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Synthesis and Pharmacological Action of bis(2-hydroxynaphthalene-1-carbaldehyde) oxaloyldihydrazone

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Abstract:- Manganese (II) complex of bis(2-hydroxynaphthalene-1-carbaldehyde) oxaloyldihydrazone has been synthesized. In view of the data obtained from the elemental analysis (CHNM), spectral (IR, ^{1}H-NMR, mass, UV-Vis.), magnetism and thermal measurements, the structure of ligand / complex has been speculated. The ligand coordinated to the manganese ion in bi-dentate manner forming mononuclear tetrahedral complex. The free oxaloyldihydrazone and its manganese (II) complex were evaluated for their antimicrobial activities against gram-positive and gram-negative bacteria as well as fungi. The obtained results uncovered the ability of the free ligand to inhibit the growth of chosen bacteria. Whereas, the proliferation hindrance towards bacteria was slightly enhanced upon coordination with the manganese (II) ions. With respect to antifungals activity, the investigated compounds revealed insensitivity.

Keyword:- *Oxaloyldiydrazone Complex; Structural Studies; Pharmacological Application.*

I. INTRODUCTION

A ligand framework having electronegative atoms like N and O improves the coordination outcomes. Among nitrogen-oxygen giver ligands, the hydrazones have an extraordinary spot because of broad applications for medication plan, organocatalysis and insecticides [1-3]. Hydrazone which are recently recognized as polyfunctional ligand has high tendency to form stable metal complexes with d-block transition metal ions like Mn(II) due to availability of donor sites and its complexing capability through keto-enol tautomerism [4]. Despite, a series of transition metal complexes [M= V(IV), Cu(II), Mn(II), Ni(II), Pd(II), Co(II) and ruthenium(II)] of hydrazones were investigated [5,6], little papers have been reported for aryl oxaloyldihydrazones complexes [7,8]. Maybe, this emerges from the poor dissolvability of oxaloyldihydrazones ligands in most common used organic solvents. Actually, some complexes of bis(2-hydroxynaphthalene-1-carbaldehyde) oxaloyldihydrazones with Cu(II), Ni(II) and Pd(II) have been reported elsewhere [8-10] and this study is an expansion of past work. In terms of biological activity, hydrazones including oxaloyldihydrazone and their metal complexes present a wide scope of pharmacological applications as antitumoral, antimicrobial and antiviral agents [8,11-13]. Coordination compounds got from arylhydrazones have been reported to act as enzyme inhibitors and are helpful in pharmaceutical field [14]. Broad investigations have uncovered that the lone pair on nitrogen atom of the azomethine group in hydrazones is liable for the biological and chemical activity [14,15]. Throughout the years a large number of organic/inorganic compounds are prepared to discover potential chemotherapeutic agent to battle pathogenic microorganisms. In this regard, complexes of Co(II), Ni(II) and Fe(III) with ampicillin and chloramphenicol were synthesized and revealed that the activity of the metal complexes was more strong antibacterial agent than the original drugs [16].

In continuation of ongoing reports on some oxaloyldihydrazones and their chelates [9,10], the present work portrays synthesis and structural characterization investigations of Mn(II) complex with oxaloyldihydrazone as ligand. Antimicrobial activity of the ligand and its manganese complex have been researched to show the plausibility of using them in pharmacology science.

II. EXPERIMENTAL

A. Materials and techniques

2-hydroxynaphthalene-1-carbaldehyde, manganese (II) acetate tetrahydrate and oxalic dihydrazide were acquired from Sigma-Aldrich. Solvents were utilized without any more refinement considering their highest purity. Elemental analysis, thermal (TG) and spectral (FT-IR, Mass, UV-Vis.) measurements were carried out as published [9]. The ^{1}H-NMR spectra were obtained using a Varian mercury VX-300 NMR spectrometer at 300 MHz in DMSO-d_6. Tetramethylsilane (TMS) was utilized as reference and chemical shifts were given in δ (ppm). Employing Faraday's strategy, effective magnetic moments (μ_{eff}) of the complexes were estimated at room temperature (RT).

B. Preparations

- *Isolation of ligand (L)*

Bis(2-hydroxynaphthalene-1-carbaldehyde) oxaloyldihydrazone was prepared by the recipe published in Ref. 9. Oxalic dihydrazide (0.01 mol, 1.181 g) was first dissolved in 40 mL distilled water by heating on hot plate and 30 mL absolute ethanol was included. The subsequent hot solution of oxalic dihydrazide was mixed with hot absolute ethanolic solution of the chosen aldehydes (keeping the molar proportion at 1 hydrazide : 2 aldehyde). Precipitation of hydrazone was observed during the

increment of aldehyde solution. The obtained mixture was refluxed for 3 h. The subsequent precipitate was separated on hot by filtration, washed first by water to avoid abundance of dihydrazide and after that by absolute ethanol to eliminate any excess of aldehyde, and dried at 80 ˚C for 2 h inside an electric oven. The chemical formula and molecular structure of the resulting hydrazone was detected from the elemental analysis and spectral (IR, ^{1}H-NMR) data, (Table 1, m.p. of ligand > 300). Furthers, mass spectra of ligand revealed molecular ion peaks (M^+) at m/z (found/calcd.) = 327.1/426.4 which matches with the proposed formulas.

➢ *Isolation of complex*

Manganese (II) complex was prepared by a direct reaction between the ligand and the metal acetate salts as follows. Dihydrazone (0.564 mmol, 0.2 g) was dissolved first in hot DMF (35 mL) and afterward 40 mL methanol was included. From that point, 25 mL methanolic solution of Mn(II) acetate salt was added gradually to the hydrazone solution in 1L:2M molar proportion. The subsequent mixture was refluxed under heating for 3 h and afterward sifted on hot. The desired precipitate was washed by methanol and left in air overnight. To expel any trace of DMF solvent, the complex was washed thoroughly with methanol and acetone, separately and respectively, sifted again and lastly dried at 80 ˚C in an electric oven for 4 h (m.p. of manganese (II) complex > 300).

C. Antimicrobial activity

The susceptibility tests were performed by NCCLS proposals (National Committee for clinical lab Standards ,1993). Assessments with respect to the restraint zone were done by the well diffusion strategy [19]. The inoculum suspension was prepared from colonies grown overnight on an agar plate, and inoculated into Mueller-Hinton broth. A sterile swab was inserted in the suspension and employed to inoculate Mueller-Hinton agar plates. The species were dissolved in dimethyl sulfoxide (DMSO) with various concentrations (2.5, 5, 10 mg/ml). The inhibition zone was estimated at 37 ºC after 24h. Controls utilizing DMSO were satisfactorily done. The inoculum suspension was blended from provinces become medium-term on an agar plate, and immunized into Mueller-Hinton stock. A sterile swab was submerged in the suspension and used to vaccinate Mueller-Hinton agar plates. The examples were disintegrated in DMSO.

III. RESULTS AND DISCUSSION

The analytical and physical results of the ligand (L) and its related Mn(II) complex ((Mn-L) are collected in Table 1.

3.1. IR Spectroscopy

The structures of chosen oxloyldihydrazone was validated on the premise: (1) $\nu(OH)_{naphthoic}$, ν(NH) and ν(C=O) for L are situated at 3476, 3166 and (1705(m) +1660(v.s)) cm^{-1}, respectively. (2) The ν(C=N) was seen at 1621 showing the interaction of dihydrazide with selected aldehyde. (3) Observation of both ν(NH) and ν(C=O) in the IR spectra of the two ligand (simultaneously) proved the existence of keto form. (4) Appearance of ν(C=O) at two positions in case of L (1660,1705 cm^{-1}) alludes to establishment of mixed [trans(staggered)-structure + cis(syn/anti-cis)-structure] isomers for first ligand, Fig. 1 [20].

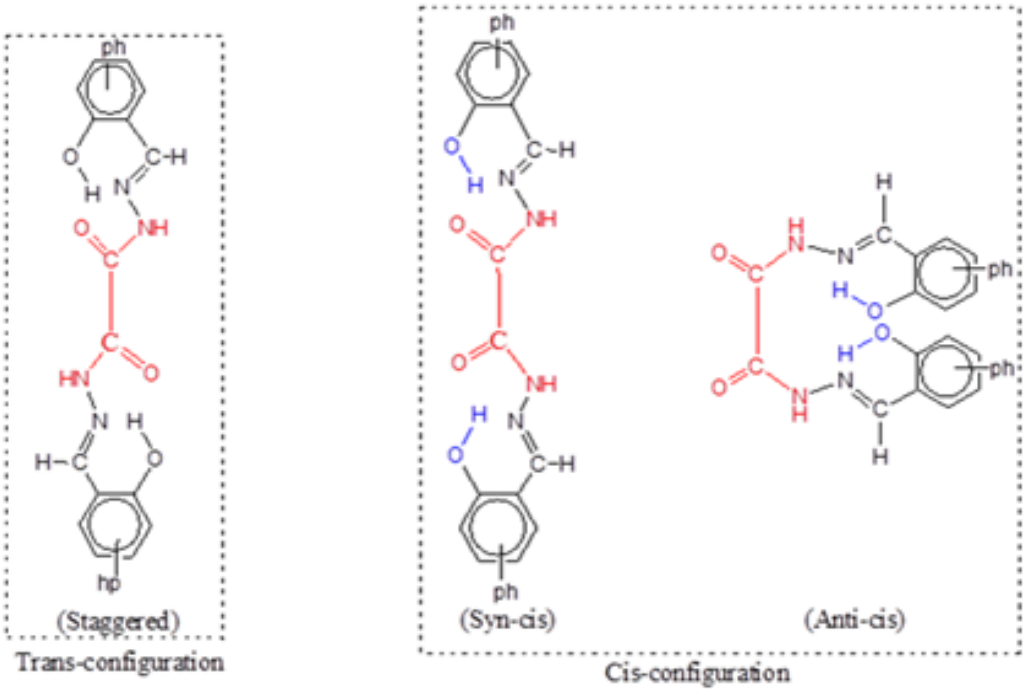

Fig. 1:- Proposed structures of oxaloyldihydrazone.

This depends on the cis isomer is absorbed at higher stretching frequency compared to the trans one owing to the field effect criteria [9]. The band at 1660 cm^{-1} demonstrates the presence of trans –form while the band centered at 1705 cm^{-1} describes cis form. Virtually, NMR spectroscopy gives a satisfactory agreement with this view as illustrated later. (5) Naphthoic OH of L was appeared at 3476 cm^{-1} and enolic OH was seen in BAO at 3227 cm^{-1}. (6) The bands located at 1287 cm^{-1} is associated to ν(C-O) of C-OH (in L) groups [21]. (7) Otherwise, the aromatic (C=C) group in ligand is situated in the area 1400-1600 cm^{-1} however $\delta(CH)_{out\ of\ plane}$ was observed in L at 741.

The IR spectra of the Mn(II) complex has been checked up and contrasted with those of related ligands. The method of chelation and structure was assured by the following actualities: (1) Disappearance of ν(NH) with recognizable of ν(C=O) at 1655 cm^{-1} in the complex give an indisputable proof to the coordination of metal ion with deprotonated NH group. (2) Doubtless the positive shift watched for ν(C-O) vibration (L:1287→complex: 1299 cm^{-1}) give some insight to deprotonation of both naphthoic (OH) groups during their coordination however remarking $\nu(OH)_{naphthoic}$ at lower value (3186 cm^{-1}) points to the existence of naphthoic (OH) in H-bonding. (3) Splitting of the azomethine band in free ligand with its shift (ligand: 1621 cm^{-1}: complex: 1600, 1618 cm^{-1}) justify the sharing of this group in coordination where two dissimilar azomethine groups are formed, Fig. 4 [22]. This supposition is boosted from the perception of $\nu(OH)_{naphthoic}$ and $\nu(OH)_{enolic}$ at 3186 and 3342 cm^{-1}. The lower offset associated with $\nu(OH)_{naphthoic}$ demonstrated the presence of H-bonding between the azomethine nitrogen and naphthoic OH group. (4) Existence of broad band at 3379 cm^{-1} in the complex is appointed to the overlapped coordinated/crystalline water molecules. The presence of new $\nu(M\text{-}O_{naphthoic})$ in Mn-L spectra at 567 cm^{-1} declares the formation of Mn-L bond.

Formula	Symbol	Color	Elemental Analyses Found (calcd.)%			
			C	H	N	M
$C_{24}H_{18}N_4O_4$	L	Yellow	68.4 (67.7)	5.0 (4.3)	12.7 (13.2)	-
$[Mn(BHO\text{-}H)(H_2O)_2].0.5H_2O$	Mn-L	Brown	54.2 (54.9)	4.3 (4.2)	10.5 (10.5)	10.3 (10.7)

Table 1:- Physical and analytical data of the oxaloyldihydrazone (L) and its related Mn(II) complex.

3.2. NMR Spectroscopy

The proton NMR spectra of the ligands showed signals at various positions. In L ligand: 12.8(NH, s), 12.6(OH, s), 9.7(CH=N, s), 6.5-8.5 (aromatic protons, m) ; In BAO: 12.3(NH, s), 11.9(OH, s), 8.9(CH=N, s), 6.8-8.5(aromatic protons, m), 3.93(OCH_3, s). Vanishing of –OH and –NH protons upon supplying of D_2O affirmed the right assignment of these groups in the ligand spectrum. The ligand is in harmony with syn-cis- or staggered conformation as the δNH, δOH and δCH=N, resonances, each showed up as a singlet [23]. But which of conformation is true? In fact, IR data information responded to this inquiry as referenced above and guaranteed that the staggered configuration.

3.3. UV-Vis. spectra and magnetic investigations

The absorption bands of the oxaloylhydrazone and its metal complex in Nujol mull have been assigned (Table 2). In addition to the ligand bands, manganese complex demonstrated d→d transitions from which the proposed geometry (tetrahedral) was predicted [24]. Effective magnetic moments ($\mu_{eff.}$, Table 2) of the manganese (II) complex, estimated at 6 ampere supported their structure obtained from the electronic information [24]. The μ_{eff} values estimated at room temperature were seem to be closed to spin only value and alluded to high spin complexes. A consequence of the much smaller value of Δ_t results in (nearly) all tetrahedral complexes being high spin.

3.4. Thermogravimetric investigation

Thermal disintegration examine of the synthesized consequential solid complexes have been performed which are exploited to distinct the type and number of solvent molecules in the complex structure as well as the nature of the final products (Table 2). The TG thermograms of Mn-L complex exhibited five stages of decomposition, concerned to the gradual disintegration of the complex with formation of metallic residue as final products. TG curves illustrated that Mn-L begin to decompose at 300 °C, signifying the Mn-L is more stable.

In the light of the prior outcomes, the manganese complex is anticipated to have structures presented in Fig. 2.

Sample	Band position (nm)	Assignment	Configuration	$\mu_{eff.}$ (B.M.)	TG		
					Temp. °C	Assignments	% Found/calcd.
L	230-270 300-330 330-360 360-380 380-420	$\pi\rightarrow\pi^*$(Phenyl) $\pi\rightarrow\pi^*$(C=O) $\pi\rightarrow\pi^*$(C=N) $n\rightarrow\pi^*$(C=O) $n\rightarrow\pi^*$(C=N)	-	-	-	-	-
Mn-L	480 590	$^6A_{1g}(S)\rightarrow{}^4T_{2g}(G)$ $^6A_{1g}(S)\rightarrow{}^4T_{1g}(G)$	Tetrahedral, T_d	4.7	45-150 620-800	$1/2H_2O_{crystalline}$ formation of $2(MnO+MnCO_3)$ mix.	2.0/1.7 70.8/71.0

Table 2:- Electronic spectral, magnetic moment and thermal data of L / Mn(II) complex.

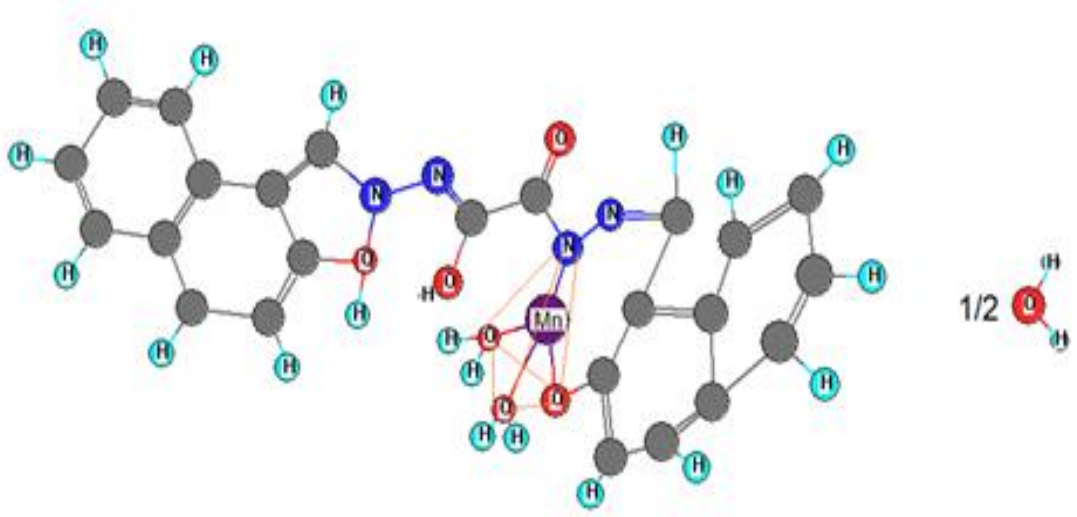

Fig. 2:- Speculated structure of manganese (II) complex.

3.6. Pharmacological evaluation

The antibacterial action of ligands (L) and its complex against gram-positive (Staphylococcus aureus, Bacillus subtilis) and gram-negative (Escherichia coli, Proteus) bacteria are shown in Table. 3. Metal complex showed higher activity in comparison to the free ligand towards all the tested strains. The higher action of metal complex can be illustrated in the light of chelation hypothesis. On chelation, the polarity of the metal ion will be diminished to a more prominent degree because of the interaction between the ligand orbitals belong to donor groups and the positive charge of the manganese (II) ion. Furthermore, complexation process will induce the delocalization of p-electrons over the chelating ring and enhances the penetration of the complex into lipid membranes and blocking of the metal binding sites in the enzymes of bacteria.

Sample / Tested microorganisms	L	Mn-L	Control
FUNGI			*Ketoconazol*
Aspergillus fumigatus (RCMB 002008)	NA	NA	17
Candida albicans RCMB 005003 (1) ATCC 10231	NA	NA	20
Gram Positive Bacteria:			*Gentamycin*
Staphylococcus aureus (RCMB010010)	11	12	24
Bacillus subtilis RCMB 015 (1) NRRL B-543	10	11	26
Gram Negatvie Bacteria:			*Gentamycin*
Escherichia coli (RCMB 010052) ATCC 25955	NA	8	30
Proteus vulgaris RCMB 004 (1) ATCC 13315	NA	7	25

Table 3:- Antimicrobial activity of L and its Mn(II) complex.

- Mean zone of inhibition in mm beyond well diameter (6 mm) produced on a range of pathogenic microorganisms.
- The test was done using the diffusion agar technique, Well diameter: 6.0 mm (100 µl was tested),
- RCMB: Regional Center for Mycology and Biotechnology.
- Ketoconazole (100 µg/ml) = positive control for fungi.
- Gentamycin (4µg/ml) = positive control for bacteria.

*NA = No activity.

The sample was tested at 10 mg/ml concentration. The metal complex additionally influences the breath process of the cell and hence obstructs the synthesis of proteins restricting further growth of the organisms [25]. The other factors, which additionally increment the action, are solubility and bond length between the metal and ligand [26]. With respect to antifungals activity, the results revealed insensitivity of the compounds towards the tested fungi.

IV. CONCLUSION

Oxaloyldihydrazone and its mononuclear manganese (II) complex can be prepared and isolated in pure form. The conventional reflux strategy might be utilized for this reason. Contrasting of theoretical and experimental percentages of elemental analyses demonstrates that the compositions of the isolated manganese (II) complex matches well with the proposed formulae. FT-IR and UV–Vis. spectroscopy, magnetism besides the change of ligand color upon complexation affirmed the formation of the desired manganese complexes. The Mn(II)-bis(2-hydroxynaphthalene-1-carbaldehyde) oxaloyldihydrazone has tetrahedral conformation. For antibacterial action against four microorganisms, the outcomes suggested that the complex is more active and might impede protein creation of certain microorganisms.

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