CHAPTER-1

Introduction

An overview of Some Main Class of Nitrogen, Oxygen and Sulphur Containing Heterocyclic Compounds

Chapter 1

An Overview of Some Main Class of Heterocyclic Compounds Containing Oxygen, Sulphur, and Nitrogen

1. Introduction

The term "heterocyclic compound" refers to cyclic organic compounds that contain at least one hetero atom (an atom other than carbon and hydrogen) in their cyclic ring systems. Such as Nitrogen (N), oxygen (O), and Sulphur (S) are the three most prevalent heteroatoms. Heterocyclic compounds are commonly available in plants and animal products and are a crucial component of about half of all natural organic compounds. Alkaloids, natural dyes, drugs, proteins, enzymes, etc., are significant groups of naturally occurring heterocyclic compounds. Heterocyclic compounds can be easily identified based on their electrical structure. The two main classifications for heterocyclic compounds are unsaturated and saturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetrahydrofuran are the traditional amines and ethers, respectively, in this category. However, due to their unusual chemical behavior, unsaturated heterocyclic compounds with rings of five and six members have been thoroughly explored. Pyridine, Thiophene, Pyrrole, Furan, and their benzo-fused derivatives are examples of unsaturated heterocyclic compounds. Quinoline, Isoquinoline, Indole, Benzothiophene, and Benzofuran are remarkable examples of benzo-fused heterocycles. Heterocyclic compounds can be divided into two types: aliphatic and aromatic.

The aliphatic heterocyclics are cyclic compounds that are analogous to ethers, amines, amides, thioethers, and other similar compounds. Heterocyclic compounds frequently occur in 5 to 7-membered ring systems however they can also comprise less prevalent 3- and 4-membered rings [1-5]. The aromatic heterocyclic compounds are very stable and do not readily decompose

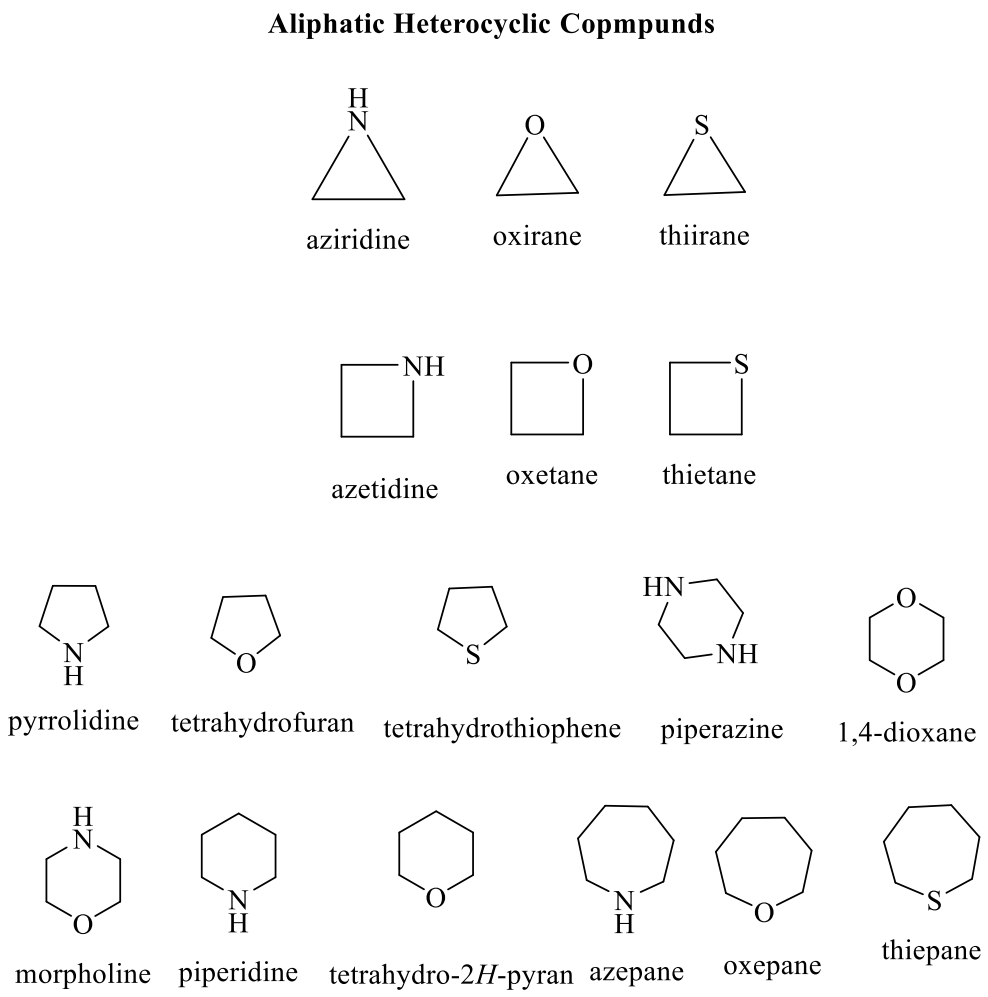


Figure 1.1: Some important aliphatic heterocyclic compounds

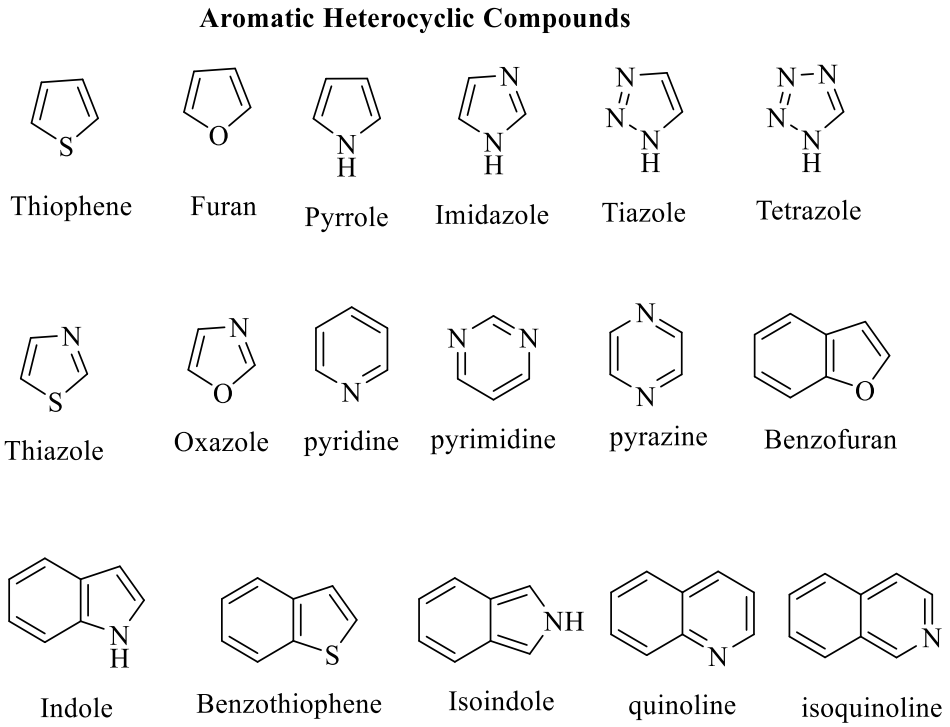


Figure 1.2: Several significant heterocyclic compounds with six members

In organic chemistry, heterocyclic compounds are the most crucial type of molecules due to their composition of chemical molecules containing at least one heterocyclic component. Heterocyclic compounds attract scientific interest due to their significance in human life and their occurrence in nature [6]. This is because they are used as crucial structural components in various herbal products, including vitamins, hormones, antibiotics, and pigments [7-8]. As a result, there is a lot of interest in developing biologically active molecules using these derivatives. Contemporary society relies on synthetic heterocycles for various applications, including pharmaceuticals, insecticides, dyes, polymers, cosmetics, solvents, antioxidants, and vulcanisation accelerators [9-10].

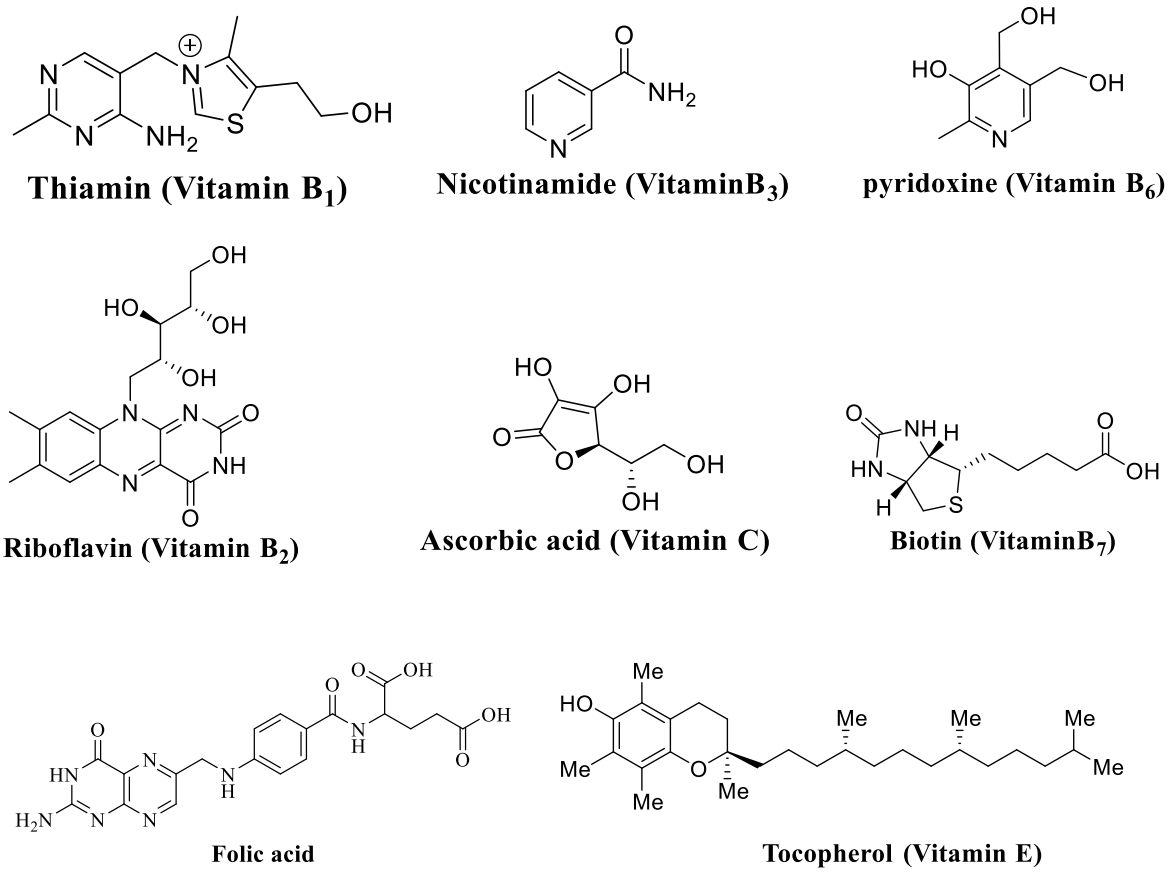


Figure 1.3: - Vitamins which contain heterocyclic compounds.

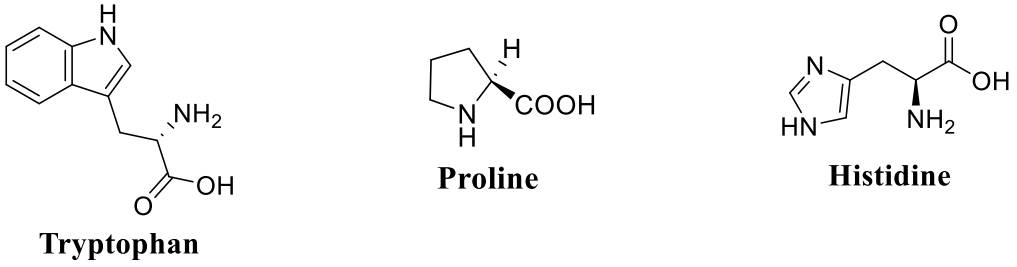


Figure 1.4: - Amino acids which contains heterocycles

Heterocycles are commonly used in industrial chemistry for the manufacture of herbicides, fungicides, pesticides [11-14], colorants, cosmetics, reprography, electronic devices, plastic materials, antioxidants, and vulcanization accelerators [15-16].

Modern and Eco-compatible approach for the synthesis of heterocyclic approach

Green Chemistry is a comparatively new developing field that strives to work at the molecular level to gain sustainability. **Green Chemistry is defined as Pal Anastas. According to Pal, "design of chemical substances and processes to reduce or eliminate the use and generation of hazardous substances**". The goals of green chemistry are broad and encompass a variety of scientific and industrial domains, in addition to safer goods, less harmful effects on the environment and energy conservation. This can ultimately encourage sustainable growth, and other chemical sectors are now adopting green chemistry due to its benefits, such as reduced waste and cost [17-19]. In this regard, we have already seen that pharmaceutical corporations look for green protocols when producing drugs. Green chemistry strategies can be seen in solvents, catalysts, and others. Green chemistry is primarily used to prevent pollution rather than to treat waste. It can be used in every phase of chemical synthesis, from synthesis to production. "Green chemistry" refers to effective chemistry that serves as an inspiration for the moral and ethical behavior of chemists". Being cost effective in disposal and regulatory compliance, the discovery of safe, environment friendly alternatives to conventional chemistry might be very profitable for academic and industrial

interests. Moreover, chemist's and customer's safety will be significantly increased by the minimization of the accidental risk during the synthesis and handling of the organic compounds. Anastas and Warner (1998) outlined the twelve principles of green chemistry, which can help chemists play their part in developing eco-compatible protocols [20–22].

In order to reduce accidents, safer chemicals, less dangerous synthesis methods, and safer solvents and reaction conditions are to be employed. The following criteria can be used to assess the Twelve Principles of Green Chemistry:

1. Prevention.
2. Maximize synthetic methods
3. Atom Economy
4. Chemical syntheses are less dangerous
5. Developing chemicals that are safer solvents and auxiliary substances.
6. Design to be energy efficient.
7. Use renewable raw resources and feedstocks.
8. Minimize the intermediate derivatives.
9. Catalysts and catalytic processes.
10. Design products which decay quickly.
11. Real-time analysis for decreasing pollution.
12. Design for degradation

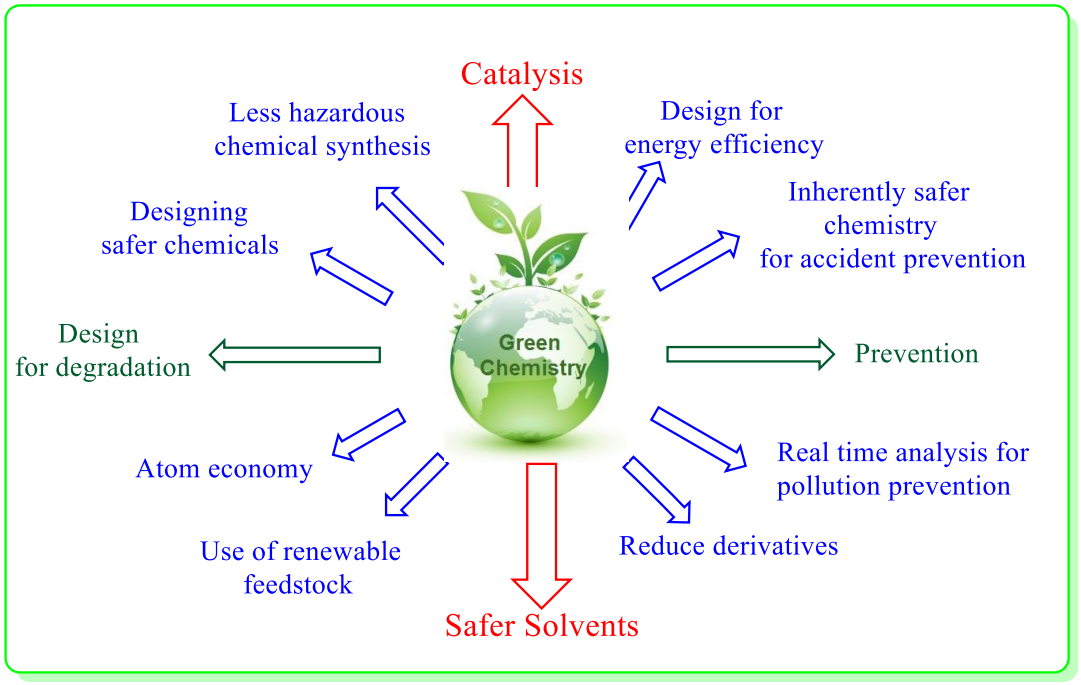


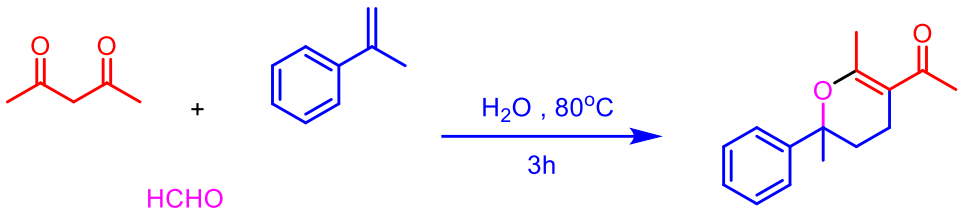
Figure 1.5: Eco-compatible approach for synthesis

Eco-compatible approach for synthesis

- **Organic Synthesis in the Green Solvent:**

Green solvents represent the goal of reducing the harmful environmental impact resulting from using solvents in the chemical process; thus, identifying green solvents is the topmost priority for organic chemists. Some common examples of green solvents are water, ionic liquid, PEG and Sc-CO_2, etc. The ionic liquid is used as a green solvent due to its incredibly cost-effective, non-toxic, and non-flammable. It does not add to greenhouse emissions, and has some additional properties, such as tunable acidity, large heat capacity, the heat of vaporization, which allows convenient control over exothermic reaction, and the coexistence of hydrogen bond donor and acceptor at high polarity functionalization, which pro-

mote catalysis [23]. Water being used as a solvent**, (Scheme1.1)** the biggest advantage is its capacity to create strong hydrogen bonds, which provide high surface tension and may encourage reactant aggregation.



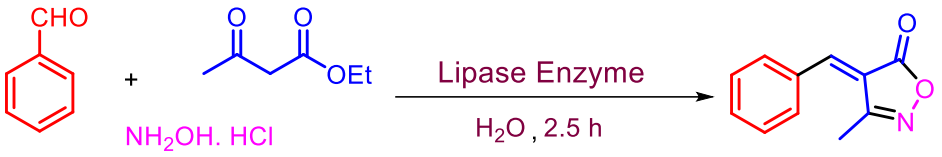
Scheme1.1: Organic synthesis in aqueous phase condition

➢ **Use of Biocatalyst in Organic Synthesis:**

Catalysts: Catalysts are those substances that are introduced into a chemical reaction to alter the rate of the reaction without any change in their properties. **Biocatalyst:** The term "biocatalyst" refers to the catalyst which is obtained from natural resources that alters the rate of the reaction without any change in the thermodynamics of the reaction. They are also called green catalysts.

- Biocatalysts are generally less polluted and can be decomposed easily. They are comparatively faster than conventional catalysts.
- The biocatalytic conversation normally involve in one step.
- Most of the reaction are performed in aqueous medium at ambient temperature and pressure.

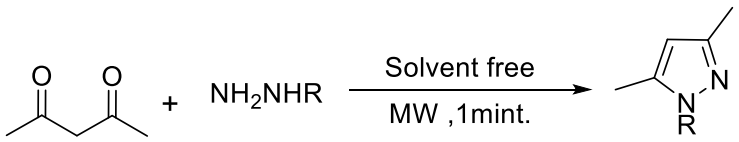
- Examples: Lipase, β-cyclodextrin and invertase enzyme [24] etc. (**Scheme 1.2**)



Scheme1.2: Organic synthesis in the presence of biocatalyst

➢ **Organic synthesis in solvent-free-condition:**

The environment friendly, solvent-free technique creates new possibilities for more efficient organic compound synthesis. The advantages of solvent-free synthesis (**Scheme1.3**) are cost savings, decreased energy consumption, short reaction times and a large reduction in reactor size and capital investment. The chemo-, stereo- or regioselective synthesis of important chemical entities and synthesis to construct small molecules will add to the increase of multi-component solvent-free organic synthetic reactions in the future of organic chemistry.



Scheme1.3: Organic synthesis in solvent-free condition:

➢ **Use of nano catalyst in Organic synthesis:**

Nanocatalysis is a fast-emerging field involving nanomaterials as catalysts in various homogeneous and heterogeneous catalysis applications (**Figure1.6**). One of the oldest indus-

trial applications of nanoscience is heterogeneous catalysis, in which nanoparticles of metals, semiconductors, oxides, and other substances are frequently utilized for critical chemical reactions

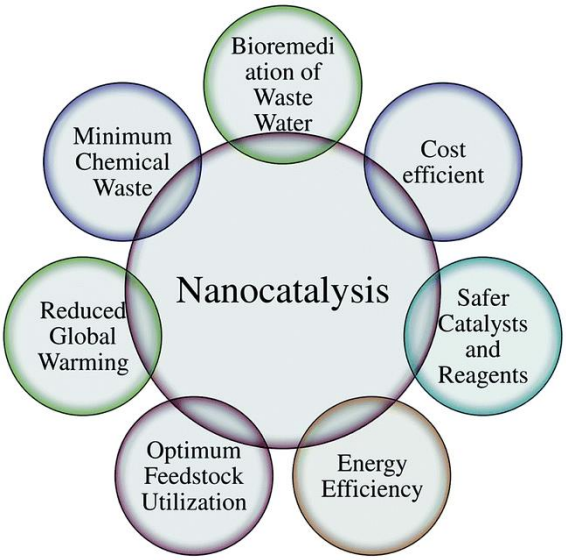


Figure 1.6: Application of Nanocatalysis.

Both homogeneous and heterogeneous catalysts have their own advantages and disadvantages, due to which there is an urgent need to develop a new catalytic system that should be active like homogeneous catalysts and should also be recoverable like a heterogeneous catalyst. In recent years, "Nanocatalysis" has been an essential and rising field in catalysis science, combining the best attributes of both homogeneous as well as heterogeneous catalysts [25]. Due to their small size (1-100 nm), active metal atoms in nanocatalysts are exposed to the surface, thereby increasing the contact between reactants and catalyst dramatically like homogeneous catalysis, whereas their insolubility in the reaction solvents

makes them heterogeneous and hence can be recovered easily from the reaction mixture [26] Furthermore, nanoparticles offer considerable active sites for increasing catalytic activity, selectivity, efficiency, and yield [27]. In particular, it can disperse into the solution and provide a higher surface-to-volume ratio. Higher selectivity of nano catalysts for reaction processes results in less waste formation and fewer contaminants, potentially leading to safer reaction conditions and a lower environmental effect [28]. An additional virtue of nano catalysts is the easy control over size, shape, and morphology, making it possible to design the materials specifically required for a particular catalytic application**.** Chemists can contribute to the development of society by creating a heterocyclic skeleton with biologically essential functions. Researchers in synthetic organic chemistry have shown a strong interest in five- and six-membered fused heterocycles and related molecules. As a result, researchers work very hard to develop novel and efficient synthetic transformations to synthesise these heterocyclic molecules. The present thesis research work is focused on synthesis of coumarin, imidazo[1,2-a] pyridine, polyfunctionalized benzofuran, and diphenyl 1, 3-thiazole.

1.2 Coumarin:

The important heterocyclic compounds with a benzopyrone structure that can be synthesized artificially as well as found in nature are called coumarins. In **1920,** Vogel extracted coumarin from tonka beans, which are also known as coumarou in French [29]. Since this is a unique benzopyrone structural moiety, its derivatives are frequently used in medicinal

chemistry since they may interact weakly, bonding with a wide range of enzymes and receptors in organisms. Coumarins are essential in various natural processes, including plant physiology, growth hormone effects, respiratory regulation, and photosynthesis [30]. Coumarin has been used for a wide range of properties in different fields**.**

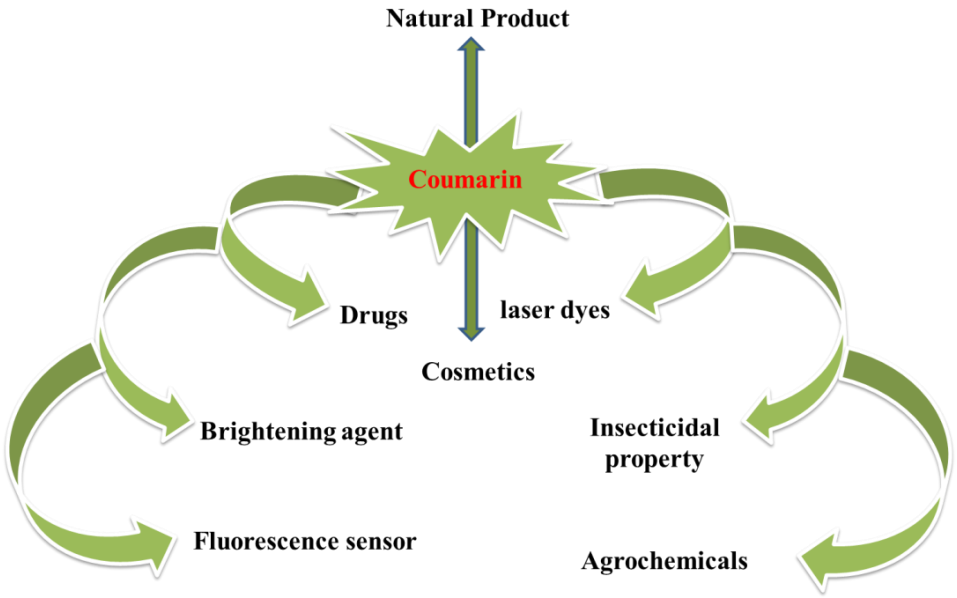


Figure 1.7: Applications of coumarin in many fields.

Numerous fields have investigated coumarin's properties, including fragrance and perfume, food and cosmetic additives, laser dyes, agrochemicals, cosmetic brightening agents, insecticides, fluorescence sensors, and pharmaceuticals [31]**. Figure 1.7** demonstrates various coumarin-containing physiologically active natural compounds **Figure 1.8**. Medicines like Umbelliferone are used as sunscreen, Dicoumarol is an anticoagulant medication, and Seselin plays an important role as a metabolite. Recent years have seen the emergence of a

new class of medications known as supramolecular medicine, including coumarins. Significant function as a metabolite, anti-tuberculosis properties of Calanolide, antibacterial properties of Chlorobiosin, and cytotoxic properties of Lamellarin D against cancer cell lines.

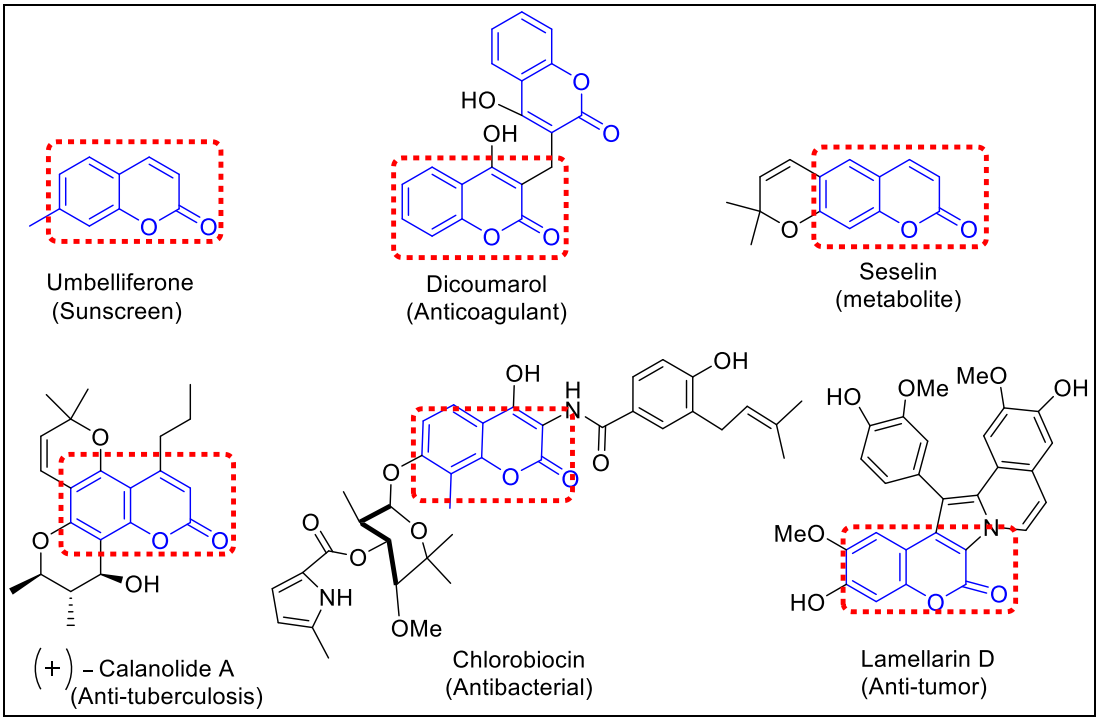
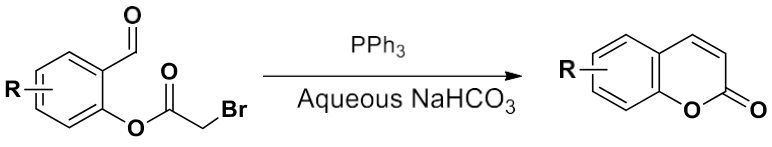


Figure 1.8: Coumarin containing biologically active molecules.

Because of their wide applications in various industries, many natural coumarins are extracted from fungi, bacteria, and plants and synthesised through chemical synthesis [32-34]**.** Organic chemists have always been interested in the synthesis of coumarin. They have devised many techniques for synthesizing this physiologically essential molecule. In literature, lots of methods have been described for the synthesis of coumarins by using different starting materials with different catalysts like Wittig reaction, Perkin reaction, Baylis-Hilmann reaction, Pechmann condensation and Knoevenagel condensation.

1.2.1 Wittig Reaction

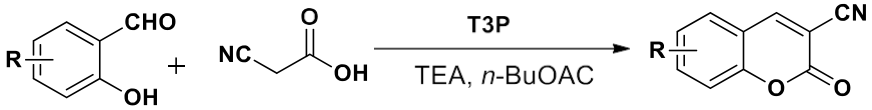
In natural product synthesis, the Wittig reaction is utilized frequently for the formation of C-C bonds. Coumarins have been synthesised using the Wittig reaction under various reaction conditions [35] as shown in scheme (**Scheme1.4**).



Scheme 1.4: Synthesis of coumarin by Wittig reaction

1.2.2 Perkin Reaction

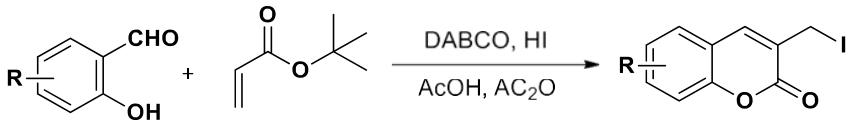
Perkin reaction is another method to synthesize coumarins. Augustine and co- workers described the synthesis of coumarins from salicylaldehyde and cyano acetic acid mediated by propylphosphonic anhydride (T3P) by Perkin reaction [36] in **(Scheme1.5).**



Scheme 1.5: Synthesis of coumarin by Perkin reaction**.**

1.2.3 Baylis-Hilmann Reaction

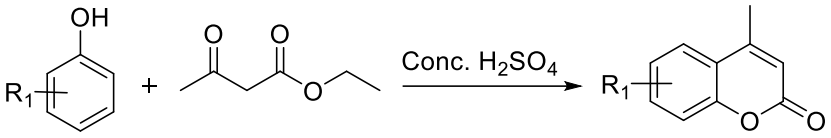
In Baylis-Hilmann methodology, coumarins are synthesized by reaction of salicylaldehyde with t-butyl acrylate in the presence of DABCO, HI and acetic acid [37] and is shown in (**scheme 1.6**).



Scheme 1.6: Synthesis of coumarin by Baylis-Hilmann reaction

1.2.4 Pechmann condensation

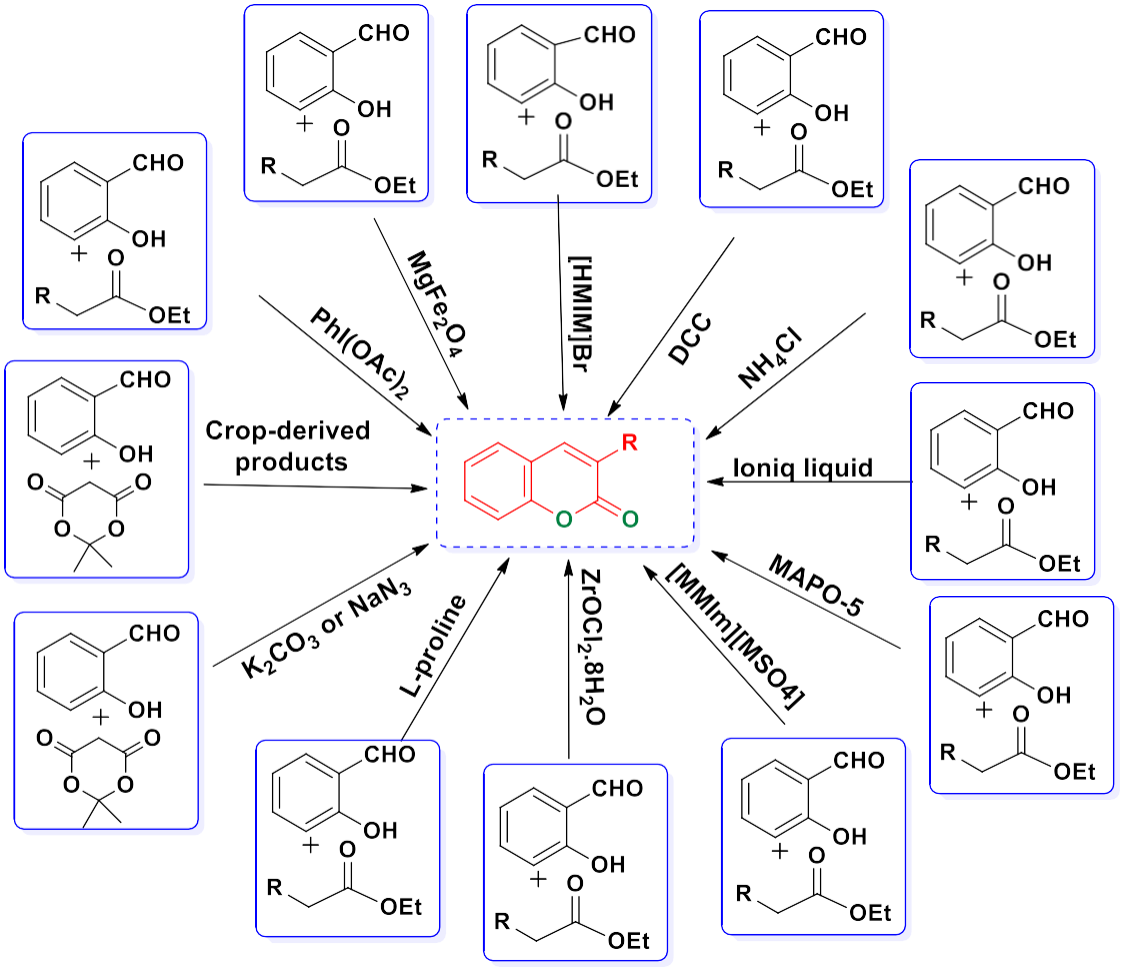
Pechmann condensation is an important method for the formation of coumarin by using different starting material such as salicylaldehyde, with active methylene compounds in the presence of different catalyst [38] (**Scheme1.7**).



Scheme 1.7: Synthesis of coumarin by Pechmann condensation

1.2.5 Knoevenagel Condensation

Coumarin was synthesised using this process by reacting o-hydroxy aldehydes, such as salicylaldehyde, with active methylene compounds combined with an alternative catalyst, like DCC [39], ammonium chloride[40], ionic liquid [41], Lewis acid metal ion-exchanged MAPO-5 molecular sieves [42],[MMIm][MSO_4] containing proline [43], $ZrOCl_2.8H_2O$[44], L-proline [45], K_2CO_3 or NaN3[46], crop-derived products [47], PhI(OAc) [48], $MgFe_2O_4$ Nano catalyst [49], [HMIM]Br, piperidine and AcOH [50] (**Scheme 1.8)**



Scheme 1.8: Synthesis of coumarin by Knoevenagel condensation.

1.3 Imidazo[1,2-*a*] pyridine

Chichibabin described the imidazo[1,2-a] pyridine ring system in 1925. One significant class of heterocyclic compounds with nitrogen ring junctions include imidazo[1,2-a] pyridines, in which the pyridine ring and imidazole moiety are joined. Chichibabin described the imidazo[1,2-a] pyridine ring system in 1925. An important type of nitrogen ring junction heterocyclic compounds is imidazo[1,2-a] pyridines, in which the pyridine ring and

imidazole moiety are joined. Due to its many uses in pharmaceutical chemistry; it is frequently referred to as a "drug prejudice" framework. Furthermore, the unique structural characteristics of this scaffold make it useful in material science. Its compounds various biological behaviors, including antibacterial, anticancer, antifungal, antiviral, antipyretic, and analgesic properties [51] **(Figure 1.9)**.

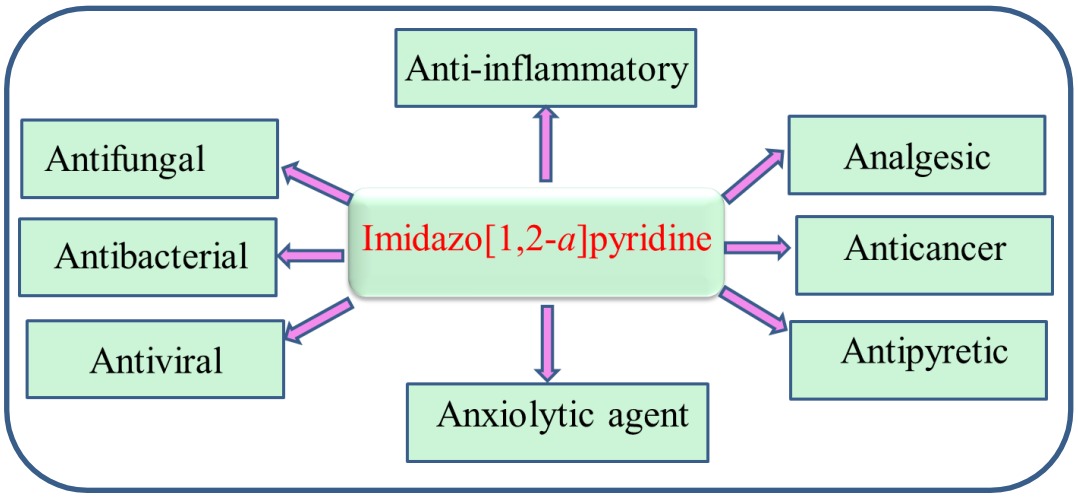


Figure 1.9: Pharmacological activity of imidazo[1,2-a] pyridines.

Many medications include the imidazo[1,2-a] pyridine (**A**) moiety, which is used to treat many kinds of disorders **(Figure 1.10)**. Zolpidem was the first medicine introduced into the market as a hypnotic. The first drug was zolpidem, introduced into the market as a hypnotic. anxiolytic2-agent, Miroprofen as an analgesic, GSK812397 as HIV infection and P13 K alpha inhibitor as an anti-cancer agent.

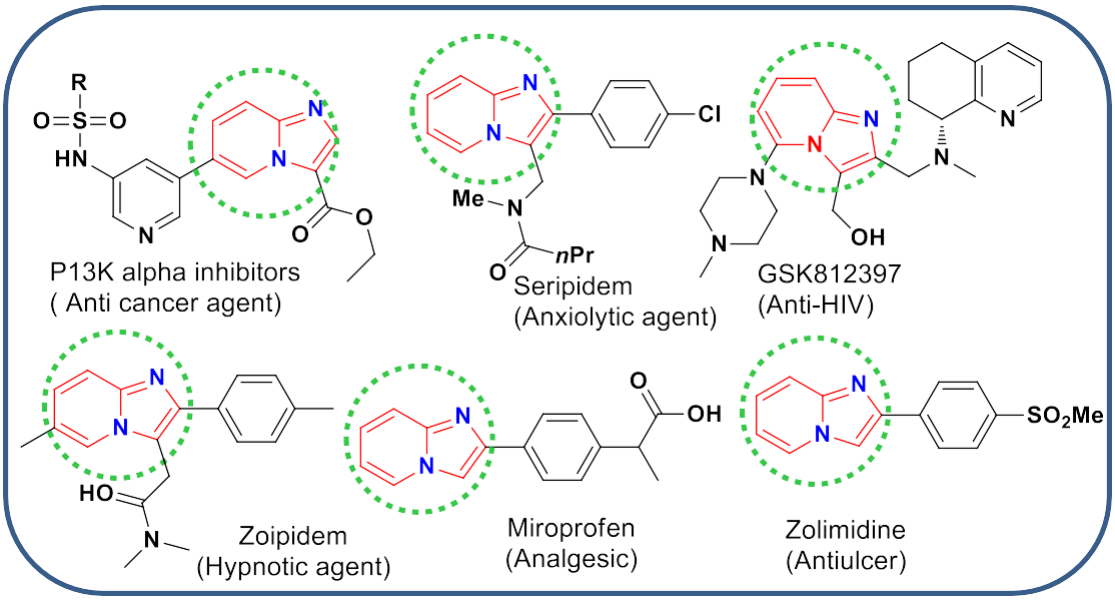


Figure 1.10: Drug-containing pyridine scaffold, imidazo[1,2-a].

For the purpose of visualizing receptors, imidazo[1,2-a] pyridine scaffolds **(B)** containing fluorescent dopamine D3 receptor ligands are helpful probes [52]. In the field of electronic devices, imidazo[1,2-a] pyridine **(C)** metal complexes are used as well. Moreover, it has been established that 2-carbonyl-3-(pyridylamino) imidazo[1,2-a] pyridine **(D)** is an excellent mercury ion probe [53] Because of its broad application in several disciplines of chemistry (**Figure1.11)**, it is better to produce this moiety synthetically using readily accessible substances.

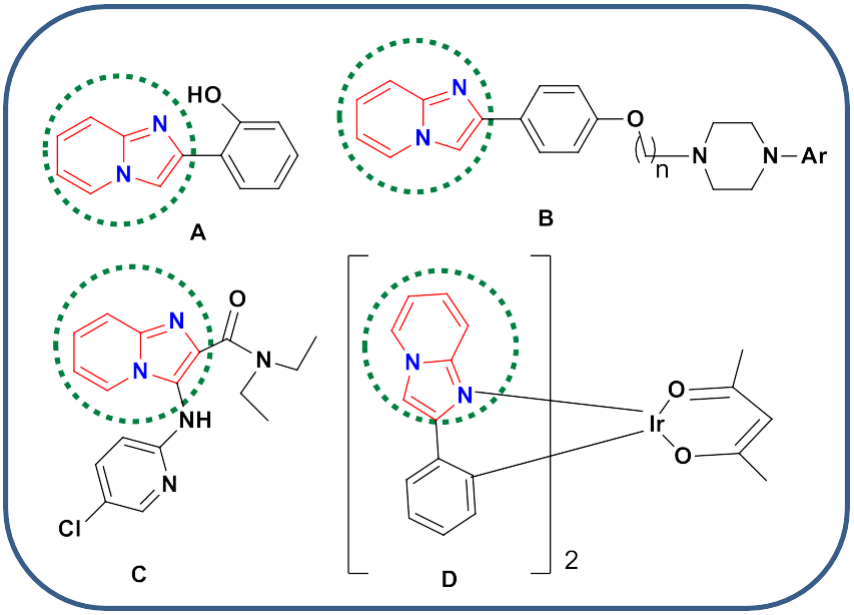
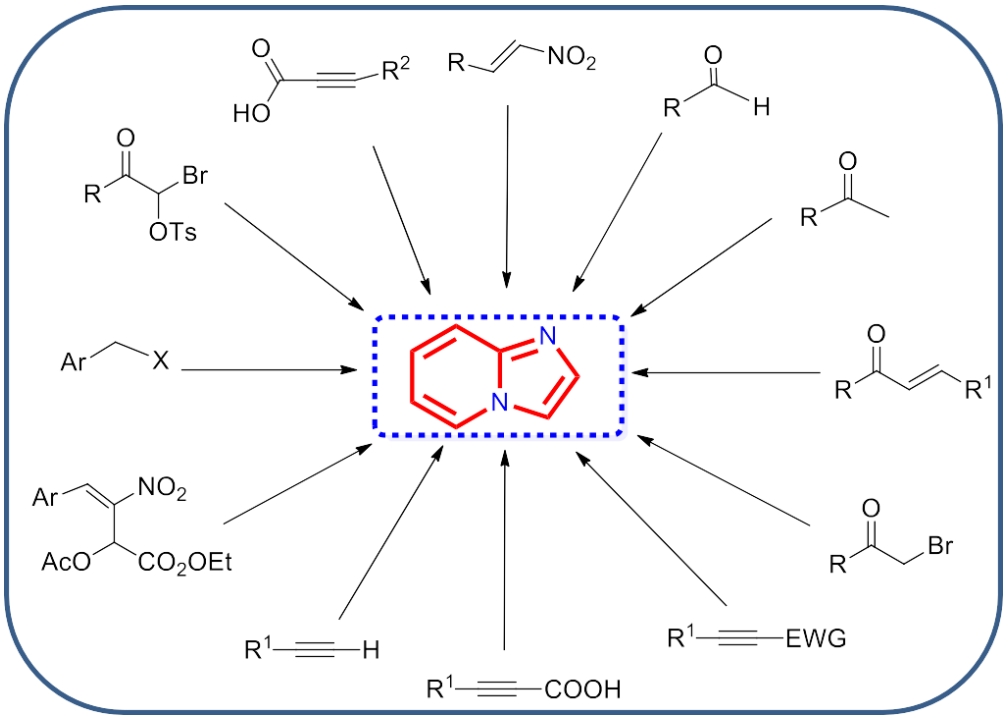


Figure 1.11: Imidazo[1,2-a] pyridine is used in materials science.

Numerous techniques for the synthesis of imidazo[1,2-a] pyridines have been developed in an effort to enhance existing synthetic approaches. Many methods have been published in the literature for the synthesis of imidazo[1,2-a] pyridines, which can be divided into multi-component, oxidative coupling, amino oxygenation, tandem reaction, hydroamination and the condensation reaction **(Scheme 1.9)**.

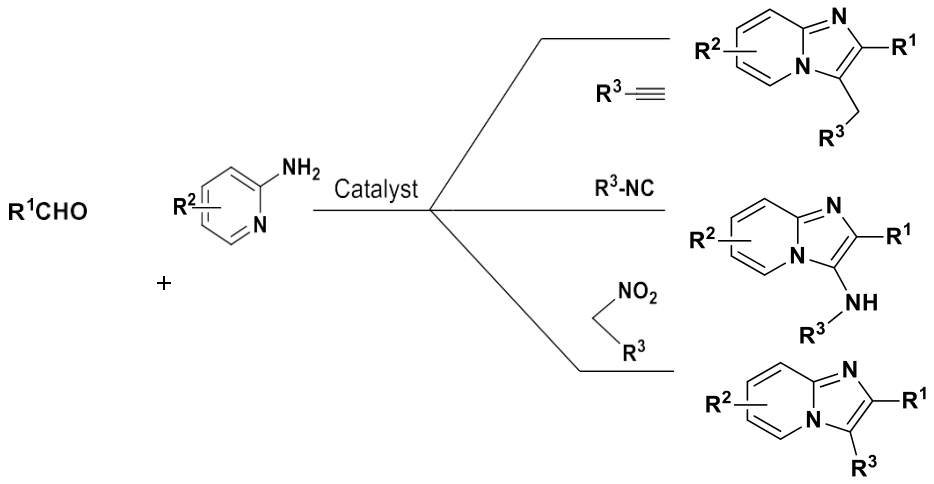


Scheme: 1.9 Different approaches for the synthesis of imidazo[1,2-a] pyridines utilizing different types of starting materials.

1.3.1Multicomponent Approach

Using a multi-component strategy, imidazo [1,2-a] pyridine have been synthesised through the reaction of 2-aminopyridine, aldehyde, and cyanide or isocyanide in the presence of different catalysts. Scandium triflate [54], copper-catalyzed [55], K_2CO_3 [56], bromodimethyl sulfonium bromide (BDMS) [57]. The imidazo[1,2-a] pyridines were also obtained by the reaction of 2-aminopyridine, aldehyde, and terminal alkyne catalysed by $Cu(OTf)_3$ [58],

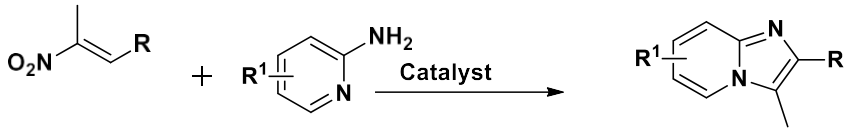
CuSO4 [59], nano-Fe_3O4-$KHSO_4$·SiO2 [60], and from the reaction of 2-aminopyridine, aldehyde, and nitromethane [61]**.** (**Scheme 1.10**).



Scheme 1.10: Imidazo[1,2-a] pyridines synthesised using a multicomponent approach

1.3.2 Tandem Reaction

Tandem reactions of 2-aminopyridine with nitroalkenes in the presence of a different catalyst, such as iron (II) [62] or iron (III) [63], were used to synthesize imidazo[1,2-a] pyridines (**Scheme 1.11)**



Scheme 1.11: Tandem process to synthesize imidazo[1,2-a] pyridines

1.4 Polyfunctionalized Benzofuran:

An efficient and facile protocol for the synthesis of a multifunctional 6,7-dihydro benzofuran-4(5H)-ones and their derivatives using iron salt in the presence of air via reactions of

readily available dimedone, acetophenone and isocyanide as starting materials. 6,7-dihydro benzofuran-4(5H)-ones and their derivatives using in Dye industries, silver photography, Agrochemical, Polymer industry and cosmetic industry shown in **Figure1.12.**

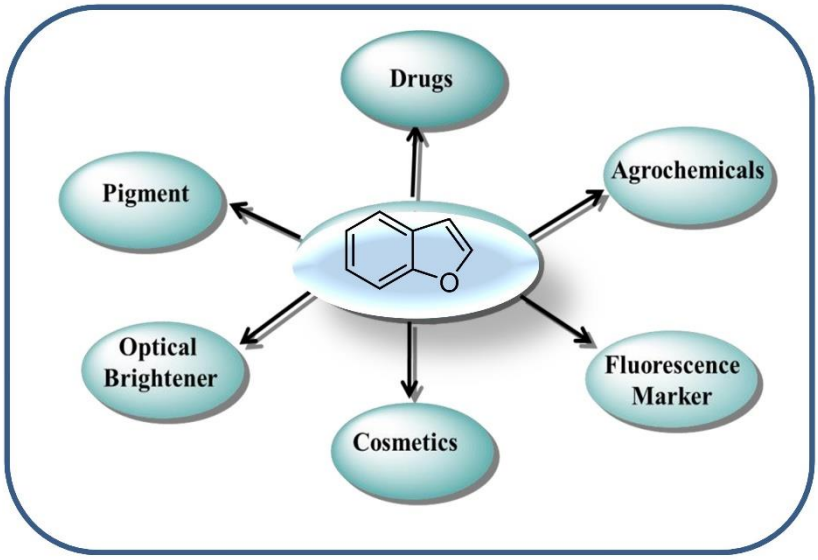


Figure1.12: Applications of benzofuran in different fields.

Benzofuran-4(5H)-ones and their derivatives are use as core unit cosmetic industry benzofuran-4(5H)-ones and their derivatives used as core unit of some bioactive molecule due to their good biocompatibility. Mainly, benzofuran functionality in 6,7-dihydrobenzofuran-4(5H)-ones played imperative utility in the treatment of various neurodegenerative diseases such as Alzheimer's disease.

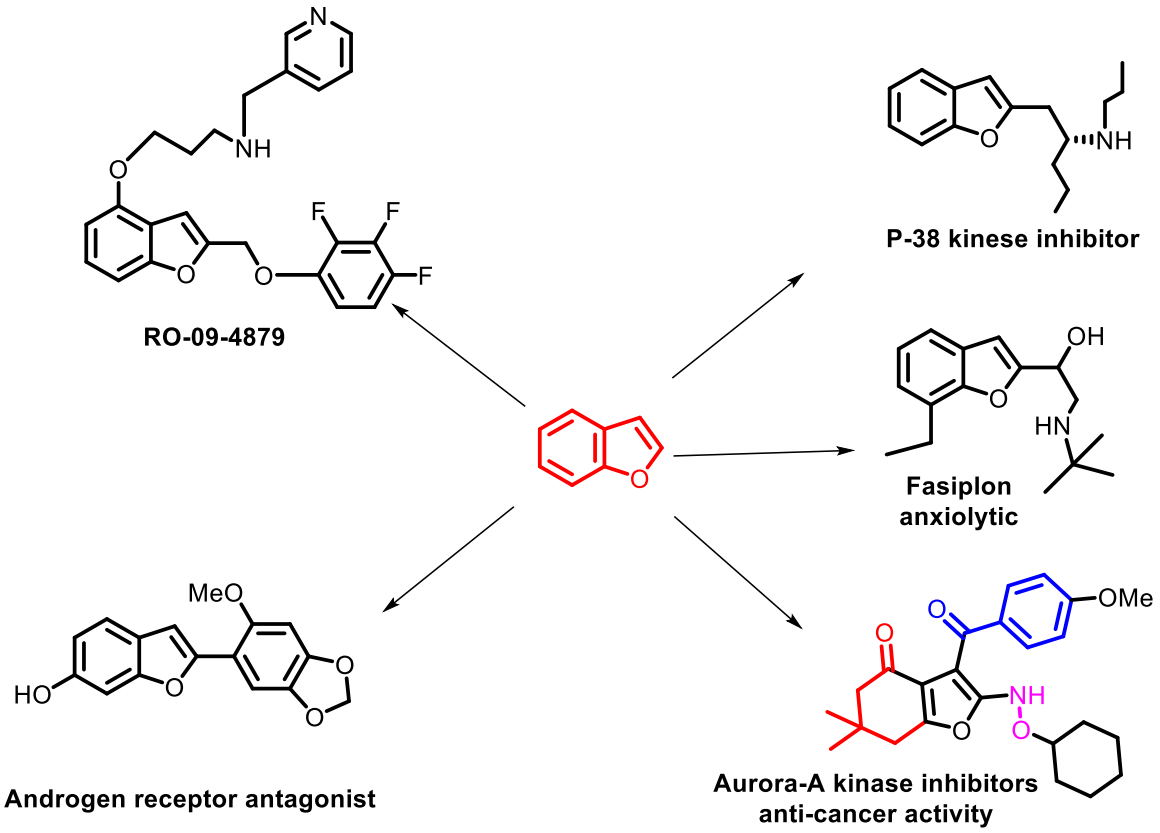
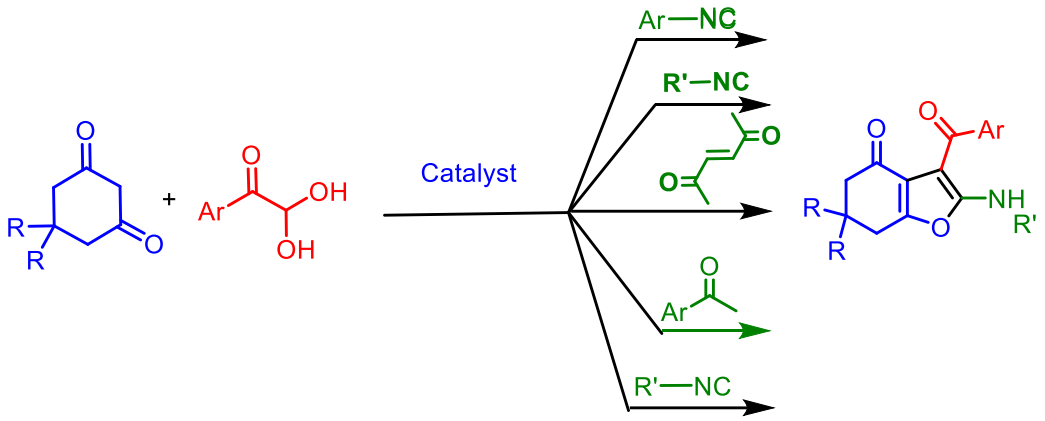


Figure 1.13: Drugs containing benzofuran-4(5H)-one's moiety

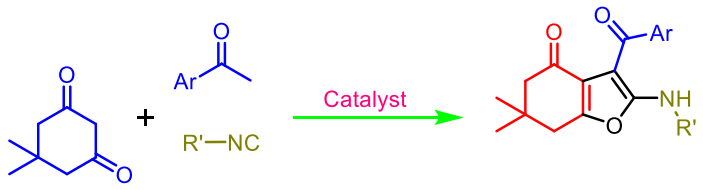
The synthesis of derivatives of 6,7-dihydrobenzofuran-4(5H)-one has been described using numerous methods, giving the significance of these molecules. The most practical and favoured technique for creating these heterocyclic compounds is the multicomponent reaction (MCR), which is one of numerous ways for synthesizing 6,7-dihydrobenzofuran-4(5H)-ones. Many methodologies for synthesizing these compounds have been developed;[64] most of them involved arene diazonium salts,[65] arylhydrazones,[66] aryl hydrazine [67] and nitriles [68] as well as aryl phenylglycine hydrazones as the starting materials (**Scheme1.12**).



Scheme 1.12: Synthesis of 6,7-dihydrobenzofuran-4(5H)-one by multicomponent approach

1.4.1Knoevenagel reaction

6,7-dihydrobenzofuran-4(5H)-one was produced by the Knoevenagel reaction between acetophenone and dimedone, isonitrile, and several catalysts, including SDS (II) [69], Ir (III) [70] (**Scheme 1.13**).



Scheme 1.13: Synthesis of 6,7-dihydrobenzofuran-4(5H)-ones by Knoevenagel reaction

1.5 Thiazole:

The five-membered heterocycle moiety thiazole has a heterocycle ring with Sulphur and nitrogen. The thiazole heterocycle moiety is highly significant for numerous biological activities, and it is present in many medicines and natural compounds. [71].

In this work, multi-component reactions (MCRs) have emerged as a powerful method in synthetic chemistry for the synthesis of novel organic molecules. [76-77]. This work one-pot reaction proceeds as MCRs, which feature three easily accessible starting materials to build eco-friendly and cost-effective procedures. [78-80]. Many medications have thiazole core in their structure and are utilized in our daily lives, such as fentiazac (a) is a non-steroidal anti-inflammatory agent [81] created for the treatment of joint and muscular pain, febuxostat (b) is used for urate-lowering treatment [82]. Similarly, Sodelglitazar (GW677954) (**c**), also known as an inhibitor of peroxisome proliferator-activated receptor delta (PPARδ) [83].

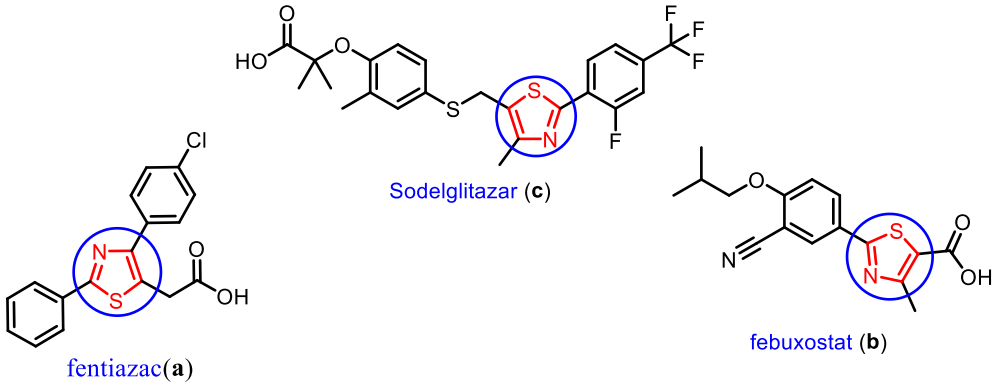
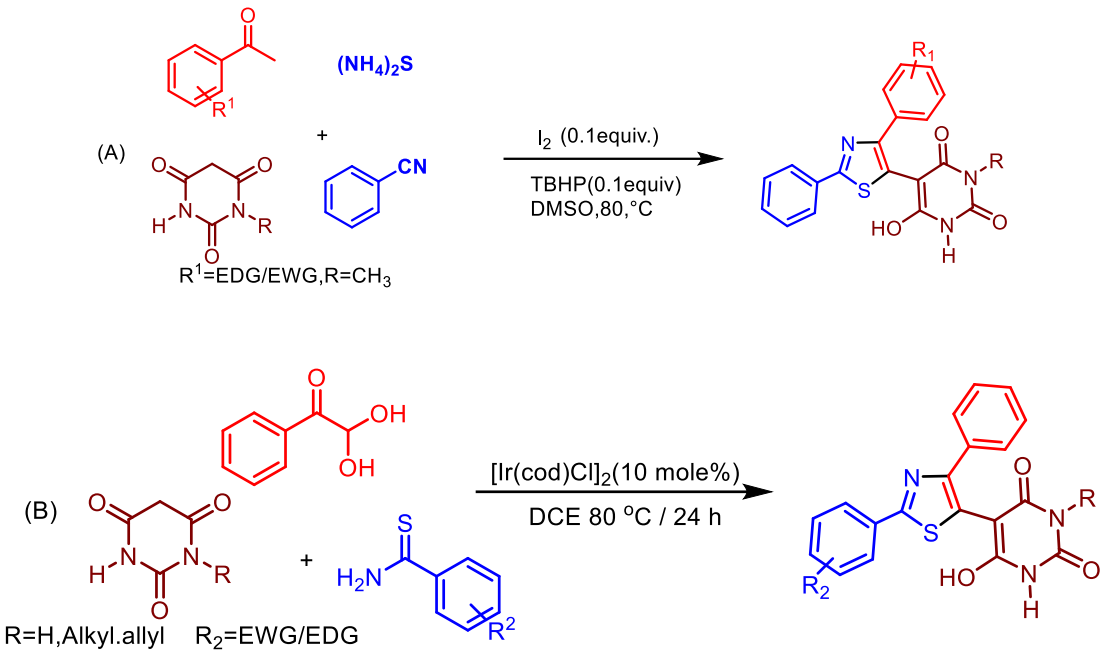


Figure 1.14: Drugs containing 1, 3-thiazole moiety as a core unit.

1.5.1Multiple Approach

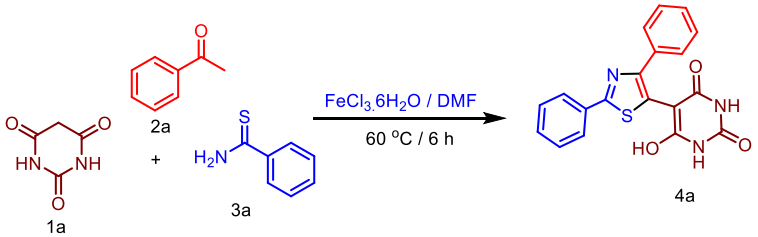
Many methodologies for synthesizing these compounds have been developed in different metal catalyst such as I_2 TBHP,[84], $[Ir(cod)Cl]_2$ [84] aryl hydra-zines [85] and nitriles [86] as well as aryl phenylglycine hydrazones the starting materials (**Scheme 1.14**).



Scheme 1.14: Synthesis of trisubstituted thiazole using different approaches

1.5.2 Michael addition

Synthesis of substituted diphenyl 1, 3-thiazole were synthesized by Michael addition reaction of barbituric acid **(1)**, acetophenone **(2)** and aryl thioamides **(3)** as the model substrates for the synthesis of trisubstituted thiazole using iron salt as a catalyst in the presence of air and DMF as reaction medium **(Scheme 1.15).**



Scheme 1.15: Synthesis of trisubstituted thiazole by Michael addition reaction

1.6 Objectives of Thesis Work

This brief introduction indicates the broad range of applications for heterocyclic compounds and many uses in fields including agriculture, material sciences, organic synthesis, biochemistry, and medicinal chemistry, among others. Consequently, we want to develop a more efficient and sustainable method for synthesizing certain substances with biological activity, which are heterocyclic molecules that can be produced using both conventional and unconventional approaches, including grinding, sun radiation, and ultrasonography. It might be beneficial to the development of green and clean chemistry.

The current thesis study is primarily focused on

1. To design a more environmentally friendly and sustainable method for the synthesis of derivatives of 3-functionalized coumarins, using beta-cyclodextrin as a catalyst.

2. To explore a Synthesis of Imidazole-fused nitrogen-bridgehead heterocycles catalysed by lipase and their antifungal and anti-microbial bioactivity.

3. To develop a Green and Efficient Iron-Catalysed Synthesis of Polyfunctionalized Benzofuran-4(5H)-one Derivatives via Cross-Dehydrogenative Coupling catalyst.

4. To demonstrate Efficient one-pot synthesis of substituted diphenyl 1, 3-thiazole through multicomponent reaction by using green and efficient Iron-catalyst via cross dehydrogenative coupling (CDC).

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