Chapter – I

INTRODUCTION

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i. An account of the general class of ligands used in the present investigation:

The ligand systems used in the present study are the Schiff bases derived from sulfonamide, carbohydrazide and pyrazinamide and so a brief account of these compounds is presented.

1. Sulfonamides:

In 1936, a year after Domagk's discovery of the anti-streptococcus activity of the dye prontosil, Ernest Fourneau of the Pasteur Institute in Paris discovered that prontosil breaks down in the human body to produce sulfanilamide which is the active agent that kills streptococcus bacteria. Fourneau's discovery triggered a flurry of research on the derivatives of sulfanilamide which resulted in the development of a family of highly successful antibiotics that have saved millions of lives.

Sulfa drugs are used for the treatment of bacterial infections, such as eye infections, influenza, meningitis, actinomices infections, and urinary tract infections. They can also be used as model compounds for mechanistic investigation of the action of drugs [1,2].

Sulfapyridine was shown to be effective against pneumonia in 1938. Sulfacetamide found highly successful use in fighting urinary tract infections. Succinoyl sulfathiazole has been in use against gastrointestinal tract infections since 1942. Sulfathiazole was used very effectively during World War II to fight infection in soldiers with battle wounds.

Sulfanilamide itself, a potent antibiotic, never gained wide-spread use due to its greater human toxicity versus its various derivatives.

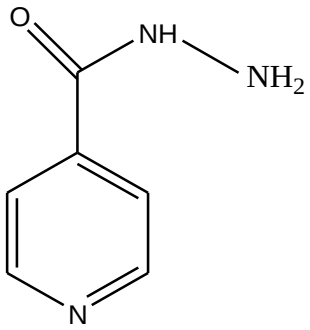
In the long history of drug discovery, an interesting phenomenon has been noted that compounds with the same structural feature show diverse biological activities. For instance, sulfonamides, with different substituted groups, display antibacterial, insulin-releasing antidiabetic, carbonic anhydrase inhibitory, high-ceiling diuretic, and antithyroid activities[3]. Recently, many papers have reported several kinds of antitumor agents possessing the structural features of sulfonamide[4,5]. It is well known that sulfadiazine is a useful antibacterial drug with the typical sulfonamide structure.

Sulpha drugs are the synthetic antimicrobial agents resulting from 4-amino benzenesulphonamide. Their antibacterial activity is thought to arise from similarity of their structures to the 4-aminobenzoic acid found in bacteria for folic acid synthesis[6].

The present work is oriented towards the synthesis of some sulfonamide based Schiff bases by condensing 4-aminobenzenesulfonamide with different aromatic aldehydes.

2. Pyridine-4-carbohydrazide:

Pyridine-4-carbohydrazide is a mono cyclic compound consisting of a nitrogen containing heterocyclic ring with keto group and hydrazide group.



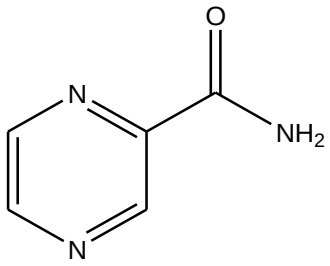
Pyridine-4-carbohydrazide

Pyridine-4-carbohydrazide is a known tuberculostatic agent. It forms metal chelates with many bivalent ions. These complexes have been used in the determination of the structure of Pyridine-4-carbohydrazide[7,8]. Numerous research papers have described the bactericidal and fungicidal properties of various mixed ligand complexes of metal ions with isoniazid and hydrazone derivatives[9,10].

Hydrazones play an important role in inorganic chemistry, as they easily form stable complexes with most transition metal ions. The development of the field of bioinorganic chemistry has increased the interest in hydrazone complexes, since it was recognized that many of these complexes may serve as models for biologically important species[11-14]. A number of complexes of transition metals with hydrazones were synthesized and characterized[15,16]. The present investigation also includes study on a schiff base derivative of pyridine-4-carbohydrazide.

3. Pyrazinamide:

Pyrazinamide is a mono cyclic compound consisting of a two para nitrogen situated pyrazine nucleus attached with an amide group.



Pyrazinamide

The pyrazine nucleus is a part of many polycyclic compounds of biological and /or industrial significance. The wide spread occurence of pyrazine derivatives in nature, especially in the flavours of many food systems, their effectiveness even at very low concentrations as well as the still increasing applications of synthetic pyrazines in the flavour and fragrance industry are responsible for the high interest in these compounds[17].

Pyrazine is a weaker base than pyridine, due to the induction effect of the second nitrogen. Some pyrazines, especially dihydropyrazines, are essential for all forms of life. Several pyrazine derivatives have been used as antioxidants. These compounds have shown important therapeutic applications[18-22]. In view of the importance of pyrazinamide, a study has been attempted on a Schiff base derivative of this moiety.

ii. Schiff bases :

The probability of synthesizing a chelating agent displaying absolute specificity is, no doubt, remote, but considerable research has been and is being undertaken toward this end. With ever-increasing knowledge of the properties of functional groups and the nature of donor and central atoms, more selective and more sensitive reagents are continually proposed. Among such promising agents is the group which is known as Schiff bases also referred to as anils, imines or azomethines. Schiff bases, first synthesized by Schiff[23], have the general formula -RC=NR', where R and R' are alkyl, cycloalkyl, aryl or heterocyclic radicals which may be variously substituted.

The most common method for preparing Schiff bases is the reaction of aldehydes and ketones with amines. The reaction is generally carried out by refluxing the carbonyl compound and amine, with an azeotroping agent, if necessary, and separating the water as formed. Schiff bases also include hydrazones, substituted hydrazones, semicarbazones, thiosemicarbazones, etc. formed respectively by the condensation of hydrazine, substituted hydrazine, semicarbazide, thiosemicarbazide, etc. with an active carbonyl group.

Schiff bases are relatively easy to prepare and because of their synthetic flexibility, they can be obtained with widely varied substitution by selection of appropriate reactants. By changing the nature and the position of donor atoms or groups, it is possible to control the size of chelate rings formed and to exploit the effect of substitution. These factors make Schiff bases, with appropriate structure, chelating agents of great potential and

analytical reagents of general interest. The preparation, properties and chemical reactions of Schiff bases have been reviewed[24-26].

A Schiff base, to be effective as a chelating agent, must possess, besides azomethine nitrogen >C=N-, an additional, appropriately located ligating group such as -OH, -SH, -$N0_2$, -NH_2, etc. so that, at least, one five- or six-membered chelate ring be formed upon complexation with a metal ion. Various aspects of the chelating characteristics of the Schiff bases are described in the work edited by Dwyer and Mellor[27]. Bayer[28] has delineated a novel approach to the structure and specificity of Schiff bases, along with other organic compounds, as chelating agents. Holm *et* al.[29] have presented an excellent review of the metal complexes formed of Schiff bases and β-ketoamines. Ever since, the studies devoted to the interaction of metals, particularly transition metals, with different types of Schiff base ligand systems and their structural characterization and biological evaluation have been in active progress.

The stereochemistries adopted by Schiff base ligands while interacting with transition metal ions depend essentially upon the presence of an additional coordination function in the ligand moiety and the charge on the ligand. As a result of these considerations, the most common stereochemistries encountered in Schiff base complexes are octahedral and square-planar. On rare occasions, other geometries such as tetrahedral, square-pyramidal, trigonal-bipyramidal, etc. are also observed.

The condensation reaction leading to a Schiff base has, in synthetic organic chemistry, a wide range of applications such as for building up of novel heterocyclic

systems; for the identification, detection and determination of aldehydes and ketones; for the purification of carbonyl or amino compounds; or for the protection of these groups during the complex or sensitive reactions[30].

In addition, Schiff bases have assumed importance in various other fields such as in coordination chemistry[31--34], analytical chemistry[35-41], pigments, dyes[42] and polymer[43-45] industries; in biochemical researches, especially as model compounds of several vitamins and enzymes[46-50] and in agriculture as fungicides, pesticides and bacteriocides[51,52].