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Anti-tubercular Activity of Dioxo Molybdenum (VI) Metal Complexes of 2-((E)-(1,5-Dimethyl-2-phenyl-3-((Z)-(quinoline-8-ylimino) methyl)-2,3-dihydro-1H-pyrazole-4-ylimino) methyl) phenol

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ABSTRACT

Dioxomolybdenum(VI) complexes tetradentate ligand 2-((E)-(1,5-dimethyl-2-phenyl-3-((Z)-(quinoline-8-ylimino)methyl)-2,3-dihydro-1H-pyrazole-4-ylimino)methyl)phenol was synthesized by conventional method. The ligands and their MoO_2^{2+} complexes have been characterized on the basis of elemental analysis, electronic. I.R., ^1H and ^{13}C-NMR spectral method, by their spectral studies, octahedral geometry of the complex has been proposed. On evaluation of in-vitro antitubercular activity of the ligand and dioxo Mo(VI) metal complex found that complex is more potent antitubercular agent than ligand.

Keywords: anti-tubercular agent, dioxo Mo (VI) metal complex

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INTRODUCTION

Molybdenum is an essential component of the nitrogenase enzyme, some vitamins, mineral supplements, and a cofactor for many enzymes required for synthesis of proteins. A variety of chemical reactions has been reported to be catalyzed by coordination compounds of molybdenum [1–3]. The complexes of molybdenum have also been studied as a model for molybdenum containing enzymes [4].

Kumar et al. synthesized the dioxomolybdenum (VI) complexes with 2-imidazolyl mercapto aceto hydrazine and ESR spectral data suggested the distorted octahedral geometry of complex. Furthermore, the ligand and dioxomolybdenum (VI) complexes were screened *in vitro* for their antibacterial properties against *Salmonella paratyphi* and *Bacillus cirroflagellosus*, which suggested that the dioxomolybdenum (VI) complexes were potent bactericides than the ligand [5].

The complexes of molybdenum with dextrofloxacin and levofloxacin antibiotic leads to the formation of green colored Mo–dextrofloxacin and yellow colored Mo–levofloxacin complexes. The microbial evaluation was made by well diffusion method against two bacterial strains, *S. aureus* and *E. coli*. It was found that the antibacterial action of Mo–dextrofloxacin and Mo–levofloxacin was substantially higher than the dextrofloxacin and levofloxacin alone against *S. aureus*, while no action was observed against *E. coli* [6]. Kehinde *et al*. synthesized the Mo(V) and VO(II), metal complexes of (E)-N′-(2,5-dimethoxylbenzylidene)nicotinohydrazide.

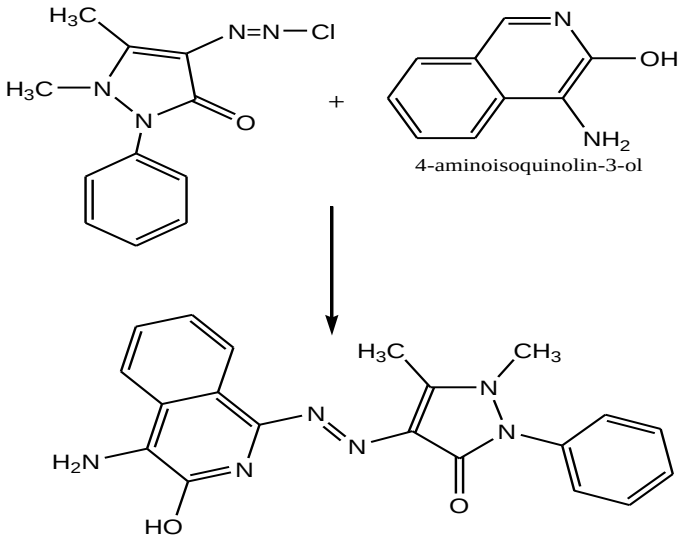
An octahedral geometry was suggested for Mo(V) complexes while tetrahedral pyramidal for VO(II) complex. *In vitro* anti-mycobacterial activity study of the compounds was evaluated against Mycobacterium tuberculosis, H37Rv, by using micro-diluted method. The metal complexes of Mo(V) displayed higher activity than the ligand and isoniazid (INH) drug [7].

The present paper exploring the synthesis and spectral characterization of dioxomolybdenum (VI) complex of tetradentate ligand 2-((E)-(1,5-dimethyl-2-phenyl-3-((Z)-(quinoline-8-ylimino)methyl)-2,3-dihydro-1H-pyrazole-4-ylimino)methyl)phenol and evaluation of their antitubercular activity against Isoniazid resistant strains of *Mycobacterium Tuberculosis*

EXPERIMENTAL

Synthesis of Ligand, 2-((E)-(1,5-Dimethyl-2-phenyl-3-((Z)-(quinoline-8-ylimino) methyl)-2,3-dihydro-1H-pyrazole-4-ylimino) methyl) phenol (MOPQHP)

25 ml, 50 m mol of 8-amino quinolin-3-ol was dissolved in 45 ml of 10% NaOH solution. The solution was cooled below 5°C in an ice bath followed by the direct addition of about 25 g of crushed ice. The cold diazonium chloride solution was added very slowly to the solution of 8-amino quinolin-3-ol with vigorous stirring. The color of solution become brown red and a solid product separated slowly. After the addition of entire amount of diazo compound. The mixture was allowed to stand in a bath for about 30 minutes with occasional stirring. The solid product obtained was then filtered under gentle suction, washed well, with cold water and recrystallized from alcohol [8].



Preparation and Isolation of Dioxo Molybdenum (VI) Complexes of MOPQHP

Preparation of $Mo(acac)_2$

The complex was prepared by the modification of literature method. $(NH_4)_6Mo_7O_{24}$ was dissolved in 100 ml water and acetylacetoacetate (acacH, 40 ml) was added. the pH of solution was adjusted to 3.5 using HNO_3 and a solid began to precipited after 1.5 hours yellow $Vo(acac)_2$ was isolated by filtration, washed with water, ethanol and dried in vaccum [9].

Synthesis of Dioxo-Molybdneum (VI) Complexes of Ligand MOPQHP

2 m mol $Mo(acac)_2$ was dissolved in minimum quantity of hot conc. HCl. This solution was added to a hot methanolic

solution of 2 m, mol of ligand with vigorous shaking.

The reddish brown solution obtained was concentration suction filtered, washed several times with aqueous methanol and finally with dry ether, it was then dried over P_4O_{10} in vacuum. The reaction was refluxed in 90% methanol [10].

The dioxo molybdneum(VI) complexes of ligands were prepared according to the following reaction.

$$2[MoO_2(acac)_2] + 2HL + 4\,H_2O \rightarrow [\{MoO_2(OH)_2\}(HL)_2] + 4acacH$$

HL = MOPQHP

RESULT AND DISCUSSION

Elemental Analysis: Analytical data indicate 1:1 metal ligand stoichiometry for all the dioxo-molybdneum (VI) metal complexes (Table 1).

Molar Conductivity and Magnetic Moment Studies

The dioxo Mo (VI) metal complex show its molar conductivity in the range of 9–12 $Ohm^{-1}cm^2mol^{-1}$ and its magnetic moment is lie in the range of 1.81 B.M. which proposed octahedral geometry (Table 2) [11, 12].

Table 1. *Elemental analysis data of the ligand and dioxo Mo(VI) metal complexes.*

Ligand/complexes	C% Calc./found	H% Calc./found	N% Calc./found	Metal % Calc./found	Mol. wt
$C_{20}H_9N_5O_2$	68.37/68.39	2.56/2.54	19.94/19.90		351
$(C_{20}H_8N_5O_4)Mo$	50.25/50.35	1.67/1.65	14.65/14.52	21.26/21.22	477

Table 2. *Analytical data of dioxo Mo(VI) metal complexes.*

Ligand/metal complexes	Solubility	Molar conductivity ($Ohm^{-1}cm^2\ mol^{-1}$)	Magnetic moment (BM)
$sC_{20}H_8N_5O_2$	DMSO, DMF	–	–
$(C_{20}H_8N_5O_4)Mo$	DMSO, DMF	12	1.81

Electronic Spectral Studies

The Electronic spectra of the dioxomalybdenum (VI) complex characterized by three d→d transitions $d_z^2 \rightarrow d_{x^2-y^2}$ and $d_{xy} \rightarrow d_{x^2-y^2}$ and $d_{xy,yz} \rightarrow d_{x^2-y^2}$ in the rage of 11,135-12,108 cm^{-1}, 8,621-19,416 cm^{-1} and 21,413-27,322 cm^{-1} proposed octahedral geometry [13].

I.R. Spectral Studies

The shifting of band appeared at 1535–1515 cm^{-1} upto 25 cm^{-1} suggested that nitrogen atom of quinolone ring participate in bonding with metal. The characteristic band of carbonyl group of pyrazolone ring decrease from 1600 cm^{-1} show involvement of oxygen atom of carbonyl group with dioxo Mo(IV) metal. The appearance of medium intensity band at 485- 495 cm^{-1} suggested the involvement of quinolone ring N-atom in bonding.

The disappearance of band appeared at 3000–3200 cm^{-1}suggested the involvement of –OH group in bonding via deprotonation.

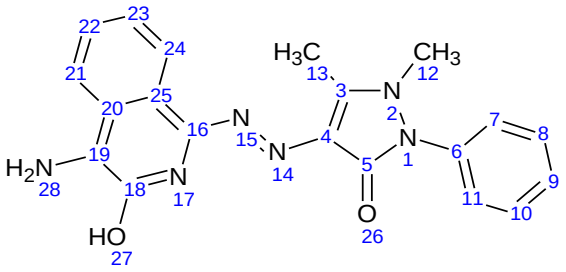
The band appeared in the region 915 cm^{-1} strongly evidenced the symmetric [ν_s(O=Mo=O)] and asymmetric [ν_{as}(O=Mo=O)] vibrations which suggested that MoO_2^+ moiety exist in *cis-form* in complex (Table 3) [14].

Table 3. *IR spectral frequencies (cm^{-1}) of MOPQHP and dioxo molybdenum (VI) metal complex.*

Ligand/complex	Quinoline ring vibrations		N=N-	-OH	NH_2	C=O	(O=Mo=O)	
	C=C	C=N					ν_s	ν_{as}
$C_{20}H_9N_5O_2$	1535	1320	150	3200	1353	1600		
$(C_{20}H_8N_5O_4)Mo$	1525	1285	1585	2955	1353	1575	910	925

^{1}H NMR Spectral Studies

The ^{1}H MNR spectra of Ligand and its corresponding dioxo-Mo(VI) metal complexes has been recorded in $CDCl_3$. The spectra of dioxo Mo(VI) metal complex show disappearance of –OH group protons signal (δ 5.0) which indicate that ligand is coordinated with metal by the deprotonation of –OH group but the $–NH_2$ group proton signal (δ 4.0) remain same in complex spectra show the presence of free amino group in complex [15]. On further comparing the ^{1}H NMR spectra of ligand and dioxo Mo (VI) metal complex a slight downfield shifting is appeared in multiplet of signal of protons at δ 7.4–7.8 ppm at position 21, 22, 23 and 24 up to δ 6.9–7.2 which suggested that N-atom of quinoline ring is participate in coordination with metal (Table 4) [16].



Numbering of Ligand

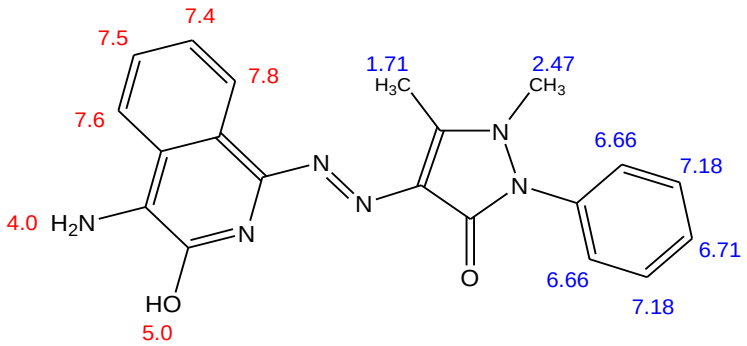
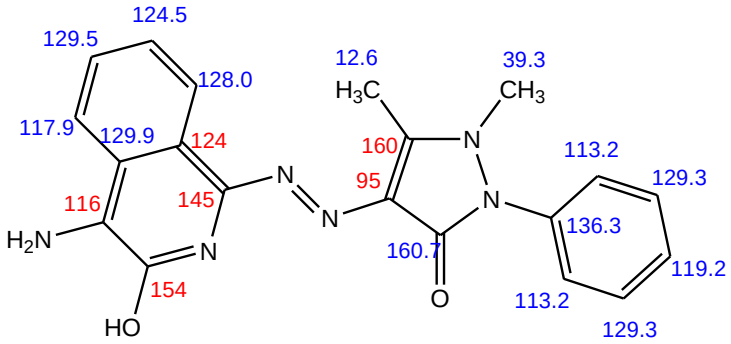


Table 4. *^{1}H NMR spectral data of ligand MOPQHP and dioxo molybdenum (VI) metal complex.*

Ligand/complex	Chemical shift in δ/ ppm					
	Quinoline ring protons	$–NH_2$	–OH	Aromatic protons	$–C–CH_3$	$–N–CH_3$
$C_{20}H_9N_5O_2$	7.6, 7.5, 7.4, 7.8	4.0	5.0	6.66 7.18 6.71	1.71	2.47
$(C_{20}H_8N_5O_4)Mo$	7.2, 7.1, 6.9, 7.5	4.0		6.66 7.18 6.71	1.71	2.47

^{13}C NMR Spectral Studies

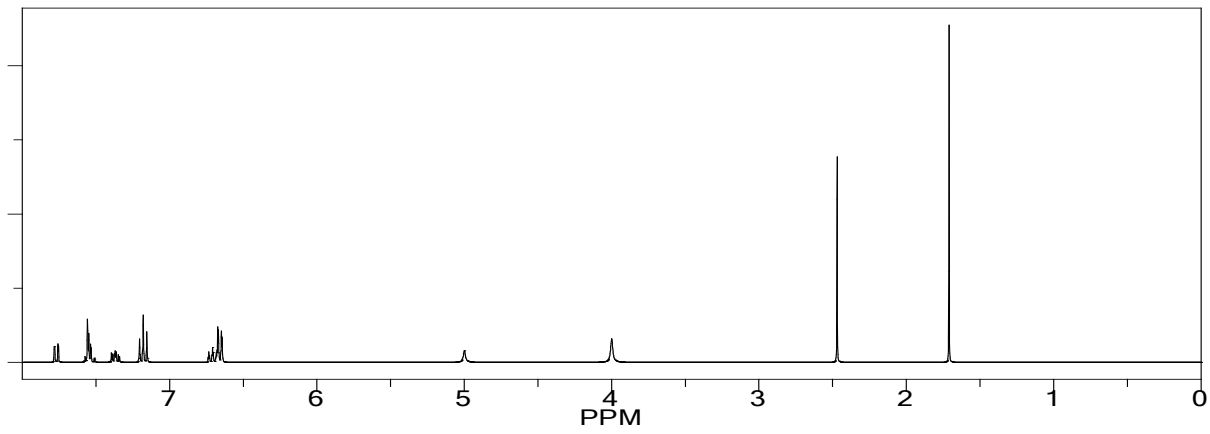
The signal of C_5 atom of ligand shift downfield upto 1.5 ppm from 160.7 ppm suggested the involvement of oxygen atom of C=O group in bonding. The signal of C_{18} atom shift downfield from 154 ppm upto 1.5 ppm indicative the involvement of N-atom of quinolone ring while the downfield shifting of C_{16} atom signal from 145 ppm suggested the involvement of -OH group in coordination with dioxo Mo(VI) via deprotonation (Table 5) [17].



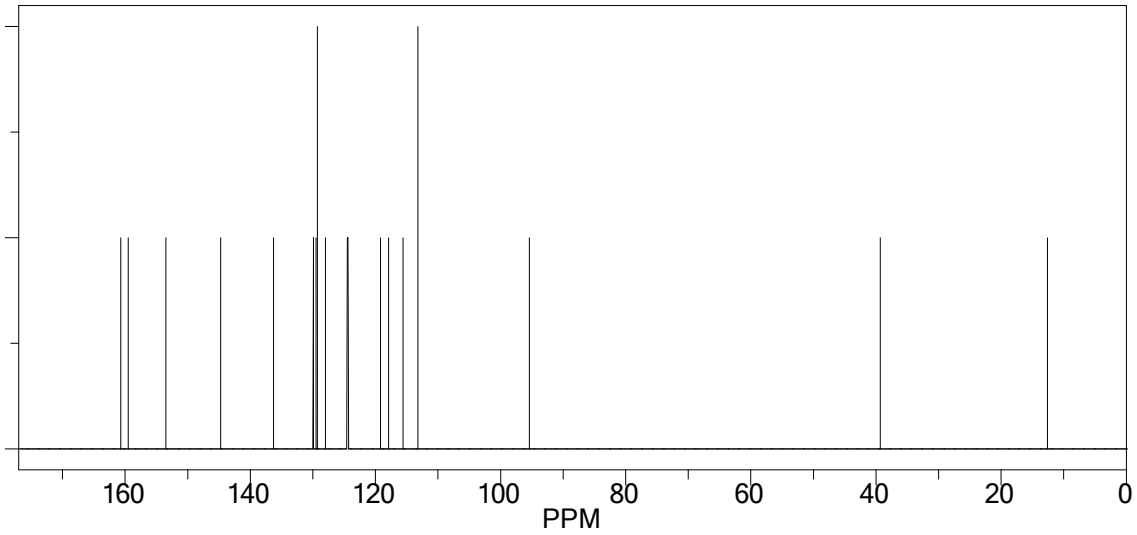
^{13}C NMR chemical shift δ/ppm of ligand MOPQHP.

Table 5. *^{13}C NMR spectral data of 2-((E)-(1,5-dimethyl-2-phenyl-3-((E)-quinolin-8-ylimino) methyl)-2,3-dihydro-1H-pyrazol-4-ylimino) methyl) phenol and dioxo Mo(VI) metal complex.*

Ligand/complex	C-atom	Chemical shift δ/ ppm	DEPT
$C_{20}H_9N_5O_2$	C-20, C-21, C-22	129.5, 117.9, 129.5	C-atom of quinoline ring
	C-23, C-24, C-25	124.5, 128, 124	C-atom of quinoline ring
	C-16	124	C-atom of quinoline ring adjacent –N=N-bridge bond
	C-18	154	Carbon atom of quinoline ring substituted by –OH group
	C-19	116	Carbon atom of quinoline ring substituted by -NH_2 group
	C-5	160.7	–C=O of pyrazolone ring
	C-4	95	Carbon atom of pyrazolone ring adjacent –N=N- bridge bond
$(C_{20}H_8N_5O_4)Mo$	C-16	122.9	Involvement of –N=N-bridge bond in coordination
	C-18	151.3	Involvement of N-atom of quinoline ring in bonding
	C-5	159.5	Involvement of oxygen atom –C=O of pyrazolone ring in bonding



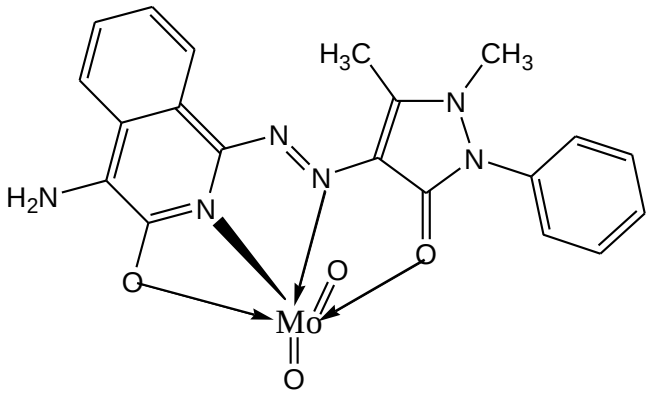
^{1}H NMR spectra of ligand MOPQHP



^{13}C NMR spectra of ligand MOPQHP

CONCLUSION

From the spectral data following structure is suggested for dioxo Mo (VI) metal complex



di-oxo Mo (VI) Metal Complex of MOPQHP

Evaluation of Anti-Tubercular Activity of Complex Bacterial Culture

The *in vitro* antitubercular activity of the synthesized ligand and its dioxo Mo(IV) metal complexes was tested against the isoniazid resistant *Mycobacterium tuberculosis*. The screening result were compared with Moxifloxacin (Zone of inhibition Z.I. = 24–26 mm) as a reference drug.

The screening culture medium was nutrients agar (Bacteriological Grade, Qualigen Fine Chem. Mumbai, India) and antitubercular screening was performed by employing by filter paper disc method [18].

The solvent used was 10% of DMSO in methanol and biological screening result was mentioned in mm (millimeter), Showing a diameter of inhibition zone and these are categories as 6 mm for mild, 7–13 mm for moderate, 14–26 mm for efficacy, respectively.

Different weights of synthesized compounds (6.250, 3.125, 1.562 µg/ml) were placed in the surface of culture and incubated at 37°C for 24 hours.

After incubation the zone of inhibition (mm) recorded in Table 6.

Table 6. *Zone of inhibition of dioxo Mo (VI) metal complex and ligand MOPQHP.*

Ligand/complex	Zone of inhibition (ZI mm)		
	Concentration		
	6.250 µg/ml	3.125 µg/ml	1.562 µg/ml
$C_{20}H_9N_5O_2$	15	11	8
$(C_{20}H_8N_5O_4)Mo$	22	19	12

A comparative study of the ligand and its complexes (MIC values) indicates the complexes of Mo (IV) metal with which exhibit higher antitubercular activity than the free ligand. Such increased activity of the complexes can be explained based on the Overtones concept.

According to Overtones concept of cell permeability, the lipid membrane that surrounds the bacterial cell favor the passage of only the lipid-soluble materials due to which lipo solubility is an important factor, which controls the antitubercular activity.

Upon chelation, polarity of the metal ion gets significantly reduced owing to overlapping of the ligand orbital and partial sharing of positive charge between the metal ion and the donor groups. Further, the delocalization of π-electrons gets increased over the whole chelate ring which enhances the lipophilicity of the complexes.

The increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocks the metal binding sites in the bacterial enzymes. These complexes are also known to interfere with the respiration process of bacterial cells which further blocks the synthesis of proteins that restrict growth of the organism.

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