

CHAPTER 1

Over View of Nitrogen Containing Compounds

Overview of Nitrogen Containing Organic Compounds

Nitrogen is a naturally occurring element that is essential structural moiety of all the living things and it is found in amino acids, nucleic acids, vitamins and hormones. They display an enormous structural diversity such as simple functional group, degrees of substitution and heterocyclic system. Nitrogen containing compounds represent as a core skeleton or exists alone in many biologically, pharmaceutically and synthetically active compounds. *N*-heterocyclic organic compounds are very important industrially, biologically and also used for the functioning of many developments in human society.

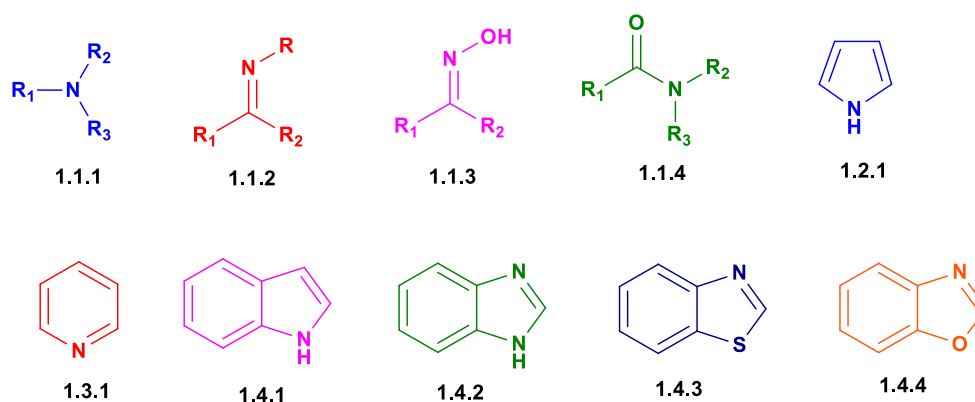


Figure 1.1 Nitrogen containing some main class of organic compounds

This chapter has covered some main class of nitrogen containing functional groups. Acyclic nitrogen containing compounds (1.1) like amine (1.1.1), imine (1.1.2), oxime (1.1.3), amides (1.1.4) and nitrogen containing five membered heterocyclic (1.2) pyrrole (1.2.1),

six membered (1.3) pyridine (1.3.1) and fused heterocycles (1.4) such as indoles (1.4.1), benzothiazoles (1.4.2) benzimidazoles (1.4.3) and benzoxazoles (1.4.4) (**Figure 1.1**).

1.1 Nitrogen containing acyclic compounds

1.1.1 Amines

Amines are the most important and widely focused organic compounds and derived from ammonia by replacing one, two or all the three protons by different carbon derivatives. Since amines are present in amino acids which involves in protein synthesis it shows that they are very important in survival of living beings. On the other hand amines are cornerstone in a variety of different industries such as dyes, drugs, surfactants, agrochemicals and plastics as auxiliaries for the rubber, textile, paper industries etc (Crozet et al. 2011).

Amines are also used in the synthesis of many drugs like Amphetamine which exists in two enantiomeric forms levoamphetamine and dextroamphetamine and are used in the treatment of attention deficit hyperactivity disorder (ADHD), obesity and narcolepsy. Chlorpheniramine is an antihistamine used to treat the symptoms of allergic conditions. Salmeterol is an adrenergic receptor agonist (LABA) used in the prevention of asthma symptoms and maintenance of chronic obstructive pulmonary disease (COPD) symptoms (**Figure 1.2**).

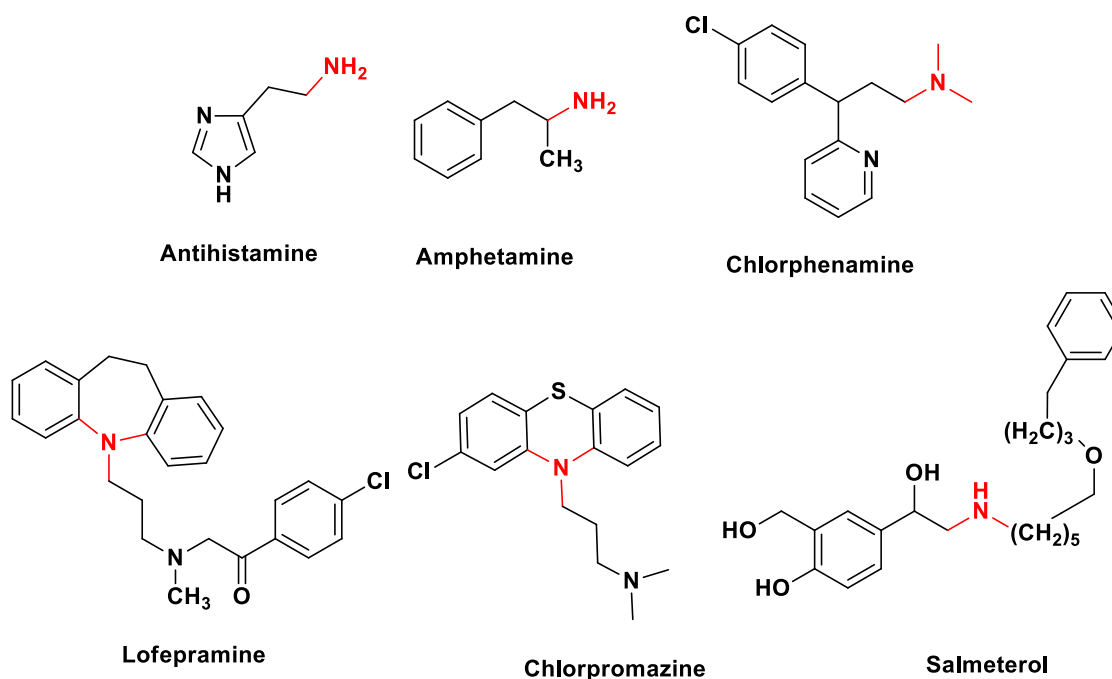
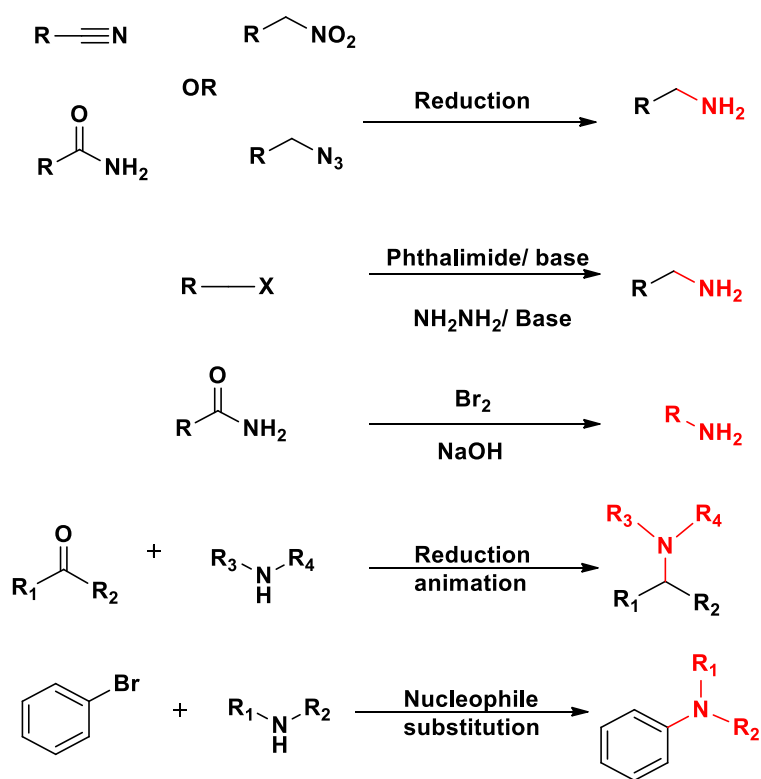


Figure 1.2 Some biological active drugs containing amine functional group

Primary amines are mainly synthesized by the reduction of amides (Bhunja et al. 2020), aliphatic and aromatic nitro compounds (Pehlivan et al. 2010, Orlandi et al. 2016, Goswamia et al. 2020), cyanides (Haddenhamet al. 2008), azides (Lee et al. 2001, Lin et al. 2002) and different oximes (aldoximes and ketoximes) (Abiraj et al. 2004, Sadighnia et al. 2019) by using different reducing agents. Primary amines are also synthesized by Gabriel synthesis method, it involves the initial alkylation of potassium phthalimide to form *N*-alkyl phthalimide, which on hydrolysis provides corresponding primary amine as final product and also by Hofmann rearrangement (Loudon et al. 1984, Gibson et al. 1968).

Secondary and tertiary amines are directly prepared by the nucleophilic substitution of primary and secondary amines with the alkyl halides to give corresponding secondary and tertiary amines respectively. They are also prepared by reductive amination of aldehydes or ketones with primary and secondary amines (Varjosaari et al. 2017) (**Scheme 1.1**).



Scheme 1.1 Synthesis of primary, secondary and tertiary amines

1.1.2 Imines

An imine is a functional group, which is commonly referred to as azomethines or Schiff bases containing a carbon–nitrogen double bond and have general formula $R_2C=NR$, when $R = H$, the compound is a primary imine, when R is hydrocarbyl, the compound is a secondary imine. The term "imine" was coined by the German chemist Albert Ladenburg in 1883. Imines and its derivative have been documented as key intermediates for synthesizing nitrogen containing biologically active heterocycles and alkaloid (Martin 2009, Dai et al. 1999) (**Figure 1.3**).

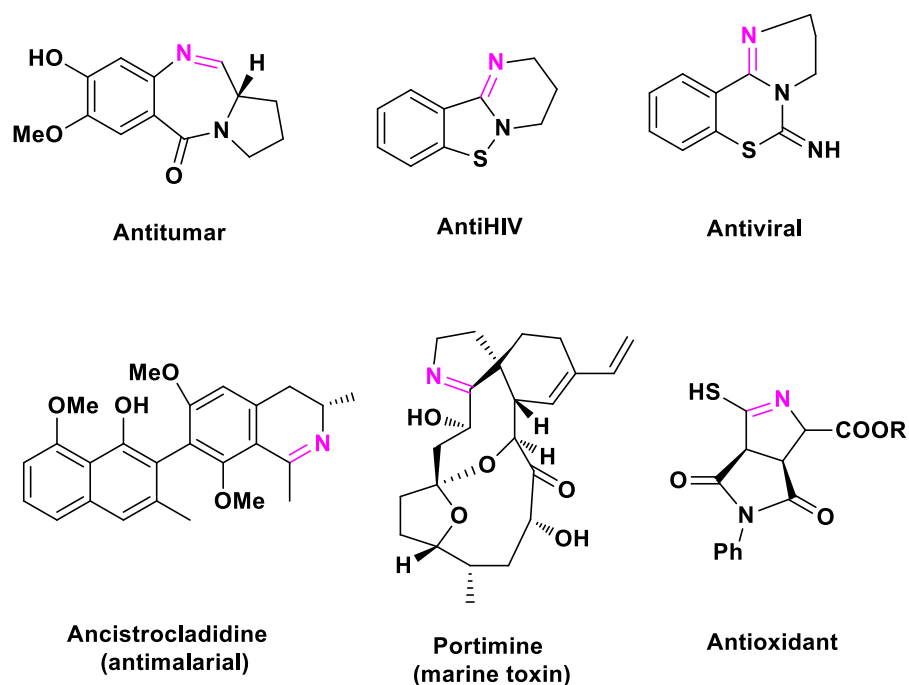
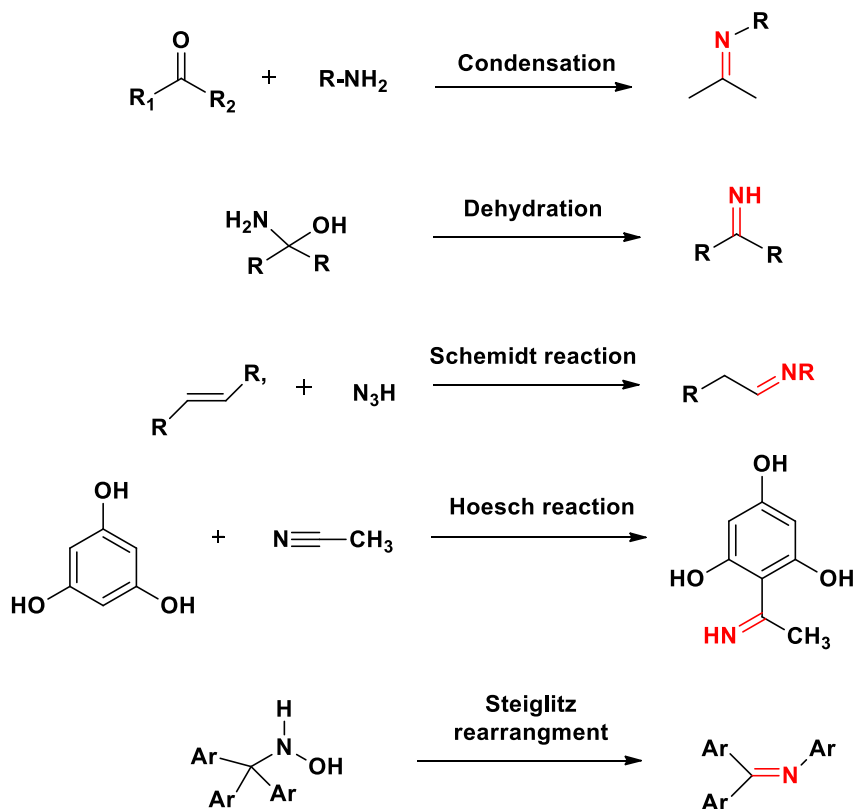


Figure 1.3 Some biological active drugs containing imine functional group

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Traditionally primary imines are synthesized by condensation reaction of aldehydes with primary amines (Baruah et al. 2017, Ali et al. 2013). Secondary imines can be synthesized by condensation of ketones, which is less common due to low reactivity of ketones. Some other methods are also known like dehydration of hemiaminals (Shu et al. 2019), Stieglitz rearrangement in which trityl hydroxylamine (Ar_3CNHOH) rearranges to a triaryl imine, in the presence of catalyst PCl_5 (Sisti et al. 1994). In Houben-Hoesch reaction nitriles react with arenes in the presence of acid gives carbonyls via imine intermediate and it is isolated as reaction intermediate (Yato et al. 1990) (**Scheme 1.2**).



Scheme 1.2 Synthesis of imine derivatives

1.1.3 Oximes

The name oxime is an abbreviation of oxy-imine, $>C=N-OH$. Two structures (A) and (B) (**Figure 1.4**) were proposed for the oxime group but on the basis of neutron diffraction study of dimethylglyoxime, the presence of $-OH$ group has been established which favours the structure (A). In solid state, oximes are found to be associated by H-bonding $O-H\cdots N$. The presence of mild acidic hydroxyl group and slightly basic nitrogen atom makes the oxime group as an amphoteric in nature. In oxime carbon and nitrogen atoms are sp^2 hybridized. There is no free rotation about $C=N$, hence oximes of aldehyde and ketone exhibit geometrical isomerism.

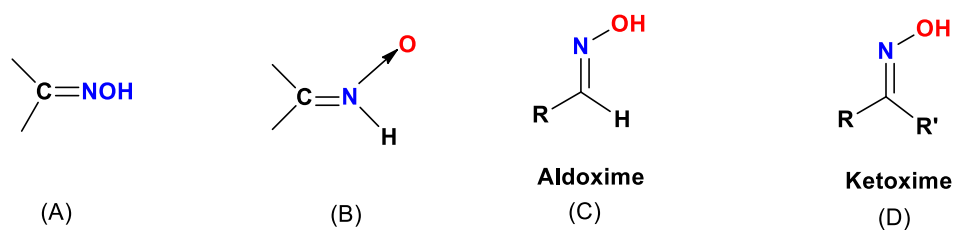


Figure 1.4 Structure (A & B) and classification (C & D) of oximes

Oxime is an important structural constituent, used as a building block for the synthesis of pharmaceuticals and agrochemicals (Ashani et al. 2008). Oxime compounds found extensive applications in different fields such as antidotes for nerve agents e.g. Pralidoxime, Obidoxime, Methoxime, Asoxime and Trimedoxime (**Figure 1.5**). Oximes are also found in antioxidants, insecticides, vasodilators, antimicrobial agents and inhibitors of P450. Diacetyloxime is used as an inhibitor of ATP-sensitive potassium ion channels

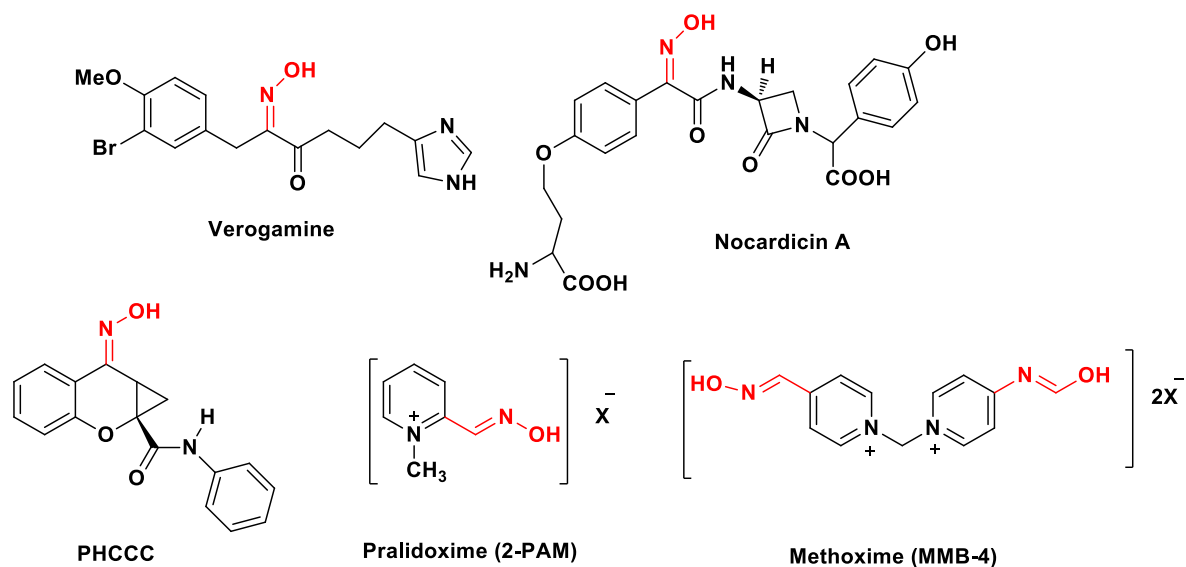
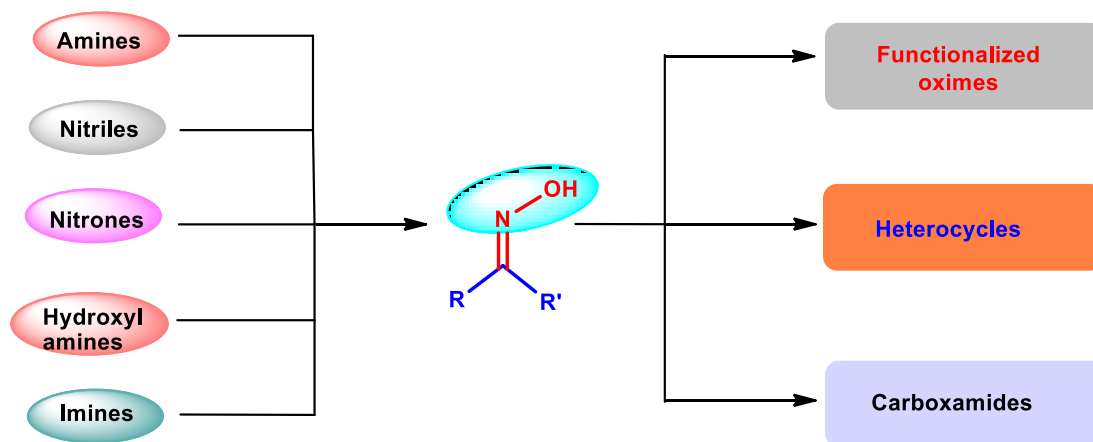


Figure 1.5 Examples of some drugs containing oxime group



Scheme 1.3 Synthesis and reactivity of oximes

(Tattersall 1993). Oximes have widely used in protecting carbonyls and different functional groups. Oxime is an important intermediate to convert different functional groups such as

amide (Martínez-Asencio et al. 2012), nitro, amine (Liu et al. 2019), isoxazolines (Zhu et al. 2019, Pohjakallio et al. 2009), isoquinolines (Deshmukh et al. 2019), hydroxylamine-*o*-ethers (Yamada et al. 1987) etc. into other functional groups (**Scheme 1.3**).

1.1.4 Amides

Amides are the compounds having general formula $R_mE(O)_nNR_1$ (R and R_1 are H or alkyl organic group) where E may be C, S, P and depending on E the corresponding amides are known as carboxamides (E=C, m=1 and n=1), sulfonamides (E=S, m=1 and n=2) and phosphoramides (E=P, m=2 and n=1). Amides represent an important class of compound in the agrochemicals, pharmaceutical, material science and chemical industries (Pattabiraman et al. 2011, Valeuret et al. 2009). Among them, carboxamide is usually found in nature and used in many drugs, natural products and polymers formation. Some examples are shown in **Figure 1.6**.

Traditionally, amides are synthesized by coupling reaction between carboxylic acid with an amine (primary and secondary) in the presence of some dehydrating agents (Grieco et al. 1979). Commonly this reaction is thermodynamically favorable and it has high activation energy because amine first deprotonating the carboxylic acid which reduces its reactivity. Therefore, carboxylic acid derivatives such as esters, acid chlorides and anhydride are used for amide synthesis (Ojeda-Porras et al. 2016, Wang et al. 2019).

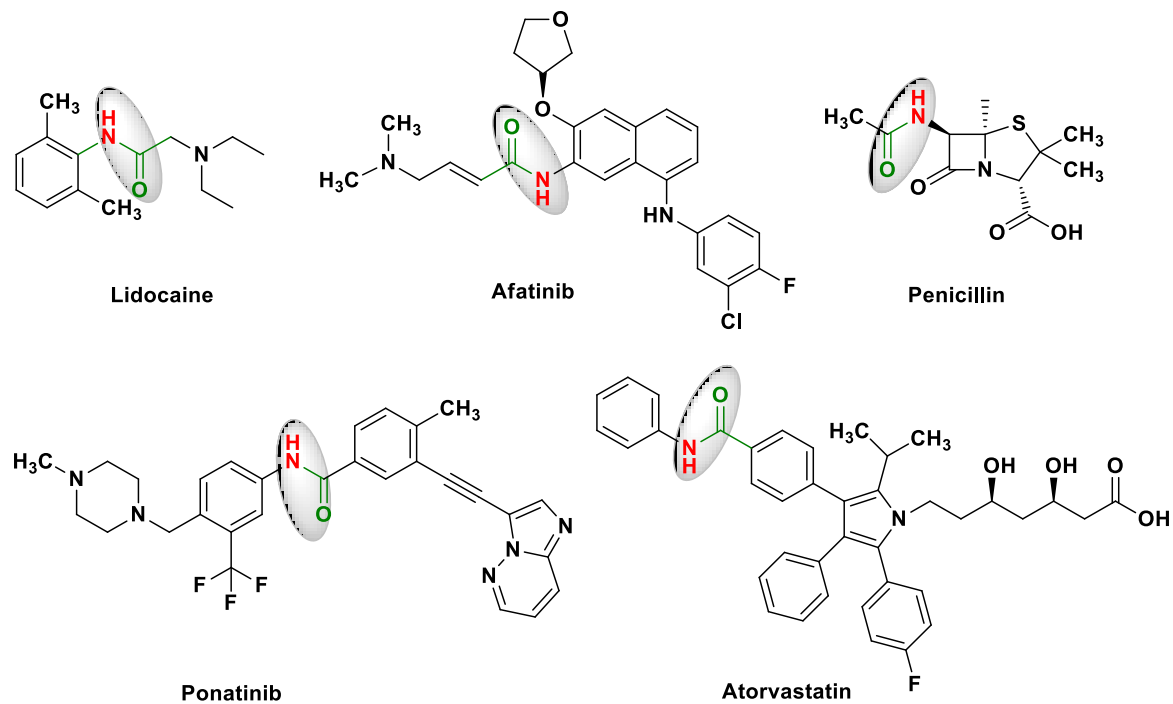
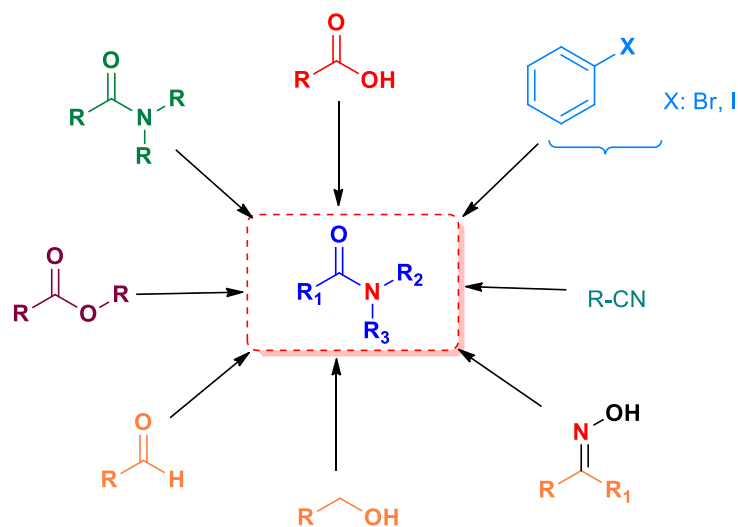


Figure 1.6 Examples of some drugs containing amide groups



Scheme 1.4 Amide bond formation through various substrates

Different name reactions are also known for amide synthesis such as Beckmann rearrangement in which oxime is converted into amide under acidic conditions (Hashimoto et al. 2007), “Ritter reaction”, is used to convert a nitrile into amide using a strong acid (Jiang et al. 2014). “Schmidt reaction” is an acid-catalyzed reaction of hydrogen azide with different electrophiles (carbonyl compounds, tertiary alcohols or alkenes) (Smith 1948, Nyfeler et al. 2006). Multicomponent reaction between carbonyl compound, amine, isocyanide and carboxylic acid to give bis-amide, “Ugi reaction” (Yang et al. 2015), conversion of one amide to other by its reaction with an amine i.e. “transamidation” (Zhang et al. 2019), oxidative amidation of aldehydes or alcohols (Kamble et al. 2020) etc.

1.2 Nitrogen containing five membered cyclic compounds

1.2.1 Pyrrole

Pyrrole is a heterocyclic compound and an important chemical motif in various drugs, natural products, catalysts and advanced materials (Bhardwaj et al. 2015, Konar et al. 2017). In 1834 Runge isolated pyrrole from coal tar and the structure was correctly formulated by Baeyer in 1870. Pyrroles are active component of complex macrocycles, including the porphyrins of heme, chlorins, bacteriochlorins, chlorophyll, porphyrinogens (Senge et al. 2014).

Pyrroles are utilized as a substrate for polymerization process, corrosion inhibitor, preservative, solvent for resins and terpenes. It is used as a functional material in various

metallurgical process, luminescence chemistry, spectrochemical analysis and transition metal complex catalyst for uniform polymerization. Furthermore, some of the compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids and synthetic heterocyclic derivatives (Estevez et al. 2010) **Figure 1.7**.

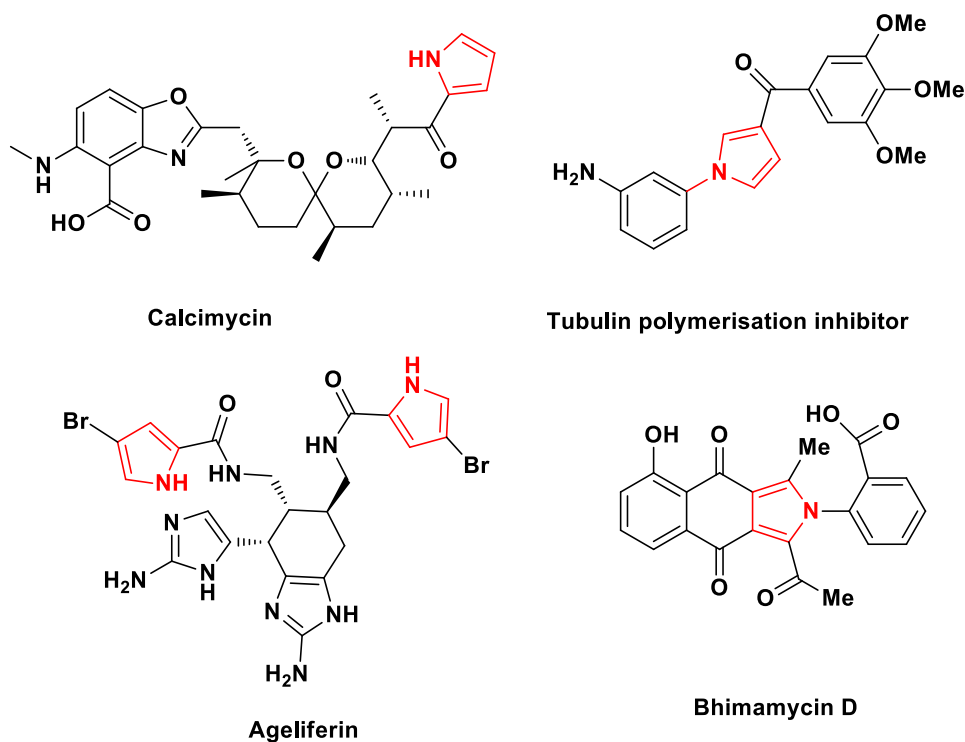
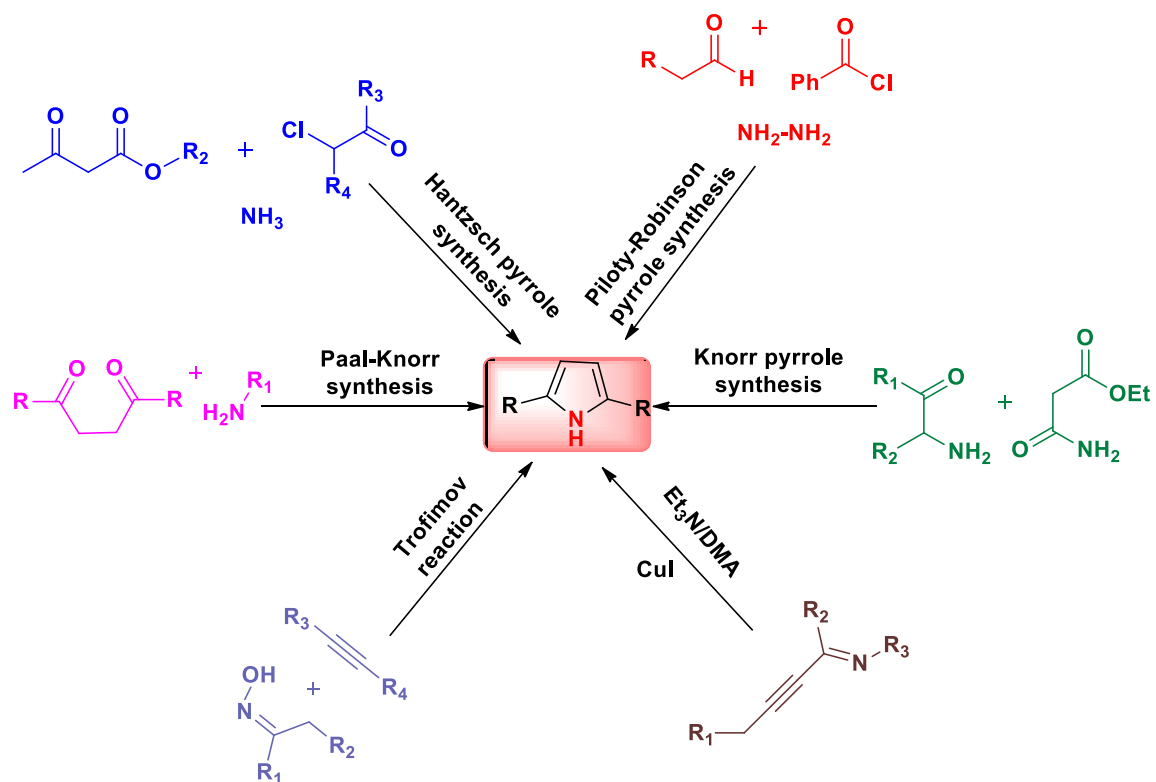


Figure 1.7 Few biologically active compounds containing pyrrole moiety

Pyrroles are synthesized by various methods such as by the reaction of 1,4-dicarbonyl compounds with ammonia or aromatic aliphatic amines (Akelis et al. 2016), ketones or secondary alcohols and β -amino alcohols (Krasniqi et al. 2019), α -amino ketones react with active methylene compounds “Knorr pyrrole synthesis” (Ma et al. 2018),

three component condensation involving aldehyde and hydrazine hydrate “Piloty–Robinson pyrrole synthesis”, ammonia and α -haloketones to give substituted pyrroles “Hantzsch pyrrole synthesis”, reaction of oxime with alkynes “Trofimov reaction” (Schmidt et al. 2005) etc. **Scheme 1.5**.



Scheme 1.5 Synthesis of pyrrole and its derivatives

1.3 Nitrogen containing six membered cyclic compounds

1.3.1 Pyridine

Pyridine is an important heteroaromatic compound having diverse and potent biological properties (Quin et al. 2010, Altaf et al. 2015). A large amount of pyridine was obtained from natural sources via coal tar distillation. Pyridines are also occurred in many significant compounds e.g. vitamins niacin (vitamin B3) (Watts et al. 2008), pyridoxine (vitamin B6) and a number of alkaloids including nicotine, quinine etc. Pyridine structure present in a number of pharmaceuticals such as anti-HIV, anticancer, antidiabetic, proton pump inhibitor (Kelgokmen et al. 2019) etc. **Figure 1.8.**

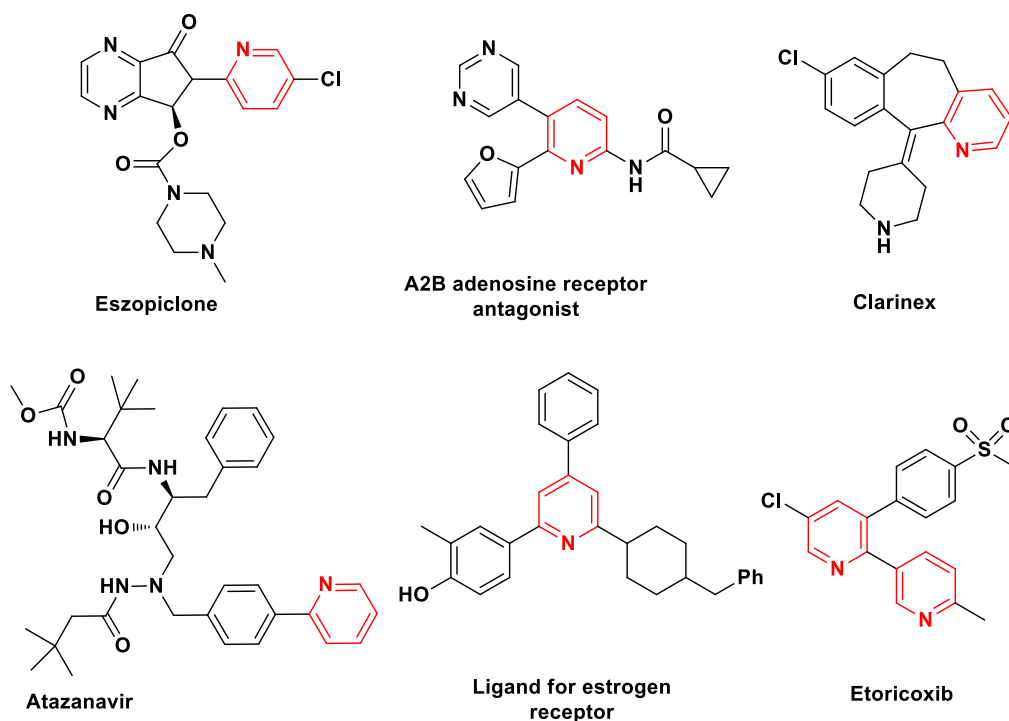
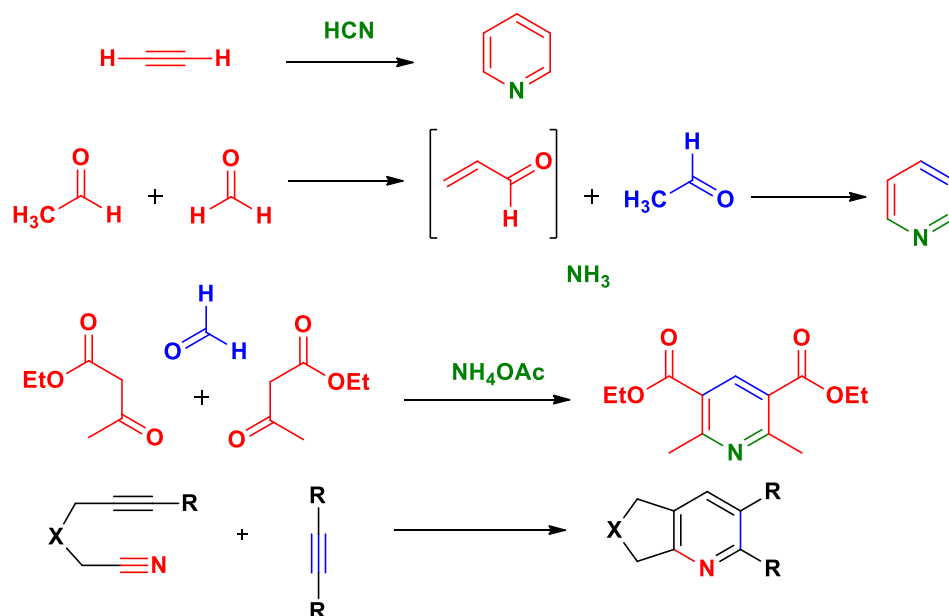


Figure 1.8 Representative compounds containing pyridine substructure

Pyridine was first synthesized in 1876 from acetylene and hydrogen cyanide (Hanmer et al. 1947). Pyridine have been synthesized by the Chichibabin pyridine synthesis and this method is still used in industries (Frank et al. 1949). Knoevenagel condensation reaction between aldehyde and formaldehyde gives acrolein after that acrolein condensed with acetaldehyde and ammonia to give dihydropyridine, which is oxidized with a solid-state catalyst gives pyridine (Jin et al. 2009). The Hantzsch pyridine synthesis is a multi-component organic reaction between an aldehyde, β -keto ester (2 equivalents) and nitrogen donor (ammonium acetate or ammonia) (Phillips 1949). Cycloaddition of alkyne nitriles and alkynes gives pyridine (D'Souza et al. 2011) (**Scheme 1.6**).



Scheme 1.6 Synthesis of pyridine and its derivatives

1.4 Nitrogen containing fused heterocyclic compounds

1.4.1 Indole

Indole derivatives show diverse biological activities and widely distributed in natural products. Indole chemistry began to develop with the study of the indigo dye. Indigo can be converted to isatin and then oxindole derivatives. Indole derivatives have many biological properties such as anti-inflammatory, anticonvulsant, cardiovascular and antibacterial etc. In particular, 3-substituted indole derivatives play a key role in the synthesis of biologically active compounds (Agarwal et al. 2005, Demurtas et al. 2019, Estevão et al. 2010). Some of the biologically active indole representatives are shown in **Figure 1.9**.

Indoles and its derivatives were synthesized by different methods such as by the reaction of phenylhydrazine and carbonyl compounds (aldehyde or ketone) under acidic conditions known as “Fischer indole synthesis” (Saikia et al. 2019), in the presence potassium *tert*-butoxide-promoted dehydrogenation of indoline (MacDonough et al. 2015), 2-fluorotoluenes and benzonitriles in the presence of base (Mao et al. 2019), α -bromoacetophenone and excess aniline to give 2-aryl-indole, “Bischler–Möhlauindole synthesis”, an aniline and ketone bearing a thioether “Gassmanindole synthesis” (Li 2014), an *ortho*-iodoaniline and a disubstituted alkyne using palladium catalyst “Larockindole synthesis” (Shan et al. 2013), thermal decomposition of 3-aryl-2-azido-propenoic ester into an indole-2-carboxylic ester “Hemetsbergerindole synthesis” (Lehmann et al. 2009), from substituted

ortho-nitrocinnamic acid and iron powder in strongly basic solution “Baeyer–Emmerlingindole synthesis (Sánchez-Viesca et al. 2018) (Scheme 1.7).

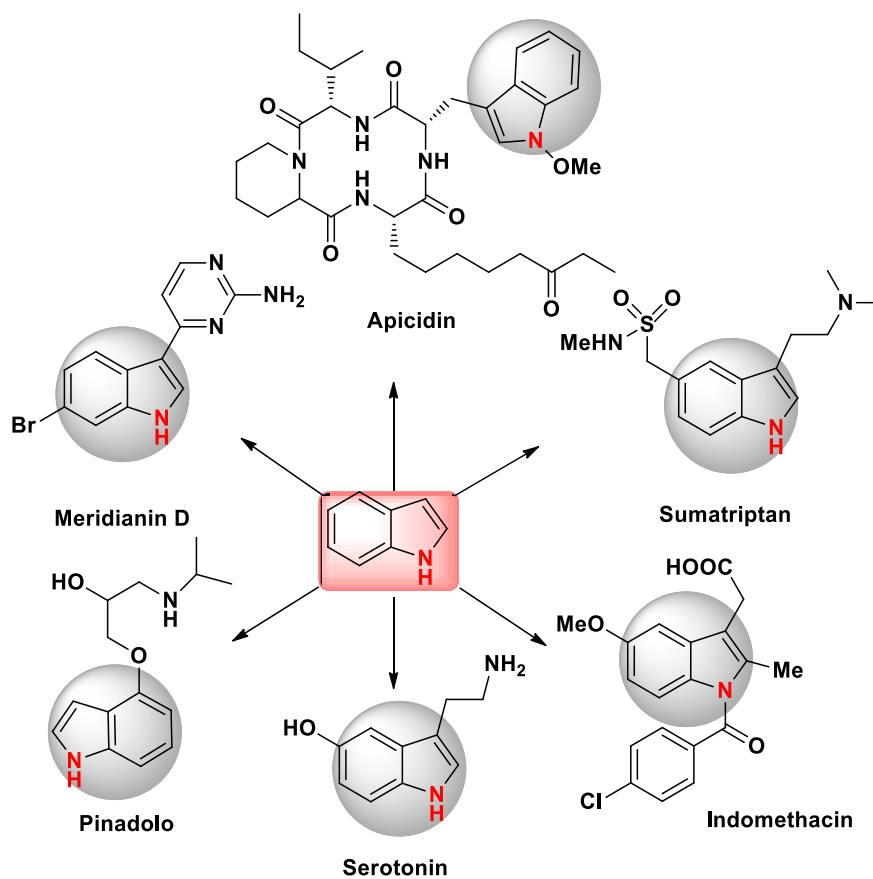
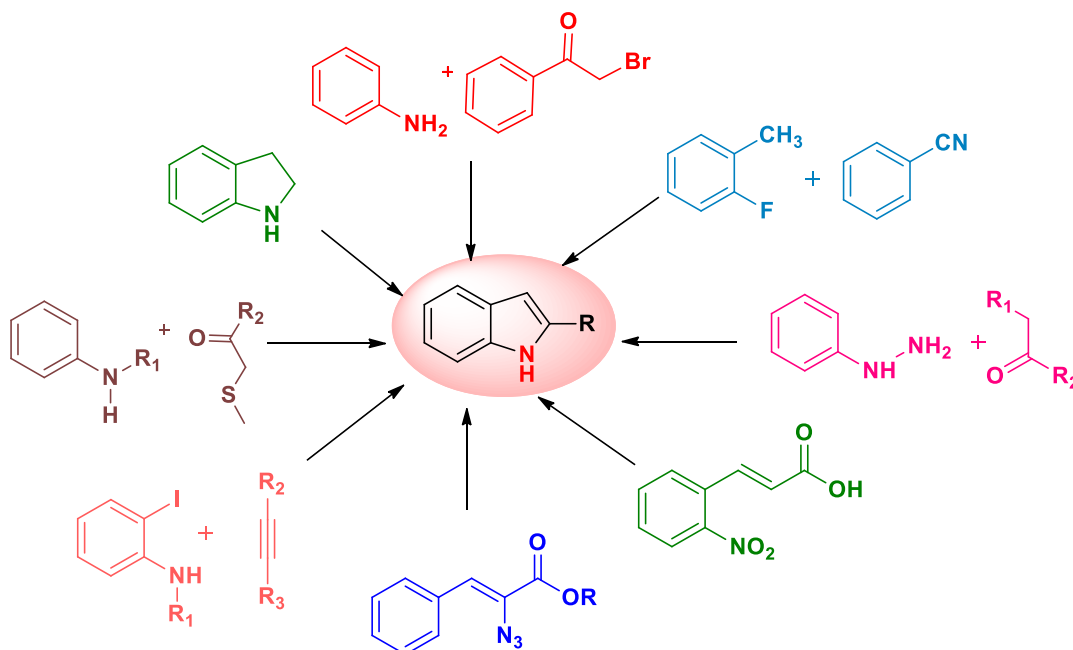


Figure 1.9 Examples of pharmacologically active indole derivatives



Scheme 1.7 Synthesis of indole and its derivatives

1.4.2 Benzothiazole

Benzothiazole has gained considerable attention because of their miscellaneous biological, pharmaceutical and interesting chemical applications (Rana et al. 2007). 2-Substituted benzothiazole derivatives have potential to use as antidiabetic, anti-inflammatory, antitumor, antifungal, anti-inflammatory, antiviral, antipsychotic, antiarrhythmic, neurodegenerative, mosquitocidal agents (Sever et al. 2019) imaging agents for Ca²⁺ channel antagonist, anti-HIV, antituberculosis, analgesia and diuretic activity etc. (Ali et al. 2013) **Figure 1.10**.

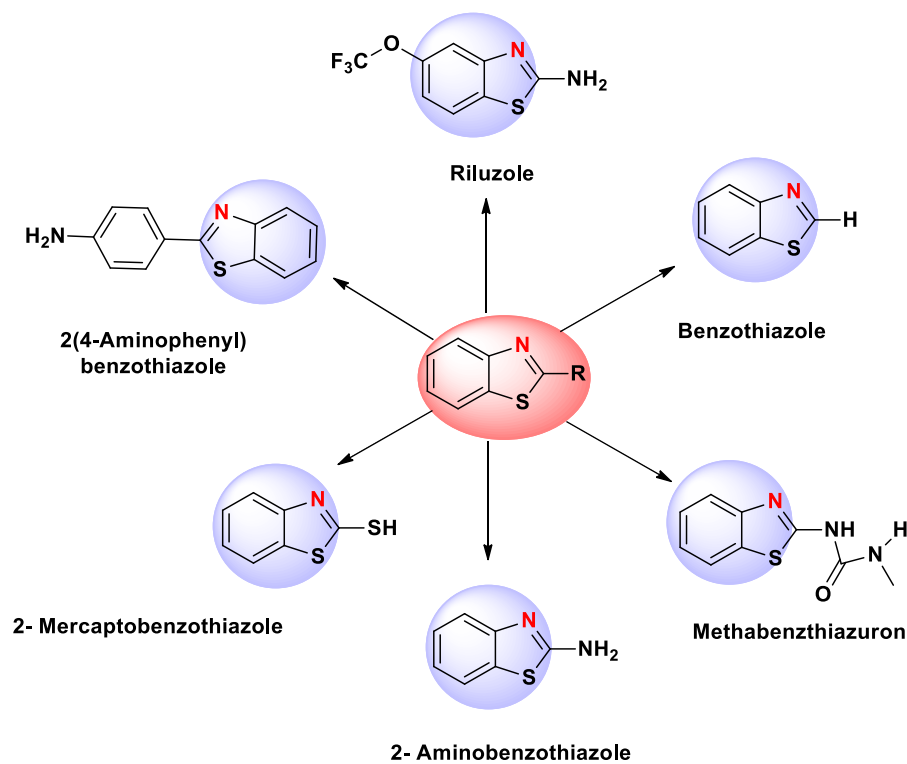
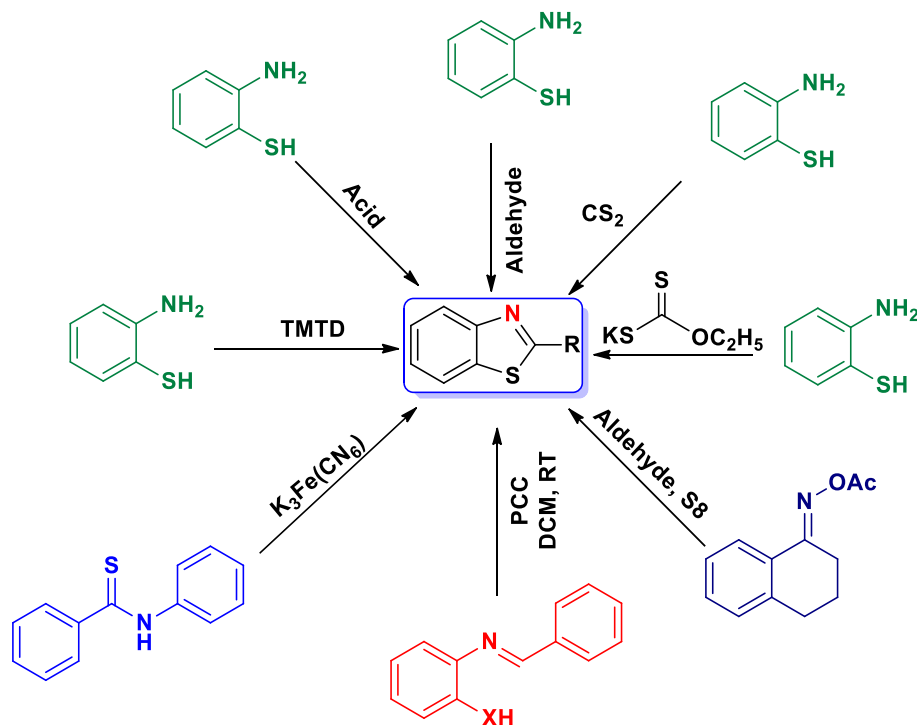


Figure 1.10 Few biologically active compounds containing benzothiazole moiety

Benzothiazoles are mainly synthesized by the reaction of 1,2-aminothiophenol with carbonyl compounds (Liu et al. 2020), 2-halogen substituted anilines and dithiocarbamates in the presence of *t*-BuOK. (Xu et al. 2017), oxidative cyclization of thiobenzanilide by potassium cyohexaferrate (Voschino et al. 1989), oxidative cyclization of Schiff's base (Praveen et al. 2008), three-component reaction of cyclohexenoneoximes, aldehydes and elemental sulfur (Xu et al. 2019), tetramethylthiuram disulfide (TMTD) and *o*-aminothiophenol (Liu et al. 2017), arylthioureas undergoes intermolecular oxidative C-H bond functionalization in the presence of pyridine (Gao et al. 2019) (**Scheme 1.8**).



Scheme 1.8 Synthesis of benzothiazole and its derivatives

1.4.3 Benzimidazole

Benzimidazole is nitrogen containing heterocyclic moiety comprising of six-membered benzene ring fused with five-membered imidazole ring. Benzimidazole and its derivatives are the part of many biological active compounds and widely used as antihypertensive, anti-inflammatory, antibacterial, antiviral, antifungal, antihelminthic, anticancer (Najajreh 2019), antiulcer, antioxidant, psychoactive drugs, anticoagulants, proton pump inhibitors, immunomodulators, hormone modulators, antidepressants and antidiabetics etc. Benzimidazole derivatives exert their actions by interacting with vital

biological targets DNA minor groove, histamine receptors, β -tubulin, serotonin receptors etc. (Alaqeel 2017, Shaharyar et al. 2017) **Figure 1.11**.

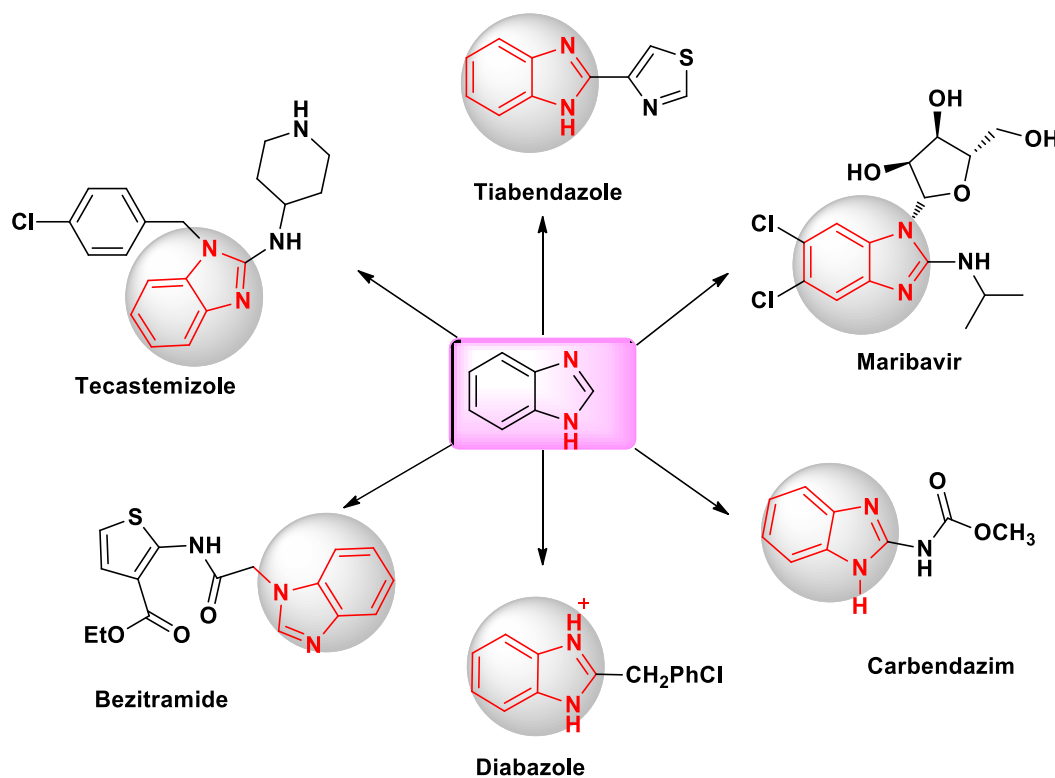
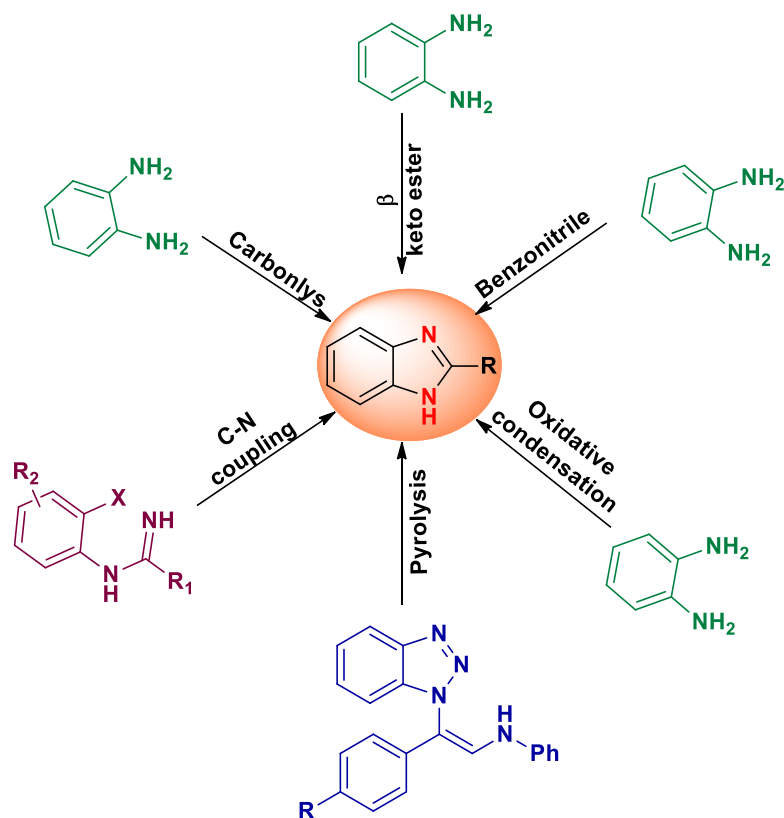


Figure 1.11 Few biologically active compounds containing benzimidazole moiety

Benzimidazole and its derivatives were prepared by different methods such as by the condensation reaction of *o*-phenylenediamine with carbonyls (Sabeti et al. 2015, Gorepatilet al. 2013, Merroun et al. 2019), oxidative condensation reaction of alcohols, methyl arenes derivatives with *o*-phenylenediamine (Das et al. 2018, Chopra et al. 2019), oxidative cyclisation of *N*-aryl amidine intermediate resulting from aniline addition to a nitrile (Arnold et al. 2019, Xiang et al. 2013), one-pot intermolecular cross coupling of

o-haloacetoanilide with guanidines (Guo et al. 2019), intramolecular C(sp³)-H imination (Bose et al. 2019) and thermolysis of benzotriazole derivatives (Al-Awadi et al. 2008) (Scheme 1.9).



Scheme 1.9 Synthesis of benzimidazole and its derivatives

1.4.4 Benzoxazole

Benzoxazoles and their derivatives are aromatic heterocyclic compounds containing nitrogen and oxygen atoms which present in numerous natural products and attended as pharmacophores in drug discovery. Further, a number of benzoxazole derivatives are

recognized as a antimycobacterials, peroxisome proliferators activated receptor γ antagonists, cytotoxic natural products, cathepsin S inhibitors, 5-HT₃ receptor antagonists, non-nucleoside reverse transcriptase inhibitors, elastase inhibitors, estrogen receptor- β agonists, antidiabetic antimicrobial, anti-cancer, anti-HIV, anticonvulsant, antiinflammatory, antinuclear and antitumor etc. (Kakkar et al. 2018, Vodnala et al. 2018)

Figure 1.12.

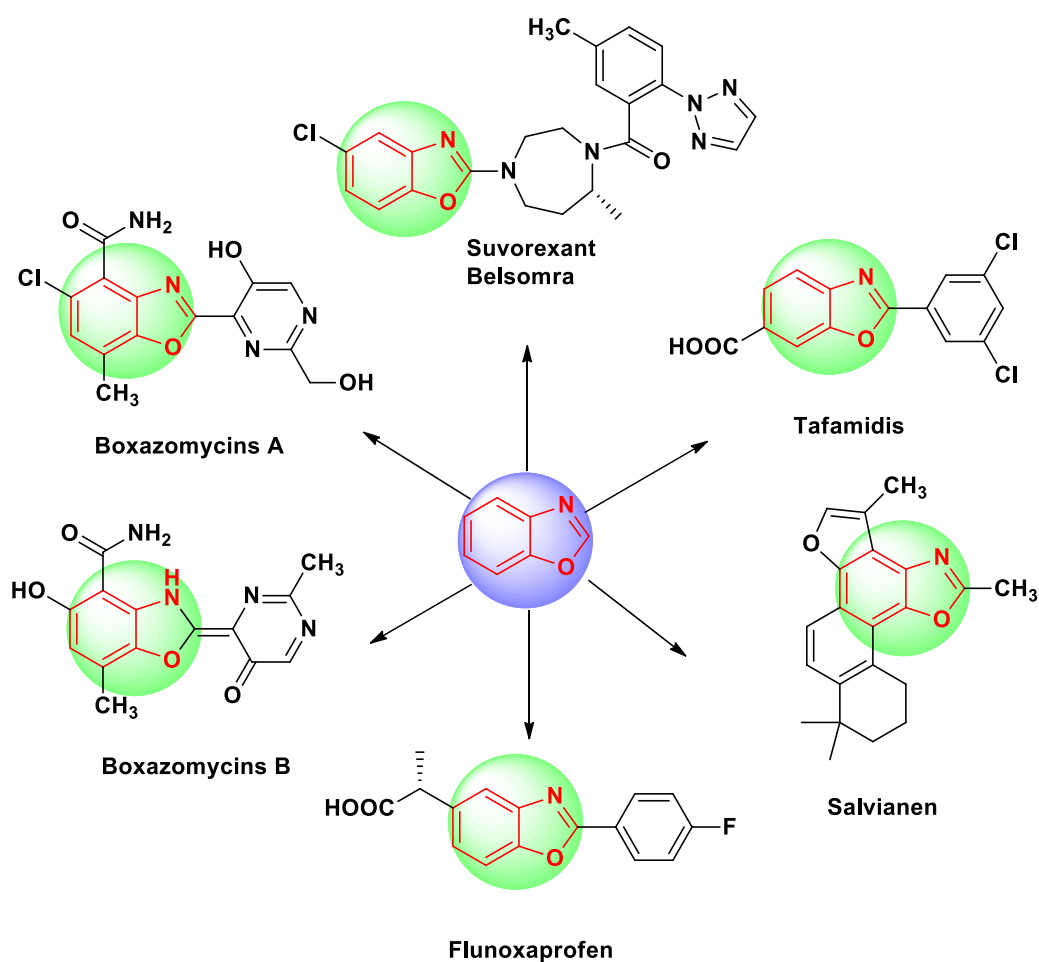
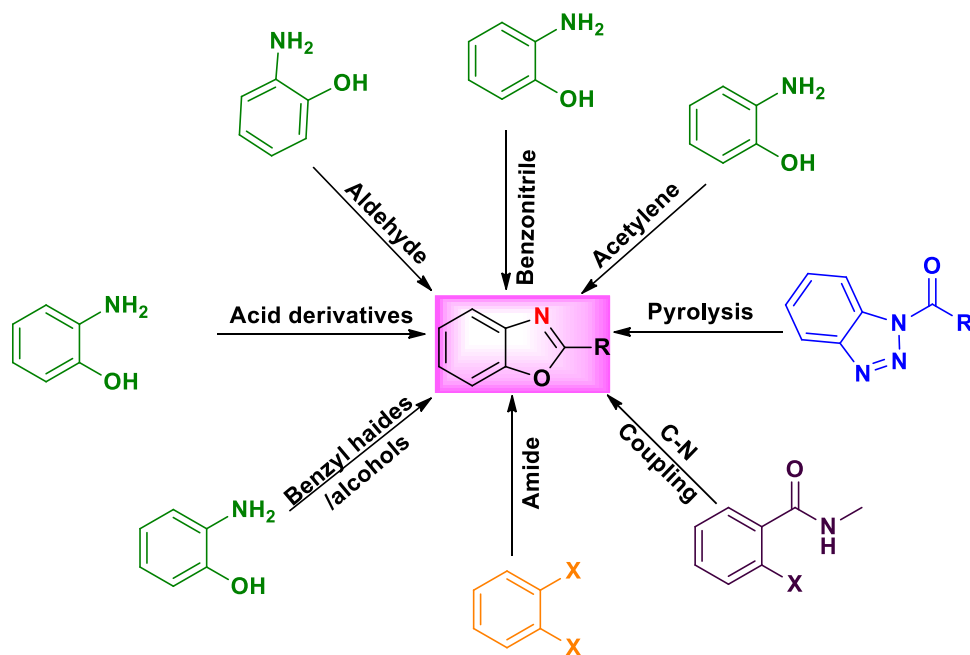


Figure 1.12 Few biologically active compounds containing benzoxazole moiety

Benzoxazole and its derivatives were prepared by different methods such as by the reaction of aldehyde/ carboxylic acids derivatives and 2-aminophenol under various conditions (Kumar et al. 2012, Niedduet al. 2012), oxidative condensation reaction between toluene/ benzyl alcohol/ benzyl amine/ styrene with 2-aminophenol (Doan et al. 2019, Safaei et al. 2018), one-pot intermolecular C-heteroatom coupling of N-(2-bromophenyl) benzamide (Singh et al. 2019), intermolecular cross coupling of 1,2-dihaloarenes with amide (Schuh et al. 2007), intramolecular C-N cross-coupling of 2-haloanilines with acyl halides/ thioacyl halides (Viirre et al. 2007), hydroamination of alkynes with 2-aminophenols (Oshimoto et al. 2019) benzotriazole rings cleavage (BtRC) of N-acyl benzotriazole gives benzoxazole derivative (Singh et al. 2017) (Scheme 1.10).



Scheme 1.10 Synthesis of benzoxazole and its derivatives

In view of importance of nitrogen containing organic compounds, our interest is to explore the chemistry (synthesis and structural characterization) of imidazopyrimidine, pyranopyrazoles, benzimidazole/ benzothiazole and amides. The studies have been described in the subsequent chapters 2-5. During the research period we have also synthesized the β -hydroxy ketones from α -methyl ketones and ninhydrin under microwave irradiations which is presented in last as an appendix.

1.5 References

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