Study of Re(II) Complex of Novel Ligand

Vijendra Yadav[1], Jinendra Singh Chauhan[2], Brijesh Singh[3]

[1]*Rabindra Nath Tagore University(Formerly AISECT University) Bhopal, M.P., India*

[2] *BPL Govt. College Mhow, Indore, M.P., India*

[3]*Rabindra Nath Tagore University, Bhopal, M.P., India*

Abstract - The synthesized new drug noble ligand (organic compound) 1 - {3- [2 -Amino -5- (5-hydroxy -5H -imidazol -4 -ylmethanesulfonyl) -benzyloxy] -4H- pyrazol -4 -yl} - ethanone derived from hydrazine and acceto-acetic ester. The drug which one used as a ligand consist pyrazol and imidazole (nitrogen derivatives), and it found that the 'N'atom, oxygen atom 'S' atom bonded with the metal Re(II) to form complex . The structure was confirmed by using elemental analysis, UV-VIS, mass spectrometry, and NMR spectroscopy and 13C NMR showing that the complex behave as antifungal complex and the analysis revealed that it is better complex for fungus.

Keywords: Pyrazol, imidazole, derivative, metal ion complexes; H-NMR, 13C-NMR.

I. INTRODUCTION

The bioinorganic chemistry dealing of elements and complexes that are present in different living organism and do biological function in this study we are working on the structure, function, properties and biological utilization of metal-drug complex such as antifungal and anti-microbial activity. These analysis of metal–drug complex paramount importance in medicine as well as in the field of environment and chemical technology.

Bioinorganic chemistry recently really useful in different area of chemical science and technology basically in filed of medicine because so many complexes are naturally found in biological system with the essential and non-essential elements which shows various importance in to different part of biological system as complex for example macro elements such as Na,K and Cl used in nurve conduction and micro-elements Fe, Co, Cu, Zn, V, Mn, Mo, F, I required in small amount for vitamin segments which help to secure biological system this elements is called essential element.

In other hand non-essential elements also help in working of biological systems, but its functions are not yet properly known, recently few scientists are define some functions of As, Ni, Ti, Si, B etc. in such way transition metal ions are given so many complexes which working as vitamins, enzyme, co-enzyme and as carrier of molecules. Moreover; these complexes useful as medicines for the treatment of cancer, anti-fungal, anti-microbial and anti-inflematry1,2.

The chemistry of metal complexes with ligands those containing oxygen and nitrogen as donor atoms have to attract for the research. So many organic ligands are known to coordinate to metal atom in two ways. 1. Metal to ligand electron pair donation and 2. Ligand to metal donation of electrons, with under the different reaction conditions1.

The drug (organic ligand) transition metal complexes of Manganese, cobalt, nickel, copper, and zinc are life-essential metallic elements and exhibit greater biological activity when associated with certain metal protein complexes3[-5], participating in oxygen transport, electronic transfer reactions, or the storage of ions [6-7]. Mn (II), Co (II), Ni (II), Cu (II), and Zn (II) complexes of the 4-chloro-2-{(E)-[(4-ophenyl)imino] methyl}phenol, has been synthesized 8-9. The new Mn (II), Co (III), Ni (II), Cu (II), and Zn (II) complexes of the 4-chloro-2-{(E)-[(4-henyl) imino] methyl}phenol has been investigated and is now reported [8]. Evaluation results and revealed that the metal complexes are given six coordinated octahedral geometry, exhibited higher activity than the free other ligand[10-11-12].

Similarly the polymeric ligands also coordinate with d-block transition metal complexes has been synthesized and reported, which are good to their high thermal stability and enormous pharmacological activity along with potential applications as functional materials16. Owing to the high thermal stability of the polymeric ligand, they specific applications such as in waste water treatment, metal recovery, protective coatings, thermally stable materials, water disinfectants, antifouling paints, antimicrobial and surgical materials, gels and ointments for medical uses, and biological activity [13-14].

The stability of complex defines in general; the complexes exist under suitable conditions may be stable for long period. However the formation of complexes analyzed in solution, for that two types of stabilities are count 1.Thermodynamic stability and 2. Kinetic stability. In the thermodynamic calculation the equilibrium constants of a reaction is determine with this the heat exchange and entropy change during reaction also determine. It also found that during the reaction the large amount of heat liberated in the reaction which indication of the most stability of reaction products. Secondly, increment in entropy during the reaction is greater the stability of products[1].

The kinetic stability of complexes is shows the speed of reaction which given transformation leading to the attainment of equilibrium. In this study we are mainly focus on the thermodynamic stability of the complex compound[15]. The determination of stability constant for the complexes in terms of stability is count in two ways thermodynamic stability and kinetic stability, the thermodynamic stability of complex deals with the bond energy (E_{bin}), stability constant (β) and redox potential(EMF), and the kinetic stability count with the rate of the reaction(K).

For that the mechanism of reaction focuses to be pointed on formation of intermediate, and activation [16-17]. The thermodynamic stability of complexes is revealed the extent to which the species will be transformed into other species under the certain conditions, when the equilibrium is occurs than metal ion (M^+) combines with ligand (L) to form complex [MLn], sofare;

$$M + nL \rightarrow MLn$$

$$K = \frac{[ML_n]}{[M][L]^n}$$

Thus by knowing the value of [M], [L] and [MLn] the value of K, stability constant of the complex [MLn] can be count[6].

For the determination of stability constant is required knowledge of data mining and MAT-LAB in that case we capable to find out computing quantitative analysis with the concentration of free metal ion, ligand and any of its complexes formed in the chemical process, under different conditions of pH. These all type of data must be exclusively employed in the field of analytical chemistry, stereochemistry, bio-inorganic chemistry, non-ferrous and rare metals, ion exchange etc. There are so many methods for the analysis of computational stability constants. Here we working on only two methods are explained known as pH-metric method and spectrophotometric method. For determination of stepwise stability constant of complex by pH-metric method as complexing processes are considered, thus it is possible to analyzed formation of stability constants which refer to the addition of ligands in a stepwise manner as follows:

$$M + nL \rightleftharpoons MLn$$

$$K = \frac{[ML_n]}{[M][L]^n}$$

$$MLn\text{-}1 + L \rightleftharpoons MLn$$

$$K = \frac{[MLn]}{[Mn-1][L]}[MLn] = [MLn\text{-}1][L]$$

The constants K1, K2, K3 ...K_n are called stepwise stability constants for the complex formation and it related to the overall stability constant as:

$$\beta 1 = K1, \beta 2 = K1.K2, \beta 3 = K1.K2.K3, \beta 4 = K1.K2.K3.K4$$

Therefore $\beta_n = K1.K2.K3. \ldots\ldots K_n$

The metal drug ligand complexes are mainly dibasic acids and heterocyclic bases which have been studied since the past few decades18 because of their antibacterial and anti-fungal properties, and also because of their activities against microbes, viruses and cancer cells19. In this way some scientists and researchers found that the complexes of platinum (IV) metal are showing good biological and clinical properties so it is very important for medical point of view. Some more complexes of platinum (IV) also exhibit anti-tumor activity[20]. And some more transition metal complexes of Ni (II), Co (II), Fe (II) and Cu (II) complexes with thiazoline legend count of their fungicidal activity[4]. Similarly the transition metal complexes of pehthalic acid studied for both from pharmacological[21] and industrial point of view.

The chlorine constituted complexes of 8-hydroxyquinoline reviled that the complexes has great efficiency as antifungal agents6, complex of Cu (II) with the 8-hydroxyquinoline are showing the anti-fouling agent7 and itself protects the fungi[22]. Recently, in this present study we are going to find antifungal activities of synthesized complexes of transition metals with metal-1 -{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone complexes and heterocyclic bases.

II. EXPERIMENTAL

In this preparation we are using AR grade chemicals, for this synthesis 25 ml of methyl-aceto- ethyl-acetate mix with the 20 ml of hydrazine hydrogen chloride in to the round bottom flask then the exothermic reaction is take place at room temperature (32^0C), and it produced compound 4-Ethoxy-4-hydrazino-butan-2-one with 12.2 gm. of yield.

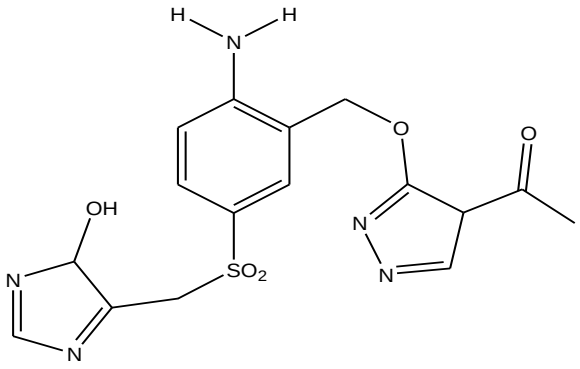


Figure 1: Structure of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone

Ethanolic solution of prepared ligand (0.02 mol) and Eethanolic solution of corresponding metal salts (0.02 mol) (MX2, where M= the Fe (III), Cu(II) and Re(IV) metal ions X=SO^4 /Cl /Acetate/NO_3) were mixed together with constant stirring in acidic media. The mixture was refluxed for 3 h at 85 ^oC. On cooling colored solid metal complexes were precipitated out. The products were filtered, washed with petroleum ether, than we get recrystallized complex.

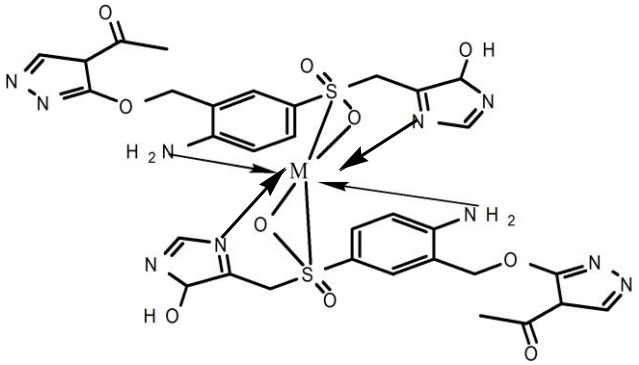


Figure 2 : Structure of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone metal complex Re(II)

Infrared spectra of the ligand and its complexes were carried out by using KBr pellets in the range 4000-400 cm^{-1}on **Bucker model** of IR instrument. The electronic absorption was carried out by Shimadzu UV-1601 using alcohol as solvent. The Mass spectra were recorded by ESI technique on **VG AUTOSPEC** mass spectrometer instrument with **GLC**. The 1-H spectra were recorded on **Varian Gemini Unity** Spectrometer by employing TMS as internal standard, with KCl.

All the analysis done at SIRT, Bhopal and the Mass spectra analyzed at RGPV, Bhopal Pharmacy department.

Drug yellow coloured 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone: Elemental analysis data for $C_{17}H_{19}N_5O_4S$ found: C 49.09%; H, 4.30%; N- 17.89% calculated: C, 49.10%; H, 4.39%; N, 17.68%. FT-IR (KBr, disc cm−1) 3423.2 υ (O-H), 1600.6, 1220.3 υ(C-O), 703.7 υ (H2O), 534.8 υ(H-N), 491.7 υ(N-N). UV-Vis λ_{max} (nm) at λ max (nm) 223.4, 270.2 and 358 nm. ^{1}H NMR): δ 7.50, 2.0(-OH), 3.23(C=O), 4 (-NH_2), 7.18–7.39 (m, 7ArH); ^{13}C NMR): COCH3 206 164–165(-NH_2), 162(N=N),193(-$COCH_3$),129 (O=(S)=O), 125(C-O),138.2(-C6H5). And the mass spectrum at the 100% abundance is 391 eg. The mass of compound is 391 and 389.3au along with the m+2 and M-2 degradation.

Re (II) Complex: Yield: 73.91%, 0.2672 g, colour: brown, m.p> 394°C, and molar conductance 24 $Ohm^{-1}cm^2mol^{-1}$. Elemental analysis data for C17H19Re (II)N_5O_4S found: C, 52.41%; H, 3.34%; N, 4.72% calculated: C, 52.47%; H, 3.39%; N, 4.69%. FT-IR (KBr, disc cm−1) 3455.6 υ(O-H), 1599.7, 1213.9 υ(C-O), 695.8 υ(H2O), 536.1 υ(Re-N), 490.8 υ(Re-O). 1H NMR): δ 7.50, 2.0(-OH), 3.23(C=O), 4 (-NH2), 7.18–7.39 (m, 7ArH); 13C NMR): COCH3 206 164–165(-NH2), 162(N=N),193(-COCH3),129 (O=(S)=O), 125(C-O),138.2(-C6H5).UV-Vis λ_{max}(nm) 243.1, 267.1 and 345.5. According to the mass spectra the mass of metal-drug complex is 968.21 au.

The center-point of each Whatman filter paper was marked for the mobility observation of metal ions. Each of the vessels was filled with 100 ml of background electrolyte containing 0.1 M $HClO_4$ and ligand reagent (1.0×10-2 M). The paper becomes moistened with the background electrolyte solution, and then the spot of each metal solution was applied at the marked center-point of the strips using micropipette. At least one strip was spotting with glucose solution for electro-osmotic correction. The next paper strips put on insulator and then thermo stated water at 25^0C. Than after the paper strip was exchanged over the insulator plates at constant temperature. The lid air tight for left to 20 minutes to insure wetting of paper strips.

Subsequently, a direct 180 volts was set in between the electrodes, and after Electrophoresis was carried out for 45 minutes after which these strips were removed from and dried. The metal ions and glucose spots were detected by specific reagents. The edges were analyzed from the center-point and the mean were counted. The distance moved by glucose point was neglected to find out the correct length. Migration of ions towards anode and cathode were denoted by negative and positive signs, respectively.

For the preparation yeast inoculums, the fungal sample sub-cultured on dextrose agar slant for Drug Designing, these sample were incubated for 24hours at 35°C. The obtained sample suspension was adjusted to 0.5 McFarland standards. Then after this process the inoculum was further adjusted to 1.5×10^5 or 2.5×10^5. The inoculums and the mold suspensions of fungi was obtained after 5 days which cultured on Sabor and dextrose agar slant incubated at 35°C.

The fungi were collected with a sterile cotton swab and transferred to a sterile tube. The suspensions were standardized by counting the conidia in a hemocytometer to 2.5×10^6 conidia/mL. The suspension was diluted 1:10 with RPMI to obtain final inoculums of 2.5×10^5 conidia/mL.

The total of 20 µL of each compound concentration and 20 µL of fungal suspension were added to each plate for the negative control, but 100 µL of broth was added to the positive control. The plate was sealed with aluminum foil and incubated at 35°C for 24 hours at humid conditions. The MIC was determined by using ELISA reader at 530 nm for the yeast species and visually for mold species after

24 hours of incubation as the lowest concentration of drug that resulted in 50% inhibition of growth, the data of all the analysis compared to that drug-free growth control.

III. RESULT AND DISCUSSION

During the analysis it found that melting points of the complexes were higher than that of the 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone ligand its Indicating that the complexes are more stable than the ligand. The chemical equations showing the preparation of its ligand and its metal (II) complexes.

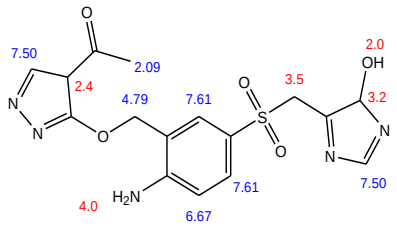
The spectral analysis were performed initially with electronic absorption spectroscopy and it was carried out by the instrument Shimadzu -1601 using alcohol as solvent The electronic spectral data of the 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone ligand and its metal complexes are given in the experimental part of unit and it showing that the 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone ligand has three bands at λ max (nm) 223.4, 270.2 and 358 nm respectively, in which the bands at 223.4 nm is due to the π–π∗ transition in ring, next for the band appearing at 270.2 nm is count to n–π∗ transition of nonbonding electrons present on the $–NH_2$, and the band at 358.1nm is due to n–π∗ transition of the Ar-OH group. The UV-Vis spectra of the 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone metal complexes are presented in the similar absorption spectra as the ligand, but it have either a blue shift or red shift.

FT-IR (KBr, disc cm−1) 3455.6 υ(O-H), 1599.7, 1213.9 υ(C-O), 695.8 υ(H2O), 536.1 υ(Re-N), 490.8 υ(Re-O) in which stretching 1601 cm^{-1},1595 cm^{-1} and 1599.7 cm^{-1} occurs for metal-NH_2 bonding in complexes, respectively. This indicated that the coordination of ligand through the nitrogen.

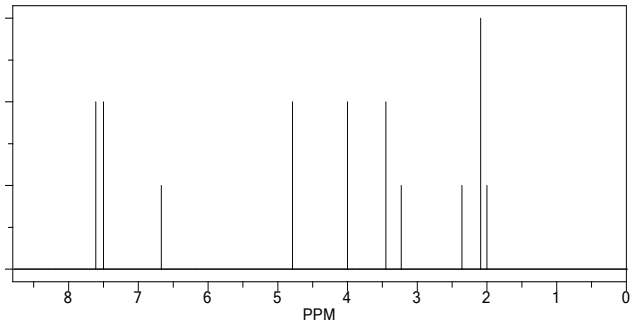
Re(II) complexes of 1 -{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone given least values of MIC against Gram-positive cocci strains: *S. aureus*, *S. pyogenes*, *E. faecalis*, *K. pneumoniae*, *S. typhi*, and *E. coli* and reveled that complexes are most active.

Re(II) is more inhibition efficiency and it also found that the imidazole and the pyrazol ring is in constitution with the one α,β-unsaturated carbonyl group which leads to electronic and steric interactions between the substituents, so furthermore; the large size of the drug ligand, the presence of an electron donating group it increases the direct resonance conjugation between the amino group and the hetro-cyclic rings which might be the reason for the low antimicrobial and antifungal activity of the complexes. Therefore, the in activity of Re(II) complex found more efficient.

ChemNMR H-1 Estimation



Estimation Quality: blue = good, magenta = medium, red = rough



Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH3	2.09	0.86	methyl
		1.23	1 alpha -C(=O)C
CH	2.4	1.50	methine
		0.86	1 alpha -C=O
		?	2 unknown alpha substituent(s)
			-> 2 increment(s) not found
CH	7.50	7.50	aldimine
CH2	4.79	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		2.20	1 alpha -O
CH	6.67	7.26	1-benzene
		-0.07	1 -C-O
		-0.80	1 -N
		0.28	1 -S(=O)(=O)-R
CH	7.61	7.26	1-benzene
		-0.07	1 -C-O
		-0.25	1 -N
		0.67	1 -S(=O)(=O)-R
CH	7.61	7.26	1-benzene
		-0.07	1 -C-O
		-0.25	1 -N
		0.67	1 -S(=O)(=O)-R
CH2	3.5	1.37	methylene
		2.08	1 alpha -S(=O)(=O)
		?	1 unknown alpha substituent(s)
			-> 1 increment(s) not found
CH	7.50	7.50	aldimine
CH	3.2	1.50	methine
		1.73	1 alpha -O
		?	2 unknown alpha substituent(s)
			-> 2 increment(s) not found
OH	2.0	2.00	alcohol
NH2	4.0	4.00	aromatic C-NH

Figure 3: ^{1}H-NMR 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone

In this present investigation we found that how these metal drug complexes can be used as antifungal agent. As variation in ligands; so, proper selection of drug and metal may be antifungal and anti-microbial agents. Therefore, the present result and analysis may open a new area of research in field of bio-inorganic chemistry.

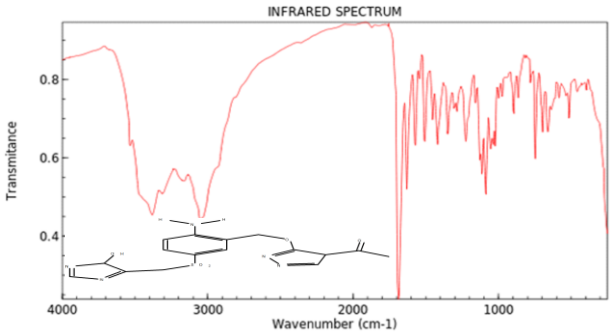


Figure 4: IR Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone

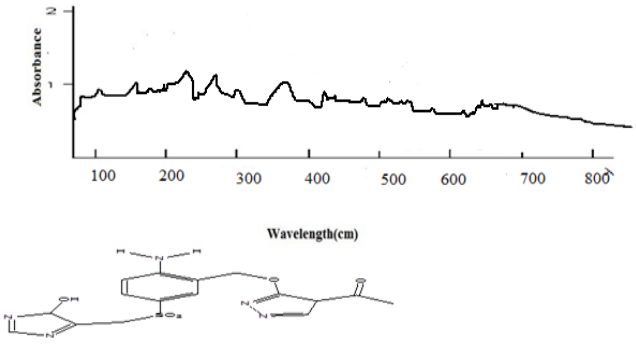


Figure 5: UV-VIS Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone

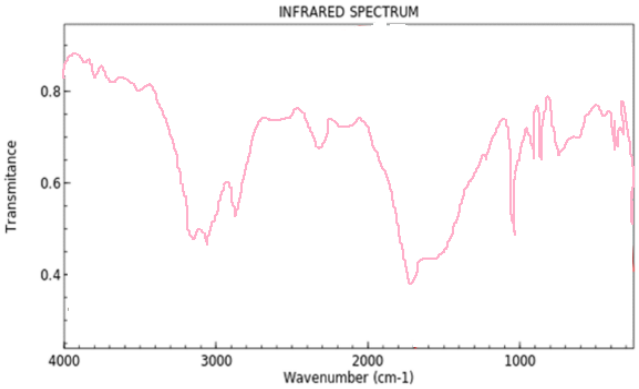


Figure 6: IR Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone Re (II) complex

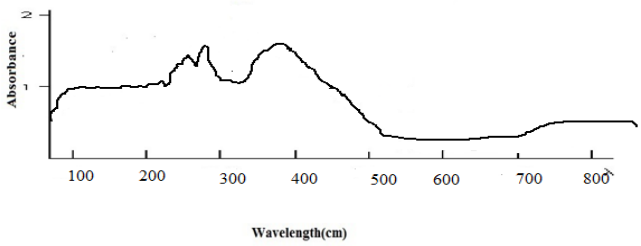
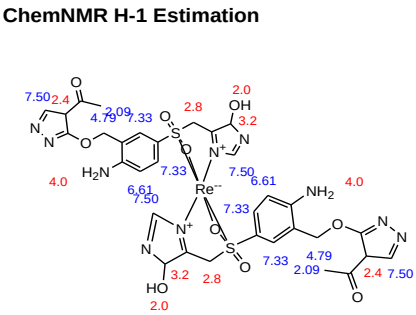
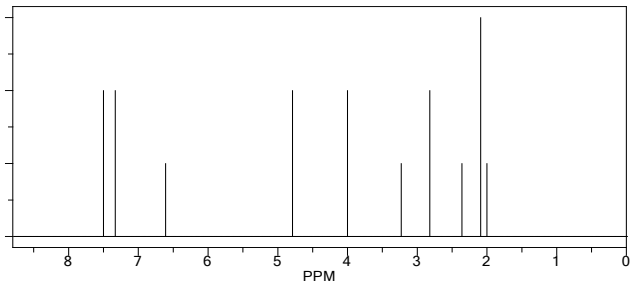


Figure 7: UV-VIS Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone Re (II) complex





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		-0.25	1 -N
		0.39	1 -S(=O)-R
CH	7.33	7.26	1-benzene
		-0.07	1 -C-O
		-0.25	1 -N
		0.39	1 -S(=O)-R
CH2	2.8	1.37	methylene
		1.45	1 alpha -S(=O)-1:C*C*C*C*C*C*1
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CH	7.50	7.50	aldimine
CH	3.2	1.50	methine
		1.73	1 alpha -O
		?	2 unknown alpha substituent(s)
			-> 2 increment(s) not found
OH	2.0	2.00	alcohol
NH2	4.0	4.00	aromatic C-NH
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		-0.80	1 -N
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		0.39	1 -S(=O)-R
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		1.45	1 alpha -S(=O)-1:C*C*C*C*C*C*1
		?	1 unknown alpha substituent(s)
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CH	7.50	7.50	aldimine
CH	3.2	1.50	methine
		1.73	1 alpha -O
		?	2 unknown alpha substituent(s)
			-> 2 increment(s) not found
OH	2.0	2.00	alcohol
NH2	4.0	4.00	aromatic C-NH

Figure 8: ^{1}H-NMR Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone Re (II) complex

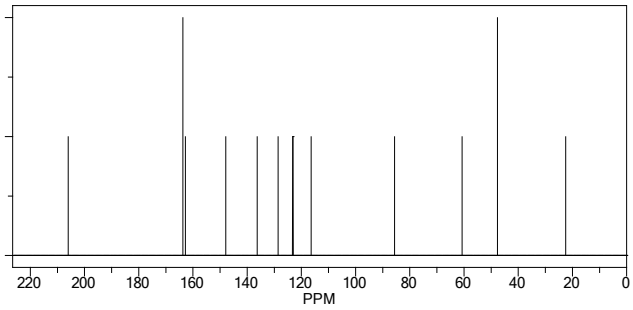

Figure 9: ^{13}C-NMR Spectra of 1-{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone Re (II) complex

IV. CONCLUSION

In this study, the synthesis of a new macro-cyclic derivative of pyrazol and imidazol is count as the 1 -{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone where, the spectroscopic analysis of data were investigated ligand complexes with Cu(II) in DMSO and ethyl alcohol.

The Electrochemical, IR, NMR, and MS analysis have been confirmed the unexpected and possibilities of metal complex formation by a new organic ligand that is 1 -{3-[2-Amino-5-(5-hydroxy-5H-imidazol-4-ylmethanesulfonyl)-benzyloxy]-4H-pyrazol-4-yl}-ethanone. The metal ligand ratio in complex is found stable 1:2 in the solvent. Furthermore, complex is attracted to nitrogen atoms and oxygen atoms. The NMR ^{1}H and ^{13}C is also revealed that the complex have tetrahedral structure and it also containing the biological activity.

V. REFERENCES

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