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Research Article

Synthesis, Characterization, Antimicrobial And Anticancer Activities of Mn(II) Mixed Ligand Complexes of Pentamethylene Dithiocarbamate With Diamines

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Abstract: A new series of binuclear Mn(II) mixed ligand complexes of pentamethylene dithiocarbamate(pmdtc) with diamines such as 1,10 phenanthroline(phen),ethylenediamine(en),diethylenetriamine(dien),triethylenetetramine(trien) are reported. The synthesized complexes were characterized by thermal, elemental, metal, nitrogen and sulphur, UV-Vis, infra-red, ESR Spectral analysis and magnetic susceptibility studies. Antibacterial, antifungal and anticancer studies have also been carried out on these complexes which show moderate activity towards some of the tested microorganisms.

Keywords: Mixed ligand Mn(II)phen/en/dien/trien, Pentamethylenedithiocarbamate, Antibacterial, antifungal, anticancer activities.

INTRODUCTION

In recent years, there has been a renewed interest in the synthesis and study of mixed ligand complexes with biologically significant ligands¹. Complexes of transition metals with mixed ligands having S and N as donor atoms have found great interest among other coordination complexes²⁻⁴. Dithiocarbamates are versatile ligands by virtue of high selectivity and sensitivity towards reaction with transition metal ions stabilizing a range of oxidation states⁵. Dithiocarbamate-metal complexes have drawn much research attention due to their diverse applications and interesting biological, structural, magnetic, electrochemical and thermal properties⁶⁻¹². They are used as accelerators in vulcanization, as high pressure lubricants, as antimicrobial and anticancer agents. The

dithiocarbamates, both as free ligands and metal complexes are used in agriculture for controlling insects and fungi¹³. Recently gold (III) dithiocarbamate complexes have been used for treatment of human cancer by suppressing tumor growth via direct inhibition of the proteasome activity¹⁴.

Dithiocarbamates, act both as unidentate and bidentate leading to tetra and hexa-coordination^{15, 16}. The wide range of applications of dithiocarbamates prompted us to prepare mixed ligand complexes with pentamethylene dithiocarbamate as one of the ligands. Herein we report Synthesis, characterization, antimicrobial and anticancer activities of Mn(II) mixed ligand complexes of pentamethylene dithiocarbamate with diamines.

EXPERIMENTAL SECTION

The chemicals employed for the preparation are of very pure grade and used without further purification. The Manganese sulphate used for the synthesis is of analytical grade. Piperidine, carbon disulphide, ethylene diamine, diethylenetriamine, triethylenetetra-amine and 1,10phenanthroline are pure grade chemicals from Merck. The chloroform used as solvent in all our studies is distilled by standard procedures. The ligand was prepared as follows, to a solution of piperidine (0.05mol) in chloroform(5ml) constantly stirred in ice added 4ml of sodium hydroxide (10N) and carbon disulphide (3ml,0.05 mol) for about 30 minutes, sodium salt of dithiocarbamate precipitated out. The obtained precipitate was washed with ether and dried in vacuum. The complexes were synthesized by mixing aqueous solution of $\text{MnSO}_4 \cdot 5\text{H}_2\text{O}$ (1mmol) and aqueous solution of 1, 10 phenanthroline/en/dien/trien (1mmol) with continuous stirring for 10 minutes. Then aqueous solution of pentamethylene dithiocarbamate (2mmol) was added drop wise with vigorous stirring for 20 minutes. The formed precipitate then filtered off, the complexes repeatedly washed with water and recrystallised from ether and dried in vacuum. The synthesized complexes were characterized by elemental analysis (Nitrogen -kjeldhal's method ,metal -ICPOES- Inductively Coupled Plasma optical emission spectroscopy- PerkinElmer Optima 5300 spectrometer, Sulphur –gravimetrically by barium sulphate method),thermal analysis-(TGA were recorded in nitrogen atmosphere using NETZSCH STA 490C/CD thermal analyser with a heating rate of 10° C/min), UV-Visible absorption spectra (as solution in chloroform- a shimadzu UV 1600 model spectrometer),Infrared spectrum (as KBr disc - shimadzu spectrometer) and EPR Spectra (JES-FA 200 electron spin resonance spectrometer in the region from 1000-8000 gauss). Magnetic susceptibility studies were carried out using Vibrating magnetometer Lakeshore VSM 7410.The antibacterial and antifungal studies were carried out by using agar disc diffusion method originally described by Baeur¹⁷. The invitro cytotoxicity of the prepared complexes were carried out by MTT based assay¹⁸ with cancer cell line, HELA (human cervical cell line). In parallel the activity was tested on normal cell line, HEK (human kidney cell line).

RESULTS AND DISCUSSION

The complexes are stable, non-hygroscopic and brown colored solids. All the complexes were found to be completely soluble in chloroform, partially soluble in DMSO and DMF and insoluble in alcohol and water. The elemental analysis data of the complexes **Table-1** confirm the proposed composition $[\text{Mn}_2(\text{phen/en/dien/trien})_2(\text{pmdtc})_2(\text{H}_2\text{O})_2\text{SO}_4]$. The electrical molar conductance of the complexes at a concentration of about 10^{-3} M in chloroformic solution was found to be 5-10 $\text{Ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$ indicating the non-electrolytic nature of the complexes. The thermal analysis data from TGA for the four complexes are furnished in table-1. The thermograms were run upto 1000° C and final residue corresponds to manganese sulphide. The IR spectral data of the complexes are given in **Table-2**.

The stretching vibration of NH of amines and ν O-H of water molecules appears at 3420cm^{-1} as a combination band. The ν NH₂ group of the primary amine appears around 3220cm^{-1} in these complexes. The aliphatic C-H of amine appears around 2860cm^{-1} and ν C-H of piperidine appears around 2930cm^{-1} . The $\nu\text{C}=\text{S}$ stretching frequency appears at 1233cm^{-1} . The two bands around $870\text{--}1010\text{cm}^{-1}$ are assigned to ν C-S group of dithiocarbamate moiety and these confirm bidentate and monoionic nature of dithiocarbamate¹⁹. The bands in the region $1250\text{--}1350\text{cm}^{-1}$ are assigned to ν N-C stretching vibration, whereas bridging SO₄ appears at $1110\text{--}1240\text{cm}^{-1}$ ²¹. The $412\text{--}519\text{cm}^{-1}$ region is associated $\nu\text{M-S}$ and ν M-N vibrations $\nu\text{M-S}$ is observed in the region $418\text{--}445\text{cm}^{-1}$ and may be taken as evidence for the coordination of metal to sulphur. This behavior may be attributed to the electron releasing of the amines, which forces high electron density towards the sulphur atoms, whereas ν M-N was observed in the $465\text{--}513\text{cm}^{-1}$ region²². The electronic spectral data on the complexes are shown in Table- 1.

Table-1: Elemental composition, Thermal analysis and electronic absorption data

Complexes	% Nitrogen (theo) exp	% inorganic Sulphur (theo) exp	% organic Sulphur (theo) exp	% metal (theo) exp	% of Residue TGA (theo) Exp	λ_{max} (nm)
[Mn ₂ (1,10phen) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	(8.7) 7.9	(3.3) 3.1	(13.3) 12.5	(11.4) 11.5	(18.1) 18.09	345,313
[Mn ₂ (en) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	(12.2) 11.8	(4.6) 4.8	(18.7) 12.3	(16.0) 15.0	(25.4) 25.32	358,450
[Mn ₂ (dien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	(14.5) 13.8	(4.1) 3.9	(16.6) 13.8	(14.2) 13.5	(22.5) 21.12	453,355
[Mn ₂ (trien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	(16.3) 15.8	(3.7) 3.1	(14.9) 12.53	(12.8) 12.5	(20.3) 20.5	458,353,302

Table-2: IR spectral data (vcm^{-1})

Complexes	$\nu\text{N-H}$ $\nu\text{O-H}$	$\nu\text{C-H}$ (amine, piperidine)	$\nu\text{N-C}$	$\nu\text{C-S}$	$\nu\text{M-S}$ $\nu\text{M-N}$	Bridged SO ₄ units	$\nu\text{C}=\text{S}$
[Mn ₂ (1,10phen) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	- 3249	2853, 2930	1381	987	412, 474	1123 1220	1230
[Mn ₂ (en) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	3340 3228	2857, 2928	1353	957	434, 500	1114 1231	1231
[Mn ₂ (dien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	3424 3216	2860, 2929	1361	956	438, 502	1115 1232	1233
[Mn ₂ (trien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	3416 3267	2853, 2930	1356	963	421, 514	1124 1234	1232

Two peaks are observed in the region $325\text{--}498\text{nm}$. In high spin d^5 manganese (II) configuration, the (d-d) electronic transitions are spin forbidden and laporte forbidden and hence low intense band

around around 450 nm is assigned to octahedral Mn(II). The peak in the region 350nm corresponds to metal to ligand charge transfer ²³. All the complexes give a single peak in the EPR spectrum and the g value corresponds to 1.97, 2.0, 2.07 and 1.98 for phen, en, dien, trien complexes respectively.

The magnetic susceptibility studies shows an increase in mass in the presence of magnetic field. The VSM plot of magnetic moment in emu vs. field shows hysteresis loop indicating ferromagnetism and negligible height loops and the coercivity suggest that these complexes have significantly small size.

Anticancer studies: The invitro cytotoxicity of Mn (II) based dithiocarbamate complexes are given in Table-3.

Table-3: Anticancer activity in HeLa cell line

Complexes	concentration (ug/ml)	Absorbance (O.D)	Cell viability (%)	Cell toxicity (%)
[Mn ₂ (1,10phen) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	cell control	1.2	100	0
	100	0.21	17.72	82.28
	50	0.23	19.3	80.7
	10	0.86	71.31	28.69
	1	1.28	96.07	3.93
[Mn ₂ (en) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	cell control	1.2	100	0
	100	0.96	80.13	19.87
	50	1.05	87.38	12.62
	10	0.97	80.92	19.08
	1	0.77	63.96	36.04
[Mn ₂ (dien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	cell control	1.2	100	0
	100	0.76	63.54	36.46
	50	0.9	74.92	25.08
	10	1.09	90.81	9.19
	1	1.04	86.31	13.69
[Mn ₂ (trien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	cell control	1.2	100	0
	100	0.86	71.69	28.31
	50	0.92	76.25	23.75
	10	0.93	77.53	22.47
	1	0.95	79.13	20.87

All the four complexes shows moderate activity against the cancer cells but seems to have less toxicity towards normal cells. The IC₅₀ value of phen, en, dien, trien complexes are 19.30, 87.38, 74.32 and 76.25.

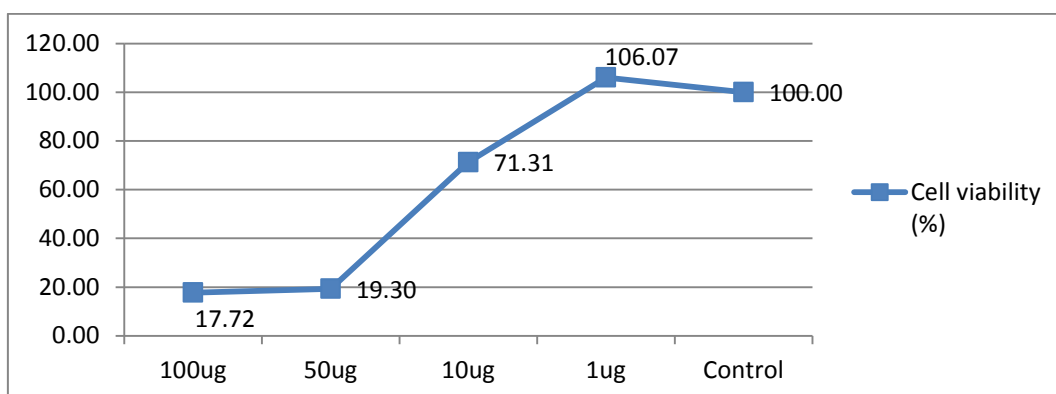


Fig-1:Anticancer activity on HELA cell line of $[\text{Mn}_2(1,10\text{phen})_2(\text{pmdtc})_2(\text{H}_2\text{O})_2\text{SO}_4]$

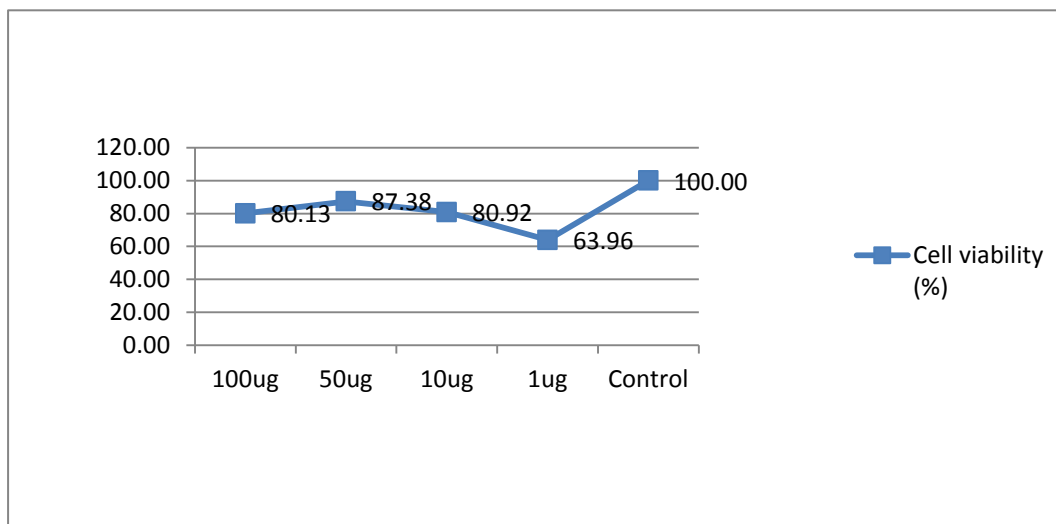


Fig-2:Anticancer activity on HELA cell line of $[\text{Mn}_2(\text{en})_2(\text{pmdtc})_2(\text{H}_2\text{O})_2\text{SO}_4]$

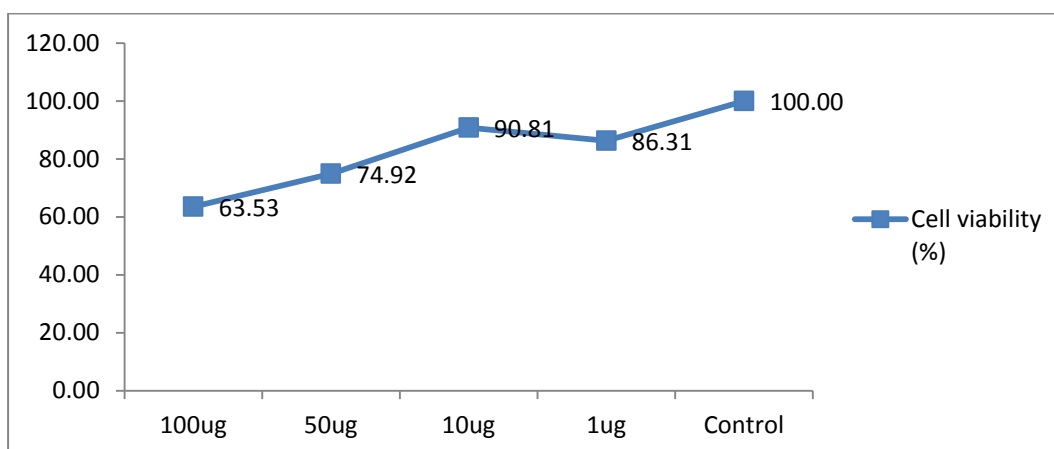


Fig-3:Anticancer activity on HELA cell line of $[\text{Mn}_2(\text{dien})_2(\text{pmdtc})_2(\text{H}_2\text{O})_2\text{SO}_4]$

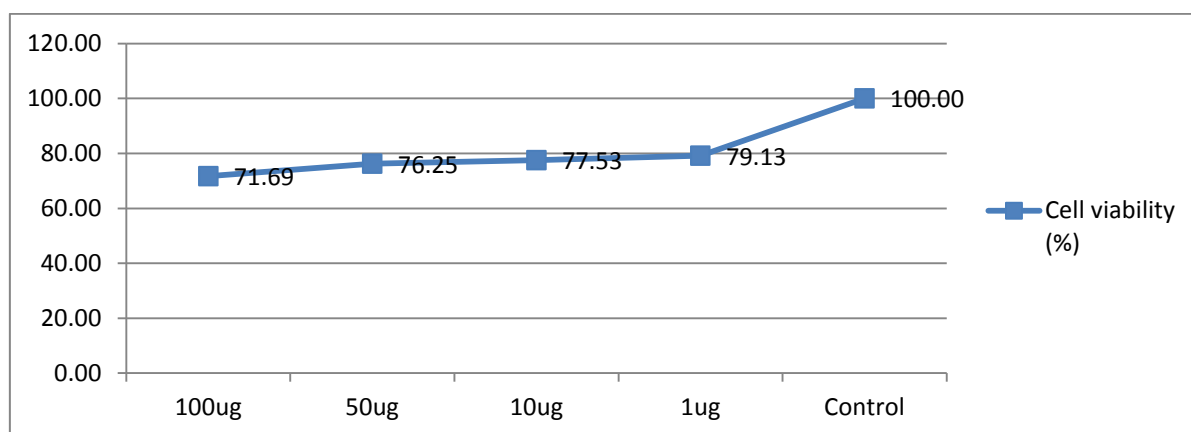


Fig-4:Anticancer activity on HELA cell line of $[\text{Mn}_2(\text{trien})_2(\text{pmdtc})_2(\text{H}_2\text{O})_2\text{SO}_4]$

Antimicrobial studies: Antimicrobial studies was performed on five bacterial species namely *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Aeromonas Spp* and *Vibrio Parahemolyticus* and three fungus namely *Candida albicans*, *Trichoderma viride* and *Aspergillus niger*. The results for the complexes and commercial antibiotics used as positive control are listed in Table-4, 5.

Table-4: Antibacterial studies

Complexes	Organisms	Zone of inhibition			Antibiotic (1mg/ml)
		Concentration(μg/ml)			
		1000	750	500	
[Mn ₂ (1,10 phen) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Bacillus Subtilis	10mm	8mm	6mm	15mm
	Aeromonas Spp	10mm	8mm	7mm	12mm
	Staphylococcus aureus	8mm	-	-	13mm
	Vibrio Parahemolyticus	9mm	7mm	-	14mm
	E.coli	11mm	8mm	7mm	12mm
[Mn ₂ (en) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Bacillus Subtilis	9mm	8mm	6mm	16mm
	Aeromonas Spp	-	-	-	13mm
	Staphylococcus aureus	11mm	8mm	7mm	15mm
	Vibrio Parahemolyticus	10mm	7mm	6mm	13mm
	E.coli	-	-	-	10mm
[Mn ₂ (dien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Bacillus Subtilis	8mm	-	-	13mm
	Aeromonas Spp	10mm	8mm	-	14mm
	Staphylococcus aureus	9mm	-	-	10mm
	Vibrio Parahemolyticus	11mm	8mm	7mm	12mm
	E.coli	10mm	8mm	6mm	10mm
[Mn ₂ (trien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Bacillus Subtilis	9mm	-	-	13mm
	Aeromonas Spp	10mm	8mm	7mm	12mm
	Staphylococcus aureus	9mm	7mm	6mm	15mm
	Vibrio Parahemolyticus	8mm	-	-	11mm
	E.coli	10mm	8mm	-	10mm

Table 5: Antifungal studies

Complexes	Organisms	Zone of inhibition			Antibiotic (1mg/ml)
		Concentration(μg/ml)			
		1000	750	500	
[Mn ₂ (1,10phen) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Candida albicans	12mm	9mm	7mm	14mm
	Trichoderma Viridi	9mm	7mm	-	12mm
	Aspergillus niger	9mm	8mm	7mm	13mm
[Mn ₂ (en) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Candida albicans	10mm	8mm	-	12mm
	Trichoderma Viridi	10mm	8mm	6mm	15mm
	Aspergillus niger	9mm	-	-	13mm
[Mn ₂ (dien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Candida albicans	8mm	7mm	-	11mm
	Trichoderma Viridi	10mm	8mm	6mm	13mm
	Aspergillus niger	10mm	8mm	7mm	12mm
[Mn ₂ (trien) ₂ (pmdtc) ₂ (H ₂ O) ₂ SO ₄]	Candida albicans	7mm	-	-	11mm
	Trichoderma Viridi	9mm	8mm	6mm	13mm
	Aspergillus niger	9mm	-	-	13mm

With increasing concentration of the dithiocarbamate complexes, an increase in the diameter of the zone of inhibition was observed indicating the complexes shows better antibacterial and antifungal activity. The dien complex does not show antibacterial activity against *Escherichia coli*, *Aeromonas* Spp even at 1000mg concentration.

CONCLUSION

From the above data and various spectral and analytical studies, it may be concluded that the complexes contain two Mn(II) linked by bridging sulphate. The two Mn(II) in the complexes have an octahedral environment with the dithiocarbamate acting bidentate through two sulphur and one aquo ligand and bidentate amine. The investigations revealed that the complexes have significant better antimicrobial and anticancer activity towards the tested organisms and cell lines.

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