GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS

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IN

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UNDER THE FACULTY OF SCIENCE AND TECHNOLOGY

BY

Miss. ABOLI CHHAPPANRAO SAPKAL
M.Sc., SET

UNDER THE GUIDANCE OF

Dr. SANTOSH B. KAMBLE

M.Sc., Ph.D.

DEPARTMENT OF CHEMISTRY
YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE
(AUTONOMOUS) SATARA, 415001
MAHARASHRTA, INDIA

2023

DECLARATION AND UNDERTAKING

I hereby declare that the thesis entitled **"GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS"** completed and written by me has not previously formed the basis for the award of any Degree or Diploma or other similar title of this or any other University or examining body. Further, I declare that I have not violated any of the provisions under the acts of Copyright/Piracy/ Cyber/ IPR etc amended from time to time.

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Place: Kolhapur **(Miss. Aboli C. Sapkal)**

Date: Research Student

YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE (Autonomous),

SATARA

DEPARTMENT OF CHEMISTRY

Dr. Santosh B. Kamble

Assistant Professor
Raman Post-Doctoral Fellow (USA)
Y. C. Institute of Science, Satara-415001
Maharashtra, India
Phone: (02162)234392 Fax: (02346)250665
Mobile: 9823524565
Email:santosh.san143@gmail.com

CERTIFICATE

This is to certify that the thesis entitled **"GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS"** which is being submitted herewith for the award of the degree of **Doctor of Philosophy** in **CHEMISTRY** of Shivaji University, Kolhapur is the result of the original research work completed by **Miss. Aboli Chhappanrao Sapkal** under my supervision and guidance. To the best of my knowledge and belief, the work embodied in this thesis has not been the basis for the award of any Degree or similar title of this or any other University or examining body.

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Miss. Aboli C. Sapkal

TABLE OF CONTENT

ABBREVIATIONS

Aq	: Aqueous
Ar	: Aryl
^{13}C NMR	: Carbon nuclear magnetic resonance
$CDCl_3$	: Deuterated chloroform
CMC	: Critical micelle concentration
DCM	: Dichloro methane
DMSO	: Dimethyl sulfoxide
DMSO-d_6	: Deuterated dimethyl sulfoxide
FT-IR	: Fourier-transform infrared spectroscopy
EtOH	: Ethanol
GCMS	: Gas chromatography-mass spectrometry
^{1}H NMR	: Proton nuclear magnetic resonance
H_2O	: Water
HRMS	: High resolution mass spectroscopy
Hz	: Hertz
ILs	: Ionic liquids
IR	: Infrared
MeOH	: Methanol
MCRs	: Multi-component reactions
MHC	: Minimum hydrotropic concentration
mmol	: Millimole
MP	: Melting point
MS	: Mass spectroscopy
MW	: Microwave
NaPTS	: Sodium para toluene sulfonate
NaBS	: Sodium benzene sulfonate
NaXS	: Sodium para xylene sulfonate

PEG	: Polyethylene glycol
Ph	: Phenyl
ppm	: Pats per million
p-TSA	: para-Toluene sulfonic acid
RT	: Room temperature
TLC	: Thin layer chromatography
TMS	: Tetramethylsilane
US	: Ultrasonic irradiation
UV	: Ultraviolet
Z.Z.	: *Zingiber zerumbet*

GENERAL REMARKS

1. All chemicals used in the study were purchased from Sigma-Aldrich and Loba Chemical companies and used without additional drying or purification.

2. The spectra concerning each chapter (2 to 5) are given just after the experimental part.

3. Proton, carbon-13, and DEPT NMR spectra were recorded with a Bruker Ascend 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 as solvents, with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm.

4. Mass spectral analyses were recorded on the GCMS-QP2010 gas chromatograph mass spectrometer.

5. Fourier transform infrared (FT-IR) spectra were recorded on a Lamda FTIR 750 spectrometer (KBr).

6. High-resolution mass spectra were recorded on the Dionex UHPLC Ultimate 3000 system.

7. Optical microscopy measurements: a drop of turbid reaction mixture was subjected to light microscopy measurement using an OLYMPUS light microscope.

8. Melting points were determined using the electrical melting point apparatus EQ 730A-EQUIPTRONICS.

9. Sonication was performed in a SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz.

CHAPTER -1

Green Chemistry: "Hurt not the earth, neither the sea, nor the trees".

-Ronald C.D. Breslow.

CHAPTER 1

Green Methodology for Organic Transformations

1.1 Introduction

In the modern progressive era chemist have responsibility to grow environment friendly synthetic routes to achieve their goals without environmental hazards. So, chemists are competing to achieve this under naming of 'green' chemical transformations. Achieving such goal is particularly called "Green Chemistry". Now days in industries various hazardous chemicals are used which causes pollution this is hazardous to environment. The green chemistry is used to reduce carbon footprint and many hazardous by-products. Now intensely established routes in this field includes use of mild reaction conditions, lessening number of reaction steps, switching to less harmful reactants and reagents, use of solvent free processes, use of renewable energy sources, developing proficient purification and isolation processes in synthetic transformation etc.

Green Chemistry

Green chemistry is type of chemistry which performs various chemical processes that reduce or eliminate the usage and generation of hazardous substances. It actually practices techniques that are environmentally friendly. The Green chemistry is applicable in whole sequence of chemical product involving its scheme, manufacturing, use and final disposal. In present era green chemistry plays crucial role in synthetic chemistry. The term green chemistry was first invented by Paul Anastas in 1998 and then John C. Warner set up principles to practice under green chemistry that worldwide known as twelve principals of green chemistry [1], [2].

Nowadays green chemistry works powerful tool and it open up new doors for researchers to think new reaction conditions that have less impact on environment. Considering these new unconventional trends are in progression.

Need of Green Chemistry

In many ways human impact on the physical environment that triggered lots of pollution that mainly comprise climate change, poor air quality, undrinkable water and soil erosion. In that utilization of chemistry is everywhere which acquired principal position for such issue. So, in emerging era use novel compounds and processes had grown up by the researchers that plays vital role to control demolition of environment.

Now, researchers adopted various concepts of green chemistry for protection of environment without affecting advancement of chemistry. The fundamental ideas and strategies for green novel techniques based on "Twelve Principles of Green Chemistry" that put forth by Paul Anastas and John C. Warner in 1998.

Thus, to conserve the environment the researchers have no other option than adopting the concept of sustainable development and green chemistry so for that purpose that advancement of chemistry and protection of environment can go on parallel to each other [3], [4]. To analyse sustainability in practises and the involvement of sustainable green approaches in research, evolution, and manufacturing, academic policies have to involvement in green chemistry principles and pointers of sustainability [5], [6]. These principles are listed in following figure 1.1.

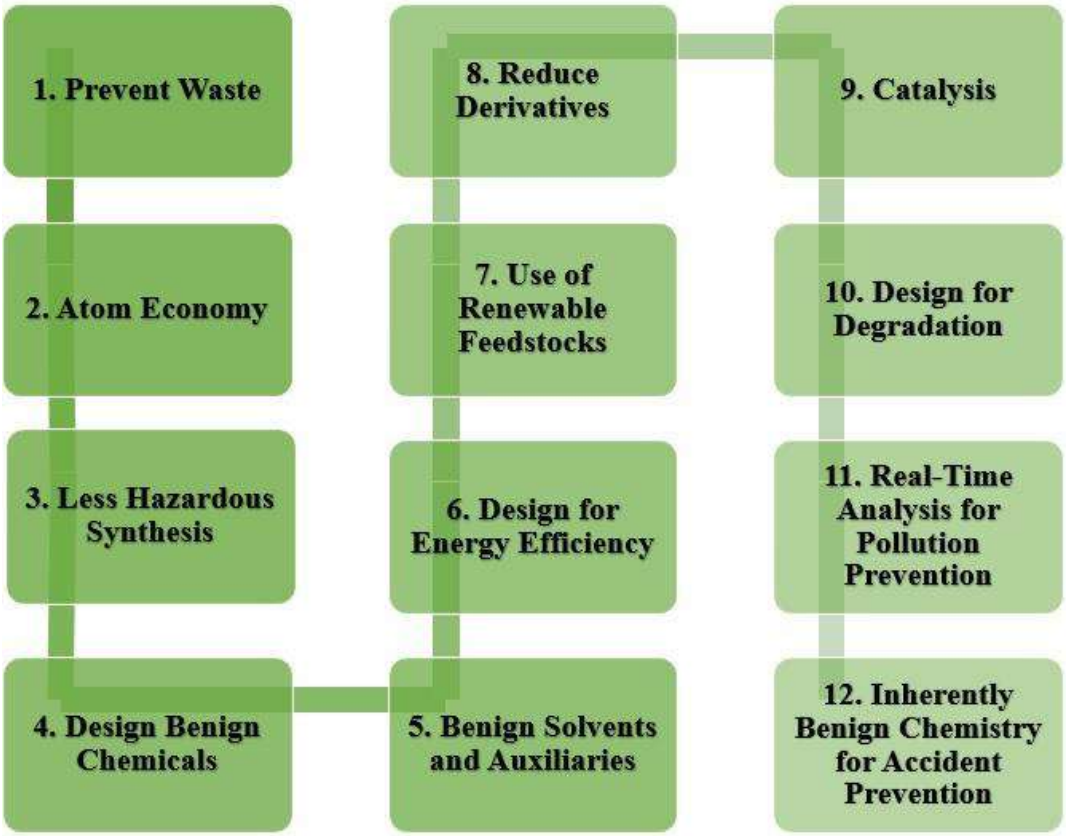


Figure 1.1 12 principles of Green Chemistry

Greener methodologies for organic transformations:

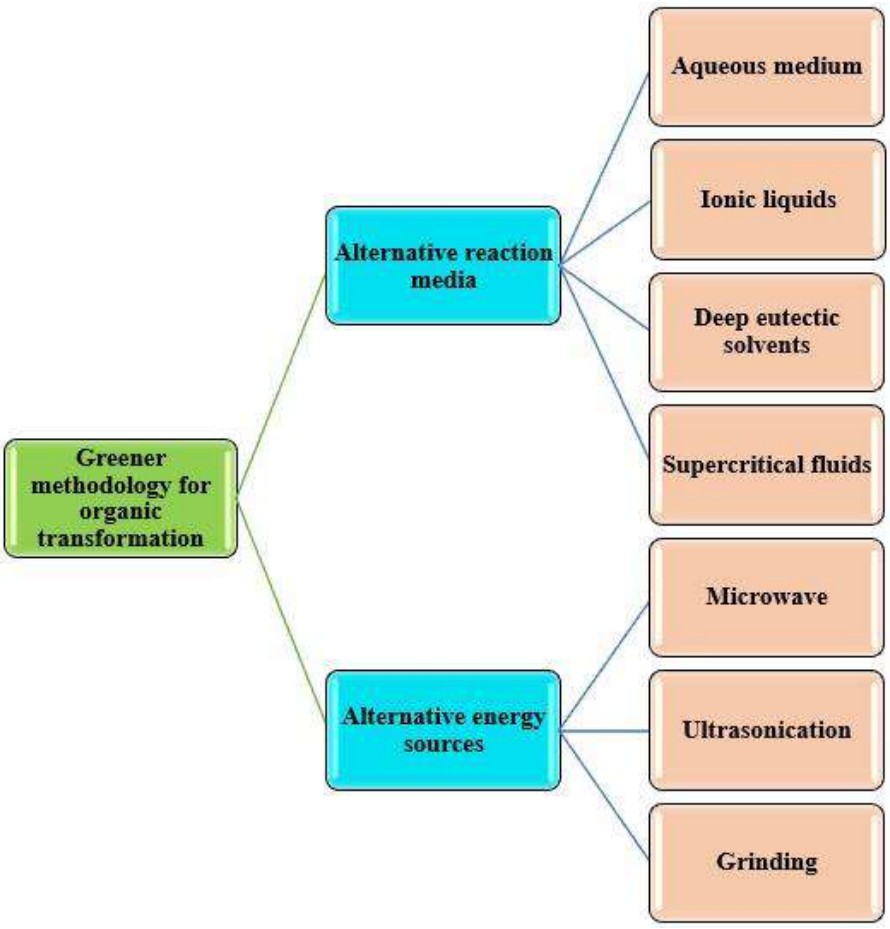


Figure 1.2 Greener methodologies for Organic Transformations

1.2 Aqueous medium

The water is an attractive medium for various organic syntheses. Multi-component reactions (MCR's) are carried out in water increases productivity of multi-component reactions as well as protect the environment from hazardous solvent which would achieve the green chemistry challenge. The use of water as a solvent is more advantageous because it is easily available, secure, inexpensive, inoffensive, noncorrosive, nonflammable and ecologically benignant; alternatively stated, it is an eco-friendly "green solvent".

Aqueous medium has a wide spectrum of applications in numerous areas involving supramolecular structures [7], interactions between protein molecules [8], etc. In recent years different groups working on aqueous mediated synthesis so they

observed that water could catalyse chemical transformations through the hydrogen bonding with substrates [9]. Breslow's group carried out Diels-Alder synthesis in water and got excellent results because water accelerates the reaction by forming hydrophobic interactions with non-polar groups [10]. Although organic preparations in aqueous media are very few due to the sparingly or incompletely soluble nature of the many organic composites. An interesting study to achieve aqueous solubilities of substrates is the utility of amphiphiles, including hydrotropes and surfactants.

1.2.1 Hydrotropes

Hydrotropes are immensely aqueous-solvable, surface-active organic salts that boost the solubilities of operationally insoluble or sparely soluble organic composites in aqueous medium [11]. In 1916, *Carl Neuberg* was first time invented the term "hydrotropes" for surface-active organic salt [12]. As reported by Neuberg, "the phenomena of accelerating the solubilities of unsolvable organic molecules in water by a third ingredient or additive are referred to as hydrotropism or hydrotropy" [13]. Neuberg furthermore recorded environmentally friendly character of various hydrotropes as a result of their basic nature and the potential there within. The salts of different organic constituents such as benzoic, benzyl sulfonic, 1-naphthyl, thiophene carboxylic, 2-furoic, and phenylacetic acid derivatives, as well as few of aromatic fatty acids, are hydrotropic substances **(Figure 1.3)**. The concept hydrotropes comes from the word hydro means water and tropes means something other. Hydrotropic salts decrease the interfacial surface tension at a particular concentration, mentioned as the *Minimum Hydrotropic Concentration* (MHC) [14]–[18]. Hydrotropes have similarities as well as differences to surfactants in the form of molecular structure and association **(Figure 1.4)**. Hydrotropes contain the hydrophilic and hydrophobic groups; however, hydrophobic groups are incapable to form micelle as result of its very small structural arrangement in contrast with a hydrophobic group of surfactants. The diversity between surfactant and hydrotrope is substantially higher Hydrophile/Lipophile balancing (HLB). Hydrotrope generates stacks type aggregates in an aqueous medium which creates associated structures that are accountable for hydrotropic behaviour. The distinctive aggregation of hydrotrope is the source of the dissolution process of a moderately soluble hydrophobic compound in an aqueous medium, which is analogous

to the micellization process. Saleh and co-workers considered the importance of planer structure for the association and hydrotropic effect.

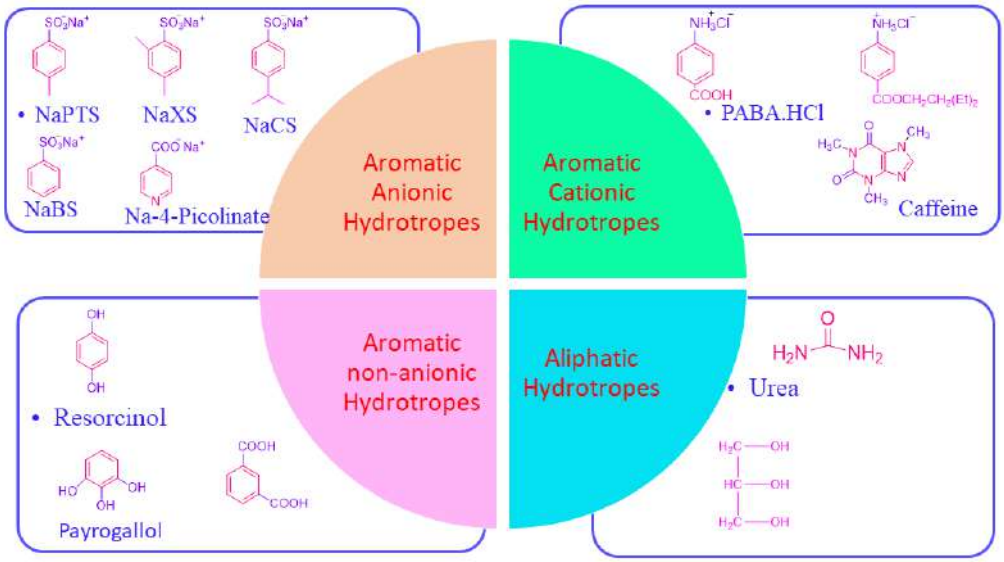


Figure 1. 3: Different examples of hydrotropes

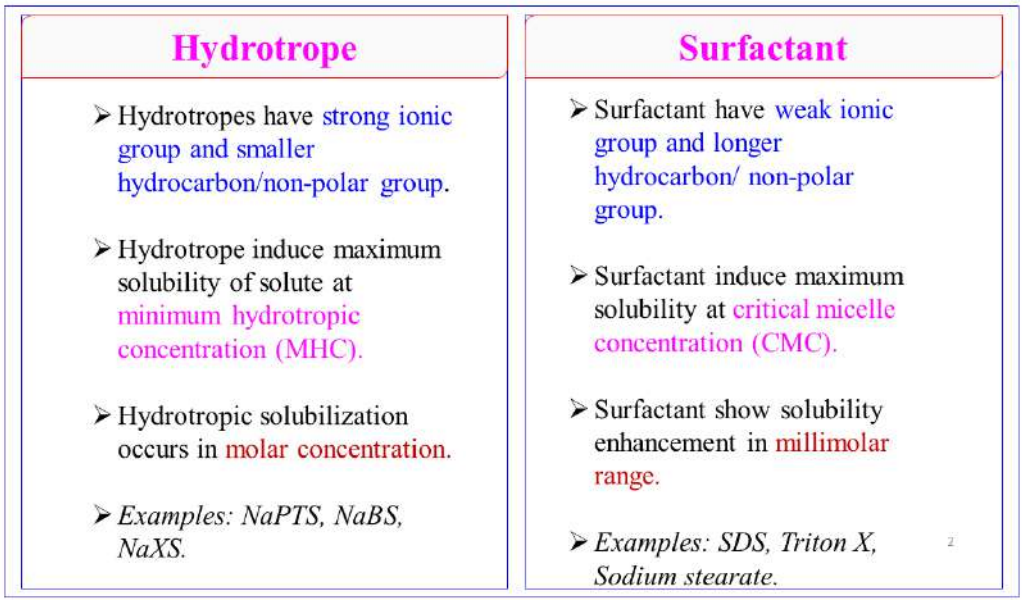


Figure 1.4. Difference between Hydrotrope and Surfactant.

The capacity of hydrotrope to enhance the solvability of organic material in aqueous media is highest whenever the hydrotrope concentration is enough to stimulate the creation of associated structure and maintain the solubility same after that point.

Surfactant carry out greatest solubility at critical micelle concentration (CMC) while hydrotrope shows highest solubility at minimum hydrotrope concentration (MHC). Hydrotropes are excellent in solubilising organic compounds in aqueous media and more exclusive than surfactant. Hydrotrope reduces the surface tension of water and at particular point surface tension becomes constant at that point self-aggregation of hydrotrope occurs. Several theories and practical approaches are used to explain the mechanistic pathway of hydrotrope in organic transformation. The reported mechanism of hydrotrope in organic transformation are show by following figure **(Figure 1.5)** [19]–[23].

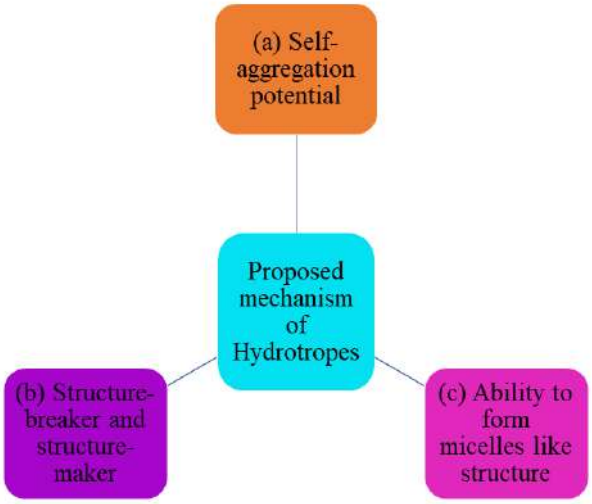


Figure 1.5 Proposed mechanism of Hydrotropes

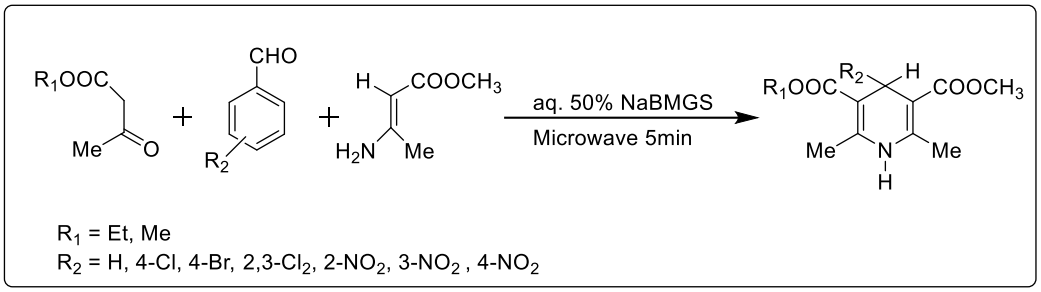
Friberg and Blute mentioned the historical growth of hydrotrope and its involvement in industrial applications [24]. Hydrotropes are mostly utilized in cleaning agent, medical treatment such drug dissolutions [25]. The different fields take advantages of hydrotropes including shampoo, creams, lotion and printing press [26].

Sodium xylene sulfonate maximizes the efficiency of water to solubilise other organic substances. Johnson and Johnson firm put to use hydrotrope sodium xylene sulfonate in cosmetics mainly in shampoos. Sodium toluene sulfonate be applied as hydrotrope and viscosity modifying agent in detergent formulations which reduces the viscosity of chain of Linear Alkyl Benzene Sulfonic Acids (L.A.B.S.).

Application of Hydrotropes in organic transformation

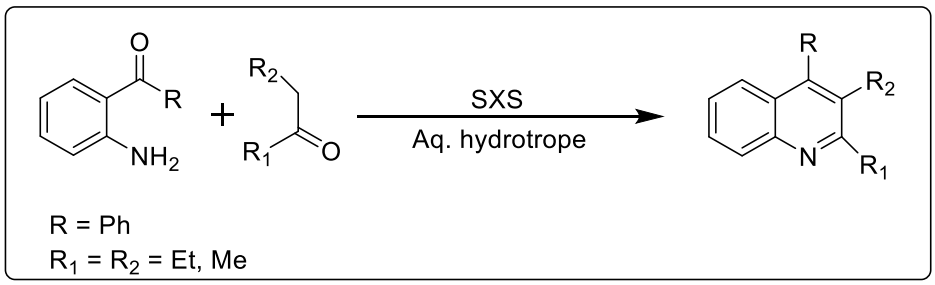
In supplement to industrial application hydrotropes also take part in organic transformation as a reaction medium, for example preparation of quinolines [27]. Hydrotropes also enhance the speed of multiphase synthesis which results in alkaline hydrolysis of aromatic esters [28], [29].

Bhushan M. Khadilkar and Virendra R. Madyar [30] reported synthesis of clinically important dihydropyridine by using aq. 50% sodium butyl monoglycol sulphate (NaBMGS) under microwave irradiation **(Scheme 1.1)**.



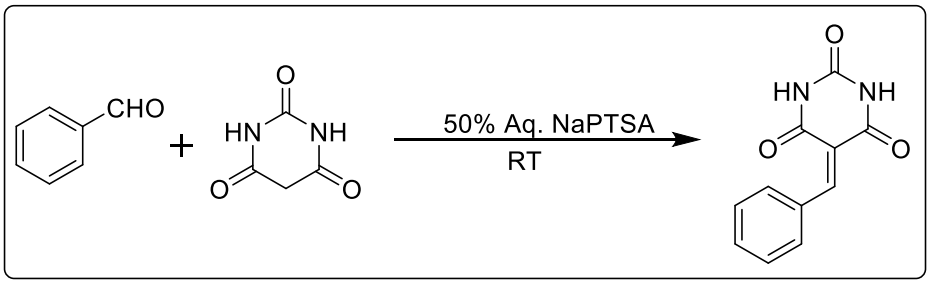
Scheme 1.1

Sharmad J. Chandratre and Zoeb A. Filmwala [31] developed synthesis quinolines in aqueous hydrotropic medium. Condensation between 2-amino ketones with aldehydes or ketones in the aqueous hydrotropic solution of sodium xylene sulphonate (SXS) afford the desired quinolines derivatives **(Scheme 1.2)**.



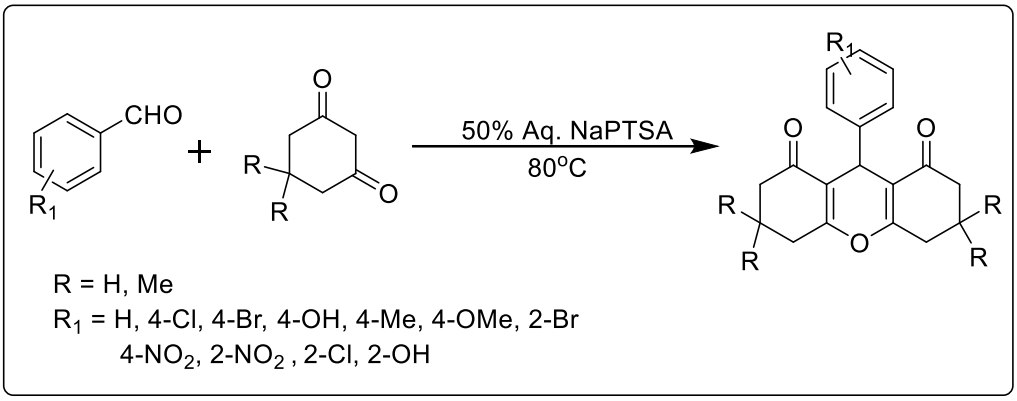
Scheme 1.2

Synthesis of 5-arylidine barbituric acid derivatives in aqueous hydrotropic medium reported by Santosh Kamble and co-workers [17]. They use an efficient Knoevenagel condensation of barbituric acid with different aromatic aldehyde in 50 % aq. NaPTS solution at room temperature providing the respective 5-arylidine barbituric acid derivatives **(Scheme 1.3)**.



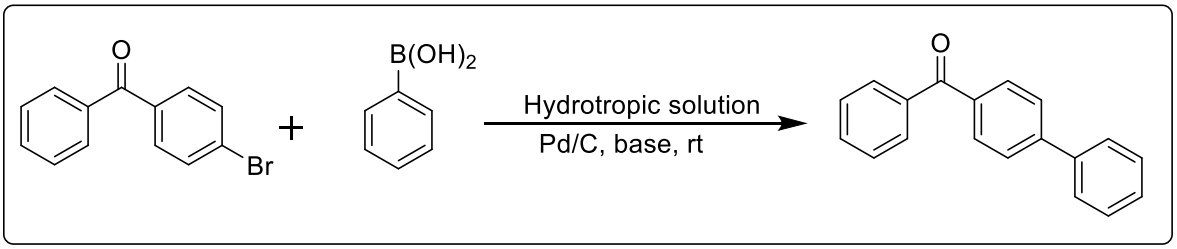
Scheme 1.3

Kamble et al. [32] uses same hydrotrope for the synthesis of 1,8-dioxooctahydroxanthenes **(Scheme 1.4)**.



Scheme 1.4

In the absence of ligand Suzuki-Miyaura and without base Heck-Matsuda cross-coupling schemes developed by Sanjay N. Jadhav and co-workers [33]. In this protocol, they developed a new catalyst by palladium grafting on activated carbon (Pd/C) in an aqueous hydrotropic environment **(Scheme 1.5)**.



Scheme 1.5

1.2.2 Surfactant

A surfactant is a combination of surface-active agents or compounds having surface-active properties that are called surfactants. Surfactants having a hydrophilic

head (polar molecule) and a hydrophobic tail (non-polar molecule), such kind of structure with two different functions, are called amphiphilic substances. Surfactants are entities that generate self-assembled molecular clusters called micelles in a solution as well as interfacial adsorption, which are characteristics properties of a surfactant [34] **(Figure 1.6)**. That has different dissolution characteristics in similar solutes. Hydrophobic group is alkyl chain with 8-12 carbons atoms that does not show affinity toward water in aqueous system but in lipid system they are called as lipophilic groups. The hydrophilic group they are functional group such as $RCOO^-$, RSO_3^-, $ROSO_3^-$, R_4N^+ etc. has affinity toward water. Thus, hydrophobic groups of surfactants attract nonpolar environment while hydrophilic groups attract with polar environment if aqueous system during aggregation. This is a characteristic property of surfactant, due to which it becomes a surface active and able to decrease the surface/ interfacial tension by aggregating at interface of two immiscible liquids which results into maximise the solubility, mobility and biodegradation of sparingly soluble organic substance. At a certain concentration, surfactant molecules form the micelle that concentration is known as critical micelle concentration (CMC).

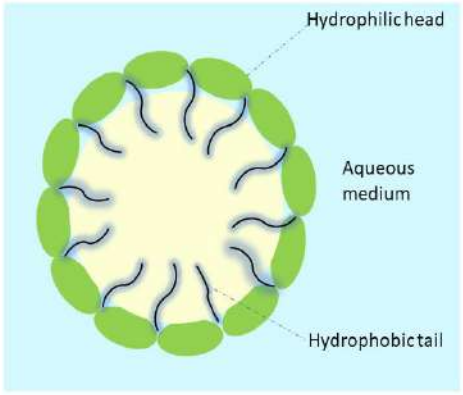


Figure 1.6: Structure of micelle formation

Classification of surfactant:

Classification of surfactant based on charge as anionic, non-ionic, cationic, amphoteric, and also on their source of availability as a biosurfactant **(Figure 1.7)**.

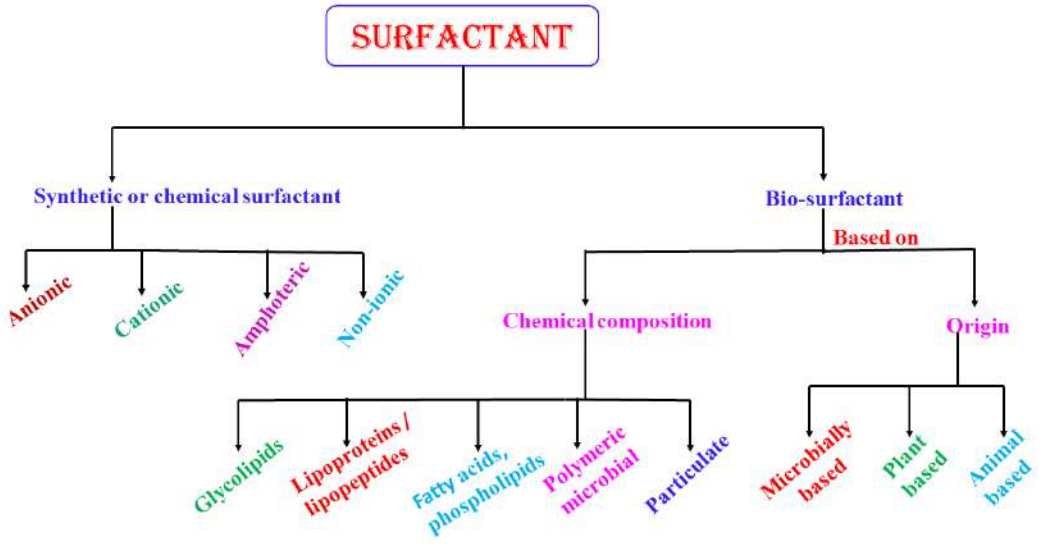


Figure 1.7 Classification of surfactant

I) Chemical or synthetic surfactant:

1.2.1 Anionic Surfactant:

In these surfactants hydrophilic group dissociate into amphiphilic anions and alkaline cations (Na^+, K^+) or a quaternary ammonium cation when dissolved in aqueous system. Anionic surfactant is mostly used in industry as a detergent such as soap. The hydrophilic head groups are carboxylate, sulfonate, sulphate and alkyl chain of hydrocarbons C_{12} to C_{18} acts as hydrophobic.

Examples: Sodium dodecyl sulphate, Sodium dodecylbenzene sulfonate, Dioctyl sodium sulfosuccinate, Sodium stearate, petroleum sulfonates, lignin sulfonates, ester sulfonates etc **(Figure 1.8)**.

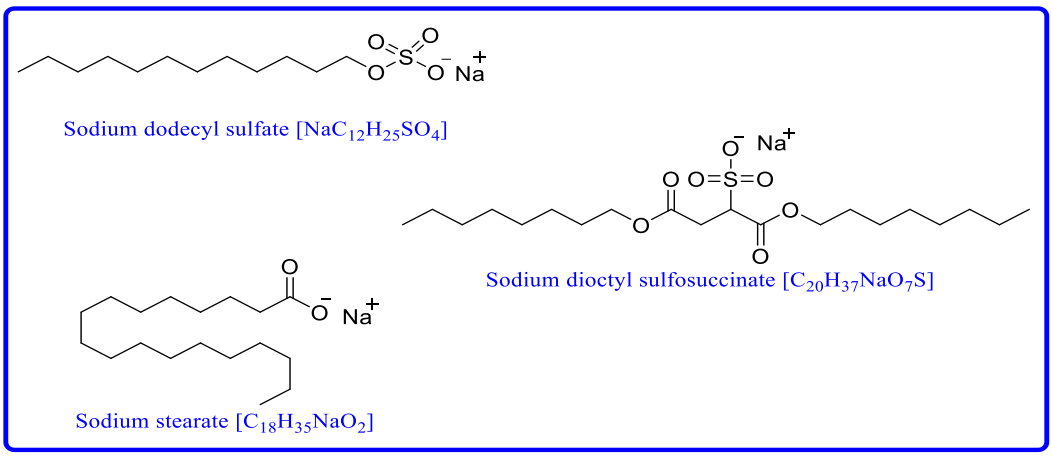


Figure 1.8 Examples of anionic surfactant

1.2.2 Cationic Surfactant:

In the aqueous system, cationic surfactant dissociates as an amphiphilic cation and halogen as an anion. These types of surfactants correspond to large proportions of nitrogen compounds such as fatty amine salts, natural fatty acids, and quaternary ammonium compounds. These surfactants are mostly used for surface modification as softeners in hair conditioners, but they also have bactericidal properties as antibacterial in hygiene formulations.

Examples: Hexadecyl trimethyl ammonium chloride, Hexadecyl pyridinium chloride, Benzethonium chloride **(Figure 1.9)**.

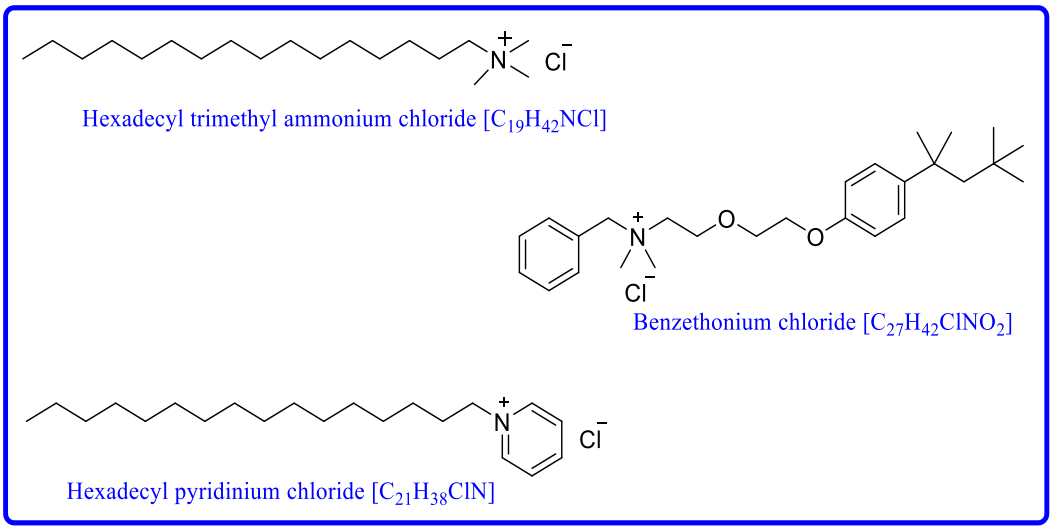


Figure 1.9 Examples of cationic surfactant

1.2.3 Amphoteric or Zwitterionic Surfactant:

Amphoteric surfactant exhibits dissociation of both cationic and anionic functional groups in their polar hydrophilic portion often depending on the pH but amphoteric behaviour shows at intermediate pH and its application in cosmetic, personal care products due to which they are quite expensive. Alkyl amino acids, alkylbetains, alkylaminobetaines are common classes of amphoteric surfactants.

Examples: N-Dodecyl-N, N-dimethylglycinate, Dipalmitoylphosphatidylcholine (Lecithin), Cocamidopropyl betaine **(Figure 1.10)**.

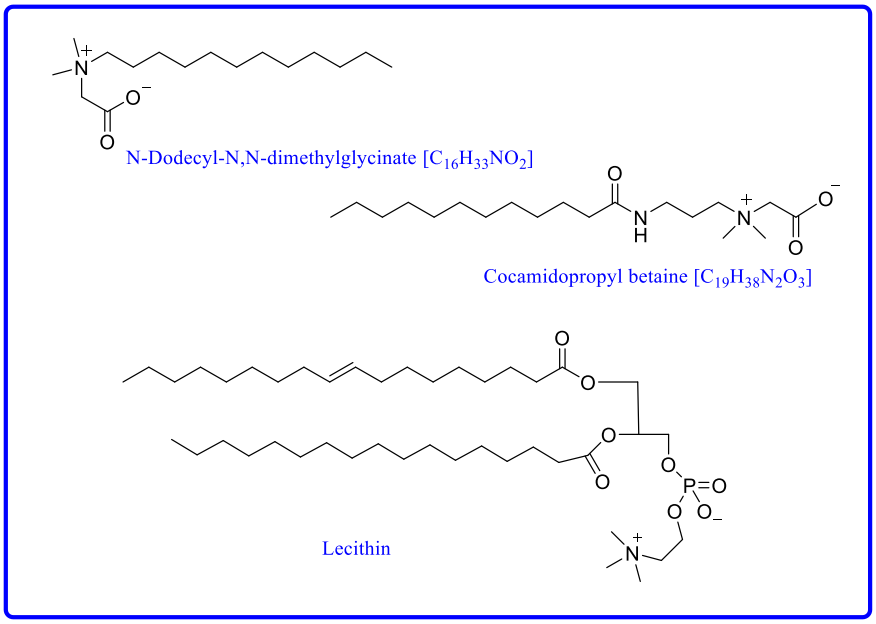


Figure 1.10 Examples of amphoteric surfactant

1.2.4 Non-ionic surfactant:

These type surfactants do not dissociate or ionizes in aqueous system due to their hydrophilic part has a non-dissociable functionality such as alcohol, phenol, ether, ester or amide. The hydrophilic part carries noncharged polyethylene oxide (PEO) or polyglycerin chains. There important application in drugs, cosmetic as personal care products.

Examples: Polyoxyethylene 20 cetyl ether (Brij 58), Triton X-100, Tween 20 etc **(Figure 1.11)**.

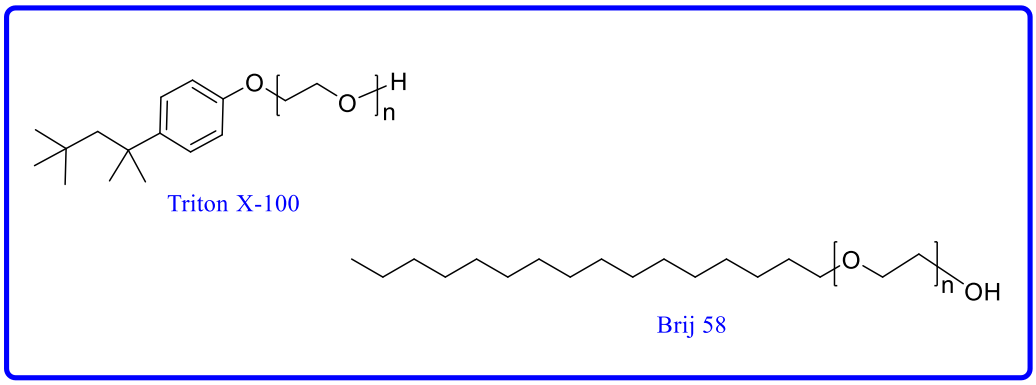


Figure 1.11 Examples of non-ionic surfactant

II) Bio-surfactant-microbial surfactant:

Surface active biomolecules are produced from microorganisms, plants and animal materials known as biosurfactant. These types of surfactants are anionic or neutral in behaviour due to hydrophilic groups are carbohydrate, amino acid, peptide, phosphate etc. while hydrocarbon chain is hydrophobic tail. Biosurfactants are better than synthetic or chemical surfactants owing to their lower toxicity, easy biodegradability, specific activity, effectiveness at extreme temperatures as well as at pH, lower surface tension, and lower interfacial tension.

Classification of biosurfactant: Classification of biosurfactant on the basis of their chemical composition and source of origin.

Based on chemical composition

1. Glycolipids: Glycolipids are the most common type of biosurfactant found in the environment, consisting of a combination of carbohydrates and long-chain aliphatic or hydroxyl acids linked by an ester or ether portion. Ex. Rhamnolipids, Trehalose lipids, Sophorolipids **(Figure 1.12)**.

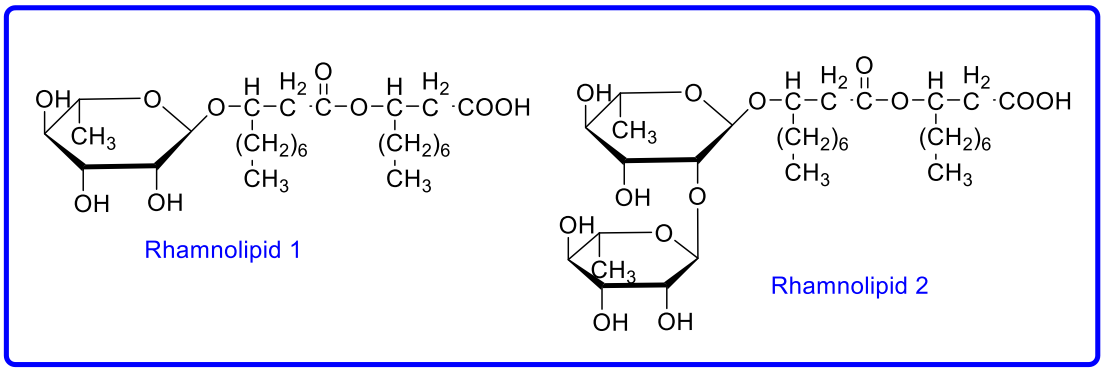


Figure 1.12 Examples of glycolipids

2. Lipopeptides and Lipoprotiens: In lipopeptides lipid acts as hydrophobic head and peptide is hydrophilic tail that lipid is attached to the polypeptide chain. Along with antimicrobial properties they are also excellent surfactant.

Examples. Surfactin, Lichenysin, Viscosin **(Figure 1.13)**.

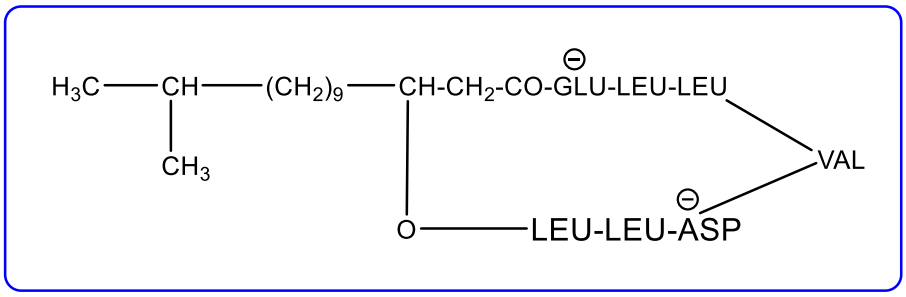


Figure 1.13 Structure of Surfactin

3. Fatty acids, phospholipids, and neutral lipids: These types of surfactants are produced by several bacteria and yeast during the microbial oxidation of n-alkanes. The equilibrium between hydrophilic and lipophilic groups is directly proportional to the length of the hydrocarbon chain in their structural frameworks. Ex. Acinetobacter sp., corynomicolic acids.

4. Polymeric Microbial Surfactants: Most commonly used polymeric microbial surfactant are polymeric heterosaccharides containing proteins. The researcher interested in studied of polymeric biosurfactants are emulsan, liposan, alasan and lipomannan. Ex. Acinetobacter calcoaceticus **(Figure 1.14)**.

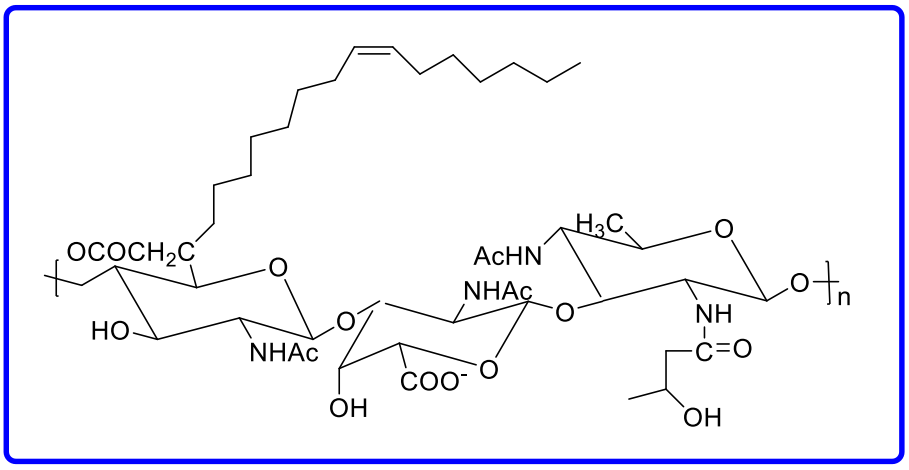


Figure 1.14 Structure of Acinetobacter calcoaceticus

5. Particulate biosurfactant: The creation of microemulsion and the presence of extracellular membrane vesicles that partition hydrocarbons play significant roles in alkane intake by microbial cells. Ex. vesicles of Acinetobacter sp. strain HO1-N.

Based on origin:

1. Microbially-based Surfactants:

These surfactants are produced by variety of microorganisms or by microbial fermentation processes using cheaper agro-based materials. They are divided into two groups depending on molecular weight. First group contains low molecular weight surfactant such as glycolipids, lipopeptides and phospholipids shows effectiveness in reducing surface and interfacial tension. High molecular weight surfactant contains polysaccharides, proteins, lipopolysaccharides, lipoproteins or complex mixtures of these biopolymers which stabilizes newly created surfaces.

2. Plant-based surfactant:

In environmentally conscious days demand increases for the natural sourced surfactant. Plant derived surfactants are good source of biosurfactant. Saponin is excellent class of plant having characteristic surface-active properties due to those plants are rich in saponin class used as biosurfactant. Plant-based saponins are largely distributed in nature offering large potential replacement for the hazardous synthetic surfactant which exhibits excellent surface and biological activities. Biological activities include antimicrobial activity, antidiabetic activity, adjuvant potentials, anticancer activity, and others are reported. They can be extracted from various parts of plants such as roots, stem, leaves, bark, seeds and fruits. Commonly found dietary based saponins are legumes: soybeans, chickpeas, peanuts, sapindus mukorossi, *Accacia concinna* pods.

3. Animal-based surfactant:

Animal derived surfactant take important position in medical field. Commonly known biosurfactants obtained from animals includes the lecithin, gelatin, casein, wool fat, cholesterol, and wax. This type of surfactant also contains low molecular weight surfactant includes lecithin and high molecular weight surfactant as like gelatin. Egg yolk provides the natural surfactant lecithin, which contains zwitterionic phosphatidylethanolamine (PE, ~18.1 %) as well as phosphatidylcholine (PC, ~78.7 %). Refined egg lecithin is good intravenous nutrition and an excipient for drug delivery. The commercially available source for gelatin is bovine skin, as well as bones and pigskin, which are applied as a stabiliser, thicker, and texturizer in food along with

non-food products. It is an inadequate source of protein surfactant yet shows excellent emulsifying qualities, which might be enhanced with enzyme-catalysed attachment of hydrophobic side chains. Different protein-based biosurfactants are available from animal sources of origin, like casein, egg albumin, bovine serum albumin, and human serum albumin. Bile acids as well as pulmonary surfactants are two physiologically significant animal-based surfactants. Clinical usage and preclinical animal research both point to the superiority of animal-derived surfactants over synthetic formulations.

Applications of Surfactants:

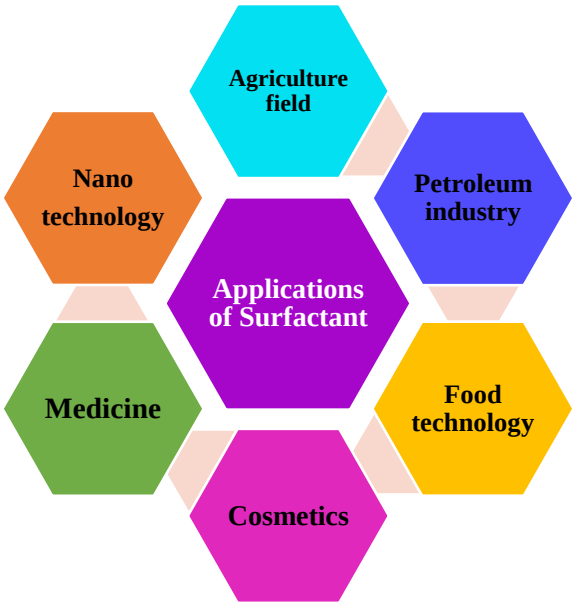
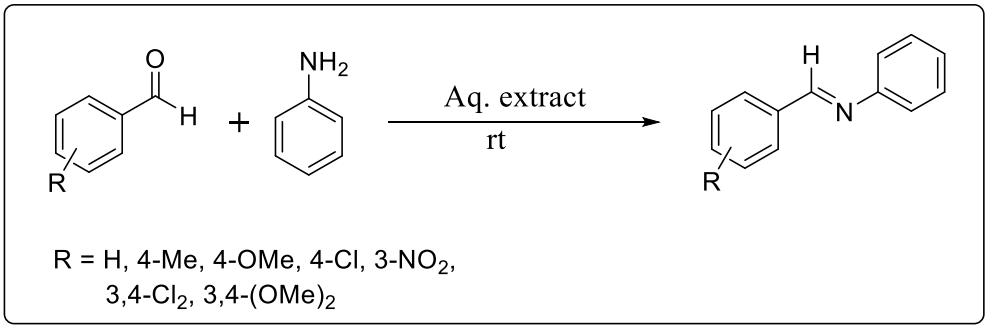


Figure 1.15 Applications of Surfactant

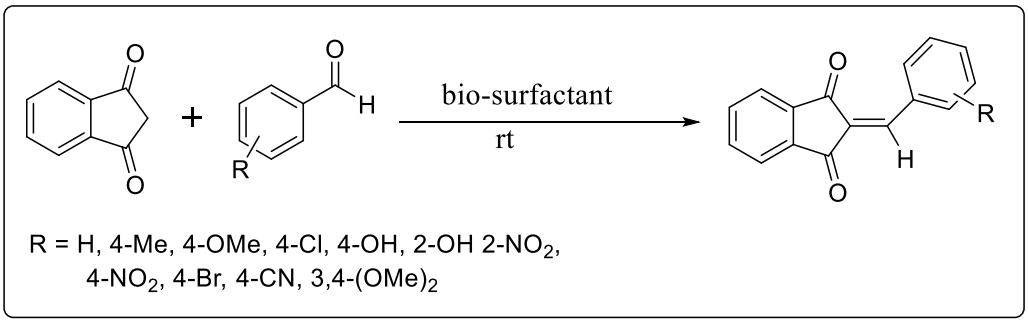
The implementation of biosurfactants as a green replacement for chemical surfactants in organic transformations has been successfully analysed by scientists in recent years. For this purpose, aqueous extracts of various fruits, plants, seeds, leaf and juice from fruit were chosen as the source of biosurfactants, including *Sapindus trifoliatus* fruit, chickpea leaf extract, *Balanites roxburghii*, and pods of *Accacia concinna.* The aqueous extracts of these fruits have an acidic pH and high surface activity due to the presence of several saponins; therefore, they show catalytic activity in various synthesises. Saponins are plant-based surfactants that contain the amphiphilic moieties in which sugars are connected to either the sterol or triterpene nonpolar groups.

Santosh Pore et al. [35] prepared a novel green catalyst from the pericarp of Sapindus trifoliatus fruits in 2010 and applied it to aldimine synthesis. The different derivatives of aldimines prepared from aromatic aldehydes and amines were catalysed by the natural extract. They observed the aromatic ketones and amines did not produce ketimines under similar reaction environments, which denotes the chemoselective nature of the extract **(Scheme 1.6).**



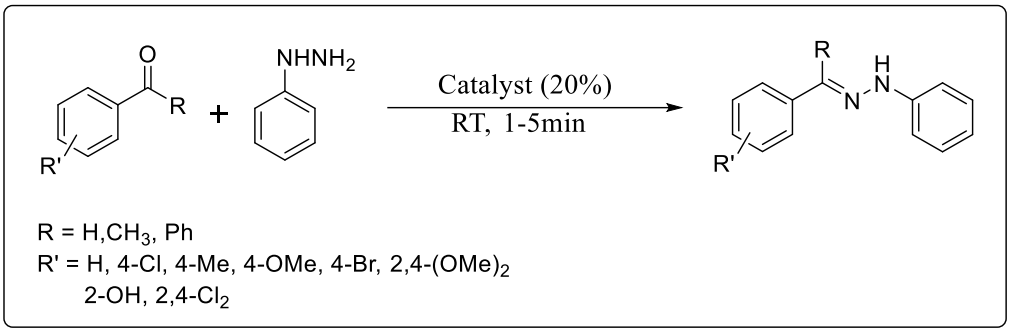
Scheme 1.6

Madhuri Barge and Rajashri Salunkhe [36] develop a protocol for C–C bond formation in an aqueous extract of Balanites roxburghii fruit. An aqueous extract of balanites roxburghii fruit is used as a biosurfactant for Knoevenagel condensation of 1,3-indanedione with aryl aldehydes, which acts as a biogenic green acidic catalyst **(Scheme 1.7).**



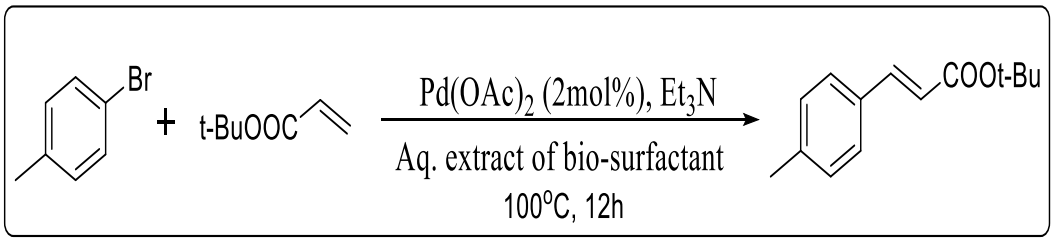
Scheme 1.7

An ecologically and economically affordable preparation of aryl-hydrazones in an aqueous extract of *Acacia* pods, which is a natural surfactant-type catalyst developed by Hemant V. Chavan and co-workers [37] **(Scheme 1.8).**



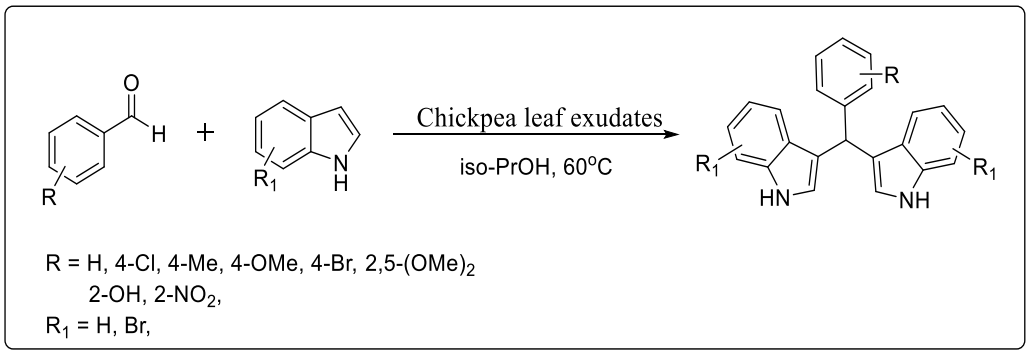
Scheme 1.8

Seema P. Patil and co-workers [38] reported a green and environmentally benign protocol for ligand free Pd-catalysed Mizoroki–Heck cross coupling reactions by using biosurfactant. The biosurfactant used in this study was prepared from the seeds of the pericarps (pods) of the *Acacia concinna* plant, which are soaked in water. The resulting extract contains saponin, which acts as a natural biosurfactant **(Scheme 1.9)**.



Scheme 1.9

Chickpea leaf exudates: a green brønsted acid type biosurfactant reported by Rupesh C. Patil et al. [39] for the synthesis of bis(indole)methane and bis(pyrazolyl)methane **(Scheme 1.10)**.



Scheme 1.10

1.3 Ionic liquid in organic transformation:

Ionic liquids (ILs) have fascinated the interest of researchers in the last decade, due to their particular properties [40], [41] [42] and their use in organic synthesis as a catalyst [43]–[45], catalysis [46]–[48], biocatalysts [49], [50], processes of nanomaterial synthesis [51], [52], polymerization reactions [53], [54], and electrochemistry [55]. Ionic liquids are polar and ionic in nature, couple with microwave irradiations very expeditiously, and are therefore the best solvent for organic reactions that are assisted by MW irradiations [56], [57]. Ionic liquids are considered as green reaction medium by chemists due to its remarkable characteristic properties including thermal-chemical stability, lower vapour pressure, recyclability, stable at high temperature in liquid state, non-combustible, easily solvates organic, inorganic and polymeric materials. Ionic liquids are molten organic salts composed of ions and exist in liquid electrolytes at temperature below 100°C. Ionic liquids are mostly organic cations by combined with inorganic anions creating crystalline moieties with less lattice energies enabling these salts to be in liquid state at or near room temperature. Ionic liquids are replacement for regular organic solvents those are harmful to the nature. The most commonly used ionic liquids are heterocyclic imidazolium, pyridonium, pyrazolium molecules in addition to another non-heterocyclic cations like as ammonium and phosphonium **(Figure 1.16)**.

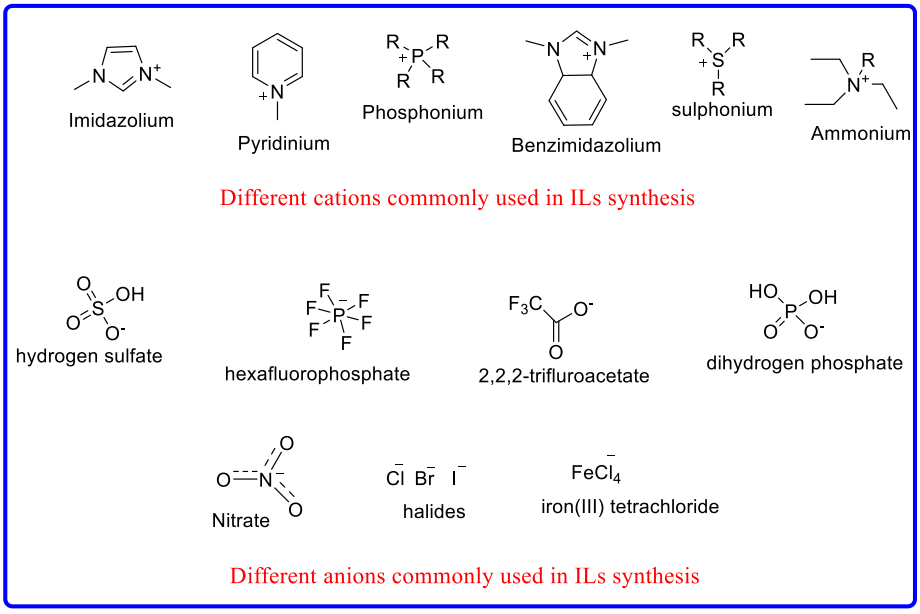


Fig. 1.16 Structures of cations and anions used in ILs synthesis.

The applications of ionic liquid in different field as shown in figure 1.17 along with its properties, advantages, and disadvantages.

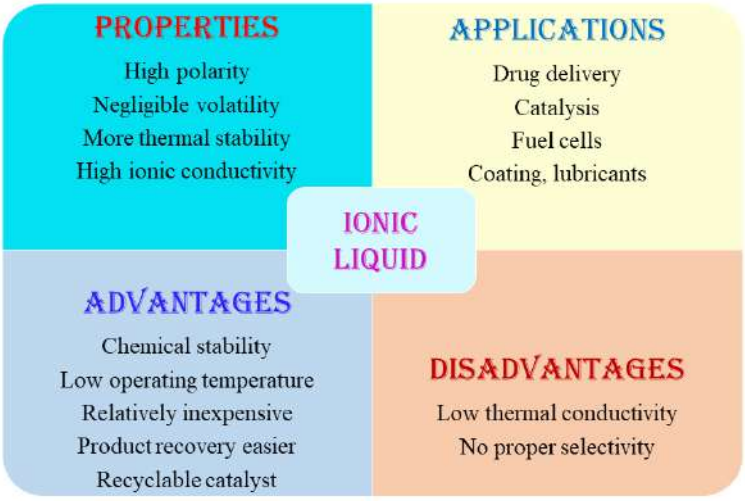
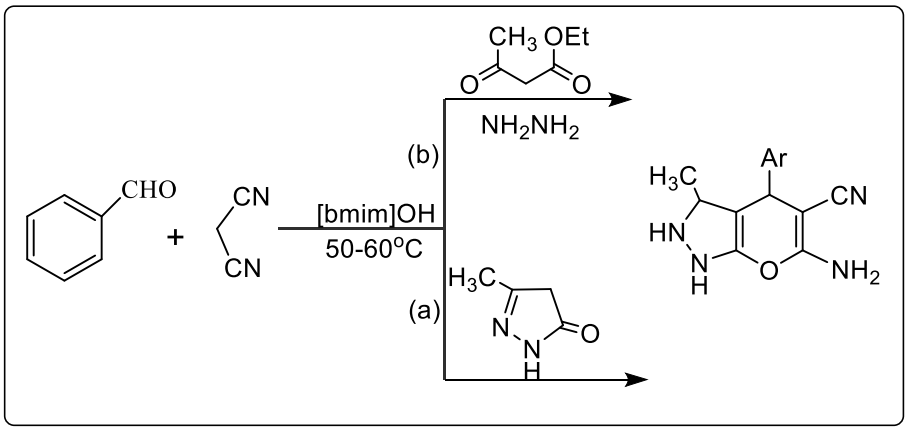


Figure 1.17 Properties, applications, advantages, and disadvantages of ILs

Applications of ILs in organic transformation

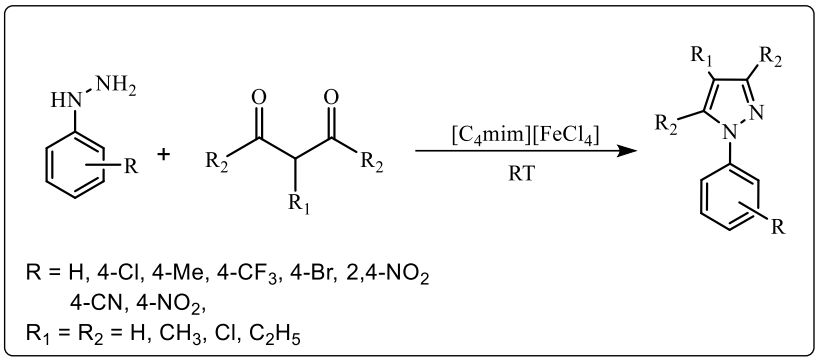
Jitender M. Khurana et al. [58] reported under solvent-free conditions, convenient and green synthesis of 4H-pyrans and 4H-pyrano[2,3-c] pyrazoles in ionic liquid 1-butyl-3-methyl imidazolium hydroxide {[bmim]OH}. [bmim]OH is a basic ionic liquid that is recyclable, inexpensive, reduces the time of reaction, and increases yield **(Scheme 1.11)**.



Scheme 1.11

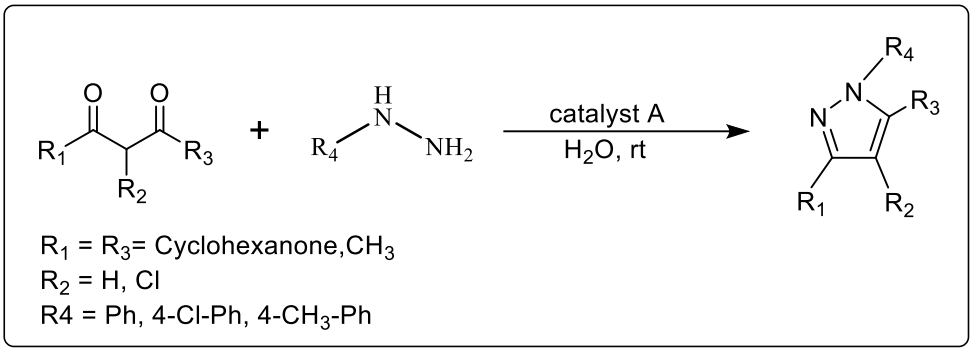
Manashjyoti Konwar et al. [59] carried out one pot synthesis of pyrazoles at room temperature in ionic liquid. Ionic liquid contains transition metal which is magnetic and also catalytic such ionic liquids are known as task-specific ionic liquids

(TSIL). There are various metal-based ionic liquids such as $[AlxCly]^-$, $[FeCl_4]^-$, $[MnCl_4]^{2-}$ $[CuCl_4]^{2-}$, $[NiCl_4]^{2-}$, $[PdCl_4]^{2-}$, etc. are used in synthesis but after screening $[FeCl_4]^-$ good result **(Scheme 1.12)**.



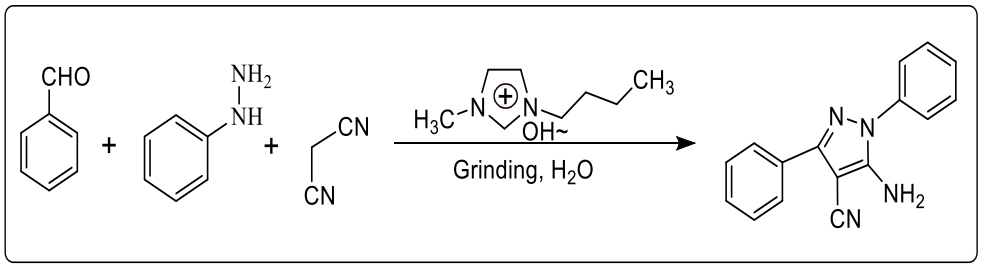
Scheme 1.12

Shirin Safaei et al. [60] synthesize pyrazoles using SO_3H brønsted acidic ionic liquid in water. The reaction between various 1,3-diketones and hydrazines or hydrazides in the presence of multi-SO_3H brønsted acidic ionic liquid at room temperature within 5 minutes gives regioselective derivatives of pyrazoles in excellent yield **(Scheme1.13)**.



Scheme 1.13

Srivastava et al. [61] carried out synthesis of functionally diverse pyrazole derivatives by ionic liquid catalysed with grinding in water. Reaction of malononitrile, phenyl hydrazine and diversified aldehyde in ionic liquid-1-butyl-3-methyl imidazolium hydroxide [(Bim)OH], with water without by-products gives desired product in good yield **(Scheme 1.14)**.



Scheme 1.14

1.4 Microwave assisted organic transformations (MAOT):

Microwave irradiation is one of the prominent non-conventional energy sources whose usefulness in synthetic chemistry have increased considerably in recent years [62]. During the second world war, Randall and Booth at the university of Birmingham, as part of the development of RADAR, devised a device for creating fixed-frequency microwaves, the magnetron [63]. Initially, it was established that microwaves warmed up water; after that, microwaves were used in household and commercial devices for heating and cooking purposes, which started in the 1950s. Tappan introduced first kitchen microwave oven in 1955 but its domestic use increases during the 1970's and 1980, s. Then scientists wonder why it is only used for domestic purposes and begin using microwave ovens for synthesis in the laboratory [64], but both household as well as laboratory ovens operate at 2.45 GHz. The electromagnetic spectrum shows microwaves are placed between infrared radiation and radio waves **(Figure 1.18)**. Researcher first investigate the mechanisms of dielectric heating and search the significances of the microwave irradiation technique in the chemical synthesis.

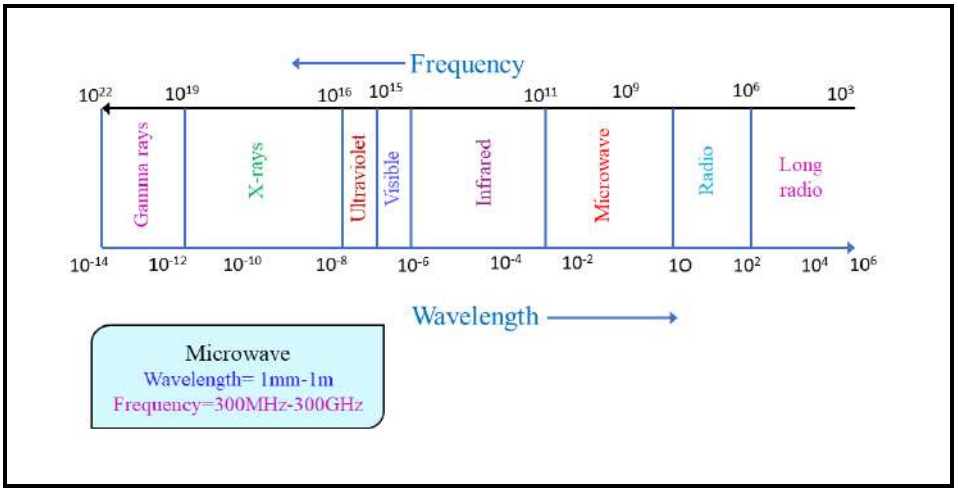


Figure 1.18 Electromagnetic spectrum

Selectivity is observed in the absorption of radiation and heating, such as when materials having high dielectric constant values have a tendency to consume microwave radiation, while less polar materials and highly ordered crystalline substances are inferior absorbers [65]. The microwaves transferred energy not only due to conduction but also due to dielectric loss. The affinity of a compound to come in contact with microwave heating is dependent on the dielectric properties, the dielectric loss factor (e''), and the dielectric constant (e'). Therefore, dielectric loss factor (e'') indicates the effectiveness with which electromagnetic radiation is transformed into heat, while the dielectric constant (e') represents the efficiency of molecules to absorb microwaves. The ratio of $\tan\delta = (e'')/(e')$, indicates the capability of these molecules to modify electromagnetic energy into heat at a given frequency and temperature. High values of dissipation factor(δ) of the sample means easy susceptibility to microwave energy [66]–[68]. Other important factors are ionic conduction, size, charge, conductivity of ions and their interaction with the solvent. In microwaves, heating starts from the inner side of the flask and radiates outside, in contrast to conventional heating, which initiate from the outside, and therefore microwave heating is less economical in terms of source energy used. Microwave radiation has some prominent microwave dielectric heating effects on organic reactions viz. thermal effect and non-thermal effect [69], [70]. Thermal effects are caused by the different temperatures created due to microwave dielectric heating.

The aquatic emulsification and polymerization of butyl acrylate, acrylic acid, and methacrylic acid in the presence of pulsed electromagnetic radiation is the first recorded application of microwave irradiation in organic transformation [71]. The first successful application of microwave heating in organic transformation was made in 1986 by Gedye et al. [70] and Giguere et al. [72]. From the 19th to the 20th centuries, diverse organic reactions were successfully conducted in commercial as well as advanced microwave with a reduction in time and increasing yield.

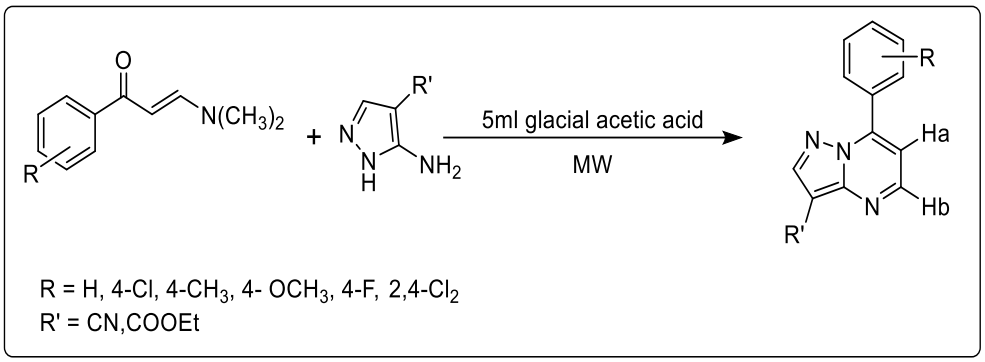
The microwave-assisted organic transformations have been carried out in two ways:

1. Microwave assisted organic transformations in presence of solvents
2. Microwave assisted organic transformations without solvent

1. Microwave assisted organic transformations in presence of solvents:

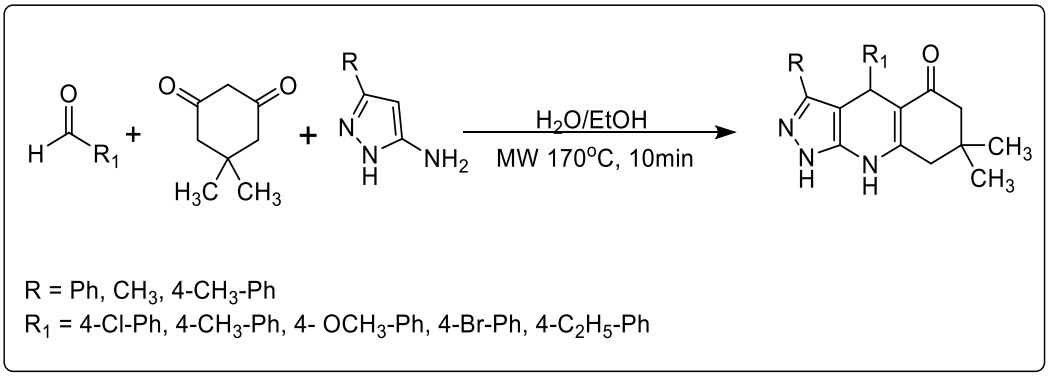
To conduct the reaction under microwave choice of solvent depend on solubility of reagent in that solvent and solvent which couples effectively with microwaves and acts as the energy transfer medium.

Li Ming et al. [73] reported MW assisted synthesis of pyrazolo [1,5-a] pyrimidine via the reaction of enaminones and 5-amino-1H-pyrazoles. This is prepared in glacial acetic acid at 120°C for 20 min under adjustable microwave 0–25 W gives excellent yield **(Scheme 1.15)**.



Scheme 1.15

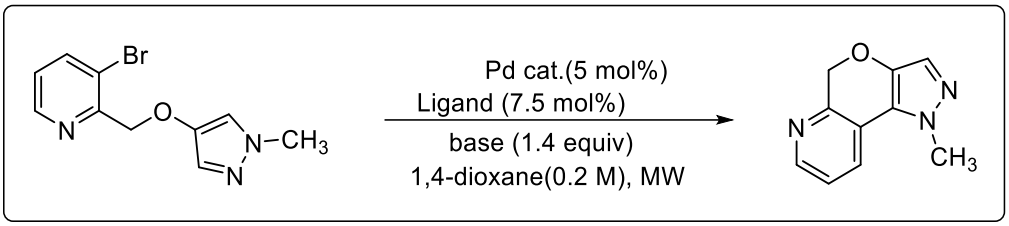
Anastasiya Yu et al. [74] reported green protocol for the synthesis of pyrazolo [3,4-b]quinolin-5-ones by using microwave irradiations. These is three component reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium at 175°C (375W) **(Scheme 1.16)**.



Scheme 1.16

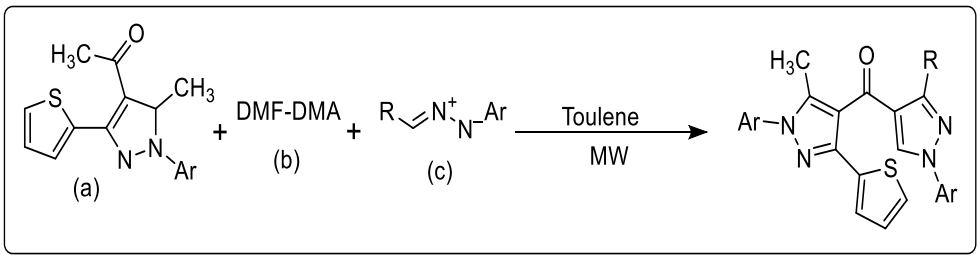
Aaron T. Garrison et al. [75] carried out synthesis of 1,5 dihydropyrazolo[3′,4′:5,6] pyrano[3,4-b]pyridines under microwave irradiation. They

develop regioselective Pd(0)-catalysed C−H arylation reaction between pyrazoles within 5 min in the microwave create 98% product **(Scheme 1.17)**.



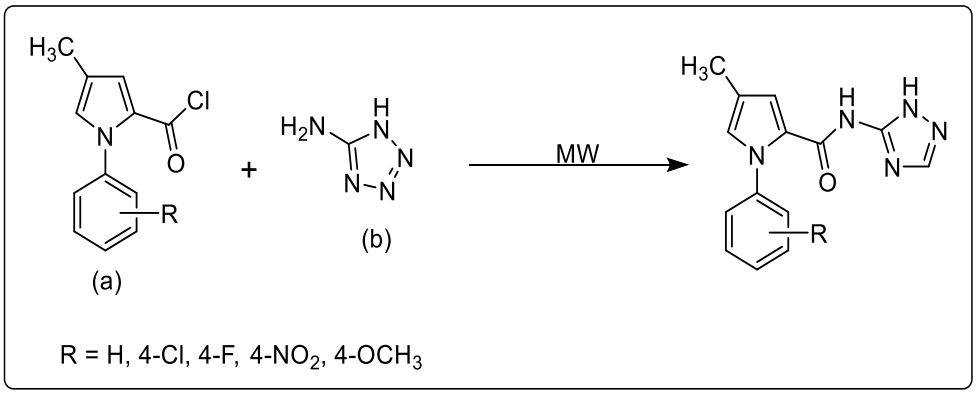
Scheme 1.18

Sobhi M. Gomhal et al. [76] demonstrate one pot multi component synthesis of some novel pyrazole (22) scaffolds as potent anticancer agents under controlled MW conditions. Multi-component reaction of acetyl pyrazole (a), dimethylformamide dimethylacetal (DMF–DMA) (b) and nitrile imine (c) in toluene under conventional heating as well as microwave irradiation at 150°C. But MW within 4-5 min. gives above 80% yield as compare to conventional heating that require 10-15hr with 60-70% yield **(Scheme 1.19)**.



Scheme 1.20

Jun Hu et al. [77] synthesize tetrazolyl pyrazole amides via microwaves. This tetrazole pyrazole amide shows various interesting biological activities such as, bactericidal, pesticidal, herbicidal and antimicrobial activities. Derivative of tetrazolyl pyrazole such as 3-methyl-1-phenyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (23) were prepared by the reaction of various 3-methyl-1-phenyl-1H-pyrazole-5-carbonyl chlorides (a) and 1H-tetrazol-5-amine (b) under microwave irradiation at 400W (110^{o}C) for 20 min obtain 78-90% yield **(Scheme 1.21)**.

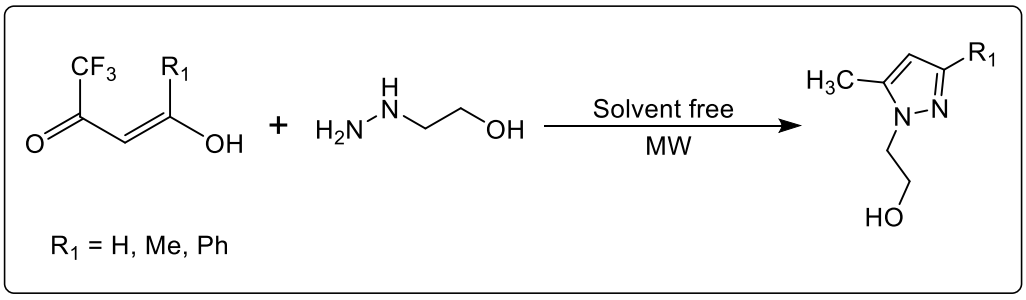


Scheme 1.21

2. Microwave assisted organic transformations without solvent:

In these environmentally conscious days, the researchers develop solvent free procedures which involve simple workup, avoid toxic solvents, economically safe, clean and efficient.

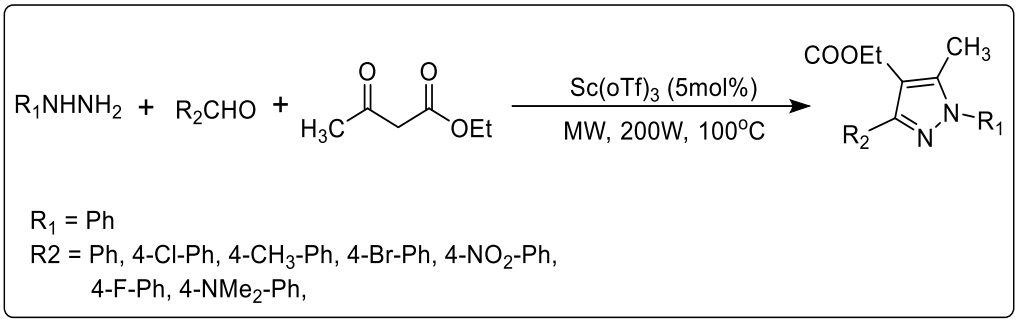
Lilian Buriol et al. [78] develop a new protocol for pyrazole synthesis under microwave irradiation and solvent-free conditions. In this synthesis they avoid use of organic solvent and conventional heating. To obtain 4,5-dihydro-1H-pyrazoles or pyrazoles there is cyclocondensation takes place between enones and hydrazine's under MW irradiation under solvent free condition. They also perform same reaction by using domestic MW oven and also conventional heating but MW equipment for synthesis gives better yield as compare to others **(Scheme 1.22)**.



Scheme 1.22

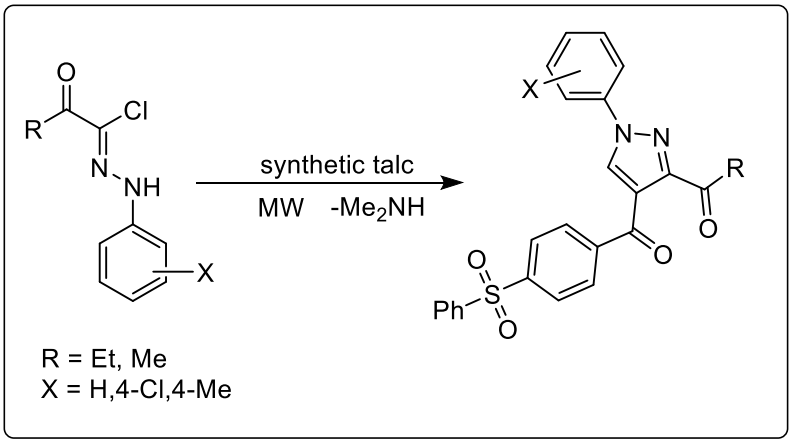
Kumkum Kumari et al. [79] carried out microwave assisted, solvent free, synthesis of functionalized pyrazoles using [$Sc(OTf)_3$] catalyst. Mixture of phenyl hydrazine, aldehydes and ethyl acetoacetate is irradiated under microwave at 200W and 100^oC in 3-6 min produces pyrazole with excellent yield (74-92%). $Sc(OTf)_3$ is a

powerful Lewis acid catalyst. It is mild reaction conditions, easy to handling, stability to moisture, and reusability, therefore $Sc(OTf)_3$ is environmental safer catalyst **(Scheme 1.23)**.

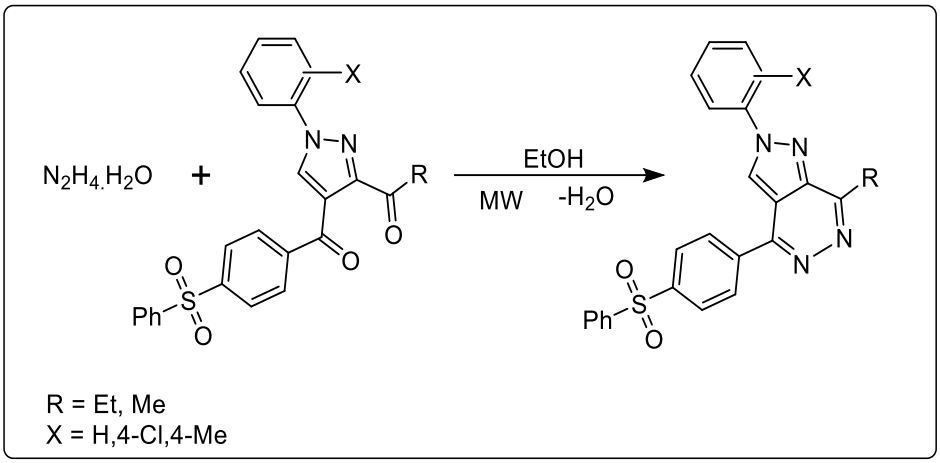


Scheme 1.23

Mohamed F. Mady et al. [80] reported synthesis of novel pyrazole and pyrazolo[3,4-d]pyridazine derivatives via microwave irradiation. Synthesis of pyrazole by using synthetic talc was added to an enaminone derivative and hydrazonyl halides under MW at (249 psi, 130°C) and pyrazolo[3,4-d]pyridazine is prepared from pyrazole derivatives in ethanol (2 ml), hydrazine hydrate (98%) was added and irradiated by microwaves using pressurized conditions (249 psi,120°C) for 3 min. Both reactions also carried out using conventional heating but MW gives excellent yield (89%) within short time **(Scheme 1.24 and 1.25)**.

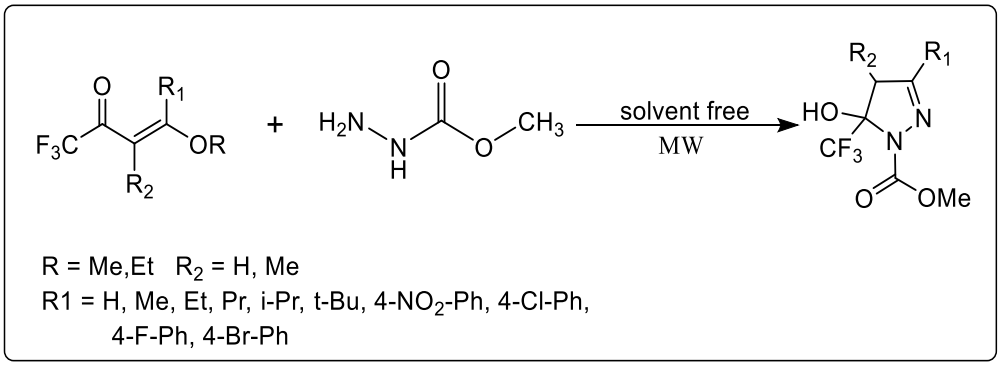


Scheme 1.24



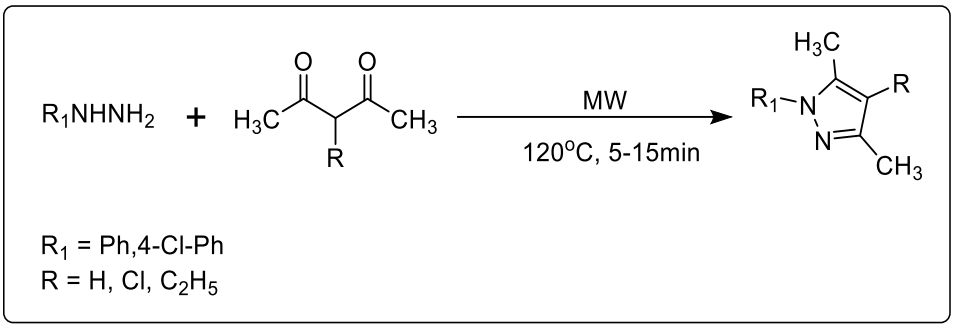
Scheme 1.25

Marcos A. P. Martins et al. [81] demonstrate 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1H-pyrazoles under microwave conditions without solvent. The product of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazoles obtained by the reaction taking place between enones and methyl hydrazinocarboxylate without solvent in microwaves is reported within 6–8 min with a high as excellent yield (50–92%). This methodology is a very effective alternative technique to regular conventional heating and produces the heterocyclic compounds in excellent yields in very little time **(Scheme 1.26)**.



Scheme 1.26

Buchi Reddy Vaddula et al. [82] gives microwave assisted catalyst and solvent free synthesis of pyrazoles and diazepines. Pyrazole is synthesized by condensation of hydrazine's/hydrazides with 1,3-diketones in 5-15min give excellent yield up to 99% that is full conversion of reactant in to product reduces generation of waste, save time, energy and cost **(Scheme 1.27)**.



Scheme 1.27

Advantages and disadvantages of microwave irradiations in organic synthesis is shows in following figure **(Figure 1.19).**

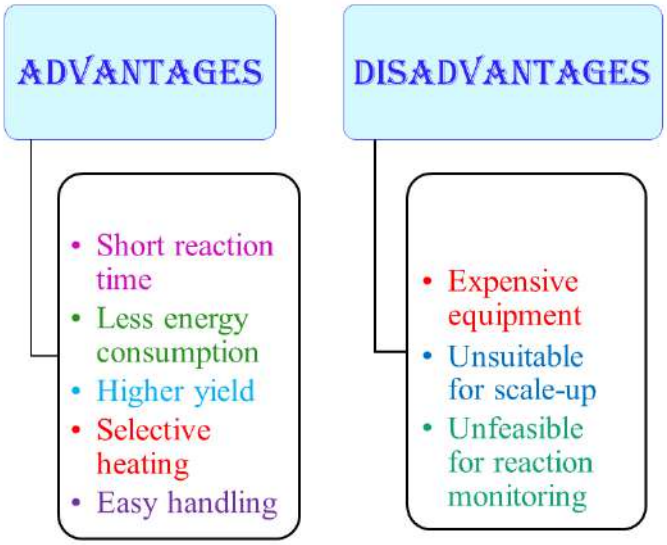


Figure 1.19 Advantages and disadvantages of MW irradiations

1.5 Organic Transformations Under Ultrasonic Irradiation:

The usefulness of ultrasonic waves to assist reactions is now a well-established field of chemistry. The innovative ultrasonics era starts with Professor Paul Langevin's (1917) design of a quartz sandwich transducer for underwater sound transmission in submarines for different purposes. Professor Alfred Lee Loomis modified the wartime acquaintance with Professor Robert Wood and provided for collaborative work and the writing of any joint research article. In 1926, Wood told Loomis of Langevin's experimental work and suggested that the topic provided a broad range of study in physics, chemistry, biology, along with in the medical field. It was this group start involvement of ultrasound into the chemistry in 1927. The actual use and application of sonochemistry took place in the 1980's, soon after [83], [84].

The effect of ultrasound waves on chemical reactivity is known as sonochemistry. Sonochemistry is a chemical application of ultrasound. The best region for initiating chemical reactions is 20-100 kHz and 1-10 MHz is most suitable for ultrasound imaging of body organs in medical science **(Figure 1.20)**. The wavelength of ultrasound for 20 to 100 kHz range is from 7.5 to 0.015 cm. The phenomenon of cavitation seems to be the origin of the Sonochemical effect and the physical phenomenon, high temperatures or electrical fields, occurs during cavitation which breaks the many bonds, mostly homolytic cleavage occurs. The effect of ultrasound waves is not due to the direct interaction of ultrasonic beam with the reaction material but it is due to the phenomenon of cavitation created during the process of implosion of cavitating bubbles [85]. Ultrasound is in fact transmitted through a medium via pressured waves by causing vibrational motion of molecules which alternately compressed and stretched the molecular structure of the medium which consequently, it breaks down and a cavity is formed [86]. This cavity is called cavitation bubble and the process "cavitation". Many of these cavitation bubbles, generated in ultrasonic field which absorb energy from the propagating sound waves. The bubble then implodes creating very high temperature, pressure and mass transfer in a very small area of bubbles **(Figure 1.21)**. These tiny spaces act as micro reactors and due to which changes chemical reactivity of reactant molecule [87].

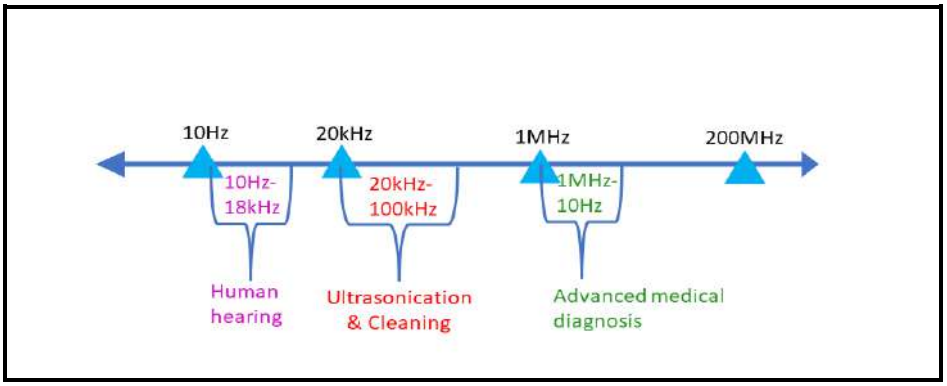


Figure 1.20 Ultrasound frequency range

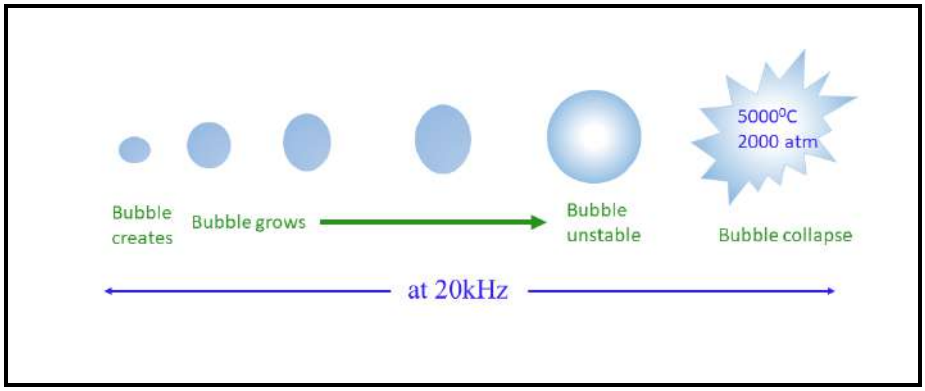


Figure 1.21 Bubble formation and collapsing.

There are two types of ultrasonic devices used in organic synthesis:

1. Introducing ultrasound waves directly into reaction mixture through the ultrasonic probe.
2. Use of ultrasonic cleaning bath which emits ultrasound waves into the water filled in the bath that propagates to the reaction vessel placed in the water of ultrasonic bath.

In laboratory simple ultrasonic bath of 10-1liter capacities has been used for synthesizing different organic compounds **(Figure 1.22)**. The reaction vessel can be properly placed in water bath through which ultrasound propagates and the wave passes through the reaction vessel irradiating the reaction mixture. The symbol **"))))))))"** is used for reaction carried out under ultrasound irradiation.

Figure 1.22 Laboratory used ultrasonication bath.

The ultrasound irradiations have applications in different fields with lots of advantages **(Figure 1.23)**. In literature survey, the different types of organic reactions that were carried out under ultrasound irradiation and studied by different researchers are given below:

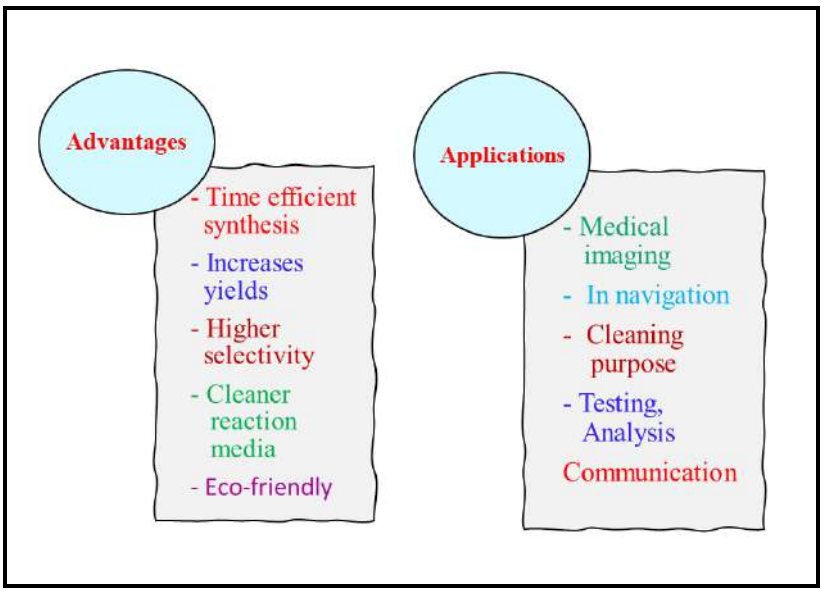
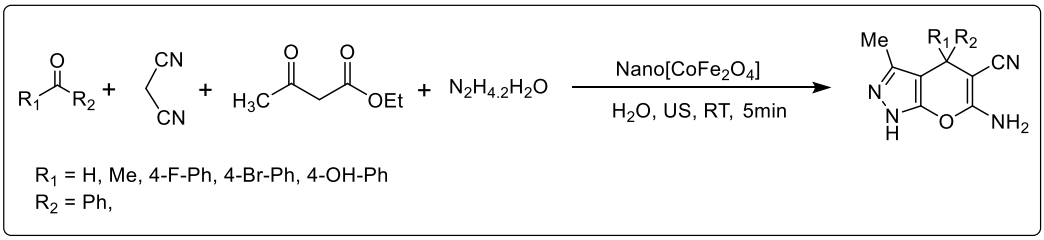


Figure 1.23 Advantages and applications of ultrasound irradiations.

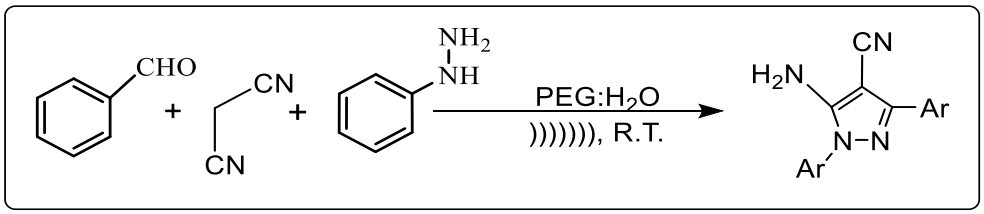
M. Mishraa et al. [88] demonstrate one-pot synthesis of magnetic nano-[$CoFe_2O_4$]-catalysed pyrano [2, 3-c] pyrazoles via ultrasound waves. Under ultrasound irradiation reaction takes place between various aldehydes as well as dialdehydes, and ketones with malononitrile, followed by addition of ethyl acetoacetate along with hydrazine hydrate in the occurrence of magnetic nano-[$CoFe_2O_4$] catalyst within 5 min. gives excellent yield (90-96%) **(Scheme 1.28).**



Scheme 1.28

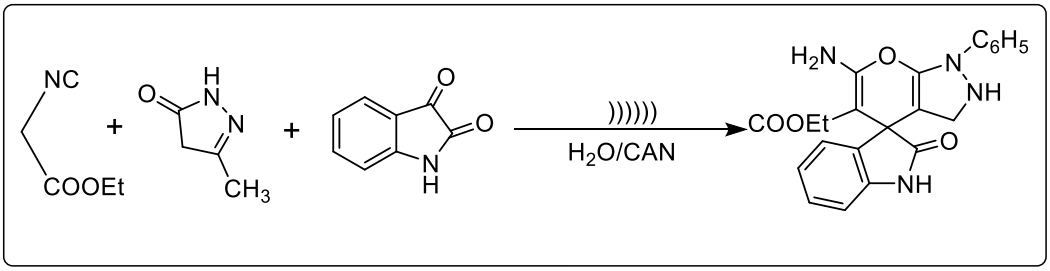
Environmental friendly protocol developed by Firouzeh Nemati et al. [89] for the catalyst-free synthesis of highly substituted pyrazole under ultrasonic radiation. These protocols cost effective, time saving, required less energy that is it follows green

chemistry principles. A mixture of aldehyde, malononitrile, phenyl hydrazine and PEG (polyethylene glycol): H_2O (1:1) was irradiated under ultrasonic irradiation at ambient temperature and at appropriate time (30 min.), product is obtained in excellent yield (99%) **(Scheme 1.29)**.



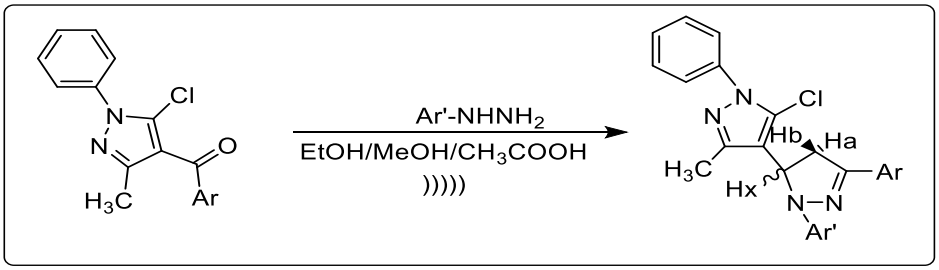
Scheme 1.29

Anshu Dandia et al. [90] carried out ultrasound assisted green synthesis of spiro[pyrano[2,3-c] pyrazoles]. The mixture of isatin, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one gives desired product by applying various conditions and catalyst but ultrasound and catalyst-CAN gives expected result with time up to 20 min yield goes to 97% **(Scheme 1.30)**.



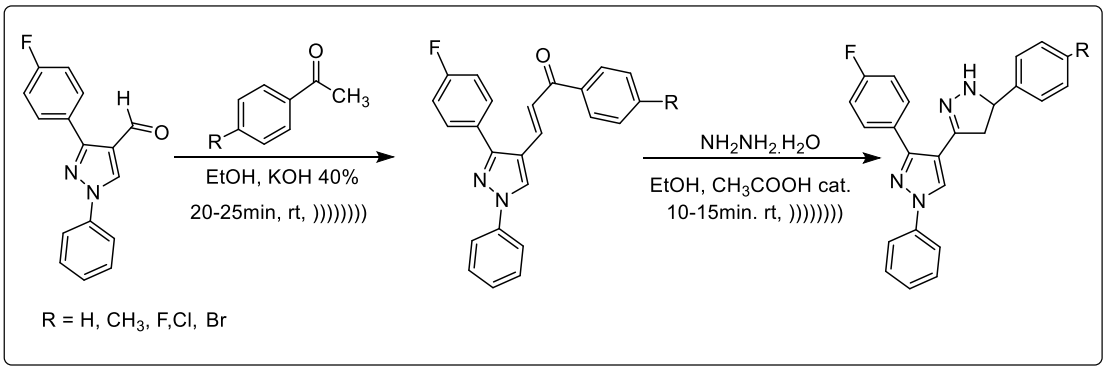
Scheme 1.31

Jorge Trilleras et al. [91] synthesize ultrasonics assisted synthesis of 5-(pyrazol-4-yl)-4, 5-dihydropyrazoles derivatives. Synthesis is done by using chalcones and hydrazine's in ethanol or methanol or acetic acid under sonication at ambient conditions in 20 min. gives 80% yield **(Scheme 1.32)**.



Scheme 1.33

Reactions under ultrasonic irradiation is a 'green' alternative methodology for organic transformation that offers many advantages over conventional synthesis, since it provides uniform heating, faster reaction times, and minimal side reactions, therefore Sharad N. Shelke et. al. [92] under ultrasonic irradiation synthesized fluorinated pyrazoline derivatives in 20-25 min. with 80% yield **(Scheme 1.34)** .



Scheme 1.34

The present introductory topic represents the significance of various green approaches that enhance organic transformations through the utilisation of hydrotrope, biosurfactant, ionic liquid, and alternative energy sources including microwave and sonochemistry. These alternative ways minimise or eliminate the environmental issues caused due to traditional chemical productions carried out at the laboratory and industrial level.

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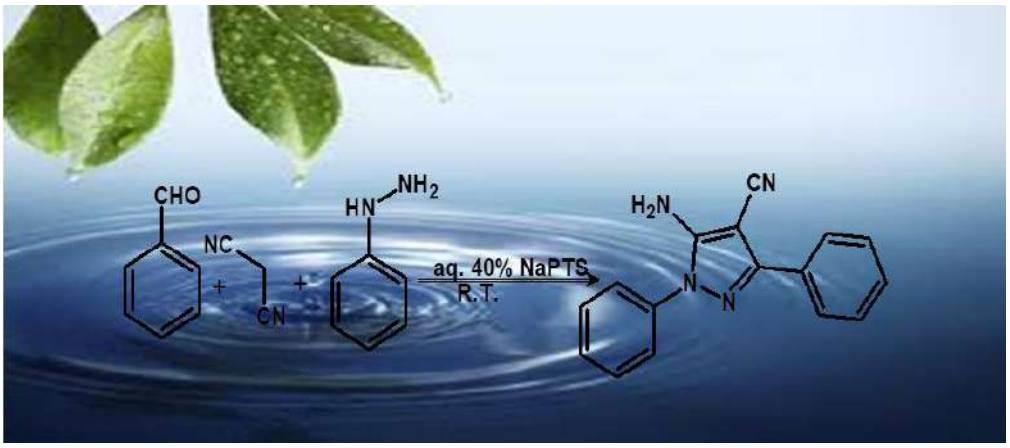
CHAPTER – 2

GREENER SYNTHESIS OF 5-AMINOPYRAZOLE-4-CARBONITRILE IN AQUEOUS HYDROTROPIC MEDIUM



JOURNAL OF HETEROCYCLIC CHEMISTRY

ARTICLE

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Review

Greener and Environmentally Benign Methodology for the Synthesis of Pyrazole Derivatives

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CHAPTER 2

Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for Greener Synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium

2.1 Introduction

Heterocycles account for more than half of all known pharmaceutical compounds due to their wide range of physical, chemical and biological properties with a broad spectrum of reactivity along with stability. Therefore, they take important position in the world of organic chemistry [1]. They have great impetus in a variety of fields, such as drugs, vitamins, natural products, hormones, agrochemicals, dyes and many others. Nitrogen-containing heterocycles are widely spread in the ecosphere which play a significant role in metabolism because of their special structural stability as well as reactivity [2]. Along with naturally occurring N-containing heterocycles, many synthetic N-heterocycles with great physiological and pharmacological properties also exist [3]. From these pharmacophores, one can arrange a diverse class of drugs with potent yield [4]. Heterocyclic compounds have solubility as well as salt-formation properties that restrict their direct oral-consumption and bioavailability [5].

Among the nitrogen-containing heterocycles, pyrazole **(Figure 2.1)** is one of the important core structures of diverse biologically active compounds, which has numerous applications in chemistry, biology and other sciences [6]. German Chemist Ludwig Knorr used the term pyrazole for the first time in 1883. He also synthesizes analgesic drugs which containing pyrazole ring known as antipyrin or phenazone (c) in 1883. The first natural pyrazole, pyrazolayl-alanine (d), was extracted from watermelon seeds (Citrullus vulgaris) in 1959 another natural pyrazole 3-n-nonypyrazole (e) extracted from Houttuynia Cordata which is a plant of the “piperaceae” family by Japanese workers **(Figure 2.2)**. Pyrazole is one of the important five-membered aromatic heterocycles that bears two nitrogen atoms and three carbon atoms in adjacent positions [7], [8].

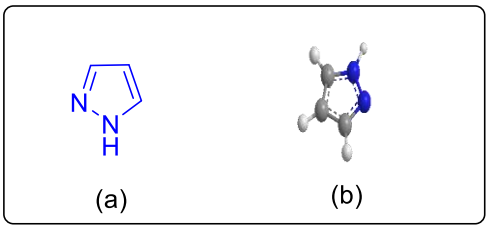


Figure 2.1 (a) Structure of Pyrazole (b) 3D structure of Pyrazole

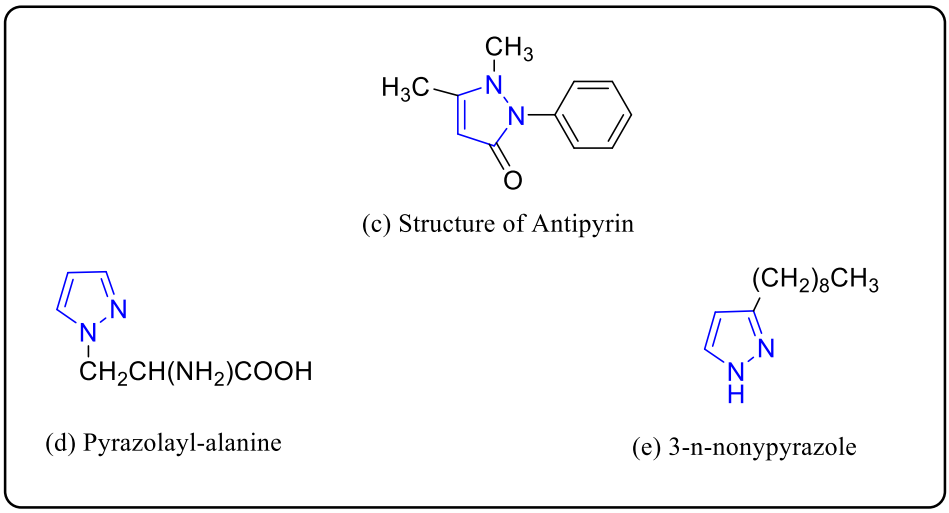


Figure 2.2. Structure of Antipyrin and some naturally occurring pyrazole molecules.

Pyrazole derivatives having deep involvement in pharmacy because of diverse biological activities including antimicrobial [9], antiviral [10], antitumor [11], anti-inflammatory [12], antioxidant [13], anticancer [14], analgesic [15], anti-HIV [16], anticonvulsant [17], antiangiogenic [18], and antidiabetic [19] **(Figure 2.3)**. It plays promising role in inhibiting the activity of against monoamine oxidase in the therapy of diseases such as Parkinson's and Alzheimer's. Pyrazole also have importance in agrochemical field mainly in herbicides, pesticides, insecticides, fungicides and dyestuffs [20], [21].

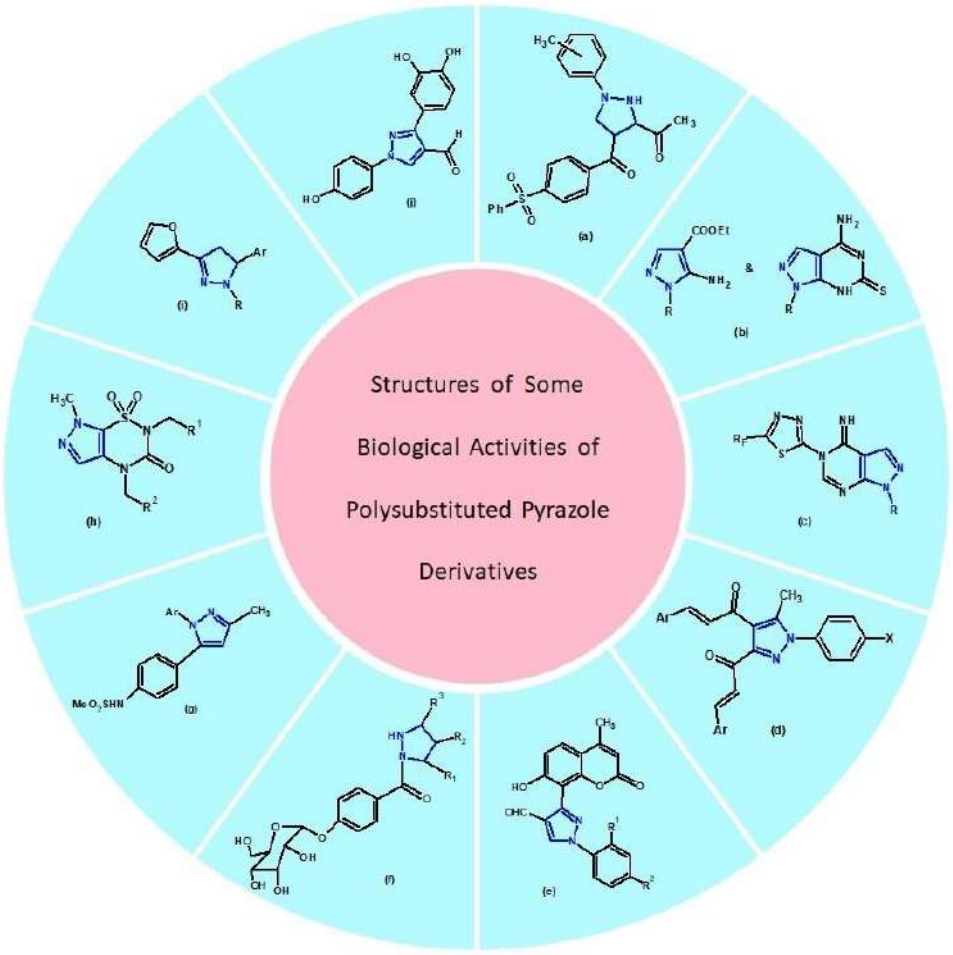


Figure 2.3 Structure of biologically active Pyrazole derivatives.

Due to the wide application of pyrazole derivatives in different fields, it is the subject of deep investigation. According to a literature survey, there are several methods that are reported for the synthesis, like as 1,3 dipolar cycloadditions of diazo compounds, reaction of chalcones with hydrazine, four component reaction between terminal alkynes, hydrazine, carbon monoxide, and aryl iodide, three component reaction between aldehyde, phenyl hydrazine, and malononitrile, and simple reaction between 1,3 diketone with hydrazine by using different conditions along with a catalyst that synthesizes different derivatives of pyrazole which contains pyrazole as a core structure.

Knorr [22] first synthesized a 5-methyl-2-phenyl-2 (f), 4-dihydro-3H-pyrazol-3- one (g), **(Figure 2.4)** by a reacting ethyl acetoacetate with phenyl hydrazine in 1883.

These derivatives (f) and (g) shows anti-inflammatory activity [23] along with promising anti-diabetic agent [24].

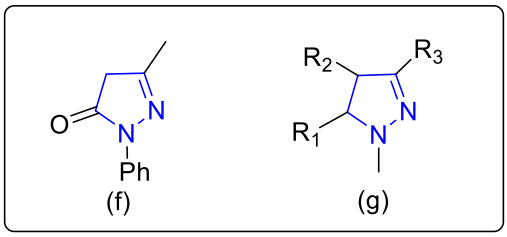


Figure 2.4 Knorr first synthesized pyrazole derivatives

In 1938 L. Ruzicka et al. [25] synthesizes first steroidal pyrazole derivative (h), cholest-4-eno-[3,2-c]-pyrazole-5-carboxylic acid **(Figure 2.5)**. In which pyrazole ring fused with steroidal scaffold that shows diverse biological activities.

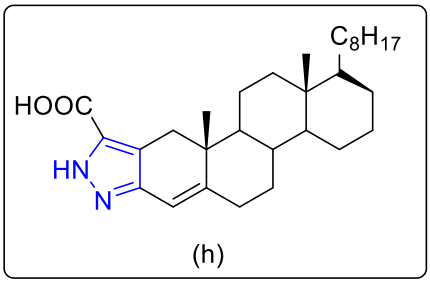
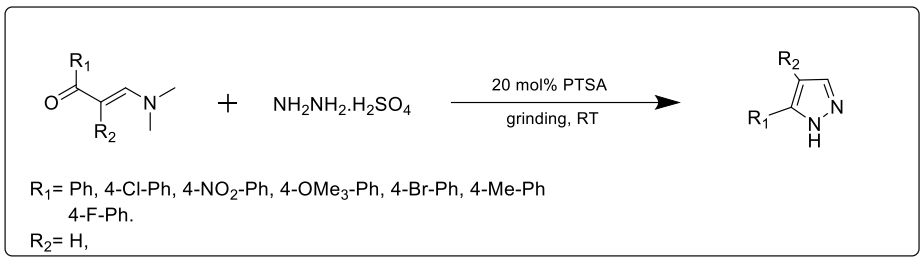


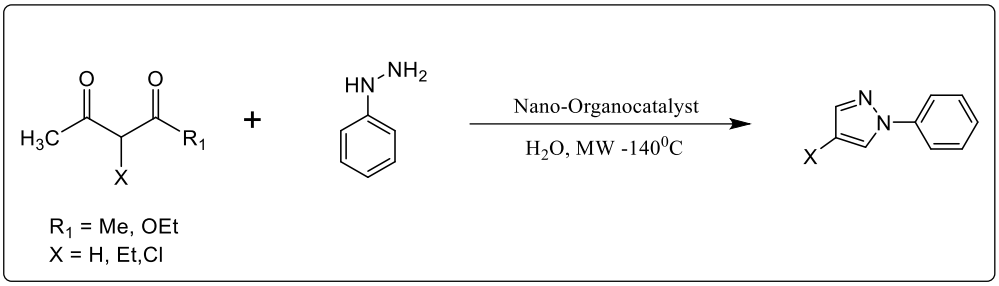
Figure 2.5 First steroidal pyrazole derivative.

Kelvis Longhi et al. [26] demonstrate an efficient synthesis of various derivatives of NH-pyrazoles from the reaction mixture of β-dimethyl amino vinyl ketones along with hydrazine sulfate with p-toluene sulfonic acid (PTSA) as a catalyst in absence of solvent, on grinding firstly liquid forms then eutectic mixture create which distribute reactants uniformly gives product in 6-12 min. with 90% yield **(Scheme 2.1)**. They show solvent free simple synthesis with minimum waste within short time develop green route of synthesis.



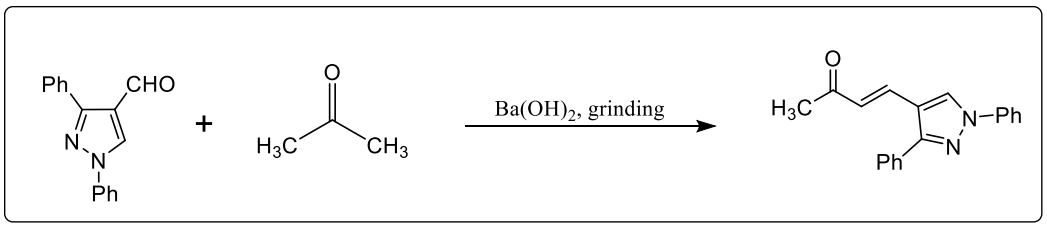
Scheme 2.1

Vivek Polshettiwar et al. [27] reported microwave-assisted pyrazole synthesis by using nano-organocatalyst. Pyrazole is synthesized by various hydrazine's along with hydrazides reacted efficiently with 1,3-diketones in presence of nano-organocatalyst (nano ferrite (Fe_3O_4) supported glutathione) was irradiated under microwave at 50-250W for 20 min obtain the product in good yields (78-96%) **(Scheme 2.2)**.



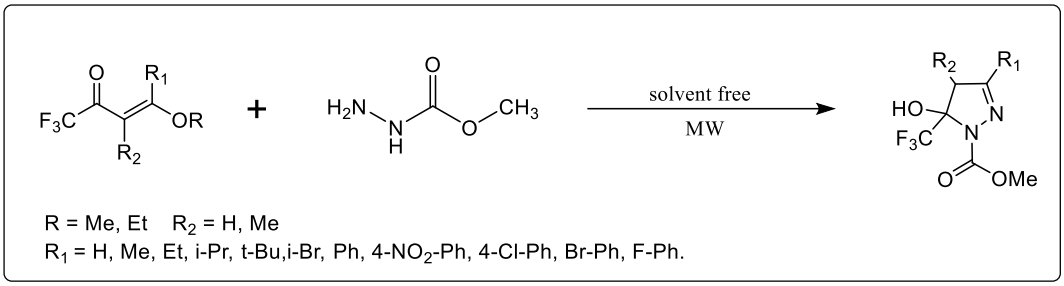
Scheme 2.2

Parvin Kumar et al. [28] synthesise pyrazole chalcones without solvent at room temperature. Activated barium hydroxide (C-200) synthesises pyrazole substituted chalcones from a mixture of pyrazole aldehydes and acetophenones by grinding with a mortar and pestle in 5–10 minutes, giving an above-average yield of 90%. It is an eco-friendly, solvent-free Claisen Schmidt condensation **(Scheme 2.3)**.



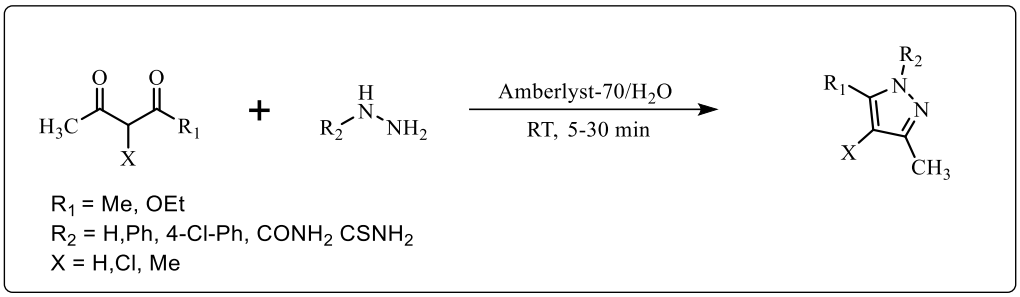
Scheme 2.3

Marcos A. P. Martins et al. [29] demonstrate the preparation of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1H-pyrazoles in the absence of solvent under microwave conditions. For the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazoles, the cyclo-condensation between 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones and methyl hydrazinocarboxylate under solvent-free microwave conditions is reported within 6–8 min with a high to excellent yield (50–92%). This methodology is an effective alternative to conventional thermal heating, which produces the heterocyclic products with excellent yields in less time **(Scheme 2.4)**.



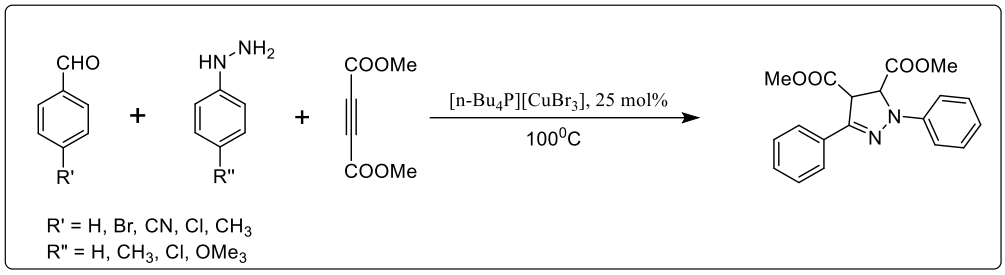
Scheme 2.4.

Recyclable catalyst attracts the attention due to it directly effect on environment together with economy therefore Nitin Lad and Dipali Dange et al. [30] demonstrate greener approach for the synthesis of pyrazole such as amberlyst-70 as a recyclable catalyst in aqueous medium. Mixture of hydrazine's/hydrazides and 1,3-dicarbonyls in presence of Amberlyst-70 at 30ºC stirred for 5-30 min, product is form which is further purified and then yield is calculated. In less time 95% yield is obtain as well as catalyst is recycled up to five cycles give good yield. Separation and reuse of catalyst is easy therefore this protocol is more favorable in green synthesis **(Scheme 2.5)**.



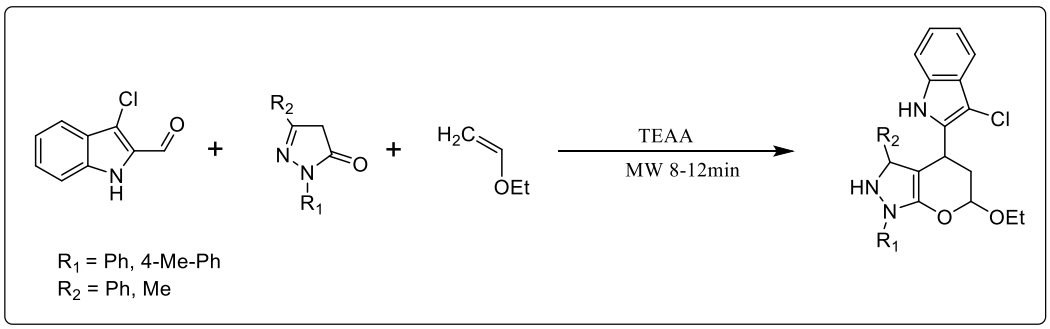
Scheme 2.5

The green synthesis of substituted pyrazole in the presence of Cu(II) ionic liquid is done by Shirin Safaei et al. [31] with a higher yield. A mixture of aldehyde, aryl hydrazine, then dimethyl acetylene dicarboxylate (DMAD) and [n-Bu_4P] [$CuBr_3$] were mixed, and the composite was heated at 100^oC without solvent for the appropriate time in 1–1.5 hrs., giving a 52–88% yield. Reusability, along with recyclability, of a catalyst is of practical importance in minimising the amount of waste and reducing pollution. Therefore, use of ionic liquid is safe as well as environmentally effective that reduce time, therefore total cost along with energy consumption also minimizes **(Scheme 2.6)**.

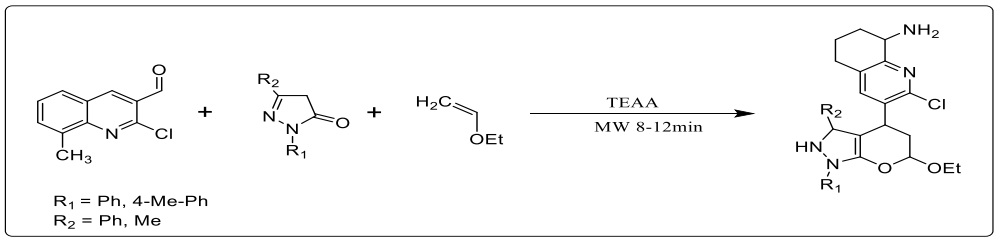


Scheme 2.6

Narsidas J. Parmar et al. [32] develop one-pot preparation of numerous heteroaryl pyrano[2,3-c]pyrazoles in ionic liquid under microwave-irradiation. It is three-component hetero-Diels–alder reaction, afforded indolyl and quinolyl pyrano[2,3-c]pyrazoles **(Scheme 2.7 & 2.8)**. Microwave reduces time from hrs. to 8-12 min with 90% yield these is main advantage of MW irradiation that minimizes time, cost, pollution along with increasing yield.

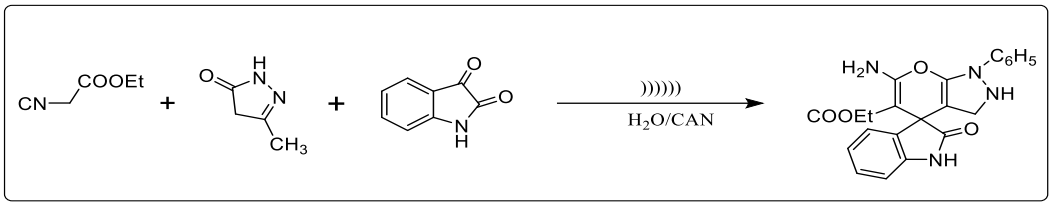


Scheme 2.7



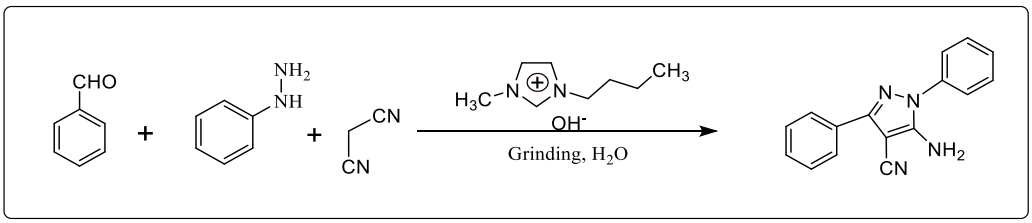
Scheme 2.8

Anshu Dandia et al. [33] carried out ultrasound-assisted green synthesis of spiro[pyrano[2,3-c] pyrazoles. The mixture of isatin, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one gives the desired product by applying various conditions together with the catalyst, but ultrasound with the catalyst CAN gives the expected result with time up to 20 min and a yield of 97% **(Scheme 2.9)**.



Scheme 2.9

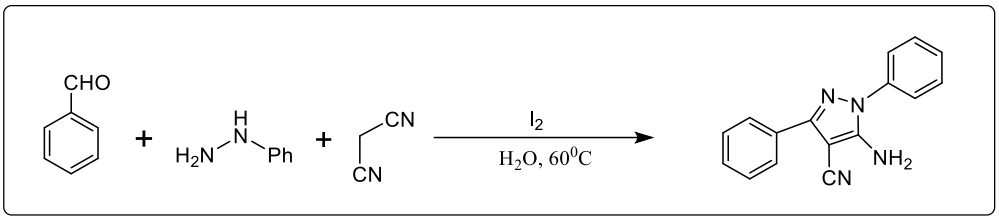
Srivastava et al. [34] carried out synthesis of functionalized pyrazole derivatives by ionic liquid catalyzed with grinding in water. These triply green routes fulfill all shades of green chemistry. Reaction of malononitrile, phenyl hydrazine and diversified aldehyde in ionic liquid-1-butyl-3-methyl imidazolium hydroxide [(Bim)OH], with water without by-products gives desired product in good yield (90%) in 10-30 min **(Scheme 2.10)**. Here combination of green route, ionic liquid with grinding in water develop environmentally as well as economically facile synthesis.



Scheme 2.10

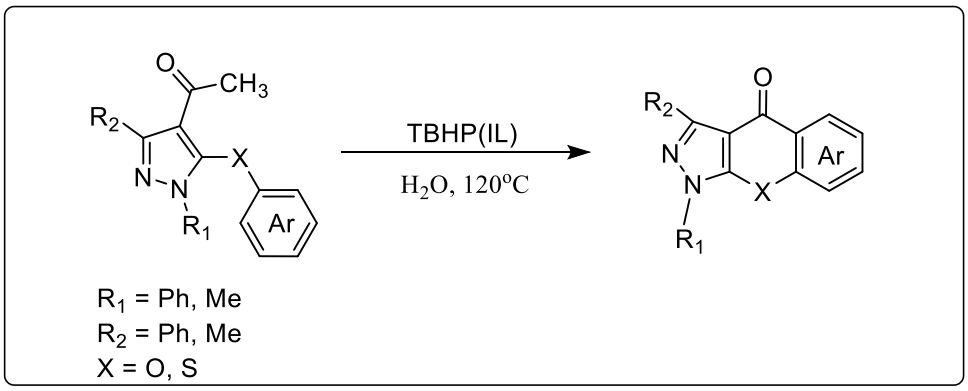
One pot synthesis of highly functionalized pyrazole, developed by Madhulika Srivastava et al. [35] in water, catalyzed by iodine. They carried out reaction at various

temperature by using different catalyst in iodine at 60°C within 20 min phenyl hydrazine, malononitrile and a diverse range of aldehydes reacted, product obtain in high yield 85-94% **(Scheme 2.11)**. Reaction goes by Knoevenagel condensation between aldehyde derivatives and malononitrile gives 1,2 unsaturated compound which attacked by phenyl hydrazine (Michael addition) after which intramolecular cyclisation gives pyrazole.



Scheme 2.11

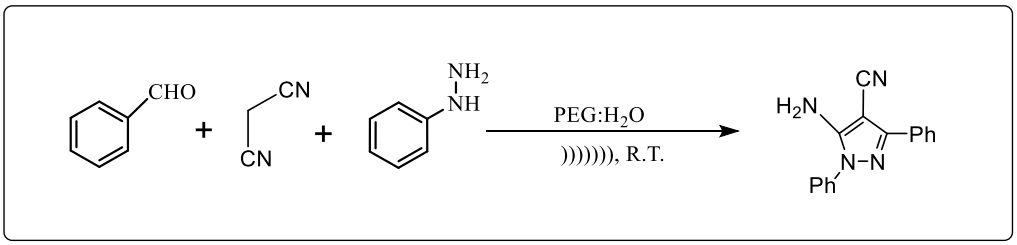
He Li et al. [36] developed green pathway for the preparation of chromeno[2,3-c] pyrazol-4(1H) through ionic liquid in aqueous media. Various kinds of ionic liquids and solvents are tested for obtaining desired product in good yield. Ionic liquids are easily recycled and reused after drying in vacuo. Reused 5-times without loss of activity, reaction of 3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with tert-butyl hydroperoxide (TBHP) in H_2O at 120°C for 24 hr. gives 73% yield **(Scheme 2.12)**.



Scheme 2.12

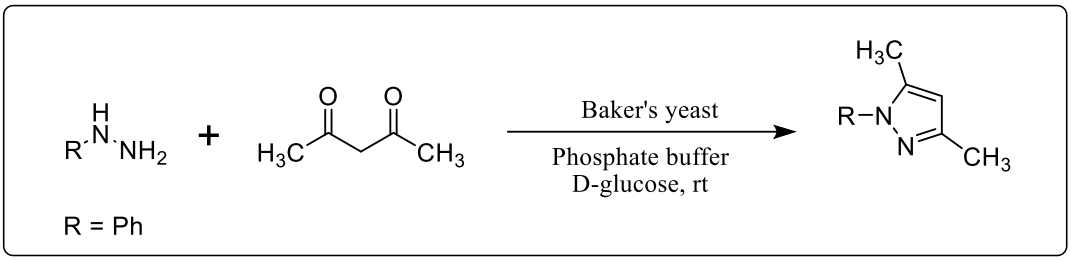
Environmentally friendly protocol developed by Firouzeh Nemati et al. [37] for the catalyst-free synthesis of pyrazole scaffolds under ultrasonic radiation. These protocols cost effective, time saving, required less energy that is it follows green chemistry principles. A mixture of aldehyde, malononitrile, phenylhydrazine in PEG

(polyethylene glycol): H_2O (1:1) was irradiated under ultrasonic waves at ambient temperature for appropriate time (30 min.), product is obtained in excellent yield (99%) **(Scheme 2.13)**.



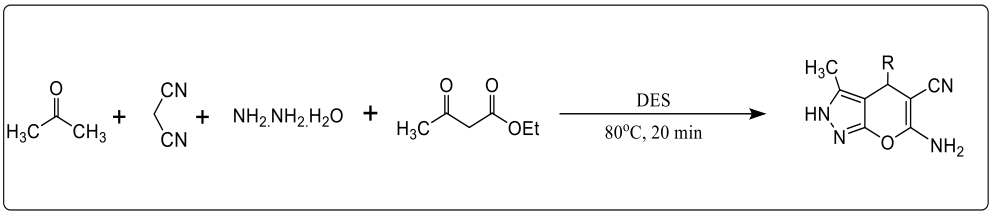
Scheme 2.13

Ananda Mane et al. [38] develop protocol for the synthesis of pyrazole by adding fermented baker's yeast to 1,3-dicarbonyl compound and hydrazine/hydrazide the resulting mixture was aroused at room temperature for indicated time gives yield (70-90%) is depend on substituent **(Scheme 2.14)**. It is a biodegradable, biocatalyst gives eco-friendly, inexpensive, easily available, less hazardous pyrazole derivatives.



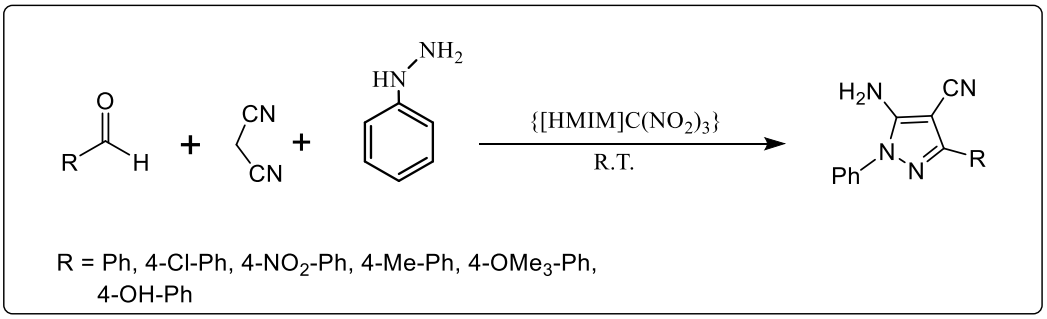
Scheme 2.14

Recently, researchers focused more attention on the utility of deep eutectic solvents (DES) for organic transformations due to Manisha R. Bhosle et al. [39] develop a protocol for production of 6-amino-2H, 4H-pyrano[2,3-F]pyrazole-5-4 carbonitriles in deep eutectic solvent such as cholinechloride: urea. Use of DES avoids toxic solvents together with catalyst. Reaction between aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate in DES at 80ºC in 20 min with 82% yield **(Scheme 2.15)**.

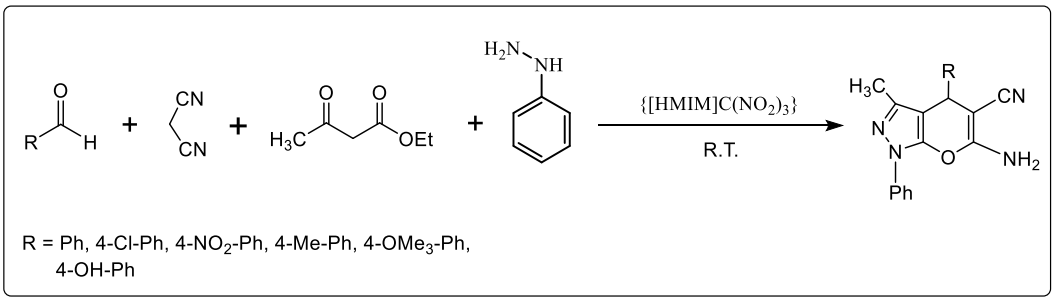


Scheme 2.15

Mohammad Ali Zolfigo et al. [40] first used 1-methylimidazolium trinitromethanide {[HMIM] $C(NO_2)_3$}: as a nano sized ionic liquid for creation of library of pyrazole molecules (58). There is Knoevengel condensation of aldehyde with malononitrile gives arylidene malononitrile then Michael addition of phenylhydrazine on it obtain the product in good yield. Also prepare 1,4-dihydropyrano-[2,3-c]-pyrazole (59) by a one-pot four-component, reaction between various aromatic aldehydes, malononitrile, phenylhydrazine, and ethyl acetoacetate in similar conditions in 20 min gives 92% yield **(Scheme 2.16 & 2.17)**.



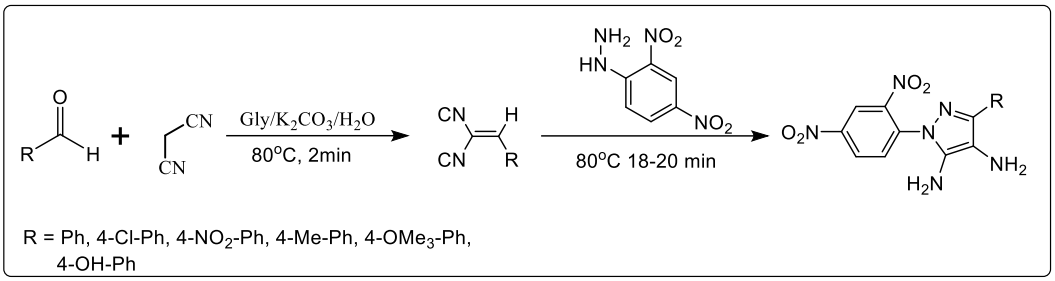
Scheme 2.16



Scheme 2.17

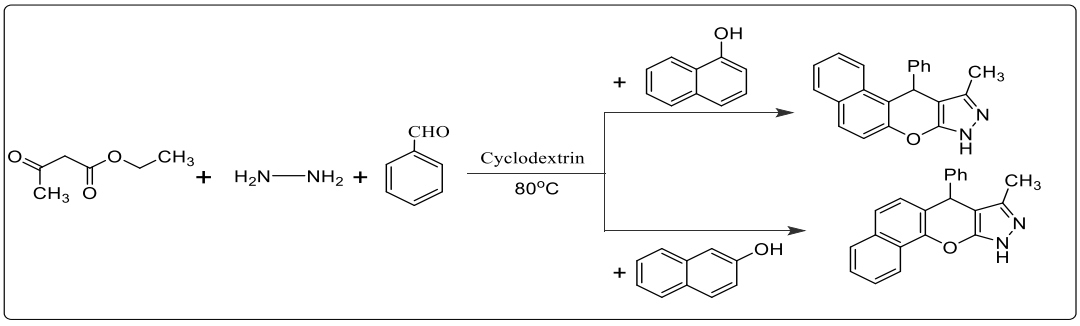
Hamid Beyzaei et al. [41] carried out green synthesis of polysubstituted pyrazoles along with study of their antimicrobial activities in presence of deep eutectic solvent (DES). Synthesis carried out between cyanoacetonitrile, 2,4-

dinitrophenylhydrazine and various aldehydes in deep eutectic solvent (DES)-glycerol/potassium carbonate at 80°C in 20 min gives 91% yield. DES acts as ecofriendly media or efficient catalyst for organic transformation **(Scheme 2.18)**.



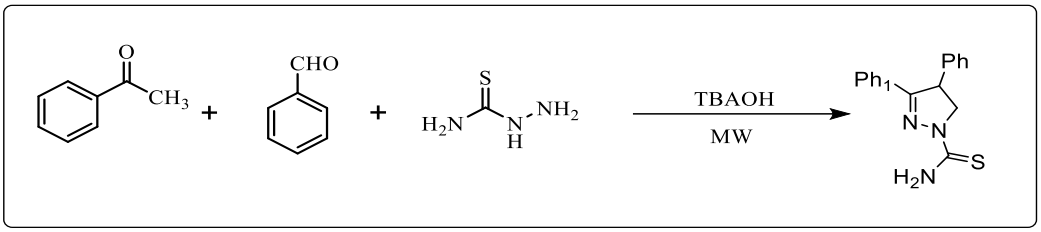
Scheme 2.18

Cyclodextrin is an efficient green catalyst used by Samahe Sadjadi et al. [42] for synthesis of benzochromeno-pyrazole. They design ionic liquid-modified cyclodextrin nano sponges. Synthesis of benzochromenopyrazole derivatives by reacting hydrazine hydrate, benzaldehydes, α or β-naphthol and ethyl acetoacetate in 15 min gives high yield 94% **(Scheme 2.19)**.



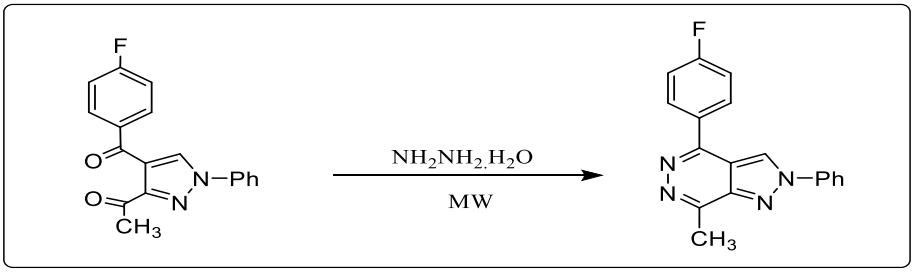
Scheme 2.19

Hamid Reza Farmani et al. [43] synthesize green protocol is microwave-assisted synthesis of 4, 5-dihydro-1H-pyrazole-1-carbothioamides in water. Aqueous medium with microwave both is environmentally green and efficient route. Mixture of aldehyde, acetophenone, thiosemicarbazide and tetrabutylammonium hydroxide [TBAOH] as base in water irradiated under MW at 300W, 70°C in 2-3 min gives 80-96% yield. This methodology provides easy, simple, environmentally safe protocol as well as improve sustainability **(Scheme 2.20)**.



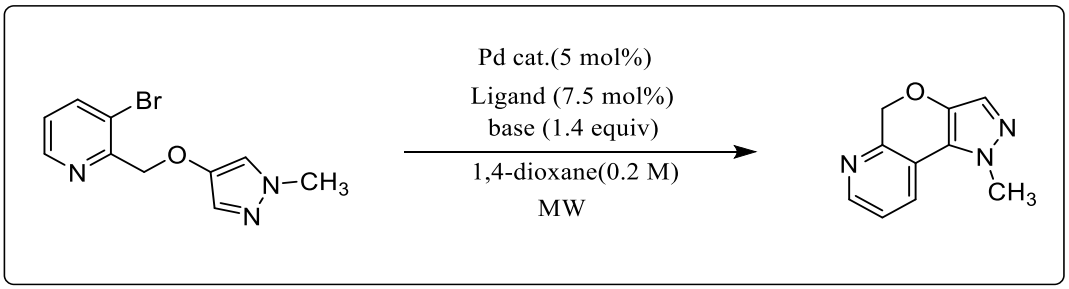
Scheme 2.20

Ismail I. Althagafi et al. [44] develop MW-assisted synthesis of novel regioselective pyrazoles and pyrazolopyridazines. They synthesise pyrazole molecules consisting of a fluorophenyl ring by the 1, 3-dipolar cycloaddition of nitrile imines and enamines using not only traditional but also advanced microwave irradiation, but MW gives good results in 10–30 min. with 85% yield **(Scheme 2.21)**.



Scheme 2.21

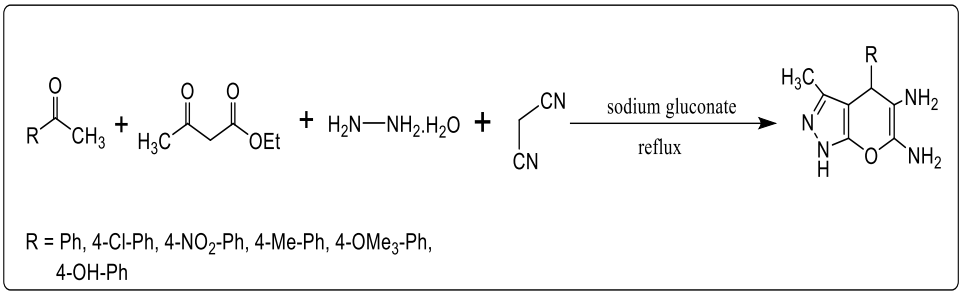
Aaron T. Garrison et al. [45] carried out the synthesis of 1,5 dihydropyrazolo[3′,4′:5,6] pyrano[3,4-b]pyridines (21) by microwave irradiation. They develop a regioselective Pd(0)-catalyzed CH arylation reaction of pyrazoles within 5 minutes in the microwave, creating 98% product **(Scheme 2.22)**.



Scheme 2.22

Amol Khandebharad et al. [46] carried out synthesis of dihydropyrano [2,3-c] pyrazole (72) in presence of biodegradable catalyst such as sodium gluconate. It is one-pot multicomponent reaction of aldehyde or ketone, Cyanoacetonitrile, ethyl

acetoacetate and hydrazine hydrate in aqueous medium obtain the high yield (92%) within short period of time (20 min) **(Scheme 2.23)**.



Scheme 2.23

2.2 Present Work:

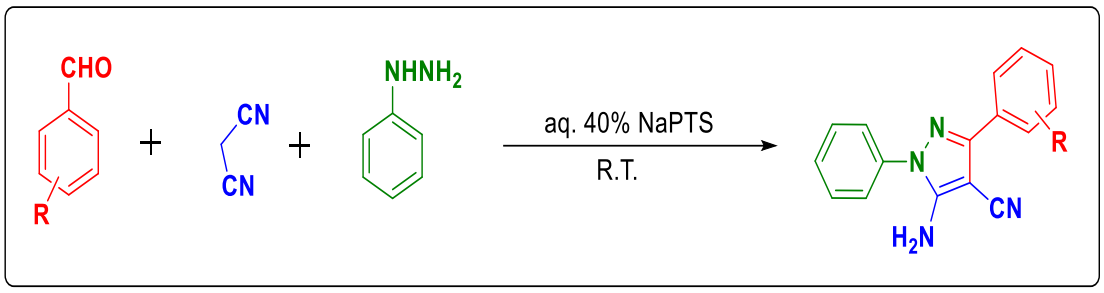
Synthesis by MCRs is more accepted aspect because it is effective, required less energy, decrease cost, time and generation of by-products. Therefore, the formation of new MCRs with green aspect has enticed more attentiveness, specifically in the field of medicinal chemistry, organic synthesis along with material science. Synthesis of heterocyclic scaffolds is performed via MCRs in the presence of various green tools as well as by using green catalyst which produces good results.

All the reported methodologies require harsh reaction conditions viz. organic solvent, metal framework catalyst, acids along with bases but this reaction conditions are not sustainable to the environment, expensive, hazardous, time consuming. Therefore now days researchers focused on develop more eco-friendly, less hazardous, environmentally safe methodologies, such as ionic liquid, [47] I_2 in water, [35] 1-methylimidazolium trinitro methanide {[HMIM]C$(NO_2)_3$}as a nano ionic liquid (NIL), [40] PEG-400 and water under ultrasound waves [37] but designing of ionic liquid and other solvent are also little costly which cause environmental issue therefore we use here hydrotrope in these synthesis which can full fill some of the conditions of green chemistry that is environmentally safe, less hazardous, cost effective, easy handling, no any toxic solvent, that is it is sustainable to environment

2.3 Result and Discussion:

Hydrotropes are increase solubility of sparingly soluble organic compounds [48]. Hydrotropes are water- soluble and surface-active compounds; they substantially increase the solvability of organic moieties such as esters, alcohols, ketones, aldehydes, hydrocarbons and fats [49]–[51]. It acts as carrier for poorly soluble drugs and also for

non-polar organic compounds [52]. The main feature is the nature of hydrotropes, on which reaction conditions depend, and the maximum solubilities of reactants or substrates observed at their minimum hydrotropic concentration (MHC). After that hydrotrope increases dissolvability of materials there is direct interaction between reactants those are insoluble in aqueous medium. The mechanism by which insoluble and sparingly soluble compounds are soluble in water is aggregation and MHC [53]. There is difference between self-aggregation of hydrotrope and micelle, that is presence of minimum hydrotrope concentration (MHC) analogues to minimum micellar concentration (CMC) [54]. Most hydrotropic solutions precipitate the solute on dilution with distilled water therefore recovery of product along with re-use of hydrotropic solvent is easy [55]. Hydrotropes are used for many purposes such as drug solubilization, detergent formulations, health care, in household applications [56], also used as extracting agent. Overall hydrotrope has various advantages such as eco-friendly; non-flammable, less toxic, inexpensive that is hydrotrope follow the green chemistry principle. Therefore, here use one of the hydrotrope is sodium p-toluene sulfonate (NaPTS) for synthesis of Pyrazole derivatives **(Scheme 2.24)**.



Scheme 2.24 Synthesis of 5-amino-pyrazole-4-carbonitrile.

Table-2.1: Screening of conditions for synthesis of 5-amino-pyrazole-4-carbonitrile.

Entry	Solvent/ Catalyst	Time	Yield
1	Water	48hrs	trace

2	Ethanol	24hrs	trace
3	Water + Ethanol (1:1)	24hrs	40%
4	**Water + 40% NaPTS**	**30 min**	**92%**

Initially focused on selection of green methodology for synthesis of present scheme **(Table 2.1)**. Initially we use water as green solvent but yield was very low and also require long reaction time, then we choose another solvent is water: ethanol (1:1) then also yield is poor due to lower solubility of organic compound in aqueous medium. Then we select hydrotrope that increase the solubility of sparingly soluble compounds in aqueous medium. Hydrotropes are surface active agent they increase solubility in many folds access. We select hydrotrope which is NaPTS at various concentrations out of which 40% NaPTS gives expected yield in 5-10 minutes at room temperature **(Table 2.2)**. We screen the reaction condition by using reactant as aldehyde (1mmol), malononitrile (1mmol), phenyl hydrazine (1mmol) we got the maximum yield in 5ml 40% aq. NaPTS at room temperature. Then use different derivatives of benzaldehyde with electron donating and withdrawing group getting good to excellent yields of corresponding pyrazoles.

Table-2.2: Optimization concentration of Hydrotrope for synthesis of 5-amino-pyrazole-4-carbonitrile:

SR. NO.	Hydrotrope (% w/v)	Temp.(^{0}C)	Time	Yield %
1.	10 % NaPTS	24^{0}C	24 hrs	-
2.	20 % NaPTS	24^{0}C	180 min	10
3.	30 % NaPTS	24^{0}C	100 min	50
4.	**40 % NaPTS**	**24^{0}C**	**30 min**	**92**
5.	50 % NaPTS	24^{0}C	100 min	90

6.	60 % NaPTS	24^0C	100 min	85
7.	40 % NaPTS	50^0C	60min	70
8.	40 % NaPTS	80^0C	80 min	70
9.	40 % NaPTS	100^0C	100 min	75

The plausible mechanism of the product formation is conceptualized in fig.2.6. The water added to hydrotrope, water fragments hydrating the head parts of hydrotrope which decreases the electrostatic attraction between these head groups of hydrotropic moieties. The two head groups separated from each other and replace the water molecules interacting hydrophobic parts. This may be the electromotive force for two hydrophobic parts to interact also it enhance the reactant molecule to solubilize and get interact with each other. Then water molecules get eliminated and easily occupied by the hydrophilic head groups. As a consequence of the overall findings, there is an enhanced speed of the reaction, and the reaction proceeds in an aqueous medium due to hydrotropism.

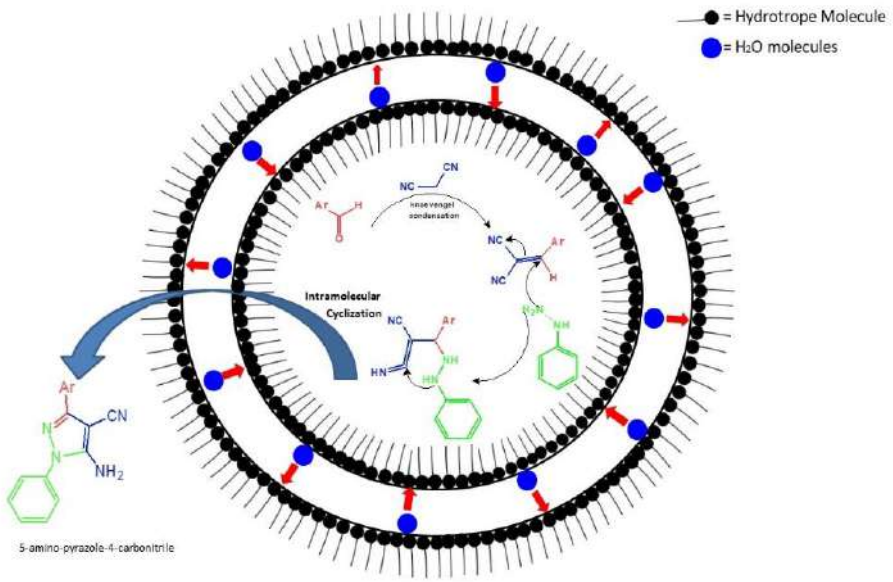
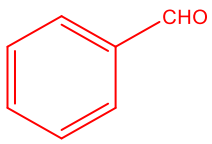
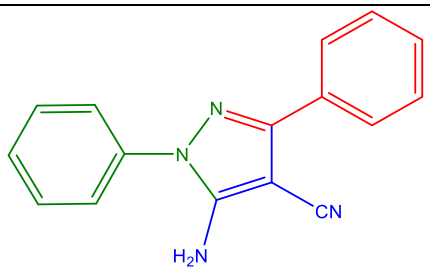
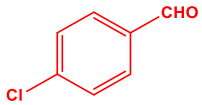
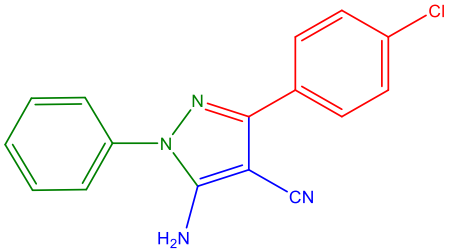
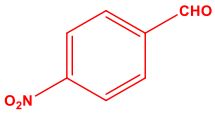
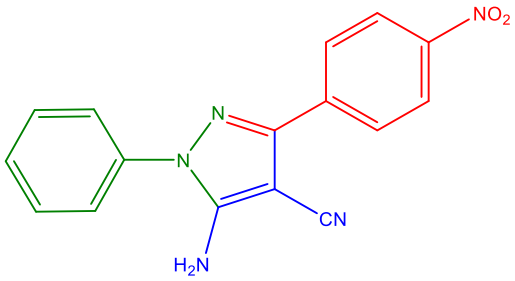
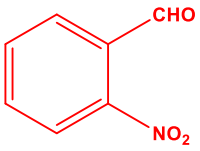
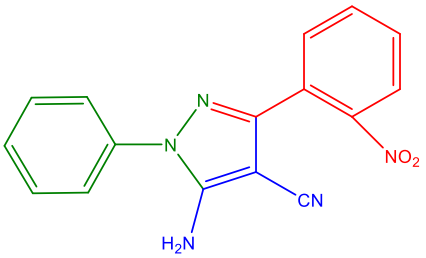
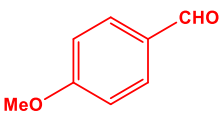
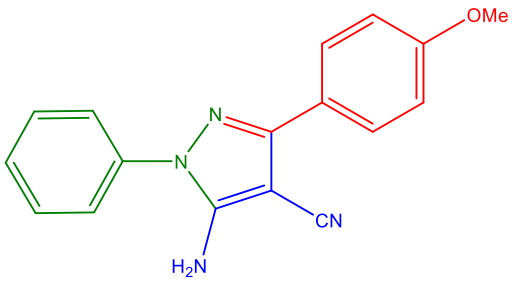
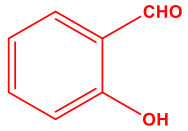
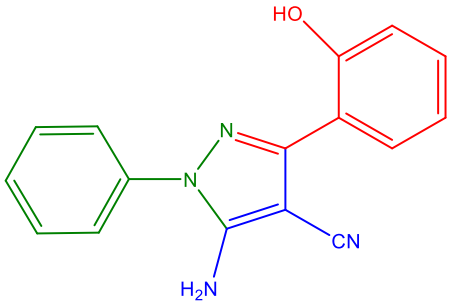
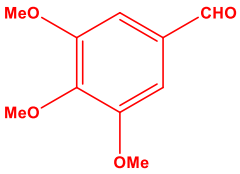
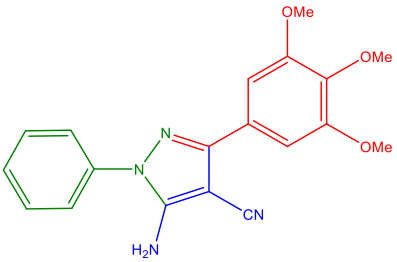
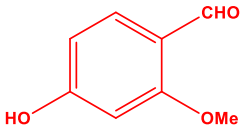
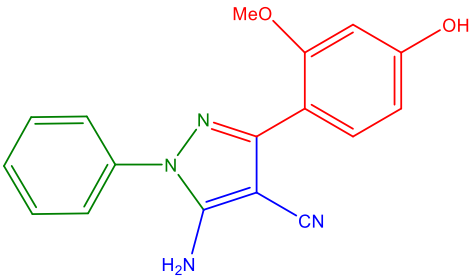
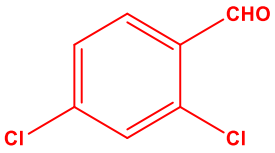
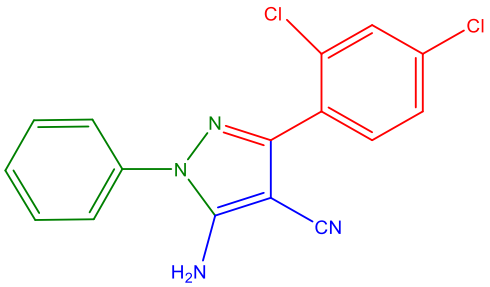
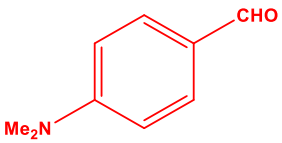
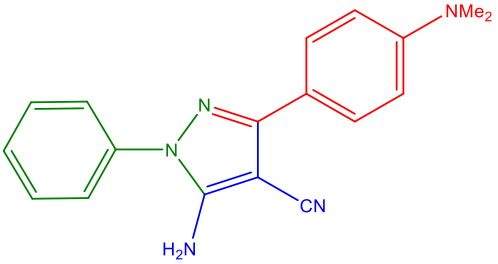
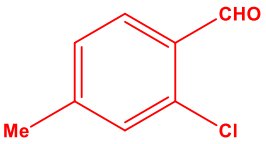
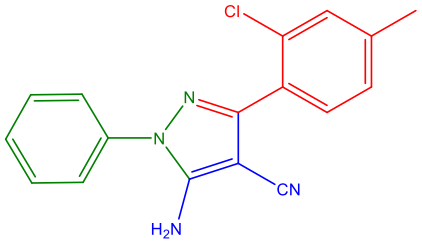
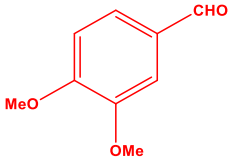
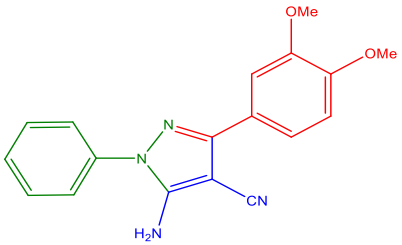
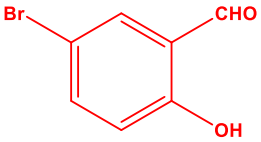
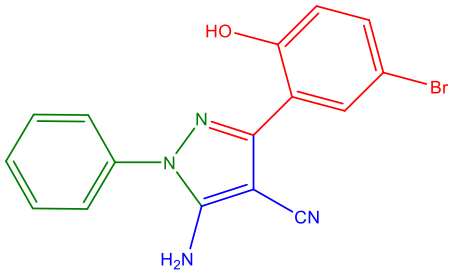


Figure 2.6 A Plausible reaction mechanism for synthesis of 5-amino-pyrazole-4-carbonitrile in aqueous hydrotropic medium.

Table-2.3: Synthesis of 5-amino-pyrazole-4-carbonitrile derivatives in 40% hydrotrope in aqueous medium.

Entry	Aldehyde	Product	M.P. (ºC) [34], [57]	Yield (%)
1			156-158	92
2			127-128	92
3			175-177	92
4			158-160	92
5			106-109	90

6			160-162	80
7			128-130	92
8			120-122	92
9			130-132	90
10			104-106	92

11			124-126	92
12			121-123	92
13			178-180	80

Recyclability of Hydrotrope:

The reuse of catalyst is very important step in synthesis because reuse of catalyst directly effects on cost along with environment. Therefore, easy recovery along with reuse of catalyst is necessary these is possible by using hydrotrope, because it is reuse only after the reaction is complete, filter the product and give washing to product then collect the filtrate along with product because that filtrate contain the hydrotrope, then keep the filtrate for evaporation after that our catalyst i.e., hydrotrope is recover, which is ready for reuse. We check the recyclability of that hydrotrope by 5 times obtain the good result with loss of small amount of yield which is shown in **figure 2.7**.

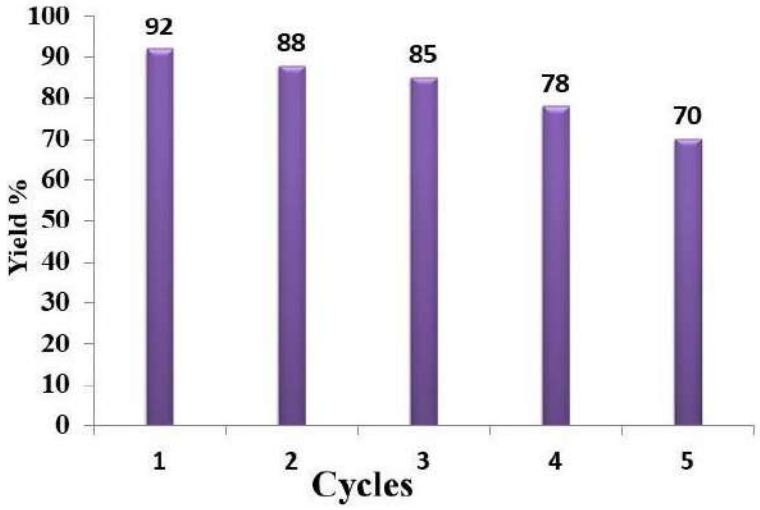
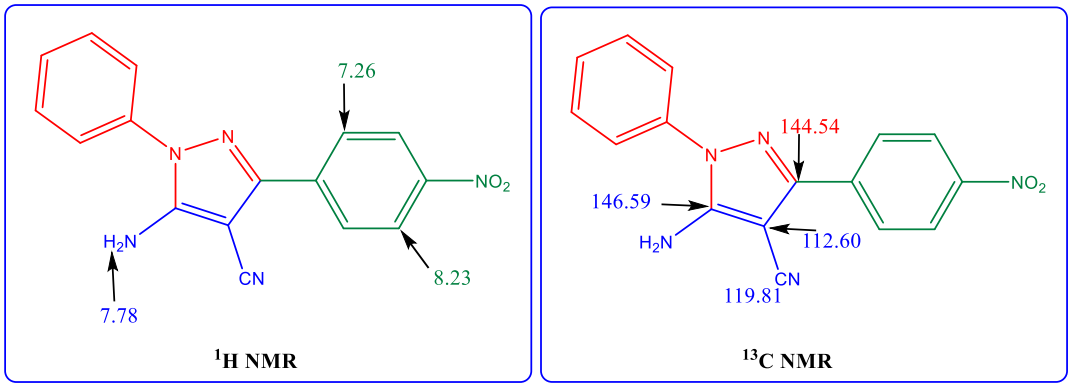


Figure 2.7 Recyclability of Hydrotrope.

Characterization of products

The synthesized products of pyrazole derivatives are confirmed on the basis of IR, ^{1}H, ^{13}C NMR spectroscopy, which is in full agreement with the proposed structures.

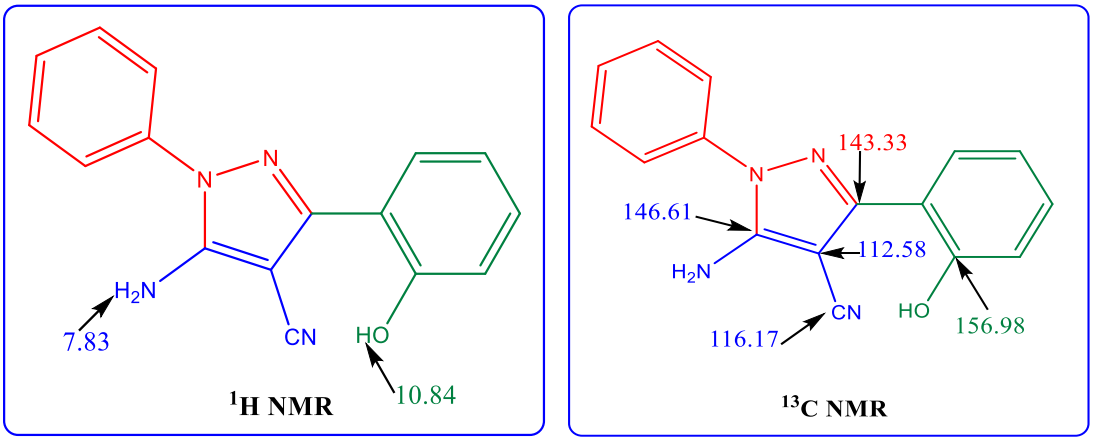
1) 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3):



In IR spectrum **(Figure 2.11)** characteristic band observed at 3467.38 and 3303.43 cm^{-1} for asymmetric and symmetric stretching vibrations of primary amine group while band at 2360.11 cm^{-1} corresponds to nitrile group. In the ^{1}H NMR **(Figure 2.12)** spectrum, singlet appeared at δ 7.78 ppm for two protons of amine group. two protons ortho to nitro groups resonated at more upfield at δ 8.23 ppm while protons at meta position appeared at δ 6.95-7.98 ppm. The remaining peaks from δ 7.15-7.26 ppm attributed to protons of aromatic ring. Similarly, in ^{13}C NMR **(Figure 2.13)** spectrum displays peak at 119.81 ppm for nitrile group however carbon adjacent to nitrile group

appeared at δ 112.60 ppm. The remaining carbons resonated in aromatic region 124.43, 125.76, 126.96, 127.52, 129.01,130.51, 130.74, 132.81, 144.54 and 146.59 ppm.

2) 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6):



IR spectrum shows **(Figure 2.14)** characteristic peak for phenolic OH appeared at 3446 cm^{-1}, NH_2 at 3320.82 and 3207.04 cm^{-1} resp. while cyanide band appears at 2188.81 cm^{-1}. In ^1H NMR **(Figure 2.15)** spectrum of the same compound showed sharp singlet at δ 10.84 ppm for hydroxyl proton, amines two proton also shows singlet at δ 7.83 ppm. four protons show multiplate at δ 6.99-7.90 ppm, remaining three protons also shows multiplate at δ 7.15-7.49 ppm of the benzene ring. ^{13}C spectrum **(Figure 2.16)** exhibited pyrazole ring carbon appeared at δ 112.58, 143.33 and 146.61 ppm. the peak at δ 116.17 ppm was for nitrile carbon while aromatic carbons noticed at δ 118.46, 119.46, 120.86, 129.52, 129.53, 129.99, 135.26, 137.24, 141.17, 156.98 ppm from which confirms the correct structure formation of corresponding product.

2.4 Conclusion:

The present protocol describes environmentally friendly synthesis of 5-aminopyrazole-4-carbonitrile. Due to harsh reaction conditions dangerous side effect on environment need to develop such safe methods therefore here we use hydrotrope in aqueous medium which is a green methodology. This methodology having lot of advantages such as less hazardous, cost effective, time saving and mild reaction condition. Present protocol suggests a promising green approach for the synthesis of 5-aminopyrazole-4-carbonitrile.

2.5 Experimental

General:

All the chemicals required for synthesis were commercially sourced and were used without further purification. Melting points of products are measured on electrical melting point apparatuses. IR spectra were obtained with lambda FT-IR 750 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 400MHZ spectrometer using $CDCl_3$as solvent and TMS is an internal standard.

General procedure for the synthesis of 5-amino-pyrazole-4-carbonitrile:

Take equimolar ratios of malononitrile (1 mmol), phenyl hydrazine (1 mmol), and substituted aldehyde (1 mmol) in 10 ml of a 40% aqueous NaPTS solution. This reaction mixture was constantly stirred at room temperature for a few minutes until the progress of the reaction was monitored by TLC in n-hexane: ethyl acetate (7:3). The solid product was separated by simple filtration. The separated solid product was recrystallized in a suitable solvent.

Spectroscopic data for some target compounds are as follows:

1) 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (1):

White solid, melting point: 156-158ºC. IR (KBr): ῡ = 3320.82, 3290, 2930, 2210, 580, 1600, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.87 (d, 1H), 7.11(dd, 2H), 7.13-7.26(m, 5H), 7.37(d,1H), 7.65(S, 2H), 7.68(d,1H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.71, 120.07, 126.15, 128.40, 128.58, 129.28, 135.26, 137.24, 143.33, 144.61, 144.75, 146.80.

2) 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6):

Yellow solid, melting point: 160-162ºC. IR (KBr): υ= 3446.17, 3320.82, 3207.04, 2927, 2188.81, 1598.70, 112.79, 1150.01 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.90-7.00 (m, 4H), 7.15-7.49 (m, 5H), 7.83 (s, NH_2), 10.84 (s, 1H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.58, 116.57, 118.46, 119.46, 120.86, 129.52, 129.53, 129.99, 135.26, 137.24, 141.17, 143.33, 146.61, 156.98.

3) 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3):

Red solid, melting point:175-177^{o}C. IR (KBr): υ 3467.38, 3303.43, 2950, 2360.11, 1580.70, 1210.05, 750.17 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.95 (d, 1H), 7.15-7.26 (m, 5H), 7.78 (S, NH_2), 7.98 (d, 1H),8.23 (dd, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δppm 112.60, 119.81, 124.43, 125.76, 126.96, 127.52, 129.01,130.51, 130.74, 132.81, 144.54, 146.59.

4) 5-amino-1-phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole-4-carbonitrile (7):

Cream color, melting point:128-126^{o}C.IR (KBr): ῡ = 3413, 3364, 2930, 2220, 1610, 1245, 1140 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 3.930 (s, 3H), 3.389 (s, 6H), 6.88 (d, 2H, ArH), 7.19-7.28 (m, 5H, ArH), 7.66(s, 2H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.60, 117.57, 119.46, 121.07, 127.2, 129.4, 130.7, 137.9, 143.2, 148.12, 150.0, 154.7.

5) 5-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (5):

Light brawn solid, melting point:106-109^{o}C. IR (KBr): ῡ = 3446.17, 3320.82, 292741, 1598.17, 1480.17, 1272.78, 1159.01, 750.04. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 3.910(S, 3H), 6.89(d, 2H, ArH), 7.60(d, 2H, ArH), 7.30-7.60(m, 5H, ArH), 7.71(s, 2H). ^{13}C NMR (100MHz $CDCl_3$): δppm 53.6, 112.60, 114.8, 116.34, 121.20, 126.2, 127.4, 129.01, 129.85, 130.07, 145.8, 152, 155.

6) 5-amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2):

Cream color solid, melting point:127-128^{o}C. IR (KBr): ῡ = 3446.17, 3313.11, 2229.11, 1594.84, 1488.78, 1255.43, 748.25. ^{1}H NMR (400MHz, $CDCl_3$): δppm 7.45-7.68 (m, 4H, ArH), 7.30-7.60 (m, 5H), 7.72 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δppm 118.45,120.86, 122.4, 126.5, 127.98, 129.25, 129.88, 130.45, 133.23, 144.46, 148.01, 153.01.

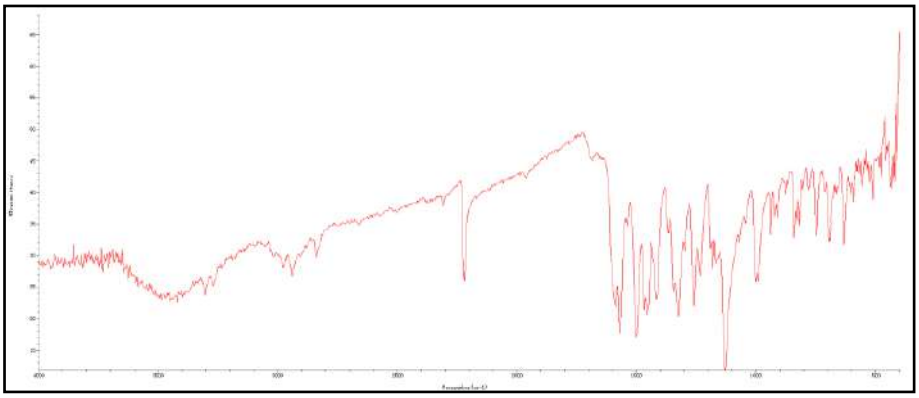


Figure 2.8: IR Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

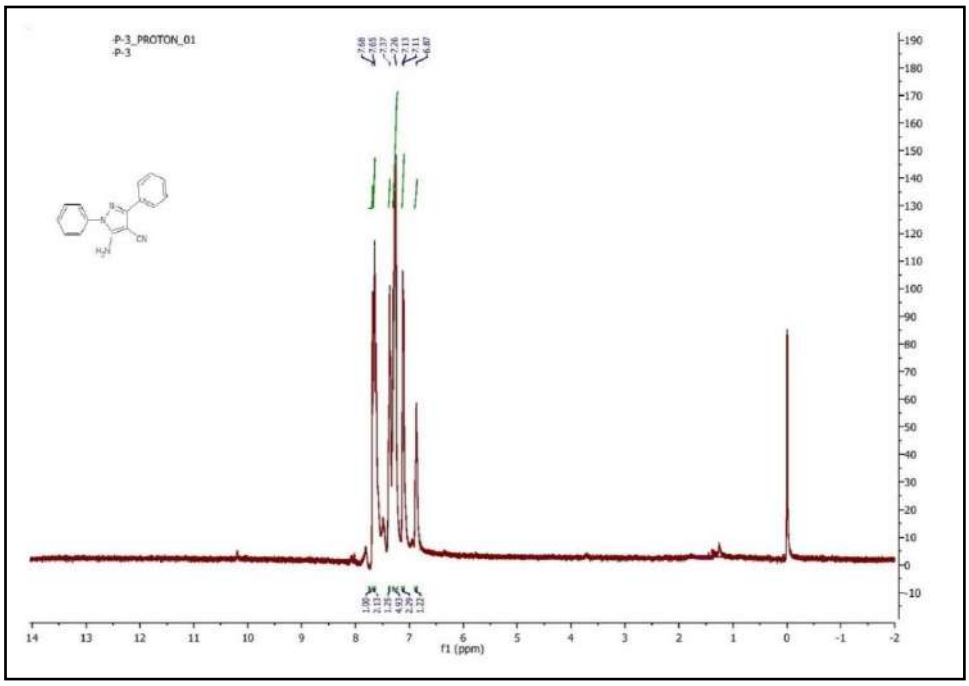


Figure 2.9: ^{1}H Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

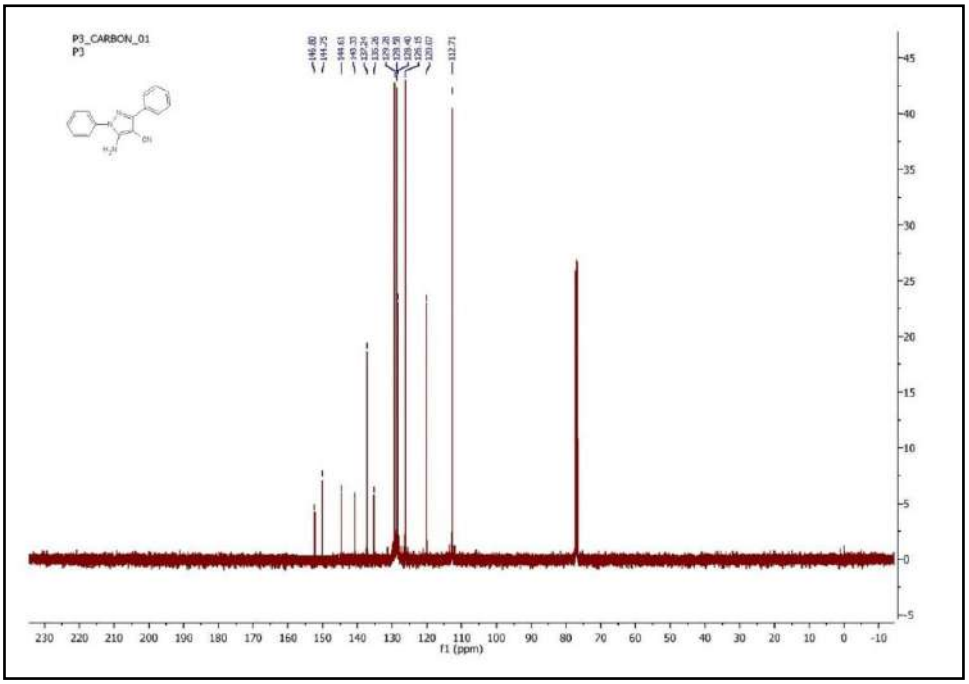


Figure 2.10: ^{13}C Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

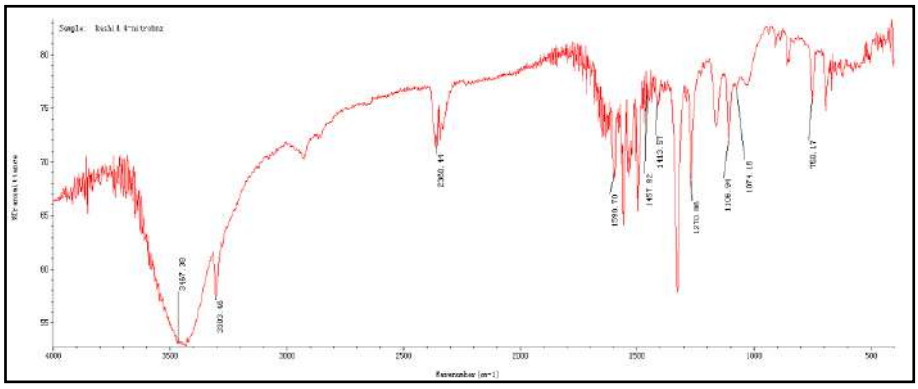


Figure 2.11: IR Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

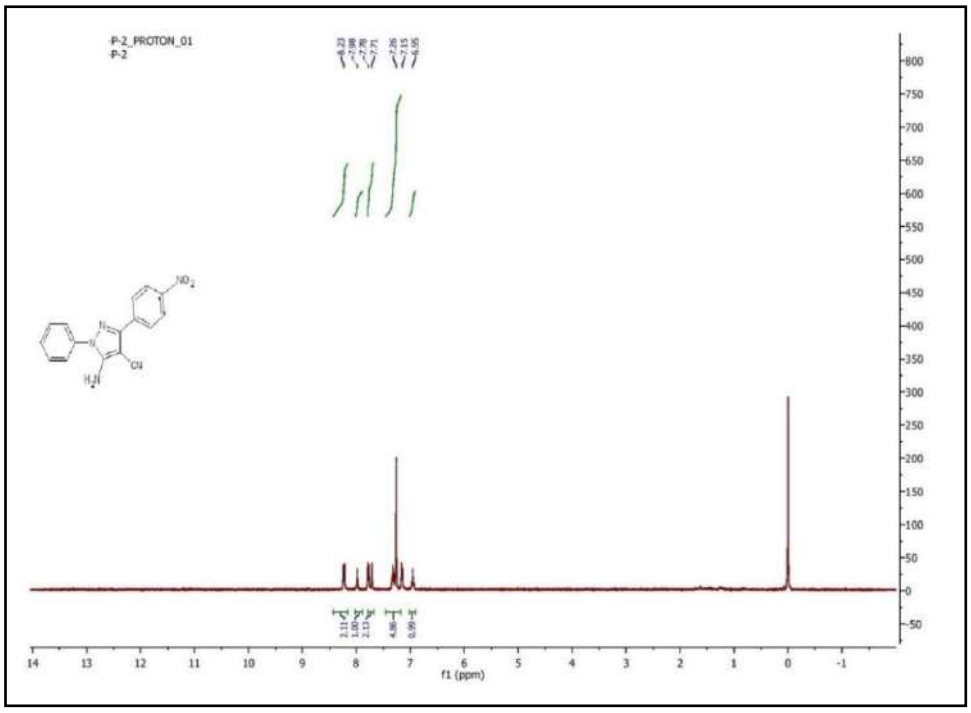


Figure 2.12: ^{1}H Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

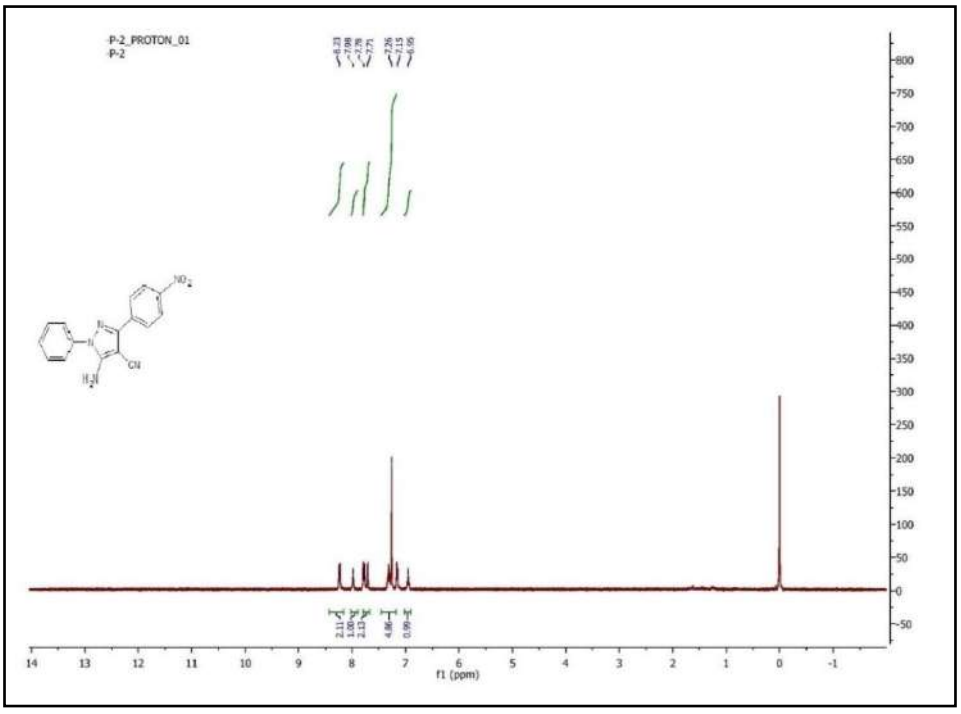


Figure 2.13 ^{13}C Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

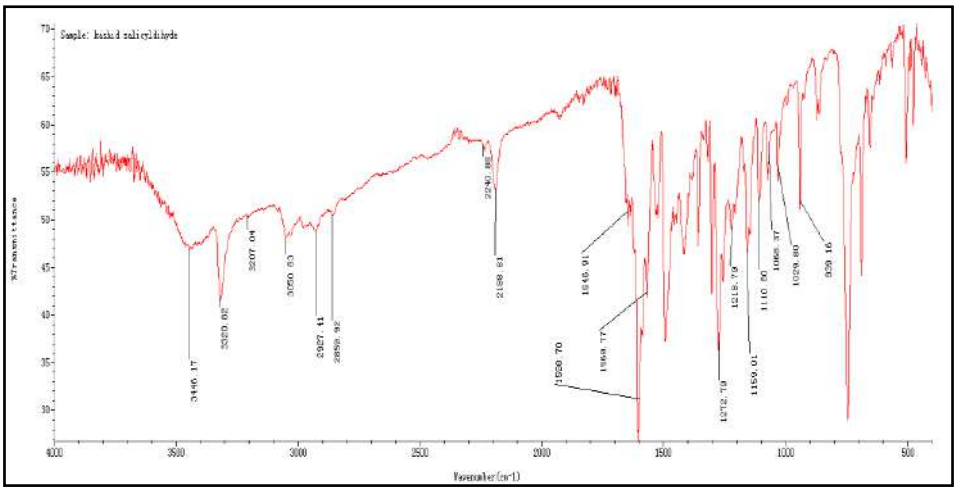


Figure 2.14 IR Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile(6)

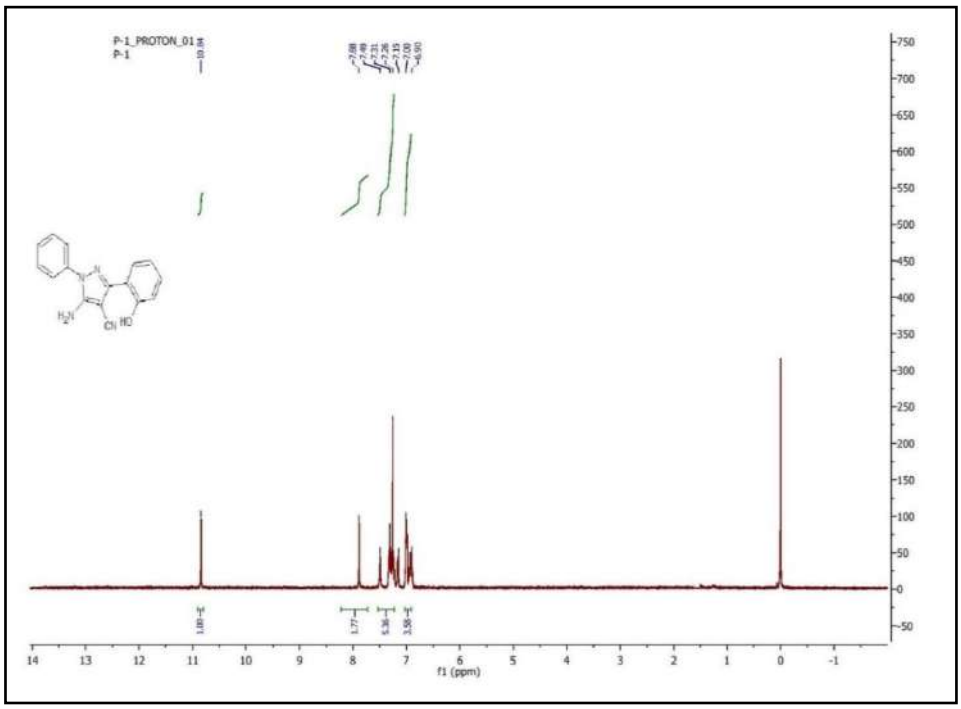


Figure 2.15 ^{1}H Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6)

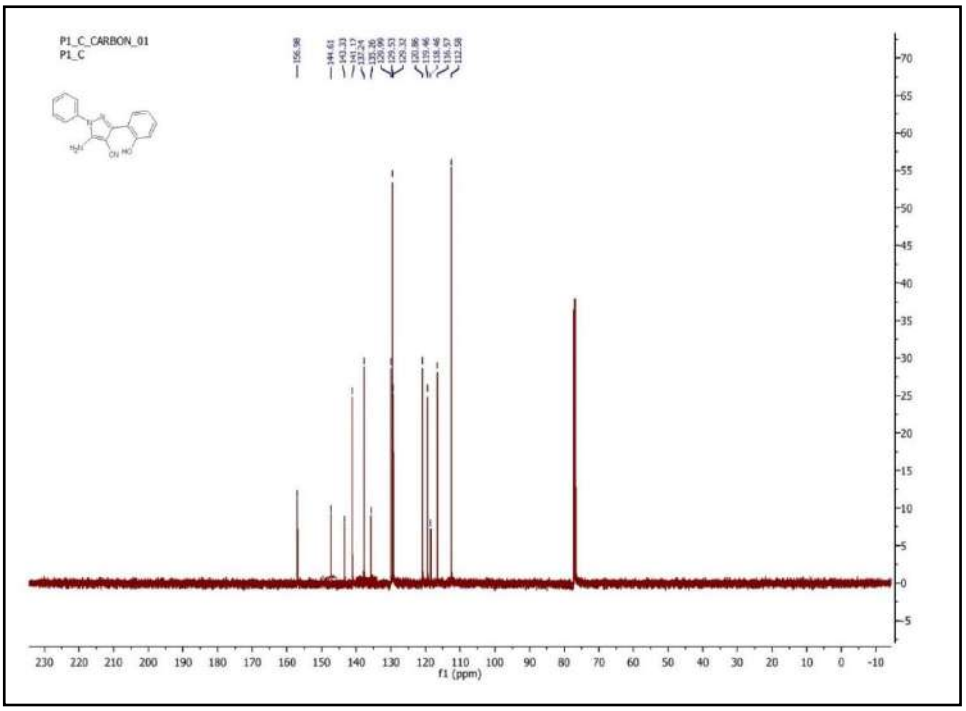


Figure 2.16 ^{13}C Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile(6)

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CHAPTER – 3

CLEAN AND GREEN APPROACH FOR SYNTHESIS OF VARIOUS DERIVATIVES OF [1,3]OXAZINE IN SUSTAINABLE AQUEOUS HYDROTROPIC MEDIUM

Research Article

Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium

Aboli Sapkal, Suraj Attar, Avdhut Kadam, Pramod Gaikwad & Santosh Kamble

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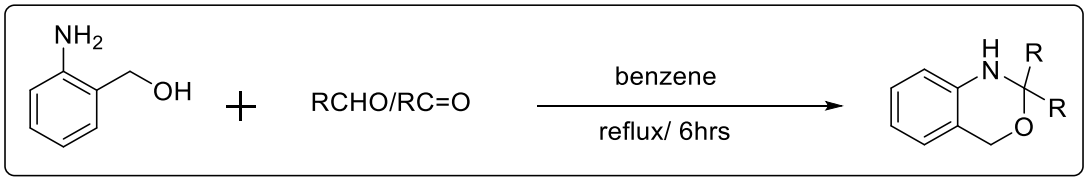
CHAPTER 3

Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium

3.1 Introduction

The importance of organic chemistry increases day by day due to heterocyclic compounds and its involvement in the pharmaceutical industry. The study of heterocyclic compounds is very innovative from both a theoretical and practical point of view. They are extensively spread in natural space and necessary to life due to their crucial role in the metabolic activities of all living cells. Some pharmaceutically active heterocyclic compounds are widely found in nature as like antibiotics penicillin and cephalosporin, alkaloids-morphine and reserpine along with these synthetic heterocyclic compounds also widely spread in different fields for example materials in applied chemistry dye stuffs, copolymers, solvents, photographic sensitizers and developers. Oxazine is one of the important heterocycles among the library of various heterocyclic compound. Holley and cope were reported first synthesis of oxazine in 1944 **(Scheme 3.1)** [1]. After that, Burke et al. also extensively contributed to the development of many benzoxazines and naphthoxazines during the 1950s and 1960s [2]–[4]. Oxazine ring bears the Oxygen and nitrogen and therefore its application in drug chemistry is tremendous. These oxazines have its own library of their various analogous oxazine scaffolds such as Oxazole (1), Isoxazole (2), 4,5-dihydroisoxazole (3), Isoxazolidine (4), 1,3-oxazolidine (5), 1,2-oxazine (6), 1,3-oxazine (7), 1,4-oxazine (Morpholine) (8), 3,6-dihydro-2H-[1,2]oxazine (9), Benzo[d]isoxazole (10), 1,4-benzoxazine (11) **(Figure 3.1)**, etc., at the different position containing oxygen and nitrogen in their structural arrangement.



Scheme 3.1 Synthesis of first Oxazine by Holly and Cope in 1944.

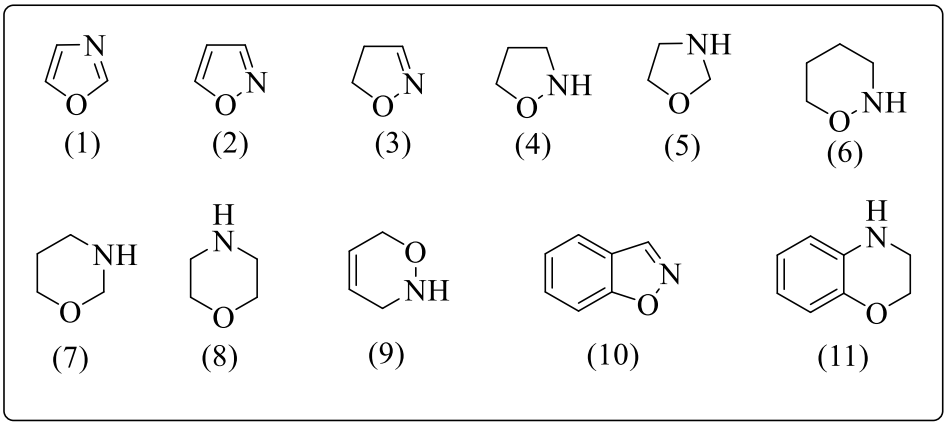


Figure 3.1. Different Oxazine Scaffolds.

The development in the chemistry of [1,3] oxazine compounds has been of interest since the 1950s and will continue to be so until the 20th century. [1,3]Oxazine contains one oxygen and one nitrogen atom at 1,3 position in six membered ring **(Figure 3.2)** [5].

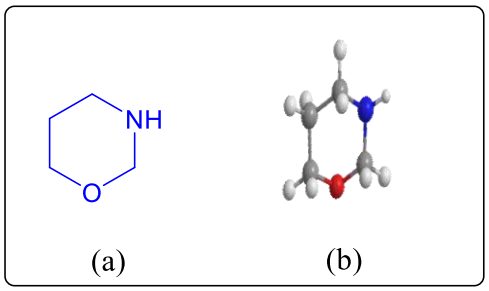


Figure 3.2. (a) Structure of [1,3]Oxazine and (b) 3D structure of [1,3]Oxazine.

Researcher focused in the synthesis of [1,3]Oxazine compounds due to its versatile role in biological as well as medicinal field [6], [7]. In the medicinal field, they cover a large spectrum of pharmacological operations, such as bactericidal [8], fungicidal [9], antiviral [10], microbiocidal, anti-cancer [11], anti-HIV [12], anti-tuberculosis [13], and anti-inflammatory agents [14]. These interesting biological activities brings the patent to some preparative schemes of [1,3]Oxazine especially tetrahydro-1,3-oxazines along with the synthetic utility of 5,6-dihydro-4H-1,3-oxazines. Therefore, **figure 3.3** shows the structures of some biologically active

[1,3]Oxazines such as anti-tumour, anti-Parkinson and potent non-steroidal progesterone receptor agonists. One potent drug-Ifosfamide having 1,3-oxazine ring fight against several types of cancers like as testicular cancer, breast tumour, lymphoma (Non-Hodgkin), Soft tissue sarcoma, Osteogenic sarcoma, Lung cancer, Cervical cancer, Ovarian cancer, Bone cancer **(Figure 3.4)**.

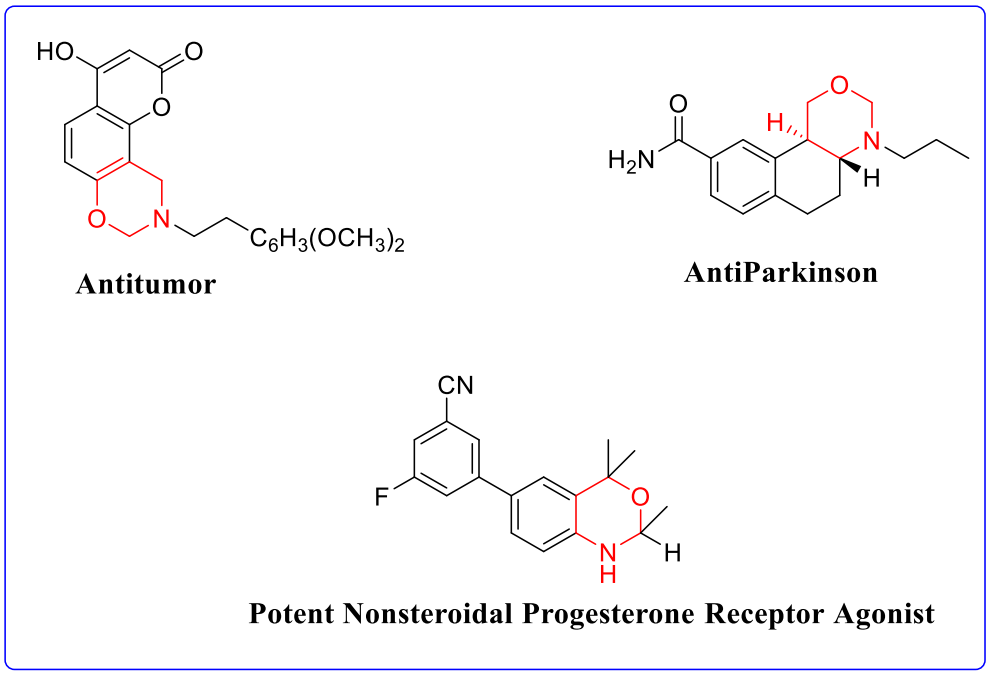


Figure 3.3. Structures of some biologically active [1,3]Oxazines.

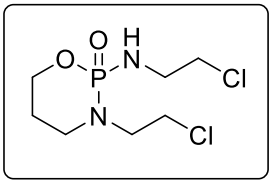
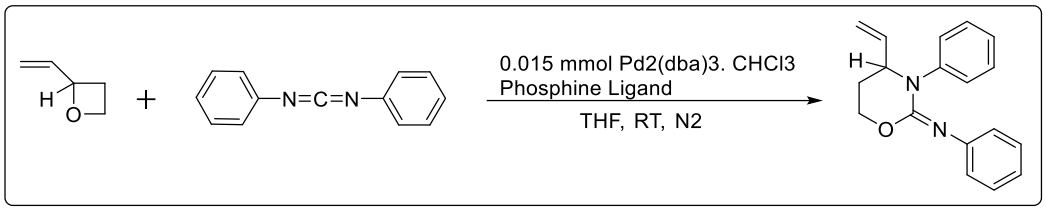


Figure 3.4. Structure Ifosfamide.

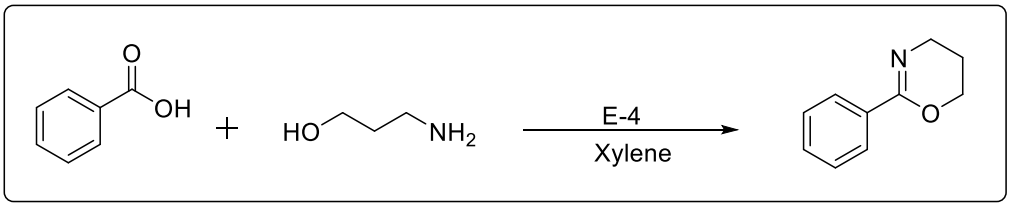
In the beginning, benzene and reduction molecules of benzene like pyridine and oxazole, which are replacements for carbon and hydrogen atoms in the benzene ring by nitrogen and oxygen, produce the oxazine molecules, but now a days tremendous development in the synthesis of oxazine compounds. Following is the literature survey of synthesis of various oxazine derivatives by incorporating different reactants, solvents and methodologies.

Chitchamai and Howard [15] synthesize stereoselective bicyclic 1,3-oxazines, cycloaddition of vinyloxetanes with heterocumulenes catalysed by palladium. They develop novel features of cycloaddition process by using $Pd_2(dba)_3$. $CHCl_3$ and phosphine ligand dppe **(Scheme3.2).**



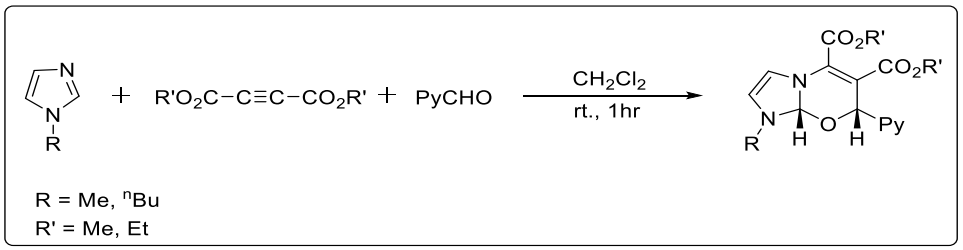
Scheme 3.2

Agnieszka Cwik et al. [16] develop simple strategies for the synthesis of oxazines. In presence of zeolite, Ersorb-4 (E-4) 3-aminopropanol and benzoic acid gave the corresponding 2-phenyloxazine. Simple workup procedure due to use of heterogenous catalyst **(Scheme 3.3).**



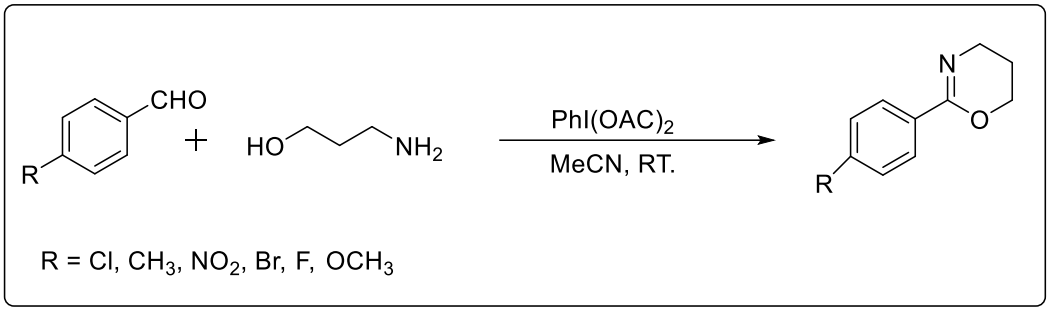
Scheme 3.3

Mehdi Adib and co-workers [17] by using pyridine carboxaldehydes produces diastereoselective 1,8a-dihydro-7H-imidazo[2,1-b][1,3]oxazine derivatives by reacting 1-Alkyl imidazoles with dialkyl acetylene dicarboxylates **(Scheme 3.4).**



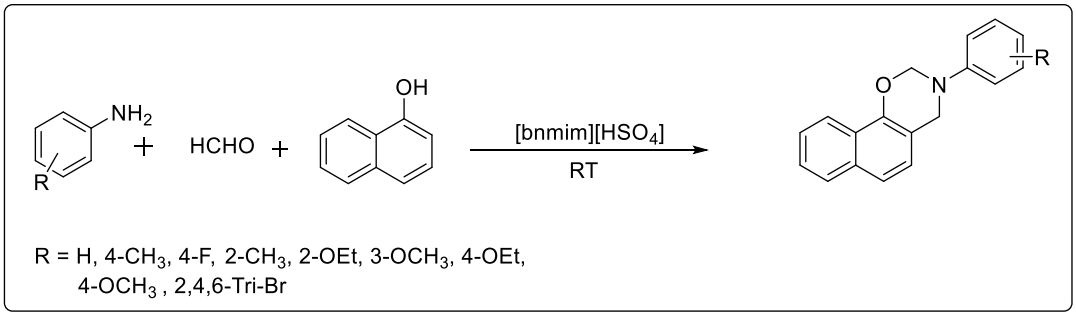
Scheme 3.4

Nandkishor N. Karade et al. [18] demonstrate oxidative conversion of aldehydes to 2-substituted oxazolines and oxazines by using mild dehydrogenating agent (diacetoxyiodo)benzene **(Scheme 3.5).**



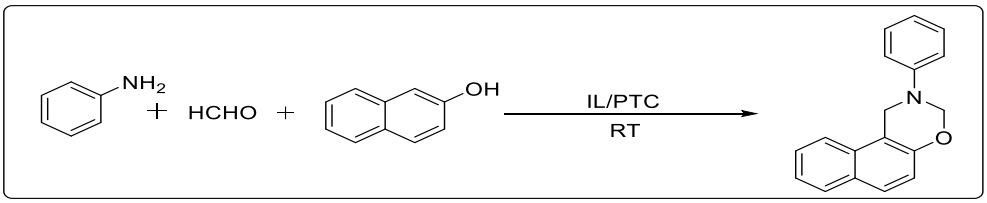
Scheme 3.5

Synthesis of 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*][1,3]oxazine derivatives, developed by Kategaonkar and co-workers [19] in ionic liquid. Mannich type reaction in presence of ionic liquid, 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim] [HSO_4] **(Scheme 3.6).**



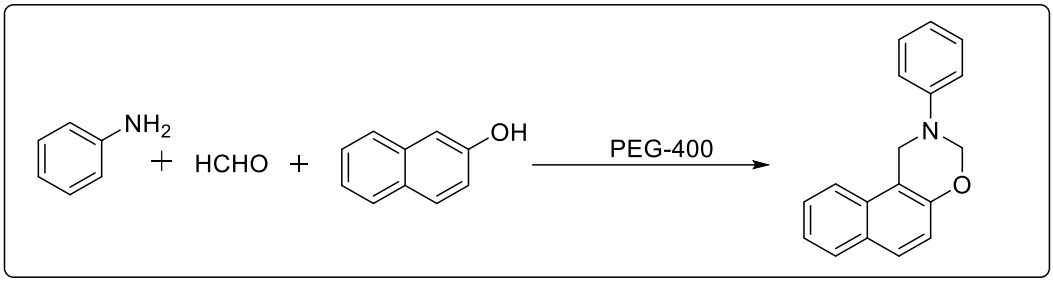
Scheme 3.6

Combination of ionic liquid (1-butyl-3-methyl imidazolium hydrogen sulphate [bmim]HSO_4) and phase transfer catalyst (n-tetra butyl ammonium bromide (TBAB)) were carried out by Suryakant B. Sapkal et al. [20] for the synthesis of [1,3]Oxazine derivatives **(Scheme 3.7).**



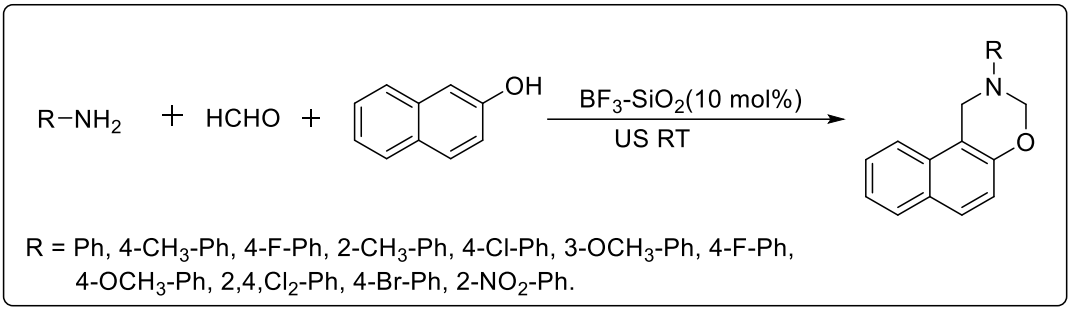
Scheme 3.7

Polyethylene glycol (PEG)-400 a safer medium that avoids the use of acid/base catalyst for the preparation of 1,3-oxazine derivatives was reported by Pravin Shinde and co-workers [21] **(Scheme 3.8).**



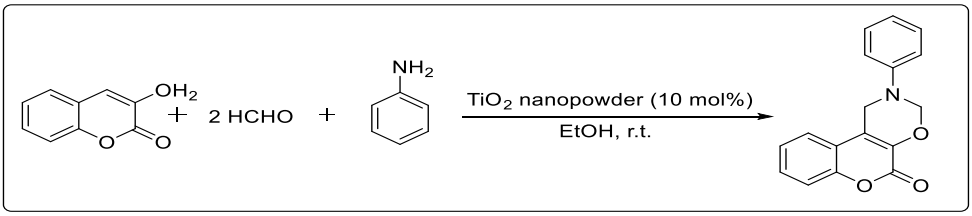
Scheme 3.8

Environment-friendly method developed by Mudumala Veeranarayana Reddy et al. [22] for the synthesis of 1,3-oxazine derivatives under ultrasound waves in presence of BF_3–SiO_2 catalyst **(Scheme 3.9).**



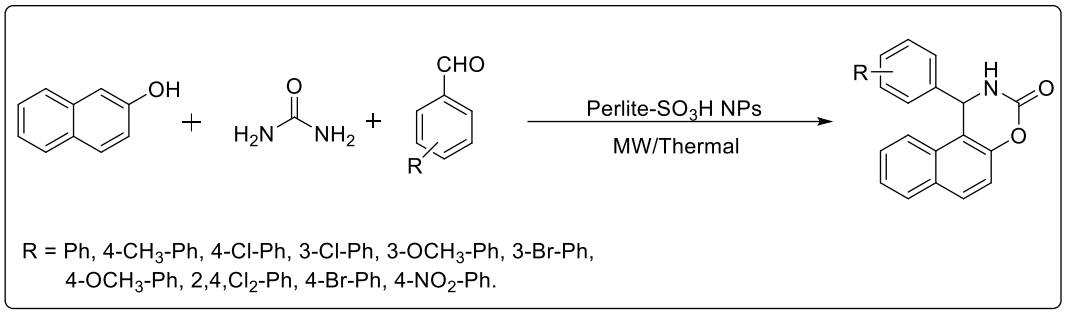
Scheme 3.9

Animesh Mondal et al. [23] reported TiO_2 nano powder catalysed synthesis of new chromeno[4,3-*e*][1,3]oxazine derivatives at room temperature. Recyclability of catalyst gives good result up to four cycles without significant loss in yield **(Scheme 3.10)**.



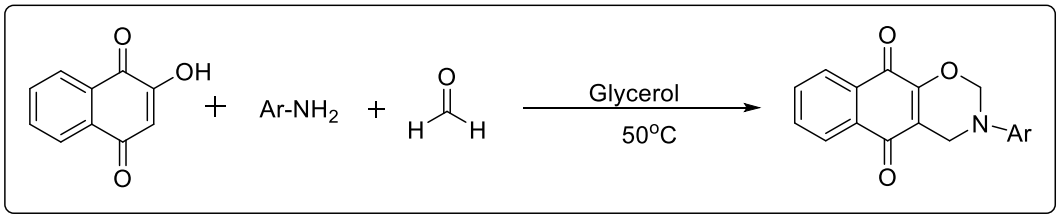
Scheme 3.10

A. Ramazani et al. [24] first prepared perlite-SO_3H nanoparticles and used those nanoparticles for the production of 1,2-dihydro-1-aryl-naphtho[1,2-*e*][1,3]oxazine-3-one molecules in accordance with microwaves and thermal heating in the absence of solvent **(Scheme 3.11)**.



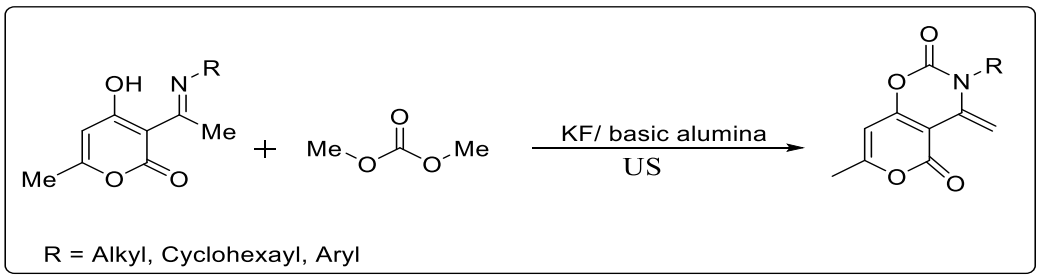
Scheme 3.11

Shruti Gupta and co-workers [25] use glycerol as a green media for the eco-friendly preparation of various derivatives of naphtho[2,3-e][1,3]oxazines **(Scheme 3.12).**



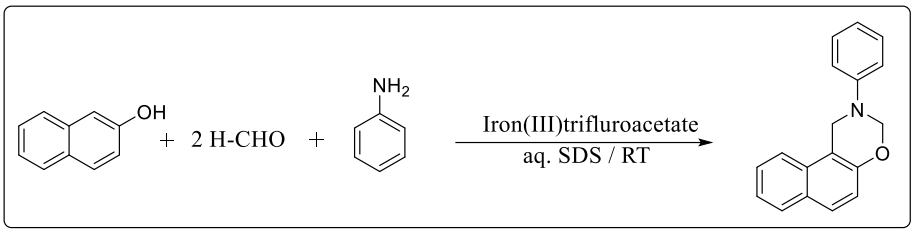
Scheme 3.12

Tamer S. Saleh et al. [26] develop green protocol under ultrasound irradiation for the synthesis of novel pyrano[3,4-e][1,3]oxazines. KF/basic alumina catalyst increases the yield within short period of time **(Scheme 3.13)**.



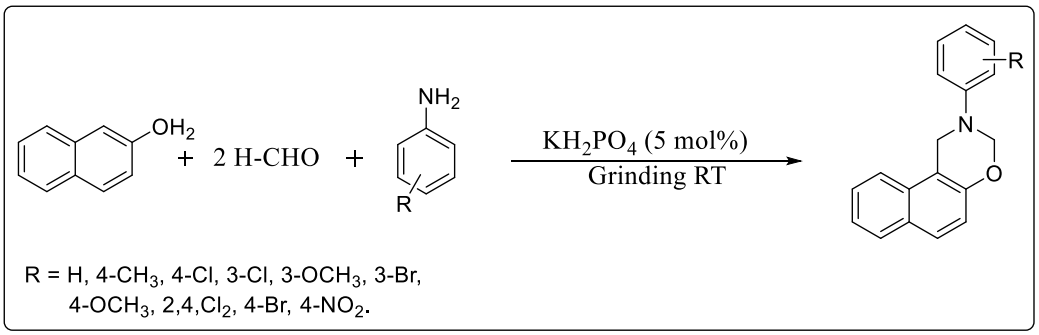
Scheme 3.13

A multipurpose water-stabilized fluorine consisting of organometallic lewis acid prepared by Trushant Lohar et al. [27] for the greener production of 1,3-oxazine scaffolds at room temperature **(Scheme 3.14)**.



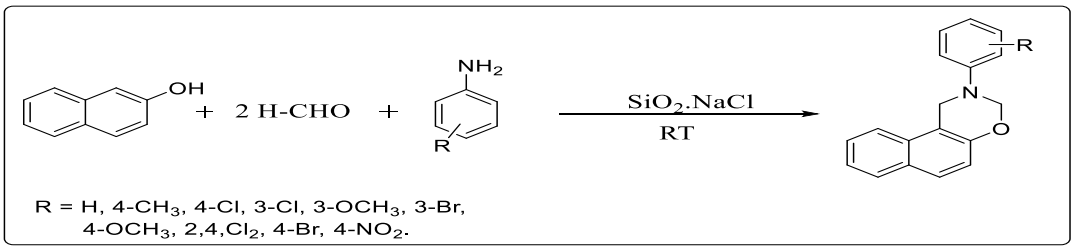
Scheme 3.14

Balasaheb Shitole and co-workers [28] demonstrate that potassium dihydrogen phosphate effectively catalyses the different molecules of naphtho-[1,2-e][1,3] oxazine by grinding with pestle and mortar in the absence of solvent at room temperature **(Scheme 3.15)**.



Scheme 3.15

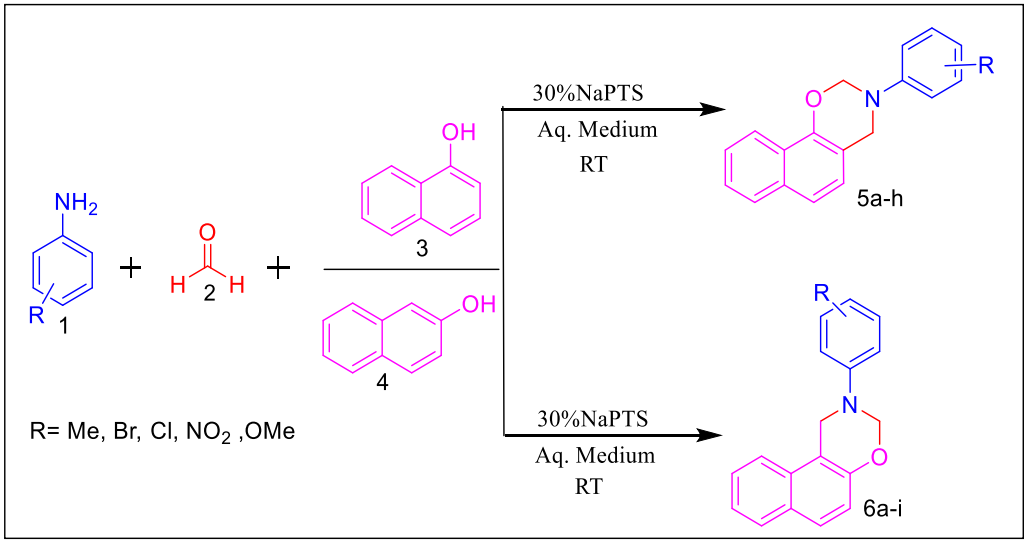
Putusenla Imchen et al. [29] synthesized of 1,3-benzoxazine and 1,3-naphthoxazine using $NaCl.SiO_2$ at room temperature and check their antibacterial activity. Uses streptomycin as a standard control for all the microbial test **(Scheme 3.16)**.



Scheme 3.16

3.2 Present Work:

Chemical synthesis via green chemistry approaches our future opportunities in working with chemical processes by introducing novel reactions that can maximise the derived products and minimise side-products; designing new chemical transformations that can modify activities in organic synthesis; and searching for greener reaction media that are naturally environmental and ecologically benign. The development of simple and sustainable synthetic methodologies and the use of readily available reagents is one of the main objectives of organic synthesis. In organic synthesis, the use of aquatic solutions of hydrotropes exhibits the characteristic properties of an alternative reaction medium. We give attention to the development of greener organic synthesis by creating aquatic hydrotropic solutions as a benign medium [30]–[32]. With the extension of our study to find the scarcely exploiting capability of hydrotropes in chemical synthesis, we report here the sustainable synthesis of 2,3-dihydro-2-phenyl-*1H*-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in an aqueous hydrotropic medium at ambient temperature **(Scheme 3.17)**.



Scheme 3.17 Synthesis of [1,3]Oxazine derivatives in 30% Aq. Hydrotropic medium.

3.3 Result and Discussion:

The selection of hydrotropes plays a significant role in the synthetic transformation involving aromatic amine, formaldehyde with α-Naphthol or β-

Naphthol in to 3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in aqueous medium. The amphiphilic character and hydrophobic region favour the solubility of organic reactants in aqueous media and thus differ from classical surfactants. The solubilities of organic substrates occur due to their amphiphilic and hydrophobic regions and differ from conventional surfactants. The hydrotrope shows maximum solubility of compounds at the minimum hydrotropic concentration (MHC), which was used as a reaction medium [33]. Those molecules are insoluble in water, but they show solubility in aquatic media by the use of hydrotropes because direct interaction takes place between reactants and hydrophobic molecules of hydrotropes, which gives solubility in many folds of excess. A wide number of synthetic methodologies were reported for these transformations.

According to a survey of previous studies for the synthesis of [1,3]Oxazine derivatives, the novelty of the present protocol is to overcome the problem of solubility of organic compounds in an aqueous medium. Due to the poor or insolubility of organic moiety, they are not interacting with each other. The hydrotropic aqueous medium is one of the best alternatives for hazardous organic solvents that solubilize insoluble organic compounds in an aqueous medium. Hydrotropes are not only recyclable but also non-toxic in nature. Hydrotrope is cheap in cost as well as can be synthesized in the laboratory, which makes it an environmentally and economically efficient protocol [34], [35].

Here we represent the comparative table of previous and present study **(Table 3.1)**.

Table 3.1. Comparative various synthetic methods for synthesis of [1,3]Oxazines derivatives

Entry	Reagents and condition	Time (m/h)	Yield (%)	References
1	(S)-BINAPO chiral lewis base with $HSiCl_3$ in DCM	10-11h	77	[13]
2	$KAl(SO_4)_2$ _$12H_2O$ (alum) in H_2O	15 min.	75	[16]
3	Solid-support catalyst, SiO_2.NaCl at room temperature	5-10 min	78	[18]

4	1-benzyl-3-methyl imidazolium hydrogen sulfate i.e. [bnmim] [HSO_4], room temperature and stirring	1min	77	[24]
5	1-butyl-3-Methyl imidazolium hydrogen sulphate [bmim]HSO_4 Ionic liquid and PTC such as tridecyl trimethyl ammonium bromide (TDTMAB) at 60ºC.	30 min	90	[25]
6	BF_3–SiO_2 Ultrasonicated room temperature	10 min	90	[26]
7	***Sodium p*-Toluene Sulphonate (NaPTS) at room temperature**	**10 min**	**94**	**Present work**

The various hydrotropes such as sodium benzene sulphonate (NaBS), sodium p-xylene sulphonate (NaXS) and sodium p-toluene sulphonate (NaPTS) were picked for this synthetic transformation. The results obtained by using various NaPTS, NaBS, and NaXS are mentioned in **Table 3.2,** which indicate that NaPTS gives better results than NaBS and NaXS. That is, NaPTS in an aqueous solution shows a better outcome for this synthetic transformation.

Table 3.2. Screening of various hydrotropes for synthesis of [1,3]Oxazines derivatives

Entry	Hydrotrope	Time (Min.)	Yield (%)[a]
1	*p*-Toluene Sulphonate (NaPTS)	10	94
2	*p*-Xylene Sulphonate (NaXS)	50	70
3	Benzene Sulphonate (NaBS)	120	40

Reaction at room temperature [a] isolated yield.

We selected to apply 30% (w/v) aqueous solutions of selected hydrotropes as a reaction medium. Selected organic reactants for the synthesis of oxazine molecules show maximum solubility at this concentration. We got excellent results for NaPTS; therefore, we applied this specific hydrotrope for subsequent analysis. then we studied

the effect of concentration of aq. NaPTS. The productivity of the model scheme changes significantly with respect to the concentration of hydrotrope and was remarkable when 30% of aq. NaPTS was used as a reaction solvent **(Figure 3.5)**. Enhance the solubility of reactant molecule at 30% conc. of NaPTS.

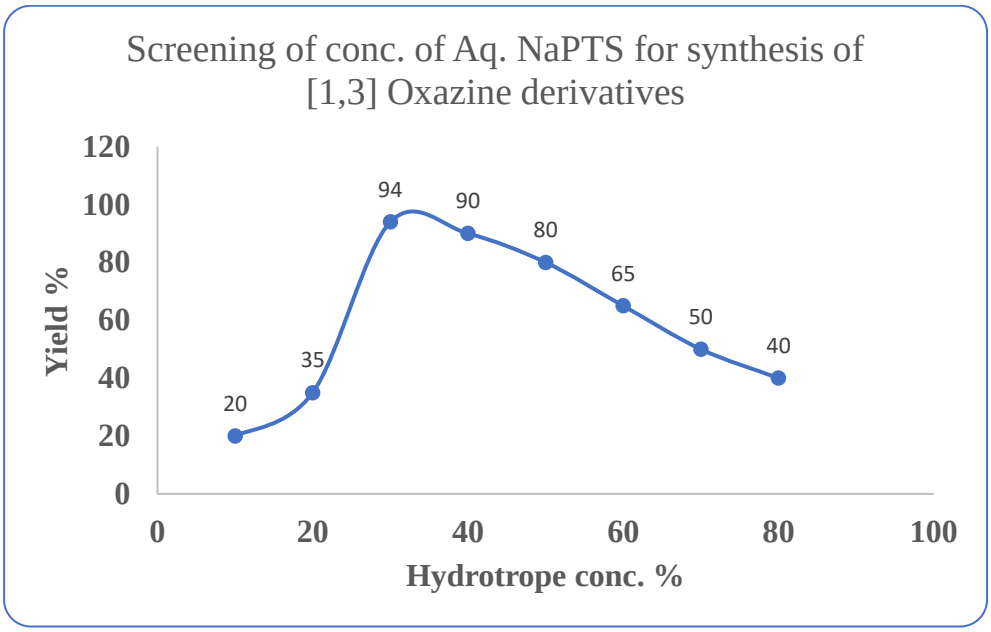


Figure 3.5. Screening of Conc. of Aq. NaPTS for synthesis of [1,3] oxazines derivatives

Our next task was to assess the efficiency of the aqueous hydrotropic solutions for this organic transformation. Accordingly, a model reaction between aniline and formaldehyde with α -Naphthol/ β -Naphthol in 30% of aq. NaBS, NaXS, and NaPTS was carried out at ambient temperature **(Scheme 3.17)**. On the completion of the reaction as confirmed by thin layer chromatography (TLC) using n-hexane/ethyl acetate (8:2) as the solvent system, the reaction mixture was diluted with cold water, during which the product gets separated out. The simple filtration of the reaction mixture gives the crude product; the high-purity products obtained after recrystallization are used for spectral analysis. In all cases, the reactions proceeded smoothly, affording the corresponding products in high yields **(Table 3.3)** and which gave correct IR, ^{1}H NMR, ^{13}C NMR and DEPT spectral analysis. The plausible mechanism of the product formation for the synthesis of [1,3]Oxazine derivatives is conceptualized in **figure 3.6**.

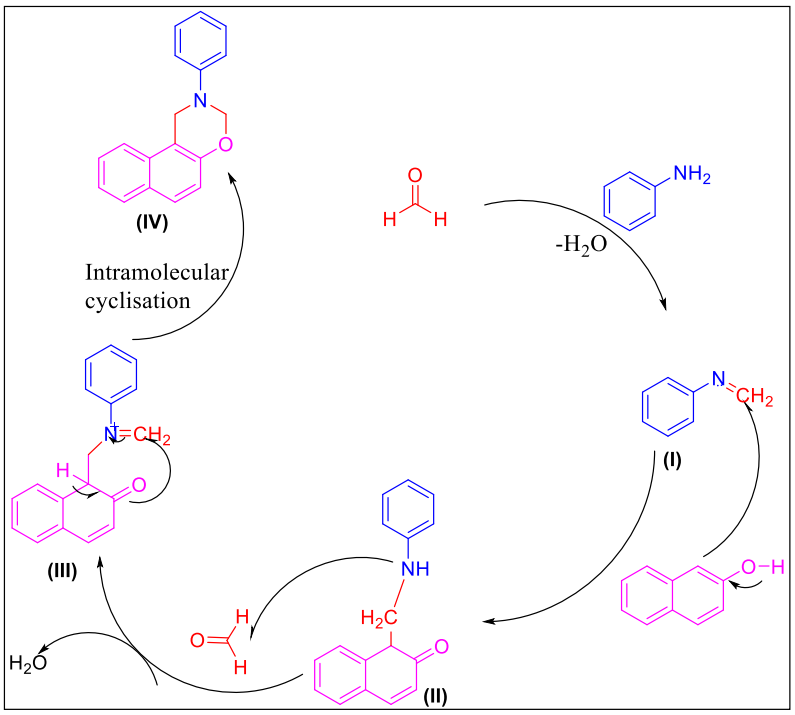
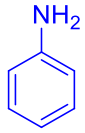
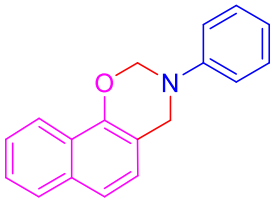
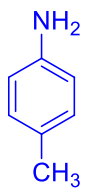
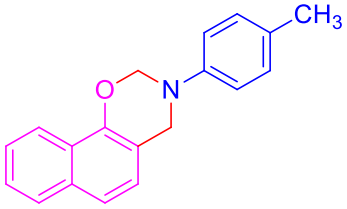
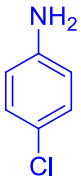
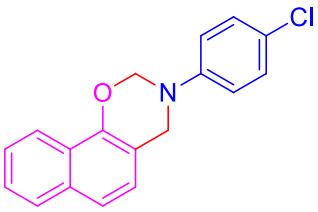
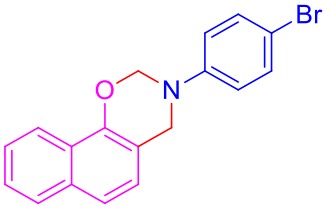
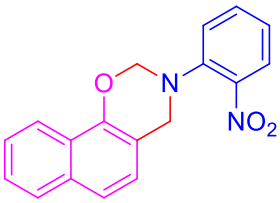
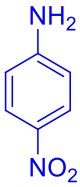
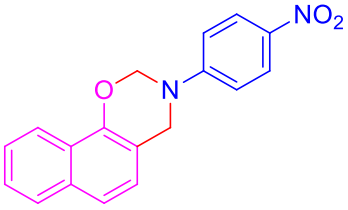
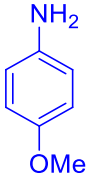
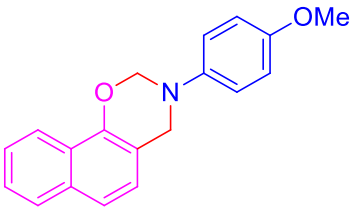
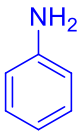
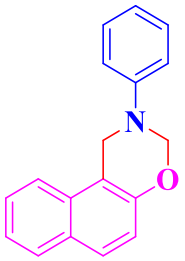
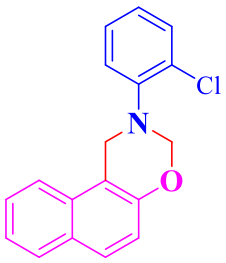
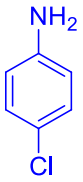
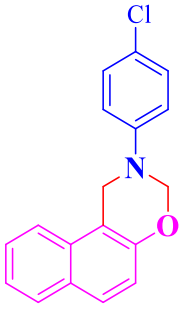
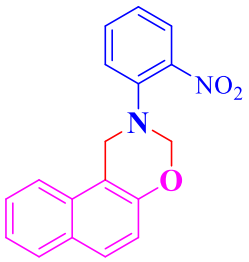
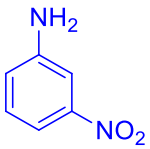
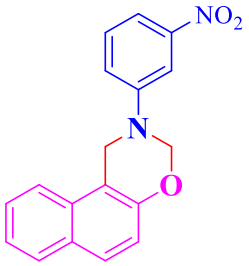


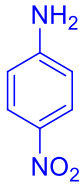
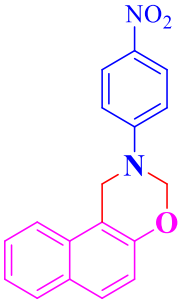
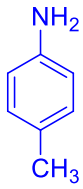
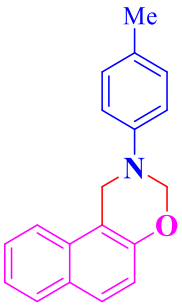
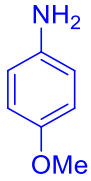
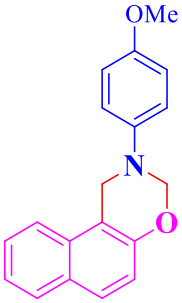
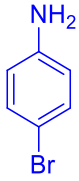
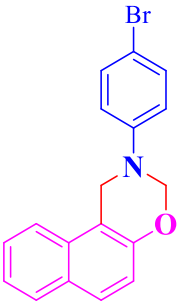
Figure 3.6. A Plausible reaction mechanism for synthesis of [1,3] oxazine derivatives.

Table 3.3. Synthesis of [1,3]Oxazine derivatives in 30% aq. NaPTS solution[a].

Entry	Aniline	Product	Time Min.	Yield %[b]	M.P.°C Lit. [16, 23,]
1.		 5a	30	90	110-111 [23]
2.		 5b	30	90	196-198 [23]

3.		 5c	40	90	80-82
4.		 5d	20	90	115-117 [23]
5.		 5e	45	85	85-87
6.		 5f	10	94	114-116
7.		 5g	10	92	298-300 [23]

8.		 6a	30	90	47-49 [23]
9.		 6b	40	84	146-148
10.		 6c	30	88	221-223
11.		 6d	40	84	132-134 [23]
12.		 6e	45	80	140-142 [24]

13.		 6f	10	94	171-173 [23]
14.		 6g	20	88	88-90 [23]
15.		 6h	20	92	78-80 [16]
16.		 6i	20	90	117-119

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and DEPT spectroscopy.

[b] Isolated yields after recrystallization.

Recyclability of Hydrotrope:

In organic synthesis, reusability and recovery of hydrotropic medium are very vital from the point of view of environmental effects and economy. Therefore, we first recovered the hydrotropes after completion of the reaction. The reaction mixture was simply filtered, the product was washed with water, and both the product and aqueous medium were collected. Then the aqueous medium was kept for evaporation to remove water, and finally we recollected the hydrotrope. The reusability of that hydrotropic solution was studied four times, including the use of freshly prepared solution for the respective synthesis. We got good results with a small amount of loss of yield, as shown in **figure 3.7**.

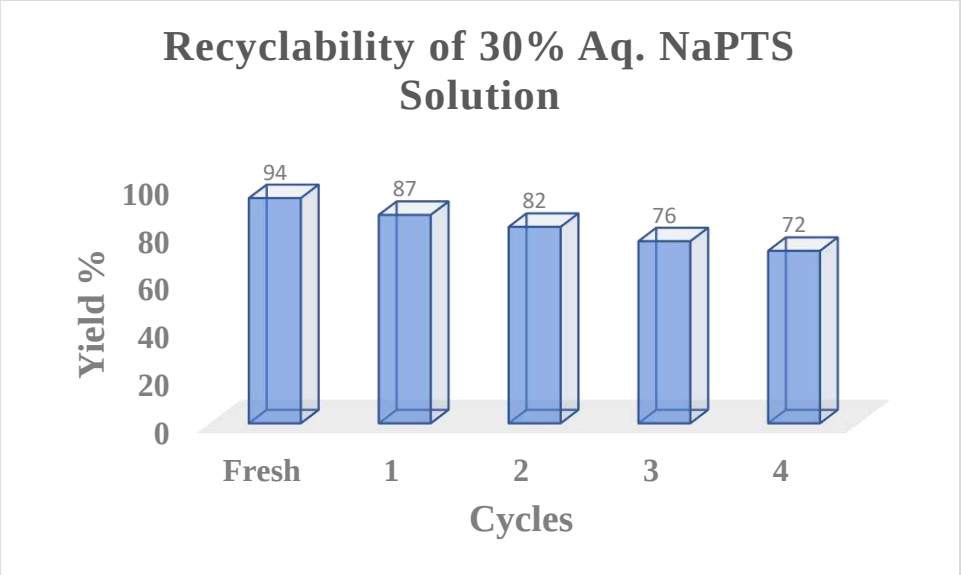
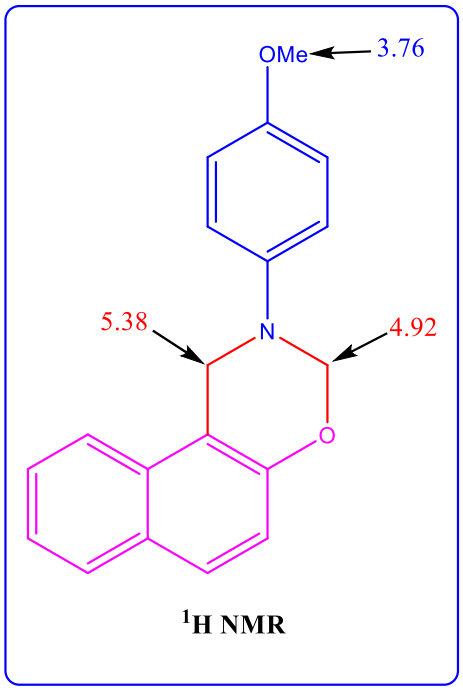


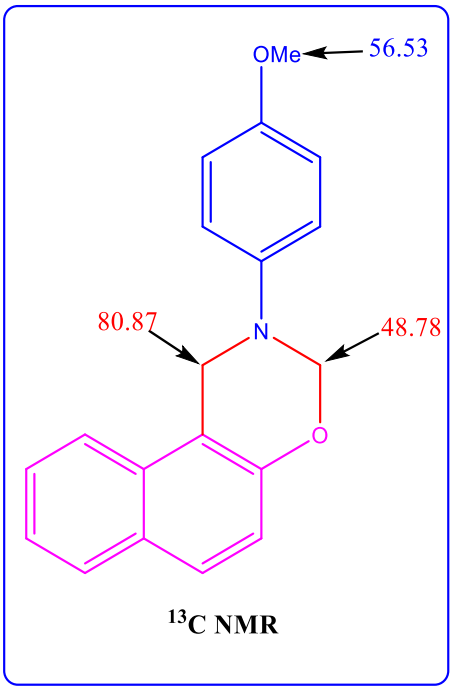
Figure 3.7. Recyclability of 30% aq. NaPTS solution

Characterization of products:

1) 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine



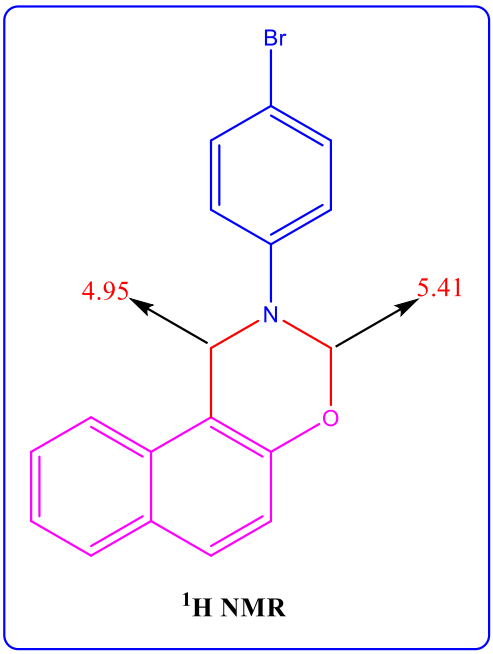
^{1}H NMR



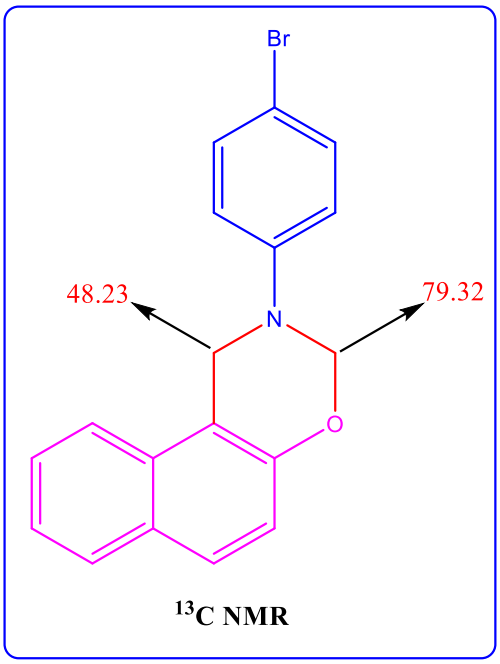
^{13}C NMR

IR spectrum **(Figure 3.8)** showed absorption band at 1626 cm^{-1} for aromatic C=C streching, at 1436 cm^{-1} for methyl C-H while band appeared at 1228 and 1037 cm^{-1} for corresponding C-N and C-O single bond. the ^{1}H NMR **(Figure 3.9)** spectrum showed three sharp singlet one at δ 3.76 ppm for three protons of methoxy group. The symmetric resonances of two singlet peaks at δ 4.92 (N-C$\underline{H}_2$-Ar) and 5.38 ppm (O-C$\underline{H}_2$-N) were assigned to the methylene groups of the oxazine ring in the compound. The rest of the peaks from 6.84 to 7.80 ppm correspond to the aromatic protons. The two negative peaks in DEPT-^{13}C NMR spectrum **(Figure 3.10)** were observed at δ 48.77 and 80.87 ppm of methylene carbons. The methoxy carbon was resonated at 56.53 ppm as a positive peak. The ^{13}C spectrum **(Figure 3.11)** also supports the oxazine formation with peaks corresponding to 1,3-oxazine ring at δ values 48.78 (N-C-Ar) and 80.87 ppm (O-C-N). The methoxy group resonates at δ 56.53 ppm. remaining peaks were due to aromatic carbons at δ 112,5, 114.5, 118.8, 120.9, 121.1, 123.6, 126.6, 128.2, 128.7, 129.0, 131.2, 142.7, 152.3, 155.1 ppm.

2) 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-16):



^{1}H NMR



^{13}C NMR

In the IR spectrum **(Figure 3.12)** the frequencies corresponding to 1597 cm^{-1} for aromatic alkene, 1199 cm^{-1} for C-O single bond. para substitution was shown by frequency 801 cm^{-1} corresponding to C-Br. The ^{1}H NMR **(Figure 3.13)** showed peaks corresponding to oxazine ring at δ values 4.95 (N-C$\underline{H_2}$-Ar) and 5.41 ppm (O-C$\underline{H_2}$-N) and the remaining chemical shift δ values from 7.06-7.80 ppm attributed to aromatic region. The two negative peaks in DEPT-^{13}C NMR spectrum **(Figure 3.14)** were observed at δ 48.23 and 79.32 ppm of methylene carbons. Similarly, the ^{13}C NMR **(Figure 3.15)** possessed peaks corresponding to methylene carbons of the 1,3-oxazine ring at δ values 48.23 (N-C-Ar) and 79.32 (O-C-N), while aromatic carbons resonates at δ values 112.1, 114.06, 118.71, 120.27, 120.81, 123.7, 126.8, 128.4, 128.7, 129.0, 131.1, 132.1, 147.8, 152.1 ppm.

3.4 Conclusion:

In conclusion, we have developed an environmentally benign, efficient and green methodology for the synthesis of [1,3]Oxazine derivatives by one-pot multi-component reaction of aniline, α-Naphthol or β-Naphthol and formaldehyde in 30% aq. NaPTS solution. The aqueous hydrotropic solution of sodium paratoulene sulphonate can be recycled after a simple work-up and reused up to four times with good efficiency

of product yield. Therefore, attractive and notable features of the present work are: shorter reaction time with high yield; environmentally friendly reaction medium; reusability of hydrotropic medium; absence of harmful organic solvents; and easy workup procedure. As a result, the current protocol plays an important role in organic synthesis by adhering to green chemistry principles.

3.5 Experimental

Melting points of products were determined on electrical melting point apparatus EQ 730A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR,^{13}C NMR and DEPT spectra were recorded on a Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal reference. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. The hydrotropes NaBS, NaXS, and NaPTS were synthesised in the laboratory by the following procedures, which were reported in the literature [36].

General procedure for synthesis of [1,3]oxazine derivatives:

A mixture of aniline (1 mmol), α-naphthol or α-naphthol (1 mmol), and formaldehyde (2 mmol) in 5 ml of a 30% aqueous hydrotropic medium was constantly stirred at room temperature. The progress of the reaction was confirmed by thin-layer chromatography. After the reaction is complete, the crude product is collected by simple filtration, and the recrystallization of the crude product in ethyl acetate produces the pure product.

Spectral data of synthesized compounds:

3,4-Dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-1)

IR (neat, thin film): υ = 1606, 1580,1214, 1028 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.70 (s, 2H, Ar-CH_2-N), 5.82 (S, 2H, N-CH_2-O), 6.88-8.20 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.6, 93.4, 113.4, 114.3, 119.6, 121.9, 122.9, 124.6, 125.2, 125.5, 127.1, 129.6, 149.6; DEPT of two –CH_2 carbon appeared at 59.6 and 93.4 resp.

3,4-Dihydro-3-(4-chlorophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-3)

IR (neat, thin film): υ = 1610, 1585, 1460, 1208, 1032, 788 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 113.4, 115.7, 119.6, 122.9, 124.6, 125.2, 125.5, 127.1, 127.2, 129.7, 132.5, 147.7, 149.0; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp.

3,4-Dihydro-3-(4-nitrophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-6)

IR (neat, thin film): υ = 1617, 1590, 1454, 1555, 1365, 1215, 1025 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 112.3, 113.4, 119.6, 122.9, 124.6, 124.8, 125.2, 125.5, 127.1, 132.5, 137.4, 149.0,155.7; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp.

2,3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-8)

IR (neat, thin film): υ = 1615, 1585, 1456, 1212, 1032 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 5.04 (s, 2H, Ar-CH_2-N), 6.12 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 53.7, 83.0, 111.5, 114.3, 118.4, 120.8, 121.9, 123.4, 126.3, 128.0, 128.3, 128.8,129.6, 131.7, 149.6, 151.7; DEPT of two –CH_2 carbon appeared at 53.7 and 83.0 resp.

2,3-dihydro-2-(*p*-tolyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-14)

IR (neat, thin film): υ = 1614, 1588, 1454, 1218, 1038 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 2.32 (s, 3H, -CH_3), 5.05 (s, 2H, Ar-CH_2-N), 6.10 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 21.3, 57.7, 93.0, 111.5, 112.8, 118.4, 120.8, 123.4, 126.3, 128.0, 128.3, 128.8, 129.9, 130.7, 131.7, 146.6, 151.7; DEPT of two –CH_2 carbon appeared at 57.7 and 93.0 resp.

2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-15)

IR (neat, thin film): υ = 1626, 1436, 1228, 1037, 793 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 3.78 (s, 3H, -OCH_3), 4.92 (s, 2H, Ar-CH_2-N), 5.38 (S, 2H, N-CH_2-O), 6.84-7.80 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm):48.7, 55.5, 80.8, 112,5, 114.5, 118.8, 120.9, 121.1, 123.6, 126.6, 128.2, 128.7, 129.0, 131.2, 142.7, 152.3, 155.1; DEPT of two –CH_2 carbon appeared at 48.7 and 80.8 resp.

2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-16)

IR(neat, thin film): υ = 1597, 1479, 1199, 801 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.95 (s, 2H,Ar-CH_2-N), 5.41 (s,2H,N-CH_2-O), 7.06-7.80 (m 10H,Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 48.2, 79.3, 112.1, 114.06, 118.71, 120.27, 120.81, 123.7, 126.8, 128.4, 128.7, 129.0, 131.1, 132.1, 147.8, 152.1; DEPT of two –CH_2 carbon appeared at 48.2 and 79.3 resp.

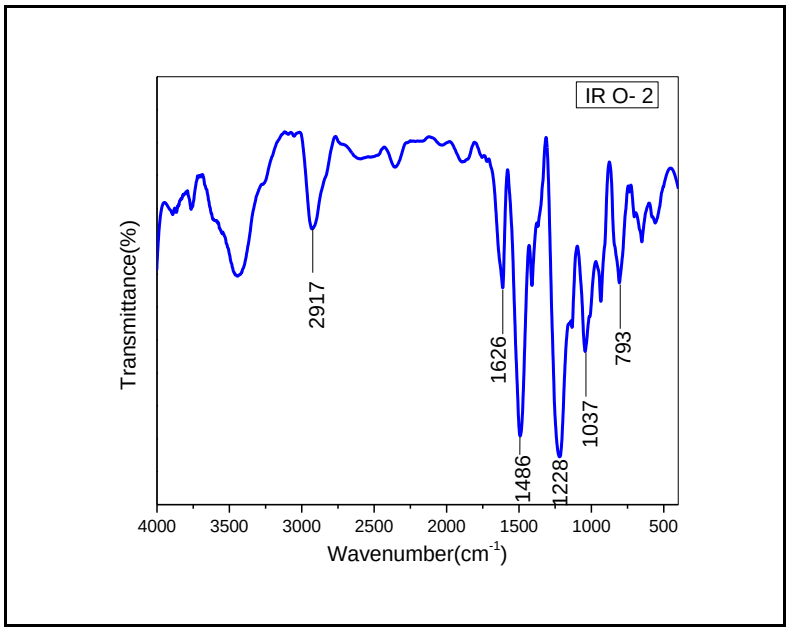


Figure 3.8: IR spectra of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

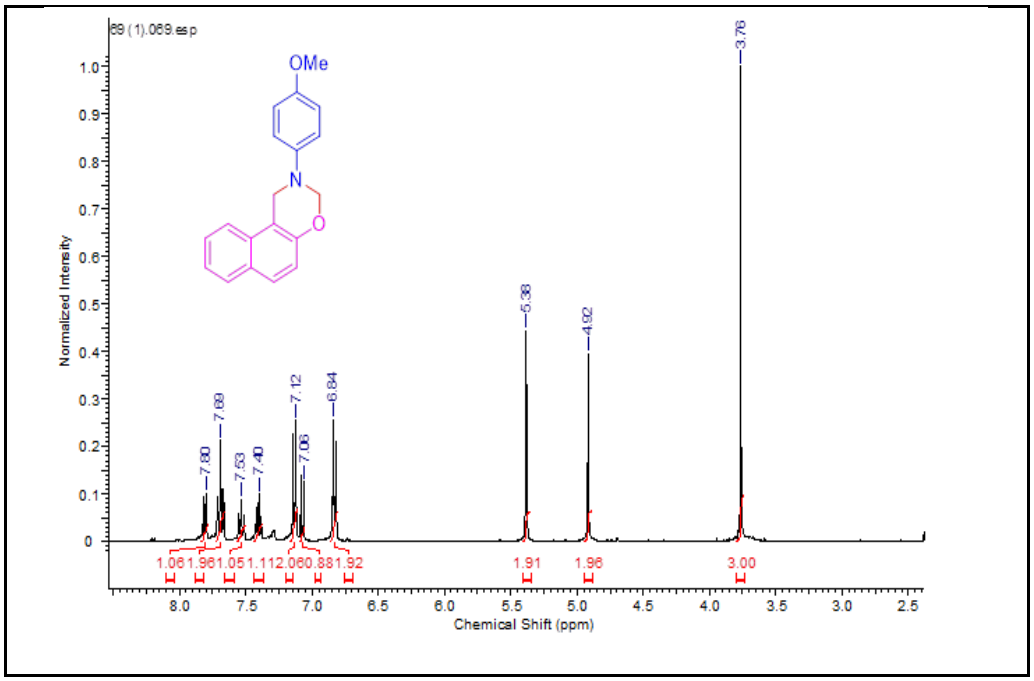


Figure 3.9: ^{1}H NMR of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

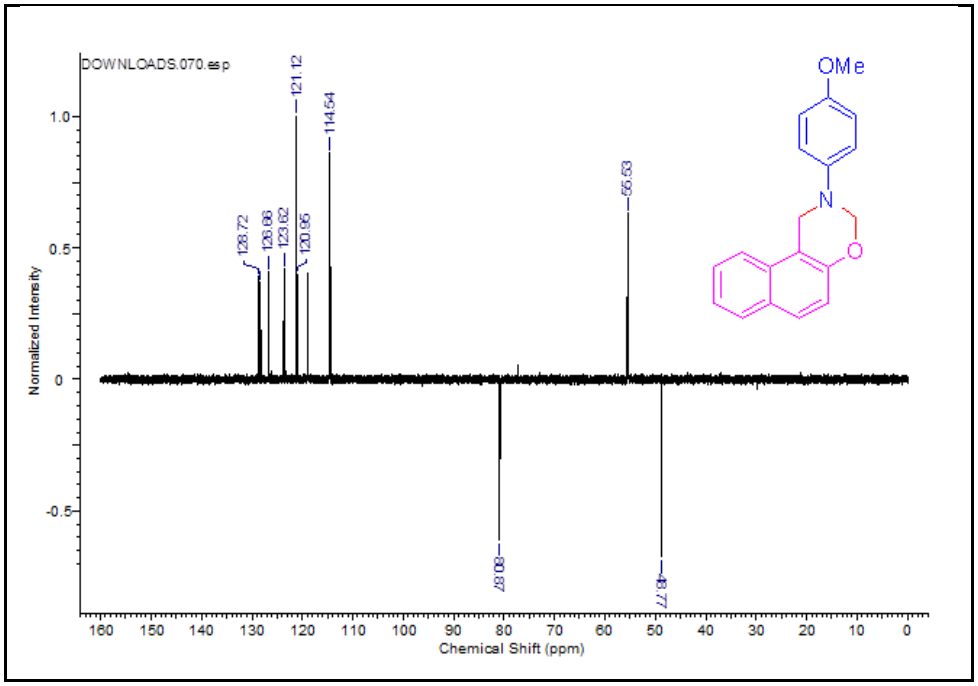


Figure 3.10: DEPT of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

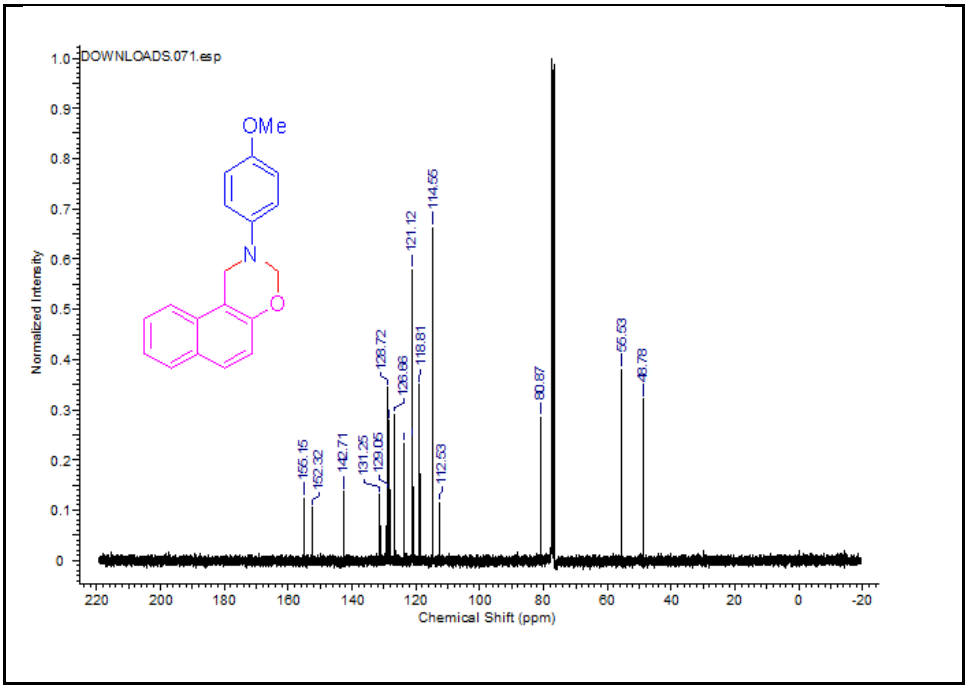


Figure 3.11: ^{13}C NMR of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

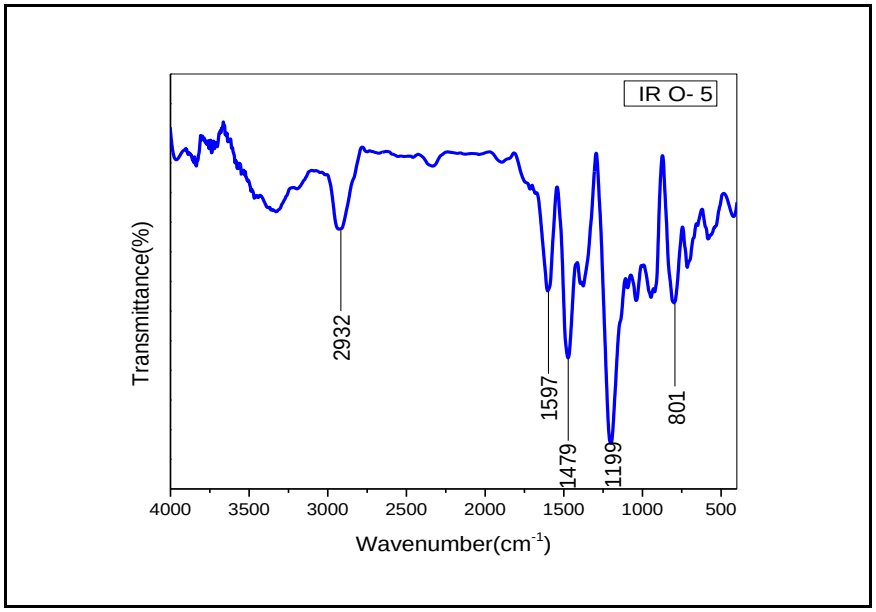


Figure 3.12: IR spectra of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

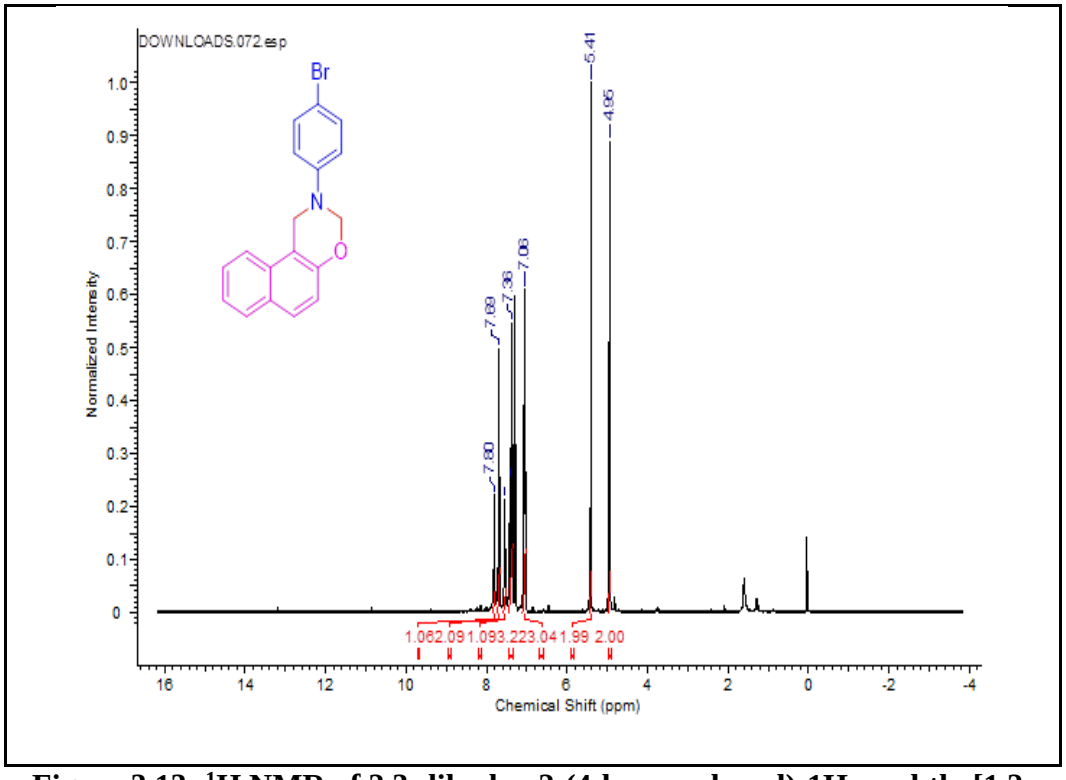


Figure 3.13: ^{1}H NMR of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

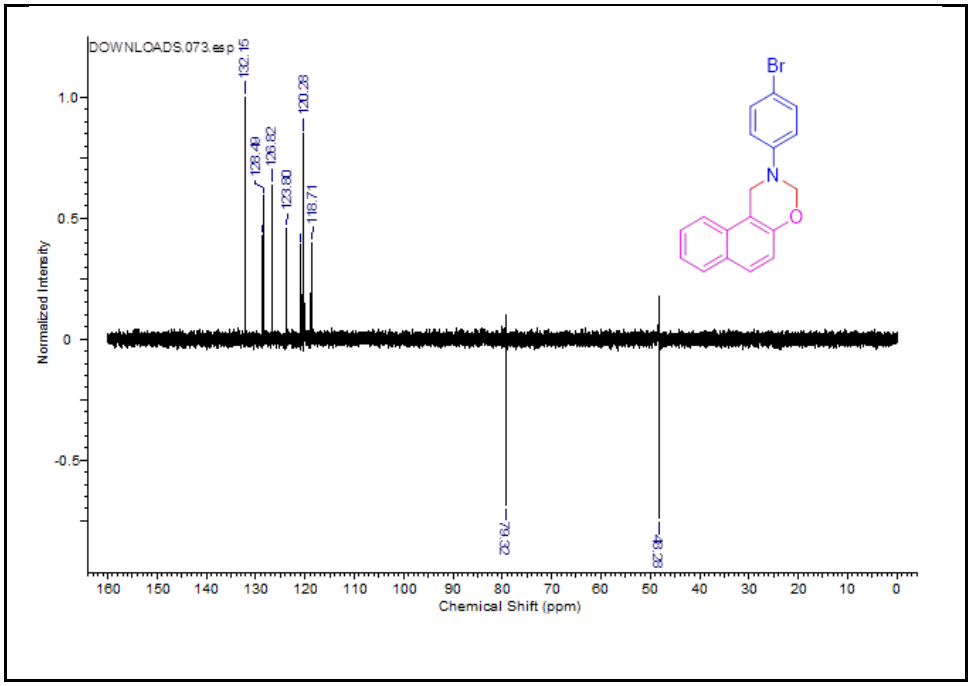


Figure 3.14: DEPT of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

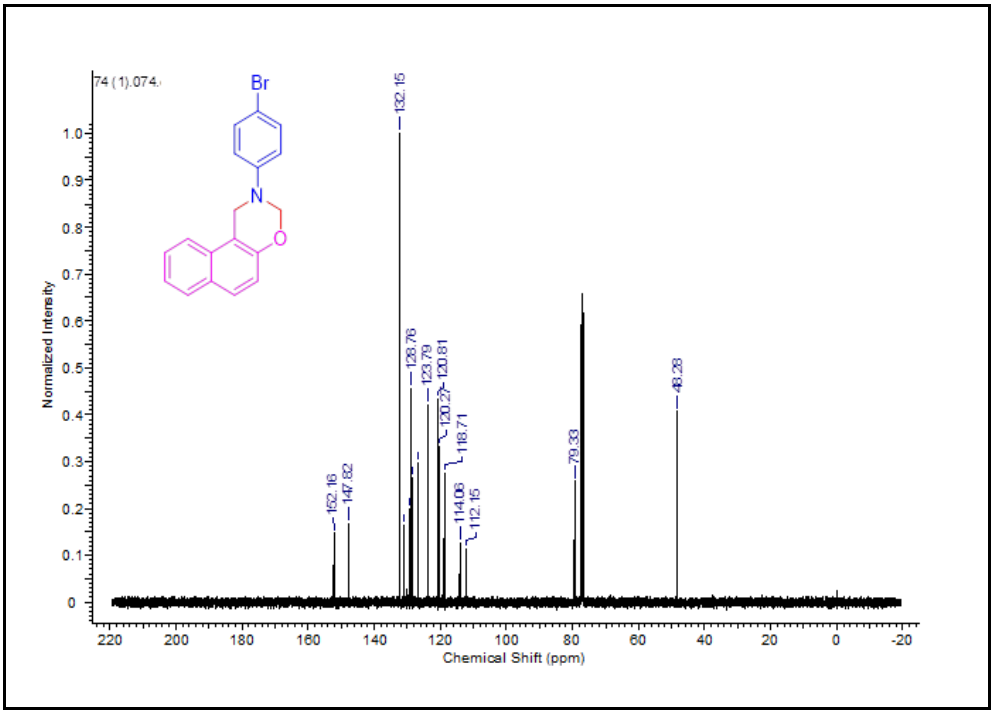


Figure 3.15: ^{13}C NMR of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

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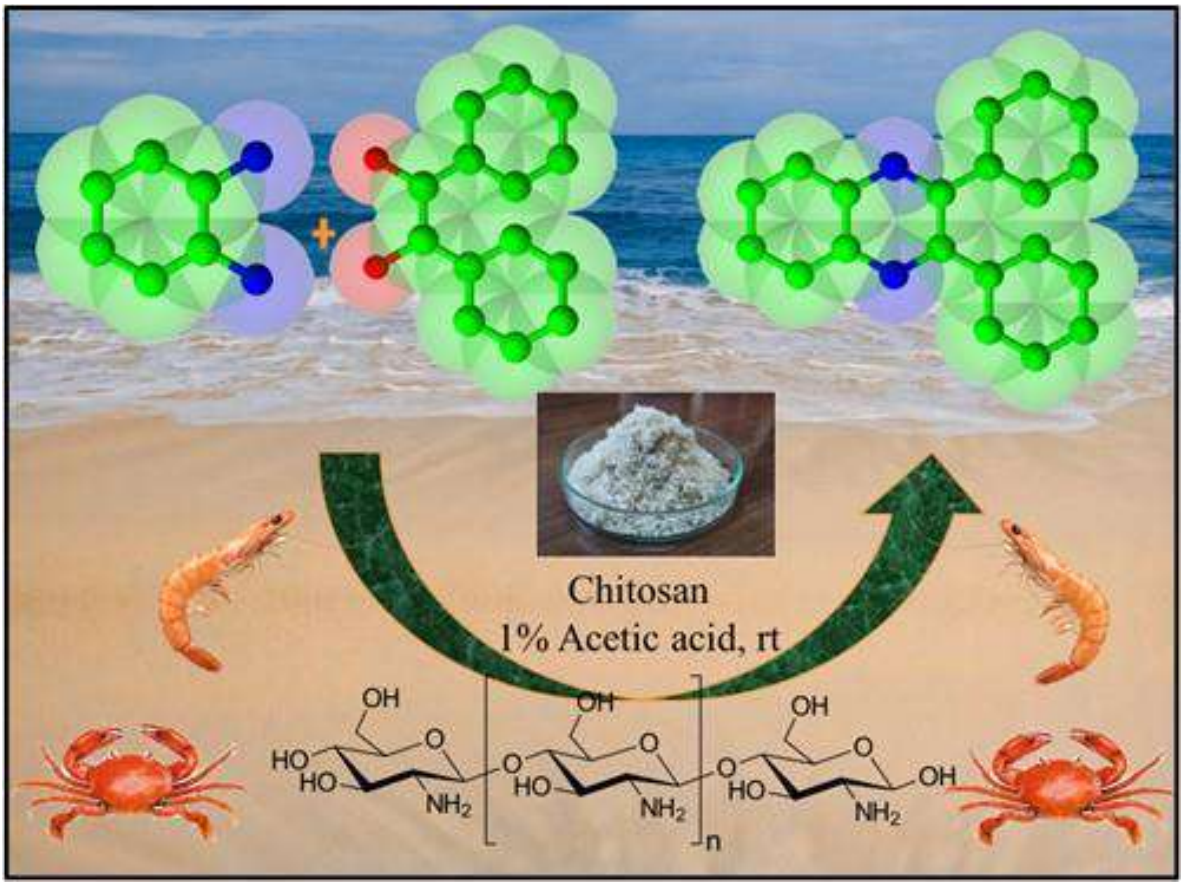
CHAPTER - 4

GREEN AND ECO-COMPATIBLE SYNTHESIS OF QUINOXALINE MOLECULES USING CHITOSAN AS A BIODEGRADABLE CATALYST IN AQUEOUS MEDIUM



CHAPTER 4

Green and Eco-compatible Synthesis of Quinoxaline Molecules using Chitosan as a Biodegradable Catalyst in Aqueous Medium

4.1 Introduction

The study of the chemistry of heterocyclic compounds is one of the interesting branches of organic chemistry. There has been a huge discovery of heterocyclic substances due to their important role in the metabolism of all living cells. As a result of the special stability of heterocyclic compounds, they have most important function in living cells, such as vitamins, co-enzymes, etc.; they resist metabolic destruction and do not easily degrade themselves. Therefore, from decades until now, researchers have focused primarily on the synthesis of heterocyclic compounds.

Quinoxaline is one of the important class of heterocycles. It has diverse applications in dyestuffs, drug and as an analytical reagent. The biological activity with other substances continually increases interest in the synthesis of new derivatives of this molecule. Quinoxaline (a) is an aromatic heterocycle produced by the fusion of two six-membered aromatic rings, one of which is benzene and the other is pyrazine, consist of two nitrogen atoms symmetrically placed at the 1 and 4 positions **(Figure 4.1)** [1].

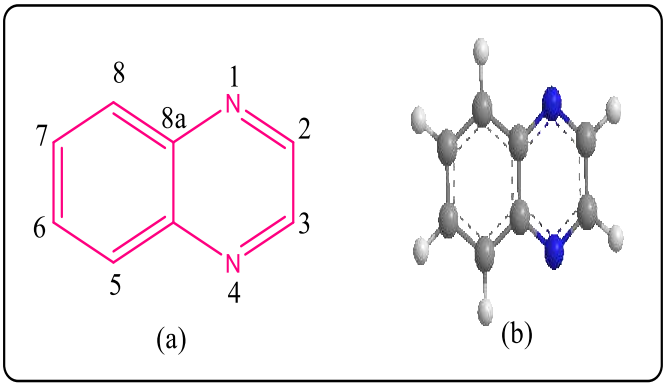
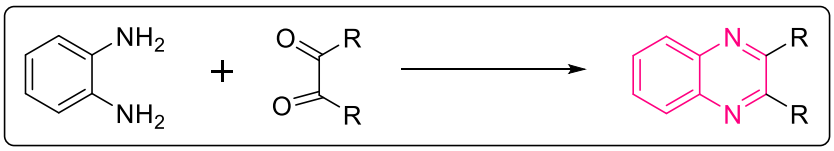


Figure 4.1. (a) Structure of Quinoxaline (b) 3D Structure of Quinoxaline.

Hinseberg first discovered the quinoxaline in 1884; according to him, in the quinoline, the methine group is replaced by a nitrogen atom at the fourth position and called it benzopyrazine. Hinseberg did a systematic study of the quinoxaline and their

derivatives and suggested the class name quinoxaline by pointing out the relationship between the quinoline and glyoxal, the dicarbonyl compound from which he prepared the first member of the series **(Scheme 4.1)** [2]. Thereafter, Gabriel and sonn confirmed the ring structure, and they demonstrated experimentally the relationship between the quinoxalines and pyrazines by oxidising the quinoxaline to pyrazine 2,3-dicarboylic acid. The physical properties of quinoxaline and pyrazine are analogous with each other. The numbering system shown in structure of quinoxaline (a) is universally used or accepted. From the resonating structure of quinoxaline depicted in **(Figure 2)** the positions 2,4,5,7 and 8a are electron deficient and hence easily attacked by nucleophile [3].



Scheme 4.1

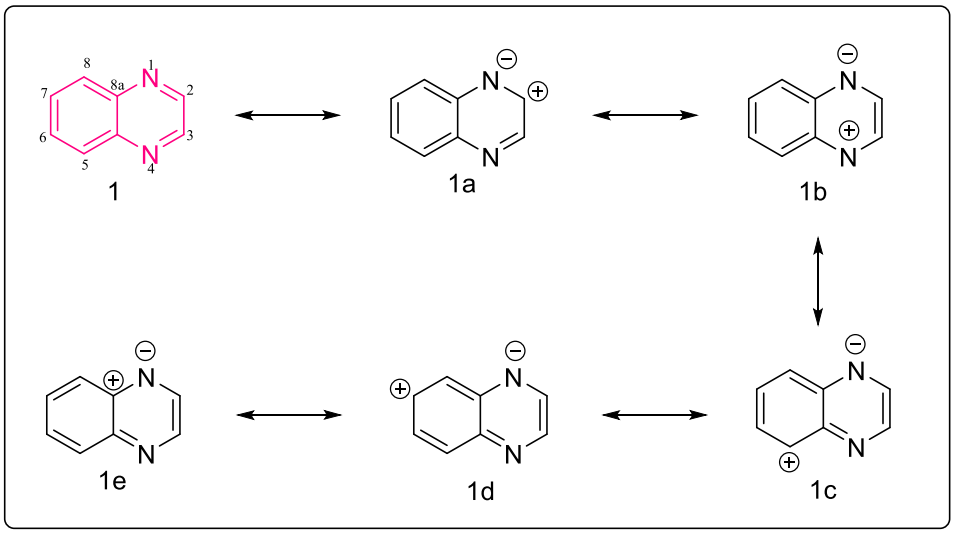


Figure 4.2 Resonating structures of quinoxaline.

Researcher's gives principal attention towards the quinoxaline molecule from the several years. The quinoxaline molecule has become great topic of universal research due to two nitrogen atoms in one of the rings. The two imine nitrogen atoms at 1,4 position displays electron-withdrawing properties. In addition to that these derivatives have extensive application because their formation takes place very easily

and smoothly with good yields [4]. The application program of quinoxaline molecules in distinct field as like dyes, or as a building block in the production of organic semiconductors [5], electroluminescent material, dye-sensitized solar cells (DSSC) [6] [7], etc. also they consisting a broad range of physicochemical [8] and biological activities [9] such as antibacterial [10], antiviral, anticancer activity [11], antitubercular activity [12], anti-inflammatory [13], anti-malarial [14], anti-hyperglycemic [15], anti-HIV [16] and anti-depressant activity [17]. Quinoxaline has a very important position in pharmacy due to its anticancer drug activity; CQS (chloroquinoxaline sulfonamide) and XK469 were both found to have activity against solid tumours **(Figure 4.3)**.

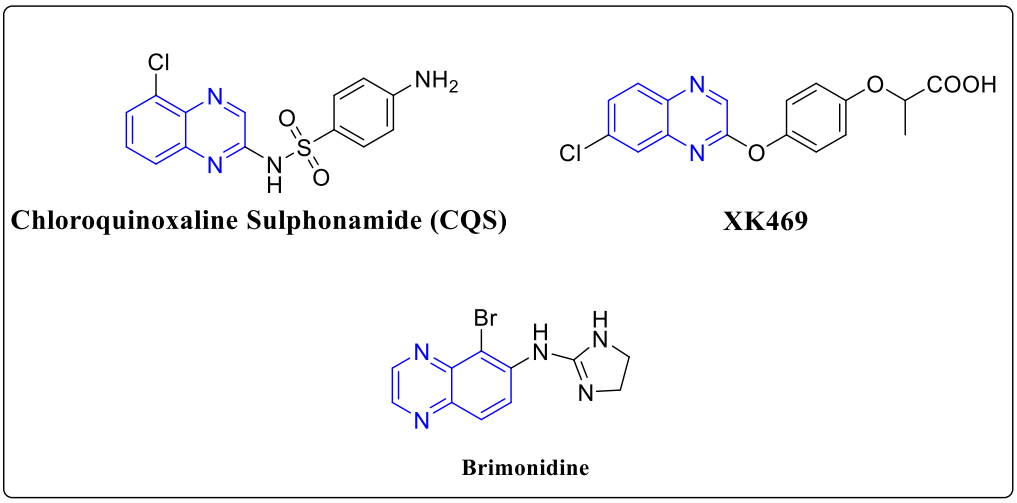
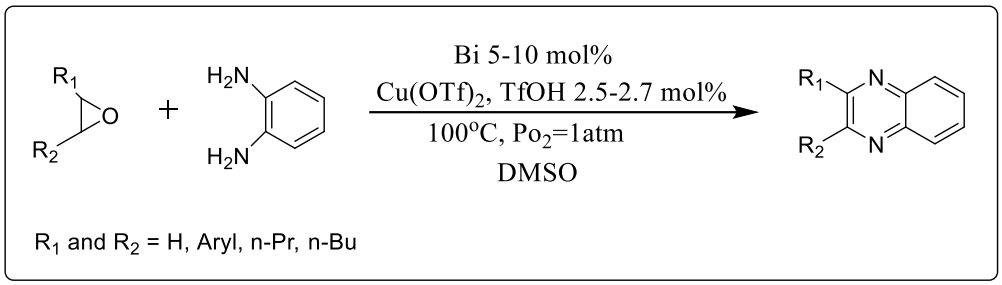


Figure 4.3 Biologically Active Quinoxaline Molecules.

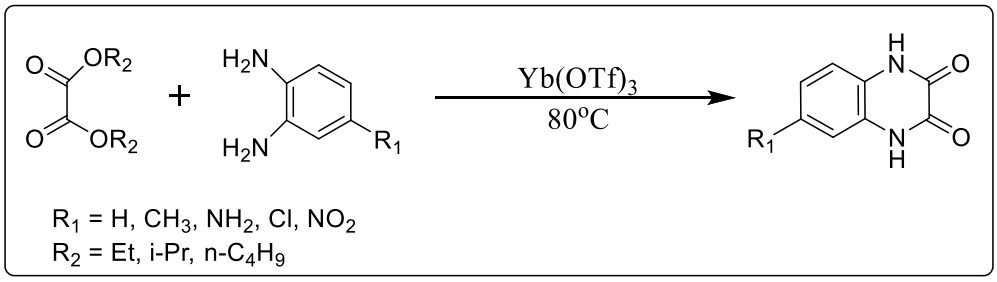
There are different methods are reported for the preparation of quinoxaline derivatives general method is condensation of O-phenylenediamine with glycoxal or an -diketone [18], 1,4-addition of 1,2-diamines to diazenylbutenes [19] and cyclization–oxidation of phenacyl bromides [20]. Various popular methods for synthesis of substituted quinoxaline derivates are reported as below;

Sylvain Antoniotti and Elisabet Dunach [21] gives direct bi-catalysed synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines by oxidative coupling **(Scheme 4.2).**



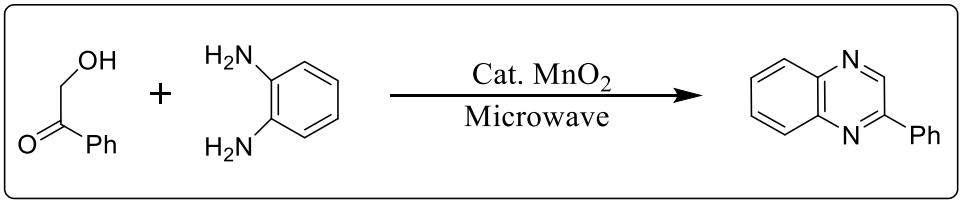
Scheme 4.2

Ytterbium triflate catalysed synthesis of quinoxaline-2,3-diones derivatives reported by Limin Wang and co-workers [22]. Heterocyclisation of 1,2-phenylenediamines and alkyl oxalates under solvent-free condition gives high yield within 1hr **(Scheme 4.3)**.



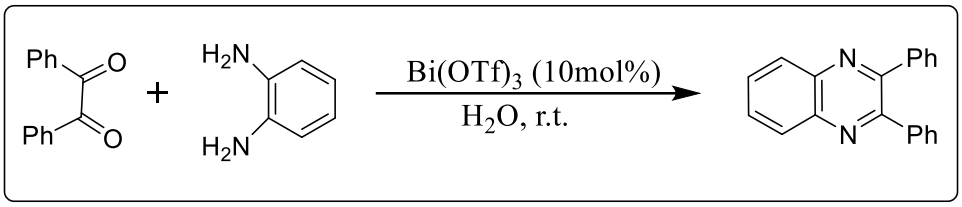
Scheme 4.3

So Yeon Kim et al. [23] under microwave irradiation developed manganese (IV) dioxide-catalysed production of quinoxalines. A variety of *a*-hydroxyketones react with aromatic or aliphatic 1,2-diamines in presence of manganese (IV) dioxide under microwave irradiation without solvent within one minute synthesize quinoxaline molecules **(Scheme 4.4).**



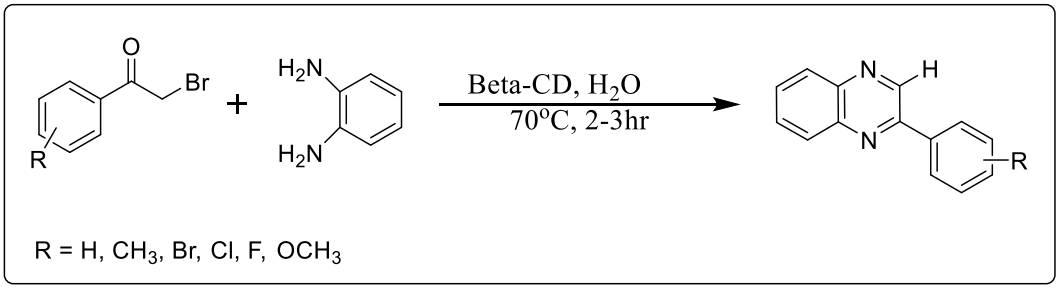
Scheme 4.4

Jhillu S. Yadav et al. [24] developed aqueous-mediated, bismuth(III)-catalysed rapid synthesis of 2,3-disubstituted quinoxalines. They prepared different kinds of 2,3-disubstituted quinoxalines with better yields under normal conditions, including room-temperature stirring of 1,2-diamines with 1,2-dicarbonyls in the presence of bismuth (III) triflate as a catalyst **(Scheme 4.5)**.



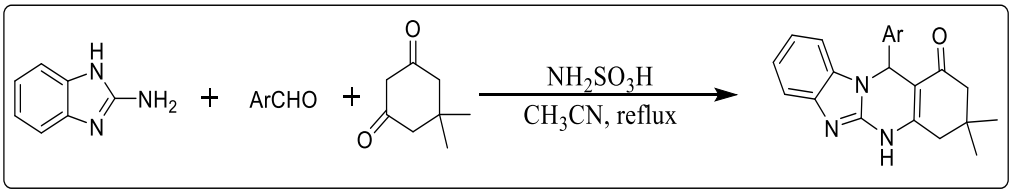
Scheme 4.5

The biomimetic synthesis of quinoxalines in water reported by B. Madhav and co-workers [25] was catalysed by β-cyclodextrin. The biomimetic study of β -cyclodextrin is understood by using ^{1}H NMR spectroscopy **(Scheme 4.6)**.



Scheme 4.6

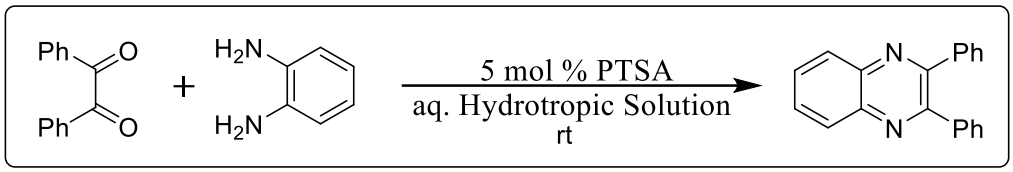
Majid M. Heravi and co-workers [26] reported sulfamic acid–catalysed synthesis of [1,2,4]triazolo/benzimidazole quinazolinone derivatives. sulfamic acid is a reusable, green catalyst **(Scheme 4.7)**.



Scheme 4.7

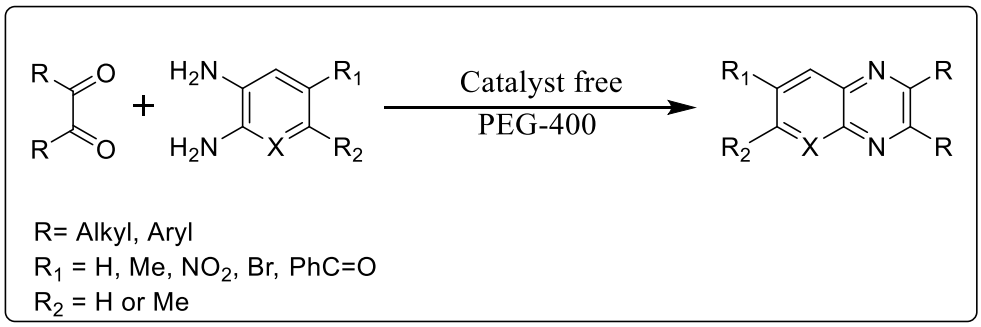
Arjun Kumbhar et al. [27] demonstrated the synthesis of quinoxalines and pyrido[2,3-b]pyrazines in aqueous hydrotropic medium. Combination of Bronsted acid

and hydrotrope avoids the utilization of organic solvents, produces excellent yield at room temperature **(Scheme 4.8)**.



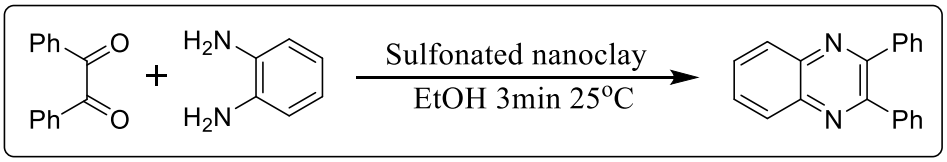
Scheme 4.8

A catalyst-free protocol was developed by Tie-Qiang Huang et al. [28] for the production of quinoxalines and pyrazines molecules in PEG. The condensation of 1,2-diketones with aromatic 1,2-diamines in polyethylene glycol (PEG) provides quinoxaline derivatives in good yields **(Scheme 4.9)**.



Scheme 4.9

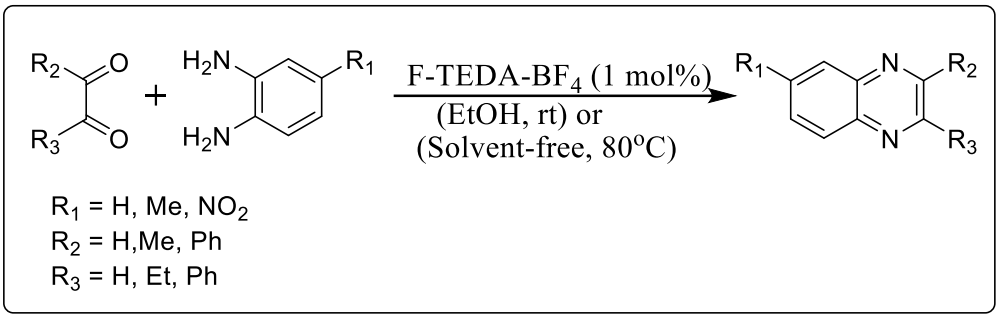
Mahgol Tajbakhsh and co-workers [29] use sulfonated nanoclay minerals as a reusable, eco-compatible catalytic agent for the development of quinoxaline molecules. Synthesized sulfonated nanoclay was used for the synthesis of quinoxaline derivatives by reacting 1,2-diamines with 1,2-diketones in ethyl alcohol as a greener medium at room temperature **(Scheme 4.10)**.



Scheme 4.10

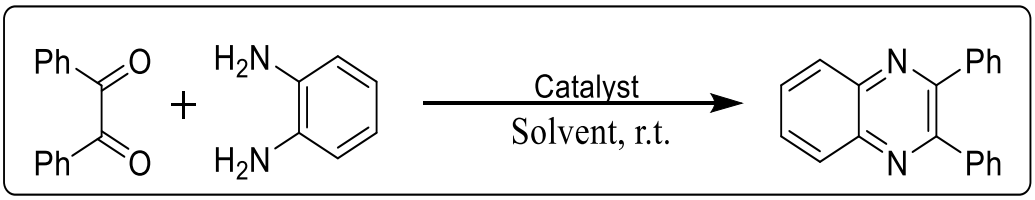
S. F. Hojati et al. [30] developed a methodology for the synthesis of quinoxaline and 2,3-dihydropyrazine derivatives using selectfluor-[1-(chloromethyl)-4-flouro-1,4-

diazoniabicyclo[2,2,2]octane bis(tetraflouroborate)] as an effective and reutilizable catalyst in solvent and under solvent free condition **(Scheme 4.11)**.



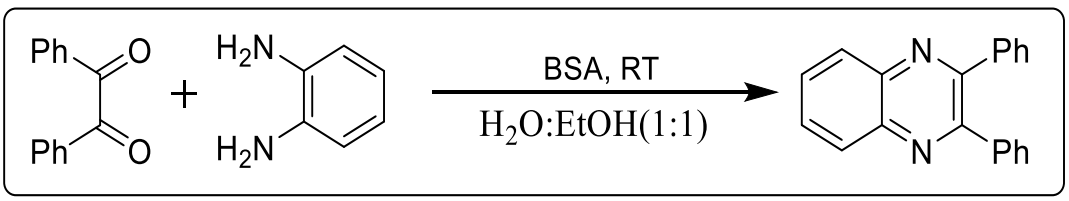
Scheme 4.11

Preparation and utilisation of polyvinylimidazole-based Bronsted acidic ionic liquid supported silica as an effective systematic heterogeneous catalyst reported by Bahman Tamami and co-workers [31] for the synthesis of quinoxaline derivatives **(Scheme 4.12)**.



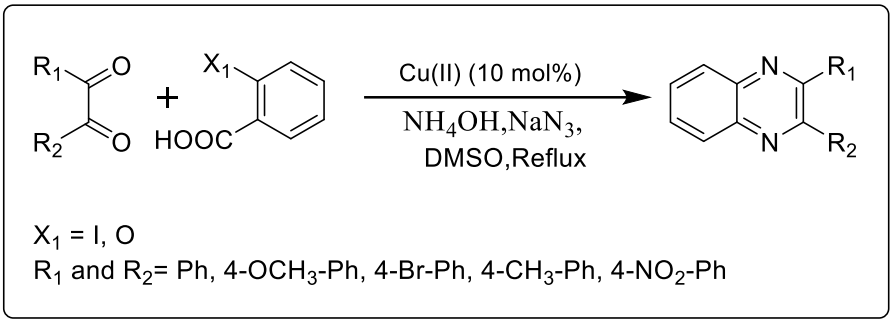
Scheme 4.12

Sami Sajjadifar [32] reported a newer and more eco-friendly catalyst, silica boron sulfonic acid, for the preparation of quinoxaline molecules at room temperature. The condensation of 1,2-diketones and 1,2-diamines using BSA in H_2O: EtOH (20 ml) produces quinoxaline derivatives in isolated high yields (**Scheme 4.13)**.



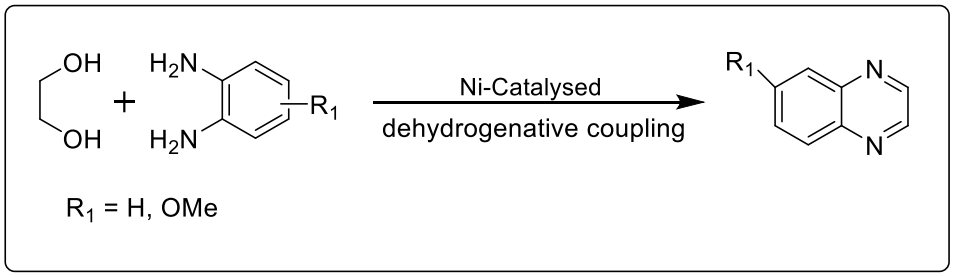
Scheme 4.13

Bittu Saha et al. [33] first reported that 2-iodo benzoic acid is an unusual reactant for the synthesis of quinoxaline using an organo-Cu (II) catalyst. The reaction pathway is a Schmidt reaction followed by a nucleophilic substitution reaction between 2-iodo benzoic acid and sodium azide, which stimulated by an organo Cu (II) catalyst that produces quinoxaline molecules **(Scheme 4.14).**



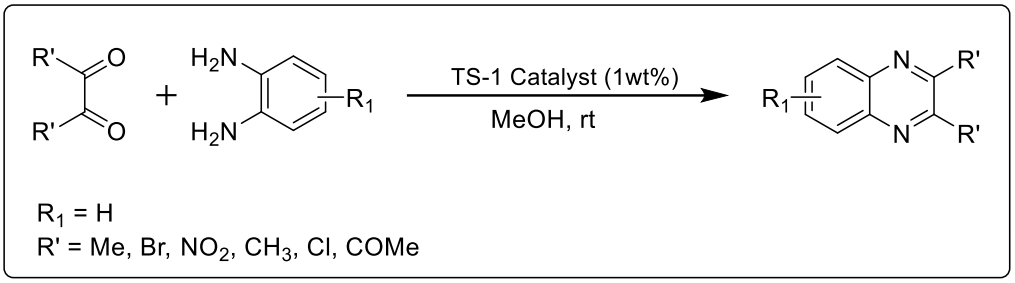
Scheme 4.14

Atanu Bera and co-workers [34] synthesise the substituted benzimidazoles and quinoxalines. There is dehydrogenative coupling that takes place between ethylene glycol and aromatic diamines for the selective synthesis of mono- and di-substituted quinoxaline, catalysed by earth-abundant $NiCl_2$ with the ligand 1,10-phenthroline **(Scheme 4.15)**.



Scheme 4.15

Pranav S. Chandrachood et al. [35] developed an effective approach for the synthesis of quinoxaline molecules catalysed through titanium silicate-1. A library of quinoxaline derivatives was efficiently produced at room temperature in better yields with 1 wt.% of titanium silicate (TS-1) as a catalyst by the reaction between 1,2-diamines and 1,2-diketones in methanol **(Scheme 4.16)**.



Scheme 4.16

Gurpreet Kaur and co-workers [36] reported camphor sulfonic acid as a systematic organic catalyst that produces the structurally diverse quinoxalines and pyrido-pyrazine derivatives at room temperature **(Scheme 4.17)**.

Scheme 4.17

4.2 Present Work:

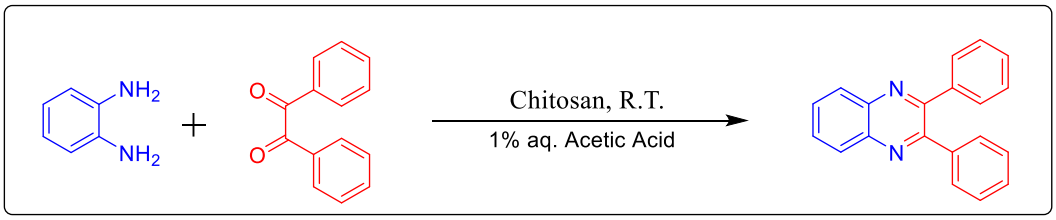
We contribute to green chemistry by developing a greener, eco-compatible synthesis of quinoxaline at room temperature using chitosan as a biodegradable catalyst. Chitosan is a natural polysaccharide and is also known as a "biopolymer", which was obtained from the alkaline hydrolysis of chitin. Chitin is obtained from the exoskeletons of crustaceans such as crabs, lobsters, and shrimp; the radulas of molluscs; as well as the beaks of cephalopods, which are abundantly present in the biosphere of the earth. Therefore, chitosan is a renewable green catalyst.

4.3 Result and Discussion:

In the present protocol, we apply chitosan without any further modification for the synthesis of quinoxaline derivatives. Fortunately, we obtained a good to excellent yield within a short period of time compared to the previous strategies. At the beginning, we focused on optimising the conditions for the synthesis of quinoxaline by

using benzil and ortho-phenylenediamine in the presence of chitosan in 5ml of 1% aqueous acetic acid solution. Initially, we focused on a systematic evaluation of the amounts of catalyst used of 0.01, 0.02, 0.04, 0.05, 0.06, and 0.08 g of chitosan (Table 4.1). We got a very excellent result at 0.04 g of chitosan. When we increase the amount of chitosan, we observe that the solubility of chitosan decreases and it forms a gel-like viscous solution in the round bottom flask. This shows the reactants are not mixed properly with each other and therefore decrease the amount of product **(Table 4.1)**. Then, after optimising the conditions, we synthesise quinoxaline by using benzil and ortho-phenylenediamine in 5 mL of 1% aq. acetic acid solution using 0.04 g chitosan as a catalyst at room temperature as a model scheme **(Scheme 4.18)**. We prepared the series of quinoxaline derivatives by using substituted benzil and ortho-phenylenediamine under optimised reaction conditions **(Table 4.2)**.

In recent days, very few protocols display direct use of chitosan in organic transformation. Researchers develop pathways that directly use chitosan for greener and eco-friendly synthesis of organic compounds in response to the demand for sustainable development in terms of the environment, safety, and economy [37], [38].



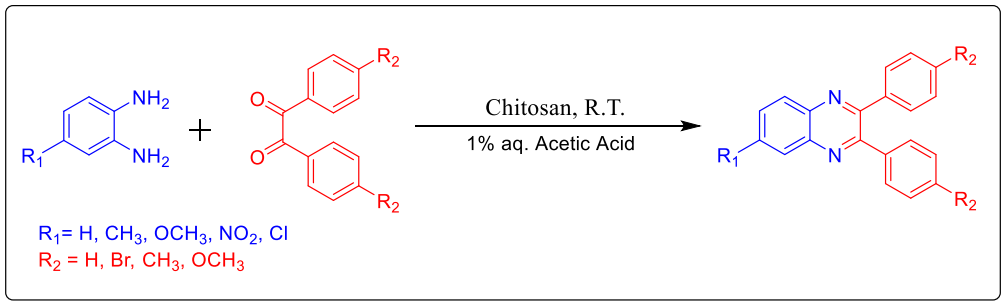
Scheme 4.18. Synthesis of Quinoxaline by using chitosan as a biocatalyst.

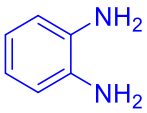
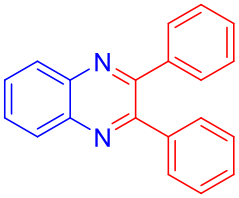
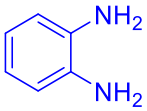
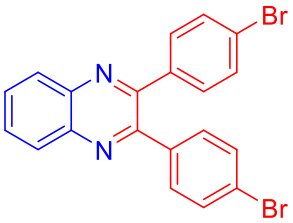
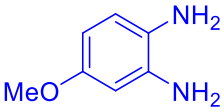
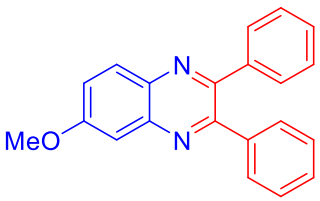
Table 4.1. Optimizing amount of catalyst for synthesis of Quinoxaline derivatives:

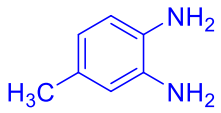
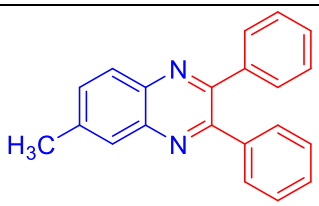
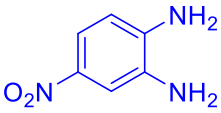
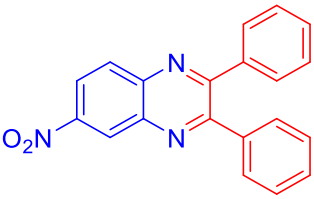
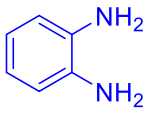
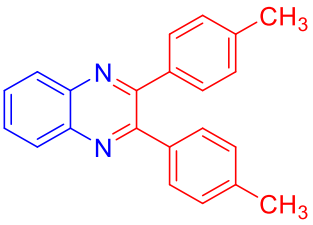
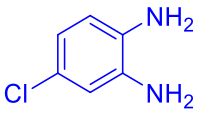
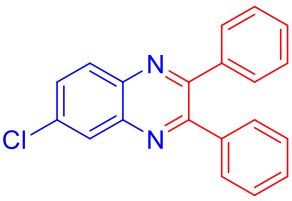
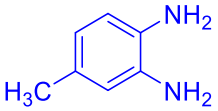
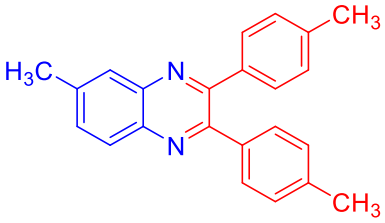
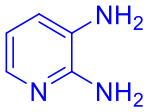
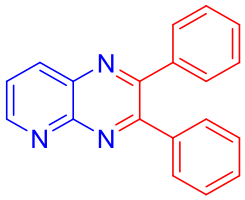
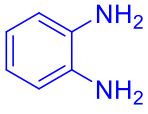
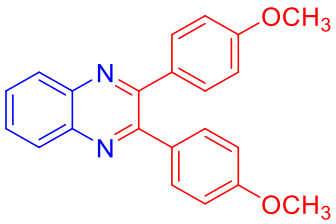
Sr. No.	Amount of Chitosan, solvent	Time	Yield (%)
1	0.01 in 1% aq. Acetic acid	24hrs	25
2	0.02 in 1% aq. Acetic acid	24hrs	47
3	0.03 in 1% aq. Acetic acid	8hrs	71
4	0.04 in 1% aq. Acetic acid	10min	92
5	0.05 in 1% aq. Acetic acid	15min	90

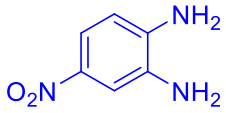
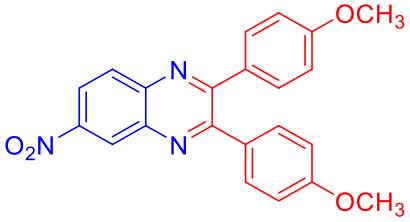
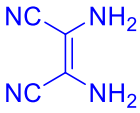
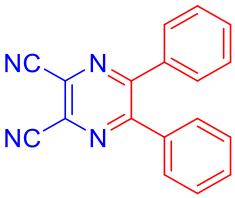
6	0.06 in 1% aq. Acetic acid	15hrs	65
7	0.08 in 1% aq. Acetic acid	24hrs	35
8	0.04 in 1% acetic acid: Ethanol (1:1)	20min	50

Table 4.2 Synthesis of Quinoxaline derivatives by using Chitosan as biodegradable catalyst.



Sr. No.	1,2-Diamine	Product	M.P. (°C) [Lit.]	Yield %[a]
1			127-128 [39]	92
2			190-192 [39]	92
3			160-162 [41]	91

4			116-118 [39]	90
5			192-194 [39]	90
6			145-146 [39]	91
7			120-121 [42]	92
8			140-142 [39]	92
9			160-162 [29]	92
10			156-158 [39]	92

11			191-192 [43]	90
12			165-166	90

[a] Isolated yield after recrystallisation.

Recyclability of Catalyst:

The synthesis of quinoxaline from benzil (1 mmol) and ortho-phenylenediamine (1 mmol) in 5 mL of 1% aq. acetic acid with 0.04 gm of chitosan after this the solid mass was filtered and the filtrate contained chitosan catalyst, which was reused without any further treatment for the next cycle of quinoxaline synthesis. This study shows that there is no reduction in catalytic efficiency up to the third cycle, after that there is a slight decrease in yield **(Figure 4.4)**.

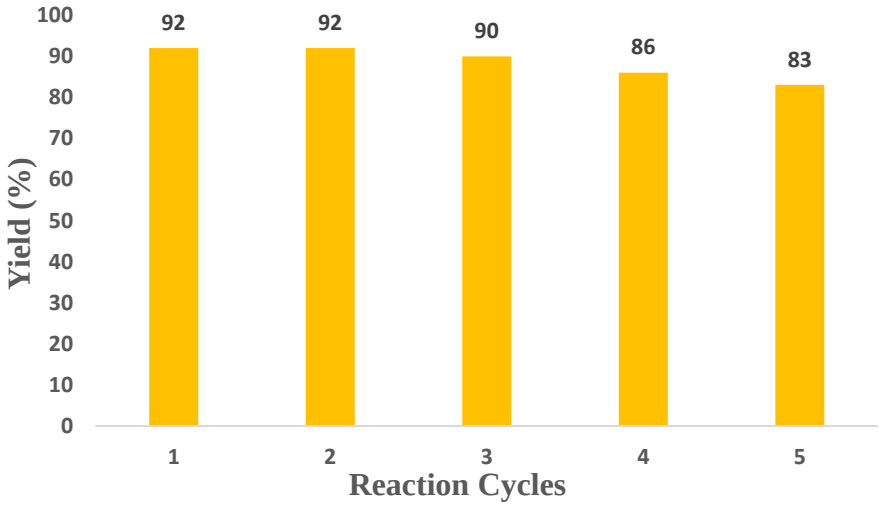


Figure 4.4. Recyaclability of Catalyst.

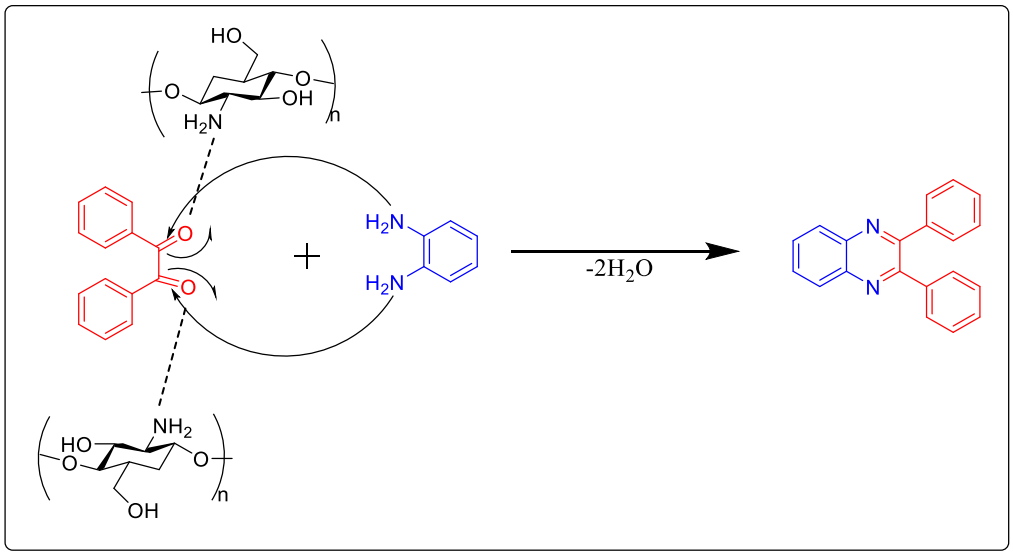
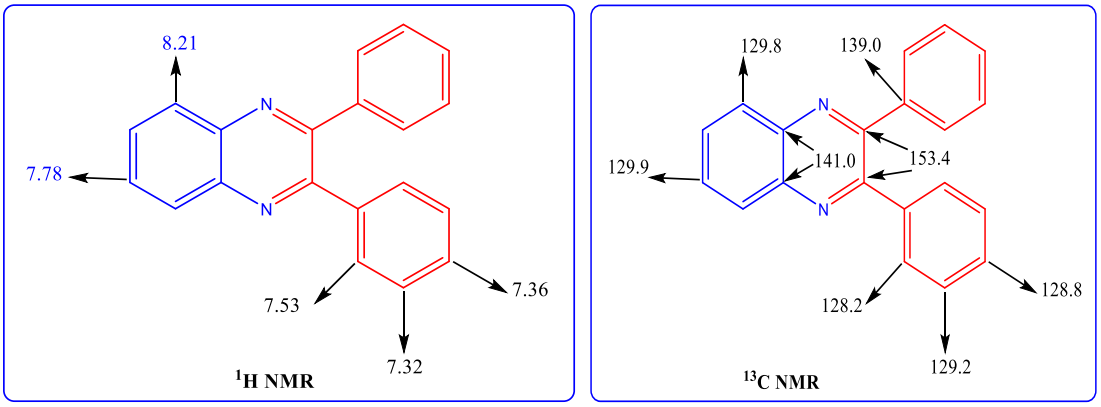


Figure 4.5. Plausible mechanism for synthesis of Quinoxaline by using Chitosan as biodegradable catalyst.

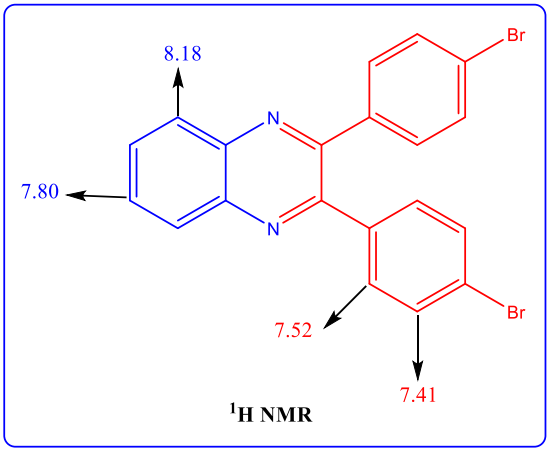
Characterization of products:

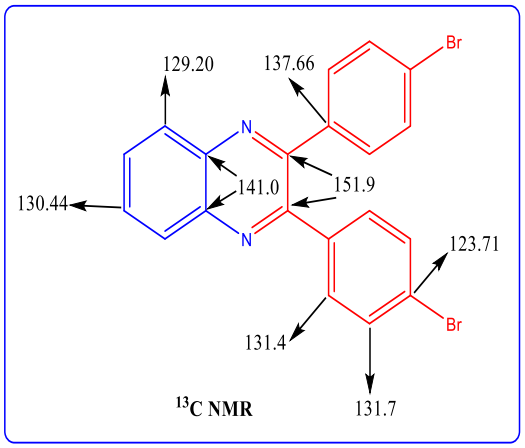
2,3-Diphenylquinoxaline:



IR spectrum **(Figure 4.6)** exhibits a characteristic band around 1443 cm^{-1} assignable to N=C-Ar, which indicates the formation of quinoxaline. The band at 1631 cm^{-1} designates the presence of alkene in aromatic rings. ^{1}H NMR spectra **(Figure 4.7)** of same compound shows all signals in the range of δ 7.34 to 8.21 ppm. The aromatic proton of quinoxaline appeared as a multiplate while aromatic protons of phenyl ring also appeared as multiplate. ^{13}C spectrum **(Figure 4.8)** exhibits all peaks at δ 151.93, 141.24, 137.66, 131.70, 131.43, 130.44, 129.20, 123.71 ppm in the aromatic region. The GCMS **(Figure 4.9 and 4.10)** shows peak at m/z: 282.

2,3-bis(4-bromophenyl) quinoxaline (Table 2. Entry-2):





IR spectrum **(Figure 4.11)** exhibits a characteristic band around 1393 cm^{-1} assignable to N=C-Ar, which indicates the formation of quinoxaline. The band at 1662 cm^{-1} designates the presence of alkene in aromatic rings and absorption at 749 cm^{-1} for the C-Br. ^{1}H NMR spectra **(Figure 4.12)** of same compound shows all signals in the range of δ 7.40 to 8.18 ppm. The aromatic proton of quinoxaline appeared as a multiplate while aromatic protons of phenyl ring appeared as doublet. ^{13}C spectrum **(Figure 4.13)** exhibits all peaks at δ 151.93, 141.24, 137.66, 131.70, 131.43, 130.44, 129.20, 123.71 ppm in the aromatic region.

4.4 Conclusion:

In conclusion, we described the new readily recovered biocatalyst for the synthesis of a series of quinoxaline derivatives. The biodegradable catalyst for organic transformation plays an important role now days because of the environmental views and the present protocol conserves environmental life and the economy by using biodegradable chitosan as a catalyst. The promising aspects of present work are high efficiency, short reaction time, clean reaction media, and operational simplicity. This protocol enhances the synthetic methodology for sustainable synthesis of various quinoxaline derivatives in aqueous medium.

4.5 Experimental Section

The melting points of the products were determined using the EQ 730A-EQUIPTRONICS electrical melting point apparatus and are uncorrected. Infrared

spectra were recorded on a Lamda FTIR 750 spectrometer. The samples were examined as KBr discs 5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. GCMS is recorded on GCMS-QP2010. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companies and used without further purification.

General Procedure for Synthesis Quinoxaline Derivatives

In a round-bottom flask, dissolve 0.04 g of chitosan in 5 ml of a 1% aqueous acetic acid solution, then add 1,2-diketone (1 mmol) and 1,2-diamine (1 mmol) derivatives. The reaction mixture was magnetically stirred at room temperature for an appropriate time (table 2). The completion of the reaction was monitored by tlc (n-hexane: ethyl acetate, 6:4). After completion of the reaction, the reaction mixture is filtered, and the product is washed with a 1% aqueous acetic acid solution. We get a crude product that has been recrystallized in ethanol. We obtain the pure product of quinoxaline.

Spectroscopic Data

2,3-Diphenylquinoxaline (Table 2. Entry-1): IR (KBr): 3051, 1630, 1528, 1348, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.18-8.21 (m, 2H), 7.77-7.80 (m, 2H), 7.52-7.54 (m, 4H), 7.34-7.37 (m, 6H); ^{13}C NMR (400 MHz, CDCl3): δ 153.48 (C), 141.23 (C), 139.08 (C), 129.98 (CH), 129.84 (CH), 129.22 (CH), 128.81 (CH), 128.28 (CH); MS (ESI): m/z = 282.

2,3-bis(4-bromophenyl) quinoxaline (Table 2. Entry-2): IR (KBr): 1662, 1575, 1393, 1200, 1059, 825, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.15-8.21 (m, 2H), 7.79-7.82 (m, 2H), 7.51-7.53 (m, 4H), 7.40-7.42 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 151.93 (C), 141.24 (C), 137.66 (C), 131.70 (CH), 131.43 (CH), 130.44 (CH), 129.20 (CH), 123.71 (C).

6-Methyl-2,3-Diphenylquinoxaline (Table 2. Entry-4): IR (KBr): 3063, 1660, 1592, 1210, 874, 719, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.1 (d, 1H), 7.96 (s, 1H), 7.63 (dd, 1H), 7.5 (m, 4H), 7.35 (m, 6H), 2.6 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$):

δppm 152.9 (C), 152.1 (C), 141.1(C), 138.7(C), 138.2(C), 137.8(C), 132.4 (CH), 129.2 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.4 (CH), 20.4 (CH).

5,6-diphenylpyrazine-2,3-dicarbonitrile (Table 2. Entry-12): IR (KBr): 2917, 2160, 1586, 1438, 1008, 1185, 775, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 7.32-7.30 (m, 4H), 7.25-7.23 (t, 2H), 7.17-7.15 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δppm 155.27 (C), 135.04 (C), 131.03 (C), 129.68 (CH), 128.98 (CH), 128.71 (CH), 113.18 (C); MS (ESI): m/z = $281(M-1)^{+}$.

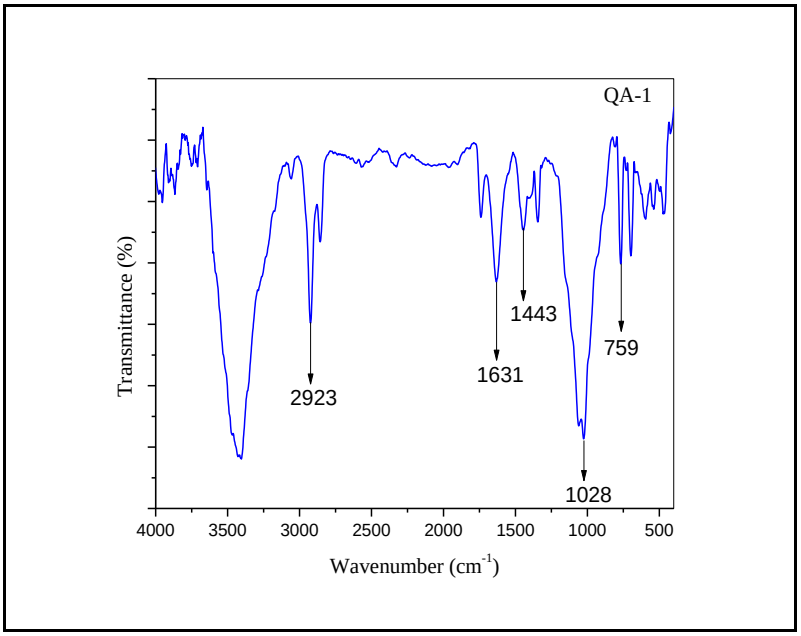


Figure 4.6: IR spectra of 2,3-Diphenylquinoxaline

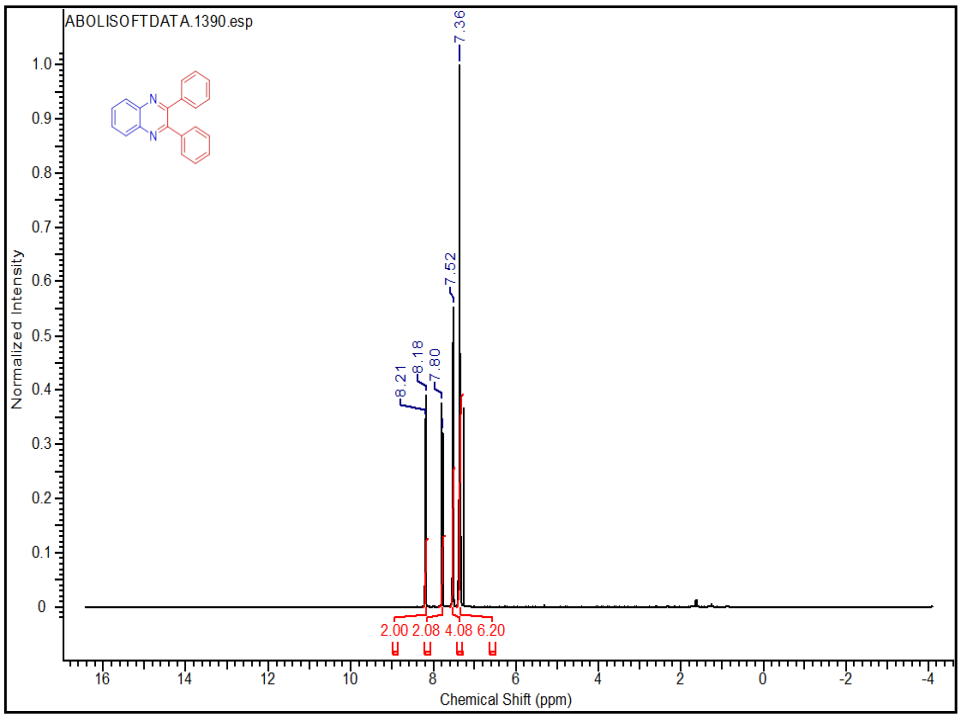


Figure 4.7: ^{1}H NMR of 2,3-Diphenylquinoxaline

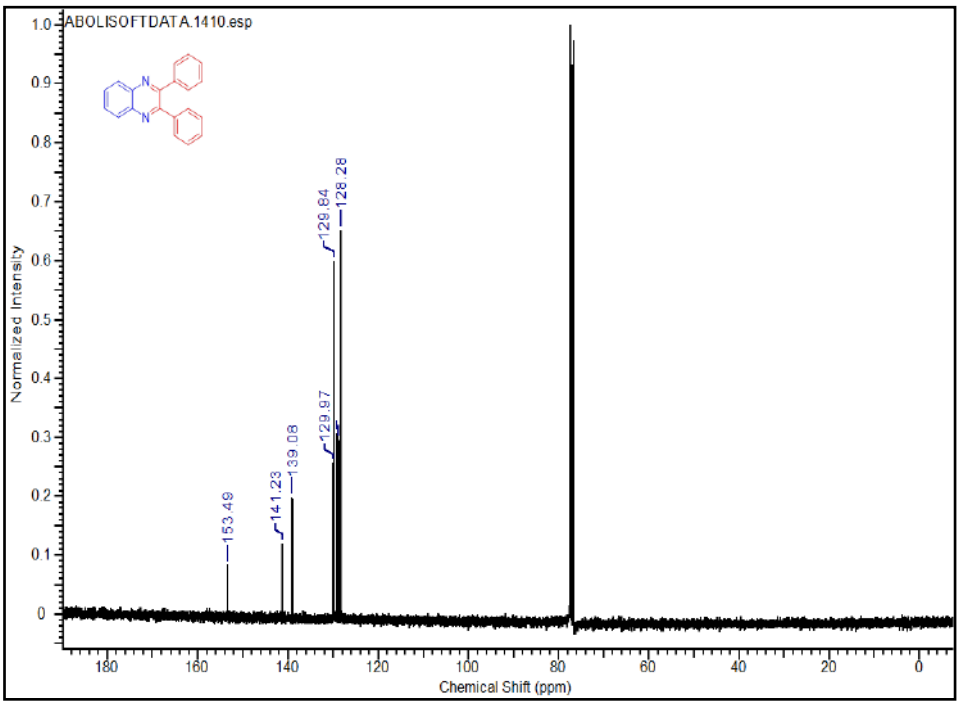


Figure 4.8: ^{13}C NMR of of 2,3-Diphenylquinoxaline

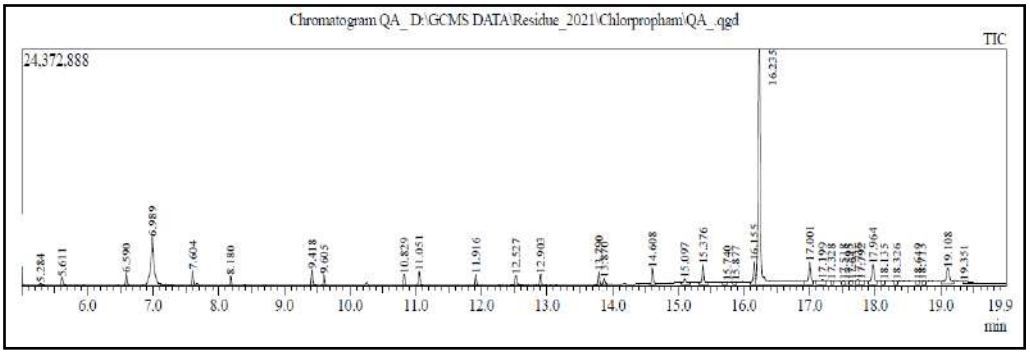


Figure 4.9: GCMS spectrum of 2,3-Diphenylquinoxaline

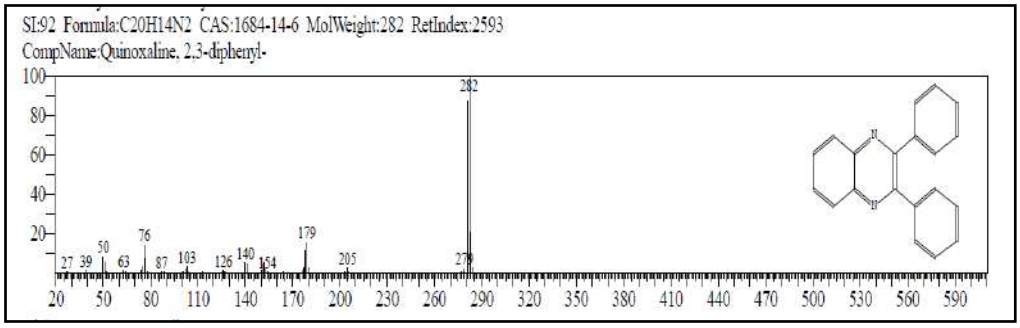


Figure 4.10: Mass spectrum of 2,3-Diphenylquinoxaline

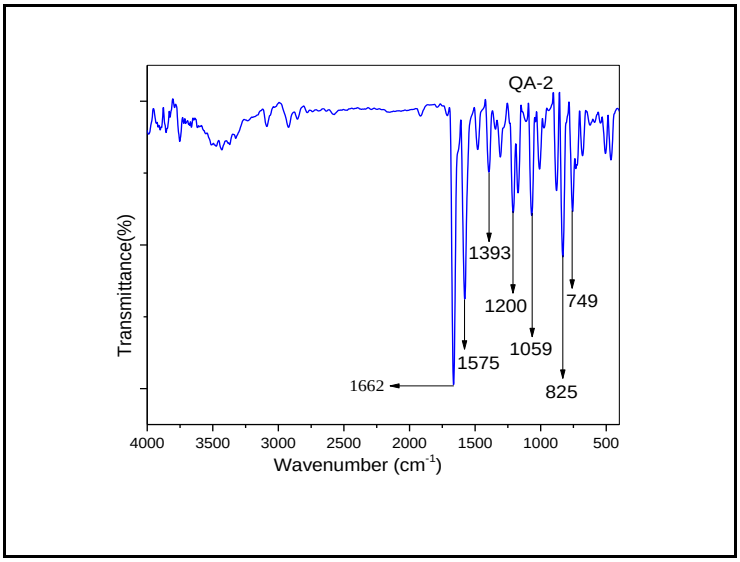


Figure 4.11: IR spectra of 2,3-bis(4-bromophenyl) quinoxaline

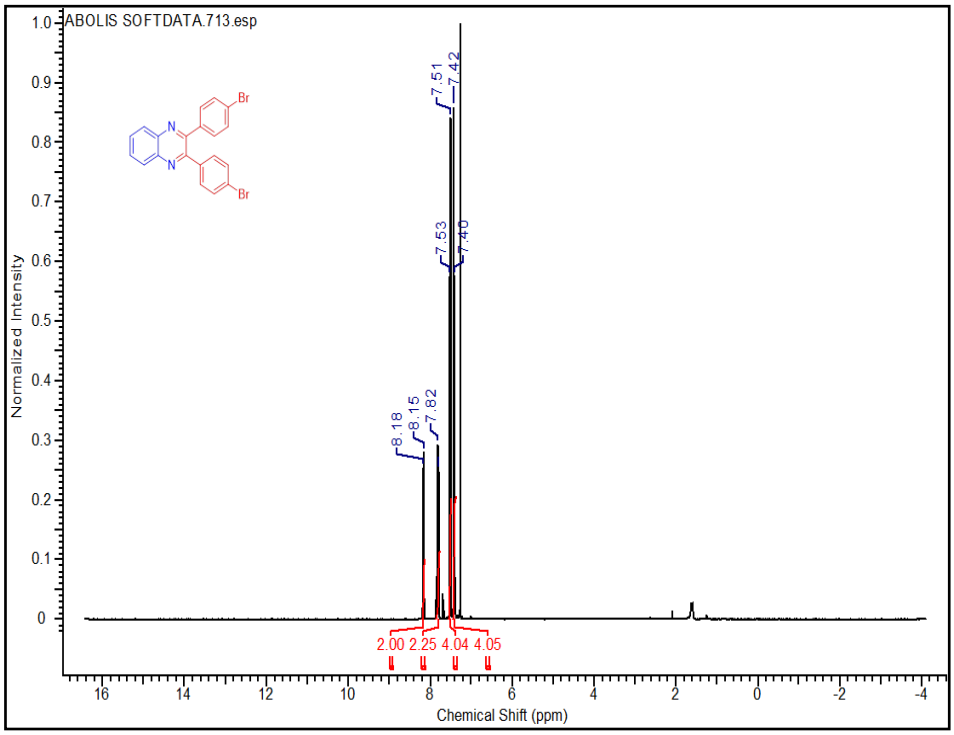


Figure 4.12: ^{1}H NMR of 2,3-bis(4-bromophenyl) quinoxaline

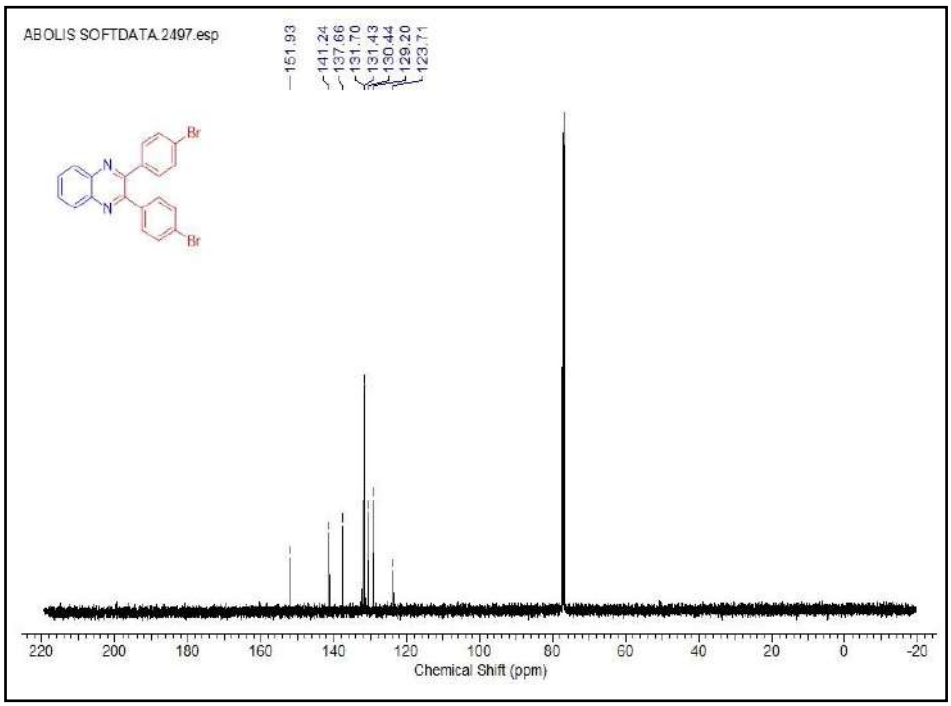


Figure 4.13: ^{13}C NMR of 2,3-bis(4-bromophenyl) quinoxaline

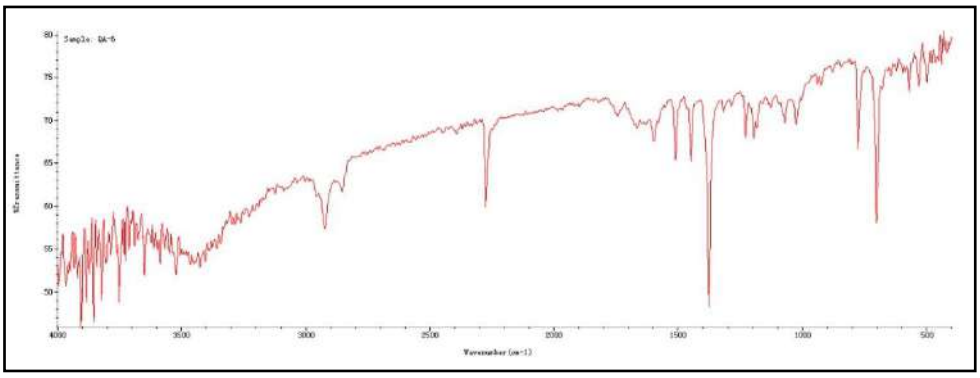


Figure 4.14: IR Spectrum of of 5,6-diphenylpyrazine-2,3-dicarbonitrile

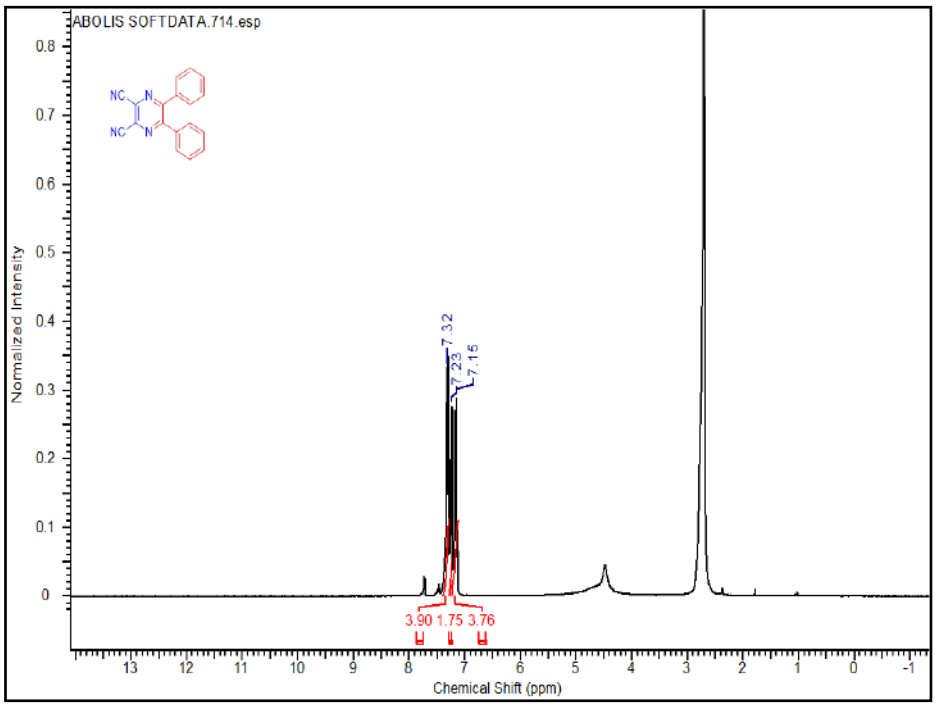


Figure 4.15: ^{1}H NMR spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

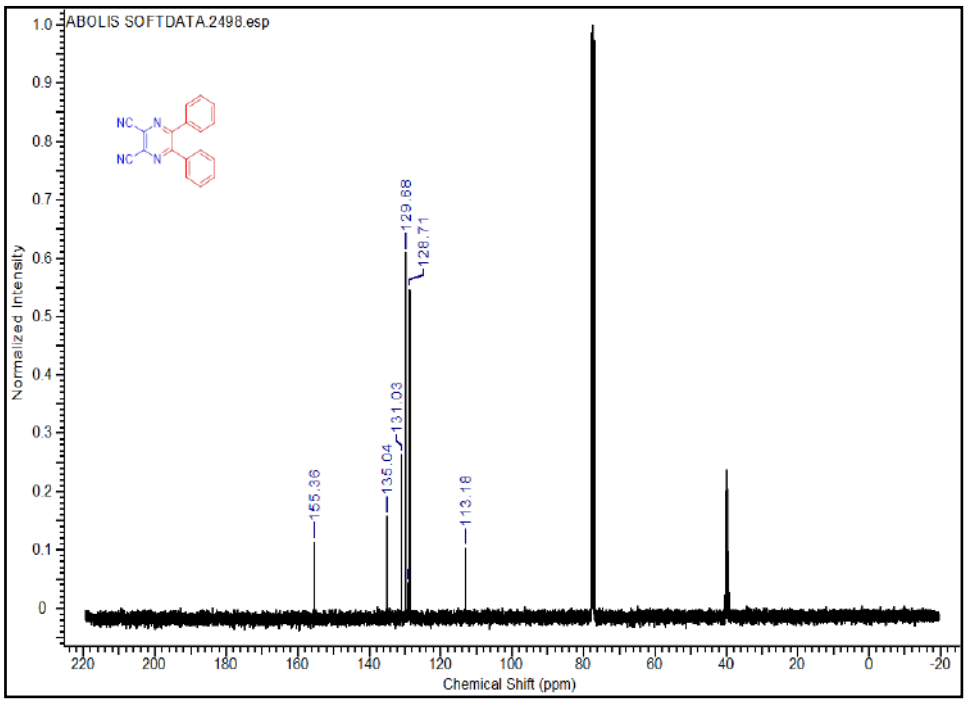


Figure 4.16: ^{13}C NMR spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

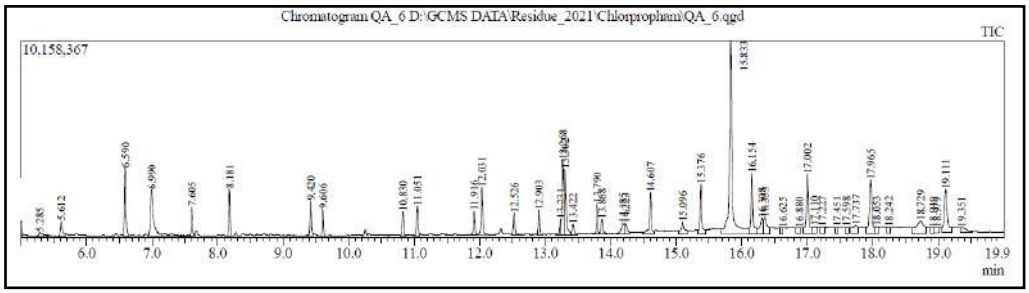


Figure 4.17: GCMS spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

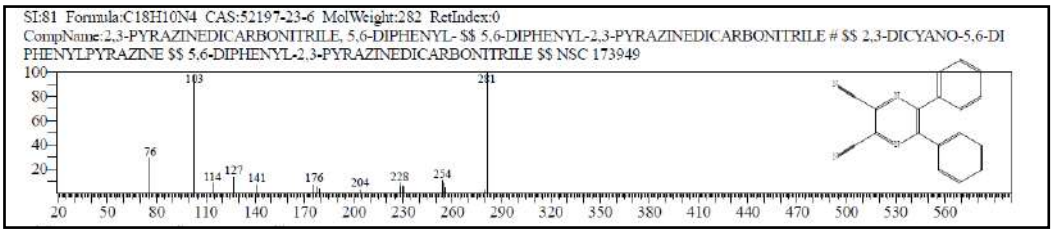


Figure 4.18: Mass spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

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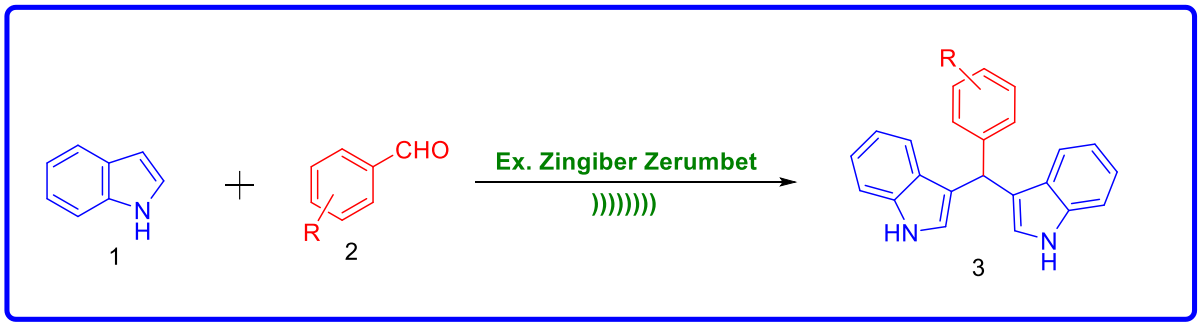
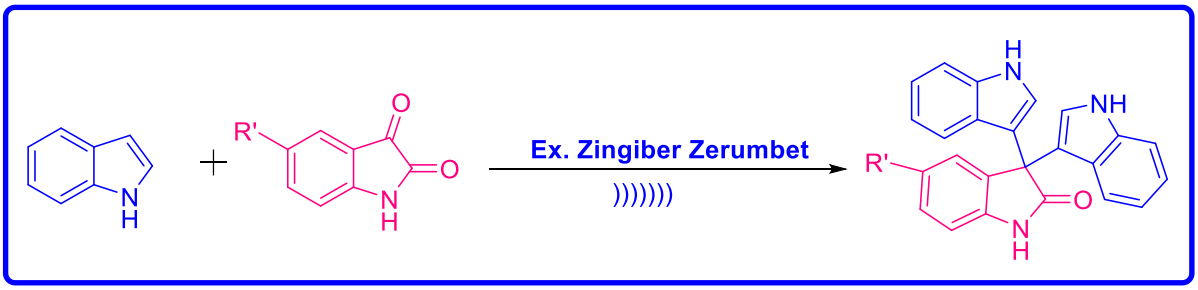
CHAPTER - 5

SECTION - I

GREENER AND ENHANCED ECO-SENSITIVE BENIGN METHODOLOGY FOR THE SYNTHESIS OF BIS(INDOLYL)METHANE AND TRISINDOLINES MOLECULES.





CHAPTER 5

Section: I

Greener and Enhanced Eco-sensitive Benign Methodology for the Synthesis of Bis(indolyl)methane and Trisindolines Molecules

5.I.1 Introduction

Chemist are very interested in the creation of diverse class of heterocyclic compounds. Heterocyclic compounds are carbocyclic compounds that replace carbon atom by one or more heteroatom such as nitrogen, oxygen or sulphur with in ring structure. They are aliphatic and aromatic found in nature, synthesized in laboratory and also in the industrial sector. The significance of these heterocyclic compounds lies in the various fields of science and technology and also in our daily life. These fields are pharmaceutical industry, agrochemicals, veterinary products, as result of developers, sanitizers, corrosion inhibitors, copolymers, dyestuffs and exhibit tremendous applications at industrial scale.

Most interesting nitrogen containing heterocycles are pyrazole, pyrazine, pyrimidine, quinoline, quinoxaline, indole etc. shows wide range of biological and medicinal activities, so their preparation always been an attractive and innovative part of organic chemistry. Among the various heterocyclic compounds' particularly indole and its derivatives, have occupied a unique place in the chemistry of nitrogen-containing heterocyclic compounds because of their miscellaneous biodynamic properties [1]. The aromatic bicyclic structure incorporating benzene ring fused with pyrrole ring is known as indole **(Figure 5.I.1)** [2]. Indole is electron rich heteroaromatic system due to having high-energy HOMO containing 10 π-electron system, 8 electrons from double bonds and 2 electrons from lone pair of electrons present on nitrogen atom. As like benzene, indole readily undergoes electrophilic substitution reactions due to delocalization of excessive π-electrons. Indole contains only one nitrogen atom, which is weakly basic in nature, like pyrrole and therefore very reactive with strong acids [3].

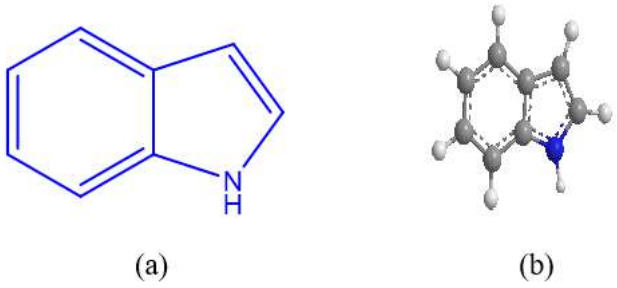
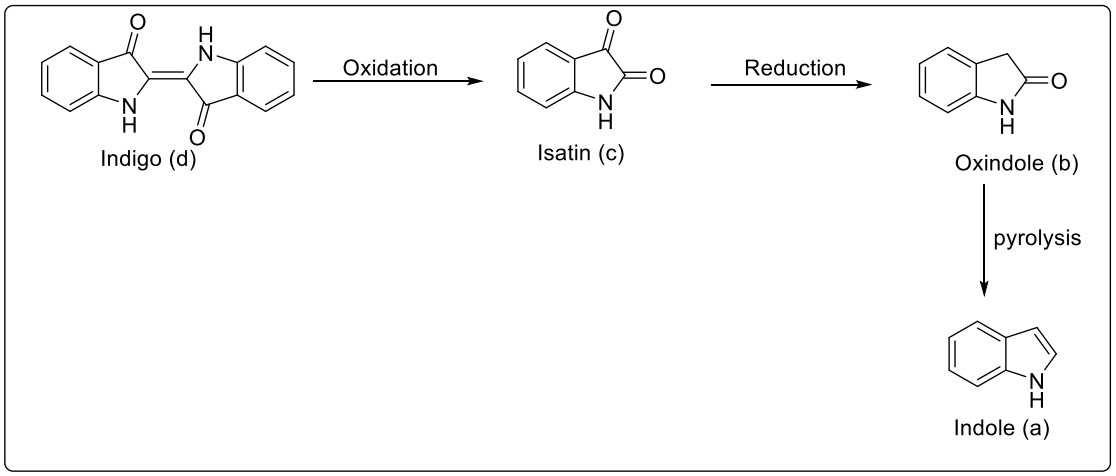


Figure 5.I.1: (a) Structure of Indole (b) 3D structure of Indole.

The research and study in the chemistry of indole (**a**) began in the mid of the 19th century with extensive search on the natural blue dye indigo (**d**), imported to Europe mainly from India. Indigo (**d**) (species of *Indigofera*) is an example of simple bisindole [4]. In 1866, Adolf Von Baeyer discovered the conversion of oxindole (**b**) into indole (**a**) by a pyrolytic technique using zinc dust (**Scheme 5.1**) and in 1869 he established a formula for indole **(Figure 5.I.2)** [5].



Scheme 5.I.1

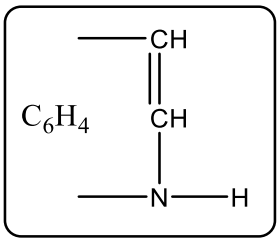


Figure 5.I.2 Baeyer formula for Indole

Indole (a), also known as 2, 3-benzopyrrole, 1H-benzo[b]pyrrole, 1-benzazole, 1-azaindene, or ketole, is a colorless, shiny, crystalline compound with a melting range of 52-54^{o}C. Indole (a) and its oxygenated derivative known as isatin having different isomers are collected in figure 5.3 out of which indole (a) is most stable isomer.

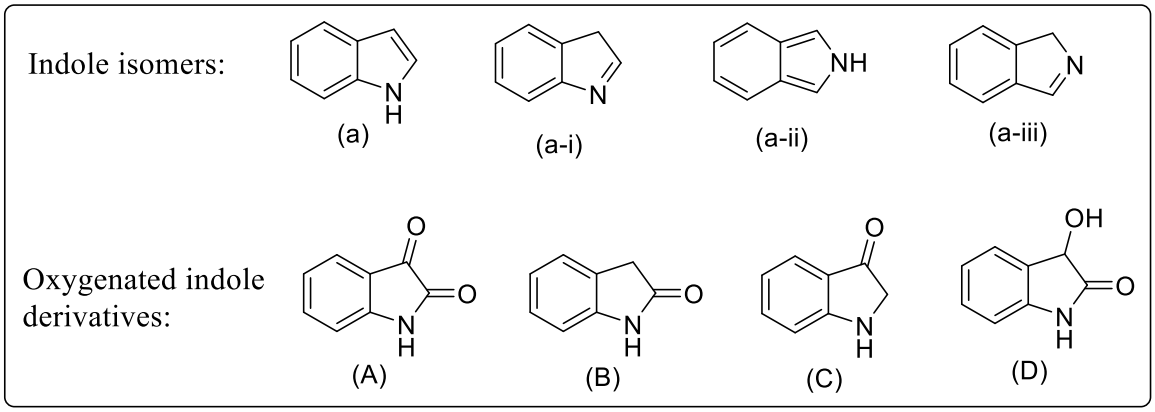


Figure 5.I.3 Indole isomers and oxygenated indole derivatives

Different derivatives of indole containing naturally occurring indole nucleus including Reserpine, Vincristine and essential amino acid Tryptophan [6]–[8]. Indole and its derivatives have been a subject of research studies due to its anticarcinogenic, antioxidant and antiathrerogenic effects [9]–[12]. Bis(indolyl)methane and tris-indoline are one of the important derivatives of indole **(Figure 5.I.4)**.

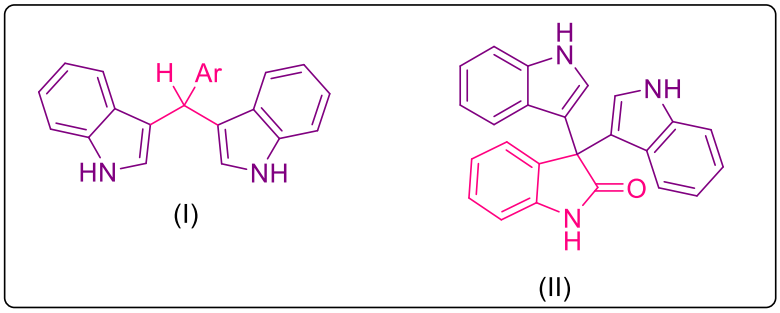
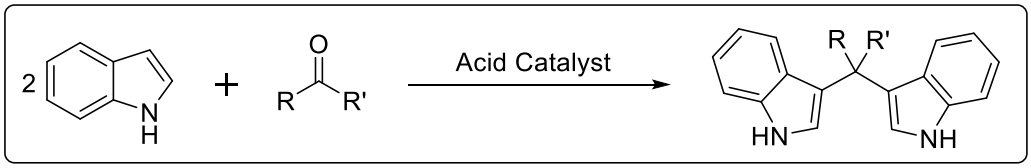


Figure 5.I.4 (I) structure if Bis(indolyl)methane (II) structure of Trisindolines

Bis(indolyl)methanes (BIMs) that having two indole units in a molecule, widely spread in various marine and terrestrial natural sources [10]. Viberindole is natural BIMs are useful in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome [13], [14], etc. Other natural sources are parasitic bacteria, sponges, tunicates, and also obtained from the assimilation of indole-3-carbinol present in Brassica

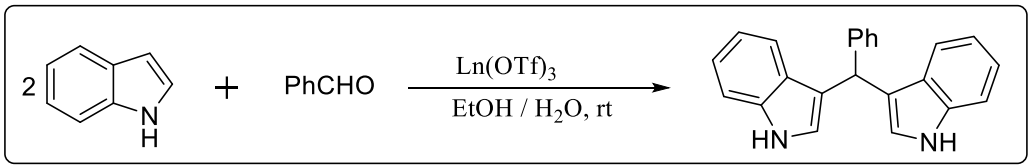
vegetables such as broccoli, cauliflower, and collard greens [15], [16]. Trisindolines are nitrogen bearing heterocyclic compounds containing an isatin core holds two indole scaffolds. Trisindolines have been prepared by reacting isatins with two indoles moieties mostly acid catalysed strategies are applied [17]. Trisindolines have wide spectrum of biological activities including anticancer [18], antimicrobial, anticonvulsant [19], antimycobacterial [20], and spermicidal activities [21]. The greatness of indole and its widespread implementation justifies it being addressed as "The Lord of the Rings" of heteroaromatic compounds [22]. Therefore, here we collect some methodologies for the synthesis of BIMs and Trisindolines, as follow;

The most famous synthetic method is Fischer indole synthesis was first reported by Fischer [23] in 1886 by Friedel-Crafts reaction between indole and aldehydes or ketones catalysed with mere acid **(Scheme 5.I.2)**.



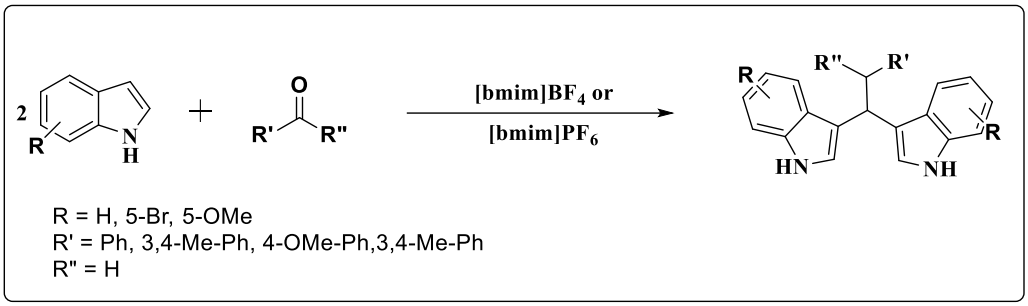
Scheme 5.I.2

After that Wang and co-workers [24] in 1996 developed a new methodology for the synthesis of BIMs using Lanthanide triflate [Ln $(OTF)_3$] as a mild and effective acid catalyst in protic media **(Scheme 5.I.3)**.



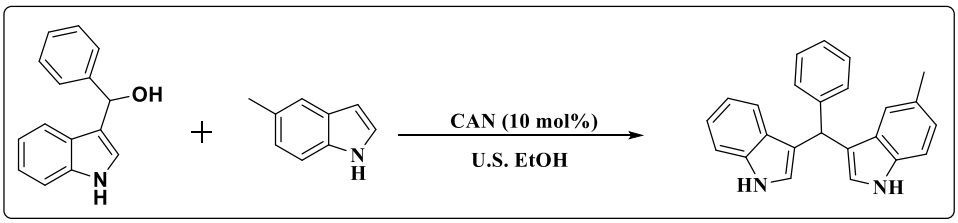
Scheme 5.I.3

J. S. Yadav et al. [25] demonstrated that ecofriendly process for the synthesis of BIMs by using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids. At room temperature stirring the indole, aldehyde or ketone in ionic liquids [([bmim]BF_4) or ([bmim]PF_6)] for 4-5hrs gives the BIMs in good yield **(Scheme 5.I.4)**.



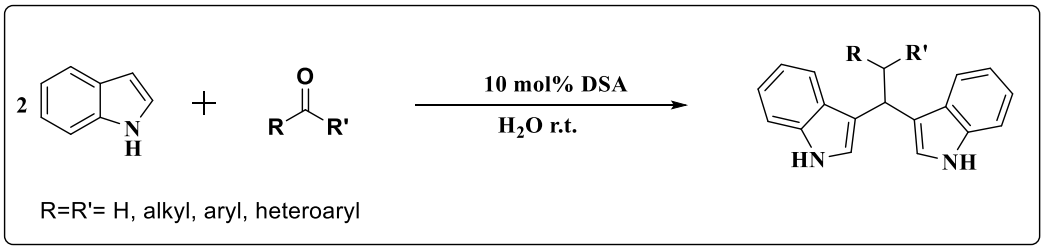
Scheme 5.I.4

Novel approach discovered by Xiao-Fei Zeng et al. [26] for synthesis of unsymmetrical bis(indolyl)alkanes under ultrasonic irradiation. In recent years many organic transformations are catalyzed by ceric ammonium nitrate (CAN) because inexpensive, easily available and soluble in less hazardous organic solvent such as EtOH and MeOH **(Scheme 5.I.5).**

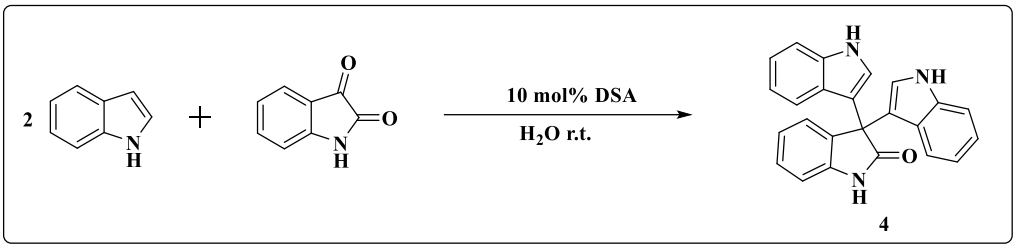


Scheme 5.I.5

Parasa Hazarika et al. [27] develop nonhazardous synthetic methodologies for synthesis of bis(indolyl)methane and tris-indolines for that they take aldehyde or ketone (1mmol) which reacts with indole (2mmol) and isatin (1mmol) treated with indole (2mmol) in presence dodecylsulphonic acid (DSA) in water at room temperature **(Scheme 5.I.6 and 5.I.7).**

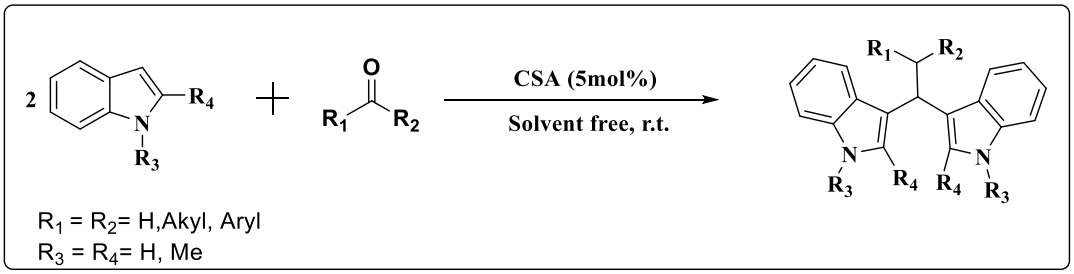


Scheme 5.I.6

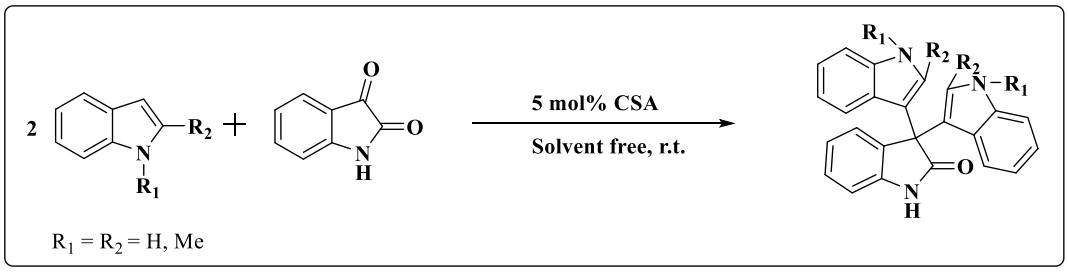


Scheme 5.I.7

Solvent free synthesis is very green protocol demonstrated for synthesis of bis(indolyl)methanes and 3,3'-indolyloxindole derivatives by Heshmatollah Alinezhad et al. [28] by using cellulosic sulphuric acid (CSA). CSA is a solid acid catalyst which is easy to handle, non-explosive and eco-friendly **(Scheme 5.I.8 and 5.I.9)**.

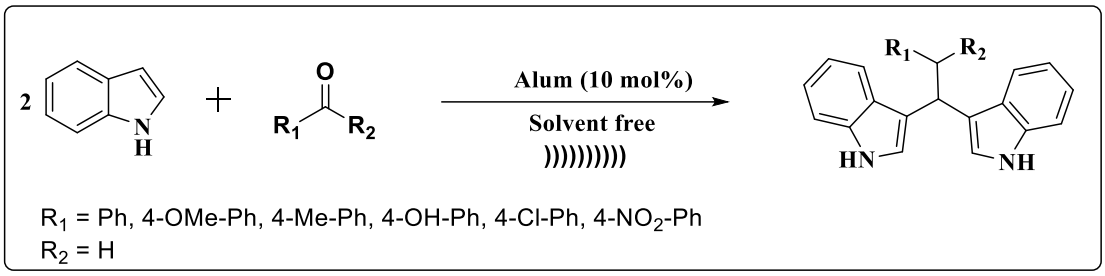


Scheme 5.I.8



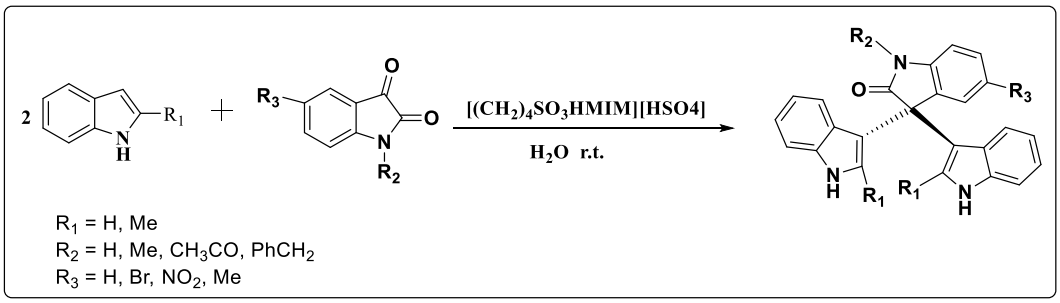
Scheme 5.I.9

Alum ($KAl(SO_4)_2.12H_2O$) catalyzed synthesis of bis(indolyl)methane under ultrasound irradiation without solvent developed by Swapnil S Sonar et al. [29] in which indole and aldehyde or ketone derivatives in presence of alum powder was irradiated under ultrasonication at ambient temperature for spectacular time gives bis(indolyl)methane with good yield (**Scheme 5.I.10**).



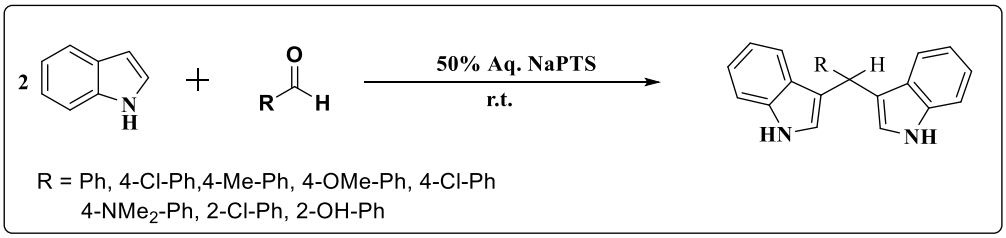
Scheme 5.I.10

Karimi, Narges et al. [30] synthesized oxindoles derivatives by using Brønsted acidic ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ in aqueous that is on water. Reaction is carried out by indole, isatin and ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ in water was stirred at room temperature that afforded oxindole in good yield **(Scheme 5.I.11)**.



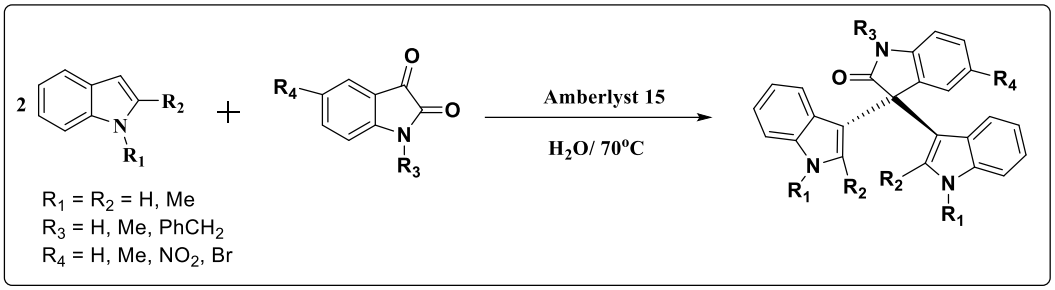
Scheme 5.I.11

Aqueous hydrotropic medium is a very attractive green solvent, which increases solubility of sparingly soluble organic reactants. Kamble et al. [31] developed the greener medium for the synthesis of bis(indolyl)methane that avoids the use of organic solvent **(Scheme 5.I.12)**.



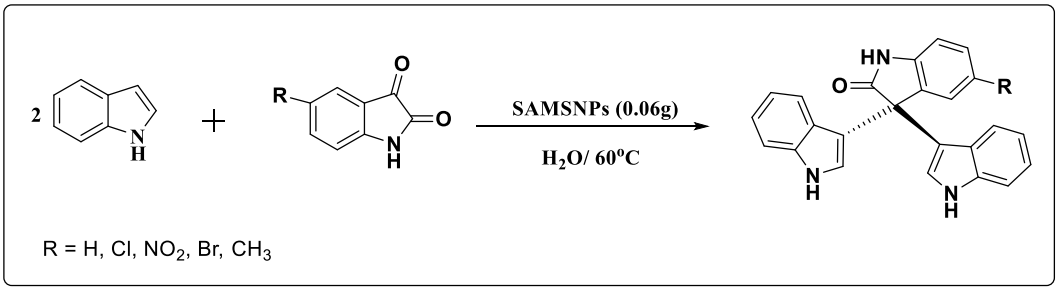
Scheme 5.I.12

Yaghoub Sarrafi et al. [32] prepared derivatives of 3,3-di(indolyl)oxindoles in excellent yield by employing Amberlyst-15 catalyst, reaction of indole and isatin in aqueous medium at 70°C **(Scheme 5.I.13)**.



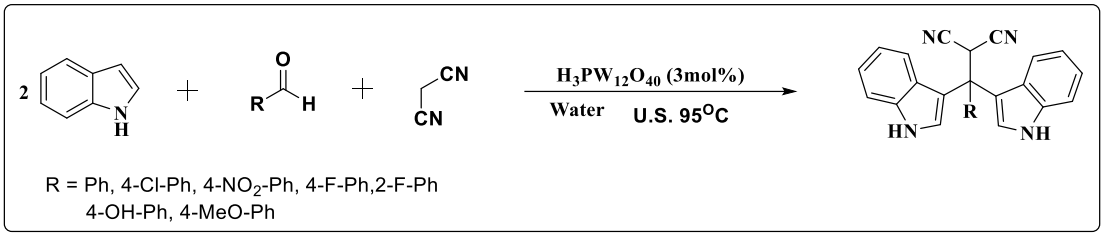
Scheme 5.I.13

Organic synthesis in aqueous medium is one of the important green prospective. Therefore, Ebrahim Mehrasbi et al. [33] prepared 3,3di(indolyl)oxindoles in the presence of mesoporous silica nanoparticles (SAMSNs) which are functionalized by sulfonic acid in aqueous media **(Scheme 5.I.14)**.



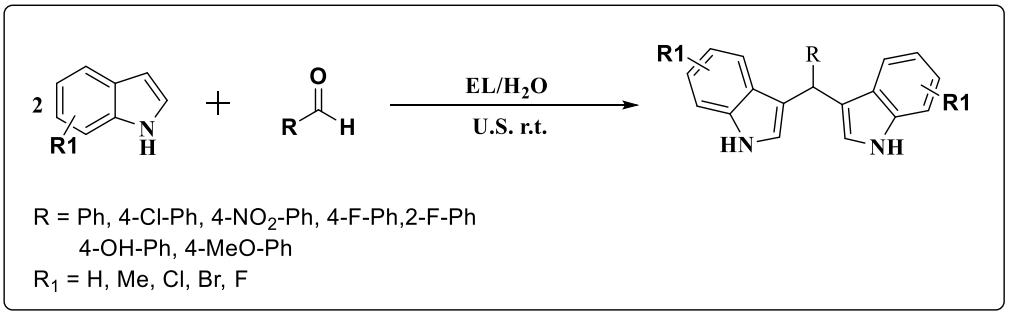
Scheme 5.I.14

Mohammad Ali Amrollahi et al. [34] again used $H_3PW_{12}O_{40}$ in aqueous media for the synthesis of bis(indolyl)methane under ultrasound irradiation**.** Here they perform reaction between aldehyde, indole and active methylene compound and catalyst $H_3PW_{12}O_{40}$ in water which was irradiated under ultrasonication gave the bis(indolyl)methane in good to excellent yield **(Scheme 5.I.15)**.

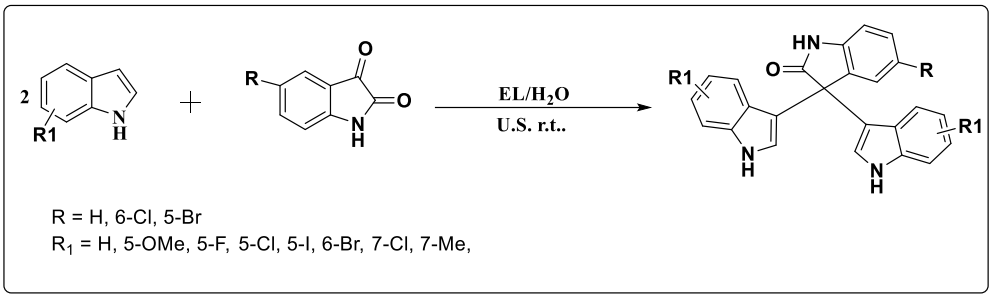


Scheme 5.I.15

Ge Gao et al. [35] demonstrated that in aqueous ethyl lactate (EL), without catalyst synthesis of bis(indolyl)methane and 3,3-bis(indolyl)oxindoles. Under ultrasound irradiation indole reacting with aldehyde or isatin in ethyl lactate: H_2O **(Scheme 5.I.16 and 5.I.17)**.

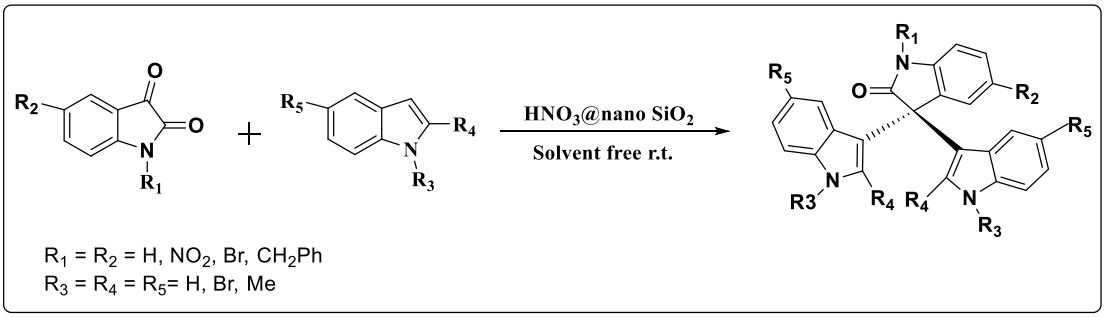


Scheme 5.I.16



Scheme 5.I.17

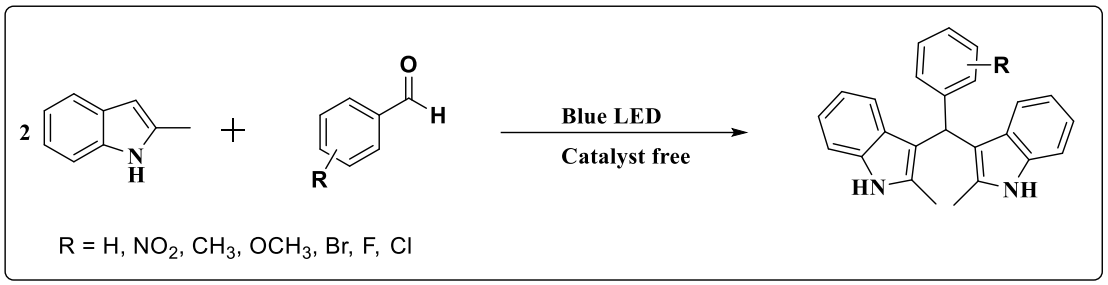
Nikoofar et al. [36] prepare the symmetrical and unsymmetrical di(indolyl)indoline-2-ones by two methods such as solvent free stirring and grinding by using HNO_3@nano SiO_2 as catalyst **(Scheme 5.I.18)**.



Scheme 5.I.18

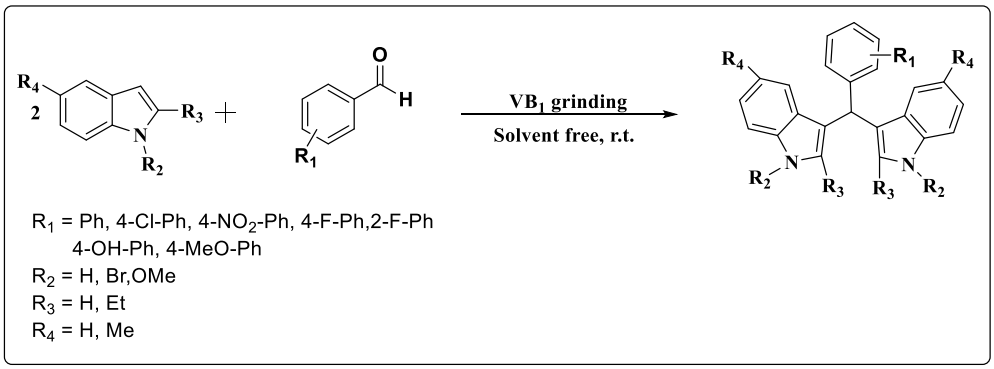
A green protocol that synthesizes the BIMs in the absence of a catalyst was disclosed by Yi-Shu Zhao et al. [37]. Reacting 2-methylindole and aryl aldehydes in

EtOH-H_2O (1:1) under blue LEDs for 4 hours produces series of BIMs with good yields **(Scheme 5.I.19)**.

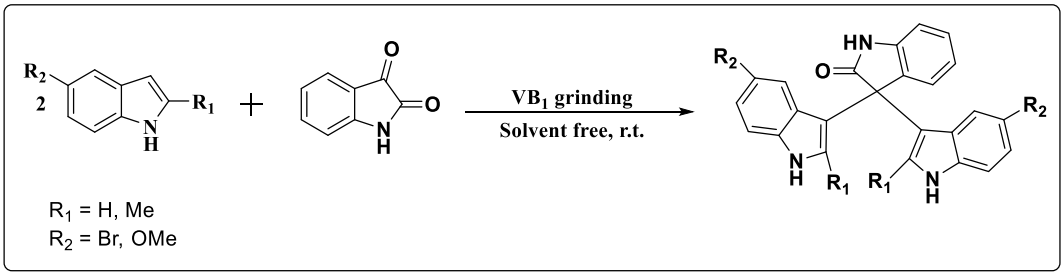


Scheme 5.I.19

According to green chemistry principles thiamine hydrochloride showed high atom economy and a small E-factor for the synthesis of indole scaffolds. Therefore, Sivagami Mathavan et al. [38] utilizes environmentally and economically friendly, recyclable amino catalyst thiamine hydrochloride for synthesis of bis(indolyl)methane's & tris(indolyl)methane's **(Scheme 5.I.20 and 5.I.21)**.

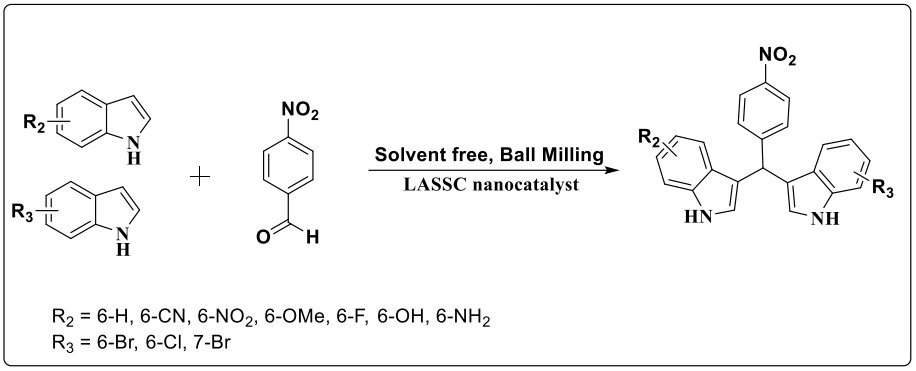


Scheme 5.I.20



Scheme 5.I.21

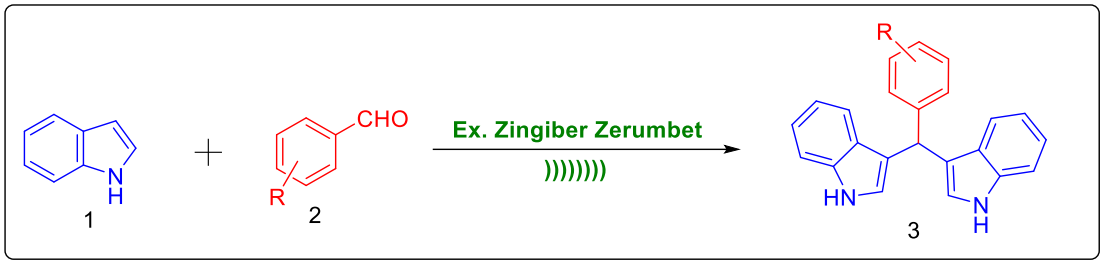
Zhiqiang Wu et al. [39] was developed ball milling solvent free synthesis of unsymmetrical bis(indolyl)alkanes using Lewis acid-surfactant-SiO_2 composite nano-catalyst (LASSC) ($AlCl_3.6H_2O$+SDS+SiO_2) **(Scheme 5.I.22)**.



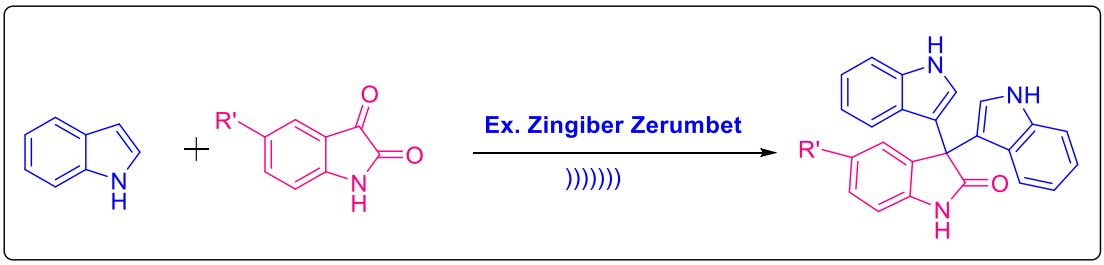
Scheme 5.I.22

5.2 Present work:

Due to diverse useful properties of molecule that containing indole as core ring structure for example bis(indolyl)methane, tris-indoline, etc. Scientists are constantly developing new methodologies for the synthesis of such indole scaffolds. Therefore, in the present work, we represent the more environmentally friendly synthesis of bis(indolyl)methane and tris-indoline by using natural surfactant "shampoo zinger" under ultrasound irradiation **(Scheme 5.I.23 and 5.I.24)**.



Scheme 5.I.23 Ultrasound assisted synthesis of bis(indolyl)methane in bio-surfactant.



Scheme 5.I.24 Ultrasound assisted synthesis of tris-indoline in bio-surfactant.

5.3 Result and Discussion:

In a continuation of our ongoing research on the development of sustainable methodologies and searching a green medium for organic transformations. Initially we

perform the model reaction, 4-nitrobenzaldehyde (1mmol) and indole (2mmol) in 5ml shampoo zinger at room temperature. We found very trace amount of yield **(Table 5.I.1 Entry 1)**. Then we focused on optimized the reaction condition to maximize the yield of product and decrease time of reaction. But significant improvement occurs when reaction perform under ultrasound irradiation. Ultrasound irradiation not only increase the yield but also minimise the reaction time **(Table 5.I.1)**. After optimizing reaction condition, we apply same strategy to different aldehyde and indole in 5ml shampoo zinger under ultrasound irradiation **(Table 5.I.2)**. Benzaldehyde with electron withdrawing group gives good yield than the electron donating group.

The scope of protocol was further extended to synthesis of tris-indoline by reacting indole (2mmol) with isatin (1mmol) as a model scheme under optimized reaction condition was in 5ml shampoo zinger under ultrasound irradiation. We obtain good result; within short period of time. We perform total four reaction by using different substituted isatins **(Table 5.I.3)**. The presence of electron donating and withdrawing group on benzene ring of isatins shows little effect on reaction yield. Ultrasound irradiation reduce the reaction time and increase reactivity due to formation of cavities, which produces high pressure and energies [40]. Shampoo zinger is extract of *Zingiber zerumbet*, fruit of zinger which acts as natural surfactant. Inflorescence of plant containing viscous juice which is rich in surfactant is known as ginger shampoo **(Figure 5.I.5)** [41]. There is saponin present in the viscous juice of *Zingiber zerumbet*, due to which it shows surfactant properties. Surfactants are detergents that are effective at dissolving non-polar compounds. This efficiency in dissolving non-polar compounds has made aqueous surfactant systems better alternatives to harmful organic solvents in various applications. Surfactant forms the micelles, which are similar to colloidal aggregation. This micelle formation occurs above the critical micelle concentration (CMC). A low concentration of CMC means requiring less surfactant to decrease the surface tension. Initially, the clear reaction mixture turned turbid, which indicates the formation of micelle-like colloidal aggregation was observed in microscopic images **(Figure 5.I.6)**. During this aggregation, reactant molecules are brought into close proximity to each other and interactions take place between them, which form the organic transformation between them. The visual exploitation of the reaction progress also observed by change in color during this synthetic transformation **(Figure 5.I.7)**. Overall, the product formation occurs very easily between the core of the

micelle. Therefore, here we report synthesis of BIMS and tris-indoline under ultrasonication in natural surfactant, zinger shampoo **(Scheme 5.I.23 and 5.I.24)**. Present strategy discloses the green and efficient methodologies.

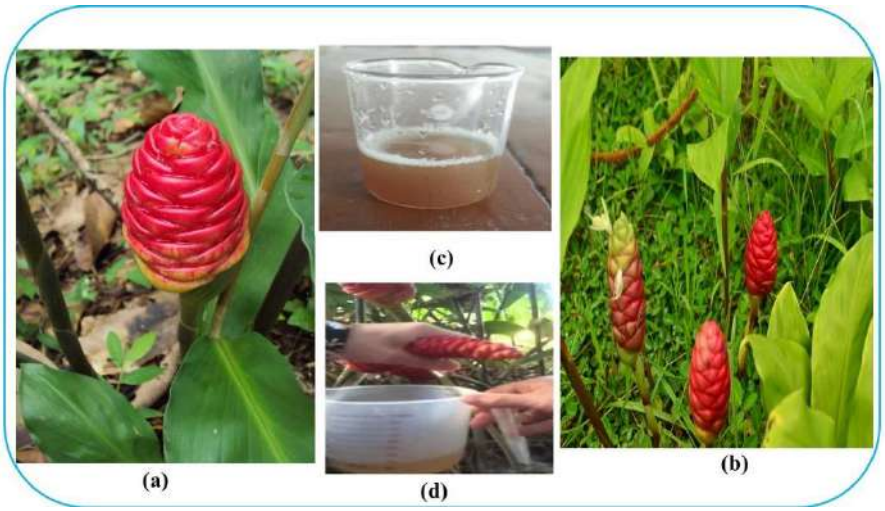


Figure 5.I.5. (a) Inflorescence of *Zingiber zerumbet*, (b)Inflorescence with flowers of *Z. zerumbet*, (c) Extract/juice of *Z. zerumbet*, (d) Collection extract/juice.

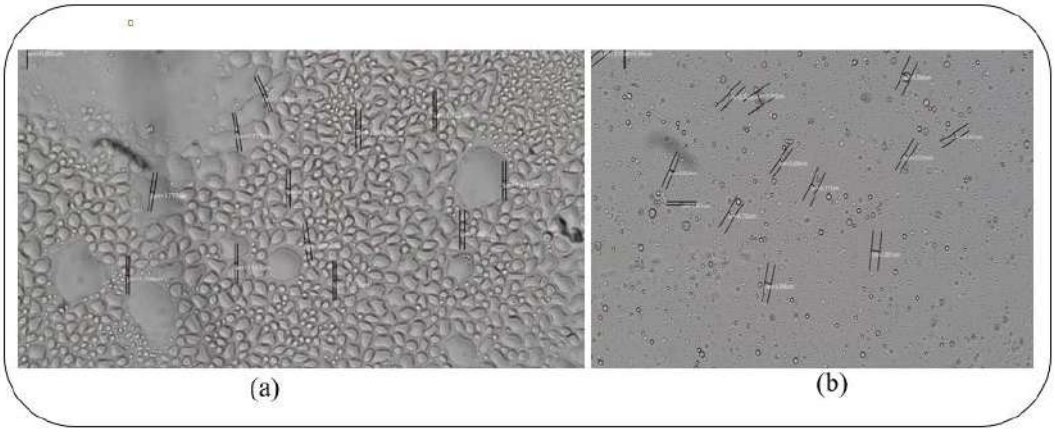


Figure 5.I.6. Microscopic Images (a) Extract of *Zingiber zerumbet* (b) Reaction mixture in *Zingiber Zerumbet*

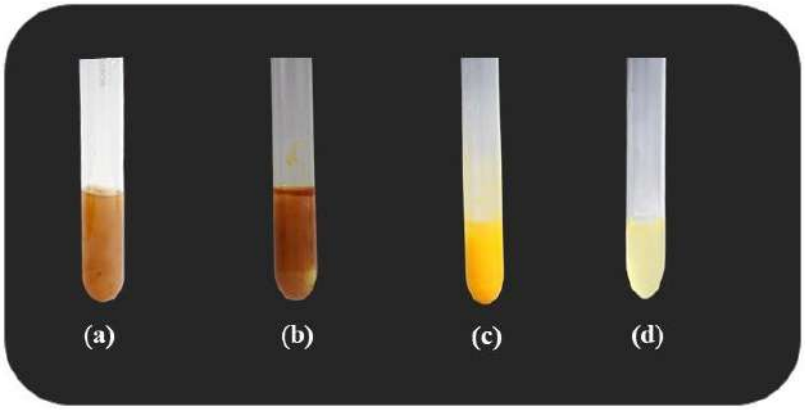
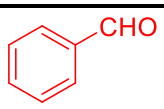
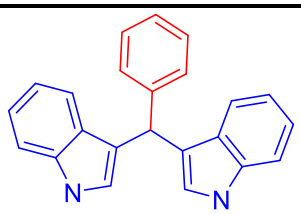


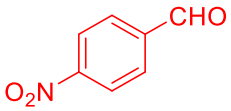
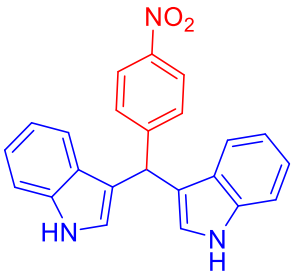
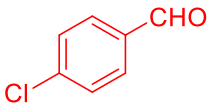
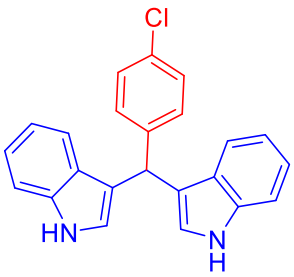
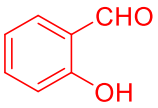
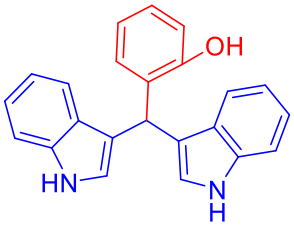
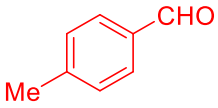
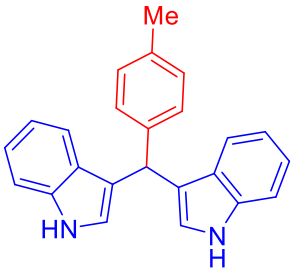
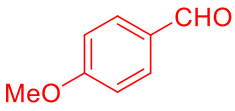
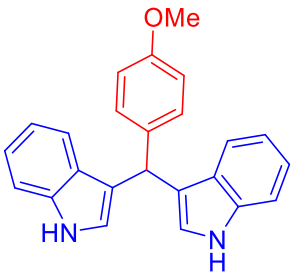
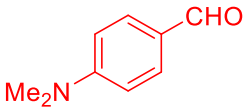
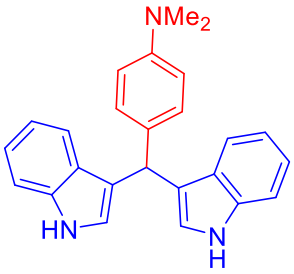
Figure 5.I.7 (a) Extract/juice of *Zingiber zerumbet* (b) Reactant in *Zingiber zerumbet extract* (c) Formation of product (d) *Zingiber zerumbet extract* after reaction

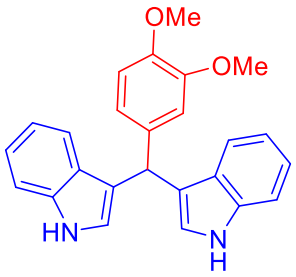
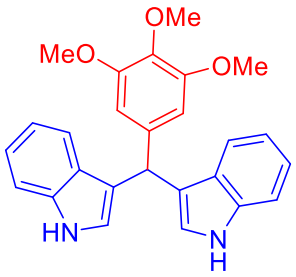
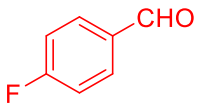
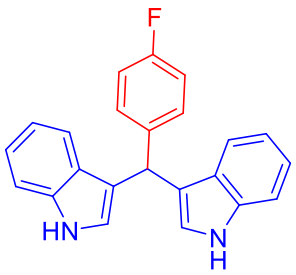
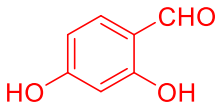
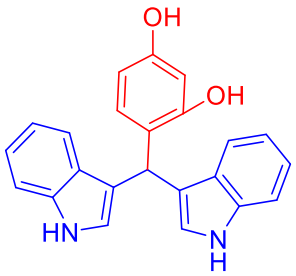
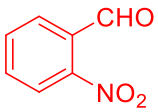
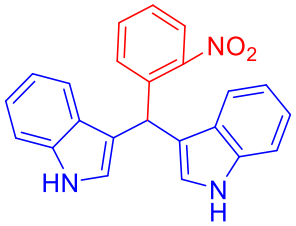
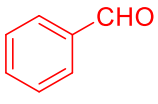
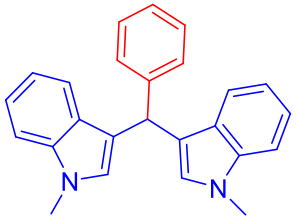
Table 5.I.1. Screening of Solvent Conditions for synthesis of bis(indolyl) methane.

Sr. No.	Solvent and Condition	Time	Yield (%)
1	*Zingiber zerumbet* at room temp.	2 days	trace
2	*Zingiber zerumbet* at reflux condition (50^oC)	24 hrs	50
3	*Zingiber zerumbet* at reflux condition (65^oC)	6 hrs	60
4	*Zingiber zerumbet* and ultrasonication at room temp.	10 min.	92
5	*Zingiber zerumbet* and ultrasonication at 45^oC.	10 min	90

Table 5.I.2. Synthesis of Bis-indoyl under ultrasound irradiation by using bio-surfactant.

Sr. No.	Aldehyde	Product	M.P.(^oC) [42], [43]	Yield (%)
1			126-128	92

2			126-128	92
3			76-78	90
4			102-104	86
5			98-100	88
6			190-192	86
7			169-171	85

8			197-199	86
9			208-210	86
10			72-74	86
11			108-110	86
12			190-192	84
13			203-203	90

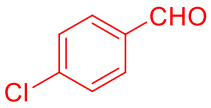
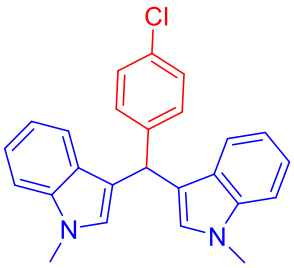
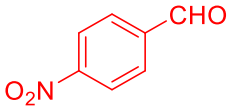
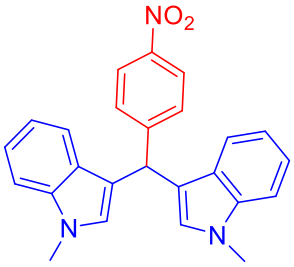
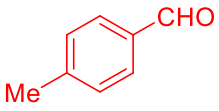
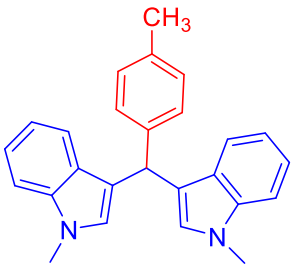
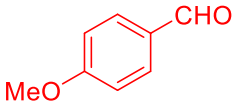
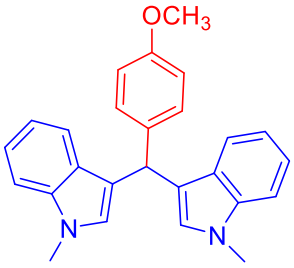
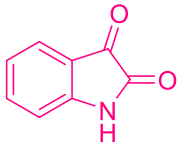
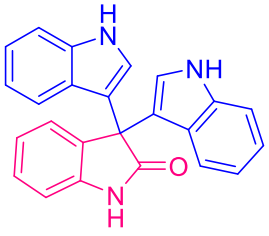
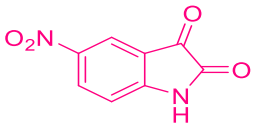
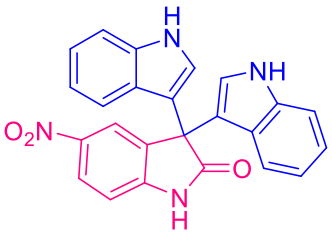
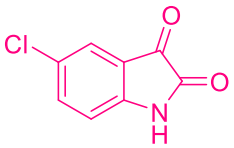
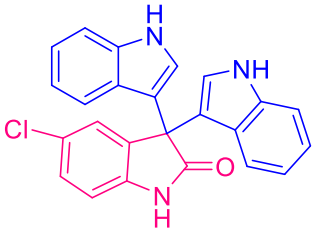
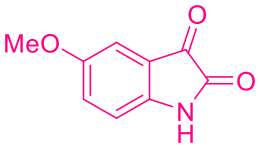
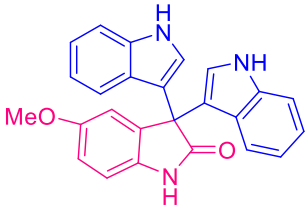
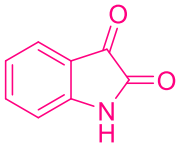
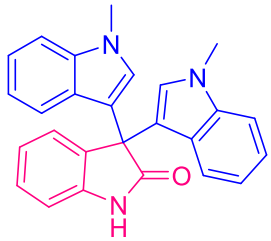
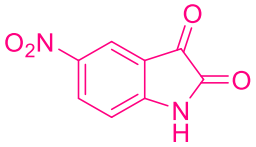
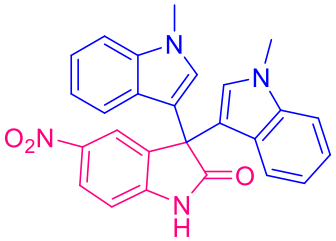
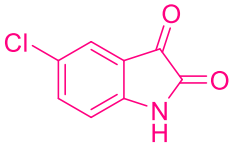
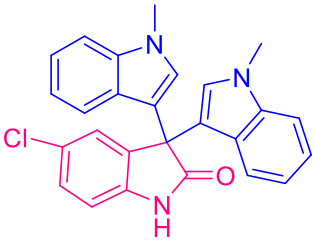
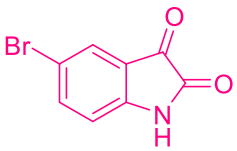
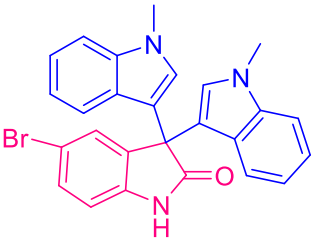
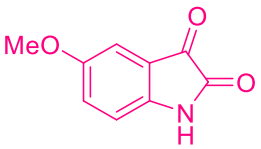
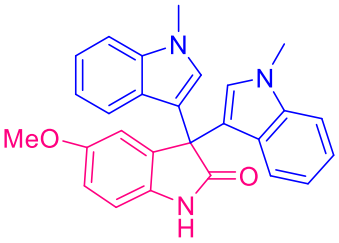
14			210-212	92
15			215-217	92
16			147-149	90
17			219-221	92

Table 5.I.3. Synthesis of Tris-indoyl under ultrasound irradiation by using bio-surfactant.

Sr. No.	Isatin	Product	MP (ºC)[35], [44]	Yield (%)
1			314-316	92

2			298-299	88
3			297-299	90
4			290-292	90
5			>300	92
6			>300	88
7			>300	90

8			>300	88
9			>300	90

Recyclability of Natural Surfactant-zingiber zerumbet:

We use only 5ml extract of zingiber zerumbet for the reaction. After completion of reaction filter the product and collect the filtrate and reuse for the reaction and monitoring any effect on yield but there is no much more effect on yield. After third cycle slightly decrease in yield. Therefore, reuse of extract is very important step as an environmental point of view which maintain the sustainability **(Figure 5.I.6.)**.

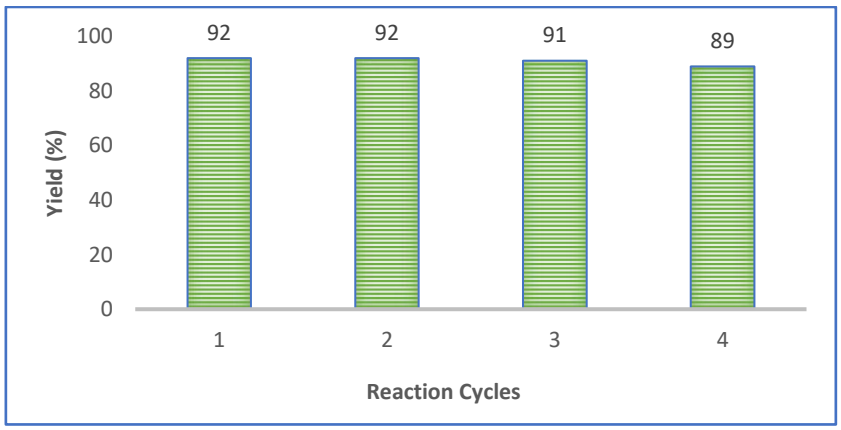
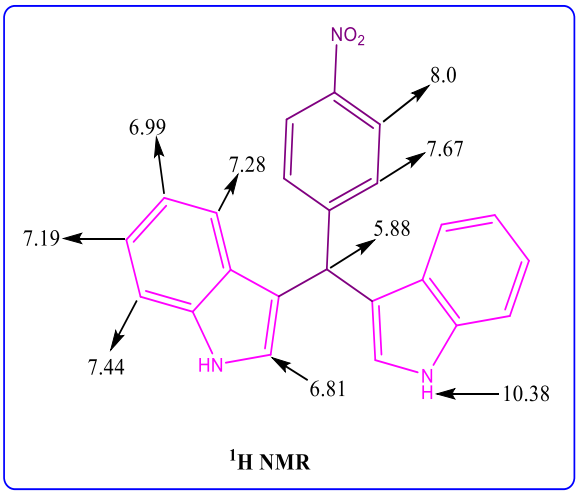


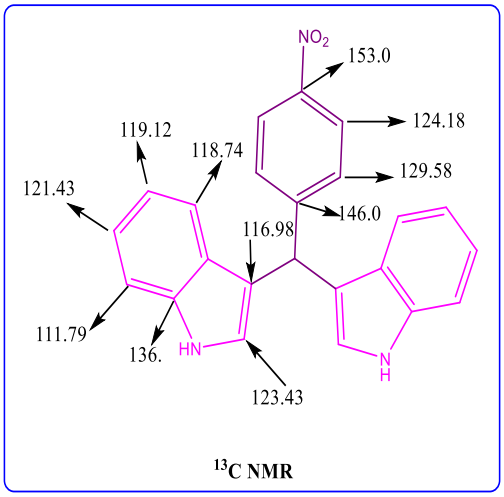
Figure 5.I.6. Recyclability of natural surfactant

Characterization of products

1) 3,3-Bis(indolyl)-4-nitrophenylmethane (Table 2.I. Entry 2):



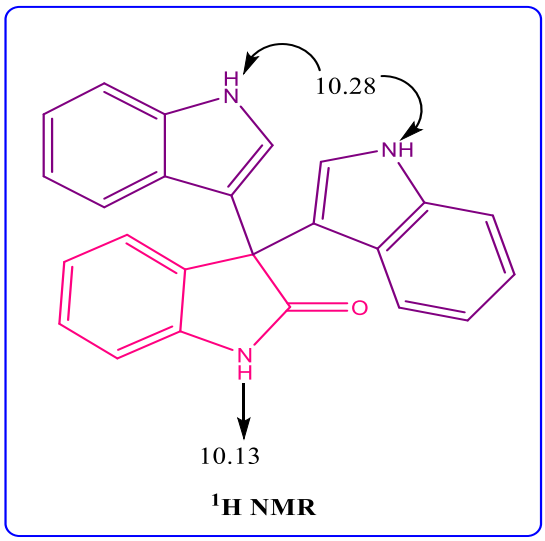
^{1}H NMR



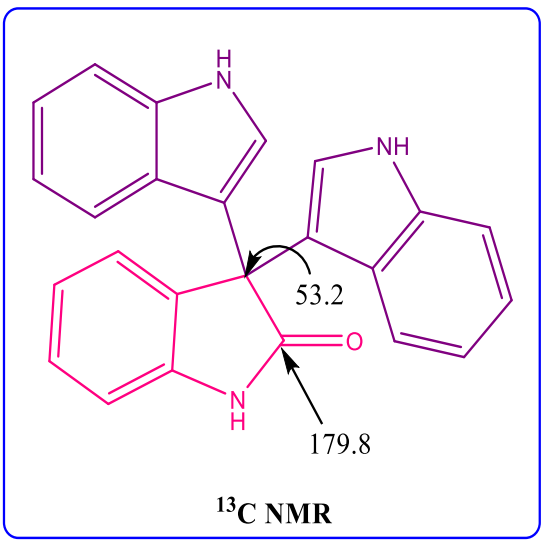
^{13}C NMR

IR spectrum **(Figure 5.I.8)** exhibits the bands at 3426 cm^{-1} for NH stretching vibration. the alkene shows frequency at 1637 cm^{-1}. In ^{1}H NMR **(Figure 5.I.9)** spectrum two NH protons of indole moiety resonated at δ10.38 ppm. The methine proton shows sharp singlet at δ 5.88 ppm which confirms the formation of bis(indolyl)methane. the protons adjacent to NO_2 group resonated at δ8.0 ppm which gives doublet, another doublet at δ 7.67 for aromatic protons meta to nitro group. The aromatic protons of indole ring observed in the range of δ 7.46 - 7.79 ppm. The ^{13}C NMR **(Figure 5.I.10)** spectrum shows peak at δ 153.0, 146.17, 136.99, 129.58, 126.62, 124.18, 123.43, 121.43, 119.12, 118.74, 116.98 and 111.79 ppm are attributed in aromatic region.

2) [3,3':3',3"-terindolin]-2'-one (Table 3.I. Entry 1):



^{1}H NMR



^{13}C NMR

The IR spectrum (**Figure 5.I.17**) of the compound showed the absorption band at 3428 cm^{-1} for NH stretching frequency. The carbonyl group for cyclic amide of indole moiety showed absorption band at 1707 cm^{-1}. The absorption band at 1106 cm^{-1} was corresponding to C-N stretching frequency. The ^{1}H NMR spectrum (**Figure 5.I.18**) displays singlet for two NH protons of indole ring appeared at δ 10.28 ppm whereas one NH proton of isatin moiety was observed at δ 10.13 ppm. The aromatic protons appeared at chemical shift δ values from 6.71 to 7.26 ppm. In the ^{13}C NMR spectrum **(Figure 5.I.19)** C3 carbon of indole moiety resonated at δ 53.16 ppm. The carbonyl carbon of the cyclic amide of isatin moiety was observed at δ 179.8 ppm. The remaining aromatic carbon noticed at 141.3, 137.6, 134.9, 127.8, 126.0, 125.2, 124.7, 121.8, 121.2, 121.1, 118.6, 114.6, 111.6 and 109.9 ppm. In the mass spectrum **(Figure 5.I.20)** molecular ion peak observed at 364 [M+H]+, 386 [M+Na]+ which confirms the formation of desired molecule.

5.4 Conclusion:

Clean and ecofriendly synthesis of bis(indolyl)methane and tris indoline by the combination of natural surfactant *Zingiber zerumbet* and ultrasound irradiation. This perspective gives the nontoxic, environmentally safe and cheap synthesis of indole derivatives. Ultrasonic irradiation saves the reaction time and significant improvement in the yield. Therefore, this protocol highlights and follows various green chemistry principle such as avoid toxic chemicals, harsh reaction condition, use of green solvent and methodology.

5.5 Experimental

General

Zingiber zerumbet fruit of zinger is collected from botanical garden of Y.C.I.S. Satara, India. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. Melting points of products were determined on electrical melting point apparatus EQ 730A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR,^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer using DMSO as solvent and TMS

as internal reference. Sonication was performed in a SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz.

Collection of "Zingiber zerumbet" fruit extract:

Zingiber zerumbet is the fruit of the zinger available in the botanical garden of Y.C.I.S. Satara. Extract was removed by hand from fruit, which is a viscous liquid known as "shampoo zinger" and also a natural surfactant. It was collected and stored in freezers and used in reactions as a natural surfactant.

Synthesis of bis(indolyl)methane:

Taken 5ml zingiber zerumbet extract in round bottom flask add to it aldehyde (1mmol) and indole (2mmol) then flask placed in bath sonicator and which was irradiated under ultrasonic irradiation at room temperature for appropriate time (Table 1.) until reaction was completed which was monitored by tlc (nHexane: EA 8:2), colored solid product was formed after completion of reaction which filtered and recrystallized in ethyl acetate getting pure product.

Synthesis of tris-indoline:

Taken 5ml zingiber zerumbet extract in round bottom flask add to it isatin (1mmol) and indole (2mmol) then flask placed in bath sonicator and which was irradiated under ultrasonic irradiation at room temperature for appropriate time (Table 1.) until reaction was completed which was monitored by tlc (nHexane: EA 8:2), solid product was formed which was filtered and recrystallized in ethyl acetate getting pure product.

Spectral data of synthesized compounds:

1) 3,3-Bis(indolyl)-4-nitrophenylmethane (Table 5.I.2 Entry 2): Yellow Solid, M.P. 221-223°C. IR (KBr): ῡ= 3426, 2925, 1741, 1637, 1550, 1457, 1342, 1016, 744 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 10.38 (s, 2H), 8.0-7.9 (d, 2H), 7.67-7.66 (d, 2H), 7.46-7.42 (d, 2H), 7.30-7.27 (d, 2H), 7.20-7.17 (t, 2H), 7.02-6.97 (t, 2H), 6.84-6.79 (s, 2H), 5.88-5.87 (s, 1H); ^{13}C NMR: 153.0, 146.17, 136.99, 129.58, 126.62, 124.18, 123.43, 121.43, 119.12, 118.74, 116.98, 111.79 ppm.

2) 4-Chlorophenyl-3,3-bis(indolyl)methane (Table 5.I.2 Entry 3): Pink Solid, M.P. 76-78°C. IR (KBr): $\bar{\upsilon}$ = 3409, 2927, 1623, 1521, 1488, 1455, 1276, 1207, 1069, 1010, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.39-7.34 (m, 4H), 7.30-7.26 (m,4H), 7.21-7.19 (t, H), 7.05-7.01 (t, 2H), 6.61 (s, 2H), 5.87 (s, 1H); ^{13}C NMR: 142.6, 136.7, 131.7, 130.1, 128.4, 126.9, 123.6, 122.1, 120.7, 119.8, 119.3, 111.2, 44.6 ppm.

3) 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole) (Table 5.I.2 Entry 13): Pink Solid, M.P. 210-212°C. IR (KBr): $\bar{\upsilon}$ = 2921, 1589, 1511, 1338, 1004, 736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d,2H), 7.30 (d, 2H), 7.27 (m, 4H), 7.25 (d, 2H), 7.02 (d, 2H), 6.52 (s,2H), 5.86 (s,1H), 3.70 (s, 6H); ^{13}C NMR: 143.0, 137.40, 131.64, 130.03, 128.33, 127.44, 126.22, 121.55, 119.91, 118.75, 117.70, 109.0, 39.48, 32.71 ppm. HRMS (ESI) m/z = 383.1320 $[M-H]^-$.

4) 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole) (Table 5.I.2 Entry 14): Yellow Solid, M.P. 215-217. IR (KBr): $\bar{\upsilon}$ = 3050, 2927, 1484, 1224, 1172, 1148, 1093, 996, 813, 732, 673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 2H), 7.52 (d, 2H), 7.32 (m, 4H), 7.26 (d, 2H), 7.02 (d,2H), 6.55(s, 2H), 5.98(s, 1H), 3.72(s,6H); ^{13}C NMR: 152.31, 146.47, 137.42, 129.47, 128.29, 127.03, 123.62, 121.82, 119.64, 119.03, 116.60, 109.33, 40.07, 32.78 ppm.

5) [3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 1): Yield: 92%; white solid; M. P.=314-318ºC, IR (KBr, cm^{-1}): 3428, 3324, 1707, 1613, 1468, 1106, 932, 736; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.28 (s, 2H), 10.13 (s, 1H), 7.26-7.24 (m, 4H), 7.20-7.12 (t, 1H), 7.11-7.08 (t, 1H), 6.96-6.93 (m, 3H), 6.91-6.82 (m, 3H), 6.80 -6.71 (s, 2H); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 179.8, 141.3, 137.6, 134.9, 127.8, 126.0, 125.2, 124.7, 121.8, 121.2, 121.1, 118.6, 114.6, 111.6, 109.9, 53.2 ppm. HRMS (ESI) m/z = 386.1241 $[M + Na]^+$.

6) 5'-nitro-[3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 2): Yield: 90 %; white solid, M.P. 298-299°C; IR (KBr, cm^{-1}): 3384, 2917, 1707, 1519, 1454, 1175, 1018, 744; ^{1}H NMR (400 MHz, DMSO-*d6*) δ10.84 (s, 1H), 10.29 (s, 2H), 8.09 (dd, 1H), 8.06 (d, 1H), 7.98-7.49 (d, 2H), 7.04-7.00 (m, 3H), 6.99-6.97 (m, 2H), 6.95-6.83 (s,

2H), 6.79-6.75 (m,2H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 179.6, 148.1, 142.5, 137.5, 135.6, 125.8, 125.6, 124.8, 121.5, 120.7, 120.2, 118.8, 112.0, 111.6, 110.1, 53.0 ppm.

7) **5'-methoxy-[3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 4):** Yield: 88 %; white solid, M.P. 290-292^{o}C; IR (KBr, cm^{-1}): 3384, 2928, 1686, 1484, 1191, 734, 572; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.91 (s,2H), 9.66 (s, 1H), 7.62 (d, 2H), 7.40 (d,2H), 7.24 (m, 2H), 7.07-6.94 (m, 4H), 6.87 (m,1H), 6.74 (s, 2H), 3.58 (s,3H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 179.4, 155.0, 137.3, 136.2, 134.9, 128.6, 126.0, 125.9, 124.6, 121.7, 118.5, 114.6, 112.0, 11.1, 110.2, 55.6, 53.2 ppm.

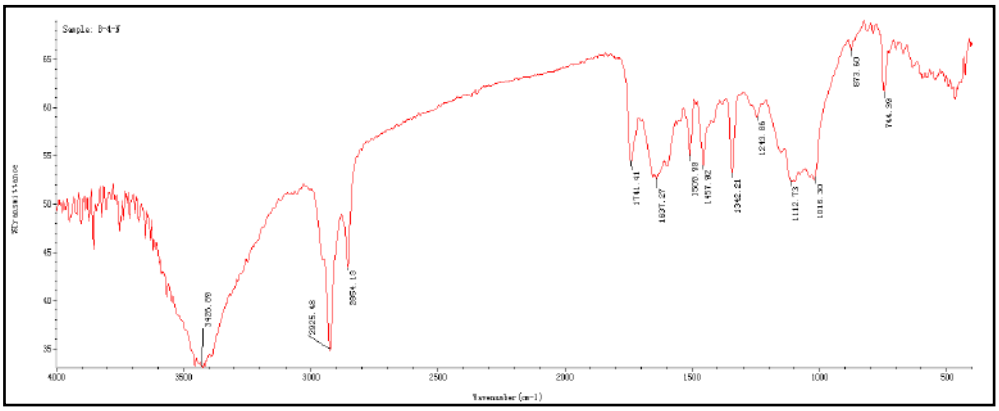


Figure 5.I.8: IR Spectra of 3,3-Bis(indolyl)-4-nitrophenylmethane.

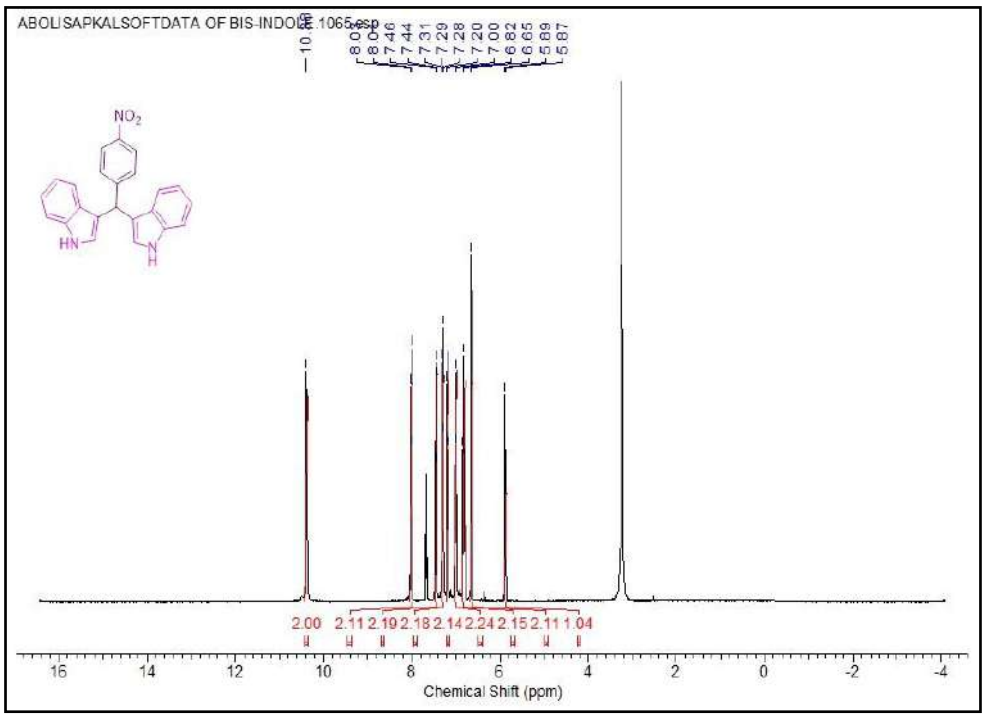


Figure 5.I.9: ^{1}H NMR of 3,3-Bis(indolyl)-4-nitrophenylmethane.

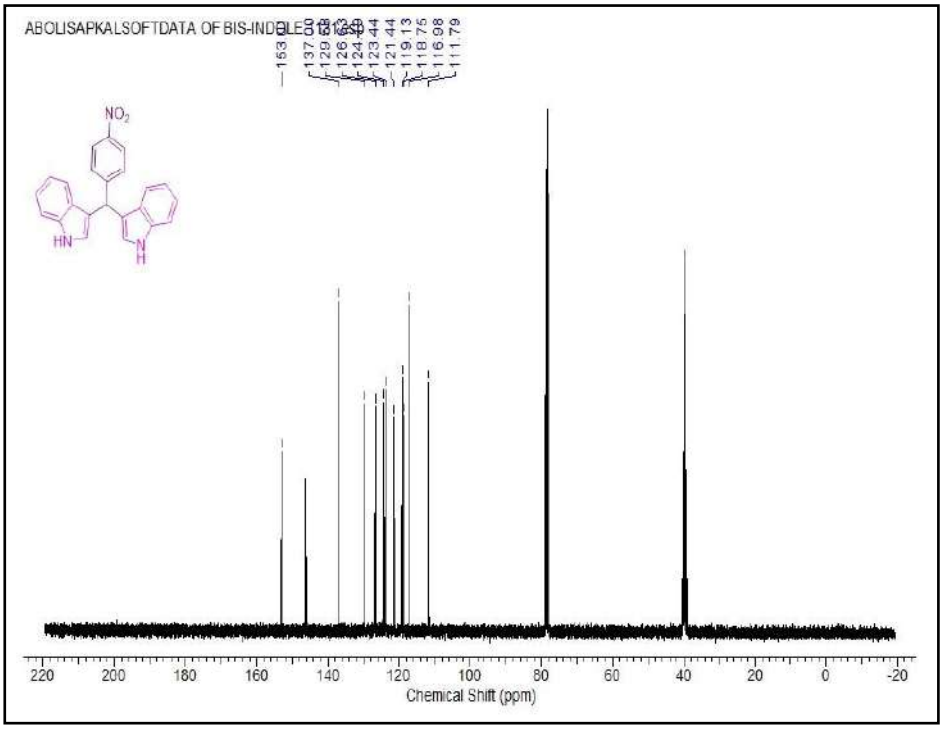


Figure 5.I.10: ^{13}C NMR of 3,3-Bis(indolyl)-4-nitrophenylmethane.

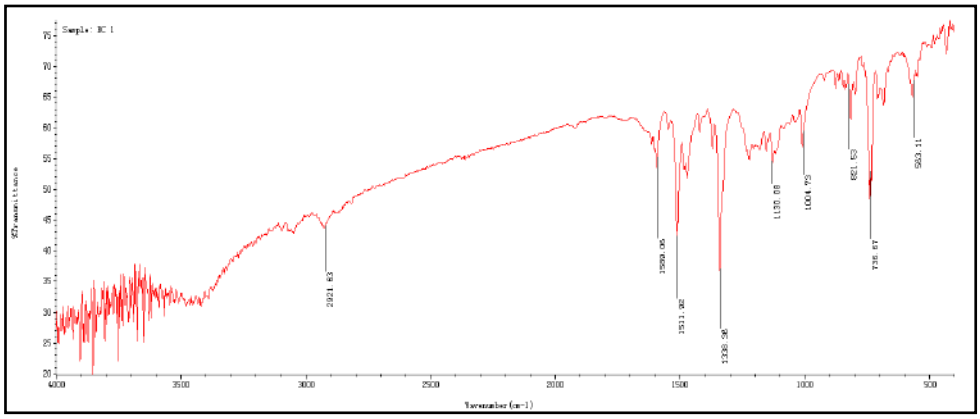


Figure 5.I.11: IR spectrum of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

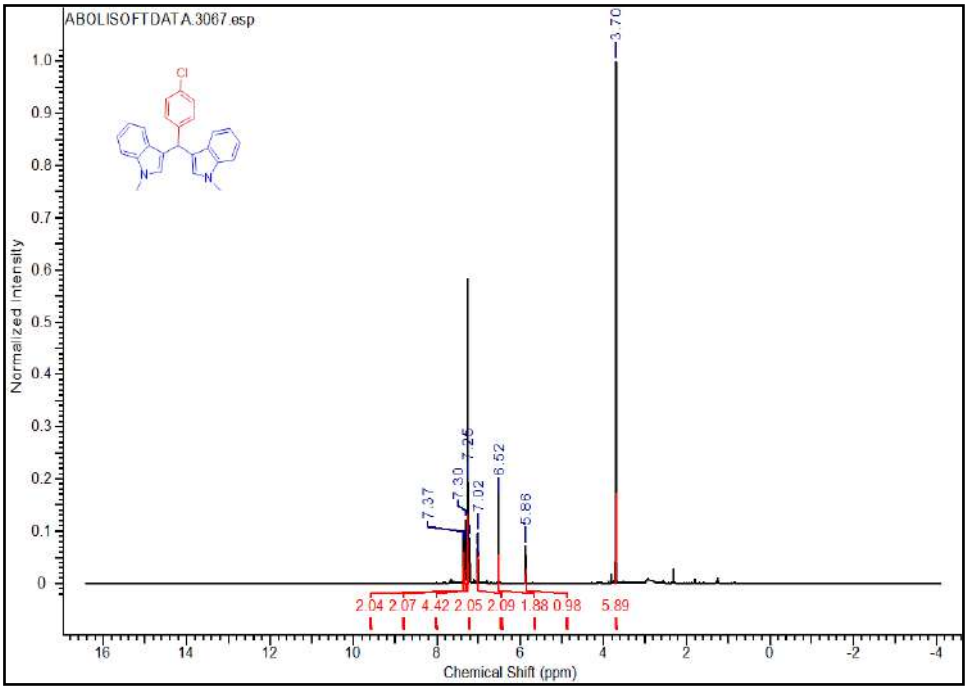


Figure 5.I.12: ^{1}H NMR of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

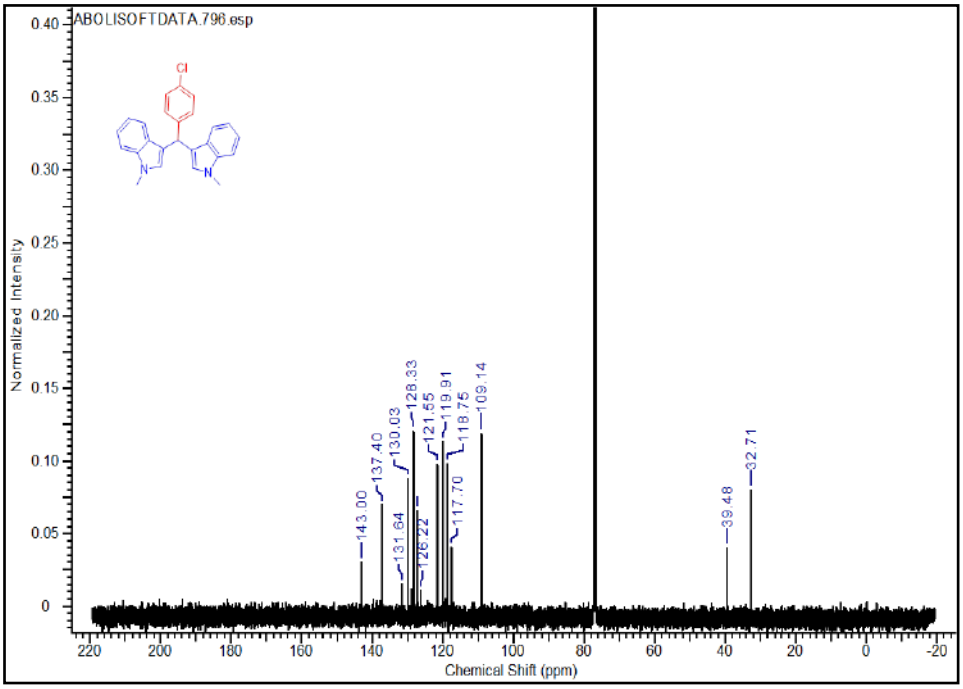


Figure 5.I.13: ^{13}C NMR of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

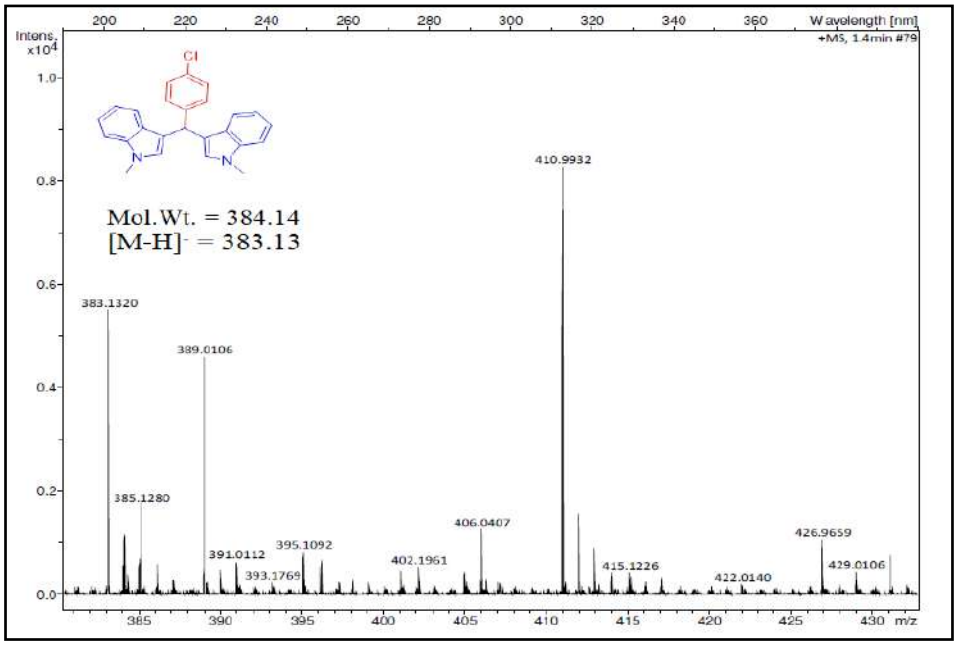


Figure 5.II.14 HRMS of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

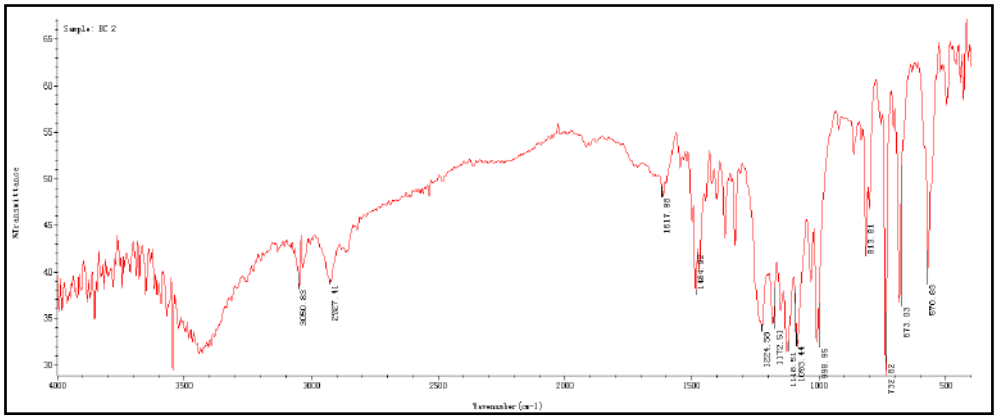


Figure 5.I.14: IR spectrum of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

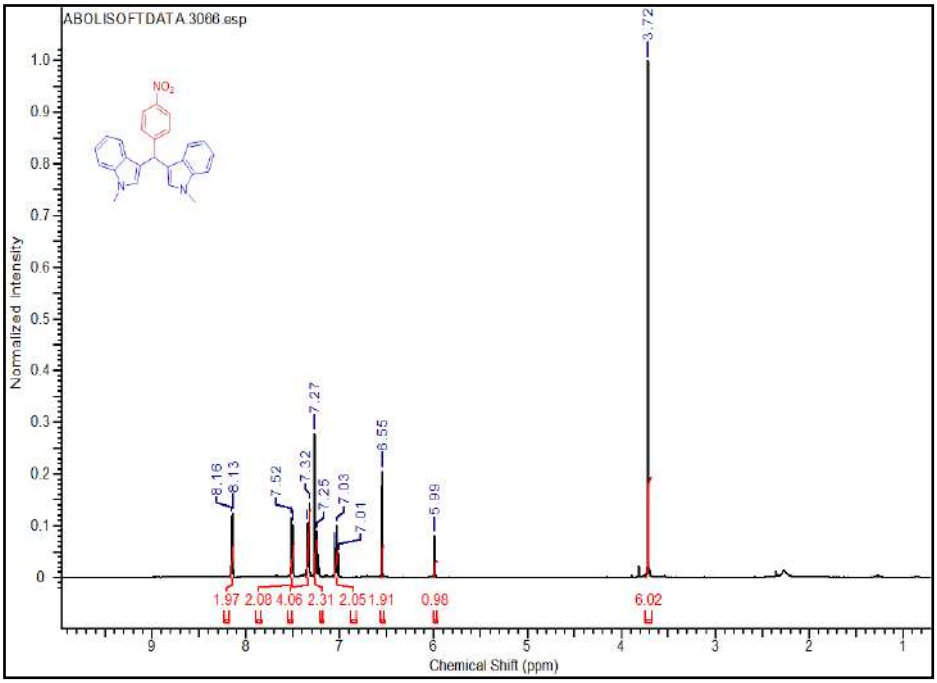


Figure 5.I.15: ^{1}H NMR of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

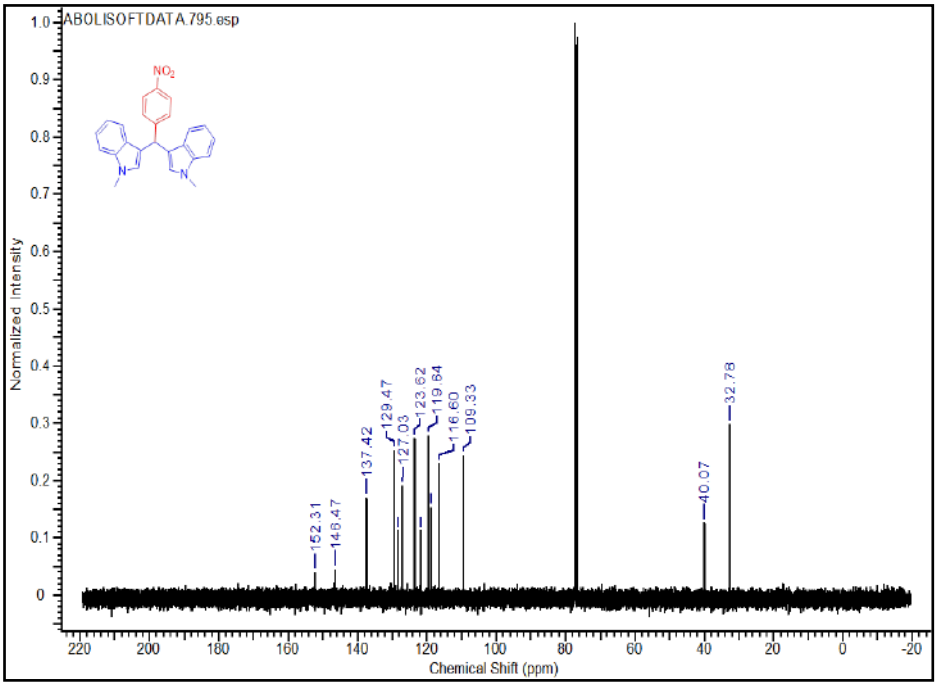


Figure 5.I.16: ^{13}C NMR of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

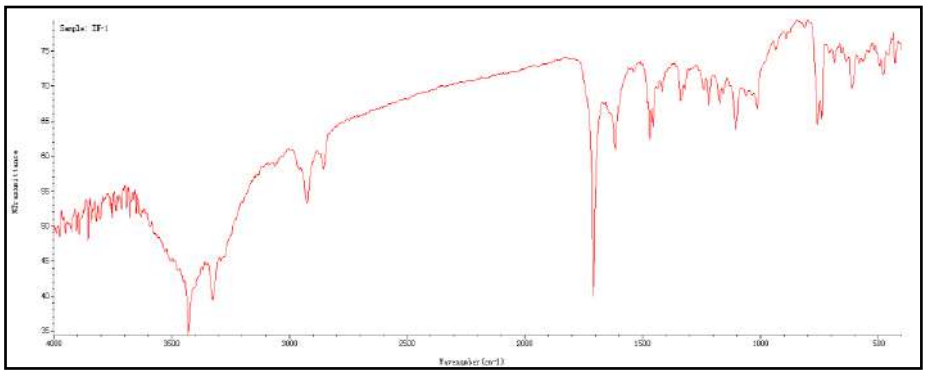


Figure 5.I.17: IR Spectra of [3,3':3',3"-terindolin]-2'-one

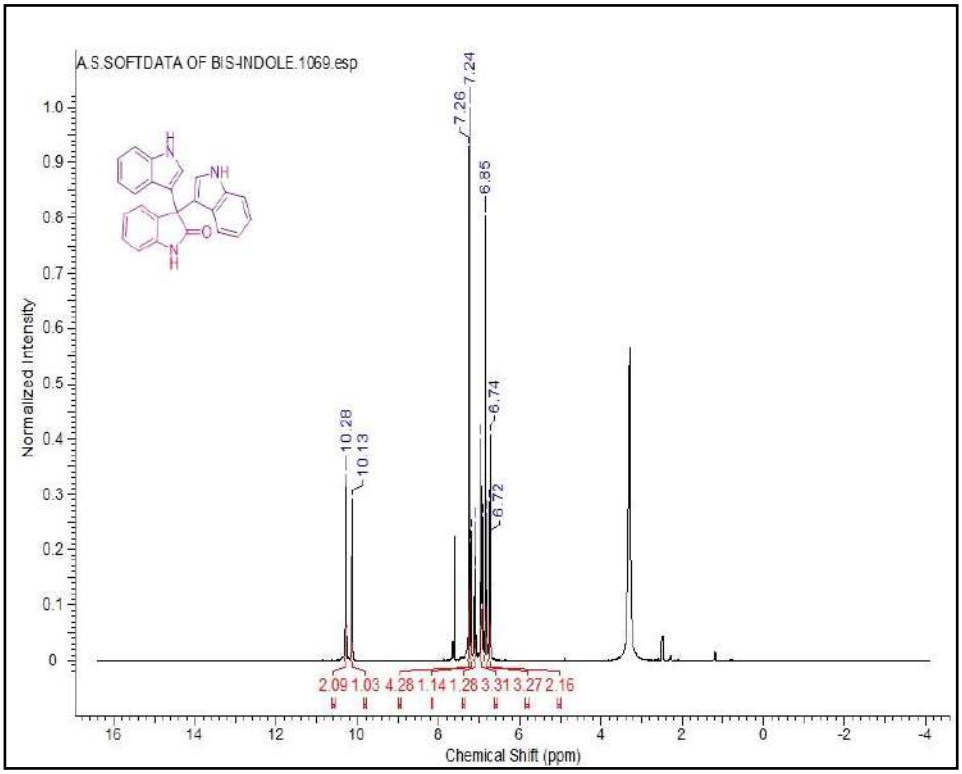


Figure 5.I.18: ^{1}H NMR of [3,3':3',3"-terindolin]-2'-one

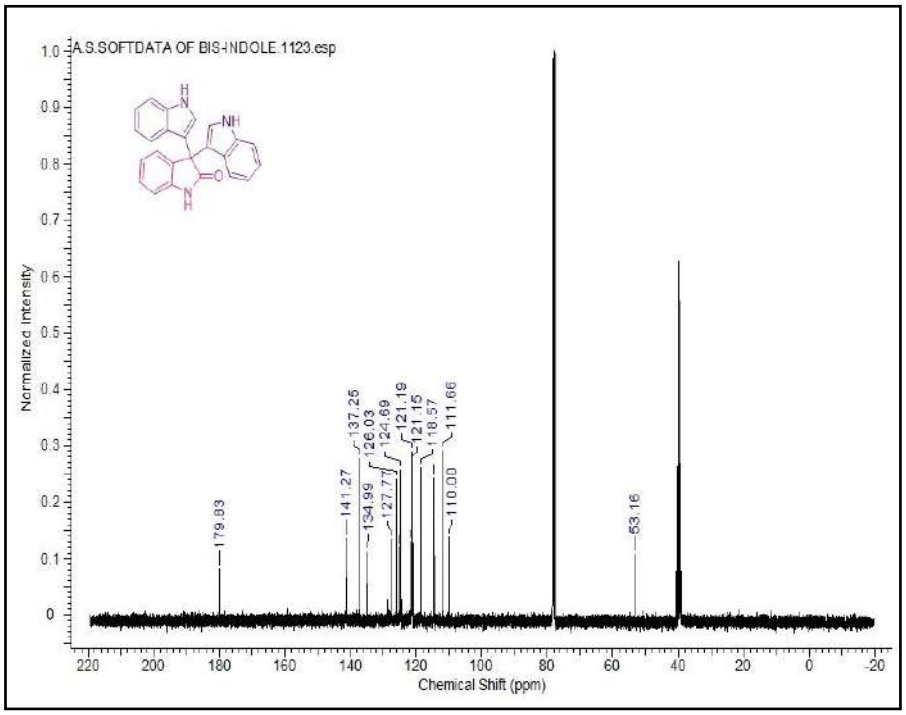


Figure 5.I.19: ^{13}C NMR of [3,3':3',3"-terindolin]-2'-one

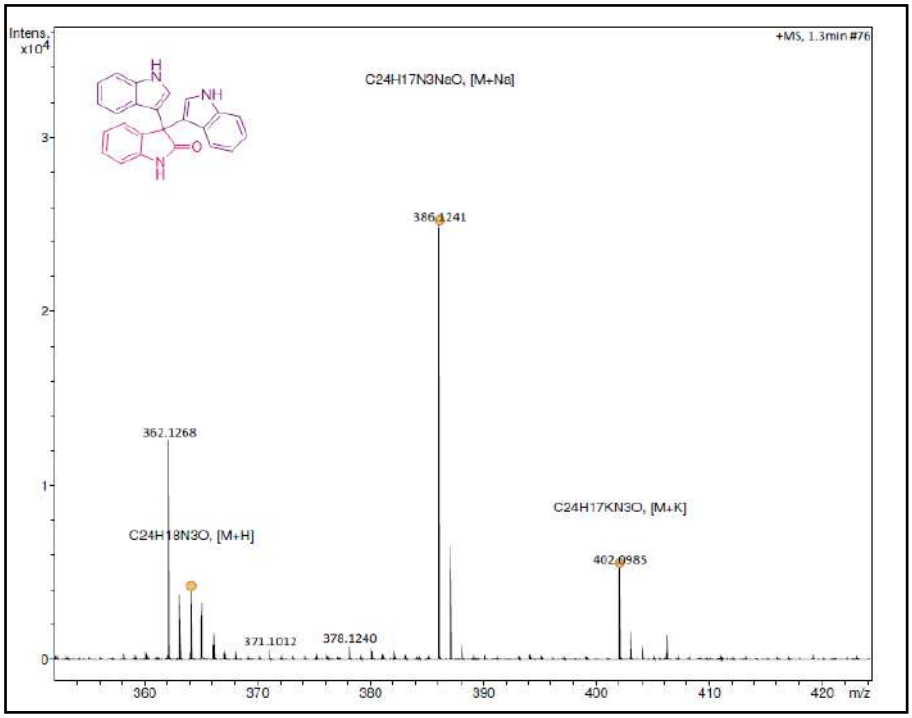


Figure 5.I.20 HRMS of [3,3':3',3"-terindolin]-2'-one.

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CHAPTER 5

Section II

Bio-catalyzed Synthesis of Spirooxindole Derivatives

5.II.1 Introduction

The spirooxindole system is one of the important parts of heterocyclic chemistry. The spirooxindole ring constitutes the core structure of pharmaceuticals and natural products, including cytostatic alkaloids such as spirotryprostatins A, B, and Strychnofoline. Spirotryprostatins B is well known anti-cancer agent found in the *Aspergillus fumigatus* fungus along with additional indole-based alkaloids [1]. The shrub *Strychnosusambarensis* was source of spiro-oxindole alkaloid from which Strychnofoline isolated [2] **(Figure 5.II.1)**. They were appealing synthetic scaffolds due to their unique structural diversity and highly influenced pharmacological activities [3]. The structural relationship shown by spiro compounds in which at least two molecular rings with one common atom are known as spiro compounds. They consisting heterocyclic or fully carbocyclic rings which are connected through two or three ring to one atom [4]. This structural diversity attracts chemists and biologists for their synthesis under novel protocols.

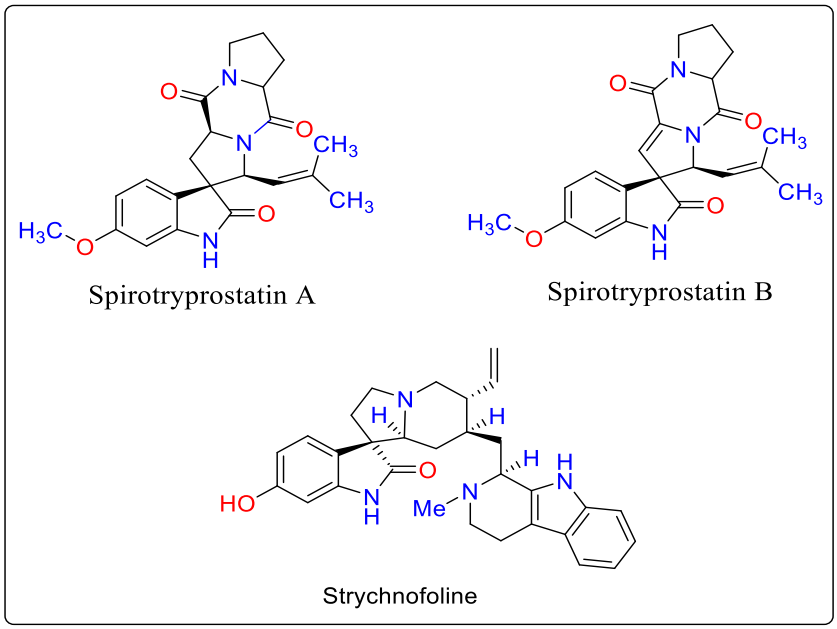


Figure 5.II.1. Structures of biologically active spirooxindole alkaloids.

Spirooxindole was discovered in the Amazon rainforest and tropical areas of South and Central America in the Uncariatomentosa plant, also known as Cat's Claw, and was first isolated from the plant Rubiaceae and Apocynaceae alkaloids family of natural products [5], [6]. The structural arrangement of spirooxindole molecule constituting two basic structural subunits: one of which is multiple functionalized oxindole, which can take acts as donors and acceptors for hydrogen bonding; the another is a cycloalkyl or heterocyclic compounds fused at the C-3 position of oxindole [7]. According to this unique special chemical structural arrangement it gives wide contribution in medical world as result of anti-cancer [8], anti-inflammatory [9], anti-microbial [10], antioxidant [11], anti-viral [12], anti-HIV [13], anti-malarial agents [14] and local anesthetic properties[15].

Spirooxindole is a very prominent structural motif present in several natural products such as horsfline [16], alantrypinone [17], citrinadin [18], welwitindolinone, elacomine and isoelacomine [19] that having potential pharmacological activities **(Figure 5.II.2)**.

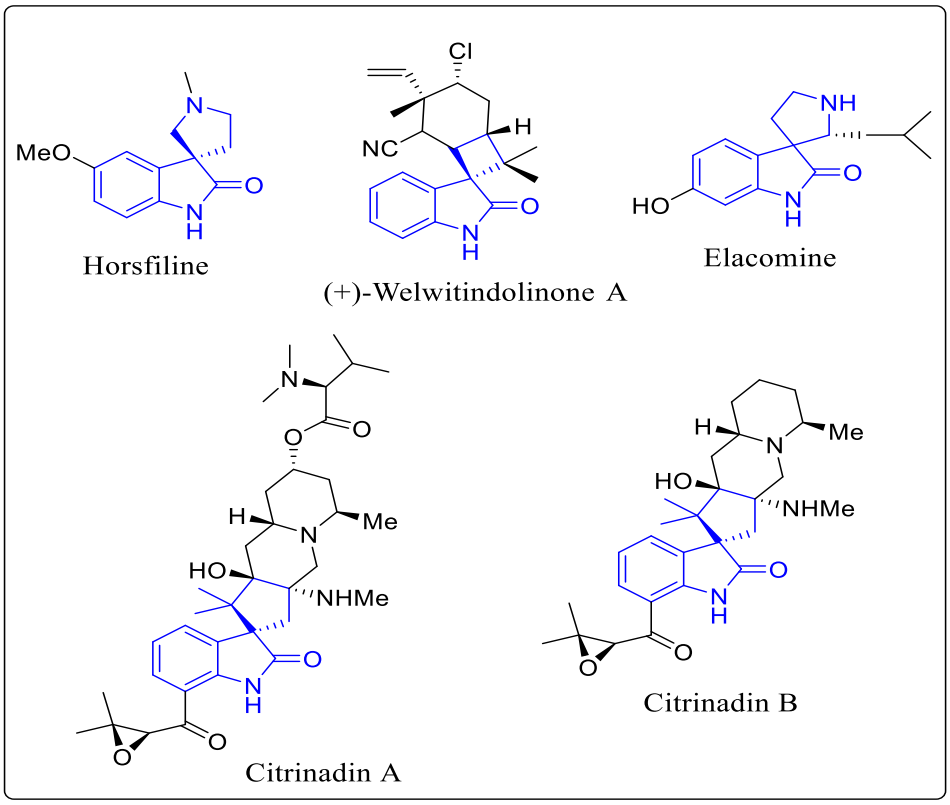
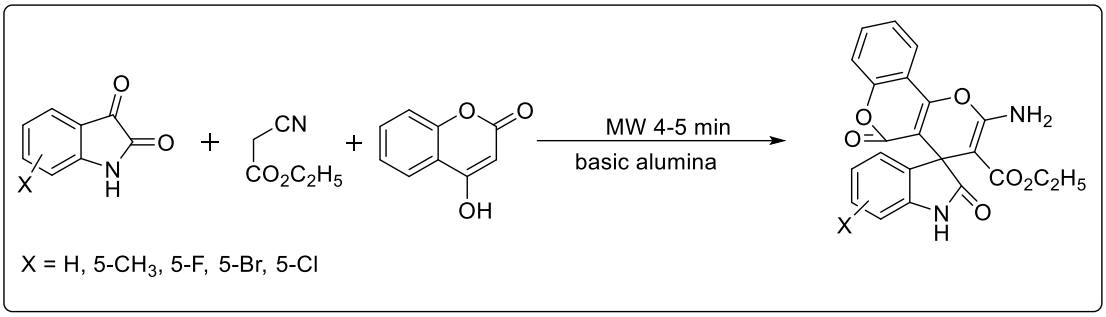


Figure 5.II.2 Spirooxindole based natural products.

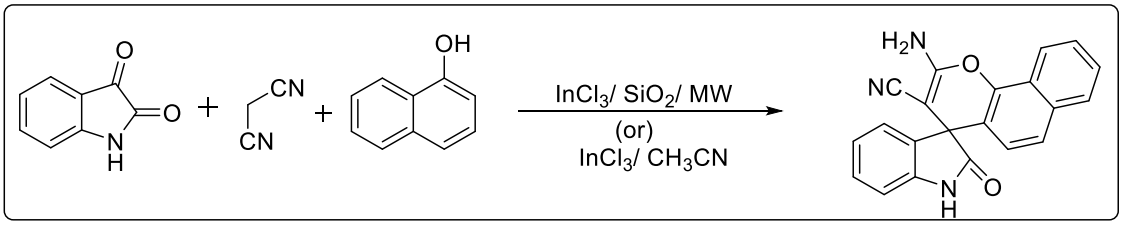
Following literature shows the how researcher constantly and innovatively involved in the synthesis of spirooxindole;

Multicomponent one-pot diastereoselective synthesis of spiro scaffold was developed by Dandia Anshu and co-workers [20] under microwaves. Reaction assisted by microwave between the reactants 1*H*-indole-2,3-dione, ethyl cyanoacetate and 4-hydroxycoumarin produces good amount products within short period of time **(Scheme 5.II.1)**.



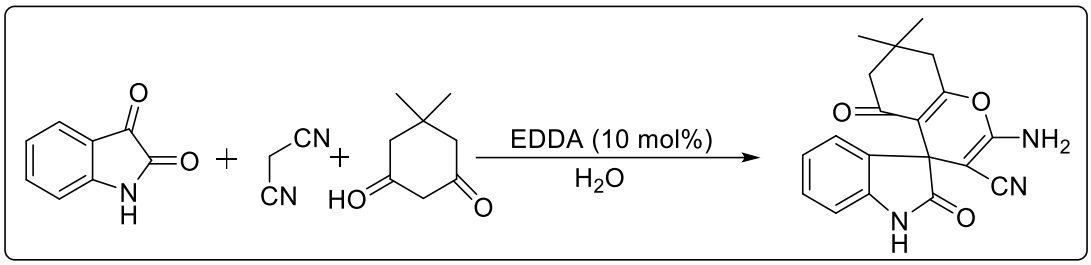
Scheme 5.II.1

Shanthi et al. [21] newly reported $InCl_3$-catalyzed, simple and efficient one-pot multi-component technique for the production of spirooxindoles by conventional heating and under solvent-free microwave irradiations **(Scheme 5.II.2).**



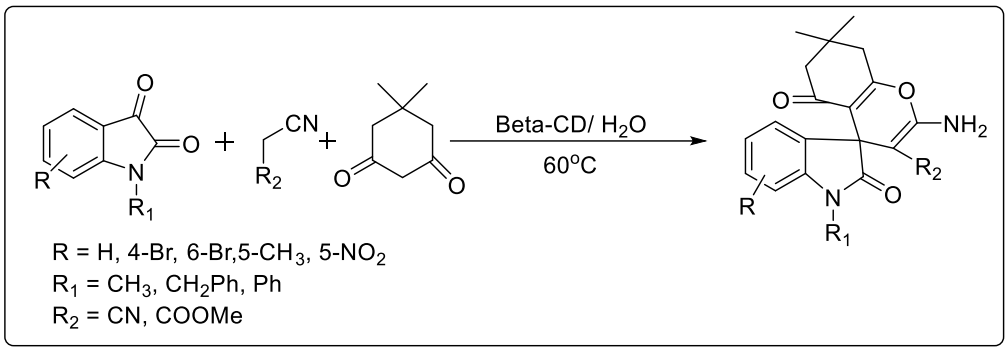
Scheme 5.II.2

G. Sri Hari and Y. Rok Lee [22] use ethylenediamine diacetate as a catalyst for the preparation of spirooxindole compounds in an aqueous medium. A three-component reaction mixture containing isatins, malononitrile, and 1,3-dicarbonyl compounds catalyzed by ethylenediamine diacetate (EDDA) in an aqueous medium affords spirooxindole compounds in high yield **(Scheme 5.II.3).**



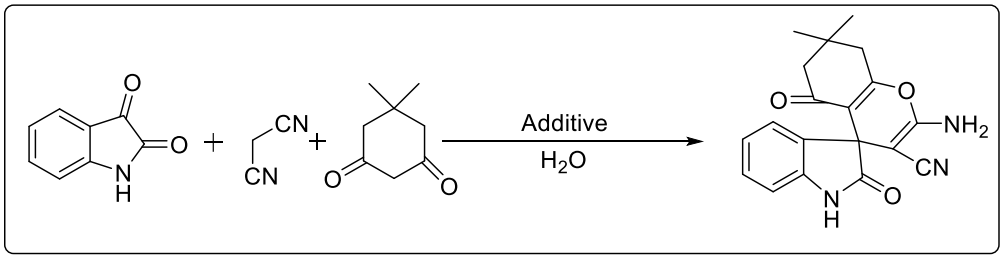
Scheme 5.II.3

Sridhar Regati and co-workers [23] reported supramolecular synthesis of spirooxindoles catalyzed by β-cyclodextrin in aqueous medium. Synthesis of various derivatives of spirooxindoles from isatin, malononitrile and 1,3-dicarbonyl compounds in high yield catalyzed by β-cyclodextrin **(Scheme 5.II.4)**.



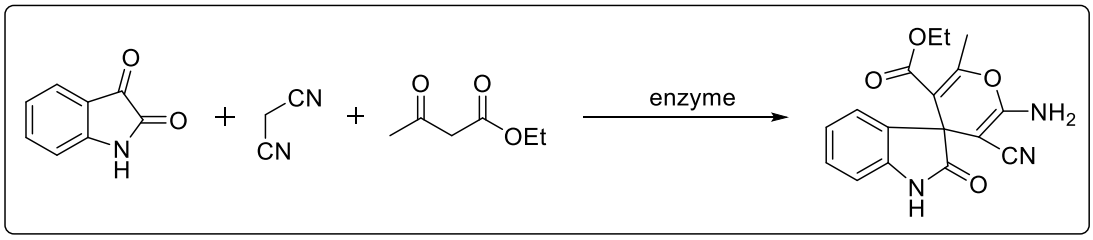
Scheme 5.II.4

Lewis base-surfactant-combined catalyst utilized in the synthesis of spirooxindoles in aqueous micellar media demonstrated by Li-Min Wang and co-workers [24]. Simple reaction takes place between isatin, malononitrile, and 1,3-dicarbonyl compounds produces the desired spirooxindoles derivatives with good results such as yield and less time **(Scheme 5.II.5)**.



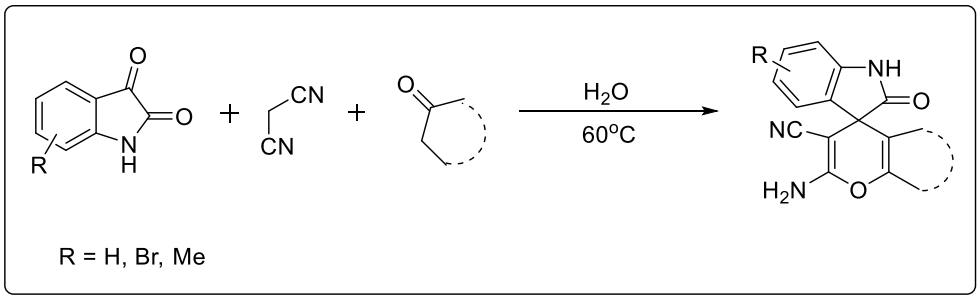
Scheme 5.II.5

She-Jie Chai et al. [25] developed enzyme catalyzed one-pot synthesis of spirooxindole derivatives. Reaction goes by Knoevengel condensation followed by Michael addition in presence of porcine pancreas lipase (PPL) produces desired product with good yield **(Scheme 5.II.6)**.



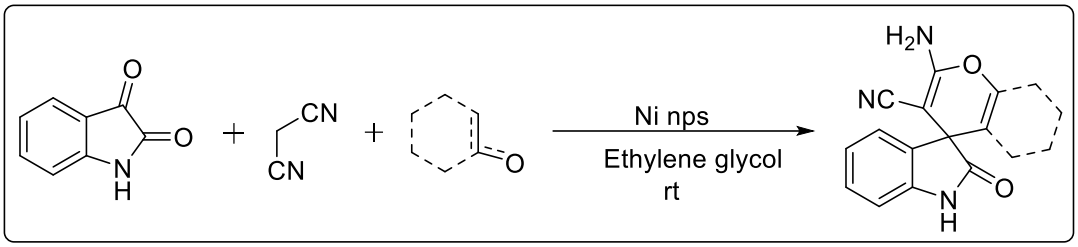
Scheme 5.II.6

Catalyst-free methodology developed by Liqin Zhao and co-workers [26] for the synthesis spirooxindole molecules in aqueous medium. The catalyst free protocol saves the environment from hazardous chemicals and decrease the final cost of synthesis **(Scheme 5.II.7)**.



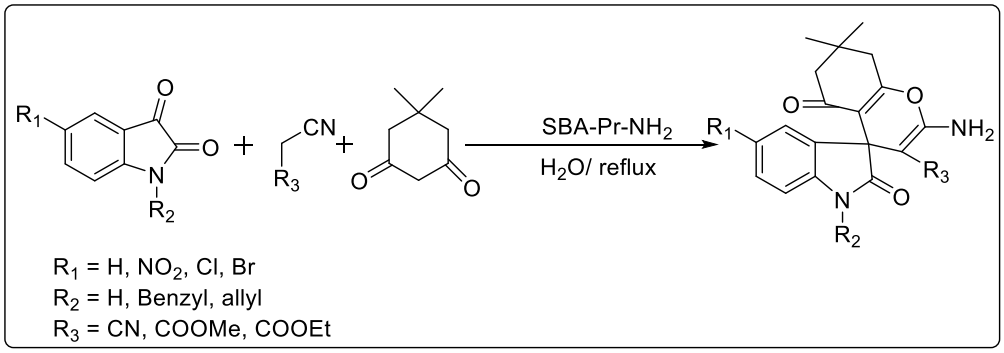
Scheme 5.II.7

Jitender M. Khurana and Sneha Yadav [27] first synthesized polyethylene glycol (PEG)-stabilized Ni nanoparticles. Use those highly effective PEG-stabilized Ni nanoparticles for the preparation of biologically important spiropyrans from the condensation between malononitrile, different 1,3-dicarbonyl compounds, and ninhydrin/acenaphthoquinone/isatin **(Scheme 5.II.8)**.



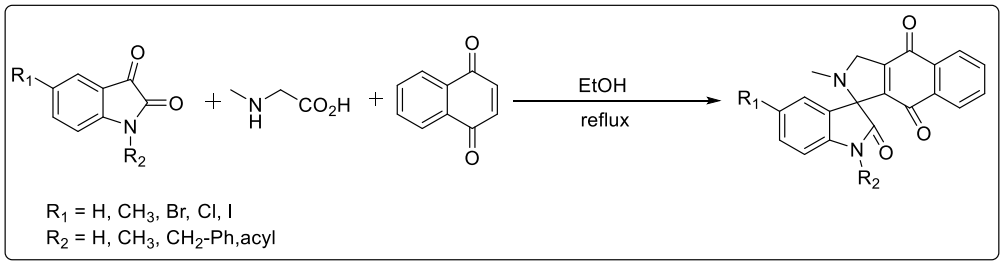
Scheme 5.II.8

Amino-functionalized SBA-15 type mesoporous silica utilized by Ghodsi M. Ziarani et al. [28] for the preparation of spirooxindoles. Amino-functionalized SBA-15 (SBA-Pr-NH_2) has been basic heterogeneous nanocatalyst can be easily handled and removed from the reaction mixture by simple filtration **(Scheme 5.II.9)**.



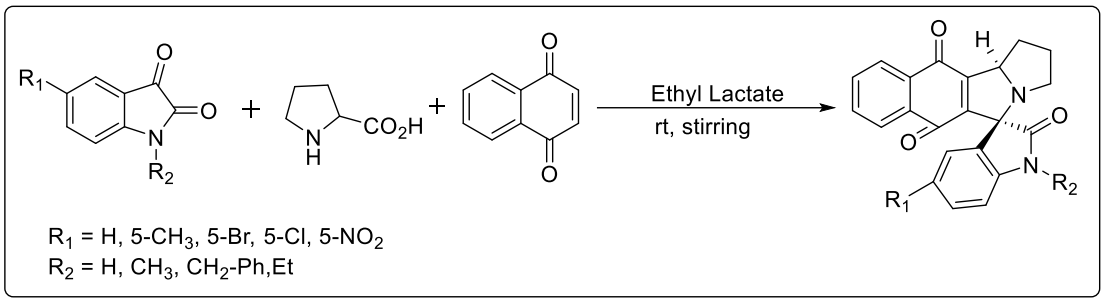
Scheme 5.II.9

Gangaru Bhaskar et al. [29] demonstrated series of novel spirooxindole products. Evaluated their antimicrobial activity against bacteria and fungi. Derivatives of spirooxindoles have been prepared by 1,3-dipolar cycloaddition of an azomethine ylide obtained from isatin with the dipolarophile 1,4-naphthoquinone **(Scheme 5.II.10)**.



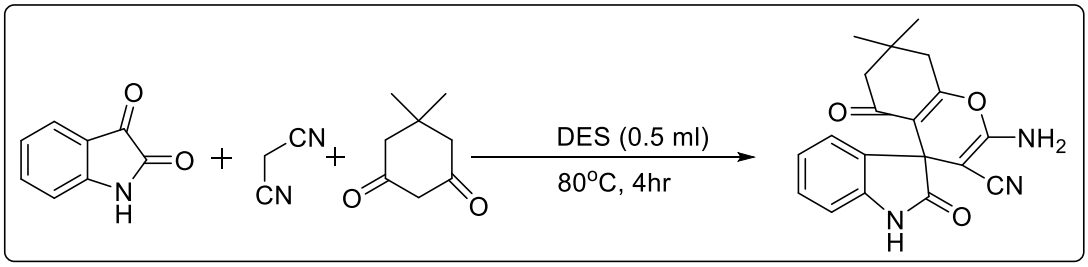
Scheme 5.II.10

Ethyl lactate was assessed as a bio-based green solvent by Anshu Dandia and co-workers [30] for the 1,3-dipolar cycloaddition reaction between azomethine ylide obtained from substituted isatin and proline with naphthoquinone as a dipolarophile, which produces spiro-pyrrolo[2,1-a]isoindole derivatives **(Scheme 5.II.11)**.



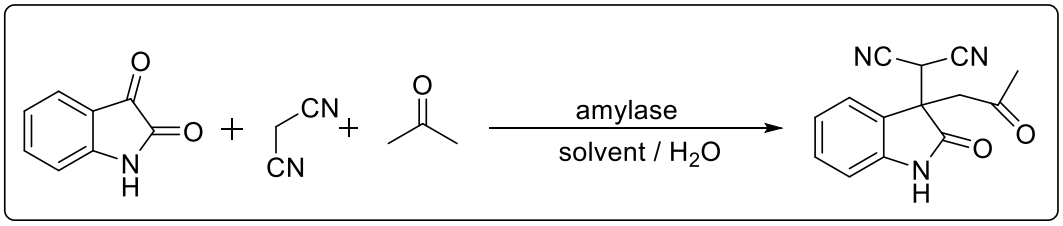
Scheme 5.II.11

Najmedin Azizi et al. [31] synthesised spirooxindole in deep eutectic solvent. Biodegradable urea:ChCl as deep eutectic solvent gives the environmental friendly preparation of spirooxindole derivatives **(Scheme 5.II.12)**.



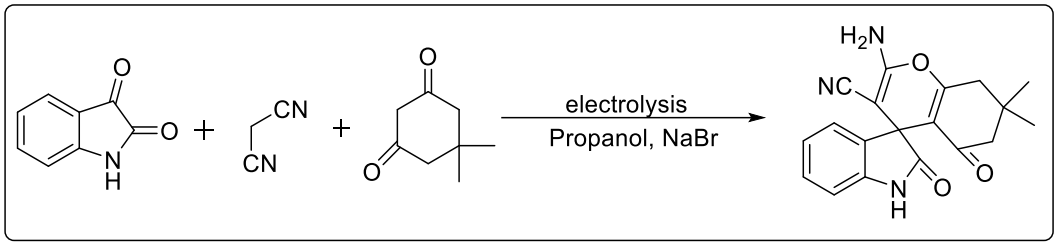
Scheme 5.II.12

Tao He et al. [32] reported α-Amylase as a biocatalyst for the production of 3,3'-oxindoles and spirooxindole pyrans. α-Amylase obtained from hog pancreas displayed biocatalytic activity and promote the synthesis within short time with excellent yield **(Scheme 5.II.13)**.



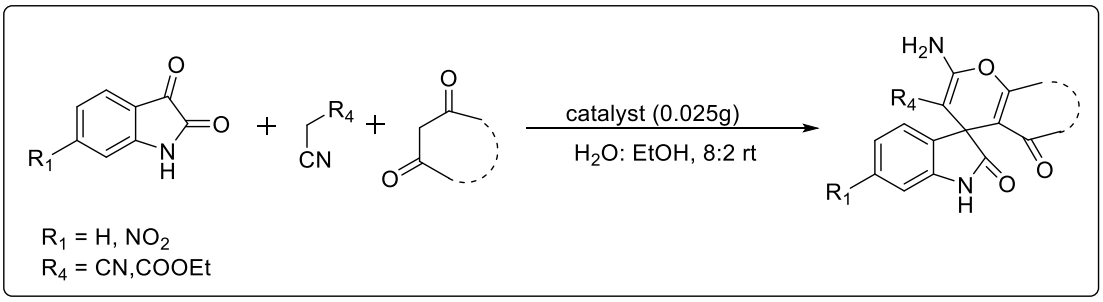
Scheme 5.II.13

Zahra Darvish et al.[33] synthesized nanoparticles of spirooxindole derivatives from isatins, malononitrile, and dimedone by electrocatalysis. Electrogenerated base of the anion of propanol from undivided cell containing the sodium bromide as an electrolyte **(Scheme 5.II.14)**.



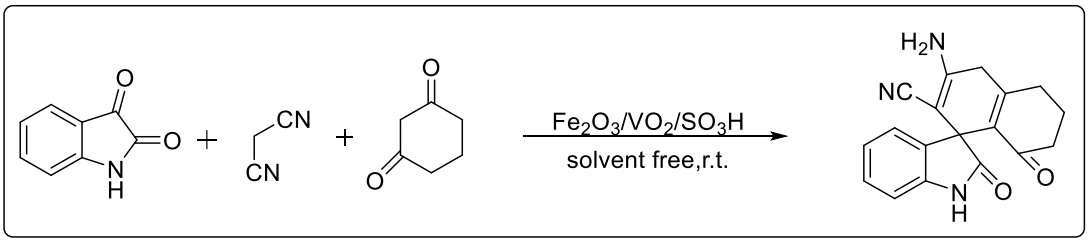
Scheme 5.II.14

Halloysite nanoclay play effective role for developing the green synthesis of spirooxindole compounds was reported by Samahe Sadjadi and co-workers [34]. Heteropolyacids, HPAs decorated Halloysite Nanoclay - HPA@HNTs-IMI-SO_3H is heterogeneous catalyst prepare by combining natural clay ($Al_2(OH)_4Si_2O_5 \cdot 2H_2O$) and ionic liquid **(Scheme 5.II.15)**.



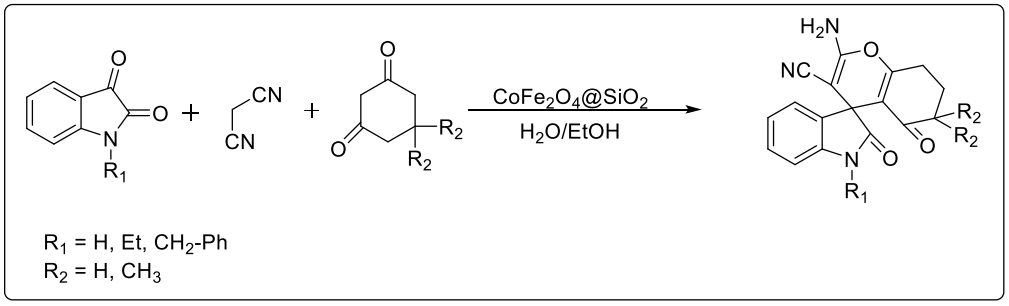
Scheme 5.II.15

Hassan Hassani et al. [35] reported synthesis of spirooxindole derivatives catalysed by sulfonic acid supported on Fe_2O_3/VO_2 nanocatalyst. The production of spirooxindole derivatives by reacting the isatin, 1,3-cyclohexadiene and malononitrile without solvent **(Scheme 5.II.16)**.



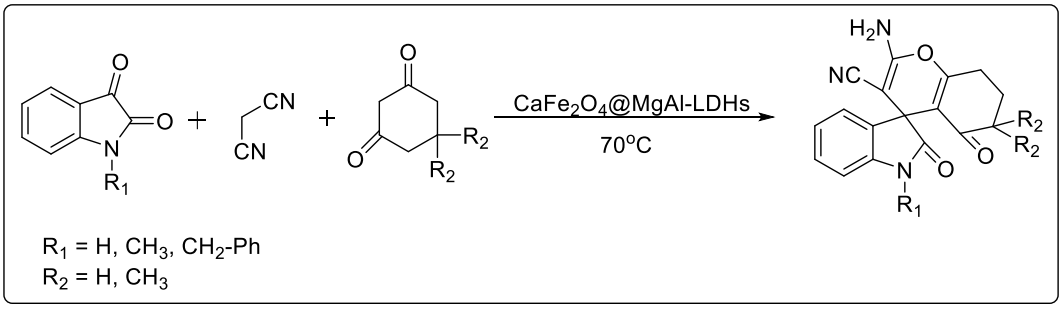
Scheme 5.II.16

$CoFe_2O_4@SiO_2$: A magnetically reutilizable heterogeneous catalyst prepared by Kaveh Hemmat and co-workers [36] is applied for the synthesis of spirooxindole. The synthesis of spirooxindoles by reacting malononitrile, various isatins with 1,3-dicarbonyl compounds in presence of $CoFe_2O_4@SiO_2$ catalyst **(Scheme 5.II.17)**.



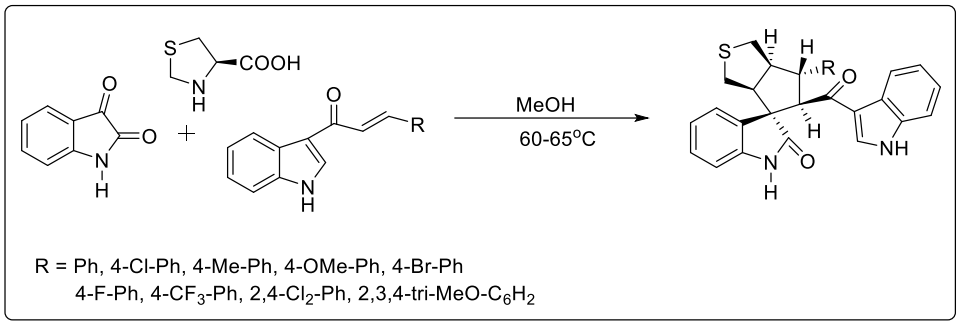
Scheme 5.II.17

Mehri Salimi et al. [37] design magnetically recyclable $CaFe_2O_4@MgAl$-LDH nanoparticles and use it for synthesis of spirooxindole scaffolds. They check biological activity of synthesized compound which shows promising chemotherapeutic agent is spirooxindole **(Scheme 5.II.18)**.



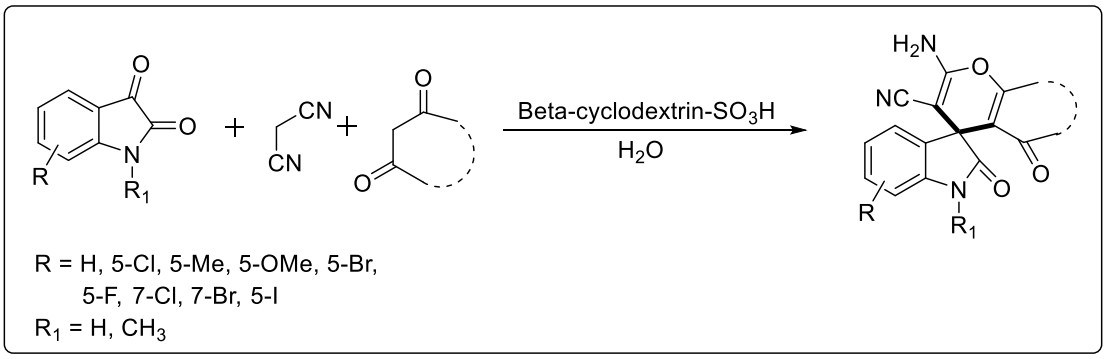
Scheme 5.II.18

Preparation of new series of thiazolo-pyrrolidine–(spirooxindole) tethered to 3-acylindole developed by M. S. Islam and co-workers [38]. Reaction between 3-acetyl indole with isatin, and l-4-thiazolidinecarboxylic acid in methanol produces desired spirooxindole in high yield **(Scheme 5.II.19)**.



Scheme 5.II.19

Fangzhou Xu et al. [39] reported simplistic development of spiroindoline molecules as potential anti-viral agent. Present protocol was disclosed appropriate and easily accessible β-cyclodextrin-SO_3H promoted strategy for development of varieties spiro indoline compounds in aqueous media **(Scheme 5.II.20)**.

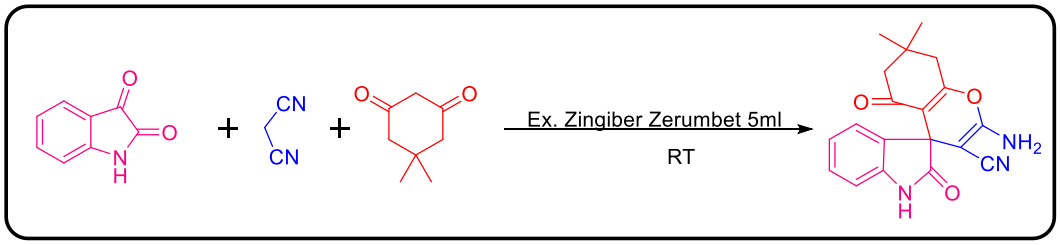


Scheme 5.II.20

5.II.2 Present work:

Bio-surfactant is a greener agent which conserve the ecosystem from addition of toxic chemical in to nature and give contribution in decreasing environmental pollution [40]. Medium for this reaction is a natural extract therefore reaction goes in greener environment and gives contribution to sustain the green principal with saving economy by using naturally available extract of *Zingiber zerumbet* and also environment by using bio-surfactant for such organic transformation (Scheme 5.II.21).

Surfactants are surface active agent, biosurfactant or natural surfactant are microbial amphiphiles extracted from plant, animals or microorganisms. *Zingiber zerumbet* (L.) Roscoe ex Sm., widely known as 'Shampoo Ginger' is an aromatic and rhizomatous herb which crop up naturally in the Himalaya and the western ghats of India [41].



Scheme 5.II.21. Synthesis of Spirooxindole derivatives in bio-surfactant.

5.II.3 Result and Discussion:

Initially we go for the selection of suitable solvent under the green perspective as result of water, ethanol, methanol, combination of water: ethanol (1:1) in which reacting equimolar quantities of isatin, malononitrile with dimedone without catalyst as the model reaction. But our effort not getting expected result, yield is poor and consumed longer time. We perform model reaction at also high temperature in similar solvent in absence of catalyst, we get nearly good results **(Table 5.II.1 and 5.II.2)**.

But our aim was developed a greener protocol for the synthesis of spirooxindole derivatives under the circumstances of green chemistry principles such as preventing the utilization of toxic or hazardous chemical substances like as catalyst, solvents, and give priorities to the use of biodegradable catalyst as well as reaction medium available from renewable feedstocks. Therefore, from previous research outcome we try to perform synthesis of spirooxindole in the extract of *Zingiber zerumbet*. We perform the model reaction by taking equimolar quantities of isatin, malononitrile with dimedone in 5ml extract of *Zingiber zerumbet*. We got the superlative results over the other solvents without use of catalyst. Shampoo zinger is extract of *Zingiber zerumbet*, fruit of zinger which acts as bio-surfactant. Inflorescence of plant containing viscous juice which is rich in surfactant is known as ginger shampoo [42]. There is saponin present in the viscous juice of *Zingiber zerumbet*, due to which it shows surfactant properties. Surfactants are detergents that are effective at dissolving non-polar compounds. This

efficiency in dissolving non-polar compounds has made aqueous surfactant systems better alternatives to harmful organic solvents in various applications. Surfactant forms the micelles, which are similar to colloidal aggregation. This micelle formation occurs above the critical micelle concentration (CMC). A low concentration of CMC means requiring less surfactant to decrease the surface tension. Initially, the clear reaction mixture turned turbid, which indicates the formation of micelle-like colloidal aggregation. During this aggregation, reactant molecules are brought into close proximity to each other and interactions take place between them, which form the organic transformation between them.

Under the optimized condition, series of spirooxindole derivative were synthesized by using different active methylene groups **(Table 5.II.4)**. In a comparison study of most reported works, this work demonstrated a high yield (92%) with a greener protocol that saves the environment and economy by using bio-surfactant in a short period of time **(Table 5.II.3)**.

Table 5.II.1: Solvent Screening for synthesis of spirooxindole derivatives.

Entry	Solvent	Time	Yield (%)
1	Water	72 hrs.	20
2	Ethanol	24 hrs.	40
3	Ethanol and Water (1:1)	48 hrs.	40
4	Methanol	48hrs	trace

Table 5.II.2: Optimization of reaction condition and solvent screening for synthesis of spirooxindole derivatives.[a]

Sr. No.	Solvent	Temperature	Time	Yield[b] (%)
1	water	60°C	10hrs	30
2	Water: ethanol	60°C	6-7hrs	50
3	ethanol	40°C	3-4hrs	70
4	Extract of *Zingiber zerumbet*	Room temperature	15 min	92

5	Extract of *Zingiber zerumbet*	40°C	15 min	90
6	Ex. Of Z.z. and ethanol (1:1)	Room temperature	15min	91

a) Reacting substrates: equimolar quantities of isatin, malononitrile and dimedone.

b) Isolated yield of product.

Spirooxindoles were synthesized by means of one-pot condensation of equimolar quantities of isatin, malononitrile and active methylene compounds by using 5ml extract of *Zingiber zerumbet* as bio-surfactant at room temperature (**Scheme 5.II.21**).

Table 5.II.3: Comparative study of published works versus present work for the synthesis of spirooxindole.

Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield (%)	References
1	Nano-ZnO	CH_3CN	Reflux 82°C	6 hrs.	93	[43]
2	-	Urea:ChCl	80°C	6 hrs.	95	[31]
3	Acylase Amano (AA)	Ethylene glycol	50°C	4 hrs.	97	[44]
4	SiO_2@g-C_3N_4	EtOH: H_2O (1:1)	Reflux	3 min	95	[45]
5	Borax	EtOH	78°C	2 hrs	94	[46]
6	$CoFe_2O_4$@SiO_2	EtOH: H_2O (1:1)	80°C	5 min	98	[47]
7	$CaFe_2O_4$@Mg Al-LDH	H_2O	70°C	4 min	97	[28]
8	Extract of *Zingiber zerumbet*	-	RT	15 min	92	This work

The proposed mechanism for the synthesis of spirooxindole derivative (4) was conceptualized in **figure 5.II.3**. The process of synthesis of spirooxindoles represents a typical cascade reaction in which first step is Knoevenagel condensation between isatin and malononitrile which gives isatylidene malononitrile (5). Then, Michael addition of dimedone on isatylidene malononitrile (5) gives intermediate (6), then followed by intramolecular cycloaddition of hydroxyl group to the cyano moiety gives corresponding spirooxindole product (4).

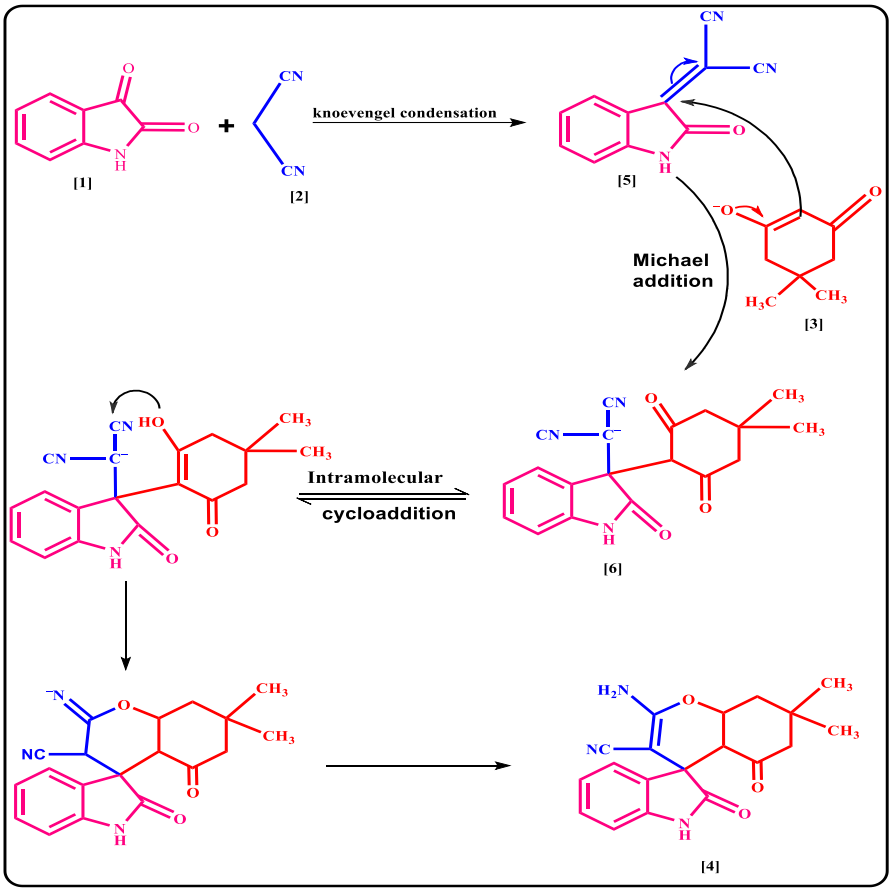
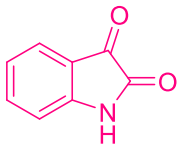
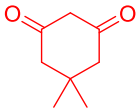
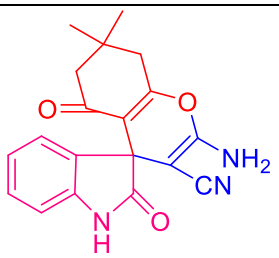
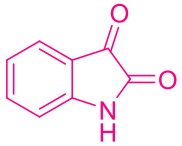
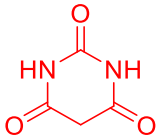
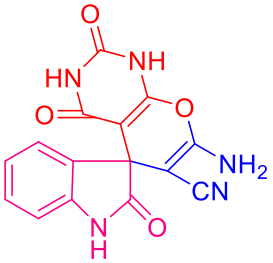
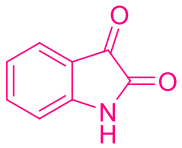
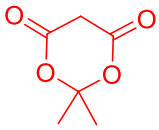
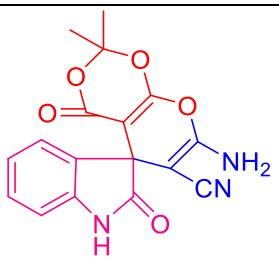
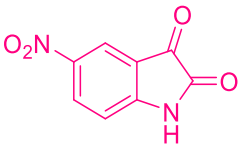
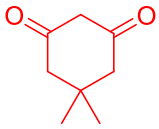
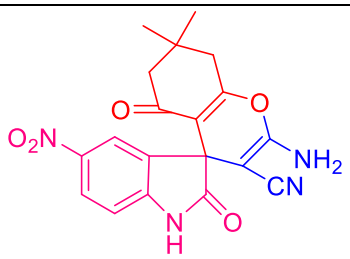
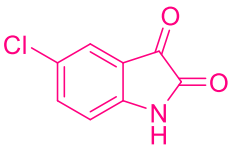
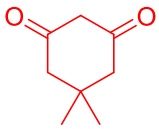
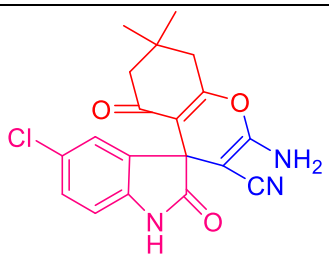
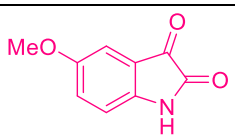
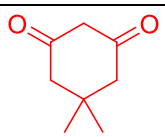
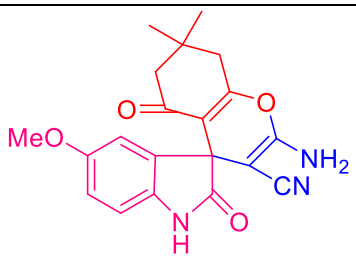
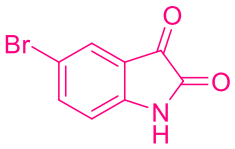
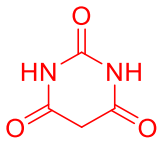
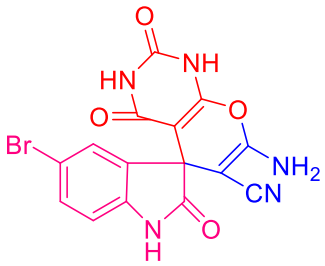
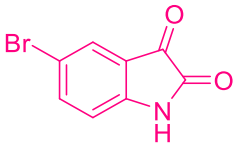
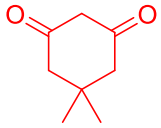
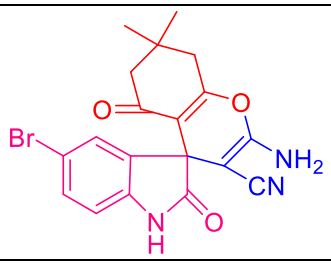
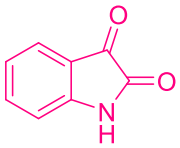
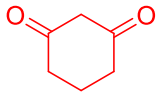
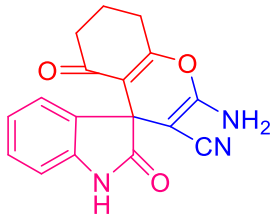
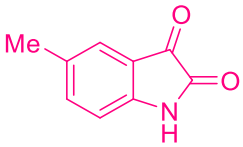
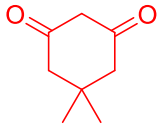
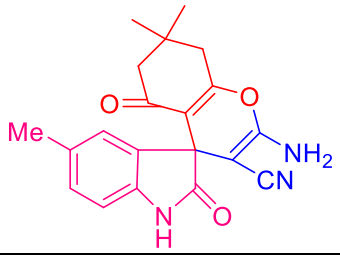


Figure 5.II.3. Plausible reaction mechanism for synthesis of spirooxindole in aqueous hydrotropic medium.

Table 5.II.4: Synthesis of spirooxindole derivatives in bio-surfactant at room temperature.

Sr. No.	Isatin	Active methylene	Product	MP (°C) [Lit]	Yield (%)[b]
1				286-288 [25]	92
2				>300 [48]	86
3				187-190 [31]	85
4				>300 [25]	94
5				290-292 [25]	91
6				285-287 [25]	91

7				225-227 [48]	90
8				>300 [49]	90
9				282-283 [25]	92
10				281-283 [49]	93

b) Isolated yield of product.

Recyclability of Bio-Surfactant, *Zingiber zerumbet*:

We use only 5ml extract of *Zingiber zerumbet* for the reaction. After completion of reaction filter the product and collect the filtrate and reuse for the reaction and monitoring any effect on yield but there is no much more effect on yield. After third cycle slightly decrease in yield. Therefore, reuse of extract is very important step as an environmental point of view which maintain the sustainability **(Figure 5.II.4)**.

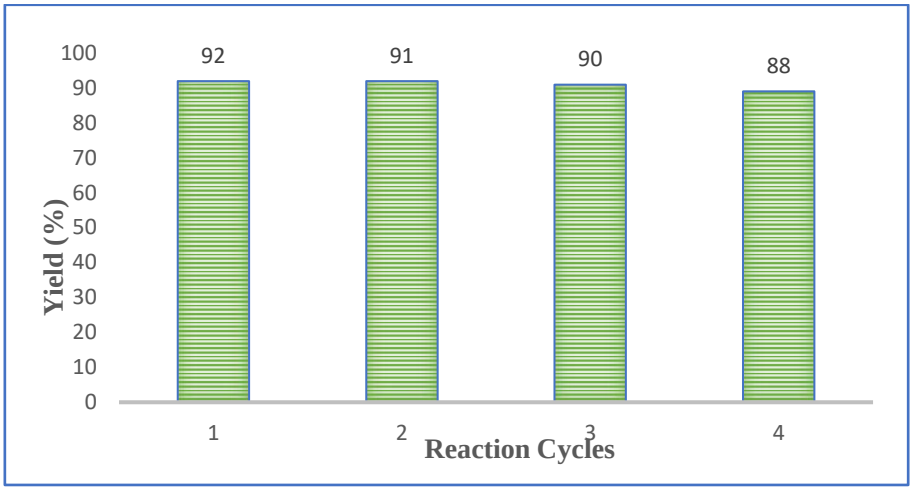
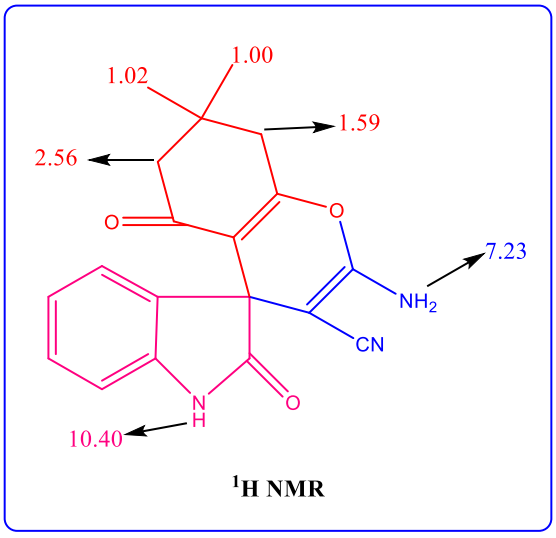
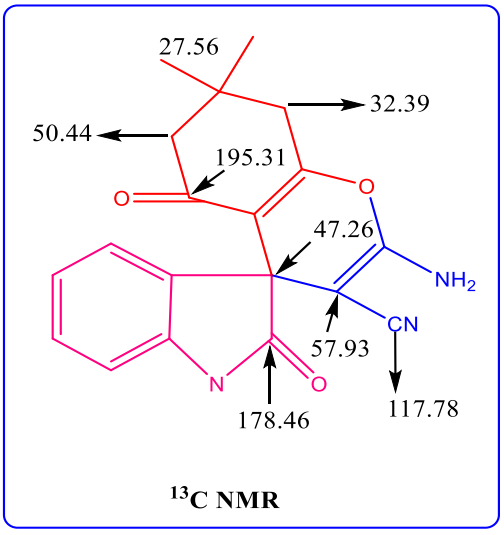


Figure 5.II.4. Recyclability of bio-surfactant

Characterization of products

1) 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile (Table 5.II.4 Entry 1):

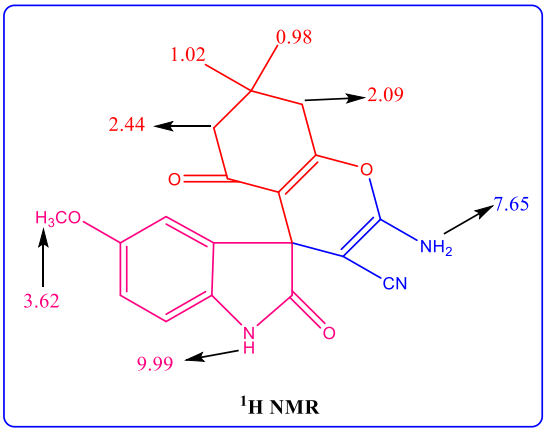


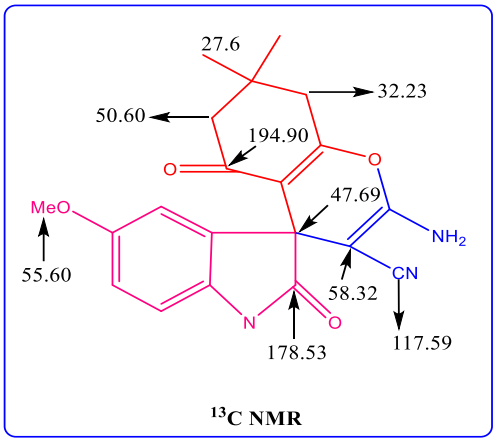


IR spectrum **(Figure 5.II.5)** exhibits characteristic peaks for asymmetric and symmetric stretching frequency of -NH_2 group at 3384 and 3318 cm^{-1} respectively. The characteristic peak for nitrile group was observed at 2194 cm^{-1}. The carbonyl functional group of dimedone moiety was show absorption at 1720 cm^{-1} while amide carbonyl group of indole ring showed a peak at 1681cm^{-1}. ^{1}H NMR spectrum **(Figure 5.II.6)** showed the two sharp singlet due to methyl protons at δ 1.00 and 1.03 ppm. Four protons of the methylene group resonate at δ 2.56 and 1.59 ppm, which exhibits multiplate. The protons of primary amine were resonated at δ 7.23 ppm while the NH proton of indole ring was observed at δ 10.40 ppm. The remaining chemical shift δ

values from 6.80-7.14 ppm were attributed to four protons in the aromatic region. The ^{13}C NMR spectrum **(Figure 5.II.7)** possessed the peak at δ 27.46 ppm due to methyl group while two methylene carbon exhibits peak at δ 32.39 and 50.44 ppm. The carbon which was adjacent to nitrile group appeared at δ 57.93 ppm, however the carbon of nitrile group resonated at δ 117.78 ppm. The carbon at spiro position was observed at δ 47.26 ppm. The unsaturated carbonyl carbon was found at δ 195.31 ppm although the carbonyl carbon of amide in the indole ring resonated at δ 178.46 ppm. The rest of the carbons resonated at δ 164.58, 159.20, 142.48, 134.85, 128.60, 123.44 and 122.12 ppm in the aromatic region. Mass spectrum **(Figure 5.II.8)** gave peak at m/z: 336.9 $[M+H]^+$.

2) 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`- indoline]-3-carbonitrile (Table 5.II.4. Entry 10):





The IR spectrum **(Figure 5.II.8)** shows absorption frequencies at 3384 and 3309 cm^{-1} for asymmetric and symmetric stretching vibrations of the NH_2 group. The nitrile group shows corresponding absorption band at 2188 cm^{-1} while conjugated carbonyl group appeared at 1718 cm^{-1}. The ^1H NMR spectrum **(Figure 5.II.9)** exhibits two sharp singlets at δ 0.98 ppm and δ 1.02 ppm for six protons of two methyl group. three protons of methoxy group of isatin moiety shows sharp singlet at δ 3.62 ppm. The multiplate peaks at δ 2.44 ppm and δ 2.09 ppm were due to four protons of two methylene groups. the two protons of NH_2 were resonated at δ 7.65 ppm although proton of NH of indole ring was observed at δ 9.99 ppm. Out of three aromatic protons, one proton was resonated at δ 6.68 while remaining two protons was observed at δ 6.45 ppm and 6.66 ppm which was adjacent to OMe_3 group. Similarly, ^{13}C NMR spectrum **(Figure**

5.II.10) exhibits the peak at δ 27.66 due to carbon of methyl group. The carbon adjacent to nitrile group was observed at δ 58.32 ppm, however the carbon of nitrile resonated at δ 117.59 ppm. The carbon of spiro ring was found at δ 47.69 ppm. the carbon of methoxy group of isatin moiety resonated at δ 55.60 ppm. The unsaturated carbonyl carbon showed the value δ 194.90 ppm, while the carbonyl carbon of amide in the indole moiety resonated at δ 178.53 ppm. The rest of the aromatic carbons appeared at δ 164.19, 159.15, 155.46, 135.77, 135.58, 112.85, 111.33, 110.22 and 110.07 ppm. Mass spectrum **(Figure 5.II.15)** gave peak at m/z: 365 $(M)^+$.

5.II.4 Conclusion

In conclusion, we report a simple and new approach for the synthesis of spirooxindole, which represents a highly efficient and environmentally benign protocol. These methods provide a good alternative to synthetics as well as those that require harsh reaction conditions. Use of bio-surfactants generates an ecologically safe protocol that eliminates the addition of hazardous solvents to nature, which is more important during these environmentally conscious days. This is achieved by synthesizing spirooxindole in a natural medium. Therefore, we develop here a greener protocol for the synthesis of spirooxindole derivatives.

5.II.5 Experimental

General

^{1}H-NMR and ^{13}C-NMR of pure compounds were recorded on a Bruker 400 MHZ spectrometer using $CDCl_3$ as solvent and TMS is an internal standard. IR spectra were obtained with lambda FT-IR 750 spectrometer. Melting points were determined using a melting/boiling point electrical apparatus (EQ 730A-EQUIPTRONICS) and are uncorrected. All the chemicals required for synthesis were purchased from Loba and Sigma-Aldrich chemical companies and were used without further purification. *Zingiber zerumbet* fruit of zinger is collected from botanical garden of Y.C.I.S. Satara, India.

Collection of "*Zingiber zerumbet*" fruit extract:

Zingiber zerumbet is the fruit of the zinger available in the botanical garden of Y.C.I.S. Satara. Extract was removed by hand from fruit, which is a viscous liquid

known as "shampoo zinger" and also a natural surfactant. It was collected and stored in freezers and used in reactions as a natural surfactant.

General procedure for the synthesis of spirooxindole

Isatin (1mmol), Malononitrile (1mmol) and active methylene compound (1mmol) was added to a 5 mL extract of *Zingiber zerumbet* in the round bottom flask. Then reaction mixture was kept for stirring at room temperature for appropriate time until the completion of the reaction was monitored by TLC (nHexane: EA 8:2). The solid product was separated by simple filtration. The isolated crude product was recrystallized with ethanol.

Spectroscopic data for some target compounds are as follows

1) **2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile (Table 5.II.4. Entry 1):** IR (KBr): $\bar{\upsilon}$ = 3384, 3318, 3153, 2959, 2194, 1720, 1681, 1658, 1473, 1343, 1224, 1055, 903cm^{-1}; ^{1}H NMR (DMSO-d_6 , 400 MHz) ∂: 10.40 (s, 1H, NH), 7.23 (s, 2H, NH_2), 7.14 (t, 1H,ArH), 6.98 (d,1H,ArH), 6.89 (t, 1H, ArH), 6.80 (d, 1H, ArH), 2.56 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.03 (s,3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.31,178.46, 164.58, 159.20, 142.48, 134.85, 128.60, 123.44, 122.12, 117.78, 111.22, 109.57, 57.93, 5 0.94, 47.26, 32.39, 28.04, 27.46. MS (ESI): m/z 336.9 $[M+H]^+$.

2) **2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile (Table 5.II.4. Entry 7):** IR (KBr): $\bar{\upsilon}$ = 3286, 3154, 2958, 2190, 1725, 1652, 1479, 1349, 1220, 1056, 809 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.33 (s, 1H, NH), 7.02 (d, 1H, ArH), 6.83 (s, 1H, ArH), 6.72 (d, 1H, ArH), 6.62 (s, 2H, NH_2), 2.45 (s, 2H, CH_2), 2.10, (s, 2H, CH_2), 1.00(s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.07, 178.31, 164.59, 159,27, 141.16, 136.36, 128.28, 126.53, 123.43, 117.42, 110.95, 110.86, 57.48, 50.52, 47.50, 32.29, 27.99, 27.66.

3) **2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile (Table 5.II.4. Entry 10):** IR (KBr): $\bar{\upsilon}$ = 3384,3309, 3160, 2925, 2188, 1718, 166, 1600, 1484, 1351, 1205, 1029, ^{1}H NMR

(DMSO-d_6, 400 MHz) ∂: 9.99(s, 1H, NH), 7.65 (s, 2H, NH_2), 6.68 (d,1H, ArH), 6.66 (d, 1H, ArH), 6.45 (s, 1H, ArH), 3.62 (s, 3H, OCH_3), 2.44 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂:194.90, 178.53, 164.19, 159.15, 155.46, 135.77, 135.58, 117.59, 112.85, 111.33, 110.22, 110.07, 58.32, 55.60, 50.60, 47.69, 32.23, 28.33, 27.66. MS (ESI): m/z 365 $(M)^+$.

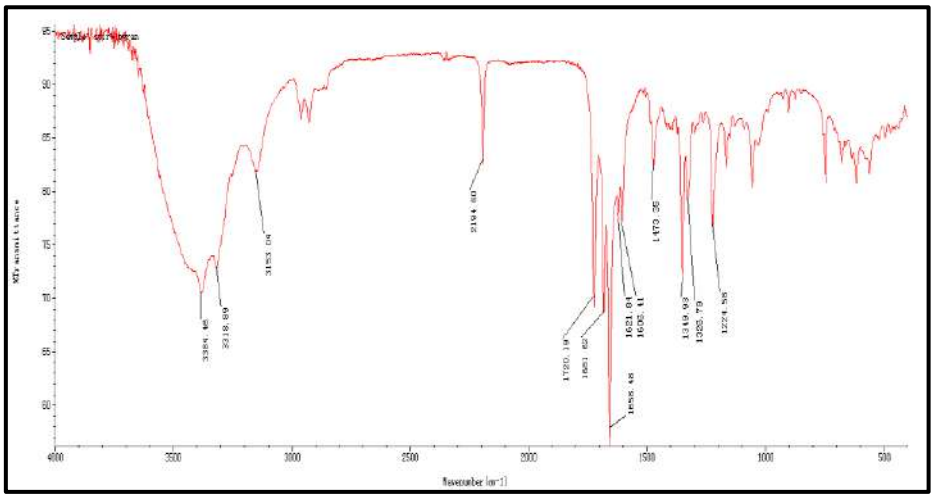


Figure 5.II.5: IR spectra of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile

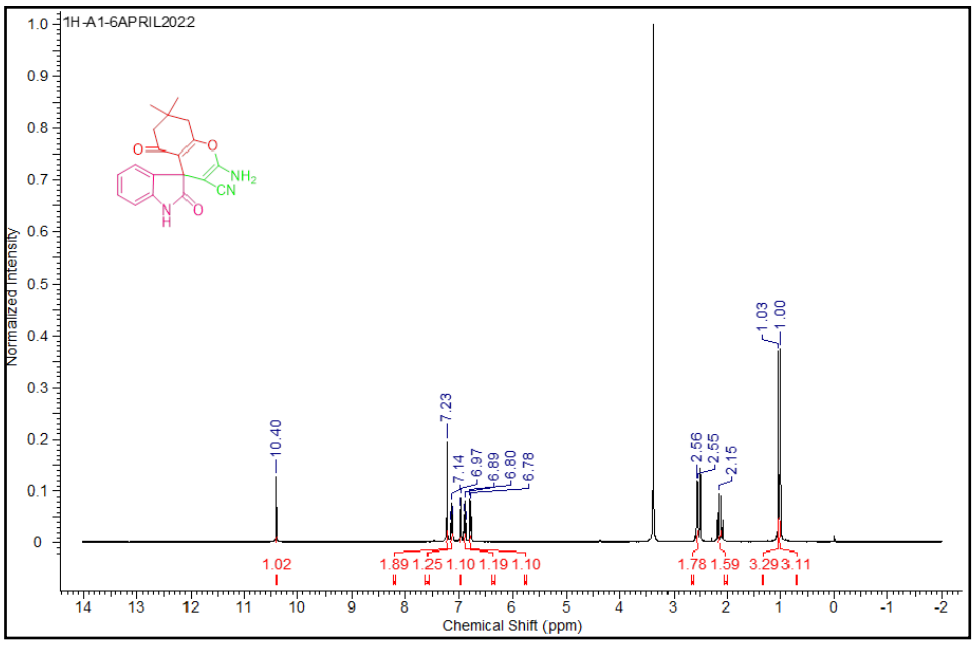


Figure 5.II.6: ^1H NMR of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile

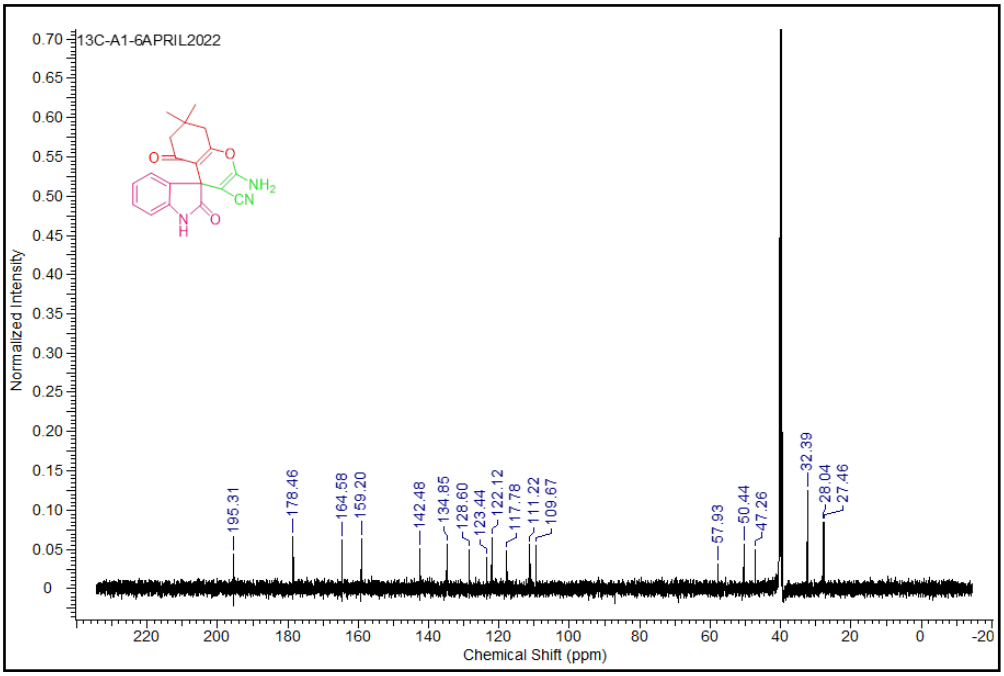


Figure 5.II.7: ^{13}C NMR of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile.

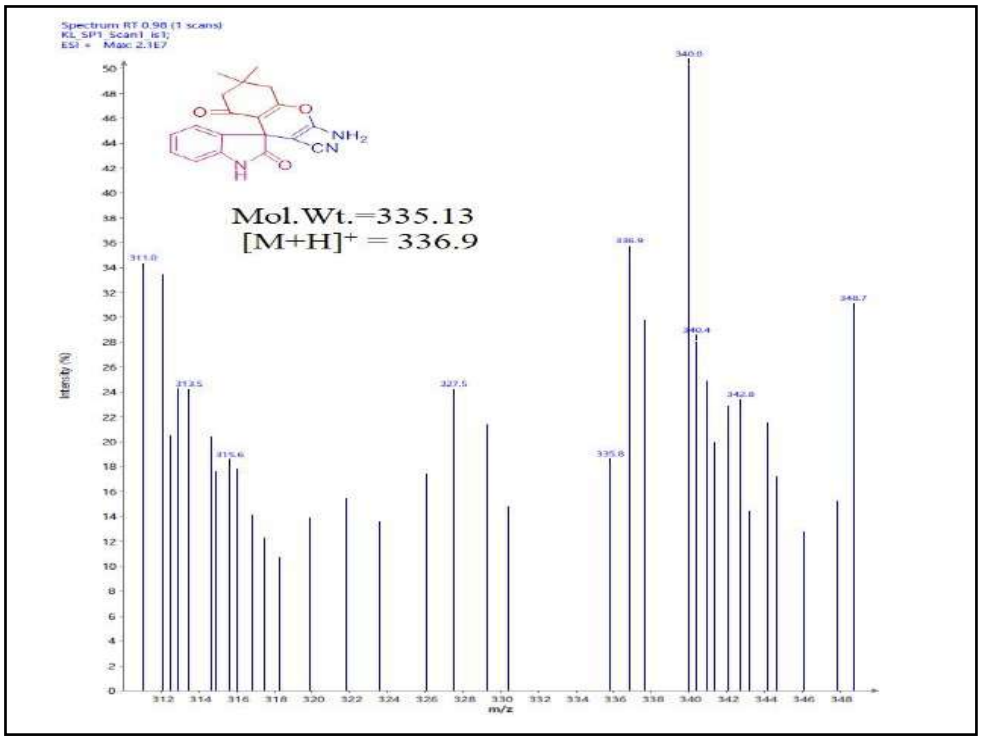


Figure 5.II.8 Mass spectrum of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile.

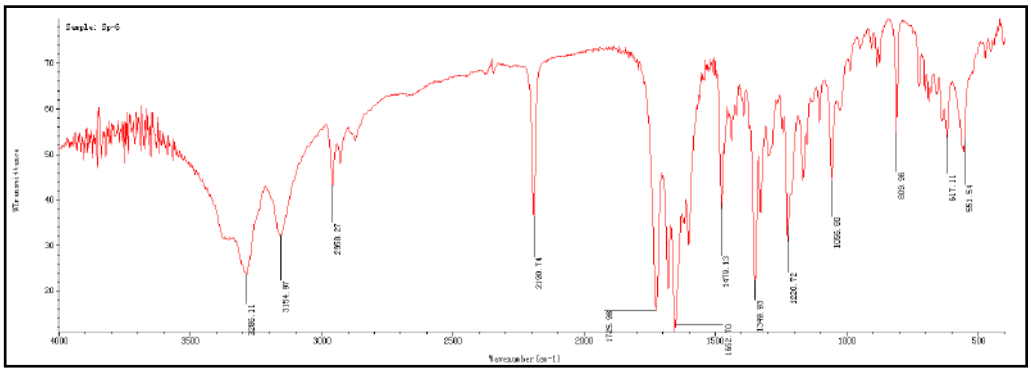


Figure 5.II.8: IR spectra of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

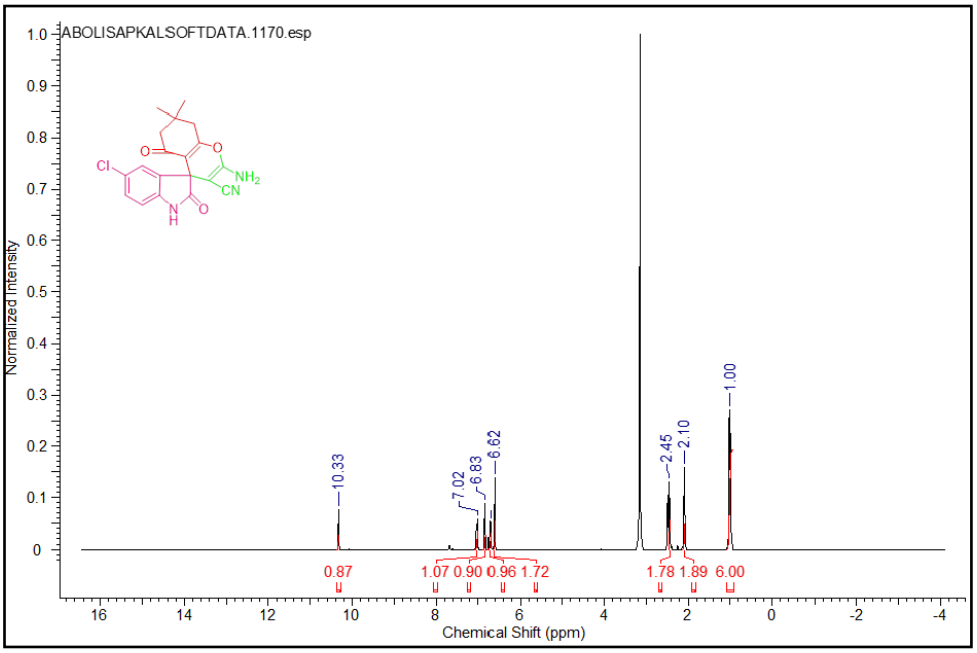


Figure 5.II.9: ^{1}H NMR of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

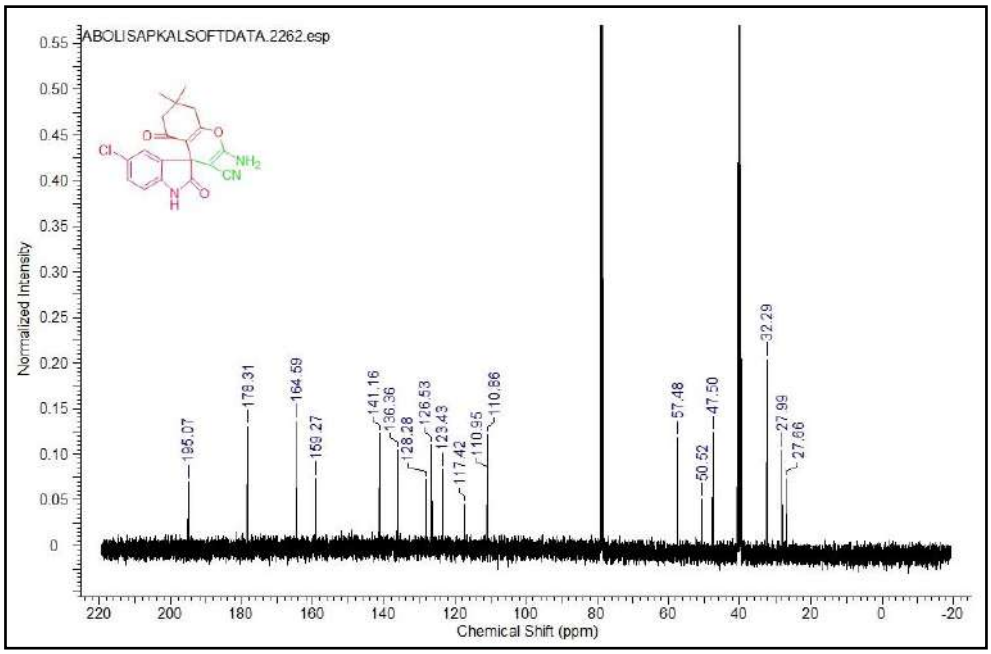


Figure 5.II.10: ^{13}C NMR of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

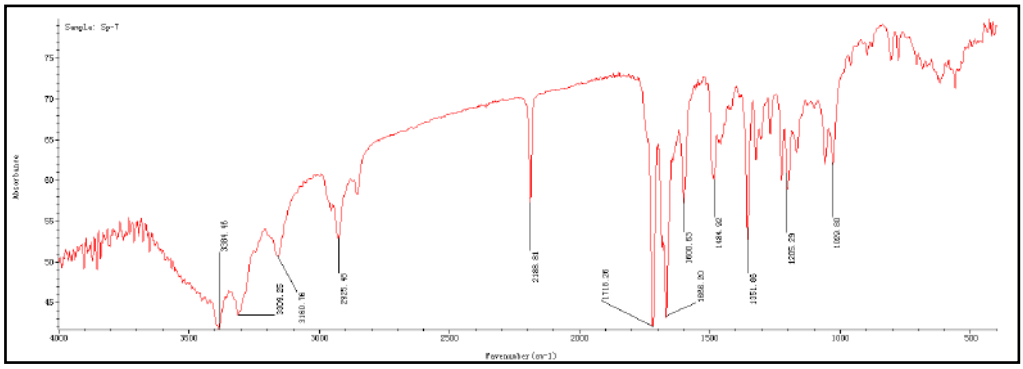


Figure 5.II.11: IR spectra of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

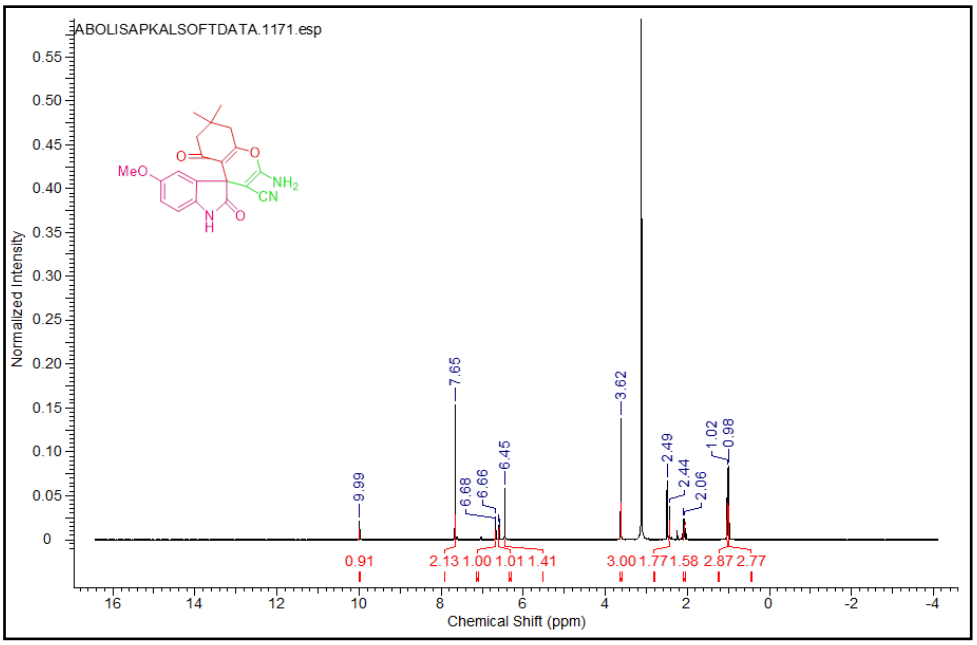


Figure 5.II.12: ^{1}H NMR of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile

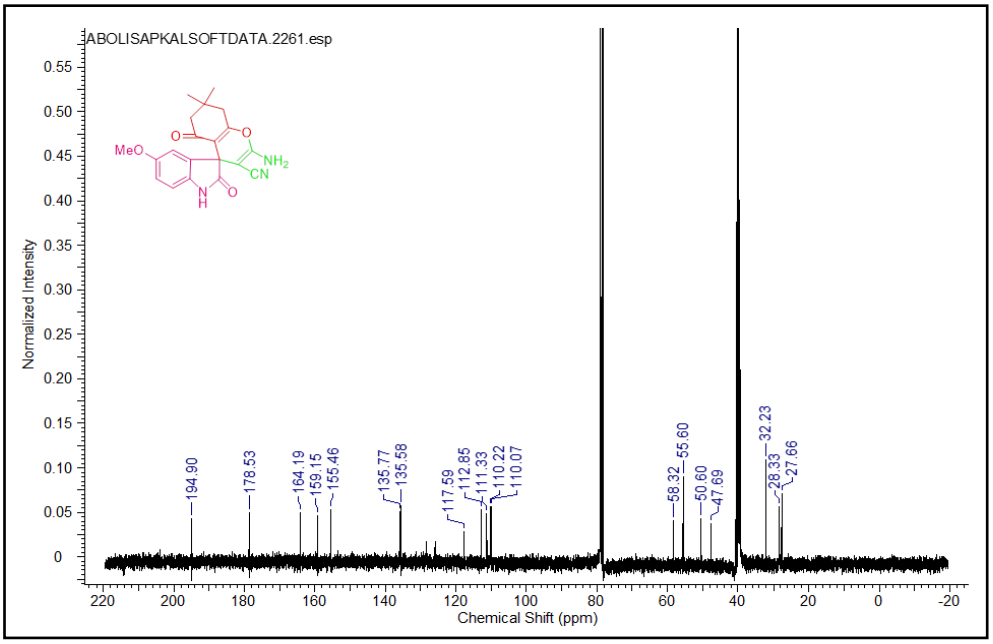


Figure 5.II.13: ^{13}C NMR of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

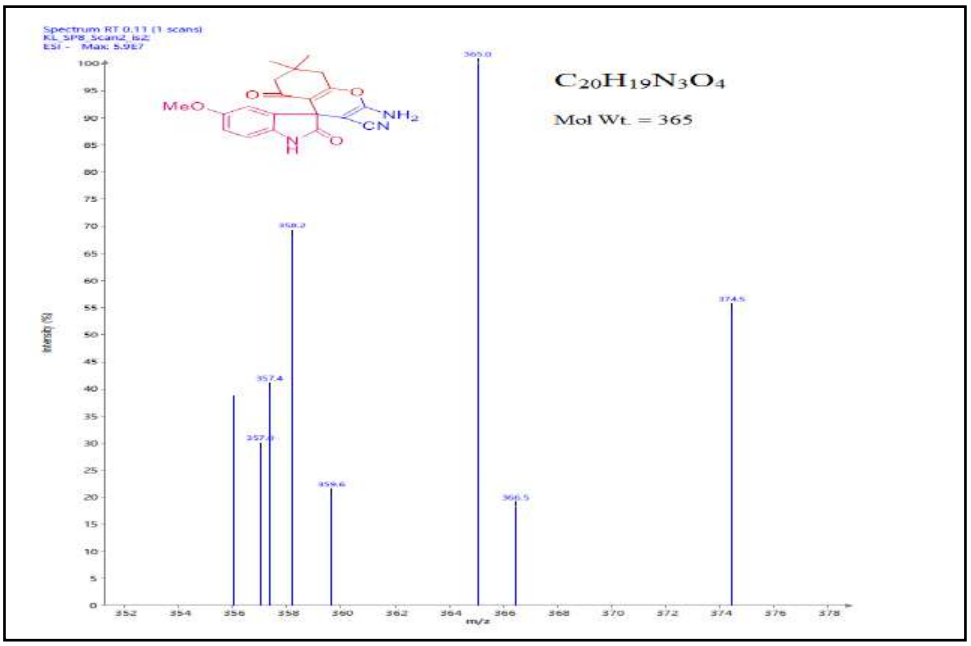


Figure 5.II.15 Mass spectrum of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8 tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile

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PUBLICATIONS

LIST OF PUBLICATIONS:

[1] "Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for Greener Synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium"
Aboli Sapkal and S. B. Kamble*
***Journal of Heterocyclic Chemistry*, 57, 3597-3604, 2020.**

[2] "Greener and Environmentally Benign Methodology for the Synthesis of Pyrazole Derivatives"
Aboli Sapkal and S. B. Kamble*
***Chemistry Select, 5*, 12971-13026, *2020*.**

[3] "Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium"
Aboli Sapkal, Suraj Attar, Avdhut Kadam, Pramod Gaikwad, Santosh Kamble*
***Polycyclic Aromatic Compounds*, 2022.**

[4] "Greener and Environmentally Benign Methodology for the Synthesis of Bis(Indole)methane and Trisindoline Derivatives"
Aboli Sapkal, Suraj Attar, S.B. Kamble*
Journal of Shivaji University.

[5] "Gel entrapped ZnO nanorods: An efficient and sustainable catalyst for the Claisen- Schmidt condensation reaction in aqueous hydrotropic media"
Suraj R. Attar, Aboli C. Sapkal, Chaitali S. Bagade, Sarfraj H. Mujawar, Santosh B. Kamble*
***Molecular Catalysis*, 542, 2023.**

[6] "Green and Eco-compatible Synthesis of Quinoxaline Molecules using Chitosan as a Biodegradable Catalyst in Aqueous Medium"
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80-RECOMMENDATIONS

GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS

A THESIS SUBMITTED

TO

SHIVAJI UNIVERSITY, KOLHAPUR

FOR

THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

UNDER THE FACULTY OF SCIENCE AND TECHNOLOGY

BY

Miss. ABOLI CHHAPPANRAO SAPKAL
M.Sc., SET

UNDER THE GUIDANCE OF

Dr. SANTOSH B. KAMBLE

M.Sc., Ph.D.

DEPARTMENT OF CHEMISTRY
YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE
(AUTONOMOUS) SATARA, 415001
MAHARASHRTA, INDIA

2023

80-RECOMMENDATIONS

Recommendations:

The research work carried out in this thesis is concerned with development of green methodologies for various organic transformation. The present work reports applications of hydrotrope, biocatalyst, and biosurfactants to be a potent catalyst-solvent system for some organic transformations. Based on the literature review it felts that there is wide scope of studying in the area of green methodologies for organic transformations. following recommendations are made –

1) Day to day increases need of development of alternative or new process or techniques for synthesis of organic moieties in laboratory or industrial importance.

2) The alternative process or techniques not only reduce cost but are also time-saving, eco-friendly, and reduce the generation of by-products.

3) There is establishment of new green catalyst, aqueous mediated organic transformations that decrease the use of toxic organic solvents as a reaction medium or having easy work-up procedure.

4) Water as a reaction medium is good choice for many organic solvents because it not only reduce cost but easy to handling and environmentally friendly solvent.

5) Biocatalyst and biosurfactant are environmentally friendly because they are biodegradable, source of them is nature which saves the ecology as well as economy.

6) The remarkable properties of the present methodologies are eco-friendly catalysts and reaction medium, which save the environment and are also cost-effective, reusable, non-hazardous, and easy to separate.

7) The main advantage is that large amounts of organic solvents can be avoided, and the catalyst can be recycled. Such fascinating features are associated with hydrotrope and surfactants which provide a new path for organic transformations by minimising the use of organic solvents with a remarkable reaction rate.

Conclusion:

We have synthesised biologically active various heterocyclic compounds such as 5-aminopyrazole-4-carbonitrile, [1,3]Oxazine by using hydrotrope-NaPTS, quinoxaline molecules using biocatalysts as chitosan, bis(indolyl)methane, and tris-indoline in biosurfactant, which is a natural extract of *Zingiber zerumbet* under ultrasound irradiation, and spirooxindole derivatives in the presence of biosurfactant is a natural extract of *Zingiber zerumbet* at room temperature. The synthesised heterocyclic compounds are confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The present methodology has promising aspects, viz., mild reaction conditions, recyclability, and high yield.

Summary:

Finally, sustainable methodologies are employed for the synthesis of 5-aminopyrazole-4-carbonitrile, [1,3]Oxazine, quinoxaline, bis(indolyl)methane, tris-indoline, and spirooxindole derivatives by utilising hydrotrope, biocatalyst, and biosurfactant as green reaction media. These catalysts exhibited high efficiency, and the products formed with a high yield in a short reaction time with an easy work-up procedure.

Future Findings:

Development of greener methodologies for organic transformations through the involvement of green solvents and catalysts that are abundantly present in nature. Screening of alternative energy sources that save the economy, time, and also ecology.

Part II

1. University Name	: Shivaji University, Kolhapur.
2. Department of	: Chemistry
3. Name of Researcher	: Miss. Aboli Chhappanrao Sapkal
4. Name of Guide	: Dr. Santosh B. Kamble
5. Type of Degree	: Ph.D.
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M.Sc., Ph.D.

DEPARTMENT OF CHEMISTRY
YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE
(AUTONOMOUS) SATARA, 415001
MAHARASHRTA, INDIA

2023

DECLARATION AND UNDERTAKING

I hereby declare that the thesis entitled **"GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS"** completed and written by me has not previously formed the basis for the award of any Degree or Diploma or other similar title of this or any other University or examining body. Further, I declare that I have not violated any of the provisions under the acts of Copyright/Piracy/ Cyber/ IPR etc amended from time to time.

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Place: Kolhapur **(Miss. Aboli C. Sapkal)**

Date: Research Student

YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE (Autonomous),

SATARA

DEPARTMENT OF CHEMISTRY

Dr. Santosh B. Kamble

Assistant Professor
Raman Post-Doctoral Fellow (USA)
Y. C. Institute of Science, Satara-415001
Maharashtra, India
Phone: (02162)234392 Fax: (02346)250665
Mobile: 9823524565
Email:santosh.san143@gmail.com

CERTIFICATE

This is to certify that the thesis entitled **"GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS"** which is being submitted herewith for the award of the degree of **Doctor of Philosophy** in **CHEMISTRY** of Shivaji University, Kolhapur is the result of the original research work completed by **Miss. Aboli Chhappanrao Sapkal** under my supervision and guidance. To the best of my knowledge and belief, the work embodied in this thesis has not been the basis for the award of any Degree or similar title of this or any other University or examining body.

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Place: Kolhapur **Dr. Santosh B. Kamble**

Date: (Research Guide)

Forwarded through

Prof. and Head
Shivaji University, Kolhapur

The Principal,
Y.C.I.S., Satara

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Miss. Aboli C. Sapkal

TABLE OF CONTENT

ABBREVIATIONS

Aq	: Aqueous
Ar	: Aryl
^{13}C NMR	: Carbon nuclear magnetic resonance
$CDCl_3$	: Deuterated chloroform
CMC	: Critical micelle concentration
DCM	: Dichloro methane
DMSO	: Dimethyl sulfoxide
DMSO-d_6	: Deuterated dimethyl sulfoxide
FT-IR	: Fourier-transform infrared spectroscopy
EtOH	: Ethanol
GCMS	: Gas chromatography-mass spectrometry
^{1}H NMR	: Proton nuclear magnetic resonance
H_2O	: Water
HRMS	: High resolution mass spectroscopy
Hz	: Hertz
ILs	: Ionic liquids
IR	: Infrared
MeOH	: Methanol
MCRs	: Multi-component reactions
MHC	: Minimum hydrotropic concentration
mmol	: Millimole
MP	: Melting point
MS	: Mass spectroscopy
MW	: Microwave
NaPTS	: Sodium para toluene sulfonate
NaBS	: Sodium benzene sulfonate
NaXS	: Sodium para xylene sulfonate

PEG	: Polyethylene glycol
Ph	: Phenyl
ppm	: Pats per million
p-TSA	: para-Toluene sulfonic acid
RT	: Room temperature
TLC	: Thin layer chromatography
TMS	: Tetramethylsilane
US	: Ultrasonic irradiation
UV	: Ultraviolet
Z.Z.	: *Zingiber zerumbet*

GENERAL REMARKS

1. All chemicals used in the study were purchased from Sigma-Aldrich and Loba Chemical companies and used without additional drying or purification.

2. The spectra concerning each chapter (2 to 5) are given just after the experimental part.

3. Proton, carbon-13, and DEPT NMR spectra were recorded with a Bruker Ascend 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 as solvents, with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm.

4. Mass spectral analyses were recorded on the GCMS-QP2010 gas chromatograph mass spectrometer.

5. Fourier transform infrared (FT-IR) spectra were recorded on a Lamda FTIR 750 spectrometer (KBr).

6. High-resolution mass spectra were recorded on the Dionex UHPLC Ultimate 3000 system.

7. Optical microscopy measurements: a drop of turbid reaction mixture was subjected to light microscopy measurement using an OLYMPUS light microscope.

8. Melting points were determined using the electrical melting point apparatus EQ 730A-EQUIPTRONICS.

9. Sonication was performed in a SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz.

CHAPTER -1

Green Chemistry: "Hurt not the earth, neither the sea, nor the trees".

-Ronald C.D. Breslow.

CHAPTER 1

Green Methodology for Organic Transformations

1.1 Introduction

In the modern progressive era chemist have responsibility to grow environment friendly synthetic routes to achieve their goals without environmental hazards. So, chemists are competing to achieve this under naming of 'green' chemical transformations. Achieving such goal is particularly called "Green Chemistry". Now days in industries various hazardous chemicals are used which causes pollution this is hazardous to environment. The green chemistry is used to reduce carbon footprint and many hazardous by-products. Now intensely established routes in this field includes use of mild reaction conditions, lessening number of reaction steps, switching to less harmful reactants and reagents, use of solvent free processes, use of renewable energy sources, developing proficient purification and isolation processes in synthetic transformation etc.

Green Chemistry

Green chemistry is type of chemistry which performs various chemical processes that reduce or eliminate the usage and generation of hazardous substances. It actually practices techniques that are environmentally friendly. The Green chemistry is applicable in whole sequence of chemical product involving its scheme, manufacturing, use and final disposal. In present era green chemistry plays crucial role in synthetic chemistry. The term green chemistry was first invented by Paul Anastas in 1998 and then John C. Warner set up principles to practice under green chemistry that worldwide known as twelve principals of green chemistry [1], [2].

Nowadays green chemistry works powerful tool and it open up new doors for researchers to think new reaction conditions that have less impact on environment. Considering these new unconventional trends are in progression.

Need of Green Chemistry

In many ways human impact on the physical environment that triggered lots of pollution that mainly comprise climate change, poor air quality, undrinkable water and soil erosion. In that utilization of chemistry is everywhere which acquired principal position for such issue. So, in emerging era use novel compounds and processes had grown up by the researchers that plays vital role to control demolition of environment.

Now, researchers adopted various concepts of green chemistry for protection of environment without affecting advancement of chemistry. The fundamental ideas and strategies for green novel techniques based on "Twelve Principles of Green Chemistry" that put forth by Paul Anastas and John C. Warner in 1998.

Thus, to conserve the environment the researchers have no other option than adopting the concept of sustainable development and green chemistry so for that purpose that advancement of chemistry and protection of environment can go on parallel to each other [3], [4]. To analyse sustainability in practises and the involvement of sustainable green approaches in research, evolution, and manufacturing, academic policies have to involvement in green chemistry principles and pointers of sustainability [5], [6]. These principles are listed in following figure 1.1.

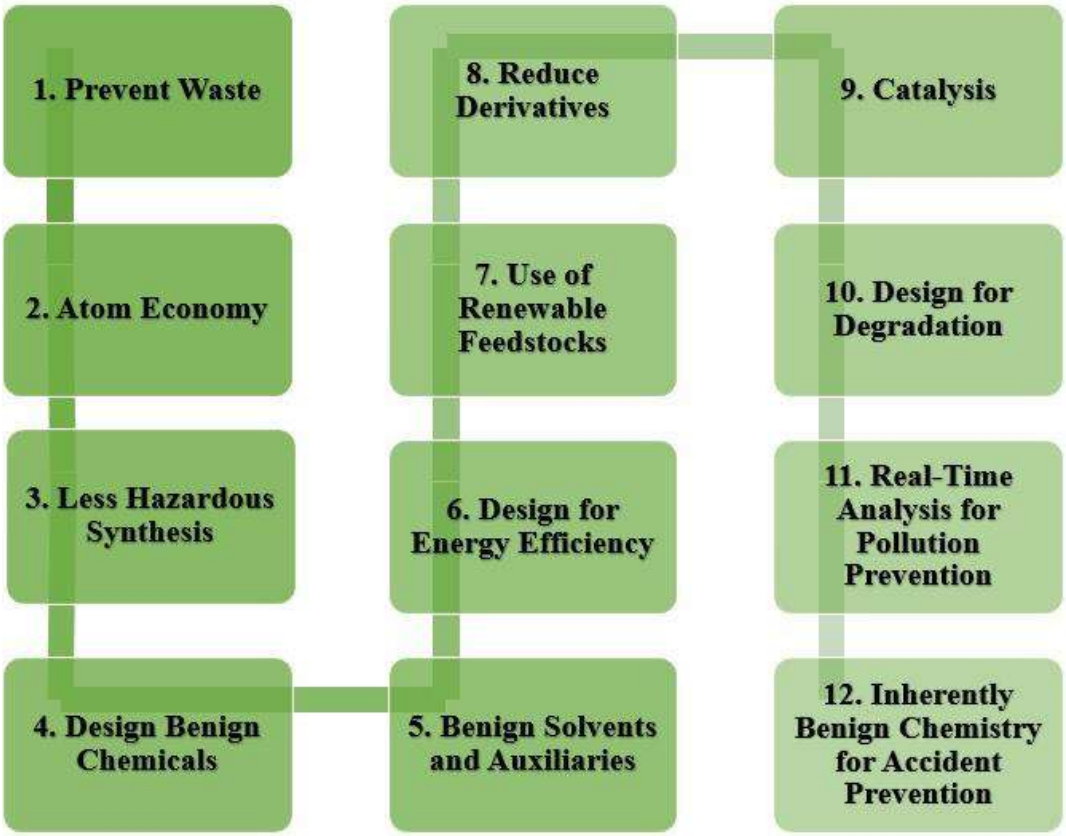


Figure 1.1 12 principles of Green Chemistry

Greener methodologies for organic transformations:

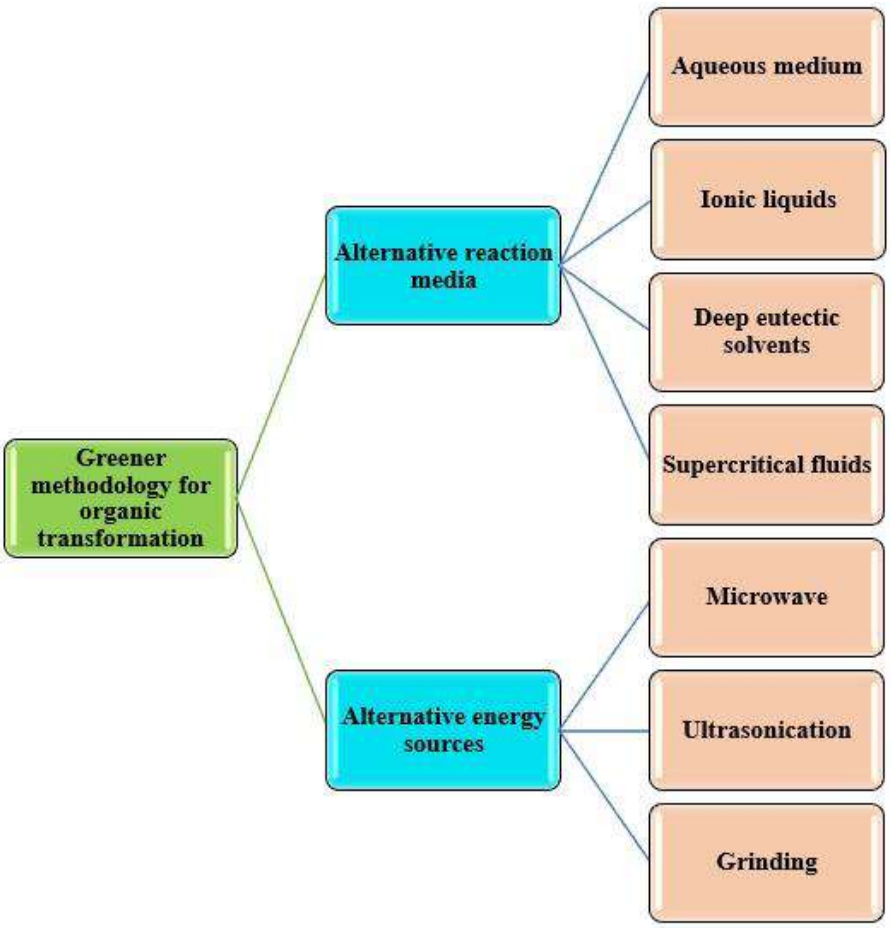


Figure 1.2 Greener methodologies for Organic Transformations

1.2 Aqueous medium

The water is an attractive medium for various organic syntheses. Multi-component reactions (MCR's) are carried out in water increases productivity of multi-component reactions as well as protect the environment from hazardous solvent which would achieve the green chemistry challenge. The use of water as a solvent is more advantageous because it is easily available, secure, inexpensive, inoffensive, noncorrosive, nonflammable and ecologically benignant; alternatively stated, it is an eco-friendly "green solvent".

Aqueous medium has a wide spectrum of applications in numerous areas involving supramolecular structures [7], interactions between protein molecules [8], etc. In recent years different groups working on aqueous mediated synthesis so they

observed that water could catalyse chemical transformations through the hydrogen bonding with substrates [9]. Breslow's group carried out Diels-Alder synthesis in water and got excellent results because water accelerates the reaction by forming hydrophobic interactions with non-polar groups [10]. Although organic preparations in aqueous media are very few due to the sparingly or incompletely soluble nature of the many organic composites. An interesting study to achieve aqueous solubilities of substrates is the utility of amphiphiles, including hydrotropes and surfactants.

1.2.1 Hydrotropes

Hydrotropes are immensely aqueous-solvable, surface-active organic salts that boost the solubilities of operationally insoluble or sparely soluble organic composites in aqueous medium [11]. In 1916, *Carl Neuberg* was first time invented the term "hydrotropes" for surface-active organic salt [12]. As reported by Neuberg, "the phenomena of accelerating the solubilities of unsolvable organic molecules in water by a third ingredient or additive are referred to as hydrotropism or hydrotropy" [13]. Neuberg furthermore recorded environmentally friendly character of various hydrotropes as a result of their basic nature and the potential there within. The salts of different organic constituents such as benzoic, benzyl sulfonic, 1-naphthyl, thiophene carboxylic, 2-furoic, and phenylacetic acid derivatives, as well as few of aromatic fatty acids, are hydrotropic substances **(Figure 1.3)**. The concept hydrotropes comes from the word hydro means water and tropes means something other. Hydrotropic salts decrease the interfacial surface tension at a particular concentration, mentioned as the *Minimum Hydrotropic Concentration* (MHC) [14]–[18]. Hydrotropes have similarities as well as differences to surfactants in the form of molecular structure and association **(Figure 1.4)**. Hydrotropes contain the hydrophilic and hydrophobic groups; however, hydrophobic groups are incapable to form micelle as result of its very small structural arrangement in contrast with a hydrophobic group of surfactants. The diversity between surfactant and hydrotrope is substantially higher Hydrophile/Lipophile balancing (HLB). Hydrotrope generates stacks type aggregates in an aqueous medium which creates associated structures that are accountable for hydrotropic behaviour. The distinctive aggregation of hydrotrope is the source of the dissolution process of a moderately soluble hydrophobic compound in an aqueous medium, which is analogous

to the micellization process. Saleh and co-workers considered the importance of planer structure for the association and hydrotropic effect.

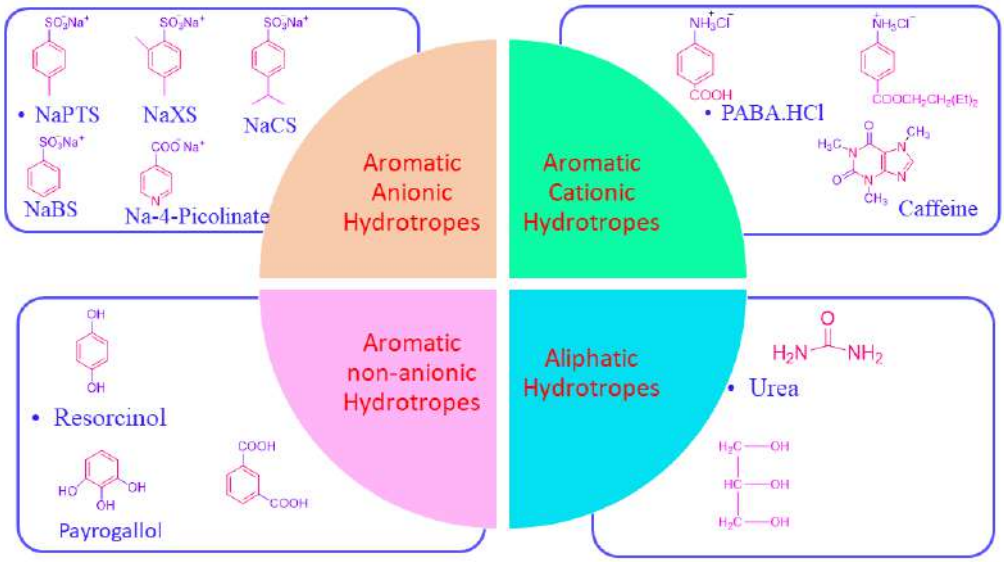


Figure 1. 3: Different examples of hydrotropes

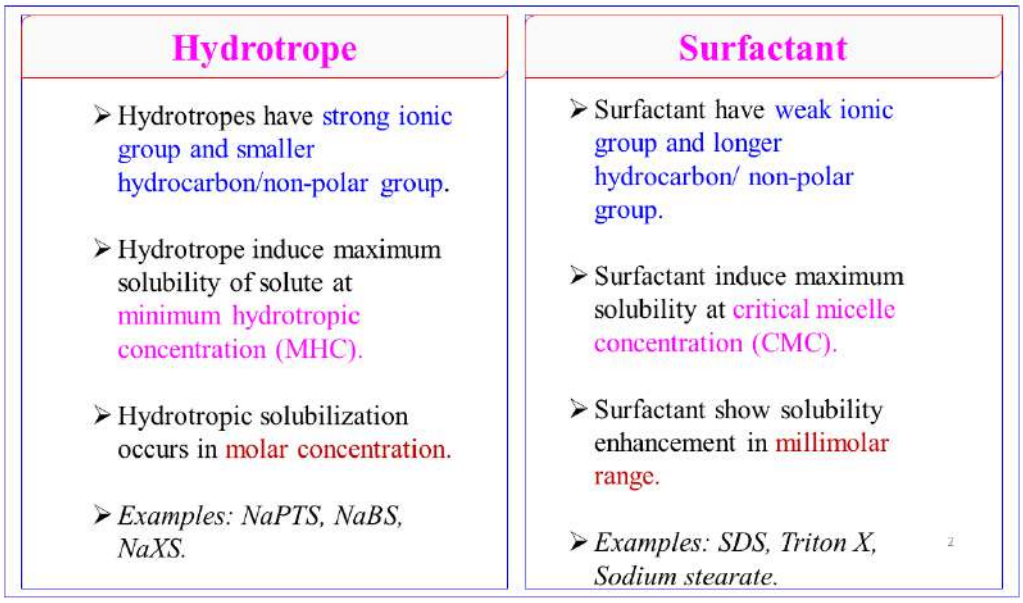


Figure 1.4. Difference between Hydrotrope and Surfactant.

The capacity of hydrotrope to enhance the solvability of organic material in aqueous media is highest whenever the hydrotrope concentration is enough to stimulate the creation of associated structure and maintain the solubility same after that point.

Surfactant carry out greatest solubility at critical micelle concentration (CMC) while hydrotrope shows highest solubility at minimum hydrotrope concentration (MHC). Hydrotropes are excellent in solubilising organic compounds in aqueous media and more exclusive than surfactant. Hydrotrope reduces the surface tension of water and at particular point surface tension becomes constant at that point self-aggregation of hydrotrope occurs. Several theories and practical approaches are used to explain the mechanistic pathway of hydrotrope in organic transformation. The reported mechanism of hydrotrope in organic transformation are show by following figure **(Figure 1.5)** [19]–[23].

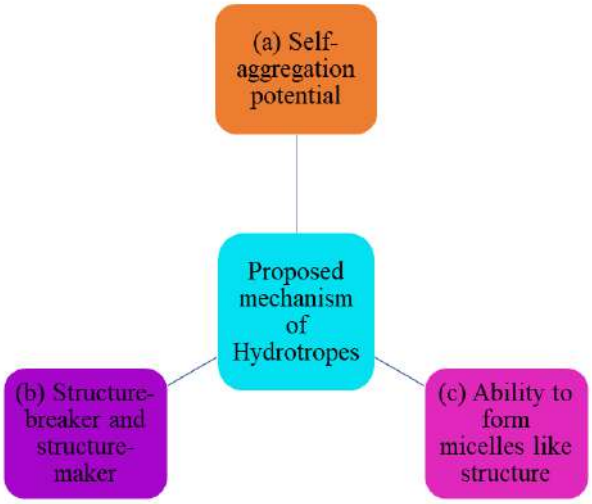


Figure 1.5 Proposed mechanism of Hydrotropes

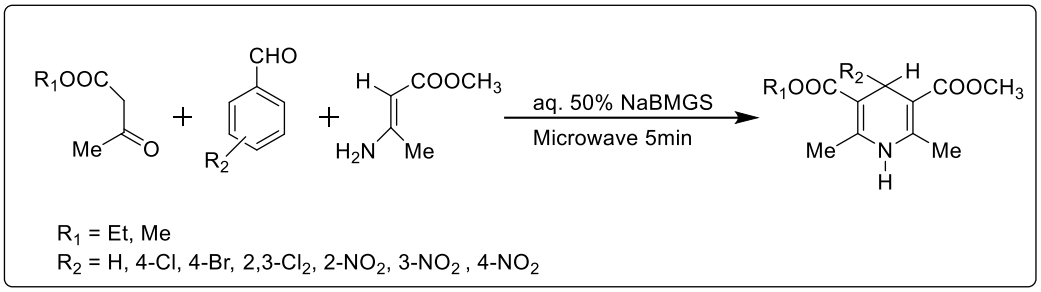
Friberg and Blute mentioned the historical growth of hydrotrope and its involvement in industrial applications [24]. Hydrotropes are mostly utilized in cleaning agent, medical treatment such drug dissolutions [25]. The different fields take advantages of hydrotropes including shampoo, creams, lotion and printing press [26].

Sodium xylene sulfonate maximizes the efficiency of water to solubilise other organic substances. Johnson and Johnson firm put to use hydrotrope sodium xylene sulfonate in cosmetics mainly in shampoos. Sodium toluene sulfonate be applied as hydrotrope and viscosity modifying agent in detergent formulations which reduces the viscosity of chain of Linear Alkyl Benzene Sulfonic Acids (L.A.B.S.).

Application of Hydrotropes in organic transformation

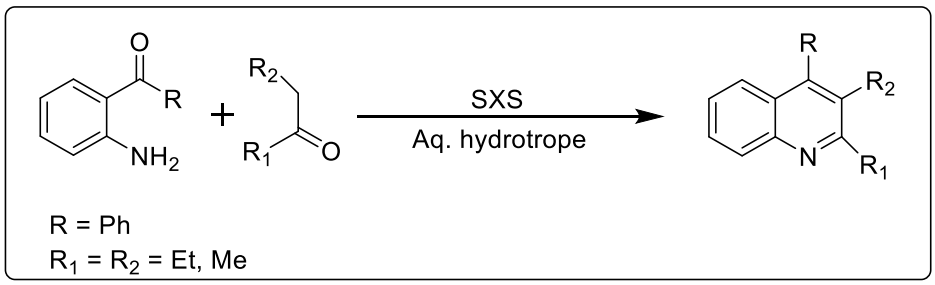
In supplement to industrial application hydrotropes also take part in organic transformation as a reaction medium, for example preparation of quinolines [27]. Hydrotropes also enhance the speed of multiphase synthesis which results in alkaline hydrolysis of aromatic esters [28], [29].

Bhushan M. Khadilkar and Virendra R. Madyar [30] reported synthesis of clinically important dihydropyridine by using aq. 50% sodium butyl monoglycol sulphate (NaBMGS) under microwave irradiation **(Scheme 1.1)**.



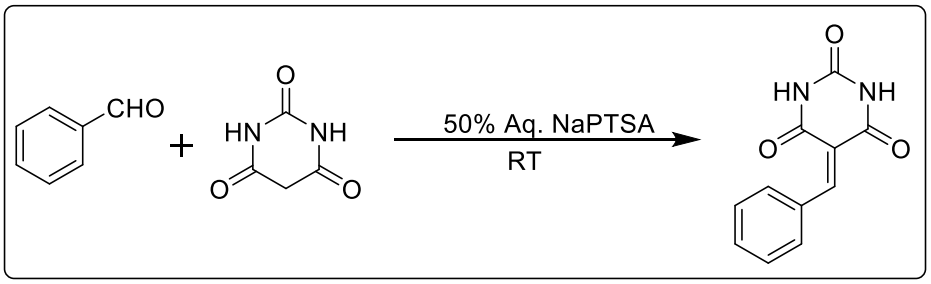
Scheme 1.1

Sharmad J. Chandratre and Zoeb A. Filmwala [31] developed synthesis quinolines in aqueous hydrotropic medium. Condensation between 2-amino ketones with aldehydes or ketones in the aqueous hydrotropic solution of sodium xylene sulphonate (SXS) afford the desired quinolines derivatives **(Scheme 1.2)**.



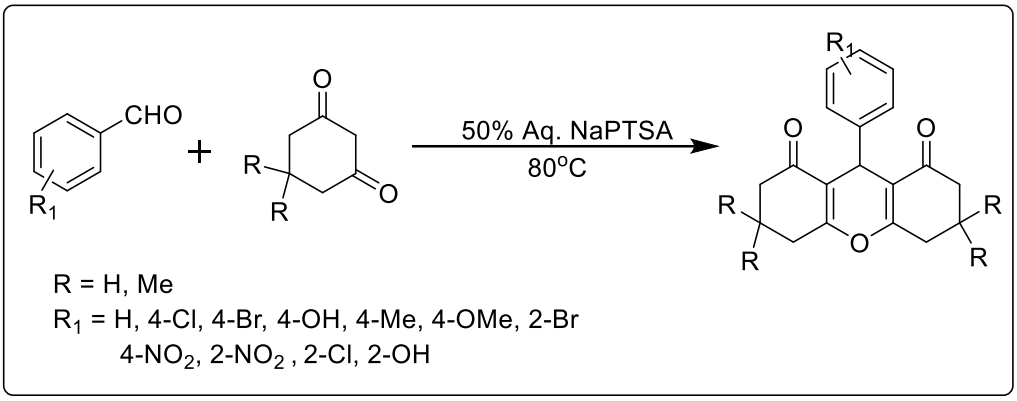
Scheme 1.2

Synthesis of 5-arylidine barbituric acid derivatives in aqueous hydrotropic medium reported by Santosh Kamble and co-workers [17]. They use an efficient Knoevenagel condensation of barbituric acid with different aromatic aldehyde in 50 % aq. NaPTS solution at room temperature providing the respective 5-arylidine barbituric acid derivatives **(Scheme 1.3)**.



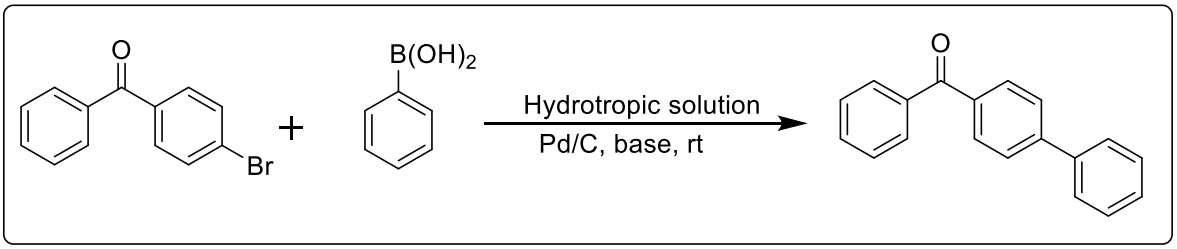
Scheme 1.3

Kamble et al. [32] uses same hydrotrope for the synthesis of 1,8-dioxooctahydroxanthenes **(Scheme 1.4)**.



Scheme 1.4

In the absence of ligand Suzuki-Miyaura and without base Heck-Matsuda cross-coupling schemes developed by Sanjay N. Jadhav and co-workers [33]. In this protocol, they developed a new catalyst by palladium grafting on activated carbon (Pd/C) in an aqueous hydrotropic environment **(Scheme 1.5)**.



Scheme 1.5

1.2.2 Surfactant

A surfactant is a combination of surface-active agents or compounds having surface-active properties that are called surfactants. Surfactants having a hydrophilic

head (polar molecule) and a hydrophobic tail (non-polar molecule), such kind of structure with two different functions, are called amphiphilic substances. Surfactants are entities that generate self-assembled molecular clusters called micelles in a solution as well as interfacial adsorption, which are characteristics properties of a surfactant [34] **(Figure 1.6)**. That has different dissolution characteristics in similar solutes. Hydrophobic group is alkyl chain with 8-12 carbons atoms that does not show affinity toward water in aqueous system but in lipid system they are called as lipophilic groups. The hydrophilic group they are functional group such as $RCOO^-$, RSO_3^-, $ROSO_3^-$, R_4N^+ etc. has affinity toward water. Thus, hydrophobic groups of surfactants attract nonpolar environment while hydrophilic groups attract with polar environment if aqueous system during aggregation. This is a characteristic property of surfactant, due to which it becomes a surface active and able to decrease the surface/ interfacial tension by aggregating at interface of two immiscible liquids which results into maximise the solubility, mobility and biodegradation of sparingly soluble organic substance. At a certain concentration, surfactant molecules form the micelle that concentration is known as critical micelle concentration (CMC).

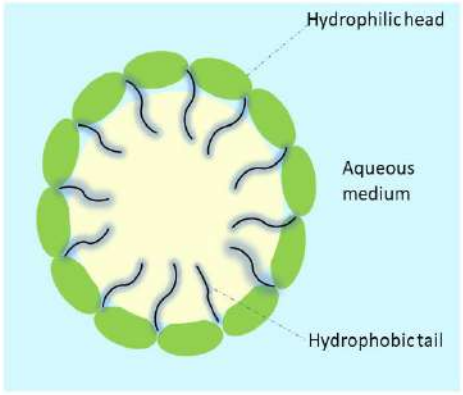


Figure 1.6: Structure of micelle formation

Classification of surfactant:

Classification of surfactant based on charge as anionic, non-ionic, cationic, amphoteric, and also on their source of availability as a biosurfactant **(Figure 1.7)**.

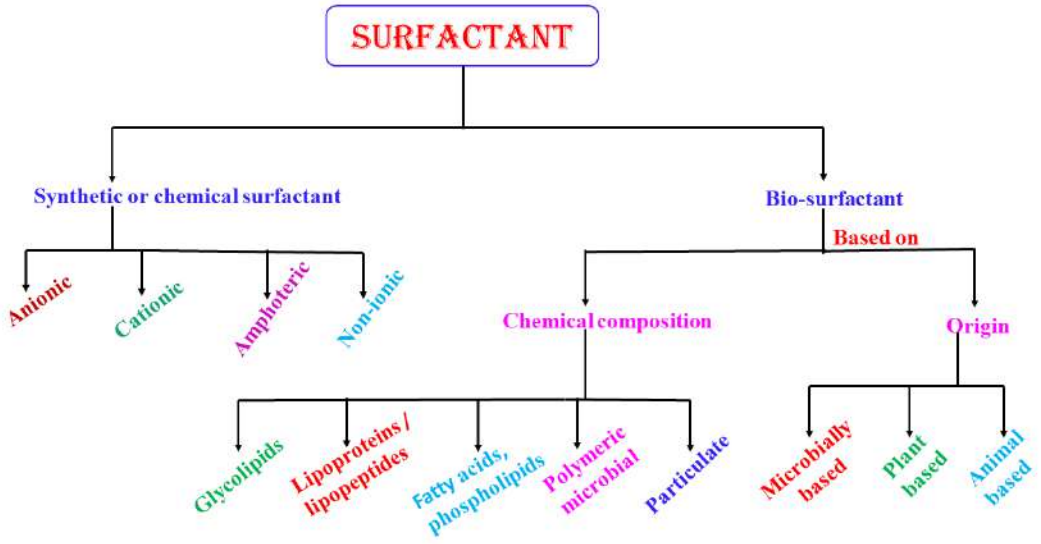


Figure 1.7 Classification of surfactant

I) Chemical or synthetic surfactant:

1.2.1 Anionic Surfactant:

In these surfactants hydrophilic group dissociate into amphiphilic anions and alkaline cations (Na^+, K^+) or a quaternary ammonium cation when dissolved in aqueous system. Anionic surfactant is mostly used in industry as a detergent such as soap. The hydrophilic head groups are carboxylate, sulfonate, sulphate and alkyl chain of hydrocarbons C_{12} to C_{18} acts as hydrophobic.

Examples: Sodium dodecyl sulphate, Sodium dodecylbenzene sulfonate, Dioctyl sodium sulfosuccinate, Sodium stearate, petroleum sulfonates, lignin sulfonates, ester sulfonates etc **(Figure 1.8)**.

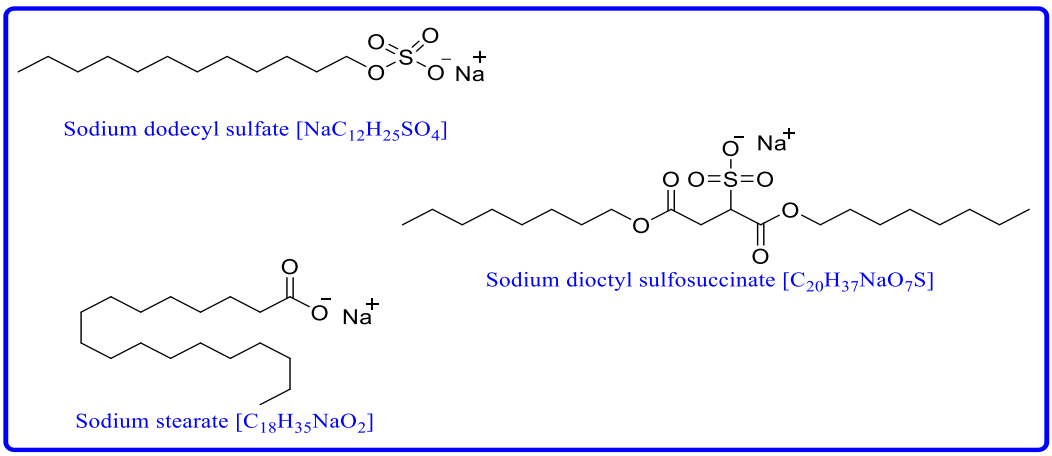


Figure 1.8 Examples of anionic surfactant

1.2.2 Cationic Surfactant:

In the aqueous system, cationic surfactant dissociates as an amphiphilic cation and halogen as an anion. These types of surfactants correspond to large proportions of nitrogen compounds such as fatty amine salts, natural fatty acids, and quaternary ammonium compounds. These surfactants are mostly used for surface modification as softeners in hair conditioners, but they also have bactericidal properties as antibacterial in hygiene formulations.

Examples: Hexadecyl trimethyl ammonium chloride, Hexadecyl pyridinium chloride, Benzethonium chloride **(Figure 1.9)**.

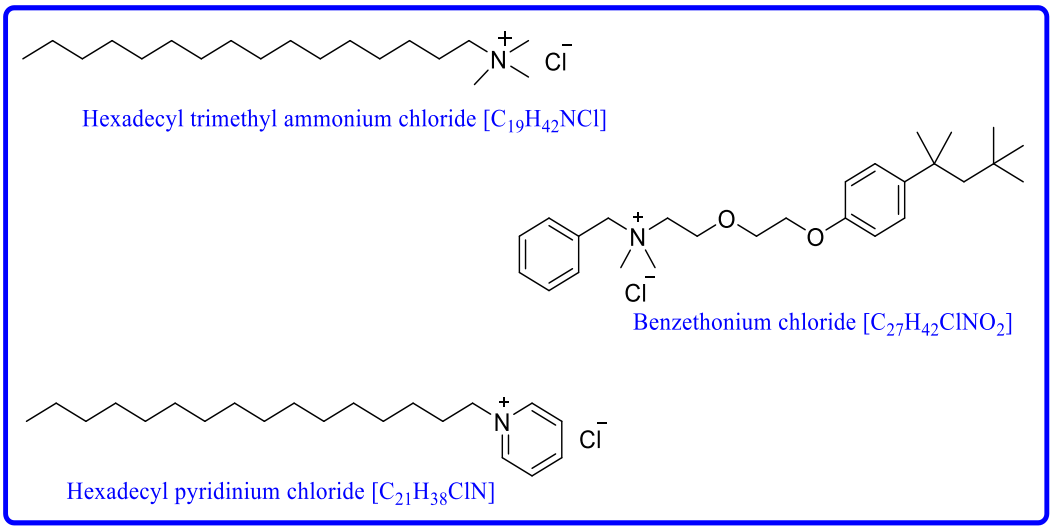


Figure 1.9 Examples of cationic surfactant

1.2.3 Amphoteric or Zwitterionic Surfactant:

Amphoteric surfactant exhibits dissociation of both cationic and anionic functional groups in their polar hydrophilic portion often depending on the pH but amphoteric behaviour shows at intermediate pH and its application in cosmetic, personal care products due to which they are quite expensive. Alkyl amino acids, alkylbetains, alkylaminobetaines are common classes of amphoteric surfactants.

Examples: N-Dodecyl-N, N-dimethylglycinate, Dipalmitoylphosphatidylcholine (Lecithin), Cocamidopropyl betaine **(Figure 1.10)**.

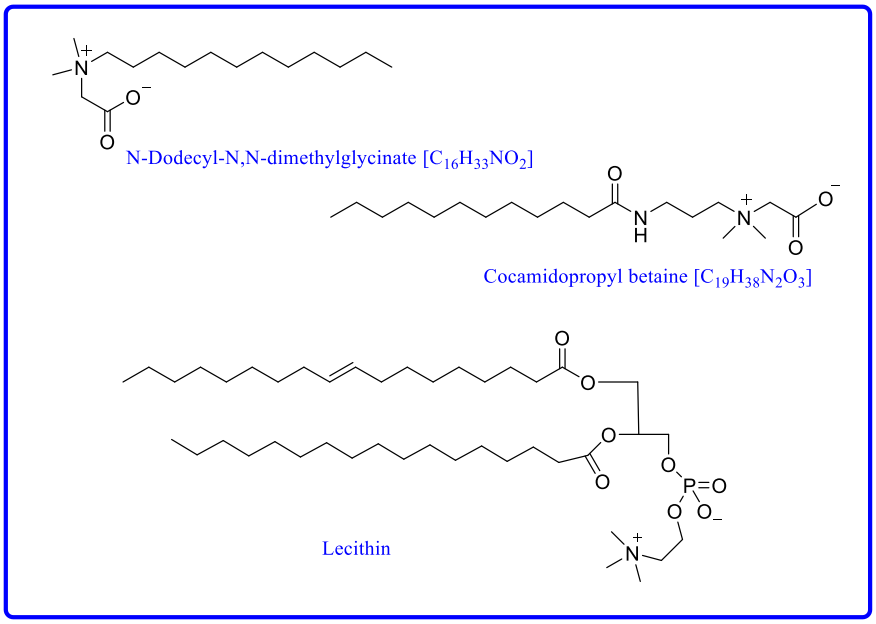


Figure 1.10 Examples of amphoteric surfactant

1.2.4 Non-ionic surfactant:

These type surfactants do not dissociate or ionizes in aqueous system due to their hydrophilic part has a non-dissociable functionality such as alcohol, phenol, ether, ester or amide. The hydrophilic part carries noncharged polyethylene oxide (PEO) or polyglycerin chains. There important application in drugs, cosmetic as personal care products.

Examples: Polyoxyethylene 20 cetyl ether (Brij 58), Triton X-100, Tween 20 etc **(Figure 1.11)**.

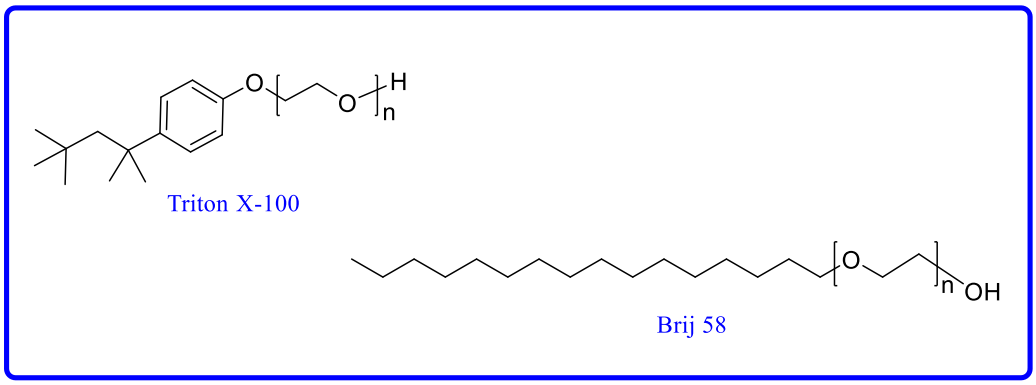


Figure 1.11 Examples of non-ionic surfactant

II) Bio-surfactant-microbial surfactant:

Surface active biomolecules are produced from microorganisms, plants and animal materials known as biosurfactant. These types of surfactants are anionic or neutral in behaviour due to hydrophilic groups are carbohydrate, amino acid, peptide, phosphate etc. while hydrocarbon chain is hydrophobic tail. Biosurfactants are better than synthetic or chemical surfactants owing to their lower toxicity, easy biodegradability, specific activity, effectiveness at extreme temperatures as well as at pH, lower surface tension, and lower interfacial tension.

Classification of biosurfactant: Classification of biosurfactant on the basis of their chemical composition and source of origin.

Based on chemical composition

1. Glycolipids: Glycolipids are the most common type of biosurfactant found in the environment, consisting of a combination of carbohydrates and long-chain aliphatic or hydroxyl acids linked by an ester or ether portion. Ex. Rhamnolipids, Trehalose lipids, Sophorolipids **(Figure 1.12)**.

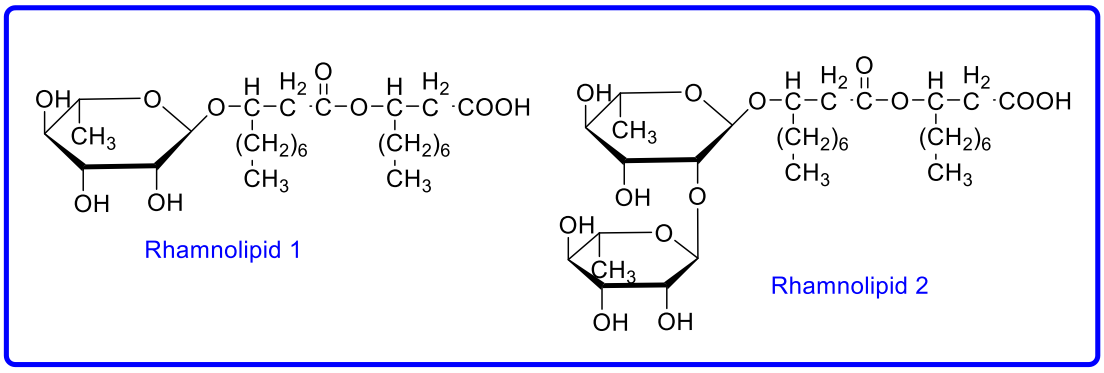


Figure 1.12 Examples of glycolipids

2. Lipopeptides and Lipoprotiens: In lipopeptides lipid acts as hydrophobic head and peptide is hydrophilic tail that lipid is attached to the polypeptide chain. Along with antimicrobial properties they are also excellent surfactant.

Examples. Surfactin, Lichenysin, Viscosin **(Figure 1.13)**.

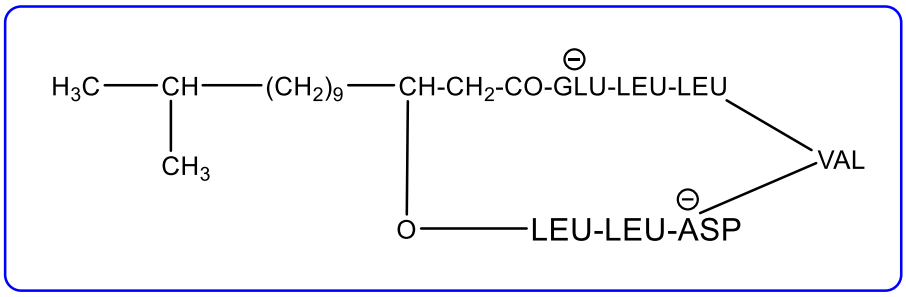


Figure 1.13 Structure of Surfactin

3. Fatty acids, phospholipids, and neutral lipids: These types of surfactants are produced by several bacteria and yeast during the microbial oxidation of n-alkanes. The equilibrium between hydrophilic and lipophilic groups is directly proportional to the length of the hydrocarbon chain in their structural frameworks. Ex. Acinetobacter sp., corynomicolic acids.

4. Polymeric Microbial Surfactants: Most commonly used polymeric microbial surfactant are polymeric heterosaccharides containing proteins. The researcher interested in studied of polymeric biosurfactants are emulsan, liposan, alasan and lipomannan. Ex. Acinetobacter calcoaceticus **(Figure 1.14)**.

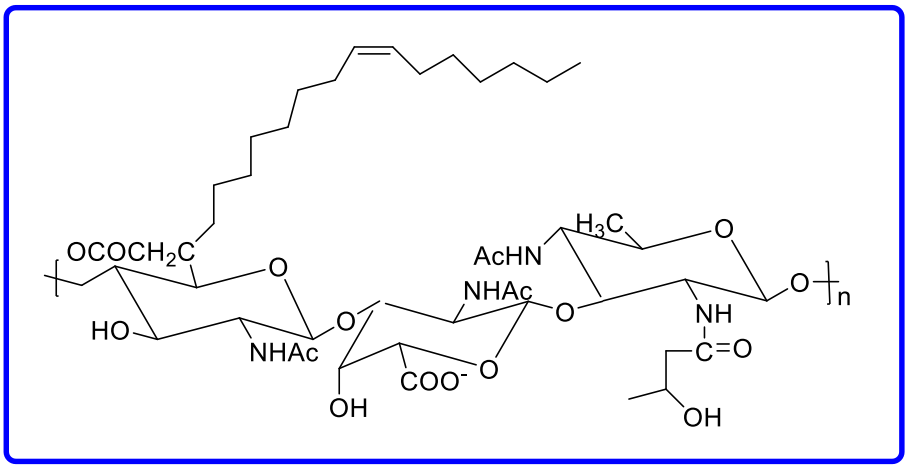


Figure 1.14 Structure of Acinetobacter calcoaceticus

5. Particulate biosurfactant: The creation of microemulsion and the presence of extracellular membrane vesicles that partition hydrocarbons play significant roles in alkane intake by microbial cells. Ex. vesicles of Acinetobacter sp. strain HO1-N.

Based on origin:

1. Microbially-based Surfactants:

These surfactants are produced by variety of microorganisms or by microbial fermentation processes using cheaper agro-based materials. They are divided into two groups depending on molecular weight. First group contains low molecular weight surfactant such as glycolipids, lipopeptides and phospholipids shows effectiveness in reducing surface and interfacial tension. High molecular weight surfactant contains polysaccharides, proteins, lipopolysaccharides, lipoproteins or complex mixtures of these biopolymers which stabilizes newly created surfaces.

2. Plant-based surfactant:

In environmentally conscious days demand increases for the natural sourced surfactant. Plant derived surfactants are good source of biosurfactant. Saponin is excellent class of plant having characteristic surface-active properties due to those plants are rich in saponin class used as biosurfactant. Plant-based saponins are largely distributed in nature offering large potential replacement for the hazardous synthetic surfactant which exhibits excellent surface and biological activities. Biological activities include antimicrobial activity, antidiabetic activity, adjuvant potentials, anticancer activity, and others are reported. They can be extracted from various parts of plants such as roots, stem, leaves, bark, seeds and fruits. Commonly found dietary based saponins are legumes: soybeans, chickpeas, peanuts, sapindus mukorossi, *Accacia concinna* pods.

3. Animal-based surfactant:

Animal derived surfactant take important position in medical field. Commonly known biosurfactants obtained from animals includes the lecithin, gelatin, casein, wool fat, cholesterol, and wax. This type of surfactant also contains low molecular weight surfactant includes lecithin and high molecular weight surfactant as like gelatin. Egg yolk provides the natural surfactant lecithin, which contains zwitterionic phosphatidylethanolamine (PE, ~18.1 %) as well as phosphatidylcholine (PC, ~78.7 %). Refined egg lecithin is good intravenous nutrition and an excipient for drug delivery. The commercially available source for gelatin is bovine skin, as well as bones and pigskin, which are applied as a stabiliser, thicker, and texturizer in food along with

non-food products. It is an inadequate source of protein surfactant yet shows excellent emulsifying qualities, which might be enhanced with enzyme-catalysed attachment of hydrophobic side chains. Different protein-based biosurfactants are available from animal sources of origin, like casein, egg albumin, bovine serum albumin, and human serum albumin. Bile acids as well as pulmonary surfactants are two physiologically significant animal-based surfactants. Clinical usage and preclinical animal research both point to the superiority of animal-derived surfactants over synthetic formulations.

Applications of Surfactants:

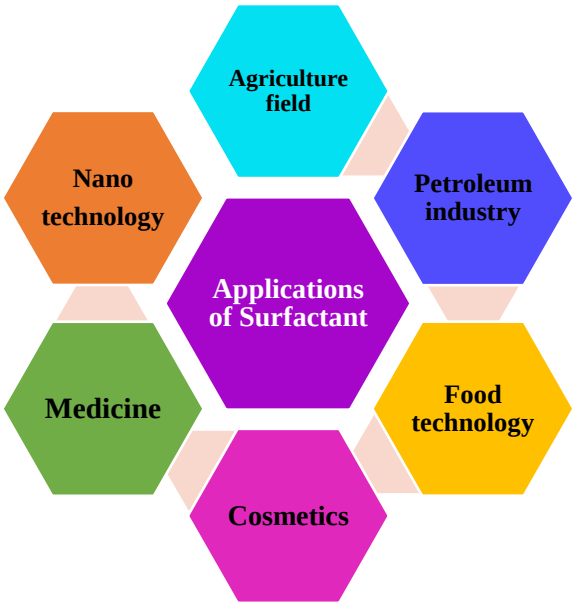
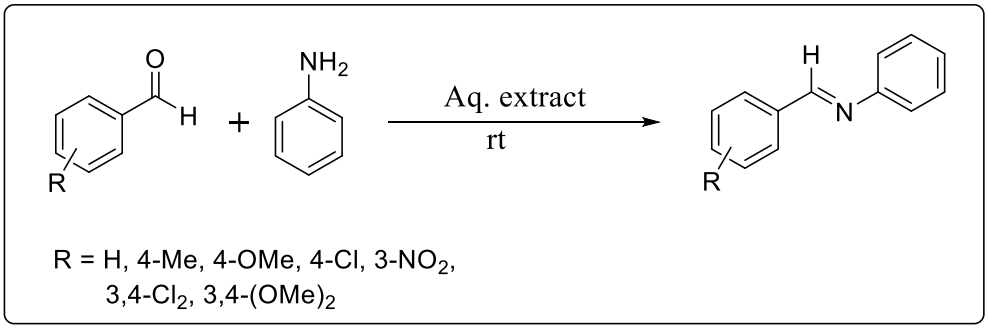


Figure 1.15 Applications of Surfactant

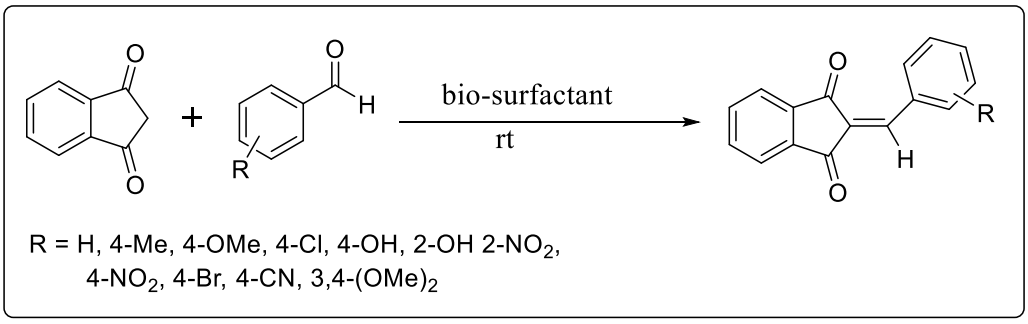
The implementation of biosurfactants as a green replacement for chemical surfactants in organic transformations has been successfully analysed by scientists in recent years. For this purpose, aqueous extracts of various fruits, plants, seeds, leaf and juice from fruit were chosen as the source of biosurfactants, including *Sapindus trifoliatus* fruit, chickpea leaf extract, *Balanites roxburghii*, and pods of *Accacia concinna.* The aqueous extracts of these fruits have an acidic pH and high surface activity due to the presence of several saponins; therefore, they show catalytic activity in various synthesises. Saponins are plant-based surfactants that contain the amphiphilic moieties in which sugars are connected to either the sterol or triterpene nonpolar groups.

Santosh Pore et al. [35] prepared a novel green catalyst from the pericarp of Sapindus trifoliatus fruits in 2010 and applied it to aldimine synthesis. The different derivatives of aldimines prepared from aromatic aldehydes and amines were catalysed by the natural extract. They observed the aromatic ketones and amines did not produce ketimines under similar reaction environments, which denotes the chemoselective nature of the extract **(Scheme 1.6).**



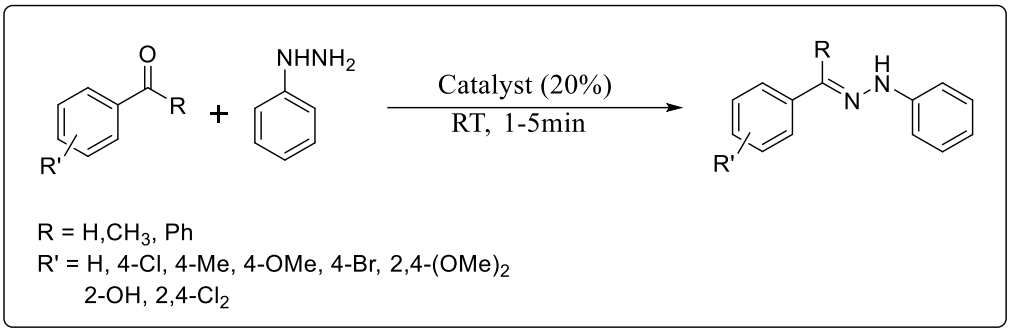
Scheme 1.6

Madhuri Barge and Rajashri Salunkhe [36] develop a protocol for C–C bond formation in an aqueous extract of Balanites roxburghii fruit. An aqueous extract of balanites roxburghii fruit is used as a biosurfactant for Knoevenagel condensation of 1,3-indanedione with aryl aldehydes, which acts as a biogenic green acidic catalyst **(Scheme 1.7).**



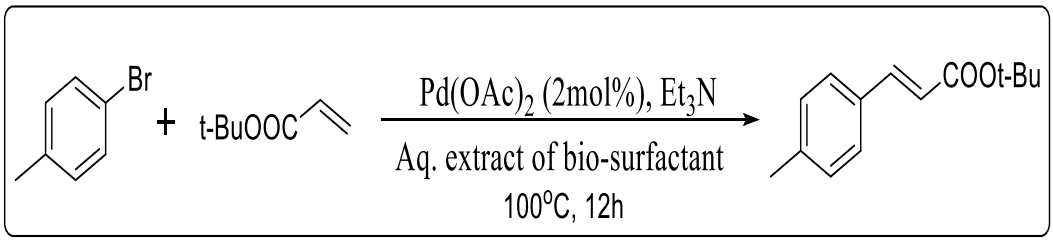
Scheme 1.7

An ecologically and economically affordable preparation of aryl-hydrazones in an aqueous extract of *Acacia* pods, which is a natural surfactant-type catalyst developed by Hemant V. Chavan and co-workers [37] **(Scheme 1.8).**



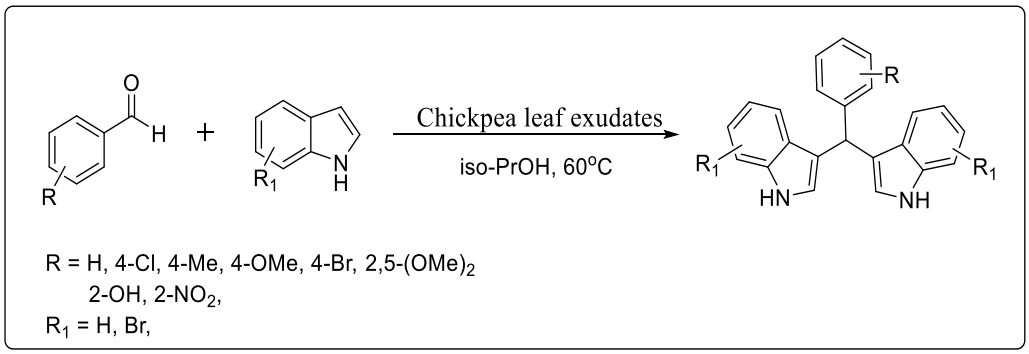
Scheme 1.8

Seema P. Patil and co-workers [38] reported a green and environmentally benign protocol for ligand free Pd-catalysed Mizoroki–Heck cross coupling reactions by using biosurfactant. The biosurfactant used in this study was prepared from the seeds of the pericarps (pods) of the *Acacia concinna* plant, which are soaked in water. The resulting extract contains saponin, which acts as a natural biosurfactant **(Scheme 1.9)**.



Scheme 1.9

Chickpea leaf exudates: a green brønsted acid type biosurfactant reported by Rupesh C. Patil et al. [39] for the synthesis of bis(indole)methane and bis(pyrazolyl)methane **(Scheme 1.10)**.



Scheme 1.10

1.3 Ionic liquid in organic transformation:

Ionic liquids (ILs) have fascinated the interest of researchers in the last decade, due to their particular properties [40], [41] [42] and their use in organic synthesis as a catalyst [43]–[45], catalysis [46]–[48], biocatalysts [49], [50], processes of nanomaterial synthesis [51], [52], polymerization reactions [53], [54], and electrochemistry [55]. Ionic liquids are polar and ionic in nature, couple with microwave irradiations very expeditiously, and are therefore the best solvent for organic reactions that are assisted by MW irradiations [56], [57]. Ionic liquids are considered as green reaction medium by chemists due to its remarkable characteristic properties including thermal-chemical stability, lower vapour pressure, recyclability, stable at high temperature in liquid state, non-combustible, easily solvates organic, inorganic and polymeric materials. Ionic liquids are molten organic salts composed of ions and exist in liquid electrolytes at temperature below 100°C. Ionic liquids are mostly organic cations by combined with inorganic anions creating crystalline moieties with less lattice energies enabling these salts to be in liquid state at or near room temperature. Ionic liquids are replacement for regular organic solvents those are harmful to the nature. The most commonly used ionic liquids are heterocyclic imidazolium, pyridonium, pyrazolium molecules in addition to another non-heterocyclic cations like as ammonium and phosphonium **(Figure 1.16)**.

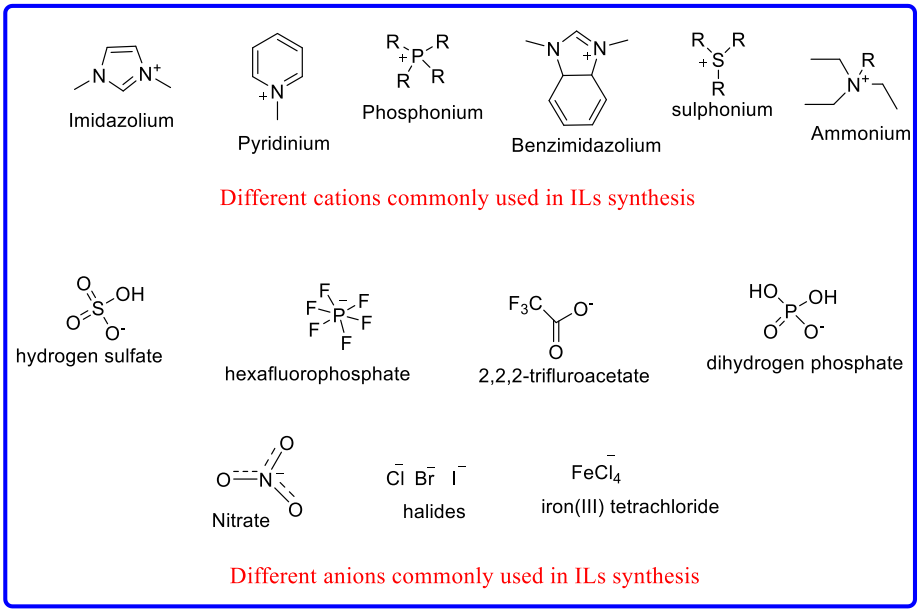


Fig. 1.16 Structures of cations and anions used in ILs synthesis.

The applications of ionic liquid in different field as shown in figure 1.17 along with its properties, advantages, and disadvantages.

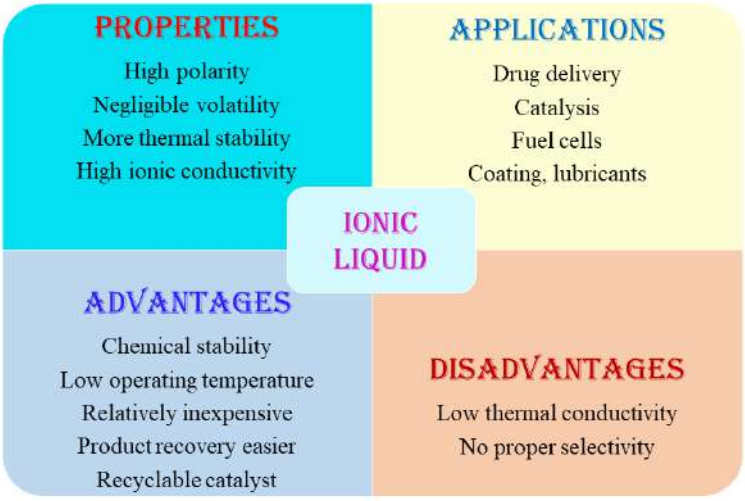
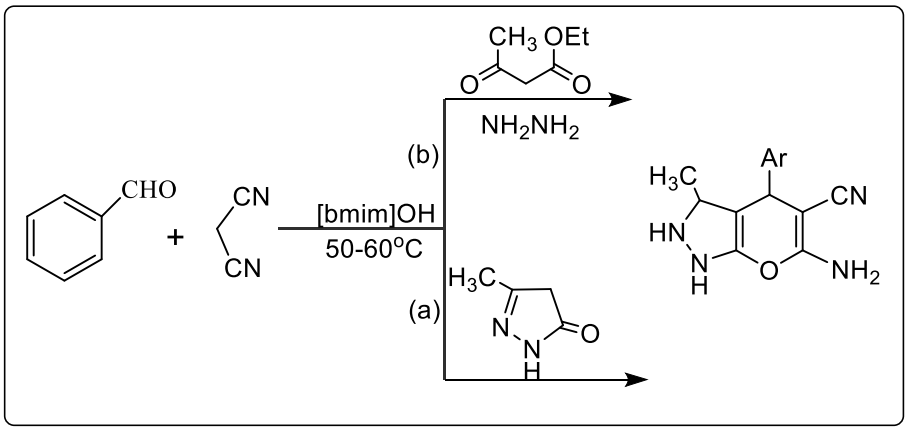


Figure 1.17 Properties, applications, advantages, and disadvantages of ILs

Applications of ILs in organic transformation

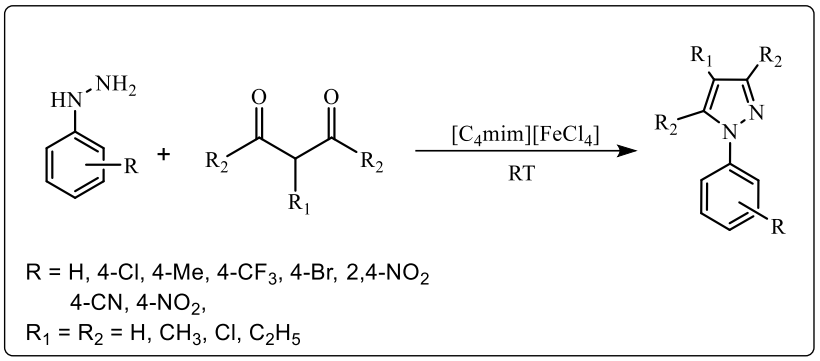
Jitender M. Khurana et al. [58] reported under solvent-free conditions, convenient and green synthesis of 4H-pyrans and 4H-pyrano[2,3-c] pyrazoles in ionic liquid 1-butyl-3-methyl imidazolium hydroxide {[bmim]OH}. [bmim]OH is a basic ionic liquid that is recyclable, inexpensive, reduces the time of reaction, and increases yield **(Scheme 1.11)**.



Scheme 1.11

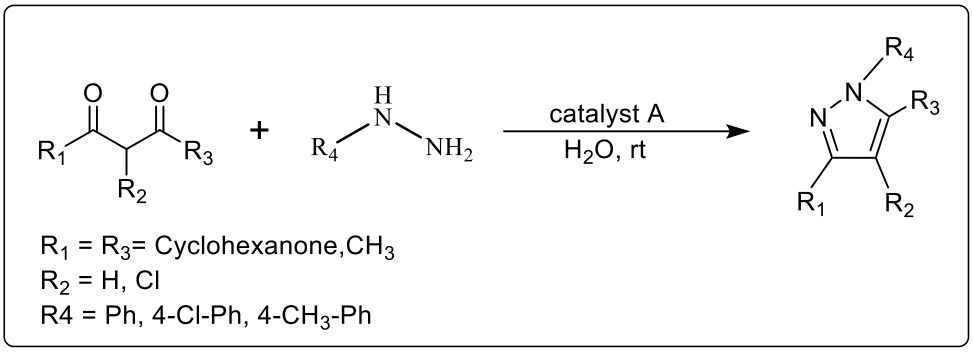
Manashjyoti Konwar et al. [59] carried out one pot synthesis of pyrazoles at room temperature in ionic liquid. Ionic liquid contains transition metal which is magnetic and also catalytic such ionic liquids are known as task-specific ionic liquids

(TSIL). There are various metal-based ionic liquids such as $[AlxCly]^-$, $[FeCl_4]^-$, $[MnCl_4]^{2-}$ $[CuCl_4]^{2-}$, $[NiCl_4]^{2-}$, $[PdCl_4]^{2-}$, etc. are used in synthesis but after screening $[FeCl_4]^-$ good result **(Scheme 1.12)**.



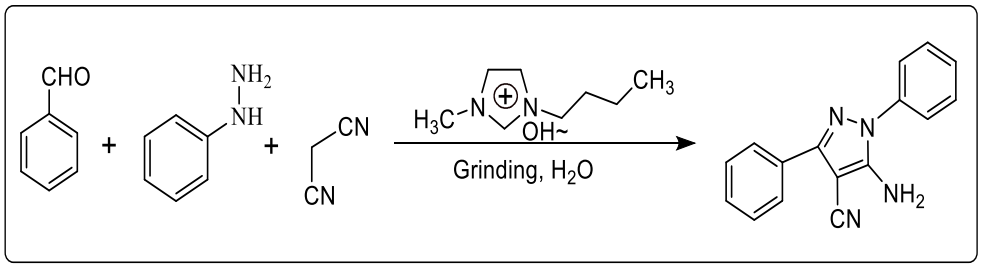
Scheme 1.12

Shirin Safaei et al. [60] synthesize pyrazoles using SO_3H brønsted acidic ionic liquid in water. The reaction between various 1,3-diketones and hydrazines or hydrazides in the presence of multi-SO_3H brønsted acidic ionic liquid at room temperature within 5 minutes gives regioselective derivatives of pyrazoles in excellent yield **(Scheme1.13)**.



Scheme 1.13

Srivastava et al. [61] carried out synthesis of functionally diverse pyrazole derivatives by ionic liquid catalysed with grinding in water. Reaction of malononitrile, phenyl hydrazine and diversified aldehyde in ionic liquid-1-butyl-3-methyl imidazolium hydroxide [(Bim)OH], with water without by-products gives desired product in good yield **(Scheme 1.14)**.



Scheme 1.14

1.4 Microwave assisted organic transformations (MAOT):

Microwave irradiation is one of the prominent non-conventional energy sources whose usefulness in synthetic chemistry have increased considerably in recent years [62]. During the second world war, Randall and Booth at the university of Birmingham, as part of the development of RADAR, devised a device for creating fixed-frequency microwaves, the magnetron [63]. Initially, it was established that microwaves warmed up water; after that, microwaves were used in household and commercial devices for heating and cooking purposes, which started in the 1950s. Tappan introduced first kitchen microwave oven in 1955 but its domestic use increases during the 1970's and 1980, s. Then scientists wonder why it is only used for domestic purposes and begin using microwave ovens for synthesis in the laboratory [64], but both household as well as laboratory ovens operate at 2.45 GHz. The electromagnetic spectrum shows microwaves are placed between infrared radiation and radio waves **(Figure 1.18)**. Researcher first investigate the mechanisms of dielectric heating and search the significances of the microwave irradiation technique in the chemical synthesis.

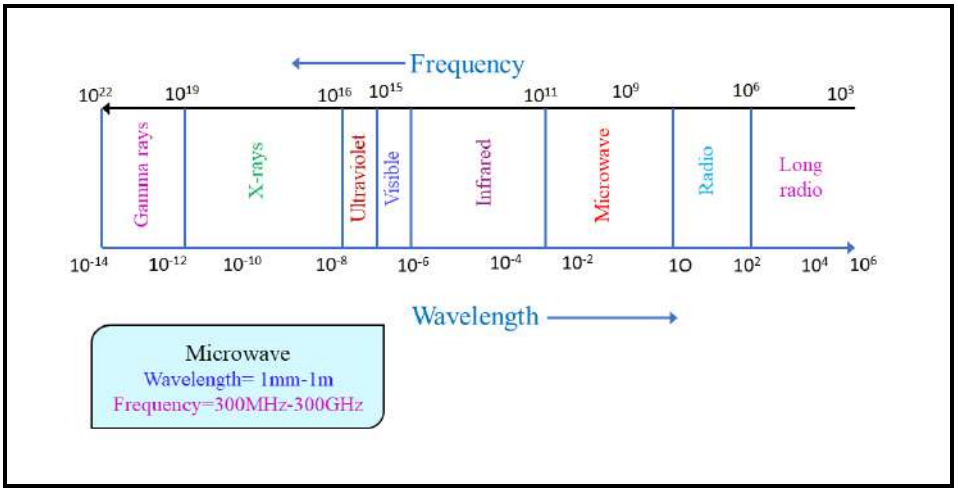


Figure 1.18 Electromagnetic spectrum

Selectivity is observed in the absorption of radiation and heating, such as when materials having high dielectric constant values have a tendency to consume microwave radiation, while less polar materials and highly ordered crystalline substances are inferior absorbers [65]. The microwaves transferred energy not only due to conduction but also due to dielectric loss. The affinity of a compound to come in contact with microwave heating is dependent on the dielectric properties, the dielectric loss factor (e''), and the dielectric constant (e'). Therefore, dielectric loss factor (e'') indicates the effectiveness with which electromagnetic radiation is transformed into heat, while the dielectric constant (e') represents the efficiency of molecules to absorb microwaves. The ratio of $\tan\delta = (e'')/(e')$, indicates the capability of these molecules to modify electromagnetic energy into heat at a given frequency and temperature. High values of dissipation factor(δ) of the sample means easy susceptibility to microwave energy [66]–[68]. Other important factors are ionic conduction, size, charge, conductivity of ions and their interaction with the solvent. In microwaves, heating starts from the inner side of the flask and radiates outside, in contrast to conventional heating, which initiate from the outside, and therefore microwave heating is less economical in terms of source energy used. Microwave radiation has some prominent microwave dielectric heating effects on organic reactions viz. thermal effect and non-thermal effect [69], [70]. Thermal effects are caused by the different temperatures created due to microwave dielectric heating.

The aquatic emulsification and polymerization of butyl acrylate, acrylic acid, and methacrylic acid in the presence of pulsed electromagnetic radiation is the first recorded application of microwave irradiation in organic transformation [71]. The first successful application of microwave heating in organic transformation was made in 1986 by Gedye et al. [70] and Giguere et al. [72]. From the 19th to the 20th centuries, diverse organic reactions were successfully conducted in commercial as well as advanced microwave with a reduction in time and increasing yield.

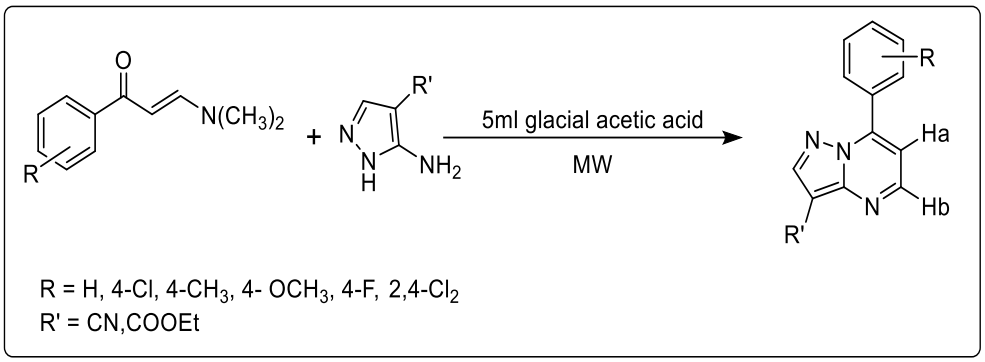
The microwave-assisted organic transformations have been carried out in two ways:

1. Microwave assisted organic transformations in presence of solvents
2. Microwave assisted organic transformations without solvent

1. Microwave assisted organic transformations in presence of solvents:

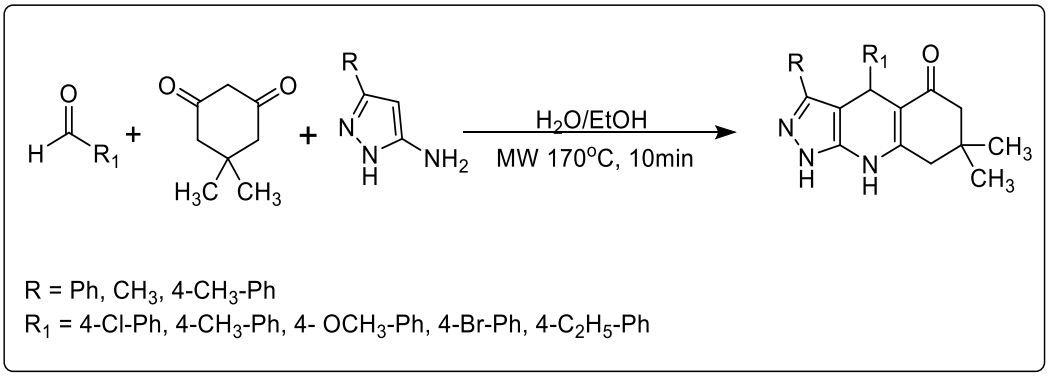
To conduct the reaction under microwave choice of solvent depend on solubility of reagent in that solvent and solvent which couples effectively with microwaves and acts as the energy transfer medium.

Li Ming et al. [73] reported MW assisted synthesis of pyrazolo [1,5-a] pyrimidine via the reaction of enaminones and 5-amino-1H-pyrazoles. This is prepared in glacial acetic acid at 120°C for 20 min under adjustable microwave 0–25 W gives excellent yield **(Scheme 1.15)**.



Scheme 1.15

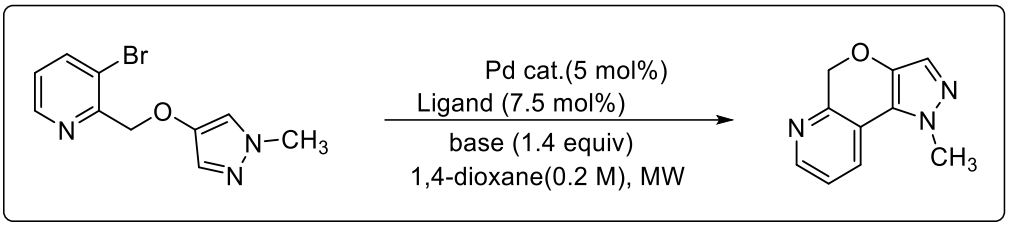
Anastasiya Yu et al. [74] reported green protocol for the synthesis of pyrazolo [3,4-b]quinolin-5-ones by using microwave irradiations. These is three component reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium at 175°C (375W) **(Scheme 1.16)**.



Scheme 1.16

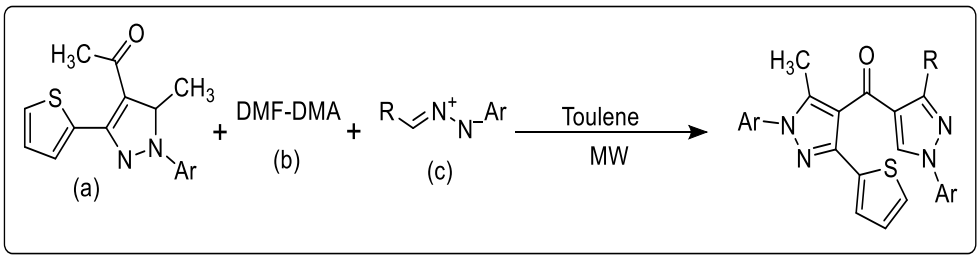
Aaron T. Garrison et al. [75] carried out synthesis of 1,5 dihydropyrazolo[3′,4′:5,6] pyrano[3,4-b]pyridines under microwave irradiation. They

develop regioselective Pd(0)-catalysed C−H arylation reaction between pyrazoles within 5 min in the microwave create 98% product **(Scheme 1.17)**.



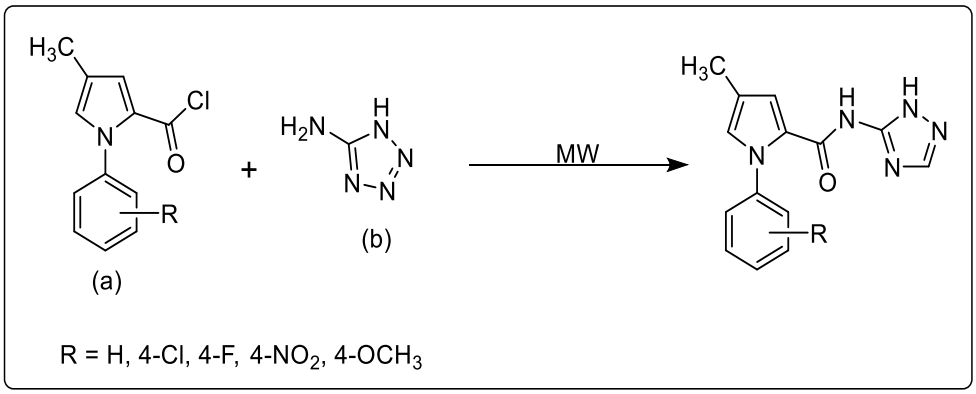
Scheme 1.18

Sobhi M. Gomhal et al. [76] demonstrate one pot multi component synthesis of some novel pyrazole (22) scaffolds as potent anticancer agents under controlled MW conditions. Multi-component reaction of acetyl pyrazole (a), dimethylformamide dimethylacetal (DMF–DMA) (b) and nitrile imine (c) in toluene under conventional heating as well as microwave irradiation at 150°C. But MW within 4-5 min. gives above 80% yield as compare to conventional heating that require 10-15hr with 60-70% yield **(Scheme 1.19)**.



Scheme 1.20

Jun Hu et al. [77] synthesize tetrazolyl pyrazole amides via microwaves. This tetrazole pyrazole amide shows various interesting biological activities such as, bactericidal, pesticidal, herbicidal and antimicrobial activities. Derivative of tetrazolyl pyrazole such as 3-methyl-1-phenyl-N-(1H-tetrazol-5-yl)-1H-pyrazole-5-carboxamide (23) were prepared by the reaction of various 3-methyl-1-phenyl-1H-pyrazole-5-carbonyl chlorides (a) and 1H-tetrazol-5-amine (b) under microwave irradiation at 400W (110^{o}C) for 20 min obtain 78-90% yield **(Scheme 1.21)**.

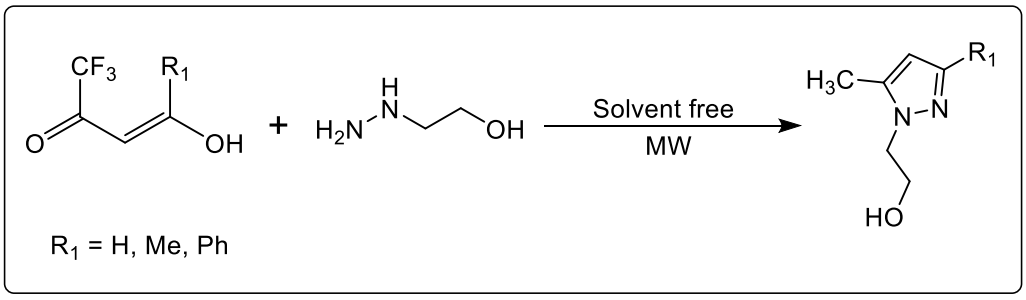


Scheme 1.21

2. Microwave assisted organic transformations without solvent:

In these environmentally conscious days, the researchers develop solvent free procedures which involve simple workup, avoid toxic solvents, economically safe, clean and efficient.

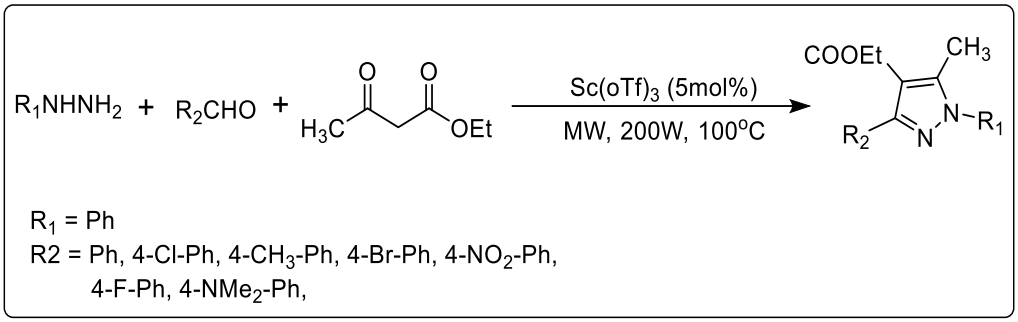
Lilian Buriol et al. [78] develop a new protocol for pyrazole synthesis under microwave irradiation and solvent-free conditions. In this synthesis they avoid use of organic solvent and conventional heating. To obtain 4,5-dihydro-1H-pyrazoles or pyrazoles there is cyclocondensation takes place between enones and hydrazine's under MW irradiation under solvent free condition. They also perform same reaction by using domestic MW oven and also conventional heating but MW equipment for synthesis gives better yield as compare to others **(Scheme 1.22)**.



Scheme 1.22

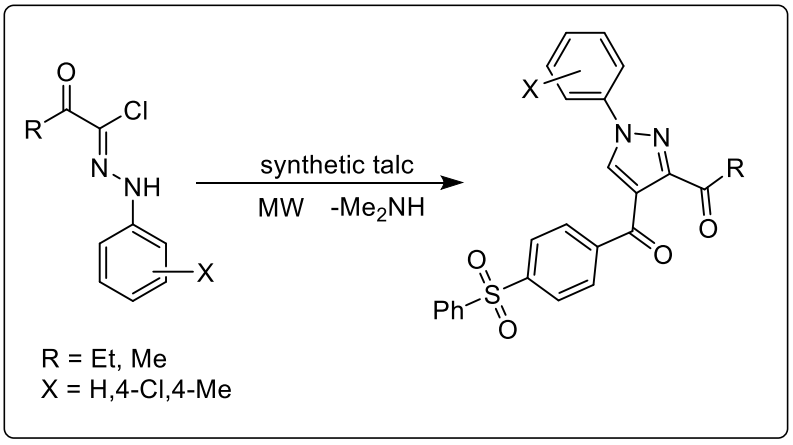
Kumkum Kumari et al. [79] carried out microwave assisted, solvent free, synthesis of functionalized pyrazoles using [$Sc(OTf)_3$] catalyst. Mixture of phenyl hydrazine, aldehydes and ethyl acetoacetate is irradiated under microwave at 200W and 100^oC in 3-6 min produces pyrazole with excellent yield (74-92%). $Sc(OTf)_3$ is a

powerful Lewis acid catalyst. It is mild reaction conditions, easy to handling, stability to moisture, and reusability, therefore $Sc(OTf)_3$ is environmental safer catalyst **(Scheme 1.23)**.

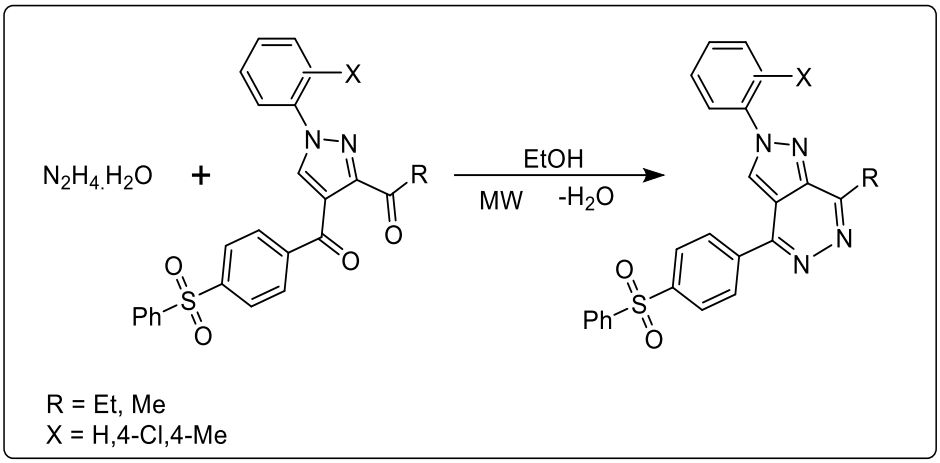


Scheme 1.23

Mohamed F. Mady et al. [80] reported synthesis of novel pyrazole and pyrazolo[3,4-d]pyridazine derivatives via microwave irradiation. Synthesis of pyrazole by using synthetic talc was added to an enaminone derivative and hydrazonyl halides under MW at (249 psi, 130°C) and pyrazolo[3,4-d]pyridazine is prepared from pyrazole derivatives in ethanol (2 ml), hydrazine hydrate (98%) was added and irradiated by microwaves using pressurized conditions (249 psi,120°C) for 3 min. Both reactions also carried out using conventional heating but MW gives excellent yield (89%) within short time **(Scheme 1.24 and 1.25)**.

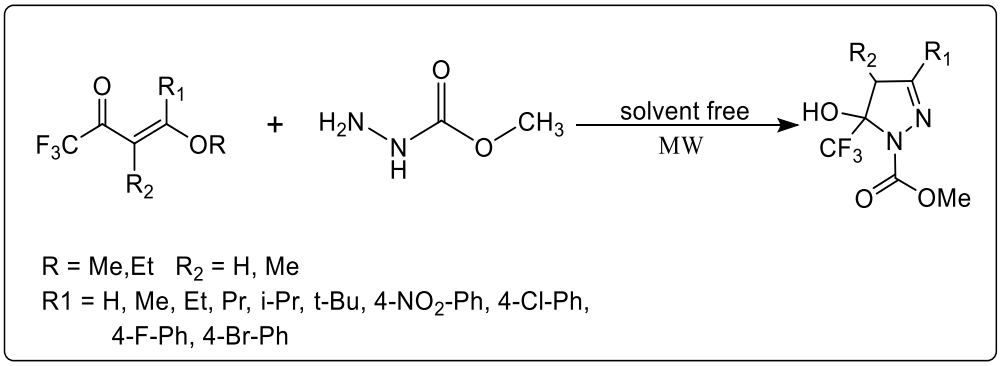


Scheme 1.24



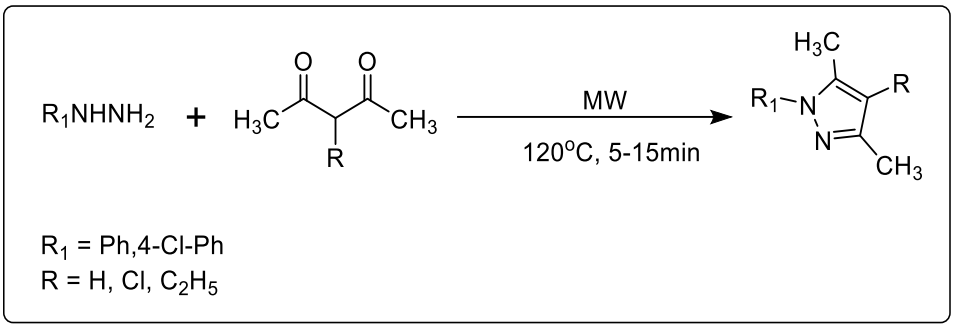
Scheme 1.25

Marcos A. P. Martins et al. [81] demonstrate 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1H-pyrazoles under microwave conditions without solvent. The product of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazoles obtained by the reaction taking place between enones and methyl hydrazinocarboxylate without solvent in microwaves is reported within 6–8 min with a high as excellent yield (50–92%). This methodology is a very effective alternative technique to regular conventional heating and produces the heterocyclic compounds in excellent yields in very little time **(Scheme 1.26)**.



Scheme 1.26

Buchi Reddy Vaddula et al. [82] gives microwave assisted catalyst and solvent free synthesis of pyrazoles and diazepines. Pyrazole is synthesized by condensation of hydrazine's/hydrazides with 1,3-diketones in 5-15min give excellent yield up to 99% that is full conversion of reactant in to product reduces generation of waste, save time, energy and cost **(Scheme 1.27)**.



Scheme 1.27

Advantages and disadvantages of microwave irradiations in organic synthesis is shows in following figure **(Figure 1.19).**

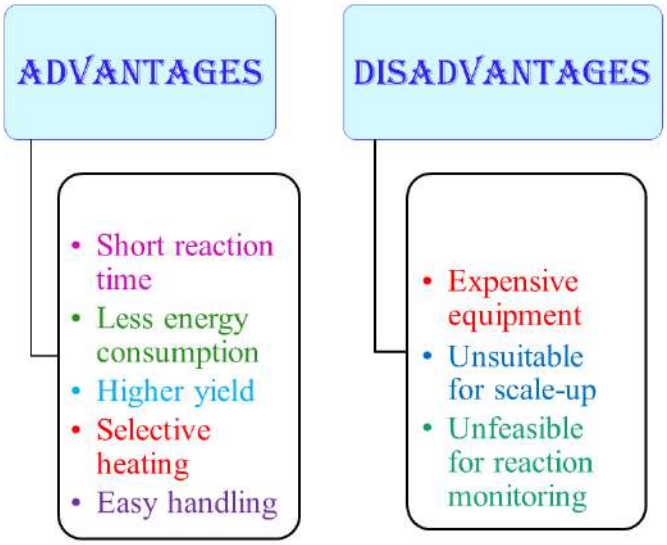


Figure 1.19 Advantages and disadvantages of MW irradiations

1.5 Organic Transformations Under Ultrasonic Irradiation:

The usefulness of ultrasonic waves to assist reactions is now a well-established field of chemistry. The innovative ultrasonics era starts with Professor Paul Langevin's (1917) design of a quartz sandwich transducer for underwater sound transmission in submarines for different purposes. Professor Alfred Lee Loomis modified the wartime acquaintance with Professor Robert Wood and provided for collaborative work and the writing of any joint research article. In 1926, Wood told Loomis of Langevin's experimental work and suggested that the topic provided a broad range of study in physics, chemistry, biology, along with in the medical field. It was this group start involvement of ultrasound into the chemistry in 1927. The actual use and application of sonochemistry took place in the 1980's, soon after [83], [84].

The effect of ultrasound waves on chemical reactivity is known as sonochemistry. Sonochemistry is a chemical application of ultrasound. The best region for initiating chemical reactions is 20-100 kHz and 1-10 MHz is most suitable for ultrasound imaging of body organs in medical science **(Figure 1.20)**. The wavelength of ultrasound for 20 to 100 kHz range is from 7.5 to 0.015 cm. The phenomenon of cavitation seems to be the origin of the Sonochemical effect and the physical phenomenon, high temperatures or electrical fields, occurs during cavitation which breaks the many bonds, mostly homolytic cleavage occurs. The effect of ultrasound waves is not due to the direct interaction of ultrasonic beam with the reaction material but it is due to the phenomenon of cavitation created during the process of implosion of cavitating bubbles [85]. Ultrasound is in fact transmitted through a medium via pressured waves by causing vibrational motion of molecules which alternately compressed and stretched the molecular structure of the medium which consequently, it breaks down and a cavity is formed [86]. This cavity is called cavitation bubble and the process "cavitation". Many of these cavitation bubbles, generated in ultrasonic field which absorb energy from the propagating sound waves. The bubble then implodes creating very high temperature, pressure and mass transfer in a very small area of bubbles **(Figure 1.21)**. These tiny spaces act as micro reactors and due to which changes chemical reactivity of reactant molecule [87].

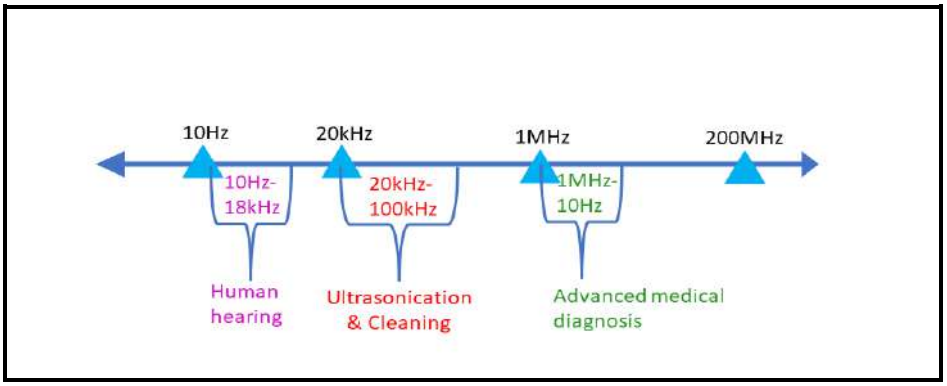


Figure 1.20 Ultrasound frequency range

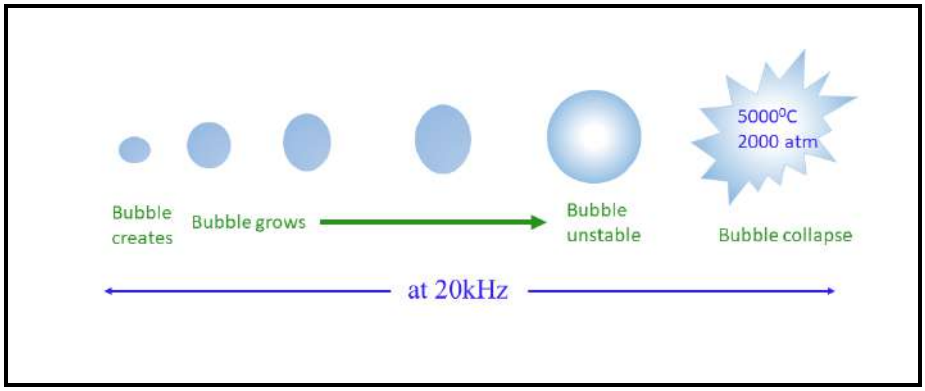


Figure 1.21 Bubble formation and collapsing.

There are two types of ultrasonic devices used in organic synthesis:

1. Introducing ultrasound waves directly into reaction mixture through the ultrasonic probe.
2. Use of ultrasonic cleaning bath which emits ultrasound waves into the water filled in the bath that propagates to the reaction vessel placed in the water of ultrasonic bath.

In laboratory simple ultrasonic bath of 10-1liter capacities has been used for synthesizing different organic compounds **(Figure 1.22)**. The reaction vessel can be properly placed in water bath through which ultrasound propagates and the wave passes through the reaction vessel irradiating the reaction mixture. The symbol **"))))))))"** is used for reaction carried out under ultrasound irradiation.

Figure 1.22 Laboratory used ultrasonication bath.

The ultrasound irradiations have applications in different fields with lots of advantages **(Figure 1.23)**. In literature survey, the different types of organic reactions that were carried out under ultrasound irradiation and studied by different researchers are given below:

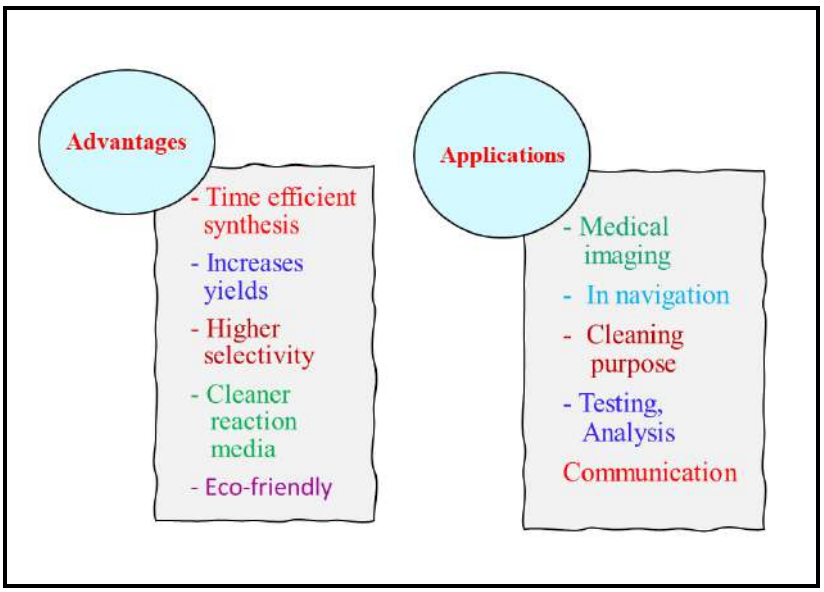
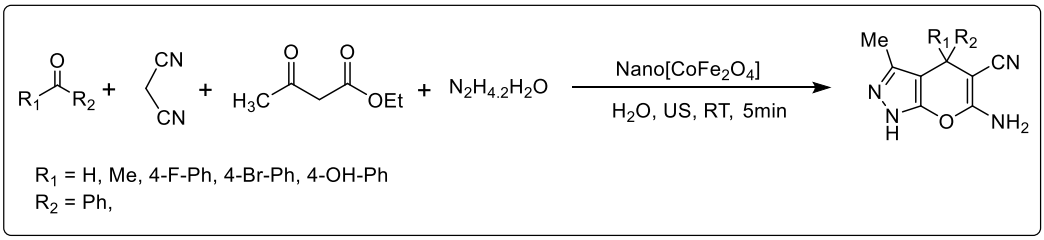


Figure 1.23 Advantages and applications of ultrasound irradiations.

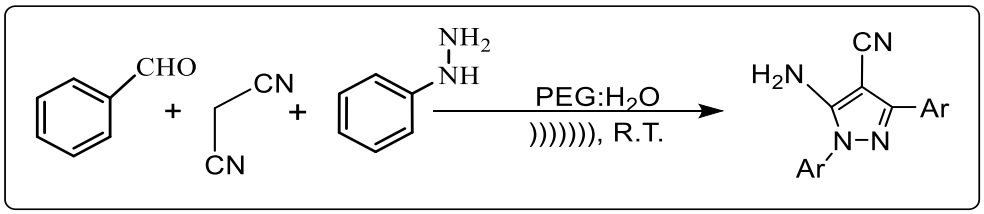
M. Mishraa et al. [88] demonstrate one-pot synthesis of magnetic nano-[$CoFe_2O_4$]-catalysed pyrano [2, 3-c] pyrazoles via ultrasound waves. Under ultrasound irradiation reaction takes place between various aldehydes as well as dialdehydes, and ketones with malononitrile, followed by addition of ethyl acetoacetate along with hydrazine hydrate in the occurrence of magnetic nano-[$CoFe_2O_4$] catalyst within 5 min. gives excellent yield (90-96%) **(Scheme 1.28).**



Scheme 1.28

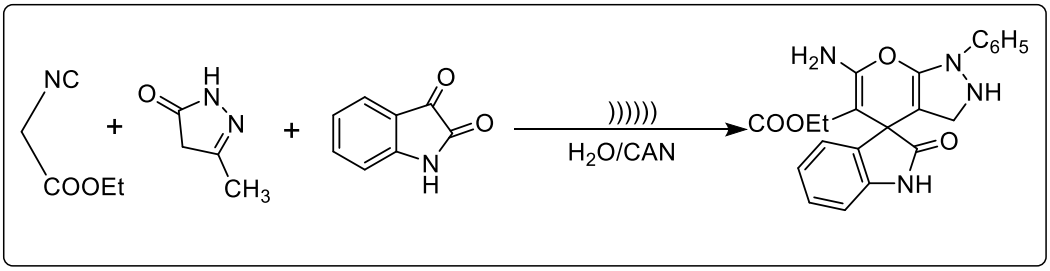
Environmental friendly protocol developed by Firouzeh Nemati et al. [89] for the catalyst-free synthesis of highly substituted pyrazole under ultrasonic radiation. These protocols cost effective, time saving, required less energy that is it follows green

chemistry principles. A mixture of aldehyde, malononitrile, phenyl hydrazine and PEG (polyethylene glycol): H_2O (1:1) was irradiated under ultrasonic irradiation at ambient temperature and at appropriate time (30 min.), product is obtained in excellent yield (99%) **(Scheme 1.29)**.



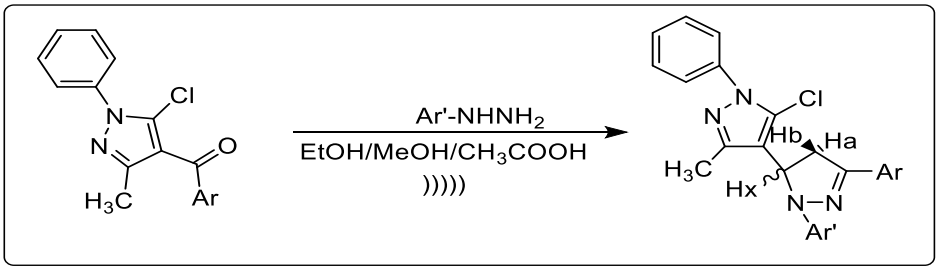
Scheme 1.29

Anshu Dandia et al. [90] carried out ultrasound assisted green synthesis of spiro[pyrano[2,3-c] pyrazoles]. The mixture of isatin, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one gives desired product by applying various conditions and catalyst but ultrasound and catalyst-CAN gives expected result with time up to 20 min yield goes to 97% **(Scheme 1.30)**.



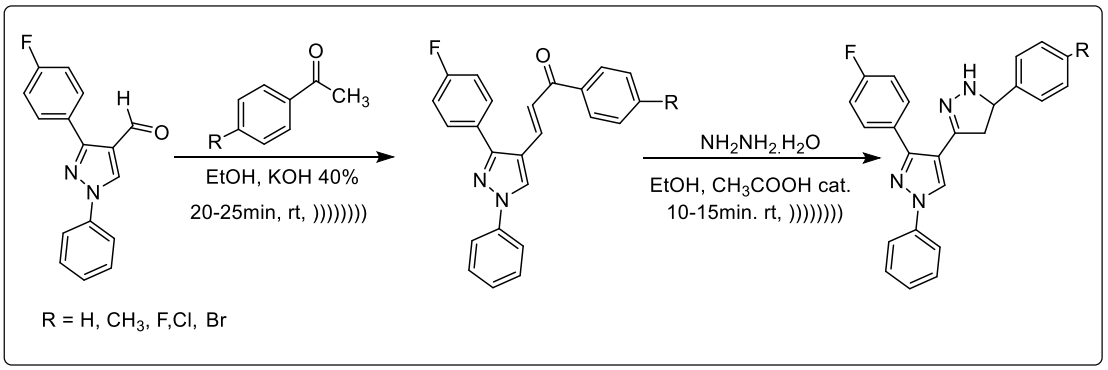
Scheme 1.31

Jorge Trilleras et al. [91] synthesize ultrasonics assisted synthesis of 5-(pyrazol-4-yl)-4, 5-dihydropyrazoles derivatives. Synthesis is done by using chalcones and hydrazine's in ethanol or methanol or acetic acid under sonication at ambient conditions in 20 min. gives 80% yield **(Scheme 1.32)**.



Scheme 1.33

Reactions under ultrasonic irradiation is a 'green' alternative methodology for organic transformation that offers many advantages over conventional synthesis, since it provides uniform heating, faster reaction times, and minimal side reactions, therefore Sharad N. Shelke et. al. [92] under ultrasonic irradiation synthesized fluorinated pyrazoline derivatives in 20-25 min. with 80% yield **(Scheme 1.34)** .



Scheme 1.34

The present introductory topic represents the significance of various green approaches that enhance organic transformations through the utilisation of hydrotrope, biosurfactant, ionic liquid, and alternative energy sources including microwave and sonochemistry. These alternative ways minimise or eliminate the environmental issues caused due to traditional chemical productions carried out at the laboratory and industrial level.

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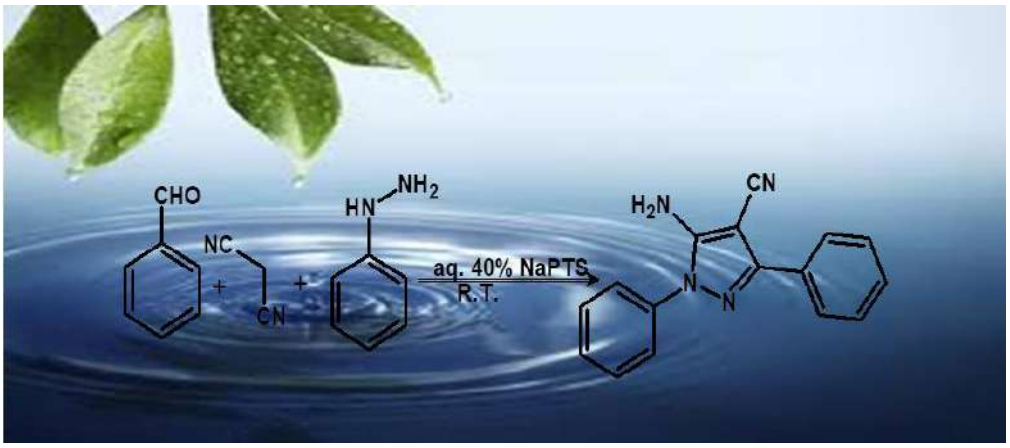
CHAPTER – 2

GREENER SYNTHESIS OF 5-AMINOPYRAZOLE-4-CARBONITRILE IN AQUEOUS HYDROTROPIC MEDIUM



JOURNAL OF HETEROCYCLIC CHEMISTRY

ARTICLE

Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for greener synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium

Aboli Sapkal, Santosh Kamble

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Greener and Environmentally Benign Methodology for the Synthesis of Pyrazole Derivatives

Aboli Sapkal, Santosh Kamble

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CHAPTER 2

Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for Greener Synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium

2.1 Introduction

Heterocycles account for more than half of all known pharmaceutical compounds due to their wide range of physical, chemical and biological properties with a broad spectrum of reactivity along with stability. Therefore, they take important position in the world of organic chemistry [1]. They have great impetus in a variety of fields, such as drugs, vitamins, natural products, hormones, agrochemicals, dyes and many others. Nitrogen-containing heterocycles are widely spread in the ecosphere which play a significant role in metabolism because of their special structural stability as well as reactivity [2]. Along with naturally occurring N-containing heterocycles, many synthetic N-heterocycles with great physiological and pharmacological properties also exist [3]. From these pharmacophores, one can arrange a diverse class of drugs with potent yield [4]. Heterocyclic compounds have solubility as well as salt-formation properties that restrict their direct oral-consumption and bioavailability [5].

Among the nitrogen-containing heterocycles, pyrazole **(Figure 2.1)** is one of the important core structures of diverse biologically active compounds, which has numerous applications in chemistry, biology and other sciences [6]. German Chemist Ludwig Knorr used the term pyrazole for the first time in 1883. He also synthesizes analgesic drugs which containing pyrazole ring known as antipyrin or phenazone (c) in 1883. The first natural pyrazole, pyrazolayl-alanine (d), was extracted from watermelon seeds (Citrullus vulgaris) in 1959 another natural pyrazole 3-n-nonypyrazole (e) extracted from Houttuynia Cordata which is a plant of the “piperaceae” family by Japanese workers **(Figure 2.2)**. Pyrazole is one of the important five-membered aromatic heterocycles that bears two nitrogen atoms and three carbon atoms in adjacent positions [7], [8].

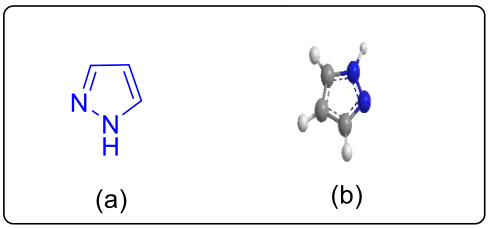


Figure 2.1 (a) Structure of Pyrazole (b) 3D structure of Pyrazole

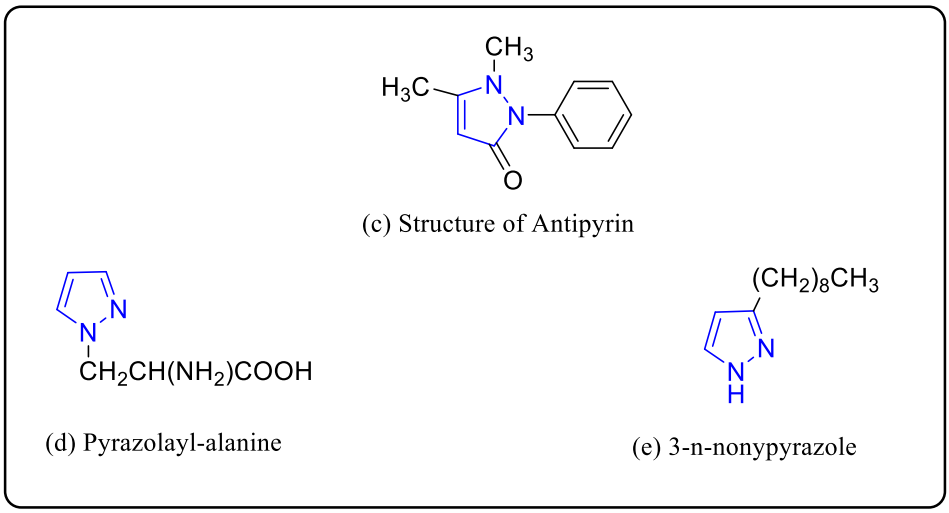


Figure 2.2. Structure of Antipyrin and some naturally occurring pyrazole molecules.

Pyrazole derivatives having deep involvement in pharmacy because of diverse biological activities including antimicrobial [9], antiviral [10], antitumor [11], anti-inflammatory [12], antioxidant [13], anticancer [14], analgesic [15], anti-HIV [16], anticonvulsant [17], antiangiogenic [18], and antidiabetic [19] **(Figure 2.3)**. It plays promising role in inhibiting the activity of against monoamine oxidase in the therapy of diseases such as Parkinson's and Alzheimer's. Pyrazole also have importance in agrochemical field mainly in herbicides, pesticides, insecticides, fungicides and dyestuffs [20], [21].

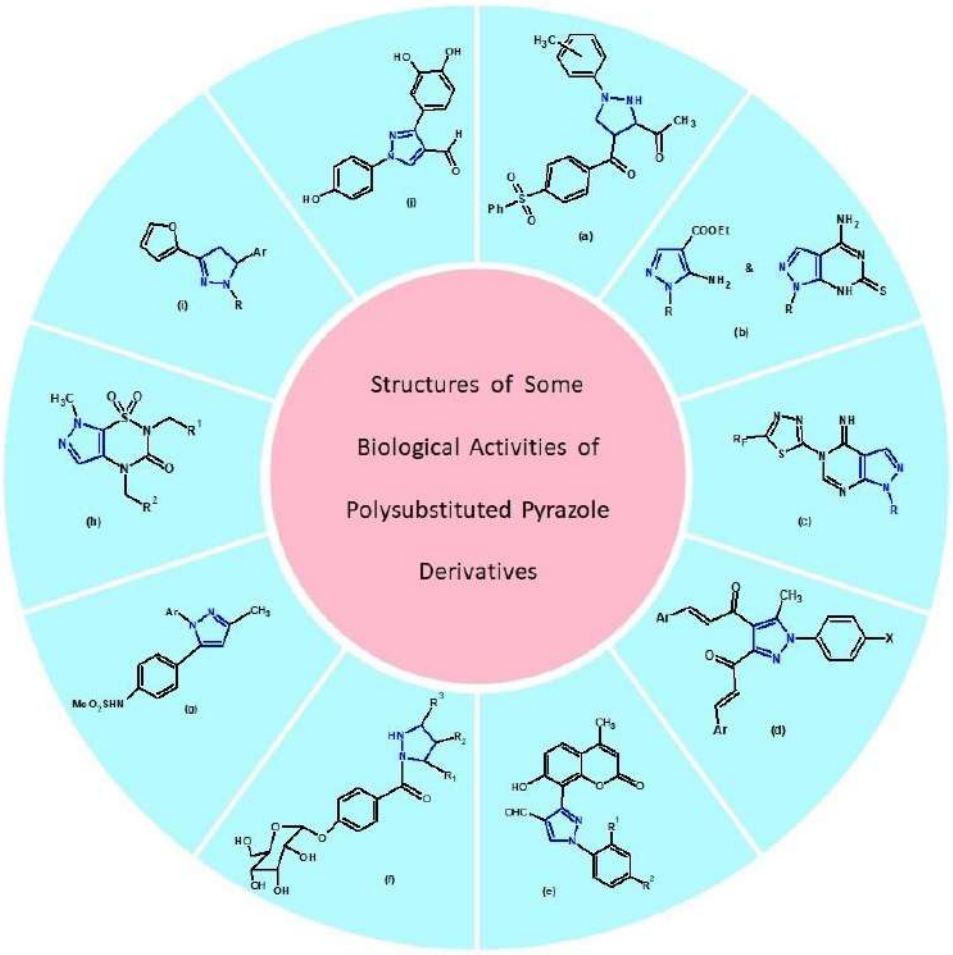


Figure 2.3 Structure of biologically active Pyrazole derivatives.

Due to the wide application of pyrazole derivatives in different fields, it is the subject of deep investigation. According to a literature survey, there are several methods that are reported for the synthesis, like as 1,3 dipolar cycloadditions of diazo compounds, reaction of chalcones with hydrazine, four component reaction between terminal alkynes, hydrazine, carbon monoxide, and aryl iodide, three component reaction between aldehyde, phenyl hydrazine, and malononitrile, and simple reaction between 1,3 diketone with hydrazine by using different conditions along with a catalyst that synthesizes different derivatives of pyrazole which contains pyrazole as a core structure.

Knorr [22] first synthesized a 5-methyl-2-phenyl-2 (f), 4-dihydro-3H-pyrazol-3- one (g), **(Figure 2.4)** by a reacting ethyl acetoacetate with phenyl hydrazine in 1883.

These derivatives (f) and (g) shows anti-inflammatory activity [23] along with promising anti-diabetic agent [24].

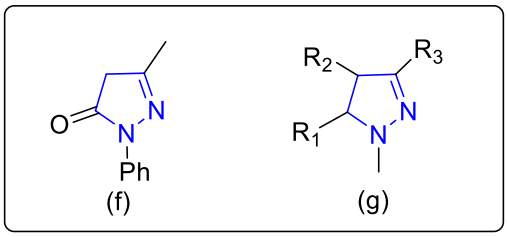


Figure 2.4 Knorr first synthesized pyrazole derivatives

In 1938 L. Ruzicka et al. [25] synthesizes first steroidal pyrazole derivative (h), cholest-4-eno-[3,2-c]-pyrazole-5-carboxylic acid **(Figure 2.5)**. In which pyrazole ring fused with steroidal scaffold that shows diverse biological activities.

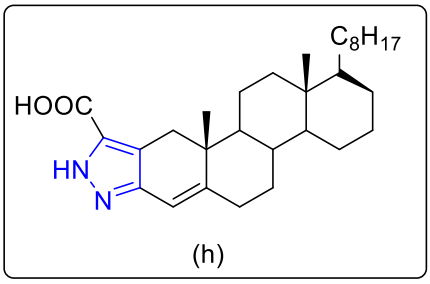
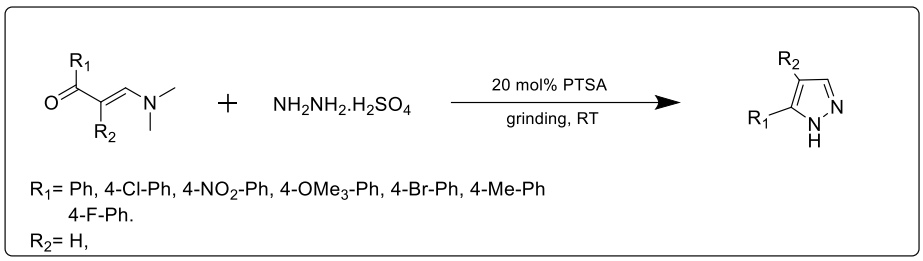


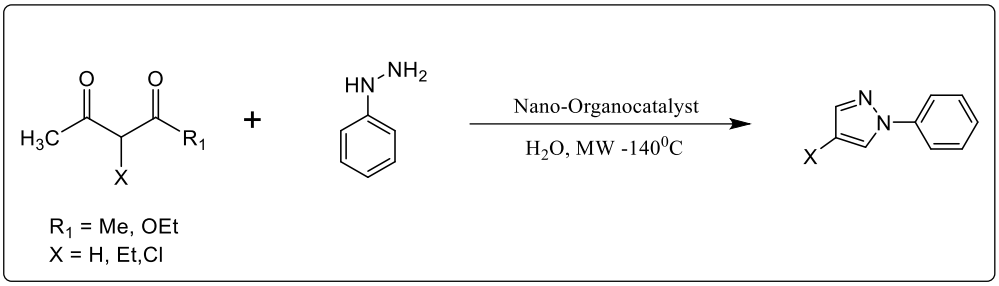
Figure 2.5 First steroidal pyrazole derivative.

Kelvis Longhi et al. [26] demonstrate an efficient synthesis of various derivatives of NH-pyrazoles from the reaction mixture of β-dimethyl amino vinyl ketones along with hydrazine sulfate with p-toluene sulfonic acid (PTSA) as a catalyst in absence of solvent, on grinding firstly liquid forms then eutectic mixture create which distribute reactants uniformly gives product in 6-12 min. with 90% yield **(Scheme 2.1)**. They show solvent free simple synthesis with minimum waste within short time develop green route of synthesis.



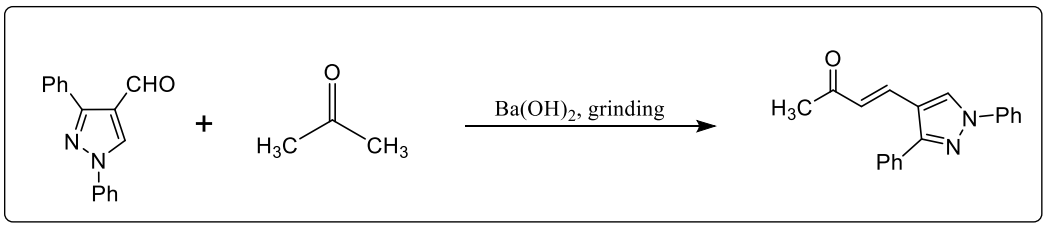
Scheme 2.1

Vivek Polshettiwar et al. [27] reported microwave-assisted pyrazole synthesis by using nano-organocatalyst. Pyrazole is synthesized by various hydrazine's along with hydrazides reacted efficiently with 1,3-diketones in presence of nano-organocatalyst (nano ferrite (Fe_3O_4) supported glutathione) was irradiated under microwave at 50-250W for 20 min obtain the product in good yields (78-96%) **(Scheme 2.2)**.



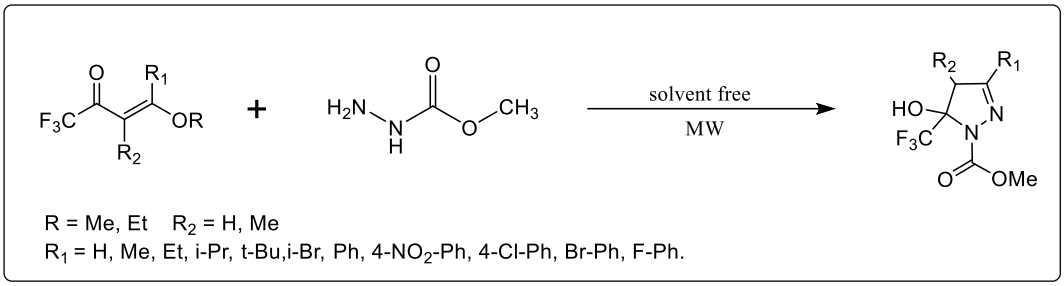
Scheme 2.2

Parvin Kumar et al. [28] synthesise pyrazole chalcones without solvent at room temperature. Activated barium hydroxide (C-200) synthesises pyrazole substituted chalcones from a mixture of pyrazole aldehydes and acetophenones by grinding with a mortar and pestle in 5–10 minutes, giving an above-average yield of 90%. It is an eco-friendly, solvent-free Claisen Schmidt condensation **(Scheme 2.3)**.



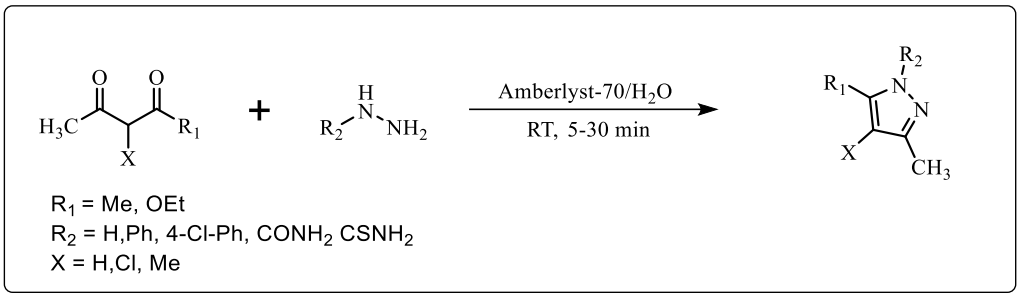
Scheme 2.3

Marcos A. P. Martins et al. [29] demonstrate the preparation of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1H-pyrazoles in the absence of solvent under microwave conditions. For the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazoles, the cyclo-condensation between 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones and methyl hydrazinocarboxylate under solvent-free microwave conditions is reported within 6–8 min with a high to excellent yield (50–92%). This methodology is an effective alternative to conventional thermal heating, which produces the heterocyclic products with excellent yields in less time **(Scheme 2.4)**.



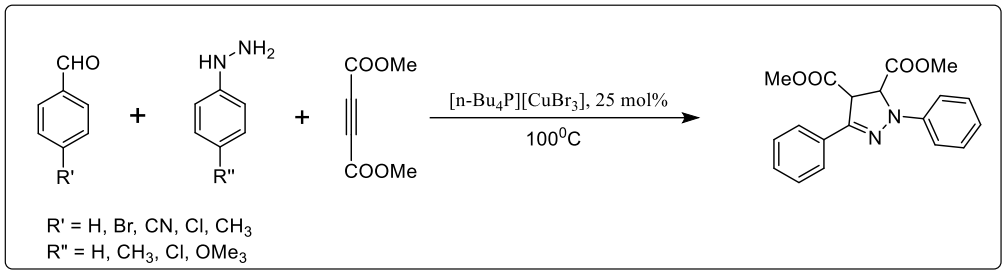
Scheme 2.4.

Recyclable catalyst attracts the attention due to it directly effect on environment together with economy therefore Nitin Lad and Dipali Dange et al. [30] demonstrate greener approach for the synthesis of pyrazole such as amberlyst-70 as a recyclable catalyst in aqueous medium. Mixture of hydrazine's/hydrazides and 1,3-dicarbonyls in presence of Amberlyst-70 at 30ºC stirred for 5-30 min, product is form which is further purified and then yield is calculated. In less time 95% yield is obtain as well as catalyst is recycled up to five cycles give good yield. Separation and reuse of catalyst is easy therefore this protocol is more favorable in green synthesis **(Scheme 2.5)**.



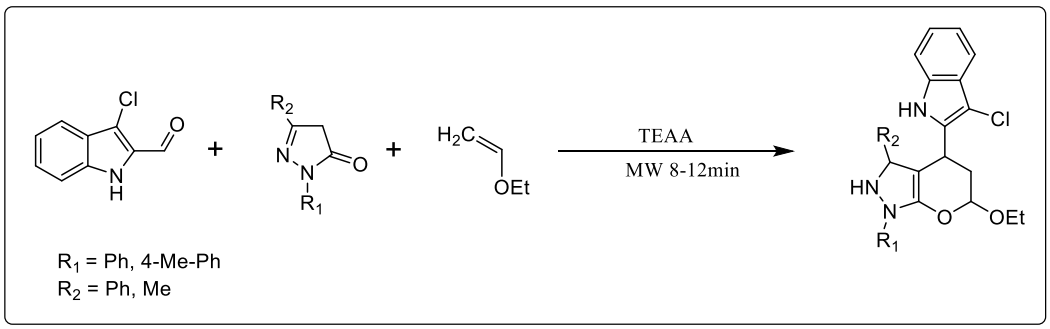
Scheme 2.5

The green synthesis of substituted pyrazole in the presence of Cu(II) ionic liquid is done by Shirin Safaei et al. [31] with a higher yield. A mixture of aldehyde, aryl hydrazine, then dimethyl acetylene dicarboxylate (DMAD) and [n-Bu_4P] [$CuBr_3$] were mixed, and the composite was heated at 100^oC without solvent for the appropriate time in 1–1.5 hrs., giving a 52–88% yield. Reusability, along with recyclability, of a catalyst is of practical importance in minimising the amount of waste and reducing pollution. Therefore, use of ionic liquid is safe as well as environmentally effective that reduce time, therefore total cost along with energy consumption also minimizes **(Scheme 2.6)**.

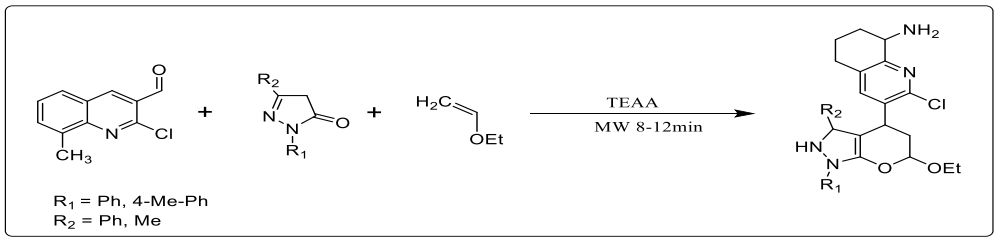


Scheme 2.6

Narsidas J. Parmar et al. [32] develop one-pot preparation of numerous heteroaryl pyrano[2,3-c]pyrazoles in ionic liquid under microwave-irradiation. It is three-component hetero-Diels–alder reaction, afforded indolyl and quinolyl pyrano[2,3-c]pyrazoles **(Scheme 2.7 & 2.8)**. Microwave reduces time from hrs. to 8-12 min with 90% yield these is main advantage of MW irradiation that minimizes time, cost, pollution along with increasing yield.

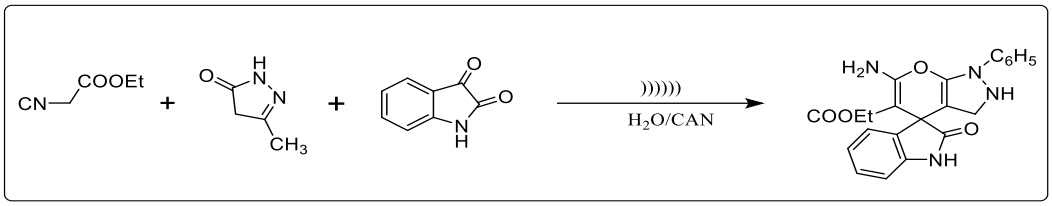


Scheme 2.7



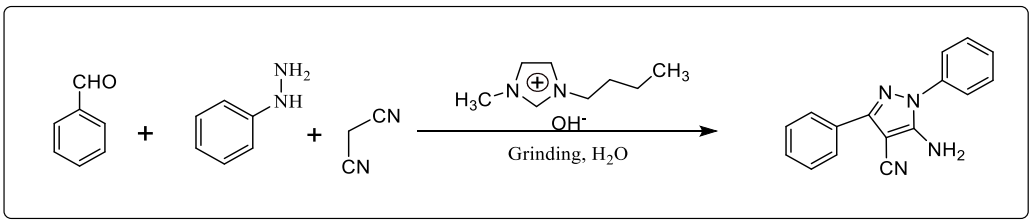
Scheme 2.8

Anshu Dandia et al. [33] carried out ultrasound-assisted green synthesis of spiro[pyrano[2,3-c] pyrazoles. The mixture of isatin, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one gives the desired product by applying various conditions together with the catalyst, but ultrasound with the catalyst CAN gives the expected result with time up to 20 min and a yield of 97% **(Scheme 2.9)**.



Scheme 2.9

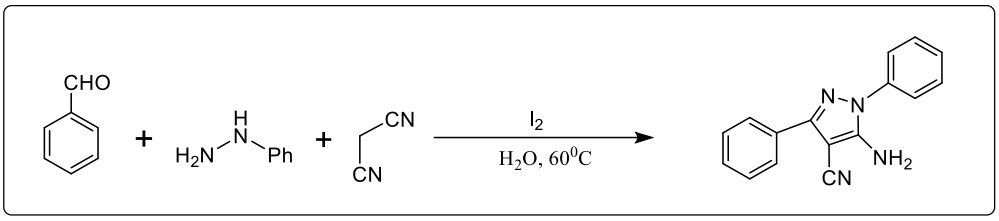
Srivastava et al. [34] carried out synthesis of functionalized pyrazole derivatives by ionic liquid catalyzed with grinding in water. These triply green routes fulfill all shades of green chemistry. Reaction of malononitrile, phenyl hydrazine and diversified aldehyde in ionic liquid-1-butyl-3-methyl imidazolium hydroxide [(Bim)OH], with water without by-products gives desired product in good yield (90%) in 10-30 min **(Scheme 2.10)**. Here combination of green route, ionic liquid with grinding in water develop environmentally as well as economically facile synthesis.



Scheme 2.10

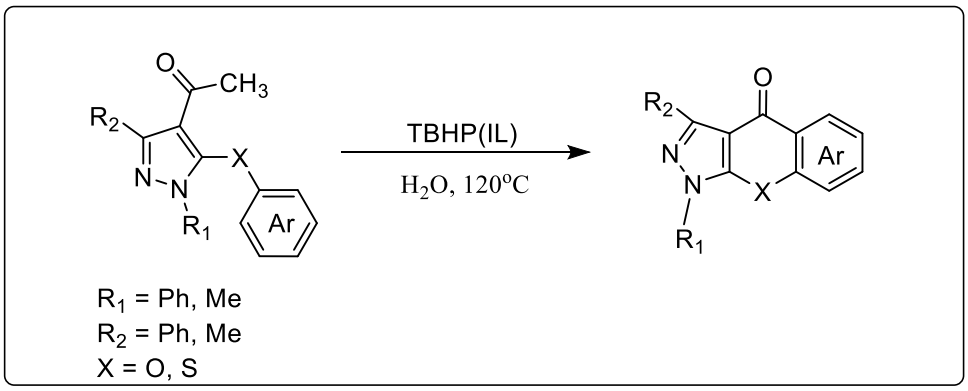
One pot synthesis of highly functionalized pyrazole, developed by Madhulika Srivastava et al. [35] in water, catalyzed by iodine. They carried out reaction at various

temperature by using different catalyst in iodine at 60°C within 20 min phenyl hydrazine, malononitrile and a diverse range of aldehydes reacted, product obtain in high yield 85-94% **(Scheme 2.11)**. Reaction goes by Knoevenagel condensation between aldehyde derivatives and malononitrile gives 1,2 unsaturated compound which attacked by phenyl hydrazine (Michael addition) after which intramolecular cyclisation gives pyrazole.



Scheme 2.11

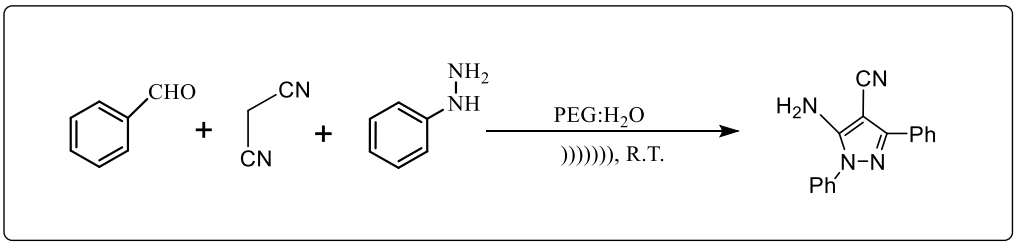
He Li et al. [36] developed green pathway for the preparation of chromeno[2,3-c] pyrazol-4(1H) through ionic liquid in aqueous media. Various kinds of ionic liquids and solvents are tested for obtaining desired product in good yield. Ionic liquids are easily recycled and reused after drying in vacuo. Reused 5-times without loss of activity, reaction of 3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with tert-butyl hydroperoxide (TBHP) in H_2O at 120°C for 24 hr. gives 73% yield **(Scheme 2.12)**.



Scheme 2.12

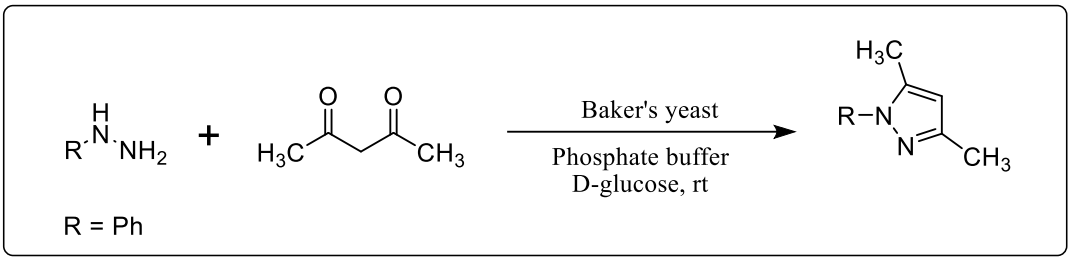
Environmentally friendly protocol developed by Firouzeh Nemati et al. [37] for the catalyst-free synthesis of pyrazole scaffolds under ultrasonic radiation. These protocols cost effective, time saving, required less energy that is it follows green chemistry principles. A mixture of aldehyde, malononitrile, phenylhydrazine in PEG

(polyethylene glycol): H_2O (1:1) was irradiated under ultrasonic waves at ambient temperature for appropriate time (30 min.), product is obtained in excellent yield (99%) **(Scheme 2.13)**.



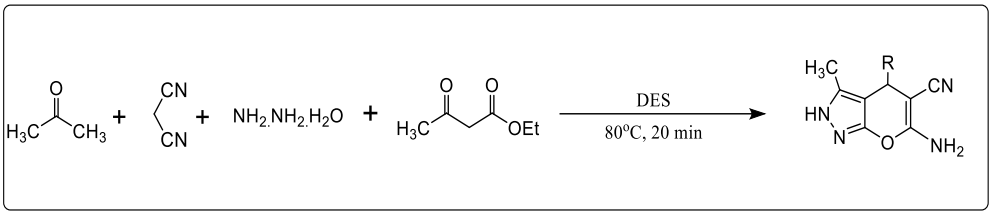
Scheme 2.13

Ananda Mane et al. [38] develop protocol for the synthesis of pyrazole by adding fermented baker's yeast to 1,3-dicarbonyl compound and hydrazine/hydrazide the resulting mixture was aroused at room temperature for indicated time gives yield (70-90%) is depend on substituent **(Scheme 2.14)**. It is a biodegradable, biocatalyst gives eco-friendly, inexpensive, easily available, less hazardous pyrazole derivatives.



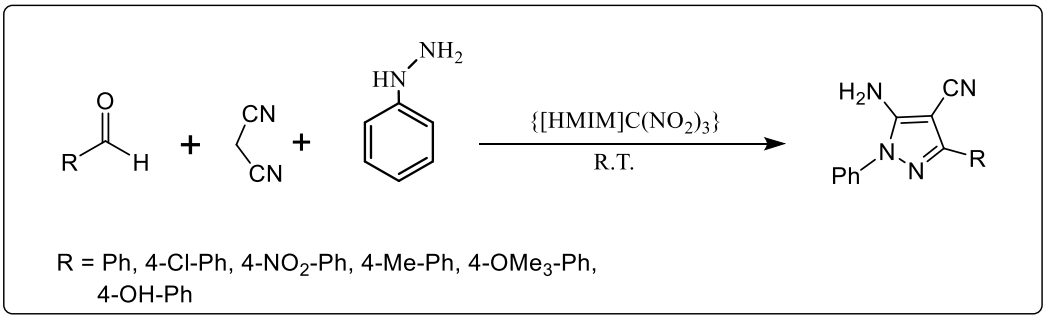
Scheme 2.14

Recently, researchers focused more attention on the utility of deep eutectic solvents (DES) for organic transformations due to Manisha R. Bhosle et al. [39] develop a protocol for production of 6-amino-2H, 4H-pyrano[2,3-F]pyrazole-5-4 carbonitriles in deep eutectic solvent such as cholinechloride: urea. Use of DES avoids toxic solvents together with catalyst. Reaction between aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate in DES at 80ºC in 20 min with 82% yield **(Scheme 2.15)**.

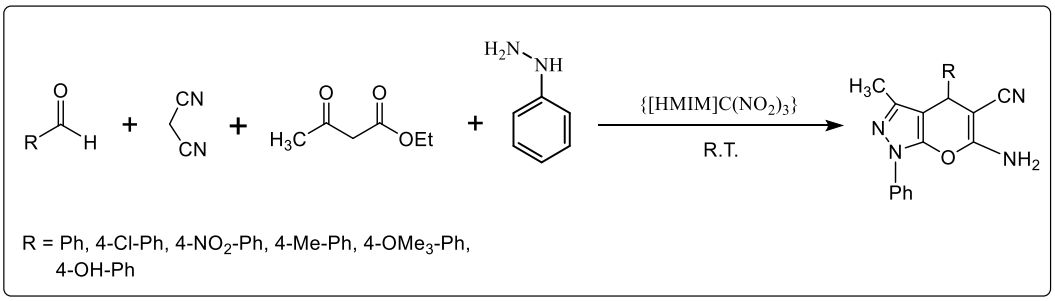


Scheme 2.15

Mohammad Ali Zolfigo et al. [40] first used 1-methylimidazolium trinitromethanide {[HMIM] $C(NO_2)_3$}: as a nano sized ionic liquid for creation of library of pyrazole molecules (58). There is Knoevengel condensation of aldehyde with malononitrile gives arylidene malononitrile then Michael addition of phenylhydrazine on it obtain the product in good yield. Also prepare 1,4-dihydropyrano-[2,3-c]-pyrazole (59) by a one-pot four-component, reaction between various aromatic aldehydes, malononitrile, phenylhydrazine, and ethyl acetoacetate in similar conditions in 20 min gives 92% yield **(Scheme 2.16 & 2.17)**.



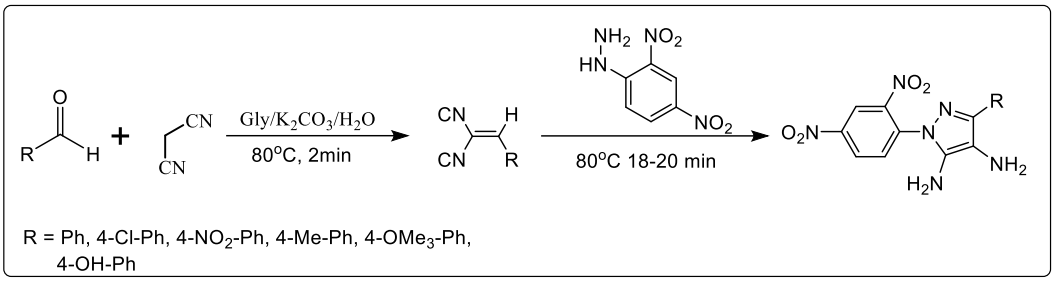
Scheme 2.16



Scheme 2.17

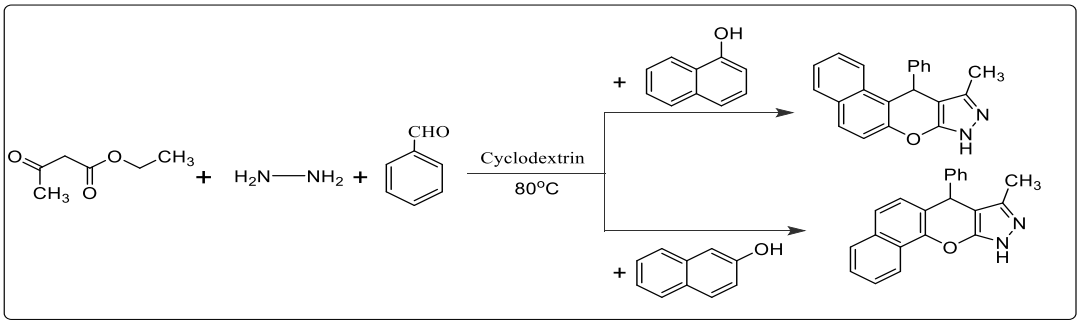
Hamid Beyzaei et al. [41] carried out green synthesis of polysubstituted pyrazoles along with study of their antimicrobial activities in presence of deep eutectic solvent (DES). Synthesis carried out between cyanoacetonitrile, 2,4-

dinitrophenylhydrazine and various aldehydes in deep eutectic solvent (DES)-glycerol/potassium carbonate at 80°C in 20 min gives 91% yield. DES acts as ecofriendly media or efficient catalyst for organic transformation **(Scheme 2.18)**.



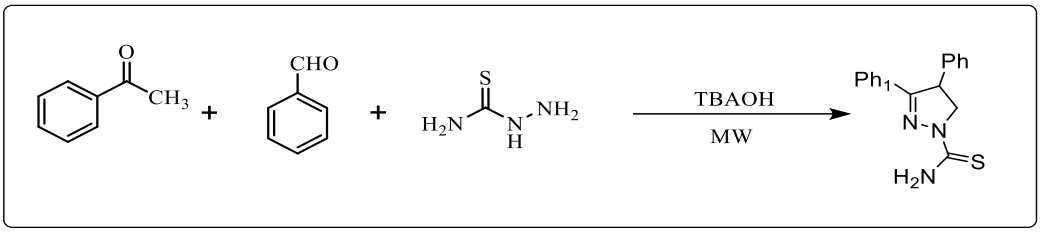
Scheme 2.18

Cyclodextrin is an efficient green catalyst used by Samahe Sadjadi et al. [42] for synthesis of benzochromeno-pyrazole. They design ionic liquid-modified cyclodextrin nano sponges. Synthesis of benzochromenopyrazole derivatives by reacting hydrazine hydrate, benzaldehydes, α or β-naphthol and ethyl acetoacetate in 15 min gives high yield 94% **(Scheme 2.19)**.



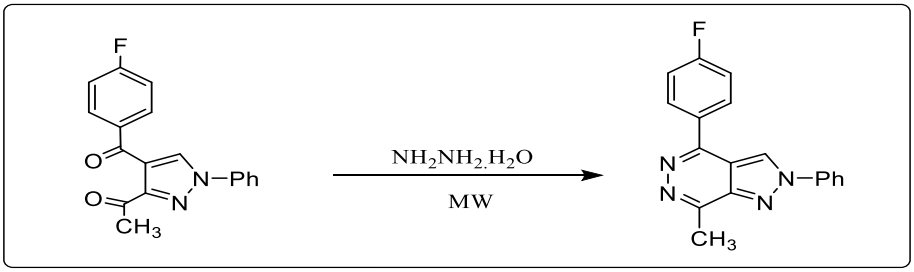
Scheme 2.19

Hamid Reza Farmani et al. [43] synthesize green protocol is microwave-assisted synthesis of 4, 5-dihydro-1H-pyrazole-1-carbothioamides in water. Aqueous medium with microwave both is environmentally green and efficient route. Mixture of aldehyde, acetophenone, thiosemicarbazide and tetrabutylammonium hydroxide [TBAOH] as base in water irradiated under MW at 300W, 70°C in 2-3 min gives 80-96% yield. This methodology provides easy, simple, environmentally safe protocol as well as improve sustainability **(Scheme 2.20)**.



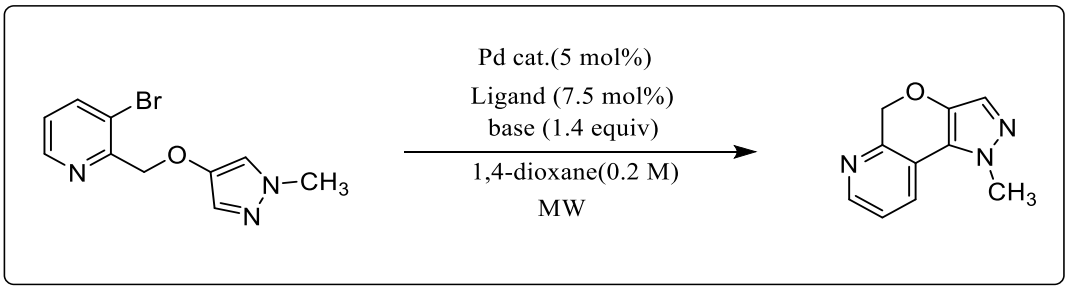
Scheme 2.20

Ismail I. Althagafi et al. [44] develop MW-assisted synthesis of novel regioselective pyrazoles and pyrazolopyridazines. They synthesise pyrazole molecules consisting of a fluorophenyl ring by the 1, 3-dipolar cycloaddition of nitrile imines and enamines using not only traditional but also advanced microwave irradiation, but MW gives good results in 10–30 min. with 85% yield **(Scheme 2.21)**.



Scheme 2.21

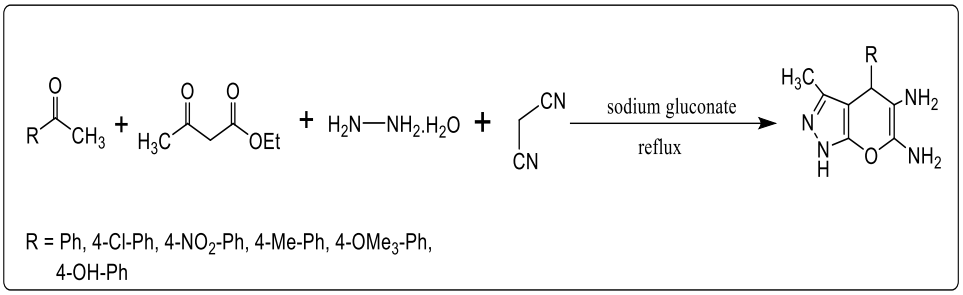
Aaron T. Garrison et al. [45] carried out the synthesis of 1,5 dihydropyrazolo[3′,4′:5,6] pyrano[3,4-b]pyridines (21) by microwave irradiation. They develop a regioselective Pd(0)-catalyzed CH arylation reaction of pyrazoles within 5 minutes in the microwave, creating 98% product **(Scheme 2.22)**.



Scheme 2.22

Amol Khandebharad et al. [46] carried out synthesis of dihydropyrano [2,3-c] pyrazole (72) in presence of biodegradable catalyst such as sodium gluconate. It is one-pot multicomponent reaction of aldehyde or ketone, Cyanoacetonitrile, ethyl

acetoacetate and hydrazine hydrate in aqueous medium obtain the high yield (92%) within short period of time (20 min) **(Scheme 2.23)**.



Scheme 2.23

2.2 Present Work:

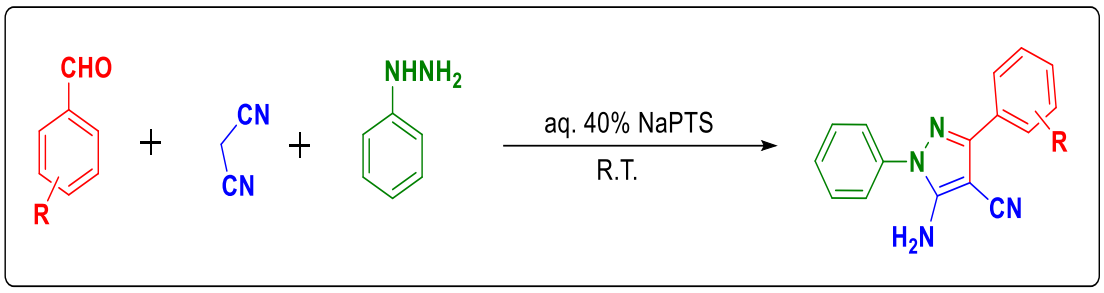
Synthesis by MCRs is more accepted aspect because it is effective, required less energy, decrease cost, time and generation of by-products. Therefore, the formation of new MCRs with green aspect has enticed more attentiveness, specifically in the field of medicinal chemistry, organic synthesis along with material science. Synthesis of heterocyclic scaffolds is performed via MCRs in the presence of various green tools as well as by using green catalyst which produces good results.

All the reported methodologies require harsh reaction conditions viz. organic solvent, metal framework catalyst, acids along with bases but this reaction conditions are not sustainable to the environment, expensive, hazardous, time consuming. Therefore now days researchers focused on develop more eco-friendly, less hazardous, environmentally safe methodologies, such as ionic liquid, [47] I_2 in water, [35] 1-methylimidazolium trinitro methanide {[HMIM]C$(NO_2)_3$}as a nano ionic liquid (NIL), [40] PEG-400 and water under ultrasound waves [37] but designing of ionic liquid and other solvent are also little costly which cause environmental issue therefore we use here hydrotrope in these synthesis which can full fill some of the conditions of green chemistry that is environmentally safe, less hazardous, cost effective, easy handling, no any toxic solvent, that is it is sustainable to environment

2.3 Result and Discussion:

Hydrotropes are increase solubility of sparingly soluble organic compounds [48]. Hydrotropes are water- soluble and surface-active compounds; they substantially increase the solvability of organic moieties such as esters, alcohols, ketones, aldehydes, hydrocarbons and fats [49]–[51]. It acts as carrier for poorly soluble drugs and also for

non-polar organic compounds [52]. The main feature is the nature of hydrotropes, on which reaction conditions depend, and the maximum solubilities of reactants or substrates observed at their minimum hydrotropic concentration (MHC). After that hydrotrope increases dissolvability of materials there is direct interaction between reactants those are insoluble in aqueous medium. The mechanism by which insoluble and sparingly soluble compounds are soluble in water is aggregation and MHC [53]. There is difference between self-aggregation of hydrotrope and micelle, that is presence of minimum hydrotrope concentration (MHC) analogues to minimum micellar concentration (CMC) [54]. Most hydrotropic solutions precipitate the solute on dilution with distilled water therefore recovery of product along with re-use of hydrotropic solvent is easy [55]. Hydrotropes are used for many purposes such as drug solubilization, detergent formulations, health care, in household applications [56], also used as extracting agent. Overall hydrotrope has various advantages such as eco-friendly; non-flammable, less toxic, inexpensive that is hydrotrope follow the green chemistry principle. Therefore, here use one of the hydrotrope is sodium p-toluene sulfonate (NaPTS) for synthesis of Pyrazole derivatives **(Scheme 2.24)**.



Scheme 2.24 Synthesis of 5-amino-pyrazole-4-carbonitrile.

Table-2.1: Screening of conditions for synthesis of 5-amino-pyrazole-4-carbonitrile.

Entry	Solvent/ Catalyst	Time	Yield
1	Water	48hrs	trace

2	Ethanol	24hrs	trace
3	Water + Ethanol (1:1)	24hrs	40%
4	**Water + 40% NaPTS**	**30 min**	**92%**

Initially focused on selection of green methodology for synthesis of present scheme **(Table 2.1)**. Initially we use water as green solvent but yield was very low and also require long reaction time, then we choose another solvent is water: ethanol (1:1) then also yield is poor due to lower solubility of organic compound in aqueous medium. Then we select hydrotrope that increase the solubility of sparingly soluble compounds in aqueous medium. Hydrotropes are surface active agent they increase solubility in many folds access. We select hydrotrope which is NaPTS at various concentrations out of which 40% NaPTS gives expected yield in 5-10 minutes at room temperature **(Table 2.2)**. We screen the reaction condition by using reactant as aldehyde (1mmol), malononitrile (1mmol), phenyl hydrazine (1mmol) we got the maximum yield in 5ml 40% aq. NaPTS at room temperature. Then use different derivatives of benzaldehyde with electron donating and withdrawing group getting good to excellent yields of corresponding pyrazoles.

Table-2.2: Optimization concentration of Hydrotrope for synthesis of 5-amino-pyrazole-4-carbonitrile:

SR. NO.	Hydrotrope (% w/v)	Temp.(^{0}C)	Time	Yield %
1.	10 % NaPTS	24^{0}C	24 hrs	-
2.	20 % NaPTS	24^{0}C	180 min	10
3.	30 % NaPTS	24^{0}C	100 min	50
4.	**40 % NaPTS**	**24^{0}C**	**30 min**	**92**
5.	50 % NaPTS	24^{0}C	100 min	90

6.	60 % NaPTS	24^0C	100 min	85
7.	40 % NaPTS	50^0C	60min	70
8.	40 % NaPTS	80^0C	80 min	70
9.	40 % NaPTS	100^0C	100 min	75

The plausible mechanism of the product formation is conceptualized in fig.2.6. The water added to hydrotrope, water fragments hydrating the head parts of hydrotrope which decreases the electrostatic attraction between these head groups of hydrotropic moieties. The two head groups separated from each other and replace the water molecules interacting hydrophobic parts. This may be the electromotive force for two hydrophobic parts to interact also it enhance the reactant molecule to solubilize and get interact with each other. Then water molecules get eliminated and easily occupied by the hydrophilic head groups. As a consequence of the overall findings, there is an enhanced speed of the reaction, and the reaction proceeds in an aqueous medium due to hydrotropism.

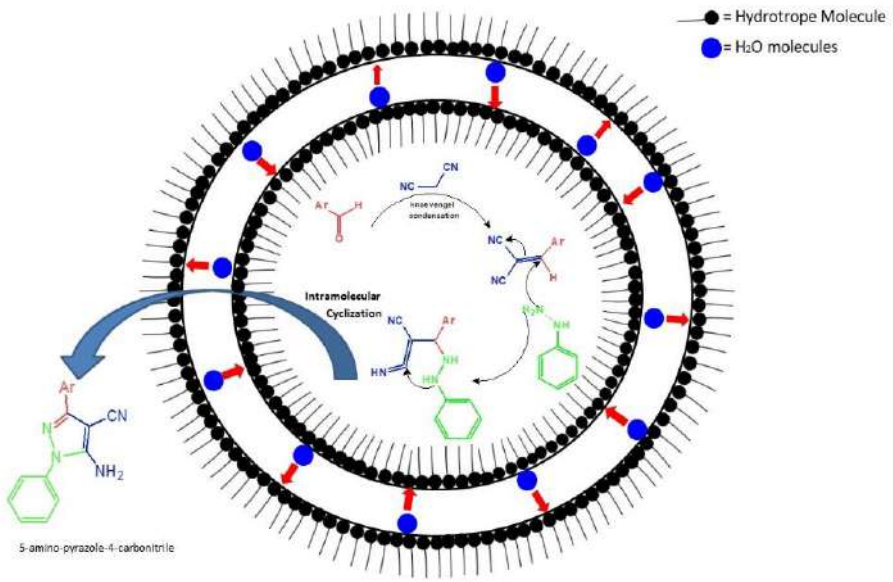
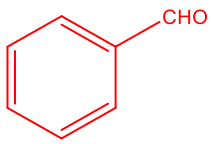
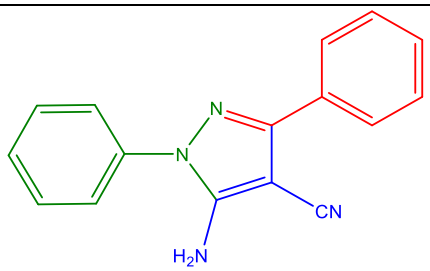
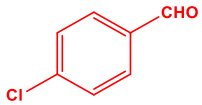
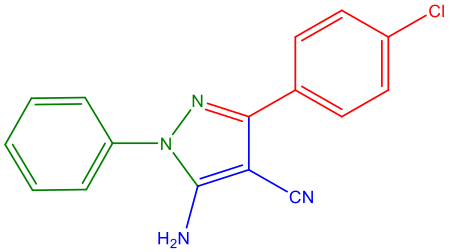
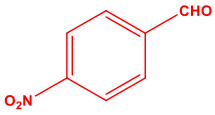
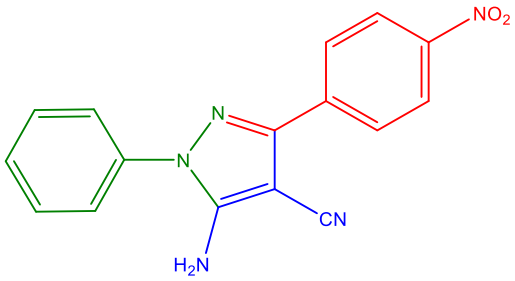
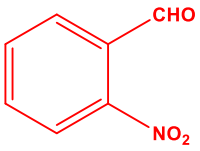
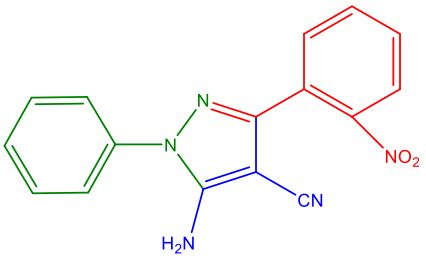
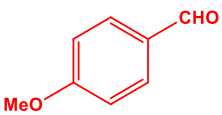
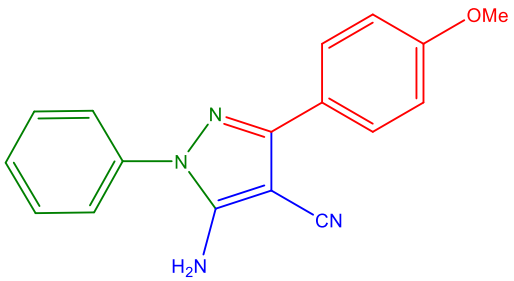
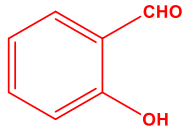
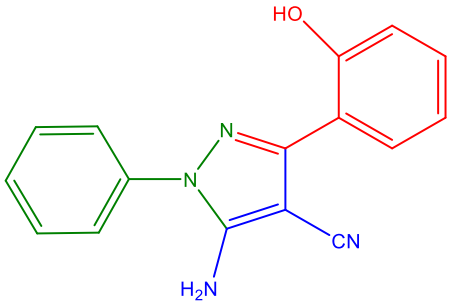
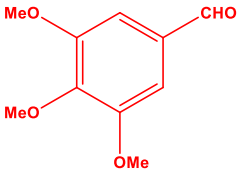
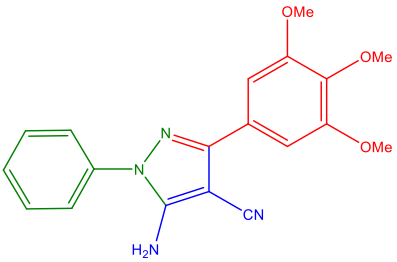
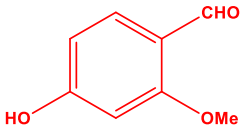
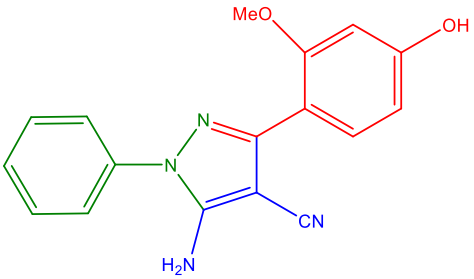
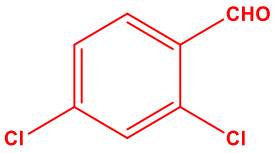
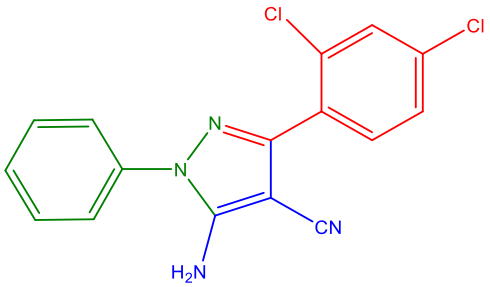
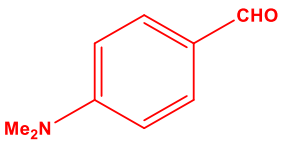
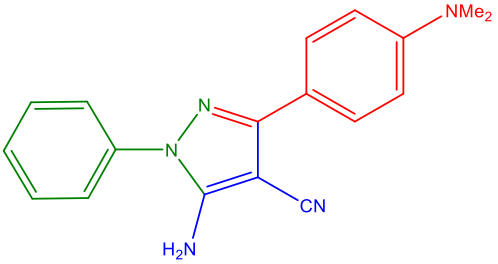
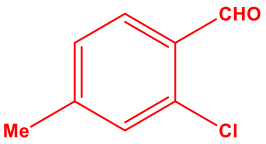
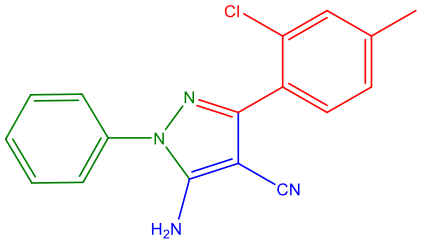
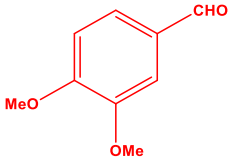
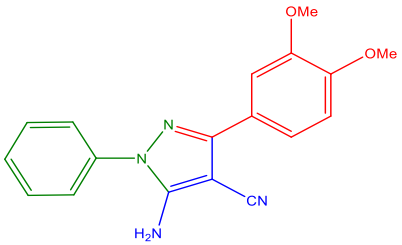
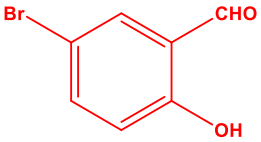
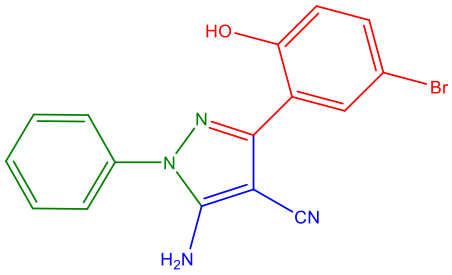


Figure 2.6 A Plausible reaction mechanism for synthesis of 5-amino-pyrazole-4-carbonitrile in aqueous hydrotropic medium.

Table-2.3: Synthesis of 5-amino-pyrazole-4-carbonitrile derivatives in 40% hydrotrope in aqueous medium.

Entry	Aldehyde	Product	M.P. (ºC) [34], [57]	Yield (%)
1			156-158	92
2			127-128	92
3			175-177	92
4			158-160	92
5			106-109	90

6			160-162	80
7			128-130	92
8			120-122	92
9			130-132	90
10			104-106	92

11			124-126	92
12			121-123	92
13			178-180	80

Recyclability of Hydrotrope:

The reuse of catalyst is very important step in synthesis because reuse of catalyst directly effects on cost along with environment. Therefore, easy recovery along with reuse of catalyst is necessary these is possible by using hydrotrope, because it is reuse only after the reaction is complete, filter the product and give washing to product then collect the filtrate along with product because that filtrate contain the hydrotrope, then keep the filtrate for evaporation after that our catalyst i.e., hydrotrope is recover, which is ready for reuse. We check the recyclability of that hydrotrope by 5 times obtain the good result with loss of small amount of yield which is shown in **figure 2.7**.

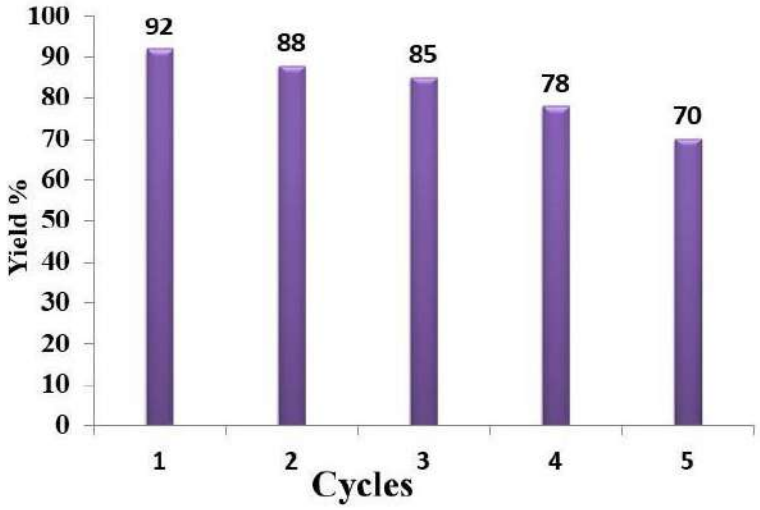
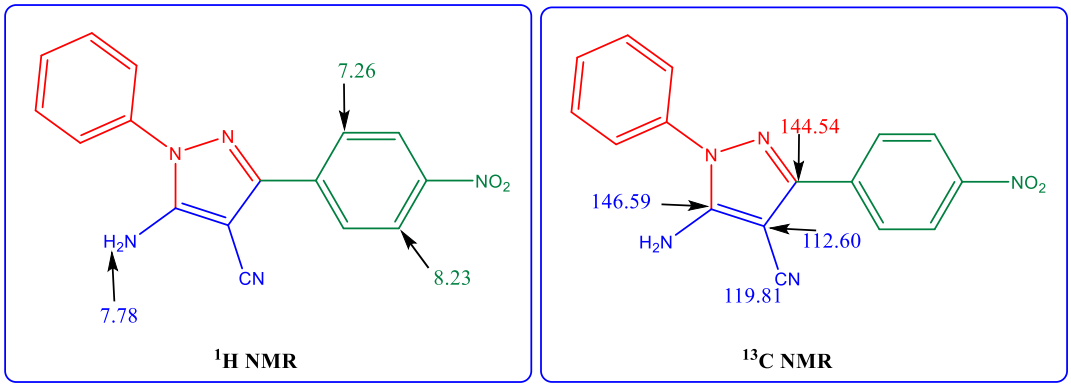


Figure 2.7 Recyclability of Hydrotrope.

Characterization of products

The synthesized products of pyrazole derivatives are confirmed on the basis of IR, ^{1}H, ^{13}C NMR spectroscopy, which is in full agreement with the proposed structures.

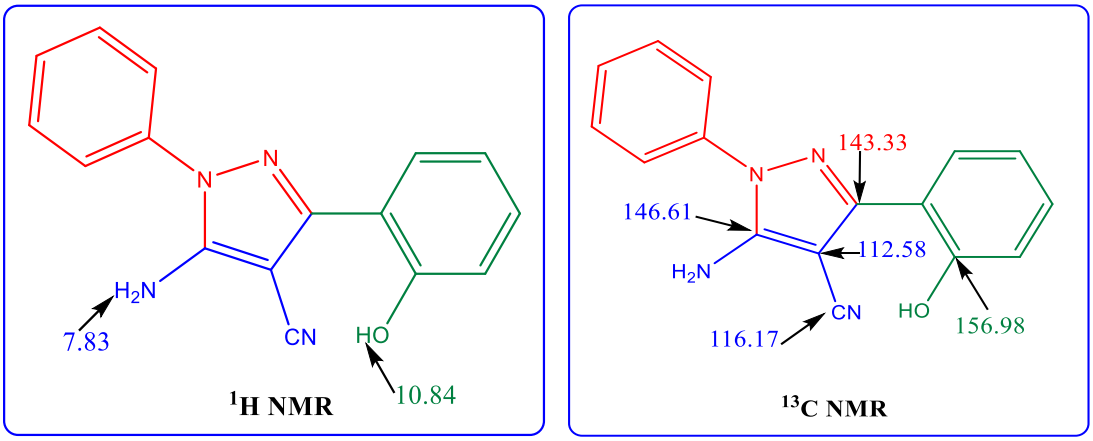
1) 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3):



In IR spectrum **(Figure 2.11)** characteristic band observed at 3467.38 and 3303.43 cm^{-1} for asymmetric and symmetric stretching vibrations of primary amine group while band at 2360.11 cm^{-1} corresponds to nitrile group. In the ^{1}H NMR **(Figure 2.12)** spectrum, singlet appeared at δ 7.78 ppm for two protons of amine group. two protons ortho to nitro groups resonated at more upfield at δ 8.23 ppm while protons at meta position appeared at δ 6.95-7.98 ppm. The remaining peaks from δ 7.15-7.26 ppm attributed to protons of aromatic ring. Similarly, in ^{13}C NMR **(Figure 2.13)** spectrum displays peak at 119.81 ppm for nitrile group however carbon adjacent to nitrile group

appeared at δ 112.60 ppm. The remaining carbons resonated in aromatic region 124.43, 125.76, 126.96, 127.52, 129.01,130.51, 130.74, 132.81, 144.54 and 146.59 ppm.

2) 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6):



IR spectrum shows **(Figure 2.14)** characteristic peak for phenolic OH appeared at 3446 cm^{-1}, NH_2 at 3320.82 and 3207.04 cm^{-1} resp. while cyanide band appears at 2188.81 cm^{-1}. In ^1H NMR **(Figure 2.15)** spectrum of the same compound showed sharp singlet at δ 10.84 ppm for hydroxyl proton, amines two proton also shows singlet at δ 7.83 ppm. four protons show multiplate at δ 6.99-7.90 ppm, remaining three protons also shows multiplate at δ 7.15-7.49 ppm of the benzene ring. ^{13}C spectrum **(Figure 2.16)** exhibited pyrazole ring carbon appeared at δ 112.58, 143.33 and 146.61 ppm. the peak at δ 116.17 ppm was for nitrile carbon while aromatic carbons noticed at δ 118.46, 119.46, 120.86, 129.52, 129.53, 129.99, 135.26, 137.24, 141.17, 156.98 ppm from which confirms the correct structure formation of corresponding product.

2.4 Conclusion:

The present protocol describes environmentally friendly synthesis of 5-aminopyrazole-4-carbonitrile. Due to harsh reaction conditions dangerous side effect on environment need to develop such safe methods therefore here we use hydrotrope in aqueous medium which is a green methodology. This methodology having lot of advantages such as less hazardous, cost effective, time saving and mild reaction condition. Present protocol suggests a promising green approach for the synthesis of 5-aminopyrazole-4-carbonitrile.

2.5 Experimental

General:

All the chemicals required for synthesis were commercially sourced and were used without further purification. Melting points of products are measured on electrical melting point apparatuses. IR spectra were obtained with lambda FT-IR 750 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 400MHZ spectrometer using $CDCl_3$as solvent and TMS is an internal standard.

General procedure for the synthesis of 5-amino-pyrazole-4-carbonitrile:

Take equimolar ratios of malononitrile (1 mmol), phenyl hydrazine (1 mmol), and substituted aldehyde (1 mmol) in 10 ml of a 40% aqueous NaPTS solution. This reaction mixture was constantly stirred at room temperature for a few minutes until the progress of the reaction was monitored by TLC in n-hexane: ethyl acetate (7:3). The solid product was separated by simple filtration. The separated solid product was recrystallized in a suitable solvent.

Spectroscopic data for some target compounds are as follows:

1) 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (1):

White solid, melting point: 156-158ºC. IR (KBr): ῡ = 3320.82, 3290, 2930, 2210, 580, 1600, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.87 (d, 1H), 7.11(dd, 2H), 7.13-7.26(m, 5H), 7.37(d,1H), 7.65(S, 2H), 7.68(d,1H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.71, 120.07, 126.15, 128.40, 128.58, 129.28, 135.26, 137.24, 143.33, 144.61, 144.75, 146.80.

2) 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6):

Yellow solid, melting point: 160-162ºC. IR (KBr): υ= 3446.17, 3320.82, 3207.04, 2927, 2188.81, 1598.70, 112.79, 1150.01 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.90-7.00 (m, 4H), 7.15-7.49 (m, 5H), 7.83 (s, NH_2), 10.84 (s, 1H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.58, 116.57, 118.46, 119.46, 120.86, 129.52, 129.53, 129.99, 135.26, 137.24, 141.17, 143.33, 146.61, 156.98.

3) 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3):

Red solid, melting point:175-177^{o}C. IR (KBr): υ 3467.38, 3303.43, 2950, 2360.11, 1580.70, 1210.05, 750.17 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 6.95 (d, 1H), 7.15-7.26 (m, 5H), 7.78 (S, NH_2), 7.98 (d, 1H),8.23 (dd, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δppm 112.60, 119.81, 124.43, 125.76, 126.96, 127.52, 129.01,130.51, 130.74, 132.81, 144.54, 146.59.

4) 5-amino-1-phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole-4-carbonitrile (7):

Cream color, melting point:128-126^{o}C.IR (KBr): ῡ = 3413, 3364, 2930, 2220, 1610, 1245, 1140 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 3.930 (s, 3H), 3.389 (s, 6H), 6.88 (d, 2H, ArH), 7.19-7.28 (m, 5H, ArH), 7.66(s, 2H). ^{13}C NMR (100MHz $CDCl_3$): δppm 112.60, 117.57, 119.46, 121.07, 127.2, 129.4, 130.7, 137.9, 143.2, 148.12, 150.0, 154.7.

5) 5-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (5):

Light brawn solid, melting point:106-109^{o}C. IR (KBr): ῡ = 3446.17, 3320.82, 292741, 1598.17, 1480.17, 1272.78, 1159.01, 750.04. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 3.910(S, 3H), 6.89(d, 2H, ArH), 7.60(d, 2H, ArH), 7.30-7.60(m, 5H, ArH), 7.71(s, 2H). ^{13}C NMR (100MHz $CDCl_3$): δppm 53.6, 112.60, 114.8, 116.34, 121.20, 126.2, 127.4, 129.01, 129.85, 130.07, 145.8, 152, 155.

6) 5-amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2):

Cream color solid, melting point:127-128^{o}C. IR (KBr): ῡ = 3446.17, 3313.11, 2229.11, 1594.84, 1488.78, 1255.43, 748.25. ^{1}H NMR (400MHz, $CDCl_3$): δppm 7.45-7.68 (m, 4H, ArH), 7.30-7.60 (m, 5H), 7.72 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δppm 118.45,120.86, 122.4, 126.5, 127.98, 129.25, 129.88, 130.45, 133.23, 144.46, 148.01, 153.01.

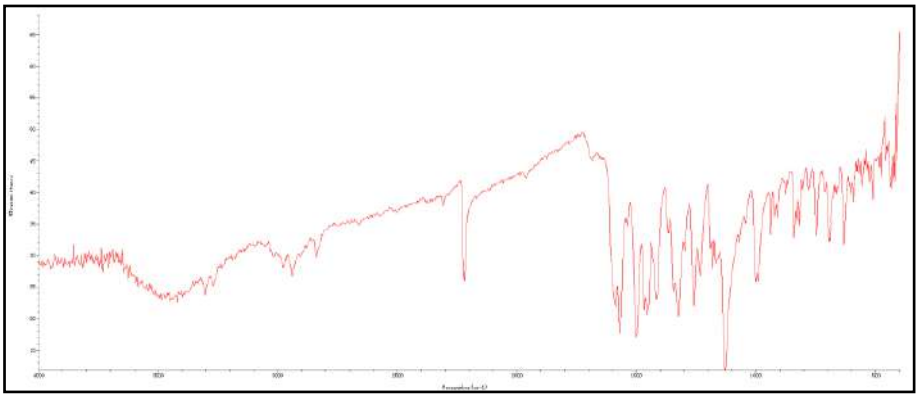


Figure 2.8: IR Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

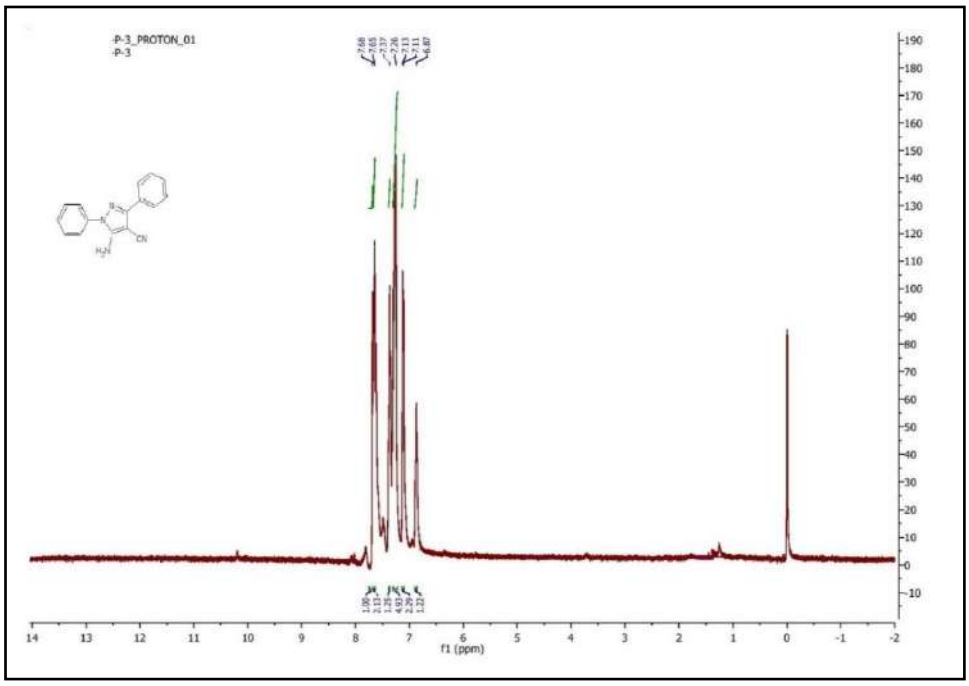


Figure 2.9: ^{1}H Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

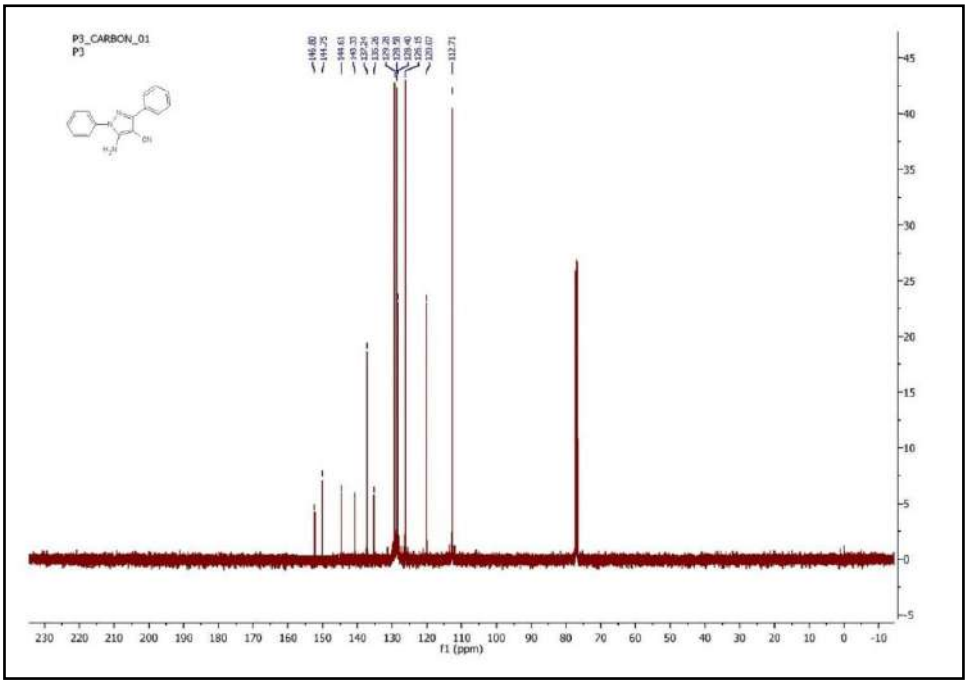


Figure 2.10: ^{13}C Spectrum of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

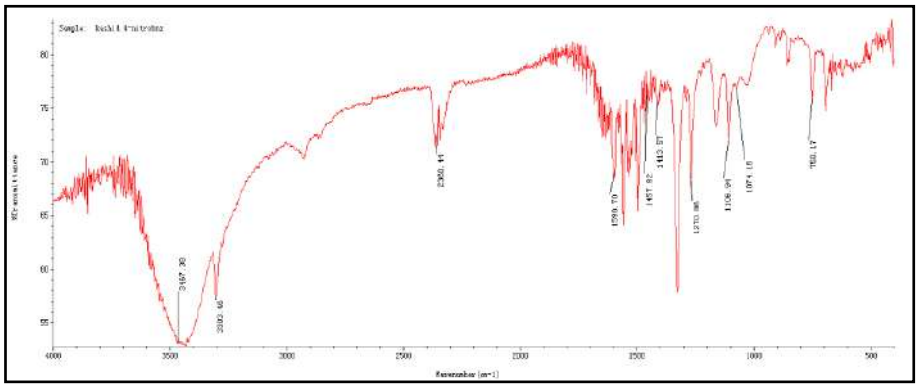


Figure 2.11: IR Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

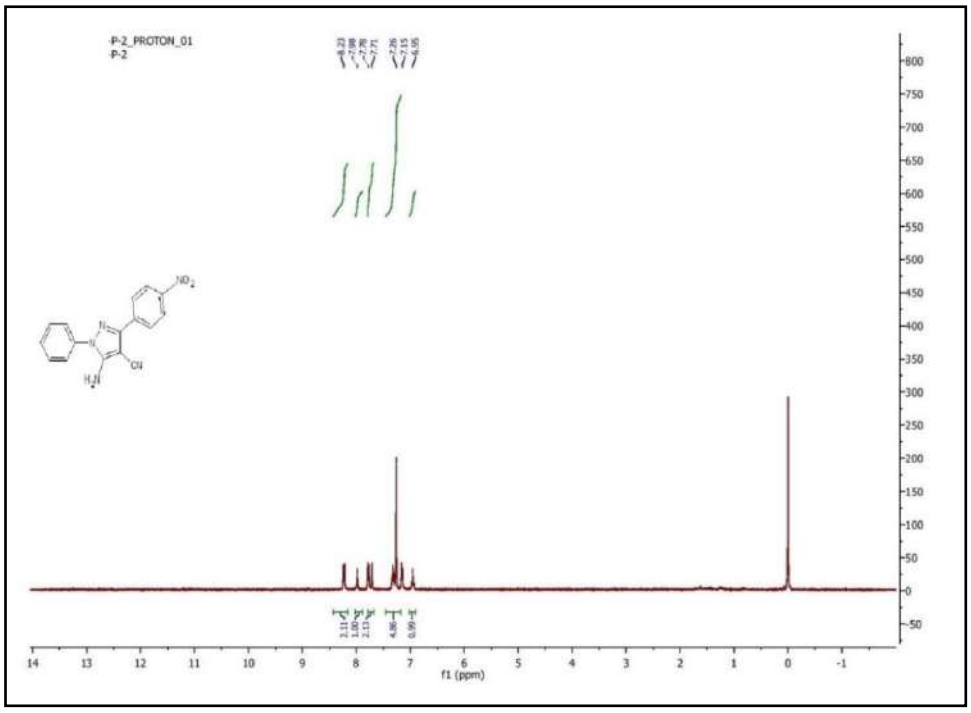


Figure 2.12: ^{1}H Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

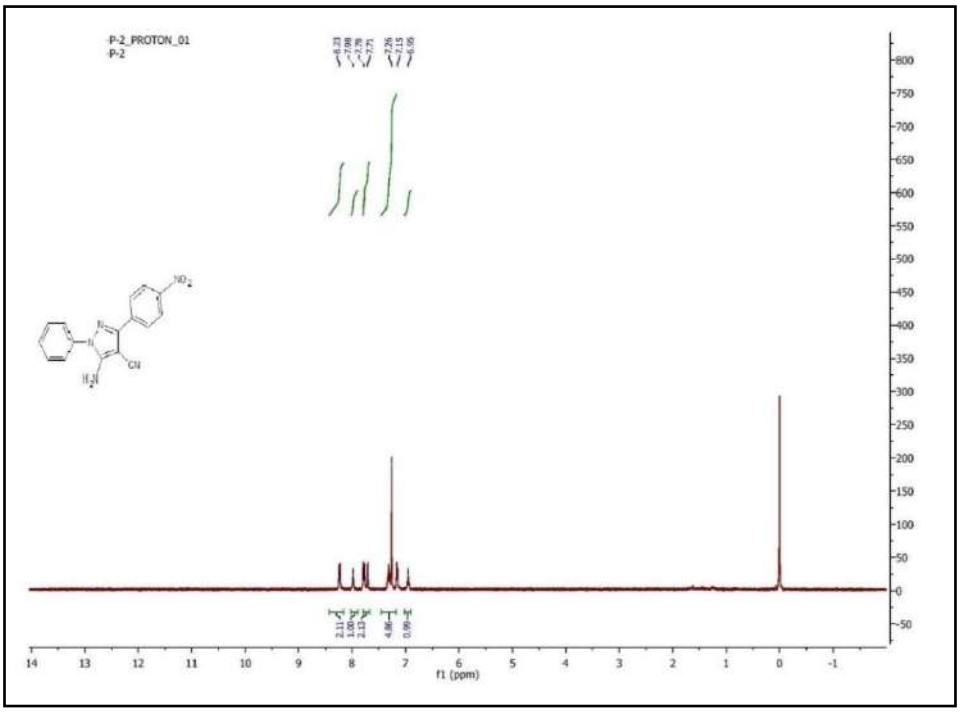


Figure 2.13 ^{13}C Spectrum of 5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile

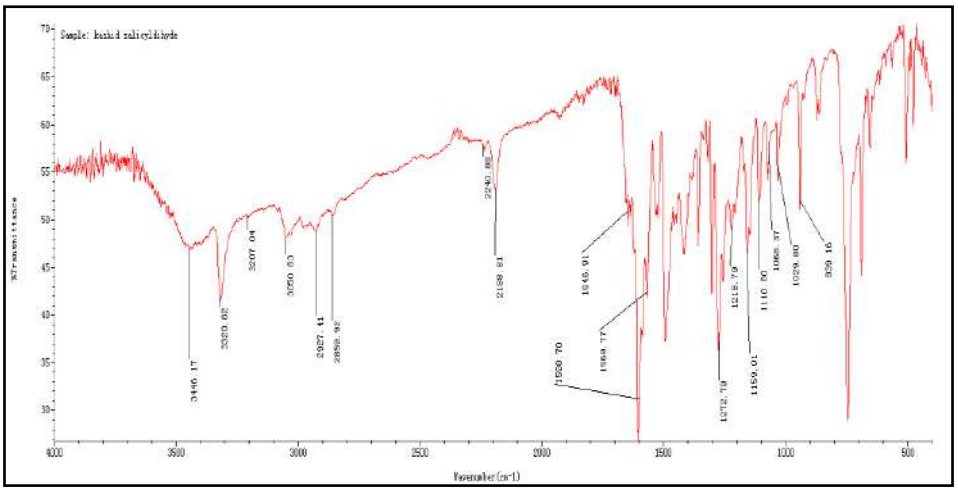


Figure 2.14 IR Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile(6)

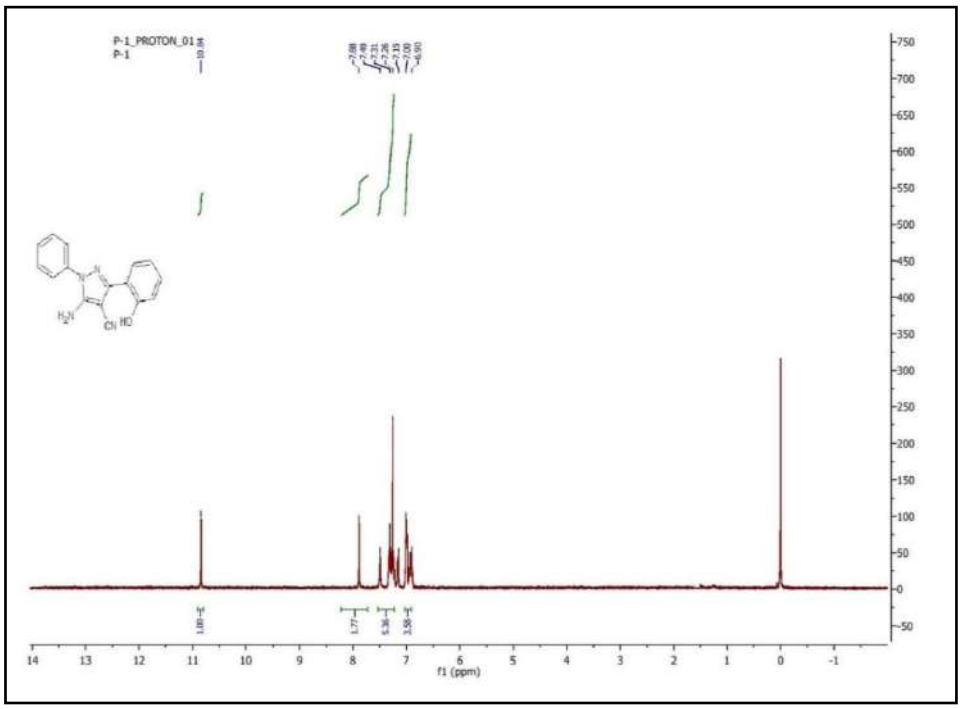


Figure 2.15 ^{1}H Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6)

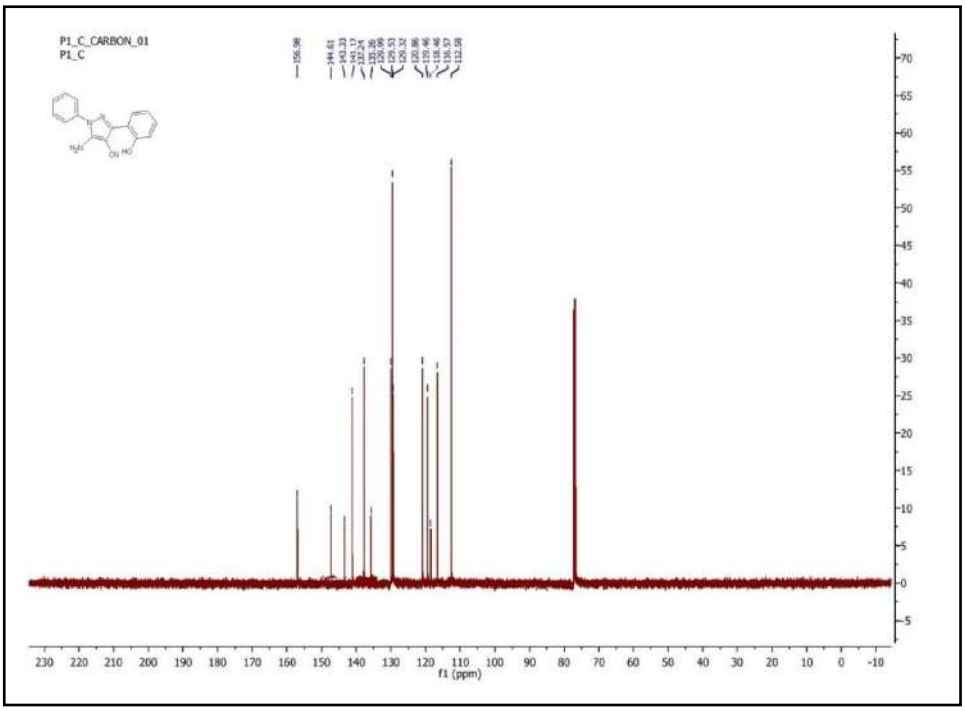


Figure 2.16 ^{13}C Spectrum of 5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile(6)

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CHAPTER – 3

CLEAN AND GREEN APPROACH FOR SYNTHESIS OF VARIOUS DERIVATIVES OF [1,3]OXAZINE IN SUSTAINABLE AQUEOUS HYDROTROPIC MEDIUM

Research Article

Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium

Aboli Sapkal, Suraj Attar, Avdhut Kadam, Pramod Gaikwad & Santosh Kamble

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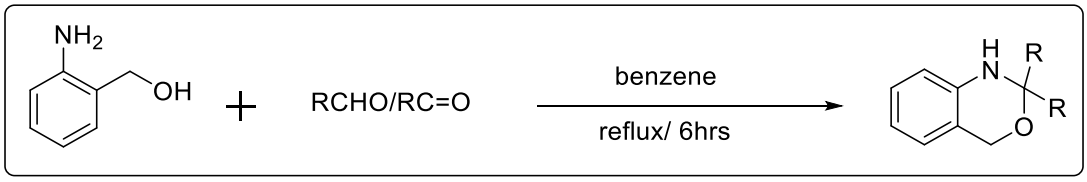
CHAPTER 3

Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium

3.1 Introduction

The importance of organic chemistry increases day by day due to heterocyclic compounds and its involvement in the pharmaceutical industry. The study of heterocyclic compounds is very innovative from both a theoretical and practical point of view. They are extensively spread in natural space and necessary to life due to their crucial role in the metabolic activities of all living cells. Some pharmaceutically active heterocyclic compounds are widely found in nature as like antibiotics penicillin and cephalosporin, alkaloids-morphine and reserpine along with these synthetic heterocyclic compounds also widely spread in different fields for example materials in applied chemistry dye stuffs, copolymers, solvents, photographic sensitizers and developers. Oxazine is one of the important heterocycles among the library of various heterocyclic compound. Holley and cope were reported first synthesis of oxazine in 1944 **(Scheme 3.1)** [1]. After that, Burke et al. also extensively contributed to the development of many benzoxazines and naphthoxazines during the 1950s and 1960s [2]–[4]. Oxazine ring bears the Oxygen and nitrogen and therefore its application in drug chemistry is tremendous. These oxazines have its own library of their various analogous oxazine scaffolds such as Oxazole (1), Isoxazole (2), 4,5-dihydroisoxazole (3), Isoxazolidine (4), 1,3-oxazolidine (5), 1,2-oxazine (6), 1,3-oxazine (7), 1,4-oxazine (Morpholine) (8), 3,6-dihydro-2H-[1,2]oxazine (9), Benzo[d]isoxazole (10), 1,4-benzoxazine (11) **(Figure 3.1)**, etc., at the different position containing oxygen and nitrogen in their structural arrangement.



Scheme 3.1 Synthesis of first Oxazine by Holly and Cope in 1944.

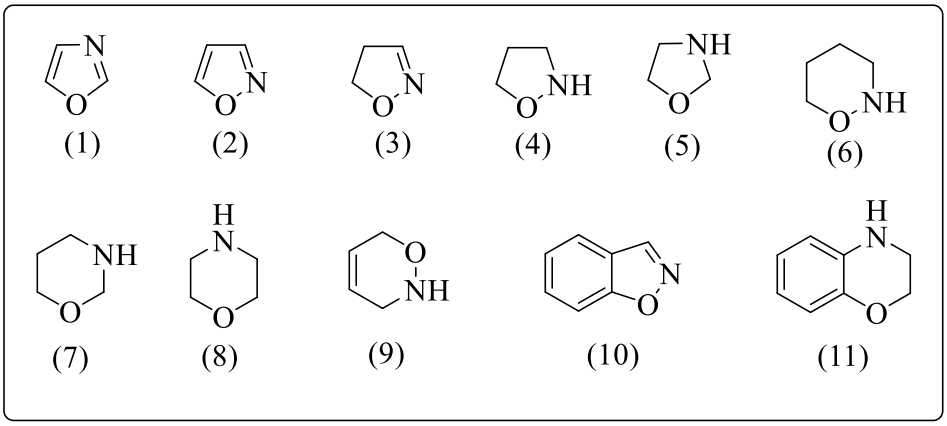


Figure 3.1. Different Oxazine Scaffolds.

The development in the chemistry of [1,3] oxazine compounds has been of interest since the 1950s and will continue to be so until the 20th century. [1,3]Oxazine contains one oxygen and one nitrogen atom at 1,3 position in six membered ring **(Figure 3.2)** [5].

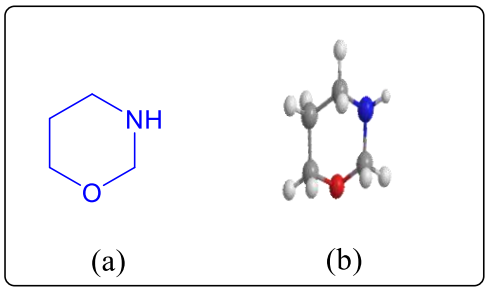


Figure 3.2. (a) Structure of [1,3]Oxazine and (b) 3D structure of [1,3]Oxazine.

Researcher focused in the synthesis of [1,3]Oxazine compounds due to its versatile role in biological as well as medicinal field [6], [7]. In the medicinal field, they cover a large spectrum of pharmacological operations, such as bactericidal [8], fungicidal [9], antiviral [10], microbiocidal, anti-cancer [11], anti-HIV [12], anti-tuberculosis [13], and anti-inflammatory agents [14]. These interesting biological activities brings the patent to some preparative schemes of [1,3]Oxazine especially tetrahydro-1,3-oxazines along with the synthetic utility of 5,6-dihydro-4H-1,3-oxazines. Therefore, **figure 3.3** shows the structures of some biologically active

[1,3]Oxazines such as anti-tumour, anti-Parkinson and potent non-steroidal progesterone receptor agonists. One potent drug-Ifosfamide having 1,3-oxazine ring fight against several types of cancers like as testicular cancer, breast tumour, lymphoma (Non-Hodgkin), Soft tissue sarcoma, Osteogenic sarcoma, Lung cancer, Cervical cancer, Ovarian cancer, Bone cancer **(Figure 3.4)**.

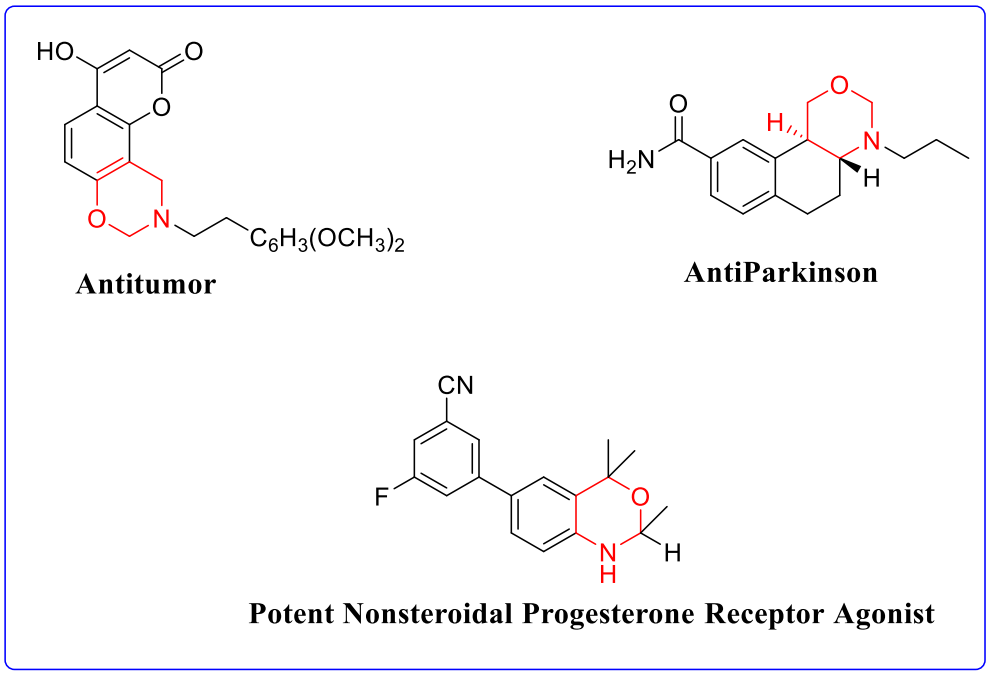


Figure 3.3. Structures of some biologically active [1,3]Oxazines.

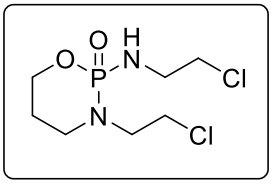
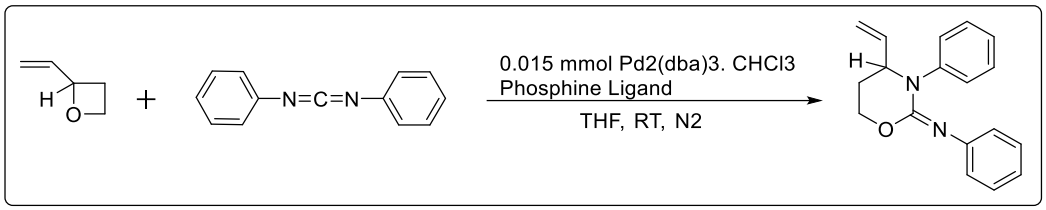


Figure 3.4. Structure Ifosfamide.

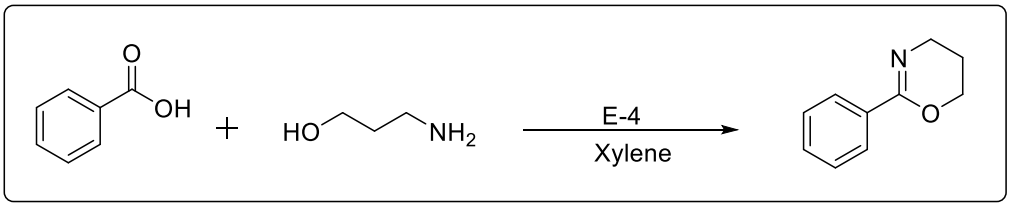
In the beginning, benzene and reduction molecules of benzene like pyridine and oxazole, which are replacements for carbon and hydrogen atoms in the benzene ring by nitrogen and oxygen, produce the oxazine molecules, but now a days tremendous development in the synthesis of oxazine compounds. Following is the literature survey of synthesis of various oxazine derivatives by incorporating different reactants, solvents and methodologies.

Chitchamai and Howard [15] synthesize stereoselective bicyclic 1,3-oxazines, cycloaddition of vinyloxetanes with heterocumulenes catalysed by palladium. They develop novel features of cycloaddition process by using $Pd_2(dba)_3$. $CHCl_3$ and phosphine ligand dppe **(Scheme3.2).**



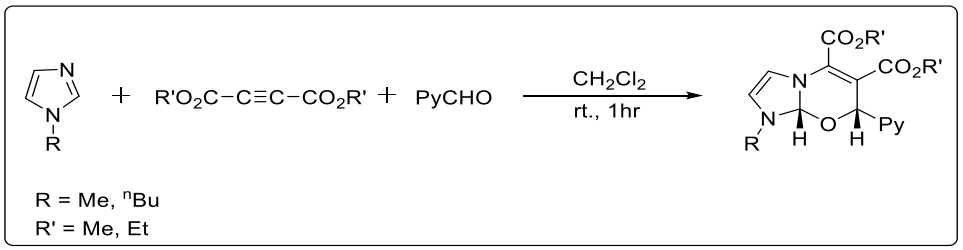
Scheme 3.2

Agnieszka Cwik et al. [16] develop simple strategies for the synthesis of oxazines. In presence of zeolite, Ersorb-4 (E-4) 3-aminopropanol and benzoic acid gave the corresponding 2-phenyloxazine. Simple workup procedure due to use of heterogenous catalyst **(Scheme 3.3).**



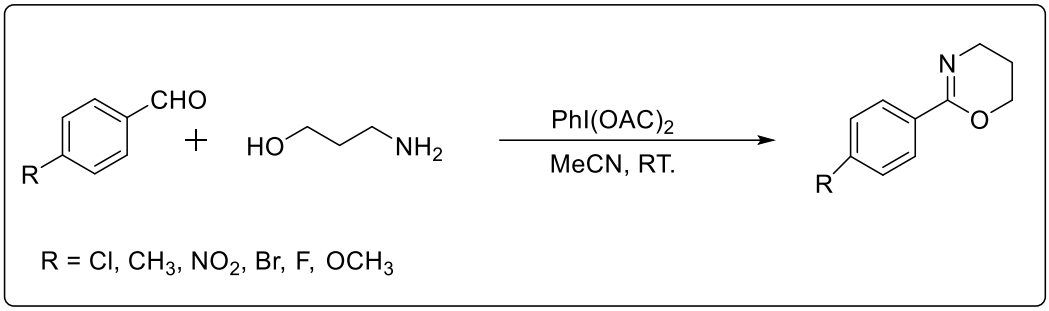
Scheme 3.3

Mehdi Adib and co-workers [17] by using pyridine carboxaldehydes produces diastereoselective 1,8a-dihydro-7H-imidazo[2,1-b][1,3]oxazine derivatives by reacting 1-Alkyl imidazoles with dialkyl acetylene dicarboxylates **(Scheme 3.4).**



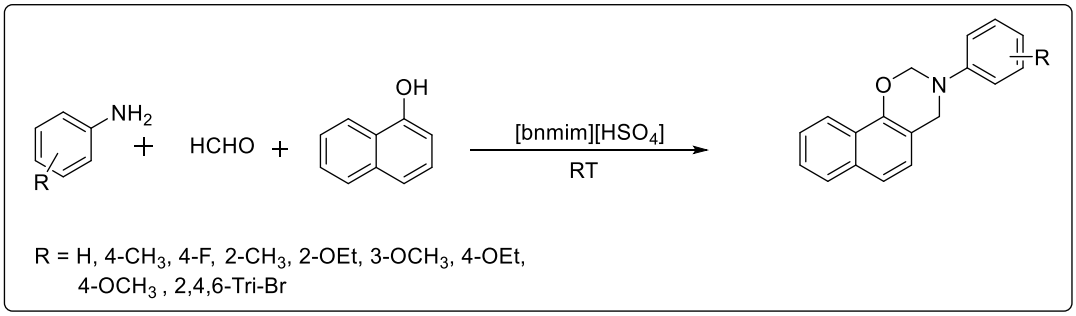
Scheme 3.4

Nandkishor N. Karade et al. [18] demonstrate oxidative conversion of aldehydes to 2-substituted oxazolines and oxazines by using mild dehydrogenating agent (diacetoxyiodo)benzene **(Scheme 3.5).**



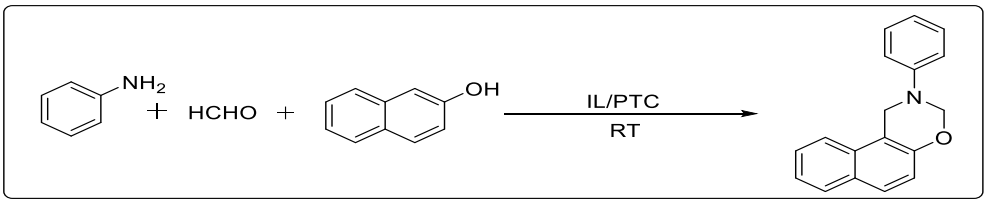
Scheme 3.5

Synthesis of 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*][1,3]oxazine derivatives, developed by Kategaonkar and co-workers [19] in ionic liquid. Mannich type reaction in presence of ionic liquid, 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim] [HSO_4] **(Scheme 3.6).**



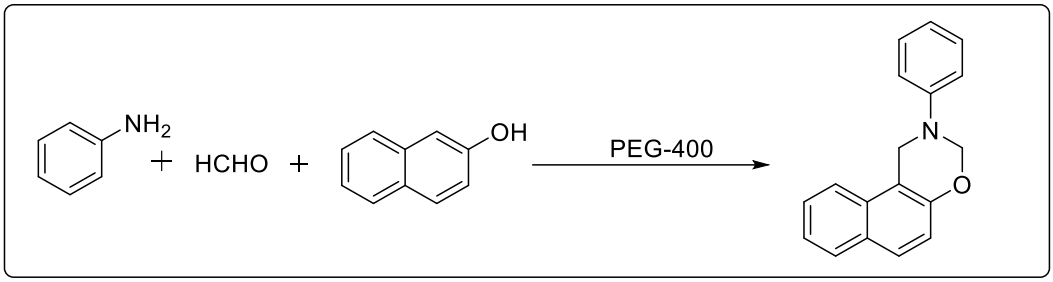
Scheme 3.6

Combination of ionic liquid (1-butyl-3-methyl imidazolium hydrogen sulphate [bmim]HSO_4) and phase transfer catalyst (n-tetra butyl ammonium bromide (TBAB)) were carried out by Suryakant B. Sapkal et al. [20] for the synthesis of [1,3]Oxazine derivatives **(Scheme 3.7).**



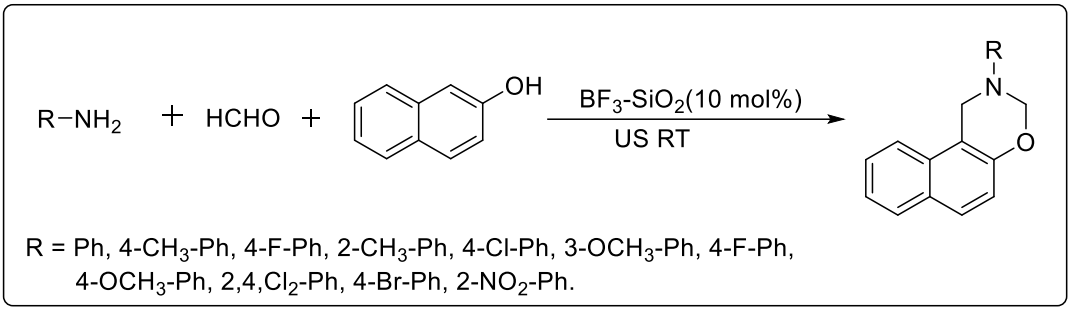
Scheme 3.7

Polyethylene glycol (PEG)-400 a safer medium that avoids the use of acid/base catalyst for the preparation of 1,3-oxazine derivatives was reported by Pravin Shinde and co-workers [21] **(Scheme 3.8).**



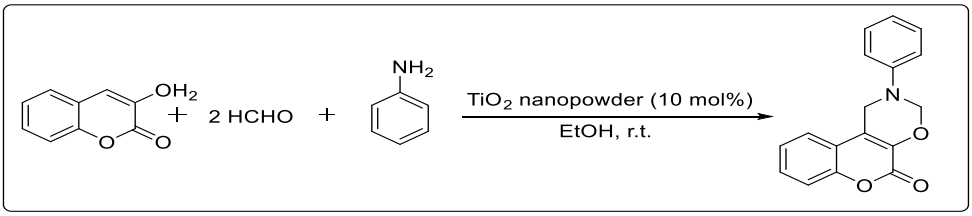
Scheme 3.8

Environment-friendly method developed by Mudumala Veeranarayana Reddy et al. [22] for the synthesis of 1,3-oxazine derivatives under ultrasound waves in presence of BF_3–SiO_2 catalyst **(Scheme 3.9).**



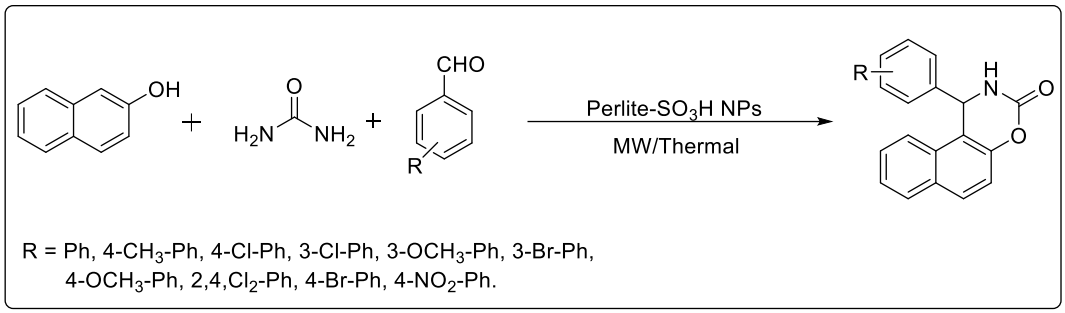
Scheme 3.9

Animesh Mondal et al. [23] reported TiO_2 nano powder catalysed synthesis of new chromeno[4,3-*e*][1,3]oxazine derivatives at room temperature. Recyclability of catalyst gives good result up to four cycles without significant loss in yield **(Scheme 3.10)**.



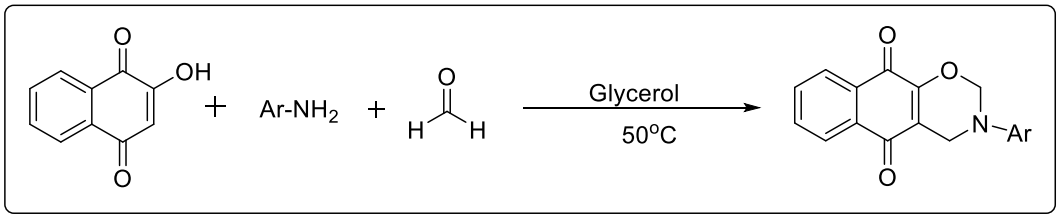
Scheme 3.10

A. Ramazani et al. [24] first prepared perlite-SO_3H nanoparticles and used those nanoparticles for the production of 1,2-dihydro-1-aryl-naphtho[1,2-*e*][1,3]oxazine-3-one molecules in accordance with microwaves and thermal heating in the absence of solvent **(Scheme 3.11)**.



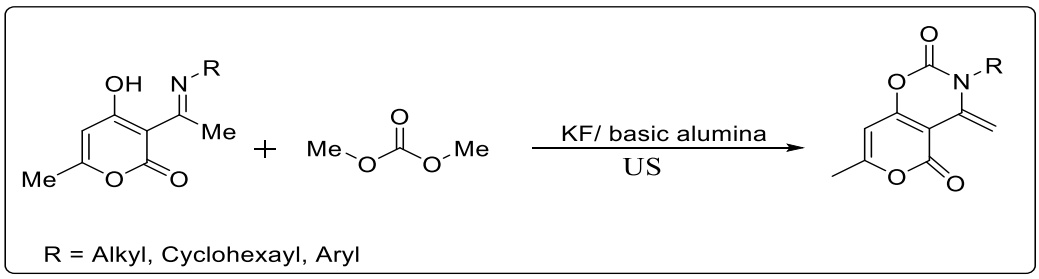
Scheme 3.11

Shruti Gupta and co-workers [25] use glycerol as a green media for the eco-friendly preparation of various derivatives of naphtho[2,3-e][1,3]oxazines **(Scheme 3.12).**



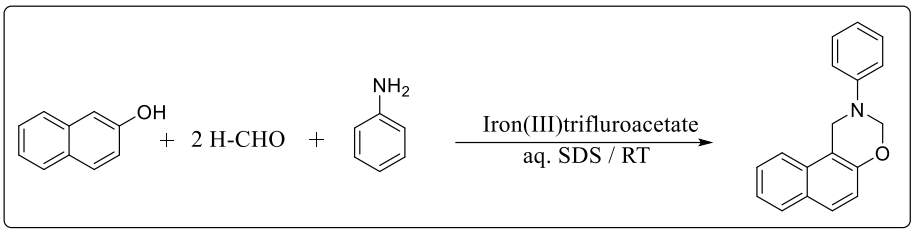
Scheme 3.12

Tamer S. Saleh et al. [26] develop green protocol under ultrasound irradiation for the synthesis of novel pyrano[3,4-e][1,3]oxazines. KF/basic alumina catalyst increases the yield within short period of time **(Scheme 3.13)**.



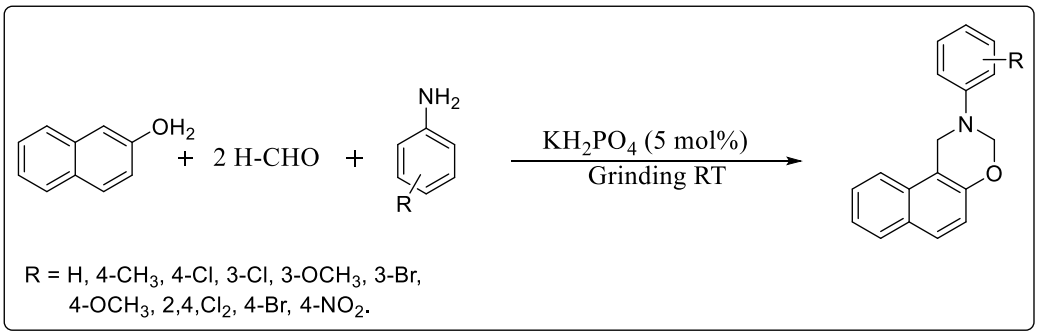
Scheme 3.13

A multipurpose water-stabilized fluorine consisting of organometallic lewis acid prepared by Trushant Lohar et al. [27] for the greener production of 1,3-oxazine scaffolds at room temperature **(Scheme 3.14)**.



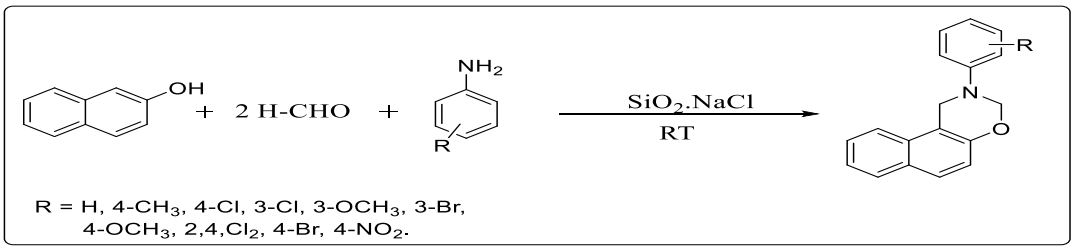
Scheme 3.14

Balasaheb Shitole and co-workers [28] demonstrate that potassium dihydrogen phosphate effectively catalyses the different molecules of naphtho-[1,2-e][1,3] oxazine by grinding with pestle and mortar in the absence of solvent at room temperature **(Scheme 3.15)**.



Scheme 3.15

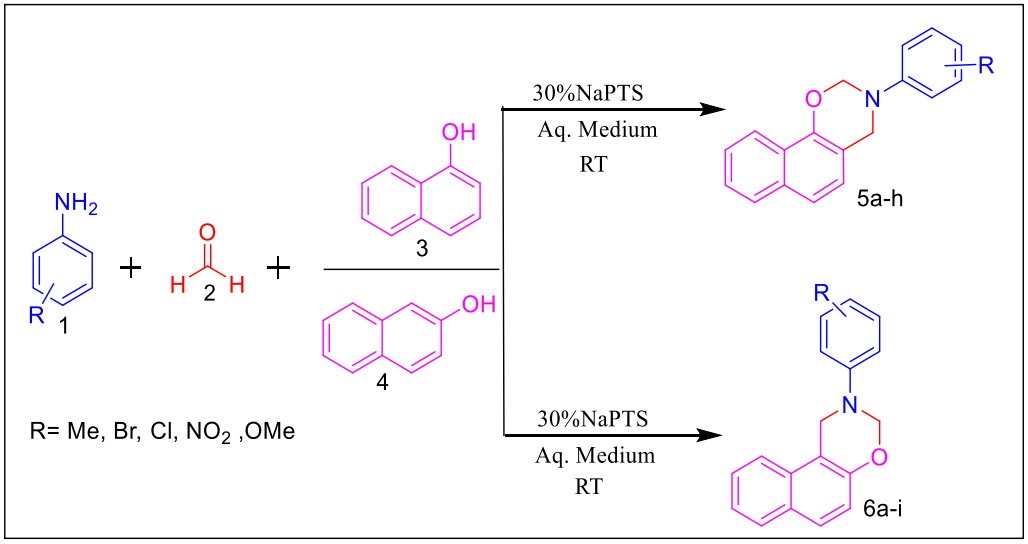
Putusenla Imchen et al. [29] synthesized of 1,3-benzoxazine and 1,3-naphthoxazine using $NaCl.SiO_2$ at room temperature and check their antibacterial activity. Uses streptomycin as a standard control for all the microbial test **(Scheme 3.16)**.



Scheme 3.16

3.2 Present Work:

Chemical synthesis via green chemistry approaches our future opportunities in working with chemical processes by introducing novel reactions that can maximise the derived products and minimise side-products; designing new chemical transformations that can modify activities in organic synthesis; and searching for greener reaction media that are naturally environmental and ecologically benign. The development of simple and sustainable synthetic methodologies and the use of readily available reagents is one of the main objectives of organic synthesis. In organic synthesis, the use of aquatic solutions of hydrotropes exhibits the characteristic properties of an alternative reaction medium. We give attention to the development of greener organic synthesis by creating aquatic hydrotropic solutions as a benign medium [30]–[32]. With the extension of our study to find the scarcely exploiting capability of hydrotropes in chemical synthesis, we report here the sustainable synthesis of 2,3-dihydro-2-phenyl-*1H*-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in an aqueous hydrotropic medium at ambient temperature **(Scheme 3.17)**.



Scheme 3.17 Synthesis of [1,3]Oxazine derivatives in 30% Aq. Hydrotropic medium.

3.3 Result and Discussion:

The selection of hydrotropes plays a significant role in the synthetic transformation involving aromatic amine, formaldehyde with α-Naphthol or β-

Naphthol in to 3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in aqueous medium. The amphiphilic character and hydrophobic region favour the solubility of organic reactants in aqueous media and thus differ from classical surfactants. The solubilities of organic substrates occur due to their amphiphilic and hydrophobic regions and differ from conventional surfactants. The hydrotrope shows maximum solubility of compounds at the minimum hydrotropic concentration (MHC), which was used as a reaction medium [33]. Those molecules are insoluble in water, but they show solubility in aquatic media by the use of hydrotropes because direct interaction takes place between reactants and hydrophobic molecules of hydrotropes, which gives solubility in many folds of excess. A wide number of synthetic methodologies were reported for these transformations.

According to a survey of previous studies for the synthesis of [1,3]Oxazine derivatives, the novelty of the present protocol is to overcome the problem of solubility of organic compounds in an aqueous medium. Due to the poor or insolubility of organic moiety, they are not interacting with each other. The hydrotropic aqueous medium is one of the best alternatives for hazardous organic solvents that solubilize insoluble organic compounds in an aqueous medium. Hydrotropes are not only recyclable but also non-toxic in nature. Hydrotrope is cheap in cost as well as can be synthesized in the laboratory, which makes it an environmentally and economically efficient protocol [34], [35].

Here we represent the comparative table of previous and present study **(Table 3.1)**.

Table 3.1. Comparative various synthetic methods for synthesis of [1,3]Oxazines derivatives

Entry	Reagents and condition	Time (m/h)	Yield (%)	References
1	(S)-BINAPO chiral lewis base with $HSiCl_3$ in DCM	10-11h	77	[13]
2	$KAl(SO_4)_2$ _$12H_2O$ (alum) in H_2O	15 min.	75	[16]
3	Solid-support catalyst, SiO_2.NaCl at room temperature	5-10 min	78	[18]

4	1-benzyl-3-methyl imidazolium hydrogen sulfate i.e. [bnmim] [HSO_4], room temperature and stirring	1min	77	[24]
5	1-butyl-3-Methyl imidazolium hydrogen sulphate [bmim]HSO_4 Ionic liquid and PTC such as tridecyl trimethyl ammonium bromide (TDTMAB) at 60ºC.	30 min	90	[25]
6	BF_3–SiO_2 Ultrasonicated room temperature	10 min	90	[26]
7	***Sodium p*-Toluene Sulphonate (NaPTS) at room temperature**	**10 min**	**94**	**Present work**

The various hydrotropes such as sodium benzene sulphonate (NaBS), sodium p-xylene sulphonate (NaXS) and sodium p-toluene sulphonate (NaPTS) were picked for this synthetic transformation. The results obtained by using various NaPTS, NaBS, and NaXS are mentioned in **Table 3.2,** which indicate that NaPTS gives better results than NaBS and NaXS. That is, NaPTS in an aqueous solution shows a better outcome for this synthetic transformation.

Table 3.2. Screening of various hydrotropes for synthesis of [1,3]Oxazines derivatives

Entry	Hydrotrope	Time (Min.)	Yield (%)[a]
1	*p*-Toluene Sulphonate (NaPTS)	10	94
2	*p*-Xylene Sulphonate (NaXS)	50	70
3	Benzene Sulphonate (NaBS)	120	40

Reaction at room temperature [a] isolated yield.

We selected to apply 30% (w/v) aqueous solutions of selected hydrotropes as a reaction medium. Selected organic reactants for the synthesis of oxazine molecules show maximum solubility at this concentration. We got excellent results for NaPTS; therefore, we applied this specific hydrotrope for subsequent analysis. then we studied

the effect of concentration of aq. NaPTS. The productivity of the model scheme changes significantly with respect to the concentration of hydrotrope and was remarkable when 30% of aq. NaPTS was used as a reaction solvent **(Figure 3.5)**. Enhance the solubility of reactant molecule at 30% conc. of NaPTS.

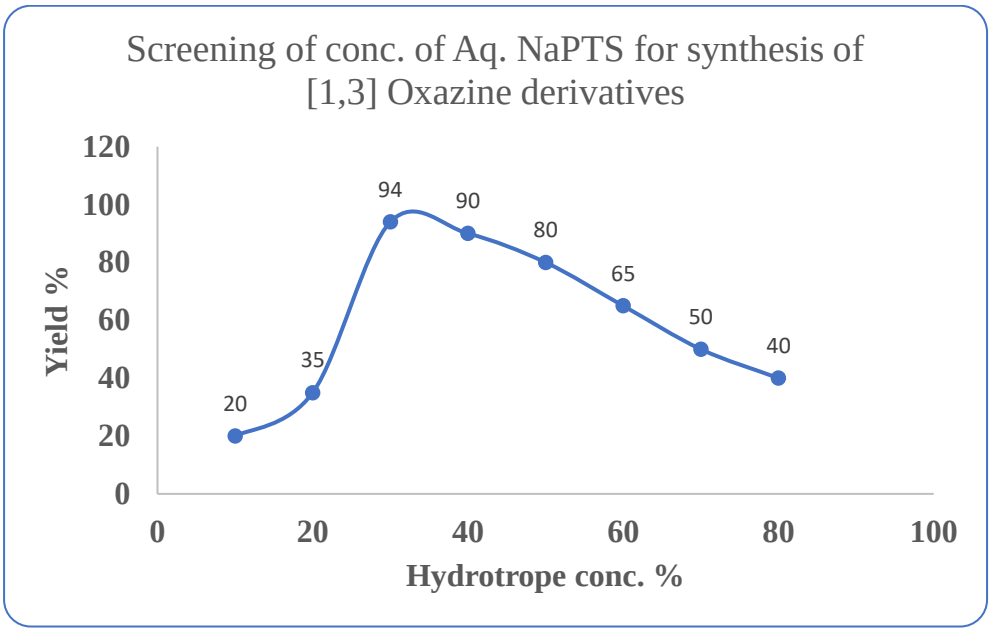


Figure 3.5. Screening of Conc. of Aq. NaPTS for synthesis of [1,3] oxazines derivatives

Our next task was to assess the efficiency of the aqueous hydrotropic solutions for this organic transformation. Accordingly, a model reaction between aniline and formaldehyde with α -Naphthol/ β -Naphthol in 30% of aq. NaBS, NaXS, and NaPTS was carried out at ambient temperature **(Scheme 3.17)**. On the completion of the reaction as confirmed by thin layer chromatography (TLC) using n-hexane/ethyl acetate (8:2) as the solvent system, the reaction mixture was diluted with cold water, during which the product gets separated out. The simple filtration of the reaction mixture gives the crude product; the high-purity products obtained after recrystallization are used for spectral analysis. In all cases, the reactions proceeded smoothly, affording the corresponding products in high yields **(Table 3.3)** and which gave correct IR, ^{1}H NMR, ^{13}C NMR and DEPT spectral analysis. The plausible mechanism of the product formation for the synthesis of [1,3]Oxazine derivatives is conceptualized in **figure 3.6**.

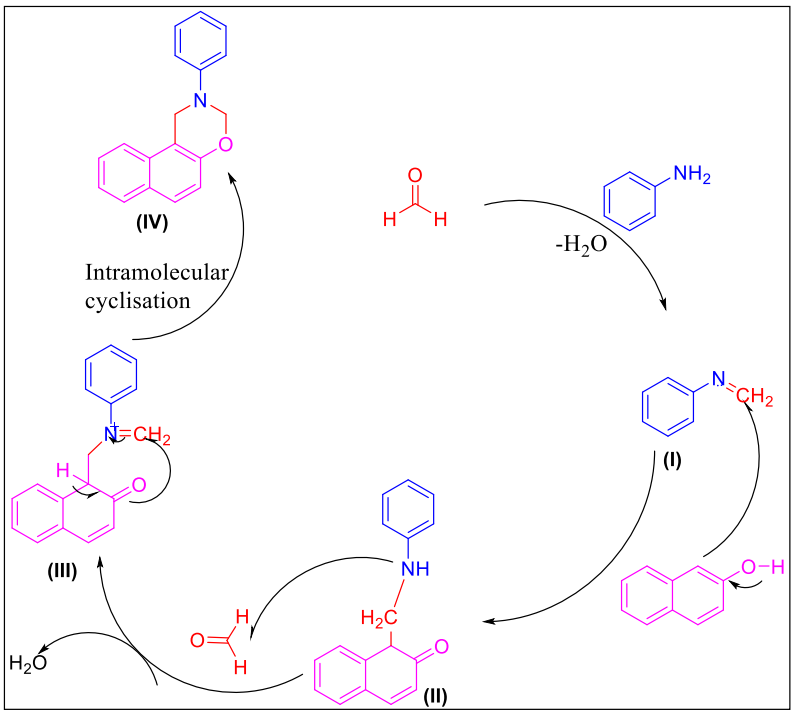
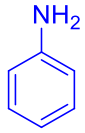
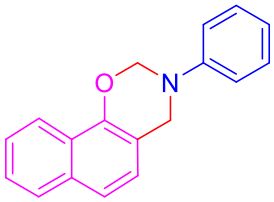
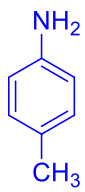
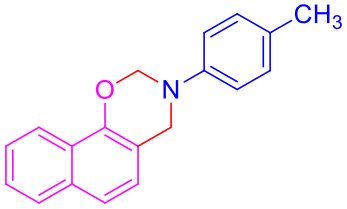
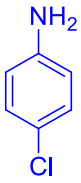
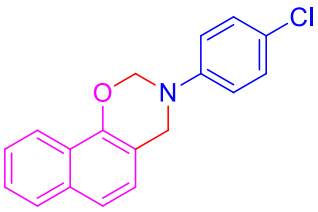
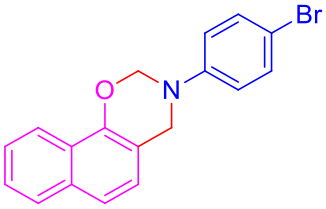
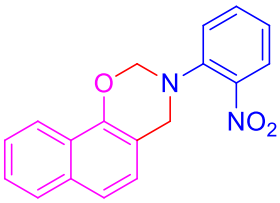
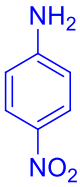
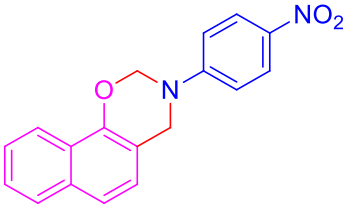
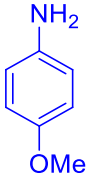
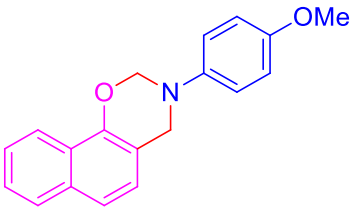
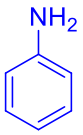
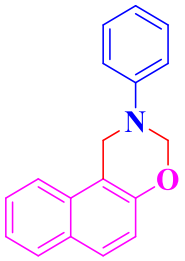
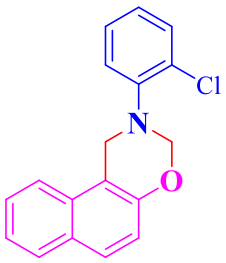
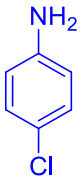
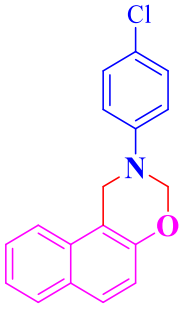
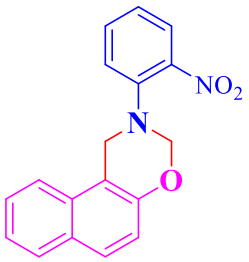
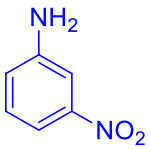
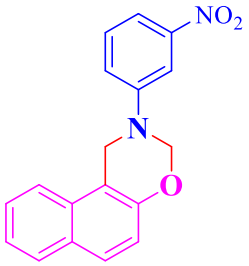


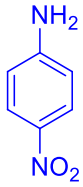
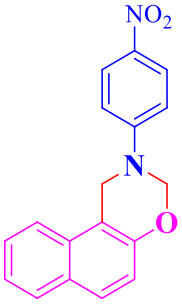
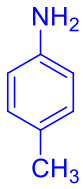
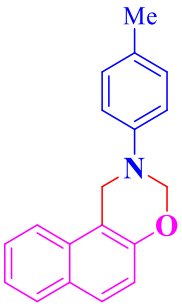
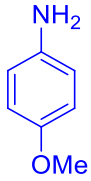
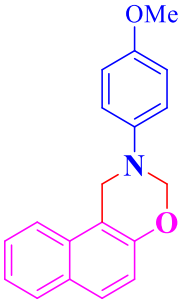
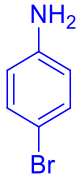
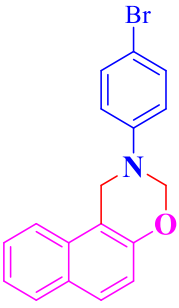
Figure 3.6. A Plausible reaction mechanism for synthesis of [1,3] oxazine derivatives.

Table 3.3. Synthesis of [1,3]Oxazine derivatives in 30% aq. NaPTS solution[a].

Entry	Aniline	Product	Time Min.	Yield %[b]	M.P.°C Lit. [16, 23,]
1.		 5a	30	90	110-111 [23]
2.		 5b	30	90	196-198 [23]

3.		 5c	40	90	80-82
4.		 5d	20	90	115-117 [23]
5.		 5e	45	85	85-87
6.		 5f	10	94	114-116
7.		 5g	10	92	298-300 [23]

8.		 6a	30	90	47-49 [23]
9.		 6b	40	84	146-148
10.		 6c	30	88	221-223
11.		 6d	40	84	132-134 [23]
12.		 6e	45	80	140-142 [24]

13.		 6f	10	94	171-173 [23]
14.		 6g	20	88	88-90 [23]
15.		 6h	20	92	78-80 [16]
16.		 6i	20	90	117-119

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and DEPT spectroscopy.

[b] Isolated yields after recrystallization.

Recyclability of Hydrotrope:

In organic synthesis, reusability and recovery of hydrotropic medium are very vital from the point of view of environmental effects and economy. Therefore, we first recovered the hydrotropes after completion of the reaction. The reaction mixture was simply filtered, the product was washed with water, and both the product and aqueous medium were collected. Then the aqueous medium was kept for evaporation to remove water, and finally we recollected the hydrotrope. The reusability of that hydrotropic solution was studied four times, including the use of freshly prepared solution for the respective synthesis. We got good results with a small amount of loss of yield, as shown in **figure 3.7**.

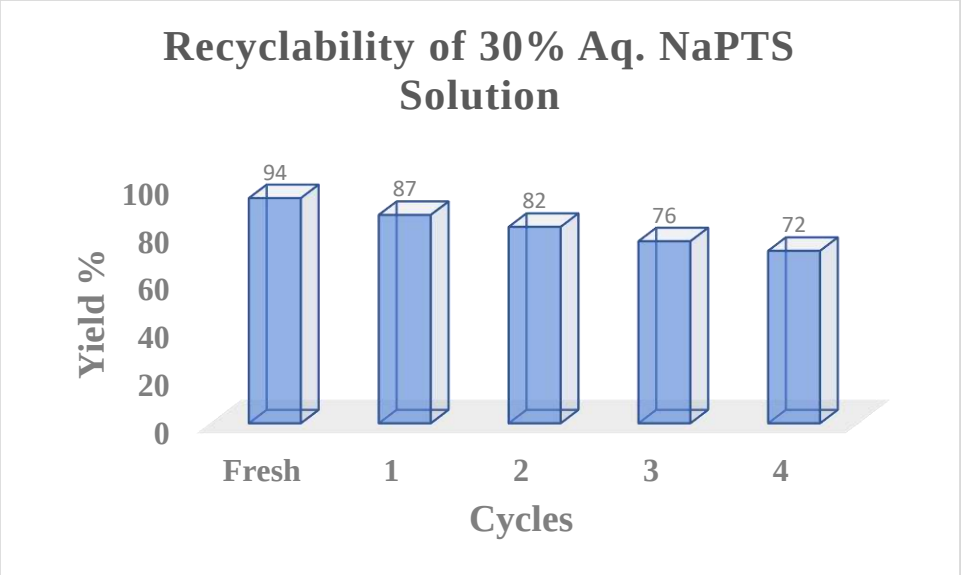
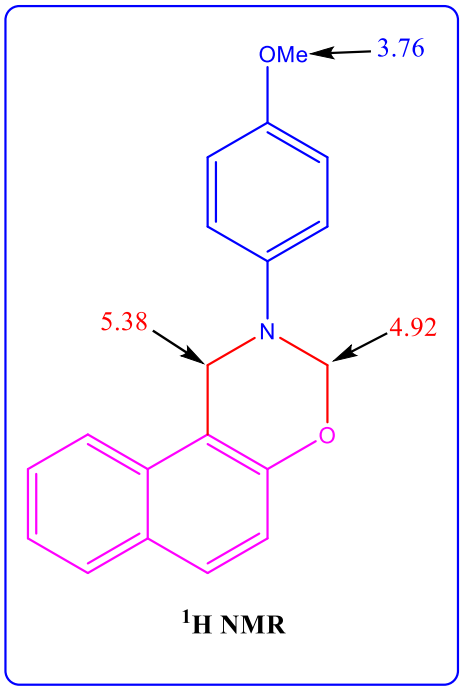


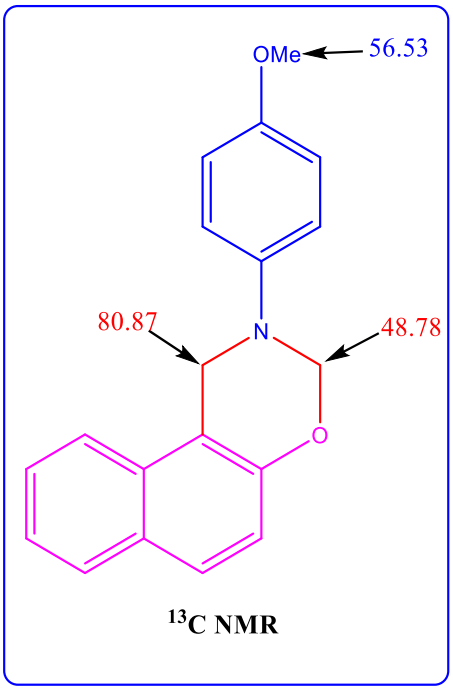
Figure 3.7. Recyclability of 30% aq. NaPTS solution

Characterization of products:

1) 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine



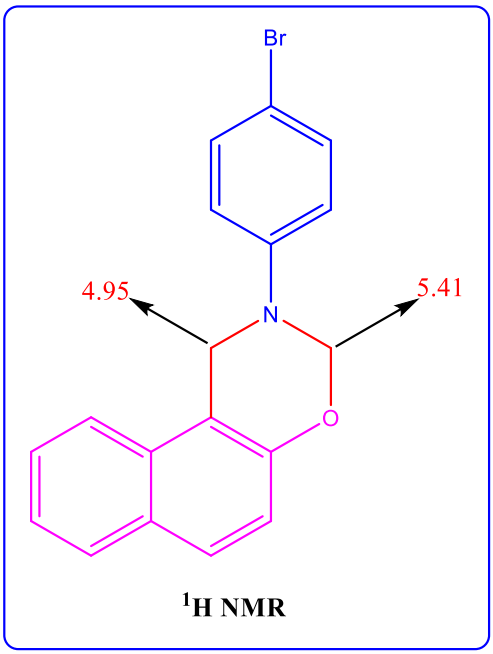
^{1}H NMR



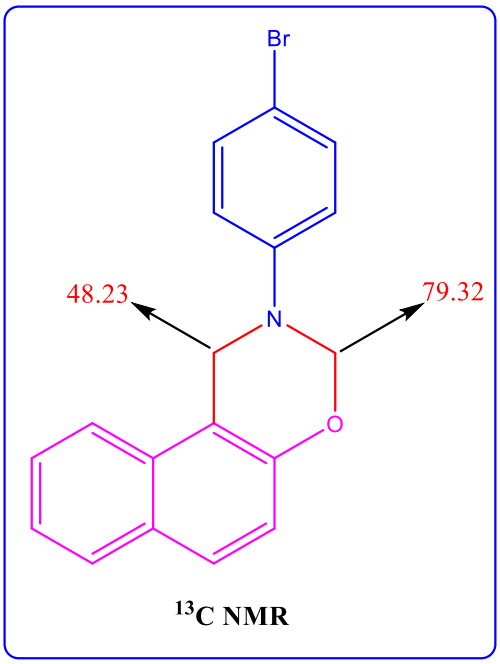
^{13}C NMR

IR spectrum **(Figure 3.8)** showed absorption band at 1626 cm^{-1} for aromatic C=C streching, at 1436 cm^{-1} for methyl C-H while band appeared at 1228 and 1037 cm^{-1} for corresponding C-N and C-O single bond. the ^{1}H NMR **(Figure 3.9)** spectrum showed three sharp singlet one at δ 3.76 ppm for three protons of methoxy group. The symmetric resonances of two singlet peaks at δ 4.92 (N-C$\underline{H}_2$-Ar) and 5.38 ppm (O-C$\underline{H}_2$-N) were assigned to the methylene groups of the oxazine ring in the compound. The rest of the peaks from 6.84 to 7.80 ppm correspond to the aromatic protons. The two negative peaks in DEPT-^{13}C NMR spectrum **(Figure 3.10)** were observed at δ 48.77 and 80.87 ppm of methylene carbons. The methoxy carbon was resonated at 56.53 ppm as a positive peak. The ^{13}C spectrum **(Figure 3.11)** also supports the oxazine formation with peaks corresponding to 1,3-oxazine ring at δ values 48.78 (N-C-Ar) and 80.87 ppm (O-C-N). The methoxy group resonates at δ 56.53 ppm. remaining peaks were due to aromatic carbons at δ 112,5, 114.5, 118.8, 120.9, 121.1, 123.6, 126.6, 128.2, 128.7, 129.0, 131.2, 142.7, 152.3, 155.1 ppm.

2) 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-16):



^{1}H NMR



^{13}C NMR

In the IR spectrum **(Figure 3.12)** the frequencies corresponding to 1597 cm^{-1} for aromatic alkene, 1199 cm^{-1} for C-O single bond. para substitution was shown by frequency 801 cm^{-1} corresponding to C-Br. The ^{1}H NMR **(Figure 3.13)** showed peaks corresponding to oxazine ring at δ values 4.95 (N-C$\underline{H_2}$-Ar) and 5.41 ppm (O-C$\underline{H_2}$-N) and the remaining chemical shift δ values from 7.06-7.80 ppm attributed to aromatic region. The two negative peaks in DEPT-^{13}C NMR spectrum **(Figure 3.14)** were observed at δ 48.23 and 79.32 ppm of methylene carbons. Similarly, the ^{13}C NMR **(Figure 3.15)** possessed peaks corresponding to methylene carbons of the 1,3-oxazine ring at δ values 48.23 (N-C-Ar) and 79.32 (O-C-N), while aromatic carbons resonates at δ values 112.1, 114.06, 118.71, 120.27, 120.81, 123.7, 126.8, 128.4, 128.7, 129.0, 131.1, 132.1, 147.8, 152.1 ppm.

3.4 Conclusion:

In conclusion, we have developed an environmentally benign, efficient and green methodology for the synthesis of [1,3]Oxazine derivatives by one-pot multi-component reaction of aniline, α-Naphthol or β-Naphthol and formaldehyde in 30% aq. NaPTS solution. The aqueous hydrotropic solution of sodium paratoulene sulphonate can be recycled after a simple work-up and reused up to four times with good efficiency

of product yield. Therefore, attractive and notable features of the present work are: shorter reaction time with high yield; environmentally friendly reaction medium; reusability of hydrotropic medium; absence of harmful organic solvents; and easy workup procedure. As a result, the current protocol plays an important role in organic synthesis by adhering to green chemistry principles.

3.5 Experimental

Melting points of products were determined on electrical melting point apparatus EQ 730A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR,^{13}C NMR and DEPT spectra were recorded on a Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal reference. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. The hydrotropes NaBS, NaXS, and NaPTS were synthesised in the laboratory by the following procedures, which were reported in the literature [36].

General procedure for synthesis of [1,3]oxazine derivatives:

A mixture of aniline (1 mmol), α-naphthol or α-naphthol (1 mmol), and formaldehyde (2 mmol) in 5 ml of a 30% aqueous hydrotropic medium was constantly stirred at room temperature. The progress of the reaction was confirmed by thin-layer chromatography. After the reaction is complete, the crude product is collected by simple filtration, and the recrystallization of the crude product in ethyl acetate produces the pure product.

Spectral data of synthesized compounds:

3,4-Dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-1)

IR (neat, thin film): υ = 1606, 1580,1214, 1028 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.70 (s, 2H, Ar-CH_2-N), 5.82 (S, 2H, N-CH_2-O), 6.88-8.20 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.6, 93.4, 113.4, 114.3, 119.6, 121.9, 122.9, 124.6, 125.2, 125.5, 127.1, 129.6, 149.6; DEPT of two –CH_2 carbon appeared at 59.6 and 93.4 resp.

3,4-Dihydro-3-(4-chlorophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-3)

IR (neat, thin film): υ = 1610, 1585, 1460, 1208, 1032, 788 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 113.4, 115.7, 119.6, 122.9, 124.6, 125.2, 125.5, 127.1, 127.2, 129.7, 132.5, 147.7, 149.0; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp.

3,4-Dihydro-3-(4-nitrophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Table 2. Entry-6)

IR (neat, thin film): υ = 1617, 1590, 1454, 1555, 1365, 1215, 1025 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 112.3, 113.4, 119.6, 122.9, 124.6, 124.8, 125.2, 125.5, 127.1, 132.5, 137.4, 149.0,155.7; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp.

2,3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-8)

IR (neat, thin film): υ = 1615, 1585, 1456, 1212, 1032 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 5.04 (s, 2H, Ar-CH_2-N), 6.12 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 53.7, 83.0, 111.5, 114.3, 118.4, 120.8, 121.9, 123.4, 126.3, 128.0, 128.3, 128.8,129.6, 131.7, 149.6, 151.7; DEPT of two –CH_2 carbon appeared at 53.7 and 83.0 resp.

2,3-dihydro-2-(*p*-tolyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-14)

IR (neat, thin film): υ = 1614, 1588, 1454, 1218, 1038 cm^{-1}.

^1H NMR(400 MHz, $CDCl_3$, δ ppm): δ 2.32 (s, 3H, -CH_3), 5.05 (s, 2H, Ar-CH_2-N), 6.10 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 21.3, 57.7, 93.0, 111.5, 112.8, 118.4, 120.8, 123.4, 126.3, 128.0, 128.3, 128.8, 129.9, 130.7, 131.7, 146.6, 151.7; DEPT of two –CH_2 carbon appeared at 57.7 and 93.0 resp.

2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-15)

IR (neat, thin film): υ = 1626, 1436, 1228, 1037, 793 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 3.78 (s, 3H, -OCH_3), 4.92 (s, 2H, Ar-CH_2-N), 5.38 (S, 2H, N-CH_2-O), 6.84-7.80 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm):48.7, 55.5, 80.8, 112,5, 114.5, 118.8, 120.9, 121.1, 123.6, 126.6, 128.2, 128.7, 129.0, 131.2, 142.7, 152.3, 155.1; DEPT of two –CH_2 carbon appeared at 48.7 and 80.8 resp.

2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine (Table 2. Entry-16)

IR(neat, thin film): υ = 1597, 1479, 1199, 801 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.95 (s, 2H,Ar-CH_2-N), 5.41 (s,2H,N-CH_2-O), 7.06-7.80 (m 10H,Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 48.2, 79.3, 112.1, 114.06, 118.71, 120.27, 120.81, 123.7, 126.8, 128.4, 128.7, 129.0, 131.1, 132.1, 147.8, 152.1; DEPT of two –CH_2 carbon appeared at 48.2 and 79.3 resp.

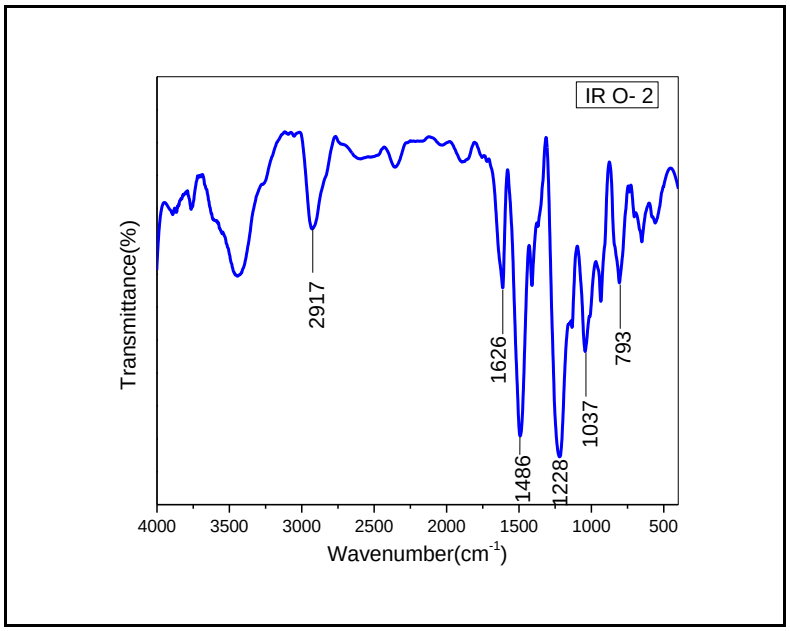


Figure 3.8: IR spectra of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

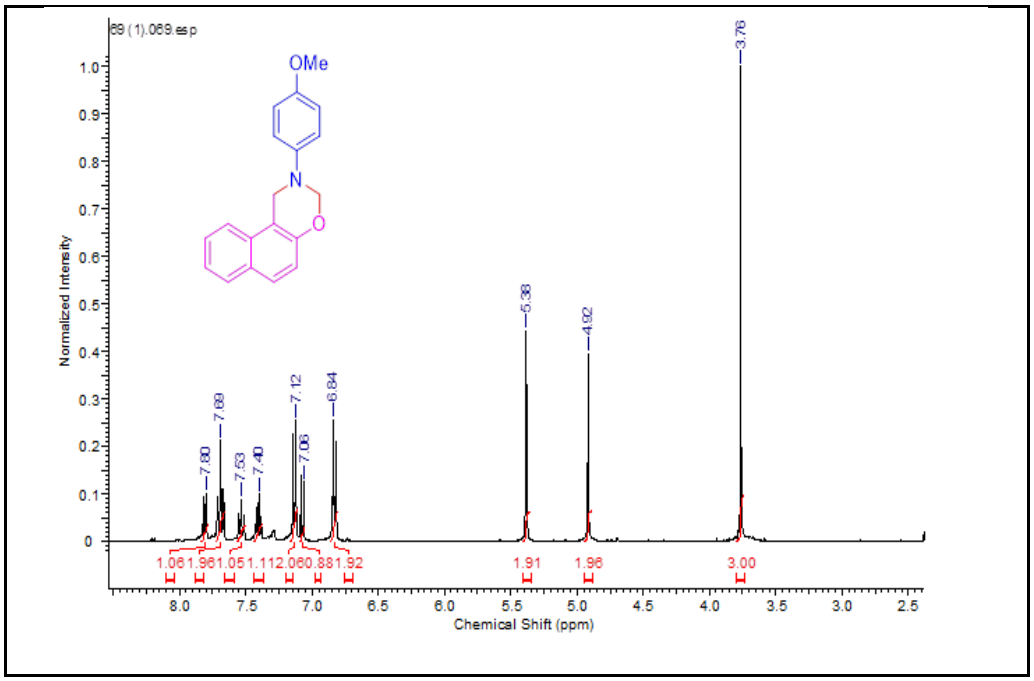


Figure 3.9: ^{1}H NMR of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

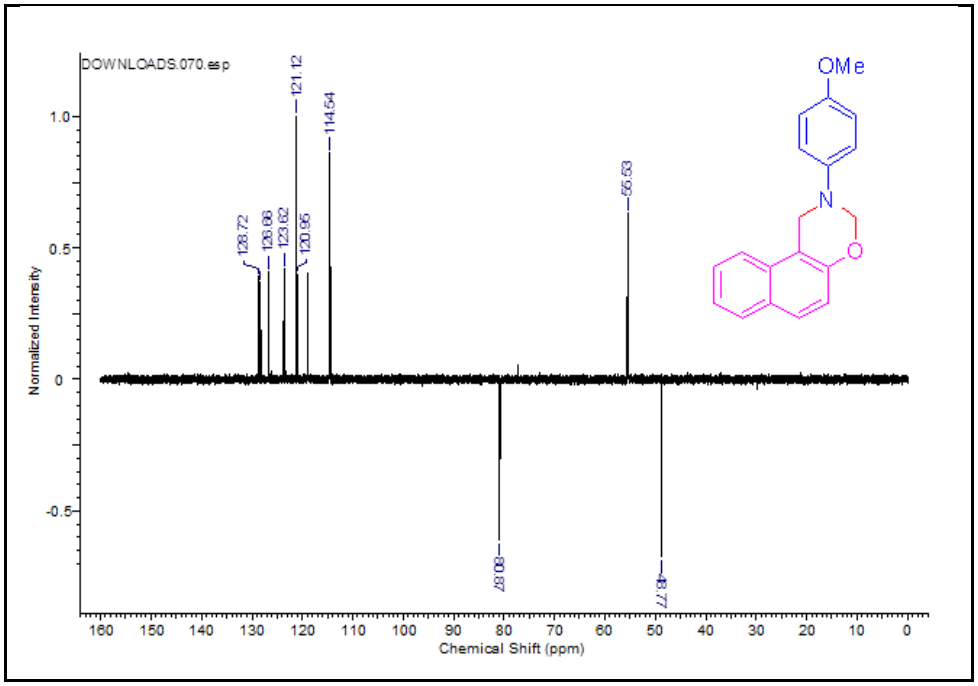


Figure 3.10: DEPT of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

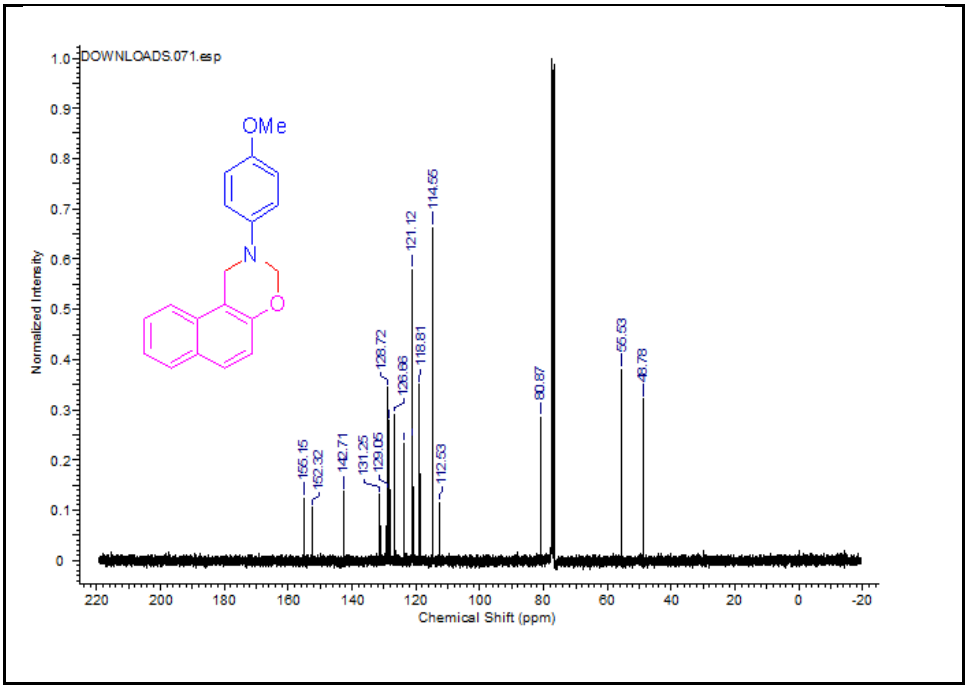


Figure 3.11: ^{13}C NMR of 2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine

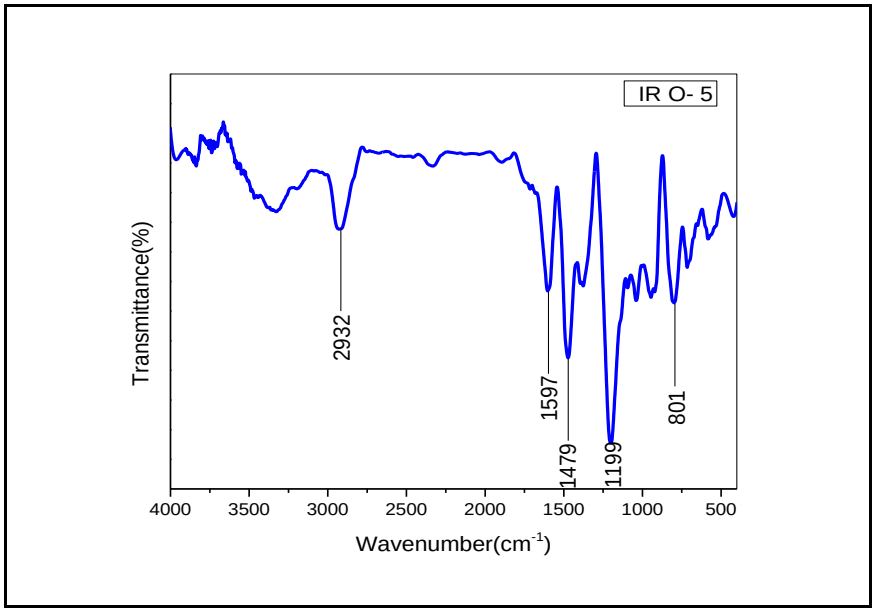


Figure 3.12: IR spectra of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

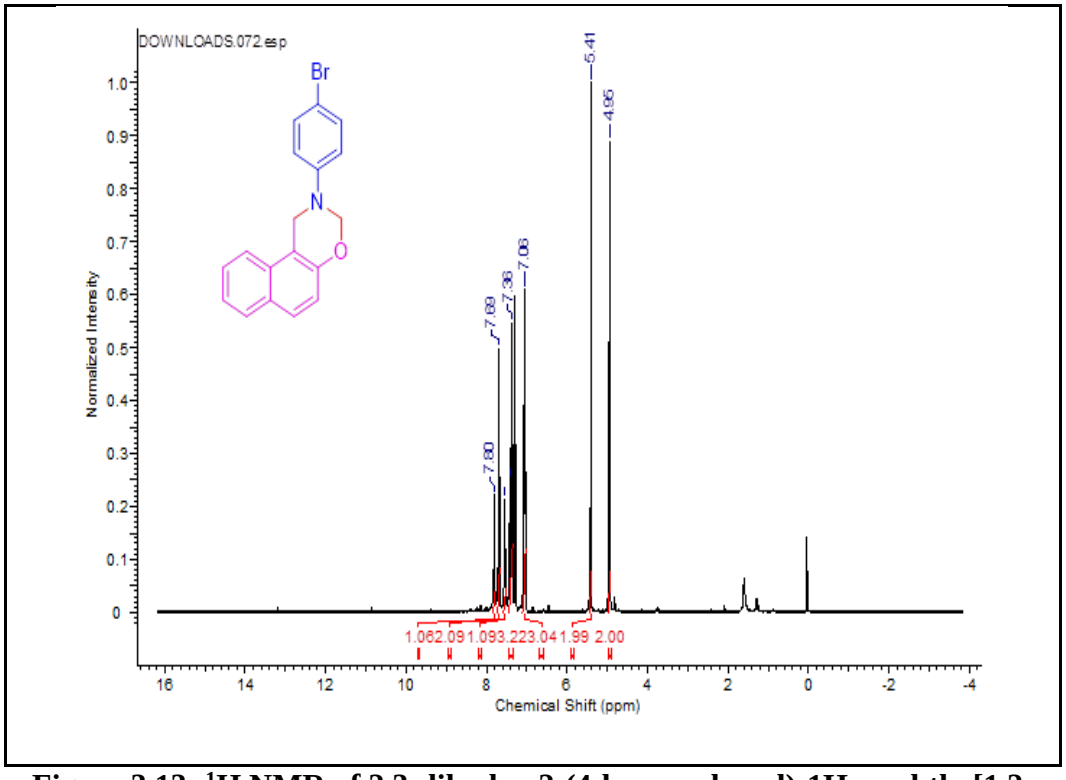


Figure 3.13: ^{1}H NMR of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

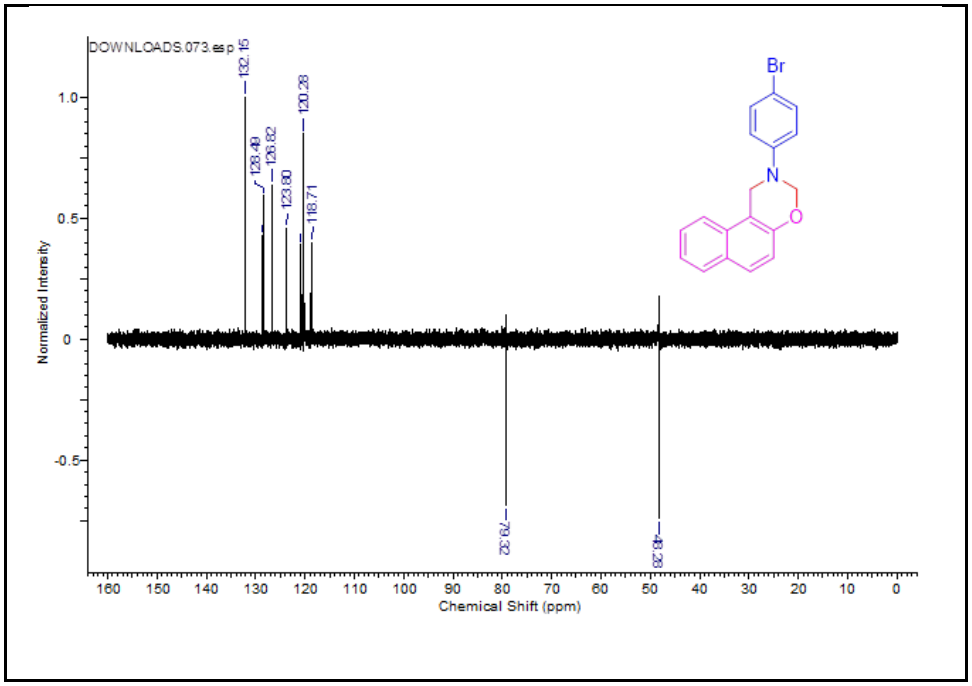


Figure 3.14: DEPT of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

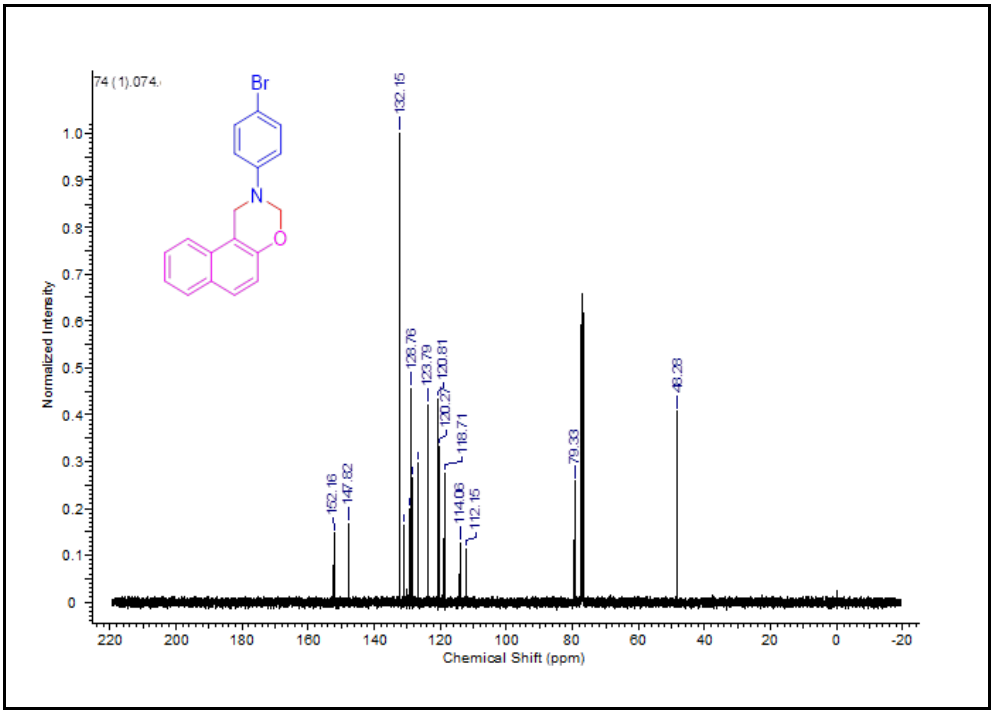


Figure 3.15: ^{13}C NMR of 2,3-dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine

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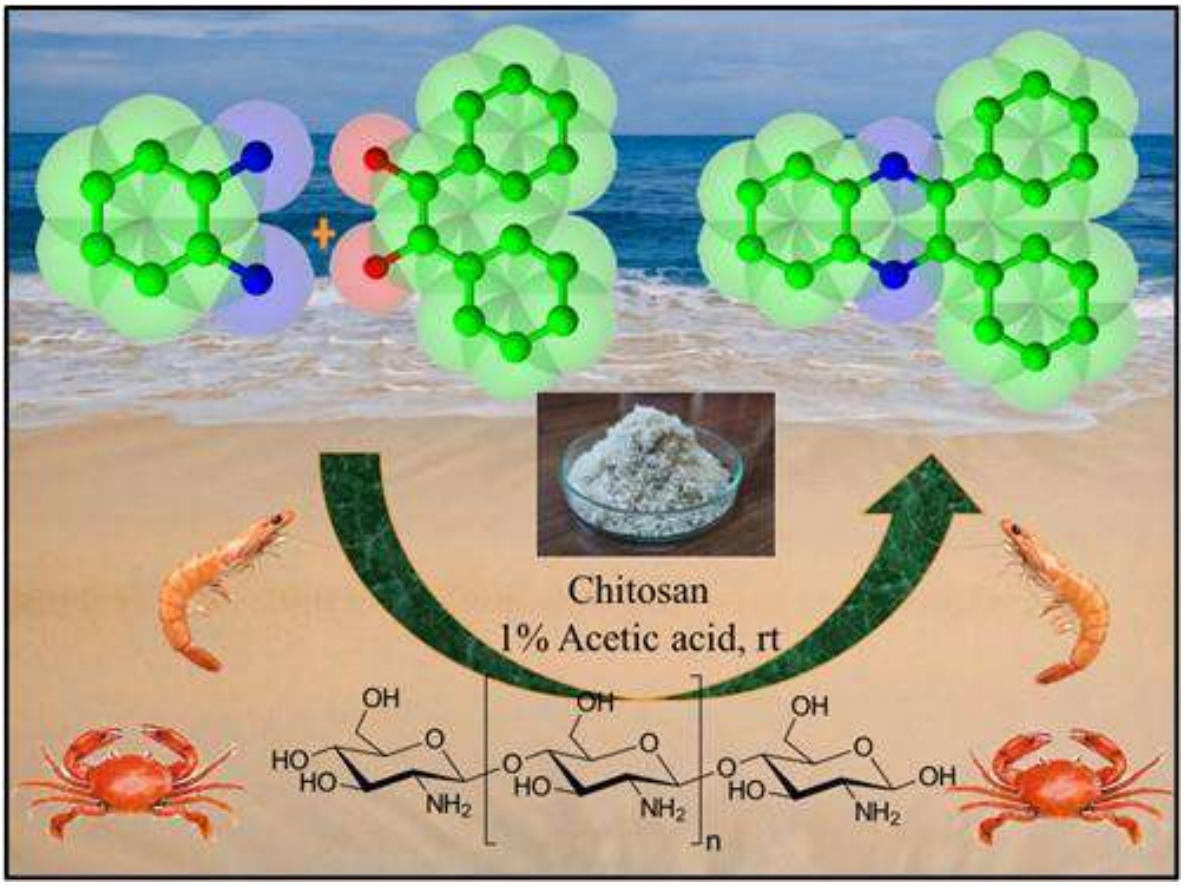
CHAPTER - 4

GREEN AND ECO-COMPATIBLE SYNTHESIS OF QUINOXALINE MOLECULES USING CHITOSAN AS A BIODEGRADABLE CATALYST IN AQUEOUS MEDIUM



CHAPTER 4

Green and Eco-compatible Synthesis of Quinoxaline Molecules using Chitosan as a Biodegradable Catalyst in Aqueous Medium

4.1 Introduction

The study of the chemistry of heterocyclic compounds is one of the interesting branches of organic chemistry. There has been a huge discovery of heterocyclic substances due to their important role in the metabolism of all living cells. As a result of the special stability of heterocyclic compounds, they have most important function in living cells, such as vitamins, co-enzymes, etc.; they resist metabolic destruction and do not easily degrade themselves. Therefore, from decades until now, researchers have focused primarily on the synthesis of heterocyclic compounds.

Quinoxaline is one of the important class of heterocycles. It has diverse applications in dyestuffs, drug and as an analytical reagent. The biological activity with other substances continually increases interest in the synthesis of new derivatives of this molecule. Quinoxaline (a) is an aromatic heterocycle produced by the fusion of two six-membered aromatic rings, one of which is benzene and the other is pyrazine, consist of two nitrogen atoms symmetrically placed at the 1 and 4 positions **(Figure 4.1)** [1].

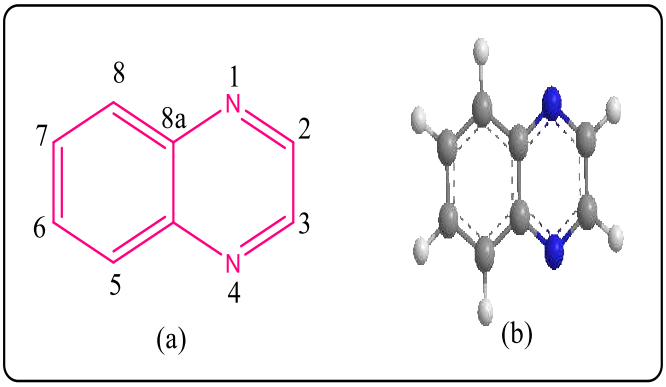
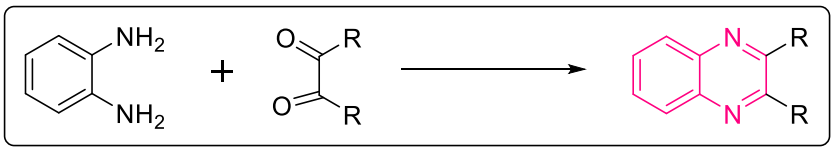


Figure 4.1. (a) Structure of Quinoxaline (b) 3D Structure of Quinoxaline.

Hinseberg first discovered the quinoxaline in 1884; according to him, in the quinoline, the methine group is replaced by a nitrogen atom at the fourth position and called it benzopyrazine. Hinseberg did a systematic study of the quinoxaline and their

derivatives and suggested the class name quinoxaline by pointing out the relationship between the quinoline and glyoxal, the dicarbonyl compound from which he prepared the first member of the series **(Scheme 4.1)** [2]. Thereafter, Gabriel and sonn confirmed the ring structure, and they demonstrated experimentally the relationship between the quinoxalines and pyrazines by oxidising the quinoxaline to pyrazine 2,3-dicarboylic acid. The physical properties of quinoxaline and pyrazine are analogous with each other. The numbering system shown in structure of quinoxaline (a) is universally used or accepted. From the resonating structure of quinoxaline depicted in **(Figure 2)** the positions 2,4,5,7 and 8a are electron deficient and hence easily attacked by nucleophile [3].



Scheme 4.1

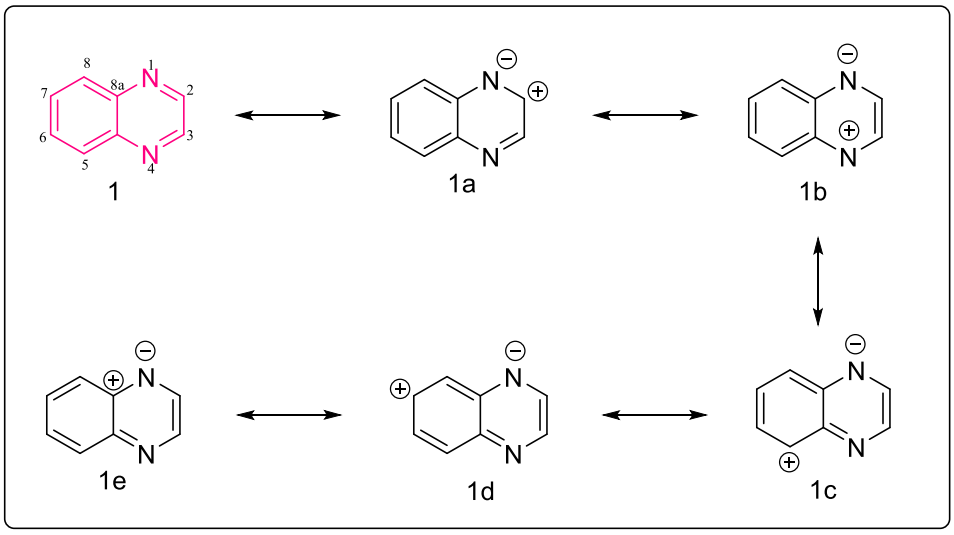


Figure 4.2 Resonating structures of quinoxaline.

Researcher's gives principal attention towards the quinoxaline molecule from the several years. The quinoxaline molecule has become great topic of universal research due to two nitrogen atoms in one of the rings. The two imine nitrogen atoms at 1,4 position displays electron-withdrawing properties. In addition to that these derivatives have extensive application because their formation takes place very easily

and smoothly with good yields [4]. The application program of quinoxaline molecules in distinct field as like dyes, or as a building block in the production of organic semiconductors [5], electroluminescent material, dye-sensitized solar cells (DSSC) [6] [7], etc. also they consisting a broad range of physicochemical [8] and biological activities [9] such as antibacterial [10], antiviral, anticancer activity [11], antitubercular activity [12], anti-inflammatory [13], anti-malarial [14], anti-hyperglycemic [15], anti-HIV [16] and anti-depressant activity [17]. Quinoxaline has a very important position in pharmacy due to its anticancer drug activity; CQS (chloroquinoxaline sulfonamide) and XK469 were both found to have activity against solid tumours **(Figure 4.3)**.

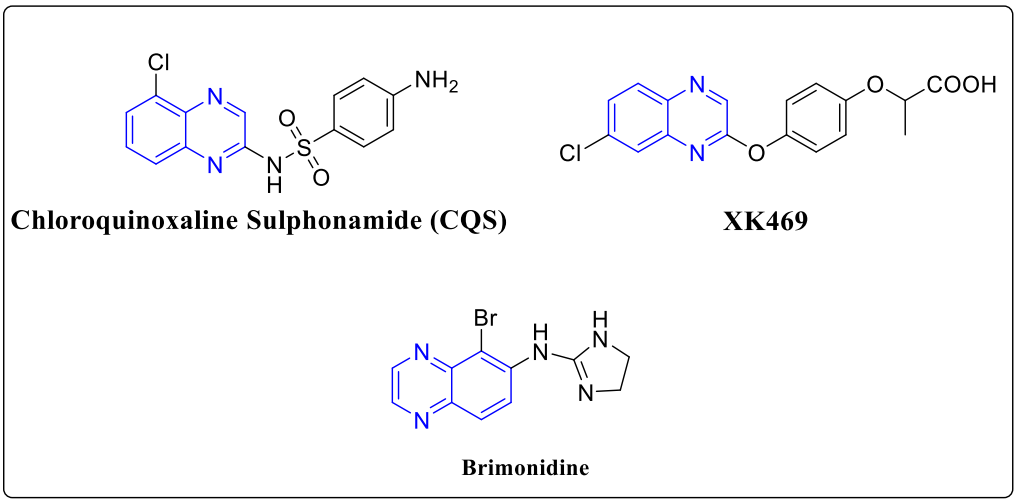
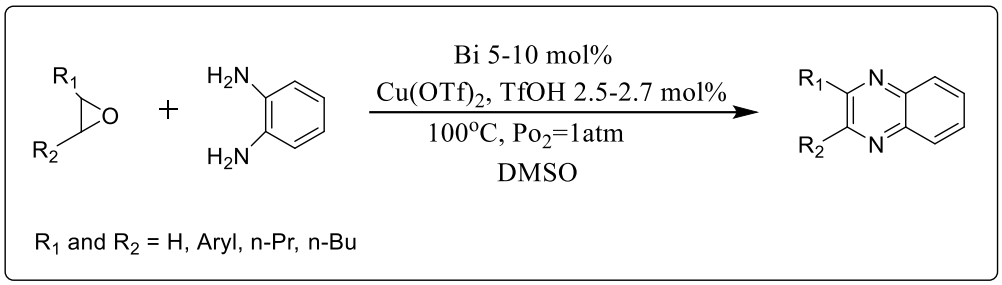


Figure 4.3 Biologically Active Quinoxaline Molecules.

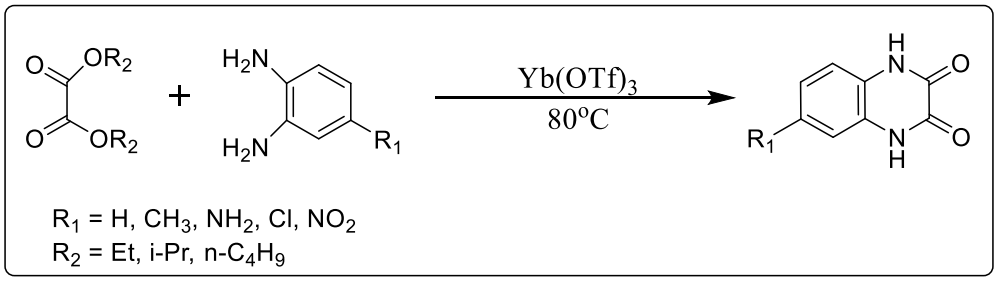
There are different methods are reported for the preparation of quinoxaline derivatives general method is condensation of O-phenylenediamine with glycoxal or an -diketone [18], 1,4-addition of 1,2-diamines to diazenylbutenes [19] and cyclization–oxidation of phenacyl bromides [20]. Various popular methods for synthesis of substituted quinoxaline derivates are reported as below;

Sylvain Antoniotti and Elisabet Dunach [21] gives direct bi-catalysed synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines by oxidative coupling **(Scheme 4.2).**



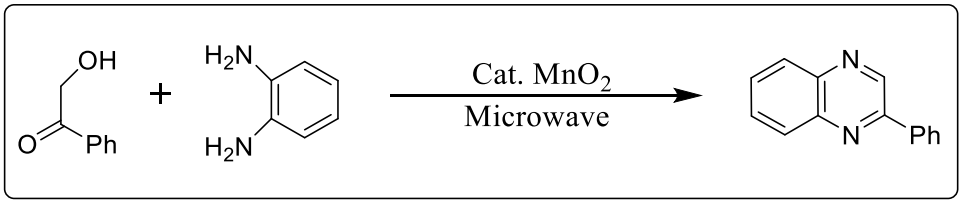
Scheme 4.2

Ytterbium triflate catalysed synthesis of quinoxaline-2,3-diones derivatives reported by Limin Wang and co-workers [22]. Heterocyclisation of 1,2-phenylenediamines and alkyl oxalates under solvent-free condition gives high yield within 1hr **(Scheme 4.3)**.



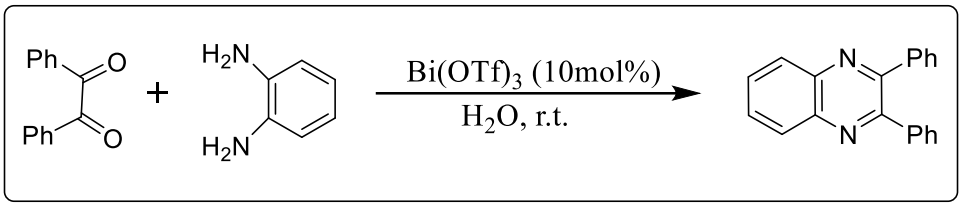
Scheme 4.3

So Yeon Kim et al. [23] under microwave irradiation developed manganese (IV) dioxide-catalysed production of quinoxalines. A variety of *a*-hydroxyketones react with aromatic or aliphatic 1,2-diamines in presence of manganese (IV) dioxide under microwave irradiation without solvent within one minute synthesize quinoxaline molecules **(Scheme 4.4).**



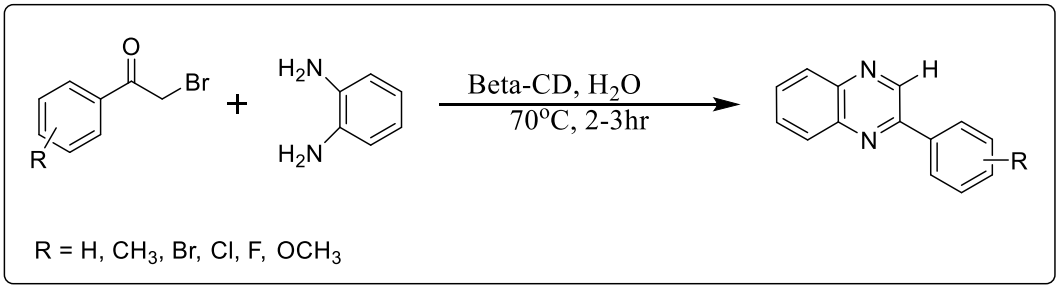
Scheme 4.4

Jhillu S. Yadav et al. [24] developed aqueous-mediated, bismuth(III)-catalysed rapid synthesis of 2,3-disubstituted quinoxalines. They prepared different kinds of 2,3-disubstituted quinoxalines with better yields under normal conditions, including room-temperature stirring of 1,2-diamines with 1,2-dicarbonyls in the presence of bismuth (III) triflate as a catalyst **(Scheme 4.5)**.



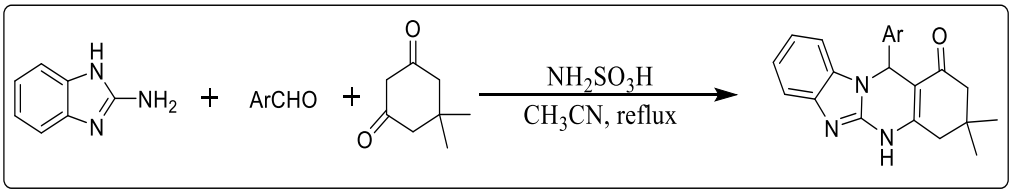
Scheme 4.5

The biomimetic synthesis of quinoxalines in water reported by B. Madhav and co-workers [25] was catalysed by β-cyclodextrin. The biomimetic study of β -cyclodextrin is understood by using ^{1}H NMR spectroscopy **(Scheme 4.6)**.



Scheme 4.6

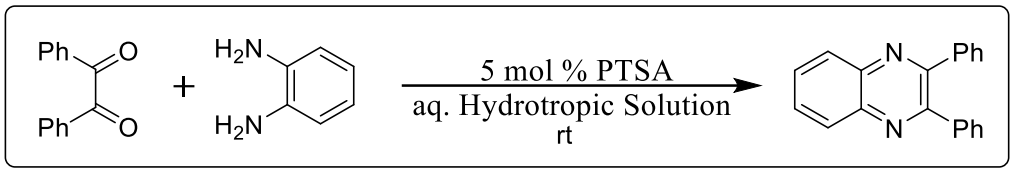
Majid M. Heravi and co-workers [26] reported sulfamic acid–catalysed synthesis of [1,2,4]triazolo/benzimidazole quinazolinone derivatives. sulfamic acid is a reusable, green catalyst **(Scheme 4.7)**.



Scheme 4.7

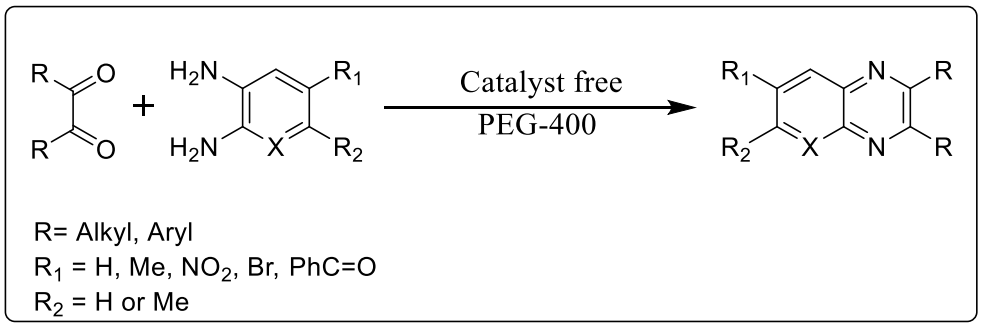
Arjun Kumbhar et al. [27] demonstrated the synthesis of quinoxalines and pyrido[2,3-b]pyrazines in aqueous hydrotropic medium. Combination of Bronsted acid

and hydrotrope avoids the utilization of organic solvents, produces excellent yield at room temperature **(Scheme 4.8)**.



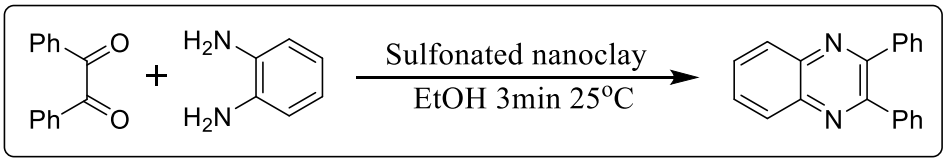
Scheme 4.8

A catalyst-free protocol was developed by Tie-Qiang Huang et al. [28] for the production of quinoxalines and pyrazines molecules in PEG. The condensation of 1,2-diketones with aromatic 1,2-diamines in polyethylene glycol (PEG) provides quinoxaline derivatives in good yields **(Scheme 4.9)**.



Scheme 4.9

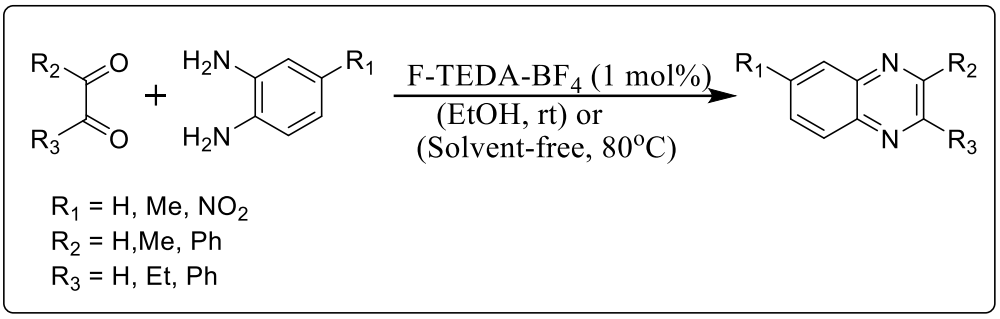
Mahgol Tajbakhsh and co-workers [29] use sulfonated nanoclay minerals as a reusable, eco-compatible catalytic agent for the development of quinoxaline molecules. Synthesized sulfonated nanoclay was used for the synthesis of quinoxaline derivatives by reacting 1,2-diamines with 1,2-diketones in ethyl alcohol as a greener medium at room temperature **(Scheme 4.10)**.



Scheme 4.10

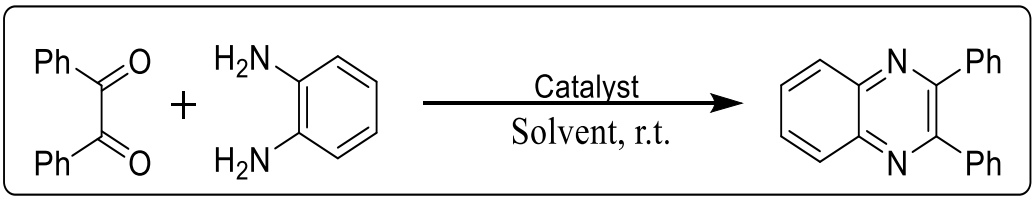
S. F. Hojati et al. [30] developed a methodology for the synthesis of quinoxaline and 2,3-dihydropyrazine derivatives using selectfluor-[1-(chloromethyl)-4-flouro-1,4-

diazoniabicyclo[2,2,2]octane bis(tetraflouroborate)] as an effective and reutilizable catalyst in solvent and under solvent free condition **(Scheme 4.11)**.



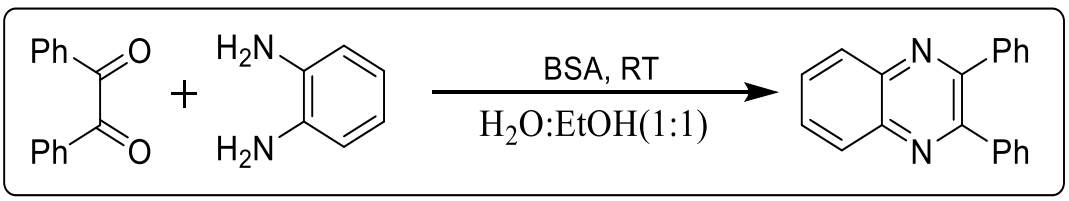
Scheme 4.11

Preparation and utilisation of polyvinylimidazole-based Bronsted acidic ionic liquid supported silica as an effective systematic heterogeneous catalyst reported by Bahman Tamami and co-workers [31] for the synthesis of quinoxaline derivatives **(Scheme 4.12)**.



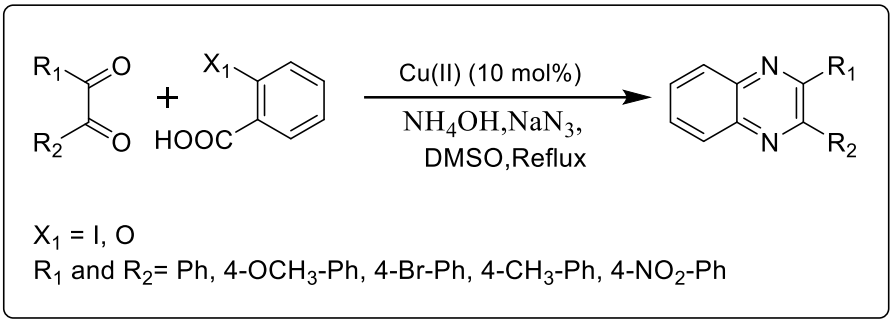
Scheme 4.12

Sami Sajjadifar [32] reported a newer and more eco-friendly catalyst, silica boron sulfonic acid, for the preparation of quinoxaline molecules at room temperature. The condensation of 1,2-diketones and 1,2-diamines using BSA in H_2O: EtOH (20 ml) produces quinoxaline derivatives in isolated high yields (**Scheme 4.13)**.



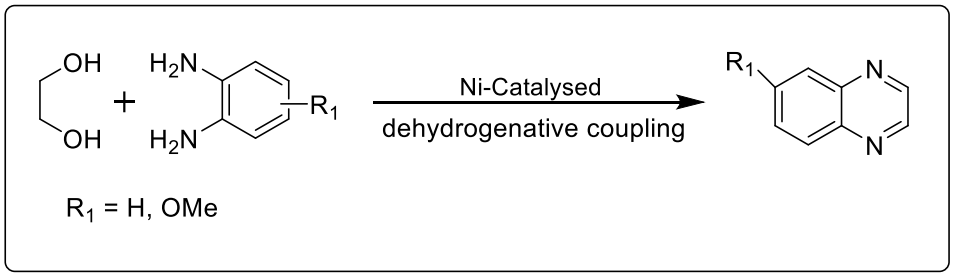
Scheme 4.13

Bittu Saha et al. [33] first reported that 2-iodo benzoic acid is an unusual reactant for the synthesis of quinoxaline using an organo-Cu (II) catalyst. The reaction pathway is a Schmidt reaction followed by a nucleophilic substitution reaction between 2-iodo benzoic acid and sodium azide, which stimulated by an organo Cu (II) catalyst that produces quinoxaline molecules **(Scheme 4.14).**



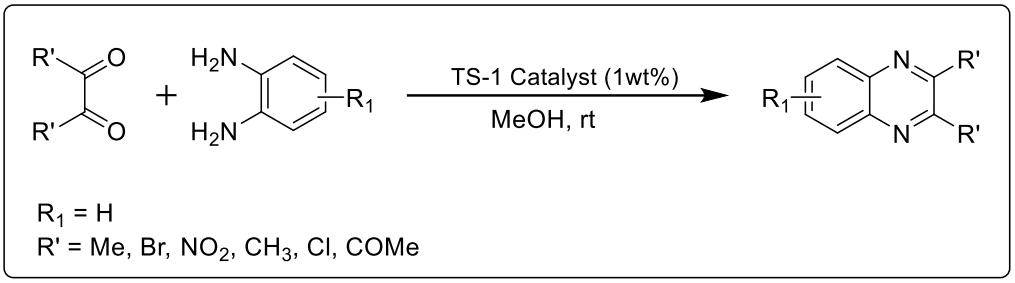
Scheme 4.14

Atanu Bera and co-workers [34] synthesise the substituted benzimidazoles and quinoxalines. There is dehydrogenative coupling that takes place between ethylene glycol and aromatic diamines for the selective synthesis of mono- and di-substituted quinoxaline, catalysed by earth-abundant $NiCl_2$ with the ligand 1,10-phenthroline **(Scheme 4.15)**.



Scheme 4.15

Pranav S. Chandrachood et al. [35] developed an effective approach for the synthesis of quinoxaline molecules catalysed through titanium silicate-1. A library of quinoxaline derivatives was efficiently produced at room temperature in better yields with 1 wt.% of titanium silicate (TS-1) as a catalyst by the reaction between 1,2-diamines and 1,2-diketones in methanol **(Scheme 4.16)**.



Scheme 4.16

Gurpreet Kaur and co-workers [36] reported camphor sulfonic acid as a systematic organic catalyst that produces the structurally diverse quinoxalines and pyrido-pyrazine derivatives at room temperature **(Scheme 4.17)**.

Scheme 4.17

4.2 Present Work:

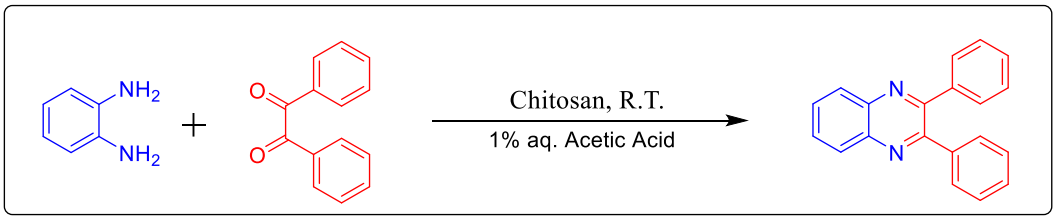
We contribute to green chemistry by developing a greener, eco-compatible synthesis of quinoxaline at room temperature using chitosan as a biodegradable catalyst. Chitosan is a natural polysaccharide and is also known as a "biopolymer", which was obtained from the alkaline hydrolysis of chitin. Chitin is obtained from the exoskeletons of crustaceans such as crabs, lobsters, and shrimp; the radulas of molluscs; as well as the beaks of cephalopods, which are abundantly present in the biosphere of the earth. Therefore, chitosan is a renewable green catalyst.

4.3 Result and Discussion:

In the present protocol, we apply chitosan without any further modification for the synthesis of quinoxaline derivatives. Fortunately, we obtained a good to excellent yield within a short period of time compared to the previous strategies. At the beginning, we focused on optimising the conditions for the synthesis of quinoxaline by

using benzil and ortho-phenylenediamine in the presence of chitosan in 5ml of 1% aqueous acetic acid solution. Initially, we focused on a systematic evaluation of the amounts of catalyst used of 0.01, 0.02, 0.04, 0.05, 0.06, and 0.08 g of chitosan (Table 4.1). We got a very excellent result at 0.04 g of chitosan. When we increase the amount of chitosan, we observe that the solubility of chitosan decreases and it forms a gel-like viscous solution in the round bottom flask. This shows the reactants are not mixed properly with each other and therefore decrease the amount of product **(Table 4.1)**. Then, after optimising the conditions, we synthesise quinoxaline by using benzil and ortho-phenylenediamine in 5 mL of 1% aq. acetic acid solution using 0.04 g chitosan as a catalyst at room temperature as a model scheme **(Scheme 4.18)**. We prepared the series of quinoxaline derivatives by using substituted benzil and ortho-phenylenediamine under optimised reaction conditions **(Table 4.2)**.

In recent days, very few protocols display direct use of chitosan in organic transformation. Researchers develop pathways that directly use chitosan for greener and eco-friendly synthesis of organic compounds in response to the demand for sustainable development in terms of the environment, safety, and economy [37], [38].



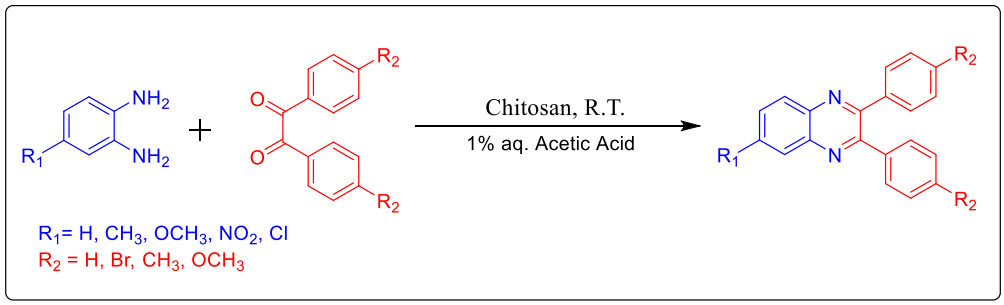
Scheme 4.18. Synthesis of Quinoxaline by using chitosan as a biocatalyst.

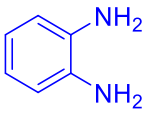
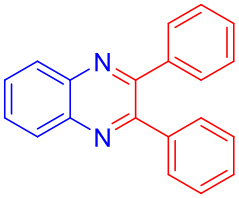
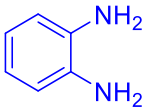
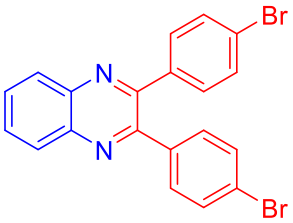
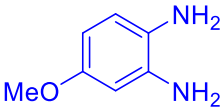
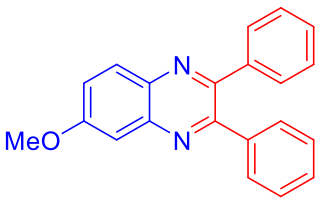
Table 4.1. Optimizing amount of catalyst for synthesis of Quinoxaline derivatives:

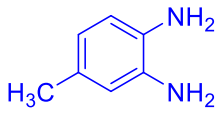
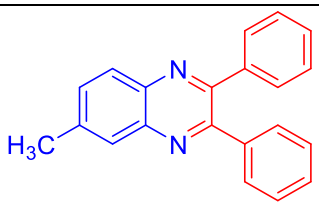
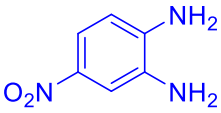
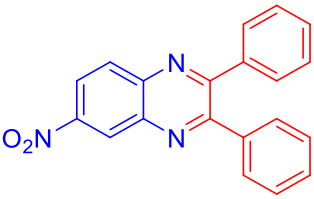
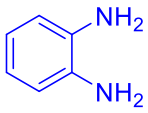
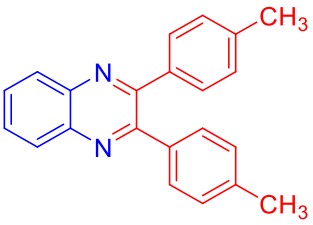
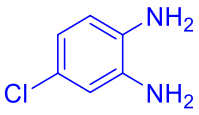
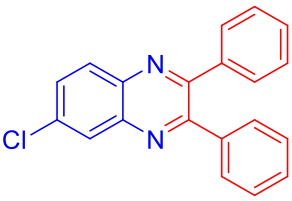
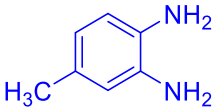
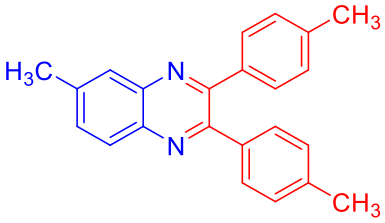
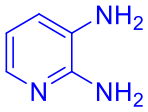
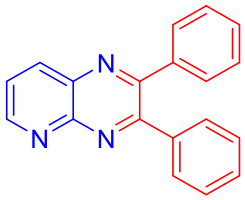
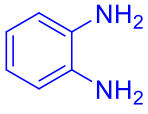
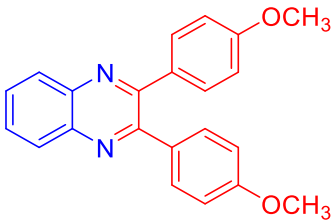
Sr. No.	Amount of Chitosan, solvent	Time	Yield (%)
1	0.01 in 1% aq. Acetic acid	24hrs	25
2	0.02 in 1% aq. Acetic acid	24hrs	47
3	0.03 in 1% aq. Acetic acid	8hrs	71
4	0.04 in 1% aq. Acetic acid	10min	92
5	0.05 in 1% aq. Acetic acid	15min	90

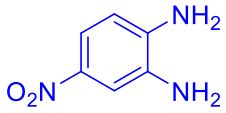
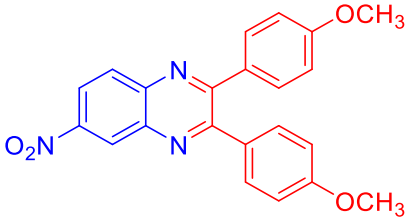
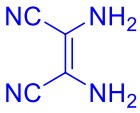
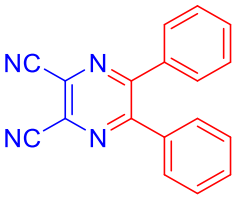
6	0.06 in 1% aq. Acetic acid	15hrs	65
7	0.08 in 1% aq. Acetic acid	24hrs	35
8	0.04 in 1% acetic acid: Ethanol (1:1)	20min	50

Table 4.2 Synthesis of Quinoxaline derivatives by using Chitosan as biodegradable catalyst.



Sr. No.	1,2-Diamine	Product	M.P. (°C) [Lit.]	Yield %[a]
1			127-128 [39]	92
2			190-192 [39]	92
3			160-162 [41]	91

4			116-118 [39]	90
5			192-194 [39]	90
6			145-146 [39]	91
7			120-121 [42]	92
8			140-142 [39]	92
9			160-162 [29]	92
10			156-158 [39]	92

11			191-192 [43]	90
12			165-166	90

[a] Isolated yield after recrystallisation.

Recyclability of Catalyst:

The synthesis of quinoxaline from benzil (1 mmol) and ortho-phenylenediamine (1 mmol) in 5 mL of 1% aq. acetic acid with 0.04 gm of chitosan after this the solid mass was filtered and the filtrate contained chitosan catalyst, which was reused without any further treatment for the next cycle of quinoxaline synthesis. This study shows that there is no reduction in catalytic efficiency up to the third cycle, after that there is a slight decrease in yield **(Figure 4.4)**.

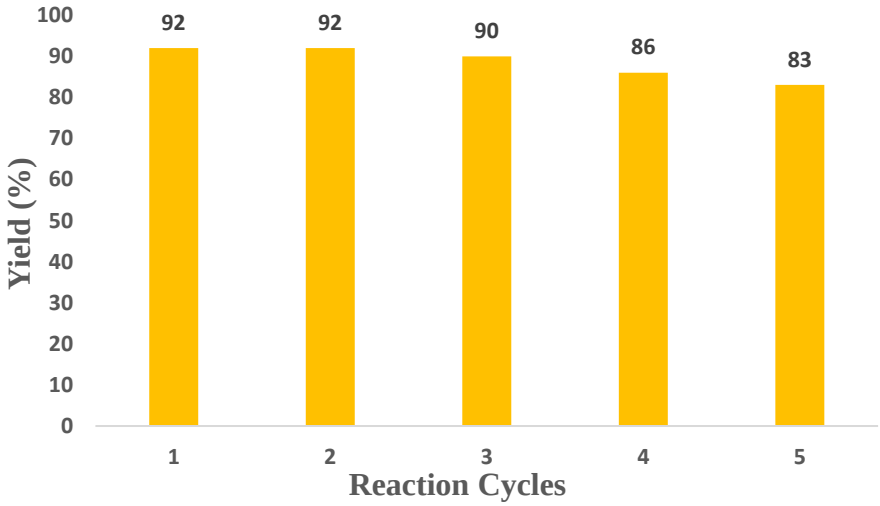


Figure 4.4. Recyaclability of Catalyst.

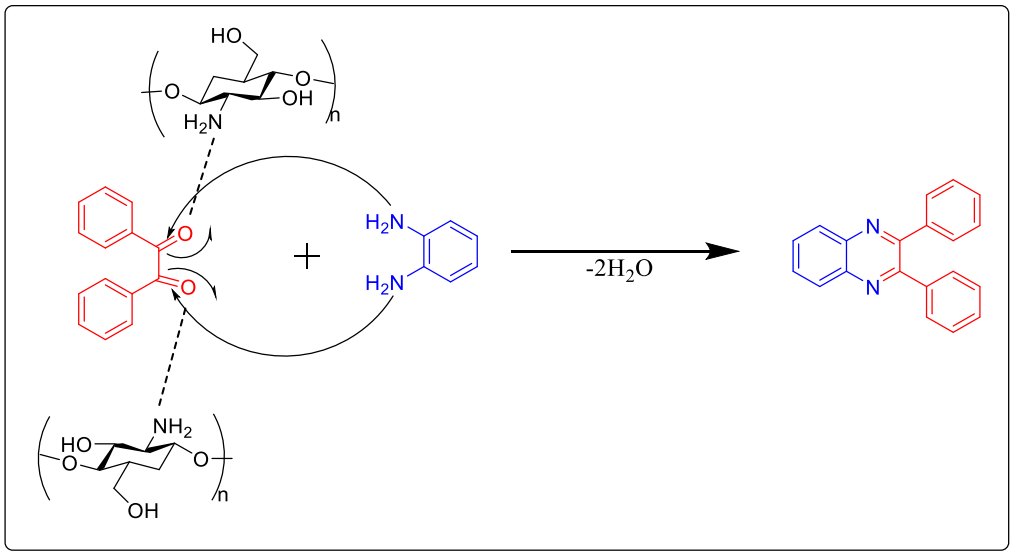
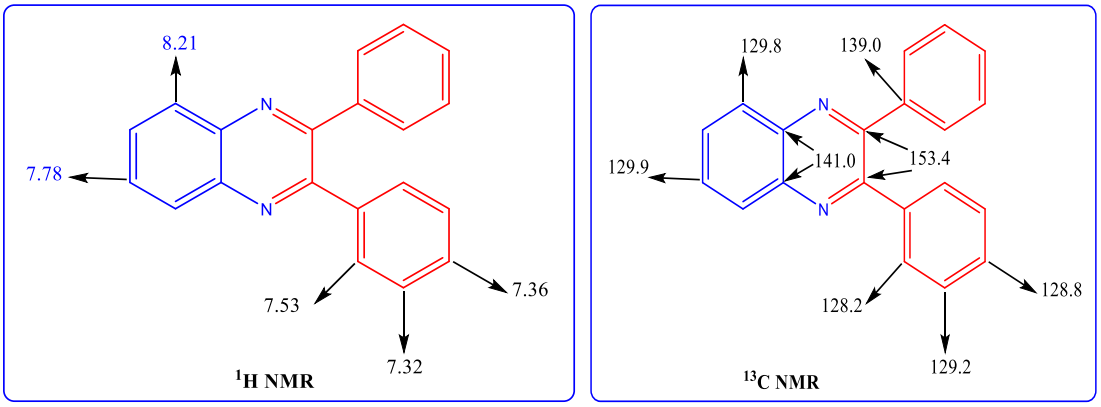


Figure 4.5. Plausible mechanism for synthesis of Quinoxaline by using Chitosan as biodegradable catalyst.

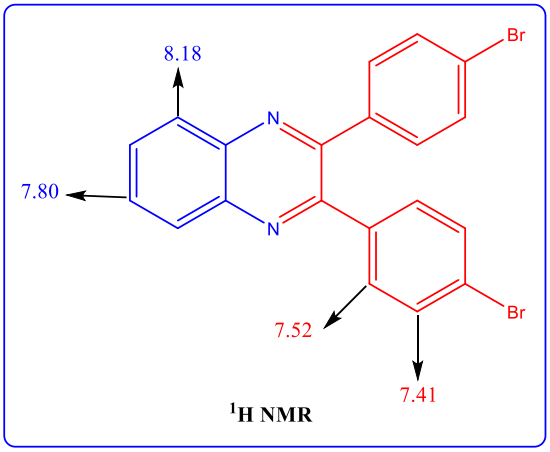
Characterization of products:

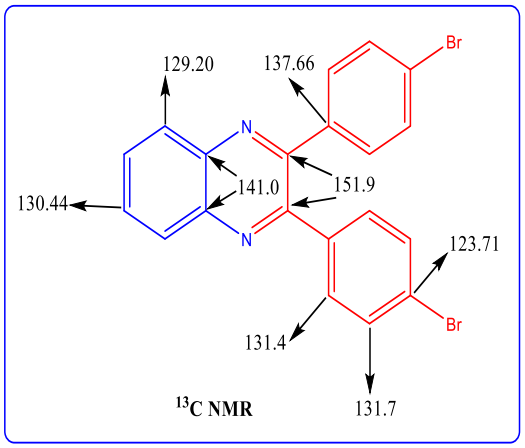
2,3-Diphenylquinoxaline:



IR spectrum **(Figure 4.6)** exhibits a characteristic band around 1443 cm^{-1} assignable to N=C-Ar, which indicates the formation of quinoxaline. The band at 1631 cm^{-1} designates the presence of alkene in aromatic rings. ^{1}H NMR spectra **(Figure 4.7)** of same compound shows all signals in the range of δ 7.34 to 8.21 ppm. The aromatic proton of quinoxaline appeared as a multiplate while aromatic protons of phenyl ring also appeared as multiplate. ^{13}C spectrum **(Figure 4.8)** exhibits all peaks at δ 151.93, 141.24, 137.66, 131.70, 131.43, 130.44, 129.20, 123.71 ppm in the aromatic region. The GCMS **(Figure 4.9 and 4.10)** shows peak at m/z: 282.

2,3-bis(4-bromophenyl) quinoxaline (Table 2. Entry-2):





IR spectrum **(Figure 4.11)** exhibits a characteristic band around 1393 cm^{-1} assignable to N=C-Ar, which indicates the formation of quinoxaline. The band at 1662 cm^{-1} designates the presence of alkene in aromatic rings and absorption at 749 cm^{-1} for the C-Br. ^{1}H NMR spectra **(Figure 4.12)** of same compound shows all signals in the range of δ 7.40 to 8.18 ppm. The aromatic proton of quinoxaline appeared as a multiplate while aromatic protons of phenyl ring appeared as doublet. ^{13}C spectrum **(Figure 4.13)** exhibits all peaks at δ 151.93, 141.24, 137.66, 131.70, 131.43, 130.44, 129.20, 123.71 ppm in the aromatic region.

4.4 Conclusion:

In conclusion, we described the new readily recovered biocatalyst for the synthesis of a series of quinoxaline derivatives. The biodegradable catalyst for organic transformation plays an important role now days because of the environmental views and the present protocol conserves environmental life and the economy by using biodegradable chitosan as a catalyst. The promising aspects of present work are high efficiency, short reaction time, clean reaction media, and operational simplicity. This protocol enhances the synthetic methodology for sustainable synthesis of various quinoxaline derivatives in aqueous medium.

4.5 Experimental Section

The melting points of the products were determined using the EQ 730A-EQUIPTRONICS electrical melting point apparatus and are uncorrected. Infrared

spectra were recorded on a Lamda FTIR 750 spectrometer. The samples were examined as KBr discs 5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. GCMS is recorded on GCMS-QP2010. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companies and used without further purification.

General Procedure for Synthesis Quinoxaline Derivatives

In a round-bottom flask, dissolve 0.04 g of chitosan in 5 ml of a 1% aqueous acetic acid solution, then add 1,2-diketone (1 mmol) and 1,2-diamine (1 mmol) derivatives. The reaction mixture was magnetically stirred at room temperature for an appropriate time (table 2). The completion of the reaction was monitored by tlc (n-hexane: ethyl acetate, 6:4). After completion of the reaction, the reaction mixture is filtered, and the product is washed with a 1% aqueous acetic acid solution. We get a crude product that has been recrystallized in ethanol. We obtain the pure product of quinoxaline.

Spectroscopic Data

2,3-Diphenylquinoxaline (Table 2. Entry-1): IR (KBr): 3051, 1630, 1528, 1348, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.18-8.21 (m, 2H), 7.77-7.80 (m, 2H), 7.52-7.54 (m, 4H), 7.34-7.37 (m, 6H); ^{13}C NMR (400 MHz, CDCl3): δ 153.48 (C), 141.23 (C), 139.08 (C), 129.98 (CH), 129.84 (CH), 129.22 (CH), 128.81 (CH), 128.28 (CH); MS (ESI): m/z = 282.

2,3-bis(4-bromophenyl) quinoxaline (Table 2. Entry-2): IR (KBr): 1662, 1575, 1393, 1200, 1059, 825, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.15-8.21 (m, 2H), 7.79-7.82 (m, 2H), 7.51-7.53 (m, 4H), 7.40-7.42 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 151.93 (C), 141.24 (C), 137.66 (C), 131.70 (CH), 131.43 (CH), 130.44 (CH), 129.20 (CH), 123.71 (C).

6-Methyl-2,3-Diphenylquinoxaline (Table 2. Entry-4): IR (KBr): 3063, 1660, 1592, 1210, 874, 719, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.1 (d, 1H), 7.96 (s, 1H), 7.63 (dd, 1H), 7.5 (m, 4H), 7.35 (m, 6H), 2.6 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$):

δppm 152.9 (C), 152.1 (C), 141.1(C), 138.7(C), 138.2(C), 137.8(C), 132.4 (CH), 129.2 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.4 (CH), 20.4 (CH).

5,6-diphenylpyrazine-2,3-dicarbonitrile (Table 2. Entry-12): IR (KBr): 2917, 2160, 1586, 1438, 1008, 1185, 775, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δppm 7.32-7.30 (m, 4H), 7.25-7.23 (t, 2H), 7.17-7.15 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δppm 155.27 (C), 135.04 (C), 131.03 (C), 129.68 (CH), 128.98 (CH), 128.71 (CH), 113.18 (C); MS (ESI): m/z = $281(M-1)^{+}$.

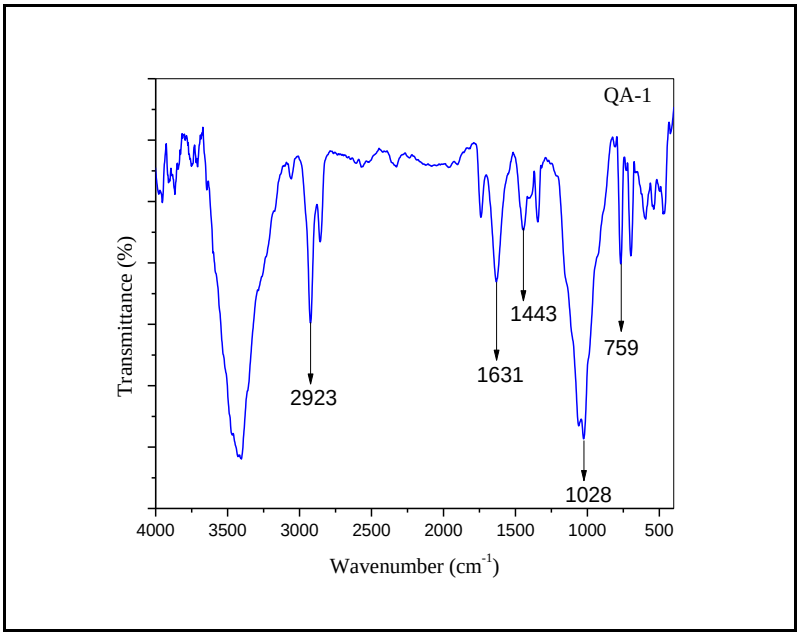


Figure 4.6: IR spectra of 2,3-Diphenylquinoxaline

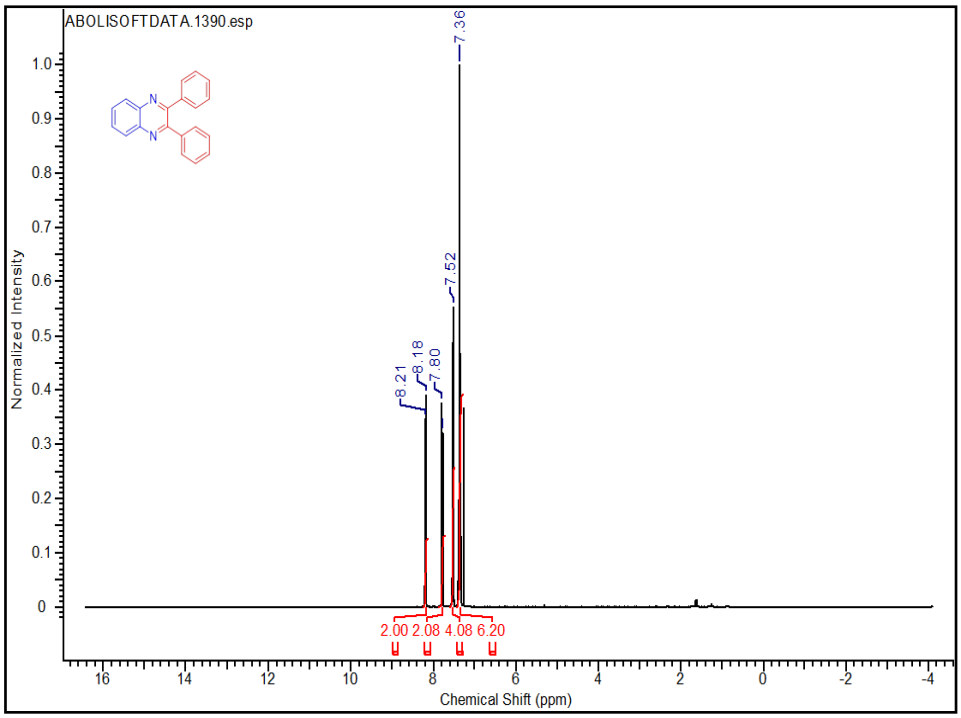


Figure 4.7: ^{1}H NMR of 2,3-Diphenylquinoxaline

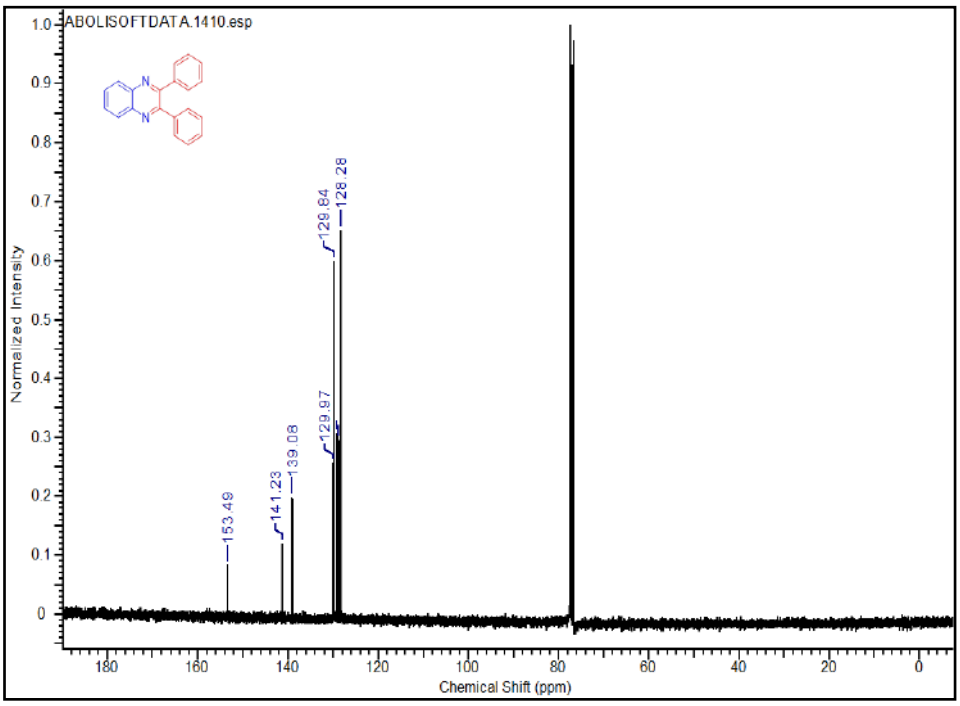


Figure 4.8: ^{13}C NMR of of 2,3-Diphenylquinoxaline

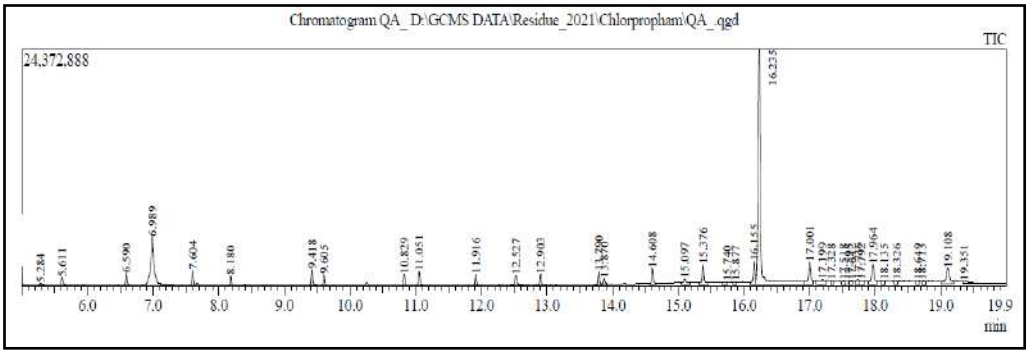


Figure 4.9: GCMS spectrum of 2,3-Diphenylquinoxaline

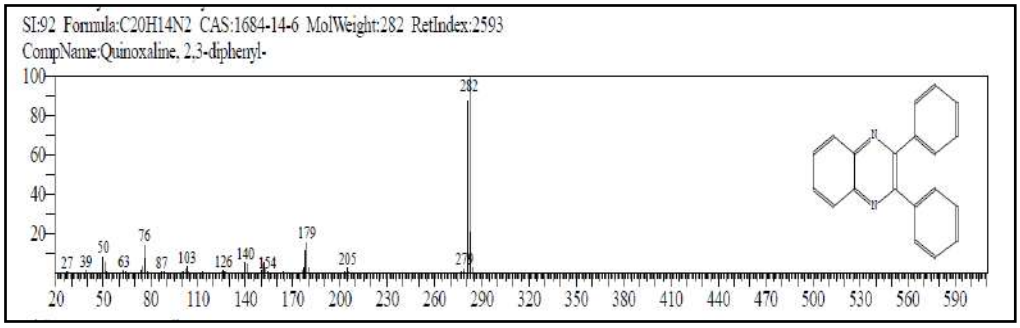


Figure 4.10: Mass spectrum of 2,3-Diphenylquinoxaline

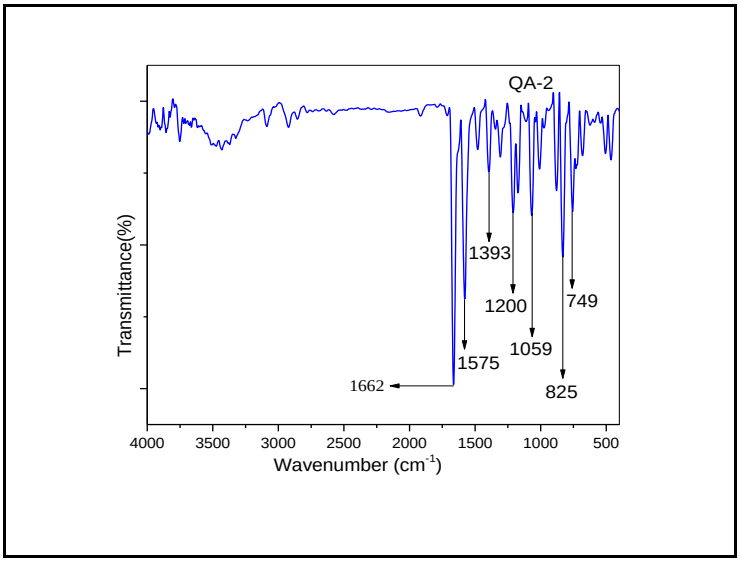


Figure 4.11: IR spectra of 2,3-bis(4-bromophenyl) quinoxaline

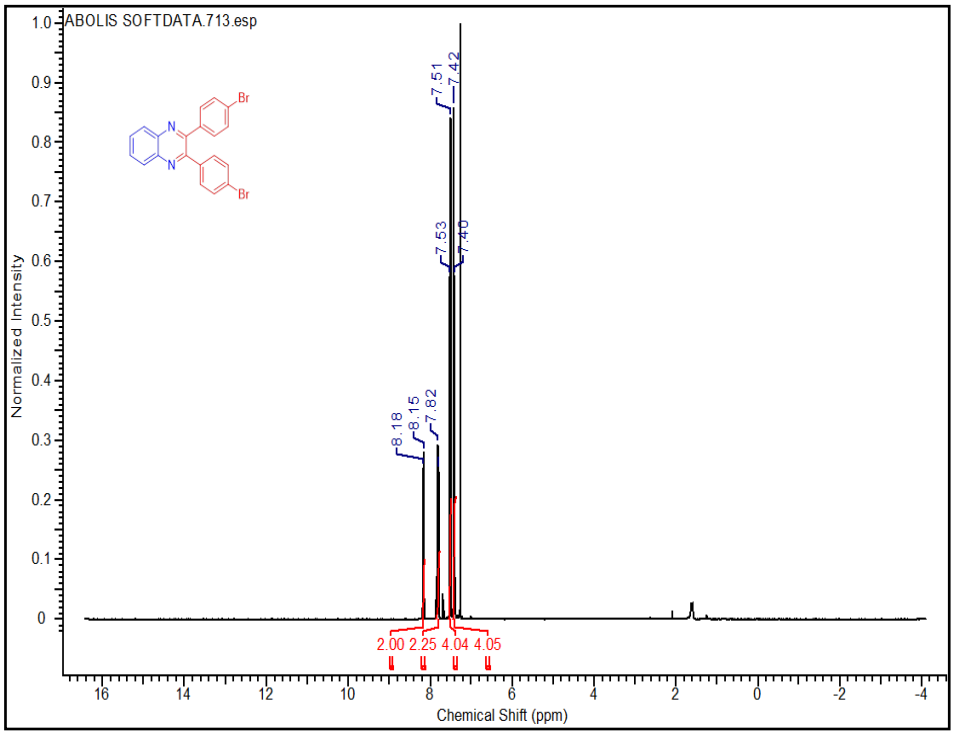


Figure 4.12: ^{1}H NMR of 2,3-bis(4-bromophenyl) quinoxaline

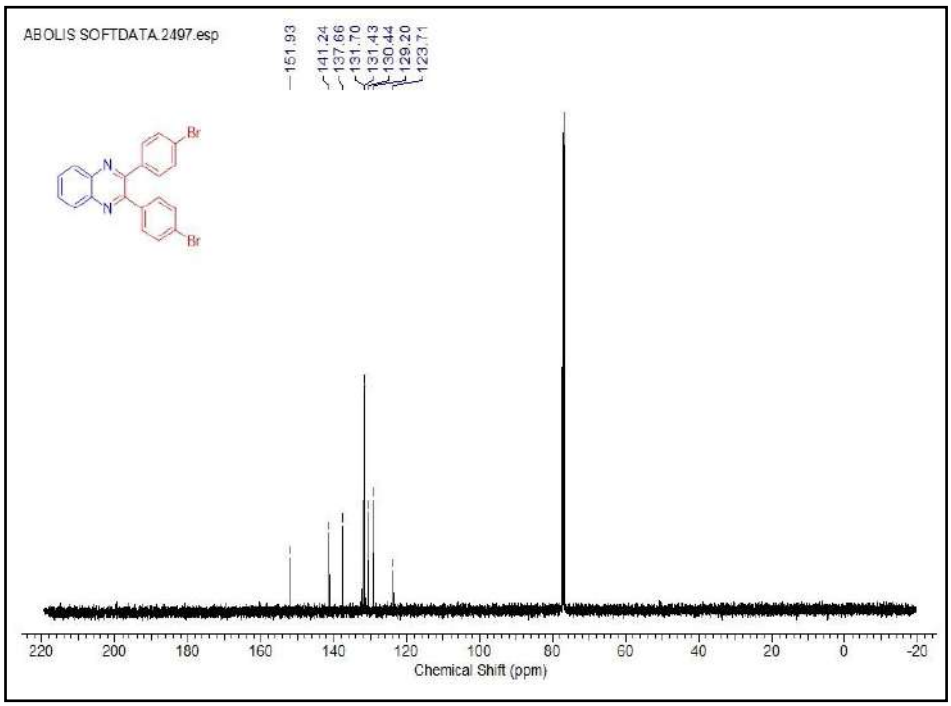


Figure 4.13: ^{13}C NMR of 2,3-bis(4-bromophenyl) quinoxaline

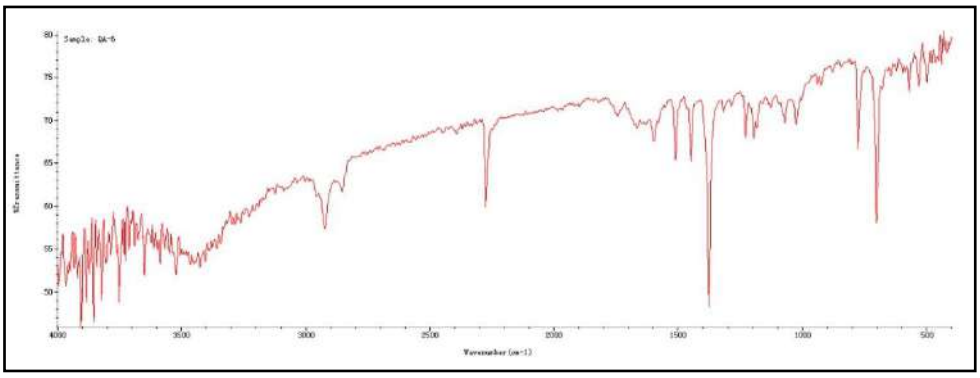


Figure 4.14: IR Spectrum of of 5,6-diphenylpyrazine-2,3-dicarbonitrile

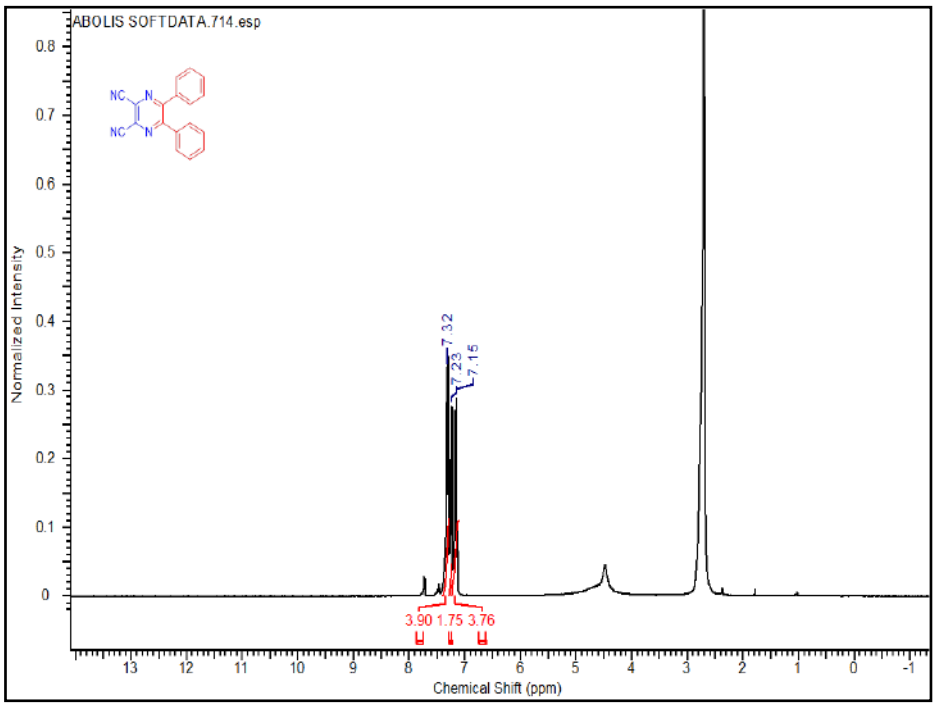


Figure 4.15: ^{1}H NMR spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

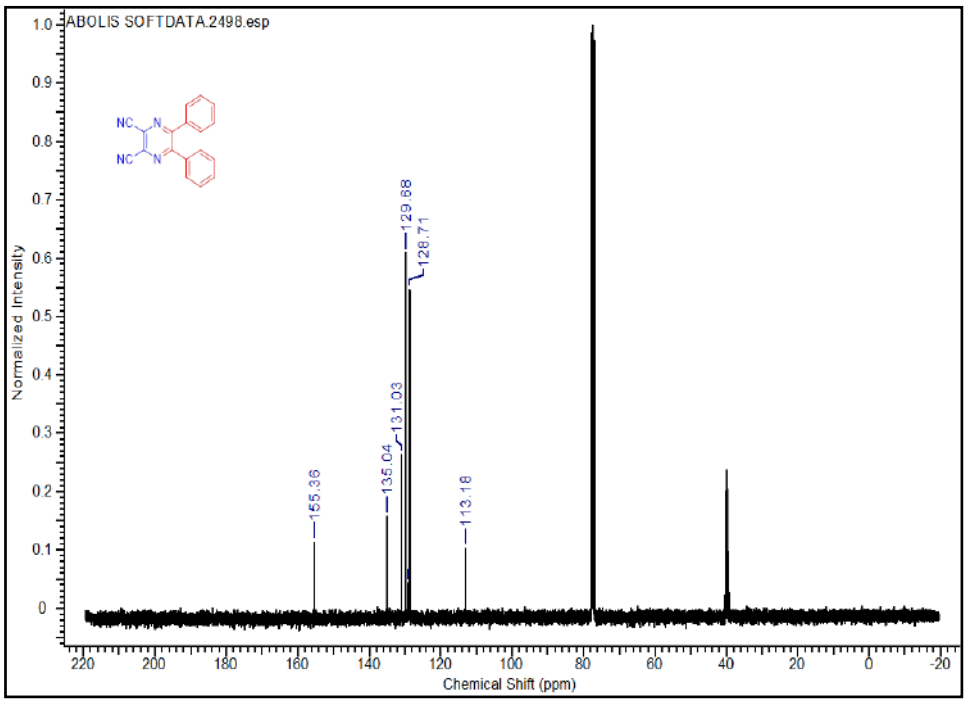


Figure 4.16: ^{13}C NMR spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

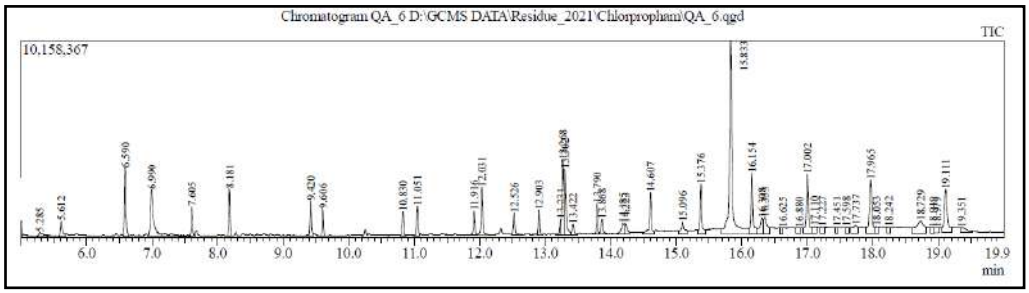


Figure 4.17: GCMS spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

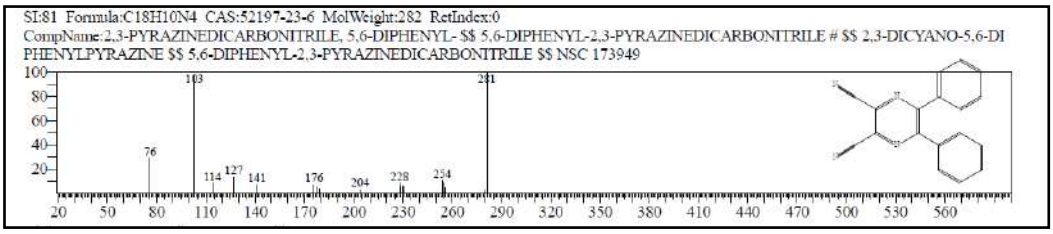


Figure 4.18: Mass spectrum of 5,6-diphenylpyrazine-2,3-dicarbonitrile

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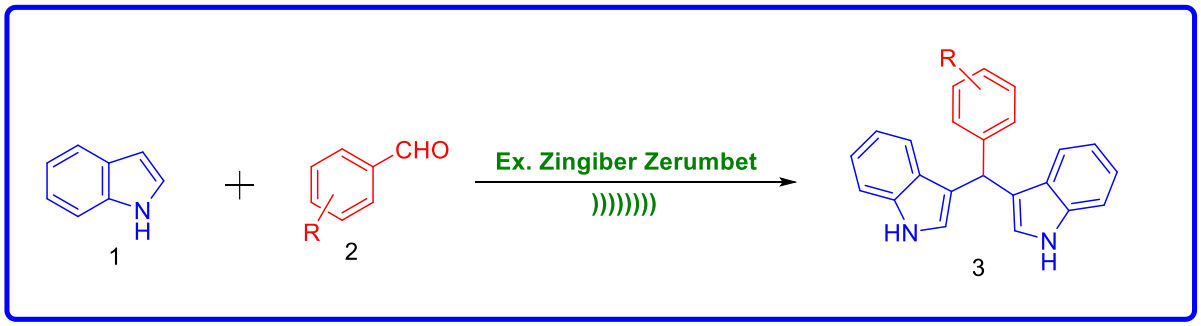
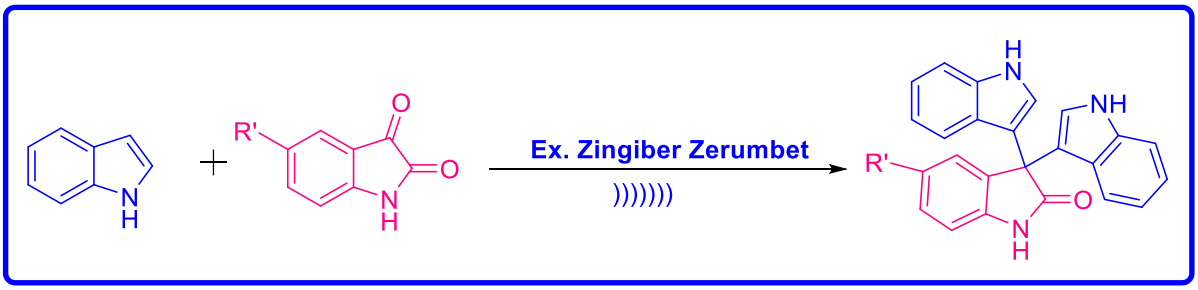
CHAPTER - 5

SECTION - I

GREENER AND ENHANCED ECO-SENSITIVE BENIGN METHODOLOGY FOR THE SYNTHESIS OF BIS(INDOLYL)METHANE AND TRISINDOLINES MOLECULES.





CHAPTER 5

Section: I

Greener and Enhanced Eco-sensitive Benign Methodology for the Synthesis of Bis(indolyl)methane and Trisindolines Molecules

5.I.1 Introduction

Chemist are very interested in the creation of diverse class of heterocyclic compounds. Heterocyclic compounds are carbocyclic compounds that replace carbon atom by one or more heteroatom such as nitrogen, oxygen or sulphur with in ring structure. They are aliphatic and aromatic found in nature, synthesized in laboratory and also in the industrial sector. The significance of these heterocyclic compounds lies in the various fields of science and technology and also in our daily life. These fields are pharmaceutical industry, agrochemicals, veterinary products, as result of developers, sanitizers, corrosion inhibitors, copolymers, dyestuffs and exhibit tremendous applications at industrial scale.

Most interesting nitrogen containing heterocycles are pyrazole, pyrazine, pyrimidine, quinoline, quinoxaline, indole etc. shows wide range of biological and medicinal activities, so their preparation always been an attractive and innovative part of organic chemistry. Among the various heterocyclic compounds' particularly indole and its derivatives, have occupied a unique place in the chemistry of nitrogen-containing heterocyclic compounds because of their miscellaneous biodynamic properties [1]. The aromatic bicyclic structure incorporating benzene ring fused with pyrrole ring is known as indole **(Figure 5.I.1)** [2]. Indole is electron rich heteroaromatic system due to having high-energy HOMO containing 10 π-electron system, 8 electrons from double bonds and 2 electrons from lone pair of electrons present on nitrogen atom. As like benzene, indole readily undergoes electrophilic substitution reactions due to delocalization of excessive π-electrons. Indole contains only one nitrogen atom, which is weakly basic in nature, like pyrrole and therefore very reactive with strong acids [3].

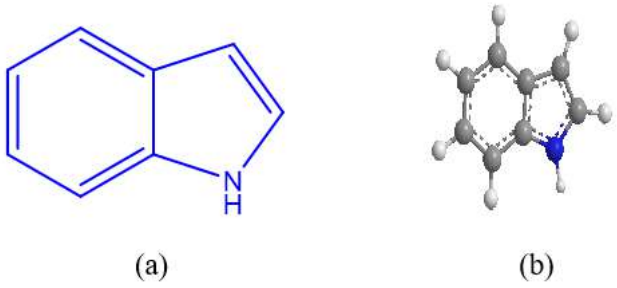
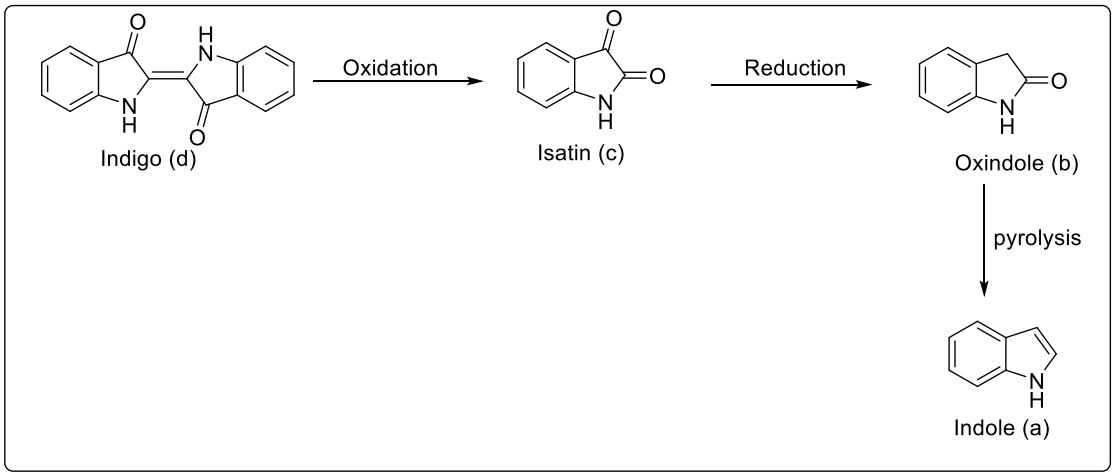


Figure 5.I.1: (a) Structure of Indole (b) 3D structure of Indole.

The research and study in the chemistry of indole (**a**) began in the mid of the 19th century with extensive search on the natural blue dye indigo (**d**), imported to Europe mainly from India. Indigo (**d**) (species of *Indigofera*) is an example of simple bisindole [4]. In 1866, Adolf Von Baeyer discovered the conversion of oxindole (**b**) into indole (**a**) by a pyrolytic technique using zinc dust (**Scheme 5.1**) and in 1869 he established a formula for indole **(Figure 5.I.2)** [5].



Scheme 5.I.1

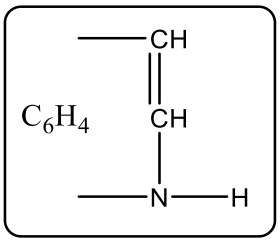


Figure 5.I.2 Baeyer formula for Indole

Indole (a), also known as 2, 3-benzopyrrole, 1H-benzo[b]pyrrole, 1-benzazole, 1-azaindene, or ketole, is a colorless, shiny, crystalline compound with a melting range of 52-54^{o}C. Indole (a) and its oxygenated derivative known as isatin having different isomers are collected in figure 5.3 out of which indole (a) is most stable isomer.

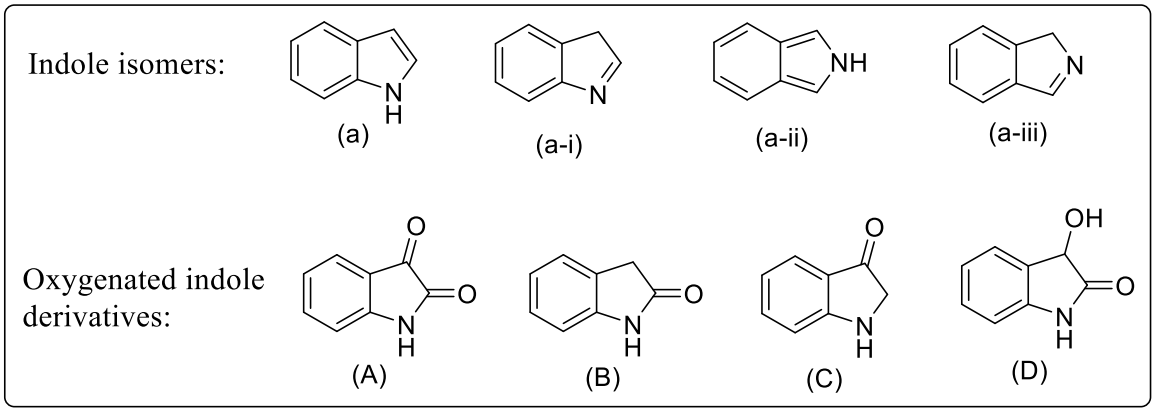


Figure 5.I.3 Indole isomers and oxygenated indole derivatives

Different derivatives of indole containing naturally occurring indole nucleus including Reserpine, Vincristine and essential amino acid Tryptophan [6]–[8]. Indole and its derivatives have been a subject of research studies due to its anticarcinogenic, antioxidant and antiathrerogenic effects [9]–[12]. Bis(indolyl)methane and tris-indoline are one of the important derivatives of indole **(Figure 5.I.4)**.

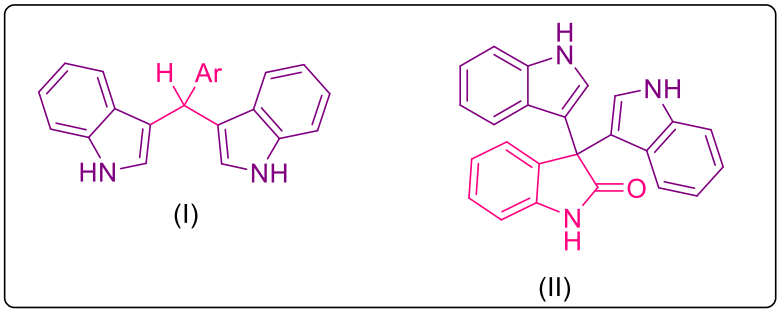
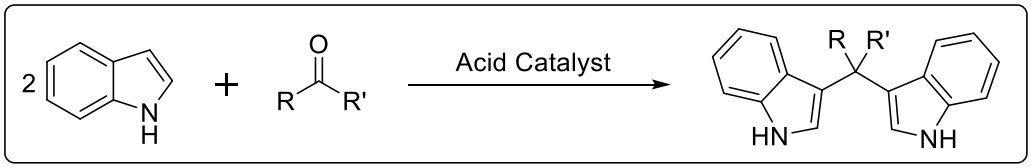


Figure 5.I.4 (I) structure if Bis(indolyl)methane (II) structure of Trisindolines

Bis(indolyl)methanes (BIMs) that having two indole units in a molecule, widely spread in various marine and terrestrial natural sources [10]. Viberindole is natural BIMs are useful in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome [13], [14], etc. Other natural sources are parasitic bacteria, sponges, tunicates, and also obtained from the assimilation of indole-3-carbinol present in Brassica

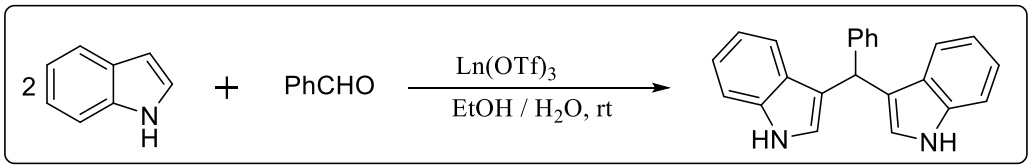
vegetables such as broccoli, cauliflower, and collard greens [15], [16]. Trisindolines are nitrogen bearing heterocyclic compounds containing an isatin core holds two indole scaffolds. Trisindolines have been prepared by reacting isatins with two indoles moieties mostly acid catalysed strategies are applied [17]. Trisindolines have wide spectrum of biological activities including anticancer [18], antimicrobial, anticonvulsant [19], antimycobacterial [20], and spermicidal activities [21]. The greatness of indole and its widespread implementation justifies it being addressed as "The Lord of the Rings" of heteroaromatic compounds [22]. Therefore, here we collect some methodologies for the synthesis of BIMs and Trisindolines, as follow;

The most famous synthetic method is Fischer indole synthesis was first reported by Fischer [23] in 1886 by Friedel-Crafts reaction between indole and aldehydes or ketones catalysed with mere acid **(Scheme 5.I.2)**.



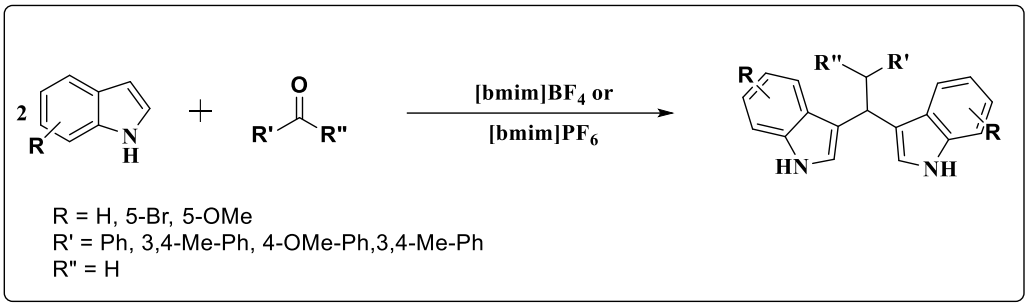
Scheme 5.I.2

After that Wang and co-workers [24] in 1996 developed a new methodology for the synthesis of BIMs using Lanthanide triflate [Ln $(OTF)_3$] as a mild and effective acid catalyst in protic media **(Scheme 5.I.3)**.



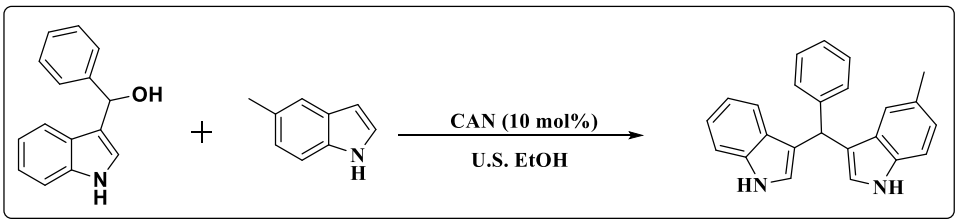
Scheme 5.I.3

J. S. Yadav et al. [25] demonstrated that ecofriendly process for the synthesis of BIMs by using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids. At room temperature stirring the indole, aldehyde or ketone in ionic liquids [([bmim]BF_4) or ([bmim]PF_6)] for 4-5hrs gives the BIMs in good yield **(Scheme 5.I.4)**.



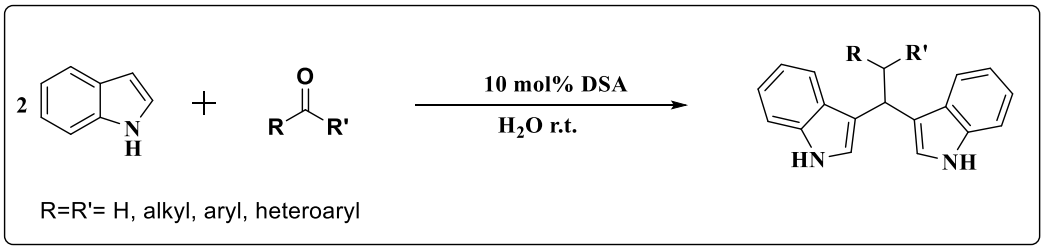
Scheme 5.I.4

Novel approach discovered by Xiao-Fei Zeng et al. [26] for synthesis of unsymmetrical bis(indolyl)alkanes under ultrasonic irradiation. In recent years many organic transformations are catalyzed by ceric ammonium nitrate (CAN) because inexpensive, easily available and soluble in less hazardous organic solvent such as EtOH and MeOH **(Scheme 5.I.5).**

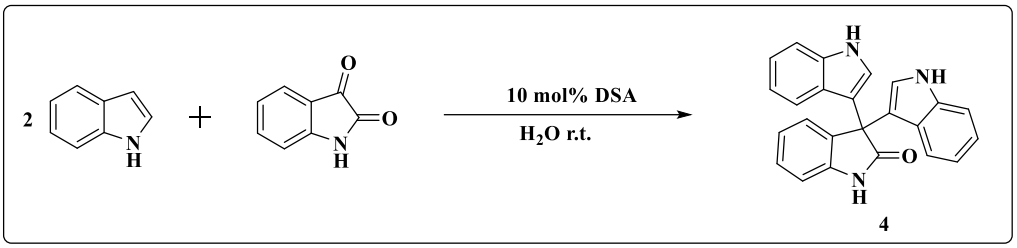


Scheme 5.I.5

Parasa Hazarika et al. [27] develop nonhazardous synthetic methodologies for synthesis of bis(indolyl)methane and tris-indolines for that they take aldehyde or ketone (1mmol) which reacts with indole (2mmol) and isatin (1mmol) treated with indole (2mmol) in presence dodecylsulphonic acid (DSA) in water at room temperature **(Scheme 5.I.6 and 5.I.7).**

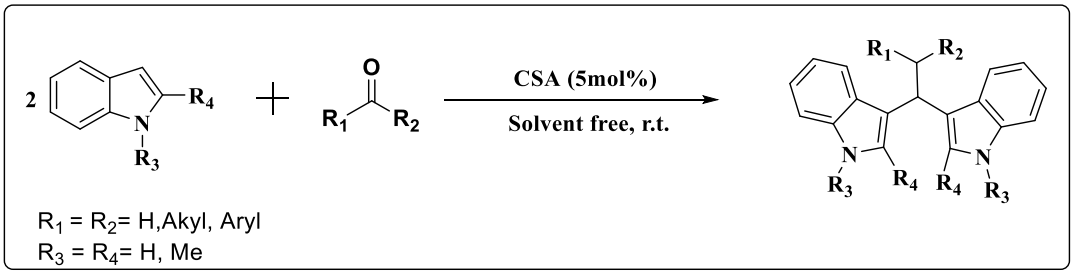


Scheme 5.I.6

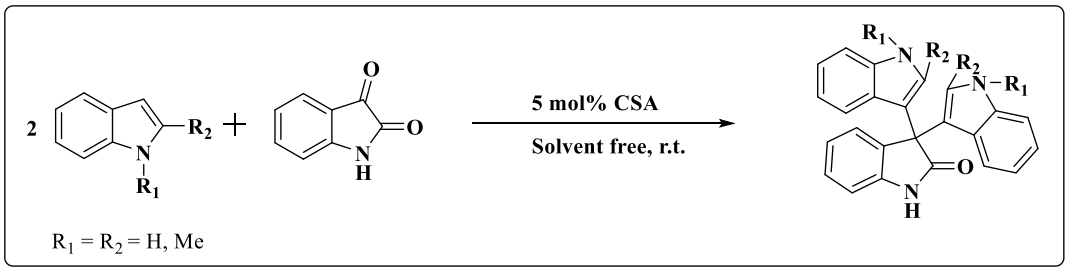


Scheme 5.I.7

Solvent free synthesis is very green protocol demonstrated for synthesis of bis(indolyl)methanes and 3,3'-indolyloxindole derivatives by Heshmatollah Alinezhad et al. [28] by using cellulosic sulphuric acid (CSA). CSA is a solid acid catalyst which is easy to handle, non-explosive and eco-friendly **(Scheme 5.I.8 and 5.I.9)**.

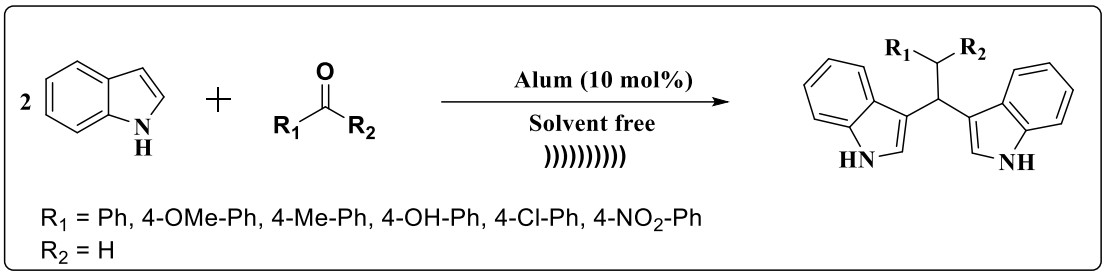


Scheme 5.I.8



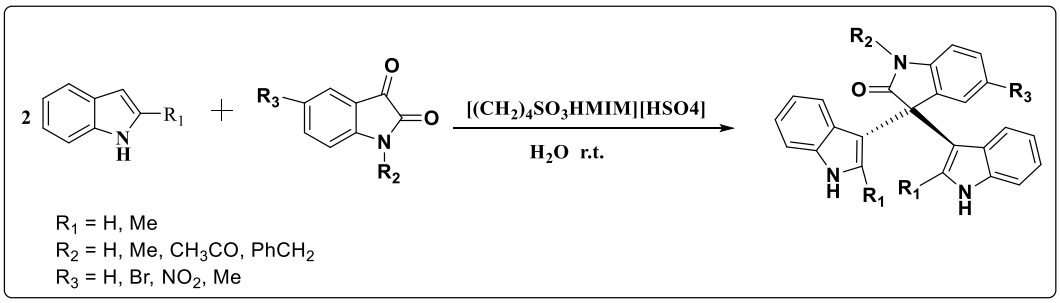
Scheme 5.I.9

Alum ($KAl(SO_4)_2.12H_2O$) catalyzed synthesis of bis(indolyl)methane under ultrasound irradiation without solvent developed by Swapnil S Sonar et al. [29] in which indole and aldehyde or ketone derivatives in presence of alum powder was irradiated under ultrasonication at ambient temperature for spectacular time gives bis(indolyl)methane with good yield (**Scheme 5.I.10**).



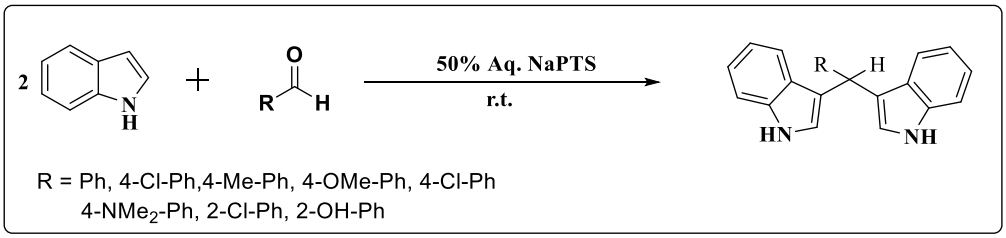
Scheme 5.I.10

Karimi, Narges et al. [30] synthesized oxindoles derivatives by using Brønsted acidic ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ in aqueous that is on water. Reaction is carried out by indole, isatin and ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ in water was stirred at room temperature that afforded oxindole in good yield **(Scheme 5.I.11)**.



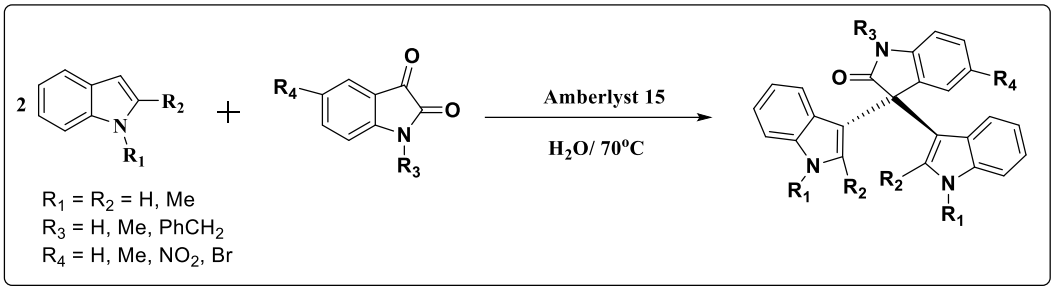
Scheme 5.I.11

Aqueous hydrotropic medium is a very attractive green solvent, which increases solubility of sparingly soluble organic reactants. Kamble et al. [31] developed the greener medium for the synthesis of bis(indolyl)methane that avoids the use of organic solvent **(Scheme 5.I.12)**.



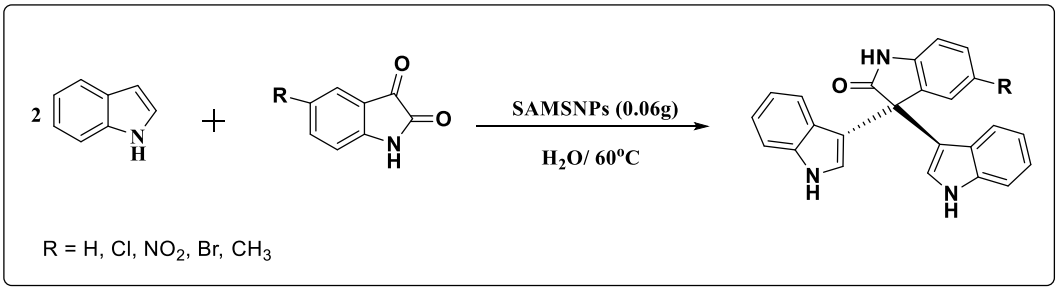
Scheme 5.I.12

Yaghoub Sarrafi et al. [32] prepared derivatives of 3,3-di(indolyl)oxindoles in excellent yield by employing Amberlyst-15 catalyst, reaction of indole and isatin in aqueous medium at 70°C **(Scheme 5.I.13)**.



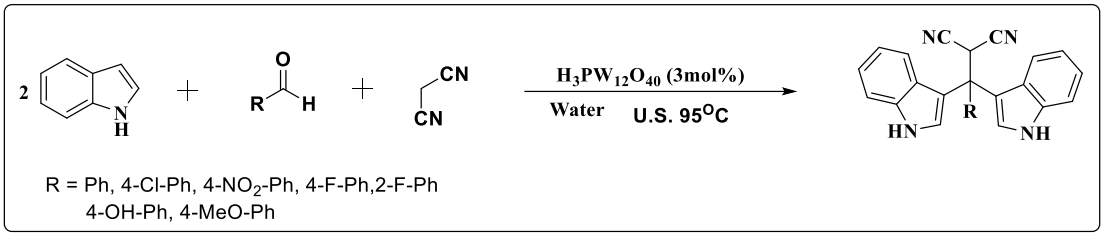
Scheme 5.I.13

Organic synthesis in aqueous medium is one of the important green prospective. Therefore, Ebrahim Mehrasbi et al. [33] prepared 3,3di(indolyl)oxindoles in the presence of mesoporous silica nanoparticles (SAMSNs) which are functionalized by sulfonic acid in aqueous media **(Scheme 5.I.14)**.



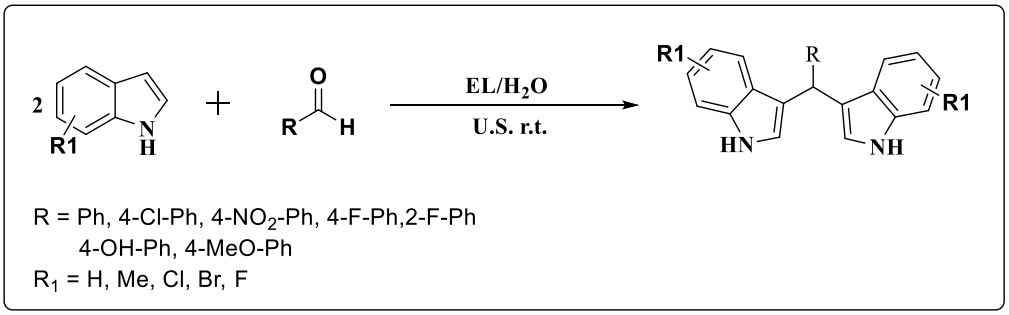
Scheme 5.I.14

Mohammad Ali Amrollahi et al. [34] again used $H_3PW_{12}O_{40}$ in aqueous media for the synthesis of bis(indolyl)methane under ultrasound irradiation**.** Here they perform reaction between aldehyde, indole and active methylene compound and catalyst $H_3PW_{12}O_{40}$ in water which was irradiated under ultrasonication gave the bis(indolyl)methane in good to excellent yield **(Scheme 5.I.15)**.

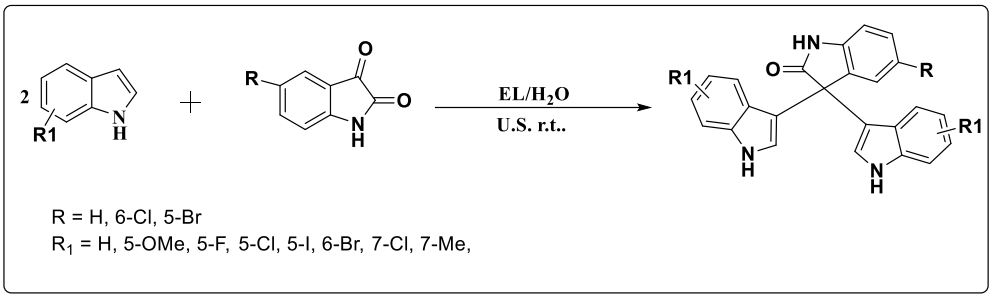


Scheme 5.I.15

Ge Gao et al. [35] demonstrated that in aqueous ethyl lactate (EL), without catalyst synthesis of bis(indolyl)methane and 3,3-bis(indolyl)oxindoles. Under ultrasound irradiation indole reacting with aldehyde or isatin in ethyl lactate: H_2O **(Scheme 5.I.16 and 5.I.17)**.

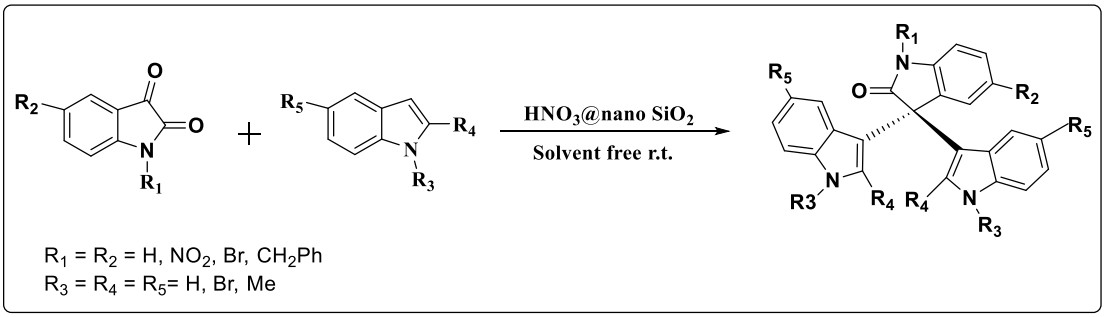


Scheme 5.I.16



Scheme 5.I.17

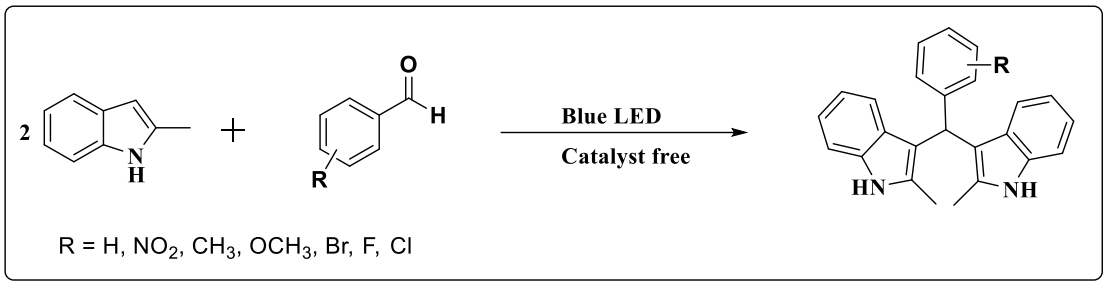
Nikoofar et al. [36] prepare the symmetrical and unsymmetrical di(indolyl)indoline-2-ones by two methods such as solvent free stirring and grinding by using HNO_3@nano SiO_2 as catalyst **(Scheme 5.I.18)**.



Scheme 5.I.18

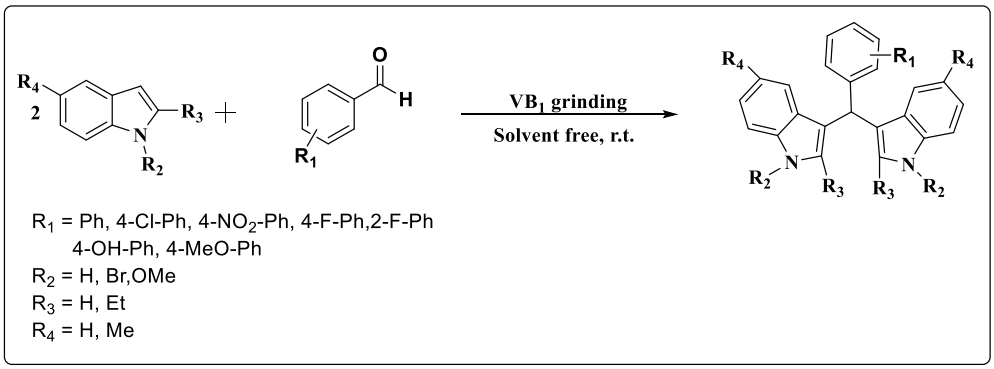
A green protocol that synthesizes the BIMs in the absence of a catalyst was disclosed by Yi-Shu Zhao et al. [37]. Reacting 2-methylindole and aryl aldehydes in

EtOH-H_2O (1:1) under blue LEDs for 4 hours produces series of BIMs with good yields **(Scheme 5.I.19)**.

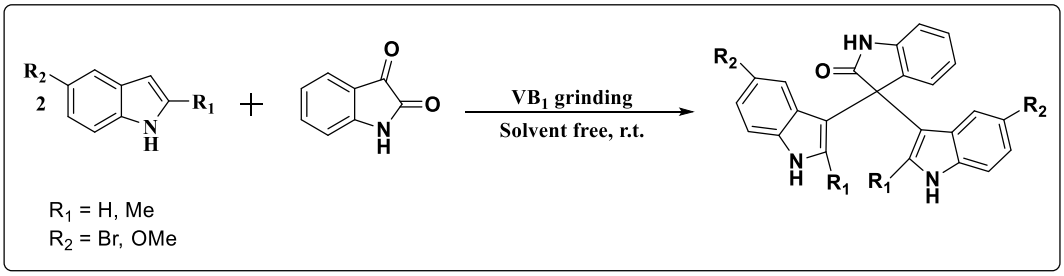


Scheme 5.I.19

According to green chemistry principles thiamine hydrochloride showed high atom economy and a small E-factor for the synthesis of indole scaffolds. Therefore, Sivagami Mathavan et al. [38] utilizes environmentally and economically friendly, recyclable amino catalyst thiamine hydrochloride for synthesis of bis(indolyl)methane's & tris(indolyl)methane's **(Scheme 5.I.20 and 5.I.21)**.

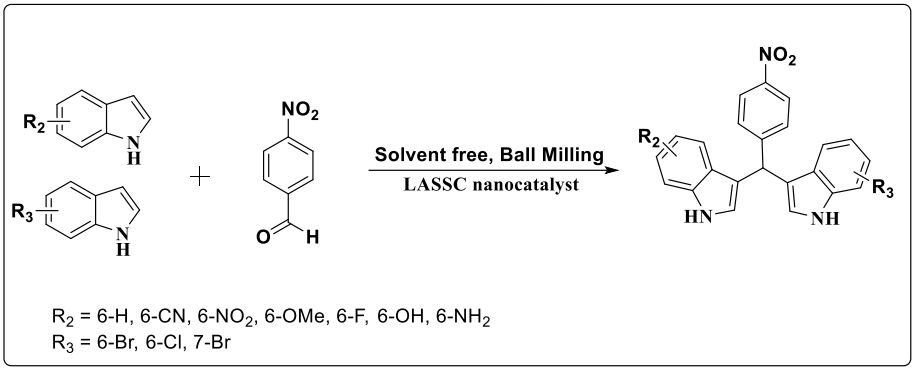


Scheme 5.I.20



Scheme 5.I.21

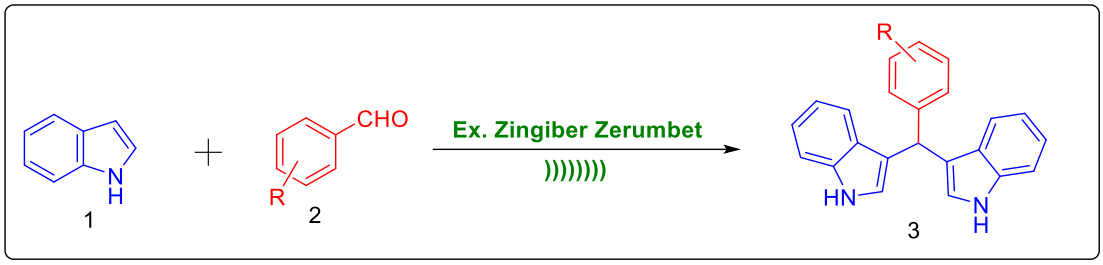
Zhiqiang Wu et al. [39] was developed ball milling solvent free synthesis of unsymmetrical bis(indolyl)alkanes using Lewis acid-surfactant-SiO_2 composite nano-catalyst (LASSC) ($AlCl_3.6H_2O$+SDS+SiO_2) **(Scheme 5.I.22)**.



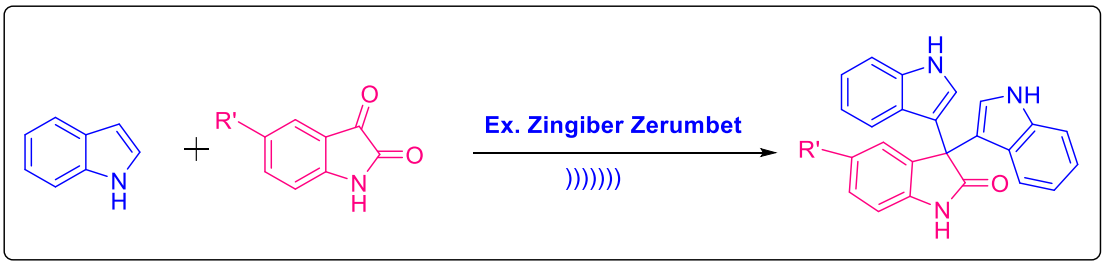
Scheme 5.I.22

5.2 Present work:

Due to diverse useful properties of molecule that containing indole as core ring structure for example bis(indolyl)methane, tris-indoline, etc. Scientists are constantly developing new methodologies for the synthesis of such indole scaffolds. Therefore, in the present work, we represent the more environmentally friendly synthesis of bis(indolyl)methane and tris-indoline by using natural surfactant "shampoo zinger" under ultrasound irradiation **(Scheme 5.I.23 and 5.I.24)**.



Scheme 5.I.23 Ultrasound assisted synthesis of bis(indolyl)methane in bio-surfactant.



Scheme 5.I.24 Ultrasound assisted synthesis of tris-indoline in bio-surfactant.

5.3 Result and Discussion:

In a continuation of our ongoing research on the development of sustainable methodologies and searching a green medium for organic transformations. Initially we

perform the model reaction, 4-nitrobenzaldehyde (1mmol) and indole (2mmol) in 5ml shampoo zinger at room temperature. We found very trace amount of yield **(Table 5.I.1 Entry 1)**. Then we focused on optimized the reaction condition to maximize the yield of product and decrease time of reaction. But significant improvement occurs when reaction perform under ultrasound irradiation. Ultrasound irradiation not only increase the yield but also minimise the reaction time **(Table 5.I.1)**. After optimizing reaction condition, we apply same strategy to different aldehyde and indole in 5ml shampoo zinger under ultrasound irradiation **(Table 5.I.2)**. Benzaldehyde with electron withdrawing group gives good yield than the electron donating group.

The scope of protocol was further extended to synthesis of tris-indoline by reacting indole (2mmol) with isatin (1mmol) as a model scheme under optimized reaction condition was in 5ml shampoo zinger under ultrasound irradiation. We obtain good result; within short period of time. We perform total four reaction by using different substituted isatins **(Table 5.I.3)**. The presence of electron donating and withdrawing group on benzene ring of isatins shows little effect on reaction yield. Ultrasound irradiation reduce the reaction time and increase reactivity due to formation of cavities, which produces high pressure and energies [40]. Shampoo zinger is extract of *Zingiber zerumbet*, fruit of zinger which acts as natural surfactant. Inflorescence of plant containing viscous juice which is rich in surfactant is known as ginger shampoo **(Figure 5.I.5)** [41]. There is saponin present in the viscous juice of *Zingiber zerumbet*, due to which it shows surfactant properties. Surfactants are detergents that are effective at dissolving non-polar compounds. This efficiency in dissolving non-polar compounds has made aqueous surfactant systems better alternatives to harmful organic solvents in various applications. Surfactant forms the micelles, which are similar to colloidal aggregation. This micelle formation occurs above the critical micelle concentration (CMC). A low concentration of CMC means requiring less surfactant to decrease the surface tension. Initially, the clear reaction mixture turned turbid, which indicates the formation of micelle-like colloidal aggregation was observed in microscopic images **(Figure 5.I.6)**. During this aggregation, reactant molecules are brought into close proximity to each other and interactions take place between them, which form the organic transformation between them. The visual exploitation of the reaction progress also observed by change in color during this synthetic transformation **(Figure 5.I.7)**. Overall, the product formation occurs very easily between the core of the

micelle. Therefore, here we report synthesis of BIMS and tris-indoline under ultrasonication in natural surfactant, zinger shampoo **(Scheme 5.I.23 and 5.I.24)**. Present strategy discloses the green and efficient methodologies.

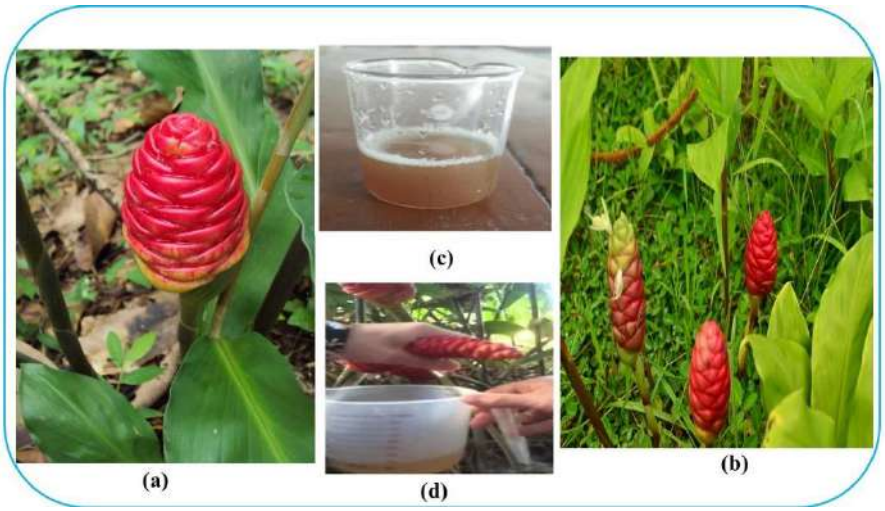


Figure 5.I.5. (a) Inflorescence of *Zingiber zerumbet*, (b)Inflorescence with flowers of *Z. zerumbet*, (c) Extract/juice of *Z. zerumbet*, (d) Collection extract/juice.

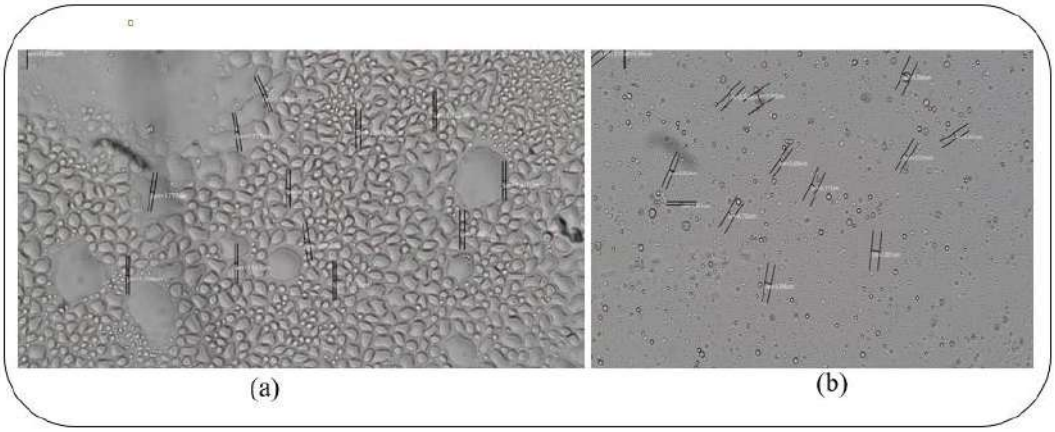


Figure 5.I.6. Microscopic Images (a) Extract of *Zingiber zerumbet* (b) Reaction mixture in *Zingiber Zerumbet*

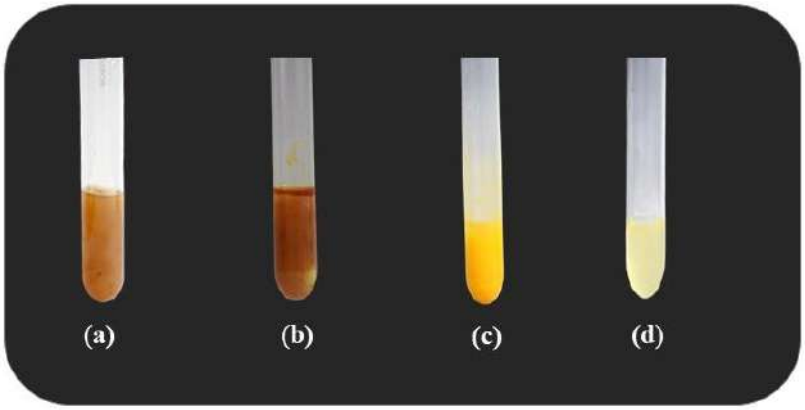
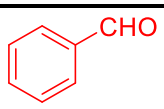
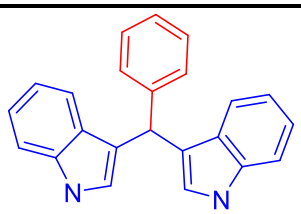


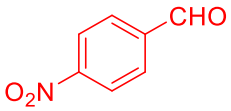
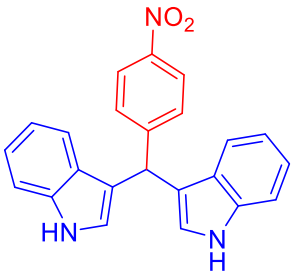
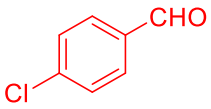
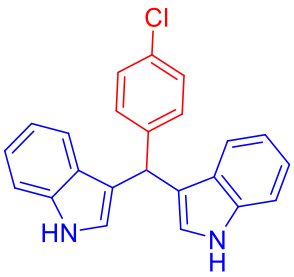
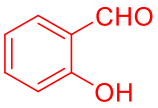
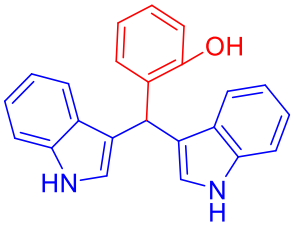
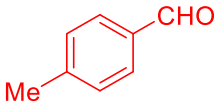
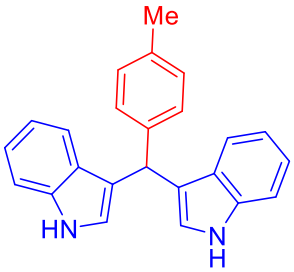
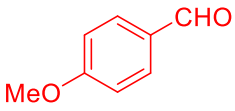
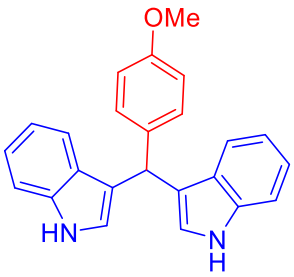
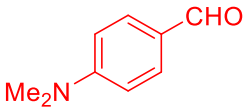
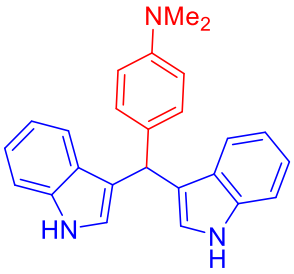
Figure 5.I.7 (a) Extract/juice of *Zingiber zerumbet* (b) Reactant in *Zingiber zerumbet extract* (c) Formation of product (d) *Zingiber zerumbet extract* after reaction

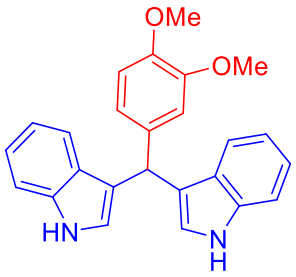
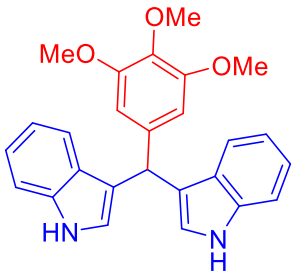
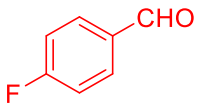
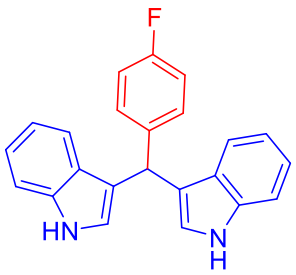
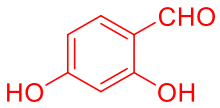
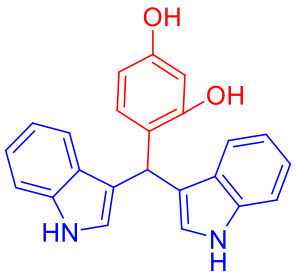
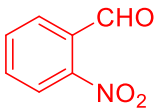
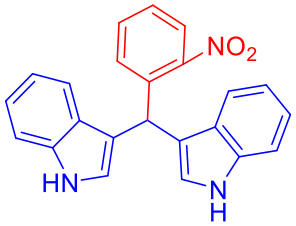
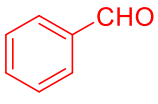
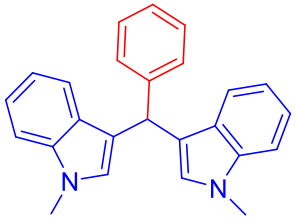
Table 5.I.1. Screening of Solvent Conditions for synthesis of bis(indolyl) methane.

Sr. No.	Solvent and Condition	Time	Yield (%)
1	*Zingiber zerumbet* at room temp.	2 days	trace
2	*Zingiber zerumbet* at reflux condition (50^oC)	24 hrs	50
3	*Zingiber zerumbet* at reflux condition (65^oC)	6 hrs	60
4	*Zingiber zerumbet* and ultrasonication at room temp.	10 min.	92
5	*Zingiber zerumbet* and ultrasonication at 45^oC.	10 min	90

Table 5.I.2. Synthesis of Bis-indoyl under ultrasound irradiation by using bio-surfactant.

Sr. No.	Aldehyde	Product	M.P.(^oC) [42], [43]	Yield (%)
1			126-128	92

2			126-128	92
3			76-78	90
4			102-104	86
5			98-100	88
6			190-192	86
7			169-171	85

8			197-199	86
9			208-210	86
10			72-74	86
11			108-110	86
12			190-192	84
13			203-203	90

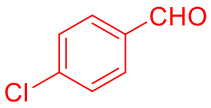
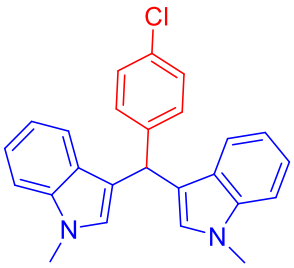
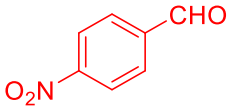
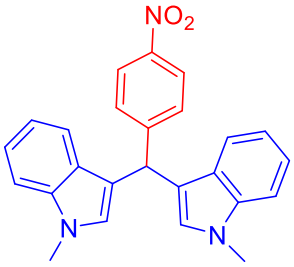
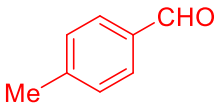
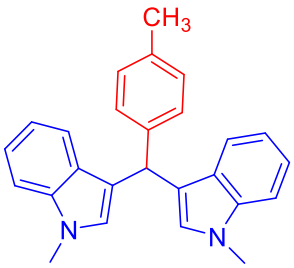
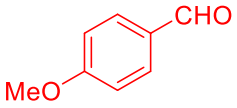
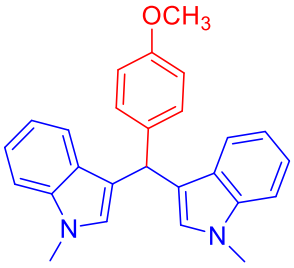
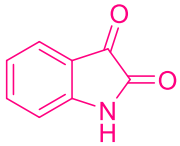
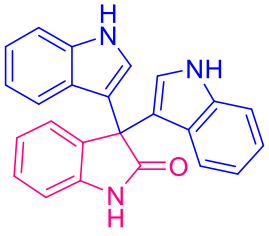
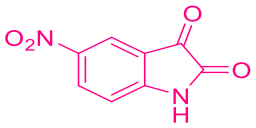
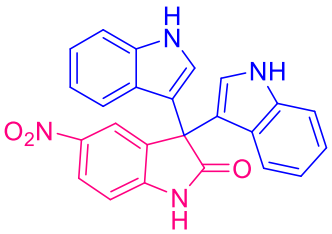
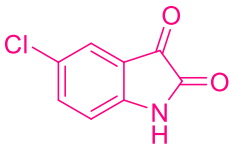
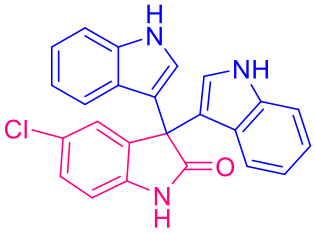
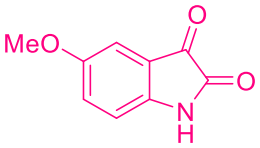
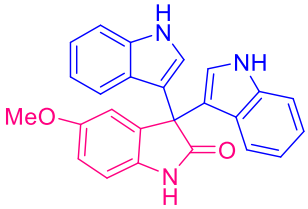
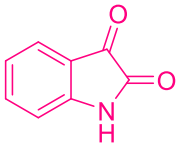
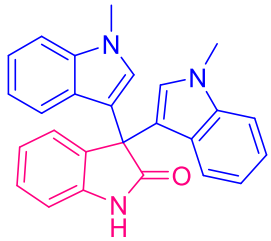
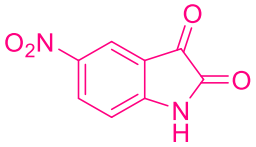
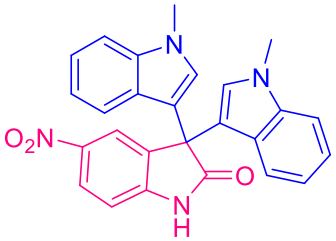
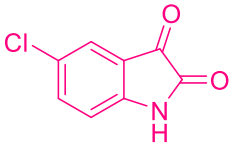
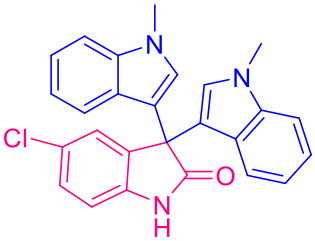
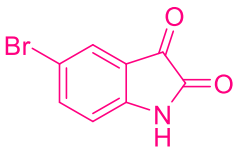
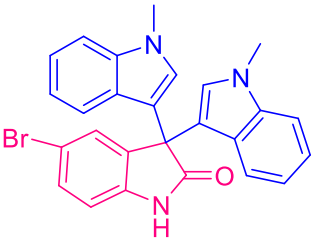
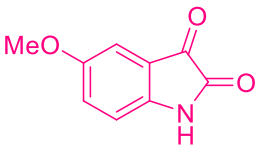
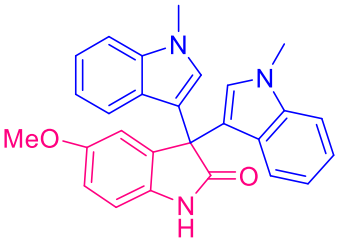
14			210-212	92
15			215-217	92
16			147-149	90
17			219-221	92

Table 5.I.3. Synthesis of Tris-indoyl under ultrasound irradiation by using bio-surfactant.

Sr. No.	Isatin	Product	MP (ºC)[35], [44]	Yield (%)
1			314-316	92

2			298-299	88
3			297-299	90
4			290-292	90
5			>300	92
6			>300	88
7			>300	90

8			>300	88
9			>300	90

Recyclability of Natural Surfactant-zingiber zerumbet:

We use only 5ml extract of zingiber zerumbet for the reaction. After completion of reaction filter the product and collect the filtrate and reuse for the reaction and monitoring any effect on yield but there is no much more effect on yield. After third cycle slightly decrease in yield. Therefore, reuse of extract is very important step as an environmental point of view which maintain the sustainability **(Figure 5.I.6.)**.

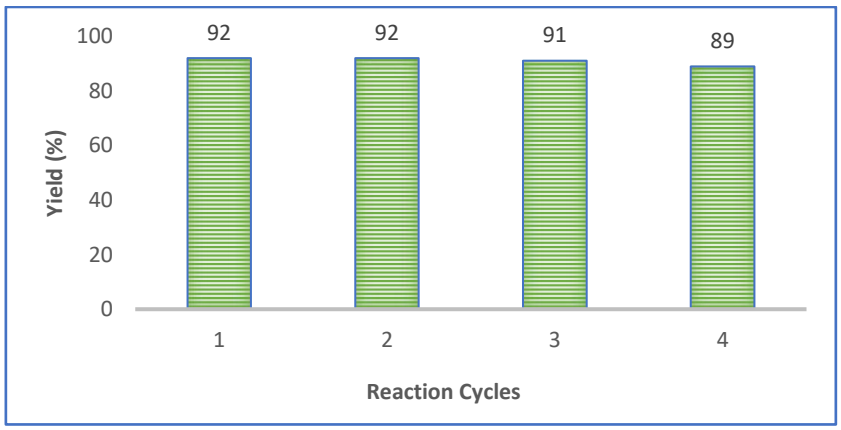
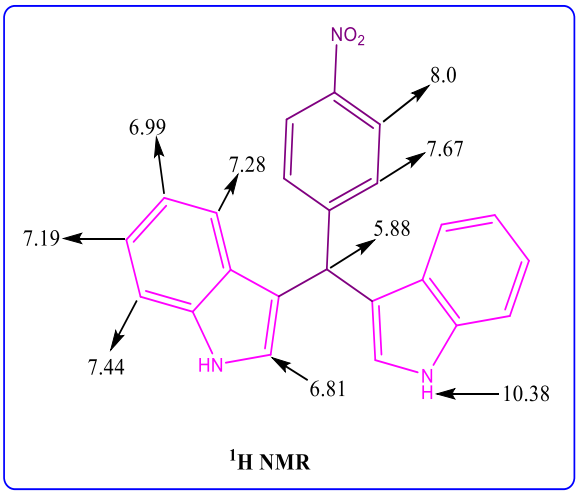


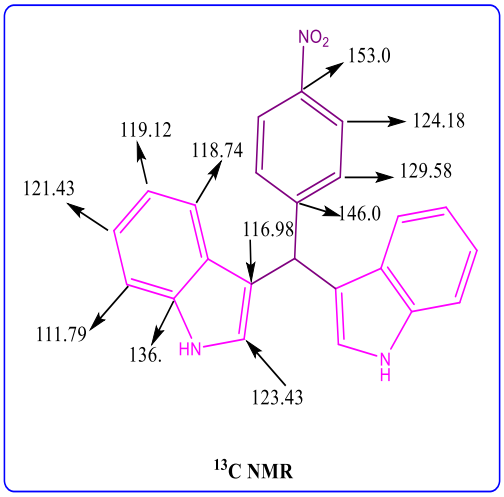
Figure 5.I.6. Recyclability of natural surfactant

Characterization of products

1) 3,3-Bis(indolyl)-4-nitrophenylmethane (Table 2.I. Entry 2):



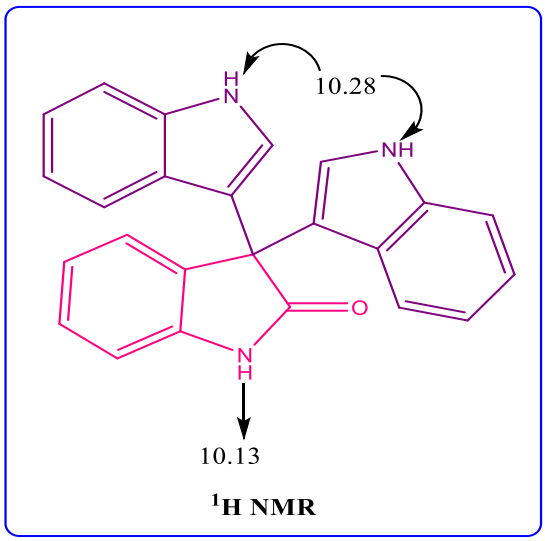
^{1}H NMR



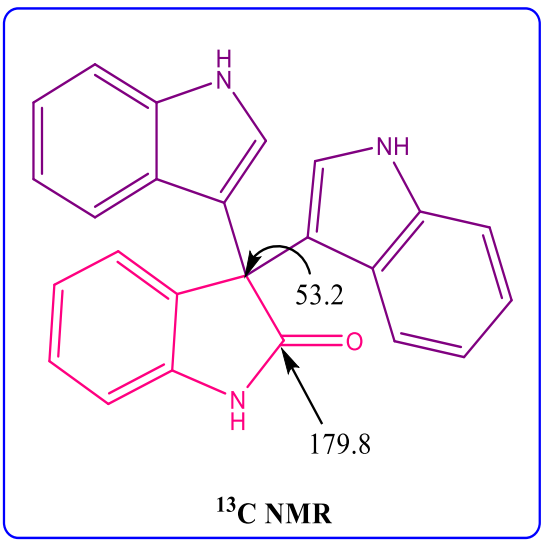
^{13}C NMR

IR spectrum **(Figure 5.I.8)** exhibits the bands at 3426 cm^{-1} for NH stretching vibration. the alkene shows frequency at 1637 cm^{-1}. In ^{1}H NMR **(Figure 5.I.9)** spectrum two NH protons of indole moiety resonated at δ10.38 ppm. The methine proton shows sharp singlet at δ 5.88 ppm which confirms the formation of bis(indolyl)methane. the protons adjacent to NO_2 group resonated at δ8.0 ppm which gives doublet, another doublet at δ 7.67 for aromatic protons meta to nitro group. The aromatic protons of indole ring observed in the range of δ 7.46 - 7.79 ppm. The ^{13}C NMR **(Figure 5.I.10)** spectrum shows peak at δ 153.0, 146.17, 136.99, 129.58, 126.62, 124.18, 123.43, 121.43, 119.12, 118.74, 116.98 and 111.79 ppm are attributed in aromatic region.

2) [3,3':3',3"-terindolin]-2'-one (Table 3.I. Entry 1):



^{1}H NMR



^{13}C NMR

The IR spectrum (**Figure 5.I.17**) of the compound showed the absorption band at 3428 cm^{-1} for NH stretching frequency. The carbonyl group for cyclic amide of indole moiety showed absorption band at 1707 cm^{-1}. The absorption band at 1106 cm^{-1} was corresponding to C-N stretching frequency. The ^{1}H NMR spectrum (**Figure 5.I.18**) displays singlet for two NH protons of indole ring appeared at δ 10.28 ppm whereas one NH proton of isatin moiety was observed at δ 10.13 ppm. The aromatic protons appeared at chemical shift δ values from 6.71 to 7.26 ppm. In the ^{13}C NMR spectrum **(Figure 5.I.19)** C3 carbon of indole moiety resonated at δ 53.16 ppm. The carbonyl carbon of the cyclic amide of isatin moiety was observed at δ 179.8 ppm. The remaining aromatic carbon noticed at 141.3, 137.6, 134.9, 127.8, 126.0, 125.2, 124.7, 121.8, 121.2, 121.1, 118.6, 114.6, 111.6 and 109.9 ppm. In the mass spectrum **(Figure 5.I.20)** molecular ion peak observed at 364 [M+H]+, 386 [M+Na]+ which confirms the formation of desired molecule.

5.4 Conclusion:

Clean and ecofriendly synthesis of bis(indolyl)methane and tris indoline by the combination of natural surfactant *Zingiber zerumbet* and ultrasound irradiation. This perspective gives the nontoxic, environmentally safe and cheap synthesis of indole derivatives. Ultrasonic irradiation saves the reaction time and significant improvement in the yield. Therefore, this protocol highlights and follows various green chemistry principle such as avoid toxic chemicals, harsh reaction condition, use of green solvent and methodology.

5.5 Experimental

General

Zingiber zerumbet fruit of zinger is collected from botanical garden of Y.C.I.S. Satara, India. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. Melting points of products were determined on electrical melting point apparatus EQ 730A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR,^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer using DMSO as solvent and TMS

as internal reference. Sonication was performed in a SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz.

Collection of "Zingiber zerumbet" fruit extract:

Zingiber zerumbet is the fruit of the zinger available in the botanical garden of Y.C.I.S. Satara. Extract was removed by hand from fruit, which is a viscous liquid known as "shampoo zinger" and also a natural surfactant. It was collected and stored in freezers and used in reactions as a natural surfactant.

Synthesis of bis(indolyl)methane:

Taken 5ml zingiber zerumbet extract in round bottom flask add to it aldehyde (1mmol) and indole (2mmol) then flask placed in bath sonicator and which was irradiated under ultrasonic irradiation at room temperature for appropriate time (Table 1.) until reaction was completed which was monitored by tlc (nHexane: EA 8:2), colored solid product was formed after completion of reaction which filtered and recrystallized in ethyl acetate getting pure product.

Synthesis of tris-indoline:

Taken 5ml zingiber zerumbet extract in round bottom flask add to it isatin (1mmol) and indole (2mmol) then flask placed in bath sonicator and which was irradiated under ultrasonic irradiation at room temperature for appropriate time (Table 1.) until reaction was completed which was monitored by tlc (nHexane: EA 8:2), solid product was formed which was filtered and recrystallized in ethyl acetate getting pure product.

Spectral data of synthesized compounds:

1) 3,3-Bis(indolyl)-4-nitrophenylmethane (Table 5.I.2 Entry 2): Yellow Solid, M.P. 221-223°C. IR (KBr): ῡ= 3426, 2925, 1741, 1637, 1550, 1457, 1342, 1016, 744 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 10.38 (s, 2H), 8.0-7.9 (d, 2H), 7.67-7.66 (d, 2H), 7.46-7.42 (d, 2H), 7.30-7.27 (d, 2H), 7.20-7.17 (t, 2H), 7.02-6.97 (t, 2H), 6.84-6.79 (s, 2H), 5.88-5.87 (s, 1H); ^{13}C NMR: 153.0, 146.17, 136.99, 129.58, 126.62, 124.18, 123.43, 121.43, 119.12, 118.74, 116.98, 111.79 ppm.

2) 4-Chlorophenyl-3,3-bis(indolyl)methane (Table 5.I.2 Entry 3): Pink Solid, M.P. 76-78°C. IR (KBr): $\bar{\upsilon}$ = 3409, 2927, 1623, 1521, 1488, 1455, 1276, 1207, 1069, 1010, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.39-7.34 (m, 4H), 7.30-7.26 (m,4H), 7.21-7.19 (t, H), 7.05-7.01 (t, 2H), 6.61 (s, 2H), 5.87 (s, 1H); ^{13}C NMR: 142.6, 136.7, 131.7, 130.1, 128.4, 126.9, 123.6, 122.1, 120.7, 119.8, 119.3, 111.2, 44.6 ppm.

3) 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole) (Table 5.I.2 Entry 13): Pink Solid, M.P. 210-212°C. IR (KBr): $\bar{\upsilon}$ = 2921, 1589, 1511, 1338, 1004, 736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d,2H), 7.30 (d, 2H), 7.27 (m, 4H), 7.25 (d, 2H), 7.02 (d, 2H), 6.52 (s,2H), 5.86 (s,1H), 3.70 (s, 6H); ^{13}C NMR: 143.0, 137.40, 131.64, 130.03, 128.33, 127.44, 126.22, 121.55, 119.91, 118.75, 117.70, 109.0, 39.48, 32.71 ppm. HRMS (ESI) m/z = 383.1320 $[M-H]^-$.

4) 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole) (Table 5.I.2 Entry 14): Yellow Solid, M.P. 215-217. IR (KBr): $\bar{\upsilon}$ = 3050, 2927, 1484, 1224, 1172, 1148, 1093, 996, 813, 732, 673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 2H), 7.52 (d, 2H), 7.32 (m, 4H), 7.26 (d, 2H), 7.02 (d,2H), 6.55(s, 2H), 5.98(s, 1H), 3.72(s,6H); ^{13}C NMR: 152.31, 146.47, 137.42, 129.47, 128.29, 127.03, 123.62, 121.82, 119.64, 119.03, 116.60, 109.33, 40.07, 32.78 ppm.

5) [3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 1): Yield: 92%; white solid; M. P.=314-318ºC, IR (KBr, cm^{-1}): 3428, 3324, 1707, 1613, 1468, 1106, 932, 736; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.28 (s, 2H), 10.13 (s, 1H), 7.26-7.24 (m, 4H), 7.20-7.12 (t, 1H), 7.11-7.08 (t, 1H), 6.96-6.93 (m, 3H), 6.91-6.82 (m, 3H), 6.80 -6.71 (s, 2H); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 179.8, 141.3, 137.6, 134.9, 127.8, 126.0, 125.2, 124.7, 121.8, 121.2, 121.1, 118.6, 114.6, 111.6, 109.9, 53.2 ppm. HRMS (ESI) m/z = 386.1241 $[M + Na]^+$.

6) 5'-nitro-[3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 2): Yield: 90 %; white solid, M.P. 298-299°C; IR (KBr, cm^{-1}): 3384, 2917, 1707, 1519, 1454, 1175, 1018, 744; ^{1}H NMR (400 MHz, DMSO-*d6*) δ10.84 (s, 1H), 10.29 (s, 2H), 8.09 (dd, 1H), 8.06 (d, 1H), 7.98-7.49 (d, 2H), 7.04-7.00 (m, 3H), 6.99-6.97 (m, 2H), 6.95-6.83 (s,

2H), 6.79-6.75 (m,2H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 179.6, 148.1, 142.5, 137.5, 135.6, 125.8, 125.6, 124.8, 121.5, 120.7, 120.2, 118.8, 112.0, 111.6, 110.1, 53.0 ppm.

7) **5'-methoxy-[3,3':3',3"-terindolin]-2'-one (Table 5.I.3 Entry 4):** Yield: 88 %; white solid, M.P. 290-292^{o}C; IR (KBr, cm^{-1}): 3384, 2928, 1686, 1484, 1191, 734, 572; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.91 (s,2H), 9.66 (s, 1H), 7.62 (d, 2H), 7.40 (d,2H), 7.24 (m, 2H), 7.07-6.94 (m, 4H), 6.87 (m,1H), 6.74 (s, 2H), 3.58 (s,3H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 179.4, 155.0, 137.3, 136.2, 134.9, 128.6, 126.0, 125.9, 124.6, 121.7, 118.5, 114.6, 112.0, 11.1, 110.2, 55.6, 53.2 ppm.

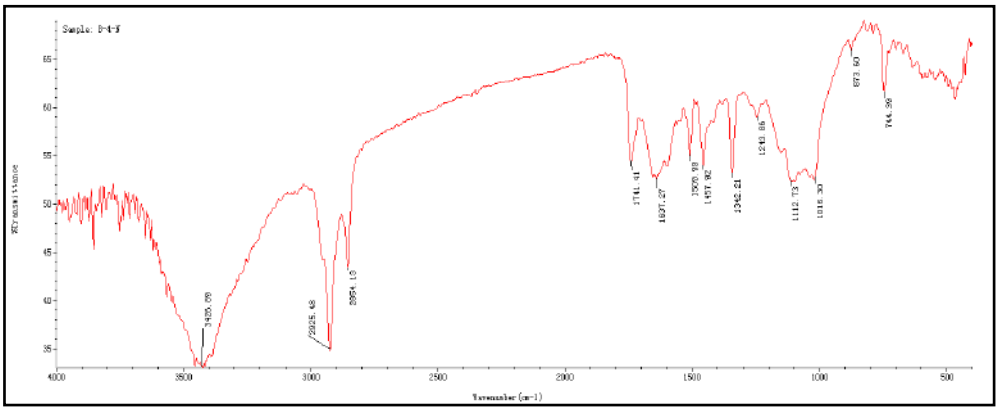


Figure 5.I.8: IR Spectra of 3,3-Bis(indolyl)-4-nitrophenylmethane.

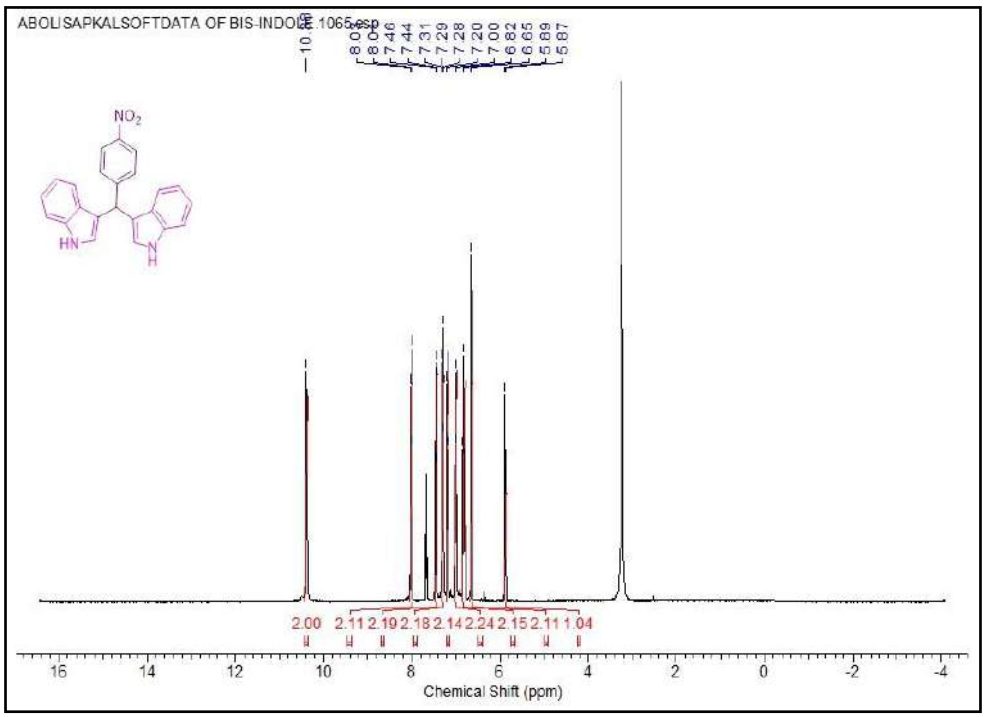


Figure 5.I.9: ^{1}H NMR of 3,3-Bis(indolyl)-4-nitrophenylmethane.

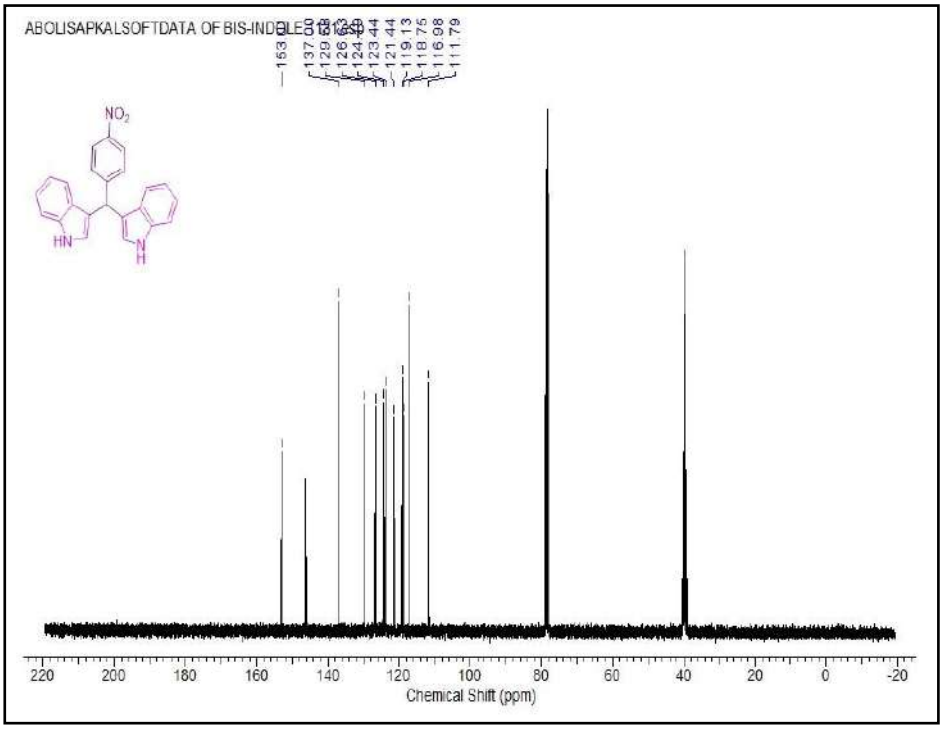


Figure 5.I.10: ^{13}C NMR of 3,3-Bis(indolyl)-4-nitrophenylmethane.

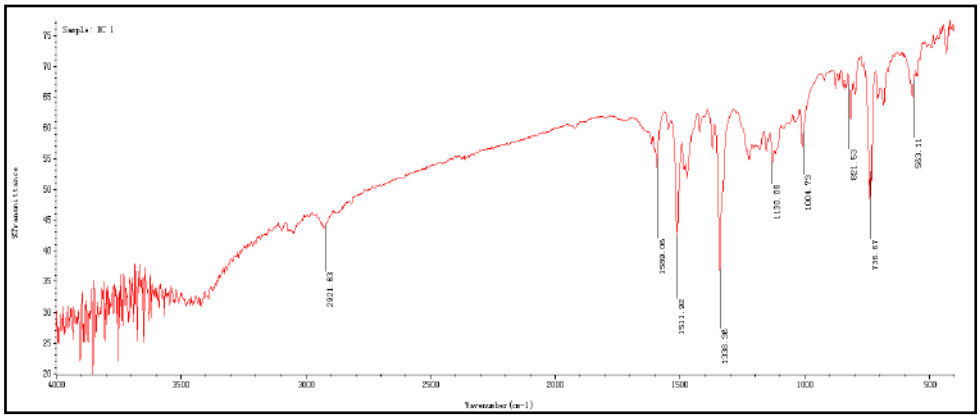


Figure 5.I.11: IR spectrum of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

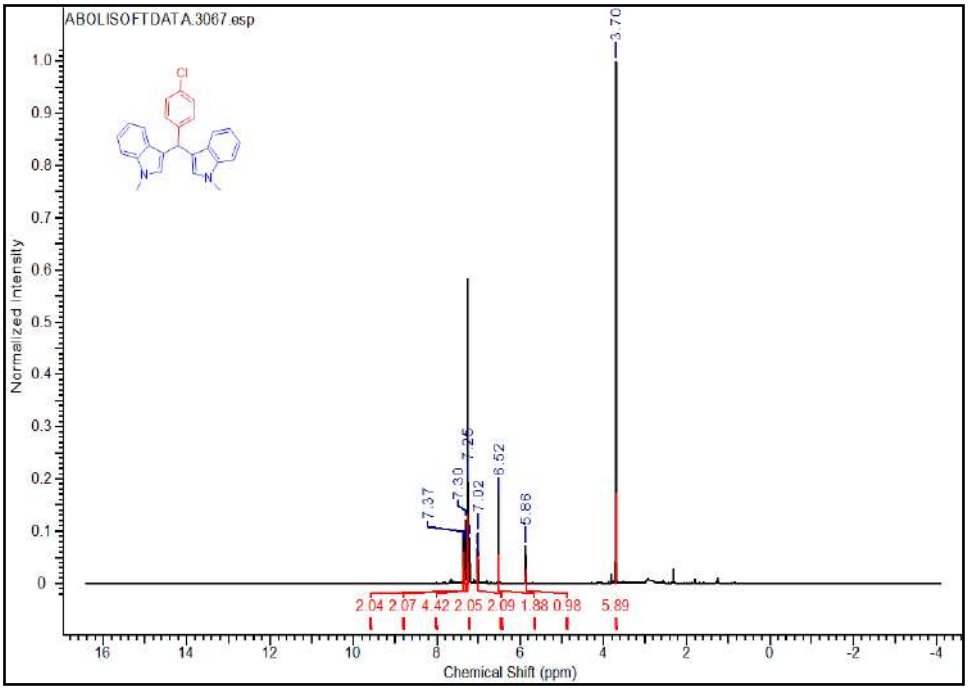


Figure 5.I.12: ^{1}H NMR of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

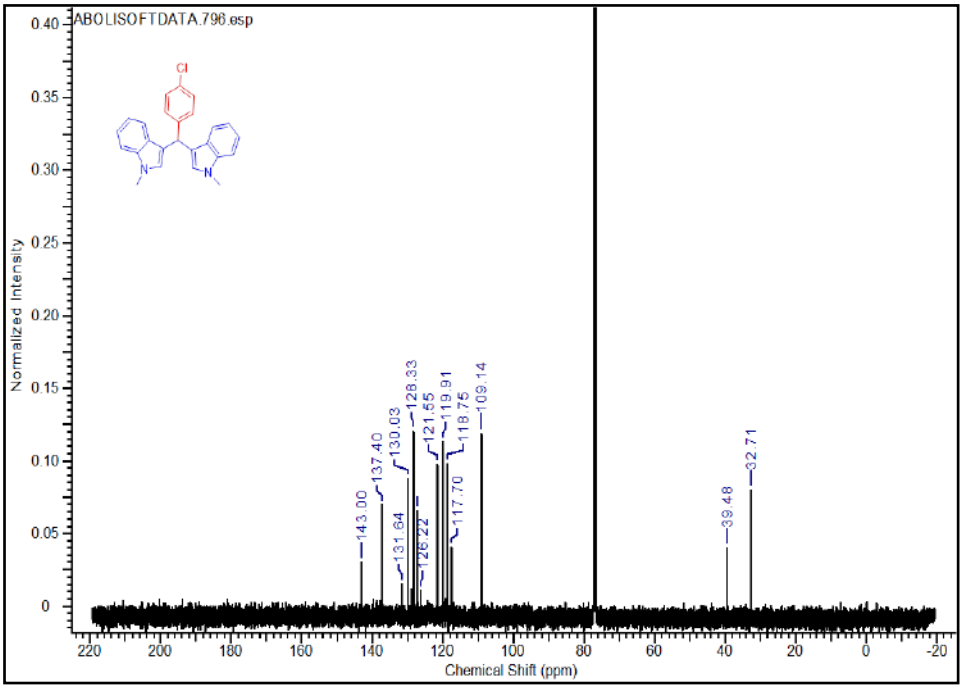


Figure 5.I.13: ^{13}C NMR of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

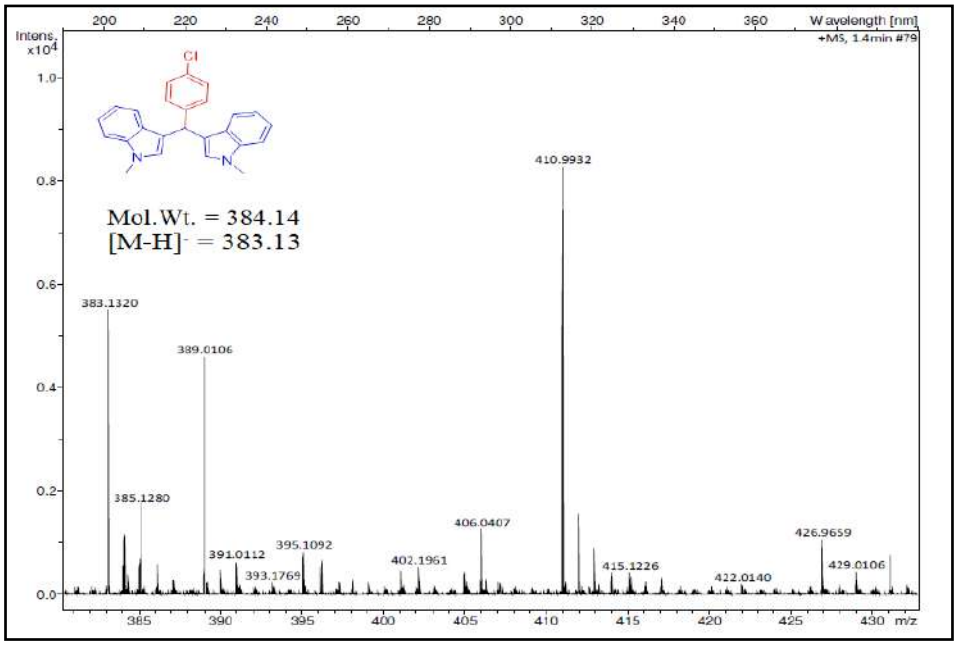


Figure 5.II.14 HRMS of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole).

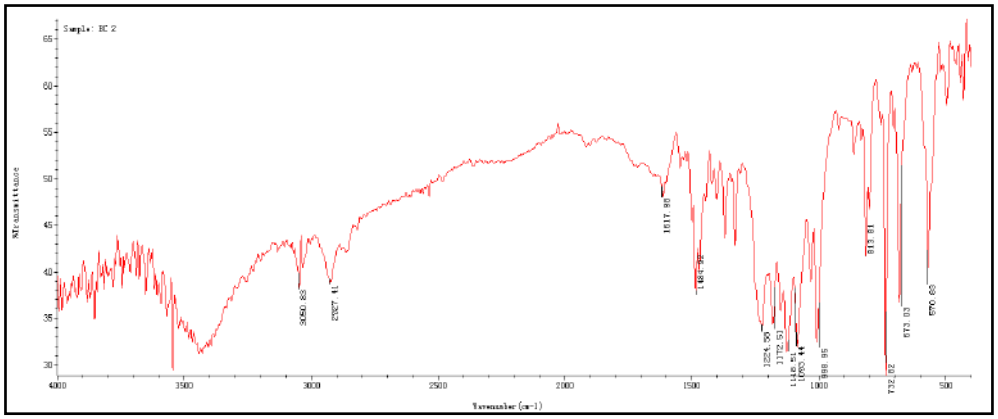


Figure 5.I.14: IR spectrum of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

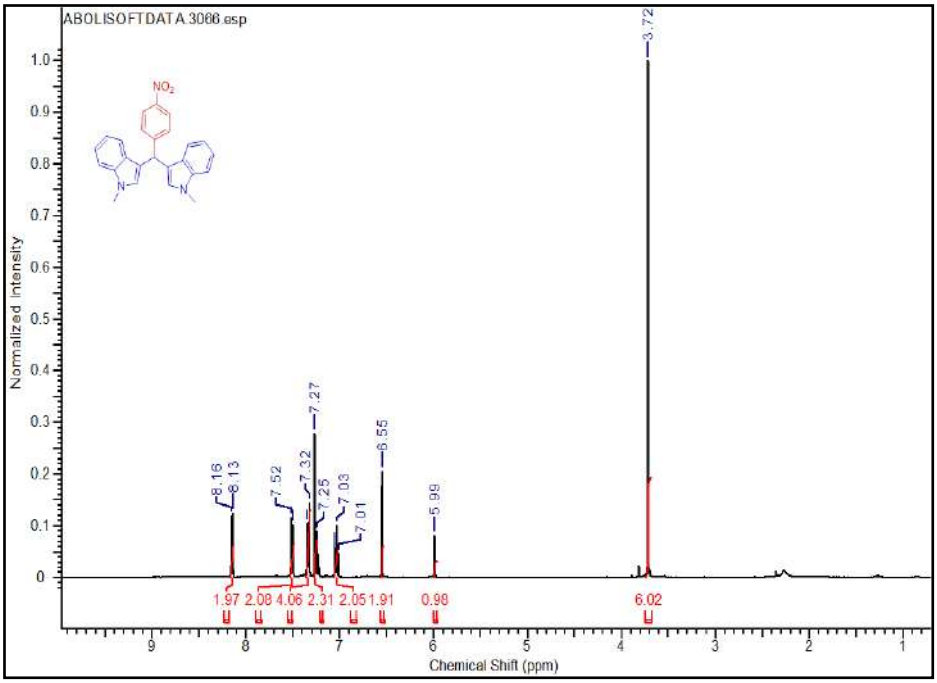


Figure 5.I.15: ^{1}H NMR of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

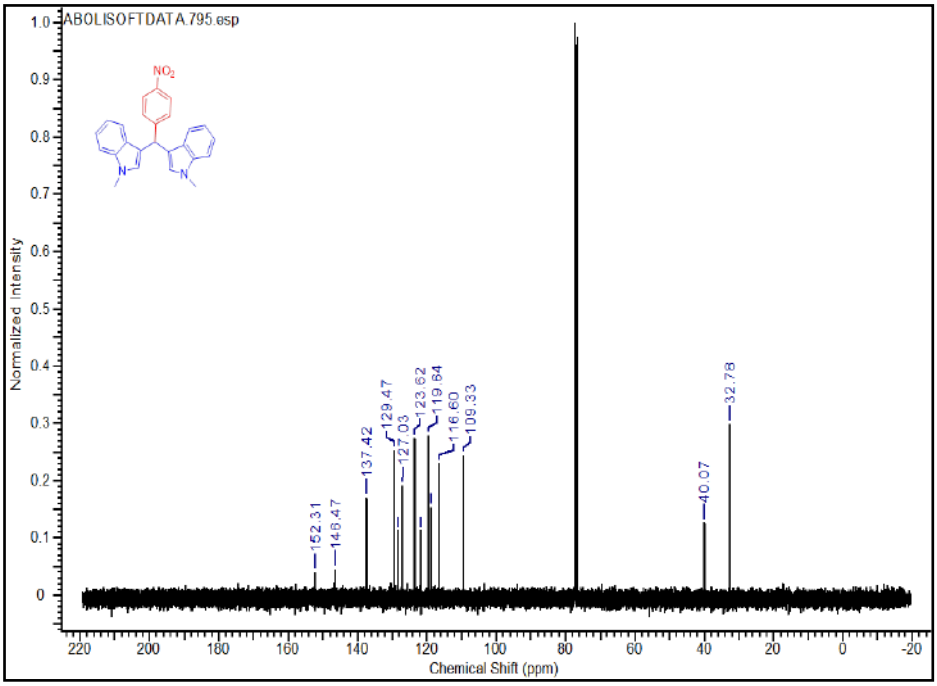


Figure 5.I.16: ^{13}C NMR of 3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole)

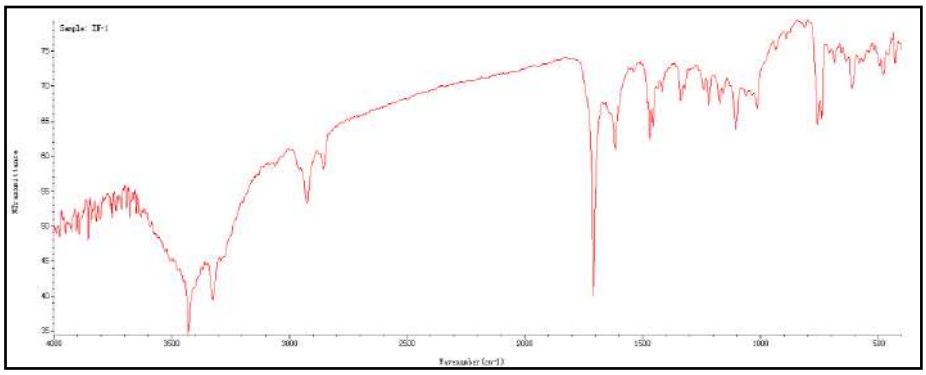


Figure 5.I.17: IR Spectra of [3,3':3',3"-terindolin]-2'-one

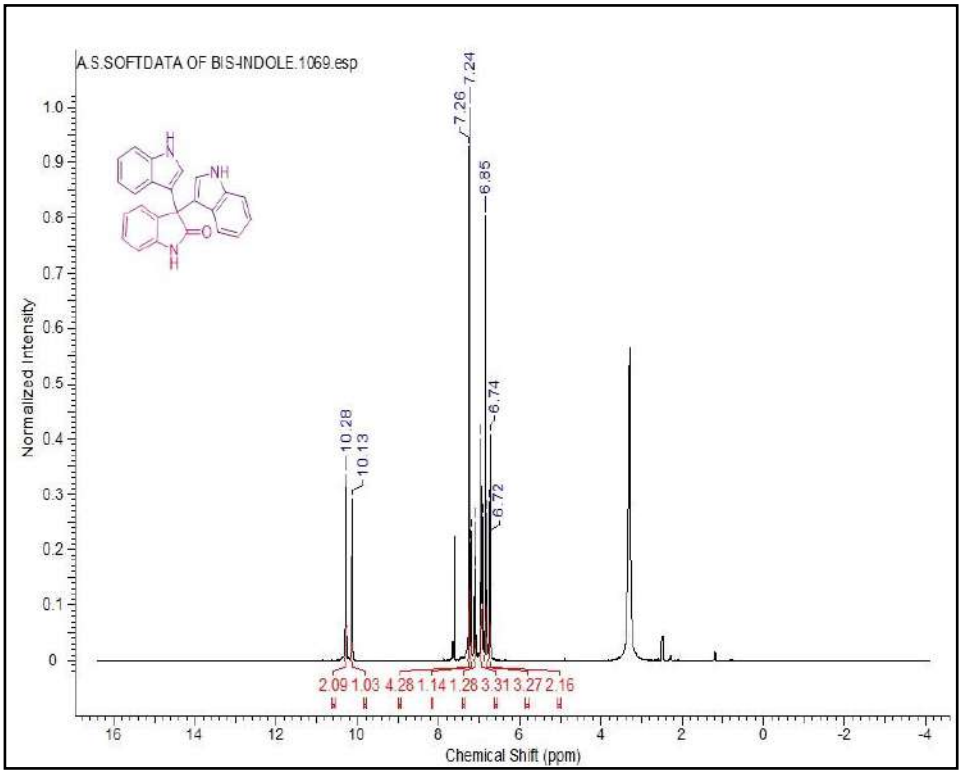


Figure 5.I.18: ^{1}H NMR of [3,3':3',3"-terindolin]-2'-one

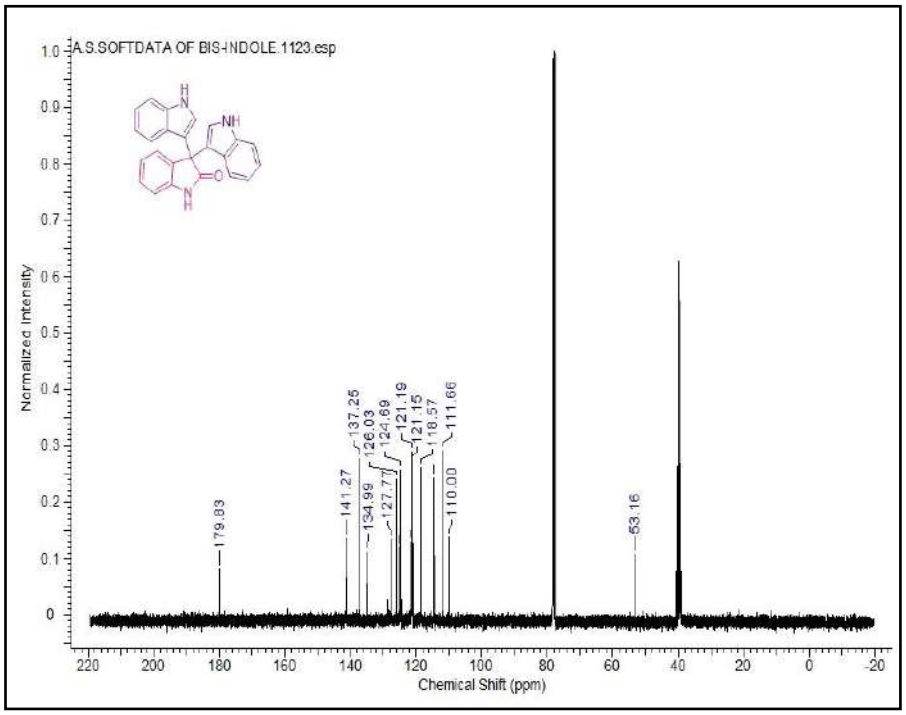


Figure 5.I.19: ^{13}C NMR of [3,3':3',3"-terindolin]-2'-one

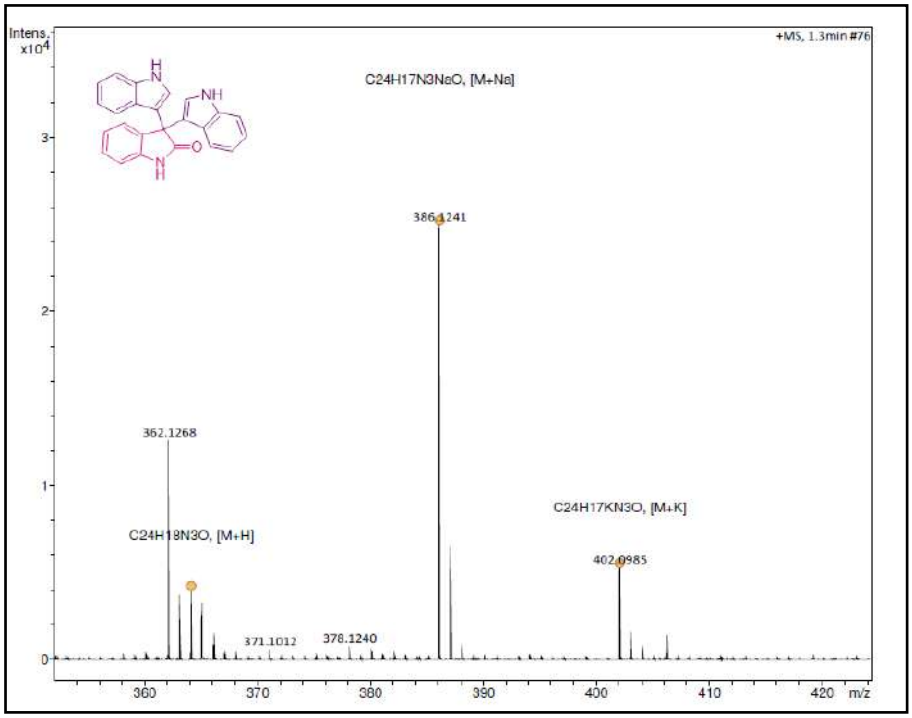


Figure 5.I.20 HRMS of [3,3':3',3"-terindolin]-2'-one.

5.I.6 References:

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CHAPTER 5

Section II

Bio-catalyzed Synthesis of Spirooxindole Derivatives

5.II.1 Introduction

The spirooxindole system is one of the important parts of heterocyclic chemistry. The spirooxindole ring constitutes the core structure of pharmaceuticals and natural products, including cytostatic alkaloids such as spirotryprostatins A, B, and Strychnofoline. Spirotryprostatins B is well known anti-cancer agent found in the *Aspergillus fumigatus* fungus along with additional indole-based alkaloids [1]. The shrub *Strychnosusambarensis* was source of spiro-oxindole alkaloid from which Strychnofoline isolated [2] **(Figure 5.II.1)**. They were appealing synthetic scaffolds due to their unique structural diversity and highly influenced pharmacological activities [3]. The structural relationship shown by spiro compounds in which at least two molecular rings with one common atom are known as spiro compounds. They consisting heterocyclic or fully carbocyclic rings which are connected through two or three ring to one atom [4]. This structural diversity attracts chemists and biologists for their synthesis under novel protocols.

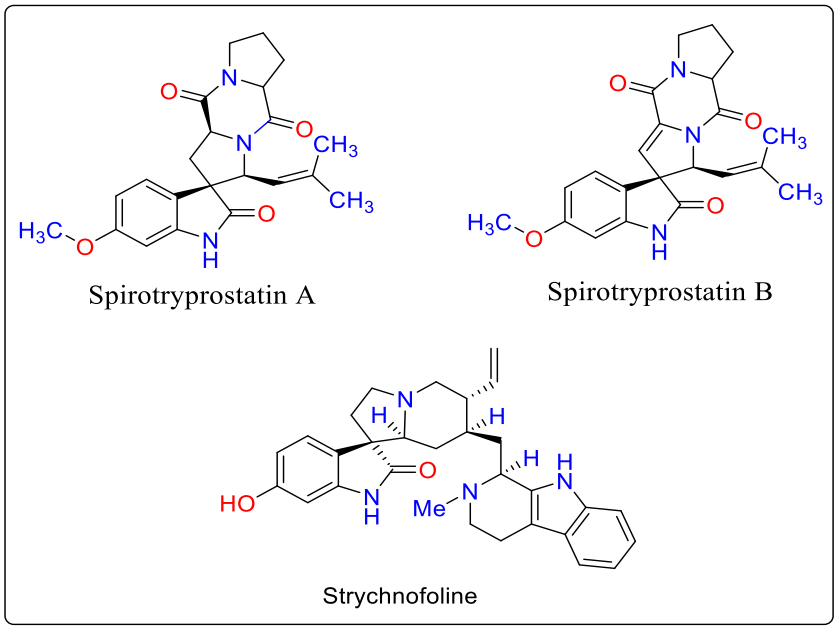


Figure 5.II.1. Structures of biologically active spirooxindole alkaloids.

Spirooxindole was discovered in the Amazon rainforest and tropical areas of South and Central America in the Uncariatomentosa plant, also known as Cat's Claw, and was first isolated from the plant Rubiaceae and Apocynaceae alkaloids family of natural products [5], [6]. The structural arrangement of spirooxindole molecule constituting two basic structural subunits: one of which is multiple functionalized oxindole, which can take acts as donors and acceptors for hydrogen bonding; the another is a cycloalkyl or heterocyclic compounds fused at the C-3 position of oxindole [7]. According to this unique special chemical structural arrangement it gives wide contribution in medical world as result of anti-cancer [8], anti-inflammatory [9], anti-microbial [10], antioxidant [11], anti-viral [12], anti-HIV [13], anti-malarial agents [14] and local anesthetic properties[15].

Spirooxindole is a very prominent structural motif present in several natural products such as horsfline [16], alantrypinone [17], citrinadin [18], welwitindolinone, elacomine and isoelacomine [19] that having potential pharmacological activities **(Figure 5.II.2)**.

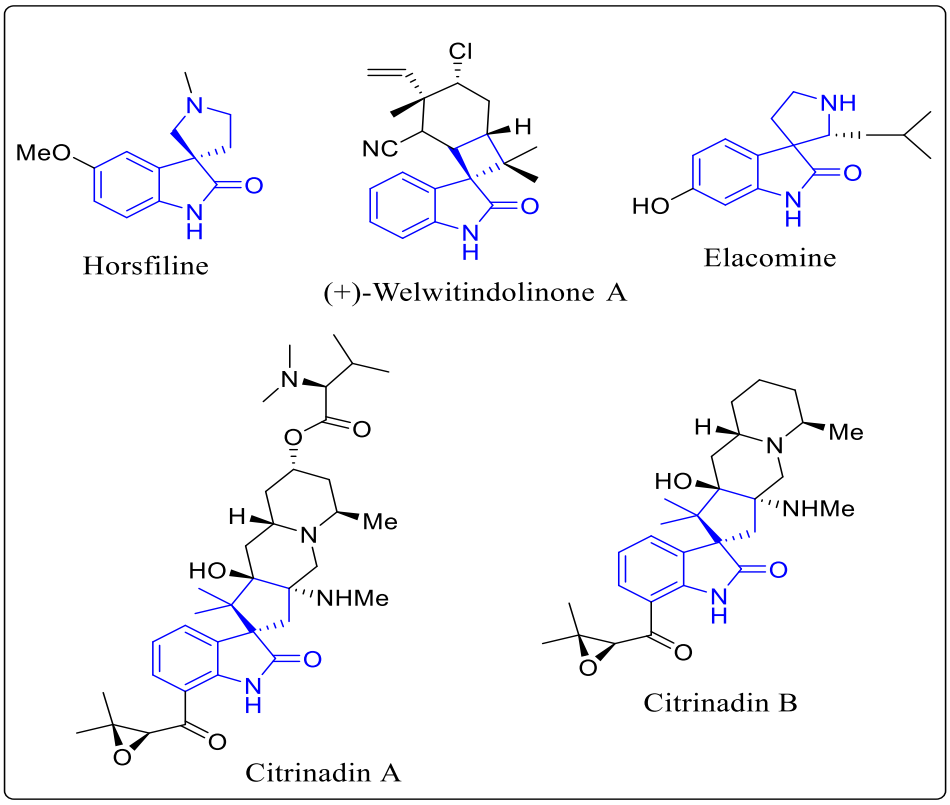
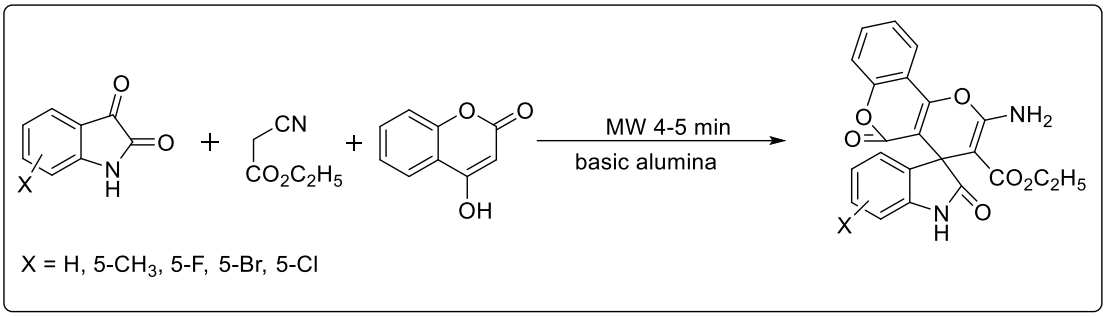


Figure 5.II.2 Spirooxindole based natural products.

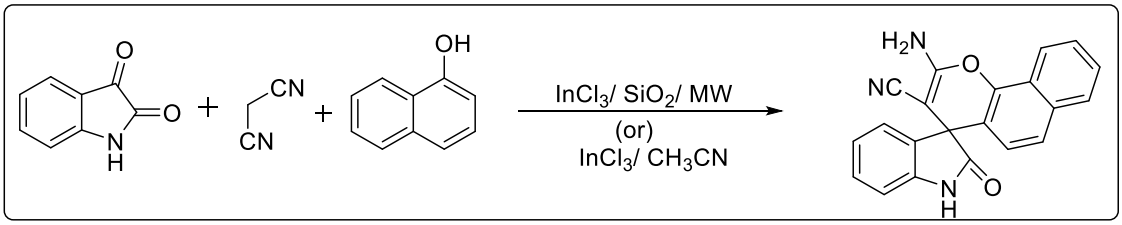
Following literature shows the how researcher constantly and innovatively involved in the synthesis of spirooxindole;

Multicomponent one-pot diastereoselective synthesis of spiro scaffold was developed by Dandia Anshu and co-workers [20] under microwaves. Reaction assisted by microwave between the reactants 1*H*-indole-2,3-dione, ethyl cyanoacetate and 4-hydroxycoumarin produces good amount products within short period of time **(Scheme 5.II.1)**.



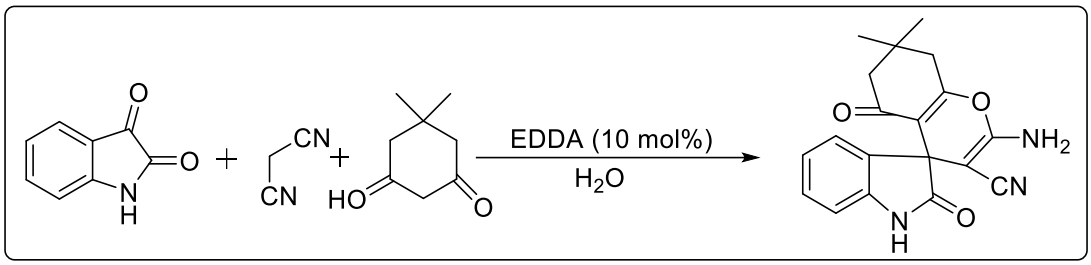
Scheme 5.II.1

Shanthi et al. [21] newly reported $InCl_3$-catalyzed, simple and efficient one-pot multi-component technique for the production of spirooxindoles by conventional heating and under solvent-free microwave irradiations **(Scheme 5.II.2).**



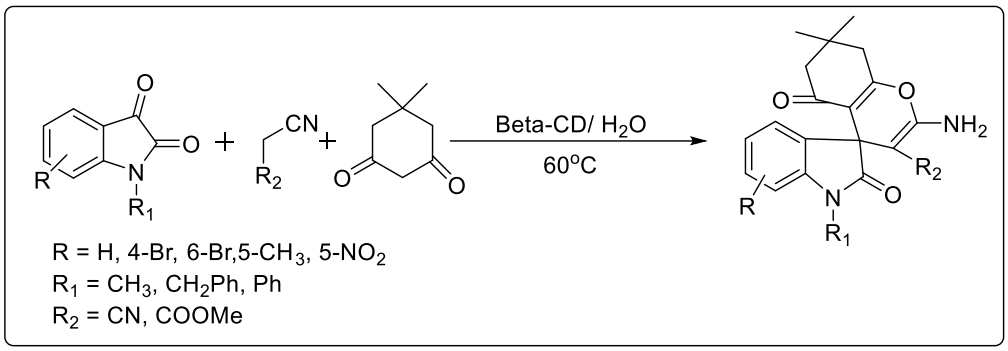
Scheme 5.II.2

G. Sri Hari and Y. Rok Lee [22] use ethylenediamine diacetate as a catalyst for the preparation of spirooxindole compounds in an aqueous medium. A three-component reaction mixture containing isatins, malononitrile, and 1,3-dicarbonyl compounds catalyzed by ethylenediamine diacetate (EDDA) in an aqueous medium affords spirooxindole compounds in high yield **(Scheme 5.II.3).**



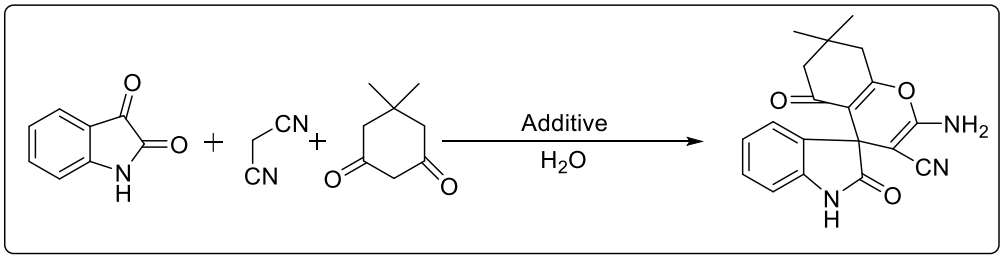
Scheme 5.II.3

Sridhar Regati and co-workers [23] reported supramolecular synthesis of spirooxindoles catalyzed by β-cyclodextrin in aqueous medium. Synthesis of various derivatives of spirooxindoles from isatin, malononitrile and 1,3-dicarbonyl compounds in high yield catalyzed by β-cyclodextrin **(Scheme 5.II.4)**.



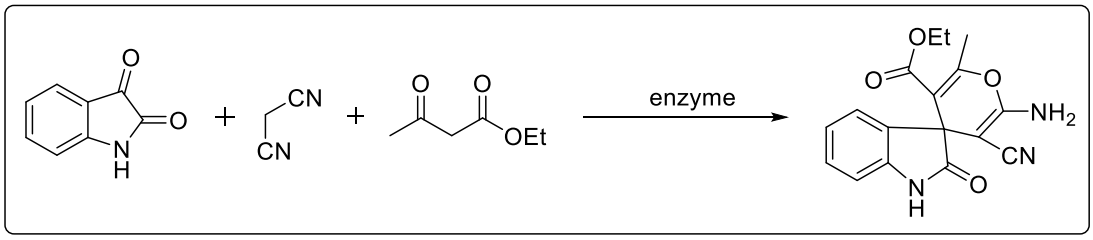
Scheme 5.II.4

Lewis base-surfactant-combined catalyst utilized in the synthesis of spirooxindoles in aqueous micellar media demonstrated by Li-Min Wang and co-workers [24]. Simple reaction takes place between isatin, malononitrile, and 1,3-dicarbonyl compounds produces the desired spirooxindoles derivatives with good results such as yield and less time **(Scheme 5.II.5)**.



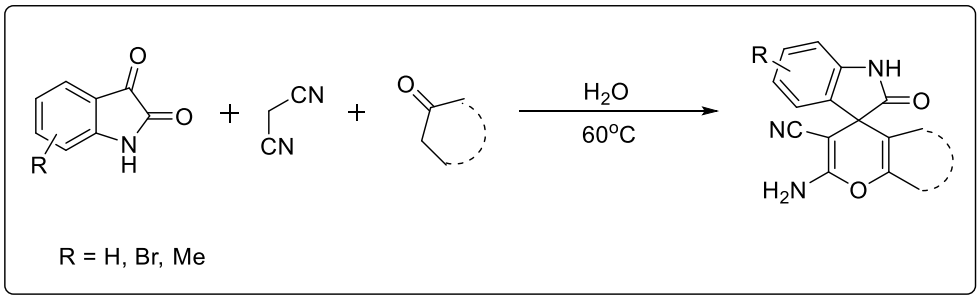
Scheme 5.II.5

She-Jie Chai et al. [25] developed enzyme catalyzed one-pot synthesis of spirooxindole derivatives. Reaction goes by Knoevengel condensation followed by Michael addition in presence of porcine pancreas lipase (PPL) produces desired product with good yield **(Scheme 5.II.6)**.



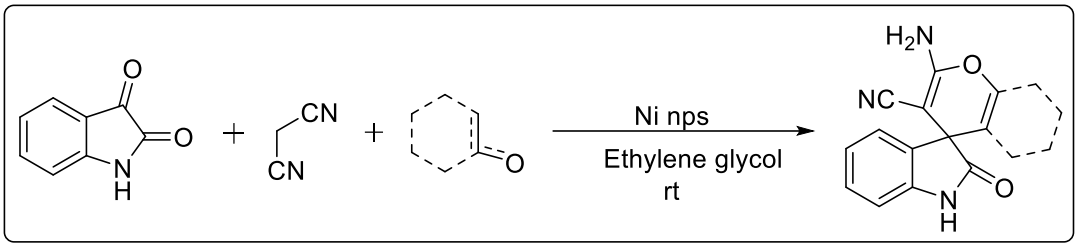
Scheme 5.II.6

Catalyst-free methodology developed by Liqin Zhao and co-workers [26] for the synthesis spirooxindole molecules in aqueous medium. The catalyst free protocol saves the environment from hazardous chemicals and decrease the final cost of synthesis **(Scheme 5.II.7)**.



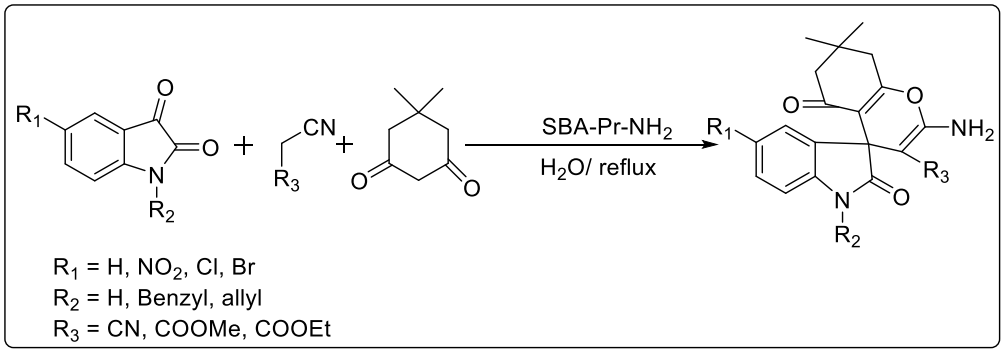
Scheme 5.II.7

Jitender M. Khurana and Sneha Yadav [27] first synthesized polyethylene glycol (PEG)-stabilized Ni nanoparticles. Use those highly effective PEG-stabilized Ni nanoparticles for the preparation of biologically important spiropyrans from the condensation between malononitrile, different 1,3-dicarbonyl compounds, and ninhydrin/acenaphthoquinone/isatin **(Scheme 5.II.8)**.



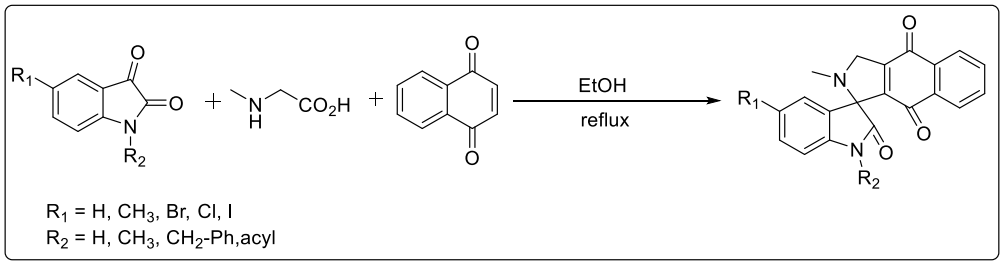
Scheme 5.II.8

Amino-functionalized SBA-15 type mesoporous silica utilized by Ghodsi M. Ziarani et al. [28] for the preparation of spirooxindoles. Amino-functionalized SBA-15 (SBA-Pr-NH_2) has been basic heterogeneous nanocatalyst can be easily handled and removed from the reaction mixture by simple filtration **(Scheme 5.II.9)**.



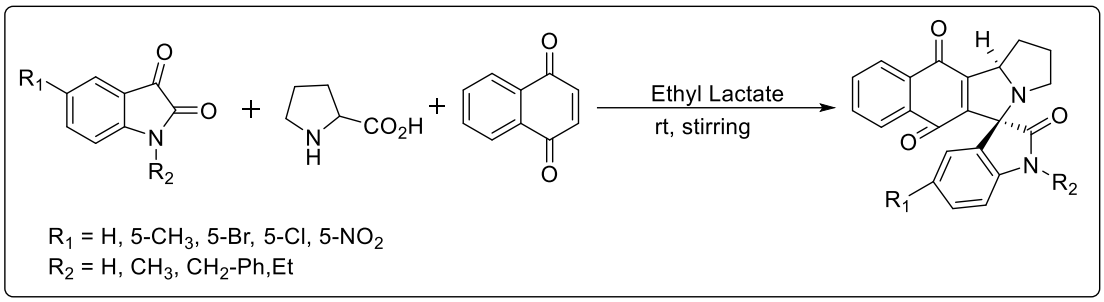
Scheme 5.II.9

Gangaru Bhaskar et al. [29] demonstrated series of novel spirooxindole products. Evaluated their antimicrobial activity against bacteria and fungi. Derivatives of spirooxindoles have been prepared by 1,3-dipolar cycloaddition of an azomethine ylide obtained from isatin with the dipolarophile 1,4-naphthoquinone **(Scheme 5.II.10)**.



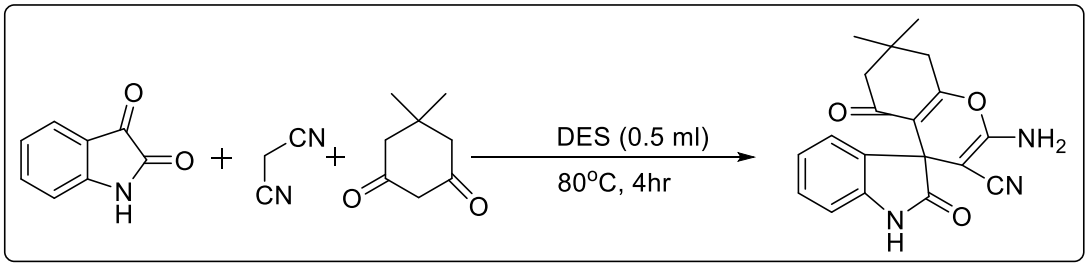
Scheme 5.II.10

Ethyl lactate was assessed as a bio-based green solvent by Anshu Dandia and co-workers [30] for the 1,3-dipolar cycloaddition reaction between azomethine ylide obtained from substituted isatin and proline with naphthoquinone as a dipolarophile, which produces spiro-pyrrolo[2,1-a]isoindole derivatives **(Scheme 5.II.11)**.



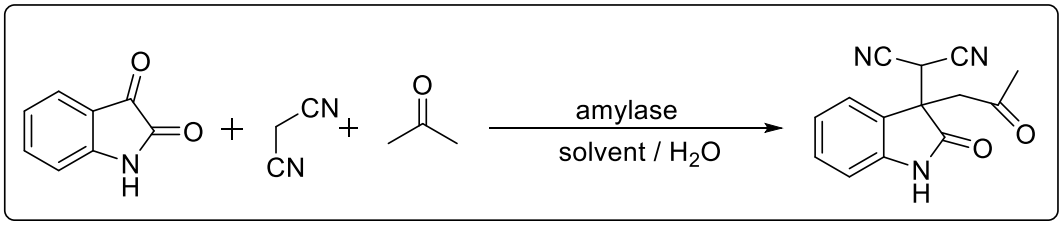
Scheme 5.II.11

Najmedin Azizi et al. [31] synthesised spirooxindole in deep eutectic solvent. Biodegradable urea:ChCl as deep eutectic solvent gives the environmental friendly preparation of spirooxindole derivatives **(Scheme 5.II.12)**.



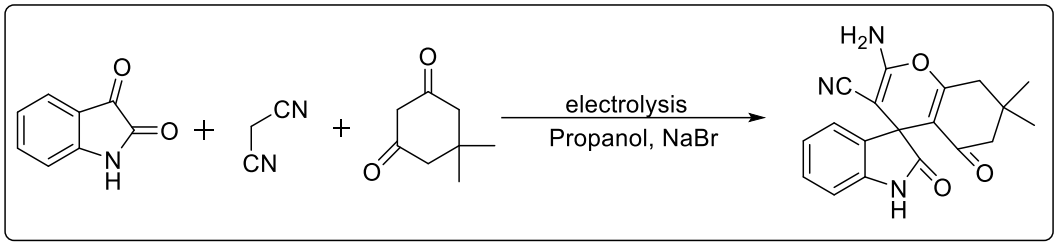
Scheme 5.II.12

Tao He et al. [32] reported α-Amylase as a biocatalyst for the production of 3,3'-oxindoles and spirooxindole pyrans. α-Amylase obtained from hog pancreas displayed biocatalytic activity and promote the synthesis within short time with excellent yield **(Scheme 5.II.13)**.



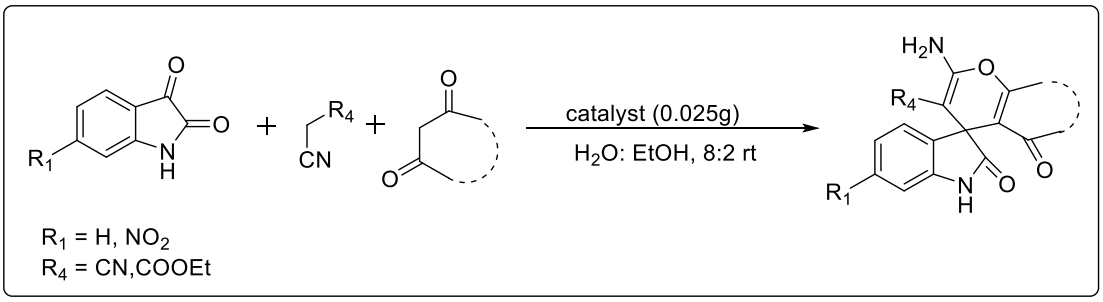
Scheme 5.II.13

Zahra Darvish et al.[33] synthesized nanoparticles of spirooxindole derivatives from isatins, malononitrile, and dimedone by electrocatalysis. Electrogenerated base of the anion of propanol from undivided cell containing the sodium bromide as an electrolyte **(Scheme 5.II.14)**.



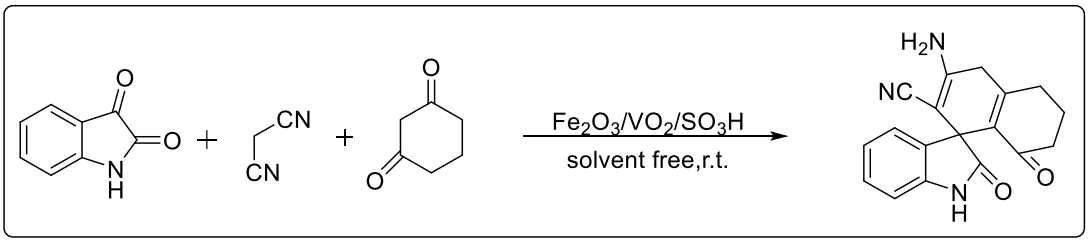
Scheme 5.II.14

Halloysite nanoclay play effective role for developing the green synthesis of spirooxindole compounds was reported by Samahe Sadjadi and co-workers [34]. Heteropolyacids, HPAs decorated Halloysite Nanoclay - HPA@HNTs-IMI-SO_3H is heterogeneous catalyst prepare by combining natural clay ($Al_2(OH)_4Si_2O_5 \cdot 2H_2O$) and ionic liquid **(Scheme 5.II.15)**.



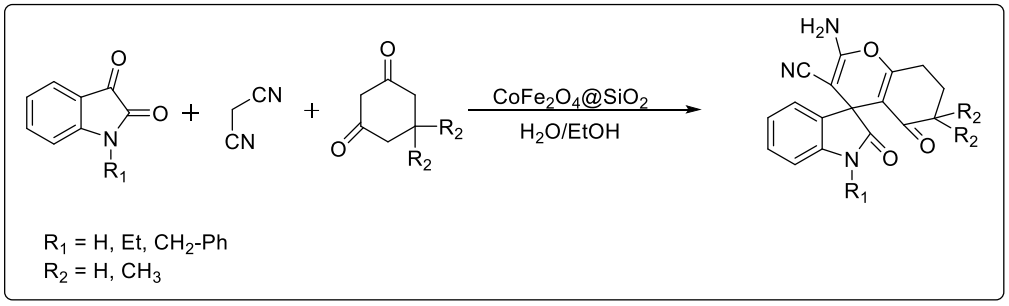
Scheme 5.II.15

Hassan Hassani et al. [35] reported synthesis of spirooxindole derivatives catalysed by sulfonic acid supported on Fe_2O_3/VO_2 nanocatalyst. The production of spirooxindole derivatives by reacting the isatin, 1,3-cyclohexadiene and malononitrile without solvent **(Scheme 5.II.16)**.



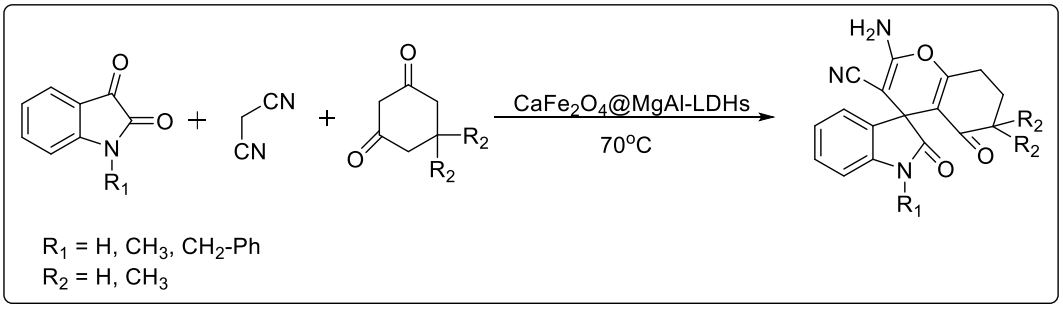
Scheme 5.II.16

$CoFe_2O_4@SiO_2$: A magnetically reutilizable heterogeneous catalyst prepared by Kaveh Hemmat and co-workers [36] is applied for the synthesis of spirooxindole. The synthesis of spirooxindoles by reacting malononitrile, various isatins with 1,3-dicarbonyl compounds in presence of $CoFe_2O_4@SiO_2$ catalyst **(Scheme 5.II.17)**.



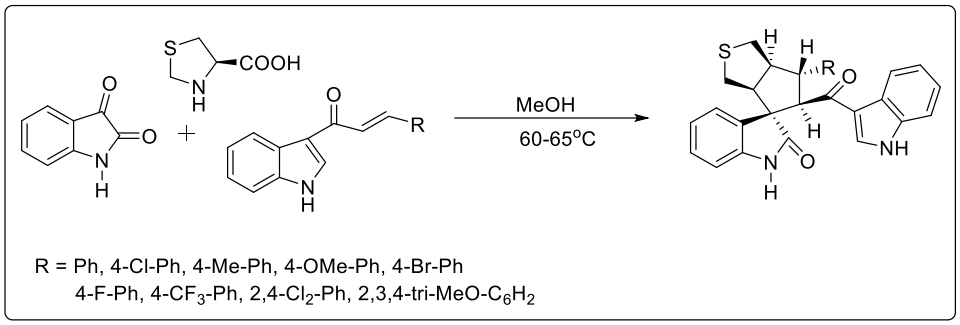
Scheme 5.II.17

Mehri Salimi et al. [37] design magnetically recyclable $CaFe_2O_4@MgAl$-LDH nanoparticles and use it for synthesis of spirooxindole scaffolds. They check biological activity of synthesized compound which shows promising chemotherapeutic agent is spirooxindole **(Scheme 5.II.18)**.



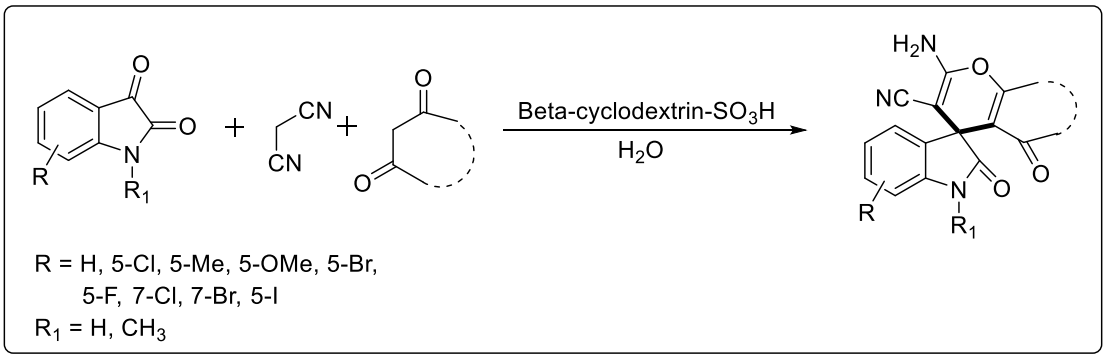
Scheme 5.II.18

Preparation of new series of thiazolo-pyrrolidine–(spirooxindole) tethered to 3-acylindole developed by M. S. Islam and co-workers [38]. Reaction between 3-acetyl indole with isatin, and l-4-thiazolidinecarboxylic acid in methanol produces desired spirooxindole in high yield **(Scheme 5.II.19)**.



Scheme 5.II.19

Fangzhou Xu et al. [39] reported simplistic development of spiroindoline molecules as potential anti-viral agent. Present protocol was disclosed appropriate and easily accessible β-cyclodextrin-SO_3H promoted strategy for development of varieties spiro indoline compounds in aqueous media **(Scheme 5.II.20)**.

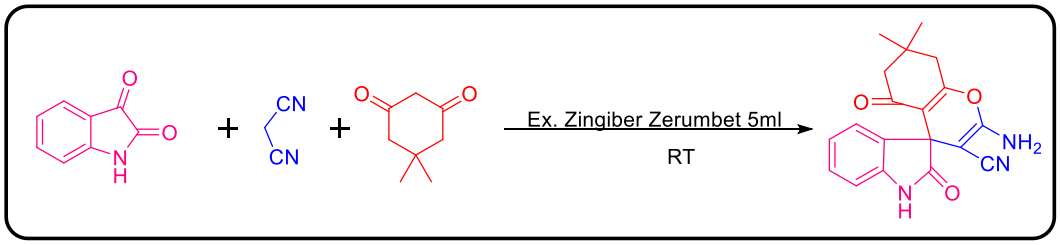


Scheme 5.II.20

5.II.2 Present work:

Bio-surfactant is a greener agent which conserve the ecosystem from addition of toxic chemical in to nature and give contribution in decreasing environmental pollution [40]. Medium for this reaction is a natural extract therefore reaction goes in greener environment and gives contribution to sustain the green principal with saving economy by using naturally available extract of *Zingiber zerumbet* and also environment by using bio-surfactant for such organic transformation (Scheme 5.II.21).

Surfactants are surface active agent, biosurfactant or natural surfactant are microbial amphiphiles extracted from plant, animals or microorganisms. *Zingiber zerumbet* (L.) Roscoe ex Sm., widely known as 'Shampoo Ginger' is an aromatic and rhizomatous herb which crop up naturally in the Himalaya and the western ghats of India [41].



Scheme 5.II.21. Synthesis of Spirooxindole derivatives in bio-surfactant.

5.II.3 Result and Discussion:

Initially we go for the selection of suitable solvent under the green perspective as result of water, ethanol, methanol, combination of water: ethanol (1:1) in which reacting equimolar quantities of isatin, malononitrile with dimedone without catalyst as the model reaction. But our effort not getting expected result, yield is poor and consumed longer time. We perform model reaction at also high temperature in similar solvent in absence of catalyst, we get nearly good results **(Table 5.II.1 and 5.II.2)**.

But our aim was developed a greener protocol for the synthesis of spirooxindole derivatives under the circumstances of green chemistry principles such as preventing the utilization of toxic or hazardous chemical substances like as catalyst, solvents, and give priorities to the use of biodegradable catalyst as well as reaction medium available from renewable feedstocks. Therefore, from previous research outcome we try to perform synthesis of spirooxindole in the extract of *Zingiber zerumbet*. We perform the model reaction by taking equimolar quantities of isatin, malononitrile with dimedone in 5ml extract of *Zingiber zerumbet*. We got the superlative results over the other solvents without use of catalyst. Shampoo zinger is extract of *Zingiber zerumbet*, fruit of zinger which acts as bio-surfactant. Inflorescence of plant containing viscous juice which is rich in surfactant is known as ginger shampoo [42]. There is saponin present in the viscous juice of *Zingiber zerumbet*, due to which it shows surfactant properties. Surfactants are detergents that are effective at dissolving non-polar compounds. This

efficiency in dissolving non-polar compounds has made aqueous surfactant systems better alternatives to harmful organic solvents in various applications. Surfactant forms the micelles, which are similar to colloidal aggregation. This micelle formation occurs above the critical micelle concentration (CMC). A low concentration of CMC means requiring less surfactant to decrease the surface tension. Initially, the clear reaction mixture turned turbid, which indicates the formation of micelle-like colloidal aggregation. During this aggregation, reactant molecules are brought into close proximity to each other and interactions take place between them, which form the organic transformation between them.

Under the optimized condition, series of spirooxindole derivative were synthesized by using different active methylene groups **(Table 5.II.4)**. In a comparison study of most reported works, this work demonstrated a high yield (92%) with a greener protocol that saves the environment and economy by using bio-surfactant in a short period of time **(Table 5.II.3)**.

Table 5.II.1: Solvent Screening for synthesis of spirooxindole derivatives.

Entry	Solvent	Time	Yield (%)
1	Water	72 hrs.	20
2	Ethanol	24 hrs.	40
3	Ethanol and Water (1:1)	48 hrs.	40
4	Methanol	48hrs	trace

Table 5.II.2: Optimization of reaction condition and solvent screening for synthesis of spirooxindole derivatives.[a]

Sr. No.	Solvent	Temperature	Time	Yield[b] (%)
1	water	60°C	10hrs	30
2	Water: ethanol	60°C	6-7hrs	50
3	ethanol	40°C	3-4hrs	70
4	Extract of *Zingiber zerumbet*	Room temperature	15 min	92

5	Extract of *Zingiber zerumbet*	40°C	15 min	90
6	Ex. Of Z.z. and ethanol (1:1)	Room temperature	15min	91

a) Reacting substrates: equimolar quantities of isatin, malononitrile and dimedone.

b) Isolated yield of product.

Spirooxindoles were synthesized by means of one-pot condensation of equimolar quantities of isatin, malononitrile and active methylene compounds by using 5ml extract of *Zingiber zerumbet* as bio-surfactant at room temperature (**Scheme 5.II.21**).

Table 5.II.3: Comparative study of published works versus present work for the synthesis of spirooxindole.

Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield (%)	References
1	Nano-ZnO	CH_3CN	Reflux 82°C	6 hrs.	93	[43]
2	-	Urea:ChCl	80°C	6 hrs.	95	[31]
3	Acylase Amano (AA)	Ethylene glycol	50°C	4 hrs.	97	[44]
4	SiO_2@g-C_3N_4	EtOH: H_2O (1:1)	Reflux	3 min	95	[45]
5	Borax	EtOH	78°C	2 hrs	94	[46]
6	$CoFe_2O_4$@SiO_2	EtOH: H_2O (1:1)	80°C	5 min	98	[47]
7	$CaFe_2O_4$@Mg Al-LDH	H_2O	70°C	4 min	97	[28]
8	Extract of *Zingiber zerumbet*	-	RT	15 min	92	This work

The proposed mechanism for the synthesis of spirooxindole derivative (4) was conceptualized in **figure 5.II.3**. The process of synthesis of spirooxindoles represents a typical cascade reaction in which first step is Knoevenagel condensation between isatin and malononitrile which gives isatylidene malononitrile (5). Then, Michael addition of dimedone on isatylidene malononitrile (5) gives intermediate (6), then followed by intramolecular cycloaddition of hydroxyl group to the cyano moiety gives corresponding spirooxindole product (4).

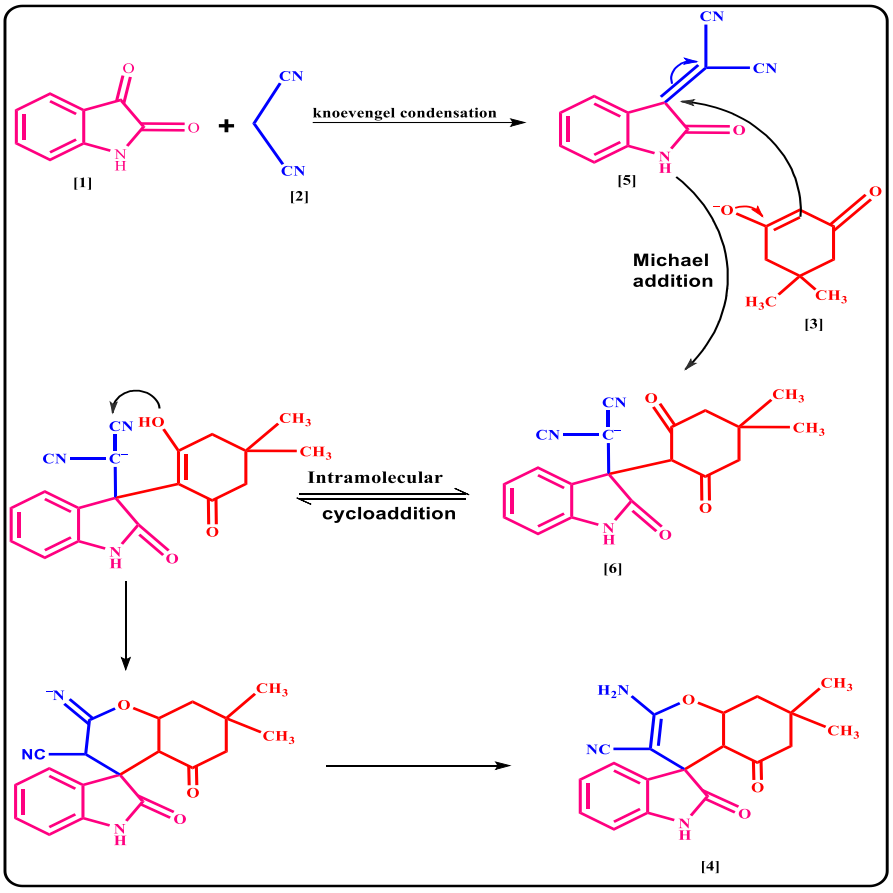
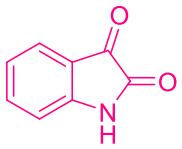
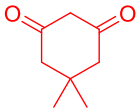
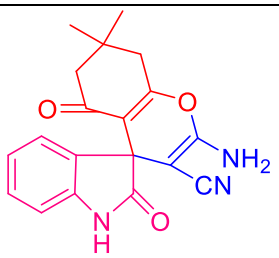
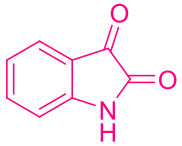
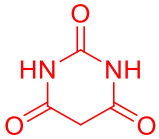
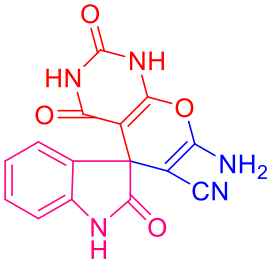
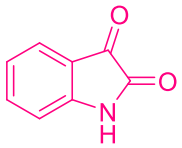
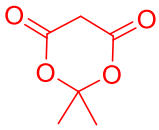
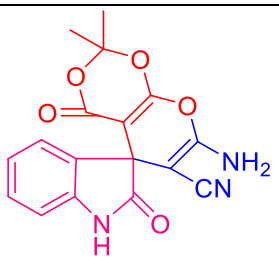
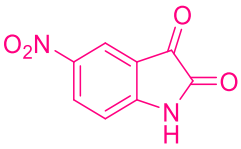
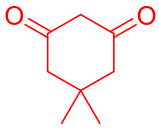
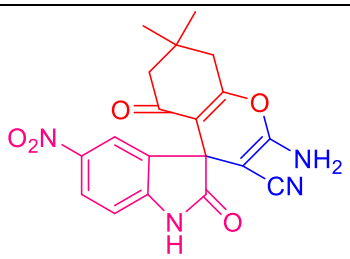
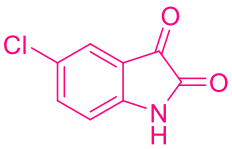
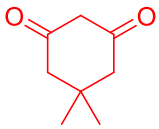
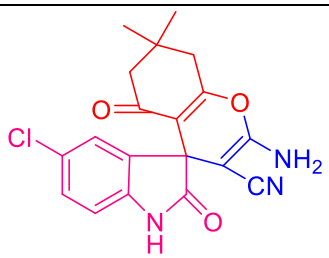
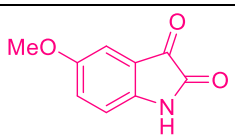
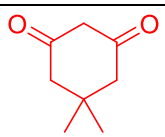
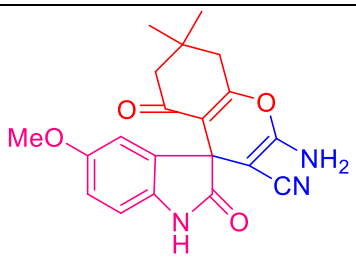
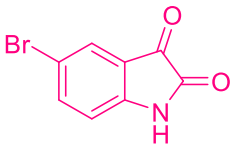
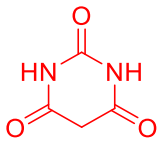
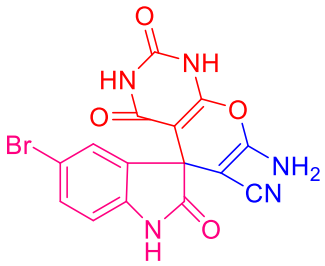
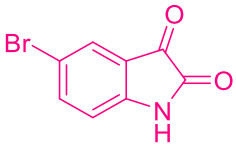
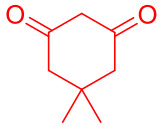
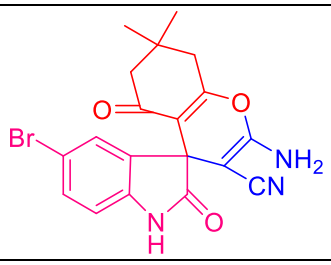
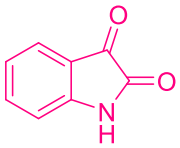
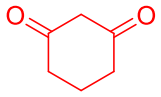
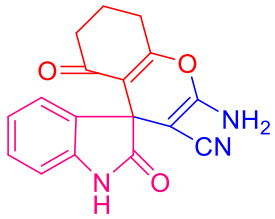
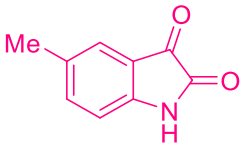
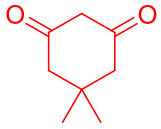
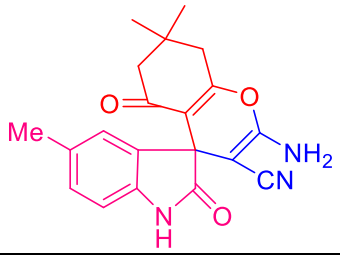


Figure 5.II.3. Plausible reaction mechanism for synthesis of spirooxindole in aqueous hydrotropic medium.

Table 5.II.4: Synthesis of spirooxindole derivatives in bio-surfactant at room temperature.

Sr. No.	Isatin	Active methylene	Product	MP (°C) [Lit]	Yield (%)[b]
1				286-288 [25]	92
2				>300 [48]	86
3				187-190 [31]	85
4				>300 [25]	94
5				290-292 [25]	91
6				285-287 [25]	91

7				225-227 [48]	90
8				>300 [49]	90
9				282-283 [25]	92
10				281-283 [49]	93

b) Isolated yield of product.

Recyclability of Bio-Surfactant, *Zingiber zerumbet*:

We use only 5ml extract of *Zingiber zerumbet* for the reaction. After completion of reaction filter the product and collect the filtrate and reuse for the reaction and monitoring any effect on yield but there is no much more effect on yield. After third cycle slightly decrease in yield. Therefore, reuse of extract is very important step as an environmental point of view which maintain the sustainability **(Figure 5.II.4)**.

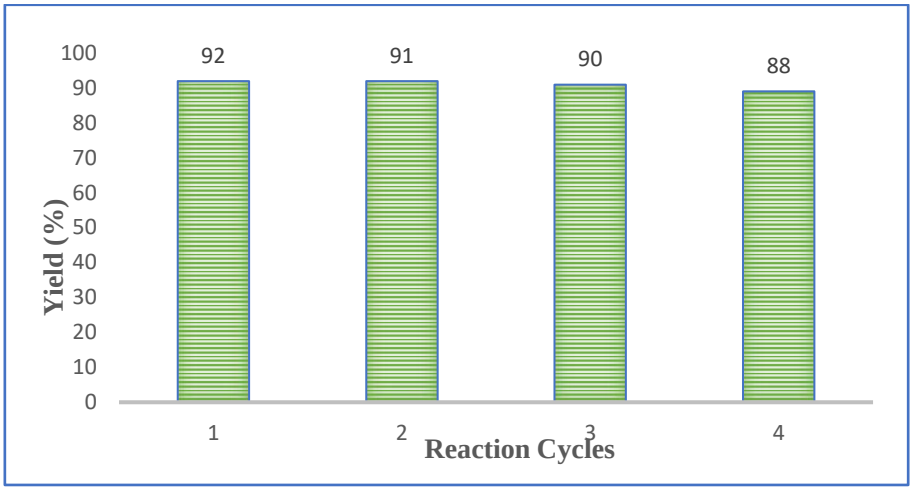
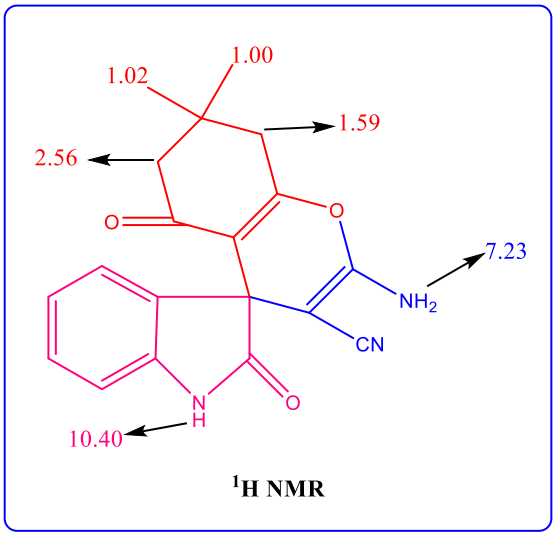
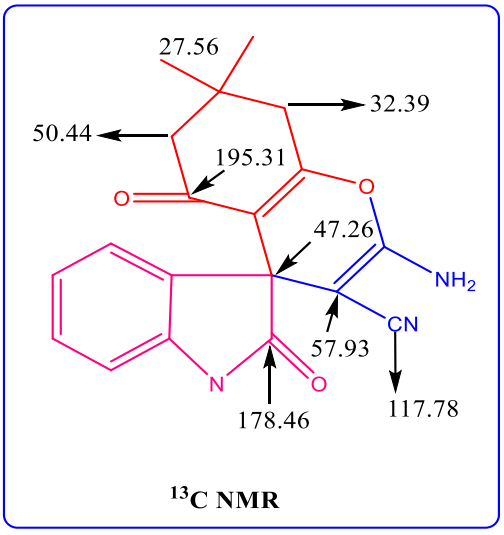


Figure 5.II.4. Recyclability of bio-surfactant

Characterization of products

1) 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile (Table 5.II.4 Entry 1):

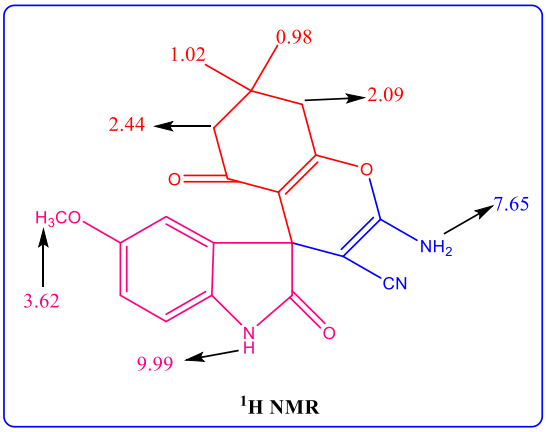


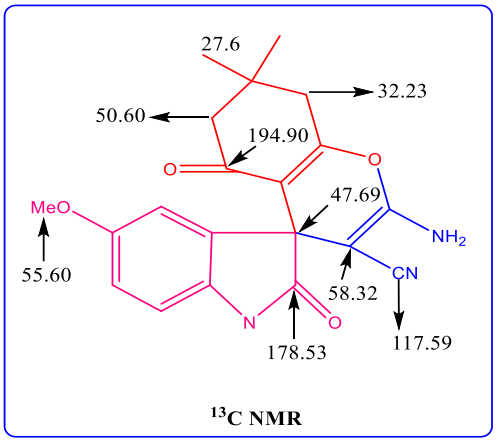


IR spectrum **(Figure 5.II.5)** exhibits characteristic peaks for asymmetric and symmetric stretching frequency of -NH_2 group at 3384 and 3318 cm^{-1} respectively. The characteristic peak for nitrile group was observed at 2194 cm^{-1}. The carbonyl functional group of dimedone moiety was show absorption at 1720 cm^{-1} while amide carbonyl group of indole ring showed a peak at 1681cm^{-1}. ^{1}H NMR spectrum **(Figure 5.II.6)** showed the two sharp singlet due to methyl protons at δ 1.00 and 1.03 ppm. Four protons of the methylene group resonate at δ 2.56 and 1.59 ppm, which exhibits multiplate. The protons of primary amine were resonated at δ 7.23 ppm while the NH proton of indole ring was observed at δ 10.40 ppm. The remaining chemical shift δ

values from 6.80-7.14 ppm were attributed to four protons in the aromatic region. The ^{13}C NMR spectrum **(Figure 5.II.7)** possessed the peak at δ 27.46 ppm due to methyl group while two methylene carbon exhibits peak at δ 32.39 and 50.44 ppm. The carbon which was adjacent to nitrile group appeared at δ 57.93 ppm, however the carbon of nitrile group resonated at δ 117.78 ppm. The carbon at spiro position was observed at δ 47.26 ppm. The unsaturated carbonyl carbon was found at δ 195.31 ppm although the carbonyl carbon of amide in the indole ring resonated at δ 178.46 ppm. The rest of the carbons resonated at δ 164.58, 159.20, 142.48, 134.85, 128.60, 123.44 and 122.12 ppm in the aromatic region. Mass spectrum **(Figure 5.II.8)** gave peak at m/z: 336.9 $[M+H]^+$.

2) 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`- indoline]-3-carbonitrile (Table 5.II.4. Entry 10):





The IR spectrum **(Figure 5.II.8)** shows absorption frequencies at 3384 and 3309 cm^{-1} for asymmetric and symmetric stretching vibrations of the NH_2 group. The nitrile group shows corresponding absorption band at 2188 cm^{-1} while conjugated carbonyl group appeared at 1718 cm^{-1}. The ^1H NMR spectrum **(Figure 5.II.9)** exhibits two sharp singlets at δ 0.98 ppm and δ 1.02 ppm for six protons of two methyl group. three protons of methoxy group of isatin moiety shows sharp singlet at δ 3.62 ppm. The multiplate peaks at δ 2.44 ppm and δ 2.09 ppm were due to four protons of two methylene groups. the two protons of NH_2 were resonated at δ 7.65 ppm although proton of NH of indole ring was observed at δ 9.99 ppm. Out of three aromatic protons, one proton was resonated at δ 6.68 while remaining two protons was observed at δ 6.45 ppm and 6.66 ppm which was adjacent to OMe_3 group. Similarly, ^{13}C NMR spectrum **(Figure**

5.II.10) exhibits the peak at δ 27.66 due to carbon of methyl group. The carbon adjacent to nitrile group was observed at δ 58.32 ppm, however the carbon of nitrile resonated at δ 117.59 ppm. The carbon of spiro ring was found at δ 47.69 ppm. the carbon of methoxy group of isatin moiety resonated at δ 55.60 ppm. The unsaturated carbonyl carbon showed the value δ 194.90 ppm, while the carbonyl carbon of amide in the indole moiety resonated at δ 178.53 ppm. The rest of the aromatic carbons appeared at δ 164.19, 159.15, 155.46, 135.77, 135.58, 112.85, 111.33, 110.22 and 110.07 ppm. Mass spectrum **(Figure 5.II.15)** gave peak at m/z: 365 $(M)^+$.

5.II.4 Conclusion

In conclusion, we report a simple and new approach for the synthesis of spirooxindole, which represents a highly efficient and environmentally benign protocol. These methods provide a good alternative to synthetics as well as those that require harsh reaction conditions. Use of bio-surfactants generates an ecologically safe protocol that eliminates the addition of hazardous solvents to nature, which is more important during these environmentally conscious days. This is achieved by synthesizing spirooxindole in a natural medium. Therefore, we develop here a greener protocol for the synthesis of spirooxindole derivatives.

5.II.5 Experimental

General

^{1}H-NMR and ^{13}C-NMR of pure compounds were recorded on a Bruker 400 MHZ spectrometer using $CDCl_3$ as solvent and TMS is an internal standard. IR spectra were obtained with lambda FT-IR 750 spectrometer. Melting points were determined using a melting/boiling point electrical apparatus (EQ 730A-EQUIPTRONICS) and are uncorrected. All the chemicals required for synthesis were purchased from Loba and Sigma-Aldrich chemical companies and were used without further purification. *Zingiber zerumbet* fruit of zinger is collected from botanical garden of Y.C.I.S. Satara, India.

Collection of "*Zingiber zerumbet*" fruit extract:

Zingiber zerumbet is the fruit of the zinger available in the botanical garden of Y.C.I.S. Satara. Extract was removed by hand from fruit, which is a viscous liquid

known as "shampoo zinger" and also a natural surfactant. It was collected and stored in freezers and used in reactions as a natural surfactant.

General procedure for the synthesis of spirooxindole

Isatin (1mmol), Malononitrile (1mmol) and active methylene compound (1mmol) was added to a 5 mL extract of *Zingiber zerumbet* in the round bottom flask. Then reaction mixture was kept for stirring at room temperature for appropriate time until the completion of the reaction was monitored by TLC (nHexane: EA 8:2). The solid product was separated by simple filtration. The isolated crude product was recrystallized with ethanol.

Spectroscopic data for some target compounds are as follows

1) **2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile (Table 5.II.4. Entry 1):** IR (KBr): $\bar{\upsilon}$ = 3384, 3318, 3153, 2959, 2194, 1720, 1681, 1658, 1473, 1343, 1224, 1055, 903cm^{-1}; ^{1}H NMR (DMSO-d_6 , 400 MHz) ∂: 10.40 (s, 1H, NH), 7.23 (s, 2H, NH_2), 7.14 (t, 1H,ArH), 6.98 (d,1H,ArH), 6.89 (t, 1H, ArH), 6.80 (d, 1H, ArH), 2.56 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.03 (s,3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.31,178.46, 164.58, 159.20, 142.48, 134.85, 128.60, 123.44, 122.12, 117.78, 111.22, 109.57, 57.93, 5 0.94, 47.26, 32.39, 28.04, 27.46. MS (ESI): m/z 336.9 $[M+H]^+$.

2) **2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile (Table 5.II.4. Entry 7):** IR (KBr): $\bar{\upsilon}$ = 3286, 3154, 2958, 2190, 1725, 1652, 1479, 1349, 1220, 1056, 809 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.33 (s, 1H, NH), 7.02 (d, 1H, ArH), 6.83 (s, 1H, ArH), 6.72 (d, 1H, ArH), 6.62 (s, 2H, NH_2), 2.45 (s, 2H, CH_2), 2.10, (s, 2H, CH_2), 1.00(s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.07, 178.31, 164.59, 159,27, 141.16, 136.36, 128.28, 126.53, 123.43, 117.42, 110.95, 110.86, 57.48, 50.52, 47.50, 32.29, 27.99, 27.66.

3) **2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile (Table 5.II.4. Entry 10):** IR (KBr): $\bar{\upsilon}$ = 3384,3309, 3160, 2925, 2188, 1718, 166, 1600, 1484, 1351, 1205, 1029, ^{1}H NMR

(DMSO-d_6, 400 MHz) ∂: 9.99(s, 1H, NH), 7.65 (s, 2H, NH_2), 6.68 (d,1H, ArH), 6.66 (d, 1H, ArH), 6.45 (s, 1H, ArH), 3.62 (s, 3H, OCH_3), 2.44 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂:194.90, 178.53, 164.19, 159.15, 155.46, 135.77, 135.58, 117.59, 112.85, 111.33, 110.22, 110.07, 58.32, 55.60, 50.60, 47.69, 32.23, 28.33, 27.66. MS (ESI): m/z 365 $(M)^+$.

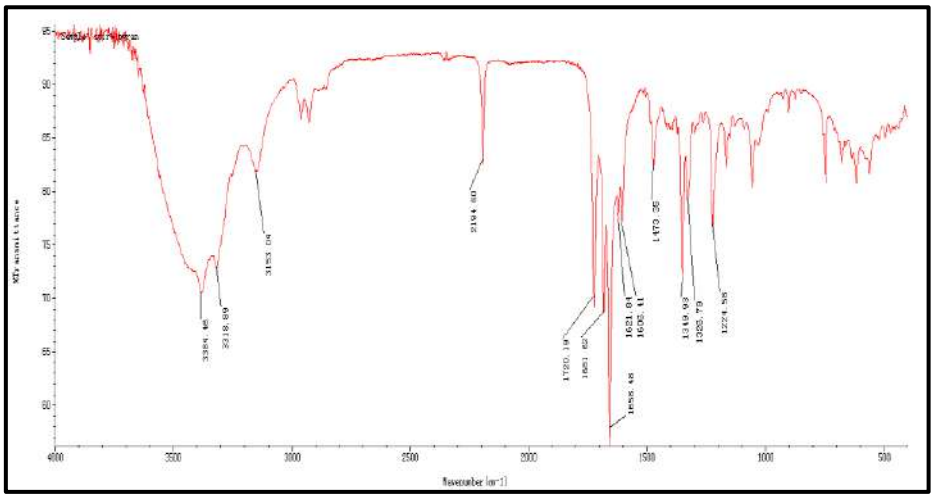


Figure 5.II.5: IR spectra of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile

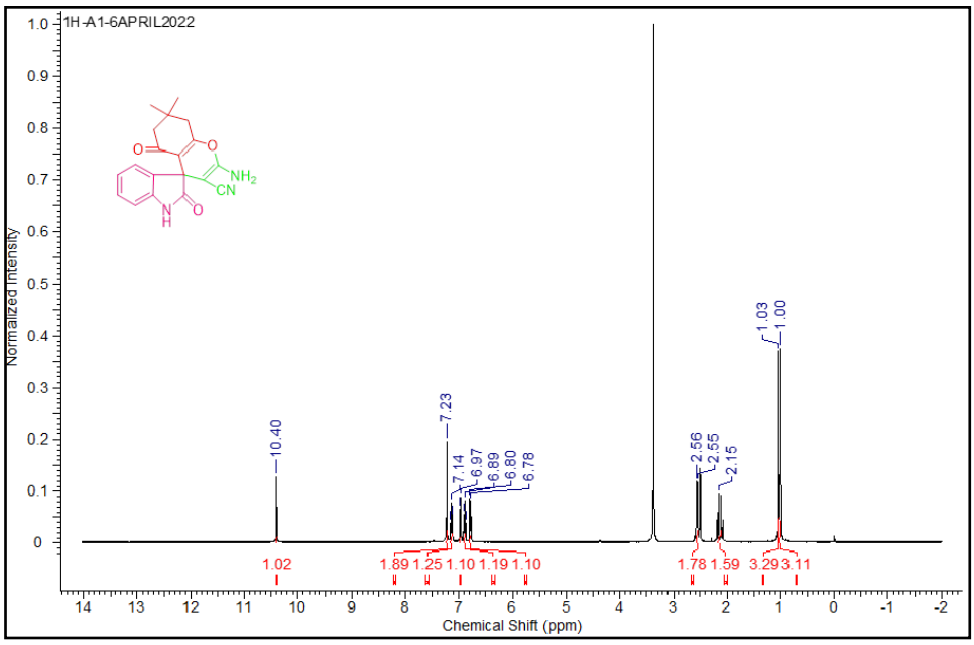


Figure 5.II.6: ^1H NMR of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile

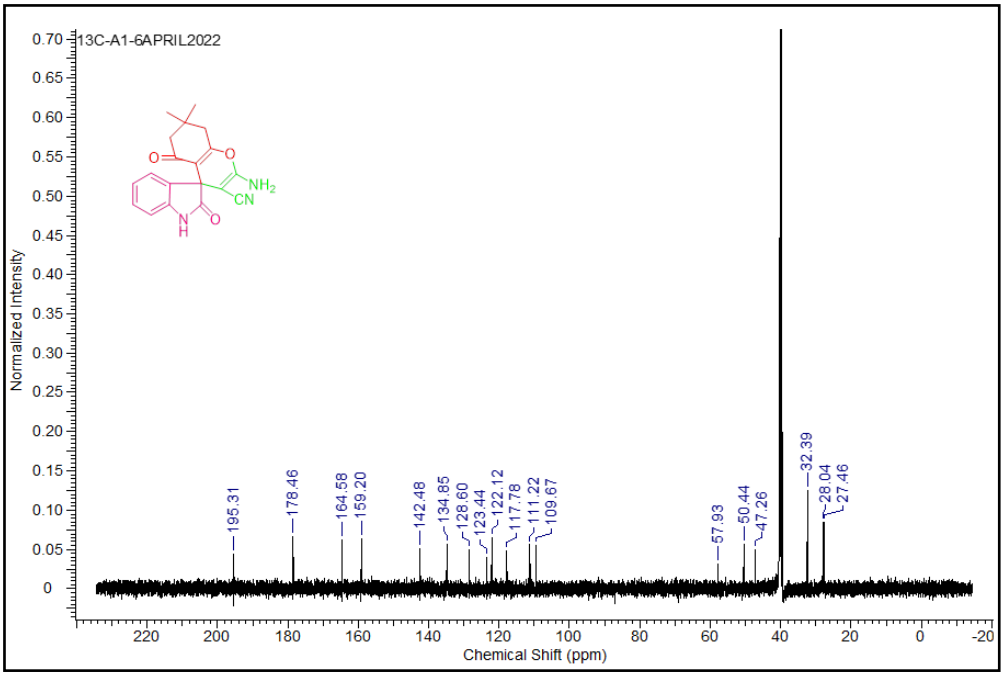


Figure 5.II.7: ^{13}C NMR of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile.

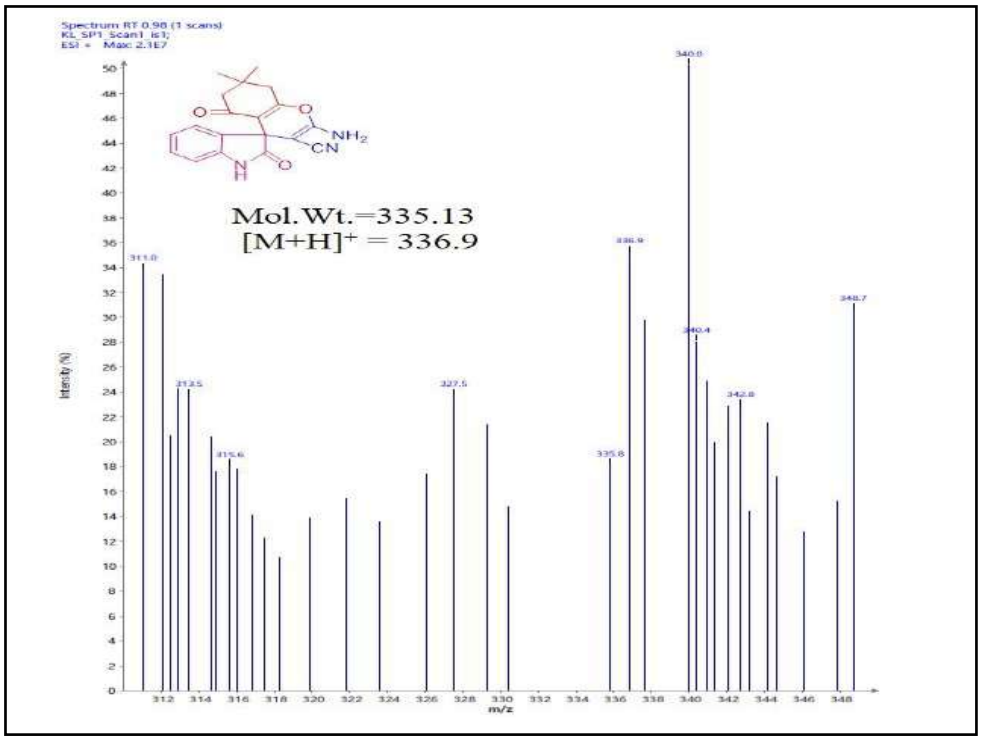


Figure 5.II.8 Mass spectrum of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8 hexahydrospiro[[1]benzopyran-4,3'-indole]-3-carbonitrile.

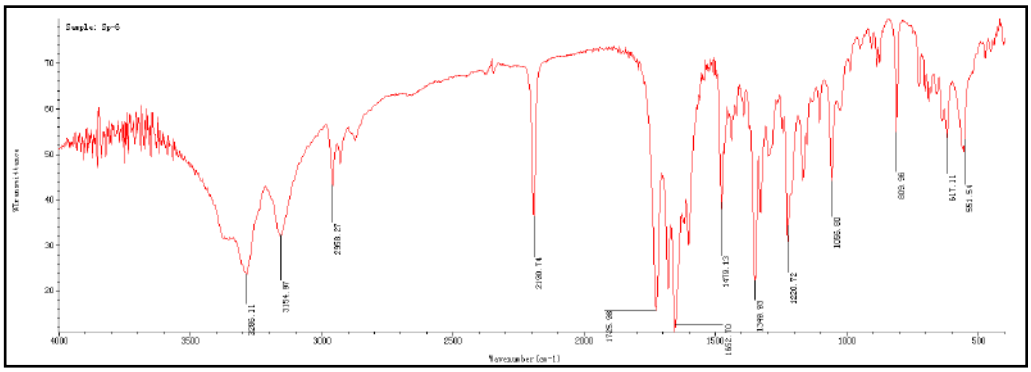


Figure 5.II.8: IR spectra of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

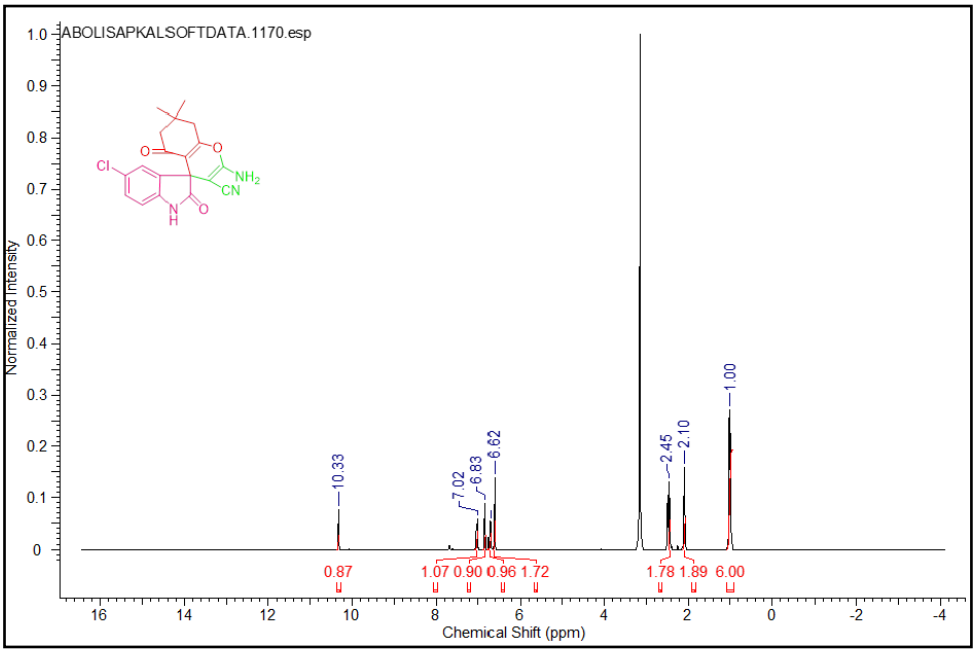


Figure 5.II.9: ^{1}H NMR of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

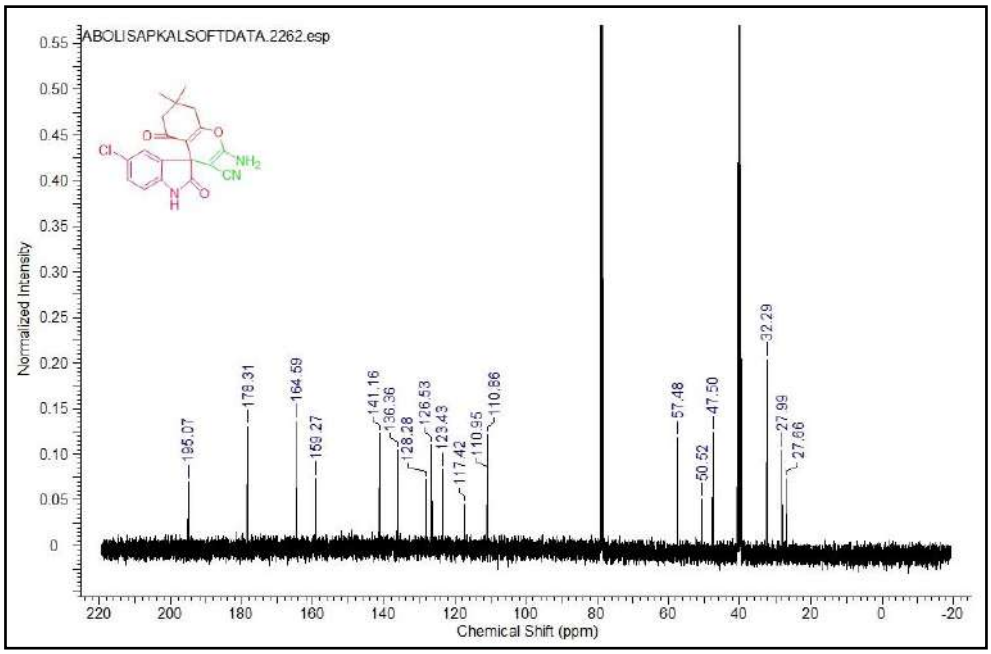


Figure 5.II.10: ^{13}C NMR of 2-amino-5`-chloro-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

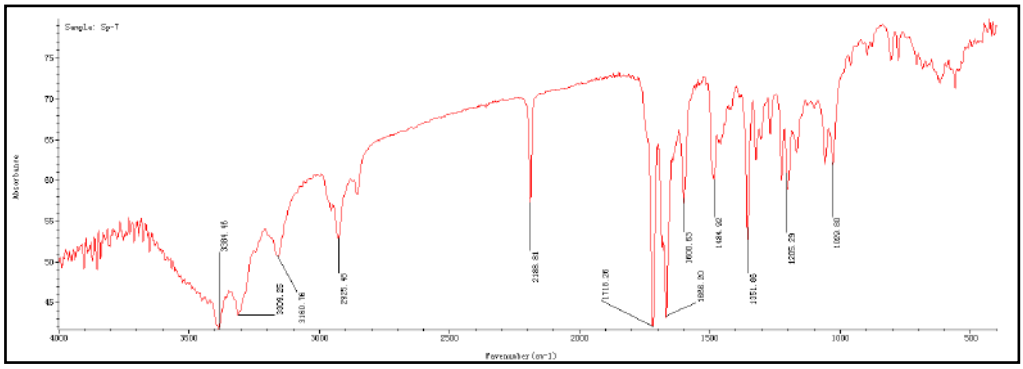


Figure 5.II.11: IR spectra of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

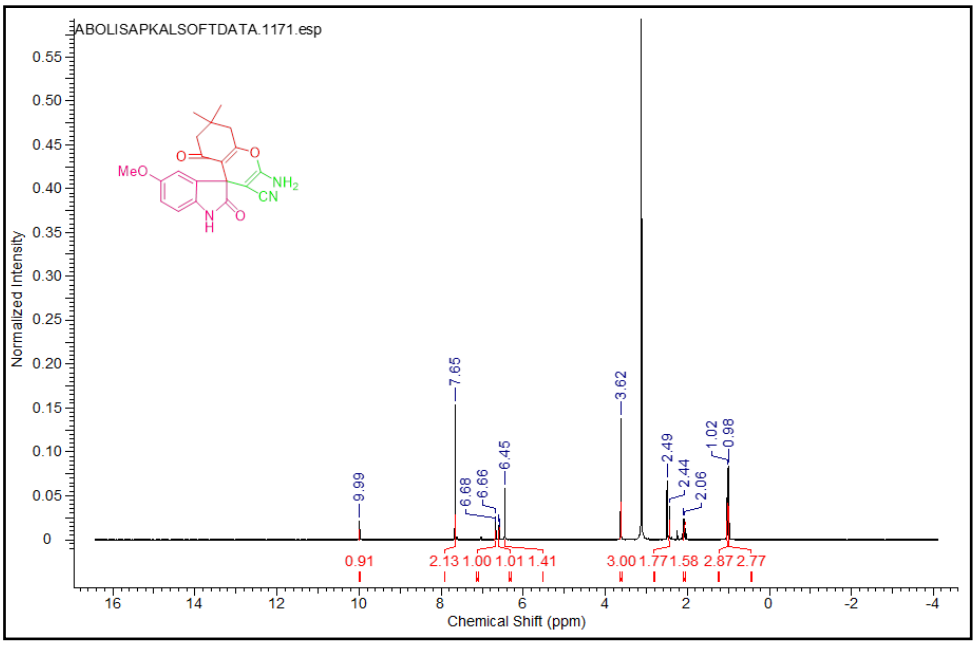


Figure 5.II.12: ^{1}H NMR of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile

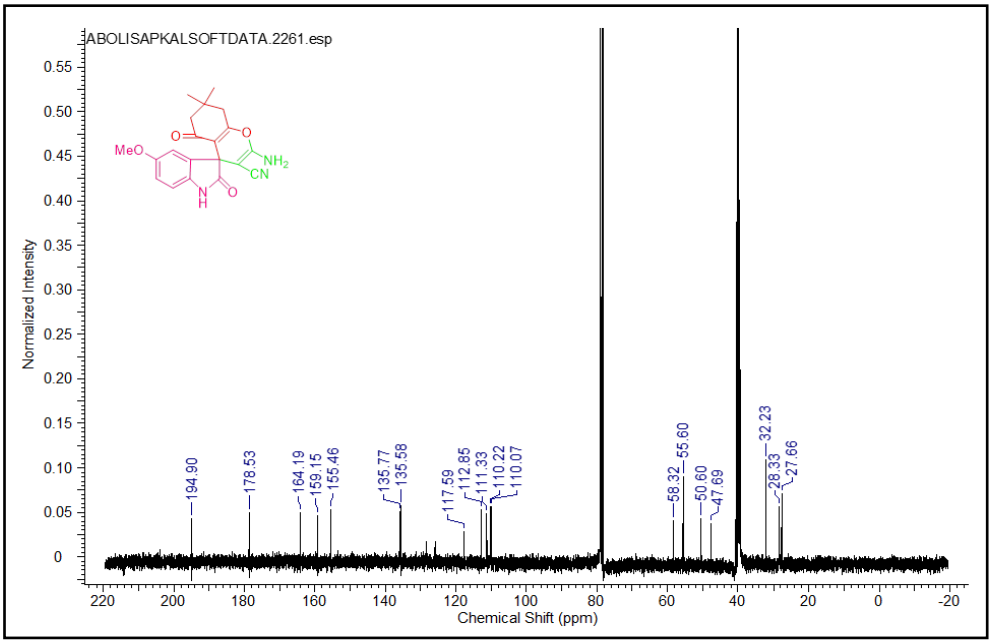


Figure 5.II.13: ^{13}C NMR of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile.

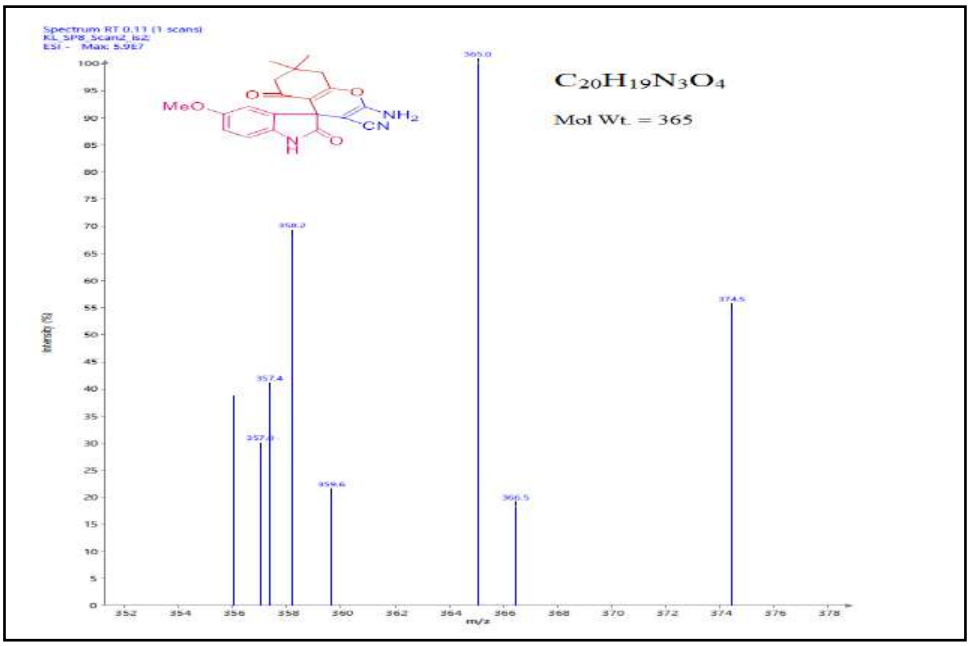


Figure 5.II.15 Mass spectrum of 2-amino-5`-methoxy-7,7-dimethyl-2`,5-dioxo-5,6,7,8 tetrahydrospiro[chromene-4,3`-indoline]-3-carbonitrile

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PUBLICATIONS

LIST OF PUBLICATIONS:

[1] "Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for Greener Synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium"
Aboli Sapkal and S. B. Kamble*
***Journal of Heterocyclic Chemistry*, 57, 3597-3604, 2020.**

[2] "Greener and Environmentally Benign Methodology for the Synthesis of Pyrazole Derivatives"
Aboli Sapkal and S. B. Kamble*
***Chemistry Select, 5*, 12971-13026, *2020*.**

[3] "Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium"
Aboli Sapkal, Suraj Attar, Avdhut Kadam, Pramod Gaikwad, Santosh Kamble*
***Polycyclic Aromatic Compounds*, 2022.**

[4] "Greener and Environmentally Benign Methodology for the Synthesis of Bis(Indole)methane and Trisindoline Derivatives"
Aboli Sapkal, Suraj Attar, S.B. Kamble*
Journal of Shivaji University.

[5] "Gel entrapped ZnO nanorods: An efficient and sustainable catalyst for the Claisen- Schmidt condensation reaction in aqueous hydrotropic media"
Suraj R. Attar, Aboli C. Sapkal, Chaitali S. Bagade, Sarfraj H. Mujawar, Santosh B. Kamble*
***Molecular Catalysis*, 542, 2023.**

[6] "Green and Eco-compatible Synthesis of Quinoxaline Molecules using Chitosan as a Biodegradable Catalyst in Aqueous Medium"
Aboli Sapkal, Suraj Attar, Santosh Kamble*
(communicated).

80-RECOMMENDATIONS

GREENER AND SUSTAINABLE METHODOLOGY FOR ORGANIC TRANSFORMATIONS

A THESIS SUBMITTED

TO

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FOR

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BY

Miss. ABOLI CHHAPPANRAO SAPKAL
M.Sc., SET

UNDER THE GUIDANCE OF

Dr. SANTOSH B. KAMBLE

M.Sc., Ph.D.

DEPARTMENT OF CHEMISTRY
YASHAVANTRAO CHAVAN INSTITUTE OF SCIENCE
(AUTONOMOUS) SATARA, 415001
MAHARASHRTA, INDIA

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80-RECOMMENDATIONS

Recommendations:

The research work carried out in this thesis is concerned with development of green methodologies for various organic transformation. The present work reports applications of hydrotrope, biocatalyst, and biosurfactants to be a potent catalyst-solvent system for some organic transformations. Based on the literature review it felts that there is wide scope of studying in the area of green methodologies for organic transformations. following recommendations are made –

1) Day to day increases need of development of alternative or new process or techniques for synthesis of organic moieties in laboratory or industrial importance.

2) The alternative process or techniques not only reduce cost but are also time-saving, eco-friendly, and reduce the generation of by-products.

3) There is establishment of new green catalyst, aqueous mediated organic transformations that decrease the use of toxic organic solvents as a reaction medium or having easy work-up procedure.

4) Water as a reaction medium is good choice for many organic solvents because it not only reduce cost but easy to handling and environmentally friendly solvent.

5) Biocatalyst and biosurfactant are environmentally friendly because they are biodegradable, source of them is nature which saves the ecology as well as economy.

6) The remarkable properties of the present methodologies are eco-friendly catalysts and reaction medium, which save the environment and are also cost-effective, reusable, non-hazardous, and easy to separate.

7) The main advantage is that large amounts of organic solvents can be avoided, and the catalyst can be recycled. Such fascinating features are associated with hydrotrope and surfactants which provide a new path for organic transformations by minimising the use of organic solvents with a remarkable reaction rate.

Conclusion:

We have synthesised biologically active various heterocyclic compounds such as 5-aminopyrazole-4-carbonitrile, [1,3]Oxazine by using hydrotrope-NaPTS, quinoxaline molecules using biocatalysts as chitosan, bis(indolyl)methane, and tris-indoline in biosurfactant, which is a natural extract of *Zingiber zerumbet* under ultrasound irradiation, and spirooxindole derivatives in the presence of biosurfactant is a natural extract of *Zingiber zerumbet* at room temperature. The synthesised heterocyclic compounds are confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The present methodology has promising aspects, viz., mild reaction conditions, recyclability, and high yield.

Summary:

Finally, sustainable methodologies are employed for the synthesis of 5-aminopyrazole-4-carbonitrile, [1,3]Oxazine, quinoxaline, bis(indolyl)methane, tris-indoline, and spirooxindole derivatives by utilising hydrotrope, biocatalyst, and biosurfactant as green reaction media. These catalysts exhibited high efficiency, and the products formed with a high yield in a short reaction time with an easy work-up procedure.

Future Findings:

Development of greener methodologies for organic transformations through the involvement of green solvents and catalysts that are abundantly present in nature. Screening of alternative energy sources that save the economy, time, and also ecology.