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Synthesis, Characterization and Preliminary Microbial Studies of 4-{[(E)–1H–Indol–3H–Lmethylidene]Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One and Its Al(III), In(III) and Tl(I) Complexes

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Abstract

4-{[(E)–1H–indol–3H–ylmethylidene]amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one and its Al(III), In(III) and Tl(I) Complexes have been synthesized and characterized by physical methods and spectral studies. All the complexes were purified and their structures were elucidated using melting point, stoichiometry, molar conductivity, UV-visible, infrared, nuclear magnetic resonance and GCMS Spectral Studies The geometry around the metals were deduced based on the spectral information and were found to be five coordinate in all the complexes. The Schiff base ligand is coordinated to the metals through the participation of its imine nitrogen, indole-nitrogen and the oxygen of the antipyrine moiety. These complexes were also tested against different bacteria and fungi using Agar well diffusion method to determine their antimicrobial potency and they were found sensitive against Escherichia Coli, Pseudomonas aeruginosa, Basillus subtilis and Candida albicans but none was found active against Staphylococcus aureus.

Key words: Biological studies; Group 13 complexes; Schiff base; Spectroscopic characterization.

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INTRODUCTION

Schiff base is a class of compounds derived from the chemical reaction (Condensation) of aldehydes or Ketones with aromatic amines (Andrea, 1897/2009). Schiff bases have many applications especially in the preparation, identification and detection of aldehydes or ketones, they equally act as herbicides, antifungal, anti-tumor and anti-microbial compounds due to their biological activities. These activities are enhanced upon complexation with metals. Other uses relate to their industrial applications as homogeneous catalyst, intermediate in some chemical reaction and as dyes and pigments as earlier reported (Hamid, Amjid, Saeed, & George, 2006, p.205). In this paper, Synthesis, Spectral Characterization and biological activity of 4-{[(E)–1H–indol–3H–ylmethylidene]amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one and its Al(III), In(III) and Tl(I) complexes were reported.

1. EXPERIMENTAL

All reagents used were of analytical grade, and these were all used without further purification.Aluminum (III) Chloride, Indium (III) chloride and Thallium (I) acetate were purchased from corresponding authors Merck, Indole-3-carboxy-aldehyde and 4-amino antipyrine were obtained from Fluka and Aldrich respectively. Melting points were determined using 4017 model of John-Fisher melting point apparatus. The stoichiometry was determined using Job's continuous variation method. The electronic spectra were recorded with ultraviolet visible spectrophotometer of serial number 2,500pc equipped with a printer, infrared spectra were recorded in the range of 4000-400cm^{-1} as kbr pellets or thin film (Nujol) on Shimadzu 8400 S Model of FT-IR spectrophotometer.^{1}H and ^{13}C NMR Spectra were recorded on 1995 YH 200MHZ model of NMR spectrophotometer using DMSO and $CdCl_3$ as an internal reference. The mass spectra were

recorded on QP2010 Plus Shimadzu, Japan model of GC-mass spectrophotometer at 70 ev.

1.1 Preparation of Schiff Base Ligand

Synthesis of 4-{[(E)–1H–indol–3H–ylmethylidene] amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one.

Equimolar amount of 4-aminoantipyrine (0.406g, 2mmol) and indol-3-carboxyaldehyde (0.290g, 2mmol) were mixed in 50ml of ethanol. The resultant mixture was refluxed with continuous stirring for 5h at 60℃ and then cooled to room temperature. The resulting yellow crystals were filtered, dried and recrystallised using methanol to get purer crystals. The crystalline product was dried in the air and stored in a desiccators containing $CaCl_2$.

1.2 Preparation of the Metal Complexes

Synthesis of Al(III), In(III) and Tl(I) complexes of 4-{[(E)–1H–indol–3H–ylmethylidene] amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one.

Generally, the metal compounds and the Schiff base ligand were reacted in a 1:2 mole ratio. The Schiff base (0.660g, 2mmol) was reacted differently with the metal salts, aluminum (III) chloride (0.130g, 1mmol), indium (III) chloride (0.221g, 2mmol) and Thallium (I) acetate (0.660g, 2mmol) respectively in 50ml of tetrahydrofuran under reflux for 6h at 60℃. the resulting crystals were filtered, washed with benzene and dried in the air. The crystals were recrystallised using methanol and stored in the desiccators for characterization. The obtained complexes were found to be amorphous colored compounds, stable at ambient temperature and soluble in ethanol, methanol, DMF, and DMSO.

1.3 Antimicrobial Studies

The evaluation of ligand and complexes for antimicrobial activity were conducted using Agar-well diffusion method (Prasadd, Agrawal, & Sharma, 2002).

2. RESULTS AND DISCUSSION

The analytical and physical data of the free ligand and its metal complexes (Table 1) indicated that the reactions of the Schiff base ligand (HL) with trivalent aluminum and indium in ethanol yielded a mononuclear and binuclear complexes respectively while the same ligand on reacting with thallium (I) acetate yielded a binuclear complexes. The following representative equations illustrate the formation of ligand and complexes. Figure 1 and scheme1 Generally, ligand and complexes were found to be colored with significant percentage yield. This ligand and complexes have high melting points and non-electrolyte with the exception of the indium complex which was found to be charged, hence could serve as a good conductor.

2.1 Electronic Spectra

The electronic spectra of the Schiff base ligand (HL) with its complexes (Table 2) with regards to band position and intensity are dissimilar to each other. These absorption bands observed are due to $\pi \rightarrow \pi^*$ transition and $n \rightarrow \pi^*$ transition of non-bonding electron in the ligand and complexes. The shift in the λ-max. in all the complexes are clear indication of complex formation as earlier reported (Hishashi et al., 1972-1976).

2.2 Infrared Spectra

The IR spectra of the complexes were compared with that of the free ligand to determine the changes that might have taken place during the complexation, all data are listed in Table 3. The band at 3,166cm^{-1} is a characteristic of the indole group (N-H) present in the Schiff base ligand[5].This absorption was shifted to higher frequency in all the complexes indicating the involvement of the indole nitrogen in coordination (Shane et al., 2004). The band assigned to the carbonyl group in the free ligand was observed at 1,750cm^{-1} and shifted to lower frequency in aluminum complex and higher frequency in thallium complex. This indicates the participation of the imine nitrogen in complex formation (Radmarkvishnan, Joseph, & Prabhakaran, 1976; Shankar, Premkumar, & Ramalingam, 1986; Ramesh, Suganthy, & Nakaranjan, 1996; Wang et al., 1999). However, this group was not involved in bonding in the thallium complex. The IR spectra of all the complexes reveal new bands at 589cm^{-1}, 446cm^{-1} and 478cm^{-1} assigned to v(M-Cl) and v (M-O) respectively. This was reported in similar work (El-Saied, 2001).

2.3 Nuclear Magnetic Resonance Spectra Studies

The assignments of the main signals in the ^{1}HNMR Spectra and ^{13}CNMR of the free ligand are listed in Tables 4 and 5, Figures 2 and 3, respectively.

The free ligand showed a signal at 8.43ppm (H_1) due to imine proton, 9.74ppm and 11.58ppm were due to indole proton. The signals within the range of 7.18-8.40ppm were all accounted for by aromatic protons (Dedley & Ian, 1980). The saturated alkyl protons of the antipyrine moiety were equally observed at 2.45 and 3.08ppm respectively.These signals confirmed the structure showing the protons numbering. (See Figure 2).

The proton and carbon spectra of the free Schiff base ligand (HL) was in good agreement with the suggested structure. Its ^{13}C NMR Table 5. was run in $CDCl_3$. Its C_9 was observed to be highly deshielded to 153 ppm due to the presence of the imine group (El-Saied, 2001). Also affected by this imine group are: Its C_{10} which appear downfield at 151 ppm. The presence of the indole group introduced an electronic effect that deshield C_6 and C_7 to give signals at 129 and 132 ppm respectively. Similarly, C_{12} and C_{15} were deshielded by the nitrogen of the antipyrine moiety assigned to signals at 135 and 137 ppm respectively. Both were confirmed using apt (attarched proton test) and the two appear as quaternary carbons. C_1, C_6, C_{10}, C_{11}, C_{12} and C_{15} are the six quaternary

carbon which appear in the apt. The signals are 116, 129, 151, 161, 135 and 137 ppm respectively. C_{11} was assigned to be 161 due to the presence of carbonyl group on the antpyrine moiety. Other carbons numbered are the aromatic carbon atoms and their various signals are assigned on Table 5.

2.4 Mass Spectra

The mass spectra data for 4-{(E)-IH-indol-3-ylmethylidene]amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-phyrazol-3-one are given in Table 6 (Scheme 2). A molecular ion peak at m/z 91 is due to $[C_6H_5N]^+$ fragment present in the compound. The m/z 92 was observed due to $[C_6H_5NH]^+$. The base peaks at m/z 43 and 89 were assigned to secondary fragmentation due to $[C_2H_5N]^+$ and $[C_6H_3N]^+$ ions respectively. The peak at m/z 41 was responsible for $[C_2H_3N]^+$ fragment while the loss of $[C_{11}H_{17}N_3]^+$ account for the primary fragmentation with the base peak at m/z 191.

3. ANTIMICROBIAL STUDIES

The antibacterial activity of the free ligand 4-{[(E)–1H–indol–3H–ylmethylidene] amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one (HL) and its aluminum (III), indium (III) and thallium (I) complexes were tested against bacterial species staphylococcus aureus, Basillus subtilis, pseudomonas aeruginosa, Escherichia coli and the antifungal activity against candida albicans were carried out.The potency of the investigated ligand and its metal complexes as antimicrobial agents were screened in addition to evaluation of some known antibiotics using penicillin as a standard antibacterial agent or reference. The results are shown in Tables 7 and 8.

The result showed that the free ligand, aluminum and thallium complexes were found active against Bacillus subtilis. The thallium complex showed activity against Escherichia Coli, Candida albicans, Bacillus subtilis and Pseudomonas aeruginosa. This activity is more than that of the free ligand. Both, thallium and indium complexes showed potency against pseudomonas aeruginosa and Candida albicans. The comparism of the biological activities of the synthesized metal complexes reveals that the thallium complex has a high range of activities against the tested organisms than all other metal derivatives.

Table 1
Analytical and Physical Data of 4-{[(E)–1H–Indol–3H– Ylmethylidene]Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3- One and Its Al(III), In(III) and Tl(I) Complexes

Compound	Mole ratio	M.W	Color	M.P (^oC)	Conductivity $ohm^{-1}cm^2mol^{-1}$	% yield
HL	1:1	329	Yellow	285-288	1.00	56
$[Al(HL)Cl_3]$	1:1	462.5	Dark yellow	270-273	18.00	60
$[In_2(HL)_3Cl_2]^{4+}$	2:3	1,217	Black	110 dec.	121.00	53
$[Tl_2(HL)_2(O_2C_2H_3)_2]$	2:2	1,066	Ash yellow	125-128	22.00	68

Table 2
Electronic Spectra Data of 4-{[(E)–1H–Indol–3H– Ylmethylidene]Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One and Its Al(III), In(III) and Tl(I) Complexes

Compound	$nm(cm^{-1})$	$nm(cm^{-1})$	$nm(cm^{-1})$
HL	742.5s(13468)		298w(33467)
$[Al(HL)Cl_3]$	741s(13495)		243w(41152)
$[In_2(HL)_3Cl_2]^{4+}$	779s(12828)	741s(13495)	417br(23980.8)
$[Tl_2(HL)_2(O_2C_2H_3)_2]$	750s(13333)	740s(13504)	331w(30211)

Legend. S= strong, br= broad and w= weak.

Table 3
Characteristic IR Bands (cm^{-1}) of 4-{[(E)–1H–Indol–3H–Ylmethylidene] Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One (HL) and Its Al(III), In(III) and Tl(I) Complexes

Compound	v(N-H)	v(C=C)	v(C=O)	v(C=N)	v(N-N)	v(M-Cl)	v(M-O)
HL	3166_w	2921_w	1750s	1609s	1124_w	-	-
$[Al(HL)Cl_3]$	3531_w	2926_w	1700s	1605s	1123_w	589_w	-
$[In_2(HL)_3Cl_2]^{4+}$	3347_w	3326_w	-	1614s	1122_w	446_w	
$[Tl_2(HL)_2(O_2C_2H_3)_2]$	3855_W	3035_W	1800s	1620s	1120_w	-	478_w

Legend. S= strong, w= weak.

Table 4
Proton NMR Data of 4-{[(E)–1H–Indol–3H–Ylmethylidene] Amino}–1,5-dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One (HL)

Position	H (∂)	Assignment
H_1	8.43 (s,1H)	Imine proton
H_2	9.74 (s,1H)	Indole proton
H_3	11.58 (s,1H)	Indole proton
H_4	8.40 (s, 1H)	Aromatic proton
H_5	7.34 (m,1H)	Aromatic proton
H_6	7.54 (m,1H)	Aromatic proton
H_7	7.50 (m,1H)	Aromatic proton
H_8	2.45 (s, 3H)	Antipyrine methyl proton
H_9	3.08 (s,3H)	N-antipyrine methyl proton
H_{10}	7.46 (m,1H)	Phenyl proton
H_{11}	7.35 (m,1H)	Phenyl proton
H_{12}	7.18(m, 1H)	Phenyl proton
H_{13}	7.31 (m, 1H)	Phenyl proton
H_{14}	7.40 (m,1H)	Phenyl proton

Table 5
^{13}C NMR Assignment for 4-{[(E)–1H–Indol–3H–Ylmethylidene] Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One (HL)

Position	^{13}C (PPM)
C_1	116.563
C_2 & C_5	112.519
C_3	122.769
C_4	121.260

To be continued

Continued

Position	^{13}C (PPM)
C_6	129.749
C_7	132.253
C_8	125.387
C_9	153.071
C_{10}	151.668
C_{11}	161.038
C_{12}	135.690
C_{13}	10.705
C_{14}	36.667
C_{15}	137.951
C_{16}&C_{20}	127.026
C_{17},C_{19}	124.583
C_{18}	123.232

Table 6
Mass Spectral Data of 4-{(E)-1H-Indol-3-Ylmethylidene]Amino}-1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Phyrazol-3-One

Molecular wt	m/z of fragment ion
$[C_{21}H_{19}N_3O]^+$	329
$[C_9H_7N]^+$	128
$[C_8H_6N]^+$	116
$[C_6H_3N]^+$	89
$C_{11}H_{11}N_3]^+$	184
$[C_6H_6N]^+$	92
$[C_6H_5N]^+$	91
$[C_3H_3]^+$	41

Table 7
Antimicrobial Activities of the Schiff Base Ligand (HL) and Its Metal Complexes Using Penicillin as Standard Drug

Organism	HL	$Al(HL)Cl_3$	$[In_2(HL)_3Cl_2]^{4+}$	$[Tl_2(HL)_2(O_2C_2H_3)_2]$
E. Coli	nil	nil	nil	14
Pseudomonas aeruginosa	nil	nil	12	20
Basillus subtilis	11	10	nil	25
Staphylococcus aureus	nil	nil	nil	nil
Candida albicans	nil	nil	11	30

Note. Zone of Inhibition (mm)

Table 8
Minimum Inhibitory Concentration (MIC) of the Ligand 4-{[(E)–1H–Indol–3H–Ylmethylidene] Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One (Hl) and Its Al(III), In(III) And Tl(I) Complexes

Organism	Compound	20	10	5	2.5	1.25	0.625	0.135
E. Coli	$[Tl_2(HL)_2(O_2C_2H_3)_2]$	20mm	18mm	15mm	13mm	10mm	nil	nil
Bacillus subtilis		25mm	18mm	15mm	nil	nil	nil	nil
Candida albicans		30mm	25mm	21mm	18mm	15mm	13mm	nil
Pseudomonas aeriginosa		20mm	18mm	15mm	13mm	10mm	nil	nil
Candida albicans	$[In_2(HL)_3Cl_2]^{4+}$	11mm	10mm	nil	nil	nil	nil	nil
Pseudomonas aeriginosa		12mm	nil	nil	nil	nil	nil	nil
Bacillus subtilis	$[Al(HL)Cl_3]$	10mm	nil	nil	nil	nil	nil	nil
Bacillus subtilis	HL	10mm	9mm	nil	nil	nil	nil	nil

Note. Concentration in µg/ml and Zone of Inhibition (mm)

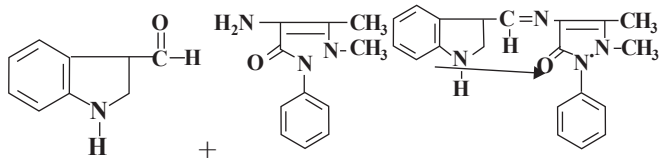


Figure 1

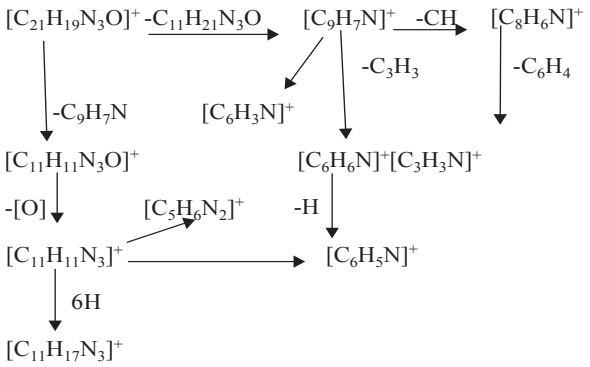
HL. ($C_{21}H_{19}N_3O$)

$AlCl_3 + HL \longrightarrow [Al(HL)CI_3$ 1:1

$InCl_3 + HL \longrightarrow [In_2(HL)_3Cl_2]^{4+}$ 2:3

$Tl(O_2C_2H_3) + HL \longrightarrow [Tl_2(HL)_2(O_2C_2H_3)_2]$ 2:2

Scheme 1



Scheme 2. Fragmentation pattern for 4-{(E)-IH-indol-3-ylmethylidene]amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-phyrazol-3-one (HL).

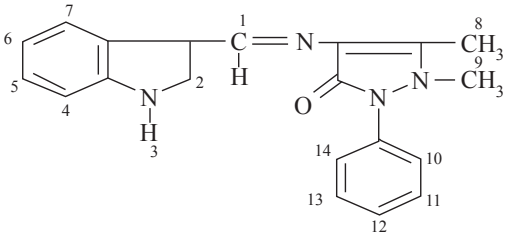


Figure 2
Structure of 4-{(E)-IH-Indol-3-Ylmethylidene]Amino}-1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Phyrazol-3-One. Showing Protons Numbering

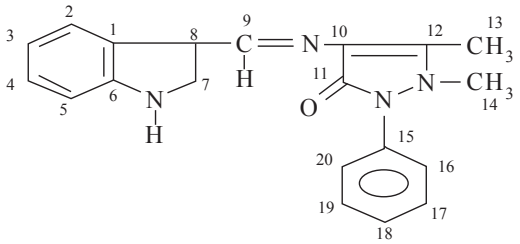


Figure 3
Structure of 4-{(E)-IH-Indol-3-Ylmethylidene]Amino}-1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Phyrazol-3-One. Showing Carbon Numbering

Proposed Structures. Following the results of the physical data and spectral information the structure of the ligand and complexes are suggested thus.

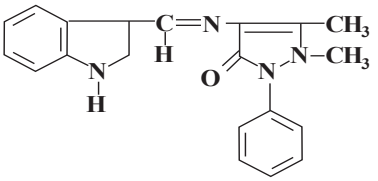
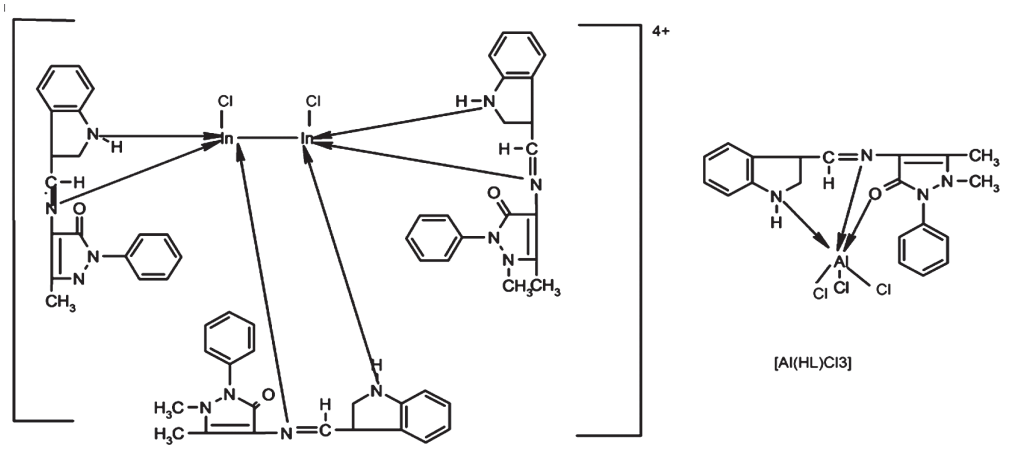
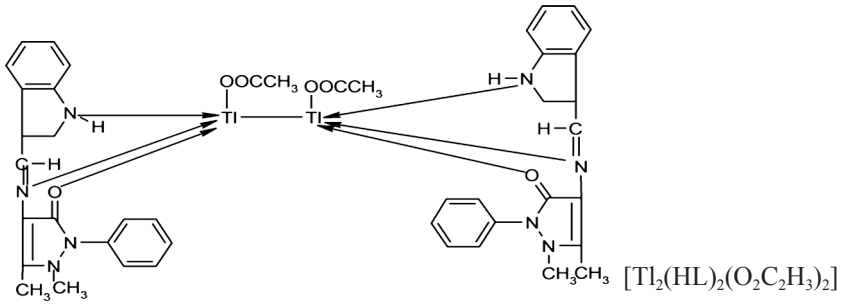


Figure 4
Structure of 4-{[(E)–1H–Indol–3H–Ylmethylidene] Amino}–1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol–3-One. (Schiff Base)



[Al(HL)Cl3]



$[Tl_2(HL)_2(O_2C_2H_3)_2]$

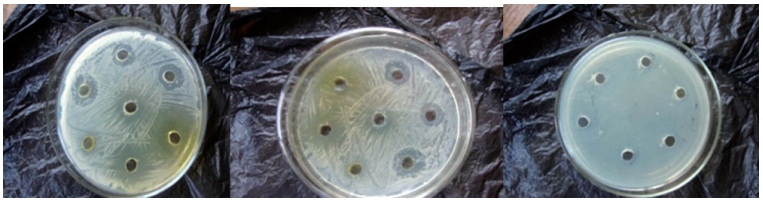


Figure 6
Plates Showing the Activities of the Organism

CONCLUSION

The synthesis and characterization of the Schiff base ligand 4-{[(E)–1H–indol–3H–ylmethylidene]amino}–1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol–3-one (HL) and its metal derivatives were successful. Following the physical data and spectral information obtained, various structures were proposed for the metal complexes. The ligand and its complexes showed antibacterial and antifungal activities. The effect was more enhanced upon complexation.

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