



Synthesis, Characterization and Antibacterial Activity and DNA cleavage Studies of tetra dentate Schiff bases and their Zn (II) Complexes

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Abstract

A new series of tetra dentate Schiff base ligands are obtained from condensation of phthalaldehyde and 2-amino benzyl alcohol, 2-amino-2-methyl-1-propanol and 2-aminobenzo hydrazine respectively, L1-L3 were reacted with Zinc acetate in aqueous methanol to give Zinc complexes (4a-c). The synthesized ligands and complexes are characterized by elemental analysis, IR, ¹H-NMR, Mass, Electronic spectra and molar conductance studies. All the complexes and ligands are examined for their anti-bacterial activities by cup plate method and their very low inhibitory concentration values verified by liquid dilution method. The DNA cleavage ability of the compounds was screened by agarose gel electrophoresis using calf thymus DNA (CT-DNA). The metal complexes are exhibited good anti-bacterial and DNA cleavage activities compared with their corresponding Schiff base ligands.

Keywords: Schiff base ligands, Zn (II) complexes, antibacterial activity, CT-DNA.

Introduction

Tetra dentate Schiff base ligands have been used as chelating agents, these are playing vital role in coordination chemistry and its metal complexes are great attention for several years¹⁻⁴. Various studies have shown that the azomethine group (>C=N-) in Schiff base complexes is responsible for various biological function⁵⁻⁹. These complexes are used as catalysts for a wide range of organic transformations such as C-H bond activation and oxidation reactions¹⁰⁻¹⁴ and several azomethines were reported to possess important antibacterial¹⁵⁻¹⁷ antifungal^{18,19} and antitumor²⁰.

Zinc metal can play key role in hydrolytic enzymes, where it is chelated by donor atoms (N/O). It has been standard at the same time a significant co-factor in bioactive molecules, each structural model in protein folding that can eagerly accept the coordination numbers 4, 5 or 6²¹⁻²³. All these considerations, the aim of this work is antibacterial activity and DNA cleavage studies²⁴ of zinc (II) complexes of the tetra dentate Schiff base ligands.

Material and Methods

All the chemicals like zinc (II) acetate, o-phthalaldehyde, 2-amino benzyl alcohol, 2-amino-2-methyl-1-propanol, 2-aminobenzohydrazides were purchased from Aldrich, USA. The solvents like ethanol, methanol, DMSO were distilled out and dried up by the standard procedures²⁵.

The percentage of carbon, hydrogen, nitrogen in Schiff base metal complexes are determined using a Perkin-Elmer CHNS

analyzer. The conductance of the Zn (II) complexes was measured on a Digisun digital conductivity meter (model DI-909). Infrared spectra in KBr/CsI pellets were recorded with a Perkin-Elmer 283 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Jeol 200MHz FT-NMR spectrometer in DMSO-*d*⁶. Mass spectra were recorded on CEC-21-110B and Finnegan MAT-1210 mass spectrometers. Hot air oven, incubator, laminar airflow unit and autoclave were used in the present investigations. The analytical data of Schiff bases and their metal compounds are given in table-1.

Synthesis of tetra dentate ligands (L1-L3): The Schiff base ligands²⁵ (L1-L3) were prepared from the condensation of 1 eq. of phthalaldehyde and 2 eq. of amine derivatives as shown in scheme-1. The general preparation strategy of Schiff base ligand (L1) is described briefly as follows: A mixture of various amines (2a-c) (0.01mol), sodium acetate (0.01 mol) and phthalaldehyde 1 (0.005 mol) in 10 ml of aqueous methanol was refluxed for 1 hour. The reaction mixture was cooled to room temperature, the solid separated was filtered, washed with water and recrystallized from ethanol.

Synthesis of Zn (II) complexes: All Zinc (II) compounds were prepared using the literature procedure²⁶ as given below as scheme-1: A mixture of L1- L3 (0.001 mole) and zinc acetate (0.001 mole) were refluxed for 4 hours. The reaction mixture was cooled to room temperature, the solid separated was filtered, washed with water and recrystallized from dichloromethane and ether to get pure complexes and directly used for analyses and biological activity.

Results and Discussion

The physical and analytical data of Zn (II) compounds are depicted in table-1. The Zn (II) complexes were extremely stable at room temperature, soluble in DMF and DMSO. Analytical data revealed the Zn (II) to ligand ratio is 1:2 in all the complexes. Molar conductance measurements of compounds were recorded in DMF (1×10^{-3} M) and values are 12.4, 15.1 and $16.3 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$. These values indicate that all the complexes are non-electrolytic nature²⁴.

Infra-red Spectral studies: In IR spectra were shown at 1677-1639 cm^{-1} which is recognized to azomethine group^{28, 29}. Schiff base ligands L1 and L3 exhibited characteristic bands at 3435 cm^{-1} and 3448 cm^{-1} which corresponding to OH group^{24, 25}. The L2 ligand showed by broad band at 3444-3359 cm^{-1} corresponding to ν_{NH} vibrations^{24, 31}, another band at 1687 cm^{-1} which is due to $\nu_{\text{C=O}}$ respectively²⁴. IR spectra of L1, L2 and L3 are presented table-2.

Infrared spectra of Zn (II) complexes explained by all the functional group bands are shifted then Zn (II) ions are coordinated with donor atoms of ligands. In all the Zn (II) complexes of azomethine group was shifted towards lower side about 40-55 cm^{-1} ^{32, 33}. In Zn (II) complexes of L1 and L3 OH bands are disappeared due to deprotonation of ligand at the time formation of complexes. Whereas Zn (II) complex of L2 ligand NH-band was shifted to lower region side which indicated that zinc metal was strongly bonded and supported to conductivity data²⁷. In fact, those two new bands are revealed by complexes of all spectra at 507 – 529 cm^{-1} assignable to $\nu_{\text{M-N}}$ vibration^{32, 33, 34} and appeared at 430 cm^{-1} and 423 cm^{-1} for M-O bonds. The band $\nu_{\text{C=O}}$ is shifted to the higher region side and observed at 1696 cm^{-1} which indicates that carbonyl group is not participated in complex formation. The coordinated water molecules show a characteristic absorption around 850 cm^{-1} in the IR spectra of complexes²⁷. The IR spectral data of [Zn (L1)

(H₂O)₂], [Zn (L2) (OAc)₂] and [Zn (L3) (H₂O)₂] are presented in table-2.

¹H –NMR and ¹³C- NMR Spectral studies: In the ¹H-NMR and ¹³C-NMR spectral data of all the ligands²⁵ L1 – L3 and respective Zn (II) complexes also represented in table-3. In all ligands important peaks which are involved in complex formation are CH=N and NH₂ (L2) and these peaks are slightly shifted towards down field compared to the respective ligand^{24, 27}. In all the ligands signals CH=N protons were appeared in the range of 8.10-8.42 δ . However, the coordination of nitrogen atom of the azomethine group to Zn (II) ion is confirmed by the appearance of signals in the range of 8.32-8.60 δ . In the spectra of Schiff base ligands L1 and L3 signals at 2.80 and 2.52 δ was appeared due to OH protons and these signals are disappearing in the Zn (II) complexes suggesting that the OH protons are deprotonated and the oxygen atoms coordinated with metal ions. In the case of Schiff base ligand L2 the signal due to aromatic NH₂ was appeared at 4.2 δ and this signal was deshielded in the respective Zn (II) complex indicating the participation of nitrogen in the coordination to the Zn (II) ion. In addition to these a new signal was observed in Zn (L2) complex at 2.12 which is due to acetyl group²⁷. There is no appreciable change in the peak positions corresponding to aromatic protons. Similarly, we are observed in ¹³C NMR spectra of all the Zn(II) complexes variation in the peak positions each spectra, which gave lot of information regarding shifting of CH=N, C-O and C_{Ar}-NH₂ peaks and suggesting that Zn(II) ions are coordinated with N and O atoms of the respective ligands. In the spectra of Zn (II) complexes, a down field shift in peak position is observed in the range of 168.40-174.02 δ is azomethine carbon atom. This evidence confirms that the ligands coordinate through nitrogen atoms and appreciable changes in peak positions were not observed with respect to aryl carbons and carbons adjacent to nitrogen/oxygen atom.

Table-1
Physical and analytical data of Schiff bases and their metal complexes

Ligand /complex, Color	M.F (M.Wt.)	Yield %	Found (Calcd.) %			
			C	H	N	Zn
L1= (BDMAB) lightyellow	C ₂₂ H ₂₀ N ₂ O ₂ (344)	(72)	76.69(76.72)	5.83(5.85)	8.19(8.13)	Nil
L2= (BDMAZ) white	C ₂₂ H ₂₀ N ₆ O ₂ (401)	(75)	65.81(65.99)	4.96(5.03)	20.89(20.99)	Nil
L3=(BDMAM) yellow	C ₁₆ H ₂₄ N ₂ O ₂ (276)	(70)	69.55(69.58)	8.68(8.75)	10.10(10.14)	Nil
[Zn L1(H ₂ O) ₂] Deep yellow	C ₂₂ H ₂₂ N ₂ O ₄ Zn (442)	(76)	59.52(59.54)	4.98(5.00)	6.28(6.31)	14.71 (14.73)
[Zn L2 (OAc) ₂] yellow orange	C ₂₆ H ₂₆ N ₆ O ₆ Zn (582)	(80)	53.46(53.48)	4.47(4.49)	14.36(14.39)	11.17(11.20)
[Zn L3(H ₂ O) ₂] yellow	C ₁₆ H ₂₆ N ₂ O ₄ Zn (374)	(78)	51.12(51.14)	6.95(6.97)	7.42(7.45)	17.37(17.40)

Table-2
IR Spectral data of ligands and its metal complexes (cm⁻¹)

Ligand / Complex	$\nu_{C=N}$	$\nu_{C=O}$	ν_{NH}/ν_{N-N^*}	ν_{M-N}	ν_{OH}	ν_{M-O}
L1	1639	Nil	Nil	Nil	3435	Nil
L2	1642	1687	3444	Nil	Nil	Nil
L3	1677	Nil	Nil	Nil	3448	Nil
[ZnL1 (H ₂ O) ₂]	1576	Nil	Nil	529	Nil	430
[ZnL2 (OAc) ₂]	1596	1696	3359/1167	507	Nil	331
[ZnL3 (H ₂ O) ₂]	1597	Nil	Nil	511	Nil	423

Table-3
¹H-NMR Spectral data of ligand and its metal complexes (δ ppm) in d⁶-DMSO

Ligand/Complex	¹ H-NMR Spectra	¹³ C-NMR spectra
L1	8.31(2H,s, CH=N),6.82-7.40 (12H,m, Ar-H),4.6 (4H, s, -CH ₂ -O), 2.80(2H, s, OH)	59.5(2C,O-C), 122.5,127.5,128.5,129.0, 129.3,131.2, 132.7, 134.1,149.3, (18C, Ar-C) 160.1 (2C, CH=N)
L2	8.10(2H,s, CH=N), 8.0(2H, s, NH-CO), 6.61-7.94(12H, m, Ar-H), 4.2(4H, s, Ar-NH ₂)	116.4,118.0,118.9, 128.3, 129.3,131.2, 133.0,134.1,148.4 (18C,Ar-C), 160.1 (2C, CH=N) 163.0(2C, C=O)
L3	8.42(2H,s, CH=N),7.50-7.86 (4H,m, Ar-H),3.84 (4H, s, O-CH ₂), 2.52(2H, s, OH),1.41 (12H, s, CH ₃)	26.20,(4C,CH ₃ -C), 55.5(2C,3 ⁰ C), 72.0 (2C,C-O) 129.30,131.2,140.20(6C,Ar-C), 160.90(2C,CH=N)
[Zn L1(H ₂ O) ₂]	8.42 (2H, s, CH=N), 6.50-7.62 (12H, m, Ar-H), 4.66 (4H, s, -CH ₂).	62.02(2C,O-CH ₂), 122.91,128.42,129.62,132.06, 134.08,136.46, 147.28(18C, Ar-C) 168.40 (2C, CH=N)
[Zn L2 (OAc) ₂]	8.32 (2H, s, CH=N), 8.02 (2H, s, NH-CO), 6.72-8.10 (12H, m, Ar-H), 4.9 (4H, s, Ar-NH ₂) 2.12 (6H, OCOCH ₃).	118.48,119.96,129.48,132.10,,136.64, 148.34(18C,Ar-C), 169.02 (2C, CH=N),164.62(2C, C=O), 23.02(2 CH ₃ , OCO), 174.02(2C, OCO)
[Zn L3(H ₂ O) ₂]	8.46 (2H, s, CH=N), 7.62-8.02 (4H, m, Ar-H), 4.02 (4H, m, -CH ₂), 1.72 (12H, s, CH ₃)	28.7, 32.24,(4C,CH ₃ -C),58.24(2C,3 ⁰ C), 71.56(2C,O-C), 132.41,134.48,146.82(6C,Ar-C), 170.21(2C,CH=N)

Mass spectral analysis: The mass spectra of ligands²⁵ viz. BDMAB (L1) and BDMAZ (L2) showed the (M⁺+Na) ion peak at m/z 367.4 (30%), 424.16(15%) and BDMAM (L3) shown molecular ion M⁺+1 peak at m/z 277(25%) respectively. This data is in good agreement with the respective molecular formulae.

The mass spectra of Schiff base Zn (II) complexes viz. [Zn (L1 (H₂O)₂] shown molecular ion peak (M⁺+Na) at (m/z) 465 (24%). However, the mass spectra [Zn (L2) (OAc)₂] and [Zn (L3) (H₂O)₂] shown (M⁺+1) peak at (m/z) 583,375 respectively. These values are equivalent with the respective molecular weights of the Zn (II) complexes calculated and experimental values are supported toward elemental analysis.

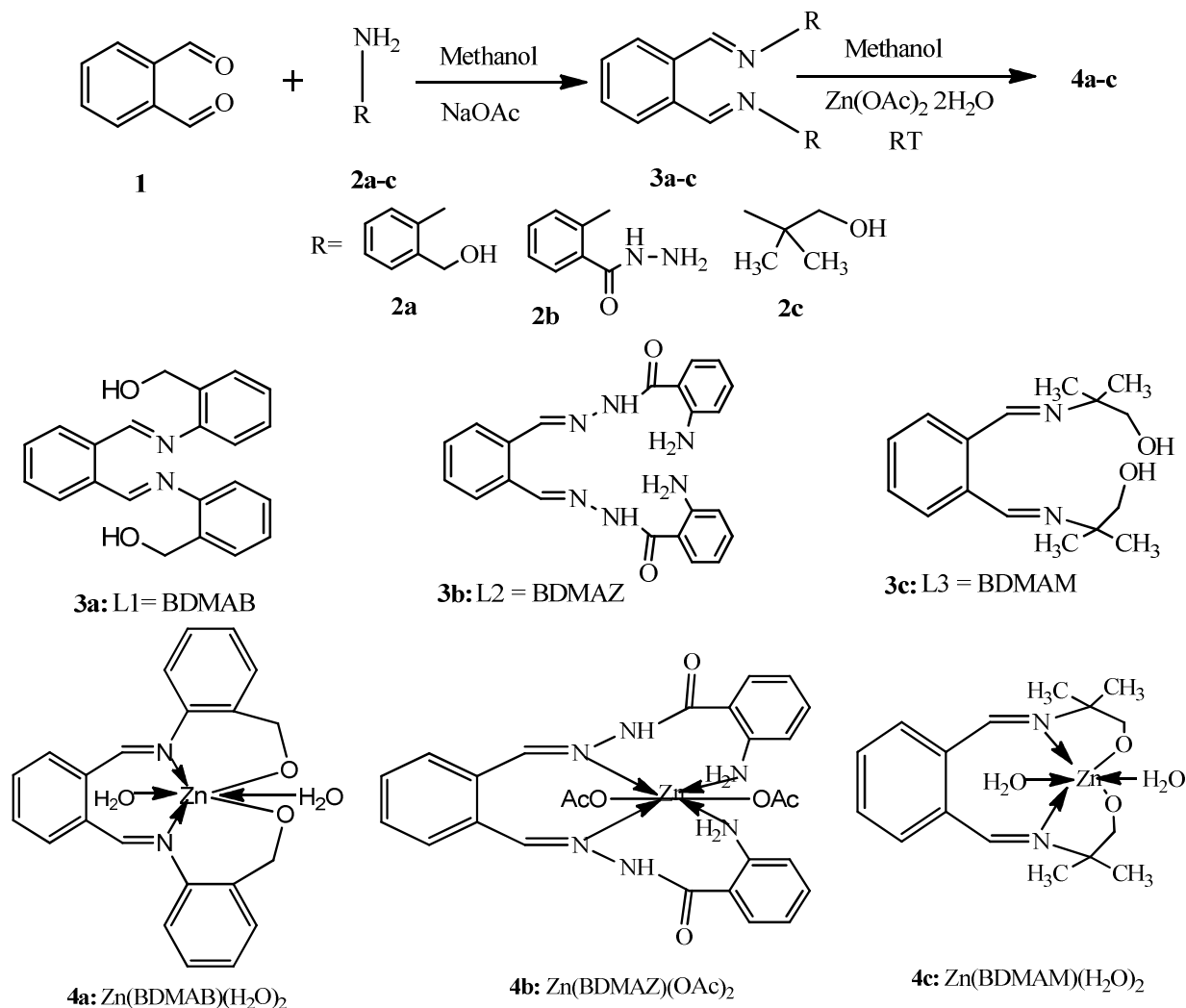
Structures of the complexes: On the basis of analytical and spectral data, octahedral structures (scheme-1) have been tentatively proposed for all of Schiff base Zn (II) complexes.

Antibacterial activity: The Schiff-base ligands and their Zn (II) metal complexes were assessed for their preliminary antibacterial activity against gram +ve and gram -ve bacteria³⁵⁻⁴¹. The activities of the Zn metal complexes are found to be more as compared to the ligands. The enhanced in the

antibacterial activity of metal chelates may be due to the effect of the metal ion in the normal cellular process. A probable mode of toxicity increase may be measured in the light of Tweedy's chelation theory⁴². Therefore, the Zn (II) complexes of ligands L2 and L3 were found to be very effective than the Zn (II) complex of L1 and all the results are given in table-4. From the results, the Zn (II) complexes with L2 and L3 ligands were found to be active at lower concentrations than the existing antibiotics like Streptomycin and Ampicillin but less than the Rifampicin.

DNA cleavage studies: The nucleic acid cleavage experiment was conducted by using calf thymus (CT) DNA (1 mg/ml) as a substrate and H₂O₂ as oxidizing agent. The cleavage ability was established by agarose gel electrophoresis. For studying cleavage capability of Transition metal complex, 1mm of corresponding metal complexes stock solution was made and used in the present study. A reaction mixture containing 30 μM of CT DNA, 50/100/150 μM of each complex and 50 μM of H₂O₂ in 50 mM of tris-HCl buffer (pH -7.2) was prepared and incubated at rt for 60 min. The cleavage pattern was studied by electrophorizing the samples for 1 h at 50 V on 1.2% of agarose gel using TBE (tris Borate EDTA) buffer, pH-8.2. Before electrophoresis, to 7 μl of these samples and 3 μl of

bromophenol blue was added as loading dye and loaded on the gel. After electrophoresis, the gel was stained using $1 \mu\text{g}/\text{cm}^3$ ethidium bromide and photographed under UV light using a gel documentation system.



Scheme-1
Synthesis of Schiff bases and their metal complexes

Table-4
Zones of inhibition of Schiff-bases and Zn (II) complexes against four different bacteria

Schiff bases & Zn Complexes	Conc. (100 $\mu\text{g}/\text{ml}$)	Zone of inhibition (mm)			
		Basillus subtilis	Staphylo coccus aureus	Escherichia Coli	Klebsiella Pneumonia
L1	1000	13	12	Nil	Nil
L2	1000	17	14	15	16
L3	1000	16	17	18	14
[Zn L1(H ₂ O) ₂]	1000	25	23	21	24
[Zn L2(OAc) ₂]	1000	45	43	44	38
[Zn L3(H ₂ O) ₂]	1000	41	34	41	36
Streptomycin	1000	10	12	6	6
Ampicillin	1000	11	13	8	7
Rifampicin	1000	51	49	48	45

In the current study, the DNA cleavage of Zn (II) complexes was monitored by agarose gel electrophoresis. All the compounds have shown modest to good DNA cleavage ability. After the electrophoresis, in all the wells loaded with compound treated calf thymus (CT)-DNA, spread was found, indicating the cleavage ability of compounds. At higher concentrations, even spread or DNA band was not observed in the region of the control DNA region representing that the DNA was totally cleaved. The Schiff base ligands L1 and L2 have shown good cleavage activity except L3. The Zn (II) metal complexes exhibited noticeable cleavage activity when compared to their Schiff base ligands. In case of [Zn L1 (H₂O)₂] exhibited good cleavage activity compared to their [Zn L2(OAc)₂] and [Zn L3 (H₂O)₂]. However, from the studies, it is found to be that Zn (II) complexes are more cleavage activity. The results of DNA cleavage studies are depicted in figure-1 and figure-2. This result indicates that, these transition metal complexes are having a potent DNA cleavage activity and can be used in drug preparation.

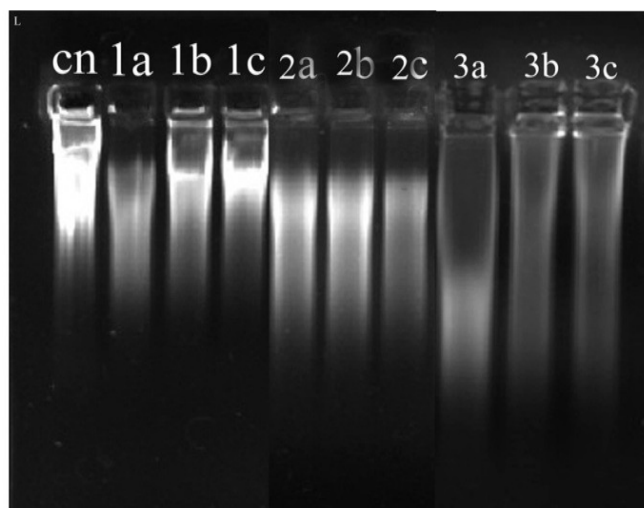


Figure-1

DNA cleavage in the absence of H₂O₂, Lane 1a: DNA+L1; Lane 1b: DNA+L2; Lane 1c: DNA+L3; DNA cleavage studies of ligands having different concentration are a, b and c, here CT= Calf Thymus, Cn = Control DNA

Conclusion

The Zn (II) complexes are acquired from the various Schiff base ligands and characterized by spectral and analytical data. The results shown that all ligands are coordinated in a tetra dentate fashion to the metal ion and the 5th and 6th position water molecules are coordinated. Based on the analytical and spectral data, the geometry of the complexes is found to be distorted octahedral nature. The Zn (II) complexes have higher antibacterial activity than the ligands. The CT-DNA cleavage studies explain that total cleavage of CT-DNA was observed by Zn (II) complexes.

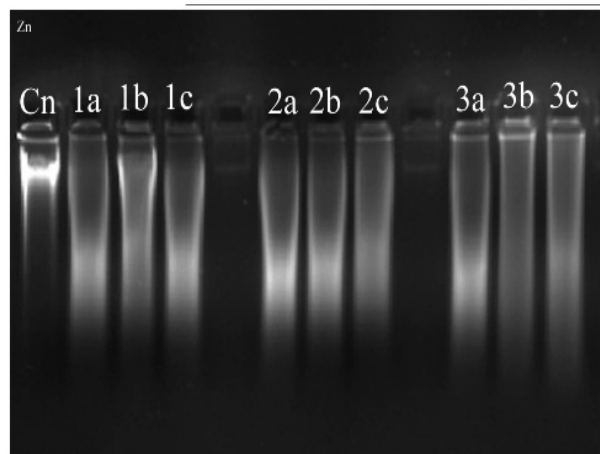


Figure-2

DNA cleavage in the Presence of H₂O₂, Lane 1a: DNA + ZnL1 (H₂O)₂ + H₂O₂; Lane 1b: DNA + ZnL2 (OAc)₂ + H₂O₂; Lane 1c: DNA + ZnL3 (H₂O)₂ + H₂O₂; Metal complexes having different concentration. Here a, b and c are concentrations a= 50 μM, b= 100 μM and c=150 μM and L1-3 = Schiff base ligands

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