Chapter 1

Synthesis and Applications of Some Main Class of Nitrogen Containing Organic Compounds

Nitrogen is a naturally occurring element that is essential for growth and reproduction in both plants and animals. It is found in amino acids that is building blocks of proteins, in nucleic acids, that comprise the hereditary material and life's blueprint for all cells and in several other organic and inorganic compounds. Additionally, most of the organic compounds containing nitrogen are key building blocks used to develop compounds of biological or medicinal interest to organic chemists. A vast number of nitrogen containing heterocyclic compounds have applications in pharmaceutical research, agriculture science, and drug discovery.

In nature, nitrogen present in the form of functional groups in organic moieties, some of the main functional groups are like amines (**1.1**), imines (**1.2**), amides (**1.3**), oximes (**1.4**),

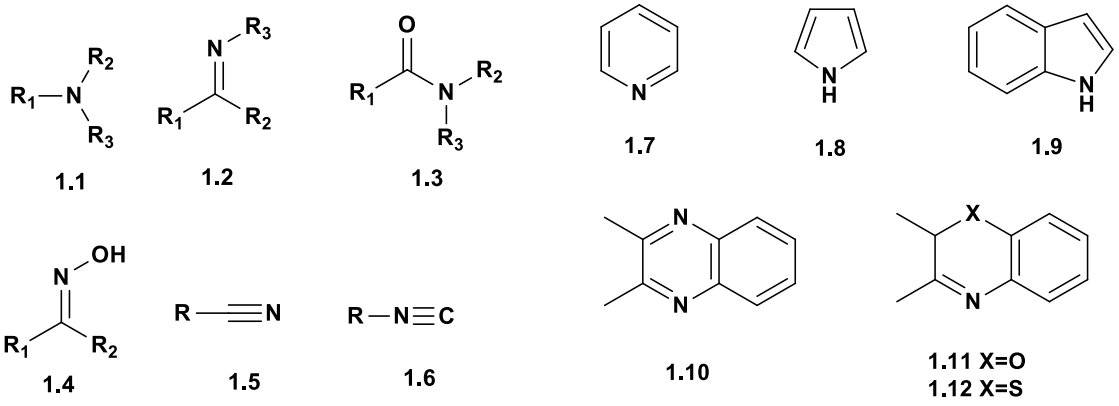


Figure 1.1: Nitrogen containing some main class of organic compounds.

cyanides (**1.5**), isocyanides (**1.6**) and nitrogen containing some main class of heterocyclic compounds are pyridine (**1.7**), indole (**1.8**), pyrrole (**1.9**), quinoxaline (**1.10**), oxazine (**1.11**) and thiazine (**1.12**) (**Figure 1.1**).

1.1 Amines

Amines are the organic compounds that are derived from ammonia by replacing one, two or all the three protons by different carbon derivatives. These compounds are important in a variety of industries including agrochemicals, dyes, drugs, surfactants and plastics; as auxiliaries for the rubber, textile, paper industries, as anticorrosion agents and process chemicals for gas scrubbing (Roose et al. 2015). Since amines are the basic building units of proteins which involved in creations of amino acids and it shows that they are very important in survival of living beings. Besides this, amines are also used in the synthesis of many drugs like Clopidogrel is an antithrombotic drug and used as an inhibitor of platelet aggregation, Aripiprazole is an antipsychotic agent, Demerol is an analgesics used to control moderate to severe pain, Salmeterol is used in treatment of asthma and chronic obstructive pulmonary disease and Novocaine is commonly used as anesthetics in oral surgery (**Figure 1.2**).

Primary amines are mainly prepared by the reduction of cyanides (Haddenham et al. 2009, Bagal et al. 2015), amides (Volkov et al. 2016), aliphatic and aromatic nitro compounds (Orlandi et al. 2016) and azides (Maiti et al. 1986, Ahammed et al. 2011) by using different

reducing agents (**Scheme 1.1**). Primary amines are also synthesized by Gabriel synthesis method (Sheehan et al. 1950) which involves the initial alkylation of potassium phthalimide to form *N*-alkyl phthalimide, which on hydrolysis provides corresponding primary amine as final product.

Secondary and tertiary amines are prepared by the nucleophilic substitution of primary and secondary amines with the alkyl halides to give corresponding secondary and tertiary amines respectively (Ruiz-Castillo et al. 2016) (**Scheme 1.2**). They are also prepared by reductive amination of aldehydes or ketones with primary and secondary amines (Tripathi et al. 2008).

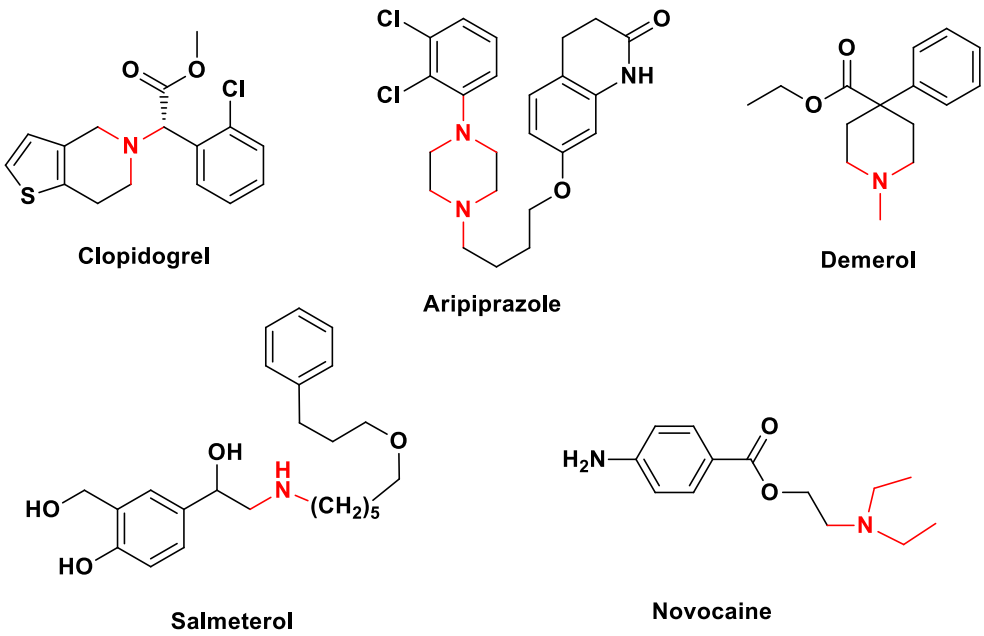
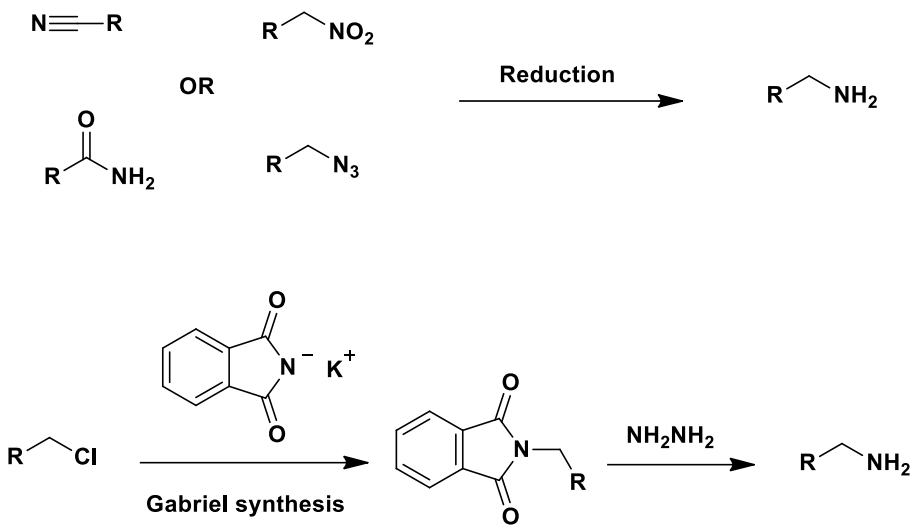
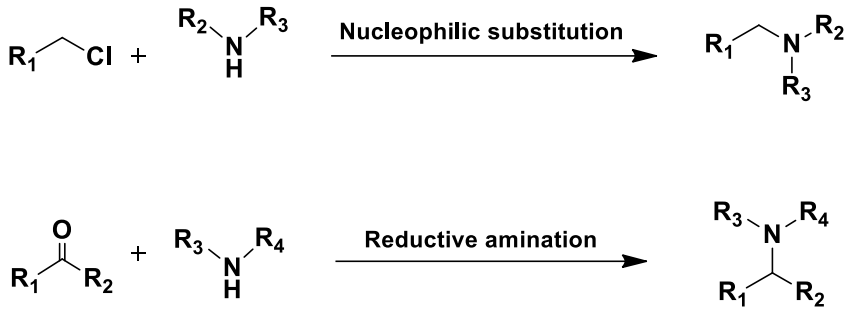


Figure 1.2: Some biological active drugs containing amine functional group.



Scheme 1.1: Synthesis of primary amines.



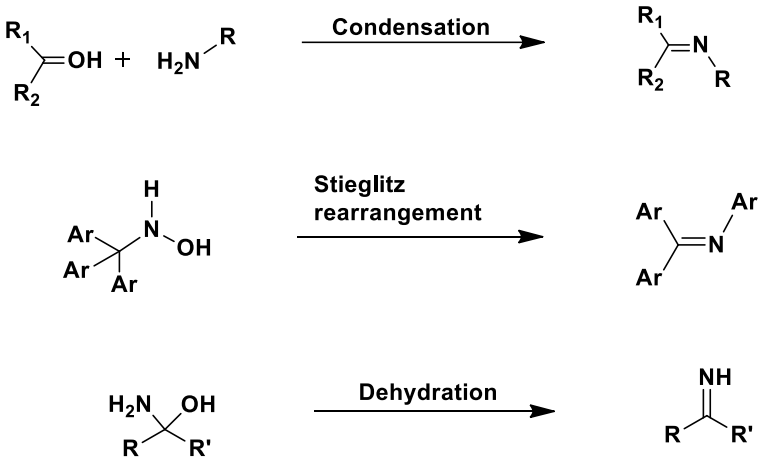
Scheme 1.2: Synthesis of secondary and tertiary amines.

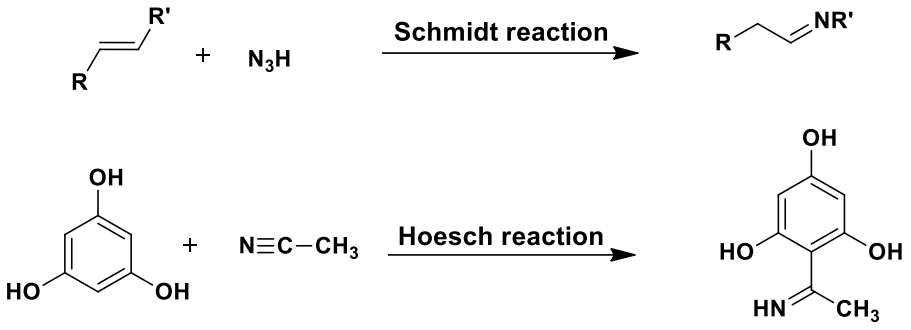
1.2 Imines

Imines or azomethines are compounds that are represented by the general formula $R_3R_2C=NR_1$. The substituents R_1, R_2 and R_3 may be alkyl, aryl, heteroaryl or hydrogen. Imine was first of all discovered by Hugo Schiff by condensation of carbonyl compounds with

primary amines in 1864 and in his respect it is also referred as Schiff bases. Imines are stable under anhydrous conditions or in anhydrous organic solvents but in aqueous medium they are easily hydrolyzed to the initial amine and the carbonyl compound. Imine hydrolysis is fast under acid catalysis and relatively slow under neutral or alkaline conditions.

Imines are generally prepared by condensation of aldehyde and ketone with amines (Qin et al. 2013) but there are some other methods for their synthesis e.g. the rearrangement of trityl N-haloamines in the Stieglitz rearrangement (Stieglitz et al. 1914, Li 2003) which involves a PCl_5 catalyzed rearrangement reaction of a trityl hydroxylamine (Ar_3CNHOH) to a triaryl imine, by dehydration of hemiaminals (Middleton et al. 1970), by reaction of alkenes with hydrazoic acid (Lang et al. 2006) as well as by the reaction of nitriles with arenes in the presence of hydrochloric acid (Gulati et al. 1935).





Scheme 1.3: Synthesis of imines.

1.3 Amides

Amides (carboxamide, sulphonamide, phosphoramide) are the compounds having general formula $R_mE(O)_nNR_2$ where E may be C, S or 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 compounds in the pharmaceutical industry, materials science, agrochemicals and chemical biology. Among them, carboxamide is very commonly found in nature. Carboxamide functional groups are found in many drugs, natural products, and polymers. It is estimated that more than 25% of all drugs contain at least one amide bond. Some examples are shown in **Figure 1.3**. Their broad utility in many fields is closely tied to the structure of the amidic moiety which confers unique features upon these compounds. Therefore, formation of amide bonds is one of the most important and studied reactions in organic chemistry.

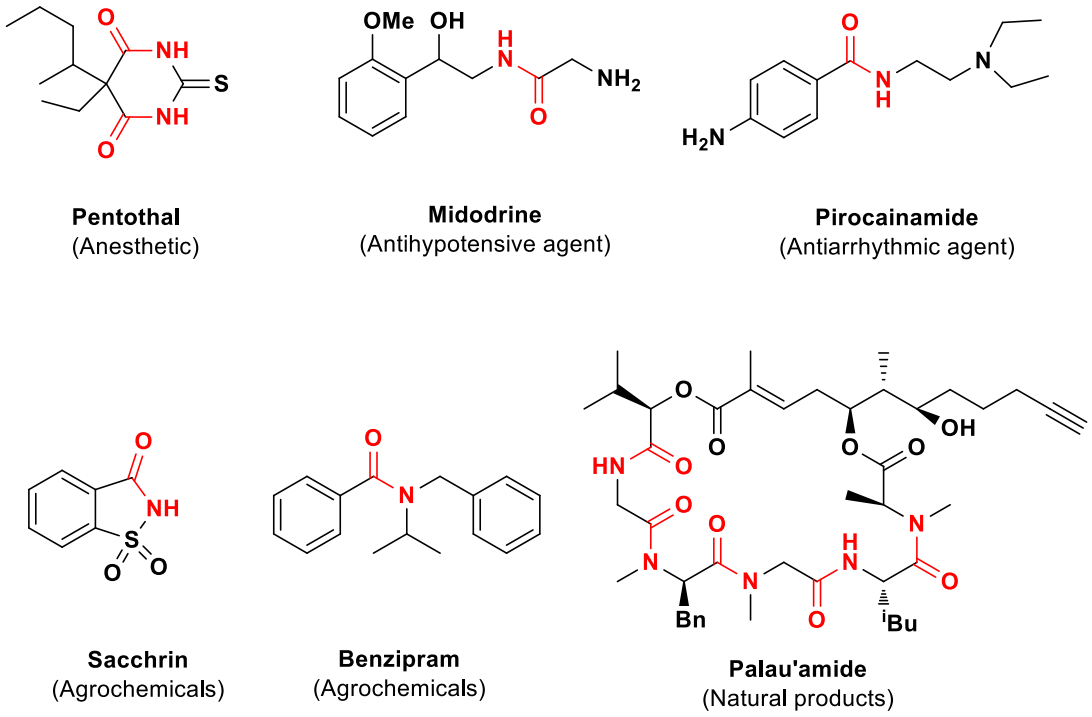


Figure 1.3: Examples of some drugs containing amide group.

The amide functionality is considered to be the most robust and resistant of the carboxylic acid derivatives. The high stability of amides is attributed to resonance delocalization of the nitrogen lone pair and carbonyl π electrons across the amidic bond (**Figure 1.4**).

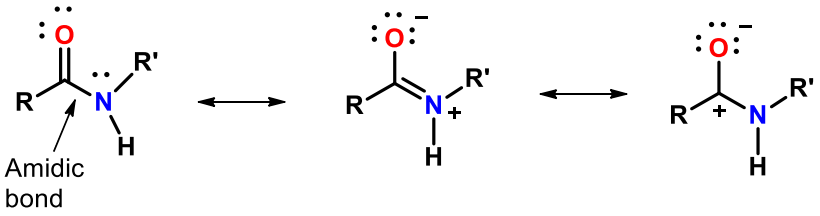
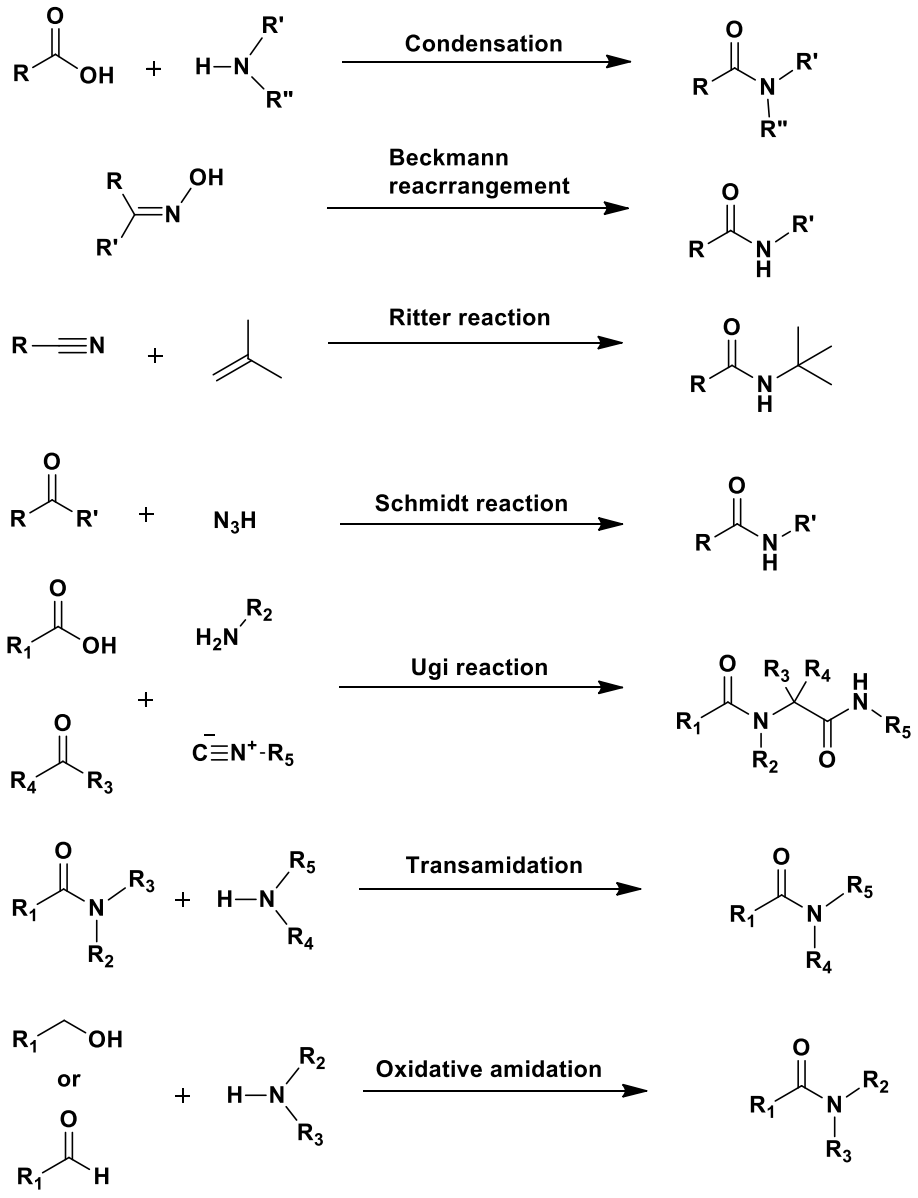


Figure 1.4: Resonance stability of amide.

Traditionally, amides were synthesized by condensation of organic acids with primary and secondary amines in the presence of some dehydrating agents (Montalbetti et al. 2005). In general, this reaction is thermodynamically favorable; however, it suffers from high activation energy, which reduces its reactivity and often requires high temperatures. Therefore, for shifting the equilibrium to the right, there is need of activation of carboxylic acid to a better electrophile such as esters, acid chlorides and anhydride (Valeur et al. 2009). Some other important methods for amide synthesis like Beckmann rearrangement which involves acid catalyzed rearrangement of an oxime functional group to substituted amides (Beckmann 1886, Gawley 2004), "Ritter reaction", a chemical transformation of a nitrile into an N-alkyl amide using various electrophilic alkylating reagents (mainly alkenes) in presence of strong acids like H_2SO_4 , reaction of carbonyl compounds with azide to give an amide "Schimdt reaction" (Wolff 2004). Multicomponent reaction between carbonyl compound, amine, isocyanide and carboxylic acid to give bis-amide, Ugi reaction" (Ugi 1959) , conversion of one amide to other by its reaction with an amine i.e. "transamidation" (Acosta-Guzmán et al. 2018), oxidative amidation of aldehydes or alcohols with amines (de Figueiredo et al. 2016) and by Umpolung reaction of amines with α-halo nitro alkanes (Shen et al. 2010) (**Scheme 1.4**).



Scheme 1.4: Synthesis of amides.

1.4 Oximes

The name oxime is an abbreviation of oxy-imine, >C=N–OH. Two structures (**A**) and (**B**) (**Figure 1.5**) were proposed for the oxime group but on the basis of neutron diffraction work on dimethylglyoxime, the presence of –OH bond was established which favors the structure (**A**). In solid state, oximes are found to be associated by H-bonding O-H·····N. The presence of slightly basic nitrogen atom and mild acidic hydroxyl group makes the oxime group as an amphoteric in nature.

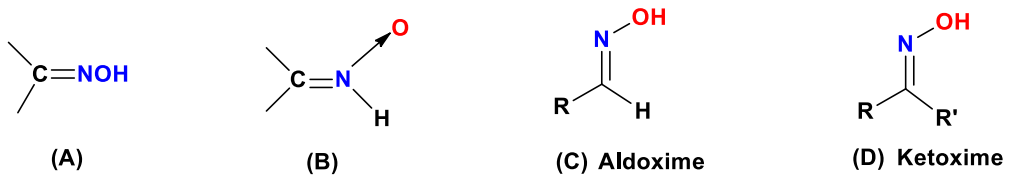


Figure 1.5: Structure (**A** & **B**) and classifications (**C** & **D**) of oximes.

Oximes are found extensive applications in different fields such as an antidotes for nerve agents e.g. Pralidoxime , Obidoxime, Methoxime, HI-6, Hlo-7, and TMB-4 (**Figure 1.6**). Methyl ethyl ketoxime is a skin-preventing additive in many oil-based paints. Perillartine, the oxime of perillaldehyde, is used as an artificial sweetener in Japan, it is 2000 times sweeter than sucrose. Buccoxime and 5-methyl-3-heptanone oxime ("Stemone") are commercial fragrances.

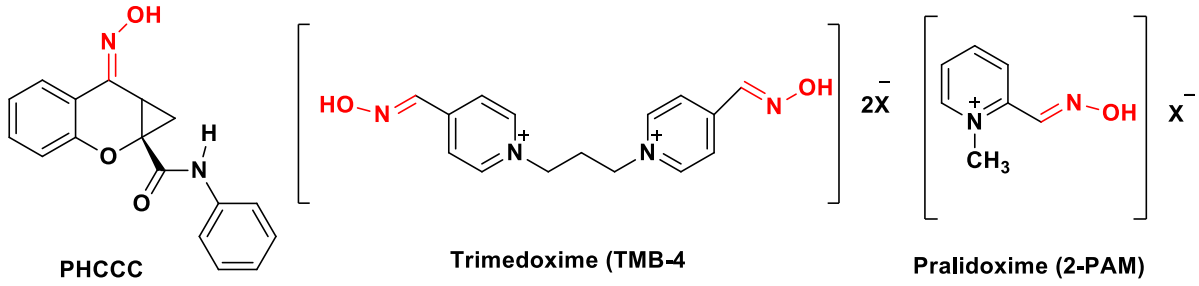


Figure 1.6: Examples of some drugs containing oxime group.

Oximes are mainly synthesized by the reaction of carbonyl compounds with hydroxylamine hydrochloride using different catalysts under different experimental conditions. Other than this, oximes are also prepared by amines, nitriles, nitrones and imines (**Figure 1.7**) (Abele et al. 2000, Bolotin et al. 2017). Oximes are highly reactive and undergo reaction very easily to synthesize functionalized oximes, heterocyclic compounds and carboxamides (**Figure 1.7**) (Freeman 1973, Bolotin et al. 2017).

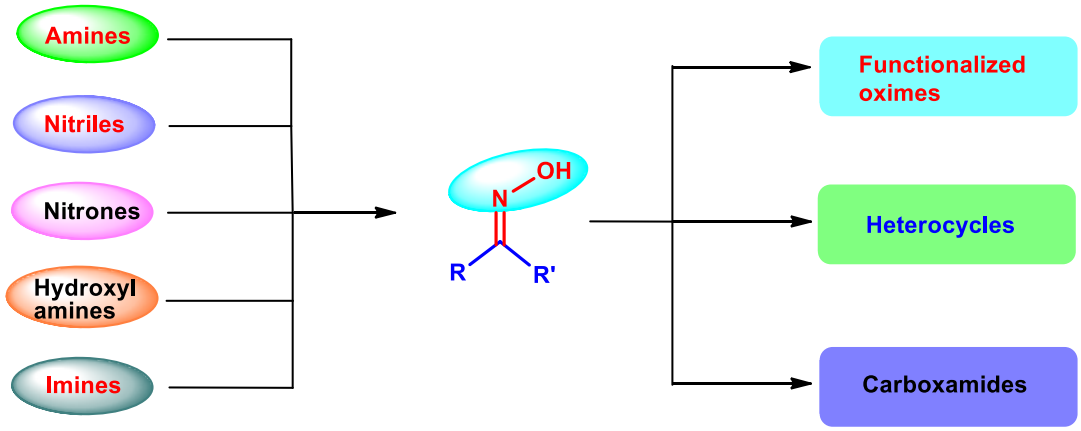
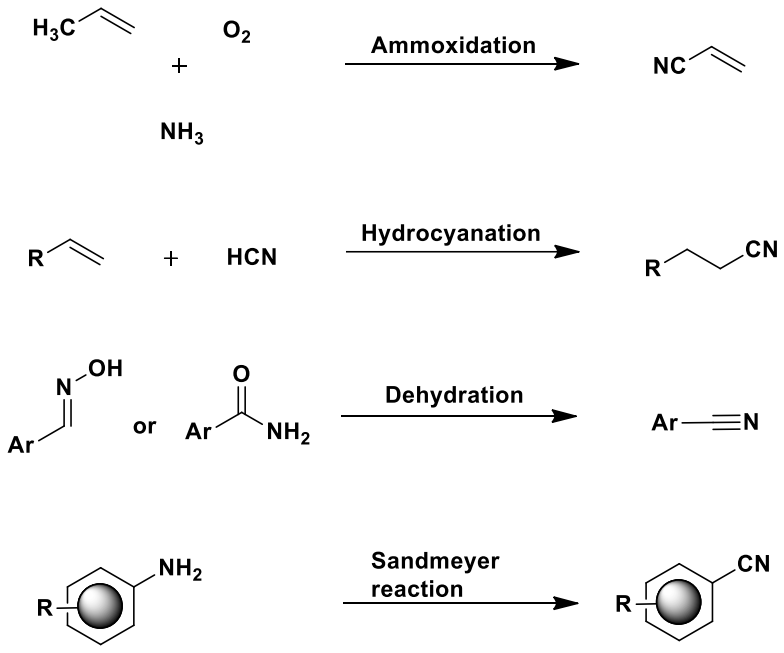


Figure 1.7: Synthesis and reactivity of oximes.

1.5 Cyanides

Nitrile functional groups are present in many useful materials e.g. methyl cyanoacrylate, used in super glue, nitrile rubber, a nitrile-containing polymer used in latex-free laboratory and medical gloves. Nitrile rubber is also widely used as automotive and other seals since it is resistant to fuels and oils.

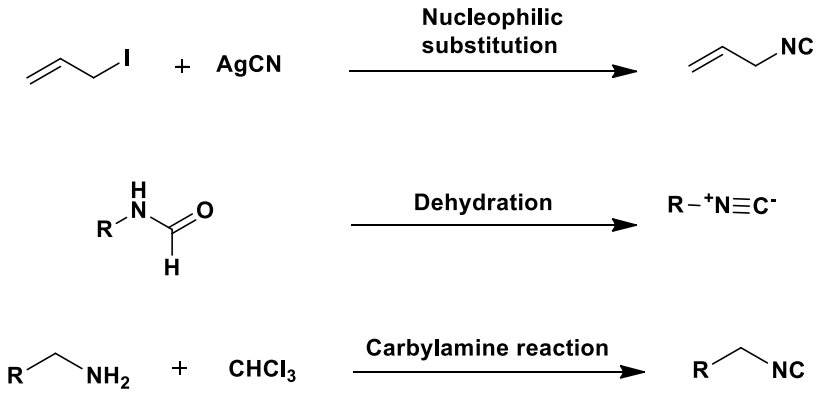
First synthesized cyanide was hydrogen cyanide by C. W. Scheele in 1782. Around 1832, benzonitrile was prepared by Friedrich Wöhler and Justus von Liebig, but due to minimum yield of the product neither physical nor chemical properties were determined. The synthesis of benzonitrile by Hermann Fehling in 1844 by heating ammonium benzoate was the first method to provide enough of the substance for chemical research. Fehling determined the structure by comparing his results to the already known synthesis of hydrogen cyanide by heating ammonium formate and named it "nitrile". Industrial method for cyanide synthesis involves the ammoxidation reaction using alkene, ammonia and oxygen (Pollak et al. 2000). This is an important method for production of acrylonitrile. The other methods for nitrile synthesis are hydrocyanation, in which HCN react with alkenes or alkynes to give nitrile (Rajanbabu 2004). Nitriles can also be prepared by organic halides and cyanide salts known as Kolbe nitrile synthesis (Friedman et al. 1960), by dehydration of amides & oximes (Kuo et al. 2007) and also by aryl diazonium salt "Sandmeyer reaction" (Clarke et al. 2003).



Scheme 1.5: Synthesis of cyanides.

1.6 Isocyanides

Allyl isocyanides were first synthesized by using silver cyanide route from the reaction of allyl iodide and silver cyanide. Some other methods for isocyanides synthesis are by dehydration of formamides with *p*-toluenesulfonyl chloride, phosphorus oxychloride, phosgene, diphosgene, or Burgess reagent and from carbylamine reaction (Hofmann isocyanide synthesis) by the reaction of amine with chloroform and potassium hydroxide (Nenajdenko 2012, Bode et al. 2016).



Scheme 1.6: Synthesis of isocyanides.

1.7 Pyridine

Pyridine derivatives are an important class of azaheterocycle found in many natural products, active pharmaceuticals and used in the *in vitro* synthesis of DNA (Katritzky et al. 1996, Henry 2004, Joule et al. 2008, Michael 2008, Altaf et al. 2015). Diploclidine (Jayasinghe et al. 2003) and Nakinadine A (Kubota et al. 2007) are two examples of recently isolated and structurally diverse natural products containing the pyridine core (**Figure 1.8**). Pyridine-derived pharmaceuticals include Atazanavir (anti-HIV) (Harrison et al. 2005), Imatinib mesylate (prescribed for chronic myelogenous leukemia) (Deininger et al. 2003), Aulfapyridine (anti-bacterial), Tripelennamine & Mepyramine (antihistaminic drugs) etc. (**Figure 1.8**). Pyridine derivatives are also incorporated into polymers such as polyvinyl pyridine (PVP) (Raje et al. 2006). Many pyridine-based alkaloid natural products are derivatives of nicotinic acid. Some nicotinic acid originated alkaloids are Nicotine and Anabasine (**Figure 1.8**) (Hill 2010).

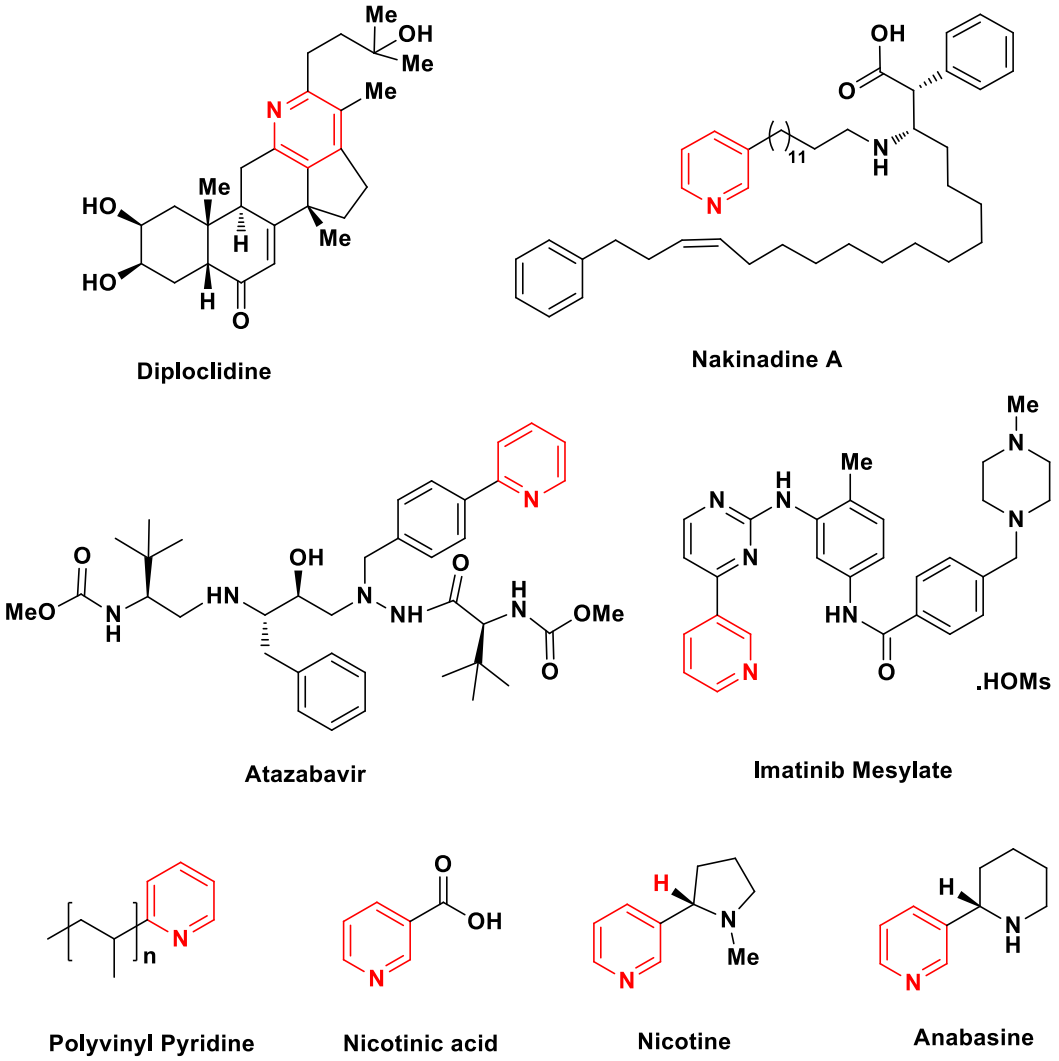
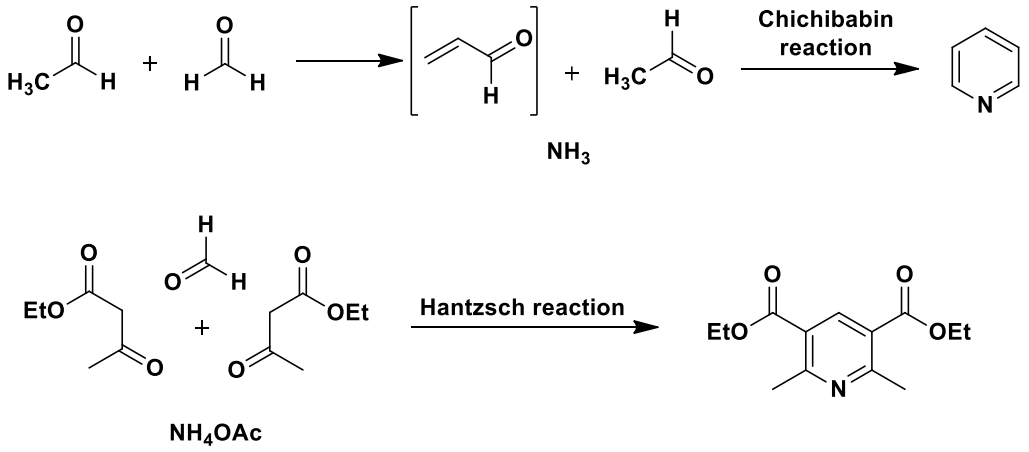


Figure 1.8: Representative compounds containing pyridine substructure.

Pyridine was discovered by Thomas Anderson in 1849 from bone oil. However, due to increasing demand of pyridine some other methods have been developed like from acetaldehyde and ammonia. It is most economical method for pyridine synthesis and

more than 20,000 tonnes pyridine are manufactured worldwide per year. Also, some other methods have been used for pyridine synthesis such as by the reaction of α,β-unsaturated carbonyl compounds (synthesized by condensation reaction between aldehyde and ketone) and ammonia or ammonia derivatives known as "Chichibabin synthesis" (Tschitschibabin 1924, Mcgill et al. 1988) and by Hantzsch pyridine synthesis which involves the reaction of β-keto acid (often acetoacetate), formaldehyde, and ammonia in (2:1:1) ratio to give hydrogenated pyridine which further oxidizes to give pyridine (Petri 1881, Knoevenagel et al. 1898, Saini et al. 2008).



Scheme 1.7: Synthesis of pyridine and its derivatives.

1.8 Pyrrole

Pyrroles are privileged scaffold with assorted nature of biological activities. Many active compounds have been developed by amalgamation of different pharmacophores in a pyrrole ring system. Pyrroles are an active component of complex macrocycles, including the porphyrins of heme, chlorins, bacteriochlorins, chlorophyll, porphyrinogens (Nakano et al. 1966). Pyrrole and its derivatives are widely used as intermediates in synthesis of pharmaceuticals, agrochemicals, dyes, photographic chemicals, perfumes and other organic compounds. The pyrrole skeleton is an imperative structural framework found in extensive range of biologically active natural products and pharmaceutically active molecules. They are an element of polymers, indigoid dyes and large aromatic rings. Pyrroles are utilized as a catalyst for polymerization process, corrosion inhibitor, preservative, solvent for resins and terpenes. It is functional in various metallurgical process, luminescence chemistry, spectrochemical analysis and transition metal complex catalyst for uniform polymerization (Rani et al. 2017). Furthermore, some of the compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids and synthetic heterocyclic derivatives. They exhibit wide range of biological activities such as antibacterial, anti-fungal, anti-viral, anti-inflammatory (Wilkerson et al. 1994), anticancer and antioxidant activity (Lee et al. 2001) (**Figure 1.9**).

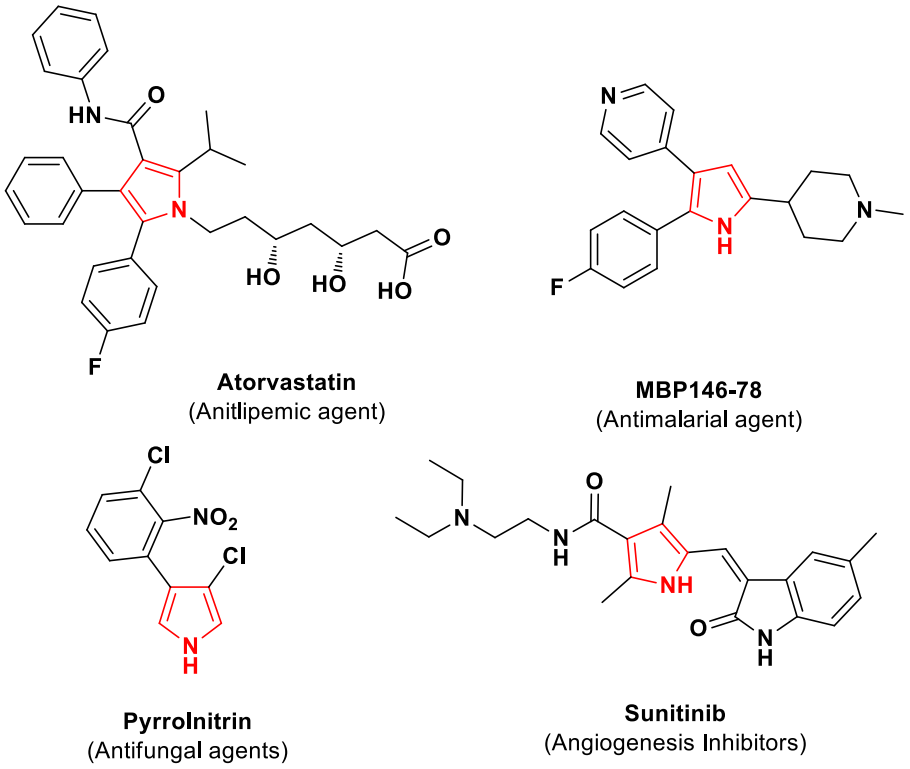
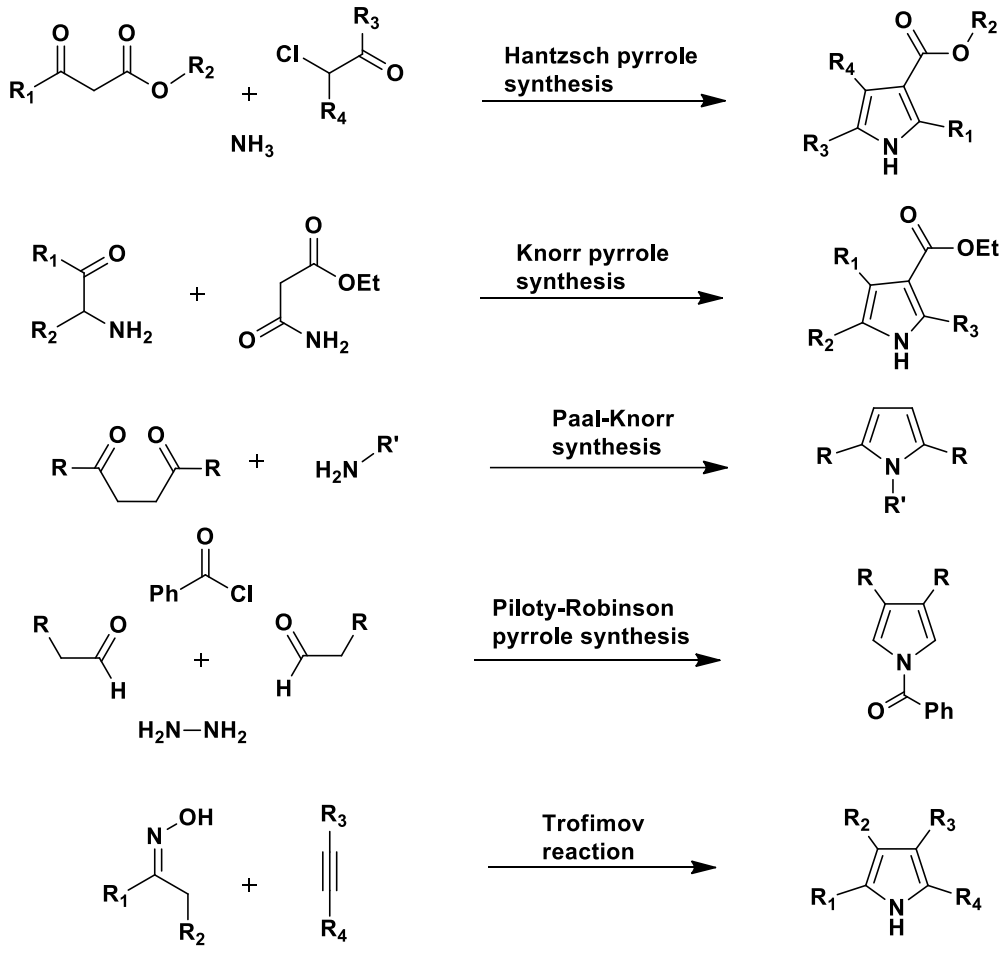


Figure 1.9: Few biologically active compounds containing pyrrole moieties.

Pyrroles are synthesizing by different methods such as by the reaction of β-ketoesters, ammonia and α-haloketones to give substituted pyrroles known as "Hantzsch pyrrole synthesis", α-amino ketone with an active methylene compound "Knorr pyrrole synthesis", from 1,4-dicarbonyl compound and ammonia or a primary amine "Paal–Knorr synthesis", by the reaction involving aldehyde, hydrazine hydrate and benzoyl chloride "Piloty–Robinson pyrrole synthesis" (D Joshi et al. 2013, Rani et al. 2017), and most importantly from the reaction of oxime with alkynes "Trofimov reaction" (Petrova et al. 1997, Schmidt et al. 2005) (**Scheme 1.8**).



Scheme 1.8: Synthesis of pyrrole derivatives.

1.9 Indole

Indole derivatives show diverse biological activities and are widely present in many important alkaloids e.g., tryptophan and auxins (Kaushik et al. 2013). Indole chemistry began to develop with the study of the indigo dye. Indigo can be converted to isatin and then to

oxindole. Adolf von Baeyer in 1866 have reduced oxindole to indole using zinc dust. **Figure 1.10** represents some examples of pharmacologically active indole derivatives.

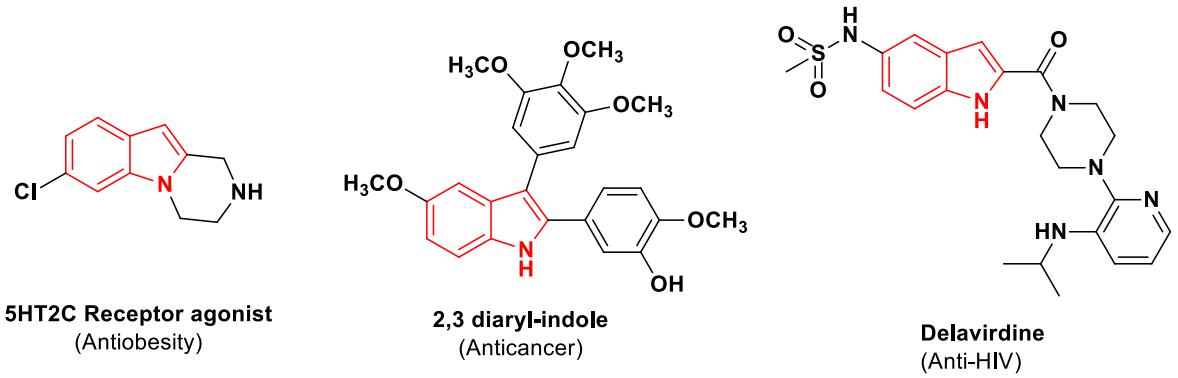
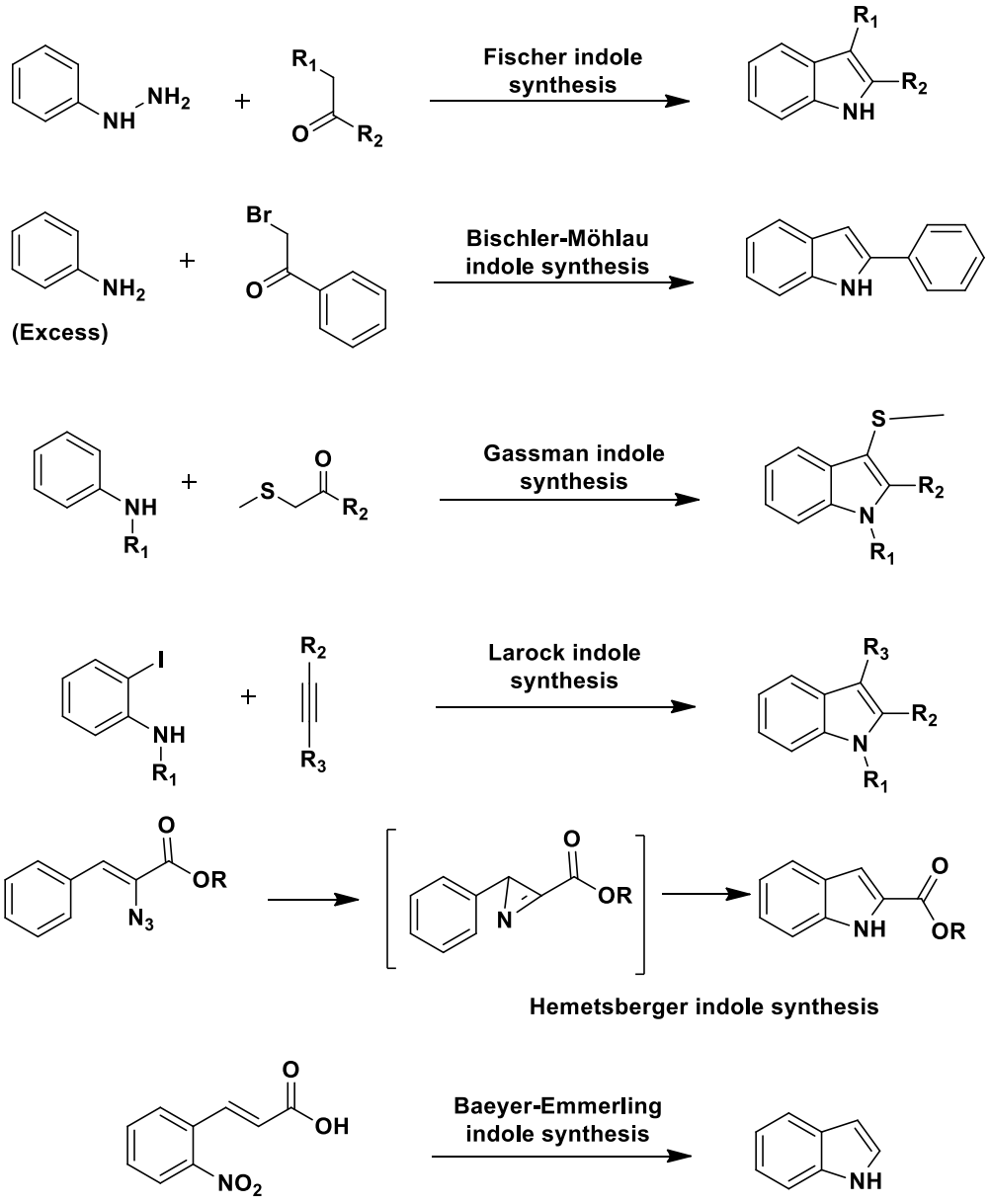


Figure 1.10: Examples of pharmacologically active indole derivatives.

Indoles and its derivatives were prepared by different methods such as by the reaction of phenylhydrazine and an aldehyde or ketone under acidic conditions known as "Fischer indole synthesis", by the reaction of α-bromo-acetophenone and excess aniline to give 2-aryl-indole "Bischler–Möhlau indole synthesis", by addition of an aniline and a ketone bearing a thioether substituent "Gassman indole synthesis", from an *ortho*-iodoaniline and a disubstituted alkyne using palladium catalyst "Larock indole synthesis", by thermal decomposition of 3-aryl-2-azido-propenoic ester into an indole-2-carboxylic ester "Hemetsberger indole synthesis", from substituted *ortho*-nitrocinnamic acid and iron powder in strongly basic solution "Baeyer–Emmerling indole synthesis" (Gribble 2003, Humphrey et al. 2006, Patil et al. 2009, Taber et al. 2011) (**Scheme 1.9**).



Scheme 1.9: Synthesis of indole and its derivatives.

1.10 Quinoxalines

Quinoxaline derivatives are a very important class of nitrogen-containing heterocycles, as they constitute useful intermediates in organic synthesis. This substructure plays an important role as a basic skeleton for the design of a number of heterocyclic compounds with different biological and pharmaceuticals activities like antitumor, anticonvulsant, antimalarial, anti-inflammatory, antiamoebic, antioxidant, antidepressant, antiprotozoal, antibacterial, and anti-HIV agents (**Figure 1.11**) and also in synthesis of fluorescent dying agents, electroluminescent materials, chemical switches, cavitands, and semiconductors (Mamedov 2016).

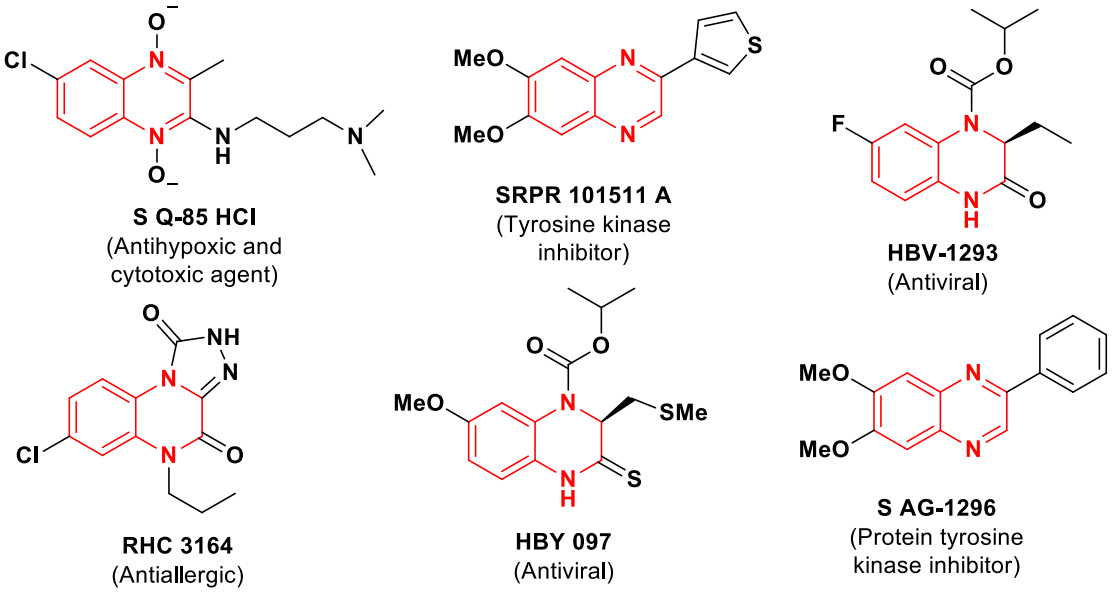
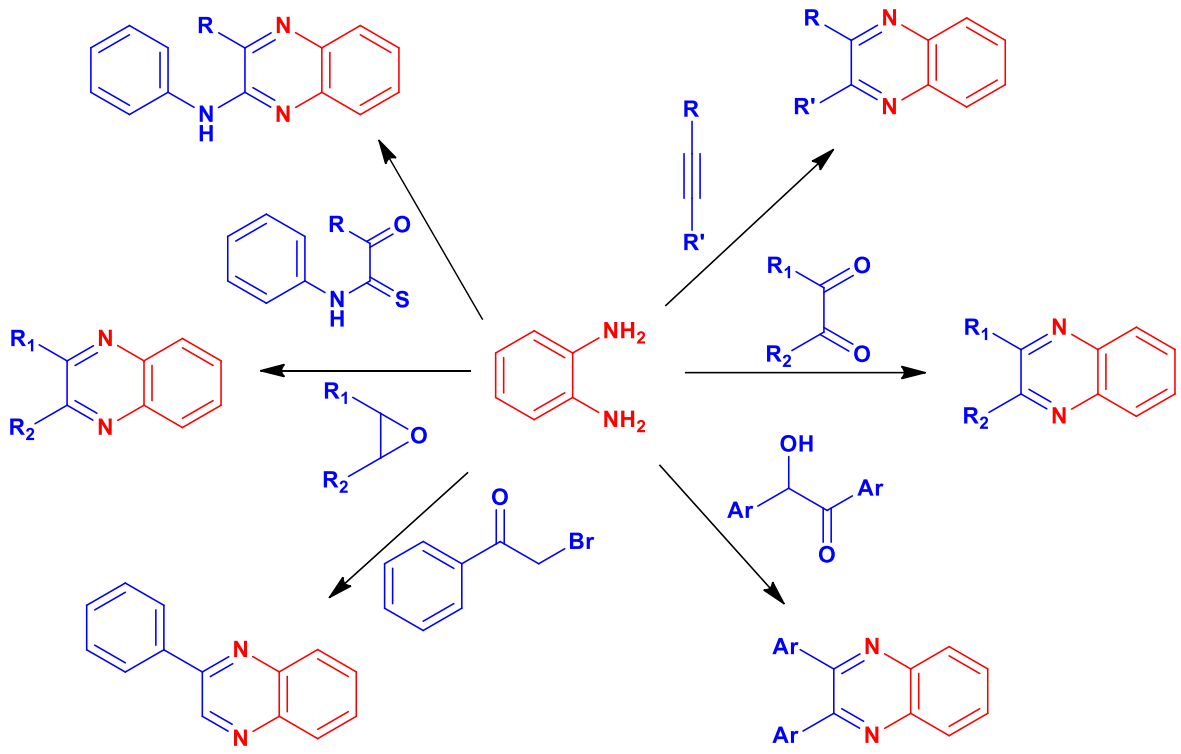


Figure 1.11: Few examples of quinoxaline containing drugs.

Quinoxalines are generally prepared by condensation of 1,2-diketones and 1,2-diamines but other than this they are also formed by using different synthons like epoxides, α-ketonic acids, α-haloketones, α-carbonyl alcohols and alkynes with 1,2-diamines (Mamedov et al. 2012, Mamedov 2016, Ramalakshmi et al. 2017).



Scheme 1.10: Synthesis of quinoxalines.

1.11 Oxazines

Oxazines are heterocyclic compounds containing one oxygen and one nitrogen atom in a six-membered ring. Depending upon the position of nitrogen and oxygen, oxazines

are classified as 1,2-oxazines, 1,3-oxazines and 1,4-oxazines. Benzo[1,4]oxazines are an important class of heterocycles which are found in many natural products as well as in several biologically active and medicinally important molecules. Natural products such as Blepharin, Cephalandole A, C-1027-chr and other pharmaceuticals incorporating 2H-1,4-benzoxazine-3(4H)one key scaffolds exhibit a wide range of biological activities such as potential activity against several diseases including heart disease, an inhibitor of bacterial histidine protein kinase, serotonin-3(5-HT3) receptor antagonists, neurodegenerative agents, antihypertensive agents, inflammatory agents, analgesic, D2 receptor antagonists, antimycobacterial and antifungal agents (**Figure 1.12**) (Didwagh et al. 2013, Sindhu et al. 2013, Jaiswal et al. 2017).

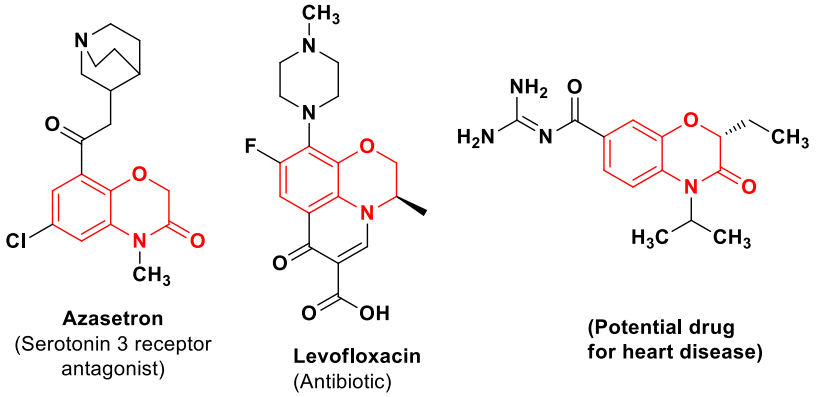
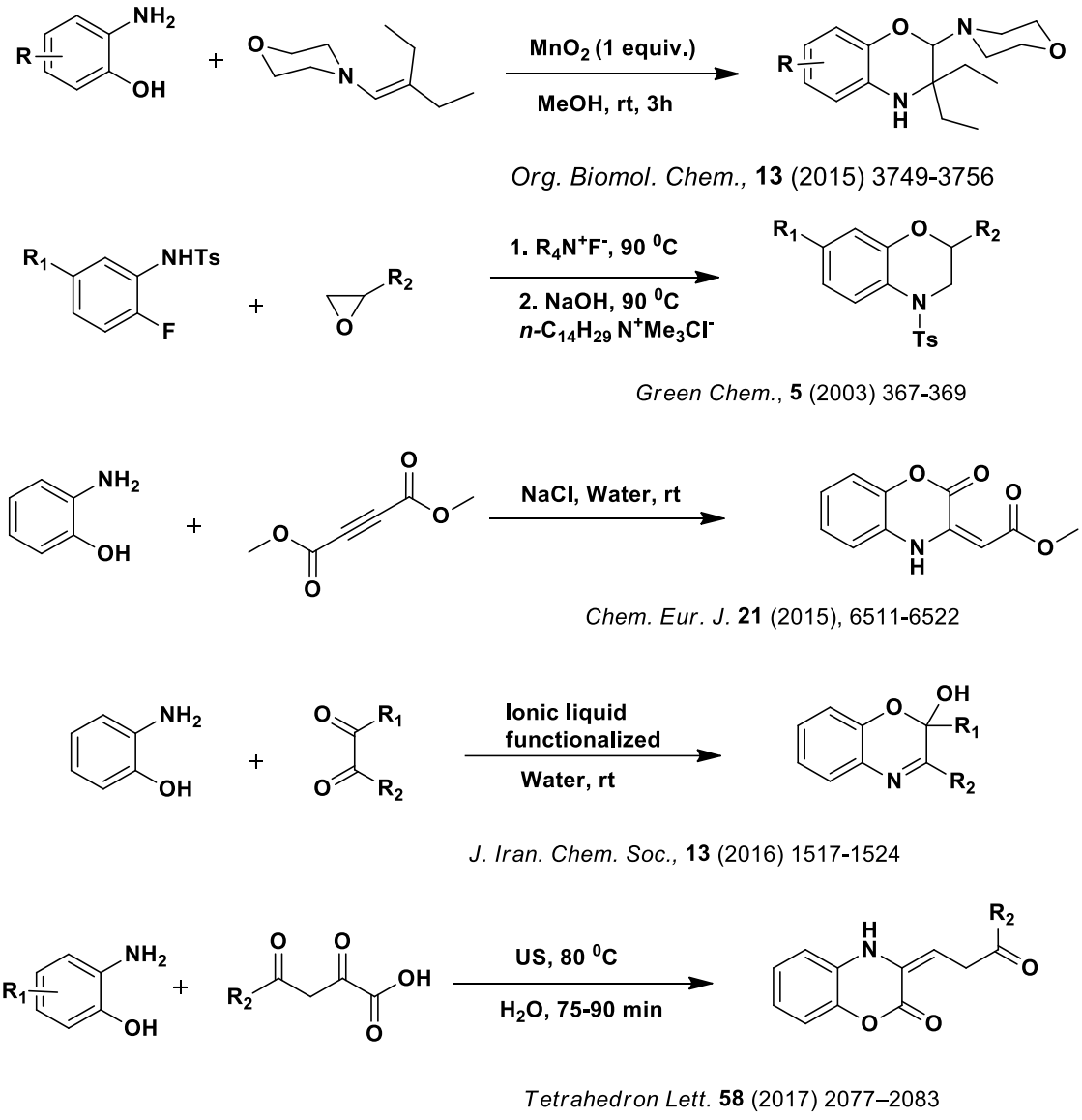


Figure 1.12: Structures of pharmaceutically active compounds possessing 1, 4-benzoxazine scaffolds.

A number of synthetic approaches for the synthesis of benzo[1,4]oxazines have been reported over the past few decades. **Scheme 1.11** shows general procedures for the synthesis of benzo[1,4]oxazine moiety (Didwagh et al. 2013, Jaiswal et al. 2017).



Scheme 1.11: Synthesis of benzo[1,4]oxazines.

1.12 Thiazines

1,4-Benzothiazines has gained considerable attention due to its wide range of biological and pharmacological activities such as antibacterial, anti-tubercular, antidiabetic, antifungal, antiarrhythmic, antitumor, antipsychotic, and neurodegenerative diseases. It is noteworthy that 1,4-benzothiazine is the pharmacophore of phenothiazines, which are well established as antipsychotic drugs namely Chlorpromazine, Fluphenazine and Mesoridazine used as antipsychotic drugs in many clinics (**Figure 1.13**) **(**Didwagh et al. 2013, Balwe et al. 2016).

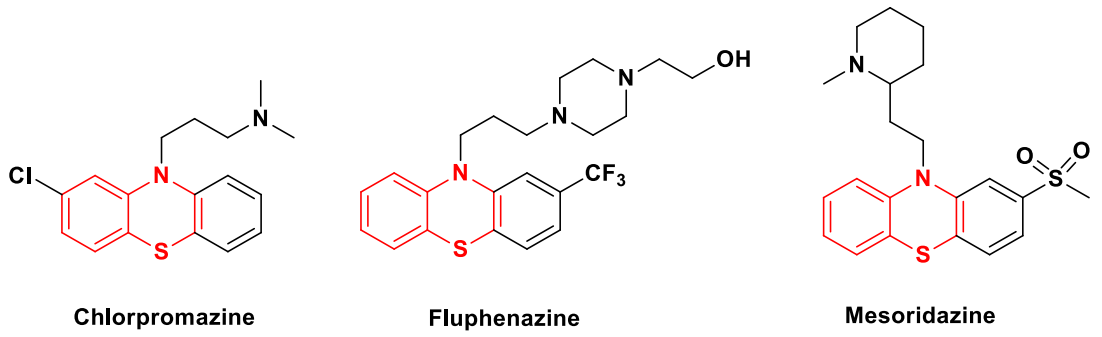
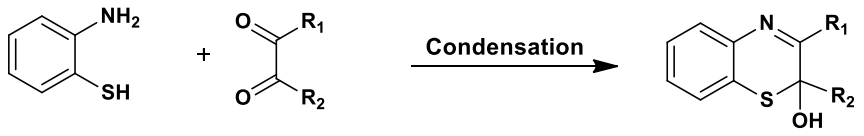
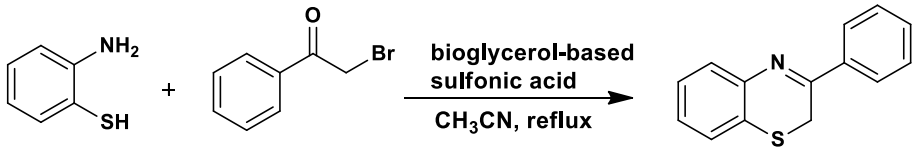


Figure 1.13: Examples of biologically active 1,4-benzothiazine derivatives.

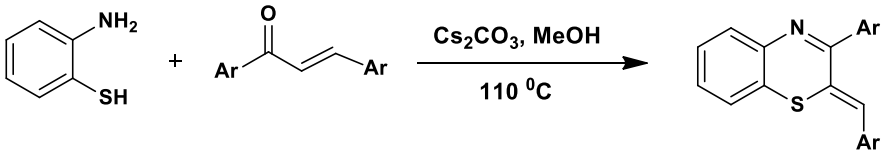
Thiazines are mainly synthesized by the reaction of 1,2-aminothiophenol with 1,2-dicarbonyl compounds (Jadamus et al. 1964, Roth et al. 1976), 1,3-dicarbonyl compounds (Bhattacharya et al. 2017), phenacyl bromide (Yang et al. 2013), chalcones (Lin et al. 2016), maleic anhydride (Kaul 1974, Jangir et al. 2015) etc. and some other methods were also reported for their synthesis involving the sulphur insertion (Charrier et al. 2001, Majumdar et al. 2014).



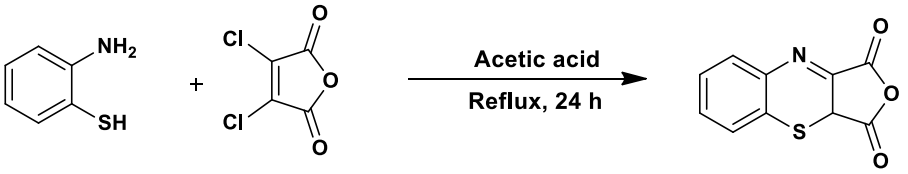
J. AM. CHEM. SOC., 86 (1964) 3056-3059



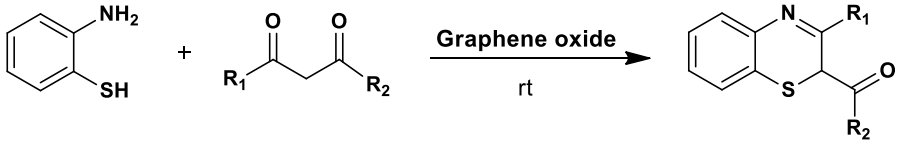
Phosphorus Sulfur Silicon Relat Elem., **188** (2013) 1327-1333



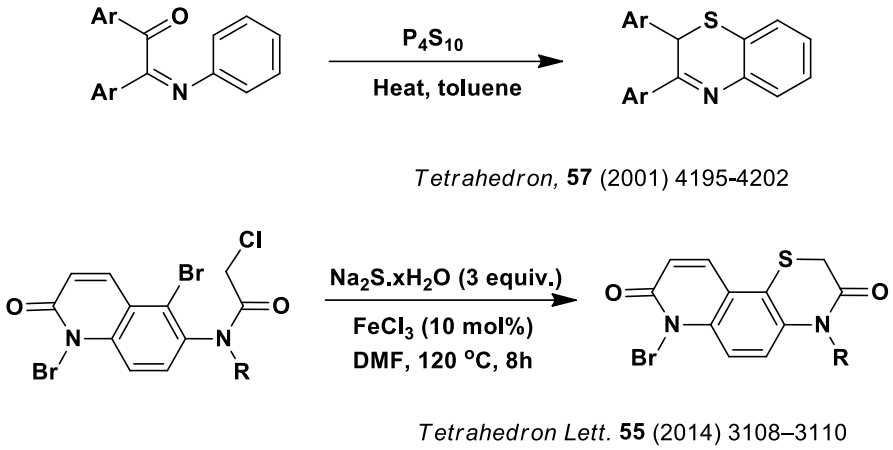
Org. Lett., **18** (2016) 6424-6427



Synthesis, 47 (2015) 2631-2634



Tetrahedron Let. 58 (2017) 926–931



Scheme 1.12: Synthesis of benzo-1,4-thiazines.

In view of the importance of above nitrogen containing organic compounds it is our interest to explore the synthesis, reactivity and structural characterization of *O*-vinyl oximes, carboxamides, quinoxalines, oxazines and thiazines, and the studies described in the subsequent chapters **2**-**6**, were undertaken.

1.13 References

Abele, E. and E. Lukevics, "Recent advances in the chemistry of oximes," *Organic Preparations and Procedures International*, **32**(3) (2000) 235-264.

Acosta-Guzmán, P., A. Mateus-Gómez and D. Gamba-Sánchez, "Direct Transamidation Reactions: Mechanism and Recent Advances," *Molecules*, **23**(9) (2018) 2382.

Ahammed, S., A. Saha and B. C. Ranu, "Hydrogenation of azides over copper nanoparticle surface using ammonium formate in water," *The Journal of organic chemistry*, **76**(17) (2011) 7235-7239.

Altaf, A. A., A. Shahzad, Z. Gul, N. Rasool, A. Badshah, B. Lal and E. Khan, "A review on the medicinal importance of pyridine derivatives," *Journal of Drug Design and medicinal chemistry*, **1**(1) (2015) 1-11.

Bagal, D. B. and B. M. Bhanage, "Recent advances in transition metal-catalyzed hydrogenation of nitriles," *Advanced Synthesis & Catalysis*, **357**(5) (2015) 883-900.

Balwe, S. G., V. V. Shinde and Y. T. Jeong, "Iron-catalyzed microwave-promoted expeditious one-pot synthesis of benzo [b][1, 4] thiazine-4-carbonitrile under solvent-free condition," *Tetrahedron Letters*, **57**(46) (2016) 5074-5078.

Beckmann, E., "Zur Kenntniss der Isonitrosoverbindungen," *Berichte der deutschen chemischen Gesellschaft*, **19**(1) (1886) 988-993.

Bhattacharya, S., P. Ghosh and B. Basu, "Graphene oxide (GO): An efficient carbocatalyst for the benign synthesis of functionalized 1, 4-benzothiazines," *Tetrahedron Letters*, **58**(10) (2017) 926-931.

Bode, M. L., D. Gravestock and A. L. Rousseau "Synthesis, reactions and uses of isocyanides in organic synthesis. An update," *Organic Preparations and Procedures International*, **48**(2) (2016) 89-221.

Bolotin, D. S., N. A. Bokach, M. Y. Demakova and V. Y. Kukushkin, "Metal-Involving Synthesis and Reactions of Oximes," *Chemical reviews*, **117**(21) (2017) 13039-13122.

Charrier, J.-D., C. Landreau, D. Deniaud, F. Reliquet, A. Reliquet and J. C. Meslin, "From benzil arylimines to 2H-benzo-1, 4-thiazines, benzothiazoles or indoles," *Tetrahedron*, **57**(19) (2001) 4195-4202.

Clarke, H. T. and R. Read, "*o*- Tolunitrile and *p*- Tolunitrile," *Organic Syntheses*, **4**(2003) 69-69.

D Joshi, S., U. A More, V. H Kulkarni and T. M Aminabhavi, "Pyrrole: chemical synthesis, microwave assisted synthesis, reactions and applications: a review," *Current Organic Chemistry*, **17**(20) (2013) 2279-2304.

de Figueiredo, R. M., J.-S. Suppo and J.-M. Campagne, "Nonclassical routes for amide bond formation, " *Chemical reviews*, **116**(19) (2016) 12029-12122.

Deininger, M. W. and B. J. Druker, "Specific targeted therapy of chronic myelogenous leukemia with imatinib," *Pharmacological reviews*, **55**(3) (2003) 401-423.

Didwagh, S. S. and P. B. Piste, "Green synthesis of thiazine and oxazine derivatives-A Short Review," *International Journal of Pharmaceutical Sciences and Research*, **4**(6) (2013) 2045.

Freeman, J. P., "Less familiar reactions of oximes," *Chemical Reviews*, **73**(4) (1973) 283-292.

Friedman, L. and H. Shechter, "Preparation of Nitriles from Halides and Sodium Cyanide. An Advantageous Nucleophilic Displacement in Dimethyl Sulfoxide1a," *The Journal of Organic Chemistry*, **25**(6) (1960) 877-879.

Gawley, R. E., "The B eckmann Reactions: Rearrangements, Elimination–Additions, Fragmentations, and Rearrangement–Cyclizations," *Organic reactions*, **35** (2004) 1-420.

Gribble, G. W., "Novel chemistry of indole in the synthesis of heterocycles," *Pure and applied chemistry*, **75**(10) (2003) 1417-1432.

Gulati, K., S. Seth and K. Venkataraman, "Phloroacetophenone," *Organic Syntheses*, **15** (1935) 70.

Haddenham, D., L. Pasumansky, J. DeSoto, S. Eagon and B. Singaram, "Reductions of aliphatic and aromatic nitriles to primary amines with diisopropylaminoborane," *The Journal of organic chemistry,* **74**(5) (2009) 1964-1970.

Harrison, T. S. and L. J. Scott, "Atazanavir," *Drugs***, 65**(16) (2005) 2309-2336.

Henry, G. D., "De novo synthesis of substituted pyridines," *Tetrahedron*, **29**(60) (2004) 6043-6061.

Hill, M. D., "Recent strategies for the synthesis of pyridine derivatives," *Chemistry–A European Journal*, **16**(40) (2010) 12052-12062.

Huang, Z., D. Zhang, X. Qi, Z. Yan, M. Wang, H. Yan and A. Lei, "Radical–Radical Cross-Coupling for C–S Bond Formation," *Organic letters***, 18**(10) (2016) 2351-2354.

Humphrey, G. R. and J. T. Kuethe, "Practical methodologies for the synthesis of indoles," *Chemical reviews*, **106**(7) (2006) 2875-2911.

Jadamus, H., Q. Fernando and H. Freiser, "Metal ion induced rearrangements of bisbenzthiazolines to Schiff-base chelates," *Journal of the American Chemical Society*, **86**(15) (1964) 3056-3059.

Jaiswal, P. K., V. Sharma, J. Prikhodko, I. V. Mashevskaya and S. Chaudhary, "“On water” ultrasound-assisted one pot efficient synthesis of functionalized 2-oxo-benzo [1, 4] oxazines:

First application to the synthesis of anticancer indole alkaloid, Cephalandole A," *Tetrahedron Letters*, **58**(22) (2017) 2077-2083.

Jangir, R., S. R. Gadre and N. P. Argade, "Sulfuryl Chloride Promoted gem-Dichlorination–Dehydrochlorination in Alkyl Benzothiazinylacetates: Synthesis of the Skeleton of Trichochrome Pigments," *Synthesis*, **47**(17) (2015) 2631-2634.

Jayasinghe, L., C. P. Jayasooriya, N. Hara and Y. Fujimoto, "A pyridine ring-containing ecdysteroid from Diploclisia glaucescens," *Tetrahedron letters*, **44**(49) (2003) 8769-8771.

Joule, J. A. and K. Mills, "Heterocyclic chemistry," *John Wiley & Sons* (2008)

Katritzky, A. R., C. W. Rees and E. F. Scriven, "Comprehensive heterocyclic chemistry I, " *Pergamon*, (1996).

Kaul, B. L., "Studies on Heterocyclic Colouring Matters Part II: $\Delta^{2,2'}$- Bi (2H- 1, 4-benzothiazines)," *Helvetica Chimica Acta*, **57**(8) (1974) 2664-2678.

Kaushik, N., N. Kaushik, P. Attri, N. Kumar, C. Kim, A. Verma and E. Choi, "Biomedical importance of indoles," *Molecules*, **18**(6) (2013) 6620-6662.

Knoevenagel, E. and A. Fries, "Synthesen in der Pyridinreihe. Ueber eine Erweiterung der Hantzsch'schen Dihydropyridinsynthese," *Berichte der deutschen chemischen Gesellschaft*, **31**(1) (1898) 761-767.

Kubota, T., T. Nishi, E. Fukushi, J. Kawabata, J. Fromont and J. i. Kobayashi, "Nakinadine A, a novel bis-pyridine alkaloid with a β-amino acid moiety from sponge Amphimedon sp," *Tetrahedron letters*, **48**(29) (2007) 4983-4985.

Kuo, C.-W., J.-L. Zhu, J.-D. Wu, C.-M. Chu, C.-F. Yao and K.-S. Shia, "A convenient new procedure for converting primary amides into nitriles," *Chemical communications*, (3) (2007) 301-303.

Lang, S. and J. Murphy, "Azide rearrangements in electron-deficient systems," *Chemical Society Reviews*, **35**(2) (2006) 146-156.

Lee, H., J. Lee, S. Lee, Y. Shin, W. Jung, J.-H. Kim, K. Park, K. Kim, H. S. Cho and S. Ro, "A novel class of highly potent, selective, and non-peptidic inhibitor of Ras farnesyltransferase (FTase)," *Bioorganic & medicinal chemistry letters*, **11**(23) (2001) 3069-3072.

Li, J. J., "Stieglitz rearrangement"*Name Reactions*, Springer (2003) 391-391.

Lin et al., "Radical Route to 1, 4-Benzothiazine Derivatives from 2-Aminobenzenethiols and Ketones under Transition-Metal-Free Conditions," *Organic letters* **18**(24) (2016) 6424-6427.

Maiti, S. N., M. P. Singh and R. G. Micetich, "Facile conversion of azides to amines," *Tetrahedron letters*, **27**(13) (1986) 1423-1424.

Majumdar, K. and D. Ghosh, "An efficient ligand-free ferric chloride catalyzed synthesis of annulated 1, 4-thiazine-3-one derivatives," *Tetrahedron Letters*, **55**(19) (2014) 3108-3110.

Mamedov, V., " A Synthesis of Quinoxalines" *Springe*r, (2016) 5-133.

Mamedov, V. A. and N. A. Zhukova "Progress in quinoxaline synthesis (Part 1). Progress in heterocyclic chemistry," *Elsevier*, **24** (2012) 55-88.

Mcgill, C. K. and A. Rappa, "Advances in the chichibabin reaction. Advances in heterocyclic chemistry," *Elsevier*, **44** (1988) 1-79.

Michael, J. P., "The quinoline alkaloids. Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds, " *Elsevier*, (2008) 423-482.

Middleton, W. and H. Carlson, "Hexafluoroacetone Imine." *Organic Syntheses*, 81-81.

Montalbetti, C. A. and V. Falque, "Amide bond formation and peptide coupling," *Tetrahedron*, **61**(46) (2005) 10827-10852.

Nakano, H., S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Noguchi, I. Ueda, H. Nakamura and T. Morimoto, "Total synthesis of pyrrolnitrin, a new antibiotic," *Tetrahedron letters*, **7**(7) (1966) 737-740.

Nenajdenko, V., "Isocyanide Chemistry: Applications in Synthesis and Material Science," John Wiley & Sons (2012).

Orlandi, M., D. Brenna, R. Harms, S. Jost and M. Benaglia, "Recent developments in the reduction of aromatic and aliphatic nitro compounds to amines," *Organic Process Research & Development*, **22**(4) (2016) 430-445.

Patil, S. A., R. Patil and D. D. Miller, "Solid phase synthesis of biologically important indoles," *Current medicinal chemistry*, **16**(20) (2009) 2531-2565.

Petri, W., "Beiträge zur kenntniss der Itaconsäure, Mesaconsäure und Citraconsäure," *Berichte der deutschen chemischen Gesellschaft*, **14**(2) (1881) 1634-1637.

Petrova, O. V., I. M. Al'bina, S. Lyubov'N, E. Y. Schmidt and E. I. Kositsyna, "Synthesis of 1 H-and 1-vinyl-2-pyridylpyrroles by the Trofimov reaction," *Mendeleev communications*, **7**(4) (1997) 162-163.

Pollak, P., G. Romeder, F. Hagedorn and H. P. Gelbke, "Nitriles," *Ullmann's Encyclopedia of Industrial Chemistry*, (2000).

Qin, W., S. Long, M. Panunzio and S. Biondi, "Schiff bases: A short survey on an evergreen chemistry tool," *Molecules*, **18**(10) (2013) 12264-12289.

Rajanbabu, T. x, "Hydrocyanation of alkenes and alkynes," *Organic Reactions*, **75**(2013) 1-74.

Raje, V. P., R. P. Bhat and S. D. Samant, "Polyvinyl pyridine as a novel solid heterogeneous, recyclable catalyst for aza-Michael reaction," *Synlett*, (16) (2006) 2676-2678.

Ramalakshmi, N., S. Chitra, S. Arunkumar and J. Arunpandiyan, "A Review On Quinoxalines," (2017).

Rani, V., V. Abbot, Y. Kapoor, D. Konar and K. Kumar, "Recent synthetic and medicinal perspectives of pyrroles: An overview," *Journal of Pharmaceutical Chemistry & Chemical Science*, **1**(1) (2017) 17-32.

Roth, H. and W. Kok, "Ninhydrin Reactions, 3. Reactions With Dimethoxyanilines And Reactive Aromatics," *Chemischer Informationsdienst*, **7**(20) (1976)

Ruiz-Castillo, P. and S. L. Buchwald, "Applications of palladium-catalyzed C–N cross-coupling reactions," *Chemical reviews*, **116**(19) (2016) 12564-12649.

Saini, A., S. Kumar and J. S. Sandhu, "Hantzsch reaction: Recent advances in Hantzsch 1, 4-dihydropyridines," (2008).

Schmidt, E. Y., I. M. Al'bina, A. M. Vasil'tsov, A. B. Zaitsev and N. V. Zorina, "A straightforward synthesis of pyrroles from ketones and acetylene: a one-pot version of the Trofimov reaction," *Arkivoc*, **7** (2005) 11-17.

Sheehan, J. C. and W. A. Bolhofer, "An improved procedure for the condensation of potassium phthalimide with organic halides," *Journal of the American Chemical Society*, **72**(6) (1950) 2786-2788.

Shen, B., D. M. Makley and J. N. Johnston,"Umpolung reactivity in amide and peptide synthesis," *Nature* **465**(7301) (2010) 1027.

Shioiri, T., "Degradation reactions," (1991).

Sindhu, T., S. Arikkatt, G. Vincent, M. Chanran, A. Bhat and K. Krishnakumar, "Biological activities of oxazine and its derivatives: a review," *Int J Pharma Sci Res*, **4** (2013) 134-143.

Stieglitz, J. and P. N. Leech, "The Molecular Rearrangement of Triarylmethyl-Hydroxylamines and The "Beckmann" Rearrangement of Ketoximes," *Journal of the American Chemical Society*, **36**(2) (1914) 272-301.

Taber, D. F. and P. K. Tirunahari, "Indole synthesis: a review and proposed classification." *Tetrahedron*, **67**(38) (2011)7195.

Tripathi, R. P., S. S. Verma, J. Pandey and V. K. Tiwari, "Recent development on catalytic reductive amination and applications," *Current Organic Chemistry*, **12**(13) (2008) 1093-1115.

Tschitschibabin, A., "Über Kondensationen der Aldehyde mit Ammonik zu Pyridinbasen," *Journal für Praktische Chemie*, **107**(1-4) (1924) 122-128.

Ugi, I., “Versuche mit isonitrilen,” Angewandte Chemie-International Edition, WILEY-VCH VERLAG GMBH MUHLENSTRASSE 33-34, D-13187 BERLIN, GERMANY, (1959).

Valeur, E. and M. Bradley, "Amide bond formation: beyond the myth of coupling reagents," *Chemical Society Reviews*, **38**(2) (2009) 606-631.

Volkov, A., F. Tinnis, T. Slagbrand, P. Trillo and H. Adolfsson, "Chemoselective reduction of carboxamides," *Chemical Society Reviews*, **45**(24) (2016) 6685-6697.

Wilkerson, W. W., W. Galbraith, K. Gans-Brangs, M. Grubb, W. E. Hewes, B. Jaffee, J. Kenney, J. Kerr and N. Wong, "Antiinflammatory 4, 5-diarylpyrroles: synthesis and QSAR," *Journal of medicinal chemistry*, **37**(7) (1994) 988-998.

Wolff, H., "The S chmidt Reaction," *Organic Reactions*, **3** (2004) 307-336.

Yang, X. and L. Wu, "Bioglycerol-Based Sulfonic Acid-Functionalized Carbon Catalyst as an Efficient and Reusable Catalyst for One-Pot Synthesis of 3-Substituted-2 H-1, 4-Benzothiazines," *Phosphorus, Sulfur, and Silicon and the Related Elements*, **188**(10) (2013) 1327-1333.