CHAPTER-1

BRIEF IDEA ABOUT BIOACTIVE COMPOUNDS AND SYNTHETIC APPROACHES OF ITS PRECURSOR

I.1. Introduction

Bioactive compounds are experiencing a flourishing interest in broad periphery of applications: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bio-science... etc. Though the range of bioactive compounds is wide, the definition of bioactive compounds remains ambiguous and dim. **What is a bioactive compound?** To answer this question, we will, firstly, discuss different definitions collected, to redraft a definition from the various concepts discussed.

The term "bioactive" is built by two words: 'bio' and 'active'. In etymology: 'bio' from the Greek "bios" refers life and 'active' from the Latin "activus" means dynamic, full of energy, with energy [1-3], or involves an activity [4]. This activity presents all the phenomena such as a form of life, a functioning or a process [5]. Simply a bioactive compound is a substance that has a biological activity [6]. In medical vocabulary, a bioactive substance is a substance having an impact on [7] or causes a reaction [8], or triggers a response in [9] the living tissue.

Generally bioactive compounds are non-essential, because same compound (or molecule) cannot play two physiological roles simultaneously in the same organism: one, nutritional (energetic metabolism and development), and other: bioactive (non-nutritional). This suggestion is aiming the contrast between two completely unlike processes: the first, which requires the degradation of the compound or molecule to liberate the essential energy for the functioning of the organism along with its maturing and the second, which requires 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. So it comes back from itself and without need to mention it after, this interaction (bioactivity) can disclose whatever the source of bioactive compound: food and non-food, integrated into an essential nutrient or not.

I.2. Sources of Bioactive compounds

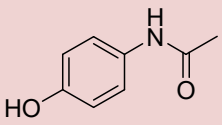
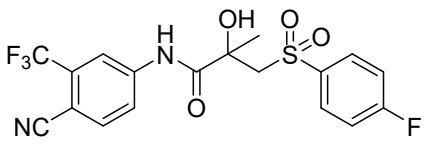
Bioactive compounds contain chemicals that are found in small amount in plants [in general] and certain foods (such as vegetables, fruits, nuts, oils and whole grains); they have actions in the body that can promote good health [10]. Typical bioactive plant compounds are produced as secondary metabolites that are not requisite for the daily functioning of the plant (such as growth) [11], but play an

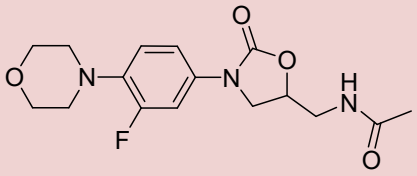
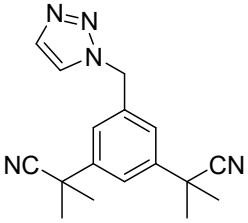
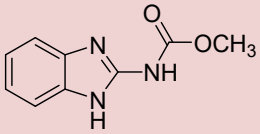
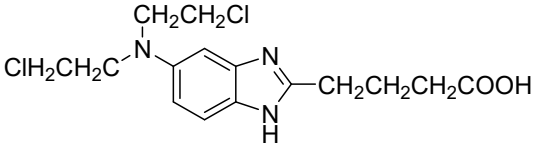
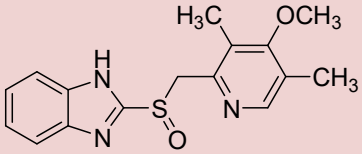
important role in the competition, defense, attraction and signaling [12]. Bioactive compounds in the plants can be explained, then, as secondary plant metabolites eliciting pharmacological or toxicological effects in humans and animals [11]. Thus, plants are not the solitary source of bioactive substances. These substances are also found in other living organisms and microorganisms, such as bacteria [13-18] mushroom [18-23] and in some groups of animals [24-28]. What is said about the terrestrial (micro-) organisms, also applies to marine (micro-) organisms. These, produce too, potentially useful substances as bioactive secondary metabolites [16-18, 24, 29-33]. It should be noted that in addition to natural bioactive substances [34, 35] the ability to synthesize a wide variety of bioactive molecules began in the early twentieth century, despite the development of pharmaceutical chemistry [36] and the emergence of new tools for chemical synthesis [37], thereby adding synthetic source of bioactive molecules. 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.

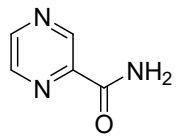
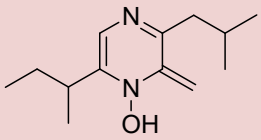
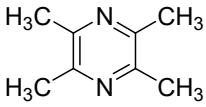
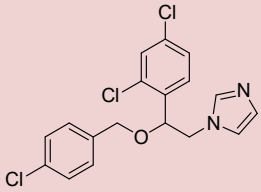
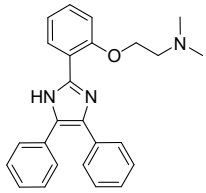
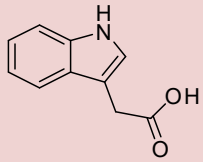
I.3. Bioactive compounds and their activity

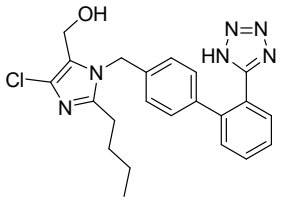
Some bioactive compounds along with their application in living tissue are shown below.

Table I.1. Examples of some bioactive compound and their bioactivity.

Sl. No.	Examples of bioactive compounds	Bioactivity
1.	Paracetamol 	Analgesic, Antipyretic
2.	Bicalutamide 	Anticancer(Prostate)

3.	Linezolide 	Antibiotic
4.	Anastrazole 	Breast-cancer treatment
5.	Carbendazim 	Fungicide
6.	Imet 3393 or Bendamustine 	Anti-cancer
7.	Omeprazole 	Treatment of GERD

8.	Pyrazinamide 	Antitubarcular
9.	Aspergillic acid 	Fungal antibiotic
10.	Ligustrazine 	Pulmonary heart disease
11.	Econazole 	Anti-fungal
12.	Trifenagrel 	Platelet aggregation inhibitor
13.	Auxine 	Plant growth regulator

14.	Losertan		Anti-hypertensive

I.4. Precursors of bioactive compounds

In chemistry, a precursor is a compound that participates in a chemical reaction that produces another compound. Simply we can say a compound from which another is formed. Therefore, precursor of bioactive compound means that a compound from which we can derive bioactive compounds. Some examples of such important precursors are shown below:

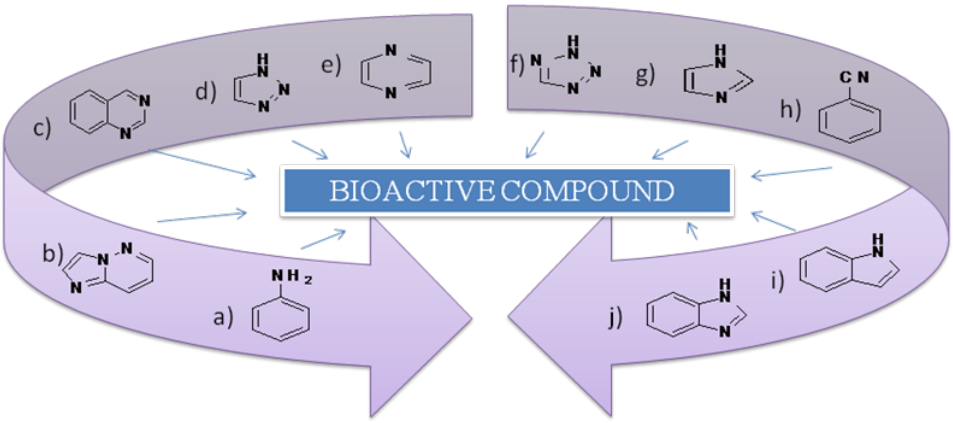


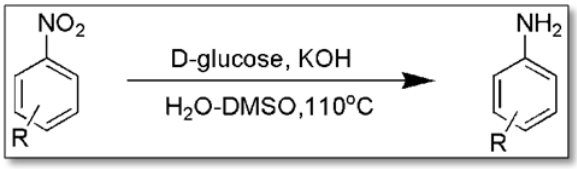
Figure I.1. Some examples of precursor of bioactive compounds. a) Aniline, b) Pyrazolopyrimidine, c) Quinazoline, d) Triazole, e) Pyrazine, f) Tetrazine, g) Imidazole, h) Nitrile, i) Indole, j) Benzimidazole.

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

As their natural availability is not so promising, researchers feel to prepare such compounds in a synthetic manner. After studying literature we came to know that there are large number of synthetic procedures are present by which we can prepare synthons of bioactive compounds. Some synthetic paths are shown below.

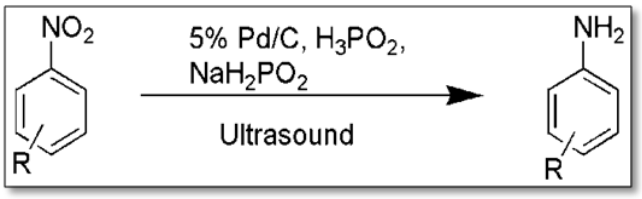
I.5.A. Synthesis of aniline

a) In 2013 M. Kumar *et al.* [38] reported reduction of aryl nitro to corresponding amine by D-glucose and KOH in water-DMSO medium at 110°C.



Scheme I.1. Reduction of aryl nitro using D-glucose-KOH.

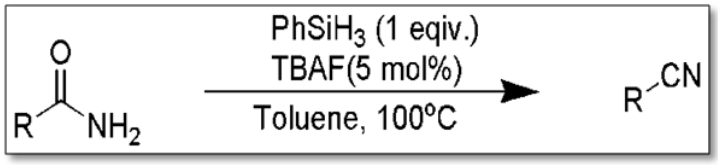
b) In the same year M. Baron *et al.* [39] reported aryl amine synthesis from aryl nitro by in-situ hydrogen generation.



Scheme I.2. Reduction of aryl nitro by in-situ hydrogen generation.

I.5.B. Synthesis of nitrile

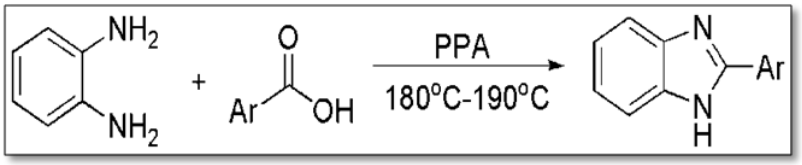
a) M. Beller *et al.* [40] converted aliphatic/aromatic amides into nitriles using catalytic amount of tetra-butyl ammonium fluoride (TBAF) and silanes.



Scheme I.3. Synthesis of nitrile using tetra-butyl ammonium fluoride (TBAF) and silanes.

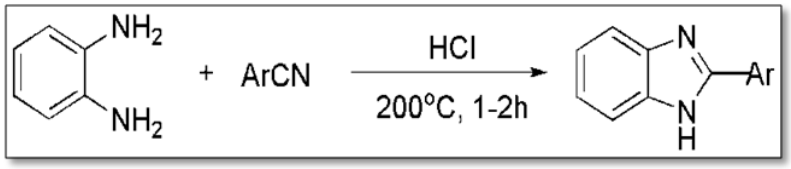
I.5.C. Synthesis of benzimidazole

a) In the presence of catalyst polyphosphate ester (PPA) at 180-190ºC, Maleki *et al*. [41], condensed *o*-phenylenediamine with aromatic carboxylic acid and got 2-arybenzimidazole.



Scheme I.4. Synthesis of 2-arybenzimidazole using catalyst polyphosphate ester (PPA).

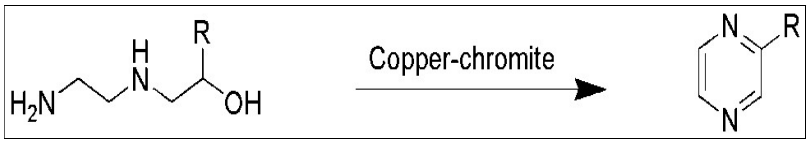
b) Hollies and Wagner obtained 2-substituted benzimidazole by the reaction of o-phenylenediamine with the substituted nitrile at 200 ºC for 1 to 2 h [42].



Scheme I.5. Synthesis of 2-substituted benzimidazole by o-phenylenediamine with substituted nitrile.

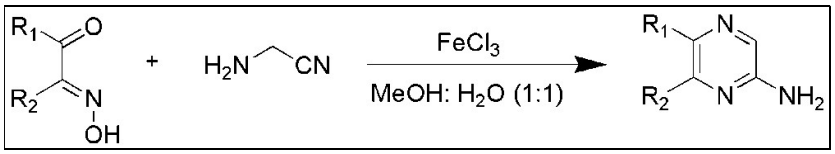
I.5.D. Synthesis of pyrazine

a) In 1990, Lee *et al.* [43] patented (U.S. Patent No. 4,966,970, 1990) the synthesis of pyrazine using copper-chromite catalyst (Scheme I.6). The catalytic reaction was carried out by adding copper-chromite catalyst to diamine compound at 300-450°C for 1-3 hours.



Scheme I.6. Synthesis of pyrazine using copper chromite.

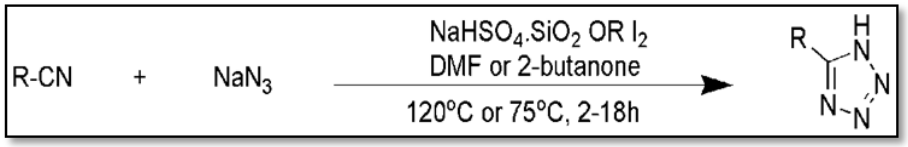
b) In year 2002, Itoh *et al.* [44] reported the reaction between isonitroso-acetophenone and aminoacetonitrile in the presence of one equivalent of $FeCl_3$ to give *N*-oxide pyrazine and subsequent hydrogenation with 10% of Pd-C to afford 55-80% pyrazine (Scheme I. 7).



Scheme I.7. Catalytic formation of pyrazine using $FeCl_3$.

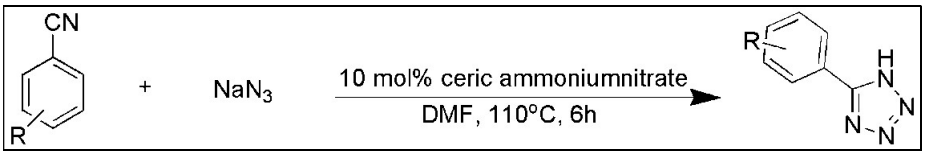
I.5.E. Synthesis of tetrazole

a) In 2009, R. Narender *et al.* [45] reported synthesis of 5-substituted 1*H*-tetrazoles using iodine or silica-supported sodium hydrogen sulfate. Here wide array of nitriles including aliphatic, aromatic, hetero nitriles as well as chloroalkyl nitriles are converted to corresponding tetrazoles with outstanding yield (Scheme I.8).



Scheme I.8. Synthesis of 5-substituted 1H-tetrazoles using iodine or silica-supported sodium hydrogen sulfate.

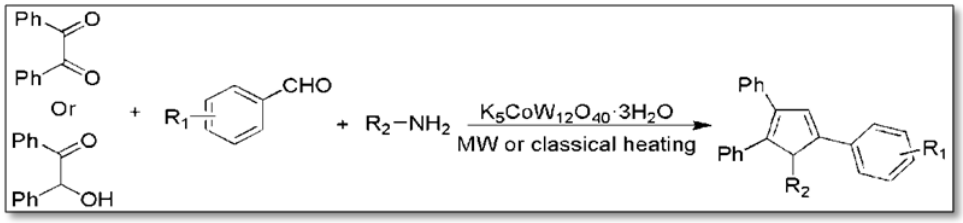
b) In 2014, S. K. Awasthi *et al.* [46] reported conversion of nitriles to 5-substituted 1H-tetrazoles using cerric ammoniumnitrate ($(NH_4)_2Ce(NO_3)_6$)as eco-friendly catalyst (Scheme I.9).



Scheme I.9. Synthesis of 5-substituted 1H-tetrazoles using $(NH_4)_2Ce(NO_3)_6$.

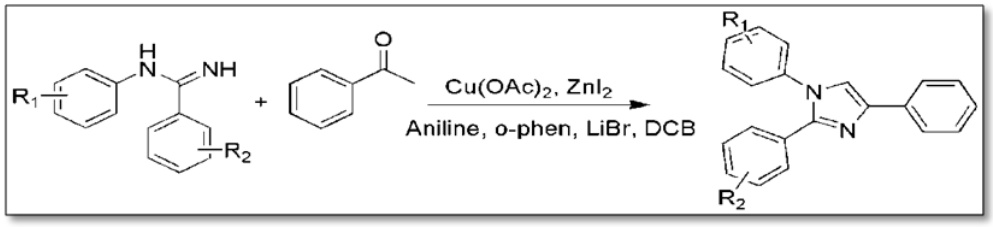
I.5.F. Synthesis of imidazole

a) In 2007, L. Nagarapu *et.al.* [47] reported potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under conventional heating and microwave irradiation.



Scheme I.10. Potassium dodecatugstocobaltate trihydrate catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles.

b) Bao-Hua Chen *et al.* [48] have reported copper and zinc co-catalyzed efficient synthetic approach to imidazoles from amidines and arylketone via oxidative coupling of (sp^3) C-H bond and N-H bond (Scheme I.11).



Scheme I.11. Copper and zinc co-catalyzed synthetic approach to imidazoles from amidines and arylketone.

I.6. Conclusion

Above synthetic procedure draw our interest to synthesize different precursors of bioactive compound in a more convenient way as the processes have large number of limitations, such as-

- Use of organic hazardous solvents

- High temperature
- Difficult reaction setup
- Use of non available reagents
- Use of corrosive chemical
- Time consuming process

In one word the processes are not environmental friendly. Henceforth, to minimize the drawback of these processes I feel to pursue my research interest to synthesize the precursor of bioactive compounds in a novel way.

I.7. References

References are given in BIBLIOGRAPHY under Chapter I.