

## Key Analytics Patterns of Biologically Active Metal Elements

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### Abstract

Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections and physicians are anxious that several bacterial infections may soon be untreatable. These concerns have led to major research efforts to discover new antibacterial agents that could be used to combat bacterial infections one of which are the Schiff bases. Schiff bases are characterized by –N=CH– (imine) groups which have biological activities such as antimicrobial, antifungal and antitumoral. Currently, more than 95% of patients with *Staphylococcus aureus* infections worldwide do not respond to first-line antibiotics such as penicillin or ampicillin. Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) were first reported in the 1960s, but have become increasingly prevalent with resistance in approximately 30% of all *Staphylococcus aureus* infections. The percentage of MRSA infection in United States hospitals increase from 2.4% (1975) to 24% (1991), with a rate of 38% at large (>200 beds) hospitals. Finally, a recent study showed that the numbers of MRSA-related deaths in the United States alone could be

higher than the numbers attributable to AIDS deaths. In the veterinary field, *S. aureus* is among the infectious agents causing mastitis in animals, predominantly in bovine species, leading to economic losses in the dairy industry.

*Keywords: Biologically Active Metals, Biologically Active Substances, Biological Substances*

The newly formed Schiff base and its complexes will have been characterized with the help of elemental analysis, condensation measurements, magnetic measurements and their structure configuration will have been determined by various spectroscopic (electronic, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, GCMS) techniques. These metal complexes and ligand will be tested for their antimicrobial inhibiting potential against the bacterial strain *Staphylococcus aureus*, *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi* (as gram negative bacteria) and fungal strain *Rizoctonia sp.*, *Aspergillus sp.*, *Penicillium sp* and compare with standard drugs Imipenem (antibacterial) and Miconazole (antifungal).

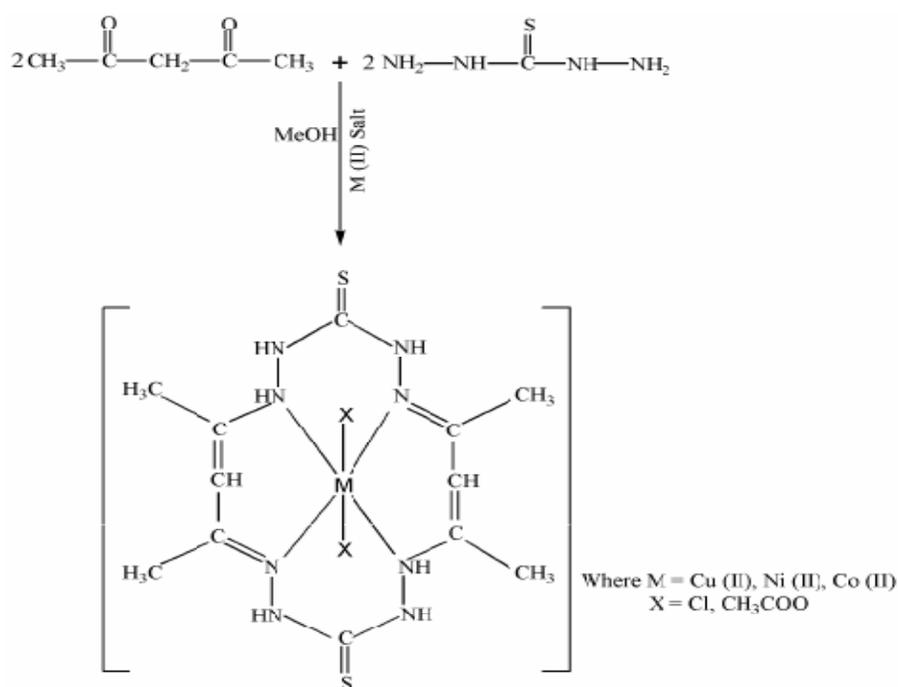
Hugo Schiff Base described the condensation between an Aldehyde and an amine leading to a Schiff base (Hugo Schiff, 1864). Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. Modern chemists still prepare Schiff bases, and now a day's active and well-designed Schiff base ligands are considered "privileged ligands". In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful catalytic transformations. In this article we show that Schiff bases are also able to transmit chiral information to produce nonracemic products through a catalytic process; chiral aldehydes or chiral amines can be used. From a practical point of view, the aspects involved in the preparation of Schiff base metal complexes are spread out in the literature. It is necessary for a macrocyclic ligand to have an enough cavity to hold more metal ions. The popular method to synthesize the

macrocyclic ligand is cyclo-condensation, such as (2+2), (3+3), (4+4) [19,20]. Mckee et al; (1988) prepared a (2+2) Schiff base tetranuclear copper complex through template condensation reaction of 2,6-diformyl-4-methyl phenyl and 1,5-diamino-3-hydroxy pentane. In this complex, the alcohol groups coordinate with copper ion as endogenous bridge ligand. Literature reports reveal that free Schiff base ligands shows less or no biological activity as comparison to their complexes. Important characteristics that can be correlated with good antimicrobial activities are as follows: (i) Lipophilicity and penetration of the complexes through the lipid membrane, (ii) the ability to form hydrogen bond with solvent molecule, (iii) a stereochemistry that allows a favorable tridimensional interaction with biomolecules and a high kinetic and thermodynamic stability in order to control the dissociation in the acidic medium, (iv) the presence of uncoordinated groups that permit the recognition by living organism and enhances the solubility.

Schiff bases are potential anticancer drugs and, when administered as their metal complexes, the anticancer activity of these complexes is enhanced in comparison to the free ligand. Schiff bases of 4-aminoantipyrine and its complexes present a great variety of biological activity ranging from antitumor, fungicide, bactericide, anti-inflammatory, and antiviral activities [30–33]. The number of transition metal complexes of Cu(II), Ni(II), Zn(II), Mn(III), Fe(III) and Cr(III) with oxygen and nitrogen donor Schiff base derivatives of 4-aminoantipyrine is limited. A small number of papers describe the synthesis and characterization of these compounds based on aminoantipyrine Schiff bases. The metal complexes derived from chromones Schiff bases have been reported and all the compounds can strongly interact with DNA via an intercalation binding mode.

It is notable that different metal ions and substitutes can affect the binding mode and affinity. In this regard, as a further research, a novel Schiff base ligand, 3-carbaldehyde chromone thiosemicarbazone and its Copper (II), Zinc (II) and Nickel (II) complexes were synthesized and

their DNA binding modes were investigated systematically. In addition, the antioxidant activities of the ligand and its metal complexes were determined by the superoxide anion ( $O_2^{*-}$ ) and hydroxyl radical ( $HO^*$ ) scavenging methods [41]. *Kumar et al;*(2011) The ligand was prepared by the condensation of acetylacetone with thiocarbohydrazide (2:2). A mixture of ethanol/1, 2-dichloroethane (1:3) was used as a solvent in the presence of anhydrous magnesium sulphate as a dehydrating agent. The metal complexes of the ligand HL were prepared by mixing a hot methanolic solution of the metal salts with required amount of a hot ethanolic solution of the ligand to form metal/ligand complexes

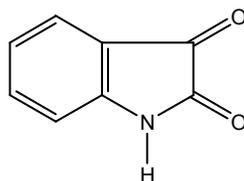


*Kumar et al;*(2016) Reaction mixture of 1,2-di(1H-indol-1-yl) ethane-1,2-dione, 1,4-dicarbonyl phenyl and solution of trivalent metal salt was refluxed for 8h. The solution was concentrated under vacuum. The precipitate was filtered off, washed with methanol and dried under vacuum

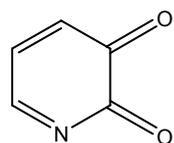
over anhydrous  $\text{CaCl}_2$ . Macrocyclic compounds containing oxalamide moiety have been synthesized and showed a variety of catalyst and biological activities. The amide groups can bind with different metal ions via nitrogen and / or oxygen atoms.

Schiff base ligand will be synthesized by the condensation of heterocyclic compounds (Indol, pyrimidine, furon, and Quinazolin etc. their derivatives) and hydrazides. The Schiff base ligand will be characterized with the help of elemental analysis, conductance measurements, magnetic measurements and their structure configuration will be determined by various spectroscopic (electronic, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, GCMS) techniques.

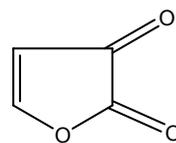
A solution of metal salt divalent [Cu(II), Zn(II), Co(II), Ni(II) etc.] and trivalent [Cr(III), Mn(III), Fe(III) etc.] in methanol will be added to a hot solution of macrocyclic ligand in ethanol, and the reaction mixture will be refluxed for 8 h. The solution will be concentrated under vacuum. The precipitate will be filtered off, washed with methanol and dried under vacuum over anhydrous  $\text{CaCl}_2$ . The newly synthesized metal complexes will be characterized by using different analytical technique



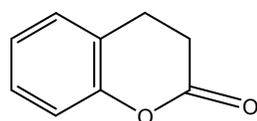
Indole 2,3 dione



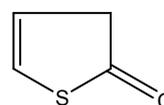
pyridine-2,3-dione



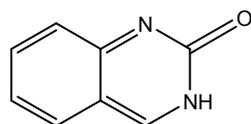
furan-2,3-dione



chroman-2-one



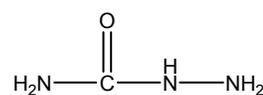
thiophen-2(3H)-one



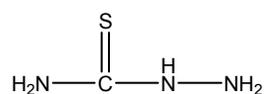
quinazolin-2(3H)-one



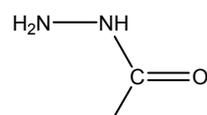
Hydrazine



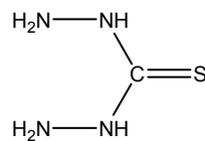
Semicarbazide



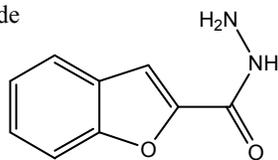
Thiosemicarbazide



Carbohydrazide



Thiocarbonylhydrazide



Benzofuran-2-carbohydrazide

Almost all the newly synthesized compounds of metal salt divalent [Cu(II), Zn(II), Co(II), Ni(II) etc.] and trivalent [Cr(III), Mn(III), Fe(III) etc.] will be screened for their biological evaluation (Antifungal and Antibacterial etc.) against various pathogens in order to evaluate their clinical utility.

The free ligand, its metal complexes, fungicide Micronazole and the control DMSO (dimethylsulfoxide) will be screen for their antifungal activity against various fungi *viz.* *Rizoctonia sp.*, *Aspergillus sp.*, and *Penicillium sp.* These species will be isolated for the infected organs of the host plants on potato dextrose agar (potato 250g+dextrose 20g+agar 20g) medium. The culture of the fungi purifies by single spore isolation technique.

The solution of different concentrations of each compound (free ligand, its metal complexes and fungicides Miconazole) in DMSO will be prepared for testing against spore germination. A drop of the solution of each concentration kept separately on glass slides. The conidia, fungal reproducing spores (approx. 200) lifted with the help of an inoculating needle, which was mixed in every drop of each compound separately. Each treatment replicates thrice and a parallel DMSO solvent control set will also run concurrently on separate glass slide. All the slides incubate in humid chambers at 25°C for 24 h. Each slide will be observed under the microscope for spore germination and percent germination finally calculated. All the results will compares with a standard fungicide Micronazole at the same concentrations.

Antibacterial activities will be evaluated using agar well diffusion method. The activity of the free ligand, its metal complexes and standard drug Imipenem will be study against the *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginoca* and *Escherichia coli* (as gram negative bacteria). The solution of each compound (free ligand, its metal complexes and standard drug Imipenem) in DMSO will prepared for testing against bacteria. Centrifuged pelletes of

bacteria from a 24h old culture containing approximately  $10^4$ - $10^6$  CFU (colony forming unit) per ml spread on the surface of Muller Hinton Agar plates. The nutrients agar media (agar 20g+beef extract 3g+peptones 5g) in 1000 mL of distilled water (PH 7.0), autoclaved and cooled down to 45°C, then it was seeded with 10 mL of prepared inocula to have  $10^6$  CFU/mL. Wells will be created in medium with the help of a sterile metallic bores and filled with the compounds. The activity will be determined by measuring the diameter of the inhibition zone (in mm). The growth inhibition was calculated according to reference.

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