Synthesis, characterization and in silico ADME study of Tris (ethylene diamine) Copper (II) Sulphate

Dr. Rahul Subhash Bhondwe[1], Bhimrao Ramchandra Torane[2], Sanjay Ranganatha Kale[3]
[1,2,3]*Department of chemistry, Tuljaram Chaturchand College, Baramati, India*

Abstract **- We here in report the synthesis of copper (II) complex Tris (ethylene diamine) Copper II Sulphate by treatment of Cu $(NO_3)_2$, ethylene diamine and excess ammonia. Synthesized complex was characterized by FTIR and ^{1}HNMR spectroscopy. Absorption, distribution, metabolism and excretion (ADME) studies were carried out for evaluating durg likeness of the complex. Pharmacokinetics properties such bioavailability, BBB penetration, solubility pharmacokinetics and skin permeation studies.**

Index Terms **- Metal complex, Cu (II) complex, FTIR, 1HNMR, ADME studies.**

I.INTRODUCTION

Metal complexes always been considered as versatile composition for various industries such as pharmaceutical, agriculture, sensors, dyes, solar cells, paint and polymer [1]. Especially the transition metal complexes have enormous importance in medicine and cosmetics. Discovery of cis Platine researchers are vigorously penetrating the area of metal complexes to explore more active pharmaceutical ingredients (API), new chemical entities (NCE) and the lead compounds [1-8]. Metal complexes have broad range of biological activities counting antibacterial, antifungal, anti-inflammatory, anti-piratic [9], anti-cancer activity [10]. Many research organization and pharmaceutical industries revealed the synthesis and characterization of numerous Cu (II) complexes and appraised for their biological activities.

Copper is an essential trace metal in human body and have a strong impact on biochemical process. Cu (II) complexes have proven to be well established ligands for many biomolecules and it is an important part of various metalloproteins. Most studied role of copper is in homeostasis, physiology of copper transport, and iron metabolism. These studies are related to oxidative stress related disorder, Wilson's disease, the Menkens disease, inflammations, Alzimer disease (AD) and Cancer. Numerous Copper (II) complexes shown cytotoxic activity by coordinated through N, S, or O atoms [11]. Lately Petronijevic et al reported the antitumor activity, DNA and BSA interaction of copper (II) complexes [12].

In our pursuit for the search of biological active and pharmaceutically important metal complexes we have synthesized copper (II) complex Tris (ethylene diamine) Copper II Sulphate with known method [13]. Its spectroscopic identification was carried out with the help of sophisticated analytical techniques such as Fourier Transform InfraRed spectroscopy (FTIR) and proton nuclear magnetic resonance (^{1}HNMR) spectroscopy. Furthermore, in silico ADME studies were performed for the pharmacokinetics parameters including bioavailability, BBB penetration, solubility, hydrophilicity and skin permeation carried out.

II. MATERIAL AND METHODS

All the chemical purchased from Yash traders and are chemically pure. The chemicals used were of AR grade. Melting Points were determined by open capillary method and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer BRUKER the ranging from 4000-400 cm-1. 1H spectra on a BRUKER AVANCE NEO 500 NMR spectrometer with DMSO-d6 as a solvent and chemical shift (δ) are expressed in ppm using TMS as internal standard. The in silico ADME studied were performed by online webserver SwissADME, the canonical smiles were generated from CHEMCD website.

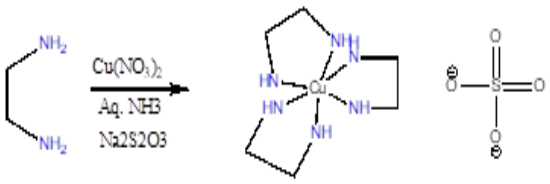

Fig 1: Preparation of Tris (ethylene diamine) Copper II Sulphate

Preparation of Tris (ethylene diamine) Copper II Sulphate

A solution of Cu(NO3)2 (1.00 mmole) in minimum amount of water was taken in round bottom flask to and cooled to 0 C, to it ethylene diamine was added dropwise and the excess ammonia (10 mmole). The mixture is heated on water bath for 1 hour and cool in ice bath for 30 min. the solution of sodium thiosulphate was added with constant stirring. The complex formed was filtered, dried under IR lamp. The product obtained (2 .1 gm) as dark orange powder. (Figure 1.)

III. RESULTS AND DISCUSSION

The complex was prepared from the condensation of Cu $(NO_3)_2$, ethylene diamine, aq. ammonia in good yield. The complex is dark orange color and stable at room temperature. FTIR analysis shown strong band at 3424 cm^{-1} and 3381cm^{-1} assigned to NH stretching frequencies, the bands at 2951, 2935 and 2878 cm^{-1} for aliphatic CH stretching from sp3 hybridized carbon atom and hydrogen. Metal nitrogen stretching bands are observed at 460-480 cm^{-1} (Figure 2) . ^{1}HNMR shown broad singlet at 2.90 ppm for NH protons and a sharp singlet at 4.88 ppm for 12 protons accounts for CH_2 groups. The down filed value of both methylene and amino protons due the coordination of nitrogen with copper metal indicates the formation of complex. (Figure 3)

ADME/tox profile:

ADME properties analysis is an essential step in the drug development, a good drug candidate must possess appropriate ADME properties besides a excellent biological activity. The Bioavailability radar of Tris (ethylene diamine) Copper II Sulphate displays most essential part in pink region, the molecule shows high polarity (Figure 4). Physicochemical properties of complex are summarized in Table 1. Molecular formula of the compound is $C_6H_{18}CuN_6O_4S$ with molecular wight 333.86 g/mol.

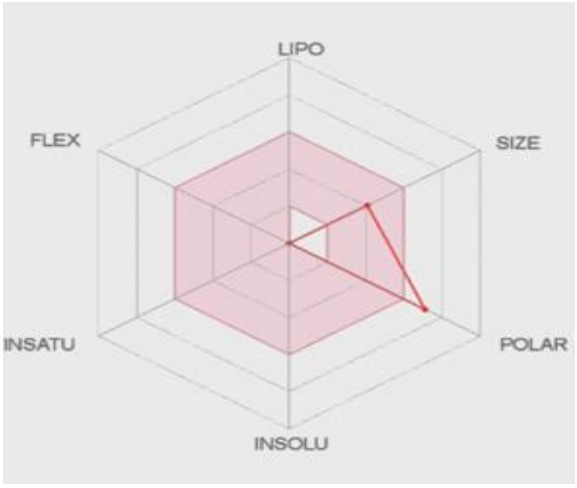

Fig 4: Bioavailability radar of Preparation of Tris (ethylene diamine) Copper II Sulphate

There are eighteen heavy atoms and absence of aromatic heavy atoms. The ratio of sp3 hybridized carbons over the total carbon count of the molecule (Fraction Csp3) should be at least 0.25 but the complex has high value 1.00, designates highly saturated compound. There is no rotatable bond hence molecule have a rigid structure. Ten H bond acceptor and six H bond donor demonstrates ability of multiple binding sites. Molar refractivity is measure of overall polarity of molecule ideal value must be in between 40 to 130, our complex has 79.99 value increasing its probability for drug likeness [14]. (Table 1)

Water solubility is another important parameter for drug to excrete from our body after effect. This also help for the formulation of drug in tablet form. Values of Log S are listed in the Table 2. The obtained values confirm high solubility of complex in water. Pharmacokinetics properties of complex exemplifies important parameter for drug likeness, the values are summarized in Table 3. GI absorption is a measurement of gastrointestinal absorption of the drug. Our complex has low GI absorption value establish its low absorption.

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF COMPLEX

Physicochemical Properties	
Formula	C6H18CuN6O4S
Molecular weight	333.86 g/mol
Num. heavy atoms	18
Num. arom. heavy atoms	0
Fraction Csp3	1.00
Num. rotatable bonds	0
Num. H-bond acceptors	10

Num. H-bond donors	6
Molar Refractivity	79.66

TABLE 2: WATER SOLUBILITY OF COMPLEX

Water Solubility	
Log *S* (ESOL)	1.65
Solubility	1.49e+04 mg/ml; 4.46e+01 mol/l
Class	Highly soluble
Log *S* (Ali)	2.93
Solubility	2.87e+05 mg/ml; 8.60e+02 mol/l
Class	Highly soluble
Log *S* (SILICOS-IT)	-2.08
Solubility	2.75e+00 mg/ml; 8.24e-03 mol/l
Class	Soluble

Blood brain barrier permeant (BBB permeant) have high impact in drug discovery, drug must not cross or permeate through BBB and must not interact with brain receptors. Our complex is not a BBB permeant and does not inhibit important enzymes as mention CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. Log *Kp* is skin penetration coefficient its optimum range is -1.2 to -1.32 cm/s, our complex has value of -12.35 cm/s having high penetration power. Finally complex is not a P-glycoprotein (P-gp) substate and not vulnerable to Drug-Drug interaction.

TABLE 3: PHARMACOKINETICS PROPERTIES OF COMPLEX

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-12.35 cm/s

IV. CONCLUSION

We have successfully carried out the synthesis of Tris (ethylene diamine) Copper II Sulphate in good yield and the complex is stable at room temperature. The structure elucidation and characterization performed with the help of advance analytical technique (FTIR and ^{1}HNMR) revealed the structure of shown complex. The ADME profile exposed that solubility is high and also it has more ability for skin penetration. Compound violated one Lipinski rule and have high polarity. Complex is not penetrating the Blood brain barrier (BBB) hence there will be no side effect which can cause neurological disfunction. Complex has moderate drug likeness and needs severe modifications before further advancements in drug discovery.

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