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Mn(III) mixed-ligand complexes with *bis*-pyrazolones and ciprofloxacin drug: synthesis, characterization and antibacterial activities

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The fluoroquinolone family member ciprofloxacin is well known for its drug design and coordinating ability towards metal ions. The coordination chemistry of this drug with metal ions of biological and pharmaceutical importance is of considerable interest. Novel Mn(III) mixed-ligand complexes of ciprofloxacin with various *bis*-pyrazolone-based dinegative bidentate ligands were synthesized and characterized on the basis of their physical properties, magnetic susceptibility measurements, (FT-IR and electronic) spectral studies. The FAB-mass spectrum of $[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$ [where H_2A^9 = 4,4′-(*p*-tolylmethylene)*bis*(3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-ol) and HL = 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid] was determined. All the synthesized compounds were screened for their bioactivity. The mixed-ligand complexes exhibited comparable activities against two Gram-negative (*Escherichia coli* and *Serratia marcescens*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) microorganisms. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: Mn(III) mixed-ligand complexes; *bis*-pyrazolones; ciprofloxacin; spectral studies; *in vitro* antibacterial studies

Introduction

Research on the coordination chemistry of manganese is driven by the biomimetic chemistry associated with manganese present in the active sites of several enzymes,[1] such as superoxide dismutase,[2] peroxidase[3,4] and oxygen evolving complex in photosystem II.[5,6] Manganese in +3 state is also very importantly found in many enzyme protein systems like conalbumin,[7] transferring,[8] concanvalinA[9,10] and pyruvate carboxylase.[11] Furthermore, the family of Mn(III) Schiff-base complexes also provides a rich series of structural types that can be used as models for the magnetic and structural properties of manganoenzymes.[12–15] Inorganic chemists have contributed to the understanding of the structural and mechanistic key motifs of these processes in different ways, but one of the most common approaches has been the modeling of biological systems with artificial inorganic complexes.[16–18]

Fluoroquinolones represent an important group of chemotherapeutic compounds, which exhibit high antibacterial activities. An efficient representative of this group, ciprofloxacin [1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid] (HL), is a second-generation fluoroquinolone family antibacterial agent and widely used in clinical practice as a broad-spectrum antimicrobial agent.[19] It is evident that a variety of functional groups originate reactivity toward unforeseen targets such as metal cations. The design of metal–drug complexes is of particular interest in pharmacological research. Metal combinations with pharmaceutical agents are known to improve the drugs' activity, to decrease their toxicity and provide the ability to act as a regulator for gene expression and a tool for microbiology.[20,21] Quinolone antibiotics are chelating agents for a variety of metal ions well known for their biological activity.[22–24]

The cordination chemistry of pyrazolones has been widely reported[25–27] and its derivatives are particularly interesting because of their potential application in medicinal chemistry[28] as analgesic,[29] anti-inflammatory[30] and therapeutic agents and for their sedative–hypnotic activity.[31–35] As an example, edaravone(3-methyl-1-phenyl-2-pyrazolin-5-one) has recently been shown to produce marked attenuation of brain damage caused by ischemia–reperfusion,[36] and its pharmacological actions were attributed to its antioxidant activity, as a potent hydroxyl radical scavenger.[37] Similarly, a few 1,5-diarylpyrazole derivatives exhibit non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[38] Recently pyrazolone derivatives have been extensively reported to have potent activity of inhibiting Protease-Resistant Proin protein accumulation.[39] In view of the importance of manganese (III) compounds and our interest in the chemistry of coordination compounds involving pyrazolone-based ligands,[40,41] we report here the synthesis of novel Mn(III) mixed-ligand complexes with *bis*-pyrazolones and ciprofloxacin drug.

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Table 1. Analytical and physical data of mixed-ligand complexes

Sample no.	Compounds	Formula weight (g mol^{-1})	Color (yield %)	Melting point (°C)	Analysis (%) Found (calcd) C	H	N	M	μ_{eff} (BM)
X	$[Mn(A^1)(L)(H_2O)_2]\cdot 2H_2O$ $C_{44}H_{46}FMnN_8O_{11}$	936.27	Dark green (74)	220	56.40 (56.41)	4.92 (4.95)	11.92 (11.96)	5.84 (5.86)	4.82
XI	$[Mn(A^2)(L)(H_2O)_2]\cdot H_2O$ $C_{44}H_{44}ClFMnN_7O_8$	907.23	Brown (81)	173	58.13 (58.19)	4.85 (4.88)	10.79 (10.80)	6.02 (6.05)	4.89
XII	$[Mn(A^3)(L)(H_2O)_2]\cdot 0.5H_2O$ $C_{44}H_{44}FMnN_7O_{7.5}$	864.26	Brown (78)	210	61.09 (61.11)	5.11 (5.13)	11.33 (11.34)	6.32 (6.35)	4.62
XIII	$[Mn(A^4)(L)(H_2O)_2]\cdot 2H_2O$ $C_{44}H_{47}FMnN_7O_{10}$	907.27	Red (80)	197	58.18 (58.21)	5.20 (5.22)	10.77 (10.80)	6.01 (6.05)	4.87
XIV	$[Mn(A^5)(L)(H_2O)_2]\cdot H_2O$, $C_{45}H_{47}FMnN_7O_9$	903.28	Brown (76)	193	59.78 (59.80)	5.22 (5.24)	10.81 (10.85)	6.06 (6.08)	4.81
XV	$[Mn(A^6)(L)(H_2O)_2]\cdot 1.5H_2O$ $C_{45}H_{48}FMnN_7O_{10.5}$	928.28	Reddish brown (82)	295	58.16 (58.19)	5.20 (5.21)	10.54 (10.56)	5.90 (5.91)	4.68
XVI	$[Mn(A^7)(L)(H_2O)_2]\cdot 2H_2O$ $C_{44}H_{46}FMnN_8O_{11}$	936.27	Reddish brown (78)	282	56.39 (56.41)	4.92 (4.95)	11.94 (11.96)	5.83 (5.86)	4.74
XVII	$[Mn(A^8)(L)(H_2O)_2]\cdot 2H_2O$ $C_{44}H_{47}FfeN_8O_{9.5}$	936.27	Red (79)	287	57.73 (57.76)	4.90 (4.95)	11.95 (11.99)	5.81 (5.86)	4.86
XVIII	$[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$ $C_{45}H_{47}FMnN_7O_8$	887.29	Orange (74)	291	60.87 (60.88)	5.33 (5.34)	11.01 (11.04)	6.17 (6.19)	4.81

Experimental

Materials and Methods

All the chemicals used were of analytical grade and used without further purification. The compound 1-phenyl-3-methyl-2-pyrazoline-5-ol was purchased from E. Merck Ltd (India). The *bis*-pyrazolone-based ligands (H_2A^n) (where $n = 1-9$) were synthesized according to the procedure described in the literature.[42] Ciprofloxacin hydrochloride was purchased from Bayer AG (Wuppertal, Germany). In this work, manganese (III) mixed-ligand complexes were synthesized using manganese (III) acetate prepared using Gündüz's method.[43] Luria broth was purchased from Hi-media Laboratories Pvt. Ltd, India.

Instruments

Carbon, hydrogen and nitrogen were analyzed with the Perkin–Elmer (USA) 2400-II CHN analyzer. Manganese was determined gravimetrically[44] after decomposing the mixed-ligand complexes with a mixture of concentrated $HClO_4$, H_2SO_4 and HNO_3 (1 : 1.5 : 2.5). Infrared spectra (4000-400 cm^{-1}) were recorded on Nicolet-400D spectrophotometer using KBr pellets. The FAB mass spectrum of the complex was recorded at SAIF, CDRI, Lucknow with a Jeol SX- 102/DA-6000 mass spectrometer. The magnetic moments were obtained by Gouy's method using mercury tetrathiocyanato cobaltate (II) as a calibrant ($g = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Diamagnetic corrections were made using Pascal's constant. Electronic spectra were recorded on a Shimadzu 160A UV–vis spectrophotometer using DMF as the solvent blank.

Antibacterial Assays – Inhibition Zone Technique

The antimicrobial sensitivity testing was performed by agar cup method. The agar medium was poured into the Petri plates. After solidifications, the Petri plates were stored in inverted position so that there was condensation of water in the upper lid. Solutions of test compounds in DMF in 500 and 1000 ppm concentrations were prepared. A 0.1 mL aliquot of young test culture was inoculated in melted top agar previously cooled to 50 °C and poured over nutrient agar and allowed to solidify. With a sterile cup borer four cups were made in each quadrant, at equal distance in nutrient agar plate previously seeded with test culture. Each cup was filled with 0.1 ml of test sample. The Petri plates having these cups on the seeded agar were first placed at low temperature for 2–4 h to allow for the diffusion of chemicals before being incubated at suitable optimum temperature of 37 ± 2 °C for 24–30 h. After the expiry of their incubation period, the zone of inhibition associated with the treated disk was measured in millimeters. The antibacterial activity of the control, standard drug (ciprofloxacin), metal salts, ligands (H_2A^n) and their mixed ligand complexes were screened against two Gram-negative (*Escherichia coli* and *Serratia marcescens*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) microorganisms using Agar-plate technique.[45] The above-mentioned four bacterial strains are the preliminary screening test organisms of choice for several reasons. *Escherichia coli* and *Serratia marcescens* are responsible for dehydration, blood transfusions and urinary tract infections, while *Staphylococcus aureus* and *Bacillus subtilis* cause pneumonia, meningitis and skin conditions.

General Procedure for the Synthesis of Mixed-ligand Complexes

The preparation of Mn(III) mixed-ligand complexes was carried out by mixing hot methanolic solution (50 ml) of $Mn(CH_3COO)_3\cdot 2H_2O$ (10 mmol) and a hot methanolic solution (50 ml) of the ligand (H_2A^n) (10 mmol) and HL ligand (10 mmol) in distilled water. The pH was adjusted to 6.0–7.0 by dropwise addition of dilute NaOH solution. The resulting mixture was heated in a water bath for 3–4 h at 60 °C. The mixture was kept overnight at room temperature. The obtained colored crystals were washed with water, methanol and finally with diethyl ether and dried over vacuum desiccators. Physicochemical parameters for all the mixed-ligand complexes are summarized in Table 1.

Table 2. The characteristic IR bands of ligand (HL)[a] and their mixed-ligand complexes

Compounds	ν(O–H)	ν(C=O)	ν(COO$^-$) Antisymmetric	ν(COO$^-$) Symmetric	$\Delta\nu$	ν(C–O)	ν(M–O)pyrazolone	ν(M–O)ketone
HL	–	1635	1618	1384	234	–	–	–
$[Mn(A^1)(L)(H_2O)_2]\cdot 2H_2O$	3410	1620	1610	1390	220	1327	452	411
$[Mn(A^2)(L)(H_2O)_2]\cdot H_2O$	3422	1622	1592	1374	218	1334	458	419
$[Mn(A^3)(L)(H_2O)_2]\cdot 0.5H_2O$	3425	1622	1597	1382	215	1326	443	422
$[Mn(A^4)(L)(H_2O)_2]\cdot 2H_2O$	3420	1625	1600	1378	222	1326	456	418
$[Mn(A^5)(L)(H_2O)_2]\cdot H_2O$	3427	1619	1595	1380	215	1329	460	415
$[Mn(A^6)(L)(H_2O)_2]\cdot 1.5H_2O$	3415	1620	1594	1384	210	1343	446	416
$[Mn(A^7)(L)(H_2O)_2]\cdot 2H_2O$	3427	1618	1599	1382	217	1326	452	418
$[Mn(A^8)(L)(H_2O)_2]\cdot 2H_2O$	3422	1618	1600	1382	218	1337	440	423
$[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$	3425	1622	1595	1387	208	1329	458	418

[a] HL = 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

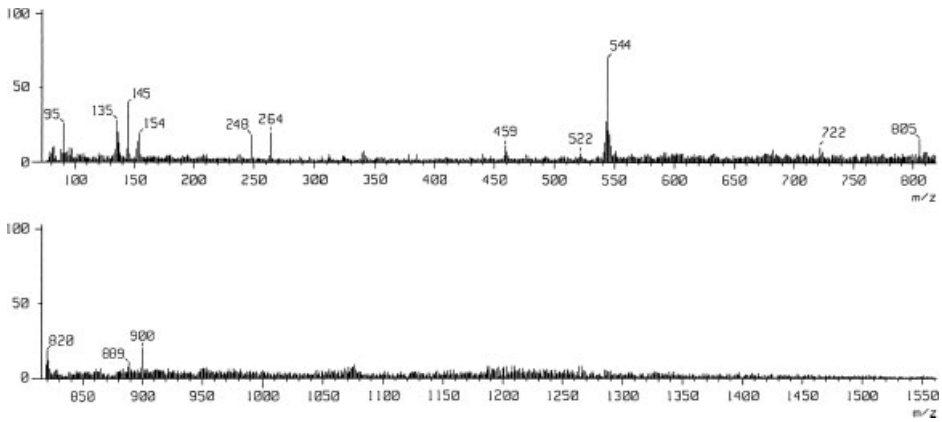


Figure 1. The typical FAB-mass spectrum of a mixed-ligand complex $[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$.

Results and Discussion

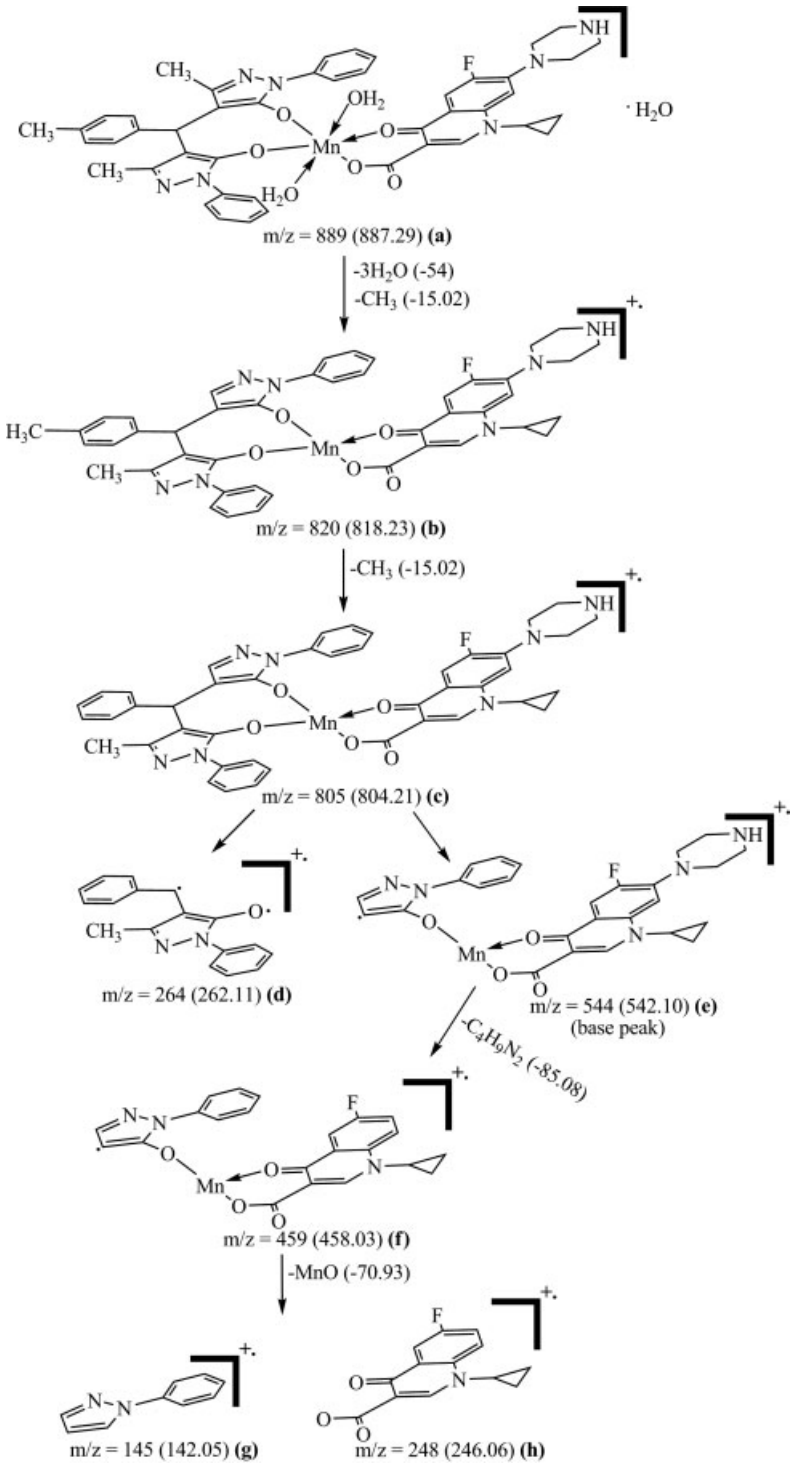
The structural investigation of all the prepared *bis*-pyrazolone ligands (H_2A^n) (where $n = 1–9$) was done using elemental analyses, IR, ^{1}H and ^{13}C NMR and DEPT-135 spectroscopy and data were published elsewhere.[42] The mixed-ligand complexes were prepared in aqueous solution by reacting manganese (III) acetate with ciprofloxacin (HL) and variable *bis*-pyrazolone ligands (H_2A^n) (where $n = 1–9$) in a 1:1:1 ratio. The pH plays a vital role in precipitating the mixed ligand complex in aqueous solution. The analytical and physical data of the mixed-ligand complexes are given in Table 1. Complexes were sparingly soluble in water, ethanol, methanol and chloroform, whereas they were completely soluble in DMF and DMSO. All the complexes were stable in air for extended period of time. When treated with KI, iodine was liberated. This was an indirect indication of Mn being in +3 oxidation state, which was further supported by the solid state magnetic moments (Table 1).

Spectroscopic Studies of Mixed-ligand Complexes

Infrared spectra

The IR spectral data of ciprofloxacin (HL) and their mixed-ligand complexes are shown in Table 2. Comparing the main IR frequencies of Mn(III) mixed-ligand complexes with that of ciprofloxacin (HL) ligand, the following results were found. Two very strong absorption peaks in the spectrum of the ligand were observed at 1707 and 1635 cm^{-1} due to ν(O–H) of the carboxylic group and ν(C=O) group, respectively. The absence of the former band in the spectra of the mixed-ligand complexes suggests that this moiety participated in the bonding to the metal ion.[46] The later band corresponding to ν(C=O) shifted to the lower frequency region (~1620 cm^{-1}) in the spectra of the mixed-ligand complexes could be due to coordination through either the ketone group or the carboxylic group bonded to the metal ion. We confirm that the coordination was through the ketonic group of the HL ligand as the antisymmetric and symmetric modes of the carboxylate group were observed at 1618 and 1384 cm^{-1}, respectively. The ν_{as}(COO$^-$) and ν_s(COO$^-$) vibrational frequencies, together with the ν(COO$^-$) values for the carboxylate group of the ciprofloxacin (HL) ligand and their mixed-ligand complexes are listed in Table 2. The frequency separation [$\Delta\nu = \nu_{as}$(COO$^-$) – ν_s(COO$^-$)] in the investigated mixed-ligand complexes was greater than 200 cm^{-1}, suggesting that the carboxylate group has a unidentate nature.[47–49] Accordingly ciprofloxacin (HL), in the isolated mixed-ligand complexes appears to act as a uninegative bidentate ligand through the oxygen atom of the carbonyl group and enolic oxygen of the carboxylate group.

The mixed-ligand complexes have similar IR spectra which differ from that of (H_2A^n) (where $n = 1–9$). All the ligands (H_2A^n) in the present investigation exhibit a broad band centered



Scheme 1. The suggested fragmentation pattern of $[Mn(A^9)(L)(H_2O)_2]^{\bullet}$ H_2O.

at 3390–3410 cm^{-1}. We assigned this peak to ν(O–H) for the intramolecular hydrogen-bonded (H···O–H) form between two 5-OH groups. In the mixed-ligand complexes, the ligand (H_2A^n) must coordinate to metal ions with the deprotonated enol form L^{2-}. The reaction of the enolic ligands with Mn^{3+} ion is revealed by the presence of a new band in the spectra of mixed-ligand complexes at 1326–1343 cm^{-1} due to the ν(C–O) (enolic).[50,51]

In the investigated complexes, the bands observed in the regions 3410–3427, 1628–1635, 845–873 and 705–715 cm^{-1} were attributed to -OH stretching, bending, rocking and wagging vibrations, respectively, due to the presence of water molecules. The presence of rocking band indicates the coordination nature of the water molecule.[47] In the far-IR region, two new bands at 440–465 and 411–423 cm^{-1} in the mixed ligand complexes were assigned to $\nu(M-O)_{pyrazolone}$ and $\nu(M-O)_{ketone}$ of HL modes, respectively.

Table 3. Electronic spectral data of free ligands (H_2A^n) and their mixed-ligand complexes

Compounds	ILCT ($\pi \rightarrow \pi^*$) transition in cm^{-1}	d–d transitions in cm^{-1}
H_2A^1	32 500	–
H_2A^2	32 600	–
H_2A^3	32 600	–
H_2A^4	32 500	–
H_2A^5	32 650	–
H_2A^6	32 600	–
H_2A^7	32 500	–
H_2A^8	32 550	–
H_2A^9	32 550	–
$[Mn(A^1)(L)(H_2O)_2]\cdot 2H_2O$	32 443	20 200
		18 181
$[Mn(A^2)(L)(H_2O)_2]\cdot H_2O$	32 467	20 050
		18 256
$[Mn(A^3)(L)(H_2O)_2]\cdot 0.5H_2O$	32 487	21 224
		18 450
$[Mn(A^4)(L)(H_2O)_2]\cdot 2H_2O$	32 450	21 324
		–
$[Mn(A^5)(L)(H_2O)_2]\cdot H_2O$	32 550	20 062
		–
$[Mn(A^6)(L)(H_2O)_2]\cdot 1.5H_2O$	33 134	20 080
		17 860
$[Mn(A^7)(L)(H_2O)_2]\cdot 2H_2O$	32 523	20 226
		17 942
$[Mn(A^8)(L)(H_2O)_2]\cdot 2H_2O$	32 367	20 050
		–
$[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$	33 464	21 342
		18 067

All of these data confirm the fact that *bis*-pyrazolones (H_2A^n) behave as a dinegative bidentate ligand, forming a conjugated chelate ring with existing mixed-ligand complexes in the enolized form.

FAB-mass spectra

The recorded FAB mass spectrum (Fig. 1.) and the molecular ion peak for the mixed-ligand complex $[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$ were used to confirm the molecular formulae. The proposed fragmentation pattern is shown in Scheme 1. The first peak at *m/z* 889 represents the molecular ion peak of the complex. Scheme 1 demonstrates the possible degradation pathway for the investigated mixed ligand complex. The primary fragmentation of the mixed-ligand complex takes place due to the loss of three H_2O molecules and one–CH_3 moiety from the species (a) to give to species (b) with a peak at *m/z* 820. The species (b) further degrades to give species (c) with the loss of one of the–CH_3 moieties. The species (c) further degrades to give species (d) (*m/z* 264) and the sharp peak (base peak) observed at *m/z* 544 represents the stable species (e) with 99.5% abundance. Species (e) further degrades with the loss of–$C_4H_9N_2$ moieties forming species (f) with a peak at *m/z* 459. The species (f) further degrades to give species (g) (*m/z* 145) and species (h) (*m/z* 248), leaving the MnO residues. The measured molecular weights for all the suggested degradation steps were consistent with expected values.

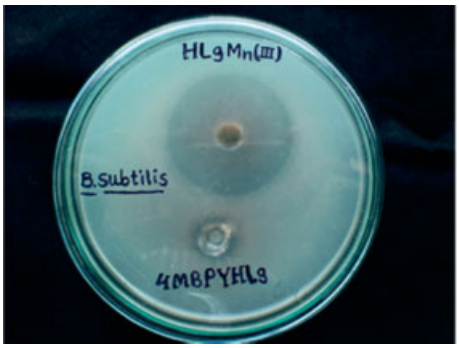


Figure 2. Zone of inhibition (mm) of *Bacillus subtilis* in ligand H_2A^9 and its mixed-ligand complex $[Mn(A^9)(L)(H_2O)_2]\cdot H_2O$.

Electronic Spectroscopy and Magnetic Moment Measurements

The information regarding geometry of the Mn(III) mixed-ligand complexes was obtained from their electronic spectra data and magnetic moment values. The magnetic moment values of Mn(III) complexes were in the range 4.62–4.89 B.M.[40] The electronic spectra data of the free ligands (H_2A^n) and their complexes are presented in Table 3. The electronic spectra of free ligands showed an intense band at ~32 600 cm^{-1}. The high intensity of this band may be due to $\pi \rightarrow \pi^*$ intra-ligand charge transfer transition. In the present work, electronic spectra of Mn(III) mixed-ligand complexes yielded one charge transfer band and multiple d–d transitions. The present mixed-ligand complexes are all six coordinated; therefore, either octahedral or distorted octahedral geometry around the metal ion is expected. The appearance of two bands in the present mixed-ligand complexes suggests them to possess distorted octahedral structures. Such distortion is most probably due to the Jahn–Teller effect as well as the steric effect of the bulky ligands. Keeping in view the distorted octahedral structures, the bands observed at ~20 200 cm^{-1} for X, XI, XIV, XV, XVI and XVII and ~21 300 cm^{-1} for XII, XIII and XVIII compounds can be assigned to the $^5B_{1g} \rightarrow {}^5E_g$ transition. Similarly, the second shoulder observed near 17860–18450 cm^{-1} can be assigned to the $^5B_{1g} \rightarrow {}^5B_{2g}$ transition.[52] The highly intense band observed near 32 500 cm^{-1} may be due to $\pi \rightarrow \pi^*$ intra-ligand charge transfer transition. From the magnetic measurement and electronic spectra data, a six-coordinated distorted octahedral stereochemistry is proposed for all the mixed-ligand complexes.

Antimicrobial Screening

The Mn(III) mixed-ligand complexes exhibit comparable activities against two Gram-negative, i.e. *Escherichia coli* and *Serratia marcescens* and two Gram-positive, i.e. *Staphylococcus aureus* and *Bacillus subtilis* microorganisms. The results concerning *in vitro* antimicrobial activity of the ligands (H_2A^n) and their mixed-ligand complexes are represented in Table 4. The antimicrobial activity of all the mixed-ligand complexes against the four microorganisms is much higher than metal salts and ligands (H_2A^n) while in competition with the ciprofloxacin. It was observed that all the complexes were more potent bacteriostatics than the ligands (H_2A^n). This is because of increase in cell permeability. The lipid membrane that surrounds the cell favors the passage of only lipid soluble materials and it is known that liposolubility is an important factor controlling antimicrobial activity. By complexation, the ionic groups and the electron delocalization over the ligand molecules participate in

Table 4. *In vitro* antimicrobial activity of the compounds (mm)

Compounds	Gram^{+ve}		Gram^{-ve}	
	Bacillussubtilis	*Staphylococcusaureus*	*Escherichiacoli*	*Serratia marcescens*
$Mn(CH_3COO)_3 \cdot 2H_2O$	12	–	11	11
Ciprofloxacin (HL)	44	52	34	44
I	17	14	–	–
II	11	13	–	–
III	11	12	–	–
IV	12	–	–	–
V	09	12	11	–
VI	10	12	–	–
VII	11	15	–	–
VIII	13	14	–	–
IX	13	11	15	–
X	38	41	31	–
XI	36	38	29	33
XII	40	37	30	30
XIII	40	38	30	40
XIV	38	39	30	–
XV	41	42	31	–
XVI	39	45	32	38
XVII	39	38	30	–
XVIII	37	–	32	40

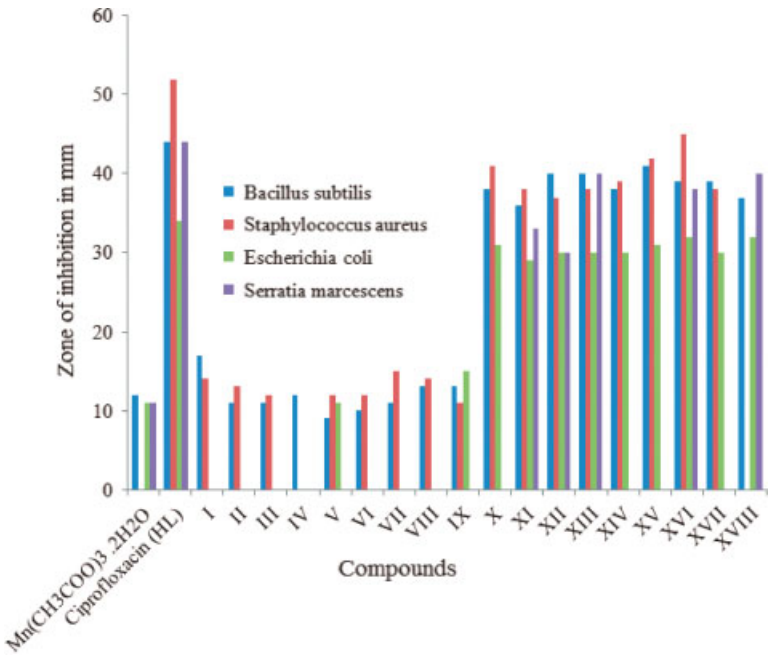
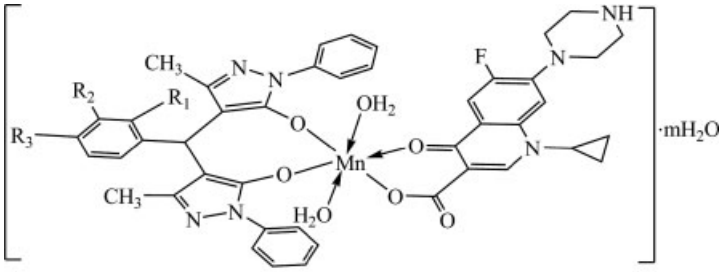


Figure 3. The plot of antibacterial activities of mixed-ligand complexes.

the complex molecule which in turn increases the hydrophobic character of the metal chelate and increases the liposolubility, thus favoring its permeation through the lipoid layer of microorganism. It therefore confirms that chelation of the nonionic ligands with transition metals tends to make the ligands act as more powerful and potent bactericides. The photograph of the zone of inhibition in the case of ligand H_2A^9 (i.e. 4 MBPYHL$_9$) and its mixed-ligand complex $[Mn(A^9)(L)(H_2O)_2]^{\bullet}H_2O$ [i.e. HL$_9$ Mn(III)] is shown in Fig. 2. The results showed that there is considerable increase in the area of inhibition of some of the complexes as compared with the ligands, metal salt and standard drug ciprofloxacin. On taking a closer look at these results, a common feature that appears is that the bioactivity enhances chelation. A possible mode for increase in biocidal activity may be considered in light of Overtone's concept[53,54] and Tweedy's chelation theory.[55,56] According to this, the chelation reduces the polarity of the central atom mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization over the whole



Compounds	R_1	R_2	R_3	mH_2O
X	-H	-H	$-NO_2$	$2H_2O$
XI	-H	-H	-Cl	H_2O
XII	-H	-H	-H	$0.5H_2O$
XIII	-H	-H	-OH	$2H_2O$
XIV	-H	-H	$-OCH_3$	H_2O
XV	-H	$-OCH_3$	-OH	$1.5H_2O$
XVI	-H	$-NO_2$	-H	$2H_2O$
XVII	$-NO_2$	-H	-H	$2H_2O$
XVIII	-H	-H	$-CH_3$	H_2O

Figure 4. The proposed structure of mixed-ligand complexes.

chelation ring. This increases the lipophilic nature of the central manganese atom, which subsequently favors its permeation through the lipid layer of the cell membrane. The comparison of the area of zone of inhibition of ligands (H_2A^n) and their mixed-ligand complexes with the standard drug ciprofloxacin and metal salt is shown in Fig. 3. It appears from the observed results that Mn(III) complexes may be able to maintain a good antibacterial activities and be an effective antibacterial broad-spectrum drug that may be able to solve some antibacterial resistance problems.

Conclusions

bis-Pyrazolone-based ligands (H_2A^n) (where $n = 1-9$) were prepared and characterized as per our earlier reports.[42] We synthesized a series of novel drug-based Mn(III) mixed-ligand complexes with ciprofloxacin and *bis*-pyrazolone-based ligands and characterized their properties. For all the mixed-ligand complexes, an octahedral environment around Mn(III) was suggested (Fig. 4). All the synthesized compounds were screened for their bioactivity. The mixed-ligand complexes exhibited strong activities against two Gram-negative (*Escherichia coli* and *Serratia marcescens*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) microorganisms. It appears from the observed results that Mn(III) complexes may be able to maintain a good antibacterial activities and be an effective antibacterial broad-spectrum drug that may be able to solve some of antibacterial resistance problems.

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