Introduction

As environmental concerns arise, organic chemists are challenged to develop eco-friendly, efficient, selective, and high-yielding processes.[1–4] The principle of Green Chemistry presents an alluring aspect within the field of chemistry, particularly about sustainable development. It encompasses a collection of principles aimed at minimizing the utilization or production of harmful substances during the process of designing, manufacturing, and employing chemical products.[5] Over the past decade, research, implementation, education, and outreach advances have increased the 'state-of-the-art' in green chemistry.[6] Such concepts include designing processes to maximize the amount of raw materials that become the product, using safe, environment-friendly substances like solvents, developing energy-efficient strategies, and minimizing waste products.

1.1 Multicomponent Reactions

A multicomponent reaction (MCR) is a reaction in which three or more reactants combine in a single reaction vessel to produce a new product containing components from all the reactants.[7–10] (**Figure 1.1**) The appealing aspect of multicomponent reactions (MCRs) lies in their integrative nature, especially when there is a need for a swift expansion in molecular diversity. By adopting a combinatorial strategy, groups of components (such as amines, carboxylic acids, alcohols, etc.) can be methodically distributed across arrays of reactions, resulting in the generation of variations based on a shared multicomponent reaction (MCR) product framework. Multicomponent Reactions (MCRs) exhibit exceptional efficiency, attributable not only to intrinsic factors like superior atom economy, selectivity, and reduced by-product formation but also to extrinsic factors

related to the processing of the reaction. These extrinsic aspects encompass streamlined procedures and equipment, cost-effectiveness, time and energy savings, and adherence to environmentally friendly criteria.[11–14]

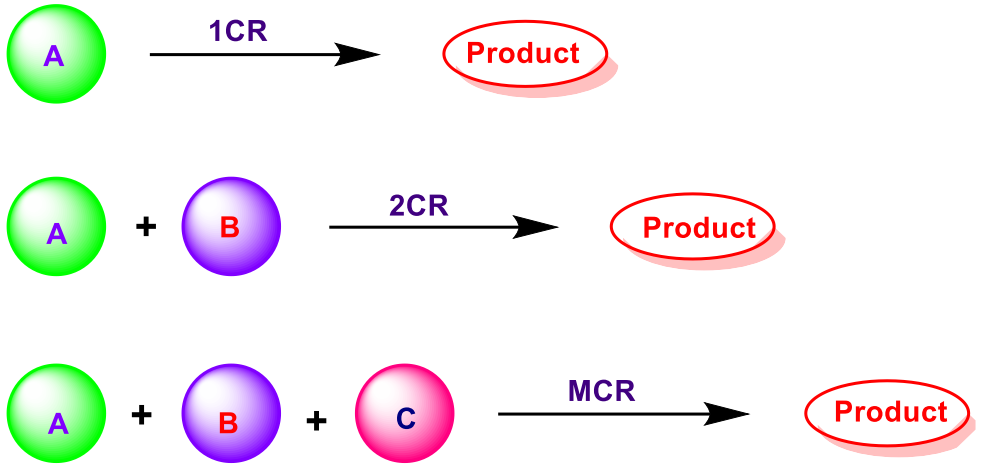


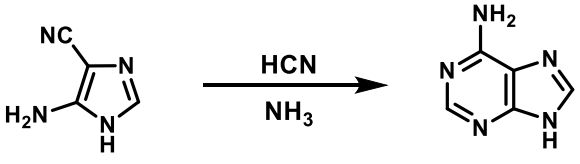
Figure 1.1 A divergent one-component reaction and convergent two- and multi-component reactions

Multicomponent Reactions (MCRs) synthesize a product through a sequential series of elementary chemical reactions. As a result, a network of reaction equilibria converges into an irreversible step, ultimately forming the desired product. The challenge lies in effectively orchestrating MCRs to ensure the network of pre-equilibrated reactions efficiently converges into the desired main product while minimizing the formation of undesired side products. The outcome is contingent upon various reaction parameters, including the choice of solvent, temperature, catalyst, concentration, starting materials, and functional groups. These considerations hold significant importance, especially when it comes to the design and exploration of new MCRs.

Unlike the typical step-by-step formation of individual bonds in the desired molecule, Multicomponent Reactions (MCRs) possess a distinctive characteristic of simultaneously creating multiple bonds in a single operation without isolating intermediates, altering reaction conditions, or introducing additional reagents. This approach effectively minimizes waste production and reduces the labor involved. The products are generated by simply combining the appropriate set of starting materials. Since the resulting product structures incorporate components from all the reactants used, MCRs with high efficiency in bond formation enable significant advancements in molecular complexity and diversity. The wide array of starting materials offers versatile opportunities for synthesizing compound libraries. Achieving generalization across as many starting materials as possible is crucial for broad applicability. Multicomponent reactions thus address the requirements for efficient and rapid synthesis of compounds in a cost-effective and time-efficient manner. These reactions, which simultaneously build C-C, C-N, and other carbon-heteroatom bonds while introducing heteroatom-containing functionalities, are particularly impressive for the swift construction of organic molecules.

Multicomponent reactions (MCRs) inherently possess broad applicability across various fields of modern chemistry-based technology. Their versatility extends beyond pharmaceutical applications, finding utility in diverse areas such as EPR-spin labeling, the development of biocompatible materials like artificial eye lenses, novel polymer properties, chiral phases for HPLC, synthesis of natural products, peptide-nucleic acids, and agrochemicals. However, this dissertation primarily focuses on the application of

MCRs in heterocyclic synthesis, as it holds significant importance due to the prevalence of heterocycles in drugs and pharmaceutically substantial compounds. The utilization of multicomponent reactions (MCRs) for heterocycle synthesis has been observed since ancient times, even predating the existence of life on Earth. In nature, this process is harnessed to create essential biomolecules, including adenine, a fundamental building block of DNA and RNA. Adenine's prebiotic formation involved the condensation of five molecules of hydrogen cyanide (HCN), an abundant component of the early Earth's atmosphere, in a multicomponent reaction catalyzed by ammonia (NH_3).[15] Similarly, multicomponent reactions involving HCN and H_2O have generated other nucleic bases. (**Scheme 1.1**)



Scheme 1.1 Multicomponent synthesis of purine

1.2 Nitrogen-Containing Organic Compound

As the universal structural motif of all living things, nitrogen can be found in vitamins, hormones, amino acids, and nucleic acids. Consequently, they showcase diverse structural attributes, encompassing simplicity, functional groups, degrees of substitution, and heterocyclic systems. Many biologically, pharmaceutically, and synthetically active compounds contain nitrogen as a core skeleton or alone. In addition to their industrial and biological importance, N-heterocyclic organic compounds play an important role in many areas of human society.

Considering the vast number of nitrogen-containing compounds, the enormous diversity of their structures, and their very different fields of application, this chapter has covered some main classes of heterocyclic compounds. Nitrogen-containing five-membered heterocycles are pyrrole and pyrazoles; six-membered is pyridine; seven-membered are azepines ring; and fused heterocycles are benzimidazole, benzothiazole, benzoxazole, and Indole (**Figure 1.2**).

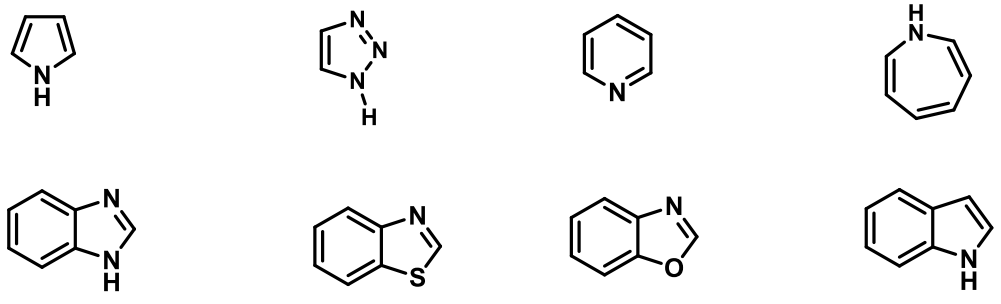


Figure 1.2 N-Heterocyclic containing some main class of organic compounds

1.2.1 Nitrogen-containing five-membered cyclic compounds

1.2.1.1 Pyrrole

Pyrrole, an essential chemical motif found in numerous drugs, natural products, catalysts, and advanced materials, is a heterocyclic compound with a five-membered ring.[16,17] In 1834, pyrrole was isolated from coal tar by Runge, and its correct structure was subsequently formulated by Baeyer in 1870. Pyrroles display activity in the presence of appropriate metal atoms, forming metal complex macrocycles encompassing heme porphyrins, chlorins, bacteriochlorins, chlorophyll, and porphyrinogens.[18] They constitute a component of polymers, indigoid dyes, and sizable aromatic rings. (**Figure 1.3**)

Pyrroles find application as a catalyst in polymerization, corrosion inhibitor, preservative, solvent for resins, and terpenes. They exhibit functionality in diverse areas, including metallurgical processes, luminescence chemistry, spectrochemical analysis, and serving as catalysts for uniform polymerization in transition metal complexes. Additionally, certain compounds serve as valuable intermediates in synthesizing biologically significant naturally occurring alkaloids and synthetic heterocyclic derivatives.[19]

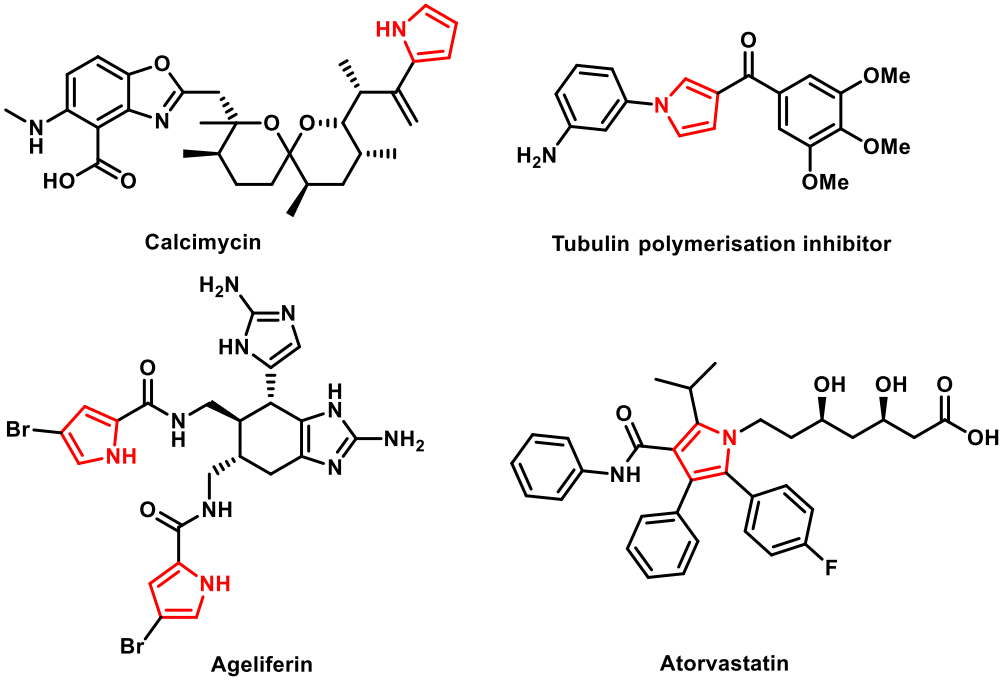
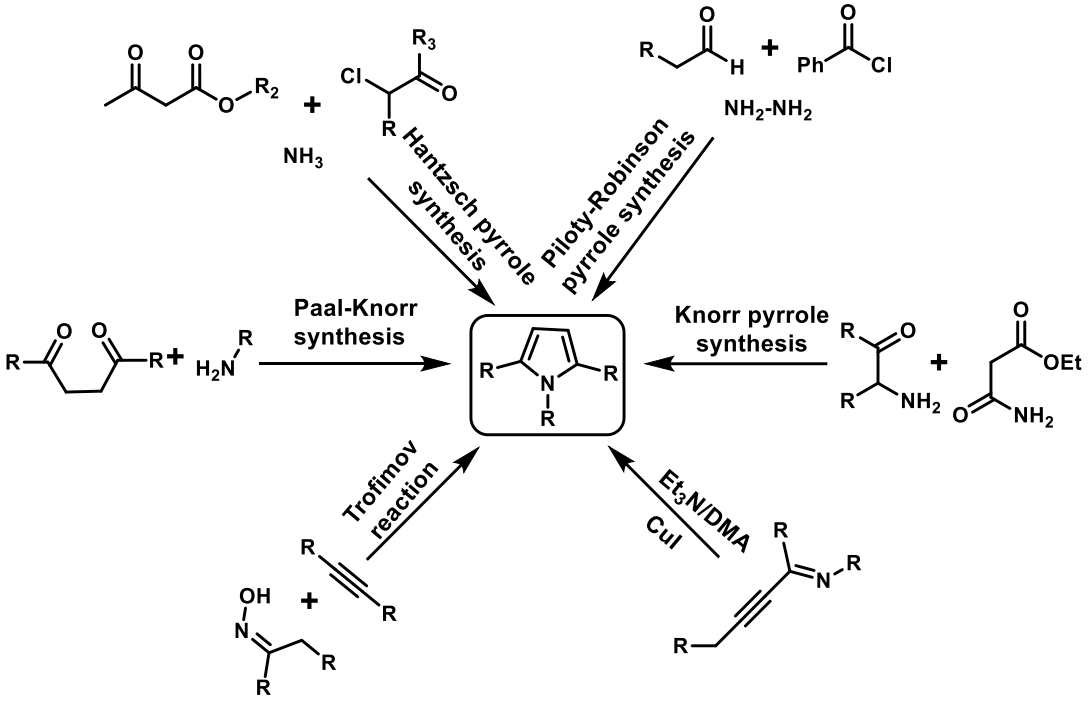


Figure 1.3 Few biologically active compounds containing pyrrole moiety

Pyrroles can be synthesized through diverse approaches, including the reaction of a 1,4-dicarbonyl compound with ammonia or aromatic/aliphatic amines (Paal-Knorr Synthesis)[20], N-butyl-substituted alkynyl imine gave intramolecular cyclization[21], by Knorr pyrrole synthesis in which α-amino-ketone react with ethyl acetoacetate[22], ketones or secondary alcohols and β-amino alcohols[23], α-halo ketones, and ammonia to give substituted pyrroles known as "Hantzsch pyrrole synthesis", by three component

condensation involving benzoyl chloride, hydrazine hydrate, and aldehyde "Piloty–Robinson pyrrole synthesis"[19], and most importantly from the reaction of oxime with alkynes "Trofimov reaction".[24] (**Scheme 1.2**)



Scheme 1.2 Synthesis of pyrrole and its derivatives

1.2.1.2 Triazoles

Triazole, a significant group of heterocyclic compounds, demonstrates a wide range of pharmacological activities. These compounds, referred to as pyrrodiazoles, possess a five-membered ring consisting of two carbon and three nitrogen atoms. Notably, they serve as fundamental structural components in commercially available drugs like cefatrizine (an antibiotic) and fluconazole (an antifungal agent). Furthermore, their medicinal potential extends to exploring antiviral properties, including anti-HIV activity.[25–27] (**Figure 1.4**)

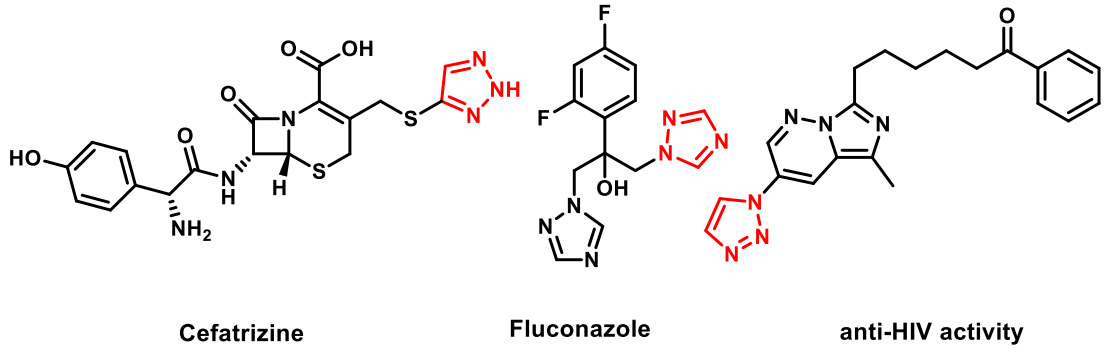
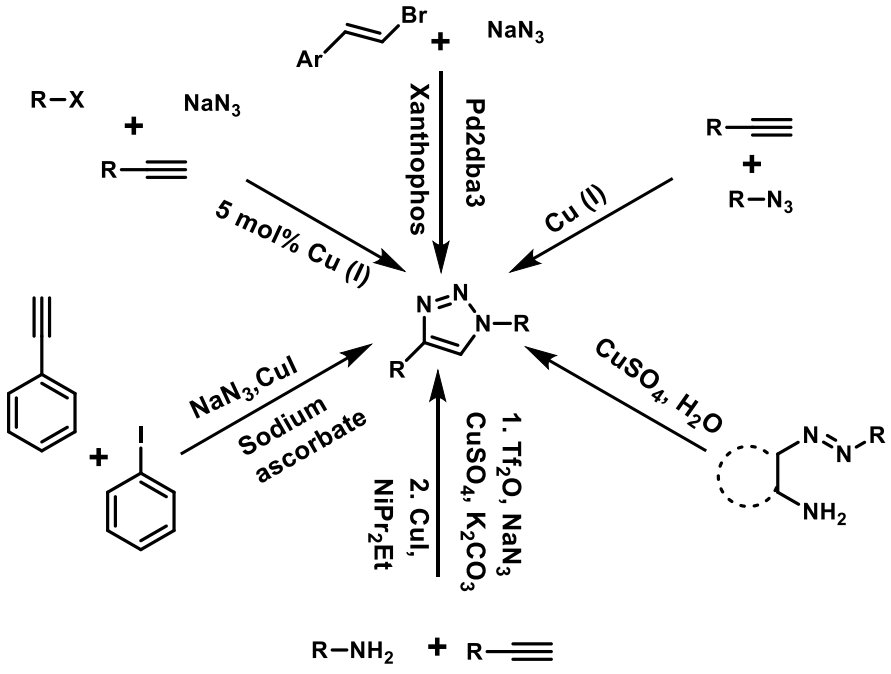


Figure 1.4 Triazoles containing marketed drugs and pharmacologically active molecules

Triazoles can be synthesized through various methods, including the reaction of an azide and a terminal alkyne in the presence of copper (I) metal or copper (II) salts. For instance, the use of copper sulfate pentahydrate facilitates this synthesis. Another approach involves a palladium-catalyzed reaction using alkenyl halides and sodium azides. Additionally, when terminal alkynes are combined with a mixture of benzyl or alkyl halides and sodium azide, in the presence of copper immobilized on 3-aminopropyl functionalized silica gel and ethanol, it leads to the formation of 1, 4-disubstituted 1, 2, 3-triazole compounds. A highly efficient method has been reported for the one-pot synthesis of triazole-linked glycoconjugates, employing 1,3-dipolar cycloaddition in the presence of Cu(I) as a catalyst. Under suitable reaction conditions, primary aliphatic amines can undergo diazo transfer to yield azides, which can further be transformed into triazoles. Condensed triazoles can be synthesized by oxidizing aryl azo heterocycles containing an amino group in the ortho position.[28–30] (**Scheme 1.3)**



Scheme 1.3 Synthesis of Triazole and its derivatives

1.2.2 Nitrogen-containing six-membered cyclic compounds

1.2.2.1 Pyridine

Heterocyclic chemistry containing nitrogen atoms encompasses half of organic chemistry. Pyridine, a significant heteroaromatic compound, possesses a wide range of potent biological properties, making it a compound of great importance.[31,32] Abundant quantities of pyridine were acquired through the distillation of coal tar, which served as a valuable natural source of this compound. Pyridines also occur in many significant compounds, e.g., pyridoxine (vitamin B_6), vitamin niacin (vitamin B_3)[33], and several alkaloids, including quinine, nicotine, etc. Pyridine structure forms many pharmaceuticals, e.g., anti-HIV, anticancer, antidiabetic, proton pump inhibitor, etc.[34] Pyridine derivatives are also incorporated into polymers, such as polyvinyl pyridine (PVP), which are utilized in light-emitting devices (LEDs).[35] (**Figure 1.5**)

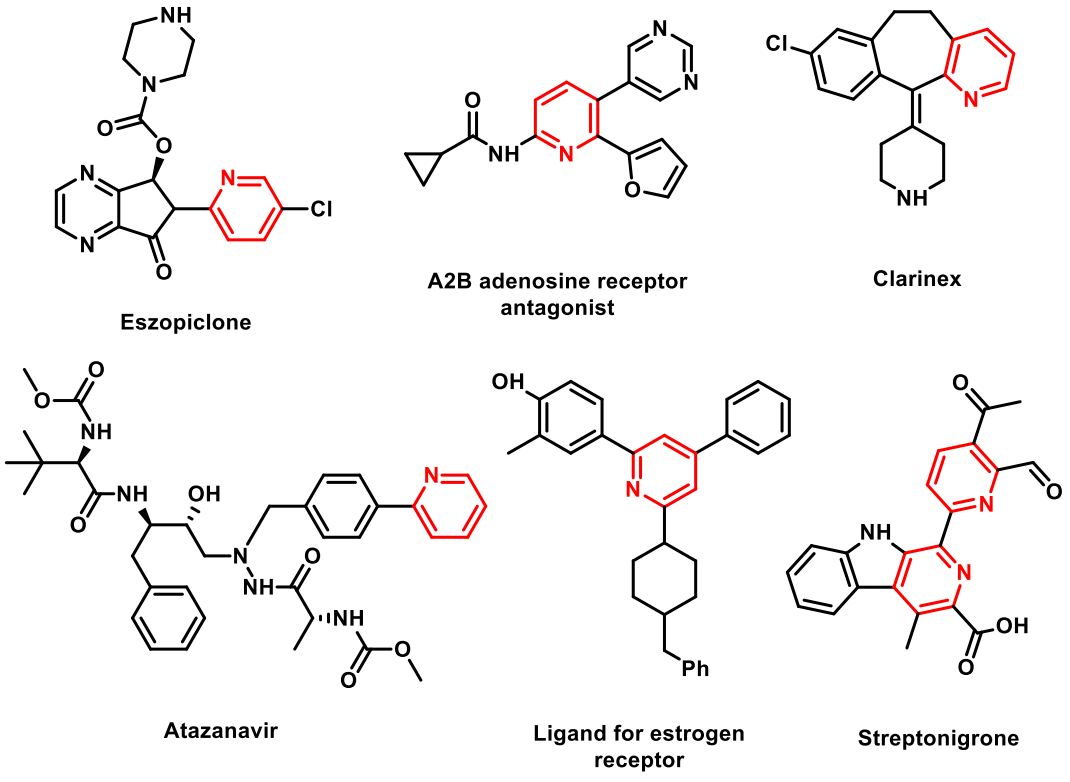
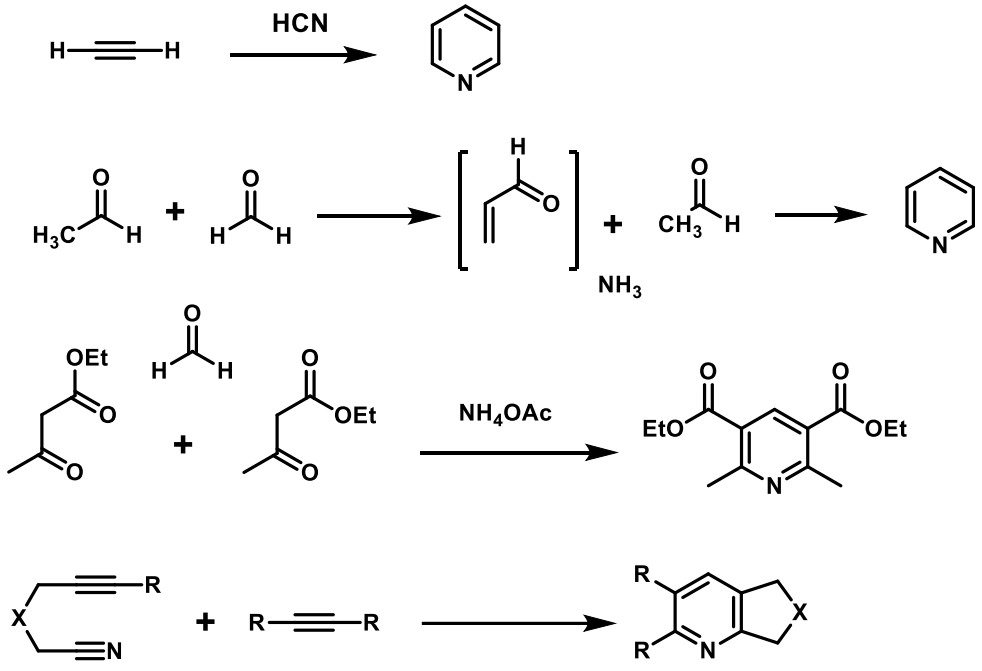


Figure 1.5 Representative compounds containing pyridine substructure

The synthesis of pyridine was initially achieved in 1876 by combining acetylene and hydrogen cyanide.[36] The Chichibabin pyridine synthesis can synthesize pyridine and is still used in industry.[37] Through the Knoevenagel condensation reaction, aldehyde and formaldehyde undergo a reaction that yields acrolein. Subsequently, acrolein undergoes condensation with acetaldehyde and ammonia, resulting in the formation of dihydropyridine. The dihydropyridine is then subjected to oxidation using a solid-state catalyst, leading to the production of pyridine.[38] The Hantzsch pyridine synthesis involves a multicomponent organic reaction that includes an aldehyde, β-keto ester (2 equivalents), and a nitrogen donor (ammonium acetate or ammonia).[39] Cycloaddition of alkynenitriles and alkynes gives pyridine.[40] (**Scheme 1.4**)



Scheme 1.4 Synthesis of pyridine and its derivatives

1.2.3 Nitrogen-containing seven-membered cyclic compounds

1.2.3.1 Azepines

Azepines are heterocyclic compounds consisting of unsaturated seven-membered rings with a nitrogen atom replacing a carbon atom. Benzoazepines, which are azepines fused with a benzene ring, have proven effective in treating a range of disorders, including hypertension (**1**) and congestive heart failure (**2**). Additionally, they are recognized for their neuroprotective properties (**3**) and their potential as agents against tuberculosis (**4**).[41–44] (**Figure 1.6**)

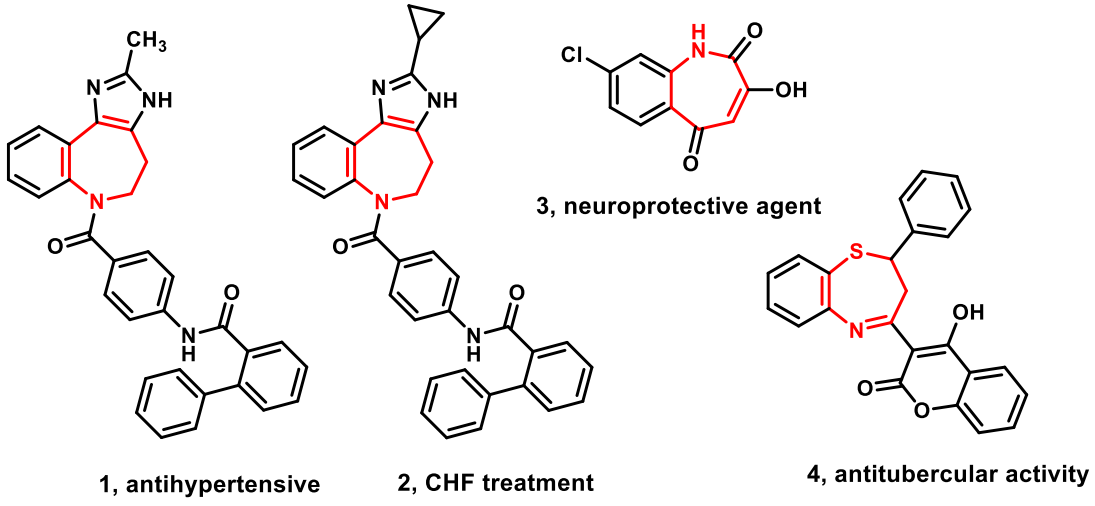
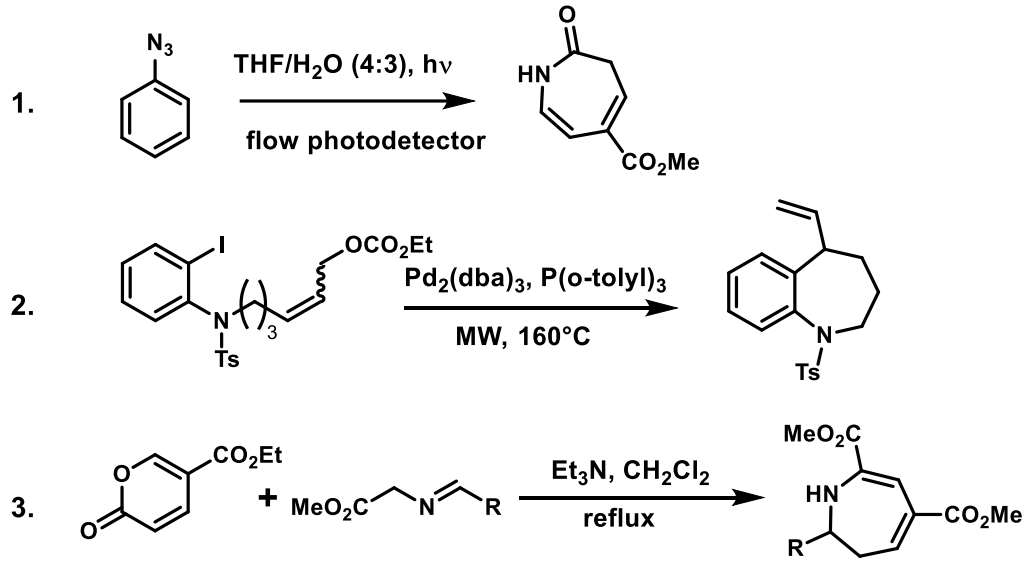


Figure 1.6 Benzoazepines based potent molecules

In due course of time, several methods have been developed for synthesizing seven-membered heterocyclic compounds. Bou-Hamdan et al. successfully synthesized substituted azepine compounds at room temperature (298K) through the photolysis of aryl azide.[45] (**Scheme 1.5.1**) Lautens and co-workers employed allyl acetates and carbonates in a microwave-assisted intramolecular coupling reaction with aryl iodides to synthesize seven-membered N-containing heterocycles.[46] (**Scheme 1.5.2**) Liu and co-workers reported the synthesis of functionalized Azepine derivatives by using methyl coumalate and glycine-derived imine ester in the presence of Et_3N as the base in CH_2Cl_2.[47] (**Scheme 1.5.3**)



Scheme 1.5 Synthesis of azepines and their derivatives

1.2.4 Nitrogen-containing fused heterocyclic compounds

1.2.4.1 Benzimidazole

Benzimidazole is a heterocyclic structure containing nitrogen consisting of a fused six-membered benzene ring and a five-membered imidazole ring. Benzimidazoles and their derivatives play a crucial role in numerous biologically active compounds and find extensive application as antihypertensive, anti-inflammatory, antibacterial, antiviral, antifungal, antihelmintic, anticancer, antiulcer, antioxidant, psychoactive drugs, anticoagulants, proton pump inhibitors, immunomodulators, hormone modulators, antidepressants, antidiabetics, and more.[48] Benzimidazole derivatives engage with essential biological targets such as DNA minor grooves, histamine receptors, β-tubulin, and serotonin receptors.[49,50] (**Figure 1.7**)

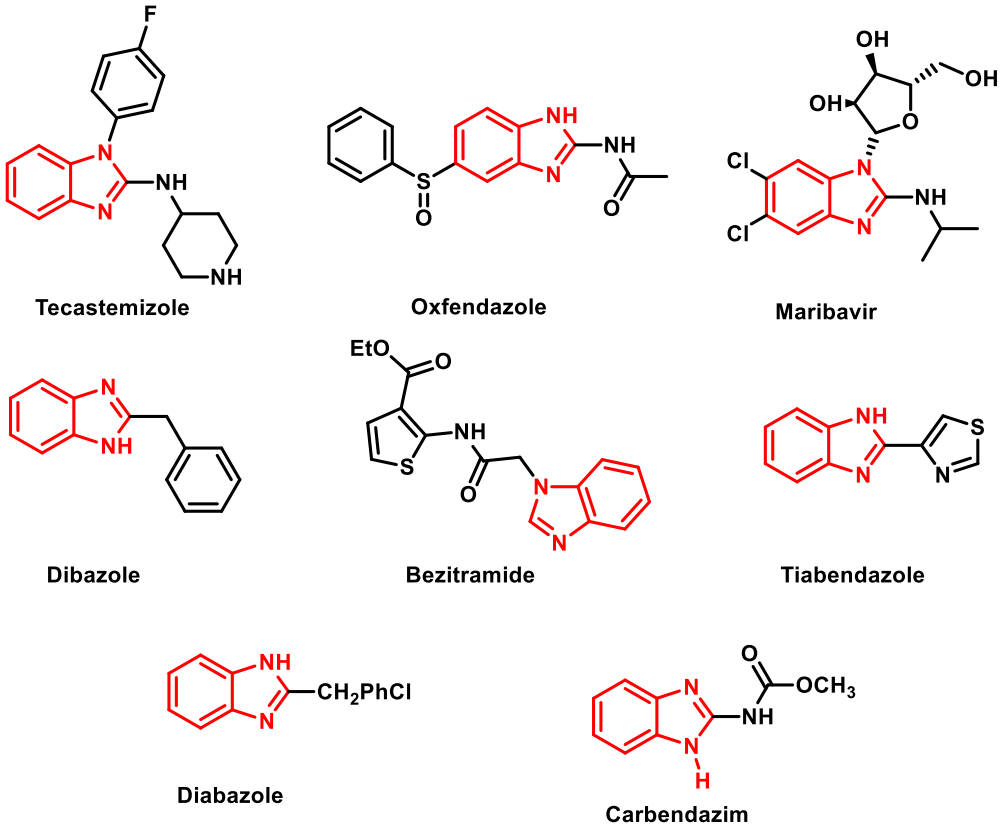
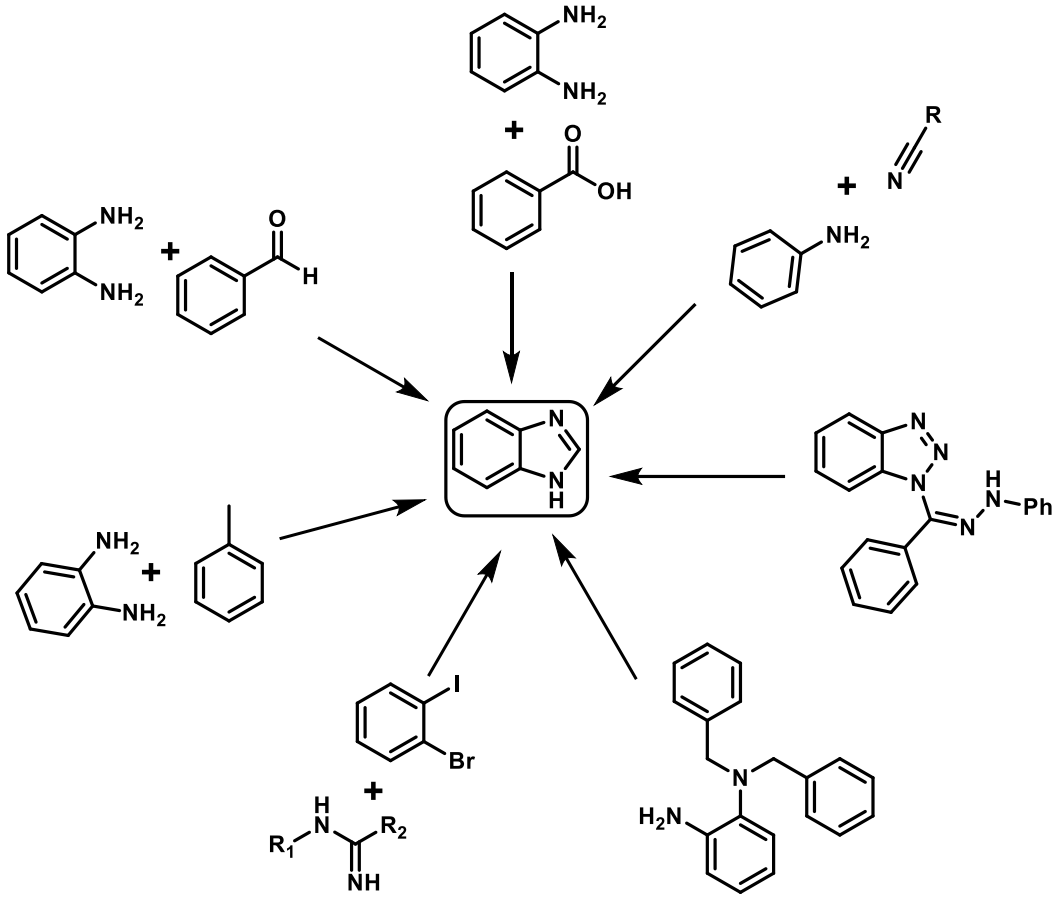


Figure 1.7 Few biologically active compounds containing imidazole moiety

Various methods have been employed to synthesize benzimidazole and its derivatives, including condensation reactions of *o*-phenylenediamine with carbonyls[51], oxidative condensation reactions of alcohols, methyl arene derivatives with *o*-phenylenediamine[52,53], oxidative cyclization of N-aryl amidine intermediates formed by the addition of aniline to a nitrile[54,55], one-pot intermolecular cross-coupling of *o*-haloacetoanilide with guanidines[56], intramolecular C(sp^3)–H imination[57], and thermolysis of benzotriazole derivatives.[58] (**Scheme 1.6**)



Scheme 1.6 Synthesis of benzimidazole and its derivatives

1.2.4.2 Benzothiazole

Benzothiazole has garnered significant interest due to its diverse range of biological, pharmaceutical, and intriguing chemical applications.[59] 2-Substituted benzothiazole derivatives exhibit promising potential for a wide range of applications, including antidiabetic, anti-inflammatory, antitumor, antifungal, antiviral, antipsychotic, antiarrhythmic, neurodegenerative, mosquitocidal properties[60] and serve as imaging agents for Ca2þ channel antagonists. Furthermore, they also demonstrate activities such as anti-HIV, antituberculosis, analgesic, and diuretic effects, among others.[61] (**Figure 1.8**)

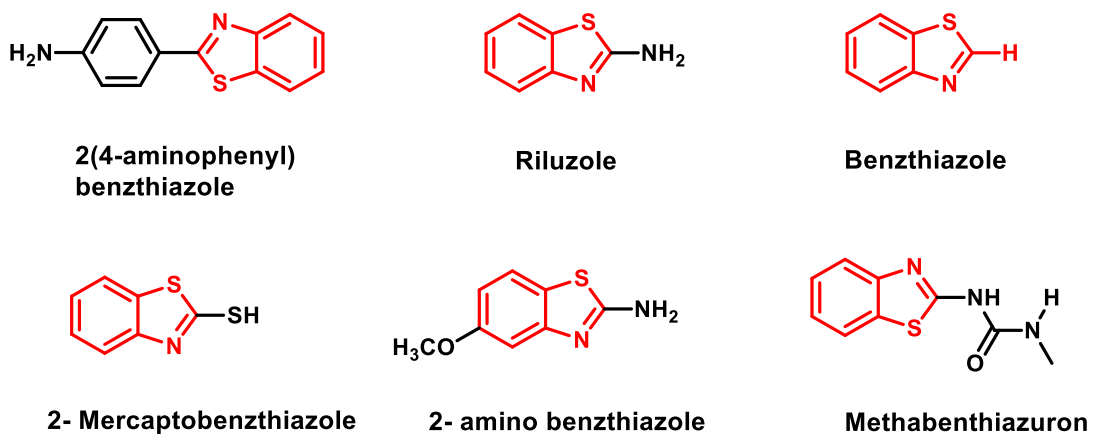
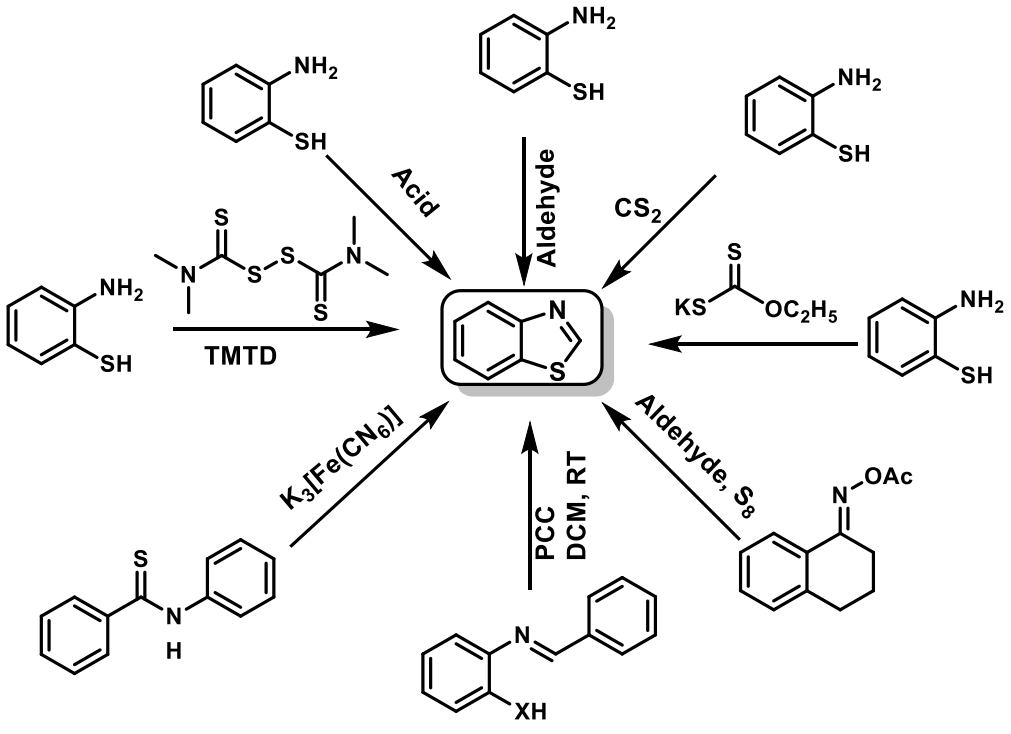


Figure 1.8 Few biologically active compounds containing Benzothiazole moiety

Benzothiazole can be synthesized through various methods, including the reaction of 1,2-aminothiophenol with carbonyl compounds[62], 2-halogen-substituted anilines, and dithiocarbamates in the presence of *t*-BuOK.[63] Other methods involve the oxidative cyclization of thiobenzanilinide using potassium cyanohexaferrate[64], oxidative cyclization of Schiff's base[65], a three-component reaction involving cyclohexenone oximes, aldehydes, and elemental sulfur[66], as well as the utilization of tetramethylthiuram disulfide (TMTD) and *o*-aminothiophenol.[67] Additionally, arylthioureas can undergo intermolecular oxidative C-H bond functionalization in the presence of pyridine to yield benzothiazole.[68] (**Scheme 1.7**)



Scheme 1.7 Synthesis of benzothiazole and its derivatives

1.2.4.3 Benzoxazole

Benzoxazoles and their derivatives are aromatic heterocyclic compounds incorporating nitrogen and oxygen atoms. These compounds are prevalent in various natural products and are recognized as valuable pharmacophores in the field of drug discovery. Moreover, numerous benzoxazole derivatives have been identified and utilized as drugs in various therapeutic areas. These derivatives possess diverse properties, serving as antimycobacterial agents, peroxisome proliferators activated receptor γ antagonists, natural cytotoxic products, cathepsin S inhibitors, 5-HT3 receptor antagonists, non-nucleoside reverse transcriptase inhibitors, elastase inhibitors, estrogen receptor-β agonists, and exhibit activities such as antidiabetic, antimicrobial, anticancer, anti-HIV,

anticonvulsant, anti-inflammatory, antinuclear, and antitumor effects, among others.[69–71] (**Figure 1.9**)

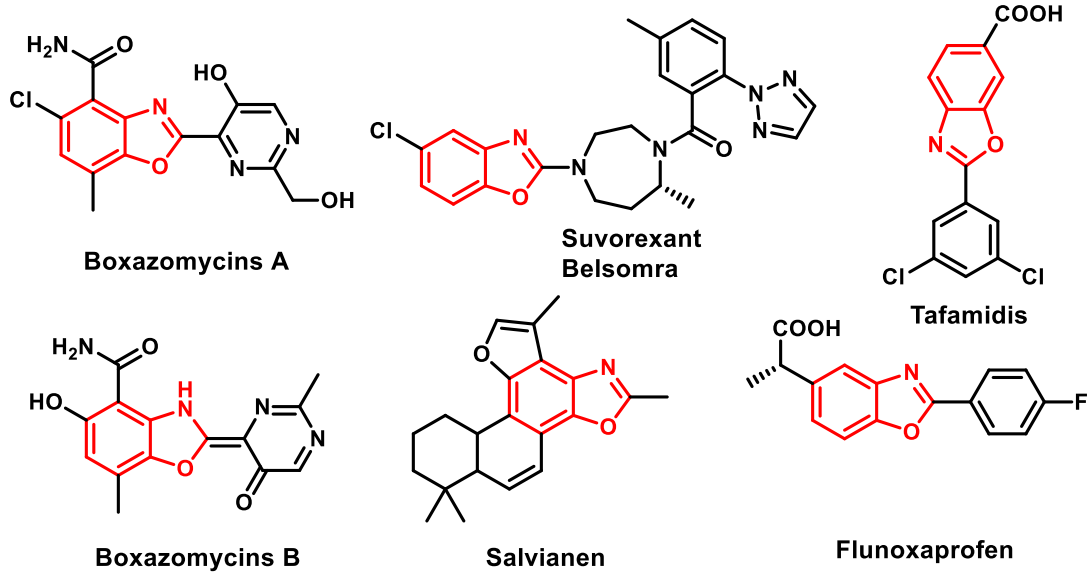
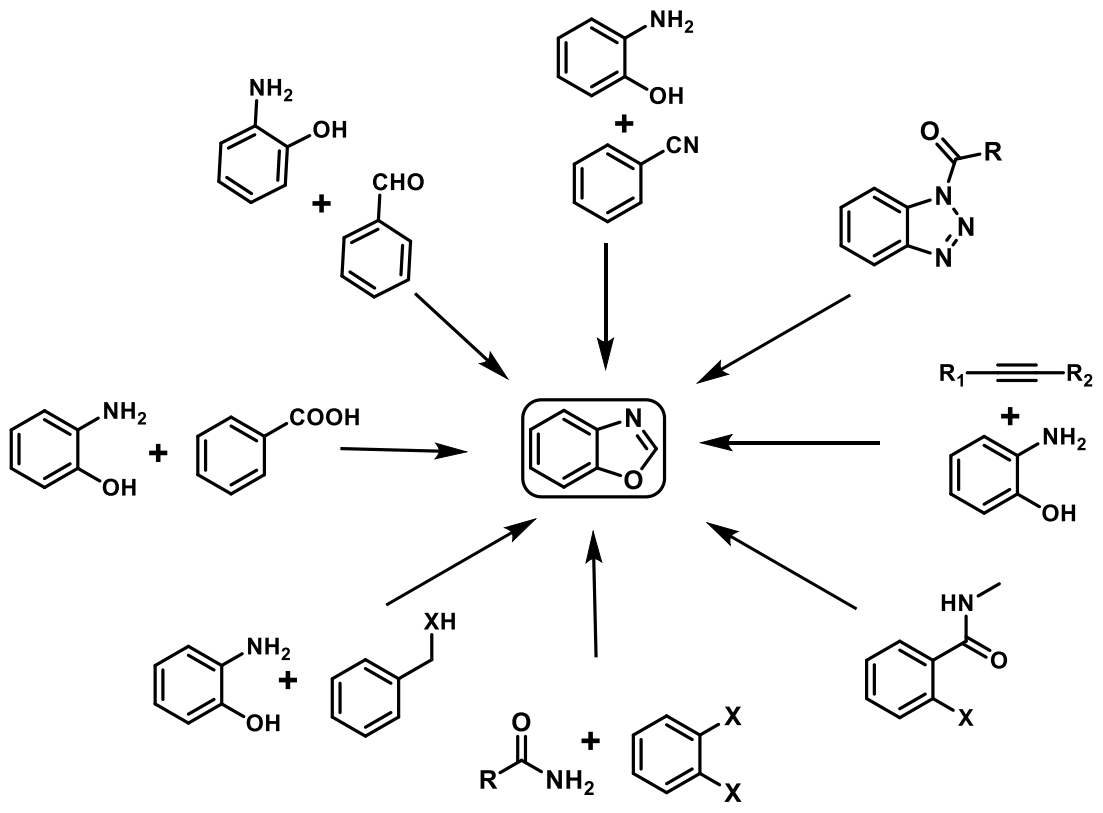


Figure 1.9 Few biologically active compounds containing benzoxazoles moiety

Benzoxazole and its derivatives have been synthesized using various methods. These include the reaction of aldehyde/carboxylic acid derivatives with 2-aminophenol under different conditions,[72,73], oxidative condensation reactions involving toluene/, benzyl alcohols/, benzyl amines/, styrene with 2-aminophenol.[74,75] Additionally, one-pot intermolecular C-heteroatom coupling of N-(2-bromophenyl) benzamide,[76] intermolecular cross-coupling of 1,2-dihaloarenes with amide[77], intramolecular C-N cross-coupling of 2-haloanilines with acyl halides/thioacyl halides[78], hydroamination of alkynes with 2-aminophenols[79] benzotriazole rings cleavage of N-acyl benzotriazole[80] have been employed as synthetic routes for benzoxazole derivatives. (**Scheme 1.8**)



Scheme 1.8 Synthesis of Benzoxazoles and their Derivatives

1.2.4.4 Indole

Indole derivatives exhibit a wide range of biological activities and are commonly found in various natural products. The exploration of indole chemistry emerged alongside the investigation of indigo dye. The conversion of indigo to isatin, followed by the formation of oxindole derivatives, is a possible pathway. Indole derivatives possess a multitude of biological properties, including but not limited to anti-inflammatory, anticonvulsant, cardiovascular, and antibacterial effects. In particular, 3-substituted indole derivatives have a crucial significance in synthesizing biologically active compounds.[81–83] **Figure 1.10** illustrates several indole compounds that exhibit biological activity.

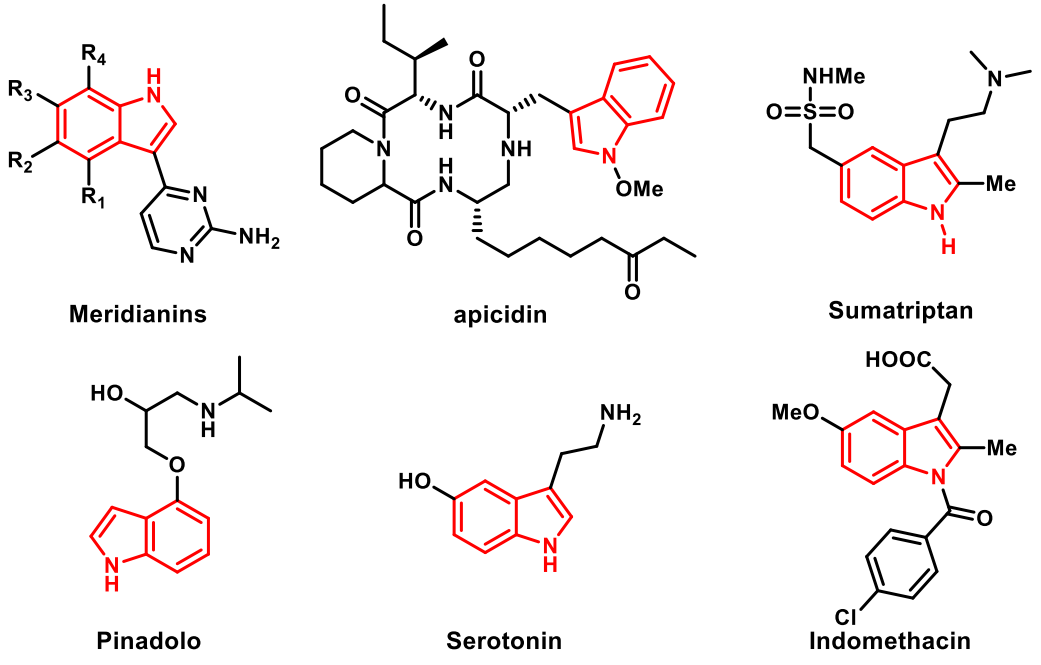
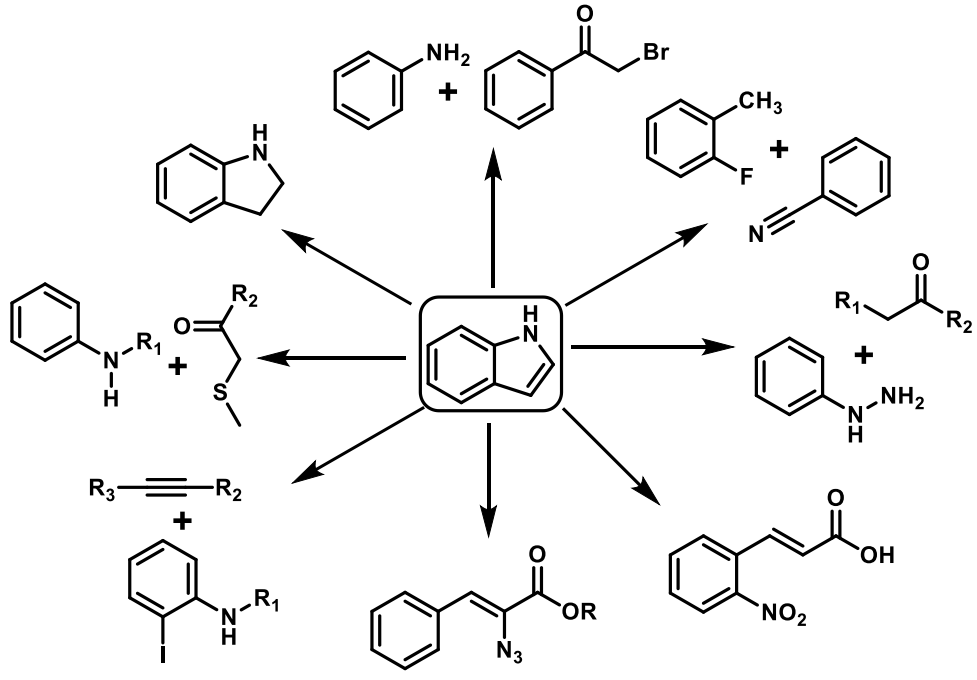


Figure 1.10 Representatives of substituted indoles

Indoles and their derivatives have been synthesized using various methods. These methods include the "Fischer indole synthesis," which involves the reaction of phenylhydrazine and carbonyls (aldehyde or ketone) under acidic conditions.[84] The "Bischler-Möhlau indole synthesis" utilizes α-bromo-acetophenone and excess aniline to yield 2-aryl-indole. The potassium tertiary butoxide-promoted dehydrogenation of indoline,[85] the reaction of 2-fluorotoluenes and benzonitriles in the presence of a base,[86] and the addition of aniline and a ketone bearing a thioether substituent are also employed for indole synthesis, known as the "Gassman indole synthesis".[87] Furthermore, the "Larock indole synthesis" involves using a palladium catalyst to react ortho-iodoaniline and a disubstituted alkyne.[88] The thermal decomposition of 3-aryl-2-azido-propenoic ester into an indole-2-carboxylic ester, referred to as the "Hemetsberger indole synthesis",[89] and the "Baeyer-Emmerling indole synthesis" using substituted ortho-nitro

cinnamic acid and iron powder in a strongly basic solution are additional methods employed for indole synthesis.[90] (**Scheme 1.9**)



Scheme 1.9 Synthesis of Indole and its derivatives

1.3 Multicomponent Synthesis of N-containing Compounds

1.3.1 Microwave-Assisted Reactions

1.3.2 Ultrasound-Assisted Reactions

1.3.3 Mechanochemical Method

1.3.4 Photochemical Synthesis

1.3.5 Transition Metal Catalyzed

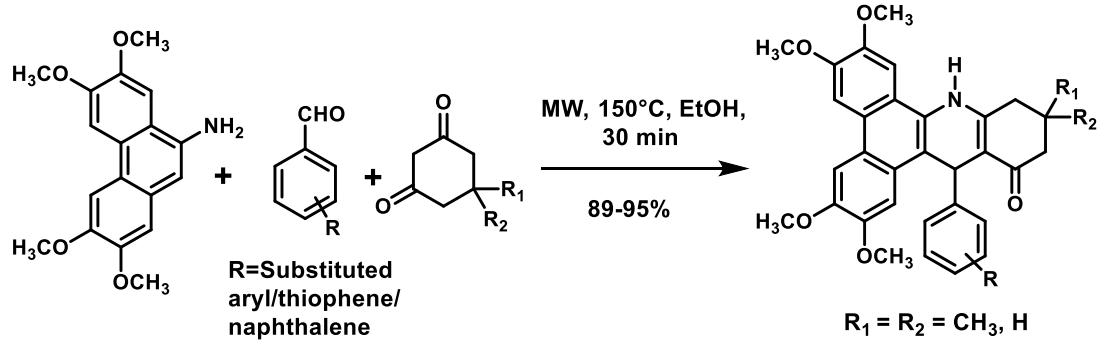
1.3.6 Nanoparticle Catalyzed

1.3.1 Microwave-Assisted Reaction

The use of microwave irradiation as an innovative energy source to initiate reactions has gained significant popularity and value in the field of organic chemistry. The efficient

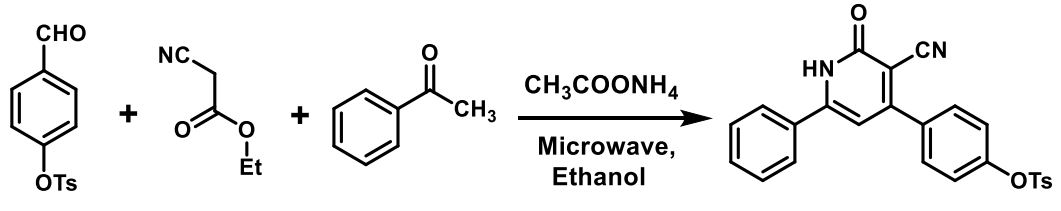
heating capabilities of microwaves often result in a noticeable enhancement of reaction rates and a substantial reduction in reaction time. Recent investigations into organic synthesis using microwave irradiation have revealed that these effects are primarily attributed to the dielectric heating properties of microwaves. Concurrently, certain studies have proposed that the non-thermal effects of microwaves have the potential to alter reaction dynamics and lower the activation energy of organic reactions.[91–95]

Under the influence of microwave irradiation, Kumar et al. devised a rapid methodology to synthesize phenanthrene-fused tetrahydrodibenzoacridinones.[96] (**Scheme 1.10)**



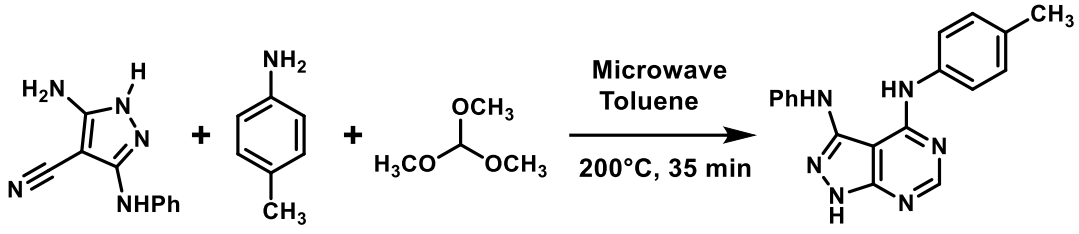
Scheme 1.10 Synthesis of phenanthrene-fused tetrahydrodibenzoacridinones

Under the influence of microwave irradiation in ethanol, Abdel-Hamid and colleagues introduced a novel class of pyridine derivatives utilizing *p*-formylphenyl-4-toluenesulfonate, ethyl cyanoacetate, acetophenone, and ammonium acetate.[97] (**Scheme 1.11**)



Scheme 1.11 Synthesis of Pyridines derivatives

Under the influence of microwave irradiation, Hui Ng and colleagues developed a new method for the synthesis of pyrazolo[3,4-d]pyrimidine.[98] (**Scheme 1.12**)



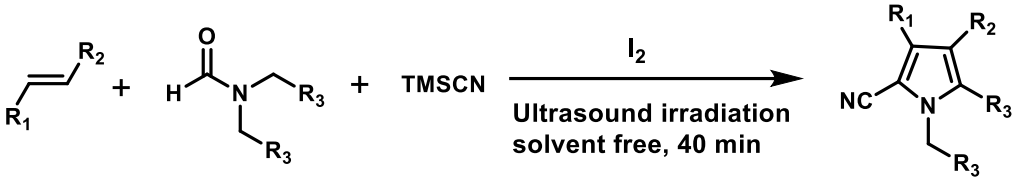
Scheme 1.12 Synthesis of Pyrazolo pyrimidine derivatives

1.3.2 Ultrasound-Assisted Reactions

In recent years, researchers have shown great interest in the rapid synthesis facilitated by ultrasound, as it addresses the societal need to produce numerous environmentally friendly and ecologically benign biologically and industrially active compounds.[99–103] Ultrasound-assisted chemistry has emerged as a comprehensive discipline that aligns with the principles of green chemistry. By leveraging ultrasound's cavitation properties, ultrasonic activation enhances mass transfer, dramatically reducing reaction times from hours to minutes. This technique also mitigates side reactions, improves reproducibility, and increases yields compared to traditional thermal heating methods. Ultrasound induces specific activation in chemical reactions through a physical phenomenon called acoustic cavitation. Cavitation disrupts the attractive forces among molecules in the liquid phase, generating a unique reaction environment within the vessel through bubbles' formation, growth, and implosive collapse. This environment accelerates reactions significantly.[104,105]

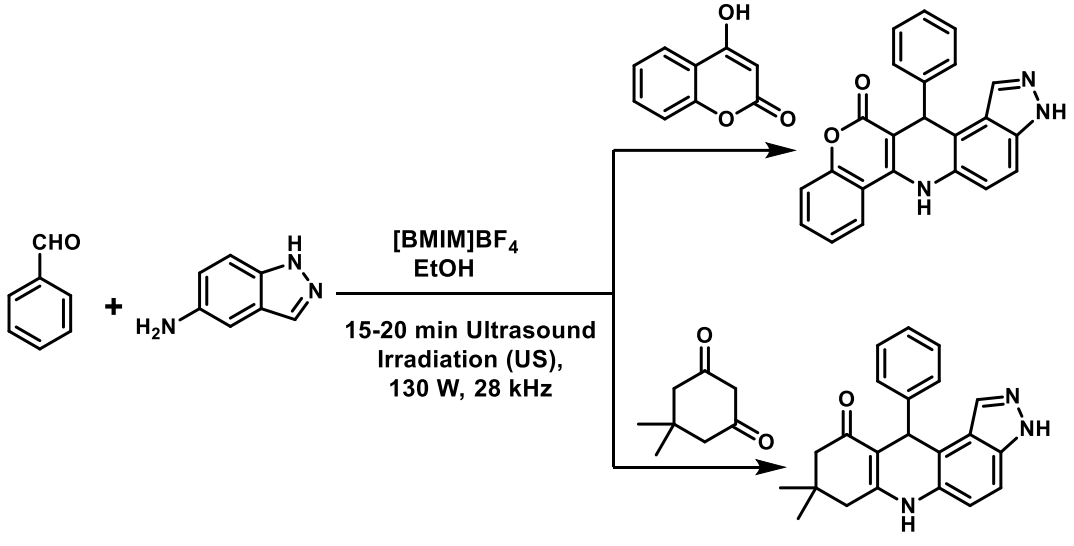
Gui et al. devised an innovative approach using the ultrasound-assisted tandem one-pot synthesis of polysubstituted pyrroles focusing on green and sustainable chemistry

principles under solvent-free conditions using iodine as both the catalyst and oxidant.[106] (**Scheme 1.13)**



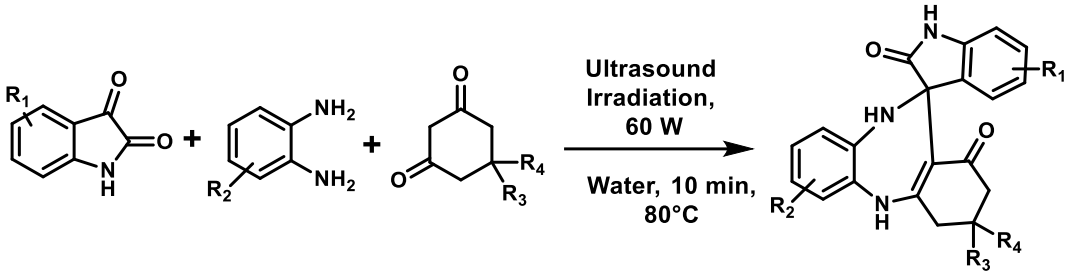
Scheme 1.13 Synthesis of polysubstituted pyrroles

Chudasama et al. have provided ultrasound-promoted convenient and ionic liquid [BMIM]BF_4 assisted green synthesis of diversely functionalized pyrazolo quinolone using 1,3-dicarbonyl compound i.e., 4-hydroxycoumarin or dimedone, benzaldehyde, and 5-amino indazole.[107] (**Scheme 1.14**)



Scheme 1.14 Synthesis of pyrazolo quinolone

In 2018, our research group developed a facile and efficient multicomponent ultrasound-assisted "on water" synthesis of benzodiazepine ring using isatin, 1, 2-phenylenediamine, and 5,5-dimethylcyclohexane-1,3-dione.[108] (**Scheme 1.15**)



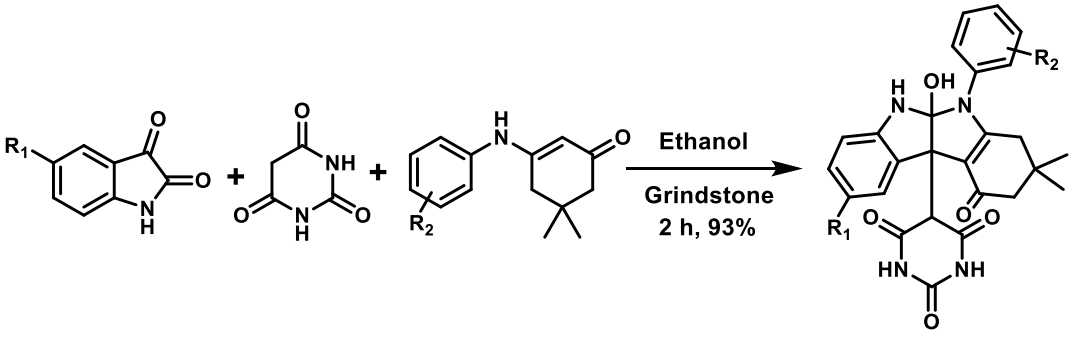
Scheme 1.15 Synthesis of benzodiazepine

1.3.3 Mechanochemical Synthesis of N-Heterocyclic Compounds

Over the past twenty years, the concept of mechanochemistry, which involves chemical transformations driven by mechanical energy, has gained significant popularity.[109,110] According to IUPAC, they have been recognized as one of the top ten transformative technologies with global impact.[111] The transformations are facilitated by the mechanical energy generated through processes such as shearing, kneading, grinding, or milling.[112] This technique encompasses various principles of green chemistry, including the reduction or elimination of solvents, environmentally friendly conditions, fast reaction kinetics, and the elimination of lengthy workup procedures.[113] Mechanochemistry's attractive potential is not confined to traditional organic synthesis or organometallics,[114] but also includes fields such as biocatalysis,[115] API synthesis,[116] polymer chemistry,[117] supramolecular chemistry,[118] and material chemistry.[119] In the latter, Mechanochemical applications have greatly aided multicomponent reactions[120–125] for the preparation of sulphur-containing[126–128] and nitrogen-containing heterocycles.[29,129–132]

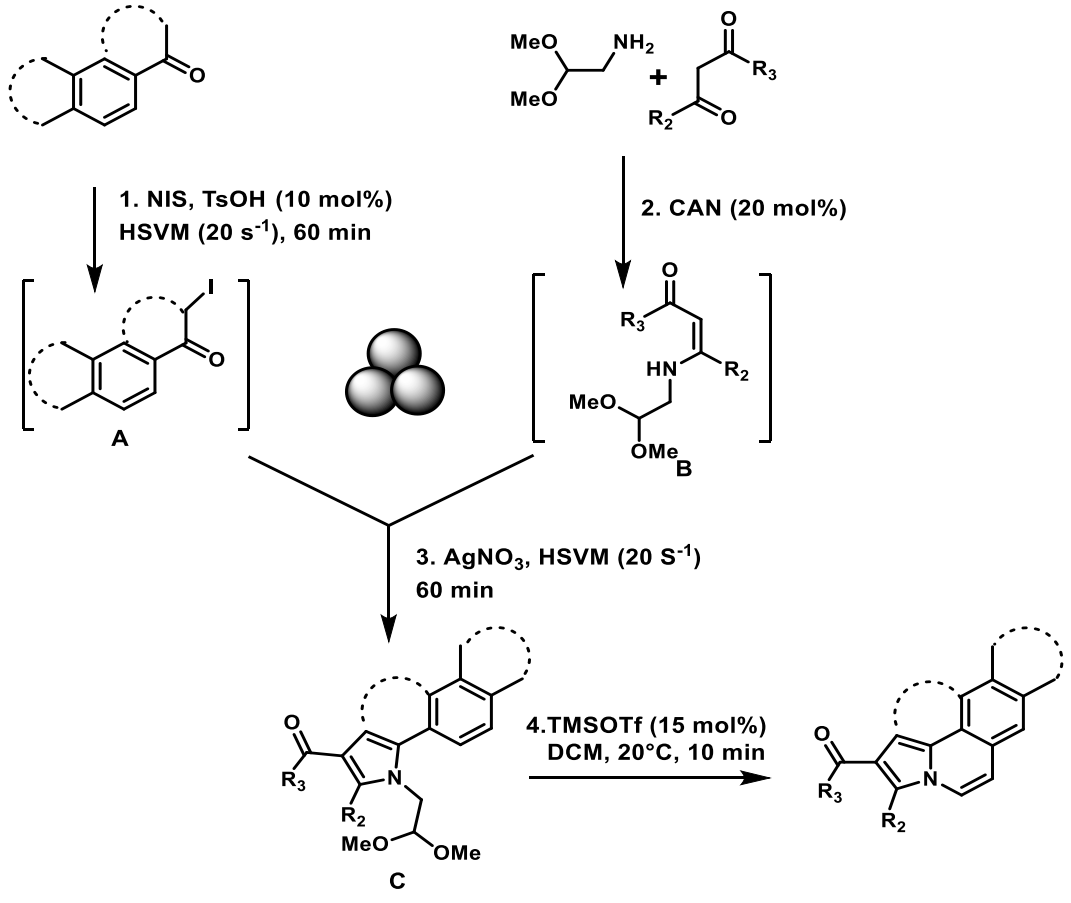
In 2020, our research team devised a highly efficient and novel approach for synthesizing indoloindolpyrimidine derivatives via multicomponent reaction utilizing isatin

derivatives, 1,3 diketones (barbituric acid), and enaminones under the grinding condition.[133] (**Scheme 1.16**)



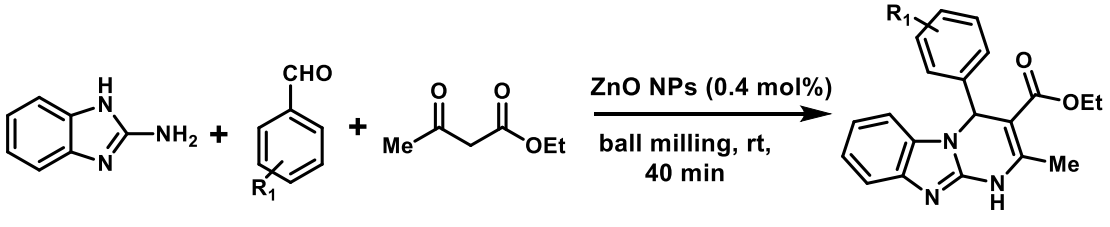
Scheme 1.16 Synthesis of indoloindolpyrimidine

Leonardi et al. reported a mechanochemical multicomponent synthesis of Pyrrolo[2,1-a]isoquinolines using ketones, 2,2-dimethoxyethylamine, and active methylene compounds.[124] (**Scheme 1.17**)



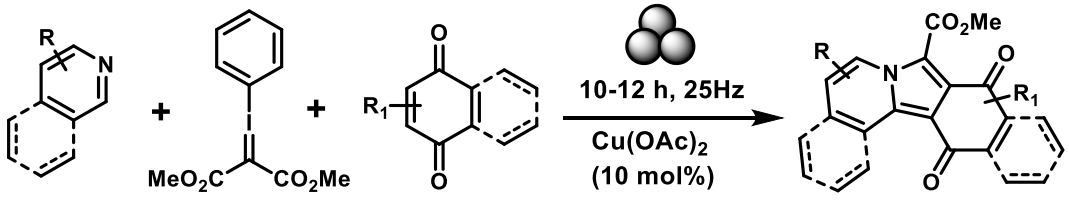
Scheme 1.17 Mechanochemical multicomponent synthesis of Pyrrolo[2,1-a]isoquinolines

Raj and co-workers reported multicomponent reactions for synthesizing pyrimidine derivatives with ZnO NPs using 2-aminobenzimidazole, ethyl acetoacetate, and benzaldehyde under a solvent-free ball milling technique.[134] (**Scheme 1.18**)



Scheme 1.18 Synthesis of pyrimidine derivatives

Sen et al. described a successful solvent-free mechanochemical multicomponent reaction that employed pyridine/isoquinoline derivatives, phenyl iodonium dimethyl malonate, and a variety of 1,4-quinones using catalyst copper acetate.[135] (**Scheme 1.19**)



Scheme 1.19 Mechanochemical synthesis of indolizines

1.3.4 Visible Light-Mediated Synthesis of N-Heterocyclic Compounds

The significance of green chemistry has become increasingly evident to chemists due to the growing concerns over pollution and waste produced during chemical processes in industrial and laboratory settings. Consequently, their focus has shifted towards substituting conventional approaches with economically viable and eco-friendly alternatives, such as green catalysts, environmentally benign solvents, and conditions that eliminate the need for solvents or catalysts.[136–138] Most chemical reactions necessitate an appropriate catalyst to facilitate the formation of desired products. While the utilization of stimuli can alleviate certain drawbacks associated with chemical processes, the absence of catalysts remains particularly enticing, particularly in industry and pharmaceuticals. Nonetheless, achieving reaction outcomes without catalysts demands the exploration of more efficient and economically viable alternatives. Furthermore, in certain instances, the indispensable role played by a catalyst renders its omission impractical.

In recent times, the utilization of visible light as an initiating source in chemical reactions has gained significant traction as a robust method for synthesizing bioactive organic compounds. This emerging research field holds promise in enhancing efficacy and synthetic versatility. The organic reaction initiated by visible light has garnered significant attention due to its utilization of pure, cost-effective, environmentally benign, user-friendly, renewable, and sustainable energy sources.[139–141] Photo-induced reactions exhibit enhanced kinetics due to light absorption from multiple directions within the reaction vessel.

In general, the application of light irradiation provides sufficient energy for the reaction to occur, eliminating the drawbacks associated with thermal activation, such as elevated temperatures or severe conditions. In order to achieve success in photochemical reactions, the reaction needs to involve the presence of light-absorbing species (such as photocatalysts or photoactive substrates).

1.3.4.1 Catalyst-free Multicomponent Synthesis under Visible Light

In general, catalyst-free reactions driven by visible light can progress through two pathways. Firstly, when at least one of the substrates can absorb light, it can undergo a single-electron transfer (SET) process, forming radical intermediates. Secondly, a complex can be formed between an electron-rich component and an electron-deficient component, known as an Electron Donor-Acceptor (EDA) complex, without needing a photocatalyst. (**Figure 1.11**) The presence of the EDA complex can be verified by the emergence of a distinct charge-transfer band associated with the complex in the UV-Vis

absorption spectrum. This results in an intense coloration in the visible-light range, shifting towards longer wavelengths.

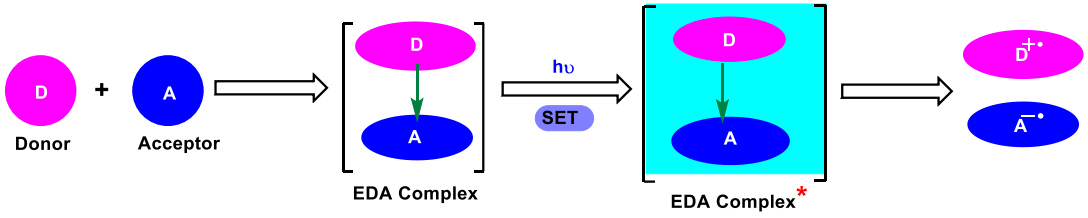
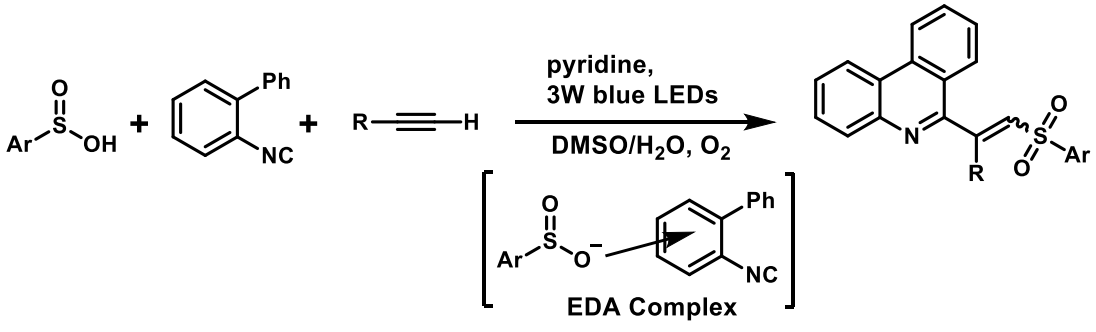


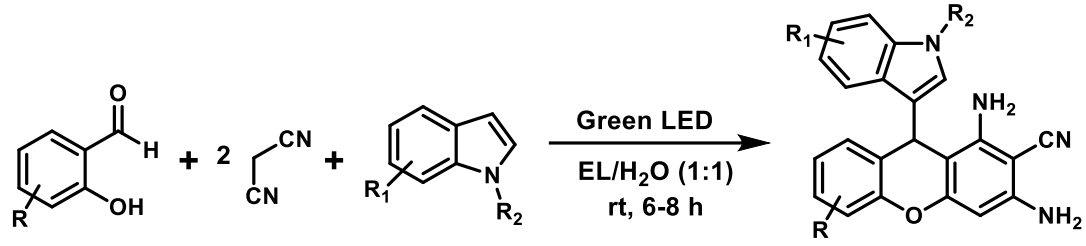
Figure 1.11 Photocatalytic pathway via EDA complex

A photo-driven method for synthesizing C6-polyfunctionalized phenanthridines through a radical cascade reaction was reported by Miao, Wang, and their colleagues in 2018. The reaction initiation involved the photosensitization of Electron Donor-Acceptor (EDA) complexes formed by arylsulfinate anions and biaryl isocyanides. Notably, the reaction exhibited high region- and stereoselectivity, yielding E-products under blue light irradiation and Z-products under UV light irradiation.[142] (**Scheme 1.20**)



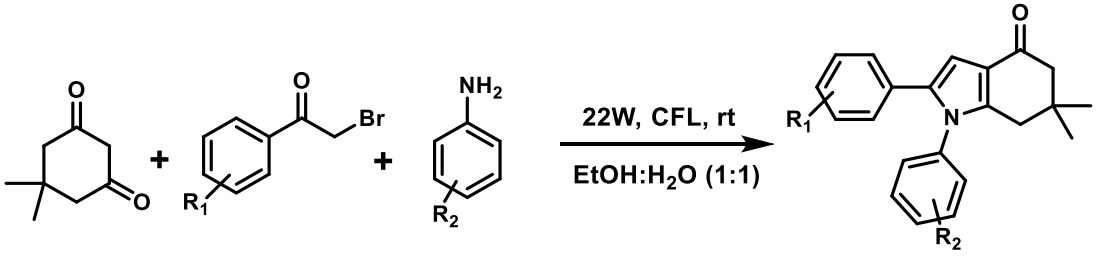
Scheme 1.20 Synthesis of phenanthridines

Zhang et al. successfully utilized visible light to synthesize numerous 5-substituted indole chromeno[2,3-b]pyridines at room temperature without needing a photocatalyst. The most favorable reaction conditions were achieved using EL/H_2O (ethyl lactate/ water) and green light irradiation.[143] (**Scheme 1.21**)



Scheme 1.21 Synthesis of 5-substituted indole chromeno[2,3-b]pyridines

Ansari et al. introduced a remarkably efficient one-pot approach mediated by visible light for synthesizing highly functionalized 4-oxo-tetrahydroindoles without a catalyst.[144] (**Scheme 1.22**)

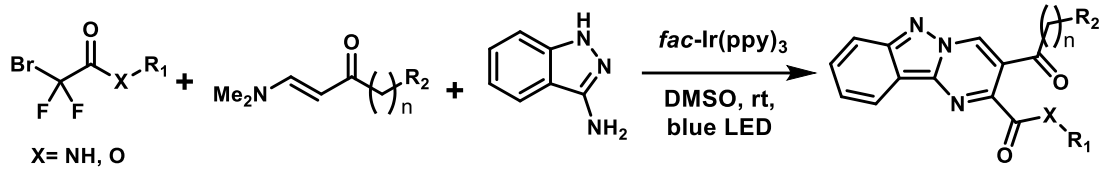


Scheme 1.22 Synthesis of 4-oxo-tetrahydroindoles

1.3.4.2 Visible-light Photo-redox Catalyzed Organic Synthesis

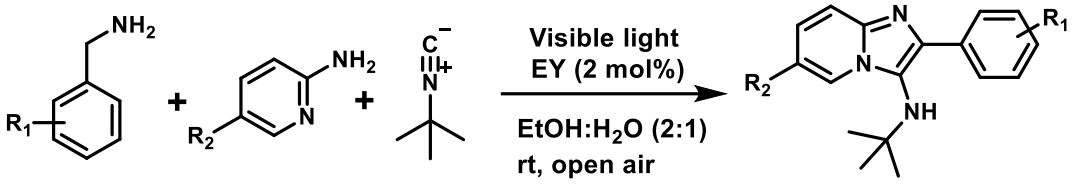
At first glance, photocatalysis can be deceiving since light (photons) is employed as a reagent, often in excessive amounts rather than in a catalytic manner. Photocatalysis refers to transformations that necessitate light as an energy source to advance, utilizing small quantities of light-absorbing photocatalysts such as metal complexes or organic dyes.[145] The excited photocatalyst can activate the substrate through various mechanisms, including single electron transfer (SET), energy transfer (ET), or hydrogen atom transfer (HAT).[146,147]

Geng and co-workers reported a synthesis of pyrimido[1,2-b]indazole from bromodifluoroacetic acid derivatives, enaminones, and 3-aminoindazoles via SET in the presence of *fac*-Ir(ppy)$_3$ as a photo-redox catalyst.[148] (**Scheme 1.23**)



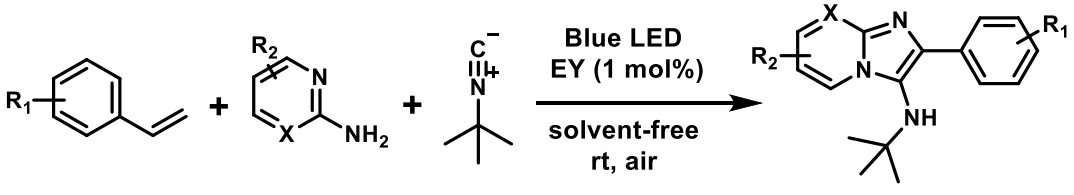
Scheme 1.23 Synthesis of pyrimidoindazole

In 2020, our research group synthesized 3- aminoimidazo[1,2-a]pyridines using benzylamine, 2-aminopyridine, and *t*-butylisocyanide under visible-light-irradiation via HAT process in the presence of eosin Y as a photo-redox catalyst.[149] (**Scheme 1.24**)



Scheme 1.24 Synthesized 3- aminoimidazo[1,2-a]pyridines

In 2021, our research group also reported the synthesis of 3-aminoimidazoheterocycles under solvent-free conditions via SET process using styrene, 2-aminoheterocycles, and tertiary butylisocyanide.[150] (**Scheme 1.25**)

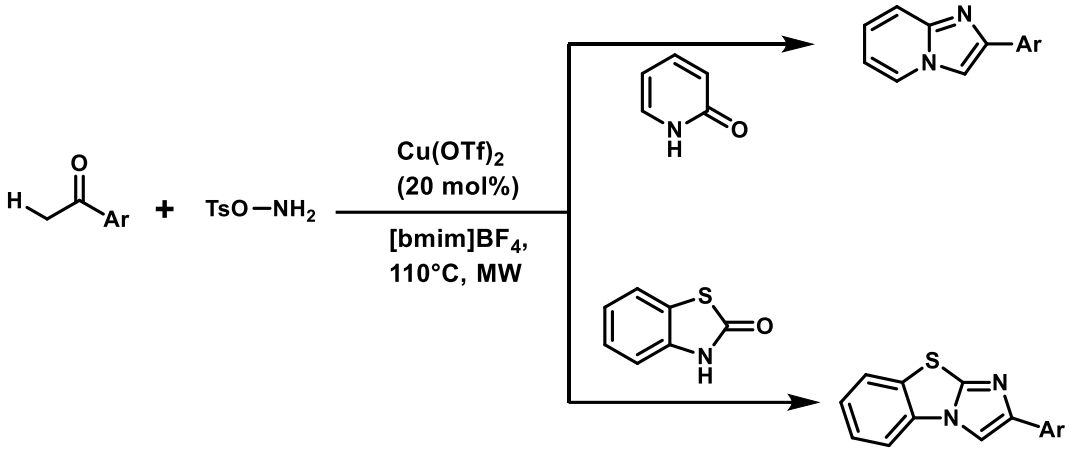


Scheme 1.25 Synthesis of 3-aminoimidazoheterocycles

1.3.5 Transition Metal-Catalyzed Synthesis of N-Heterocyclic Compounds

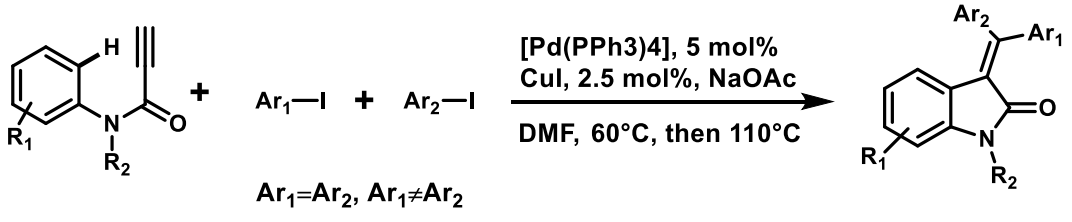
The introduction of the preamble to transition metal-catalyzed reactions in organic synthesis has unlocked the potential to functionalize traditionally unreactive C–H bonds, as well as achieve other extraordinary transformations. The exceptional characteristics of transition metal-catalyzed reactions have played a significant role in the growing popularity of transition metal-catalyzed multicomponent reactions (MCRs).[151] These MCRs involving transition metals have been integrated into various reaction sequences, resulting in an impressive diversity of molecular ensembles. While palladium-catalyzed processes have rightfully taken a central position, other transition-metal complexes are also gaining ground, implying the involvement of organometallic elementary steps that extend beyond cross-coupling and carbometallation. In addition to domino MCRs solely based on organometallic catalysis, the chronological and sequential combination of condensation, addition, and cycloaddition steps offers a vast playground for developing new sequences in heterocyclic synthesis. Some important transition metal-catalyzed multicomponent reactions are briefly described below:

Meshram et al. utilized a $Cu(OTf)_2$ catalyst and performed reactions of methyl ketones, *O*-tosylhydroxylamine, and either pyridin-2(1H)-one or thiazo/benzo[d]thiazol-2(3H)-ones in an ionic liquid medium [bmim]BF_4, leading to the successful synthesis of imidazole fused heterocycles.[152] (**Scheme 1.26**)



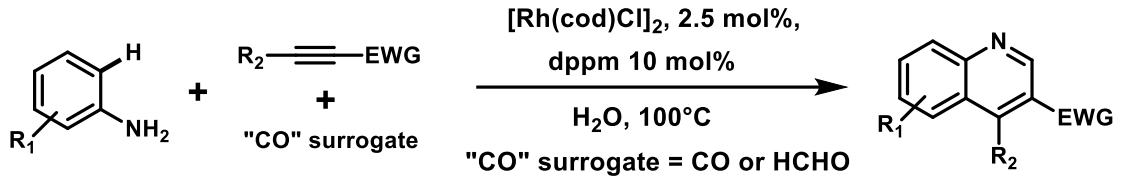
Scheme 1.26 Multicomponent synthesis of fused N-heterocycles

A three-component protocol for synthesizing 3-(diarylmethylene)oxindoles was reported in 2007 by Zhu and co-workers. The desired products were obtained through subsequent Sonogashira coupling and carbopalladation, which initiated aryl C–H vinylation.[153] (**Scheme 1.27**)



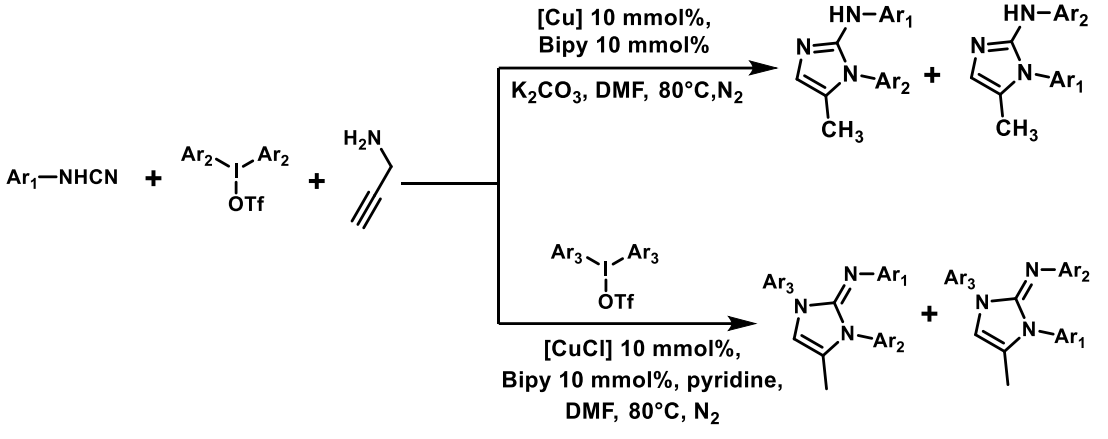
Scheme 1.27 Three-component synthesis of 3-(diarylmethylene)oxindoles

Balaraman et al. accomplished the tandem synthesis of quinolines by employing $[Rh(cod)Cl]_2$ as a catalyst. This process involved the formation of new C─C and C═N bonds through reactions between anilines, an electron-withdrawing group (EWG) functionalized alkynes, and a CO surrogate (CO or HCHO).[154] (**Scheme 1.28**)



Scheme 1.28 Three-component synthesis of quinolones

Xu et al. recently reported the successful utilization of Copper catalysts in three-component and four-component cascade reactions involving cyanamides, dirayliodonium triflates, and propargylamine. This innovative approach enables the efficient synthesis of polysubstituted 2-aminoimidazoles and 2-iminoimidazoles, employing K_2CO_3 and pyridine as the base under an N_2 atmosphere.[155] (**Scheme 1.29**)



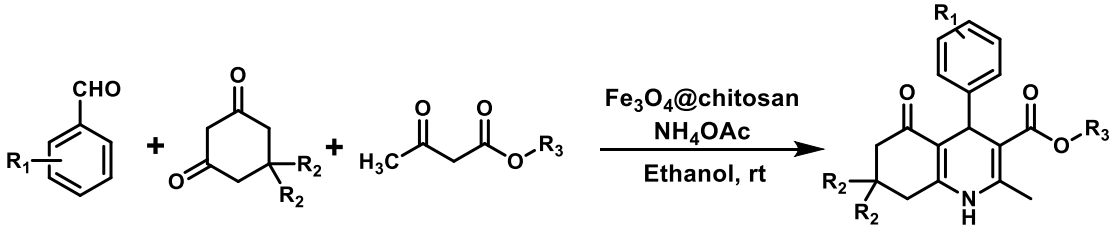
Scheme 1.29 Multicomponent synthesis of 2-aminoimidazoles and 2-iminoimidazoles

1.3.6 Nanoparticle Catalyzed Synthesis of N-Heterocyclic Compounds

In recent decades, nanostructured materials have emerged as appealing candidates for heterogeneous catalysts in a variety of organic transformations. These materials align well with the principles of green and sustainable chemistry.[156–158] Notably, significant progress has been achieved by scientists and researchers in synthesizing well-defined nanostructured materials.[159] Within these advancements, novel approaches have allowed

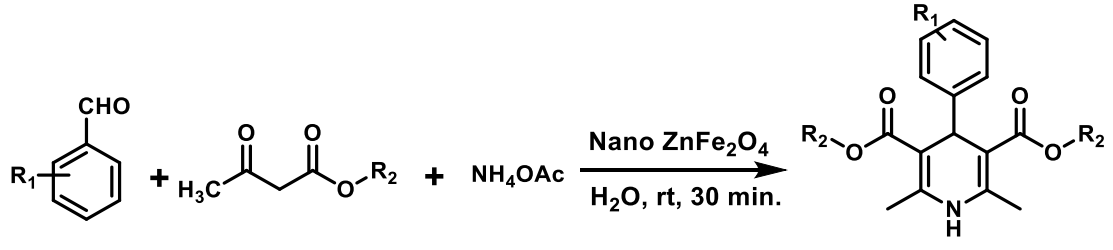
for the deliberate design and synthesis of highly active and selective nanostructured catalysts through precise control of the structure and composition of the active nanoparticles.[160] Furthermore, the ease of separating, recovering, and reusing these nanoparticles further enhances their appeal as green and sustainable catalysts.[161,162]

Maleki et al. employed a green and heterogeneous catalyst, Fe_3O_4@chitosan, to synthesize 1,4-dihydropyridine derivatives in a convenient single-step reaction.[163] (**Scheme 1.30**)



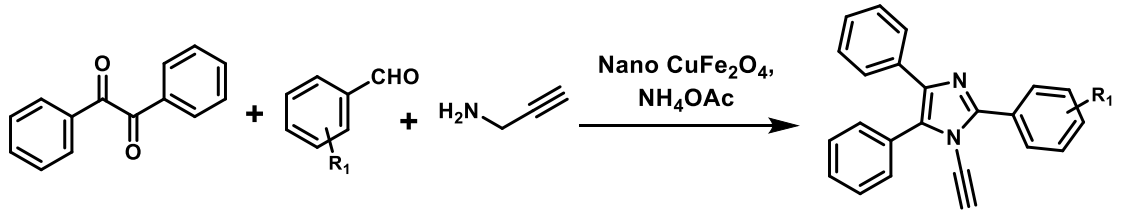
Scheme 1.30 One-pot synthesis of 1, 4-dihydropyridine derivatives

A highly efficient, rapid, and environmentally friendly Hantzsch synthesis of 1,4-dihydropyridines (DHPs) was developed by Naik and co-workers[164] using $ZnFe_2O_4$ NPs as a bimetallic nanocatalyst. (**Scheme 1.31**)



Scheme 1.31 Synthesis of 1,4-dihydropyridine

Remaily et al. reported the synthesis of 1,2,4,5-tetrasubstituted imidazoles through the reaction of benzil, aldehyde, propargylamine, and ammonium acetate using an heterogeneous magnetic nano-catalyst, $CuFe_2O_4$.[165] (**Scheme 1.32**)



Scheme 1.32 Synthesis of 1,2,4,5-tetrasubstituted imidazoles

In view of the importance of multicomponent synthesis of nitrogen containing heterocyclic compounds, our interest is to explore the chemistry (synthesis and structural characterization) of 3-Aminoimidazo[1,2-a]Pyridines, 1,4-dihydropyridines, N-heterocyclic Pyrimido [4,5-b] Quinolines and Pyrido [2,3-d] Pyrimidines under visible light irradiation, and mechanochemical approach etc. The studies have been described in subsequent **chapters 2-5**.

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