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RESEARCH ARTICLE

Potential Antimicrobial Properties of Two New Synthetic Metal Complexes Containing a Tetradentate Schiff Base.

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Abstract

Two new Schiff base metal complexes namely [Mn(H_2L)$(NCS)_2$] (1) and[Co (H_2L)$(NCS)_2$] (2)where L= [{2, 2´-[(1E, 2E)-ethane-1,2-diylidenedi (E) azanylylidene] dibenzenethiol}], have been synthesized by reacting equimolar amounts of the respective metal perchlorate and the tetradentate Schiff base, H_2L in methanol. The complexes have been characterized by spectroscopic and physicochemical studies. The antibacterial and antifungal activities of the ligand and complexes (1and 2) have been tested against some Gram positive, Gram negative bacteria and fungal strain. Manganese complex (compound 1) had higher antibacterial and antifungal effect in comparison to cobalt complex (compound 2). Again Gram positive bacteria were more susceptible to the metal complexes than the Gram negative bacteria. The metal complexes had moderate effect in human pathogenic fungus *Candida albicans* but stronger effect in plant pathogen *Aspergillus niger*. Both metal complexes had higher antimicrobial and antifungal effect than the free ligands.

INTRODUCTION

Many biologically active compounds when coordinated to metals like cobalt, manganese, zinc, copper, nickel may exhibit modified pharmacological and toxicological potential which can have medicinal importance (Ming, 2003). A large number of Schiffbases and their complexes are of significant interest and attention because of their biological activity including anti-tumor, antibacterial, fungicidal and anti-carcinogenic properties (Ren et al., 2002), (Raman et al., 2003) which are due to have their azomethine linkage (Etaiw et al., 2011). Schiff bases can be easily prepared by condensing carbonyl compounds and amines in different conditions and in different solvents with the elimination of water molecules. Schiff base ligands are able to coordinate different metals (Cozzi 2004) and to stabilize them in various oxidation states. Commonly used metals to form Schiffbase metal complexes are cobalt, copper, nickel, zinc, manganese, because of their low molecular weight and therefore prove to be more beneficial against several diseases (Ruiz et al., 1995),(Castillo-Blum and Berhans-Barba 2000). Metal complexes of Schiff bases containing nitrogen, sulfur and/or oxygen as chelating atoms are considered as simple structural models of more complicated biological systems (Sakyan et al., 2004). In recent years, the metal complexes with tridentate S, N, N types have attracted the attention of chemist because of their applications found in the field of pesticides and medicine. Recently, wide varieties of Co(II) Ni(II), Cu(II) and Zn(II) complexes of Schiff base derivatives were tested in vitro for their antibacterial activities against human pathogenic bacteria (Sang and Lin, 2010),(Issa et al., 2009),(Xiong, 2013) and for cytotoxic activity (Li et al., 2012),(Chohan et al., 2010) where the metal complexes have higher antimicrobial and antifungal activity than the free ligands.

In the present work, we have reported the synthesis of a Schiff base ligand H_2L [{2, 2´-[(1E, 2E)-ethane-1,2-diylidenedi (E) azanylylidene] dibenzenethiol}] and its metal complexes such as [Mn(H_2L)$(NCS)_2$] and[Co (H_2L)$(NCS)_2$] and characterization of the ligand and metal complexes by IR and NMR spectroscopy and tested against bacteria and fungus with the main aim to investigate if the novel compounds are potent antimicrobial agents as well as to make a comparison of their biological activities.

EXPERIMENTAL PROTOCOL

Materials and Methods

All the chemicals and solvents used in the syntheses were of reagent grade and used as received without further purification. Elemental analyses were carried out on a Perkin-Elmer 2400-II elemental analyzer. The infrared spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrophotometer with KBr discs (4000−400 cm^{-1}). ^1H NMR spectra of compounds and ligand were recorded with a Bruker DRX500 using $CDCl_3$ as solvent. Melting point/decomposition temperature was determined with a Mettler FP62 melting point analyzer. Analytical and physical data of ligand and their complexes are presented in Table 1.

Synthesis of ligand

H_2L [{2, 2'-[(1E, 2E)-ethane-1, 2-diylidenedi (E) azanylylidene] dibenzenethiol}]

To a solution of glyoxal (0.232gm, 4 mmol) in methanol (50 ml) was added 2-aminothiophenol (1gm, 8 mmol). The mixture was refluxed for six hours and cooled to room temperature. The volume was reduced to approximately 10 ml and the solution was stored overnight. The orange red precipitate that formed was separated and dried. MP. 95°C IR: 417.95cm^{-1}, 455.99cm^{-1}, 728.68 cm^{-1}, 749.13 cm^{-1}, 1685.54 cm^{-1}, 2075.43 cm^{-1}, 3367.17 cm^{-1}. ^1H NMR: δ 1.61, δ 5.23, δ 6.5, δ 8.16.

Synthesis of complexes

Synthesis of compound 1 [$Mn(H_2L)(NCS)_2$]

To a methanolic solution (20 ml) of manganese perchlorate hexahydrate(0.361gm, 1 mmol) a methanolic solution (20 ml) of Schiff base (0.272gm,1 mmol) was added with constant stirring, followed by addition of a methanolic solution (5ml) of NH_4SCN (0.078gm,1mmol). Stirring was continued for further half an hour and the solution was left as such for slow evaporation. Fine crystalline compound was obtained after 15 days. MP 121°C. IR:421.06 cm^{-1}, 452.98 cm^{-1}, 729.97cm^{-1}, 762.15 cm^{-1}, 1626.47 cm^{-1}, 2076.79 cm^{-1}, 3434.93 cm^{-1}. ^1H NMR: δ 7.5, δ 8.165, δ 7.99.

Synthesis of compound 2 [$Co (H_2L)(NCS)_2$]

Compound 2 was also synthesized in the same way as previous methods. Cobalt perchlorate hexahydrate (0.365gm, 1 mmol) was used for the synthesis and the compound was obtained after 11 days. MP 136°C. IR: 422.1 cm-1, 460.43 cm^{-1},729.75 cm^{-1}, 762.07 cm^{-1}, 1618.63 cm^{-1}, 2085.75 cm^{-1}, 3430.11 cm^{-1}. ^1H NMR: δ 7.46, δ 8.12, δ 8.0.

Microbial strains

Freeze dried microbial culture were purchased from Institute of Microbial Technology, Chandigarh (MTCC).The fungal microorganisms chosen to test antimicrobial activity of the synthesized compounds were *Candida albicans*(MTCC 183) and *Aspergillus niger* (MTCC 10180). On the other hand two Gram positive bacteria *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 96) and two Gram negative bacteria *Klebsiella pneumoniae* (MTCC 39) and *Proteus mirabilis* (MTCC 425) were used as the bacterial microorganism.

Antimicrobial screening

The standardized disc agar diffusion method (Bauer-Kirby 1966) was applied to determine the activity of the new compounds against the sensitive organism. The test compounds were dissolved in dimethylsulfoxide (DMSO) to get concentration of 2 mg/ml. Gentamicin disc (Himedia, Mumbai, India) was used as a standard reference in case of bacteria while Fluconazole disc (Himedia, Mumbai, India) was used as a standard antifungal reference and DMSO were used as negative control as they have no inhibition activity. After incubation for 24 hrs at 37ºC in case of bacteria and for 48 hrs at 30ºC in the case of fungi, inhibition of the organism evidenced by class zone surround each disc was measured and used to calculate mean of inhibition zones (mm).

The activity of test compounds were categorized as i) low activity= mean zone diameter $\leq$ 1/3 of the mean zone diameter of control ii) intermediate activity= mean zone diameter $\leq$ 2/3 of the mean zone diameter of control and iii) high activity= mean zone diameter $\geq$ 2/3 of the mean zone diameter of control.

Determination of minimum inhibitory concentration (MIC)

The minimal inhibitory concentration (MIC, µg/mL) of the compounds were estimated by broth microdilution method (NCCLS 1999) against the bacterial strain in a 96 well microtiter plates over the range 0.02-2 mg/ml. All tests were performed in Muller Hinton broth (Himedia, Mumbai, India). The inoculated plates were then incubated for 37ºC for 24 h. The minimal inhibitory concentration (MIC) was detected as the lowest concentration of the test compound in plate at which no visible growth of microorganism found. All tests were performed in triplicate for each microorganism tested.

RESULT AND DISCUSSION

IR spectra

IR spectroscopy have proven to be the most efficient technique to give enough information to illustrate the way of bonding of the ligands to the metal ions, particularly in the absence of a commanding technique such as X-ray crystallography. In order to study the binding mode of the Schiff base to the metal ion in the complexes, the IR spectrum of the free Schiff base was compared with the spectra of the transition metal complexes. These peaks change either in their positions and/or their intensities upon chelation. In the IR spectra of ligand (Fig. 1a), the absence of υ SH absorption band in the region 2600-2550 cm^{-1} and appearance of a strong and sharp υ (NH) and ∂ (NH) at 3375 cm^{-1} and 1676 cm^{-1} respectively in the ligands is a strong evidence for the existence of benzothiazoline structure of these ligands (Sharma et al., 1980) and not the Schiff base structure.

In the spectra of metal complexes (Fig 1. b and c), band due to N-H vibration disappear, indicating the chelation of nitrogen with the metal ion, and a new band at 1600 cm^{-1} is observed, which can be assigned to υ (C=N). This band suggests that in the presence of metal ion, the benzothiazoline ring rearranges (Scheme 1) to give the Schiff Base which finally acts as the tri-or tetradentate ligand.

Presence of thiocyanate, for which strong absorptions in the 2110-2075 cm^{-1} region remain isolated, is confirmed by infrared spectroscopy. As thiocyanate is a heteroatomic ambidentate ligand(Dakovic et al., 2008b),(Bai et al.,2008)it shows different molecular architectures through its versatile ligational modes (Scheme 2). The spectra of Co and Mn complexes exhibit a very strong and sharp absorption band in the region of (2075 to 2100 cm^{-1}) (Fig 1. b and c) corresponding to the asymmetric stretching vibrations of the terminal N-bondedthiocyanate ion (Dakovic et al., 2008a),(Xiong, 2013).

The involvement of the SH group in coordination was ascertained from the shift of the υ C–S to lower frequencies from 760.54 cm^{-1} in the free ligand to 729–730 cm^{-1} in the spectra of the complexes (Priyarega et al., 2012),(Tamizha et al., 2012). The appearance of a very weak band at 421–422 $cm^{-1}$and 529- 532 cm^{-1} due to υ M–S(Soliman and Linert, 1999),(Tamizha et al., 2012) and υ M–N (Nakamoto, 2006)respectively, also provides an additional evidence for the participation of the SH group in complex formation.

^{1}H NMR spectra

The azomethine proton signals appear at δ8.00 ppm in the ligand (Fig. 2a), and these are shifted downfield on complexation (δ 8.17 ppm – 8.18 ppm) (Fig. 2b and c). A downfield shift in the resonance signal of aryl protons has also been observed and this may be ascribed to the deshielding of protons due to the coordination of azomethine nitrogen to metal.

The NMR spectra of ligand show NH proton signals at 5.23 ppm, which disappear in the corresponding metal complexes indicating their deprotonation on complexation. The azomethine proton signals of these ligands shift downfield in the spectra of the complexes because of the formation of a coordinate linkage between nitrogen and metal ion (Sharma and Chandra, 2011).

Antimicrobial activity

The results of the antimicrobial activities are summarized in Table 2. The inhibition zone diameter ranged from 8 mm to 23 mm. The Schiff base ligand exhibited very low activity against all the microbial species studied. Both the newly synthesized compounds exhibited considerable antimicrobial properties and the degree of inhibition enhanced in comparison with the parent Schiff base (Table 2). Compounds 1 showed strongest bactericidal activity against all microbial strain studied. It is very clear from the inhibition zone values that both the compounds showed higher activity against Gram positive in comparison to Gram negative bacteria. Again, plant pathogenic fungus was more susceptible to the Mn complex (compound 1) than the human pathogen. The MIC values (Table 3) assessed by broth microdilution method support the results obtained from agar disc diffusion method (Table 2). Lower MIC value indicates more toxic the compound and higher MIC value indicates less toxicity of the compound. Thus the MIC values and IZD (inhibition zone diameter) values indicate both complexes were more toxic towards Gram positive strains than Gram negative strains. Both the strains of the Gram positive bacteria are more sensitive to the Mn complex, but highest activity was found against *B. subtilis*. On the other hand, *K. pneumoniae* was more sensitive toward Mn complex than *P. mirabilis*. The stronger activity of metal complexes against the Gram positive bacteria can be explained by the difference in the cell wall structure (Singh et al.,2009). The walls of the Gram negative cells are more complex and multilayered than those of Gram positive cells because of relatively high lipid content in addition to protein and mucopeptide. The outer layer consists of lipopolysaccharide (LPS) which provide a permeability barrier to the hydrophobic compound (Cohen, 2011).The greater susceptibility of the Gram positive bacteria toward metal complexes in comparison to Gram negative bacteria may be due to the lack of LPS in their outer membrane.

The comparison of antimicrobial activity of the free ligand and its complexes indicates that complexation with metals has a synergistic effect on the antimicrobial activity of these compounds and the antimicrobial activity depends upon the type of metal ion present (Li et al., 2012). The possible reason of higher antimicrobial activity shown by the newly synthesized compounds than it parent ligand can be explained by chelation theory (Emara, 2010). In chelated complex the positive charge of the metal is partially shared with donor groups of the ligands and there is an electron delocalization over the whole chelated ring (Emara, 2010).Thus chelation considerably reduces the polarity of the metal ion thereby enhancing its lipophilic character which subsequently favors its permeation through the lipid layer of the bacterial membrane (Rehman et al., 2005). Further, it has also been suggested that some functional groups such as azomethine (-C=N-) present in these compounds play an important role in antibacterial and antifungal activity (Chohan et al., 2009). However, in Gram negative bacteria an unusual lipid, lipopolysaccharide (LPS) in the outer membrane (outside the peptidoglycan layer) serves as an effective barrier against lipophilic molecules and thus slower the penetration rate of the hydrophobic molecules (Cohen, 2011).

From the in vitro antimicrobial assay, both the novel compounds are found to possess antimicrobial properties but the compound 1 is more potent against all microbes studied. However, bioactivities of synthesized metal complexes are lower than those of the tested commercial antibiotics at similar concentrations. These results suggest that antibacterial activities of the ligand increased after coordination with metal ions. These observations are similar to the bioactivities of those previously reported Mn(II) and Co(II) Schiff-base complexes (Chohan et al., 2010), (Bal and Bal, 2014).

Compound	**Molecular formula**	**Mol. wt. (g/mole)**	**M.P.(ºC)**	**Yield(%)**	**Found (Calc)%**			
					C	**H**	**S**	**N**
Ligand	H_2L	272.88	95	83	61.73%	4.44%	23.54%	10.28%
Mn complex	$[Mn(H_2L)(NCS)_2]$	443.49	121	64	43.33%	2.73%	28.92%	12.63%
Co complex	$[Co(H_2L)(NCS)_2]$	447.48	136	69	42.94%	2.70%	28.66%	12.52%

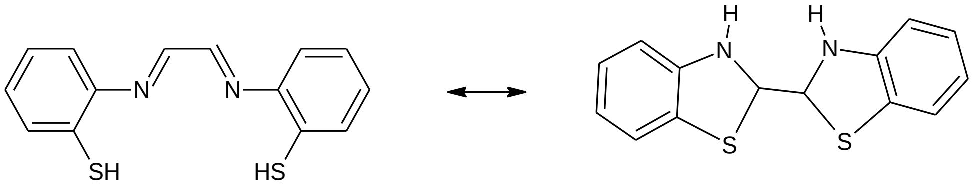
Table 1. Physical measurements and analytical data of the ligand and metal (II) complexes (1&2)

Compound	**Gram-negative bacteria**		**Gram-positive bacteria**		**Fungus**	
	K. pneumoniae	***P. mirabilis***	***S. aureus***	***B. subtilis***	***C. albicans***	***A. niger***
Ligand (H_2L**)**	6 ± 0.80	8 ± 0.40	8 ± 0.60	8 ± 0.30	6 ± 0.90	6 ± 0.50
$[Mn(H_2L)(NCS)]$	14 ± 0.50	10 ± 0.90	14 ± 0.80	23 ± 0.40	14 ± 0.60	20 ± 0.70
$[Co(H_2L)(NCS)_2]$	8 ± 0.80	8 ± 0.70	9 ± 0.70	10 ± 0.40	8 ± 0.50	10 ± 0.60
Gentamicin	25 ± 0.02	22 ± 0.09	23 ± 0.02	33 ± 0.04	-	-
Fluconazole	-	-	-	-	34 ± 0.00	30 ± 0.00

Table 2. Disc diffusion study showing the inhibition zone diameter (mm) of metal complexes (1and 2) and the ligand against bacterial and fungal strain. Results are mean ± S.E of triplicate experiments.

Compounds	***K. pneumoniae***	***P. mirabilis***	***S. aureus***	***B. subtilis***
$[Mn(H_2L)(NCS)]$	> 80	> 100	> 50	< 50
$[Co(H_2L)(NCS)_2]$	>200	> 400	< 300	< 200
Gentamicin	15	15	10	10

Table3. MIC value (µg/mL) of metal complexes (1 & 2) for different microorganism tested. Lower MIC value was found in Compound 1 against Gram positive bacteria.



Scheme 1. Rearrangement of benzothiazoline ring

$$\text{S-C-N}\rightarrow\text{M};\quad \text{N-C-S}\rightarrow\text{M};\quad \text{M}\leftarrow\text{N-C-S}\rightarrow\text{M}$$

$$\begin{array}{c}\text{N-C-S}\rightarrow\text{M};\\ \downarrow\\ \text{M}\end{array}\qquad\begin{array}{c}\text{S-C-N}\rightarrow\text{M}\\ \downarrow\\ \text{M}\end{array}$$

Scheme 2. Different ligational motifs of thiocyanate

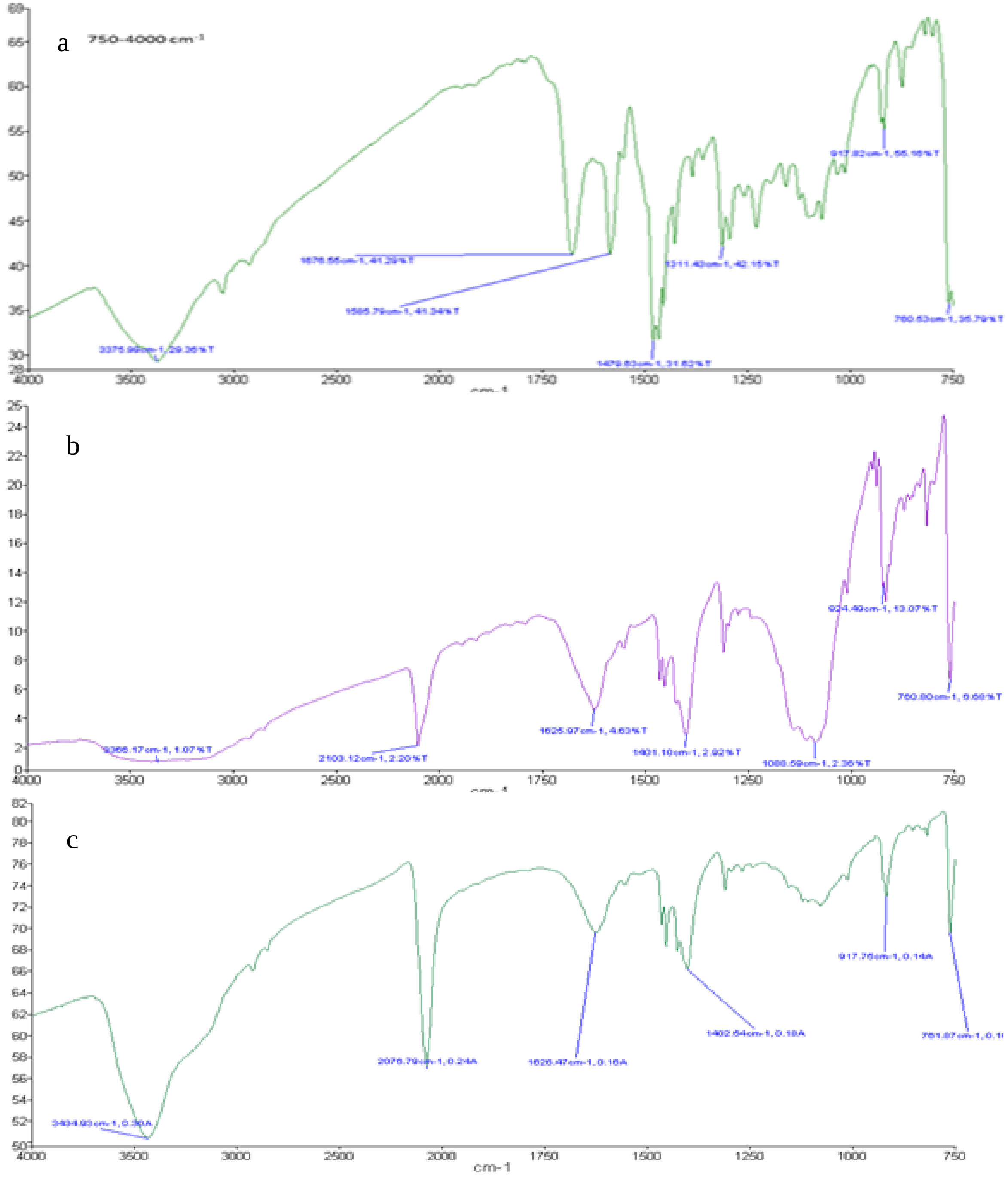


Fig.1.FT- IR spectra of (a) H_2L (b)[Mn(H_2L)$(NCS)_2$]**(**c) [Co (H_2L)$(NCS)_2$]from 750-4000 cm^{-1}

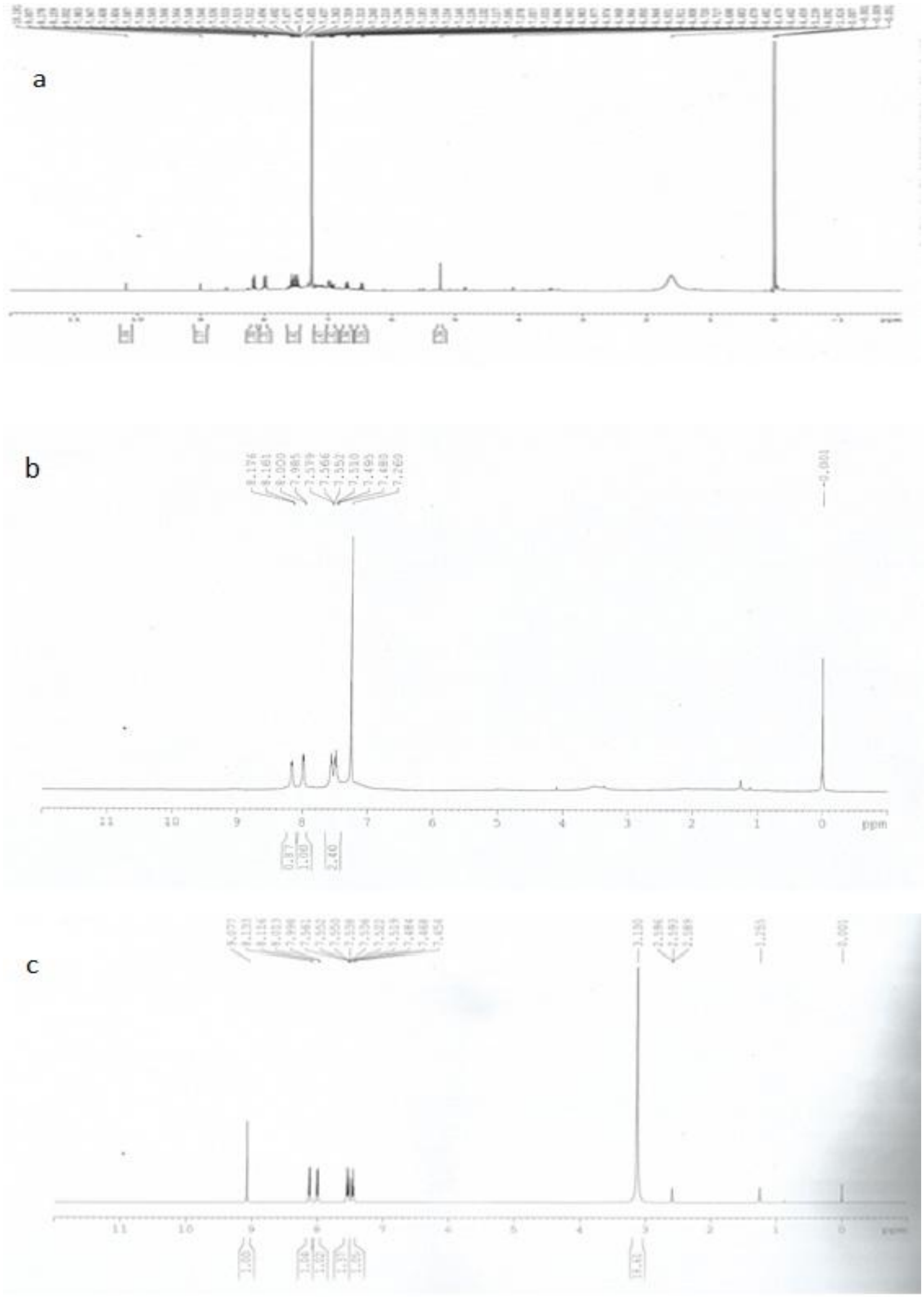


Fig. 2. ^{1}H NMR spectra of (a) H_2L (b)$[Mn(H_2L)(NCS)_2]$ **(**c) $[Co(H_2L)(NCS)_2]$

CONCLUSION

The newly synthesized complexes exhibited good antibacterial and antifungal potentiality. The bioactivity of ligand was shown to increase upon coordination due to chelation make the compound more lipophilic and, thereby, facilitating rapid penetration through microbial cell wall. However, presence of lipopolysaccharide in the outer membrane of Gram negative bacteria affects the penetration rates of lipophilic molecules. As a result, lipophilic metal complexes may show reduced activity (smaller inhibition zone diameter and higher MIC value) in Gram negative bacteria than Gram positive bacterial strain as found in the present study in both manganese and cobalt complexes.

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