Nickel(II) Schiff Base Compounds

M.Sc. Dissertation

by

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DISSERTATION

Submitted in partial fulfilment of
The degree of M.Sc. (Inorganic Chemistry)

By
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To

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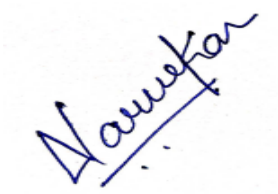
DECLARATION

I hereby declare that the work embodied in this report entitled "**Nickel(II) Schiff Base Compounds**" was carried out by me during the year 2021-2022 under the guidance of Dr. Kedar Umakant Narvekar. In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.



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CONTENT

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Introduction

Coordination chemistry plays a important role in bioinorganic, development in the field of bioinorganic chemistry has increased because of discovery of various Schiff base and their increasing properties. There are Schiff base complexes which may serve as model for biological species since the biological activities of metal complexes are discovered. Schiff base ligands are known to coordinate to metal atom in different way. Metal complexes are known to play major roles in medicinal and industrial chemistry. Various metal ions such as Copper, Cobalt and Nickel metal shows antimicrobial activity. Metal complexes with active drug as ligand is a research area of increasing interest for inorganic and medicinal chemistry. Schiff bases are condensation products of primary amines and carbonyl compounds. These were discovered by German Chemist Hugo Schiff in 1864. He was conferred with Nobel prize for the same[1]. Schiff base which is also known as imine or azomethine is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group[2]. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R1, where R and R1 are alkyl, aryl, cyclo, alkyl or heterocyclic groups which may be variously substituted[1].

Most of the Schiff bases are derived from salicylaldehyde and its derivatives which can be good chelating ligands, when they condensed with primary amines. Biological activity of Schiff bases is because of its ability to form chelate complexes with metal ion. Such biological activities include antifungal, antimalarial, anti-inflammatory, antiviral, anti-bacterial, antiproliferative, antipyretic properties[3].

1.1 Synthesis of Schiff bases.

A variety of methods for the synthesis of imines/Schiff bases have been described[4]. The classical synthesis was reported by Schiff which involves the condensation of a carbonyl compound with an amine under azeotropic distillation[5]. An in situ method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate in 1990s[6].

Studies demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. It was proposed as an alternative use of substances that function as Bronsted-Lowry or Lewis acids to activate the carbonyl group of aldehydes, catalyze the nucleophilic attack by amines, and dehydrate the system, eliminating water as the final step[7]. Formation of Schiff base generally takes place under acids or base catalysis or with heat. The common Schiff base are crystalline solids, which are feebly basic but at least some form insoluble salts with strong acids. Schiff base are used as intermediates for the synthesis of amino acids or as ligands for Preparation of metal complexes having a series of different structures[8].

1.2 Schiff Base Ligands.

A Schiff base behaves as a Flexi-dentate ligand and commonly co-ordinates through the O atom of the de-pronated phenolic group and the N atom of azomethine group. Schiff base ligands have significant importance in chemistry, especially in the development of Schiff base complexes, because Schiff base complexes are potentially capable of forming stable complexes with metal ions, many Schiff base complexes show excellent catalytic activity in various reaction at high temperature and in the presence of moisture. Over the past few years, there have been many report on their applications in homogeneous and heterogeneous catalysis, hence the need for a review article highlighting the catalytic activity of Schiff base complexes[8].

1.3 Denticity and Basicity of Schiff Bases.

Ligands are classified according to the number of donor atoms contained and are known as uni, di, tri, or quadridentate ligands. When donor sites of a ligand occupy two or more coordination positions on the same central metal ion, a complex possessing a closed ring is formed. The phenomenon of ring formation is called chelation and ring formed is called chelate ring. The term ‘chelate’ was first introduced in 1920 by Morgan and Drew. Schiff bases primarily possess nitrogen donor atoms, though many can act as bi-, tri-, tetra- or polydentate mixed donor capabilities. In general, the donor nature of the ligands depends both on the type of aldehyde/ketone used and the nature of primary amine/diamine amine/diamine[9].

1.4 Metal ion in biological system.

Nickel is transition element belonging to group (10) and period (4). Its atomic number is 28, and its atomic weight is 58.71. The stable oxidation states of nickel are 0 and +2. Also, some of the complexes shows +3 and +4 oxidation state[10]. Though Nickel is considered as hazardous due to the toxicity and carcinogenicity caused by chronic exposure, Nickel compounds have gained importance in bioinorganic chemistry[11]. Nickel complexes have been reported to act as anticonvulsant, antiepileptic agent or vitamins, antibiotic. They are reported as antifungal, antioxidants, anticancer. Nickel complexes interact with biomolecules like serum albumins or DNA and their interaction is studied which that they act as DNA intercalator or DNA cleaving agent. Ni(II) Schiff base complexes with some drugs like Mefenamic acid , Diclofenac have been prepared, and being characterised[12].

1.5 Mechanism of formation of metal Schiff base complexes.

Schiff base ligands are easily prepared by simple one pot condensation of an aldehyde and primary amines. Schiff base ligand can coordinate to metal ion through Nitrogen of the imine group that is the metal ion is coordinated to azomethane. Ligand binds with metal ion in the way that Nitrogen of the azomethane donate its lone pair of electrons into empty metal orbital with coordinate covalent bond to form stable complex. Here Schiff base ligand acts as Lewis base and metal ion acts as Lewis acid. Transition metal complexes possess varied coordination geometries such as octahedral, square planar, tetrahedral, pyramidal, etc. Many of the transition metal in +2 or higher oxidation state are hard 10 acids and prefer to coordinate with hard bases such as ligands containing N- and O- donor sites according to the HSAB principle. Nickel Schiff base complexes plays an important role in coordination chemistry of Nickel due to their importance as synthetic models for Nickel containing enzymes[4].

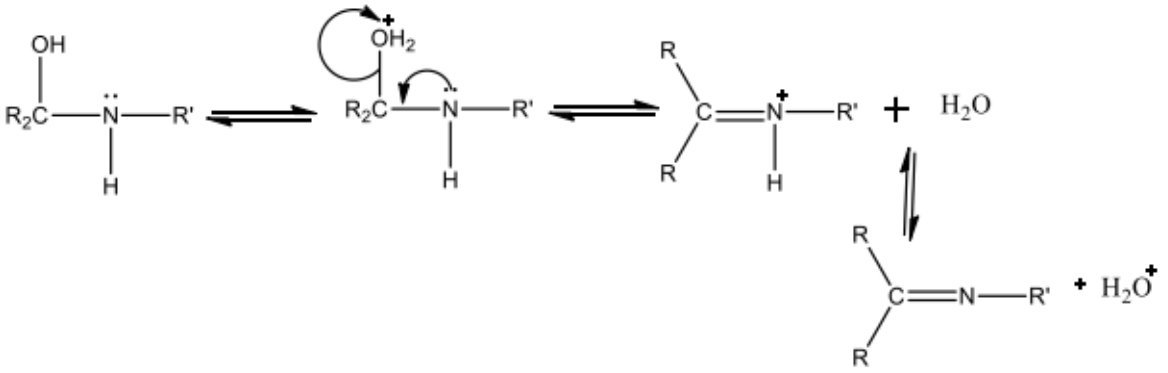


Fig.1.1: Formation of metal Schiff base complex[4].

1.6 Biological importance of Schiff bases.

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylation agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis[13]. Stereo chemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases[8].

Antibacterial properties: Schiff bases are considered as promising antibacterial agent. For example, N-(Salicylidene)-2-hydroxyaniline (Fig.1.2) is active against Mycobacterium tuberculosis[14]. The development of new antibacterial drugs enriched by innovatory and more effective mechanisms of action is clearly an urgent medical need.

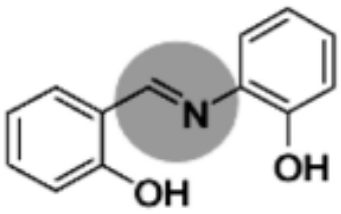


Fig. 1.2: N-(Salicylidene)-2-hydroxyaniline[14].

Other Schiff bases derivatives, which possess antibacterial activity are: benzimidazole, thiazole, pyridine, glucosamine, pyrazolone, hydrazide, thiazolidiones, indole, thiosemicarbazone, p-fluorobenzaldehyde.

Antifungal properties: Fungal infections usually are not only limited to the contamination of surface tissues. Recently, there was a considerable increase in the incidence of systemic fungal infections, which are potentially life threatening. Exploration and development of more effective antifungal agents is necessity, and the individual Schiff bases are considered to be promising antifungal medicines. Some of them, such as imine derivatives of quinazolinones possess antifungal properties against Candida albicans, Trichophyton rubrum, T. mentagrophytes, Aspergillus niger and Microsporum gypseum[15].

Anticancer properties: Cancer is a group of diseases which has the potential to attack or spread to other parts of the body since it involves abnormal cell growth. Metal complexes can offer unique mechanisms of drug action because of wide range of co-ordination numbers, geometries and kinetic properties, which are not possible with pure organic molecules[16]. In addition, they have ability to rebuild depleted haematological parameters, such as hemoglobin, red blood cells (RBC) and white blood cells (WBC) towards the right content. They also show protective effect on hematopoietic system.

Antimalarial properties: Malaria is a disease which when is neglected causes serious health problems. Schiff bases are interesting compounds, which could be part of antimalarial drugs. For example, the compound with such effect is Ancistrocladidine, which is a secondary metabolite produced by plants of the family Ancistrocladaceae and Dioncophyllaceae, and presenting an imine group in a molecular chain[17].

1.7 Metal complexes

Schiff base ligands are considered privileged ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. These compounds and their metal complexes had a variety of applications including clinical, analytical, industrial they also play important roles in catalysts. Schiff`s bases are able to coordinate metals through imine nitrogen, and there is a wide use of these metal complexes as catalysts. Schiff base ligands have significant importance in chemistry; especially in the development of Schiff base complexes, because Schiff base ligands are potentially capable of forming stable complexes with metal ions[18].

Schiff bases enhance research activity in the field of coordination chemistry leading to very interesting conclusions. The carbon-nitrogen double bond of Schiff bases like the carbon-

oxygen double bond is readily reduced by complex metal hydrides. Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers[19].

The chelating ability is enhanced when nitrogen atom is present in the vicinity of one or more donor groups. The excellent capability of Schiff bases to stabilize the metal ions in various oxidation states has enhanced their uses in metal complexes. The transition metal complexes have been study recently due to their broad applications in wide ranging areas from natural sciences to material science[20].

Schiff bases are capable of chelating various metal ions and the resultant complexes possess a wide range of magnetic, photo physical and electrochemical properties. Schiff base complexes are important class for bioinorganic chemistry, supramolecular chemistry, catalysis, biomedical applications, separation and encapsulation processes. A large number of Schiff bases and their complexes have been used for their complexing ability towards some toxic metals[21].

Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers. Metal complexes are extensively used in the treatment of cancer. Large number of complexes have been synthesized and studied for anticancer activity. Schiff bases are responsible to have a great flexibility in the structure with interesting magnetic and spectral properties. Hence variety of Schiff base ligands with diverse structure has been synthesized. The research area on all sides of the coordination compounds with azomethinic bis-imines is broadly studied due to their potential significance in different interdisciplinary fields i.e. catalysis, magneto chemistry and bioinorganic chemistry[22].

Metal complexes of various organic compounds found to be active against different organisms. Recently several metal complexes have been reported to be used as catalyst to enhance the rate of reactions. The stability and activity of metal complexes is because of polar bond between ligand and metal. The Schiff base ligands and their metal complexes find applications in the field of food and dyes industry as well as in agricultural, analytical chemistry. Versatility of Schiff base ligands and biological, analytical and industrial applications of their complexes make further investigations in this area highly desirable. It is well known that some drugs have higher activity when administered as metal complexes than free ligands[23].

Literature Review

On perusal of literature survey some structural reports of Schiff bases, Ni(II) Schiff base complexes are mentioned below. Schiff base ligand 1-(phenethylimido)methylnaphthalene 2-ol is synthesized by Hatim et. al. Formed by the condensation of phenyl ethyl amine and 2-hydroxy-naphthaldehyde in 1:1 molar 11 ratio[24].

Asymmetrical ligand L_1 and L_2 are formed by condensation of free amine group with pyridine-2-carboxaldehyde. While ligand L_3 is symmetrical formed by condensation of 1,3 diaminopropane and pyridine-2-carboxaldehyde structure in fig.1.3**.** Asymmetric ligands L_1 and L_2 are formed by the condensation of pyridine-2-carboxaldehyde with ethylenediamine and 1,3 diaminopropane structure of the ligand in fig.1.4. All these three ligands are reported by M.S. Ray et. al[25].

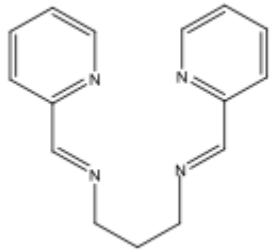


Fig 1.3

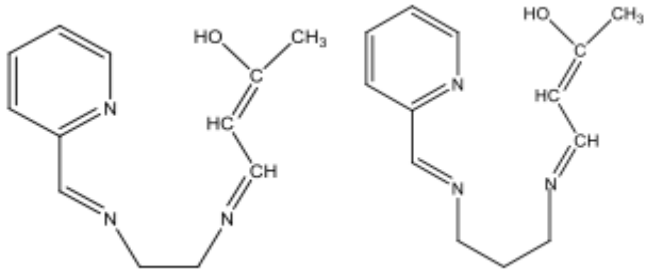


Fig 1.4

Synthesis of [Ni(AMAO)(NCS)] have been reported by A. Ghosh et. al. Here the ligand is synthesised by 1:1 condensation of 2,4-pentanedione and 1,2–diaminopropane, then the ligand is readily reacted with Ni(II) thiocyanate in presence of methanol to yield red coloured crystals of [Ni(AMAO)(NCS)]. This complex shows slightly distorted square planar geometry, the structure is shown in the fig. 1.5[26]. CCDC no. of crystal structure of this complex is **245075** and its reference code is **XEGFIZ**.

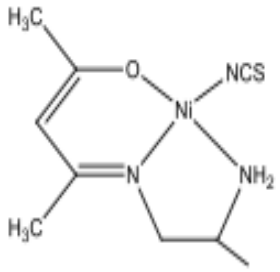


Fig.1.5 [Ni(AMAO)(NCS)][26]

[Ni(bae)]. ½ H2O is a reported complex synthesized by S.K. Gupta et. al. (2015). This complex is synthesized from template condensation of 2,4- pentanedione (acetylacetone) with ethylenediamine in the presence of NiCl2 .6H2O. The ligand of the complex is 1:2 condensation of ethylenediamine and acetylacetone. [Ni(bae)] .1/2 H2O complex is brown colour crystals suitable for single crystal XRD, structure of the complex is shown in fig.1.6[27].

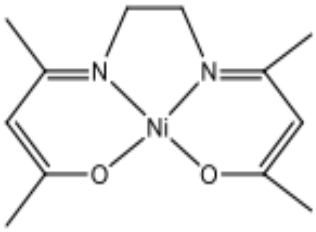
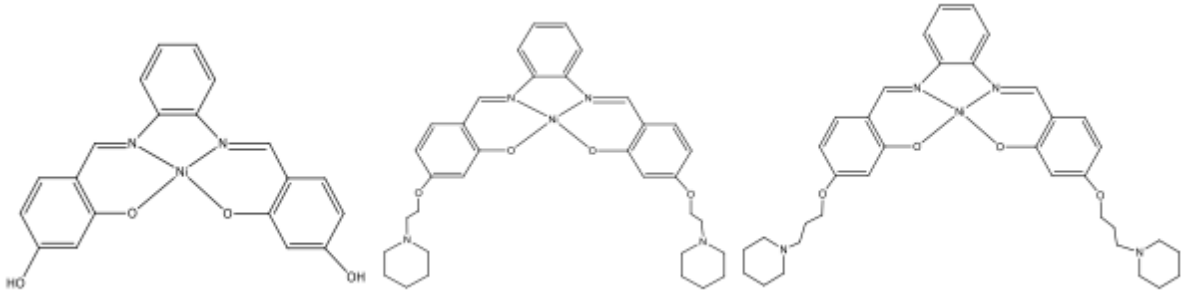


Fig.1.6: [Ni(bae)]. ½ H2O[27].

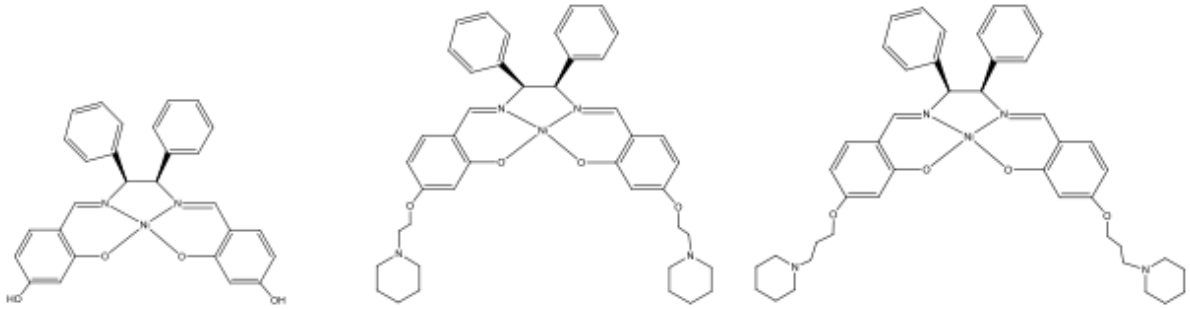
Series of Nickel (II)-Salph Complexes I – III shown in fig. 1.7 are reported. These are the square planar complexes reported by J.E. Reed, et. al. These series of complexes possess good anti-microbial activity, complexes bind with a duplex DNA[28].



I II III

Fig.1.7 Nickel (II)-Salph Complexes(I-III)[28]

Nickel complexes I-III shown in fig. 1.8 has been reported earlier by K.J. Davis et. al. (2015). These complexes contain the meso-1,2-diphenylethylenediamine moiety and possess square planar geometry. The crystals suitable for single crystal X-ray analysis were grown from methanol-DMSO solvent mixtures[29].



I II III

Fig.1.8: Nickel(II) complexes with meso-1,2-diphenylethylenediamine moiety[29].

The Ni-Salpn complex (nickel-N, N-bis(salicylidene)-1,3-propanediamine) consists of N, N'-bis(salicylidene)-1,3-propanediamine ligand (Sigma-Aldrich) and nickel acetate. Films of the Ni-Salpn complex is synthesized using electrodeposition method. Ni-Salpn solution is prepared in 1,2 -dichloroethane containing 0.1 mol L-1 tetrabutylammonium perchlorate as supporting electrolyte[30]. The structure of Ni-Salpn is shown in the Fig. 1.9.

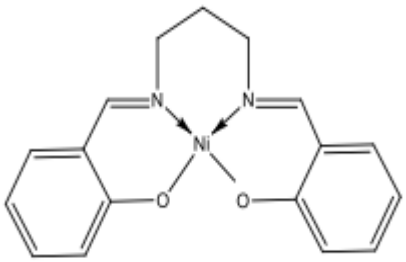


Fig.1.9: Nickel-N, N-bis(salicylidene)-1,3-propanediamine[30].

Ligand (1H-imidazole-yl) acetophenone anthranilic acid and its chelates with Co(II), Cd(II), Ni(II) ion were reported by I.A. Arbab et. al. The ligand is formed by the condensation of Anthranilic acid and Imidazole acetophenone in 1:1 molar ratio[31]. The ligand (4-fluoroaniline)(5-chlorosalicylaldehyde) and its Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)

complexes were reported by F.K. Ommeny et.al[32]. The ligand of these complexes is formed by unsymmetrical condensation of 4-fluoroaniline and 5-chlorosalicyaldehyde in 1:1 molar ratio. Nickel complexes of this ligand has highest activity against E. coli and P. aeruginosa than other metal complexes. 2,2'-((1E,1'E)-(1,4-phenylene-bis(methanylylidene))bis-(azanylydidene))-diphenol. This ligand and its copper, cobalt, Nickel complexes have been documented by J. Saranya et. al. The ligand is formed by the condensation of terepthaldehyde and 2-aminophenol in 1:2 molar ratio. Complexes of such ligand shows wide range of antibacterial activity against Salmonella enterica, Klebsiella pneumoniae, and E. coli and antifungal activity against Aspergillus flavus, Rhizopus nigricans and Penicillium notatum[33].

Mefenamic acid (fig. 1.10) is a derivative of anthranilic acid. It is used effectively as an analgesic and antipyretic agent and its side effects are headache, diarrhoea and vomiting. Some of the other derivatives of anthranilic acid are shown in the fig. 1.11. The active binding site of Mefenamic acid with metal ion is the oxygen atom of carbonyl group. Mefenamic ligand can acts as a monodentate ligand and also bidentate ligand. Metal complexes with mefenamic acid shows more biological activity than the parent drug. On perusal of Literature survey on Nickel complexes with mefenamic acid, it was found out that [Ni(mef)2(3-pic)2] is Nickel complex with mefenamic acid and picoline prepared by E. Dilek et. al, the complex shows distorted octahedral structure[34].

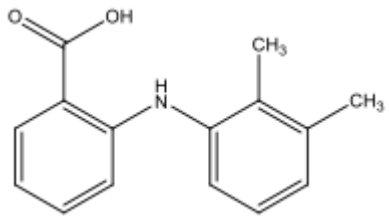
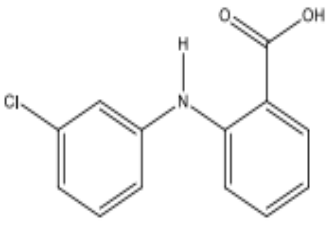
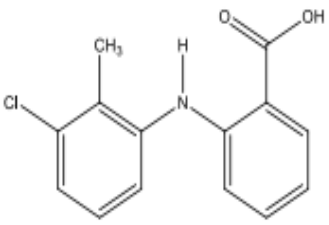


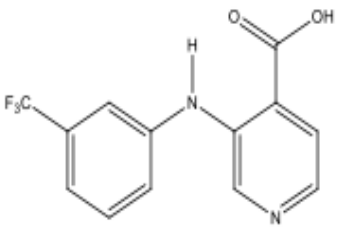
Fig.1.10: Mefenamic acid[34].



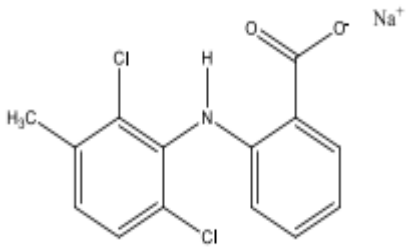
Flufenamic acid



Tolfenamic acid



Niflumic acid

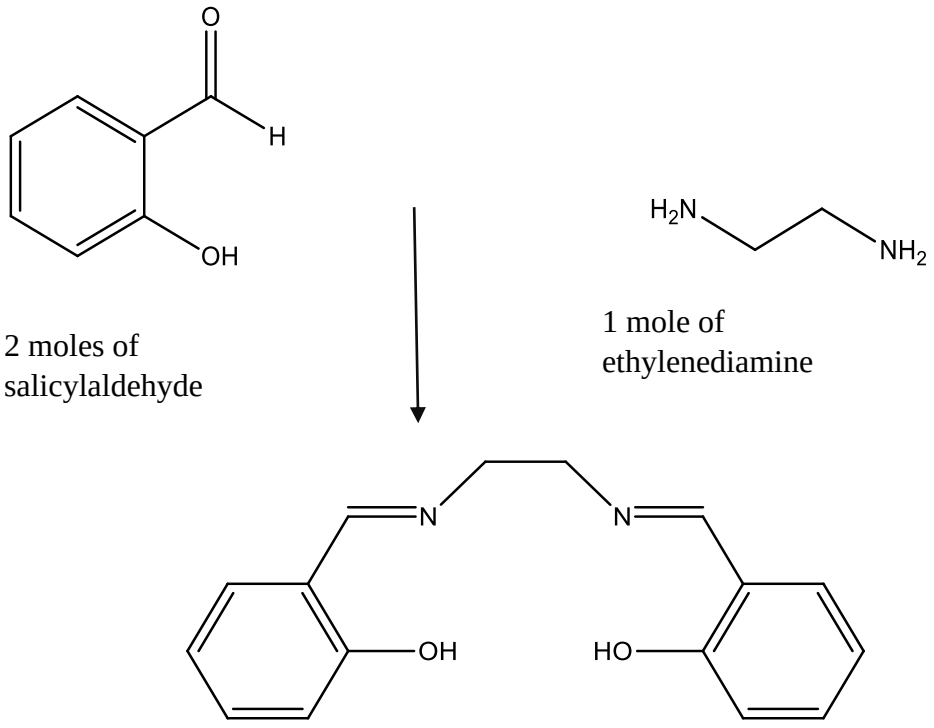


Sodium meclofenamate

Fig.1.11: Derivatives of anthranilic acid[34].

Mostly Schiff bases contains two donor atoms that is N and O donor sites. Nitrogen atoms in the ligand have a higher tendency to co-ordinate with metal ion than oxygen atom, because of which there is increased basicity of nitrogen atoms over the oxygen atoms[35].

One of the example of Schiff base ligand is Salen. It is well known tetradentate Schiff base ligand. It is easily synthesized from salicylaldehyde and ethylenediamine where ethanol is used as a solvent. The product can be easily obtain without nitrogen atmosphere and also the presence of some moisture cannnot affect the yield of product. Salen ligand possesses the C_2 symmetry.



2 moles of salicylaldehyde

1 mole of ethylenediamine

Apo Salen

Transition metals complexes with Schiff bases has various applications such as magnetic property, catalytic properties. Schiff bases have picked up significance in medicinal and pharmaceutical field because of its biological activities. Biological activity of Schiff bases is because of its ability to form chelate complexes with metal ion. Such biological activities includes antifungal, antimalarial, anti-inflammatory, antiviral, anti-bacterial, antipyretic properties. Schiff bases are the important moieties for the designing of antimalarial agents[17].

Conclusion

Schiff bases are one of the most important chemical classes of compounds having a common integral feature of a variety of medicinal agents. Schiff bases can be synthesised from various aldehyde and amine under different reaction conditions. Schiff base compounds have been shown to be promising leads for the design of more efficient antimicrobial agents. Schiff base complexes of Ni(II), the environment at coordination center can be modified by changing the chain length or introducing substitution in carbon atom of the diamine. The study shows that Schiff bases and their metal complexes are interesting research subject that constantly provides us with new information about newly created compounds. Schiff bases present a very important class of organic compounds due to their ability to form complexes with transition metal ions and of their pharmacological properties.

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