CHAPTER 1

Introduction

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The term "Green Chemistry" was first introduced by the US EPA (United States Environmental Protection Agency) in 1990 to describe chemical processes that avoid creating or releasing toxic or harmful substances [1, 2]. As outlined by Paul T. Anastas and John C. Warner (1998), "Green chemistry" encompasses a set of principles (**Figure 1.1**) focused on minimizing or eliminating the use of hazardous chemicals in reaction design, reducing waste, maximizing atom efficiency, using cleaner solvents, minimizing by-product formation, and improving energy efficiency techniques [3].

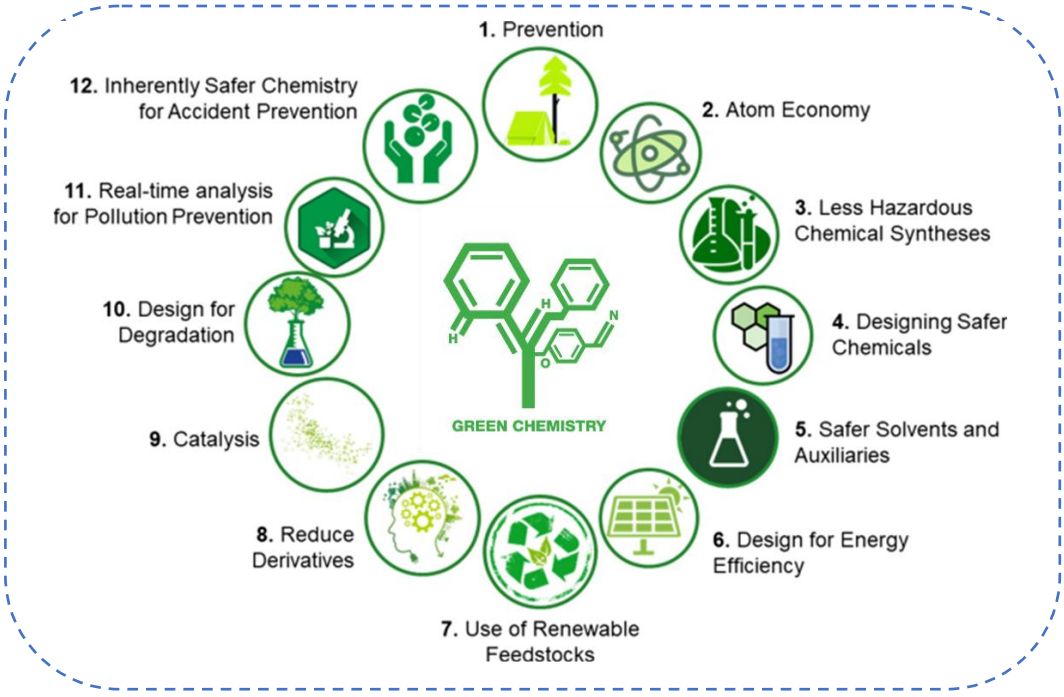


Figure 1.1 Principles Green Chemistry.

Consequently, it became imperative to devise synthetic methodologies aligned with these twelve green chemistry principles to produce valuable organic compounds with minimal environmental impact [4–6]. The two most critical "green chemistry' principles for

synthetic chemists are using green solvents or solvent-free reactions and designing for energy efficiency [7]. Our synthetic methodology considers the use of microwave and solvent-free green reaction conditions. We have also conducted a comparison of synthetic processes for related or identical reactions. This involves utilizing different inorganic and organic catalysts, as well as different non-polar and polar solvents, and without solvent, among other variables [8–10].

Our goal is to promote the use of safer solvents and auxiliaries, which means utilizing green solvents or adopting solvent-free organic synthesis methods. Green solvents offer significant advantages over traditional solvents in terms of environmental sustainability and health [11]. They are often derived from renewable resources or have low toxicity, minimizing their impact on ecosystems and human health. Green solvents also reduce or eliminate the use of volatile organic compounds (VOCs), which are known contributors to air pollution and health hazards [12, 13]. Additionally, many green solvents are biodegradable or have low toxicity, reducing the risk of environmental contamination and facilitating easier waste disposal [8, 14].

On the other hand, solvent-free technology has many advantages from the viewpoint of both academia and industry [15]. Solvent-free techniques often lead to higher reaction yields and selectivity, thereby increasing efficiency and reducing resource consumption [16]. Additionally, they reduce waste generation by eliminating the necessity for solvent disposal or purification procedures, leading to cost savings and a reduced environmental footprint. These approaches enhance workplace safety by reducing exposure

to potentially hazardous solvents, promoting a healthier working environment for researchers and operators [17–19]. Overall, the adoption of green solvents or solvent-free organic synthesis represents a crucial step towards achieving more sustainable and environmentally friendly chemical processes [15, 20]. Designing for energy efficiency can involve green synthetic approaches to reduce energy consumption, and enhance reaction selectivity and yield of products [21], also involves an easy setup, environmental friendliness, cost-effectiveness, and utilization of more environmentally friendly energy resources. As a result, there has been a need to replace thermal methods in synthesizing organic compounds with alternative non-conventional techniques, such as microwave, ultrasonic radiations, and visible light-mediated reactions, combined with traditional resources [22, 23].

1.1 Microwave-assisted reactions

Microwave irradiation has become a prized and widely embraced energy source for initiating reactions in organic chemistry. Its ability to heat efficiently often results in quicker reaction rates and significant reductions in reaction time [24, 25]. Recent studies in organic synthesis employing microwave irradiation have revealed that these improvements mainly derive from the dielectric heating properties inherent in microwaves. Microwave-assisted synthesis operates by aligning the dipoles of the material in an external field through the excitation generated by microwave electromagnetic radiation [26, 27]. Microwave heating is widely used as a convenient source of heating in organic synthesis.

The benefits of microwave-assisted organic synthesis are that microwaves can accelerate the rate of reaction, provide better yields and higher purity, uniform, and selective heating with lower energy usage, achieve greater reproducibility of reactions and help in developing convenient and cleaner synthetic routes [28–30]. It offers eco-friendly green protocol in synthesis additionally, some investigations suggest that the non-thermal effects of microwaves could potentially modify reaction dynamics and decrease the activation energy of organic reactions [31, 32]. Overall, adopting green solvents or solvent-free organic synthesis and designing for energy efficiency represents a crucial step towards achieving more sustainable and environmentally friendly chemical processes [33].

1.2 Multicomponent Reactions

Multicomponent reactions offer a powerful approach to synthesis that can contribute to the development of more sustainable and environmentally friendly chemical processes, aligning with the principles of green chemistry [34, 35]. A multicomponent reaction (MCR) involves the simultaneous combination of three or more reactants within a single reaction vessel, resulting in the formation of a novel product incorporating elements from all the initial reactants [36] (**Figure 1.2**). Multicomponent reactions (MCRs) demonstrate high remarkably, attributed not only to inherent characteristics like superior atom economy, selectivity, and minimized by-product formation as well as external factors such as streamlined procedures, simpler equipment requirements, cost-effectiveness, time and energy savings, and alignment to environmentally friendly standards [37–39].

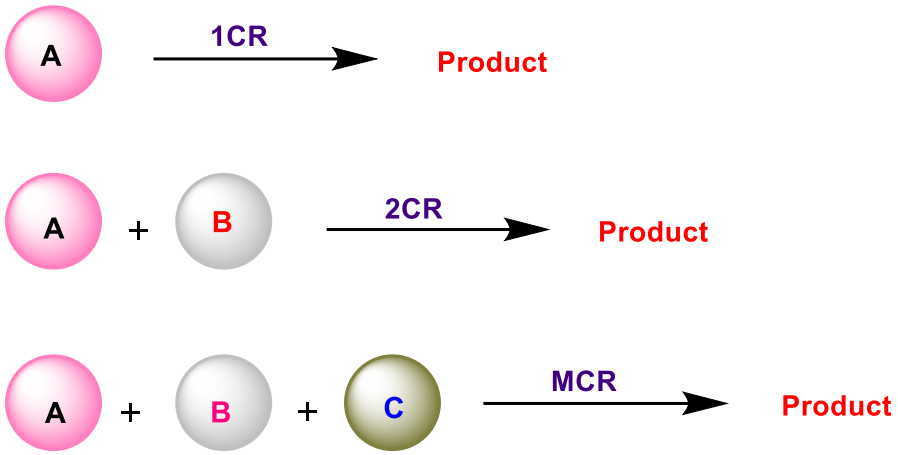
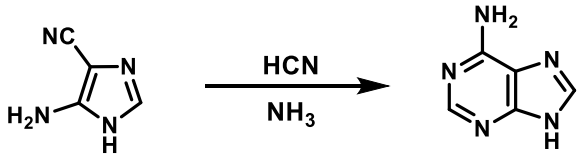


Figure 1.2 A divergent one-component reaction and convergent two- and multi-component reactions.

In contrast to the step-by-step and gradually forming individual bonds in a target molecule, MCRs stand out for their unique ability to generate multiple bonds simultaneously in a single step without the need to isolate intermediates, modify reaction conditions, or introduce extra reagents. This method efficiently reduces waste production and minimizes labor requirements [40]. Therefore, multicomponent reactions fulfill the need for efficient and swift synthesis of compounds in a manner that is both cost-effective and time-efficient. The ability of these reactions to concurrently form C-C, C-N, and various other carbon-heteroatom bonds, while incorporating functionalities containing heteroatoms, is particularly remarkable for the rapid assembly of organic molecules [41–43]. In nature, this mechanism is utilized to produce crucial biomolecules, such as adenine, which serves as a fundamental building block of DNA and RNA. The prebiotic synthesis of adenine entailed the condensation of five hydrogen cyanide (HCN) molecules, which were abundant in the early Earth's atmosphere, in a multicomponent reaction catalyzed by ammonia (NH_3) [44].

Likewise, other nucleic bases have been generated through multicomponent reactions involving HCN and water (H_2O) (**Scheme 1.1**)



Scheme 1.1 Multicomponent synthesis of purine.

1.3 Overview of Nitrogen-Containing Organic Compounds

Nitrogen is a naturally existing element that serves as a vital structural component in all living organisms. It is present in amino acids, nucleic acids, vitamins, and hormones. These compounds exhibit significant structural variations, ranging from basic functional groups to diverse degrees of substitution and heterocyclic systems [45, 46]. Nitrogen-containing compounds form the foundation or stand independently in numerous biologically, pharmaceutically, and synthetically active substances. *N*-heterocyclic organic compounds hold immense industrial, biological, and societal significance, contributing to various advancements in human society [47–49].

This chapter has covered some main classes of nitrogen-containing functional groups. Acyclic nitrogen-containing compounds (1.4) like amine (1.4.1), imine (1.4.2), oxime(1.4.3), amide (1.4.4) and nitrogen-containing five-membered heterocyclic (1.5) pyrrole (1.5.1), six-membered (1.6) pyridine (1.6.1), pyrimidine (1.6.2) and fused heterocycles (1.7) such as indoles (1.7.1), and benzimidazoles (1.7.2) (**Figure 1.3**).

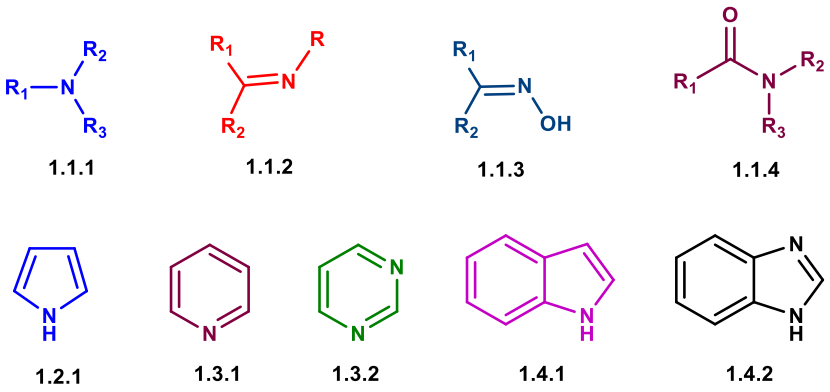


Figure 1.3 Nitrogen containing some main class of organic compounds.

1.4 Nitrogen-containing acyclic compounds

1.4.1 Amines

Amines are an important class of organic compounds containing nitrogen atoms bonded to carbon atoms and are recognized as the most crucial and extensively studied organic compounds, originating from ammonia through the substitution of one, two, or all three protons with various carbon derivatives [50]. Their significance is emphasized by their presence in amino acids, in protein synthesis, and their vital role in supporting living organisms. Amines also serve as fundamental building blocks in industries including dyes, pharmaceuticals, surfactants, agrochemicals, and plastics in the rubber, textile, and paper sectors, etc. They can act as both bases and nucleophiles due to the lone pair of electrons on the nitrogen atom [51–53].

Amines find application in the synthesis of various medications. For instance, Labetalol is employed in the management of hypertension, including during pregnancy. Exelon serves as a treatment for Alzheimer's disease, while chlorphenamine functions as an antiallergic agent. Amphetamines are utilized in the treatment of narcolepsy, obesity, and attention deficit hyperactivity disorder (ADHD). Clobenzorex may be employed to prevent weight gain, and Sensipar can help prevent the overactive functioning of the parathyroid glands [54, 55] (**Figure 1.4**).

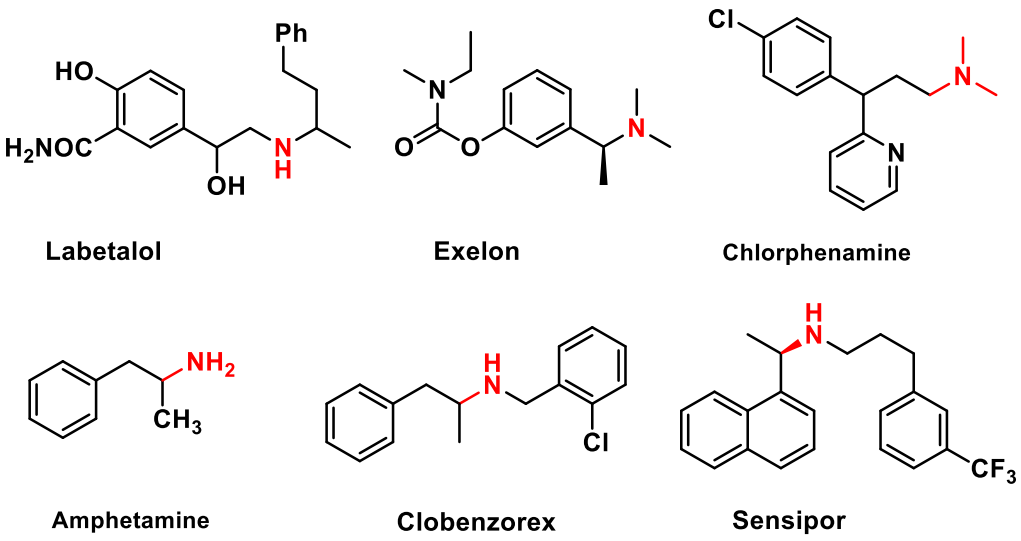
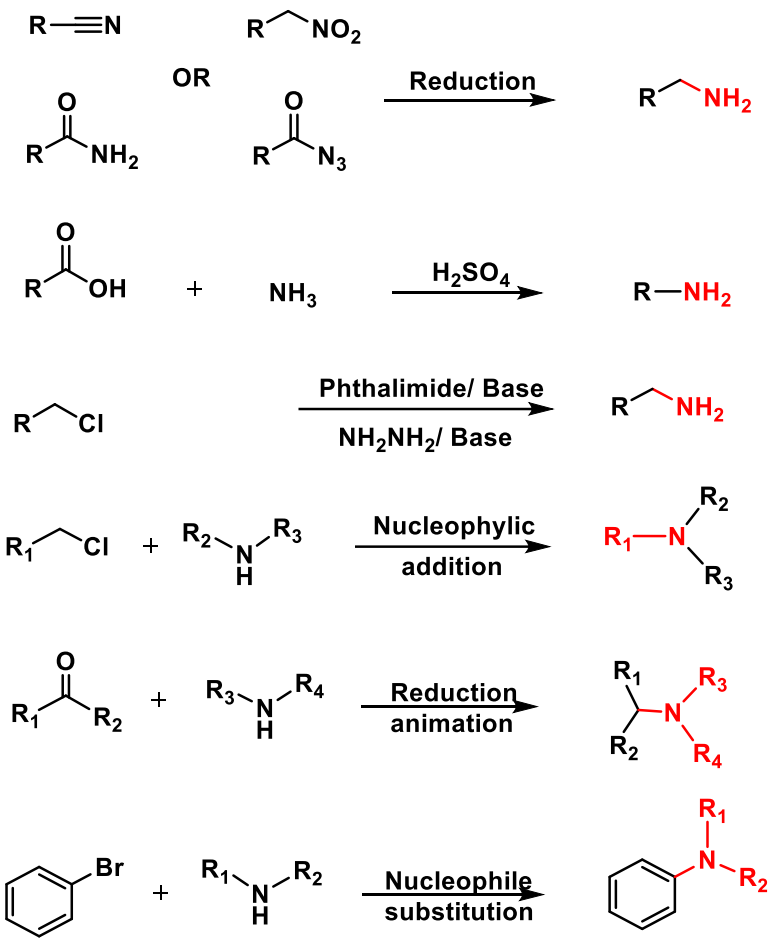


Figure 1.4 Some biologically active compounds containing amine group.

The predominant method for synthesizing primary amines involves reducing amides [56], aliphatic and aromatic nitro compounds [57–59], cyanides [60]**,** azides [61, 62], and different oximes. Certain named reactions are reported for the synthesis of primary amines, including the Gabriel synthesis method and Hofmann rearrangement [63, 64].



Scheme 1.2 Synthesis of amines.

Secondary and tertiary amines can be synthesized through direct nucleophilic substitution and addition reactions involving primary and secondary amines reacting with alkyl halides to yield secondary and tertiary amines, respectively. Additionally, they can be prepared via the reductive amination of aldehydes or ketones using primary and secondary amines [65, 66] (**Scheme 1.2**).

1.4.2 Imines

Imines, are also known as azomethines or Schiff bases, constitute a functional group featuring a carbon–nitrogen double bond with the general formula $R_2C=NR$. These compounds can exist in various forms, including primary, secondary, and tertiary imines, depending on the nature of the substituent groups attached to the nitrogen Imines, their derivatives have diverse applications in organic synthesis, medicinal chemistry, and materials science [67, 68].

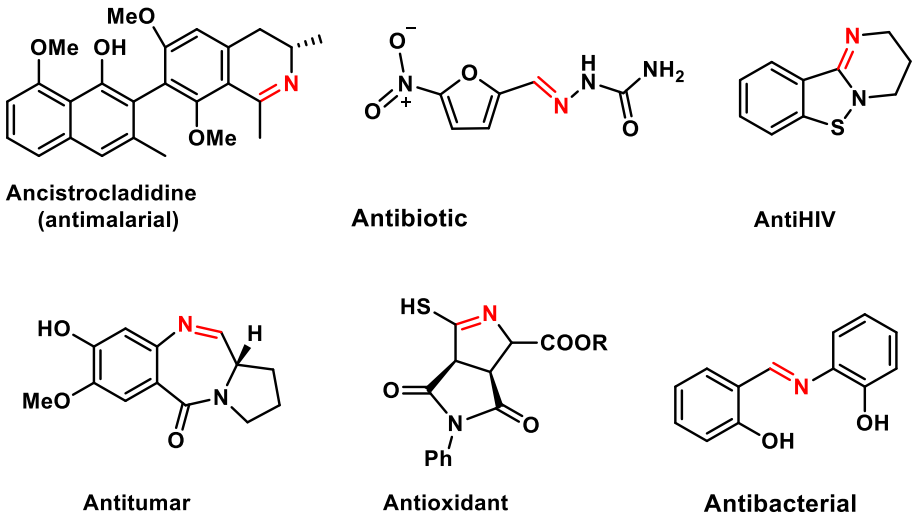
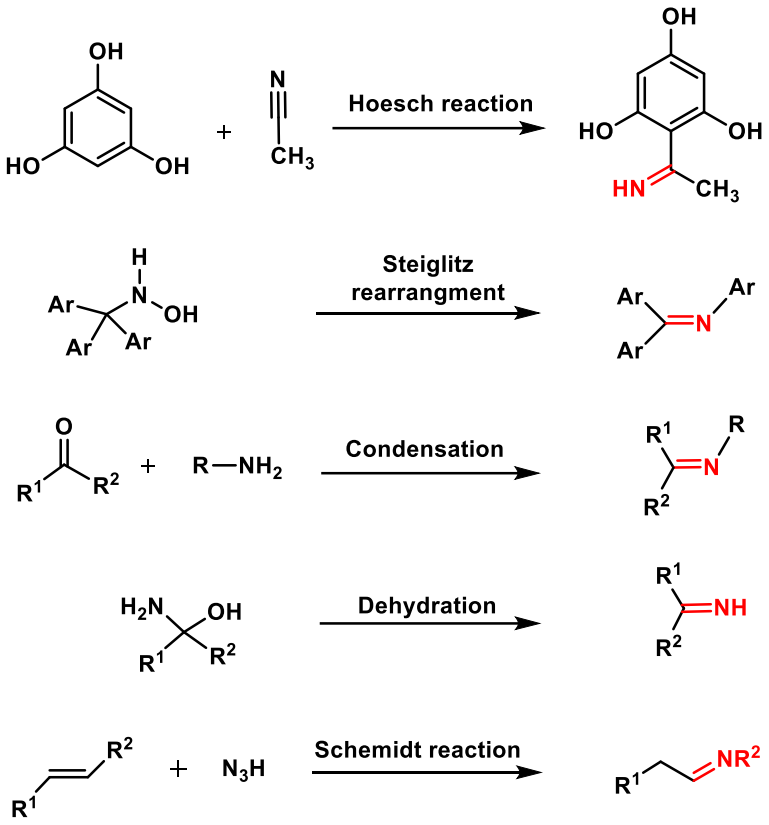


Figure 1.5 Some biologically active drugs bearing imine group.

They serve as versatile intermediates for the preparation of various nitrogen-containing compounds, including pharmaceuticals, agrochemicals, and dyes [69] (**Figure 1.5**).

Traditionally, primary imines are synthesized by condensation reaction of aldehydes with primary amines [70, 71]. Various name reactions are utilized for imine synthesis, including the Stieglitz rearrangement [72], and the Houben-Hoesh reaction [73] (**Scheme 1.3**).



Scheme 1.3 Synthesis of imine derivatives.

1.4.3 Oximes

The term "oxime" originates from "oxy-imine," denoted by >C=N–OH. Two proposed structures (A) and (B) (**Figure 1.6**) exist for the oxime group, the neutron diffraction analyses of dimethylglyoxime have confirmed the presence of the –OH group, and supporting structure (A). The oxime group displays amphoteric behaviour due to the presence of a mildly acidic hydroxyl group and a slightly basic nitrogen atom [74]. In oximes, both the carbon and nitrogen atoms are sp^2 hybridized. The restricted rotation

about the C=N bond results in geometrical isomerism in oximes derived from aldehydes and ketones.

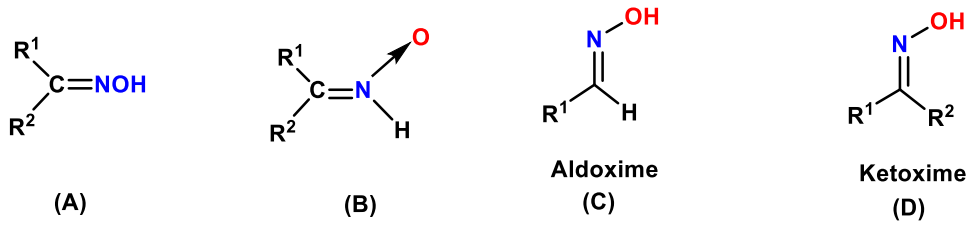


Figure 1.6 Structure (A & B) and classification (C & D) of oximes.

Oximes play a crucial role as fundamental components in synthesizing pharmaceuticals and agrochemicals and exhibit diverse applications across various fields [75]. They serve as essential antidotes for nerve agents, including Obidoxime, DAM, Pralidoxime, Methoxime, and Verogamine [76]. Additionally, oxime compounds find utility in pesticides, vasodilators, and antimicrobial agents, as well as in the treatment of migraine disorder. Notably, Methoxime is employed to treat hypotension due to hemorrhage [77] (**Figure 1.7**).

Oximes are extensively utilized in the protection of carbonyls and various other functional groups. They serve as crucial intermediates for the conversion of different functional groups such as amides [78], nitro compounds, amines [79], isoxazolines [80, 81], isoquinolines [82], among others [83], into different functional moieties (**Scheme 1.4**)

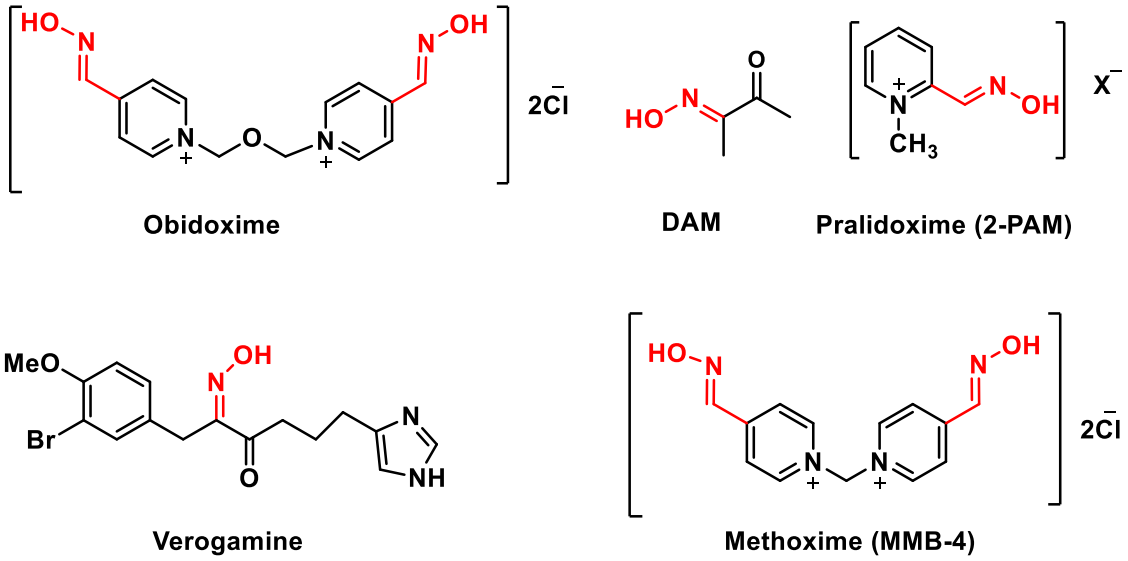
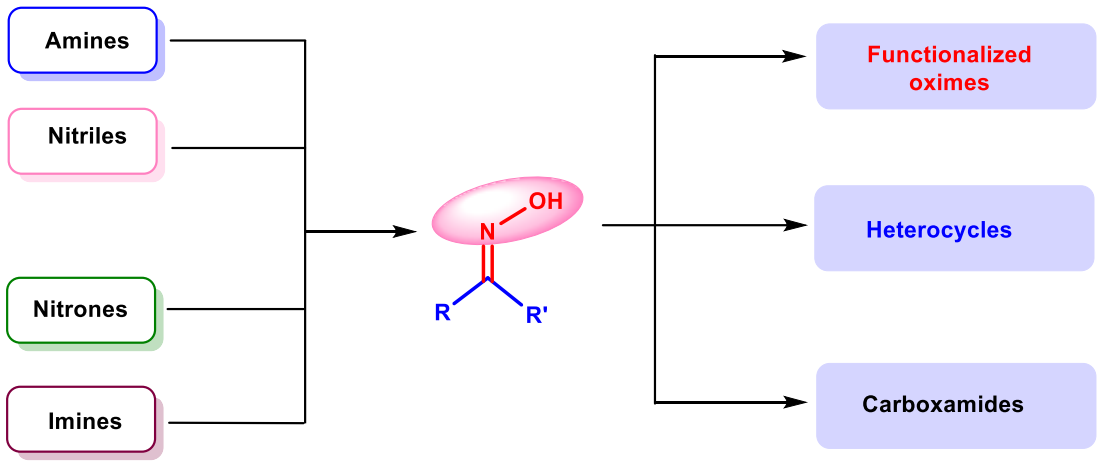


Figure 1.7 Some drugs containing oxime functional group.



Scheme 1.4 Synthesis and application of oximes.

1.4.4 Amides

Amides also known as carboxamides and, are the derivatives of carboxylic acids [84]. Carboxamides are significant compounds across diverse industries such as agrochemicals, pharmaceuticals, materials science, and chemical manufacturing [85, 86], and serve as essential building blocks in the synthesis of numerous drugs, polymers, and natural products. Consequently, the formation of amide bonds ranks among the most vital and extensively investigated reactions in organic chemistry [87]. Studies suggest that over a quarter of all drugs incorporate at least one amide bond. Some examples are shown in [88, 89] (**Figure 1.8)**.

Amides have a generic structure as $RCONH_2$, where the NH_2 group is free and is called a primary amide. When one hydrogen of NH_2 is replaced by an alkyl or aryl group such as RCONHR', it is known as a secondary amide, and tertiary amides are RCONR'R", where both the hydrogens of amine are substituted. In the molecular structure of amides [R-(C=O)-N], the central carbon atom possesses a double bond with oxygen and also a single bond with nitrogen atoms.

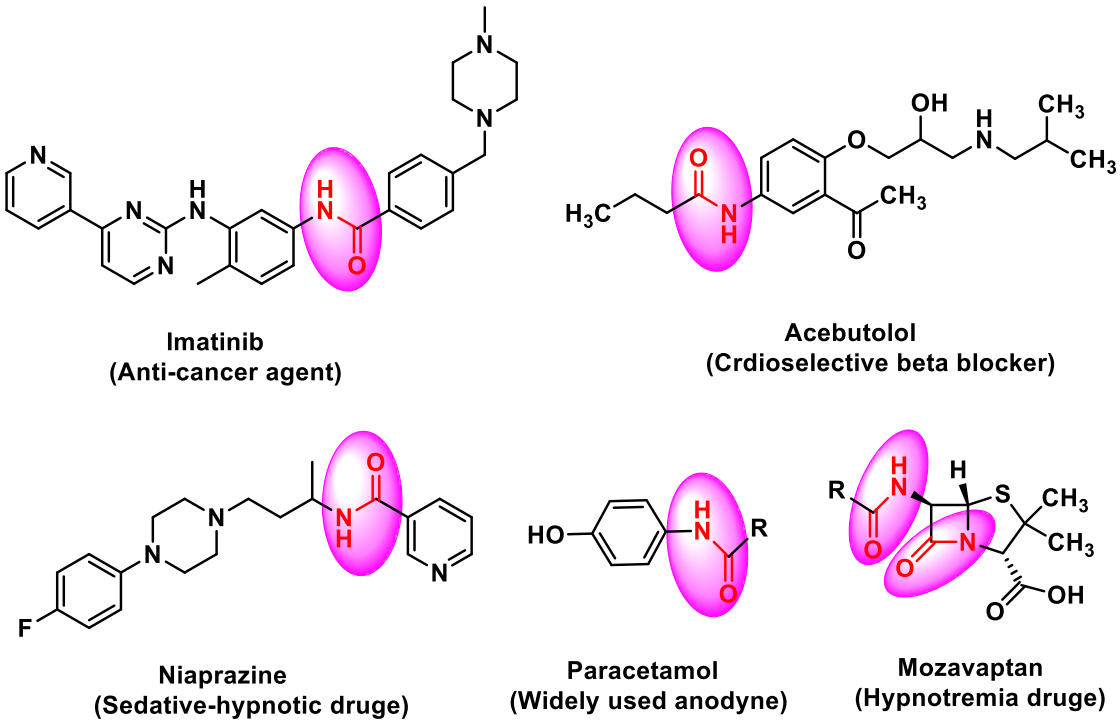


Figure 1.8 Examples of some drugs containing amide groups.

The lone pair of the nitrogen atom becomes delocalized over the carbonyl group, resulting in a partial double bond character between nitrogen and carbon. This resonance phenomenon contributes to the distinctive planarity of amides and due to a double bond character to the C-N bond **(Figure 1.9)**.

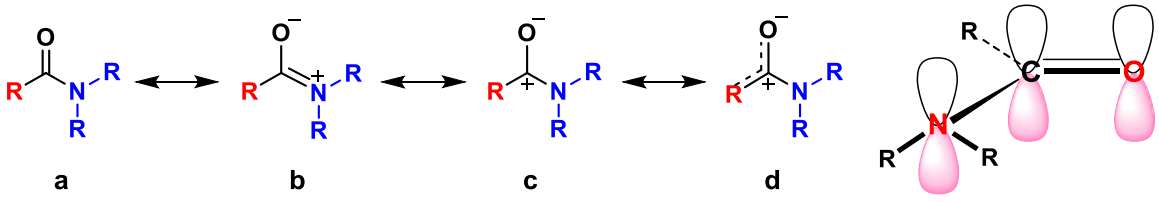
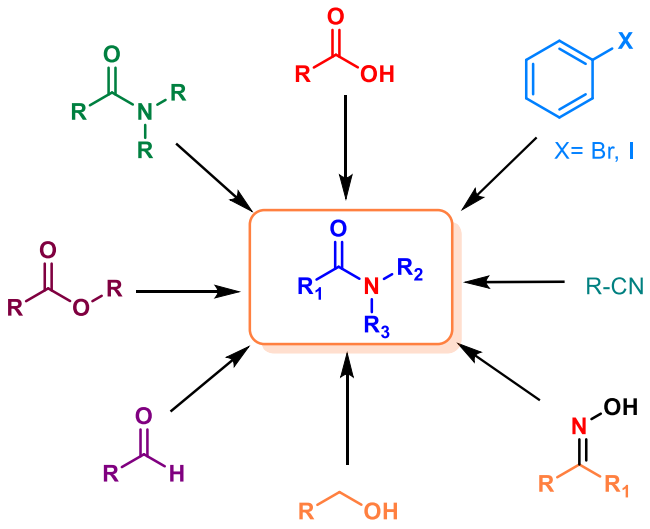


Figure 1.9 Resonance in amide bonds.

Consequently, amides exhibit enhanced stability owing to these resonance effects [90, 91]. Traditionally, amide synthesis entails a coupling reaction between a carboxylic acid and an amine (primary or secondary), facilitated by dehydrating agents [92]. While this reaction is usually thermodynamically favoured, its high activation energy is attributed to the initial deprotonation of the carboxylic acid by the amine, thereby reducing its reactivity. Consequently, derivatives of carboxylic acids such as acid chlorides, esters, and anhydrides are frequently employed in amide synthesis [93, 94] (**Scheme 1.5**).

Various name reactions are utilized for amide synthesis, such the Beckmann rearrangement [95], the Ritter reaction [96], the Schmidt reaction [97], and the Ugi reaction [98]. Transamidation is another notable reaction, which involves the conversion of one amide to another through its reaction with an amine [99, 100].



Scheme 1.5 Amide bond formation through various substrates.

Among all these alternative methods for the synthesis of amides, transamidation is one of most attractive method for the diversification of amides.

The persistent challenge in synthetic chemistry lies in achieving amide transamidation due to the equilibrium maintained between the product and substrate during the process [101]. The less reactivity of amide transamidation is due to (1) The resonance stability of the amide C-N bond results in a significant kinetic energy barrier to nucleophilic addition, known as the kinetic barrier. Furthermore, thermoneutral exchange contributes to the high thermodynamic barrier of amide transamidation, leading to the formation of an equilibrium mixture of product and substrate [102]. The two main challenges of this process have been worked out as follows. The primary challenge of this process has been addressed by reducing the kinetic energy of the system through the activation of the nitrogen in the amide group with a bulky group. (Boc, Ts Cbz or engaging lone pair of electrons of nitrogen with electron-withdrawing), which weakens the C-N bond strength; (2) The thermodynamic obstacle of achieving thermoneutral exchange is overcome by replacing the less nucleophilic amine with a more nucleophilic amine [103, 104]. The conceptualization of the two-step approach for secondary amide transamidation was initially formulated by Garg in 2016 [100]. It involves the activation of amides with *tert*-butyloxycarbonyl(Boc) group, and in the second step, *N*-activated amide undergoes transamidation by using base or additive or catalyst [105].

1.5 Nitrogen containing five-membered cyclic compounds

1.5.1 Pyrrole

Pyrrole stands as a significant heterocyclic compound found in a plethora of drugs, natural compounds, catalysts, and advanced materials [106, 107]. Pyrroles play a crucial role as active constituents within complex macrocycles, which encompass various compounds such as porphyrins found in heme, chlorins, bacteriochlorins, chlorophyll, and porphyrinogens [108]. Pyrroles find extensive applications as a substrate in polymerization processes, as well as in corrosion inhibition and preservation, and as solvents for resins and terpenes.

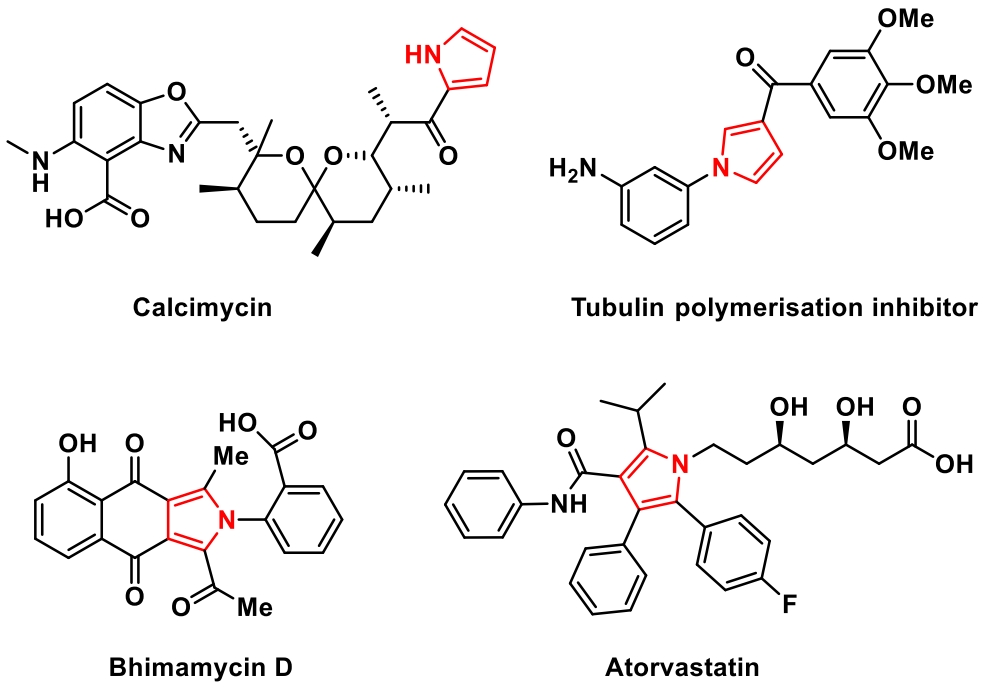
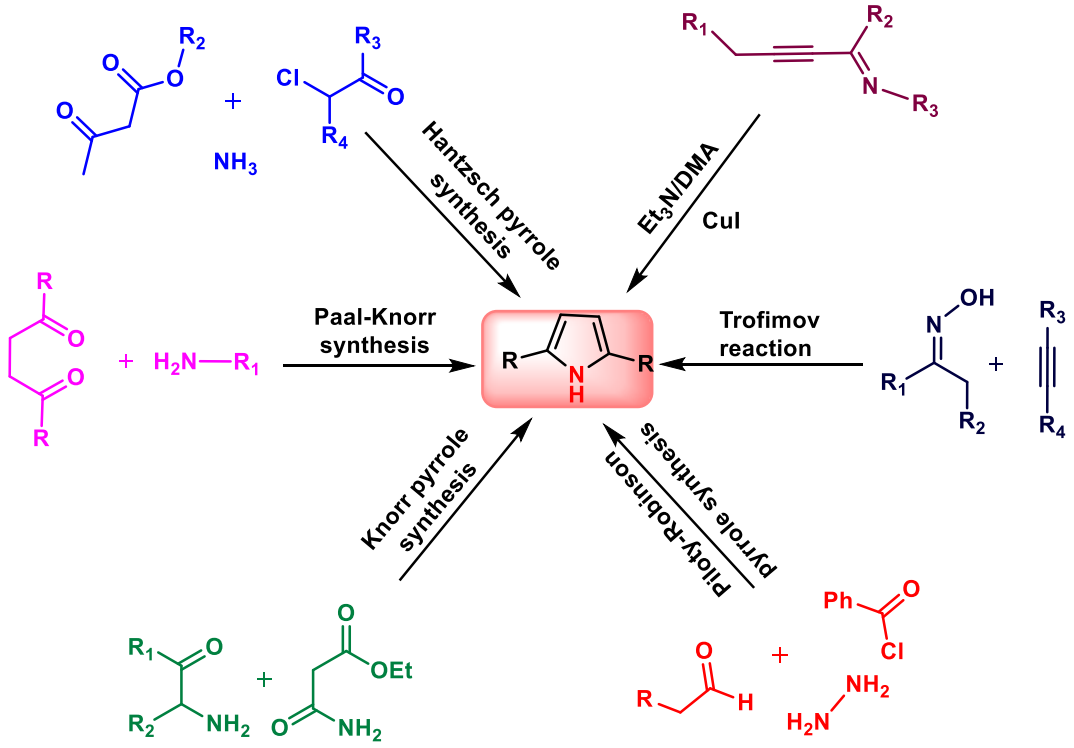


Figure 1.10 Some biologically active compounds bearing pyrrole functional group.

They serve as functional materials in diverse metallurgical processes, spectrochemical analysis, luminescent chemistry, and as transition metal complex catalysts for achieving uniform polymerization. Additionally, specific pyrrole compounds play a crucial role as intermediates in the synthesis of biologically active drugs and synthetic heterocyclic compounds [109–112] (**Figure 1.10**).

Pyrroles can be produced through diverse methods, such as the reaction between 1,4-dicarbonyl compounds and ammonia or aromatic/aliphatic amines [113].



Scheme 1.6 Synthesis of pyrrole and its derivative.

Various name reactions are utilized for the pyrrole synthesis, such as Knorr pyrrole synthesis [114], the Piloty-Robinson pyrrole synthesis [115], the Hantzsch pyrrole synthesis [116], and the Trofimov reaction [117] (**Scheme 1.6**).

1.6 Nitrogen Containing Six Membered Cyclic Compounds

1.6.1 Pyridine

Pyridine stands as a crucial heteroaromatic compound renowned for its diverse and potent biological properties [118]. Historically, a significant quantity of pyridine was obtained from natural sources through coal tar distillation. Pyridines are integral components of several vital compounds, including niacin (vitamin B3), pyridoxine (vitamin B6), and numerous alkaloids such as nicotine and quinine [119].

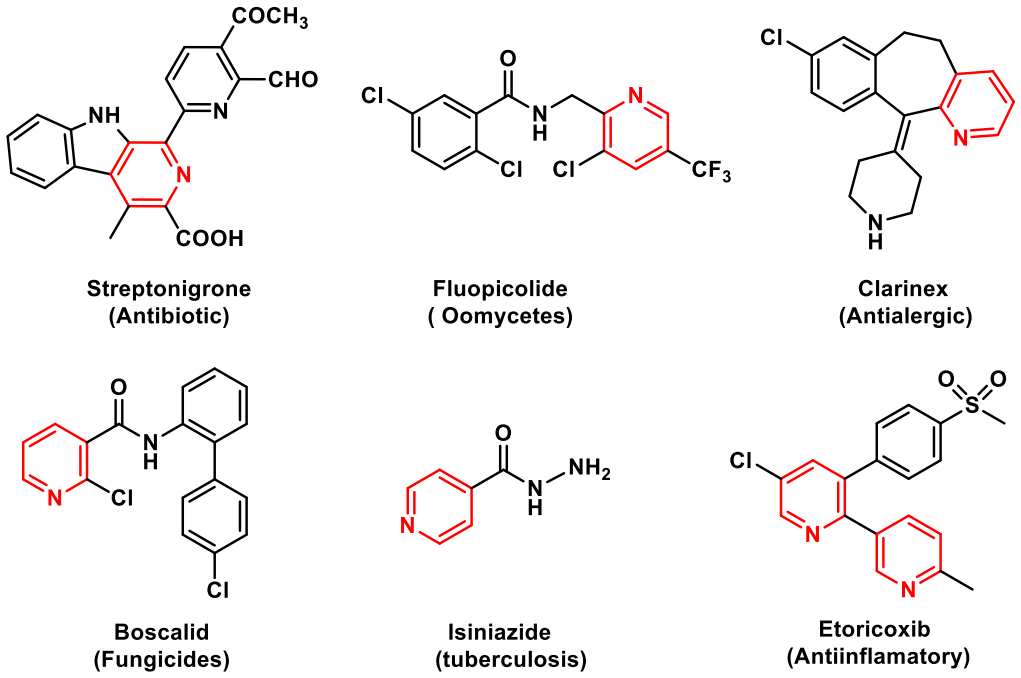
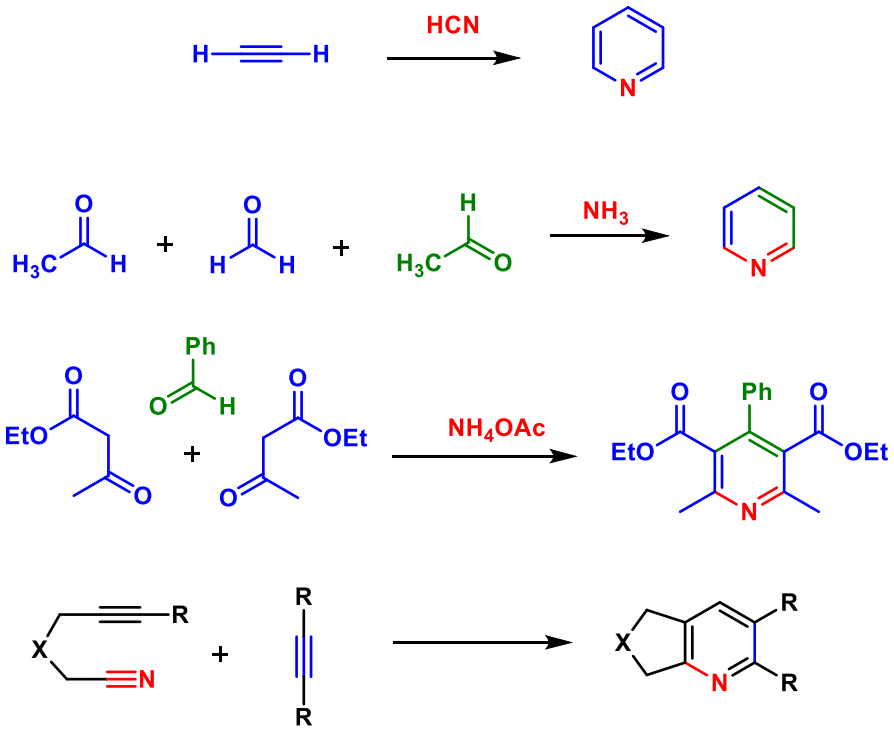


Figure 1.11 Representative compounds containing pyridine substructure.

Pyridine structure is prevalent in numerous pharmaceuticals, including anti-HIV medications, anticancer drugs, antidiabetic agents, and proton pump inhibitors [120] (**Figure 1.11**).

Pyridine was initially synthesized in 1876 through the reaction of acetylene and hydrogen cyanide [121]. There are many well-known name reactions like the Chichibabin pyridine synthesis [122], the Knoevenagel condensation reaction [123], and the Hantzsch pyridine synthesis [124]. Additionally, pyridine can be obtained through the cycloaddition of alkyne nitriles and alkynes and oxidization of dihydropyridines [125] (**Scheme 1.7**).



Scheme 1.7 Synthesis of pyridine and its derivatives.

1.6.2 Pyrimidine

Pyrimidine is a fundamental heterocyclic compound with a six-membered ring containing two nitrogen atoms located at positions 1 and 3 [126]. Its simple yet versatile structure lends itself to a multitude of biological, pharmaceutical, and industrial applications. Pyrimidine and its derivatives are integral components of essential biomolecules, including nucleic acids like DNA and RNA, where they play crucial roles in storing genetic information, transfer, and expression [127, 128]. Beyond their biological significance, pyrimidines feature prominently in the synthesis of pharmaceuticals, agrochemicals, dyes, and materials science [129, 130] (**Figure 1.12**). The diverse array of synthetic methods available for pyrimidine production underscores its importance in modern chemistry.

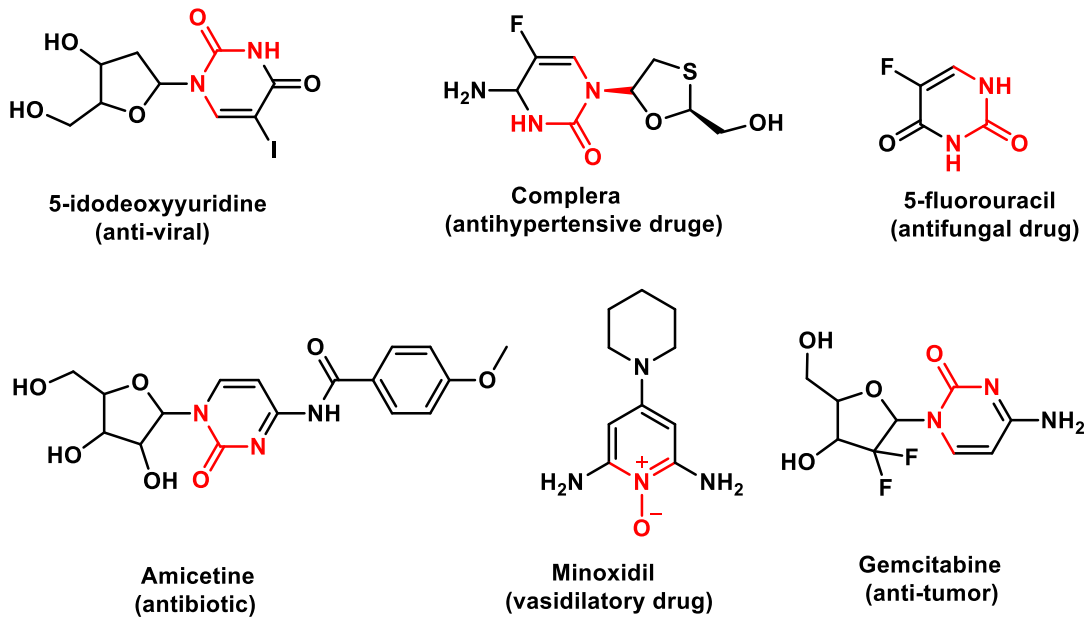


Figure 1.12 Few biologically active compounds containing pyrimidine moiety.

One classical approach involves the fusion of cyanoacetylene with ammonia, yielding 4-aminopyrimidine. This intermediate can undergo subsequent transformations to yield various pyrimidine derivatives [131]. There are many well-known name reactions like the Biginelli reaction [132], the Gewald reaction [133]. Amidine derivatives can also undergo cyclization with carbonyl compounds in the presence of ammonia or amines to yield pyrimidines via the Biginelli-type reaction [134].

1.7 Nitrogen containing fused heterocyclic compounds

1.7.1 Indole

Indoles represent highly researched heterocyclic ring systems and are abundant in natural compounds. Derivatives of indole demonstrate a broad spectrum of properties and biological activities such as anticancer, antiviral, anti-inflammatory, anti-HIV, antimicrobial, antioxidant, antimalarial, antitubercular, antidiabetic, anticholinesterase activities, etc [135, 136]. Notably, 3-substituted indole derivatives play a pivotal role in synthesizing pharmaceutically active compounds [137]. Representative examples of biologically active indole derivatives are highlighted in **(Figure 1.13).** The indole nucleus found in the amino acid tryptophan renders it significant in various phytoconstituents, including perfumes, neurotransmitters, plant hormones (auxins), and indole alkaloids. The unique molecular structure of indoles positions them as promising candidates for drug development. This gathered knowledge serves as a foundation for modifying current ligands to craft new, potent molecules with reduced side effects [45].

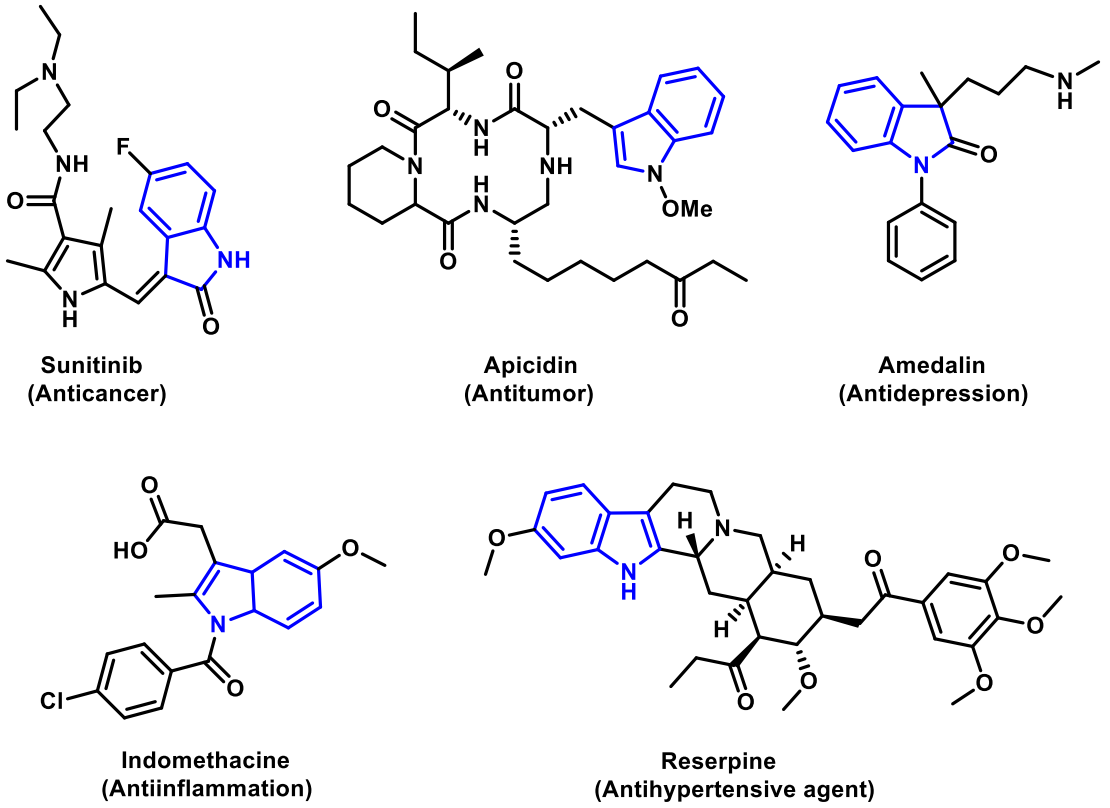
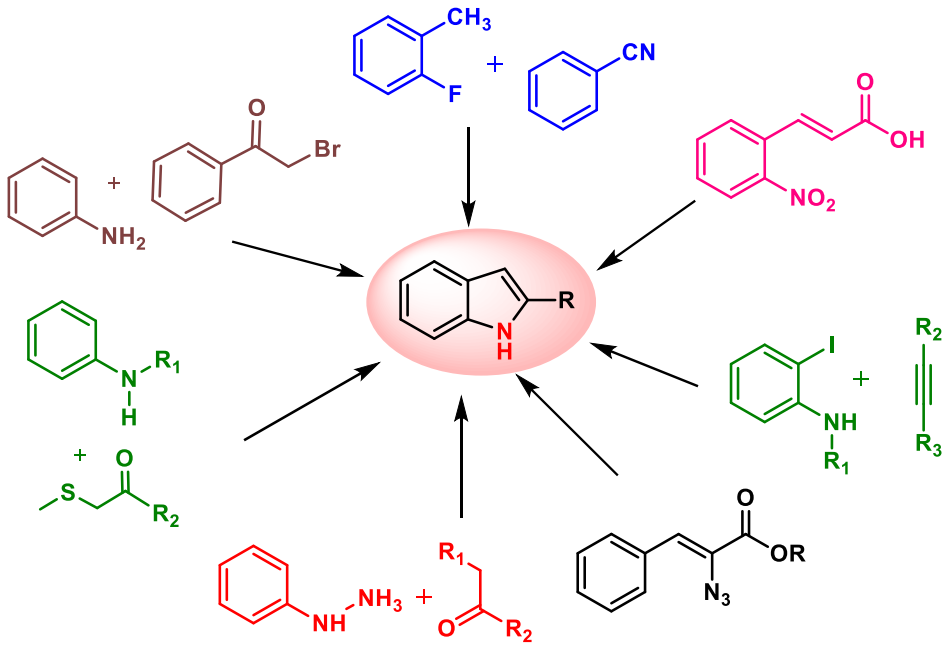


Figure 1.13 Biological activity of some substituted indoles.

Several techniques have been utilized to synthesize indoles and their derivatives. A widely used method is the Fischer indole synthesis, which involves reacting phenyl hydrazine with carbonyl compounds (aldehydes or ketones) under acidic conditions [138]. 2-Fluorotoluenes and benzonitriles react in the presence of a base [139], α-bromo-acetophenone, and an excess amount of aniline to produce 2-aryl-indole, a method known as the "Bischler–Möhlau indole synthesis" [140]. Another approach, termed the "Gassman indole synthesis", involves aniline and a ketone bearing a thioether [141]. The "Larock indole synthesis" utilizes an ortho-iodoaniline and a disubstituted alkyne with a palladium

catalyst [142]. Additionally, the "Hemetsberger indole synthesis" involves the thermal decomposition of 3-aryl-2-azido-propenoic ester into an indole-2-carboxylic ester [143]. Lastly, the "Baeyer–Emmerling indole synthesis" employs substituted ortho-nitro cinnamic acid with iron powder in a highly basic state [144] (**Scheme 1.8)**.



Scheme 1.8 Synthesis of indole derivatives.

1.7.2 Benzimidazole

Benzimidazole is a nitrogen-containing heterocyclic structure composed of a six-membered benzene ring fused with a five-membered imidazole ring [145]. It is a key component of many biologically active compounds and finds widespread use in various therapeutic areas such as antibacterial, antihypertensive, anti-inflammatory, antiviral, antihelmintic, antifungal, anticancer, antioxidant, antiulcer, psychoactive drugs, proton pump inhibitors,

antidepressants, hormone modulators, anticoagulants, immunomodulators, and antidiabetics [146, 147] (**Figure 1.14).** Benzimidazole derivatives exert their pharmacological impacts by engaging with vital biological targets, including the serotonin receptors, histamine receptors, β-tubulin, and DNA minor groove etc [148].

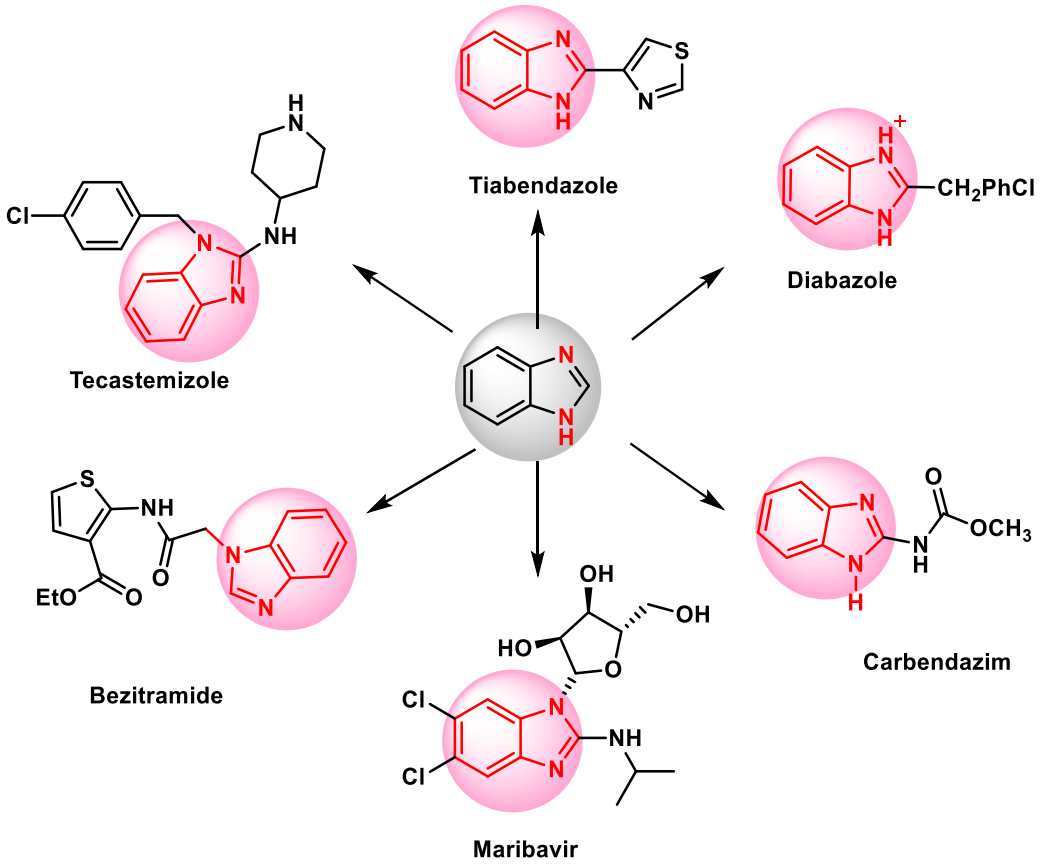
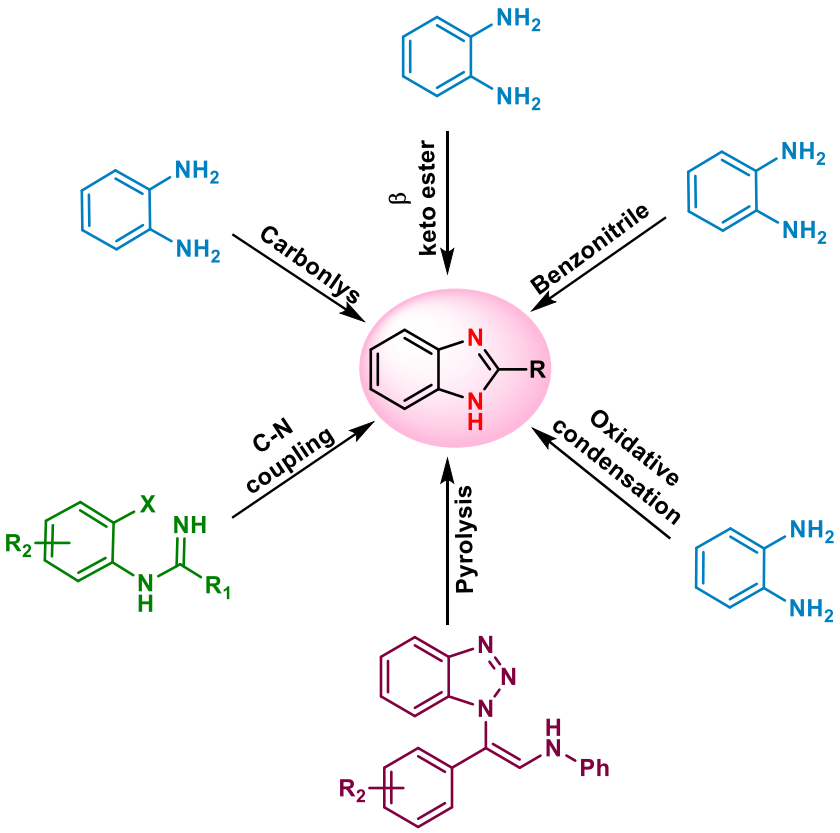


Figure 1.14 Some biologically active compounds bearing benzimidazole functional group.

There are several ways to synthesize benzimidazole and its analogs, including the condensation reaction of *o*-phenylenediamine and carbonyl compounds [149–151], oxidative condensation reactions involving alcohols and methyl arene derivatives with *o*-

phenylenediamine [152, 153], the oxidative cyclization of *N*-aryl amidine intermediates derived from the addition of aniline to a nitrile [154], one-pot intermolecular cross-coupling of *o*-haloacetoanilide with guanidine [155], intramolecular C(sp3)–H imination [156], and the thermolysis of benzotriazole derivatives [157] (**Scheme 1.9**).



Scheme 1.9 Synthesis of benzimidazole and its derivatives.

In view of the importance of nitrogen-containing organic compounds, it is our interest to explore the synthesis, reactivity and structural elucidation of carboxamides, 1,2,3,4 tetrahydropyrimidinones, and Hantzsch 1,4-dihydropyridine derivatives under sustainable and green conditions. The studies have been described in the subsequent **chapters 2-6**.

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