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REVIEW OF SYNTHESIS AND ANTIMICROBIAL ANALYSIS OF SOME BINUCLEAR COMPLEXES DERIVED FROM NITROGEN DONOR LIGANDS

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Abstarct: It is well known that copper is an important metal found in living organisms. Cu(II) plays vital roles in chemistry and biology. It is important for the function of several proteins and enzymes involved in energy metabolism, respiration and DNA synthesis, notably cytochrome oxidase, superoxide dismutase (SOD) as corbate oxidase and tyrosinase. Copper plays a significant role in cell physiology as a catalytic cofactor in the redox chemistry of mitochondria respiration, iron absorption, free radical scavenging and elastin cross linkages. Copper toxicity comes about from its ability to produce reactive oxygen species (ROS), displace other metal ions, peroxidize lipids, and directly leave DNA and RNA. Copper is included into a number of metalloenzymes implicated in formation of hemoglobin, drug/xenobiotic metabolism, carbohydrate metabolism, biosynthesis of catecholamine and the cross-linking of collagen, elastin, and hair keratin as well as in the antioxidant defense mechanism. Chemicals obtained from copper show utility as bactericides, algaecides and fungicides. In many agricultural products copper is used to fight fungi and for crop protection. In textiles, paints and woods industries, copper is an important metal. The outbreaks of serious diseases can be decreased by using copper surfaces in kitchens and food processing industries.

Keywords: Mitochondria, Collagen, Catecholamine, Antioxidant, Fungicides, Bactericides.

REVIEW :

Chemistry of heterocyclic compounds is a field of particular interest of the organic chemists. Heterocyclic compounds have attracted a considerable interest for their highly electron-donating and strong coordination abilities, and still receive much attention because of their applications in synthetic chemistry. Synthesis of secondary and tertiary amines through the N-alkylation of primary amine is the furthermost important and essential reaction.

A heterocyclic compound is one which has a cyclic structure in which along with carbon, one or more atoms of other elements are present in the ring. Nitrogen, oxygen, and sulphur are the most common heteroatoms.

For experimental drug design, various heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds. Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with applications in drug discovery.

N-substituted amines are prepared by N-alkylation using alkyl halides in a traditional manner[1]. Polyimides (PIs) show remarkable physical and chemical properties and they are used extensively in microelectronic manufacturing as interlayer dielectrics (ILDs), passivation layers and stress buffers[2]. PIs rigid imide and phenyl structure cause high modulus, glass transition temperature (Tg) and thermal stability. However, most of them have low solubility in common organic solvents. By spin-casting of polyamic acids on a Si/metal substrate, followed by the thermal dehydration reaction, the PIs film can be obtained. However, deformation of PIs film[3] takes place due to the release of water molecules in the thermal immunization process. Due to the versatile reaction chemistry of benzocyclobutene (BCB)-functionalized thermosets and their attracting properties, they become high performance materials for microelectronic applications[4-6] By incorporating the reactive alkyl group to the molecular structure, solubility of the BCB monomers increase, and also provides the photosensitivity when reacted with acid photo crosslinking agents. In this context, we discuss further the chemistry of heterocyclic moieties, synthesis and their applications.

Literature review revealed the potent inhibition of human immunodeficiency virus type 1 (HIV-1) replication by HIV-1 protease inhibition, anti tumor, analgesic and anti-inflammatory, antimalarial, antifungal, anticandidal activities[7] of Benzothiazole. 2-methylphenyl thiourea (I), 2-amino-4-methylbenzothiazole (II) and 2-hydrazino-4-methylbenzothiazole (III) are the origin

intermediates for the synthesis of 5-methyl-1, 2,4-triazolo (3,4b) benzothiazole (IV). It is a important fungicide for controlling of rice blast (pyricularia orazae) in transplanted and direct seeded rice. There are various methods for production of aminobenzothiazoles from phenyl thioureas with chlorine in aprotic solvents in the presence of catalytic quantities of bromine or preferably iodine which in these manners, the conversion to Review of Literature 16 benzothiazoles with chlorine alone leads to products likewise chlorinated in the benzene ring.

Benzothiazole compounds and their derivatives were found to numerous pharmacological activities like anticonvulsant, antimicrobial, anthelmintic, antileishmanial, anti-tubercular, schictosomicidal, antifungal, anti-inflammatory antipsychotic and anti-diabetic activities. The present review focuses on the benzothiazoles with potential activities that are now in development.

2-(4-aminophenyl) benzothiazoles are ideal class of potent and selective antitumor agents and display specific profile of cytotoxic response across the cell lines. In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties. It was reported in last few years that benzothiazole, its bioisosters and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacteria (e.g., Enterobacter, Pseudomonas aeruginosa, E. coli, and Staphylococcus epidermidis etc.) and the yeast (e.g., Candida albicans). Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. The core structure of thiazole and many pharmacologically and biologically active compounds is formed by S and N atoms.

The main problem that we are facing in the context of infectious diseases is the persistent increase and spread of antimicrobial resistance. Thus, studies for the identification of new targets and drugs for the action of infectious diseases are at the forefront. Many heterocyclic nuclei, benzimidazole, triazine, benzothiazole have been lately reviewed as antimicrobial agents[8-9]. Our attention was focused to the benzothiazole nucleus. Benzothiazole can serve as unique and versatile scaffolds in research area, especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. Under specific condition of reaction when any primary amine is treated with a ketone or an aldehyde, Schiff bases are synthesized, which are named after Hugo Schiff. [10] Schiff bases are very important organic compounds being used as pigments, catalysts, dyes and as polymer stabilizers.[11] Schiff bases have been observed to show a wide array of biocidal activities i.e. anti-inflammatory, antiviral, antimalarial, antibacterial, antifungal, anti-proliferative and antipyretic properties[12]. In various natural, non natural and naturally-derived compounds, Imine or azomethine groups are present, which show various biocidal activities.

In recent years, the field of antiepileptic drug development has become quite dynamic, affording many promising research opportunities[13]. Therefore, the continued search for safer and more effective antiepileptic drugs is necessary. As per the literature survey reveals, various derivatives of Benzothiazole, quinazoline derivatives have shown promising anticonvulsant activity, along with other pharmacological activities[14]. Further the degree of success varies as a function of seizure type, cause and other factors. Disappointingly, despite all efforts, the Review of Literature 20 complete control of seizures can be achieved in up to 50% of patients. Most of the epileptic patients not only suffer from stigmatization, they usually suffer from depression, muscular spasm, strange sensations, abnormal behavioural changes, convulsions, loss of consciousness and are highly prone to suicide and sudden, unexpected death[15]. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity.

Urea is the first organic compound that was synthesized in lab in 1982, which became the important step in the history of synthetic organic chemistry and played important physiological and biological roles in animal kingdom[16-18]. Interest has grown rapidly in the preparation and the study of the critical effects of compounds containing systems N-N-S or O-N-S with three claws of these compounds that have an energetic effects against cancers as well as it's objection vital role for the synthesis of amino acids have been prepared and the study of many derivatives of thiourea compounds that have effects against the types of microbes and viruses. Thiourea and its derivatives represent a well-known important group of organic compound due to their diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry. They moreover can be used as selective analytical reagents, especially for the determination of metals in complex interfering materials. Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century. Also these complexes display a wide range of biological activity including antibacterial, antifungal properties[19,20]. One of the important thiourea derivatives is thayazol thiourea which was known to have a wide range of biological activities including antiviral, antibacterial, antifungal, antitubercular, herbicidal, insecticidal. In addition, thayazol thiourea derivatives were often used in analytical and biological applications. Metal complexes of ligands containing sulfur as donor atoms are known to possess antifungal and antibacterial activities.

The complex with thiourea derivatives which has biological activity has been successfully screened for various biological actions: antidepressant, anticonvulsant, anthelmintic, antihistaminic, anesthetic, antitussive, analgesic etc.[21]. Cisplaten is successfully used in chemotherapy, but is effective only against a narrow range of tumors[22]. Development of analogues has resulted in a few clinically useful complexes, most of which, however, are cross-resistant to Cisplaten[23]. Next to platinum, ruthenium is also used for the construction of anticancer agents. Many ruthenium complexes have been evaluated for the treatment of cancer, in part because ruthenium(II) and ruthenium(III) complexes exhibit relatively low ligand exchange rates, which are comparable to those of platinum(II) complexes. Recently researchers working on the developments of poly nuclear metals complexes are focusing on their anticancer activity. The compounds presented are often supposed to exert their anticancer activity by different modes of action as compared to established drugs, including newly proposed mechanisms such as enzyme inhibition, cross linking of biomacromolecules or through photo-activation, though many of the examples are also capable of binding to DNA nucleon bases.

There are two types of triazole, the 1,2,3-triazoles and the 1,2,4- triazoles. Amine and thione-substituted triazoles have been studied as anti inflammatory and anti-microbial agents and other applications. Triazole are considered to be good coordinating ligands, because they involved both hard nitrogen and soft sulfur atom as thio amide group. This ligand have donor group that coordinate with wide range of metal ions. The tatumerisum form could occur in triazole. The potential coordinating sites are: (i)

sulfur of thiol group, (ii) nitrogen of the primary amino group, (iii) two nitrogen atoms at position 1 and 2 in triazole ring system. This S=C_ N_ N unit is present in the ligand that permit for bidentate coordination to metal ions. Thus this ligand is polydentate, it has been shown and experimentally verified that Complexes of polydentate ligands are called chelate complexes. They tend to be more stable than complexes derived from monodentate ligands, Furthermore five or six membered chelate is by far the most common and the most stable. A new thio- Triazole complexes with selected metals was prepared[24]. In this paper, the preparation and characterization of Cu(II), Ni(II), Zn(II), Cd(II) and Sn(II) complexes with 4-amino-5-(pyridyl)-4H-1,2,4-triazole-3- thiol are described.

Based on the survey made in the literature, it has been found that good work has been reported on polymers/copolymers/ terpolymers acting as various types of ligands with transition metal ions. The chemical properties of benzothiazole based compounds have been intensively investigated in several research fields especially in polymer field, because of their high thermal stability and pharmacological activity. The thiazole ring dramatically increases the diversity of certain biological properties such as antibacterial, antiviral, and antitubercular activities. These activities are probably due to the presence of the –N=C–S group present in the thiazole moiety.

The role of benzoyl thioureas derivatives in coordination chemistry has been extensively studied and quite satisfactory elucidated. Because benzoyl thioureas have suitable C=O and C=S function groups, they can be considered as useful chelating agents due to their ability to encapsulate into their coordinating moiety metal ions. Therefore, new thiourea derivatives and their structures have received attention of several research groups because of their complexation capacity[25]. Some derivatives are biologically active, such as antifungal, antitumour, antiviral, antibacterial, pharmacological, herbicidal, and insecticidal properties. In addition, some of the research groups have reported thermal behaviour and the acidity constants of ligands of some benzoylthiourea derivatives and their metal complexes.

In addition, fluorine-containing organic compounds have been frequently applied to biorelated materials, medicines, and agrochemicals because of their unique properties, such as high thermal stability and lipophilicity. Metal complexes with potentially tridentate and tetradentate ligands have evoked much interest in coordination chemistry. Schiff base complexes of transition metals have played prominent role in the development of coordination chemistry. Several Schiff base metal complexes have been studied because of their industrial and biological applications.[26].

In recent years main emphasis is given on the studies of polynuclear transition metal complexes. Many strategies have been applied to build such molecular architectures with different terminal and bridging ligands to facilitate ferro and anti ferromagnetic interactions among the metal centres.

Copper ions are found in the active sites of a large number of metalloproteins involved in important biological electron transfer reactions, as well as in redox processing of molecular oxygen. The former comprises 'blue' copper sites in electron-transfer proteins or multi copper oxidase while the latter includes hermocyanins (arthopodal and malluscan blood O2 carrier proteins).

In earlier studies, it has been shown that certain heterocyclic compounds such as clioquinol and pyrrolidine, dihiocarbamate act as potent antitumor compounds by binding to endogenous copper in prostate and breast cancer cells. It has been proposed that highly elevated levels of copper can be tumor specific and use of copper can be tumor specific and use of copper cheaters might be one of the useful strategies for cancer therapies.

Copper complexes of thiosemicarbazones of imidazole-2-carbaldehyde, pyrrole-2-carbaldehyde and indole-3-carbaldehyde were synthesised and characterised. The antimicrobial properties of the free ligands and their complexes were evaluated against yeasts, moulds and bacteria (Gram-positive and Gram negative). Some copper chelates exhibited a moderate inhibitory activity, better than that of the corresponding free ligands. In particular, the pyrrole derivative [Cu(HL2)2] proved to be a wide spectrum agent, showing an interesting inhibition of the growth of all Gram-positive bacteria and fungi tested at concentrations of 12-15 mg/mL. In contrast, a selective effect was observed for imidazole and indole chelates against fungi and Gram-positive bacteria, respectively.

Literature study reveals that copper complexes having N & S donor ligand show potent biological activities present work. The antibactericidal activity of the cupric chloride, fluoroquinolones and its complexes were tested against two Gram(+) S. aureus, B. subtilis, and three Gram (-) S. marcescens, E. coli and P. aeruginosa organisms using double dilution method. An acceptable reason for this increase in bactericidal activity may be explained on the basis of chelation theory and Overtone's concept. Lipid membrane surrounding the cell allows the flow of only those materials which are lipid soluble. So the liposolubility is an important factor which controls bacterial activity. This enhanced lipophicity increases the infiltration of the complexes into lipid membranes and finally obstructs the metal binding sites in bacterial enzymes. The antimicrobial activity of all complexes against five microorganisms (MIC from 0.36 to 2.07 mg/mL) is much higher than metal salt. The complex shows better antimicrobial activity than the metal salt ~3000 mg/mL), another quinilones (1.1-5.7 mg/mL), and enrofloxacin (1.4-3.9 mg/mL).

However to the best of our knowledge the combination product of soaps and ligands have not been studied thoroughly. Therefore we have chosen the system, soap-ligand complex in various compositions of non-polar solvent benzene and polar solvent propanol to understand the effect of polarity, various interactions between solute-solvent molecules and their miceller features. In the present work we synthesized complexes of Copper(II) soap with nitro and methoxy substituted benzothiazole as well as with nitro and methoxy substituted phenyl thiourea ligands. Antifungal activity was performed for the synthesized complexes against Candida albicans and Trichoderma harizianum by Kirby-Baur and Stokes' method. In the same way antibacterial activity was performed against Staphylococcus aureus (ATCC2913), Escherichia coli (ATCC25922). The synthesized complexes are quite efficient

antifungal and antibacterial agents. Some areas are still open for further research in the field of wood preservatives, in formation of more stable lubricants (for oxidative deterioration), crop protection.

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