CHAPTER-1
Introduction

1.1. Introduction.

Rapid progress of synthetic organic chemistry is associated with searching and synthesis of new organic compounds with desired properties. The great challenge for the pharmaceutical industry is to proceed to innovate, to provide clinically discriminated medicines and really make a significant change in patient's livelihood. For every 5,000-10,000 organic compounds that enter the research and development (R&D) pipeline, eventually only one could be able to receive the approval and clinical development takes about 10-12 years.

Human genome decoding has made confident and encouraged the researchers to discover large number of drug targets. In human genomes at least 1,000 genes among 30,000 genes were involved significantly in the course of syndrome. Since each of these genes linked to the function of between five and ten proteins, so there might be 5,000 – 10,000 drug targets for one new chemical entities (NCEs). [1, 2]

In order to find the new drugs and their biological activity, generally organic or medicinal chemists perform the literature search for commercially feasible combinatorial libraries. The large numbers of heterocyclic building blocks were identified for their varied applications in drug discovery and pharmaceutical research. The majority of heterocyclic organic compounds containing nitrogen have been confirmed to have the better biological activity than heterocyclic organic compounds without nitrogen. So in this regard, nitrogen containing indole and pyridine derivatives are chosen as vital building blocks for drug discovery.

Heterocycic ring having organic compounds promotes the activity against the definite organism depends on its binding affinity towards specific site of the enzyme receptor.

1.2. Importance of indole and its derivatives:

Indole (**1**) is the nitrogen containing bicyclic heterocyclic compound consists a bezene ring fused to pyrrole at 2, 3 positions. In nature the indole ring system is the most extensively distributed heterocyclic compound. The name of indole is combination of the words indigo and oleum, since indole was first isolated from indigo dye with oleum.

Indole is having pleasant flowery smell in lower concentration also and it is constituent in many perfumes, flower scents and organic blossoms. Indole was first prepared by reduction of oxindole with Zn dust by Adolf von Baeyer in 1886 [3, 4].

1.3. Nomenclature:

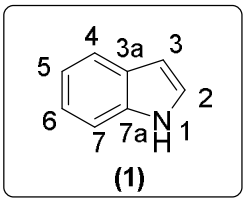


Figure 1.1: Structure of indole.

The numbering for indole ring system is as shown above. Indole, many of indole derivatives and related compounds are referred by the common or classical names though their IUPAC names are different.

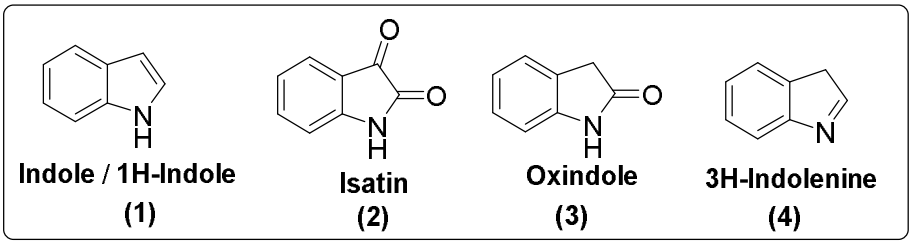


Figure 1.2: Common names for some of the indole derivatives.

1.4. Phamocological importance of indole and its derivatives:

Indole ring system was found in many natural products like alkaloids, aminoacids, hormones and etc., Majority of Indole ring system having alkaloids derived from (S)-Tryptophan **(5)**, which is a natural amino acid having Indole ring system,

Seratonin **(6)**, Tryptamine **(7)**, Psilocin **(8)**, β-indoleacetic acid **(9)**, Bufotenin **(10)**, Melatonin **(11)** and etc., Seratonin **(6)** is neurotransmitter and involves in functions of central nervous system of mammals [5, 6]. β-indoleacetic acid **(9)** is a growth regulating harrmone in plants. Melatonin **(11)** involves in the rhythm of the physiological functions in animals [7]. Psilocin **(8)** and Bufotenin **(10)** are the alkaloid compounds having hallucinogenic activity [8].

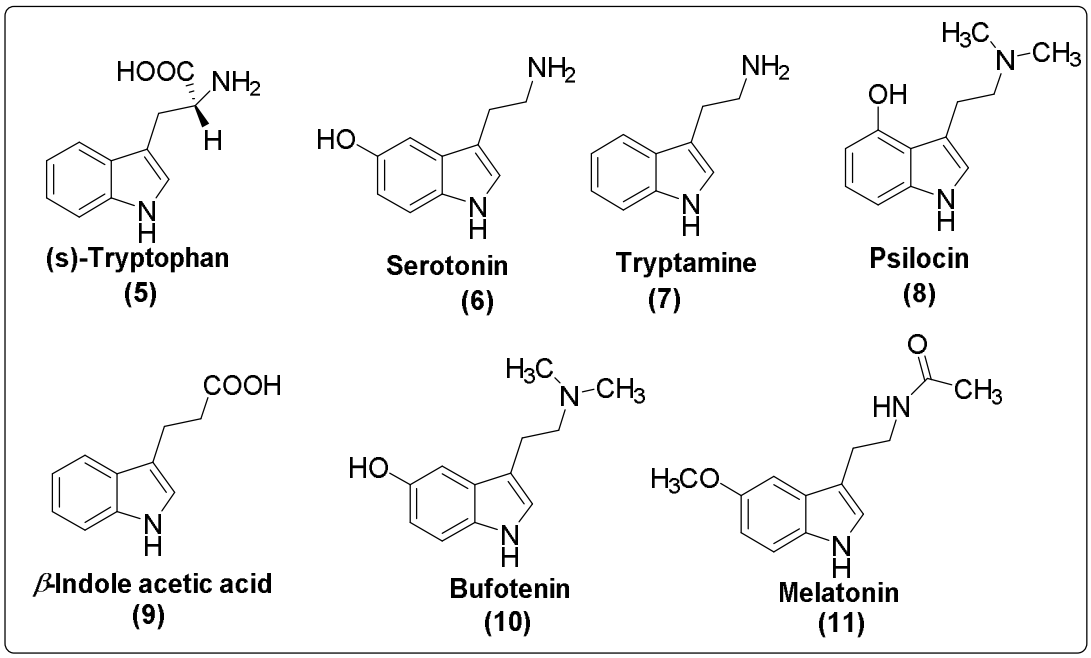
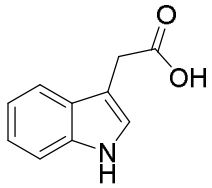
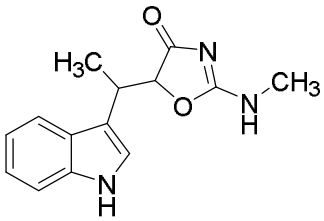
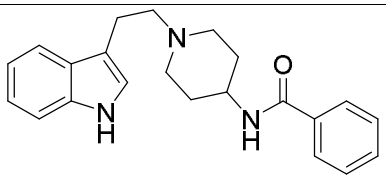
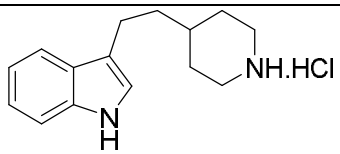
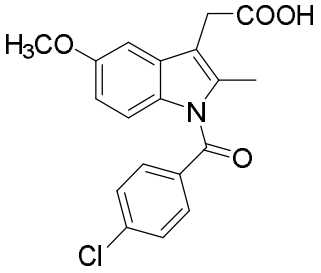
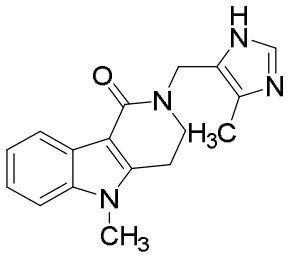
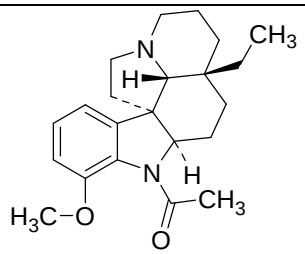
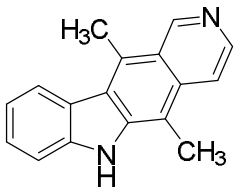
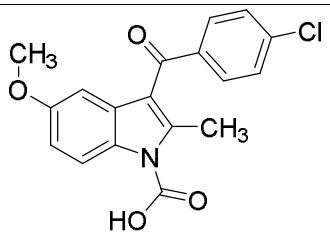


Figure 1.3: Some of the biologically active indole derivatives

Additional example of biologically active indole derivatives, their structure and therapeutic activitys are shown in below **Table 1.1**.

Table 1.1: Some of the indole derivatives and their therapeutic activity

Compound No.	Name	Structure	Therapeutic activity
12	Indole-3-acetic acid (IAA)		Heteroauxin[9] (Plant growth hormone)
13	Indolmycin (Antibiotic PA 155A)		Antibiotic[10]
14	Indoramin		Antihypertensive [11]
15	Indalpine		Antidepressant [12]
16	Indomethacin		Analgesic, Anti inflammatory &Anti pyretic[13]
17	Alosetran		IBS (Irritable bowel Syndrome)[14]

18	(-)-Aspidospermine		Naturally occurring Alkoloid[15]
19	Ellipticine		Antitumor[16]
20	Clometacin		Analegesic[17]

1.5. Physical and chemical properties of indole:

Physical properties:

Indole is a white solid and having feces or jasmine like odor. Indole melting point is 52-54^{o}C and boiling point is 253-254^{o}C. It is highly soluble in many organic solvents. Indole is readily soluble in hot water and sparingly soluble in cold water. The physical properties of substituted indoles or indole derivatives are varying depend on nature of subtituents.

Chemical properties of indole:

Indole chemical properties are very similar to pyrroles. In indoles electrophile attacks on five membered ring (pyrrole ring) rather than six membered ring [18]. The different bonds of indole ring bond lengths were determined by X-ray data and shown below [19].

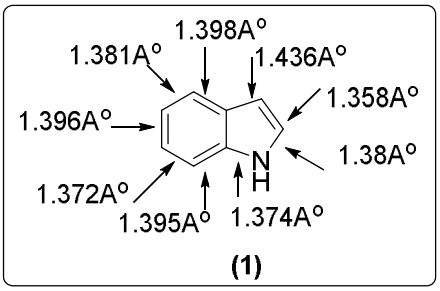


Figure 1.4: Bond lengths of indole.

By using molecular orbital method π-electron density in indole ring have been calculated [20].

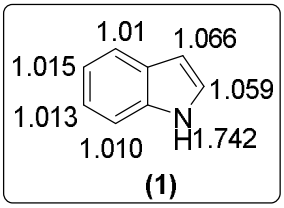


Figure 1.5: π –electron density of indole.

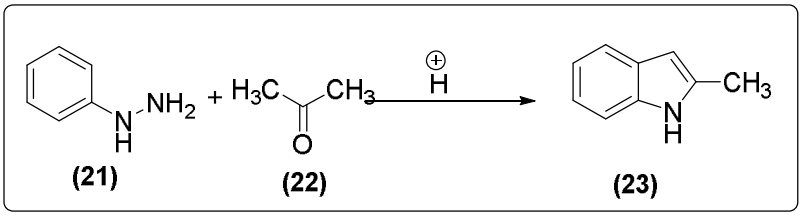
Based on above results, 3rd position in Indole ring has the higher electron density than other positions and hence 3rd position in Indole is the more preferable position to attack the electrophiles [21, 22].

Indole is a hetero aromatic ring and it undergoes electrophilic substitution reactions like Friedel-crafts alkylation, acylation, halogination, nitration and etc., at 3rd position. Moreover, Indole can undergo some special reactions like Vilsmeier Hack formylation [23], Mannich reaction [24, 25], Michael addition [26, 27], Riemer-Tiemann reaction [28, 29] and etc.,

1.6. Synthetic approaches for indoles and its derivatives:

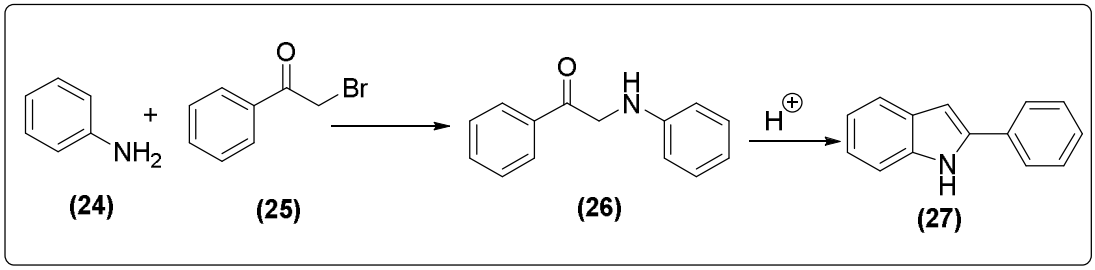
1.6.1. Fisher indole synthesis: Indole was prepared by Hermann Emil Fischer in 1883 by reacting phenylhyrazine with *α*-hydrogen having carbonyl compound under acidic conditions [30]. In this reaction along with various subtituents having phenyl

hyrdrazines and different types of carbonyl compounds were used to get various substituted indoles (**Scheme 1.1**).



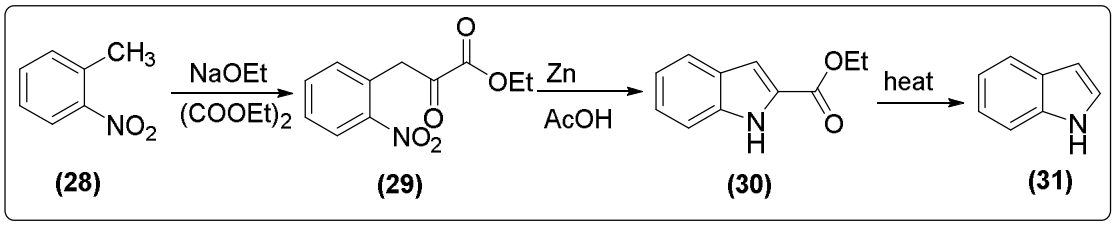
Scheme 1.1: Fisher's indole synthesis.

1.6.2. Bischler Synthesis: This reaction is also acid catalyzed reaction. It involves the reaction between aniline and *α*-haloaryl ketones and followed by cyclization of *α*-amino aryl ketones. By using this reaction 2-aryl and 2, 3-diarylindoles can be prepared [31] (**Scheme 1.2**).



Scheme 1.2: Bischler's 2-phenyl Indole synthesis.

1.6.3.The Reissert Synthesis: In this method condensation of activated aryl compound (such as *o*-nitrotoluene) and diethyloxalate gives ketoester intermediate which on reduction followed by cyclization yields an indole [32] (**Scheme 1.3**).



Scheme 1.3: Reissert's Indole synthesis.

1.7. Importance of pyridine and its derivatives:

Pyridine **(32)** is aromatic heterocyclic compound; its molecular formula is C_5H_5N. Pyridine **(32)** is a precursor to many agrochemicals, pharmaceuticals and it is also used as an important reagent and solvent in many orgaic reactions. Pyridine was first isolated and characterized by Anderson in 1846. Pyridine **(32)** cyclic nature was characterized by Dewar and Korner in 1869 [33]. Since 12th century pyridine derivatives are commercially very prominent and important molecules in medicinal and organic chemistry.

1.8. Structure and Nomenclature:

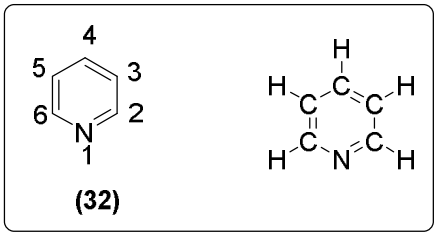


Figure 1.6: Structure of pyridine.

The Pyridine ring numbering system is shown above. Pyridine and many of pyridine derivatives are reffered by the classical or common names eventhough, IUPAC names are different.

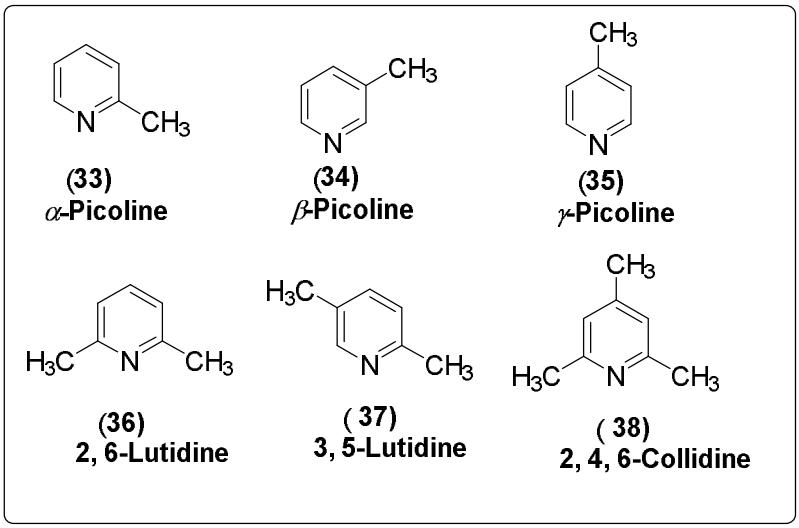


Figure 1.7: Structures of the common pyridine derivatives.

1.9. Pharmacological importance of pyridine derivatives:

Pyridine ring is considered as one of most important heterocyclic aromatic compound. Pyridine ring system is found in many naturally occurring important organic compounds such as vitamins Pyridoxine (vitamin B_6), Niacin (vitamin B_3) (**40**), in biological redox enzymes NAD/NADP/NADPH and in alkaloids like nicotine (**39**). Pyridine ring system is very important for most of the biological activities [34]. In pharma industry more than 7000 existing drugs having the pyridine ring system.

Amrinone **(41)** is the phosphodiesterase-3 inhibitor, Bupicomide **(42)** is the β-hydroxylase inhibitor and Amlexanox **(43)** is used as anti-inflammatory and anti allergic agent.

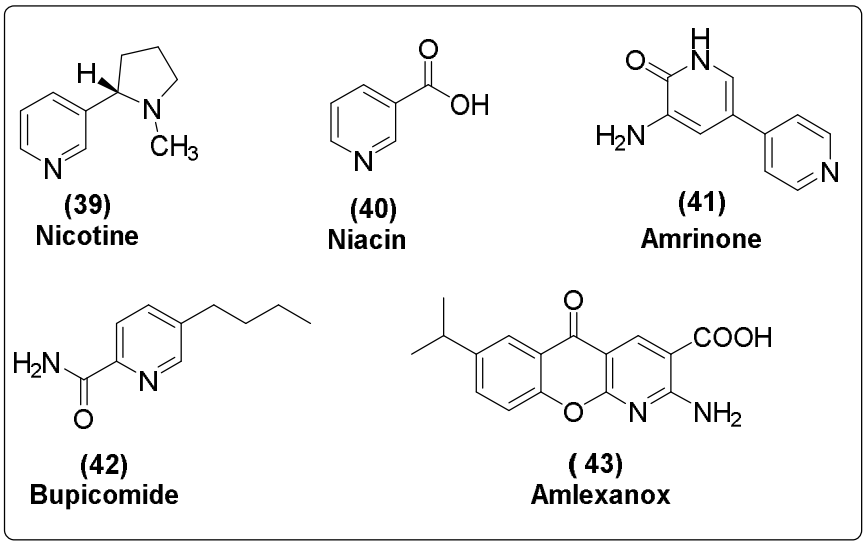
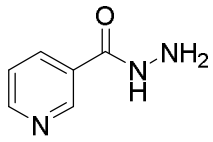
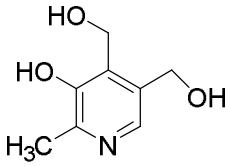
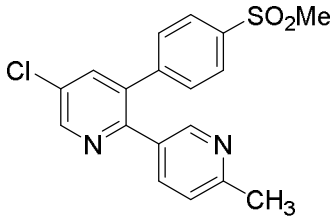
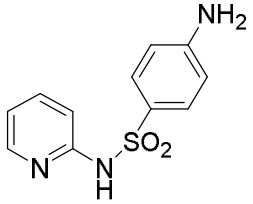
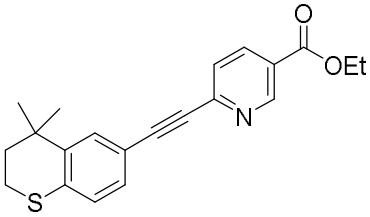
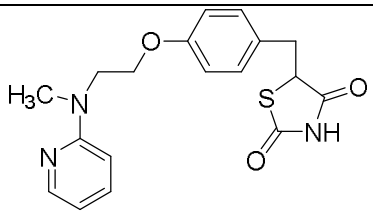
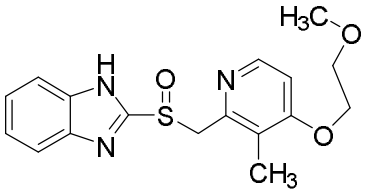
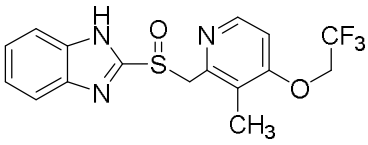


Figure 1.8: Structures of some biologically active pyridine derivatives.

Additional examples of biologically active pyridine derivatives, their structure and therapeutic activitys are shown in below **Table 1.2**.

Table 1.2: Some of the pyridine derivatives and their therapeutic activity.

Compound No.	Structure	Name	Therapeutic activity
44		Isoniazid	Antituberculosis [35]
45		Pyridoxin (vitamin-B_6)	Vitamin[36]
46		Etoricoxib	Anti inflammatory[37]
47		Sulfapyridine	Antibacterial[38]
48		Tazarotene	Treating Psoriasis[39]
49		Rosiglitazone	Anti diabetic[40]

50		Rabeprazole	Treating ulcers[41]
51		Lansoprazole	Treating ulcers[42]

1.10. Physical and chemical properties of pyridine:

Physical properties:

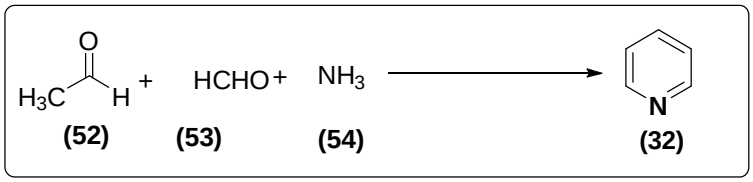
Pyridine is the color less liquid having nauseating, fish like smell. Pyridine boiling point is 115.2^{o}C, soluble in all organic solvents and miscible with water. The physical properties of pyridine derivatives are varying depend on nature of subtituents.

Chemical properties:

Pyridine is a weak organic base and p^{ka} is 5.25. Because of electronegative nitrogen in the ring, pyridine is the electron deficient aromatic system and does not react with electrophiles, but activated pyridines undergo electrophilic substitution recation at 3rd position. Pyridine undergoes nucleophilic substitution reaction at 2nd and 4th positions [43, 44].

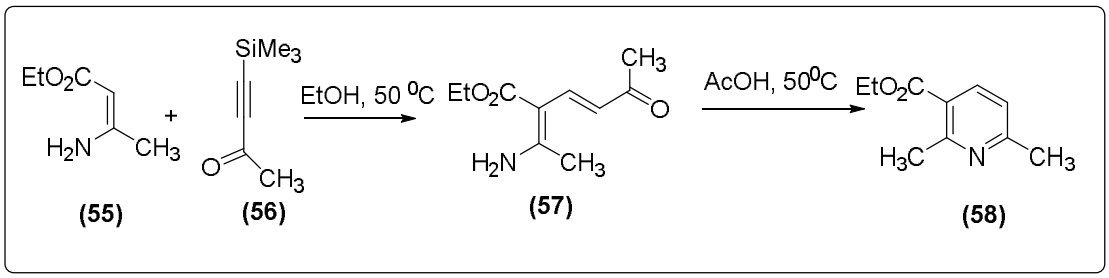
1.11. Pyridine and its derivatives- common synthetic approaches:

1.11.1. Chichibabin pyridine synthesis: This is the most general method to prepare pyridine and its derivatives.This reaction involves the condensation of ketones or aldehydes or α, β-unsaturated carbonyl compounds or any combination of above carbonyl compounds with ammonia or ammonia derivatives to yield pyridine or its derivatives [45] (**Scheme 1.4**).



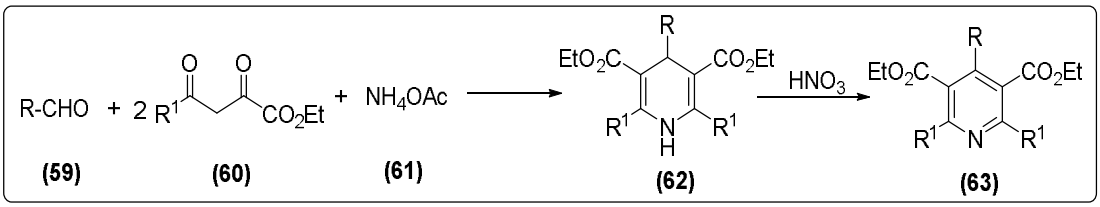
Scheme 1.4: Chichibabin pyridine synthesis.

1.11.2. Bohlmann-Rahtz pyridine Synthesis: This method involves condensation of enamines with ethynylketones and followed by cyclization under heating conditions **[46] (Scheme 1.5)**.



Scheme 1.5: Bohlmann-Rahtz pyridine synthesis.

1.11.3. Hantzsch pyridine synthesis: Aldehyde on condensation with 2 equivalents of *β*-ketoester in presence of ammonia yields dihydropyridine derivative. This intermediate undergoes oxidation and produces pyridine derivatives [47] (**Scheme 1.6**).



Scheme 1.6: Hantzsch pyridine synthesis.

1.12. Introduction and importance of Multicomponent reactions (MCR):

In organic chemistry, if more than two components are converted to the products usually it is required sequence of chemical reactions. In such cases intermediate must be isolated and purified for each step. So it takes more time, overall yield of final compound decreases, overall cost also increases and generates more waste.

In a chemical reaction three or more than three chemical components are made to react in one pot and produce desired final compound or product known as Multicomponent reaction (MCR) [48]. Multicomponent reactions have more advantages than conventional reactions in many aspects, such as; a) reduces cost and reaction time b) It can be prepared by using easily available raw materials c) Resource effective d) Easy to operate e) Multiple bond forming efficiency f) Atom economy g) Environmentally benign.

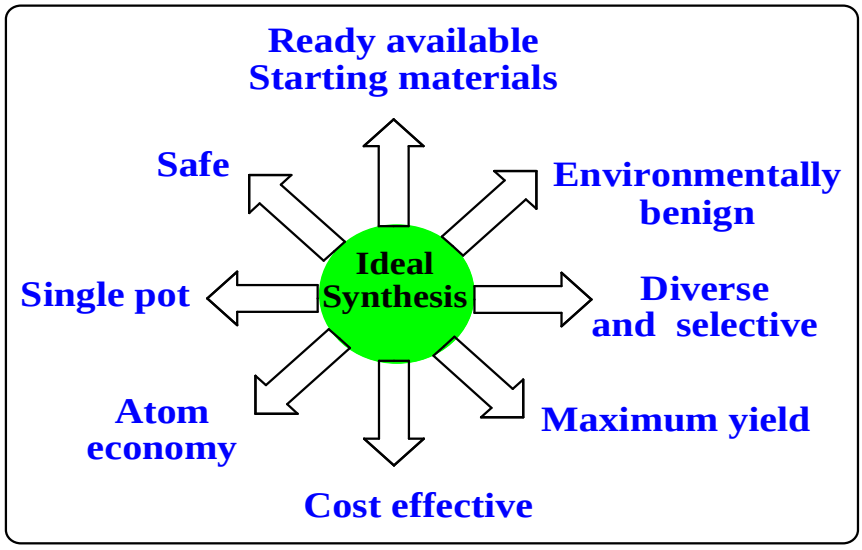


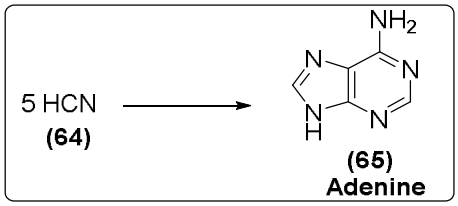
Figure 1.9: Ideal synthesis- Multicomponent reactions (MCR).

A Multicomponent reaction is a domino process and in that, subsequent conversions are determined by functionalities formed in previous stage. Multicomponent reactions afford very easy and quick access to great number of libraries of organic compounds or molecules with varied substitution patterns. The ideal synthesis of organic

compounds must lead to desired product with good yield and having less number of steps by using environmentally benign conditions and reagents.

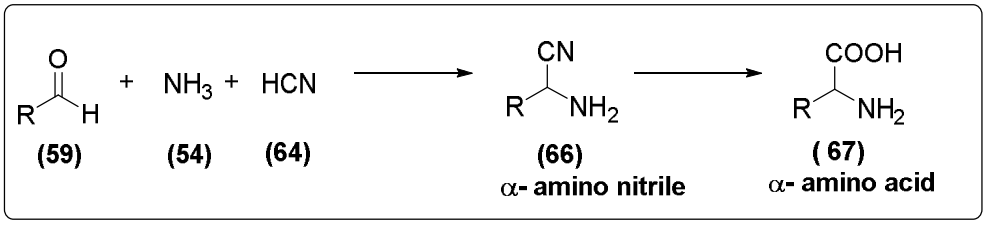
Thus, the study and discovery of new mullticomponent recations have acquired tremendous significance in heterocyclic chemistry. So, here we wish to represent our research work on the novel synthesis of Indole and Pyridine analogues by means of new multicomponent reactions strategy or approach.

The MCR concept is known in nature and it is very important in evolution. Adenine **(65)** is the nucleobase and which is the constituent in nuclic acids such as RNA and DNA [49] (**Scheme 1.7**).



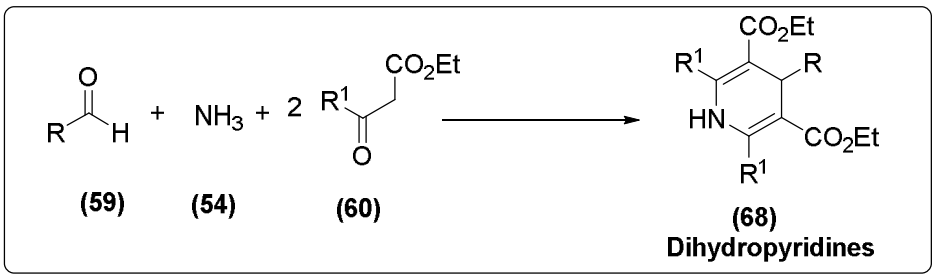
Scheme 1.7: Adenine prebiotic synthesis.

In 1850, Strecker has synthesized α-amino acids **(67)** by using multicomponent chemistry. This reaction is the first modern multicomponent reaction. This is three-component reaction and components are aldehyde, NH_3 and HCN. These three-components reacts in one pot and forms α-amino nitrile **(66)** and subsequent hydrolysis of these intermediate yields α-amino acids [50] (**Scheme 1.8**).



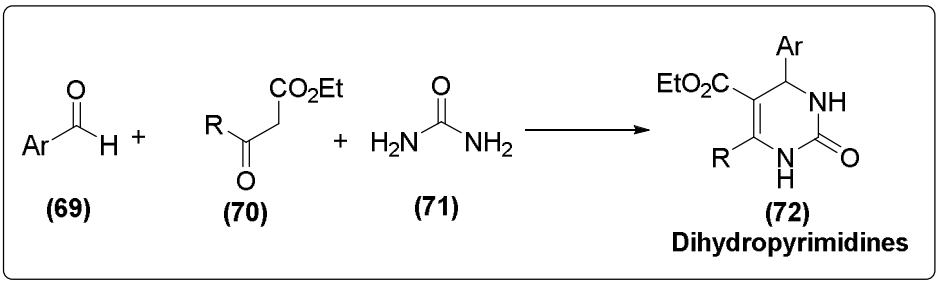
Scheme 1.8: Syntheis of α-amino acids by Strecker synthsesis.

Further progress in multicomponent recaction was done by Hantzsch in 1882. Substituted dihydropyridines **(68)** were synthesized from aldehydes, two equivalents of β-ketoesters and NH_3 [51] (**Scheme 1.9**).



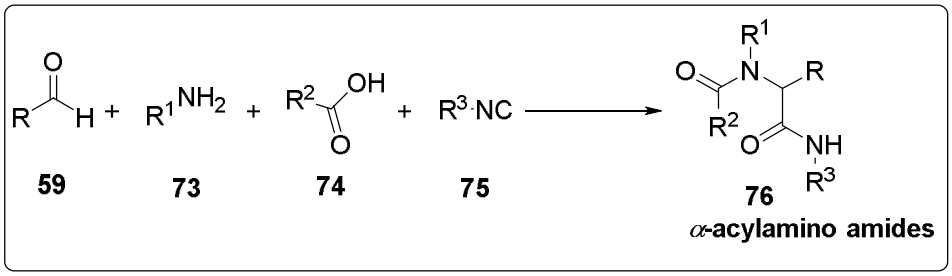
Scheme 1.9: Synthesis of dihydropyridines by Hantzsch multicomponent reaction

Substituted dihydropyrimidines **(72)** were synthesized by using Beginelli reaction in 1893. This reaction is acid catalyzed condensation of urea, aromatic aldehyde and *β*-ketoester [52] (**Scheme 1.10**).



Scheme 1.10: Synthesis of di hydropyrimidines by Beginelli multicomponent synthesis.

In 1959 Ugi *et* al. synthesized *α*-acylamino amides **(76)** by four-component reaction and the components are isocyanides, carboxylic acids, primary amines and aldehydes [53] (**Scheme 1.11**).



Scheme 1.11: Synthesis of *α*-acylamino amides by Ugi four-component reaction.

So, here we wish to present our research work on the novel synthesis of indole and pyridine derivatives by means of new multicomponent and environmentally benign approach.

1.13. Aim and objectives of the present research work.

Among the nitrogen heterocyclic compounds, Indole and Pyridine moieties are part of the many API compounds and natural products. 3-substituted indole derivatives are very important as they are extensively distributed in nature and expose a wide range of biological activities. 4, 5, 6, 7-tetrahydro-4-oxoindole derivatives have fascinated great interest for their vital physiological medicinal activity and their extensive applications in medicinal chemistry and as well as pharmaceutical chemistry. 2-arylamino-3-cyano pyridine derivatives are very important and useful intermediates in the preparation of variety of heterocyclic biological active compounds.

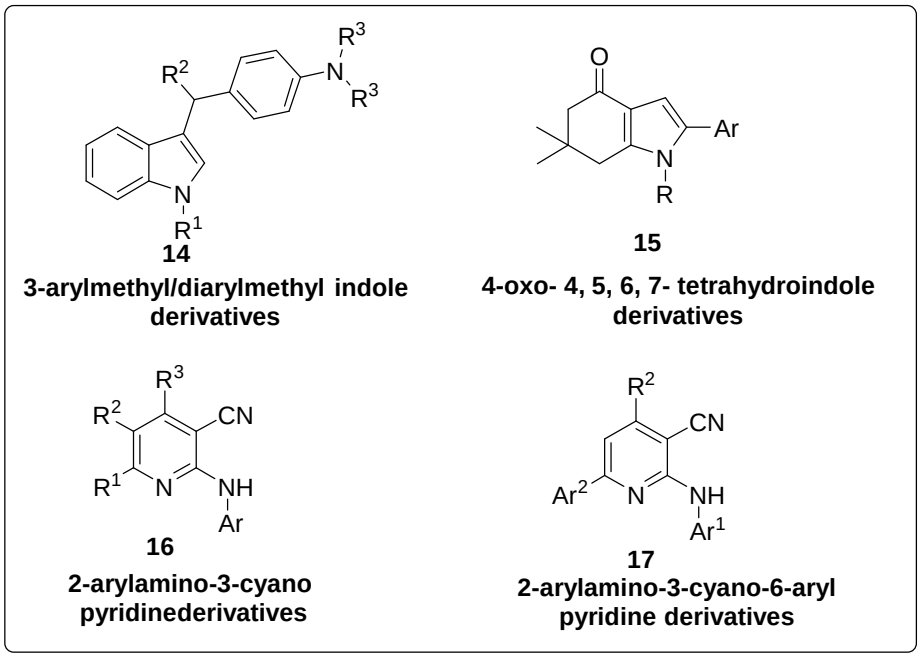


Figure 1.10: Core area of the present research work.

Aim and objective of present research work is to develop the methodologies to synthesize the above mentioned indole and pyridine derivatives by one pot

multicomponent reaction using readily available starting materials under environmentally benign conditions like inexpensive, environmentally benign catalyst, ecofriendly solvent, safe and easily operartable process.

Present research work deals with, i) Development of a simple, efficient and multicomponent methodology for the synthesis of 3-arylmethyl/ diarylmethyl indoles by a greener aza-Friedel-Crafts reaction catalyzed by PMA-SiO_2 in PEG-400, leading to 3-arylmethyl/diarylmethyl indole derivatives.

ii) Development of an efficient approach for the synthesis of 2-arylamino-3-cyanopyridine derivatives by four-component reaction catalyzed by $SnCl_2.2H_2O$ in water.

iii) Development of an efficient and ultra sound assisted methodology for the synthesis of 2-arylamino-3-cyano-6-arylpyridine derivatives by four-component reaction catalyzed by FeF_3 in PEG-400.

iv) Development of highly efficient and simple strategy for the synthesis of 4-oxo-4, 5, 6, 7-tetrahydroindole derivatives promoted by Wang resin supported sulfonic acid in water.