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POTENTIALLY ACTIVE TRANSITION METAL COMPLEXES SYNTHESIZED AS SELECTIVE DNA BINDING AND ANTIMICROBIAL AGENTS

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Abstract

Unique mononuclear complexes were synthesized from their precursor compounds by Schiff base condensation. The mononuclear manganese(III) and zinc(II) complexes were spectrally characterized. Elemental, hydrolysis activities were also carried out. The complexes were screened to probe their potential for DNA binding, antifungal and antibacterial activities.
Keywords: Manganese(III) & Zinc(II) complexes, Spectral, DNA binding and In vitro studies.

1. Introduction

Interest in macrocyclic poly-amines has been on the increase as a result of their attractive structures and their possible applications in many fields.[1-3] The reason for that is their possibility to react or coordinate with many different metal ions as well as organic molecules *via* nitrogen atoms.[4,5] Apart from the known applications of cyclam, some of its derivatives block the entry of HIV into cells and can be highly potent anti-HIV drugs[6,7], they also show antimicrobial activities .[8] As a molecule, cyclam has four nitrogen atoms, in derivatives these atoms are often substituted with different groups which can increase the number of coordination sites. Transition metals can form mono or di or trinuclear complexes, while it can be coordinated using two, three or four nitrogen atoms from cyclam. Potentially active metal complexes particularly, Mn and Zn metals with cyclam ligands and their stability has been meticulously studied. Understanding the factors enhancing the electrochemical and kinetic studies of the synthesized complexes will be helpful for drug discovery in future. In vitro screening has also been carried out.

2. Materials and methods

3-bromomethyl-5-bromosalicylaldehyde, 3-bromomethyl-5-methylsalicylaldehyde,[9] Ligands 1 & 2 were systematically prepared.[10] 5-bromo salicylaldehyde, 5-methyl

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salicylaldehyde,1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane and solvents were purchased from Genesys Inc.

2.1. Synthesis of macrocyclic mononuclear Mn(III) and Zn(II) complexes

Methanolic solution of metal chlorides (1 mmol) is refluxed with appropriate ligands (1 mmol) for 20 h. The product filtered was evaporated yielding pure complexes.

1.[MnL^1]Cl$_3$: Dark green compound. Yield: 0.5 g (92%), Anal.Calc for [$C_{28}H_{40}N_4O_4Mn$]Cl_3: C,51.13; H,6.11; N,8.55; Mn,8.33**,** Found : C,51.11; H,6.12; N,8.51; Mn,8.35**,** EI mass (m/z): [MnL^1] 657 **,**Conductance (Λ_m) : 37**,** IR (KBr,cm^{-1}): 3350 ν(OH), 3295 ν(NH), 1625 ν(CHO); λ_{max}, nm in DMF: 293,383,419 and 584 nm.

2.[MnL^2]Cl$_3$: Dark green compound. Yield: 0.6 g (92%), Anal.Calc for [$C_{26}H_{34}N_4O_4Br_2Mn$]Cl_3: C,39.65; H,4.33; N,7.10; Mn,6.96 ,Found : C ,39.64; H,4.34; N,7.11; Mn,6.97 , EI mass (m/z): [MnL^2] 787 ,Conductance (Λ_m): 39, IR (KBr,cm^{-1}): 3348 ν(OH), 3280 ν(NH), 1620 ν(CHO); λ_{max}, nm in DMF: 261,380,452 and 590 nm.

3.[ZnL^1]Cl$_2$: Dark yellow compound**:** Yield: 0.4 g (83%) **,** Anal.Calc for [$C_{28}H_{40}N_4O_4Zn$]Cl_2: C,53.12; H,6.32.; N,8.82; Zn, 10.73**,** Found : C,53.13; H,6.36; N,8.85; Zn, 10.33**,** EI mass (m/z): [ZnL^1] 632 ,Conductance (Λ_m):40**,** IR (KBr,cm^{-1}): 3354 ν(OH), 3265 ν(NH), 1623 ν(CHO); λ_{max}, nm in DMF: 295,367 and 400 nm.

4.[ZnL^2]Cl$_2$: Dark yellow compound**:** Yield: 0.5g(86%) **,**Anal.Calc for [$C_{26}H_{34}N_4O_4Br_2Zn$]Cl_2: C,40.90; H,4.45; N,7.30; Zn, 8.58**,** Found : C,40.94; H,4.49; N,7.34; Zn, 8.56**,** EI mass (m/z): [ZnL^2] 762 ,Conductance (Λ_m): 41**,** IR (KBr,cm^{-1}): 3349 ν(OH), 3260 ν(NH), 1620 ν(CHO); λ_{max}, nm in DMF: 298,370 and 405 nm.

3. Results and Discussion

Mononuclear manganese and zinc complexes synthesized from their ligands with corresponding metal chlorides are shown in scheme-1. The crystal structure of L^1 has already been reported.[11] The spectroscopic, magnetic, electrochemical and in vitro studies has been done for all the complexes.

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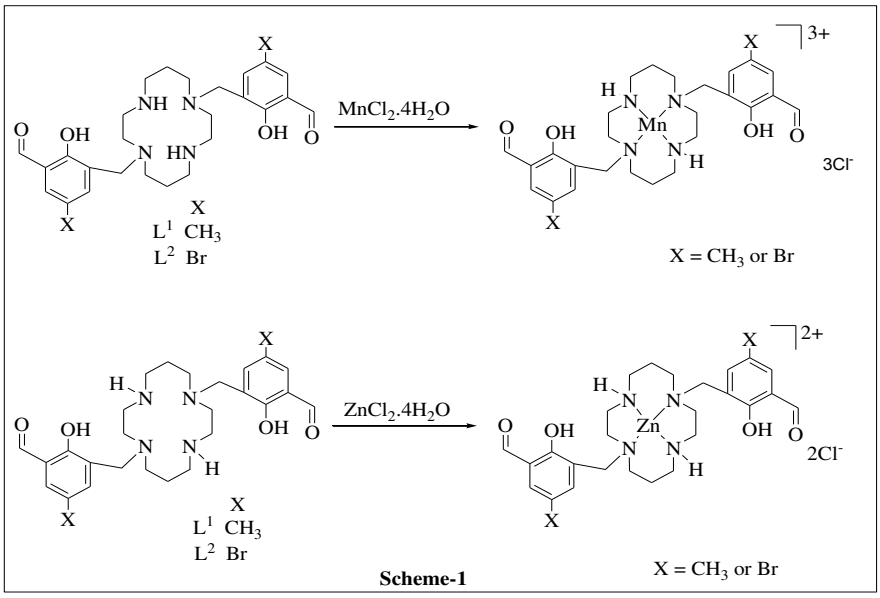

Scheme-1

3.1. Spectral investigation

The **^{1}H NMR spectra** of zinc complex shows a peak at 13.80 ppm (phenolic proton), a peak at 10.10 ppm (aldehyde proton) indicating the non coordination of phenolic OH and aldehyde with metal ion. **EI mass spectra** of complexes were obtained as 657(1), 632(2), 787(3) & 762(4) respectively.

IR spectra of the complexes show band at 1620-1650 cm^{-1}, attributing νC=O(-CHO) group, indicating the non-coordination of C=O group with metal ion. A peak at 3350 cm^{-1} indicates the non-coordination of OH group with metal ion.[12] Existence of NH group is confirmed by peak at 3295 cm^{-1}.

UV-Vis spectra (DMF medium) of manganese(III) complexes exhibit peaks around 250-340 nm (π-π* transition) , 380-420 nm (ligand to metal charge transition) and a weak d-d band around 570-630 nm. The d–d band of manganese(III) ion of L^2 shows a slight red shift in λ_{max} due to the presence of Br atom which is highly electronegative compared to CH_3 atom in L^1. Zinc(II) complexes show two peaks at 250-300 nm (π- π* transition) and 350-400 nm (ligand to metal charge transition).[13-15]

ESR spectra of {[MnL^2] Cl_3} complex were obtained as shown in the **Fig 1**. A wide spectrum indicates +3 oxidation state for manganese ion.[16] The calculated room temperature magnetic moment value is 4.89 BM.

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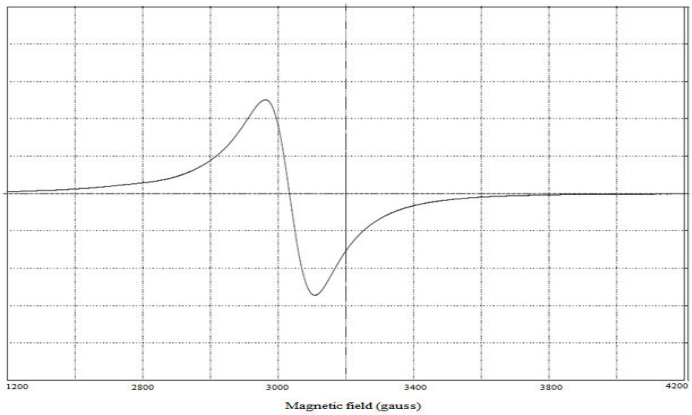

Fig 1. ESR spectrum of {[MnL^2] Cl_3}

3.2. Electrochemical studies

Cyclicvoltammetry is used to study the electrochemical behavior of the complexes.

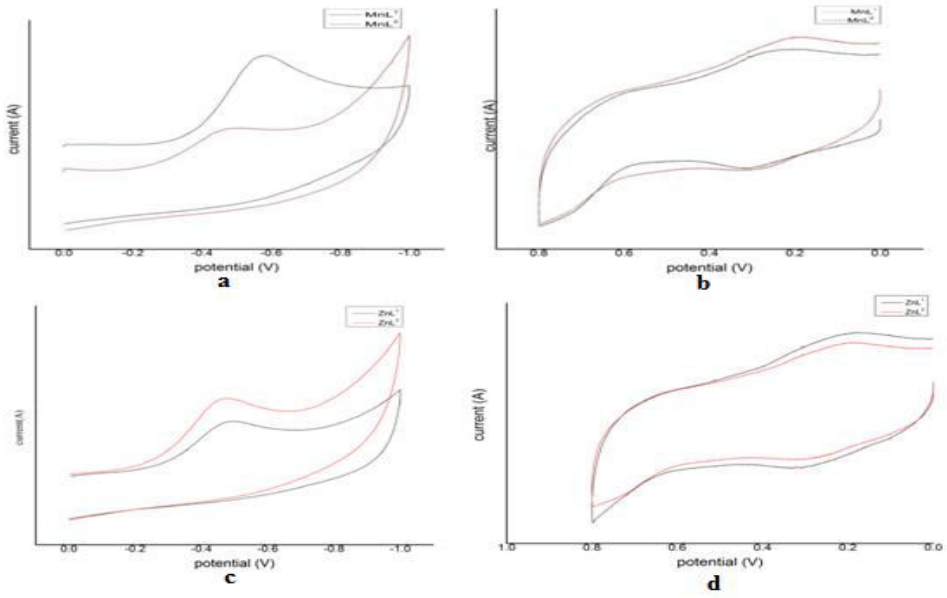

Fig 2. CV of mononuclear complexes

(a) { [MnL^1] Cl_3}$^{3+}$ & { [MnL^2] Cl_3}$^{3+}$ (Reduction), **(b)** { [MnL^1] Cl_3}$^{3+}$ & { [MnL^2] Cl_3}$^{3+}$(Oxidation)
(c) {[ZnL^1] Cl_2}$^{2+}$ & {[ZnL^2] Cl_2}$^{2+}$ (Reduction), **(d)** {[ZnL^1] Cl_2}$^{2+}$ & {[ZnL^2] Cl_2}$^{2+}$(Oxidation)

The cyclic voltammograms recorded around +1.0 to -1.0 V in DMF is given in **Fig 2**. Electrochemical data are given in **Table 1**. An irreversible reduction wave in the cathodic region and quasi reversible oxidation wave in the anodic region were observed .The reduction potential were around -0.5 to -0.7 V for MnL^1 and -0.4 to -0.6 V for MnL^2. The oxidation potential lies

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around E_{pc}= 0.28 and E_{pa}=0.32 for MnL^1 and E_{pc}=0.20 and E_{pa}= 0.24 for MnL^2. The oxidation $Mn^{III} \rightarrow Mn^{IV}$ is difficult in [MnL^2], whereas the reduction $Mn^{III} \rightarrow Mn^{II}$ is easier in [MnL^1] due to bromine atom on the redox potentials.[17] The Zn(II) complexes shows irreversible metal centered reduction around -0.4 to -0.6 and quasi-reversible oxidation around E_{pc}= 0.21 and E_{pa}=0.31 for ZnL^1 and E_{pc}=0.20 and E_{pa}= 0.28 for ZnL^2.

Table 1. Electrochemical data for Mn(III) and Zn(II) complexes

ΔE(mV)	$E_{1/2}$	E_{pc}(V) (oxidation)	E_{pa}(V)	E_{pc}(V) (reduction)	Complexes	No
40	0.30	0.32	0.28	-0.58	[MnL^1](Cl_3)	1
40	0.22	0.24	0.20	-0.48	[MnL^2] (Cl_3)	2
100	0.26	0.31	0.21	-0.50	[ZnL^1] (Cl_2)	3
80	0.24	0.28	0.20	-0.48	[ZnL^2] (Cl_2)	4

3.3. Hydrolysis of 4-nitrophenylphosphate

Hydrolysis of 4-nitrophenylphosphate by Mn(III) complexes were determined spectrophotometrically.[18] The hydrolysis activity of the complexes were obtained from log (A_α /A_α -A_t) versus time as shown in **Fig 3.** The initial rate constant values are given in **Table 2**. The higher rate constant value of complex 2 is because of Br atom and lesser rate constant value of complex 1 is because of CH_3 group.

Rate constant x $10^{-3}min^{-1}$	Complex	No
5.22	[MnL^1](Cl_3)	1
5.47	[MnL^2] (Cl_3)	2

Table 2. Rate constant of complexes

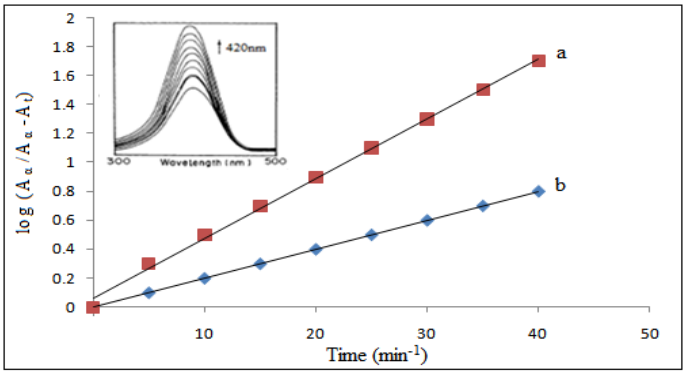

Fig 3. Hydrolysis of 4-nitrophenylphosphate by Mn(III) complexes
(a)[MnL^2](Cl_3) (b) [MnL^1](Cl_3)

3.4. DNA binding activity

The binding affinity of DNA with complexes was inspected by absorption titrations at

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room temperature.[19] Tests were done with fixed concentration (30 μM) of the metal complex and an increasing concentration of *ct*DNA (0-10 μM). The binding constant (K_b) of the complexes were determined from eqn. 1, through a plot of [DNA]/(ε_a–ε_f) *vs.* [DNA]. [20]

$$[DNA]/(\varepsilon_a-\varepsilon_f) = [DNA]/(\varepsilon_b-\varepsilon_f) + 1/Kb\ (\varepsilon_b-\varepsilon_f) \qquad (1)$$

The complexes show hypochromic effect with red shift, an interaction between the base pairs of DNA and aromatic ring of the ligand enhances hypochromism.[21] The binding constant K_b for complexes are 1.25 x 10^4 M^{-1} (1) ,1.18 x 10^4 M^{-1} (2) ,1.31 x 10^4 M^{-1} (3),1.15 x 10^4 M^{-1} (4) respectively. The larger K_b value for complex 1 show its better binding affinity to DNA compared to complex 2. DNA binding affinity is enhanced by the hydrophobic interaction of methyl group with the hydrophobic DNA surface. The lesser binding affinity of complex 2 is due to larger Br atom. The same is observed for complex 3 compared to complex 4.[22] The DNA binding absorption spectrum of **[MnL^1](Cl$_3$) & [ZnL^1](Cl$_2$)** is shown in **Fig 4** & **Fig 5.**

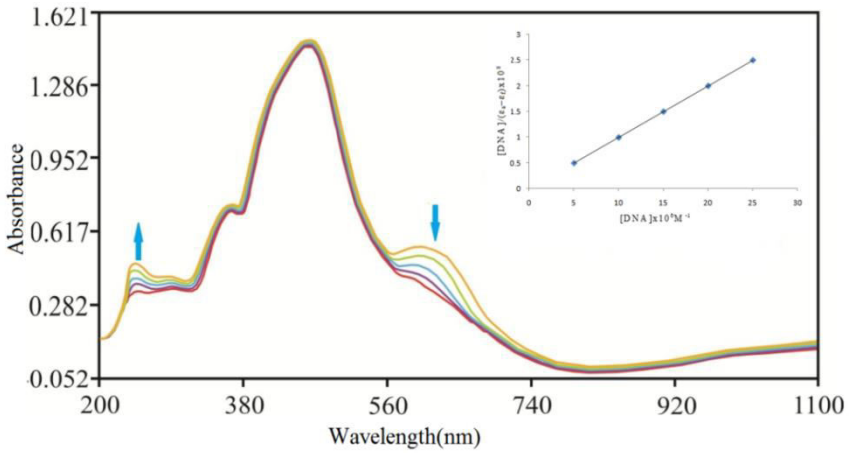

Fig 4. DNA binding absorption spectrum of [MnL^1](Cl$_3$) complex

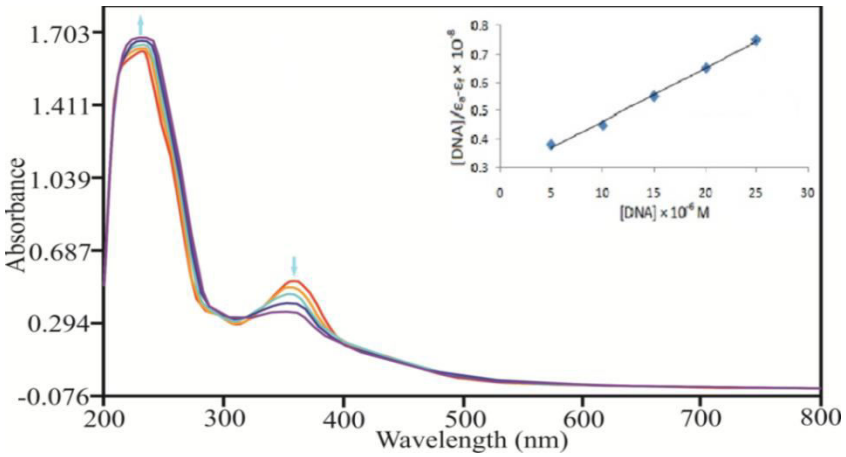

Fig 5. DNA binding absorption spectrum of [ZnL^1](Cl$_2$) complex

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3.5. Antimicrobial studies

The cup plate method using nutrient agar is used to test the in vitro activity of the complexes. Staphylococcus aureus, Bacillus subtilis, Pseudomonaas aeruginosa and Escherichia coli standard stems were used as reference cultures for in vitro experiment. Comparing with N-substituted tetraazamacrocycles[23] the complexes show better potency against tested pathogenic bacteria. Antifungal activities were tested against phytopathogenic fungus Candida albicans and Aspergillus niger which showed good antifungal activity. Manganese complexes show better activity than Zinc complexes.[24] The screening results of inhibition of pathogens are given in T**able 3** and **Fig 6.**

Table 3. Antimicrobial activity of complexes (zone of inhibition diameter in nm)

Antibacterial activity			Antifungal activity			
A.n	C.a	E.c	P.a	B.s	S.a	Complex
13	12	16	15	16	14	$[MnL^1](Cl_3)$
12	11	16	16	16	15	$[MnL^2]$ (Cl_3)
11	10	14	14	15	13	$[ZnL^1]$ (Cl_2)
11	11	15	13	14	14	$[ZnL^2]$ (Cl_2)

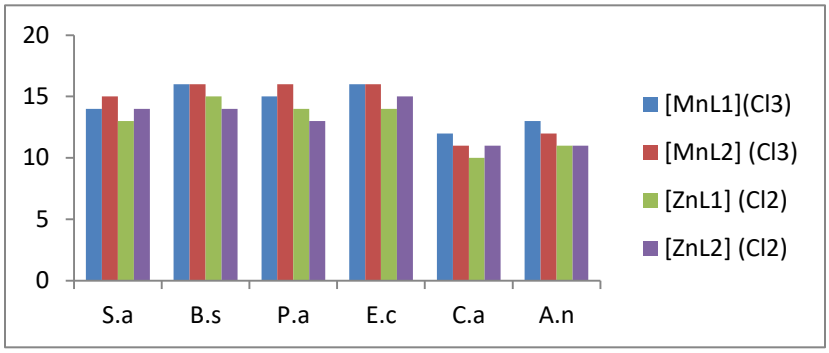

Fig 6.Antimicrobial activity of mononuclear complexes

3.6. Conclusion

Macrocyclic mononuclear Mn(III) and Zn(II) complexes have been synthesized. Their spectral datas are in good agreement with the literature. Cyclic voltammograms of the complexes have shown considerable reduction and oxidation. Kinetic study shows that complex 2 has higher rate constant than complex 1 because of Br atom on phenyl ring. The binding strength of the complexes with CT-DNA has been calculated and compared with the literature. Good results have been obtained for antibacterial and antifungal activity.

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