IMPACT: Journal of Research in Applied Natural and Social Sciences (IMPACT: JRANSS)
ISSN(E): Applied; ISSN(P): Applied
Vol. 1, Issue 2, Dec 2015, 85-92

SCHIFF BASES: AN EVERGREEN PHARMACOPHORE IN MEDICINAL CHEMISTRY

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ABSTRACT

Schiff bases are used widely in pharmaceutical industry and have interesting pharmacological activities. Schiff bases possess excellent characteristics, structural similarities with natural biological substances, relatively simple preparation procedures and the synthetic flexibility that enables design of suitable structural properties. Many biologically important Schiff bases have been reported in the literature possessing, antibacterial, antifungal, antimicrobial, anticonvulsant, anti-HIV, anti-inflammatory, antitumor and catalytic activities. Schiff bases have been studied for their important properties in catalysis. They show catalytic activity in hydrogenation of olefins, applications in biomimetic catalytic reactions and an interesting application of schiff bases is their use as an effective corrosion inhibitor. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the schiff bases function more efficiently in many cases.

KEYWORDS: Schiff Base, Antitumor, Catalyst, Biomimetic

INTRODUCTION

Structurally, schiff base is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen.[1] Schiff bases in a broad sense have the general formula $R_1R_2C=NR_3$, where R is an organic side chain. *Schiff base* is synonymous with azomethine. Some restrict the term to the *secondary aldimines* (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula RCH=NR'. Several studies showed that the presence of a lone pair of electrons in an sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance.[2-5]

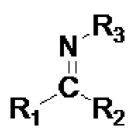


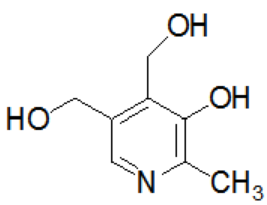
Figure 1: General Structure of Schiff Base

Because of the relative ease of preparation, synthetic flexibility, and the special property of C=N group, schiff bases are generally excellent chelating agents,[5-7], especially when a functional group like –OH or –SH is present close to the azomethine group so as to form a five or six membered ring with the metal ion. Schiff bases are used widely in pharmaceutical industry and have interesting pharmacological activities. Schiff bases possess excellent characteristics, structural similarities with natural biological substances, relatively simple preparation procedures and the synthetic flexibility that enables design of suitable structural properties. Many biologically important Schiff bases have been reported in the literature possessing, antibacterial, antifungal, antimicrobial, anticonvulsant, anti-HIV, anti-inflammatory, antitumor and catalytic activities.[8-12] On the other hand, they are fundamental material for synthesis of various Schiff base ligands which are used as chiral auxiliaries in asymmetric synthesis. Metal complex Schiff bases have also been used in oxidation reactions. They also serve as a back bone for the synthesis of various heterocyclic compounds.[13]

Versatile Applicatons of Schiff Base

Versatility of schiff base ligands and biological, analytical and industrial applications of their complexes make further investigations in this area highly desirable. Schiff bases have been found to be active against a wide range of organisms for example; *Candida Albicans*, *Escherichia coli Staphylococcus aureus*, *Bacillus polymxa*, *Trychophyton gypseum*, *Mycobacteria*, *Erysiphe graminis* and *Plasmopora viticola.* A large number of different Schiff base ligands have been used as cation carriers in potentiometric sensors as they have shown excellent selectivity, sensitivity, and stability for specific metal ions such as Ag(II), Al(III), Co(II), Cu(II), Gd(III), Hg(II), Ni(II), Pb(II), Y(III), and Zn(II). Schiff bases have been studied for their important properties in catalysis. They show catalytic activity in hydrogenation of olefins. They find applications in biomimetic catalytic reactions. An interesting application of schiff bases is their use as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the schiff bases function more efficiently in many cases. Schiff bases have been reported in their biological properties, such as, antibacterial, antifungal activities. Their metal complexes have been widely studied because they have anticancer and herbicidal applications. They serve as modals for biologically important species. *O-phenylenediamine* schiff bases show clinical properties.[13-20]

Isatin Schiff bases were reported to possess antiviral, anti-HIV, antiprotozoal and anthelmintic activities. They also exhibit significant anticonvulsant activity, apart from other pharmacological properties. Certain cobalt Schiff base complexes are potent antiviral agents. Schiff bases derived from 4-dimethylamine benzaldehyde shows antibacterial activity. In medicines they are used as antibodies and anti-inflammatory agents. Pyridoxal phosphate coenzyme links to enzymes by a Schiff base and play an important role in biological system. Schiff base (imine) formation is a very important reaction in biological chemistry. One example involves the chemistry of pyridoxal phosphate (PLP), a derivative of pyridoxine, commonly known as vitamin B_6.(Fig-7)[21-25]



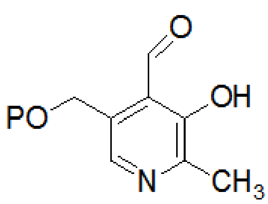


Figure 7: Pyridoxine **Pyridoxal Phosphate (PLP)**

Schiff bases are also used for treating tuberculosis. But due to some serious side effects there is urgent requirement of combining them with such a nucleas so that all the side effect may get reduced. So, for this schiffs bases of pyrazinamide is prepared. Pyrazinamide(Figure 8) is a drug used to treat tuberculosis. The drug is largely bacteriostatic, but can be bacteriocidal on actively replicating tuberculosis bacteria.

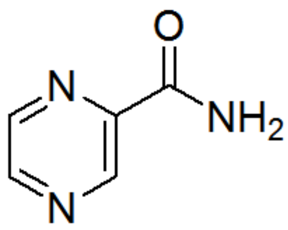


Figure 8: Pyrazinamide

Pyrazinamide is only used in combination with other drugs such as isoniazid and rifampicin in the treatment of *Mycobacterium tuberculosis*. It is never used on its own. It has no other indicated medical uses.[26] Various schiff's bases were synthesised and evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using Lowenstein-Jensen medium method.[27]

Schiff bases, 4-({[3-(4-chlorophenyl)-1*H*-pyrazol-4-yl] methylene}amino)-5-[(4 methylphenoxy) methyl]-1,2,4-triazole-3-thiol(14), 4-({[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl] methylene} amino)-5-[(4-methylphenoxy) methyl]-1,2,4-triazole-3-thiol(15) and 4-({[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl] methylene}amino)-5-[(2-methylphenoxy) methyl]-1,2,4-triazole-3-thiol(16) were prepared evaluated for their antitumor activity against various human cancer cell lines like hepatic carcinoma cell lines and Ehrlich ascites carcinoma (EAC) cells. All these compounds showed promising antitumor activity against various human cancer cell lines which were selected for carrying out activity. The antitumor activity was compared to standard antitumor drug cisplatin.[28]

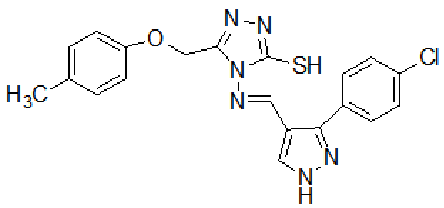


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Figure 9

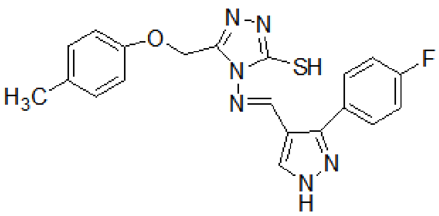

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Figure 10

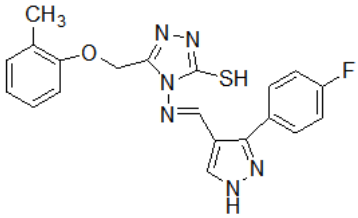

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Figure 11

Schiff base derived from sulfane thiadizole and salicylaldehyde or thiophene-2-aldehydes and their complexes show toxicities against insects. Schiff bases (thiadiazole derivatives with salicylaldehyde or o-vanillin) and their metal complexes with Mo(II) show insecticidal activities against bollworm and promote cell survival rate of mung bean sprouts.[29]

Schiff bases show remarkable activities on plant hormone such as the auxins on root growth. Schiff base of ester and carboxylic acid show remarkable activity as plant growth hormone. Schiff bases of thiodiazole have good plant growth regulator activity towards auxin and cytokine. Schiff base of chitosan and carboxymethyl-chitosan shows an antioxidant activity such as superoxide and hydroxyl scavenging. Furan semicarbzone metal complexes exhibit significant anthelmintic and analgesic activites Schiff bases are used as catalyst in large number of reactions. For example, Co(II), Fe(III) and Ru(III) complexes of Schiff bases derived from hydroxy benzaldehyde are used in oxidation of cyclohexane into cyclohexanol and cyclohexanone in presence of hydrogen peroxide. About 20 Zinc enzymes are known in which Zinc is generally tetrahedrally four coordinate and bonded to hard donor atoms such as nitrogen or oxygen. The Schiff base complexes of 2-pyridinecarboxaldehyde and its derivatives have been reported to posses high super oxide dismutase activities. Recently, the interaction of DNA with complexes [Cr(Schiff base) $(OH_2)_2]ClO_4$ was reported. Ternary complexes of Cu(II) containing NSO donor Schiff base showed DNA cleavage activity. So Schiff bases have promising antifertility and enzymatic activity which can be used to develop medicinally important moieties.[30-35]

Schiff base derivatives are being developed as dyes. For example-chromium azomethine complexes, cobalt complex Schiff base, unsymmetrical complex 1:2 chromium dyes give fast colours to leathers, food packages, wools etc. Azo groups containing metal complexes are used for dying cellulose polyester textiles. Some metal complexes are used to mass dye polyfibers. Cobalt complex of a Schiff base (salicylaldehyde with diamine) has excellent light resistance and storage ability and does not degrade even in acidic gases (CO2). Novel tetradentate Schiff base acts as a chromogenic reagent for determination of Ni in some natural food samples.[36]

Photochemical degradation of natural rubber yield amine terminated liquid natural rubber(ATNR) when carried out in solution, in presence of ethylenediamine. ATNR on reaction with glyoxal yield poly Schiff base, which improves aging resistance. Organocobalt complexes with tridentate Schiff base act as initiator of emulsion polymerization and co-polymerization of dienyl and vinyl monomers. Amino acid Schiff base complexes derived from 2-hydroxy-1-naphthaldehydes are important due to their use as radiotracers in nuclear medicine. Schiff bases are well known in the pharmaceutical industry and have been shown to possess abroad spectrum of biological activities. In light of these significances, a variety of synthetic strategies have been developed for the preparation of Schiff base, despite the progress, the synthesis of these compounds remains less than ideal. Thus, the development of environmentally friendly benign

(Green Chemistry), high-yielding and clean approaches for the synthesis of Schiff base is still remains a highly desired goal in organic synthesis.[37-40]

Some Special Schiff Base

Some workers had previously used several catalysts to overcome on the reversibility of imine formation. Now it has been reported that the use of sodium hydroxide as catalyst for the first time during synthesis of schiff bases under study overcame this problem with high yield of products. This developement in the procedure of synthesis by adding sodium hydroxide as a new catalyst is highly accepted from kinetic point of view. Following schiff bases(4-8) namely salicylidene glycine, salicylidene L-methionine, benzylidene glycine, salicylidene ß–alanine, benzylidene DL-alanine prepared by this new method has efficient yields than usual method of preparation of schiff base.[40]

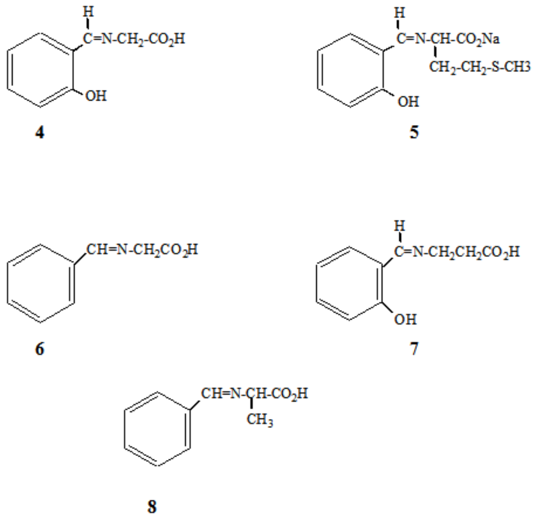

Figure 12

ACKNOWLEDGEMENTS

Authors are thankful to Khalsa college of Pharmacy, Amritsar for providing opportunity and inspiration to do this work.

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