72
4	8	85
5	10	96
6	12	97

Reaction conditions: 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol), water solvent and 10 mg catalyst at 80 °C

Table 1 Optimization of reaction parameters for the C–S coupling reaction[a]

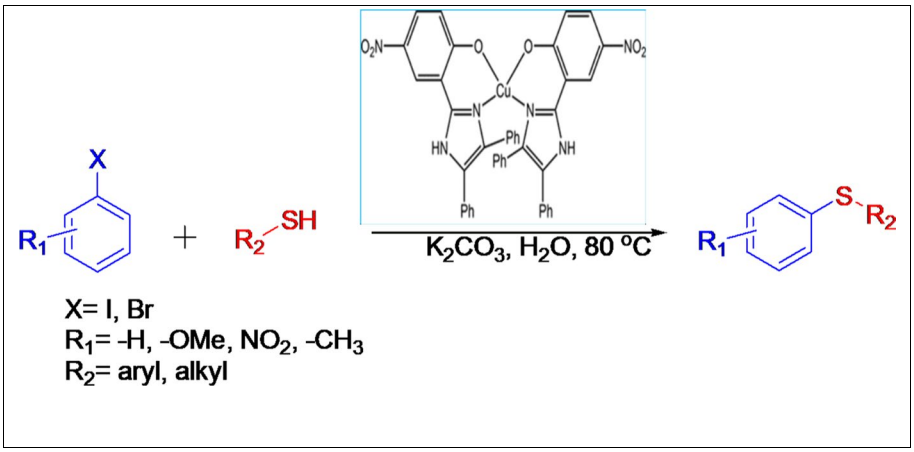


Entry[a]	Catalyst (mg)	Time (h)	Solvent (5 mL)	Base	Temperature (°C)	Yield[b] (%)
1	10	10	DMF	K_2CO_3	80	90
2	10	10	DMSO	K_2CO_3	80	87
3	10	10	CH_3CN	K_2CO_3	80	90
4	10	10	Toluene	K_2CO_3	80	92
5	10	10	Ethanol	K_2CO_3	80	91
6	**10**	**10**	**Water**	**K_2CO_3**	**80**	**96**
7	10	10	Water	K_2CO_3	100	97
8	10	10	Water	K_2CO_3	60	40
9	10	10	Water	K_2CO_3	RT	Nil
10	Nil	24	Water	K_2CO_3	80	Nil
11	10	10	Water	Cs_2CO_3	80	97
12	10	10	Water	KO^tBu	80	60
13	10	10	Water	Et_3N	80	62
14	10	10	Water	KOH	80	70

[a]Reactions carried out with 10 mg (corresponds to 0.09 mol% of copper) of synthesized copper catalyst, 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol)

[b]Yield based on column chromatography, Nil stands for in absence of catalysts well as no yield of desired product

Table 3 Synthesized copper-catalysed C–S cross-coupling of aryl halides and aryl thiols[a]



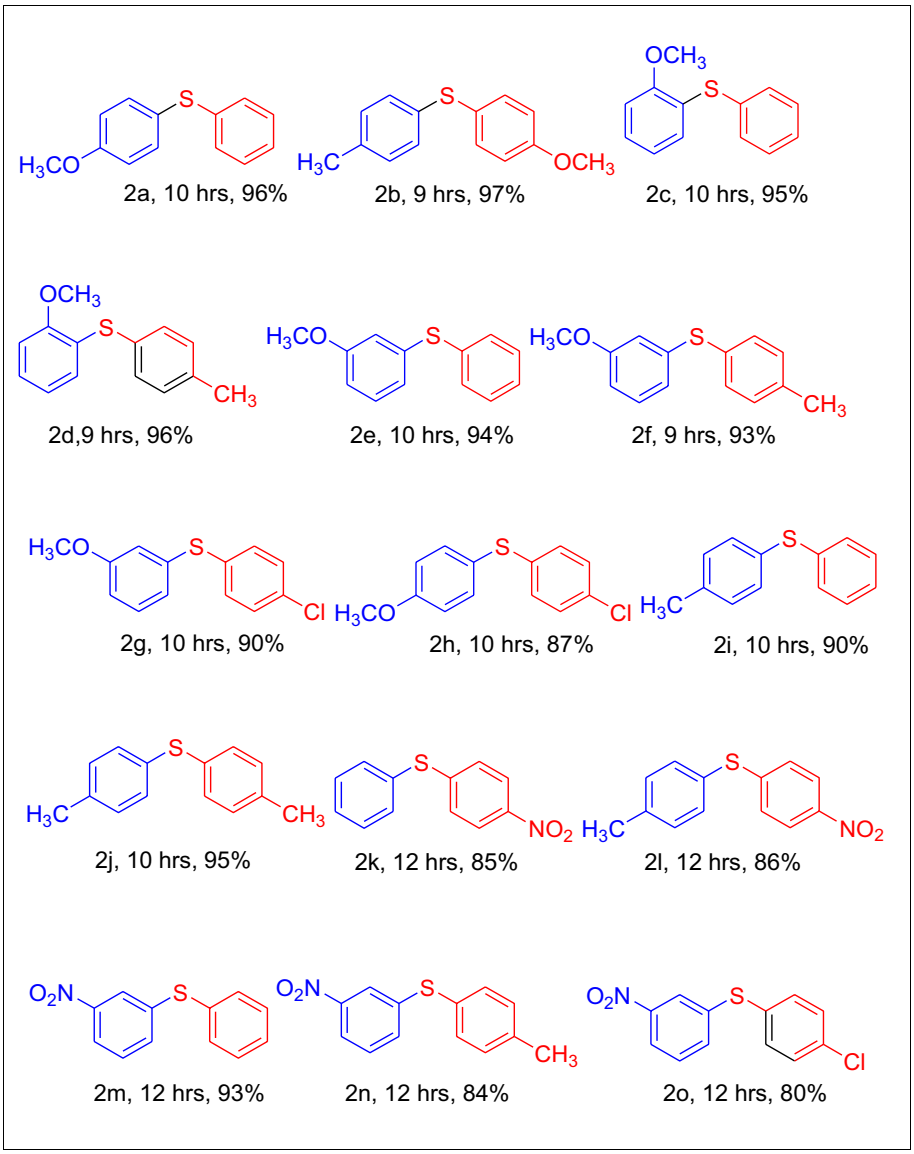
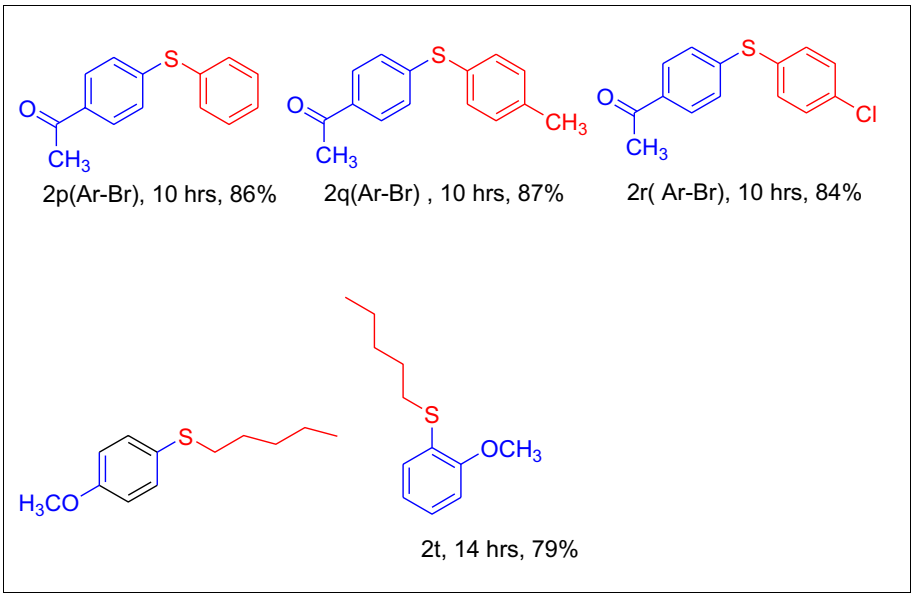


Table 3 (continued)



[a]Reactions carried out with 10 mg of synthesized copper catalyst, 4-iodoanisole (1 mmol), thiophenol (1 mmol), K_2CO_3 (1.2 mmol) in water medium at 80 °C

[b]Yield based on column chromatography

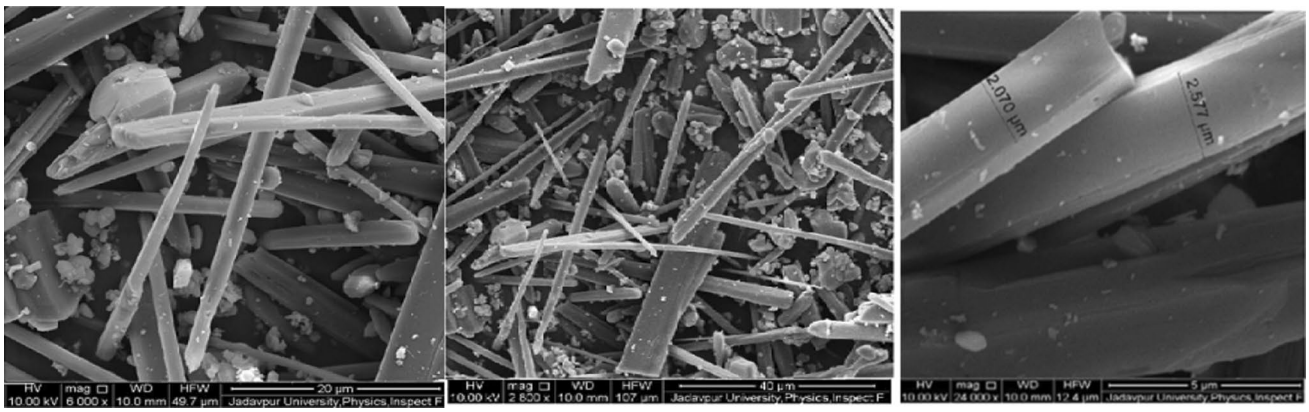


Fig. 1 SEM image of the synthesized fresh catalyst, catalyst after third run and fifth run

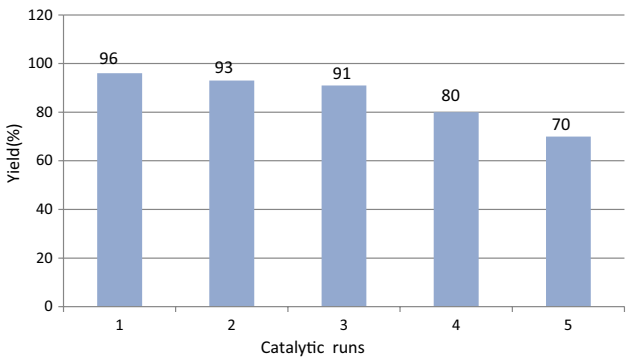


Fig. 2 Reproducibility of the catalyst in reaction

(Table 2, entry 5). Further increasing the amount of catalyst, the yield of the product did not increase considerably. We also examined the protocol using various solvents, such as DMF, DMSO, CH_3CN, toluene and ethanol, but none of them could able to beat the efficiency of water as a solvent. Keeping this observation in mind, water was chosen as the optimal medium of the reaction. Further, in order to optimize the reaction temperature, the model reaction was carried out at 60, 80 and 100 °C. Among them, 80 °C was found to yield the best result (Table 1, entry 6). We also studied the reaction by using various bases (Table 1), and among them, K_2CO_3 and Cs_2CO_3 were found to produce the best

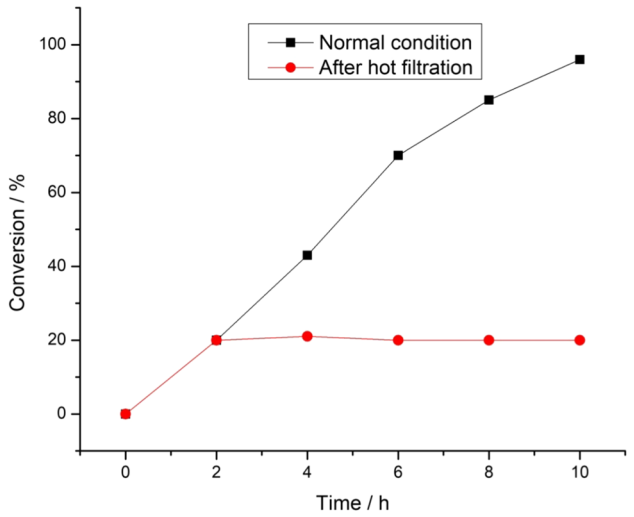


Fig. 3 Comparison of normal time profile with hot filtration test. Conversions (±2%) at different time intervals for each plot were measured by HPLC

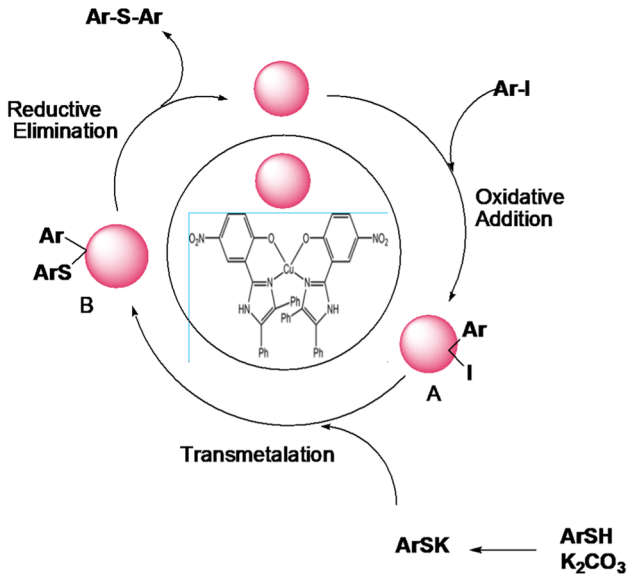


Fig. 4 Proposed reaction mechanism for C–S cross-coupling reaction

yield of the desired product. However, considering the cost of Cs_2CO_3 and the product yield is not considerably greater than K_2CO_3, the latter was chosen as the optimized base of the reaction. With this optimized greener reaction condition, we performed the reaction with various substituents (Table 3).

To investigate the catalytic activity of the synthesized catalyst and to cheek the generality of the C–S coupling reaction, we carried out the reaction with a variety of haloarenes and aliphatic as well as aromatic thiols. Both the electron-donating/electron-withdrawing groups of the haloarenes were employed with the thiols. Haloarenes with electron-donating groups afforded the desired product with good yields, which might be due to the increase in the electron density towards the nucleus of the haloarenes, thereby facilitating the reaction faster (Table 3). Bromo and iodobenzene were tried, which afforded the product with excellent yields and the order of reactivity of the haloarenes are I > Br (Table 3). Haloarenes with electron-withdrawing group such as NO_2 needed more time for completion but gave good yield (Table 3, entry 2k, 2l, 2m, 2n, 2o) of the product. On the other hand, aromatic thiols with electron-donating group also produce a better result (Table 3). The reaction was also examined with the aliphatic thiol, which also gave the corresponding product in good yield (Table 3, entry 2s, 2t). Thus, it appeared that (Table 3) the newly developed catalyst might direct the C–S coupling reaction with a wide range of substrates.

Experimental

Preparation and characterization of catalyst

Synthesis of the catalyst The Cu(II) catalyst has been prepared by the procedure reported [47]. In a multicomponent template synthesis of tri-aryl imidazole, the titled copper complex was obtained when 2-hydroxy 5-nitro benzaldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2.5 mmol) were allowed to react in the presence of CuB_4O_7 (1 mmol) at a temperature 130 °C in the presence of silica

Table 4 Comparative study of catalytic action of the synthesized organo-copper catalyst in S-arylation reaction with previously reported organo-metal systems

Entry	Catalyst	Solvent	Base	Temperature (°C)	Time (h)	Yield (%)	Ref.
1	[Tpm*CuI]	Dioxane	LiO*t*Bu	110	24	95	[52]
2	PS-C22-CuI	DMF/H_2O	Cs_2CO_3	90	7	91	[53]
3	[MNP-Si-NHC(Bz)-Ni]	DMF	Cs_2CO_3	100	10	87	[54]
4	$[Cu(C_{21}H_{14}N_3O_3)_2]\cdot 2H_2O$	H_2O	K_2CO_3	80	10	96	This work

Tpm*(tris(pyrazolyl)- methane ligands), PS-C22- CuI(polystyrene resin-supported copper(I) iodide-cryptand-22 complex), [MNP-Si-NHC(Bz)-Ni] (magnetite/silica nanoparticle-supported N-heterocyclic carbene nickel catalyst)

gel as a solid support. After completion of the reaction, blue coloured crystal was obtained and the product was washed with methanol followed by diethyl ether to afford the pure complex. Melting point > 300 °C, IR (KBr, cm^{-1}): 3430 (O–H stretching of H_2O), 3065 (N–H Stretching), 2926 (Aromatic C–H Stretching), 1578 (C=N Stretching), 1487, 1135 (C–H stretching), 466 (Cu–N stretching) (Figs. 1, 2).

Leaching of metal from the heterogeneous organo-copper catalyst was examined by the hot filtration test as described in the literature [48]. After 2 h of reaction, the reaction mixture was filtered to separate out the catalyst and HPLC was carried out with the obtained filtrate (20% conversion). The AAS analysis of the filtrate showed the absence of any copper. The filtrate was then heated for another 4 h. At 80 °C without the addition of catalyst, the corresponding HPLC pattern (Fig. 3) did not show any noticeable conversion, which implied that metals are not getting leached from the solid organo-copper catalyst during first 2 h of the reaction.

From the earlier reports [49–51], a plausible mechanism was proposed to access for the S-arylation reaction under the catalysis of organo-copper complex (Fig. 4). The first step is the oxidative addition of the copper complex to the aryl halide to form corresponding species A. Reaction with anionic thiols, which produced by reaction of the thiols and base, via trans metalation forms the species B. Reductive elimination of the desired product restores the original organo-copper catalyst and completes the catalytic cycle (Fig. 4).

The present catalyst was found to be excellent in case of S-arylation reaction between iodobenzene and thiophenol and its substituents. A comparative study is shown in Table 4.

Conclusions

We investigate the catalytic activity of our synthesized copper(II) catalyst in the C–S cross-coupling reaction of haloarene and thiols in water medium and obtain the expected product in a good yield. The recyclability of the synthesized catalyst was found to be capable up to fourth run without significant loss of the yield of the product. The catalyst was also easily recovered after completion of the reaction.

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Orginal Research Article

A greener and sustainable approach towards the synthesis of propargylamine using multicomponent A^3-coupling reaction

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ABSTRACT

The abundance of toxic contaminated effluents from the pharmaceutical industries and the serious risk of contamination of the aquatic systems were combined to provide strong motivating factors to tackle this environmental problem. Use of non-hazardous chemicals in aqueous medium is an interesting ecological alternative for the bulk production of important drugs and fine chemicals. Taking advantage of the remarkable ability of the selected catalytic systems, alternative sustainable methods have been exploited for the decontamination of industrial effluents and exhausts. In this work, we presented a newly developed metal-organic complex [Bis(picolinate-$\kappa^2N:O$) Cu(II)] catalysed A^3-coupling reaction in water which has established an excellent greener protocol to yield propargylamine. Low toxicity, easy access to active sites, high surface area, high thermal stability, recyclability of the catalyst, and easy way to separate the catalyst from the reaction mixture are the added advantage of this developed greener and sustainable protocol.

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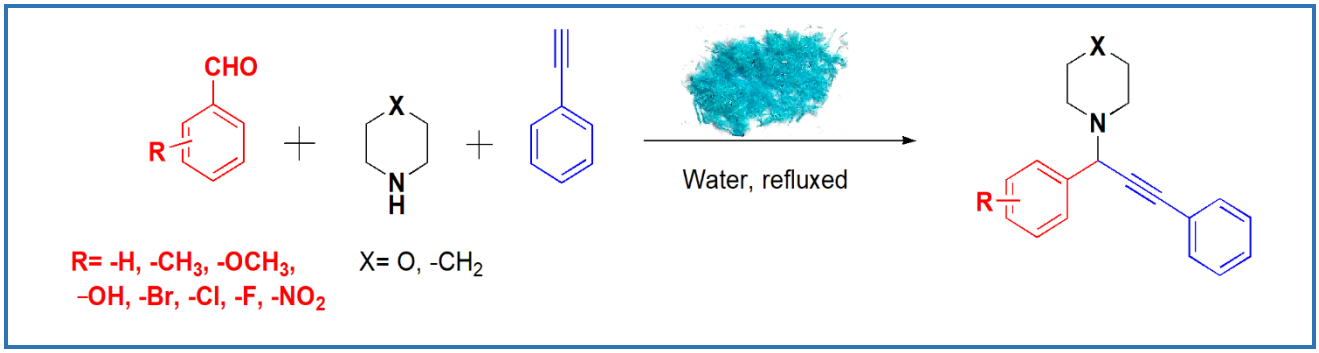
Graphical Abstract



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Introduction

Development of multicomponent reaction through the sustainable and cost effective greener approach for the synthesis of biologically active compounds and fine chemicals have attracted a great deal of attention from the researchers [1]. The modern organic synthesis multicomponent reactions (MCR) are established as most efficient tools for developing a simple, cost efficient process, maintaining atom economy and the designing of straight forward reaction protocol [2–10]. Amongst the recently developed various methods established so far for the synthesis of bio-active compounds, A^3-coupling reaction is one of the most fascinating approach. It is also well documented that three component A^3-coupling reaction is one of the most important synthetic tools for the synthesis of various propargylamine through the C-H activation of terminal alkynes [11–16]. Propargylamines are widely utilized as a key intermediate for building various nitrogen containing heterocycles and biologically active compounds [17–20]. The amine functional group were used as a precursor to develope various important biologicall y active *N*-heterocycles such as, pyrrolo[1,2-α]-quinoline, quinolones, amino indolizine setc [21], compounds possessing a wide variety of biological and medicinal properties such as alzheimer [22], antiparkinson [23], and anti-apoptotic [24]. Due to their wide range of applications, development of a very simple, cost effective and sustainable protocol has always been a challenge for the researchers and as a consequence, variety of catalytic procedure has so far been reported for the synthesis of these important classes of amines, propargylamines. Various transition metal-based catalysts such as, NHC-Ag (I) complex [25a], $AuBr_3$ [25b], Fe_3O_4 nanoparticles [26], Ni-Y zeolite [27], Chitosan/Zn $(NO_3)_2$ composite [28a], silica-immobilized CuI [28b], $InCl_3$ [29], $CoCl_2(PPh_3)_2$ [30], $[IrCl(cod)]_2$ [31], $BiCl_3$ [32], CdI_2 [33], $MnCl_2$ [34], Hg_2Cl_2 [35] have reported so far for their synthesis and copper is the most commonly studied metal among the various metal catalyst applied for the A^3-coupling reaction [36, 37]. However, homogeneous nature of the catalytic system has been the major drawback of their usage in practical application. Some of the heterogeneous catalytic system such as silica-immobilized CuI, [38], amberlyst A-21 supported CuI [39], lanthanum loaded CuO NPs [40], Cu-Ni bimetallic [41], copper ferrite NPs [42], graphene oxide-supported $CuCl_2$ [43], Cu (II) Schiff base complex immobilized on graphene oxide [44] have been reported so far. However, most of them suffer from several disadvantages including, low thermal stability, separation problem, significant leaching after several cycles of the reaction and the use of toxic solvents in most of the cases. A close observation of the results indicated a dire need of cleaner approach to enrich the scope and applicability of such reaction (A^3-coupling) in the present context of establishing green and sustainable protocols. Therefore, improvement in the area of development of suitable catalyst, solvent, the reaction temperature, and reaction hours would certainly make the protocol much more applicable to accept it as a clean and green method for the synthesis of the versatile biological

precursor, propargylamine, over the existing methods. Furthermore, it is also apparent that, in line with the current trends in sustainable and green chemistry, copper-based heterogeneous catalytic reactions are reported in the literature. This area of research continues to evolve as a more suitable approach because of its crucial advantages such as the easy separation of products from catalyst, a high stability of the heterogeneous catalysts, and most importantly, their recyclability. In that aspect, protocols comprising heterogeneous copper catalysts employing C-C coupling reaction are certainly worth mentioning.

Keeping these views in mind we have synthesized a very specific organo-copper complex, and simultaneously applied it to establish a greener and efficient multicomponent A^3-coupling reaction for the synthesis of propargylamine.

Experimental

Materials and methods

All the chemicals and solvents were purchased from the Sigma-Aldrich and Alfa aeser chemical suppliers. All the synthesized products were purified by column chromatography on 60-120 mesh silica gel (SRL, India). IR spectra were recorded on KBr disc for the compounds at the range of 4000-400 cm^{-1} on Shimadzu FT-IR 8300 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on 400 MHz and 300 MHz Bruker avance FT-NMR spectrometer using $CDCl_3$.

General procedure for synthesis of propargylamine

A mixture of benzaldehyde (1 mmol), phenylacetylene (1 mmol), and morpholine (1 mmol) in 5 mL water was stirred at 80 °C and the progress of the reaction was monitored using the TLC. After completion of the reaction, the reaction mass cooled, then the solution was poured in 100 mL water and extracted with ethyl acetate, washed several time with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate (95:5) as eluent to afford the pure product.

4-(1,3-diphenylprop-2-ynyl)morpholine (3a)

Brown oil, yield 95%, ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 4H), 3.62 (s, 4H), 4.68 (s, 1H), 7.20-7.28 (m, 6H), 7.39-7.43 (m, 2H), 7.53 (d, J = 7.2 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.4, 49.4, 61.6, 66.7, 84.6, 88, 117.6, 122.5, 127.3, 127.7, 127.8, 128.1, 131.3, 137.4.

4-(3-phenyl-1-o-tolylprop-2-ynyl)morpholine (3b)

White liquid, yield 96%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.52 (s, 4H), 3.56-3.60 (t, J = 9.3, 4H), 7.09-7.11 (m, 3H), 7.20-7.22 (m, 3H), 7.40-7.43 (m, 2H), 7.58-7.60 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 18.6, 49.3, 59.3, 66.7, 84.6, 88.1, 122.6, 124.9, 127.3, 127.7, 127.8, 128.5, 130.2, 131.3, 135.3, 137.

4-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)morpholine (3c)

Brown oil, yield 96%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 4H), 3.73 (s, 3H), 3.80 (s, 4H), 4.73 (s, 1H), 6.89 (d, J = 9Hz, 2H), 7.31-7.33 (m, 3H), 7.49-7.55 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49.3, 54.8, 60.9, 66.6, 84.8, 87.7, 113, 122.5, 127.7, 127.8, 129.2, 131.3, 158.7, 161.8.

4-(3-phenyl-1-p-tolylprop-2-ynyl)morpholine (3d)

White liquid, yield 96%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.66-2.67 (m, 4H), 3.77 (s, 4H), 4.79 (s, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.35-7.37 (m, 3H), 7.54-7.56 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20, 48.8, 60.7, 66, 84.3, 87.2, 122, 127.1, 127.2, 127.4, 127.8, 130.7, 133.7, 136.3, 161.8.

4-(1-(2-bromophenyl)-3-phenylprop-2-ynyl)morpholine (3e)

Brown oil, yield 90%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 4H), 3.68 (s, 4H), 5.06 (s, 1H), 7.12-7.17 (m, 1H), 7.22-7.31 (m, 4H), 7.48-7.59 (m, 3H), 7.73-7.75 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49.7, 61.3, 67.1, 84.6, 88.6, 122.8, 125.2, 126.9, 128.3, 129.3, 130.6, 131.8, 133.3, 137.2.

4-(1-(naphthalen-3-yl)-3-phenylprop-2-ynyl)morpholine (3f)

Orange oil, yield 92%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 4H), 3.74 (s, 4H), 4.92 (s, 1H), 7.33-7.35 (m, 3H), 7.46-7.49 (m, 2H), 7.54-7.57 (m, 2H), 7.72-7.75 (m, 1H), 7.82-7.85 (m, 3H), 8.08 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49.5, 61.7, 66.7, 84.5, 88.3, 122.5, 125.6, 126, 127, 127.1, 127.5, 127.6, 127.8, 131.3, 132.6, 134.9.

4-(1-(naphthalen-8-yl)-3-phenylprop-2-ynyl)morpholine (3g)

Orange oil, yield 93%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 4H), 3.65 (s, 4H), 5.40 (s, 1H), 7.29 (m, 3H), 7.39-7.52 (m, 5H), 7.77-7.92 (m, 3H), 8.35 (d, J = 7.8 Hz, 1H). ^{13}C NMR (300 MHz , $CDCl_3$): δ 49.9, 60.2, 67.2, 85.1, 89.1, 123.1, 124.8, 125.7, 126, 127.2, 128.3, 128.4, 128.6, 129, 131.7, 131.9, 133.2, 134.1.

4-(3-phenyl-1-(thiophen-2-yl)prop-2-ynyl)morpholine (3h)

Brown oil, yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 4H), 3.76 (s, 4H), 6.97-6.98 (m, 1H), 4.99 (s, 1H), 7.24-7.34 (m, 5H), 7.51 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49.6, 57.8, 67.1, 84.2, 87.5, 122.6, 125.7, 126.3, 126.3, 128.3, 128.4, 131.8, 142.8.

4-(1-(4-fluorophenyl)-3-phenylprop-2-ynyl)morpholine (3i)

Brown oil, yield 85%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60-2.62 (m, 4H), 3.71-3.73 (m, 4H), 4.75 (s, 1H), 7.01-7.07 (m, 2H), 7.31-7.33 (m, 3H), 7.49-752 (m, 2H), 7.58-7.59 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49, 57.3, 66.3, 81.4, 90.1, 121.9, 123.8, 127.9, 128.1, 128.3, 129.6, 130.9, 131.3, 131.6, 149.4.

4-(1-(2-nitrophenyl)-3-phenylprop-2-ynyl)morpholine (3j)

Brown oil, yield 84%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 2H), 2.62 (s, 2H), 3.63 (s, 4H), 5.65 (s, 1H), 7.26-7.56 (m, 7H), 7.71 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 49, 57.3, 66.3, 81.4, 90.1, 121.9, 123.8, 127.9, 128.1, 128.3, 129.6, 130.9, 131.3, 131.6, 149.4.

1-(3-phenyl-1-p-tolylprop-2-ynyl)piperidine (3k)

Pale yellow oil, 94%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.05 (d, J = 7.2 Hz, 2H), 7.19-7.20 (m, 2H), 7.40-7.42 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.6, 24, 25.7, 50.2, 61.7, 85.9, 87.2, 123, 127.5, 127.7, 128, 128.3, 131.3, 135.2, 136.5.

1-(3-phenyl-1-o-tolylprop-2-ynyl)piperidine (3l)

Pale yellow oil, yield 93%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 2H), 1.47-1.49 (m, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.65 (s, 1H), 7.06 (d, J = 7.2 Hz, 2H), 7.19-7.20 (m, 3H), 7.40-7.42 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20, 25.1, 28.6, 49.6, 61.1, 85.3, 86.5, 122.4, 126.9, 127.2, 127.4, 127.7, 130.7, 134.6, 135.9.

1-(1-(4-fluorophenyl)-3-phenylprop-2-ynyl)piperidine (3m)

Brown oil, yield 88%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43-1.59 (m, 6H), 2.53 (s, 4H), 4.76 (s, 1H), 7.00-7.05 (m, 2H), 7.31-7.32 (m, 3H), 7.49-7.51 (m, 2H), 7.57-7.61 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.3, 25.6, 49.5, 60.5, 84.6, 87, 113.5, 113.8, 127, 127.1, 127.8, 130.6, 133.3.

1-(1,3-diphenylprop-2-ynyl)piperidine (3n)

Pale yellow oil, yield 96%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32-1.64 (m, 8H), 2.60-2.62 (m, 4H), 4.85 (s, 1H), 7.29-7.47 (m, 7H), 7.56-7.71 (m, 3H), 7.85-7.91 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 25.7, 29.1, 50.2, 61.9, 85.6, 87.3, 121.7, 122.9, 128.4, 130, 131.3, 132.2, 138.2, 144.3.

2-(3-phenyl-1-(piperidin-1-yl)prop-2-ynyl)phenol (3o)

Brown oil, yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 2H), 1.67 (s, 4H), 2.70-2.73 (m, 4H), 5.08 (s, 1H), 6.83-6.87 (m, 2H), 7.18-7.25 (m, 1H), 7.34-7.38 (m, 3H), 7.51-7.57 (m, 3H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 24, 26, 50, 61, 82.3, 89.8, 116.3, 119, 121.3, 122.6, 128.4, 128.4, 128.5, 129.3, 131.9, 157.6.

4-benzyl-1-(1,3-diphenylprop-2-ynyl)piperidine (3p)

Pale yellow, yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43-1.47 (m, 1H), 1.50-153 (m, 1H), 1.59-1.67 (m, 2H), 1.75-1.78 (m, 1H), 2.21-2.27 (m, 1H), 2.53-2.61 (m, 3H), 2.72-2.75 (m, 1H), 3.02-3.05 (m, 1H), 4.89 (m, 1H), 7.19-27 (m, 3H), 7.31-7.44 (m, 8H), 7.56-7.58 (m, 2H), 7.69-7.71 (m, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 32.1, 37.5, 42.8, 46.9, 52.2, 61.6, 85.5, 87.5, 122.8, 125.3, 127.1, 127.6, 127.7, 127.8, 128.1, 128.7, 131.4, 138.1, 140.4.

4-(1,5-diphenylpent-2-ynyl)morpholine (3q)

Brown oil, yield 86%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35-2.46 (m, 4H), 2.58-2.62 (m, 2H), 2.84-2.88 (m, 2H), 3.61-3.68 (m, 4H), 4.45 (s, 1H), 7.03-7.30 (m, 8H), 7.37-7.45 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.5, 29.3, 34.8, 49.3, 61.2, 66.7, 87.3, 125.9, 127.1, 127.6, 127.8, 128, 128.1, 128.4, 137.8, 140.2.

2-(1-(4-benzylpiperidin-1-yl)-3-phenylprop-2-ynyl)phenol (3r)

Yellow viscous liquid, yield 85%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26-1.48 (m, 2H), 1.56-1.81 (m, 3H), 2.33-2.40 (m, 1H), 2.52-2.54 (m, 2H), 2.65-2.74 (m, 2H), 3.00-3.04 (m, 1H), 5.10 (s, 1H), 6.82-6.86 (m, 2H), 7.10-7.34 (m, 9H), 7.49-7.55 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 31.9, 32.5, 37.7, 42.9, 46.4, 52, 60.7, 89.9, 116.4, 119.1, 121.3, 122.5, 125.9, 128.2, 128.4, 128.6, 129.1, 129.4, 131.9, 140.3, 157.6.

2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-ynyl)phenol (3s)

Pale yellow semisolid, yield 90%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87-1.89 (m, 4H), 2.78-2.88 (m, 4H), 5.29 (s, 1H), 6.82-6.87 (m, 2H), 7.19-7.27 (m, 1H), 7.34-7.37 (m, 3H), 7.51-7.54 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.8, 48.9, 57.1, 83, 89, 116.2, 118.9, 122.2, 122.6, 127.8, 128.4, 128.5, 128.8, 129.9, 131.9, 157.6.

1-(1-phenylpent-1-yn-3-yl)pyrrolidine (3t)

Light brown viscous liquid; yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06-1.10 (m, 3H), 1.69-1.80 (m, 5H), 2.69-2.78 (m, 5H), 3.61 (s, 1H), 7.25-7.29 (m, 3H), 7.41-7.43 (m, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 10.06, 23.05, 27.72, 49.40, 56.47, 84.93, 87.58, 122.98, 127.85, 129.06, 131.27.

1-(1-phenylnon-1-yn-3-yl)pyrrolidine (3u)

Pale yellow oil, yield 70%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.37 (m, 3H), 1.44-1.49 (m, 5H), 1.53-1.59 (m, 2H), 1.68-1.69 (m, 2H), 1.71-1.75 (m, 4H), 1.99 (s, 1H), 2.68-2.77 (m, 4H), 3.67-3.69 (m, 1H), 7.41-7.42 (m, 2H), 7.25-7.28 (m, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 13.6, 22.1, 23, 26.2, 28.6, 31.3, 34.6, 49.2, 54.7, 84.8, 87.8, 123, 127.3, 127.7, 131.2.

1-(1-(2-chlorophenyl)-3-phenylprop-2-ynyl)piperidine (3v)

Brown oil, yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52-1.54 (m, 2H), 1.66-1.68 (m, 4H), 2.73 (s, 4H), 5.22 (s, 1H), 7.14-7.60 (m, 6H), 7.67-7.76 (m, 2H), 7.86-8.01 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 25.7, 29.2, 50.3, 58.9, 85.4, 87.3, 122.8, 125.7, 126.7, 127.8, 128.9, 129.3, 130.1, 131.3, 134.3, 136.12.

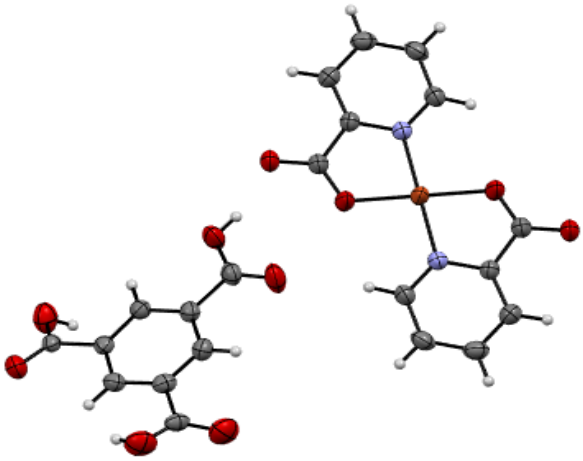


Figure 1. Single crystal X-ray analysis

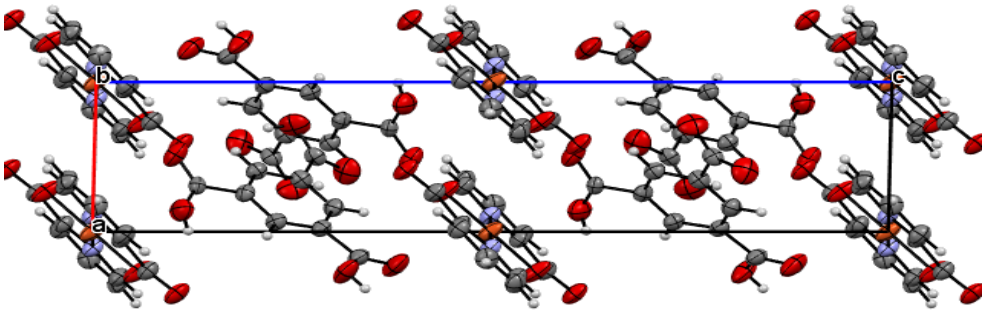


Figure 2. Packing diaram of the synthsized catalyst

Synthesis of Copper complex

The copper (II) complex [45] was synthesized using a typical hydrothermal reaction. 1 mmol (0.123 g) pyridine-2-carboxylic acid, 1 mmol (0.21 g) trimesic acid and 1 mmol (0.242 g) of copper nitrate di-hydrate was grinded in an agate motor and pastel. The blue colored mass obtained was then carefully transferred in a 10 mL teflon lined stainless steel autoclave and 5 mL of distilled water was added. The reaction mixture was stirred for 30 min with the help of magnetic stirrer to get a suspension. It was then heated in an automated hot air oven at a temperature of 150 °C for 48 h. The autoclave was then cooled to room temperature and the obtained product was filtered, washed with ethanol and water to remove the impurities in the compound. The compound was then dried over the vacuum pump.

Results and Discussion

Characterization of copper (II) complex

The copper (II) complex was characterized using various analytical techniques including, single crystal X-ray diffraction analysis, field emission scanning electron microscope (FE-SEM), and Fourier-transform infrared spectroscopy (FT-IR). The synthesized blue coloured copper (II) complex was air stable and has the melting point of above 300 °C. Single crystal analysis of the complex revealed that, the complex was crystallized in monoclinic crystal system with space group P 121/c1. The crystal structure and the packing of the complex are demonstrated in Figure 1 and Figure 2, respectively.

FE-SEM analysis

The field emission scanning electron microscopy (INSPECT F-50, FEI, Netherland) analysis was carried out to analyze the morphology of the symthesized copper (II) complex. From the electron micrograph of the complex, it is clear that the crystals have rod like morphology having several millimeters in length and thickness of 0.6-1 μm. As seen in the SEM micrographsof the copper (II) complex (Figure 3), the complex has same morphology and the bulk of the crystal has rectangular morphology or squared cross section. It is also evident from the ruptured crystal that the single crystals are composed of long filamentous grains running along the length of the crystals.

FT-IR analysis

The FT-IR spectra of the synthesized copper (II) complex showed peaks (ν/cm^{-1}) at 3091 (m), 1718 (s), 1599 (s), 1320 (s), 471 (w), 423 (w) and all these data mathes well with the earlier reported complex [45].

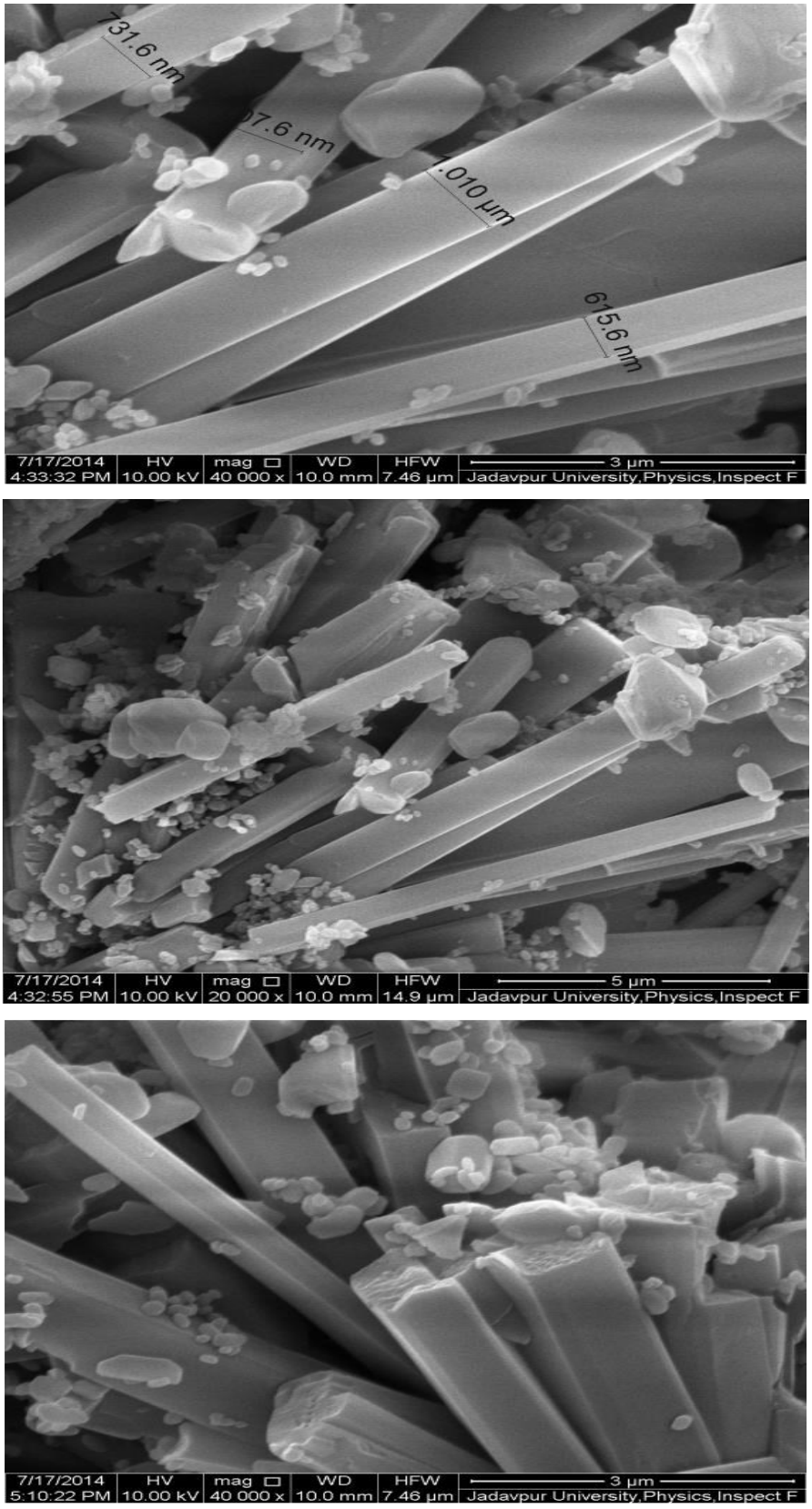


Figure 3. SEM image of the synthesized catalyst

In order to explore the catalytic activity of the newly developed greener catalyst, we put this in A^3-coupling reaction with benzaldehyde (1 mmol), phenylacetylene (1 mmol) and morpholine as a model reaction under reflux using water as solvent. The reaction was completed in 8 h with a 95% yield of the desired product (Table 1, entry 6). However, when the same reaction was attempted under the similar condition in the absence of catalyst we did not get the desired product. Therefore, we can conclude that the reaction did not occur in absence of catalyst (Table 1, entry 1).

Table 1. Optimization of reaction parameters for the synthesis of propargylamine derivatives[a]

Entry	Catalyst (mg)	Time (h)	Temperature (°C)	Solvent (5 mL)	Yield[b] (%)
1	-	24	80	Water	NR
2	2	12	80	Water	30
3	4	12	80	Neat	50
4	6	8	80	Water	80
5	8	8	50	Water	73
6	10	8	80	Water	95
7	10	12	80	Water	96
8	12	8	80	Water	95
9	14	8	80	Water	93
10	10	8	60	Water	75
11	10	8	70	Water	80
12	10	8	90	Water	90
13	10	8	80	Toluene	60
14	10	8	80	DMSO	59
15	10	8	80	DMF	86
16	10	8	80	Ethanol	87
17	10	24	RT[c]	Water	NR

[a] Reaction conditions: Benzaldehyde (1 mmol), phenylacetylene (1 mmol), morpholine (1 mmol), Copper catalyst (10 mg) at different temperatures and solvent

[b] Isolated yields

[c] Room temperature reaction

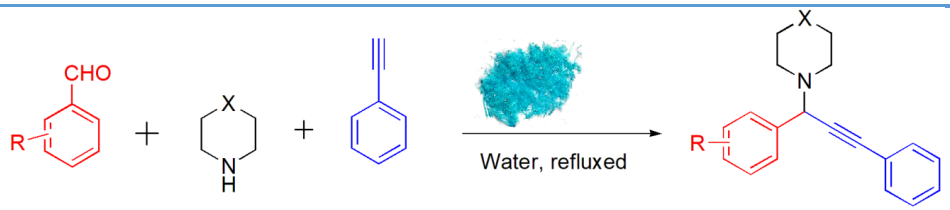
Therefore, to optimize the protocol, the model reaction was repeated with varying amount of the synthesized copper catalyst (Table 1) and out of all attempts we established that 10 mg of the catalyst (per mmol of the reactants) yielded the best result. We also tried various solvents including, DCM, DMF, toluene, DMSO, however could not beat the superiority of water as solvent.

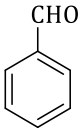
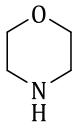
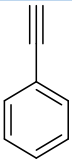
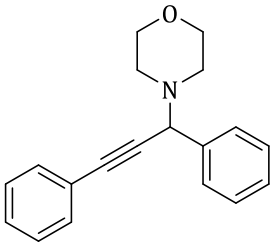
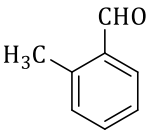
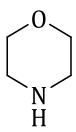
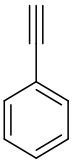
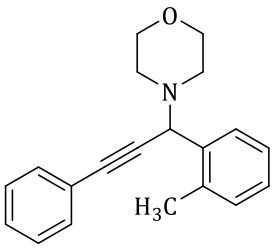
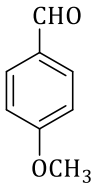
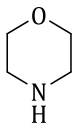
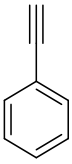
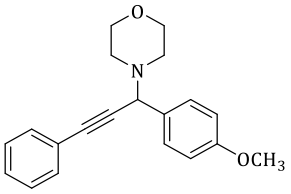
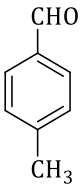
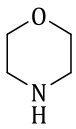
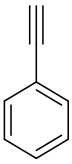
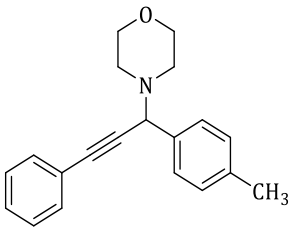
Thus, the fortunately water was established as the optimal medium of the reaction. The reaction was also carried out in solvent free condition which also afforded the corresponding product but with only moderate yield (Table 1, entry 3). Further, to optimize the temperature, the model reaction was carried out at 50, 60, 70, 80, and 90 °C. Among them, the best yield was obtained at 80 °C (Table 1, entry 6). As seen in Table 1, yields were gradually increased with enhancing the temperature and the best result was obtained at 80 °C. At a temperature beyond 80 °C the increase of yield was not considerable and as a result, 80 °C was taken as an optimal temperature. The reaction was also tried at room temperature and even after 24 h of reaction we failed to isolate minimum yield of the product (Table 1, entry 17).

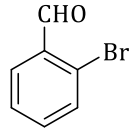
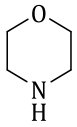
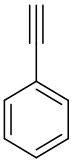
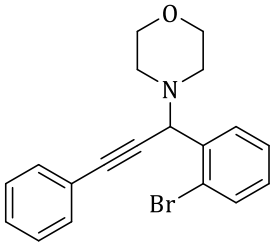
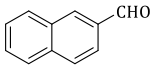
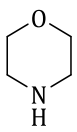
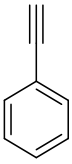
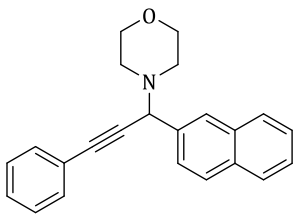
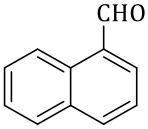
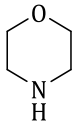
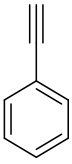
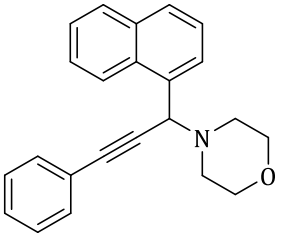
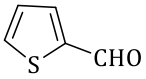
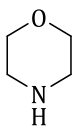
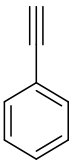
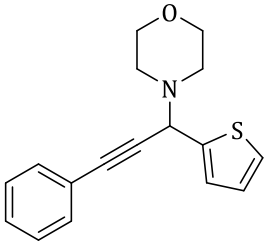
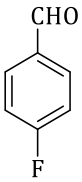
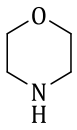
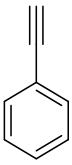
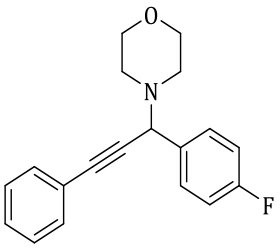
With this optimized condition we also carried out the same reaction by using the various amount of catalyst *viz.,* 2, 4, 6, 8, 10, 12, and 14 mg. We found that 10 mg catalyst (per mmol of the reactants) was sufficient for the complete conversion of the reaction to the desired product (Figure 4). Further increase in the amount of catalyst did not improve the yield of the product considerably. With this optimized greener and optimized reaction condition we performed the reaction with various substituents (Table 2). To investigate the generality and scope of the catalytic activity of the synthesized catalyst in A^3-coupling reaction, we carried out the reaction with a variety of aldehydes and terminal alkynes with different secondary amines. Both the electron donating/electron with drawing groups were employed with secondary amine. Aldehyde with electron donating groups afforded the desired product with high yield which might be due to the increased electron density in the aldehyde nucleus and thereby facilitating reaction faster (Table 2, entries 1-22). Bromo, chloro, and fluorobenzaldehydes were also tried and afforded excellent yields and the order of reactivity of aromatic halo aldehyde was –Br>-Cl>-F (Table 2, entries 5, 9, 13, 22). Aldehyde with electron withdrawing group such as $-NO_2$ was needed more time to complete and afforded low yield of the product (Table 2, entry 10). However, hetero aldehyde provided with good yield of the product (Table 2, entry 8). The above protocol was also examined with aliphatic aldehydes (Table 2, entries 20, 21), which yielded the corresponding product in good yield. Napthaldehydes were tried to determine the substrate scope of this reaction and the results afforded the desired product in good yield (Table 2, entries 6 and 7). As seen in Table 2, it is obvious that the newly developed greener catalyst may direct the A^3-coupling reaction for a wide range of substrate applicability for the synthesis of the propargylamine derivatives.

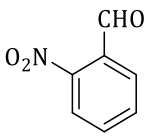
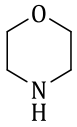
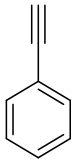
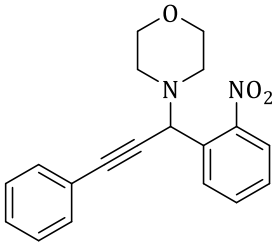
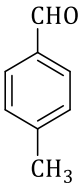
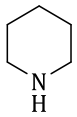
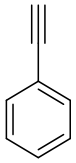
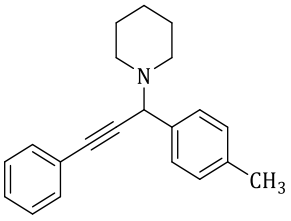
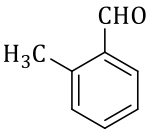
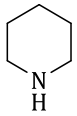
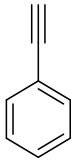
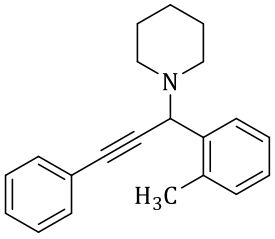
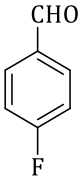
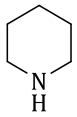
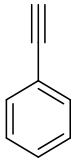
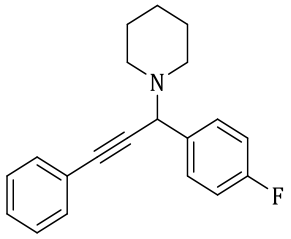
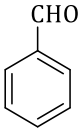
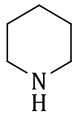
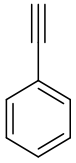
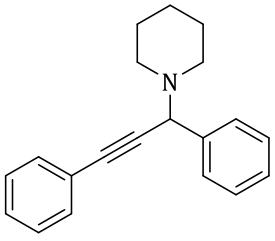
A plausible mechanism to access propargylamine involving aldehyde, phenylacetylene and morpholine at the presence of the synthesized catalyst is depicted in Scheme 1. It is assumed that, the reaction initiated by the nucleophilic attack of the amine to the activated electrophilic carbon of the aldehydic group, followed by removing the H_2O molecule to yield the iminium ion [46, 47].

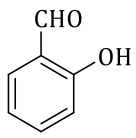
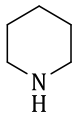
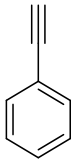
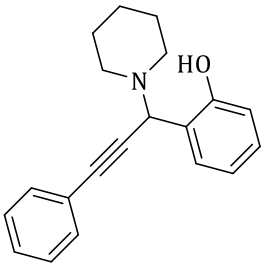
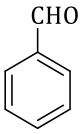
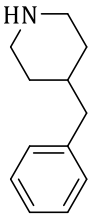
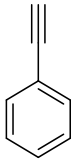
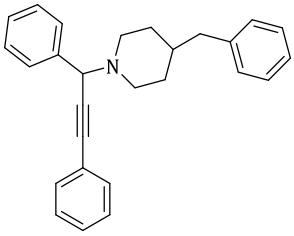
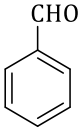
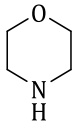
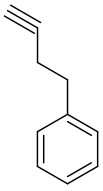
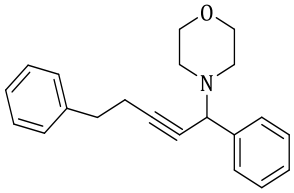
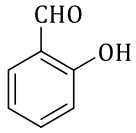
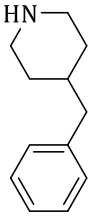
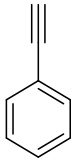
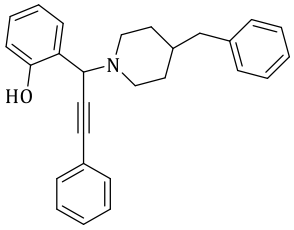
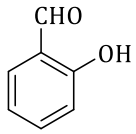
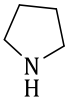
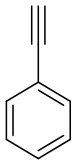
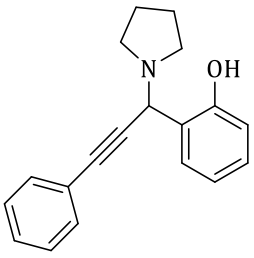
Table 2. Substrate scope of amines and aldehydes for the synthesis of Propargylamine[a]

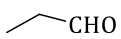
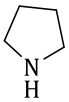
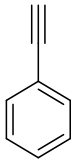
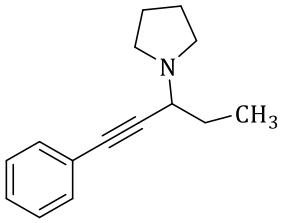
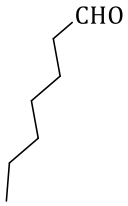
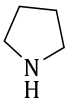
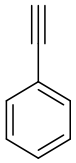
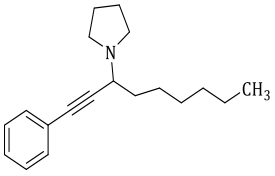
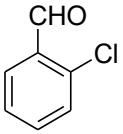
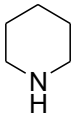
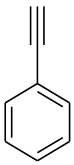
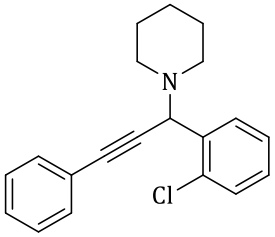


Entry	Aldehyde	Amine	Acetylene	Product	Time (h)	Yield[b] (%)
1				 **3a**	8	95
2				 **3b**	8	96
3				 **3c**	8	96
4				 **3d**	8	96

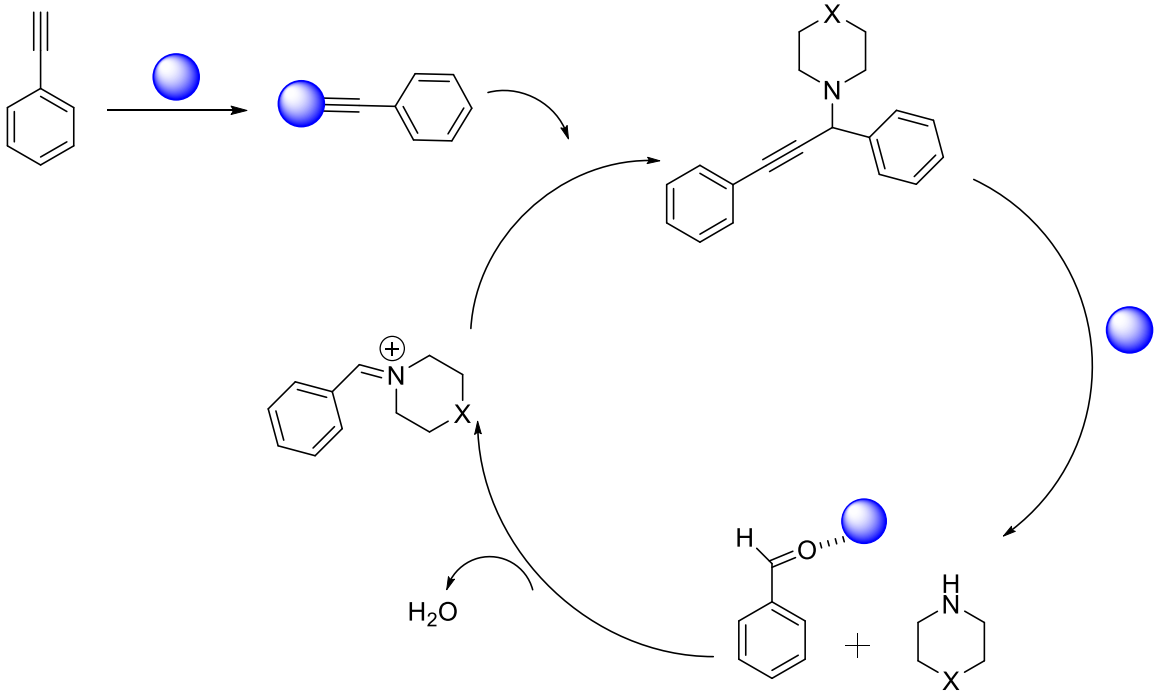
5				 **3e**	8	90
6				 **3f**	8	92
7				 **3g**	8	93
8				 **3h**	8	87
9				 **3i**	8	85

10				 **3j**	8	84
11				 **3k**	8	94
12				 **3l**	8	93
13				 **3m**	8	88
14				 **3n**	8	96

15				 **3o**	8	87
16				 **3p**	8	89
17				 **3q**	8	86
18				 **3r**	8	85
19				 **3s**	8	90

20				 **3t**	8	75
21				 **3u**	8	70
22				 **3v**	8	87

[a] Isolated yield



Scheme 1. Proposed mechanism of A[3]- coupling reaction

Simultaneously, the catalytically activated C-H bond of the phenylacetylene formed the active acetylidine complex [46, 47]. Finally, the activated acetylidine complex was added with the iminium ion to yield the corresponding propargylamine.

The comparison as depicted in Table 3, clearly indicates that the developed catalyst with significant TOF and TON value (entry 3) together with its calculated atom economy (93.89%) established the protocol as a greener and sustainable approach.

Table 3. Comparison of conventional Cu(II) catalytic systems with the newly developed catalyst for the synthesis of propargylamine at 80 °C

Entry	Catalyst	Mol% (Cu)	TOF (h^{-1})	TON	Ref
1	Cu(II)-MOF	3.0	16.33	32.67	36
2	CMC-Cu	5.0	2.1	18	37
3	[Bis(picolinate-$\kappa^2N:O$) Copper(II)]	1.37	86.58	692.70	Present work

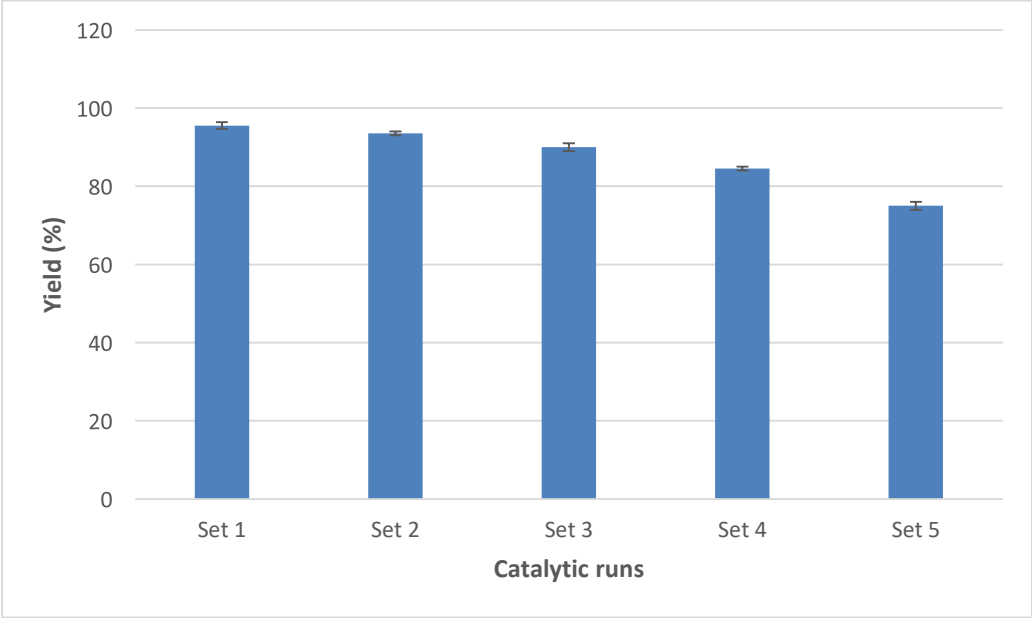


Figure 4. Recycling of [Bis (picolinate-$\kappa^2N:O$)copper(II)]di(benzene1,3,5-tricarboxylic acid)

Conclusions

In this work, the synthesized copper catalyst was applied in a greener and sustainable version of multicomponent A^3-coupling reaction of aldehyde, amine and terminal alkynes in water to obtain the desired product in good yield with excellent TOF, TON and atom economy. The recyclability of the

synthesized catalyst was found to be capable up to fifth run without any aggregation and significant metal leaching. The catalyst was also recovered easily after the completion of the reaction.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at DOI: http://dx.doi.org/10.22034/ajgc.2021.113192.

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Original Research Article

Transformative reaction on triterpenoids: action of hydrogen peroxide in presence of selenium dioxide on oxime derivative of taraxerone and antimicrobial activity of isolated compounds

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ABSTRACT

Although studies on oxidation of triterpenoid ketones with hydrogen peroxide and selenium dioxide have been reported, literature reports on the effect of the oxidizing agent on the oxime derivative of triterpenoid ketones are scanty. Thus in continuation of our previous studies on the transformative reactions on pentacyclic triterpenoids of lupane and friedelin skeleton and in order to examine the nature of the products formed on the oxidation of oxime derivatives of 3-keto-triterpenoids having gem dimethyl group at C4 and a double bond at ring D (between C14-C15), the oxidation of keto-oximes of taraxerone with hydrogen peroxide and selenium dioxide was taken up and characterisation of the products (A -D) along with the evaluation of their preliminary biological activity were studied in this work. The oxime derivative of taraxerone (1a) in tertiary butanol was refluxed with selenium dioxide and hydrogen peroxide. The residue obtained after recovery of solvent by distillation was extracted with ether and separated into neutral and acid parts using usual method.

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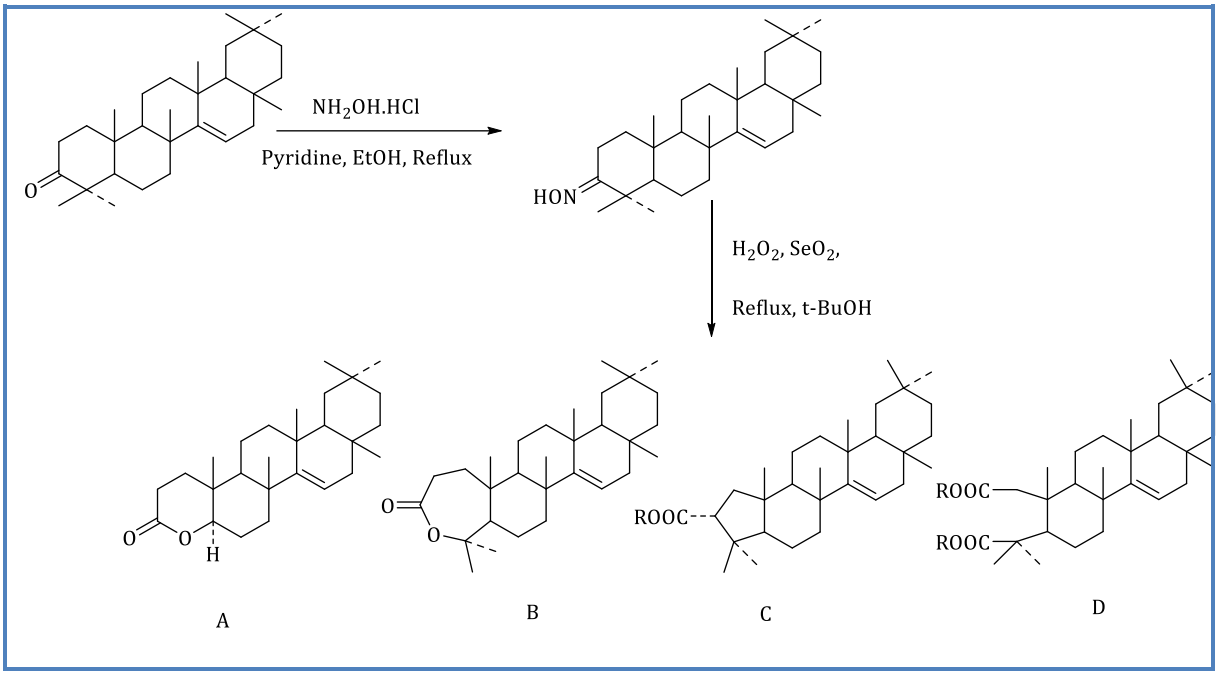
Graphical Abstract



Introduction

Plants derived triterpenoids natural products have attracted a great deal of attention for their efficient biological activity. These triterpenoids are consisted of five rings with some methyl groups in their skeleton. So, basically these are of C30-isoprenoid compounds with few functional groups in their skeleton [1]. Triterpenoids are the secondary metabolites widely present in plants and are traditionally used as medicines [2]. They show many biological activities including, antioxidant, antimicrobial, antiviral, antiallergic, antipruritic, antiangiogenic, and spasmolytic activity [3, 4]. To exploit the therapeutic potential of the natural triterpenoids or their derivatives, intense pharmacological and mechanistic studies have been carried out. Antitumor, antiviral, anti-inflammatory, antidiabetic, antiparasitic, antimicrobial, cardio-hepato and gastro-protective, analgesic and wound-healing effects are included in these bioactivities. So, we carried out the transformative reaction on the oxime derivative of taraxerone and antimicrobial activity of the isolated compounds.

Materials and Methods

Plant Material

Plants of Sapium baccatum ROXB used in this experiment were collected from North Bengal, India in May, 2016. We submitted specimens of Sapium baccatum with the tag numbers to Taxonomy and Environmental Biology Laboratory, Department of Botany, University of North Bengal, Darjeeling, India. After collection, all the plants were washed thoroughly by plenty of water and stem bark were separated by simple cutting through a knife in wet condition and separated these from the rest parts.The plant's materials were shade dried and cut into small pieces. It was then grinded in small lots in a mechanical grinder and used for the extraction process. IR spectra were recorded on KBr disc at the range of 4000-

400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 500 and 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard.

Isolation of Taraxerone from Sapium Baccatum ROXB:

Dried and powdered stem bark of Sapium baccatum ROXB (2 kgs) was extracted with toluene in a soxhlet apparatus for 20 h. On cooling the toluene extract, a yellow insoluble compound separated out, this was collected by filtration and was kept aside. This was identified as 3, 3/-di-o-methyl ellagic acid. From the clear filtrate, toluene was distilled off and the residual gummy solid (30 gms) was taken up in ether (2 ltrs). A cloudy precipitate which remained in the ether extract was separated by filtration. The clear ether solution was washed with 10% aqueous sodium hydroxide solution for three to four times and then washed with cold water till washings were neutral and dried over anhydrous Na_2SO_4.

The solvent was evaporated when the neutral material (11 gms) was obtained as a yellow gummy solid, which after chromatography and crystallisation from chloroform-methanol mixture gave shining crystals (1.3 gm) m.p 238-240 ˚C, [D]+ 10.80 identical in all respect

with authentic sample of taraxerone (mixed m.p. Co-1R ; Co-TLC). Other compounds isolated were 1-hexacosanol, taraxerol and baccatin.

Preparation of Oxime Derivative of Taraxerone

To a solution of taraxerone (3 g) dissolved in pyridine (30 mL) was added hydroxylamine hydrochloride (3 g) and ethanol (150 mL).The mixture was then refluxed in a water bath for 4 h. It was then cooled and poured over ice-cold water when white solid separated out. It was washed with water filtered through suction and dried. The dried mass was crystallised several times with chloroform-methanol mixture when taraxerone oxime m.p 250 ˚C was obtained.

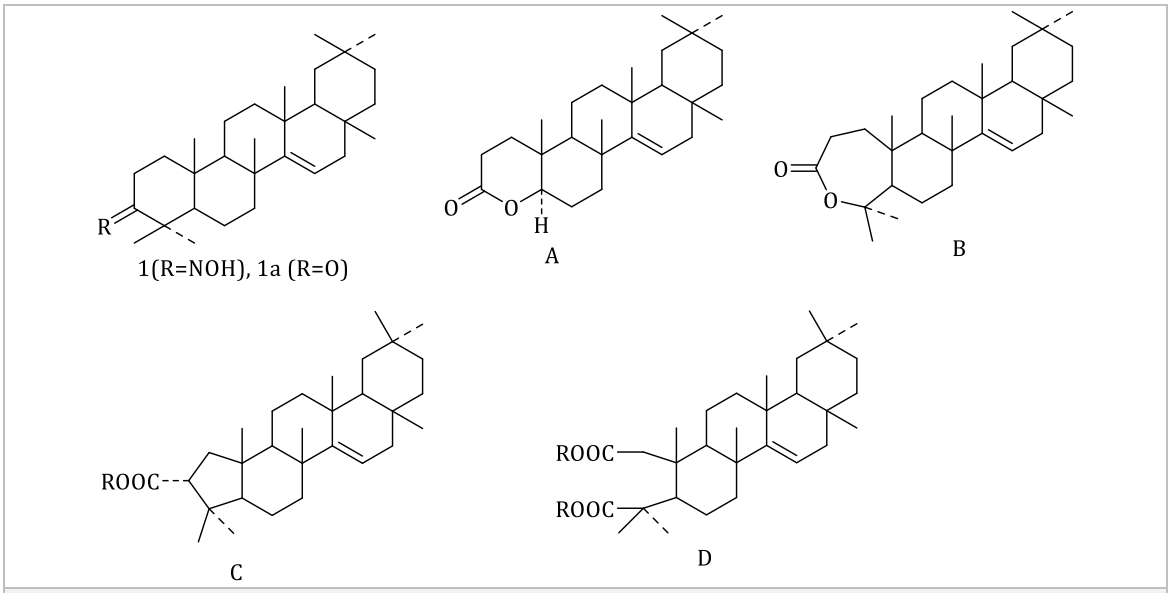


Figure 1. (1a) Taraxerone, (1) Oxime derivative of taraxerone, (A) 4,23,24-tri-nortaraxerene-3-5α H olide, (B) taraxerene-ϵ-lactone, (C) 2α-carbomethoxy-A-nor-taraxerene, (D) 2, 3-seco-methyl taraxerene dicarboxylate

Reaction of Taraxerone oxime (1) with molar proportion of hydrogen peroxide and catalytic amount of selenium-dioxide in tertiary butanol

Taraxerone oxime (1) prepared from taraxerone (1a) was subjected to oxidation with molar proportion of hydrogen peroxide and catalytic amount of selenium-dioxide in tertiary butanol by refluxing over water-bath for 20 h. The completion of the reaction was indicated by the precipitation of black selenium metal. After recovery of solvent by distillation, the residue was extracted with ether and separated into neutral and acid parts by the usual method.

The neutral part was chromatographed over silica-gel, the column on elution with petroleum ether: ethylacetate (2:3) mixture afforded a solid which on fractional crystallisation from chloroform-methanol afforded two solid compound A and B. Compound A was analysed for $C_{27}H_{42}O_2$ and compound B was analysed for $C_{30}H_{48}O_2$.

Structure Elucidation of Compound A

Compound A was recrystallized from chloroform-methanol mixture m.p 228-30 ˚C. It was analysed for $C_{27}H_{42}O_2$. Its IR-spectroscopy showed sharp absorption peak at 1750 cm^{-1} indicating the presence of a lactone carbonyl group and the other at 810 cm^{-1} indicating the presence of trisubstituted double bond that was supported by TNM test. Elemental analysis showed the molecular formula of compound A found to be $C_{27}H_{42}O_2$ which is in agreement with its mass-spectrum. It showed molecular ion peak at m/z 398(M^+) with the other fragment of prominence appeared at m/z 383(18.45); 274(100); 259; 204(75).The PMR-spectrum of Compound A showed the presence of a lactonic proton (-CO-O-CH-CH_2-) at 3.92 ppm as a quartet (q, Jae=5Hz; Jaα=12Hz) the appearance of multiplet at 2.26 ppm due to presence of methylene proton adjacent(alpha) to the carbonyl group (m, 2H,-O-CO-CH_2-CH_2-), the multiplet centered at 5.57 ppm was due to the presence of trisubstituted double bond proton of olefinic proton (m, 1H) and six tertiary methyls as singlet from 0.83 to 1.12 (6s, 18H, 6xt-CH_3) ppm. The high J-value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. Thus, from the study of IR, mass-spectrum and PMR-spectrum, the structure of the Compound A was assigned as 4, 23, 24-tri-nor-taraxerene-3-5α H olide (A).

Structure Elucidation of Compound B

Compound B was recrystallized from chloroform-methanol mixture m.p 218 ˚C. It was analysed for $C_{30}H_{28}O_2$. Its IR-spectroscopy showed sharp peak at 1720 cm^{-1} indicating the presence of a ϵ-lactone carbonyl group and the other at 810 cm^{-1} indicating the presence of trisubstituted double bond. The presence of the olefinic double bond is confirmed by the generation of yellow colour in TNM test. Elemental analysis revealed that the molecular formula of the compound B was $C_{30}H_{48}O_2$ which is in agreement with its mass-spectrum. It showed molecular ion peak at m/z 440 (M^+) and the other fragments of prominence at m/z 425, 316, 301, 205, 204, and 189. Thus, from the study of IR-spectrum and mass spectral analysis, the structure of the compound B was assigned as taraxerene-ϵ-lactone.

The genesis of the ion fragment m/z 316, 301, 204 and, 189 of the compound B is explained in Figure 2 shown below which stands as support for the structure (B).

The acid part showed two spots on chromoplate. The gummy mass was esterified with diazomethane and the products were separated by column chromatography on a deactivated alumina column. Elution with pet.ether (b.p 60-80 ˚C) furnished compound C which was crystallised from chloroform-

methanol mixture and analysed for $C_{31}H_{50}O_2$ m.p. 161-163 ˚C. Further elution of the column with pet.ether:ethylacetate (1:1) gave a white solid compound D which was crystallised from chloroform-methanol mixture and analysed for $C_{32}H_{52}O_4$, m.p. 151 ˚C.

Structure Elucidation of Compound C

Compound C was recrystallized from chloroform-methanol mixture m.p 161-163 ˚C. It was analysed for $C_{31}H_{50}O_2$. Its IR-spectroscopy showed peak at 1735 cm^{-1} indicating the presence of carbomethoxy group, at 1155 cm^{-1} for –C-O stretching vibration of the ester group and at 815 cm^{-1} indicating the presence of trisubstituted double bond. Elemental analysis showed the molecular formula of compound C is $C_{31}H_{50}O_2$ which in agreement with its mass-spectrum. It showed molecular ion peak at 454(M^+) (32) and the other fragments at 439(13); 330(14); 315(10); 287(20); 204(75).

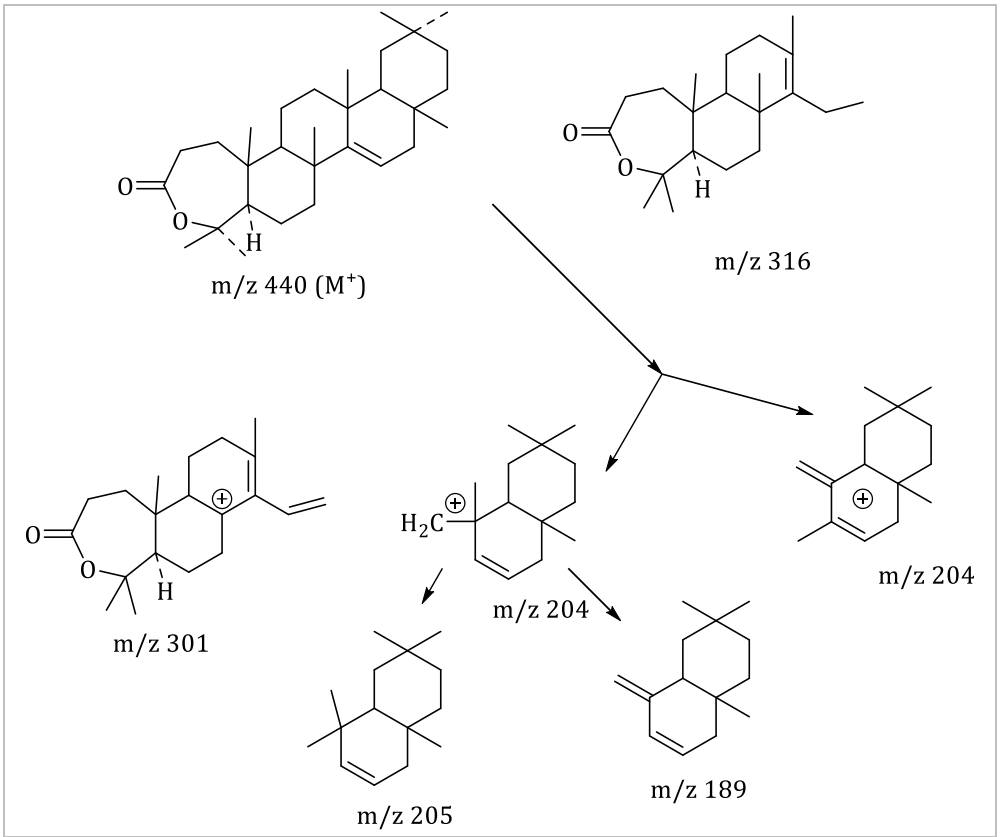


Figure 2. Genesis of the ion fragment m/z 316, 301, 204 and 189 of the compound B.

The 1H NMR-spectrum of compound C demonstrated the presence of eight tertiary methyl-group which resonated at 0.82; 0.85; 0.90; 0.92 ; 0.95; 0.99; 1.08 and 1.12 (8s;24H;8xt-CH_3) (ppm). A three proton singlet at 3.6 ppm shows the presence of carbomethoxy group in the compound (s, 3H;-$COOCH_3$). A quartet centered at 2.75 ppm integrablefor one proton may be assigned to the hydrogen atom germinal to the carbomethoxy group (q; 1H; J_{ae}=5 Hz, J_{aa}=11 Hz; -CH_2-C-CO-O). The J value also indicate that the proton is axially oriented with one axial and one equatorial neighbours. The multiplet at 5.54 ppm integral for one

proton indicate the presence of trisubstituted olefinic proton (m, 1H –C=CH). Thus, on the basis of spectral data the structure of compound has been assigned as 2α-carbomethoxy-A-nor-taraxerene(C).

Structure Elucidation of Compound D

Compound D was recrystallized from chloroform-methanol mixture m.p. 151 ˚C. It was analysed for $C_{32}H_{52}O_4$. Its IR-spectroscopy showed absorption peaks at 1725 cm^{-1} and 1730 cm^{-1} indicating the presence of two carbomethoxy group. Stretching frequency at 810 cm^{-1}indicates the presence of trisubstituted double bond. The absorption at 1440 cm^{-1} and 1140 cm^{-1} are due to $–CH_3$ vibration of ester group and –C-O stretching vibration of the ester group respectively.

The ^1H NMR-spectrum of the compound D showed eight singlet tertiary-methyl groups which resonated in the range 0.81-1.25 (8s; 24H; 8x t-CH_3) ppm. Two three proton singlet each 3.60 ppm and 3.65 ppm indicate the presence of two carbomethoxy group in the compound. The two proton multiplet centred at 2.3 is attributed to a methylene group alpha to a carbomethoxy group. The multiplet centred at 5.54 ppm is due to the presence of trisubstituted double bond. The mass-spectrum of the compound D showed molecular ion peak at m/z 500 (M^+), 485(6), 470(7), 468(9), 440(6), 399(7), 376(7), 361(2), 344(20), 316(12), 287(17), 204(100). All these spectral data analysis of the compound D assigned the structure as 2, 3-seco-methyl taraxerene dicarboxylate (D).

Biocidal Activity of Isolated Compounds

In this present work the in vitro antifungal, antibacterial activities and the phytotoxicity of isolated taraxerone (1a), 4,23,24-tri-nor-taraxerene-3-5α H olide [A], taraxerene-ϵ-lactone [B], 2α-carbomethoxy-A-nor-taraxerene [C], 2, 3-seco-methyl taraxerene dicarboxylate [D], have been studied. Five different fungal pathogens namely, Colletrichum gloeosporioides, Fusarium equisitae, Curvularia eragrostidies, Alternaria alternata and Colletotrichum camelliae were used for the antifungal study. For antibacterial study Escherichia Coli, Bacillus subtilis, Staphylococcus aureus, Enterobactor were used as bacterial pathogens. Suitable strains of these organisms were procured from the microbiology laboratory of our institute (for details see experimental). MICs (minimum inhibitory concentrations) of the triterpenoids against bacterial pathogens are presented in Table 1 and 2.

Table 1. MICs of 1a to D against different bacteria

Compounds	**MIC in µg/mL against different bacterial strains**			
	EC	BS	SA	EB
1a	100	100	98	96
A	130	<150	100	100
B	150	100	200	100
C	200	170	130	200
D	150	150	<150	100
Ampicillin	128	64	64	128

EC- Escherichia coli, BS- Bacillus subtilis, SA-Staphylococcus aureus, EB-Enterobactor, MIC-Minimum inhibitory concentration.

Table 2. MICs of 1a to D against different fungi

Compounds	MIC in µg/mL against different fungal strains				
	CG	FE	CE	AA	CC
1a	<5.0	20.0	40.0	10.0	<5.0
A	5.00	20.0	35.0	20.0	39.0
B	4.50	19.0	35.0	20.0	40.0
C	4.00	15.0	32.5	15.5	35.0
D	3.70	10.5	30.5	15.0	32.5
Bavistan	3.50	3.50	3.70	4.00	4.20

CG-Colletotrichum gloeosporioides, FE-Fusarium equisiti, CE- Curvularia eragrostidis, AA-Alternaria alternata, CC-Colletotrichum camelliae.

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