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Synthesis, Characterization and Antimicrobial Activity of Embelinthiosemicarbazone and its Transition Metal Complexes

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Embelinthiosemicarbazone (ETSC) has been synthesized by condensing embelin with thiosemicarbazide. The complexes of ETSC with metal ions Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Cd(II), VO(II), UO_2(II), MoO_2(II), Fe(III) and Cr(III) were synthesized and characterized using various spectral techniques like UV, IR, ^{1}H NMR and magnetic and conductance measurements. Embelin, ETSC and a few metal complexes of ETSC were screened for their antibacterial, antifungal and anthelmintic activities.

Key Words: Antimicrobial activity, Embelinthiosemicarbazone, Transition metal complexes.

INTRODUCTION

Thiosemicarbazones have gained special attention due to their activity against protozoa, influenza, smallpox, malaria, tuberculosis and cancer[1]. Metal thiosemicarbazonate compounds have emerged as a new class of experimental anticancer chemotherapeutic agents which exhibit inhibitory activities against most cancers through inhibition of a crucial enzyme, obligatory for DNA biosynthesis and cell division[2]. Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), a natural product, exhibits potential anthelmintic, antibacterial, antifertility, analgesic and antibiotic activities[3]. Owing to the wide range of medicinal properties of thiosemicarbazones and of embelin and their ability to form chelates with metal ions, the synthesis, characterization and antimicrobial activity of embelinthiosemicarbazone and its transition metals (*viz.*, Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Cd(II), VO(II), UO_2(II), MoO_2(II), Fe(III) and Cr(III)) complexes were investigated and presented in this paper.

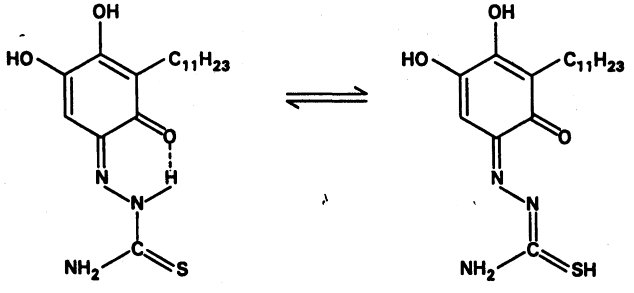

Fig. 1. Embelinthiosemicarbazone (ETSC)

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EXPERIMENTAL

Pure natural embelin was isolated from the dried berries of *Embelia ribes* Burm by the method of Fieser and Chamberline[4]. All other chemicals used for the synthesis were of AR grade while solvents were distilled prior to their use.

Molar conductance measurements of complexes in methanol and nitrobenzene were made in an Elico conductivity cell. Magnetic moments of the complexes were measured at 300 K using EG&G Model 155 VSM at RSIC, Madras. IR spectra were recorded as KBr disc in the range 4000–200 cm^{-1} on a Perkin-Elmer 1650 FTIR spectrophotometer. Electronic spectra were recorded on UV-visible spectrophotometer at the Department of Chemistry, University of Kerala, Thiruvananthapuram. NMR spectrum of the ligand was recorded on a Perkin-Elmer R-32 90 MHz spectrometer. Antimicrobial studies were conducted at the Department of Biotechnology in the University of Kerala, Thiruvananthapuram.

ETSC and the complexes were screened for their antibacterial activity against *S. aureus*, *E. coli*, *B. licheniformis*, *B. subtilis*, *Pseudomonas aeruginosa* and *Klebsiella aeruginosa* by disc diffusion method at different concentration levels of 10, 20, 30 μg/disc[5, 6]. Antifungal activity of the ligand and the metal complexes were tested by incorporating the test solution (1 mg/mL) in sabouraud dextrose agar (SDA) media against human pathogens, *Pencillium* species and *Candida albicans*, plant pathogens, *Rhizopus* species, *Phytophthora infestans* and *Aspergillus* species, industrially important strain and *Saccharomyces* species. Anthelmintic activities of the complexes were tested using earthworm[8]. All the test solutions were prepared in an aqueous ethanol.

Synthesis of Embelinthiosemicarbazone (ETSC)

Thiosemicarbazone of embelin was synthesized by refluxing 0.01 mol of embelin and 0.01 mol of thiosemicarbazide in 50 mL ethanol for 2 h. The mixture was allowed to cool when brown coloured crystals of embelinthiosemicarbazone were separated. They were filtered, washed well with hot water and then with aqueous ethanol and dried over P_4O_{10} in vacuum. It was recrystallized from methanol, yield 80%, m.p. 125°C.

Synthesis of metal complexes

For preparing metal complexes, a mixture of 0.01 mol ETSC in 20 mL methanol and 0.015 mol of the metal salt dissolved in 20 mL aqueous methanol, was refluxed on a water bath for 1 h. Afterwards, on concentrating the solution, the solid complex formed (yield 60%) was filtered, washed well with hot water and finally with dilute alcohol and dried over P_4O_{10} in vacuum.

RESULTS AND DISCUSSION

Analytical, spectral data and magnetic moment values of all the metal complexes are given in Table-1. The molar conductance measurement data in methanol and nitrobenzene clearly show that all the complexes are non-electrolytes except iron and chromium complexes which are 1 : 1 electrolytes.

TABLE-1
ANALYTICAL, CONDUCTANCE, MAGNETIC MOMENT AND ELECTRONIC SPECTRAL BANDS OF THE METAL COMPLEXES

S.No.	Complex	Metal (%), found (calcd.)	Electrolytic nature	Magnetic moment (BM)	Electronic spectra (cm^{-1})
1.	$[Mn(ETSC)_2]$	6.20 (6.90)	Non-electrolyte	5.92	25000
2.	$[Cr(ETSC)_2]Cl$	6.10 (6.19)	1 : 1	3.80	25710
3.	$[Fe(ETSC)_2]Cl$	6.10 (6.60)	1 : 1	5.90	28000
4.	$[Co(ETSC)_2]$	8.00 (7.40)	Non-electrolyte	4.90	19200 26000
5.	$[Ni(ETSC)Cl]$	12.90 (12.70)	Non-electrolyte	Diamagnetic	18870 26500
6.	$[Cu(ETSC)Cl]$	14.00 (13.60)	Non-electrolyte	1.80	19531 12195 26400
7.	$[Zn(ETSC)_2]$	14.60 (14.00)	Non-electrolyte	Diamagnetic	27000
8.	$[Cd(ETSC)_2]$	21.00 (20.70)	Non-electrolyte	Diamagnetic	26500
9.	$[VO(ETSC)Cl]$	10.52 (10.88)	Non-electrolyte	1.78	13070 16260 25970
10.	$[UO_2(ETSC)Cl]$	35.15 (35.39)	Non-electrolyte	Diamagnetic	21200 24690
11.	$[MoO_2(ETSC)Cl]$	18.00 (18.13)	Non-electrolyte	Diamagnetic	25000

IR spectra of ETSC show bands (cm^{-1}) at 3490, 3418 $\nu(NH_2)$, 3300 $\nu(OH)$, 3181 ν(N—H), 1607 ν(C═O), 1498 [ν(C═N) + δ(NH) + δ(CH)], 820 ν(C═S). Lower IR absorption frequencies for C═O and NH groups show that they are hydrogen bonded.

NMR spectrum of ETSC in ($CDCl_3$) displayed signals at δ 0.9 (3H, t) methyl protons, δ 1.3 (18H, m) methylene protons of the side chain, δ 2.4 (2H, t) methylene attached to the ring, δ 2.75 (1H, t) SH protons, δ 4.2 (1H, s) NH protons, δ 5.4 (1H, s) ring proton at C-6, δ 7.25 (2H, s) OH protons.

The peaks shown by IR spectrum of ETSC at 3490 and 3418 cm^{-1} are due to asymmetric and symmetric stretch of the NH_2 group. The absorption at 3300 cm^{-1} is due to the hydrogen bonded hydroxyl group. On complexation, ν(C═S) of the thiocarbonyl band at 820 cm^{-1} as well as the ν(N—H) band at 3181 cm^{-1}, both of the ligand, disappear, with simultaneous appearance of new bands around 1600 and 700 cm^{-1} indicating coordination of the thiocarbonyl sulphur in the thiol form after deprotonation[9–12]. Bands observed at 1607 and 1498 cm^{-1} which are due to ν(C═O) and azomethine groups of ETSC are found shifted by 15–20 cm^{-1} to lower energy side upon complexation[13]. The vanadyl chelate shows a band at 960 cm^{-1} suggesting the presence of V═O group[14]. In dioxouranium complex the band at 930 cm^{-1} corresponds to the symmetric stretch confirming the linear nature of the UO_2 group[15]. Two strong bands at 910 cm^{-1} and 930 cm^{-1} are observed in the complexes of dioxomolybdenum which are attributed to asymmetric and symmetric stretch of *cis*-MoO_2 moiety[16]. The coordination of N, O and S atoms of the ligand to the metal ions is proved by the appearance of new bands around 500, 400 ad 300 cm^{-1} in the far IR due to ν(M—N), ν(M—O) and ν(M—S) respectively.

In all the complexes the ligand band at 3300 cm^{-1} of ν(O—H) is found unaffected. Therefore ETSC coordinates to metal ion in its thiol form and acts as monovalent tridentate ONS donor ligand in all these complexes.

Electronic spectra of all the metal complexes show intense broad absorption bands in the region 28,000–24,000 cm^{-1} due to the ligand to metal charge transfer transition. In addition to this, Cu(II) complex gives bands at 19531 cm^{-1} and 12195 cm^{-1} corresponding to $^2B_{1g} \rightarrow {}^2E_g$, and $^2B_{1g} \rightarrow {}^2A_{1g}$ transitions respectively. In case of Ni(II) absorption at 18870 cm^{-1} is observed corresponding to $^1A_{1g} \rightarrow {}^1B_{1g}$ transition of square-planar geometry. Diamagnetic behaviour also confirms this geometry of the complex. Co(II) complex gives a band at 19200 cm^{-1} which is due to $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition for the octahedral geometry.

The magnetic values also agree with the octahedral gcometry for Mn(II), Cr(III) and Fe(III) complexes. In the case of Zn(II) and Cd(II) complexes only charge transfer transitions are seen around 26000 cm^{-1}. The electronic spectrum of oxovanadium chelate exhibits two bands at 13070 and 16260 cm^{-1}. Though three transitions are expected for a square pyramidal vanadyl complex[17], the third absorption is not observed as it is buried beneath the high intensity charge transfer band at 25970 cm^{-1}. In the spectrum of uranyl complex, two series of bands are observed, one in the region 23300-20200 cm^{-1} assigned to charge transfer transitions coupled with some UO_2^{2+} vibration frequency. Second series observed at 24690 cm^{-1} is due to charge transfer transitions from ligand to metal. From the above data tentative structures are proposed for the complexes as given in Fig. 2.

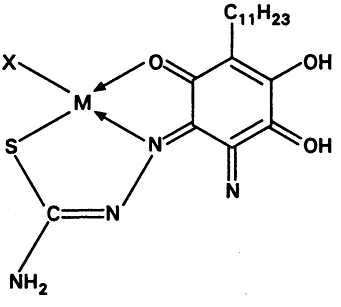

Fig. 2. (a) M = Cu(II), Ni(II), Co(II), VO(II), MoO_2(II),UO_2(II)

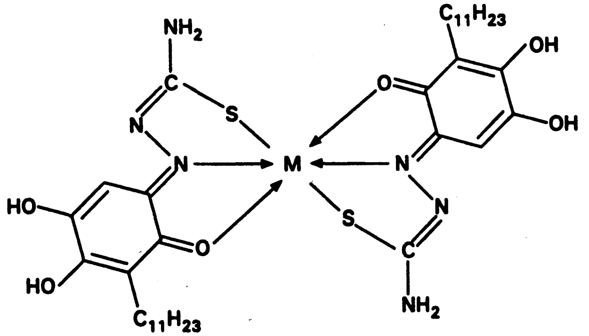

Fig. 2. (b) M = Mn(II), Co(II), Zn(II), Cd(II); X = Cl$^-$

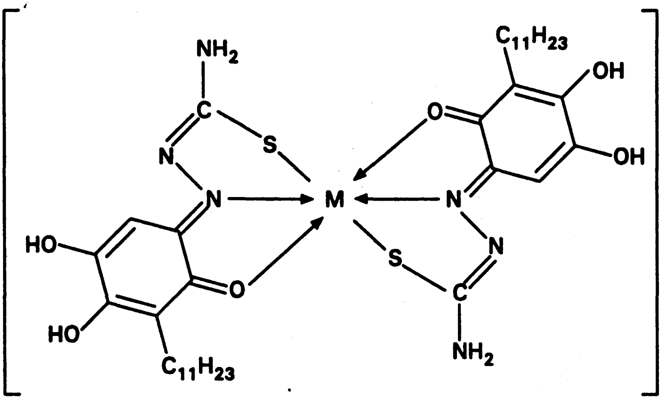

Fig. 2. (c) M = Fe(III), Cr(III); X = Cl$^-$

Antimicrobial activity

Embelin, ETSC and the complexes [Zn(ETSC)$_2$] and [VO(ETSC)Cl] were screened for antibacterial activity and the inhibition zone diameters in mm are presented in Table-2. Embelinthiosemicarbazone is found to be a more effective antibacterial agent than embelin and the metal complexes of ETSC and it inhibited the growth of *S. aureus* more than the other bacteria. All the above compounds were inactive against *P. aeruginosa*. Embelinthiosemicarbazone exhibited antifungal activity against *Pencillium, Rhizopus* and *Saccharomyces* species while moderate activities observed against *Candida albicans* and *Phytophthora infestans*. No activity is seen for embelin, its thioscmicarbazone and the metal complexes of the thiosemicarbazone against *Aspergillus* species (Table-3).

TABLE-2
ANTIBACTERIAL ACTIVITY AT 30 μg/DISC (ZONE FORMATION IN mm)

Compound	*S. aureus*	*E. coli*	*B. licheniformes*	*B. subtilis*	*B. brevis*	*P. aeruginosa*	*K. aeruginosa*
Embelin	7	11	7	7	8	Nil	7
ETSC	18	8	15	15	16	Nil	12
$[Zn(ETSC)_2]$	9	6	10	8	7	Nil	7
[VO(ETSC)Cl]	10	8	10	7	7	Nil	12
STD tetracycline	24	7	20	21	24	9	20

TABLE-3
RESPONSE OF THE TEST COMPOUND (AT 1 mg/mL) AGAINST FUNGI

Compound	*Penicillin* species	*Candida albicans*	*Rhizopus* species	*Phytophthora infestans*	*Aspergillus* species	*Saccharomyces* species
Embelin	+	+	–	–	+	+
ETSC	–	+/–	–	+/–	+	–
$[Zn(ETSC)_2]$	+	–	–	–	+	–
[VO(ETSC)Cl]	–	–	–	+/–	+	–
Control	+	+	+	+	+	+

+ not active
– active
+/- moderately active

Anthelmintic activity

Anthelmintic activity of embelinthiosemicarbazone and the complexes $[Zn(ETSC)_2]$ and [VO(ETSC)Cl] were tested using earthworm. The study was conducted at a concentration of 1 mg/mL for ligand and the metal complexes. The death of the parasite was observed after 1 h in all the cases.

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