Section A-Research paper
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A review of the chemistry of Schiff base metal complexes, examining their potential applications with medicinal value

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Abstract: The field of study surrounding the chemistry of Schiff base-containing compounds has been noteworthy throughout antiquity. The role played by Schiff bases in inorganic chemistry is significant due to the formation of very stable complexes with various transition and inner-transition metals. Schiff bases, which are synthesized from the combination of an amino group and a carbonyl group through the condensation of an amino compound with carbonyl compounds, are commonly used in industrial processes and demonstrate a wide range of biological activities, including antibacterial, antifungal, antiviral, antimalarial, anticancer, anti-HIV, anthelminthic and antipyretic properties. As a result, Schiff base is a crucial class of compounds for the creation of new drugs. A contentious topic in medicinal chemistry is the continued search for Schiff base-containing compounds with higher selectivity and lower side effects. This analysis examines the various applications of Schiff bases and their complexes, including their uses in birth control, food packaging and as an O_2 detector. The current interest in Schiff bases and their metal complexes is drawing the attention of medicinal chemists. This review compiles the various synthesis procedures and application of Schiff bases and their metals complexes.

Keywords: Schiff bases, Metal complexes, biological activity, nonlinear optical properties, Antibacterial, Antifungal, Antimicrobial Biological activities, enzymatic activities,

1. Introduction:

The Schiff bases have been recognized since 1864, when Hugo Schiff reported the formation of primary amines through the condensation of amine with carbonyl compounds (Z. Cimerman . et al. 2000). While Schiff bases of aliphatic aldehyde are unstable in nature, they are more likely to be polymerized than those with an aromatic aldehyde structure. A Schiff base is a type of chemical compounds containing a carbon-nitrogen double bond as a functional group, in which the nitrogen atom is connected to an aryl group or alkyl group (R) but not hydrogen. The

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Schiff base is closely tied to azomethine-like compounds, which were named after Hugo Schiff in honor of his contributions and possess the general structure outlined above.

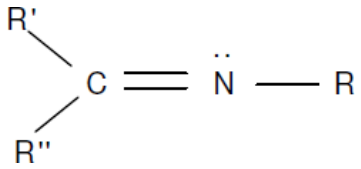

Figure 1. Schiff base structure

The reaction of an aldehyde or ketone with a Schiff base is a reversible process, and can be carried out under acidic or basic conditions or through heating.

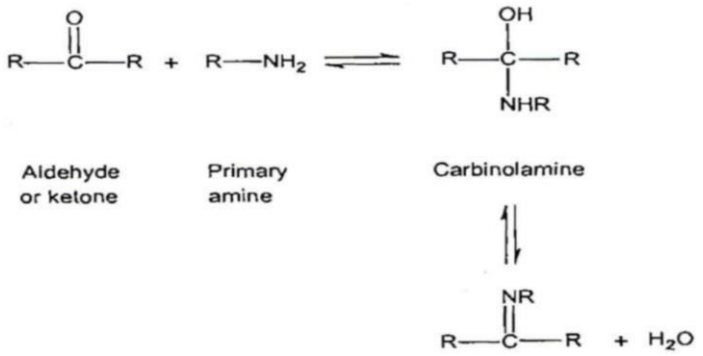

Figure 2. A Schiff base formed by Reversible reaction with an aldehydes or ketones.

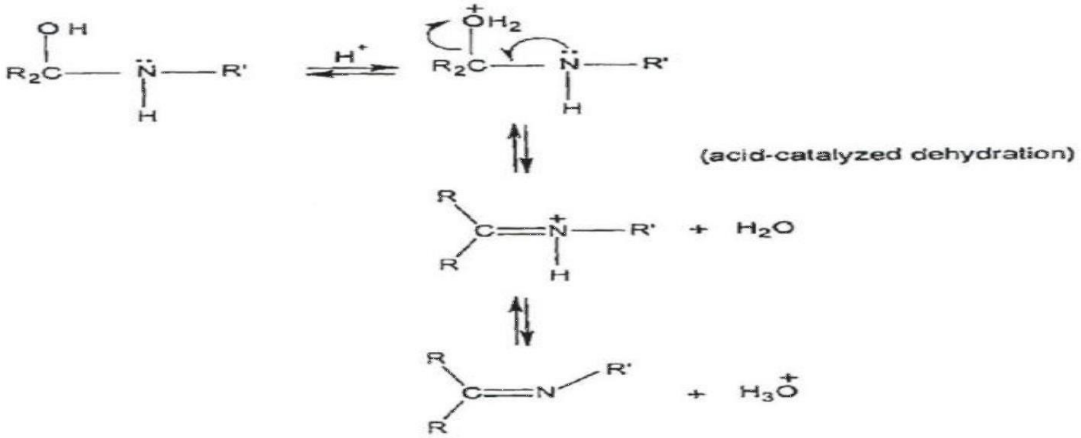

Figure 3. Mechanism used for the formation of Schiff base

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Schiff bases, a type of ligand, are primarily composed of amino acids and bind to metal ions through the formation of azomethine nitrogen bonds (T. Rosu and et al. 2006). The presence of heteroatoms such as N, O, S and C=N linkage is crucial for biological activities. The electron pairing arrangement observed in the nitrogen atom of the azomethine is of considerable chemical and biological importance, as it has an influence on both chemical and biological processes (N. S. Gwaram and et al. 2012 and K.T. Joshi et al. 2011). Schiff bases are effective chelating agents; ligands that are bidentate or tridentate tend to produce the most stable complexes with transition metals. The investigation of metal complexes for various antimicrobial, antifungal, antibacterial, antimigratory, diuretic and enzymatic properties led Schiff to develop a strong focus on this research field (A. P. Mishra et al.2012).

2. Schiff Base: Half-sandwich arene metal complexes bearing ferrocenyl-pyridine azine Schiff base:

Heterometallic complexes, which are crucial for organometallic medicinal chemistry (S.J. Lippard. (2004)], are defined as two or more metals contained inside the same molecular framework. Due to their capacity to replicate the biological activity of metalloenzymes, which frequently contain multinuclear metal centers, heterobimetallic complexes have drawn a lot of attention over the years (Joshi, R. K. et al. 2022). It is known that the redox characteristics, total charge, and interaction with biomolecules are all impacted by the interaction of the two metal centers in the molecular framework (Sadler, P. J. et al 2007). Complexes with a redox unit, like ferrocene, are very important because their electrical characteristics can be precisely controlled. A suitable substitution in the ferrocene ring's Cp allows for the alteration of the ferrocene moiety, which may then be subjected to further reactions with other ligands to produce a complex that can then interact with metals to form an organometallic bridge between the two metal centers (Chalana, A., Rai et al. 2019). Additionally, adding a biologically active group to a molecule with an iron center has been demonstrated to improve biological activity [Vikky Singh et al. 2022]. This increase in biological activity may be related to the compound's dual nature, which is known to exhibit Fenton type chemistry. Numerous organometallic compounds containing ferrocene are well known for their potential biological activity. For instance, ferrocifen (Figure 4), an organometallic counterpart of cis-tamoxifen, has excellent in vitro activity against breast cancer.

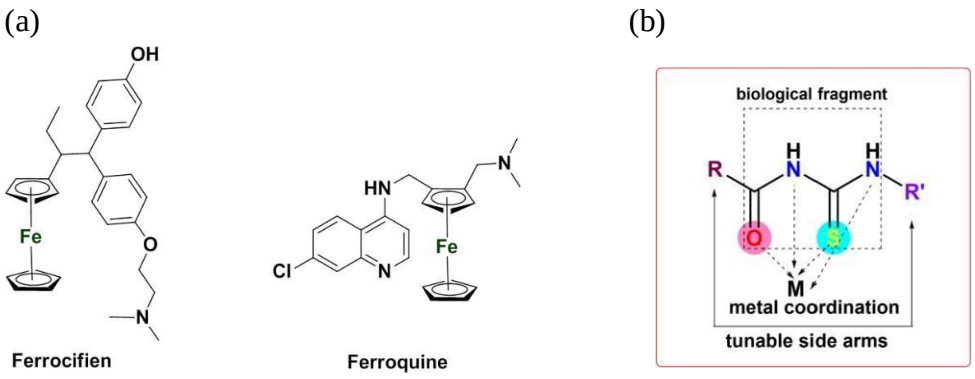

Figure 4: (a) Structure of ferrocenyl drugs (b) Pictogram of acylthiourea fragment

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cell lines. Similar to this, another ferroquine-containing organometallic complex is a viable contender. It has excellent antiplasmodial action and is even effective against strains that are resistant to chlorquine. Many works have been done to include arene metal complexes into this ferrocene framework, which is expected to demonstrate promising activity, motivated by the activity of this ferrocene derivative and Transition Metal Complexes of Tri-Thiocarbonate and Phenol-Thiourea Based Ligand [Vikky singh 2020].

In addition, analogues of urea are a class of organic compounds well known as thiourea where oxygen atom is replaced by sulphur. The amino hydrogens in thiourea when replaced by alkyl or aryl groups provides a platform for the synthesis of heterocyclic thiourea derivatives which are bioactive organic compounds. These thiourea derivates have been widely explored for their various applications such as anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory,anti-cancer and anti-fungal properties. The basic skeleton of alkyl/aryl thiourea fragment is shown in Figure 4b and we can see that it has a rich source of donor atoms which makes it a diverse ligand possessing interesting properties and having ability to coordinate various metal ions in a mono or bi-dentate ligands through its oxygen, sulfur, or nitrogen donor atoms.

3. Antibacterial Activities-

The emergence of methicillin resistance staphylococcus aureus poses significant challenges due to the increasing difficulty in treating infections. Studies and data from many countries show that vancomycin-resistant s.aureus (VISA) and VRSA (vancomycin-resistant s.aureus), which are two different forms of vancomycin-resistant s.aureus, are becoming more common than previously thought. Schiff base ligands formed through the condensation of 1-naphtylamin and 2-hydroxynapthalene-1-carbaldehyde (HL) and 1, 2-bis-(p-aminophenoxy) ethane with the addition of 2-hydroxynaphthalene-1-carboxaldehyde (H2L') to Gram-positive bacteria and Gram-negative bacteria enhanced growth. The ligand H2L' and its complexes have a significant impact on the metals Co, Zn, Cu and Ni on both Grampositive (Staphylococcus aureus) and Gram-negative (pseudomonas aeruginosa). The colony of E. coli decreased in response to Schiff base complex concentration of 4.8 μg/100 ml, similar to the decrease in the complex with HL and its ligands Ni and Cu on Gram-positive (Staphylococcus aureus) and Gram-negative (pseudomonas aeruginosa) when the concentration was 4.8 μg/100 ml. The research found that Schiff Base complexes formed primarily with Cu had a more pronounced inhibitory effect on E. coli, P. acutilgineus, A. niger, Barilium sp and Penisilium rubrum and A 1 aspergillus ferreus than those formed with other metals.

The Schiff base derived from 2-furancarboxaldehyde and 2-aminobenzoic acid, as well as its metal complexes with Cu (II), Ni (II), Co (II), and Fe (III), possesses biological activities against bacteria staphylococcus pyogenes, E.coli and pseudomonas aeruginosa (Duca, E et al. 1979), Using Mueller-Hinton agar as a medium and streptomycin as a standard, the group conducted experiments utilizing 2% glucose as a source of energy. The size of inhibition could be discerned after 24 hours at 37°C and confirmed to be effective against them.

The formation of Schiff bases through the condensation of 1, 6- bis (2-formylphenylehthn) hexane as a starting material and the microbial activity of glutaraldehyde with dihydrazide of isophthalic acid and dihydrazide of terephthalic acid was examined against four bacterial species Bacillus subtilis, staphylococcus aureus (Gram-negative), Salmonella typhi and study the effects of varying concentrations of E. coli (Gram-positive) on individual cells, E. coli (Gram-positive), at different concentrations, were dissolved in DMSO and tested

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individually. The measured inhibition zone for bacteria was 24 hours and 37 degrees Celsius, as this was the end point of the incubation period with Ciprofloxacin as a reference material for bacteria. By utilizing a different method, Schiff bases derived from indoline-2, 3-dione and 2-aminobenzoic acid and its complex with Tin metal, which have antibacterial activity against Gram-positive bacteria such as Staphylococcus, can be produced. It is possible that this activity is caused by the presence of phenyl and hydroxyl groups. A greater effect was observed in terms of potency when comparing the result of the comparison with standard drug imipinem, revealing a superior performance over Schiff base complex with Tin metal (H.E.Ali et al. 2008).

The formation of Schiff bases from the condensation of 3-OH-4-MOBH with furan-2 carboxylic acid hydrazide and thiophene -2 carboxylic acid hydrazide resulted in the creation of L1, which was primarily composed of Co (II) and Cd (II). The metal complexes and Schiff base ligands were examined against both gram-positive and gram-negative bacteria to determine their potential as an antibacterial agent by diffusion methatography. The ligand exhibited superior antibacterial properties compared to its metal complexes (L. Juh´asz et al. 2000). When metal complexes and ligands are used in combination, their effects on inhibition of bacterial activities are diminished, while the ligand has higher antibacterial activity than its metal complexes (Riyadh M. et al. 2013). The Schiff base complexes of the new lanthanide elements were examined for their antibacterial abilities against bacteria E.Coli and B.Subtilis (Jayabalakrishnan et al. 2002). Both ligand and metal complexes are effective against E.Coli and B.Subtilis, as seen in this study. The study findings indicate that metal complexes of praseodymium and erbium possess high levels of antibacterial activity, while lanthanum and samarium have a moderate level of antibacterial activity. While B.subtilis showed strong activity against cerium, praseodymium, and erbium complexes, it was slightly less active with lanthanum complex (Neelima Mishra et al. 2013).

A dark orange-colored ligand, potassium 2-N(4-N,Ndimethylaminobenzylidene)-4-trithiocarbonate1,3,4-thiadiazole and its complex with metals Co(II),Cu(II) and Ni(II) have anti-bacterial properties. The study discovered that Schiff base ligand K2N(4-N, N dimethylaminobenzylidene)-4-trithiocarbonate1, 3, 4-thiadiazole has no antibacterial activity towards Gram-positive (Staphylococcus aureus) and Gram-negative (pseudomonas aeruginosa). The Cu (II) complex shows minimal impact on both bacteria used, whereas the Co (II) complex exhibits moderate activity against Staphylococcus aureus, and modest activity against pseudomonas aeruginosa (Mahasin Alias et al. 2014). The concept of overtone and the chelation theory can explain the increased activity of metal complexes over those of ligands. The proposed theories indicate that metal complexes can penetrate the lipid membranes, increasing the penetration of metal complexes into the enzyme of microorganisms, thereby blocking the metal binding sites (Sundriyal S et al. 2006).

4. Antiviral Activities

The gossypol bases have exceptional antiviral properties. Silver complexes in oxidation state I displayed an effective level of 74% against Cucumber mosaic virus, which was confirmed by their ability to inhibit the growth of C.mosaic virus (F.Meng et al. 2003). The 2-(3-allyl-2-hydroxybenzylidene)-N-hydroxy hydrazinecarboximidamide derivative of a Schiff base derived from 1-amino-3-hydroxyguanidine tosylate has proven to be an effective treatment option for mouse hepatitis virus (MHV). To prepare the Schiff bases derived from 3-(benzylidenceamino)-2-phenylquinazoline-4(3H)-ones, various carbonyl compounds were used as substitution agents. Their antiviral impact was evaluated against KOS, G, vesicular stomatitis virus, herpes simplex

virus-1 TK-KOS ACVr, and para influenza-3virus (Kumar Ks. Et al. 2010). The research has focused on synthesizing and evaluating Schiff bases derived from abacavil to determine their potential as an alternative to abacavir for the treatment of viruses (Qin, W. et al. 2013). The Schiff bases demonstrated a susceptibility to attack HIV-1.

5. Antifungal Activities

A study has found that certain areas of the Schiff Base, particularly those close to the skin's surface, are highly effective in preventing fungal infection (Nucci M et al. 2005 and Neres ATM et al. 2009). Fungi, such as Alterneria brassicae and Alterneria brassicicola, are responsible for the production of nearly all cruciferous crops, including cauliflower, cabbage, mustard, and radish (Przybylski P, et al. 2009). At a concentration of 500 ppm, Schiff Base N-(salicylidene)-2-hydroxyaniline inhibited the growth of both fungi by 67-68% (V et al. 2011). Chitosan-derived Schiff Base had a strong inhibitory effect on Botrytis cinerea and caused significant inhibition on Colletotrichum lagenarium fungi, reducing their growth by 26-33% and 35-38% at a concentration of 1000 ppm (Guo Z, et al. 2007).

The results of evaluating the antifungal activities of 2-amino-benzthiazole and 4-aminosalicylic acid Schiff bases against A. niger and C. corda were assessed through the use of Sabarod's agar (agar disc-diffusion method) by pouring about 50 µL Schiff base dissolved in DMSO(25 mg/ml), incubated at 270c for 3-7 days. The study revealed that benzthiazole Schiff base are more effective against all tested Fungi than the salicylic Schiff base, which indicates their superiority in antifungal activity(Muhammad Aqeel Ashraf, et al. 2011).

Studied for their vitro antifungal activity are against Aspergillus Niger and Candida albicans using the agar dilution method with Sabouraud's dextrose agar (Panneerselvam P, et al. 2003). The microorganisms, 105cfu/ml, were incubated with diluted Schiff base compounds prepared of a 10 µg/ml concentration for 48 to 72 hours at 26°C and a minimum inhibitory concentration, MIC. The concentration of inhibition was found to be highest for 4-(2-(phenyl propyliden imino) henyl) morpholines against Aspergillus Niger, with a zone of inhibition of 4.2 (phenyl propylideneimino) phenyl morpholines. The results show that 4(2-benzylideneimino)phenyl)morpholines have the highest ability to inhibit Candida albicans (Gana Ruba Priya et al. 2011)

6. Enzymatic Activities

By utilizing the Schiff base linkage with pyridoxal 5’ phosphate (PLP) as a substitute for pyridoxine, vitamin B6, the enzyme activities of proteins were eradicated. The interaction between specific enzymes and PLP is crucial in supporting their catalytic functions. The majority of enzymes that bind PL contacts PLP to facilitate reactions related to the metabolism of amino acids. In many cases, the enzyme-bound Lysine residue forms a Schiff base link with PLP, demonstrating the importance of PLP in enzymatic reactions. A Schiff base complex of 2-pyridine carboxyaldehyde and its derivative exhibit high super oxide dismutase activity (M.Sivasankaran, et al 2000). The DNA cleavage activity observed in the ternary complex of copper containing NSO donar Schiff base was due to the presence of NSO donar Schiff base.

7. Anticancer activity

Cancer remains a deadly condition, and the treatment for it includes surgery and chemotherapy with severe side effects. The research finds that Schiffbases are capable of producing noteworthy anticancer results. Schiff's studies on L-phenylalanine salicylaldehyde and

2-acetylpyridine tested the K562 tumor cell (Maity, D. 2019) and MDA-MB-231 against tryptophan, respectively (Chang, X. et al. 2012) The potential proteaseome inhibitors were identified. Schiff's studies on amino acid-derived compounds have been evaluated for their ability to interact with salmon sperm DNA. The molecules have been tested against various cell lines, including HL-60, KB, BGC-823 and Bel-7402, demonstrating effective anticancer properties (Li, L. et al. 2013). S-benzyldithiocarbazate through the combination of pyridine-2-carboxaldehyde and salicaldedyhe, which have ONS and NNS donor atoms, is found to be moderately effective against leukemia (Toffazzal, M. et al. 2000). In a study by Demirbas et al. 2004, the authors have investigated the antitumor properties of hydrazide-hydrazones containing 5-oxo-[1,2,4]triazole rings and found them to be effective against breast cancer cells.

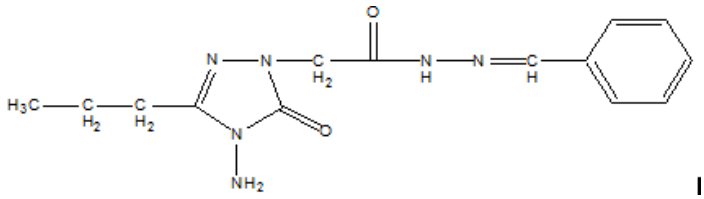

Figure 5 Hydrazide -hydrazones containing 5-oxo-[1,2,4]triazole derivatives.

8. Anticonvulsant Activity

Schiff bases derived from phthalimidine, 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-N'-(substituted phenyl) methylene/ethylidene benzohydrazide have been evaluated for their anticonvulsant activity (Bhat, M, et al. 2011). The studies of Schiff on 3-aryl-4(3H)-quinazolinone derivatives and their thiosemicarbazones have shown anticonvulsant properties, which may be attributed to the presence of thiosemicarbazone in these compounds (Aly, M. et al. 2010).

9. Conclusion

The versatility of Schiff bases is due in part to their diverse range of applications, including intermediates, chemosensors, as dyes and pigments, and various biological properties, such as the presence of azomethine nitrogen. The ability for Schiff bases to coordinate with metal atoms belonging to the main group, transition metals and rare earths is bolstered by their bi-, tri- or multidentate nature and structural flexibility. The study of the metal complexes, including their catalytic activity, has focused on their physical and chemical characteristics, including the composition of their Schiff base ligands. It has been found that these metal complexes can move across the membrane through diffusion. Amongst other issues requiring attention, the presence of toxicity and Schiff base solubility is to be considered. These findings suggest that Schiff-base is a crucial pharmacomplex for the antiepileptic properties. The insights we gained showed that Schiff-base derivatives are an invaluable tool for medicinal chemist or scientist in discovering new drug therapies. The high efficacy and low side effects make this ring a potential tool for new light in modern therapy.

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