



**SYNTHESIS, SPECTROSCOPIC AND BIOLOGICAL CHARACTERIZATION
MANGANESE (II), COBALT (II) AND NICKEL (II) COMPLEXES WITH AN
ASYMMETRIC BIDENTATE THIAZOLIDINE DERIVATIVE**

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ABSTRACT

Mn(II), Co(II) and Ni(II) complexes with a bidentate ligand ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate were synthesized and characterized on the basis of elemental analysis, molar conductance measurements, magnetic susceptibility values, UV-vis and IR spectral data. Spectral studies show that the ligand behaves as bidentate chelating agent and bonded to the metal ion through two oxygen atom. Electronic spectra and magnetic susceptibility measurement reveal octahedral geometry for Ni(II) and Co(II) complexes and tetrahedral configuration for Mn(II) complex. The complexes are found to be non-electrolytic in nature on the basis of low molar conductance. These metal complexes were also screened for its antibacterial activity against pathogenic strains causing urinary tract infections and were found to be effective.

KEYWORDS: bidentate, Schiff base, Antibacterial.

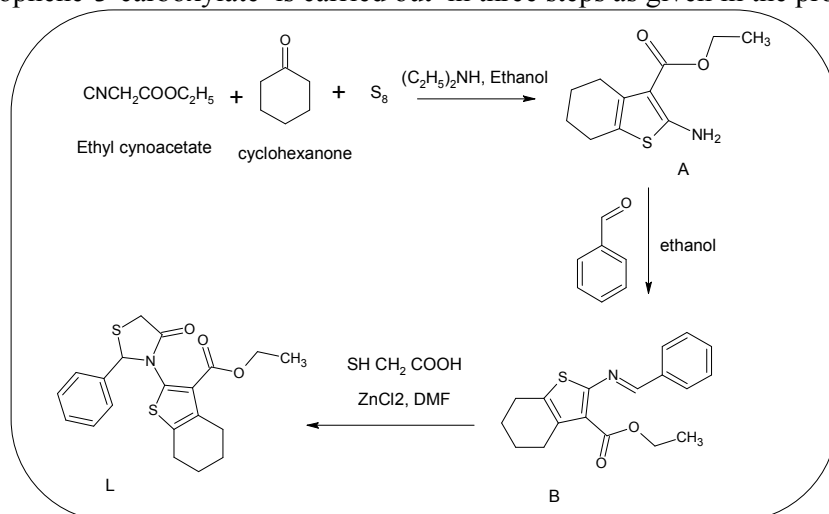
INTRODUCTION:

The heterocyclic compounds are an integral part in organic chemistry branch and constitute a modern research field that is being currently pursued by many researchers. The biological response of thiazolidine derivatives had attracted the attention of many researchers for its study of their biological potential. These compounds have been reported for their antioxidantⁱ, anti-inflammatoryⁱⁱ, antibacterial/antifungalⁱⁱⁱ, antitumor^{iv}, antidiabetic^v and antiarthritic^{vi} effects. Metal complexes of Schiff bases prepared from heterocyclic system constitute a interesting class of compound with diverse analytical, technological and biological application^{vii-ix}. Among the variety of heterocyclic Schiff base ligand system those containing thiophene moiety deserve special attention because of the biosteric relationship of thiophene to benzene that has led to several studies on drug analogue in which benzene rings have been replaced by thiophene rings^x. At present, we face threats in the form of Multi drug resistant pathogens evolving into super bugs like Extended Spectrum β -lactamase (ESBL) and Metallo- β -lactamase (MBL) producers capable of hydrolyzing β -lactam antibiotics, screening of antimicrobial properties of these complexes will provide a novel approach in the field of pharmacy^{xi}.

In continuation of our research^{xii}, the aim of this work, is to prepare and investigate the complexes of Mn(II), Co(II) and Ni(II) with Schiff base ligand ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate. The complexes were characterized by elemental analysis, magnetic moments, Molar conductance, along with electronic, infrared and NMR spectral analysis. The antibacterial activities of these metal complexes have been screened against ESBL (Extended spectrum β -lactamase) and MBL (Metallo- β -lactamase) producers which are able to hydrolyze β -lactam antibiotics including 3rd generation cephalosporins and carbapenems.

MATERIALS AND METHODS

All chemical used in the project work were of AR grade and was recrystallised while the solvent were purified and double distilled before use. Metal content was determined by the standard methods^{xiii}. Molar conductance was measured in DMF (10^{-3} M solution) on an ELICO Digital Conductivity meter Model CM-180. The electronic spectra of the complex in DMF were recorded on UV-Systronic spectrophotometer. The IR spectra were recorded in KBr disc on a Perkin Elmer Model 1600 FTIR Spectrophotometer, where as the presence of $\nu(\text{M-Cl})$ in complexes was recorded on Plytec 30 spectrometer using CsI disc. The ¹H-NMR Spectra was recorded in DMSO on a VXR-300S Varian Supercon NMR Spectrometer using TMS as the internal reference. Magnetic Susceptibility measurements were carried out by employing the Gouy method using Hg [Co (SCN)₄] as a calibrant. Preparation of ligand ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate is carried out in three steps as given in the procedure^{xiv-xvi}.



Scheme 1: Synthesis of ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (L)

Preparation of metal complexes: The metal complexes were prepared by the following general procedure. To a magnetically stirred and warmed DMF solution (20ml) of the ligand (0.01mol) added an DMF solution of metal (II) chloride in appropriate ratios dissolved in ethanol (10ml) in small parts. After complete additions of the metal salt solution, the pH was adjusted to 7.5 by adding ammonia. It was then refluxed for about six hours and the resulting solution was reduced to half the initial volume and allow standing overnight. The complex formed was filtered, washed successively with aqueous ethanol and ether. Finally the complex was dried in vacuum over P₄O₁₀.

Test organisms used in the study: 19 MDR (Multi-Drug Resistant) gram negative uropathogens were used in the study including 6 ESBL (Extended spectrum β -lactamase) and 7 MBL (Metallo- β -lactamase) producers (Table-1).

Table-1: Test organisms used in the study

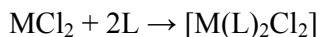
ESBL Producing uropathogens	MBL Producing uropathogens	Non- ESBL and MBL Producing uropathogens
<i>E.coli</i> strain 1	<i>E.coli</i> strain 1	<i>Proteus vulgaris</i>
<i>Citrobacter diversus</i> strain 1	<i>E.coli</i> strain 2	<i>Proteus mirabilis</i>
<i>E.coli</i> strain 2	<i>Pseudomonas aeruginosa</i>	<i>E.coli</i>
<i>Pseudomonas aeruginosa</i>	<i>E.coli</i> strain 3	<i>Morganella morganii</i>
<i>Citrobacter diversus</i> strain 2	<i>Klebsiella pneumoniae</i> strain 1	<i>C.diversus</i>
<i>Proteus vulgaris</i>	<i>Klebsiella pneumoniae</i> strain 2	<i>Pseudomonas aeruginosa</i>
	<i>C.diversus</i>	

Antimicrobial susceptibility of uropathogens: Antibiotic sensitivity test of the pathogens was carried out using Kirby Bauer method so as to obtain Antibiogram pattern^{xvii}.

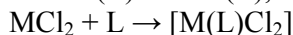
Antibacterial activity: Antibacterial activity of the metal complexes was determined by Agar cup method. The metal complexes were dissolved in HPLC grade ethanol to obtain final concentration of 200 $\mu\text{g}/\mu\text{l}$. A loopful of the test isolates were inoculated in 10 ml of Brain Heart infusion (BHI) broth and incubated at 37°C for 24 hours in order to obtain actively growing log phase isolates. Sterile 20 ml of Luria Bertani agar was melted, cooled to around 40°C and 0.4 ml test strain (0.1 O.D. at 530nm) was seeded and poured into a 9cm diameter aneubra Petri plates. Using a sterile cork borer (8 mm in diameter), wells was punched in each plate after solidification of the medium. 50 μl of the test sample (metal complex) was then added to the wells and incubated at 37°C for 24 hours to observe the zones of inhibition against each metal complex. Control wells were also set up using 50 μl of ethanol (solvent) for each isolate. The mean value obtained for three individual replicates was used to calculate the zone of inhibition for each isolate^{xviii}.

RESULTS AND DISCUSSION

Analytical data indicated that ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (L) and the metal chloride formed well defined complexes. Formation of the complexes can be symbolized as follows:



M= Co(II) and Ni(II),



M= Mn(II)

Formulation of the complexes has been based on their elemental analytical data, molar conductance values and magnetic susceptibility data. The stiochiometry of the complexes 1:1 (Metal: ligand) of Mn (II) complex, where as 1:2 (metal: ligand) of Co (II) and Ni (II) complexes. All complexes are brightly colored, non hygroscopic and decomposed above 180°C. The molar conductance values support the non-electrolyte nature of the metal complexes^{xix} as shown in Table-2

Table-2

Physico-chemical characteristic of Schiff base ligand and its metal complexes

Compound	Colour	F.Wt	Elemental analysis (%)					Molar Cond. ($\Omega^{-1}\text{cm}^2\text{mol}^{-1}$)
			Found(calcd)					
			C	N	S	Cl	M	
L	yellow	387.51	62.45 (62.02)	4.23 (3.86)	15.25 (15.56)	-	-	-----
[Mn(L)Cl ₂]	Light brown	513.35	47.43 (46.79)	3.53 (2.73)	11.08 (12.49)	12.93 (13.81)	9.85 (10.70)	8.59
[Co(L) ₂ Cl ₂]	Red	904.87	52.22 (53.09)	4.05 (3.10)	13.55 (14.17)	7.23 (7.84)	5.97 (6.51)	10.68
[Ni(L) ₂ Cl ₂]	brown	904.63	57.24 (53.11)	4.17 (3.10)	14.29 (14.18)	6.98 (7.84)	5.74 (6.49)	9.62

The spectral data of the compounds and their tentative assignments are shown in Table 3. It can be seen that the characteristic absorption peak present in IR spectra of both the complexes are similar which indicate that the complexes have similar arrangement of ligand atom around metal ions. The bonding of the ligand to the metal ions is investigated by comparing the IR spectra of the free ligand with its metal complexes. The IR spectra of the complex show that the $\nu(\text{C}=\text{O})$ band at 1647 cm^{-1} in the spectra of the ligand made a distinct shift towards lower frequency by $50\text{-}60\text{ cm}^{-1}$. This suggests that the bonding of the ligand through the carbonyl oxygen in the keto form^{xx}. The appearance of new bands in the $550\text{-}610\text{ cm}^{-1}$ range for all the complexes was taken as an indication of the presence of covalent metal oxygen bond which may be taken as an indication to the coordination between the metal ions with oxygen atom respectively^{xxi}. The band at 395 cm^{-1} and 385 cm^{-1} can be assigned to the presence of $\nu(\text{M}-\text{Cl})$ in copper and zinc complexes^{xxii} respectively, which was recorded on Plytec 30 spectrometer using CsI disc. Absence of $\nu(\text{M}-\text{S})$ band in the far infrared spectra of the metal complexes gives direct evidence to non-involvement of ring sulphur in bond formation Table-3.

TABLE -3

Important IR spectral data of Schiff base and its metal complexes.

Tentative assignment	$\nu(\text{C}-\text{H})$	$\nu(\text{C}=\text{C})$	$\nu(\text{C}-\text{O})$	$\nu(\text{Ar}-\text{H})$	$\nu(\text{C}-\text{N})$	$\nu(\text{C}-\text{S})$	$\nu(\text{C}=\text{O})$	$\nu(\text{M}\leftarrow\text{O})$	$\nu(\text{M}-\text{Cl})$
L	2846s	1590s	1284s	3085s	1375s	778s	1645s	-	-
[Mn(L)Cl ₂]	2847s	1591s	1280s	3085s	1375s	778s	1593s	552m	395m
[Co(L) ₂ Cl ₂]	2845s	1590s	1279s	3086s	1374s	777s	1586s	585m	387m
[Ni(L) ₂ Cl ₂]	2846s	1590s	1280s	3086s	1376s	778s	1588s	610m	392m

Proton NMR spectral data of the ligand supported the conclusion drawn on the basis of UV and IR spectral data. The absence of NH₂ proton signal in the NMR spectrum of ligand in DMSO-d₆ indicates successful Schiff base formation by replacement of the C=O group of ethyl -2-amino-4,5, 6,7 tetrahydro-1-benzothiophene-3-carboxylate. The signals at 1.4δ (t) of three hydrogen of OCH₂CH₃, 1.8δ (m) of four hydrogen of C5 and C6, 2.5δ (d) of two hydrogen of C4, 2.7δ (d) of two hydrogen of C7, 3.4δ (s) of two hydrogen of CH₂ of thiazolidine, 4.3δ (q) of two hydrogen of OCH₂CH₃, 5.9δ (s) of one hydrogen atom of N-CH group and at 7.1δ (m) due to five hydrogen atom of Ar-H is observed.

The electronic absorption spectrum of the ligand in DMF showed three bands at 295, 345 and 360 nm. The first one may be assigned to intraligand $\pi \rightarrow \pi^*$ transition which is nearly unchanged on complexation, whereas the second and third bands may be assigned to the $n \rightarrow \pi^*$ and charge transfer transition of the thiazolidine and ester C=O group. It is found that these bands were shifted to lower energy on complexation, indicating participation of this group in coordination with the metal ions. In addition, the spectra of the complexes showed new bands observed in the 420-440 nm range which may be attributed to the charge transfer transitions.

The electronic spectra from 6A_1 ground state of Mn(II) complex to higher energy state are spin forbidden and thus transitions are not observed in the spectrum of the Mn(II) complex. The electronic spectrum of Co(II) shows absorption bands at 9110, 14940 and 18510 cm^{-1} attributed to the transitions ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)(\nu_1)$, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)(\nu_2)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)(\nu_3)$ respectively. This confirms octahedral geometry for the Co(II) complex^{xxiii}. The ν_3/ν_1 value in the Co(II) complex is 2.03 and it lies in the usual range (2.00-2.80) reported for octahedral complexes. The electronic parameters were calculated using the standard method^{xxiv,xxv} and the values are as follows $Dq=1019\text{cm}^{-1}$, $B=699.4\text{cm}^{-1}$, $\beta = B'/B=0.72$, $\beta^0 = 28\%$ and $\text{CFSE} = -99.97 \text{ kJmol}^{-1}$. The low value of Racah parameters compared to the free ion value of 971cm^{-1} β^0 value of 28% indicates the covalent nature of Co-L bond. The spectrum of Ni(II) complex shows three absorption bands at 10120, 17620 and 28140 cm^{-1} , which may be assigned to the transitions ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)(\nu_1)$, ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)(\nu_2)$ and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)(\nu_3)$ respectively indicating octahedral geometry. The ν_2/ν_1 value in the Ni(II) complex is 1.74 and it lies in the range (1.60-1.82) for octahedral Ni(II) complexes. The electronic spectral parameters values are as follows $Dq=1012\text{cm}^{-1}$, $B=944\text{cm}^{-1}$, $\beta = B'/B=0.92$, $\beta^0 = 8\%$ and $\text{CFSE} = -145.51 \text{ kJmol}^{-1}$. The low value of Racah parameters compared to the free ion value of 1030 to 944cm^{-1} of the complex and β^0 value of 8% indicates the covalent nature of Ni-L bond.

Magnetic susceptibility measurements: magnetic moment of Mn(II) complex is 5.23 BM which shows the presence of five unpaired electrons. Magnetic moment of Co(II) and Ni(II) complexes are 4.53 BM and 3.20 BM respectively, indicating an octahedral configuration.

Antimicrobial susceptibility testing using Kirby Bauer method of gram negative uropathogens was carried out and it was found that these uropathogens were resistant to most of the antibiotics as shown in Table-5. All isolates were found to be Multiple Drug Resistant (Resistant to more than 3 antibiotics) including 3rd generation Cephalosporins (Ceftazidime, Cefotaxime and Ceftriaxone). The effect of metal complexes on these test isolates is shown in Table-6 below. The antibacterial activity of these complexes can be credited to its lipophilic nature which may allow easy binding and penetration of the complex in the cellular structure of the pathogens. It can also be explained with the help of Tweedy's chelation theory which predicts that co-ordination of metal ions to ligands reduces the metal atom polarity due to partial sharing of positive charge with donor groups and delocalization of π electrons over the entire chelate. This enhances the lipophilicity of the chelates increasing their permeation through the lipid membrane of the bacterial cell. The metal complexes interfere destructively with the synthesis of cellular walls, leading to alteration in cell permeability characteristics, a consequence of disorganized lipoprotein arrangement and therefore death of cell^{xxvi}. Impairment of normal cellular processes due to denaturation of one or more cellular enzymes^{xxvii, xxviii}.

The different properties of the metal complexes upon chelation may enhance their activity. Metal ion polarity is reduced as a consequence of overlap of ligand orbitals and partial sharing of the positive charge of the metal ion with donor groups. This action enhances the

complex penetration into the bacteria's lipid membrane and formation of irreversible covalent bond which blocks the metal binding sites in the enzymes of the micro-organisms^{xxix}.

Table-4
Antibiotic resistance profile of the uropathogens

Isolates	Antibiotic resistance profile		
ESBL Producing uropathogens			
	Sensitive	Intermediate	Resistant
<i>E.coli</i> strain 1	AS, AK, GF		BA, CF, PC, CH,RC, CI, TE, ZN, GM, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Citrobacter diversus</i> strain 1	AS, BA, CH		CF, PC,RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>E.coli</i> strain 2	AS, CH, AK, GF	ZN	BA, CF, PC, RC, CI, TE, GM, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Pseudomonas aeruginosa</i>	CH, AK, GF		AS, BA, CF, PC, RC, CI, TE, ZN, GM, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Citrobacter diversus</i> strain 2	ZN, AK, GF	NX, CU, CP, PB, AS, CF, RC, GM	BA, PC, CH, CI, TE, TT, OX, RP, ZX, CB, NA, AG, FG
<i>Proteus vulgaris</i>	NX, AS, GM, AK	TT, RP, PC, RC, GF	BA, CF, CH, CI, TE, ZN, OX, ZX, CB, NA, AG, CU, CP, FG, PB
Non- ESBL and MBL Producing uropathogens			
<i>Proteus vulgaris</i>	AK, LOM, SPX, NET, CAZ, CIP, CPX, GEN, A/S, CZX, OF, PF, NX, CTR, CPZ, CTR, CFM, CPO, CPM		NA
<i>Proteus mirabilis</i>	CI, CF, BA, PB, CU, NA, NX, OX	TT, AG, CP, TE, AK	GF,GM, ZN, RC, CH, PC, AS, FG, CB, ZX, RP
<i>E.coli</i>	AG, CU, PB, PC	CB, CI	GF, AK, GM, ZN, TE, RC, CH, CF, BA, AS, FG, CP, CU, NX, NA, ZX, RP, OX, TT
<i>Morganella morganii</i>	RC, CI, TE, PC, PB, AG, CU, OX	AK, GM, CH, CP	TT, RP, ZX, CB, NA, NX, FG, AS, BA, CF, ZN, GF
<i>C.diversus</i>	AS, BA, CF, PC, CH,RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB		
<i>Pseudomonas aeruginosa</i>	TT, RP, AG, CU, FG, AS, CF, CH, CI, TE,	OX, CB, PB, ZN, PC	BA, RC, GM, AK, GF, ZX, NA, NX, CP

MBL Producing uropathogens			
<i>E.coli</i> strain 1	CH	PC	AS, BA, CF, RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>E.coli</i> strain 2	CH	AK	AS, BA, CF, PC, RC, CI, TE, ZN, GM, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Pseudomonas aeruginosa</i>			AS, BA, CF, PC, CH, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>E.coli</i> strain 3	RC		AS, BA, CF, PC, CH, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Klebsiella pneumonia</i> strain 1			AS, BA, CF, PC, CH, RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>Klebsiella pneumonia</i> strain 2	CH	AK	AS, BA, CF, PC, CH, RC, CI, TE, ZN, GM, AK, GF, TT, OX, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB
<i>C.diversus</i>	OX, BA, CH, GM	TE, AK, GF	AS, CF, PC, CH, RC, CI, ZN, GM, TT, RP, ZX, CB, NA, NX, AG, CU, CP, FG, PB

Key:

TT -Ticarcillin/clavulanic acid, OX- Oxytetracycline, RP – Ceftriaxone, ZX – Cefepime, CB – Cefuroxime, NA - Naladixic acid, NX- Norfloxacin, AG - Amoxicillin/clavulanic acid, CU – Cefadroxil, CP - Cefoperazone, FG- Ceftazidime, PB - Polymixin B, AS – Ampicillin, BA - Co-trimazole, CF – Cefotaxime, PC- Piperacillin, CH – Chloramphenicol, RC – Ciprofloxacin, CI – Cefizoxime, TE – Tetracycline, ZN – Ofloxacin, GM – Gentamicin, AK –Amikacin, GF – Gatifoxacin.

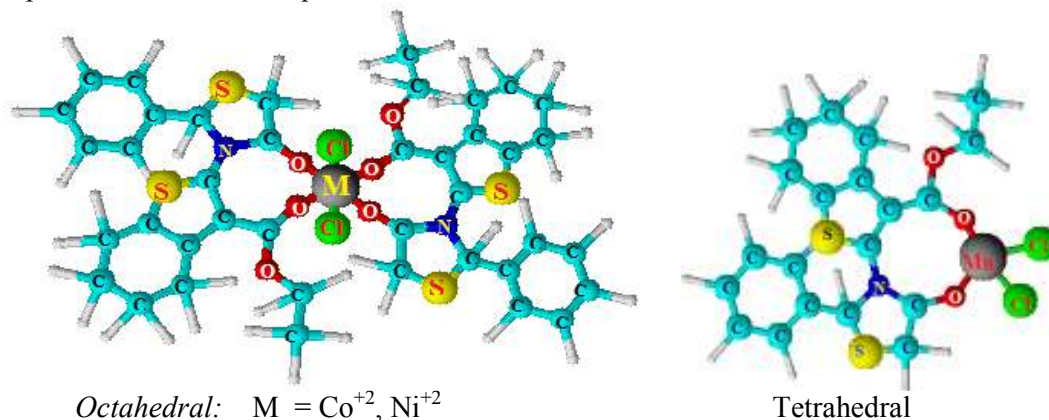
Table -5
Antibacterial activity of Schiff base metal complexes against drug resistant uropathogens

Isolates	Metal complexes (200µg/µl)		
	[Mn(L)Cl]	[Co(L) ₂]	[Ni(L) ₂]
<i>E.coli</i> strain 1	-	15	12
<i>Citrobacter diversus</i> strain 1	-	-	-
<i>E.coli</i> strain 2	-	-	-
<i>Pseudomonas aeruginosa</i>	12	14	-
<i>Citrobacter diversus</i> strain 2	15	15	12
<i>Proteus vulgaris</i>	15	-	-
<i>Proteus vulgaris</i>	25	30	-
<i>Proteus mirabilis</i>	17	18	20
<i>E.coli</i>	-	18	-
<i>Morganella morganii</i>	-	-	-
<i>C.diversus</i>	17	25	-
<i>Pseudomonas aeruginosa</i>	22	17	16
<i>E.coli</i> strain 1	12	12	15
<i>E.coli</i> strain 2	12	14	12
<i>Pseudomonas aeruginosa</i>	-	15	12
<i>E.coli</i> strain 3	-	13	16
<i>Klebsiella pneumonia</i> strain 1	15	-	-
<i>Klebsiella pneumonia</i> strain 2	-	-	-
<i>C.diversus</i>	17	-	-

CONCLUSION:

Based on the above analytical and physico-chemical properties it has been observed that a ligand ethyl 2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (L) behaves as a bidentate chelating agent and bonded to the metal ion through ester carbonyl and keto oxygen atom. Electronic spectra and magnetic susceptibility measurement reveal octahedral geometry for Ni(II) and Co(II) complexes and tetrahedral configuration for Mn(II) complex. Antibacterial studies have indicated that the complexes show higher activities than the free ligands. Structures proposed for the complexes are designated in figures below.

Proposed structure of complexes



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