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N/S/O FUNCTIONALIZED LIGANDS AND THEIR METAL COMPLEXES: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES

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ABSTRACT

A few N/S/O functionalized ligand was prepared from condensation of Boc protected gabapentin drug with different amino acids from coupling reaction method. Ligand form 1:1 complexes with Cu(II), Co(II), Mn(II), Sr(II) and Cd(II) in good yield. Characterizations of the ligand and metal complexes have been done from Elemental analysis, Infrared spectra, ^{1}H NMR, Electronic absorption spectra and molar conductance measurements. Antioxidant and Antimicrobial activity of prepared ligand and metal complexes has been carried out by using DPPH assay. The results suggested that the prepared complexes posses significant activities comparable to the standards.

Key words: N/S/O donor ligands, Metal complexes, Antioxidant activity, Antimicrobial activity.

1. INTRODUCTION

Recently, the research relating with metal complexes of N/S/O functionalized ligands has expanded enormously and now comprising their interesting aspects in coordination chemistry with a special emphasis in bioinorganic chemistry. A use of organosilicon and organotin compounds as reagents or intermediates in the inorganic synthesis has further strengthened their applications[1]. On the other hand, N/S/O functionalized ligands and their transition metal complexes have been of great interest in view of their structural features such as ligand rigidity, type of donor atoms, their disposition and resemblance to natural systems of metalloenzymes[2]. These transition metal complexes of N/S/O functionalized ligands are used

as growth inhibiting agents for most of bacteria and fungi and applied in the agrochemical and pharmaceutical industries[3]. They are extensively used as potential therapeutics[4]. Recently, dramatic progress in the chemistry of tetraazamacrocyclic complexes in particular has been evident since these structural units are involved in a variety of catalytic, biochemical and industrial process [5].

N/S/O donor ligands are potential anti-cancer, anti-bacterial and anti-viral agents and this activity tends to increase in metal(II) Schiff-base complexes[6]. The cleavage of plasmid DNA by square planar nickel (salen) [bis-(salicylidene) ethylenediamine] under the influence of magnesium monoperoxyphthalic acid (MPPA) or iodosylbenzene has been well-reported[7]. The stereospecific transformation of Cu(II) complexes as groove binder and intercalative mode of binding of the complex to the DNA was studied by electron spin resonance (ESR)[8]. Bhattacharya et al. also reported the spontaneous cleavage of DNA under ambient aerobic conditions by a new water-soluble Co–salen complex[9]. Coumarins which is one of the effective N/S/O functionalized ligand have long been recognized to possess antiinflammatory antithrombotic, antiallergic, hepatoprotective, antiviral and anticarcinogenic[10-13] activities. The hydroxycoumarins are typical phenolic compounds and therefore act as potent metal chelators and free radical scavengers. They are powerful chain-breaking antioxidants.[14] The coumarins display a remarkable array of biochemical and pharmacological actions. The antitumor effects of coumarin and its major metabolite, 7-hydroxycoumarin, were tested in several human tumor cell lines.[15] Furthermore, cytotoxic effects of complexes of coumarin derivatives were examined on several neuronal cell lines.[16]

It is well known that N and S atoms play a key role in the coordination of metals at the active sites of numerous metallobiomolecules. Metallo-organic chemistry is becoming an emerging area of research due to the demand for new metalbased antibacterial and antifungal compounds.[17] The serious medical problem of bacterial and fungal resistance and the rate at which it develops have led to increasing levels of resistance to classical antibiotics. The discovery and development of effective antibacterial and antifungal drugs with novel mechanism of action have become an urgent task for infectious diseases research programs.[18] Many investigations have proved that binding of a drug to a metalloelement enhances its activity and in some cases, the complex possesses even more healing properties than the parent drug.[19] A large number of reports are available on the chemistry and the biocidal activities of transition metal complexes containing O, N and S, N donor atoms. The transition

metal complexes having oxygen and nitrogen donor Schiff bases possess unusual configuration, structural liability and are sensitive to molecular environment.[20] And in continuation to this, in the present paper, the synthesis, characterization, and biological activities of new N/S/O functionalized ligands and their metal complexes have been carried out.

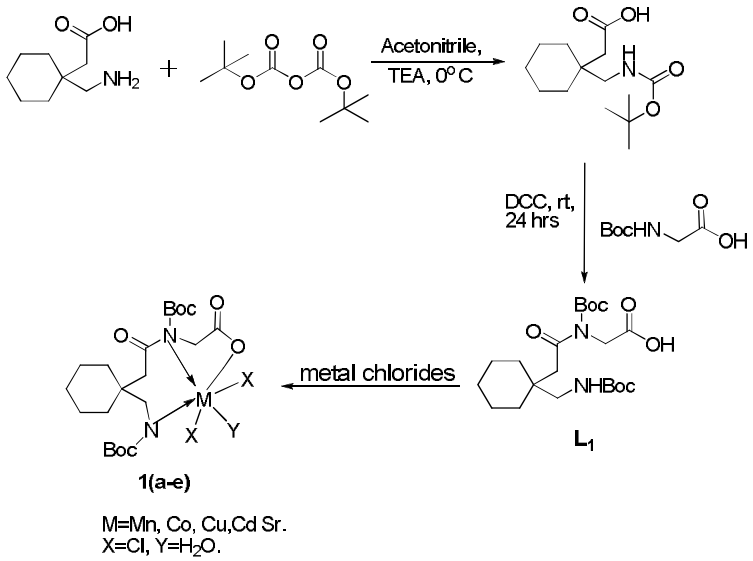
2. MATERIAL AND METHODS

All the reagents were of AR grade and used as received from Merck reagent, Germany, BDH, England and Sigma-Aldrich chemical company, USA. Melting point of the complexes were determined using Thomas Hoover apparatus and uncorrected. Molar conductance of the complexes were determined using Digisum Electronics DI-909/9009 direct reading digital conductivity meter, consisting of a cell with cell constant=0.9. IR spectra were recorded using Shimadzu 8201 PCFT-IR spectrometer by KBr technique. 400 MHz spectrophotometer using DMSO-d_6 as solvent and TMS as an internal standard. Elemental analysis was done using Vario-EL III CHN and S elemental analyzer.

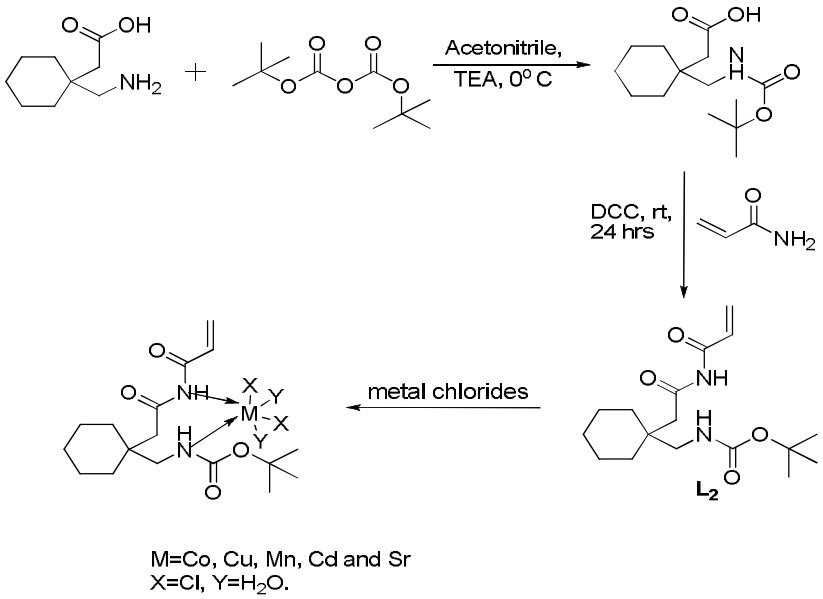
2.1. Synthesis Of Ligand (L_1) & (L_2)

The Ligand: 2-(2-(1-((tert-butoxycarbonylamino)methyl) cyclohexyl)acetamido)acetic acid (**L_1**) and *tert*-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate (**L_2**) prepared by the Methanolic solution of Boc protected gabapentine (0.01 mol) was added drop wise to a solution of 2-amino acetic acid (0.01 mol) dissolved in methanol[21]. The mixture was stirred for 24 h in 0 ^{o}C then room temperature for 3 h and filtered. Yield was about 70–80%.

Scheme 1. Synthesis of ligand L_1 and their metal complexes



Scheme 2. Synthesis of ligand L_2 and their metal complexes



2.2. Synthesis of metal complexes (1a-1e) & (2a-2e)

Equal aliquots of 0.1M ethanolic solution of the ligands was added to 0.1M ethanolic solution of the respective metal salts with constant stirring. The reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complexes. The metal complexes were prepared by refluxing in aqueous media. The obtained metal complexes were collected by filtration and purified by thorough washing with distilled cold ethanol and then with ether and dried over fused calcium chloride in vacuo.

(2-(2-(1-((tert-butoxycarbonylamino) methyl) cyclohexyl) acetamido) acetic acid) Copper(II) 1a

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $CuCl_2.nH_2O$ (0.1 M) where n=1, 2, 3… In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 85%, M.P=201-205 ^oC, Anal. Calcd. for $[Cu(C_{16}H_{28}N_2O_5)(H_2O)_2Cl_2]$: C, 34.98; H, 5.18; Cu, 10.89; N, 4.80; O, 13.70; Y, 30.46, In the low-frequency region, two bands were observed for complexes at ~ 445 and 460 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(2-(2-(1-((tert-butoxycarbonylamino)methyl)cyclohexyl) acetamido) acetic acid)Cobalt(II) 1b

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $CoCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was

refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 72%, M.P=188-191^{o}C, Anal. Calcd. for [Co($C_{16}H_{28}N_2O_5$)(H_2O)$_2Cl_2$] : C, 35.25; H, 5.22; Co, 10.18; N, 4.84; O, 13.81; Y, 30.70, In the low-frequency region, two bands were observed for complexes at ~ 450 and 460 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(2-(2-(1- ((tert-butoxycarbonylamino) methyl) cyclohexyl) acetamido) acetic acid) Manganese (II) 1c

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $MnCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 74%, M.P=185-187 ^{o}C, Anal. calcd. for [Mn($C_{16}H_{28}N_2O_5$)(H_2O)$_2$ Cl_2] : C, 35.50; H, 5.26; Mn, 9.55; N, 4.87; O, 13.91; Y, 30.91, In the low-frequency region, two bands were observed for complexes at ~ 360 and 475 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(2-(2-(1-((tert-butoxycarbonylamino) methyl) cyclohexyl) acetamido) acetic acid) Cadmium (II) 1d

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $MnCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 48%, M.P=188-190 ^{o}C, Anal. Calcd. for [Cd ($C_{16}H_{28}N_2O_5$)(H_2O)$_2$ Cl_2] : C, 32.27; H, 4.78; Cd, 17.77; N, 4.43; O, 12.64; Y, 28.11, In the low-frequency region, two bands were observed for complexes at ~ 380 and 476 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(2-(2-(1-((tert-butoxycarbonylamino) methyl)cyclohexyl) acetamido) acetic acid) Strontium (II) 1e

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $MnCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 67%, M.P=191-197 ^{o}C, Anal. Calcd. for [Sr($C_{16}H_{28}N_2O_5$)(H_2O)$_2$ Cl_2]: C, 33.59; H, 4.97; N, 4.61; O, 13.16; Sr, 14.41; Y, 29.25, In the low-frequency region, two bands were observed for complexes at ~395and 480 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) Copper(II) 2a

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $CuCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 82%, M.P=198-200 ^oC, Anal. Calcd. for $[Cu(C_{17}H_{28}N_2O_4)(H_2O)_2Cl_2]$: C, 36.09; H, 4.99; Cu, 11.23; N, 4.95; O, 11.31; Y, 31.43, In the low-frequency region, two bands were observed for complexes at ~374and 481 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) Coblt(II) 2b

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $CoCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 75%, M.P=182-185 ^oC, Anal. Calcd. for $[Co(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$: C, 36.39; H, 5.03; Co, 10.50; N, 4.99; O, 11.40; Y, 31.69, In the low-frequency region, two bands were observed for complexes at ~380and 467 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) Manganes(II)2c

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $MnCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 70%, M.P=195-197 ^oC, Anal. Calcd. for $[Mn(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$: C, 36.65; H, 5.07; Mn, 9.86; N, 5.03; O, 11.49; Y, 31.91, In the low-frequency region, two bands were observed for complexes at ~394and 486 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) Cadmium(II) 2d

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $CdCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 51%, M.P=155-157 ^oC, Anal. Calcd. for $[Cd\ (C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$: C, 33.22; H, 4.59; Cd, 18.29; N, 4.56; O, 10.41; Y, 28.93, In the low-frequency region, two bands were observed for complexes at ~378and 490 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

(tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) Strontium(II) 2e

The resulting white product 1 was obtained by addition of the ligand (0.1M) in ethanol (5 mL) to $SrCl_2.nH_2O$ (0.1 M) where n=1, 2, 3... In methanol (6 mL), the reaction mixture was refluxed on water bath for 30-45 min to obtain the respective solid metal complex. Yield 63%, M.P=168-170 ^oC, Anal. Calcd. for$[Sr(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$: C, 34.62; H, 4.78; N, 4.75; O, 10.85; Sr, 14.85; Y, 30.15, In the low-frequency region, two bands were observed for complexes at ~390and 488 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively.

3. BIOLOGICAL TESTING

3.1. DPPH free radical scavenging assay

The evaluation of antioxidant activity of newly synthesized compounds was done by DPPH radical scavenging activity assay. Internal standard BHA and the synthesized compounds of different concentrations were prepared in distilled ethanol, 1 mL of each compound solutions having different concentrations (10 µM, 25 µM, 50 µm, 100 µM, 200 µM and 500 µM) were taken in different test tubes 4 mL of 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at RT for 20 min. A DPPH blank was prepared without compound, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration, and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage and was calculated using the formula:

$$\text{Radical scavenging activity (\%)} = [(A_o\text{-}A_1)/A_o \text{ X } 100]$$

Where A_o is the absorbance of the control (blank, without compound) and A_1 is the absorbance of the compound[22].

3.2. Antimicrobials

3.2.1. Antibacterial studies

The antibacterial activities of newly synthesized compounds were determined by well plate method in Mueller-Hinton Agar. The antibacterial activity was carried out against 24 hr old cultures of bacterial strains. In this work, *E. coli*, *S.aureus*, *P. aeruginosa* and *R.solanacearum* were used to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentration of 1 and 0.5 mg/mL. 20 mL of sterilized agar

media was poured into each pre-sterilized Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 ºC for an hour. About 60 mL of 24 hr old culture suspension were poured and neatly swabbed with the pre-sterilized cotton swabs. Six millimeter diameter well were then punched carefully using a sterile cork borer and 30 mL of test solutions of different concentrations were added into each labeled well. The plates were incubated for 24 hr at 37 ºC. The inhibition zone that appeared after 24 hr, around the well in each plate were measured as zone of inhibition in mm. Experiments were triplicates and standard deviation was calculated[23].

3.2.2. Antifungal studies

Antifungal studies of newly synthesized compounds were carried out against *A. flavus, C. keratinophilu, C. albicans.* Sabourands agar media was prepared by dissolving peptone (10 g), D-glucose (40 g) and agar (20 g) in distilled water (1000 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species[22]. 20 mL of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 ºC for 1 hr. Using sterile cork borer punched carefully, wells were made on these seeded agar plates different concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 25 ºC for 72 hr. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with fluconazole as standard and zones of inhibition were determined for all the synthesized compounds[24].

4. RESULTS AND DISCUSSION

Chemistry. 2-(2-(1-((tert-butoxycarbonylamino)methyl) cyclohexyl)acetamido)acetic acid (**L_1**) and *tert*-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate (**L_2**) prepared by the Methanolic solution of Boc protected gabapentine (0.01 mol) was added drop wise to a solution of 2-amino acetic acid (0.01 mol) dissolved in methanol. The mixture was stirred for 24 h in 0 ^{o}C then room temperature for 3 h and filtered (Scheme 1) and (Scheme 2). The reaction was monitored by TLC. The resulting solution was evaporated under reduced pressure and recrystallized from methanol to get yellow crystals. Yield was about 70–80%.

Conductometric studies

All the complexes were anhydrous in nature and insoluble in methanol, ethanol, acetone and benzene. They are soluble in dimethyl sulphoxide and in dimethyl formamide. The general structures of the metal complexes were shown in Figure 1. The 10^{-3}M solution of the complex in dimethyl sulphoxide (DMSO) was used to determine the molar conductance. The conductivity data are in Table 1 and the data reveals that the complexes are non-electrolytic in nature (Geary W J 1971). The metal and anions are estimated using standard procedure (Vogel A I 1962), the data is predicted in Table 1. Elemental analysis data are in well agreement with the calculated value and the data are presented in Table 1.

Magnetic susceptibility measurements

Table 1. Yield, Elemental analysis, Melting point, Magnetic measurements and Molar conductance of metal complexes

Sl no	Complex	Yield (%)	Calculated(Found) %						Melting point (^oC)	eff $^{\mu}$ BM	Molar conductance (ohm's cm^2 mol^{-1})
			M	C	H	N	Anions	O			
1a	$[Cu(C_{16}H_{28}N_2O_5)(H_2O)_2Cl_2]$	85	12.20 (11.92)	39.56 (38.94)	6.08 (5.98)	5.05 (4.94)	15.65 (14.96)	21.65 (20.56)	201-205	4.83	18.7
1b	$[Co(C_{16}H_{28}N_2O_5)(H_2O)_2Cl_2]$	72	11.65 (10.85)	40.77 (39.25)	6.56 (5.75)	5.69 (4.98)	12.36 (11.26)	22.23 (21.12)	188-191	4.96	16.9
1c	$[Mn(C_{16}H_{28}N_2O_5)(H_2O)_2\ Cl_2]$	74	10.51 (9.59)	40.18 (39.36)	6.35 (5.95)	5.65 (4.69)	12.75 (12.94)	22.75 (21.95)	185-187	5.01	21.2
1d	$[Cd\ (C_{16}H_{28}N_2O_5)(H_2O)_2\ Cl_2]$	48	20.72 (19.15)	36.23 (35.46)	6.10 (5.20)	4.88 (3.56)	21.34 (22.48)	19.65 (18.26)	188-190	--	20.4
1e	$[Sr(C_{16}H_{28}N_2O_5)(H_2O)_2\ Cl_2]$	67	16.75 (15.26)	38.42 (37.25)	6.63 (5.87)	5.25 (4.65)	17.48 (18.27)	20.75 (19.25)	195-197	--	17.5
2a	$[Cu(C_{17}H_{28}N_2O_4)(H_2O)_2Cl_2]$	82	12.54 (12.28)	41.86 (46.99)	6.59 (5.52)	5.46 (5.75)	14.79 (15.01)	19.43 (6.80)	198-200	4.85	19.25
2b	$[Co(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$	75	12.12 (10.51)	41.68 (40.39)	6.78 (4.50)	5.79 (5.03)	28.37 (28.43)	19.78 (5.70)	182-185	4.95	15.32
2c	$[Mn(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$	70	11.40 (9.88)	41.89 (37.93)	6.68 (4.50)	5.56 (4.65)	11.33 (11.75)	19.64 (5.95)	195-197	5.11	23.54
2d	$[Cd\ (C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$	51	20.47 (11.83)	37.75 (46.02)	5.18 (4.95)	5.25 (5.56)	19.35 (18.96)	17.69 (13.05)	155-157	--	21.75
2e	$[Sr(C_{17}H_{28}N_2O_4)(H_2O)_2\ Cl_2]$	63	16.78 (10.98)	39.32 (53.02)	6.28 (6.00)	5.44 (5.51)	17.68 (17.95)	18.70 (6.23)	168-170	--	17.68

The magnetic susceptibility measurements of the complexes were obtained at room temperature using Gouy balance. Pure $Hg[Co(SCN)_4]$ was synthesized is used as calibration standard. The effective magnetic moment values of the complexes are in Table 1. The metal complexes are paramagnetic in nature. The magnetic moment (μ_{eff}) values for complexes are in the range 4.83-5.20 BM, which suggests that the complexes have high spin octahedral geometry[25].

FT-IR spectra studies

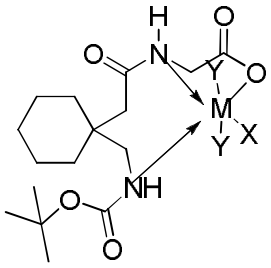
The structure of ligand confirmed by using IR spectra. The IR spectra of the prepared Ligand showed a broad band centered at 3425 cm^{-1} indicated the presence of the OH group in the ligand which is disappeared in the next step which also confirms the formation of C-N group and a medium band at 1360-1250cm^{-1}, which was assigned to the formation of the C-N group. In addition, the bands of the NH_2 groups disappeared as a broad signal at about 1550-1650 cm^{-1}.

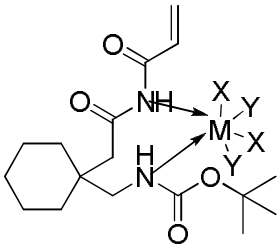
IR spectra of all the complexes exhibited a broad band around 3280-3540 cm^{-1} and a sharp peak in the range of 1640-1550cm^{-1}, these peaks can be assigned to O-H and N-H stretching and bending vibration which present in ligand. In the low-frequency region, two bands were observed for complexes at ~ 445 and 460 cm^{-1}, which were attributed to υ(M-N) and υ(M-O), respectively. These bands were not found in the spectra of the ligand[26, 27], suggesting that coordination of the ligand with the metal ions takes place via the nitrogen atoms and also via the deprotonated phenolic oxygen. It was found that the characteristic band of the C-N group in the free ligand at 1360-1250cm^{-1} was shifted to lower frequency of 1348-1350 cm^{-1} in the complexes as shown in (**Table 2)**. This alter indicates coordination of the nitrogen to the metals in the complexes. This shift also indicates that bonding in the complexes occurred through the nitrogen atom.

Table 2: Important IR of metal complexes of L_1 and L_2

Compounds	(N-H)(Cm^{-1})	(C=O)(Cm^{-1})	(C-N)(Cm^{-1})	(M-N)(Cm^{-1})	(M-O)(Cm^{-1})	(M-X)(Cm^{-1})	(H_2O)(Cm^{-1})
L_1	3300-3350	1655-1660	1080-1100	----	----	----	-----
L_2	3200-3225	1650-1655	1085-1150	----	----	----	----
1a	3190-3200	1600-1650	1070-1080	370	475	550	3365-3360
1b	3190-3200	1655-1665	1075-1085	365	473	545	3355-3340

1c	3200-3250	1700-1750	1090-1100	360	475	542	3358-3362
1d	3185-3190	1668-1170	1095-1105	380	476	523	3364-3355
1e	3250-3255	1658-1670	1080-1110	395	480	541	3362-3352
2a	3190-3200	1550-1600	1075-1090	374	481	550	3363-3360
2b	3180-3200	1600-1650	1078-1088	380	467	558	3360-3350
2c	3200-3300	1655-1665	1086-1095	394	486	548	3367-3355
2d	3220-3330	1670-1680	1195-1150	378	490	565	3361-3355
2e	3200-3250	1680-1690	1065-1090	390	488	554	3364-3354





L_1 metal complexes **L_2 metal complexes**

Fig.1. General structures of metal complexes

Biological evolution

All the synthesised compounds exhibited potent antioxidant scavenging activities. From all the synthesized compound analogues of ligand L_1 and their respective metal complexes 1(a-e) and also the ligand L_2 and their metal complexes 2(a-e) with nitro moiety was the most active with scavenging of Free radical activity. Initially, 2-(2-(1-((tert-butoxycarbonylamino)methyl) cyclohexyl)acetamido)acetic acid (L_1) and (tert-butyl (1-(2-acrylamido-2-oxoethyl)cyclohexyl)methylcarbamate) (L_2) exhibited considerable activity. The reason would be the presence of electron releasing hydroxyl and electron donating Nitrogen groups in ligand moiety endowed notable improvement in radical scavenging activity. After the complexation with metal ions reveals that the antioxidant activity increase. The complexes L_1, L_2, 1a, 1c, 2b and 2c shows moderate activity and complexes remain complexes shows less activity, all the tested ligands and metal complexes responds against the free radical scavenging strain significantly (Table 3 and Figure 2).

Table 3: *In vitro* antioxidant activity of L_1, L_2 and metal complexes.

Compounds	IC_{50}
L_1	2.86
L_2	3.41
1a	3.98
1b	2.95
1c	3.01
1d	2.85
1e	2.87
2a	3.59
2b	4.05
2c	4.28
2d	3.45
2e	3.04
Ascorbic acid	6.45

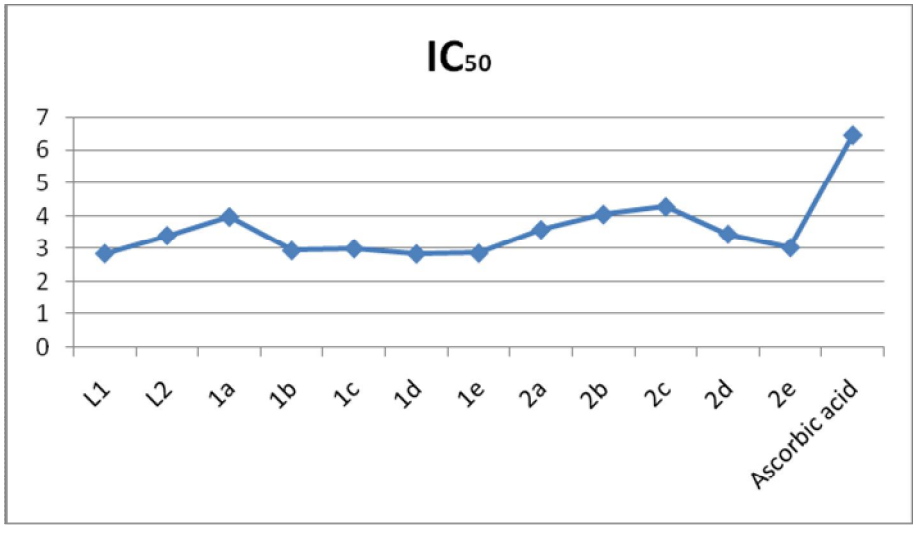


Fig.2: IC_{50} Values of ligand and metal complexes

The new Complexes were assayed *in vitro* to assess their ability to inhibit the growth of selected species of bacteria and fungi. The data is summarized in Table 4. On the basis of observed zones of inhibition, it was found that, in general, all the prepared ligand and their metal complexes responded against all the tested bacterial and fungal strains significantly (Table 4 and Figures 3). The investigation of antibacterial screening data revealed that all the

tested compounds showed moderate to good antibacterial and antifungal activities against *B. subtilis, S. aureus, P. aeruginosa, R.solanacearum, E. coli, C. albicans* and *A. niger* respectively. The compounds L_1, L_2, 1a, 1b, 1c and 2c displayed excellent antibacterial activity while 1d and 1e showed moderate antibacterial activity and the compounds 2a, 2b, 2d and 2e are less active as compare to standard drug Chloramphenicol. In case of antifungal activity compounds 1e, 1d, 2a, 2b and 2e exhibit significant activity while the compounds L_2 and 1b showed moderate activity. All the synthesized complexes found moderate antimicrobial activity[28].

Table 4: *In vitro* Antimicrobial Activity and metal complexes.

Compounds	**Antibacterial**		**Antifungal**					
			Zone inhibition					
	B.subtilis	*E.coli*	*S.aureus*	*R.solanacearum*	*A.niger*		*A. flavus*	*A.solani*
L_1	21	20	12	08	7		4	9
L_2	23	21	21	14	9		8	4
1a	18	19	10	29	12		10	14
1b	20	16	19	23	17		15	12
1c	20	21	12	27	19		15	14
1d	23	19	17	19	26		19	21
1e	26	20	16	18	20		14	21
2a	15	14	13	12	24		15	19
2b	14	15	17	14	18		12	20
2c	19	16	20	21	19		17	18
2d	18	18	17	18	16		18	14
2e	20	17	13	19	20		13	19
Chloramphenicol	29	26	23	32	--		--	--
Fluconazole	--	--	--	--	27		23	25

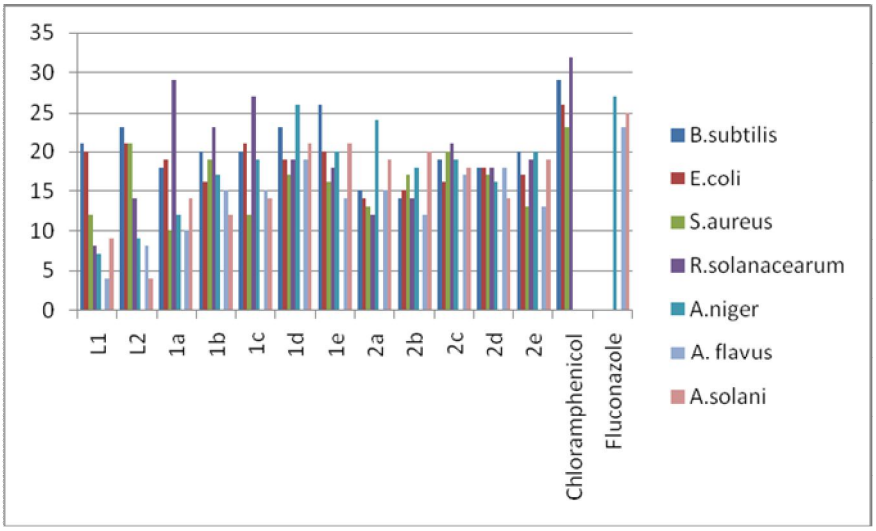


Fig.3: Zone inhibition of ligands and metal complexes

5. CONCLUSION

The work described in this paper involved the synthesis and spectroscopic characterization of a series of cobalt, copper, manganese, cadmium and strontium complexes with a new N/O/S functionalized ligands derived from 2-[1-(aminomethyl)cyclohexyl]acetic acid. These complexes were characterized by using different physiochemical techniques. These complexes are all neutral and found to have a octahedral geometry with the six donor atoms. The synthesized compounds have *in vitro* antimicrobial screening effects evaluated against three bacterial strains namely *Bacillus Subtilis, Escherichia coli, Staphylococcus aureus* and *Ralstonia solanacearum* and three fungal strains namely *Aspergillus niger, Aspergillus flavus* and *Alternaria solani* by disc diffusion method using nutrient agar medium for antibacterial studies and potato dextrose agar medium for antifungal studies And also these synthesized complexes revels effective antioxidant activity by DPPH assay.

REFERENCES

1) M. Pereyre JP, Quintard AR. *Tin* in Organic Synthesis; *Butterworths*: *London, UK*, 1987.

2) Chandra S, Monika T, Agrawal S. Synthesis and characterization of a tetraaza macrocyclic ligand and its cobalt(II), nickel(II) and copper(II) complexes, Journal of .Serberian Chemical society. 2010;75(7):935–941.

3) Zolezzi S, Spodine E, Decinti A. Electrochemical studies of copper(II) complexes with Schiff-base ligands Polyhedron, 2002;21:55–59.

4) Ali MA, Kadir MH, Nazimuddin M, Majumder SMM, Tarafder MTH, Khair MA. Coordination chemistry and bioactivity of ni2+, cu2+, and zn2+ complexes containing a bidentate ns ligand,β-n-henyldithiocarbazic acid, and the crystal structure of β-hydroxy-β-phenylmethylene-α-phenylimine, Indian Journal of Chemistry. 1988;27:1064–1071.

5) Sulok CD, Bauer JL, Speelman AL, Weber B, Lehnert N. A Detailed Investigation into the Electronic Structures of Macrocyclic Iron(II)-Nitrosyl Compounds and their Similarities to Ferrous Heme-Nitrosyls, Inorganic Chimica Acta, 2012;380:148-160.

6) Sagarika P, Dash SP, Saswati, Majhi P, Patil YP, Nethaji M, Dash HR, Das S, Dinda R. Mixed-ligand aroylhydrazone complexes of molybdenum: Synthesis, structure and biological activity, Polyhedron. 2012;38:198–204.

7) Marrow JR, Kolasa K, Cleavege of DNA by Nickel Complexes, Inorganic Chimica Acta. 1992;195:245–248.

8) Lamata M. P., Ferrer J, Modrego J, Perales M, Lahoz, FJ, Atencio R, Oro LA. Synthesis, characterization and molecular structure of the hydroperoxo complex $[(\eta^5C_5Me_5)Ir(\mu\text{-}pz)_3Rh(OOH)(dppe)][BF_4]$; Hpz = pyrazole, dppe β 1,2-bis (diphenylphosphino) ethane. Daniel Carmona, Journal of Chemical Society and Chemical Communications.1994;575-576.

9) Maggini M, Karlsson A, Scorrano G, Sandonà G, Farnia G, Maurizio P. Ferrocenyl fulleropyrrolidines: a cyclic voltammetry study, Journal of Chemical Society and Chemical Communications. 1994;589-595.

10) Zalman LS, Brothers M A, Dragovich PS, Zhou R, Prins TJ, Worland ST. Patick AK. Inhibition of Human Rhinovirus-Induced Cytokine Production by AG7088, a Human Rhinovirus 3C Protease Inhibitor, Antimicrob Agents Chemother. 2000;44(5):1236–1241.

11) Yang JX, Tan XM, Wang XH, Wang Y. 4,7,8-Trimethyl-2*H*-chromen-2-one. Acta Crystallography Sect E. 2012;68:1010-1014.

12) Kostova S, Raleva P, Genova, Argirova R. Structure-activity relationships of synthetic coumarins as HIV-1 inhibitors. Bioinorganic Chemistry Application. 2006;1-9.

13) Kostova I, Anti-Cancer Agents, Current Medicinal Chemistry. 2005;5:29-46.

14) Scozzafava A, Supuran CT. Protease inhibitors: Synthesis of potent bacterial collagenase and matrix metalloproteinase inhibitors Journal of medicinal chemistry. 2000;43:3677-3687.

15) Bagihallia GB, Patila SA, Badami P.S. Synthesis, Physicochemical Investigation and Biological Studies of Zinc(II) Complexes with 1,2,4-Triazole Schiff Bases, Journal of Iranian Chemical Society. 2009;6:259-270.

16) Lippard S.J., Berg J.M., Principles of Bioinorganic Chemistry, University Science Books, Mill Valley, CA, 1999.

17) Ibotomba Singha U, Bhubon Singha RK, Radhapiyari Devi W, Singh B. Schiff base complexes of Copper (II) ions: Synthesis, Characterization and Antimicrobial studies. Journal of Chemical and Pharmaceutical Research, 2012;4(2):1130-1135.

18) Adao P, Pessoa JC, Henriques RT, Kuznetsov ML, Avecilla F, Maurya MR, Umesh Kumar, Correia I. Synthesis, Characterization, and Application of Vanadium Salan Complexes in Oxygen Transfer Reactions. Inorganic Chemistry. 2009;48(8):3542-3561.

19) Fang T, Marshall HL, Bryan GL, Canizares CR. Chandra observations of two high-redshift quasars", the Astrophy Journal. 2001;555:356-363.

20) Ott I, Kircher B, Gust RJ. lnorg. Biochem. 2004;98:485-491.

21) Nuhn P. Naturstoffchemie, Hirtzel, S. Stuttgart, 1997, 157-67.

22) Blois MS. Antioxidant Determinations by the Use of a Stable Free Radical, Nature, 1958;181:1199-1200.

23) Ware DC, Palmer BD, Wilson WR, Denny WA. Journal of Medicinal Chemistry. 1993; 36:1839-42.

24) Quintal SMO, Qu Y, Quiroga AG, Moniodis J, Nogueira HIS, Farrell N. Inorganic Chemistry. 2005;44:5247-52.

25) Gryz M, Starosta W, Leciejewicz JJ. Coordination Chemistry. 2007;60:539-547.

26) Sanchez-Guadarrama O, Lopez-Sandoval H, Sanchez- Bartez F, Gracia-Mora I, Barba-Behrens, N. Journal of Inorganic Biochemistry. 2009;103:1204-1211.

27) Murukan B, Mohanan KJ. Enzyme Inhibition Medicinal Chemistry. 2007;22:65-71.

28) Al-Amiery AA, Kadhum AAH, Mohamad AB. Antifungal and Antioxidant Activities of Pyrrolidone Thiosemicarbazone Complexes. Bioinorganic Chemistry Application. 2012, Article ID 795812, 6 pages doi:10.1155/2012/795812.