CHAPTER I

BRIEF IDEA ABOUT THE SYNTHETIC APPROACHES TOWARDS THE SYNTHEIS OF HETEROCYCLIC MOIETIES OF BIOACTIVE HETEROCYCLIC COMPOUNDS AND BRIEF IDEA ABOUT THE HOMOGENEOUS AND HETROGENEOUS CATALYST FOR CATALYSI

I.1. Introduction

Bioactive compounds are active organic molecules having a broad range of application in several fields such as medicinal chemistry, bio organic materials, plant science, modern pharmacology, agrochemicals, cosmetics, food industry, nano-bio-technology etc. Though the range of bioactive compounds is wide, the definition of “bioactive compounds” is quite ambiguous. To answer this, the term "bioactive" should be noticed first. According to etymology: the term ‘bio’ has been derived from the Greek word "bios" which refers life and ‘active’ word has been derived from Latin word "activus" which means full of energy or with energy or involves an activity [1-4]. In broad sense, the activity means a functioning or a process and thus a bioactive compound is a substance that has a biological activity. In medical vocabulary, a bioactive substance is a substance having an impact in living tissues or cells or triggers a response in the living tissue [5-6]. Generally bioactive compounds are non-essential and cannot play two physiological roles simultaneously in the same organism such as nutritional role and bioactivity. Nutritional roles involve the degradation of the compound or molecule to liberate the essential energy for the functioning of the organism and the bioactivity involves the interaction of the compound or molecule in its integrality with one or more components of the living tissue. Therefore, a bioactive compound is a compound which has the capability to interact with one or more component(s) of the living tissue.

I.2. Sources of bioactive heterocyclic compounds

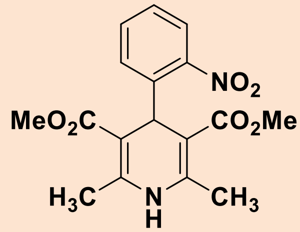
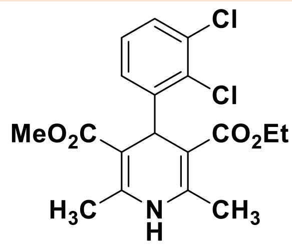
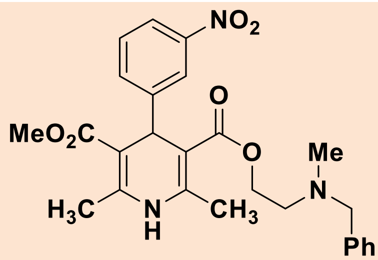
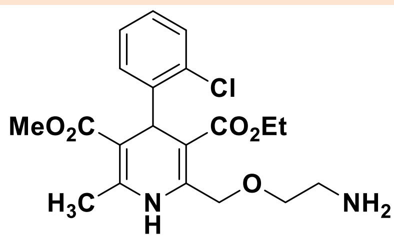
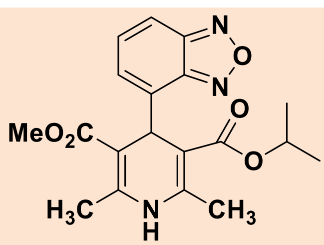
Sources of bioactive compounds are generally from plants, medicinal plants but there are also synthetic source of bioactive substances. Certain foods such as citrious fruits, nuts, unprocessed vegetables oils have actions in the body that can promote good health which is due to the presence of specific bio-active substances naturally added to it [7-8]. For example, citrious fruits contain vitamin C, some vegetable oils contain high amount of ergosterol which helps to produce vitamin D in body in presence of sunlight.[9-10] Thus essential food along with other natural food materials naturally contain bioactive substances and participates in the biological functions of the body.[11] Typical and certain bioactive compounds are produced by plants as secondary metabolites not used for daily functioning of cells of tissues but play important role in the competition, defense, attraction and signaling [13-14]. Bioactive compounds in the plants have pharmacological or toxicological effects in humans and animals and plants are not the solitary source of bioactive substances there are substances also found in other living organisms and microorganisms, such as bacteria, mushroom and in some groups of animals.[14-19]. It should be noted that natural bioactive substances had the ability to synthesize a wide variety of bioactive molecules in past, but the development of pharmaceutical chemistry and the emergence of new tools for chemical synthesis thereby adding synthetic source of bioactive molecules.[20-21]. Thus a bioactive compound may be of natural or synthetic origin. This is a very encouraging area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis.[22-23]

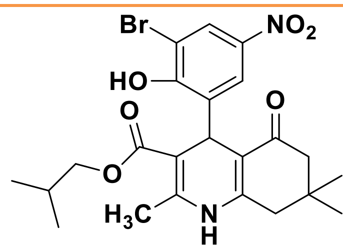
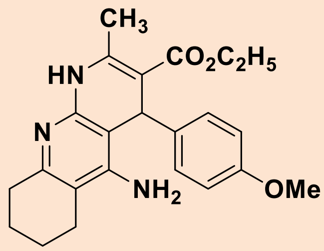
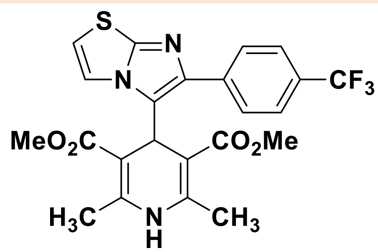
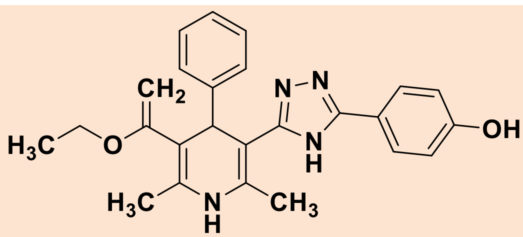
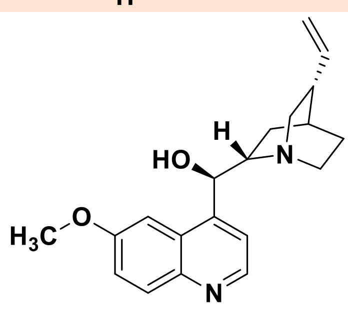
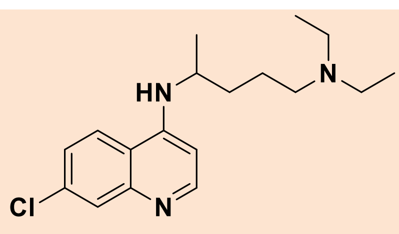
I.3. Bio active compounds and their activities

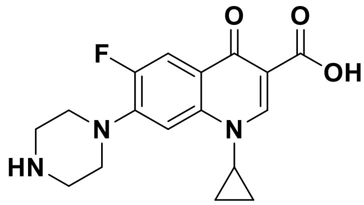
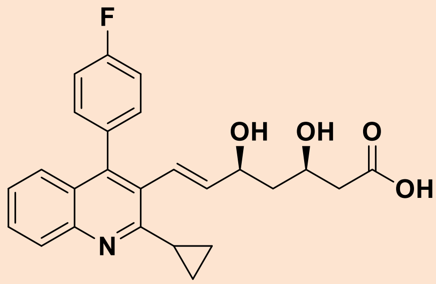
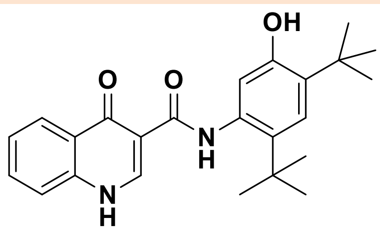
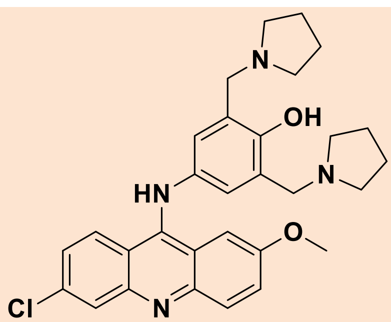
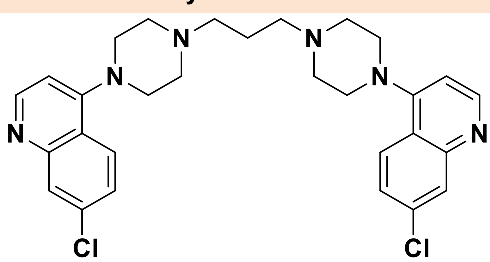
Some examples of bioactive compounds along with their application in living tissue are shown below.

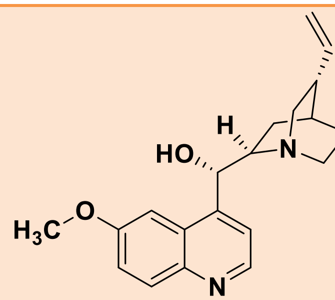
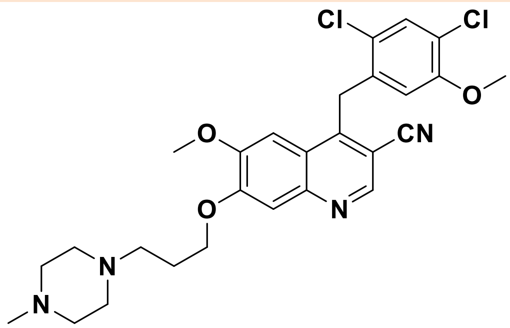
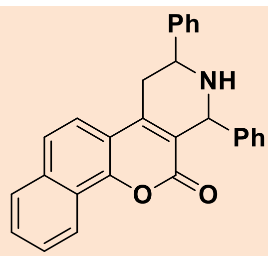
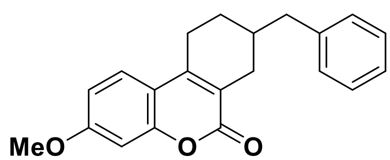
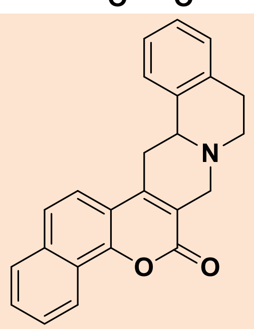
Table I.1. Examples of some bio-active compounds and their bio activity

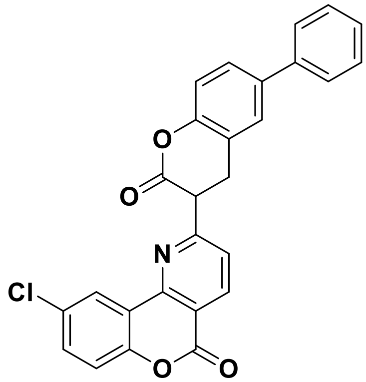
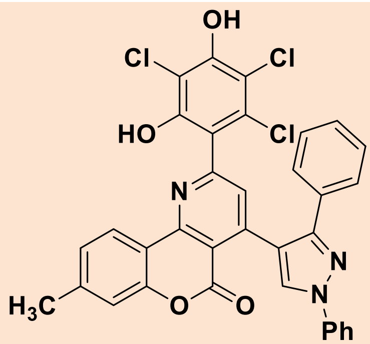
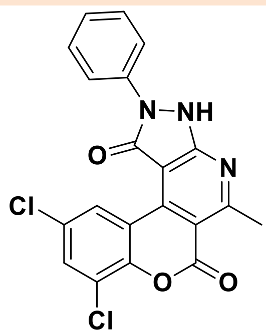
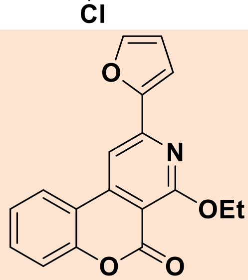
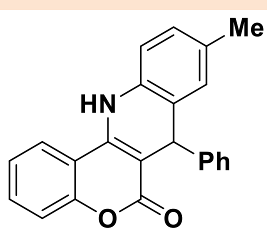
Entry	Examples of bioactive compounds	Bio activity

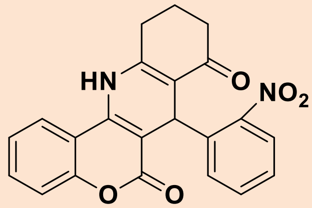
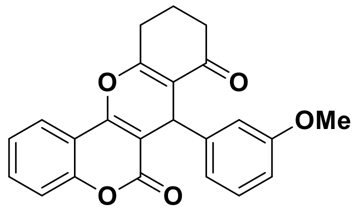
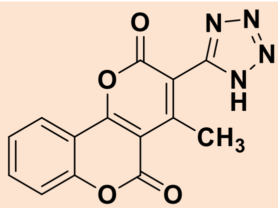
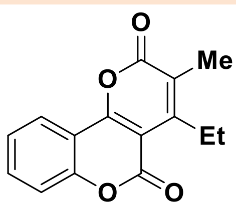
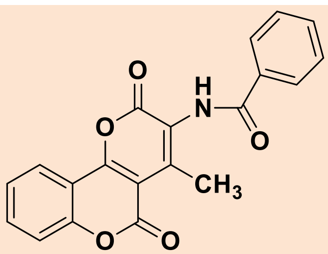
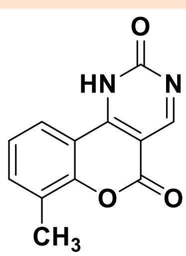
1	 Nifedipine	Calcium channel blocker
2	 Felodipine	Calcium channel blocker
3	 Nicardipine	Calcium channel blocker
4	 Amlodipine	Anti-bacterial
5	 Isradipine	Calcium channel blocker

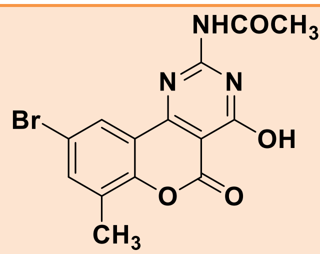
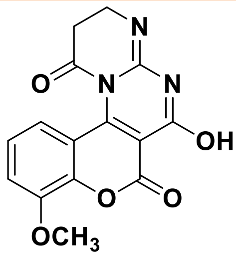
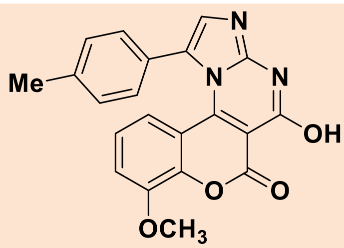
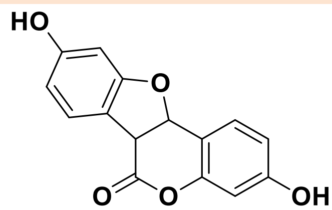
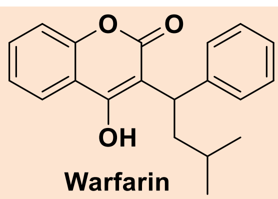
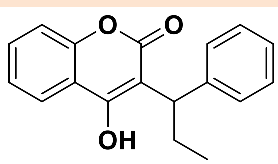
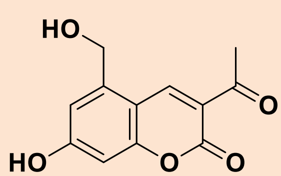
6		**Cardiovascular Activity**
7		**Anti- Alzheimer active**
10		**CFTR activity**
11		**Analgesic**
12	 Quinine	**Antimalarial**
13	 Chloroquine	**Antimalarial**

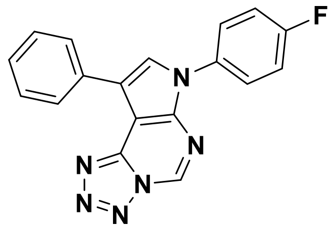
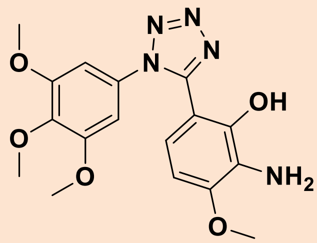
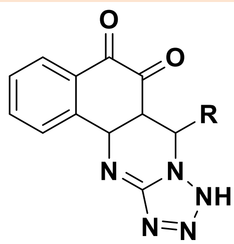
14	 Ciprofloxacin	Antibiotic
15	 Pitavastatin	Hypolipidemic
16	 Ivacaftor	Cystis fibrosis
17	 Pyronaridine	Antimalarial
18	 Piperaquine	Antimalarial

19	 **Quinidine**	**Antimalarial**
20	 **Bosutinib hydrate**	**Anti-leuckemic**
21		**Antifungal**
22		**Antipsychotic**
23		**Antimicrobial**

24		**Antimicrobial**
25		**Antibacterial**
26		**Antibacterial**
27		**Anti-inflamatory**
28		**Anticancer**

29		**Anticancer**
30		**Anticancer**
31		**Antibacterial**
32		**Antibacterial**
33		**Antibacterial**
34		**Antibacterial**

35		Antibacterial
36		Anti cancer
37		Anti cancer
38	 Cumestrol	Estrogenic activity
39	 Warfarin	Anticoagulant
40	 Phenprocoumon	Anti-thrombotic
41	 Armillarisin A	Antibacterial

42		**Antibacterial**
43		**Anticancer**
44		**Anti-tumour**

I.4. Precursor of bioactive compounds

In chemistry, precursors are smaller chemical compounds that participate in chemical reaction and produces another compound important for various applications. Therefore, precursors of bioactive compounds means that a compound from which desired bioactive compounds can be derived for medicinal and pharmaceutical usage. Some examples of precursors of bio-active compounds are shown below.(**Figure I.1**)

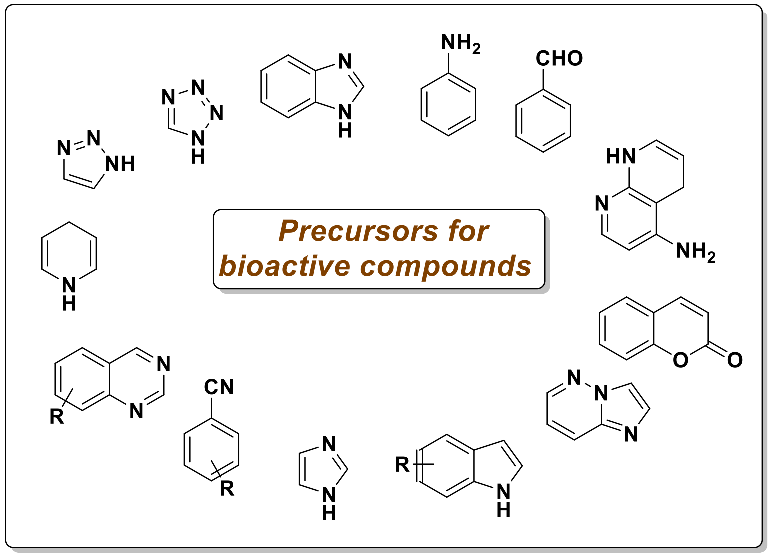
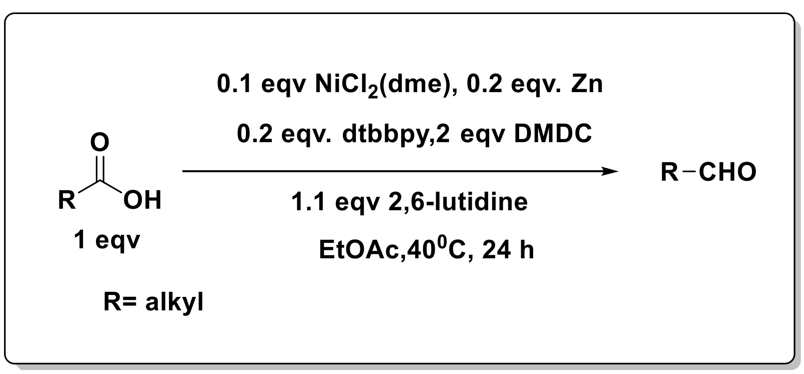


Figure I.1 Some examples of precursors of bioactive compounds

I.5. Some synthetic approaches towards the precursor of bioactive compounds

I.5.A. Synthesis of aldehydes

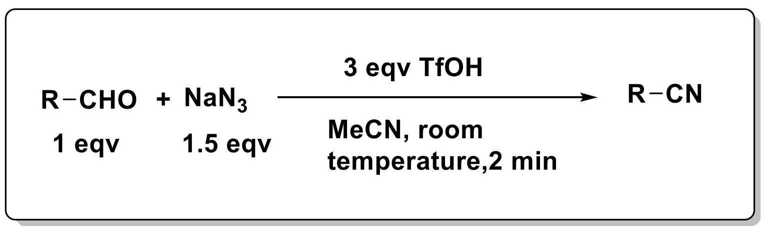
Recently, in 2019, Iosub *et. al* synthesized a wide range of aldehydes from carboxylic acids by direct but controlled reduction using a combination of Ni precatalyst, dimethyl dicarbonate as an activator and diphenylsilane as reductant (**Scheme I.1**). [24]



Scheme I.1 Synthesis of aldehydes from carboxylic acids

I.5.B. Synthesis of nitriles

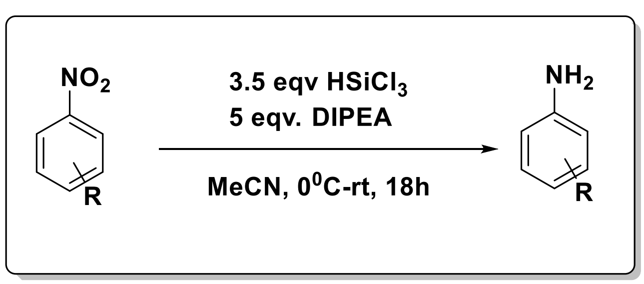
Recently in 2012, Rokade *et. al* reported a varty of nitriles which are synthesised from aldehydes by Schmidt reaction in a quantitative yield in presence of TfOH as catalyst and in acetonitrile solvent under room temperature condition(**Scheme I.2**).[25]



Scheme I.2 Synthesis of nitriles from aldehydes

I.5.C. Synthesis of anilines

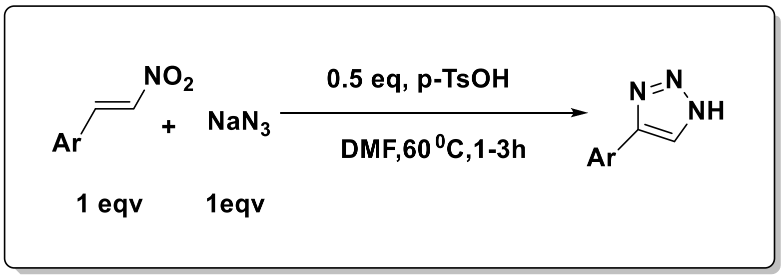
Recently in 2015, Orlandi *et. al* reported a metal free reduction of substituted nitrobenzenes to synthesise a varty of anilines in a quantitative yield with a combination of $HSiCl_3$ and tertiary amine and in acetonitrile solvent under freezing to room temperature condition(**Scheme I.3**).[26]



Scheme I.3 Synthesis of substituted anilines from substituted nitobenzaldehydes

I.5.D. Synthesis of triazoles

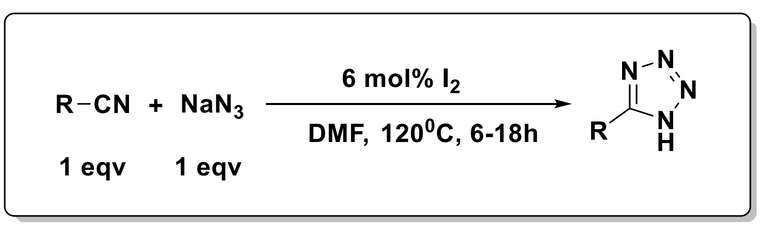
In 2014, Quan *et.al* repoted a synthesis of a variety of substituted triazoles from *β*-nitrostyrenes in presence of catalytic amount of *p*-TsOH in DMF solvent at 60^0C within a short reaction time(**Scheme I.4**).[27]



Scheme I.4 Synthesis of substituted triazoles from *β*-nitrostyrines

I.5.E. Synthesis of tetrazoles

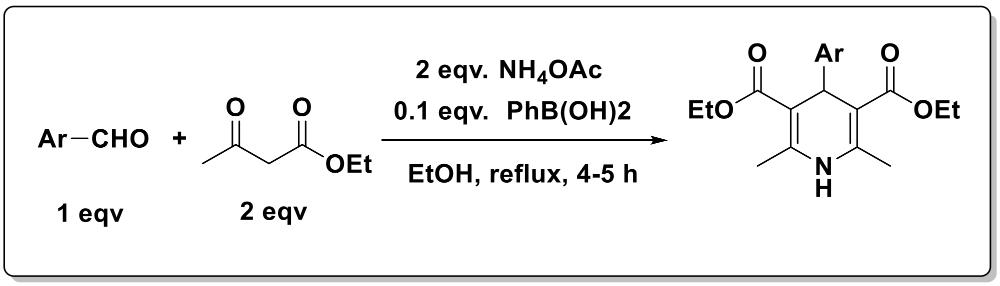
In 2010, Das *et. al* reported a synthesis of a variety of tetrazoles from nitriles in presence of iodine catalyt at 120^0C in DMF solvent (**Scheme I.5**). [28]



Scheme I.5 Synthesis of substituted tetrazoles from nitriles

I.5.F. Synthesis of dihydropyridines

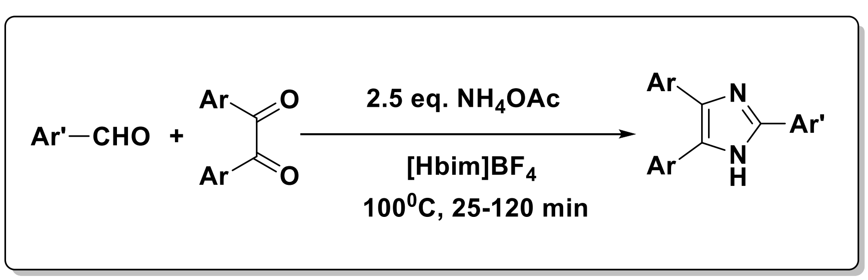
In 2008, Debache *et. al* reported a facile synthesis of a variety of dihydropyridines using aldehyde and 1,3-dicarbonyl compounds and ammonium acetate in presence of phenyl borronic acid as catalyt in ethanol solvent under reflux condition (**Scheme I.6**).[29]



Scheme I.6 Synthesis of substituted dihydropyridines from aromatic aldehydes

I.5.G. Synthesis of imidazoles

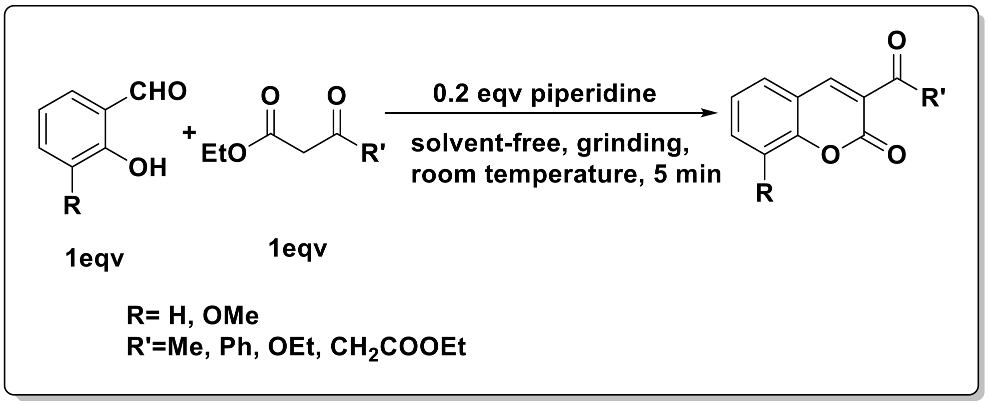
In 2005, Siddiqui *et. al* reported a facile synthesis of a variety of of imidazoles using aldehyde and 1,2-dicarbonyl compounds and ammonium acetate in presence of ionic liquid as catalyt at 100^{0}C under solvent free condition (**Scheme I.7).[**30]



Scheme I.7 Synthesis of substituted imidazoles from aromatic aldehydes

I.5.H. Synthesis of coumarine derivative

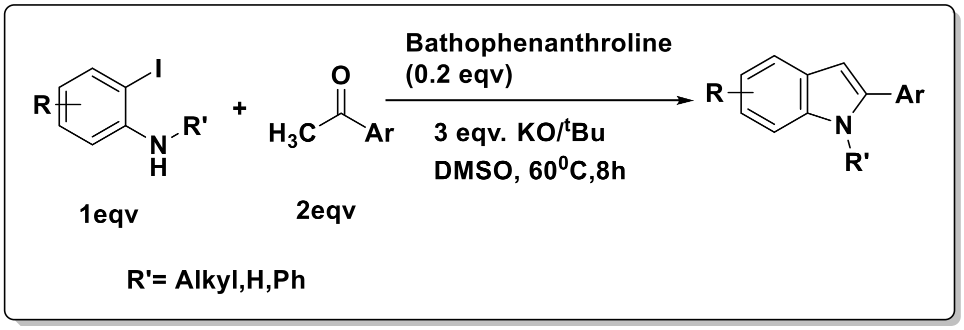
In 2001, Sugino *et. al* reported synthesis of a variety of a variety of coumarin derivatives using substituted *o*-hydroxy benzaldehydes and 1,3-dicarbonyl compounds in presence of base catalyt under solvent free condition (**Scheme I.8**).[31]



Scheme I.8 Synthesis of substituted coumarine derivatives from aromatic aldehydes

I.5.I. Synthesis of indoles

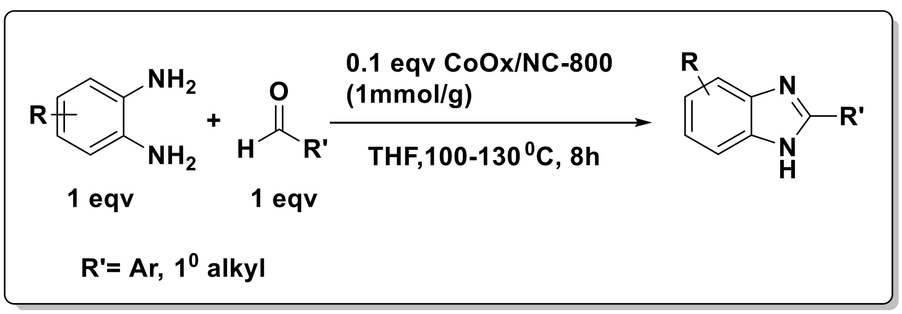
Recently in 2001, Chung *et. al* reported synthesis of a variety of a variety of indole derivatives from *o*-iodoanilines and aryl substituted keto-methyl compounds in presence of base catalyt in DMSO solvent (**Scheme I.9**).[32]



Scheme I.9 Synthesis of substituted indoles from o-iodoanilines and aryl substituted keto-methyl compounds

I.5.I Synthesis of benzimidazoles

Recently in 2019, Wang *et. al* reported synthesis of a variety of a variety of bezimidazole derivatives from *o*-dianilines and aldehydes in presence of Co-oxide catalyt at 100-130^{0}C in THF solvent (**Scheme I.10**). [33]



Scheme I.10 Synthesis of substituted benzimidazoles from o-iodoanilines and aryl substituted keto-methyl com-pounds

The above synthetic procedures draw an interest to synthesise different types precursors useful for the synthesis of a variety bioactive heterocyclic compounds in a more convenient way but some of the processes have large number of limitations such as (i) Use of non available reagents (ii) High temperature (iii) Use of corrosive chemical (iv) Use of organic hazardous solvents (v) Difficult reaction setup (vi) Time consuming process (vi) costly and hazardous catalyst and some of the processes are not environmentally and economically friendly and also some processes are not viable to do due to absence of sophisticated industry grade laboratory set up and hence minimizing the drawbacks of those processes above, I feel to pursue one my research interest to synthesize some important precursors (which are not easily available in market and are also inconvenient to prepare) by following pevious convenient methods given in literature for my targeted research interest about bioactive heterocyclic compounds in a novel and convenient way.

I.6. Catalyst

In chemistry, catalyst is a substance which when added to any progress of the chemical reaction that increases the rate of the reaction by lowering the activation energy of the reactants without itself being consumed. There are so many examples of organic and inorganic chemical reactions involving chemical reactions. On the basis of physical behavior there are two types of catalyst present in the literature of chemical science - (A) homogeneous catalyst and (B) heterogeneous catalyst and all the kinds of catalysts involving metallic, non metallic, toxic, non-toxic, enzymatic, bio-derived and biodegradable catalyst involve these two catagories. But sometimes there there occurs chemical reactions without any addition of catalysts and on that case reactants acts as autocatalyst to perform the reaction easily.

I.6.A Homogeneous catalyst

In this type of catalyst, it involves catalysts and reactants remaining in the same physical states of matter and the process is referred to as homogeneous catalysis. For example, the common homogeneous catalyst involves mineral acids and alkalies. Usually homogeneous catalyst and substrates dissolves in solvent and participate in desired reaction. There are so many examples of homogeneous catalysis such as hydrolysis, solvolysis, esterification, hydrogenation, metathesis and coupling reactions.

I.6.B Heterogeneous catalyst

In this type of catalyst, the physical state of the catalyst is different from the physical state of the reaction medium, reacting specieses. For example, preparation of ammonia by Haber's process, manufacturing of sulphuric acid by contact process, hydrogenation in unsaturated hydrocarbons involves the use of heterogeneous catalysts. Organic chemical reactions involving amorphous silica, mesoporous silica, functionalized resin, graphite powder, grapheme oxide etc. are also examples of heterogeneous catalysts.

I.6.C Difference between homogeneous and heterogeneous catalyst

Based on the literature survey and the experiences shared in reported journals and also with practical experiences, a few distinct points between homogeneous and heterogeneous catalysts has been shown in the table (**Table I.2.**)

Table I.2. Difference between homogeneous and heterogeneous Catalyst

Entry	Homogeneous catalyst	Heterogeneous catalyst
1	Activity of homogeneous catalyst is slightly higher due to its solubility in reaction medium.	Activity of heterogeneous catalyst is slightly lower to that of homogeneous catalyst but depends upon the density of functional groups attached and the porous nature of the catalyst.
2	Catalyst shows reproducible results.	Catalyst shows difficulty in reproducible results.
3	Catalyst shows relatively higher selectivity.	Catalyst shows difficulty to control selectivity.

4	Catalyst has low volume, high cost and have economically disadvantages.	Catalyst has high volume but have lower cost and is effective for large scale industrial production also.
5	Molecular active sites for this Catalyst are well defined here.	Molecular active sites for this Catalyst are not well defined rather it has random active sites.
6	Catalyst life is relatively shorter and it is rarely reusable.	Catalyst life is longer and it is reusable up to several times depend upon the reaction conditions.
7	Catalyst is less susceptible and sensitive to water and oxygen.	Catalyst is highly susceptible.
8	Catalyst shows accessible reaction kinetics, mechanism & catalytic activity.	Reaction kinetics and mechanism for this catalyst is complex and difficult to establish.
9	Used in for specific and fine chemicals manufacturing.	Used in bulk scale for industrial product manufacturing.
10	Catalysts are not diffusion controlled.	Catalysts are diffusion controlled.
11	Catalysts are difficult to	Catalysts are quite easy to

	separate from reaction mixture.	separate from the reaction mixture.

I.6. Conclusion

Finally in conclusion, I feel to pursue my research interest to synthesize bioactive heterocyclic compounds by following pevious convenient methods and by gathering knowledge from literature survey for my targeted research interest about bioactive heterocyclic compounds in a novel and convenient way. And minimizing the drawbacks of the previous processes for the synthesis of bioactive heterocyclic compounds, I also feel to pursue my research interest to synthesise new convenient greener heterogeneous catalyst and use it for the synthesis of bioactive heterocyclic compounds under greener condition.

I.7. References

References are given BIBLIOGRAPHY under Chapter I.