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Structural and Pharmacological Studies of Transition Metal Complexes

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Chromium(III) and manganese(II) complexes were synthesized with tetra-binding chelating agent. The condensation product of 1,4-diformylpiperazine and 4-aminoantipyrine coordinate to the metal ion through nitrogen and oxygen donor sites to give the complexes having stoichiometry $[M(L)X_2]X_n$, where M = Cr(III) and Mn(II), L = ligand, X = NO_3^-, CH_3COO^-, and Cl^-, and n = 0 or 1. The compounds were structurally studied with a number of analytical methods like physical methods: elemental analyses, molar conductance measurements, magnetic susceptibility measurements, and spectral methods: IR, UV/visible, NMR, ESIMS, and EPR. The studies of the compounds reveal that the ligand L is bonded to the metal ion via ONNO binding sites. The resulting complexes were found to have octahedral geometry. The pharmacological studies of the compounds were examined against the opportunistic pathogens.

Keywords complexes, ligand, pharmacological investigations, spectral characterization

INTRODUCTION

The piperazine derivatives constitute an important class of compounds that have diverse applications in the pharmaceutical array like anti-HIV activity, antidepressant, anxiolytic drug, anticancerous, etc.[1–5] Moreover, 4-aminoantipyrine incorporated compounds have also been studied in the pharmaceutical field and have multiple drug actions such as analgesic, anti-inflammatory, antifungal, antibacterial, etc.[6–9] The chelating modes of the piperazines and antipyrines have been modified to have a variety of ligand systems, as they have been used as the precursors to give interesting products on reaction with substituted amines as well as carbonyl compounds. The coordinating properties of these derivatives have also been widely examined with transition metals as well as lanthanides with the help of physicochemical, spectral, thermal, x-ray, and other forms of analysis, frequently used and powerful analytical tools.[10]

Views of these studies and their fruitful results encourage biochemists to further explore these two class of the compounds (piperazine and 4-aminoantipyrine) in the widespread pharmaceutical field. In the present studies, we have synthesized a derivative of piperazine and 4-aminoantipyrine and its transition metal complexes. The compounds have also been investigated for the fungicidal studies.

EXPERIMENTAL

Materials

All the chemicals, solvents, and metal salts are commercial products and procured from Sigma-Aldrich, Fluka, S. D. Fine, E. Merck, and Thomas Backer.

Physical Measurements

Nuclear magnetic resonance (NMR) spectra were recorded with a model Bruker Advance DPX-300 spectrometer operating at 300 MHz using dimethyl sulfoxide (DMSO)-d_6 as a solvent and TMS as an internal standard. Infrared (IR) spectra were recorded as KBr/CsI pellets in the region 4000−200 cm^{-1} on a Fourier transform (FT)-IR spectrum BX-II spectrophotometer. Electrospray ionization (ESI) mass spectra were recorded on a model Q Star XL LCMS−MS system. The stoichiometric analyses were carried out on a Carlo-Erba 1106 analyzer. The electronic spectra were recorded on Shimadzu UV mini-1240 spectrophotometer. Electron paramagnetic resonance (EPR) spectra were recorded as solids and solutions on an E4-EPR spectrometer at room temperature as well as liquid nitrogen temperature operating at the X-band region using diphenylpicrylhydrazyl (DPPH) as a standard. The molar conductance of complexes was measured in DMSO at room temperature on an ELICO (CM 82T) conductivity bridge. The magnetic susceptibility was measured at room temperature on a Gouy balance using $CuSO_4 \cdot 5H_2O$ as calibrant.

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Synthesis of Ligand 1,4-Diformylpiperazine Bis(4-imino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) (Figure 1)

The requisite quantity of the 4-aminoantipyrine (0.04 mol) was dissolved in acetonitrile (25 mL) and the solution was heated for 15 min in the presence of 1–2 drops of conc. HCl. To this warmed solution, a hot solution of 1,4-diformylpiperazine (2.8432 g, 0.02 mol) in acetonitrile (15 mL) was added dropwise with continuous stirring. The reaction mixture was refluxed for 5 h at 85°C, allowed to stay at room temperature, and then kept in a refrigerator overnight. The white shiny microcrystalline product was precipitated out, filtered, washed several times with acetonitrile, and dried under vacuum over P_4O_{10}. Yield 60%, m.p. 210°C. Elemental analyses: Found (Calcd.) for $C_{28}H_{32}N_8O_2$: C, 65.58 (65.62); H, 6.21 (6.25); N, 21.82 (21.87)%. IR (cm^{-1}, KBr pellets): 1667 ($\nu_{C=O}$), 1606 ($\nu_{C=N}$); ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 2.11 (s, 6H, H_3C-C), 2.88 (s, 6H, H_3C-N), δ 3.24-3.48 (m, 8H, piperazine ring), 7.16-7.35 (m, 10H, Ph), 7.97 (s, 2H, H-C = N) (Figure 2); ^{13}C-NMR (300 MHz, DMSO-d_6): δ (ppm): 10.68 (2C, H_3C-C), 35.58 (2C, H_3C-N), 127.13, 128.90, 129.35, 129.61 (4C, piperazine ring), 129.66, 130.34, 130.47, 131.90, 134.59, 135.30 (6C, aromatic rings); 137.62 (2C, MeC, ring), and 138.04 (2C, N-C, ring), 150.08 (2C, C = N), 196.62 (2C, C = O) (Figure 3); ESI MS: *m/z* = 512 (M^+), 513 ($M^+ + 1$) isotopic, 187 ($C_{11}H_{11}N_2O^+$) base peak ion with pyrazolone moiety, 15, 26, 112, 138, 325, 358, 435, 482, and 497 fragments (Figure 4).

Synthesis of the Complexes

The requisite amount of the ligand (1 mmol) was dissolved in acetonitrile and the solution was heated for 10 min. To this solution, a hot solution of metal salt (nitrate, chloride, or acetate) (1 mmol) in acetonitrile was added slowly dropwise with constant stirring. The resulting mixture was refluxed for 8–10 h at 80–90°C. After refluxing, the mixture was allowed to stay at room temperature for 2 h and than cooled overnight at 0°C. The precipitate of the complex was separated out, filtered, washed with cold acetonitrile, and dried under vacuum over P_4O_{10}.

Pharmacological Studies

The food poison technique was employed to investigate the fungicidal studies and dilution technique was used to determine the minimum inhibitory concentration (MIC).[11,12] The stock solutions of the compounds were prepared in DMSO solvent. The diluted solution of the compound to be tested was directly added to the PDA (potato dextrose agar) medium and the mixture was poured into a petri plate. The petri plates were kept for a day to check the sterility. A disc of 5 mm diameter of test fungal culture was placed at the center of the petri plate with the help of an inoculum needle. The petri plates were sealed with parafilm and incubated at 29 ± 2°C for a week.

All determinations were performed in duplicate. The results of the fungicidal capacity of the compounds were determined in percentage terms from the growth of the fungus in the test plate to the respective control plate. DMSO and captan were employed as a control and a standard fungicide, respectively.

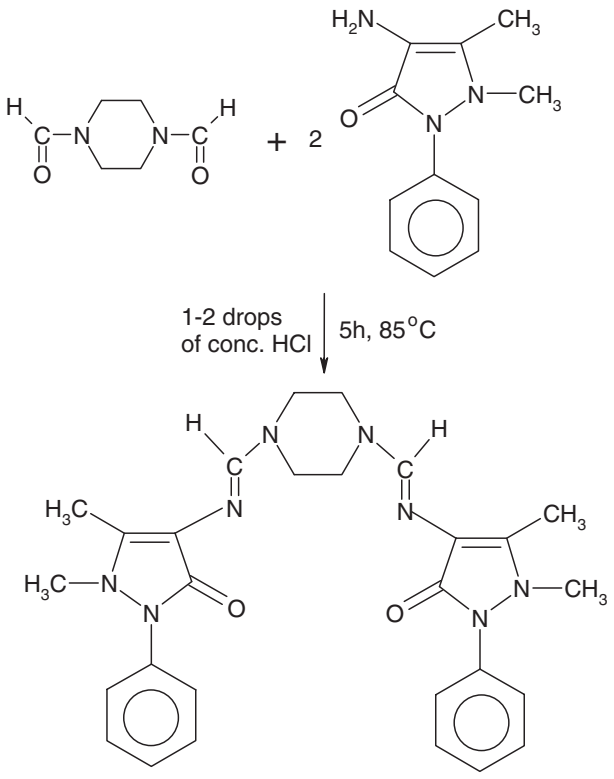


FIG. 1. Synthesis of ligand.

RESULTS AND DISCUSSION

The reaction of the Schiff's base ligand with the Cr(III) and Mn(II) metal ions gave complexes having the compositions $Cr(L)X_3$ and $Mn(L)X_2$, where ligand is L and X = NO_3^-, CH_3COO^-, and Cl^- ions. The physicochemical and stoichiometric data of the compounds are given in Table 1. The conductometric studies reveal that the complexes have $[Cr(L)X_2]X$ and $[Mn(L)X_2]$ compositions.[13] The magnetic moments lie in the range 3.76–3.90 B.M. for Cr(III) complexes and 5.97–6.01 B.M. for Mn(II) complexes, respectively, which correspond to the high spin nature of the complexes.

IR Spectra

The key IR bands of the synthesized compounds with their assignments are listed in Table 2. The IR spectrum of the ligand shows bands at 1667 and 1606 cm^{-1}, which may be assigned to the ν(C = O) and ν(C = N) stretching vibrations, respectively.[10,14,15] On complexation, the position of these bands is altered, which reveals that the carbonyl oxygen and azomethine nitrogen are bonded to the central metal ion. The IR spectra of complexes display the new bands centered in the range 375–401 and 450–572 cm^{-1}, which may be due to the ν(M−O) and ν(M−N) stretching vibrations,[16] respectively. The appearance of these additional bands also supports the bonding of ligands

TABLE 1
Stoichiometric and physical data of the complexes

Substance number	Complex	Color	μ_{eff} (B.M.)	Molar conductance (Ω^{-1} cm^2 mol^{-1})	m.p. (°C)	Analytical data (%), calcd. (found)			
						M	C	H	N
1	$[Cr(L)(NO_3)_2]NO_3Cr$ $C_{28}H_{32}N_{11}O_{11}$	Parrot green	3.88	108	292	6.93 (6.87)	44.80 (44.73)	4.27 (4.23)	20.53 (20.47)
2	$[Cr(L)Cl_2]Cl$ $CrC_{28}H_{32}N_8O_2Cl_3$	Green	3.90	116	288	7.76 (7.71)	50.11 (50.06)	4.77 (4.68)	16.70 (16.66)
3	$[Cr(L)(OAc)_2]OAc$ $CrC_{34}H_{41}N_8O_8$	Dark green	3.76	97	282	7.02 (6.96)	55.06 (55.00)	5.53 (5.49)	15.12 (15.05)
4	$[Mn(L)(NO_3)_2]$ $MnC_{28}H_{32}N_{10}O_8$	White	6.01	20	288	7.95 (7.88)	48.63 (48.57)	4.63 (4.58)	20.26 (20.21)
5	$[Mn(L)Cl_2]$ $MnC_{28}H_{32}N_8O_2Cl_2$	White	5.99	18	264	8.61 (8.55)	52.67 (52.61)	5.02 (4.97)	17.57 (17.51)
6	$[Mn(L)(OAc)_2]$ $MnC_{32}H_{38}N_8O_6$	White	5.97	15	>300	8.02 (8.07)	56.06 (56.12)	5.55 (5.50)	16.35 (16.41)

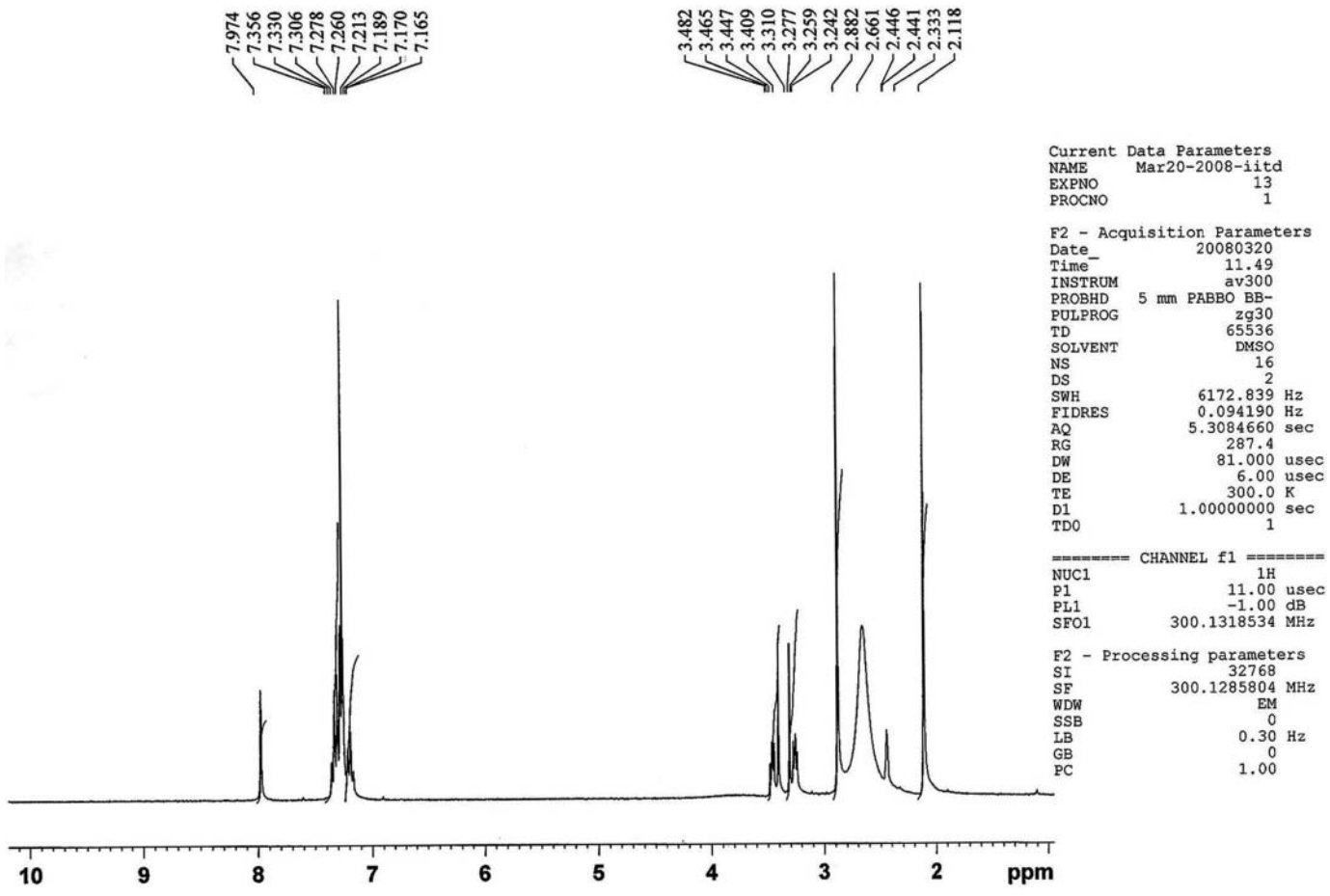


FIG. 2. ^{1}H-NMR spectrum of ligand.

to the metal ion through nitrogen and oxygen binding sites, and the ligand acts as a tetradentate ONNO donor. In the IR spectra of complexes, the bands also appear due to the coordinated anions. The chloro complexes show IR bands in the region 330−340 cm^{-1} due to ν(M−Cl). The nitrato complexes display IR bands in the regions 1390−1496 (ν_5), 1298−1354 (ν_1), and 1059−1102 cm^{-1} (ν_2) due to NO stretching vibration of nitrate anion. The difference of the IR frequencies, ν_5 and ν_1, (92−142 cm^{-1}) indicates the coordination of NO_3^- ion in unidentate fashion. The acetato complexes give IR bands at 1428−1456 (ν_{asym} stretching vibration) and 1261−1270 cm^{-1} (ν_{sym} stretching vibration), and the $\Delta\nu$ (167−186 cm^{-1}) values correspond to coordination of acetate anion through one donor atom.[17–19]

TABLE 2
Comparative IR data of compounds

Substance number	Compound	ν(C = N)	ν(C = O)	ν(M−O)	ν(M−N)	Anion bands
1	Ligand	1606	1667	—	—	—
2	$[Cr(L)(NO_3)_2]NO_3$	1564	1637	401	572	1496, 1354, 1059
3	$[Cr(L)Cl_2]Cl$	1572	1643	396	499	330
4	$[Cr(L)(OAc)_2]OAc$	1580	1622	412	507	1456, 1270
5	$[Mn(L)(NO_3)_2]$	1626	1676	382	450	1390, 1298, 1102
6	$[Mn(L)Cl_2]$	1553	1638	393	510	340
7	$[Mn(L)(OAc)_2]$	1571	1617	375	488	1428, 1261

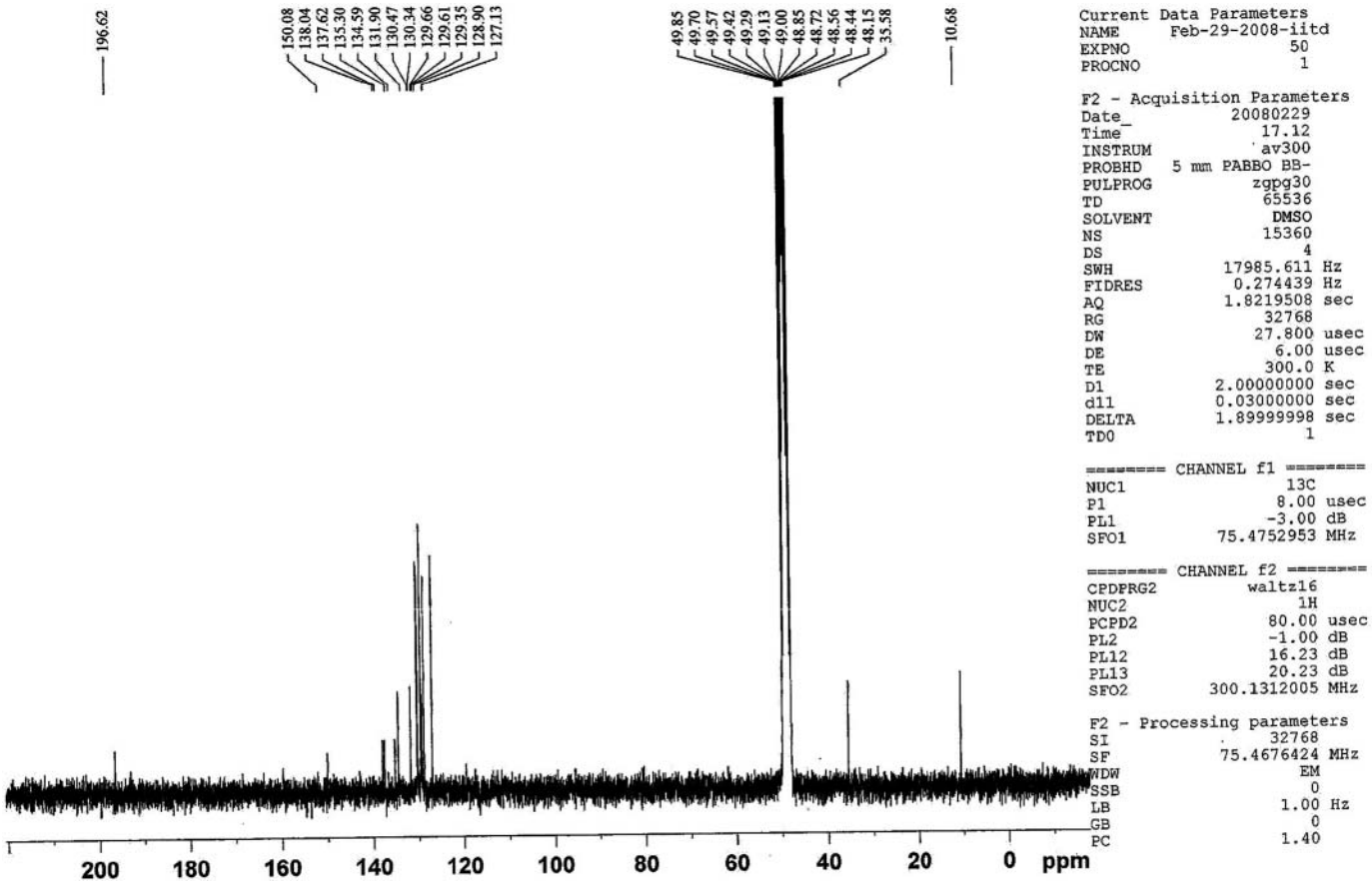


FIG. 3. ^{13}C-NMR spectrum of ligand.

TABLE 3
Electronic spectral data and ligand field parameters of complexes

Substance number	Complex	λ_{max} (cm^{-1})	D_q (cm^{-1})	B(cm^{-1})	C(cm^{-1})	β	LFSE ($kJmol^{-1}$)	F_4	F_2
1	$[Cr(L)(NO_3)_2]NO_3$	17452,37735	1745	712	—	0.69	250.21	—	—
2	$[Cr(L)Cl_2]Cl$	16231,25042, 37068	1623	662	—	0.64	232.70	—	—
3	$[Cr(L)(OAc)_2]OAc$	18621,27322	1862	760	—	0.74	266.97	—	—
4	$[Mn(L)(NO_3)_2]$	19476,23530, 28500, 34125	781	710	3286	0.74	—	93.9	1179.4
5	$[Mn(L)Cl_2]$	19260,24128, 27660, 37120	554	504	3816	0.53	—	109.0	1049.1
6	$[Mn(L)(OAc)_2]$	17295,24480, 27450, 35730	466	424	4047	0.44	—	115.6	1002.1

TABLE 4
EPR spectral data of complexes

Substance number	Complex	Polycrystalline form				Solution form			
		$g_\perp$ (LNT)	$g_\parallel$ (LNT)	g_{iso} (RT)	g_{iso} (LNT)	g_{iso} (RT)	A_{iso} (RT)	g_{iso} (LNT)	A_{iso} (LNT)
1	$[Cr(L)(NO_3)_2]NO_3$	—	—	1.9872	—	—	—	—	—
2	$[Cr(L)Cl_2]Cl$	—	—	1.9584	—	—	—	—	—
3	$[Cr(L)(OAc)_2]OAc$	—	—	1.9902	—	—	—	—	—
4	$[Mn(L)(NO_3)_2]$	—	—	2.0122	2.0451	2.0048	90.5	2.0193	92.5
5	$[Mn(L)Cl_2]$	—	—	2.0006	2.0602	1.9974	96.0	2.0161	88.5
6	$[Mn(L)(OAc)_2]$	—	—	2.0212	2.3865	2.0022	92.5	2.2016	90.0

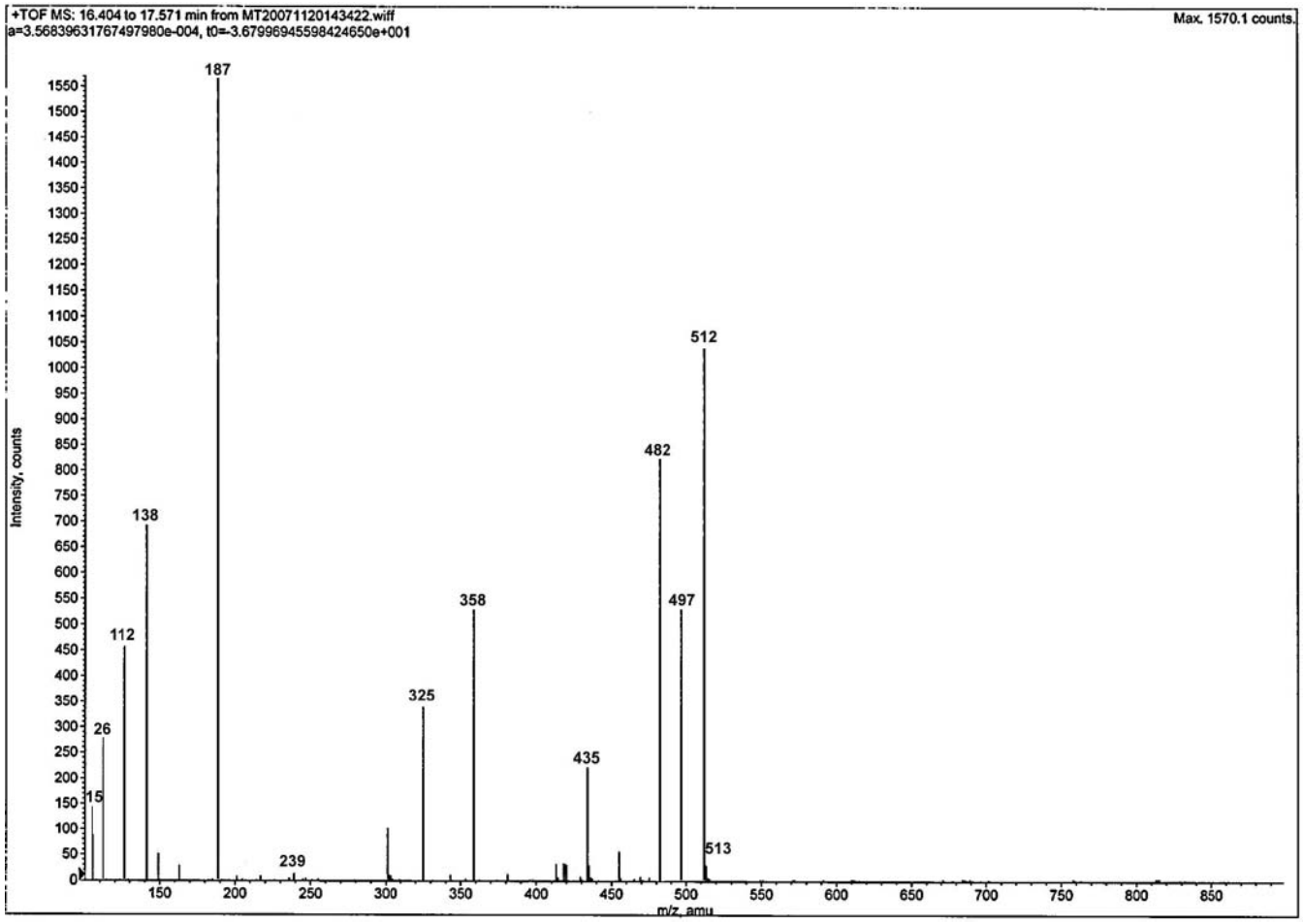
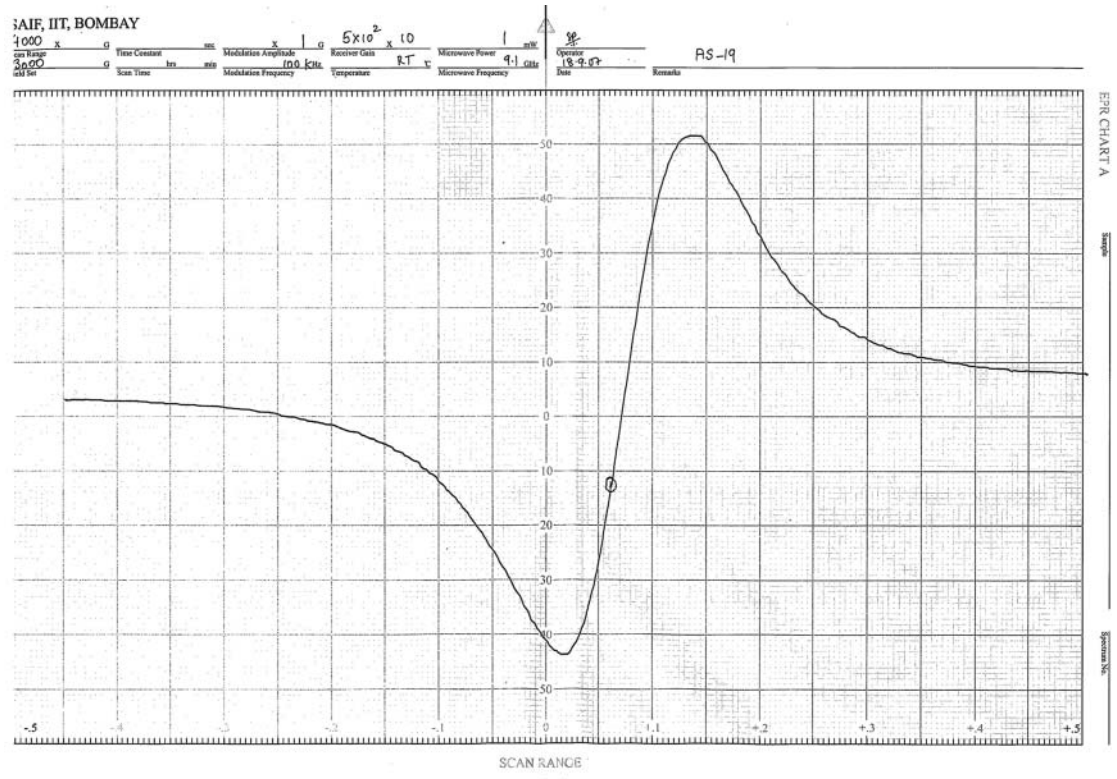


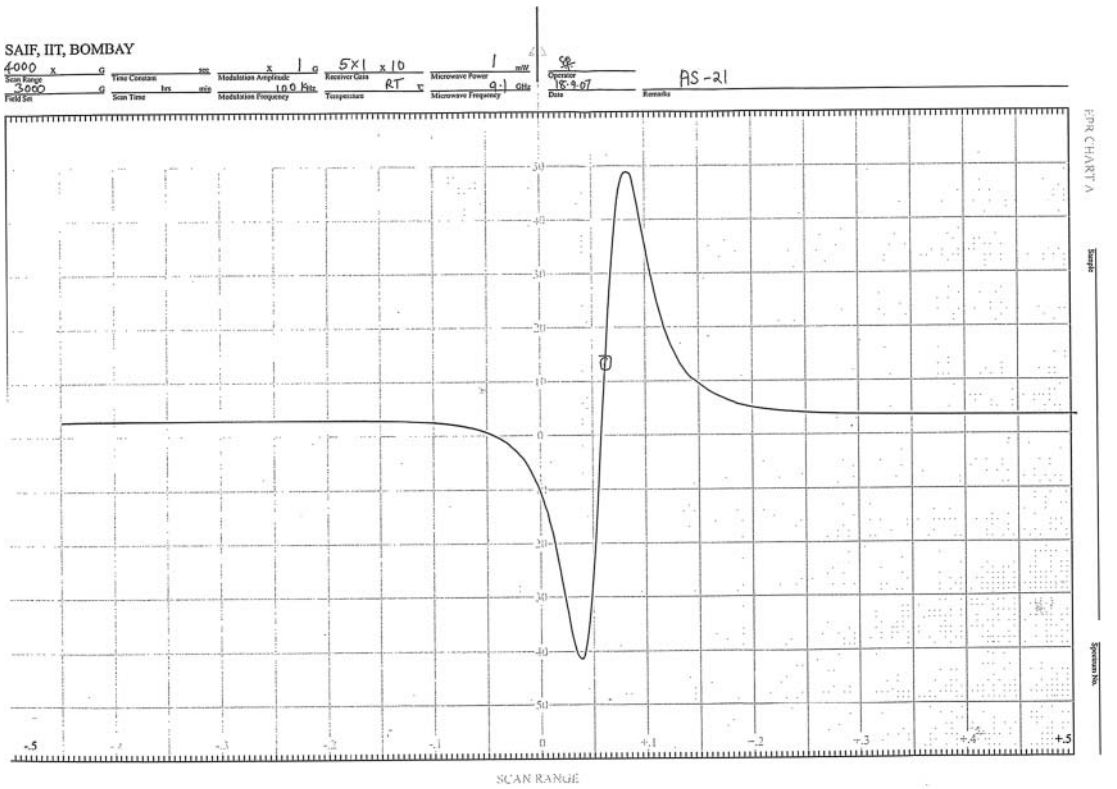
FIG. 4. Mass spectrum of ligand.

TABLE 5
Fungicidal screening data of the compounds

	Fungicidal activity (%) (conc., μg mL^{-1})								
	A. brassicae			*A. niger*			*F. oxysporum*		
Compound	200	300	500	200	300	500	200	300	500
Ligand	30	40	58	30	42	60	33	45	64
$[Cr(L)(NO_3)_2]NO_3$	36	50	62	34	45	65	39	50	67
$[Cr(L)Cl_2]Cl$	35	48	60	32	43	64	38	49	66
$[Cr(L)(OAc)_2]OAc$	38	44	60	32	44	64	36	48	65
$[Mn(L)(NO_3)_2]$	39	52	63	37	50	68	41	53	68
$[Mn(L)Cl_2]$	35	51	61	36	47	66	40	50	66
$[Mn(L)(OAc)_2]$	36	50	60	36	48	65	40	51	67
Standard (captan)	70	80	100	75	90	100	65	75	100



(a)



(b)

FIG. 5. EPR spectra of, (a) $[Cr(L)Cl_2]Cl$ and (b) $[Mn(L)Cl_2]$ complexes.

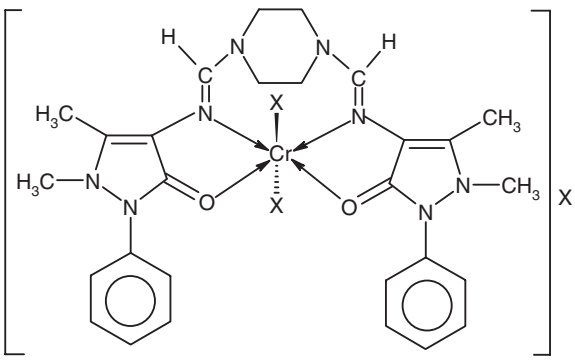
Electronic Spectra

The electronic spectral data along with ligand field parameters are presented in Table 3. The electronic spectra of Cr(III) complexes exhibit the transitions at wavelength 16231–18621 and 25042–27322 cm^{-1}, which may be assigned to the $^4A_{2g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1) and $^4A_{2g}(F) \rightarrow {}^4T_{1g}(F)$ (ν_2) spin-allowed d–d transitions. These transitions indicate the octahedral environment around the Cr(III) metal ion.[20,21] The spectra also display the bands at wavelength 37068–37735 cm^{-1}, which may be due to the charge transfer transition.

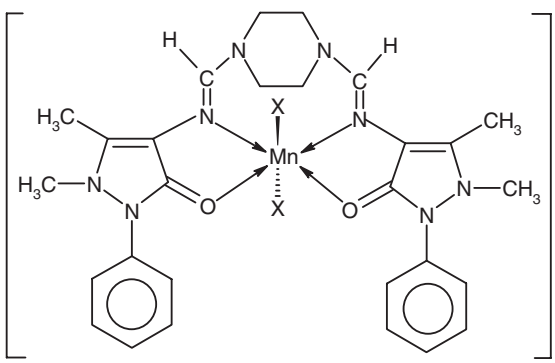
The electronic spectra of Mn(II) complexes show four absorption bands at wavelength 17295–19476, 23530–24480, 27450–28500, and 34125–37120 cm^{-1}. These bands may be assigned to the $^6A_{1g} \rightarrow {}^4T_{1g}$ (^4G), $^6A_{1g} \rightarrow {}^4E_g$, $^4A_{1g}$ (^4G), $^6A_{1g} \rightarrow {}^4E_g$ (^4D), and $^6A_{1g} \rightarrow {}^4T_{1g}$ (P) transitions, respectively. The observed transitions suggest octahedral geometry for the complexes.[20,21] The parameters like B and C (Racah parameters), Dq, covalency factor β, LFSE, and F_2 and F_4 have been calculated for the complexes. The value of the covalency factor β being less than unity (0.44–0.74) suggests the partial covalent character in the metal–ligand bonding.

EPR Spectra

The EPR spectral data of the complexes are presented in Table 4. The X-band EPR spectra of Cr(III) complexes at room



(a)



(b)

FIG. 6. Structure of the complexes: (a) $[Cr(L)X_2]X$, (b) $[Mn(L)X_2]$, where $X = NO_3^-$, Cl^-, and CH_3COO^-.

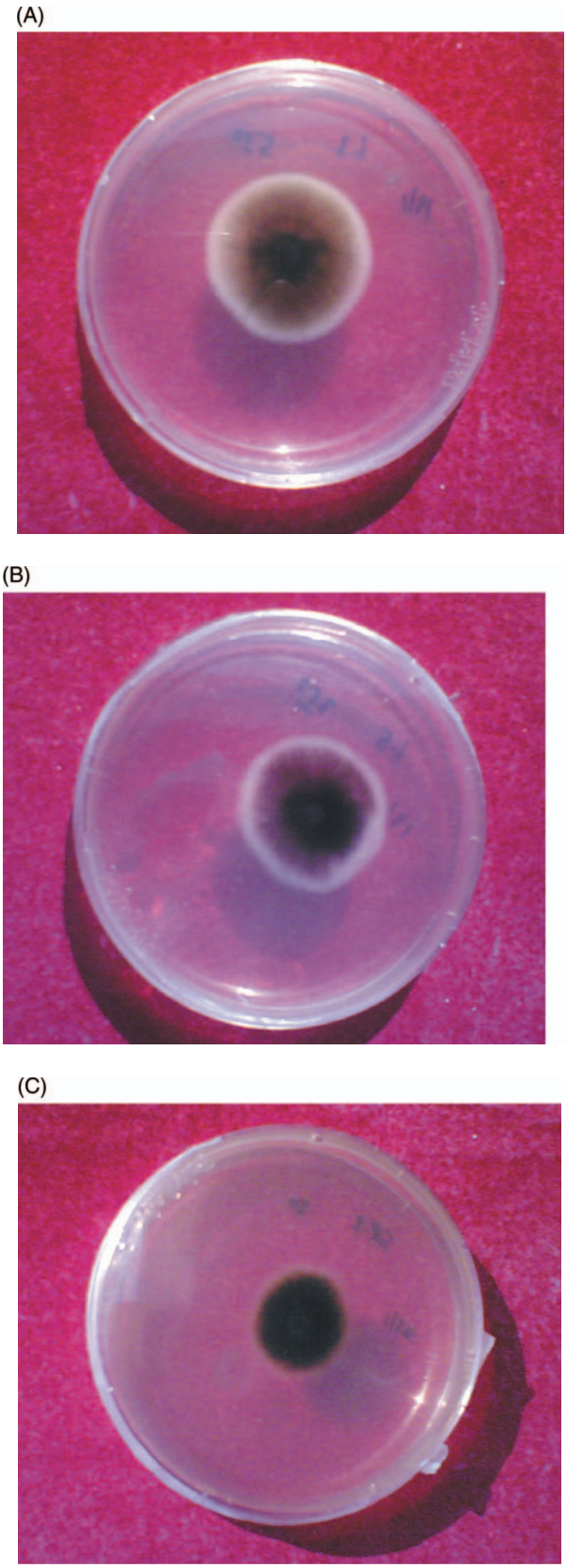


FIG. 7. Fungicidal screening against *A. brassicae* of: (A) ligand, (B) $[Cr(L)(NO_3)_2]NO_3$, and (C) $[Mn(L)Cl_2]$ (color figure available online).

temperature show a broad signal at $g_{iso} = 1.9584-1.9902$ in solid state (Figure 5a). The EPR results of complexes are also consistent with the hexacoordinated environment around the Cr(III) metal ion and octahedral geometry (Figure 6a).[22–24]

The X-band EPR spectra of Mn(II) complexes in polycrystalline form at room temperature as well as liquid nitrogen temperature give only one signal at $g_{iso} = 2.0006–2.3865$ (Figure 5b). However, the EPR spectra in solution form show the hyperfine splitting and give the sextet at $g_{iso} = 1.9974–2.2016$ due to electron spin–nuclear spin coupling (^{55}Mn, $I = 5/2$). The electron spin–nuclear spin hyperfine coupling constant A_{iso} values (88.5–96.0) are consistent with hexabonded environment around Mn(II) metal ion having octahedral geometry (Figure 6b).[22–24]

Pharmacological Studies

The fungicidal investigation data of the compounds are summarized in Table 5. The results of the investigations account for the antipathogenic behavior of the compounds, and this efficacy is positively modified on complexation (Figure 7). Overtone's concept and chelation theory explain well this drug action.[25,26] Moreover, the affinity for genetic material DNA/RNA of microorganisms and the binding of redox metal ion cofactor are key features for pharmaceutical action of the compounds.[27–29]

CONCLUSIONS

The synthesis and mycological investigations of a novel metal binding chelate derived from antipyrine and piperazine derivatives and its complexes have become successful efforts in exploring the pharmaceutical strategies of these two class derivatives (antipyrine and piperazine). The structural analysis of the compounds with physicochemical and spectral studies accounts for the monomeric, stable, paramagnetic, and non-electrolytic or electrolytic nature of the complexes having six-coordinated octahedral chelating environment. Solid-state EPR spectra of both Cr(III) and Mn(II) complexes do not show any hyperfine splitting, but the solution-form EPR spectra of the Mn(II) complexes give six lines due electron spin and nuclear spin interaction. The findings of the fungicidal investigation of the compounds against the opportunistic pathogens reveal that the synthesized compounds have antipathogenic potential.

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