A SYNOPSIS

of the thesis

Syntheses, crystal structures, magneto-structural correlation and biomimetic study of copper(II) complexes

To be Submitted
As a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in
Chemistry

By
Abhay Kumar Patel

Under the supervision of
Dr. R. N. Jadeja

Department of Chemistry
Faculty of Science
Maharaja Sayajirao University of Baroda
Vadodara 390 002
India

January 2021

Synopsis of the Thesis

To be submitted to The Maharaja Sayajirao University of Baroda for the award of the degree of DOCTOR OF PHILOSOPHY in Chemistry.

Name of Student: Abhay Kumar Patel

Title of the Thesis: "Syntheses, crystal structures, magneto-structural correlation and biomimetic study of copper(II) complexes "

Name of the Supervisor: Dr. R.N. Jadeja
The Maharaja Sayajirao University of Baroda

Faculty: Faculty of Science,The Maharaja Sayajirao University of Baroda.

Department: Department of Chemistry

Registration No.:FOS/2111

Date of Registration: 25th July 2018

Abhay Kumar Patel
Research Student

11/1/21

Dr. R. N. Jadeja
Research Guide

The Thesis will be presented in form of the following chapters:

Chapter 1: Introduction

Chapter 2: Copper(II) complexes with hydrazone blocking ligands

(A) ***Pseudohalidescopper(II) complexes with a hydrazide blocking ligand: Synthesis, spectral characterization and evaluation of antioxidant superoxide dismutase activity***

(B) ***Copper(II) tetrahedral complex derived from N'-[(2E,3Z)-4-hydroxy-4-phenylbut-3-en-2-ylidene]acetohydrazide: Synthesis, molecular structure, quantum chemical investigations, antioxidant and antiproliferative properties***

Chapter 3: Copper(II) complexes incorporating NNN-tridentate hydrazone as proligand

(A) ***Synthesis and structural characterization of copper(II) complexes with flexible hydrazone: Structural diversity, Hirshfeld analysis, density functional calculations and biological study***

(B) ***Penta-coordinated copper(II) complexes with hydrazide based ligand and imidazole as auxiliary ligand: Synthesis, spectral characterization and SOD mimetic activities***

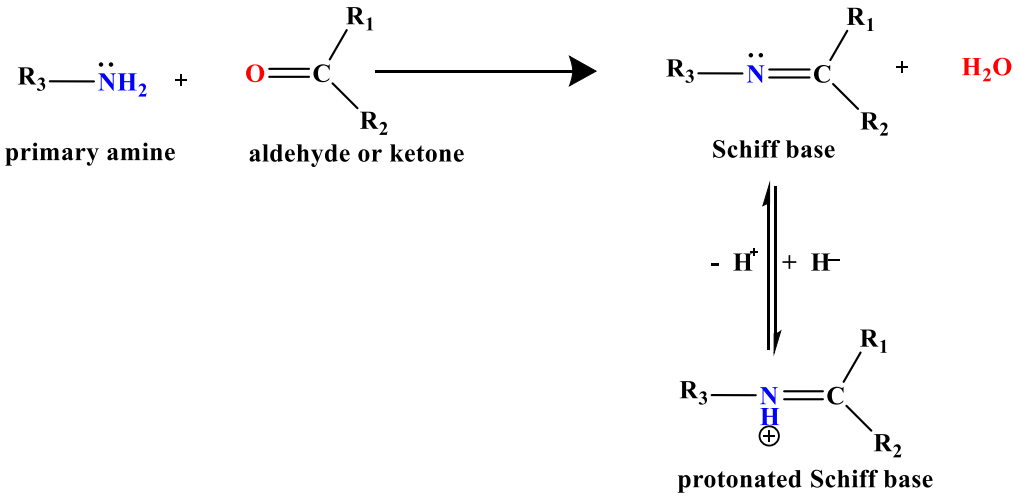
(C) ***Synthesis, spectral characterization and biomimetic activity of homobinuclearcopper(II) 2-[(E)-phenyl(pyridine-2-yl-hydrazone)methyl]pyridine complexes containing inorganic salts***

Chapter 4: Copper(II) hydrazone complexes with different nuclearties and geometries: Synthesis, structure, spectral properties, electrochemical behaviour, density functional study and *in vitro* catalytic activity

Chapter: 1
Introduction

In recent decades, hydrazone Schiff base ligands and their transition metal complexes have attracted much attention.[1,2] To mention the reasons, we can point out their structural similarities with the biological units, facile synthesis and applications in several areas. A wide range of biological properties such as antibacterial, anti-fungal,[3] anti-malarial,[4] anti-cancer[5] and other biochemical process[6] have been reported for hydrazone derivatives. Among these, different applications of Cu(II) complexes are documented in various fields.[7,8]

In the area of bioinorganic chemistry, the interest in the Schiff base complexes lies in that they provide synthetic models for the metal-containing sites in metalloproteins and enzymes.Schiff bases were first reported by Hugo Schiff in 1864. Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group.Since the free Schiff base are not always stable, many Schiff base complexes are prepared by template synthesis which implies carrying out the condensation reaction in the presence of a metal ion. This is a very common method for the preparation of macrocyclic Schiff base complexes.Schiff base ligands are easily synthesized and form complexes with almost all metal ions. Schiff base complexes of transition metal ions are efficient catalysts both in homogeneous and heterogeneous reactions and the activity of these complexes varied with the type of ligands, coordination sites and metal ions.[7,8,9]



Synthetic route of Schiff base formation

Copper exists in the biological system as asymmetric multi-dentate chelates.[9] The role of copper in both the etiology and growth of tumours has been extensively studied.10 Also many of the Cu(II) Schiff base complexes can be good models for simulating and

representing their function and providing models for the metal-containing sites in copper-containing proteins and enzymes such as ascorbic oxidase.[11]

In spite of the rapid development of novel anticancer drugs, outbreak of drug resistance and undesirable side effects have created many problems in cancer therapy. Thus, it is necessary to identify new compounds with improved properties in this regard.[12] One of the characteristics of metal ions is their potential to undergo redox processes, as determined by their redox potentials. Especially, transition metal ions are usually able to switch between several oxidation states. Due to the redox activity of metals and, therefore, a possible disturbance of the sensitive cellular redox homeostasis, a tight regulation of the metal and redox balance is crucial for health and survival.[10,13,14] Copper has a crucial role in redox reactions and triggers generation of reactive oxygen species (ROS) in human cells. Cu(II) complexes are well known for their redox activity, which seems to be, at least in part, involved in the most of their defined biological activities.[15–20]

Herein, we describe the synthesis, characterization of a new mixed-ligand Cu(II) complex.

Aim and Objectives

- ✓ Synthesis of Schiff base ligand and characterized them.
- ✓ Synthesis of metal complexes of Schiff base derivatives.
- ✓ Characterize of synthesized compounds by various technique such as IR, NMR, Mass, etc.
- ✓ Synthesized copper complexes will be screened for anticancer and SOD activity.
- ✓ The geometry optimization of copper complexesneeds to be done using DFT calculation. The optimized geometry and experimental evidence (crystal structure) will be compared.

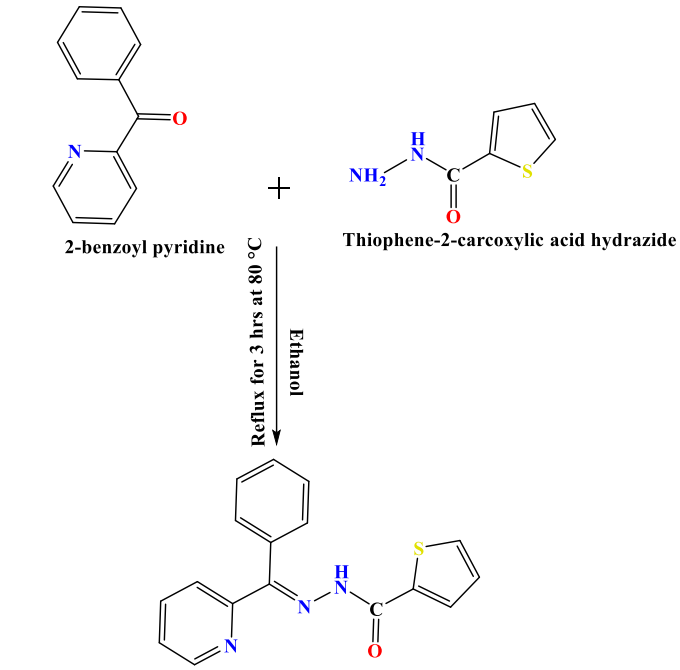
Chapter: 2

Copper(II) complexes with hydrazone blocking ligands

(A) Pseudohalidescopper(II) complexes with a hydrazide blocking ligand: Synthesis, spectral characterization and evaluation of antioxidant superoxide dismutase activity

Synthesis of ligand (HL) and metal complexes

The pro-ligand was synthesized by condensing thiophene-2-carboxylic acid hydrazide (0.71 g, 10 mmol) with 2-benzoylpyridine (0.96 g, 10 mmol) in ethanol 40 mL according to the procedure as reported previously.[42,43] The reaction mixture was refluxed for 1 h. The resulting solution was filtered and filtrate left for evaporation at RT, whereas solid mass was obtained. The obtained solid mass was washed with cold ethanol and stored in calcium chloride desiccators. The ligand was characterized by elemental analysis and NMR method.



HL = (*E*)-*N*'-(phenyl(pyridin-2-yl)methylene)thiophene-2-carbohydrazide

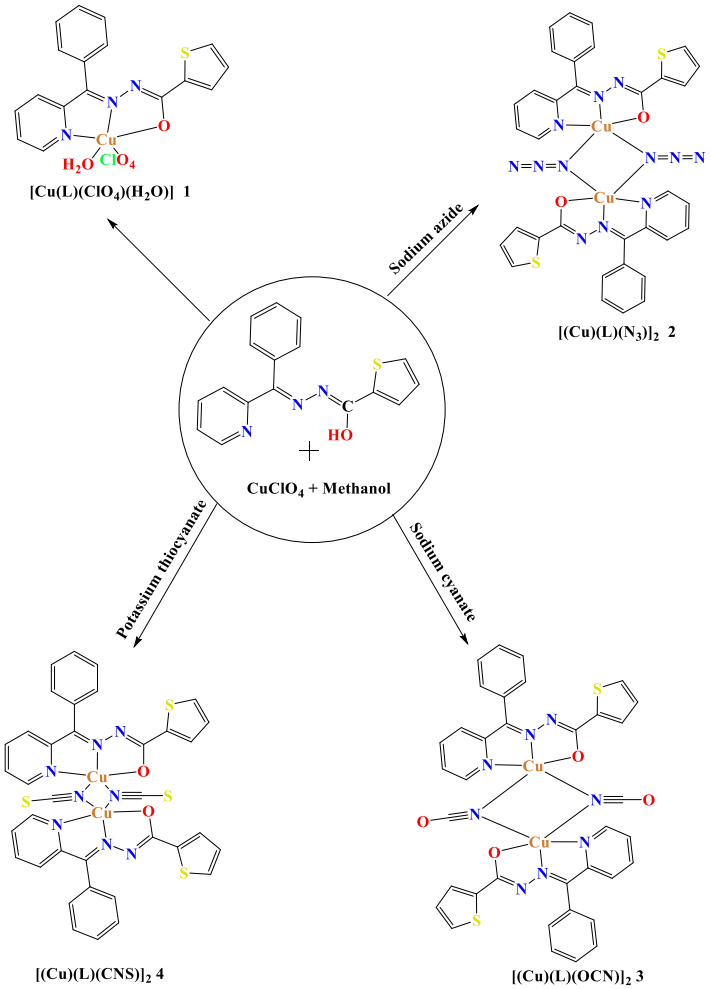
Synthesis of hydrazone ligand (HL)

Synthesis of [Cu(L)(ClO_4)(H_2O)] 1 : To a 10 mL methanolic solution of Cu(ClO_4).6H_2O (0.370g, 1 mmol) was added 10 mL methanol solution of HL (0.307g, 1 mmol) and stirred for 1 h. The mixture was filtered and filtrate was left for evaporation at RT. After one-week blue coloured complex separated out. The product was collected by filtration, washed with cold methanol and stored in calcium chloride desiccators.

Synthesis of [Cu(L)(N_3)]$_2$ 2: To a 20 mL methanolic solution of Cu(ClO_4).6H_2O (0.379 g, 1 mmol) and HL (0.307 g, 1 mmol) was added sodium azide (0.065 g, 1 mmol) solution prepared in a minimum volume of water and methanol. The reaction mixture was stirred for 1 h and filtered. The filtrate was left for slow evaporation in air at RT. After few days polycrystalline green product was obtained. The product was collected by filtration, washed with methanol and dried in calcium chloride desiccators.

Synthesis of [Cu(L)(NCO)]$_2$3: The complex **3** was prepared in a similar manner as discussed for 2, except that potassiumthiocynate (0.097 g, 1 mmol) was used in place of sodium azide. Green microcrystalline powder collected by filtration and stored in calcium

Synthesis of [Cu(L)(NCS)]$_2$4: This complex was synthesized by following similar methods as described for complex 2 and 3. In this synthesis potassiumthiocynate(0.065 g, 1 mmol) was taken in place of N_3 or NCO. The green-colored microcrystalline powder was separated after a week. The product was filtered, washed with methanol and kept in calcium chloride desiccators.



Synthetic route of complexes (1-4).

Physical Properties and Elemental Analysis

Compound	Yield (%)	m.p. (°C)	M.wt. g/mol	Colour	Λ[a]	Elemental Analysis[b](%)		
						C	H	N
HL	80	125	307.37	Greenish white	8.34	66.45(66.28)	4.21 (4.25)	13.66(13.60)
1	74	> 250	487.37	Green	15.26	41.85(41.90)	2.90 (2.95)	8.62 (8.65)
2	68	> 250	823.86	Green	18.25	49.60(49.57)	2.94 (2.95)	20.38(20.40)
3	76	> 250	823.85	Green	14.56	52.49(52.48)	2.98 (2.94)	13.61(13.60)
4	79	> 250	855.97	Green	16.78	50.54(50.52)	2.83 (2.83)	13.09(13.10)

[a]Molar conductance (Ω^{-1} cm^2 mol^{-1}) of 10^{-3} M solutions in DMSO.
[b]Calculated values are given in parentheses

FTIR Spectra

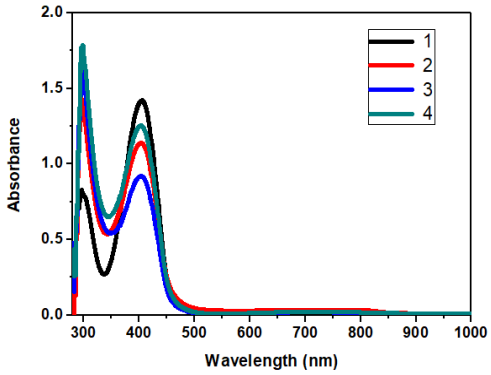
FTIR spectra of complexes (**1-4**) were analysed in comparison to free unbound ligand (HL). The important bands of FTIR of ligand and complexes is shown below in the Table.

FTIR important peaks in compounds

Compound	ν(N−H)	ν(OH)	ν(C=O)	ν(C=N)	ν(N−N)	ν(C−O¯)	ν(M−O)	ν(M−N)
HL	3174	3306	1645	1604	858			
1	-	3418	-	1575	972	1292	526	479
2	-	-	-	1572	928	1289	567	491
3	-	-	-	1573	1026	1285	423	406
4	-	-	-	1599	1089	1289	542	479

Electronic spectra

The electronic spectra of complexes recorded in DMSO solutions (3.0×10^{-3}M) of all complexes. The absorption band observed in the range 402-405 nm may be attributed to the ligand-to-metal charge transfer (LMCT) transition for each complexes. In the visible region all complexes display a single absorption band in the range 680-705 nm, agreeing with the expected five coordinate geometry around copper center.



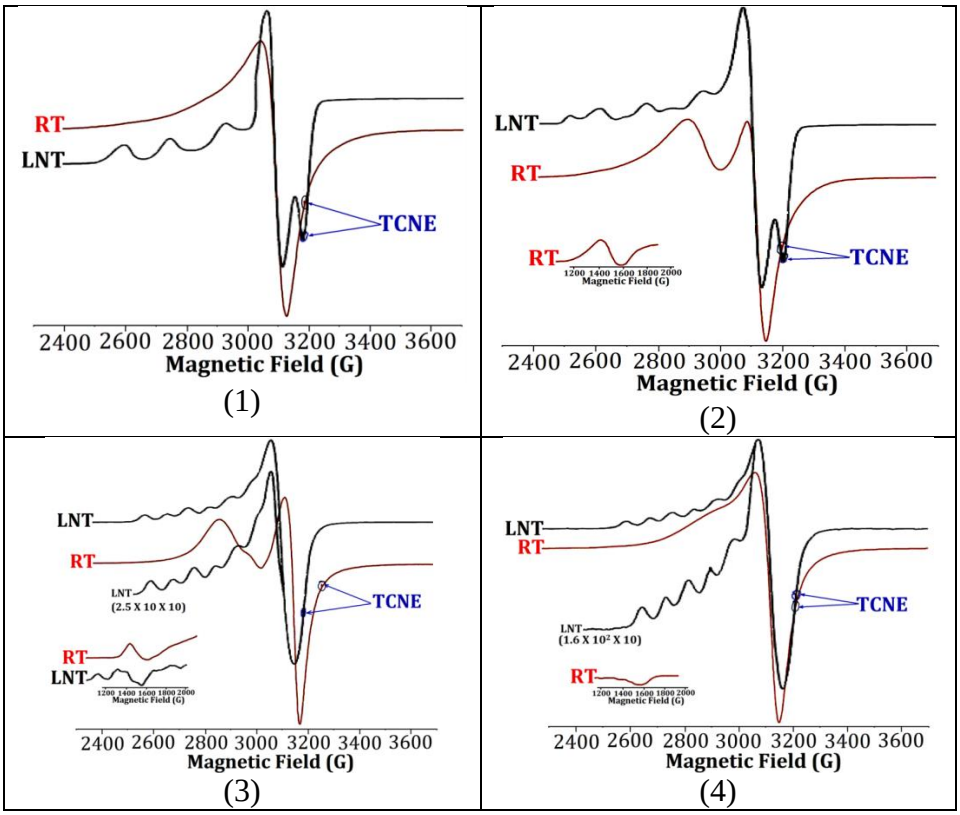
UV-visible spectra of copper(II) complexes in 3.0×10^{-3} M DMSO solution.

Epr studies

X-band epr spectra of four new copper(II) complexes were recorded of polycrystalline samples at room temperature (RT) and liquid samples in DMSO (3.0×10^{-3}M) at liquid nitrogen temperature(LNT). Epr spectra are shown below and epr spectral parameters are collected in Table.

Spin Hamoltonian parameters for complexes 1-4.

Complex	RT (Polycrystalline)				LNT (Solution)				
	$g_{\parallel}$	$g_{\perp}$	G	ΔB_{pp}(G)	$g_{\parallel}^{1}$	$g_{\parallel}^{2}$	$A_{\parallel}^{1}$(G)	$A_{\parallel}^{2}$(G)	$g_{\perp}$
1	2.224	2.055	4.21	140	2.210	-	160	-	2.068
2	2.210	2.055	3.89	103	2.241	2.203	157	159	2.067
3	2.218	2.068	3.281	105	2.233	2.203	170	170	2.058
4	2.218	2.061	3.61	107	2.207	2.213	160	160	2.065



Epr spectra of complexes in RT and LNT 1-4.

Electrochemical Studies

Electrochemical properties of complexes **1-4** were studied using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in DMSO solution containing 0.1M tetra butyl ammonium perchlorate (TBAP). The cyclic voltammograms for complexes **1-4** are shown below.All complexes show two reduction potentials corresponding to two separate couples (1) and (2) in:

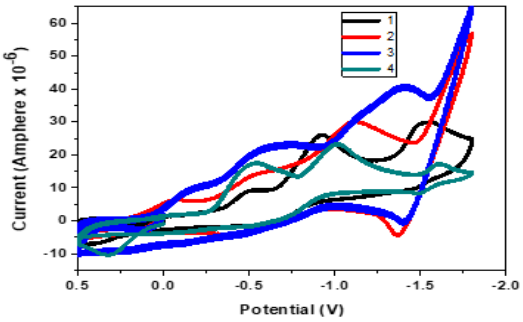
$$Cu^{II}\,Cu^{II} \rightleftharpoons Cu^{II}\,Cu^{I} \qquad (1)$$

$$Cu^{II}\,Cu^{I} \rightleftharpoons Cu^{I}\,Cu^{I} \qquad (2)$$

The anodic counter parts of these redox waves are not well defined. Similar electrochemical observations were made from the DPV experiments. The obtained electrochemical data are summarized in Table.

Electrochemical data for complexes 1-4 in DMSO (6.0×10^{-3} M).

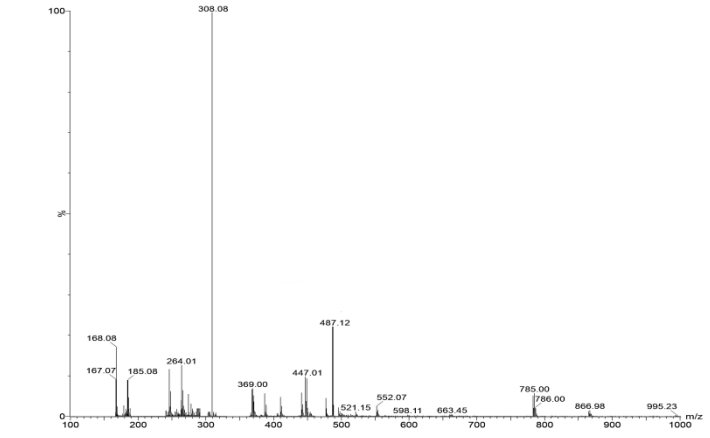
Compound	E_{pc1}(V)	E_{pa1}(V)	E_{pc2}(V)	E_{pa2}(V)	DE_{pc1}(V)	DE_{pc2} (V)	ΔEpc(V)	$E^1_{1/2}$(V)	$E^2_{1/2}$ (V)	$\Delta E_{1/2}$ (V)	K_{con}
1	-0.343	+0.257	-0.739	-0.435	-0.237	-0.576	0.339	-0.043	-0.587	0.544	1.5×10^9
2	-0.343	+0.308	-0.901	-0.730	-	-0.786					
3	-0.442	-	-1.176	-	-0.238	-0.633	0.395				
4	-0.379	-0.379	-0.831	-0.386	-0.373	-0.576	0.203	-0.287	-0.601	0.314	2.0×10^5



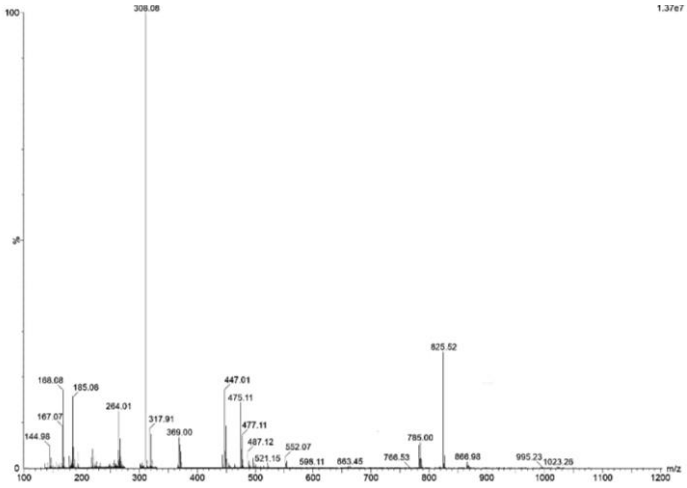
Cyclic voltammograms for complexes 1-4 in DMSO at an Ag/AgCl electrode with scan rate 100 mVs^{-1} and at temperature of 25°C.

ESI-MS of Complexes

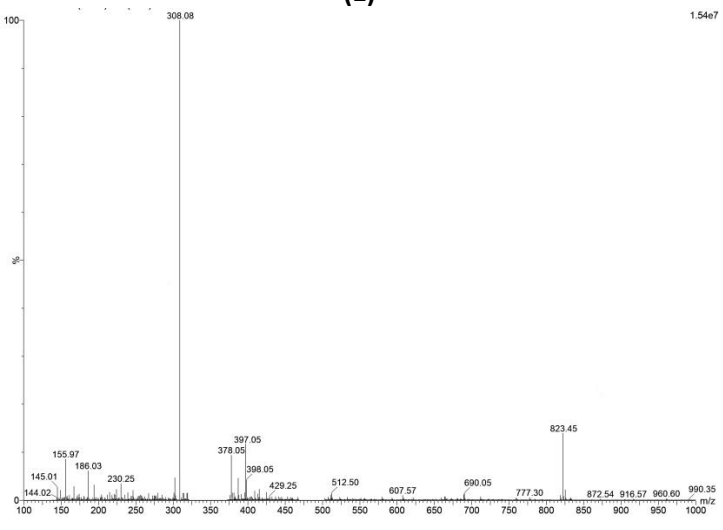
We have done ESI-Mass of all complexes to conform the molecular weight of the complexes. The ESI-Mass of complexes is shown below.



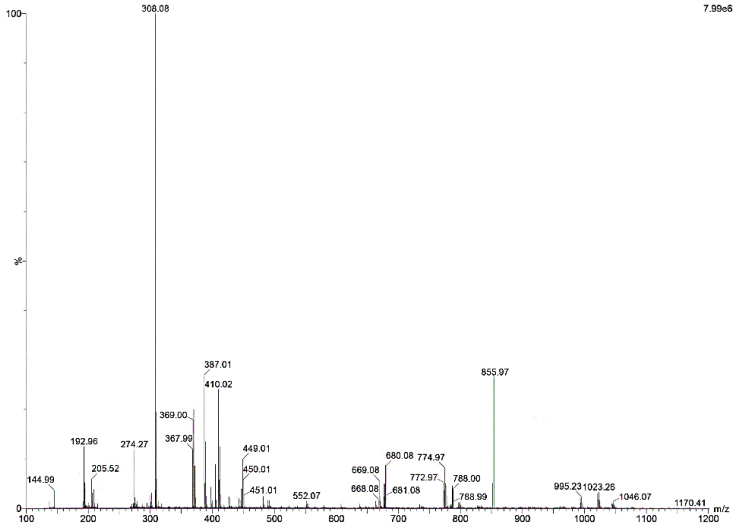
(1)



(2)



(3)

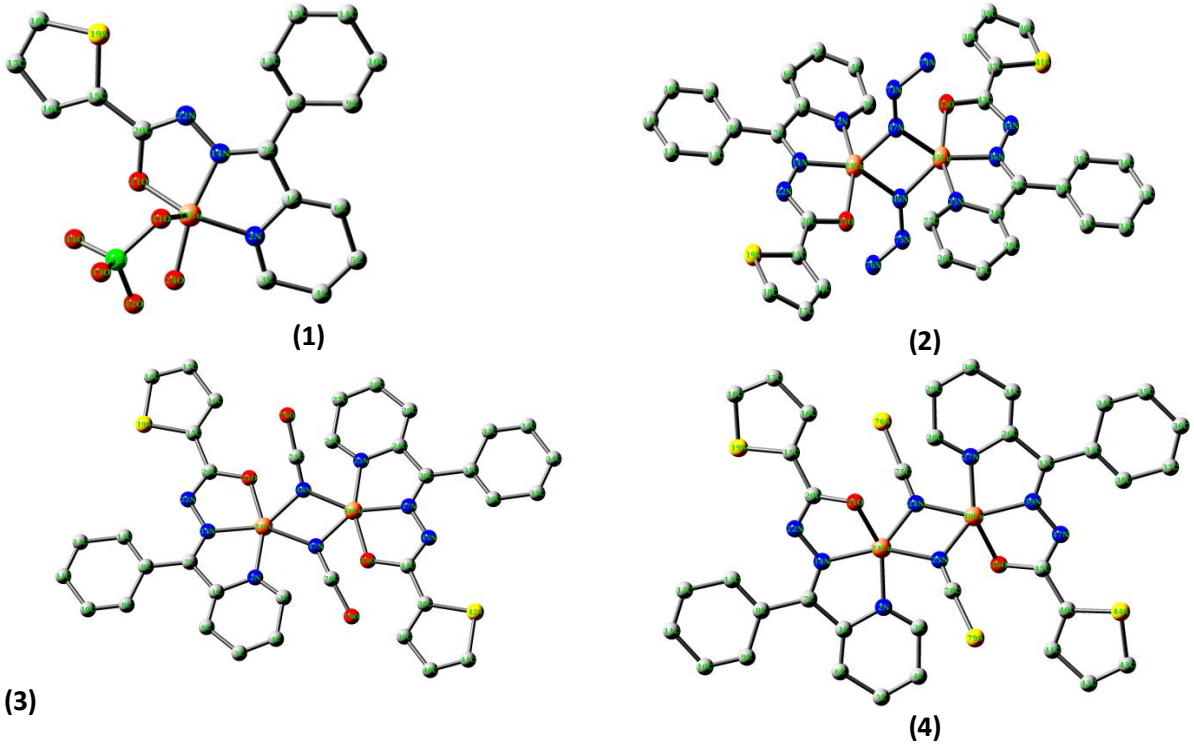


(4)

ESI-Mass of complexes 1-4.

DFT Calculations

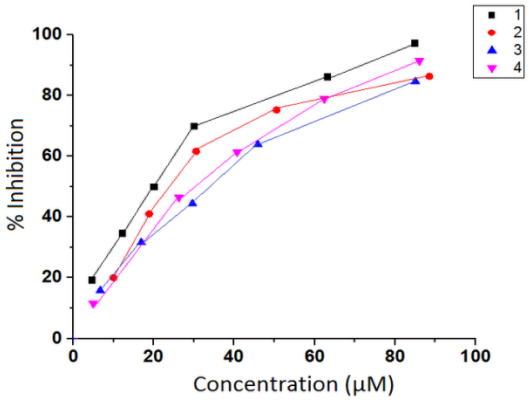
B3LYP estimated interatomic distances and bond angles of **1-4**. The optimized molecular structure is shown below. All calculations were performed with the GAUSSIAN09 program, with the aid of the Gauss View visualization program.



(1) (2) (3) (4)

DFT optimized structure of complexes 1-4.

Catalytic activity



SOD graph of complexes 1-4.

The superoxide dismutase (SOD) catalytic activities were carried out in phosphate buffer of pH 7.8 by NBT assay method.The concentrations of catalysts required to yield 50% inhibition of the reduction nitro blue tetrazolium chloride (NBT) defined as IC_{50} was calculated. The relative high SOD activity of complexes **1-4** show good SOD activity may be attributed to the flexible nature of hydrazone ligand, which can facilitate the reduction of copper(II) to copper(I) associated with variation of coordination geometry and the

accommodation of copper(I). On perusal of k_{McCF}values, it is clearly indicated that **1-4** can be used as an antioxidant superoxide scavenger. On the basis of SOD data, it is obvious that **1-4** are more efficient antioxidant scavengers than the standard antioxidant (vitamin c).

Conclusions

In this part, we have reported the synthesis of a new Schiff base ligand, N'-(phenyl-pyridine-2-yl-methylene)-thiophene-2-carboxylic acid hydrazide (HL) and its metal complexes. The ligand and its complexes are well characterized by analytical and spectral method. The molar conductance values of the complexes 1-4 in DMSO at room temperature are observed in the range 8.34–18.24 (Ω^{-1} cm^2 mol^{-1}) indicating that they are non-electrolytes nature.The distorted square pyramidal geometry (τ_5 = β-α/60° = 0.288) of copper(II) ion in Complex 1 the coordination geometry of each copper centres in 2-4 may be described as a distorted square pyramid, as evidenced by the low value of the geometrical structural index (τ_5). The geometrical structural index (τ_5) fall in the range 0.01-0.117 in complexes 2-4. The distortion in polyhedron results from the Jahn-Teller Cu^{2+} ions with d^9 configuration which is typical of a square-based pyramidal geometry. The G value of these complexes is also of less than 4, revealing the interaction in between two dipole units. As these complexes are binuclear in nature, therefore the nature of interaction is dipole-dipole intramolecular interaction.

Chapter: 2

(B) Copper(II) tetrahedral complex derived from N'-[(2E,3Z)-4-hydroxy-4-phenylbut-3-en-2-ylidene]acetohydrazide: Synthesis, molecular structure, quantum chemical investigations, antioxidant and antiproliferative properties

Synthesis of HL

To a solution of 1-benzoylacetone (1.62g, 10 mmol) in absolute ethanol (50 ml), acetylhydrazide (0.78g, 10 mmol) was added. The resultant mixture was stirred at room temperature for 30 min. The resulting suspension was refluxed at 75 °C for 3 h. The yellowish solution was filtered and the filtrate was kept for slow evaporation at room temperature to yield a light-yellow polycrystalline sample. The Schiff base was washed with ethanol and dried over fused $CaCl_2$.

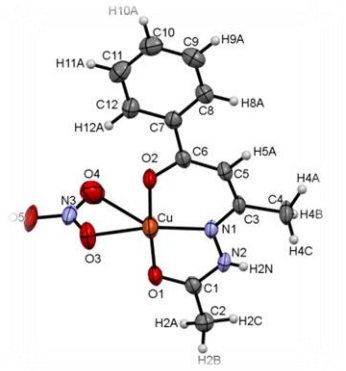
Synthesis of Complex

The Schiff base ligand (0.281g, 1.0 mmol) was dissolved in methanol (20 mL). A solution of Cu $(NO_3)_2.3H_2O$ (0.241 g, 1.0 mmol) in methanol (20 mL) was added dropwise to the above solution with stirring for 5 h to give a green clear solution. The resulting solution was filtered. The filtrate was left for slow evaporation at room temperature. Plate-like crystals were formed from the solution two weeks later. These crystals were washed with hot distilled water and then ethanol to remove impurities. The crystals were dried under vacuum.

Crystal structure of Complex

The copper(II) centre in this complex is four coordinated by two oxygen atoms (O1 and O2) and one nitrogen atom (N1) of the Schiff base and one oxygen atom (O3) of the nitrate ligand, forming a psuedotetrahedral geometry.Oxygen atom of nitrate is weakly coordinated

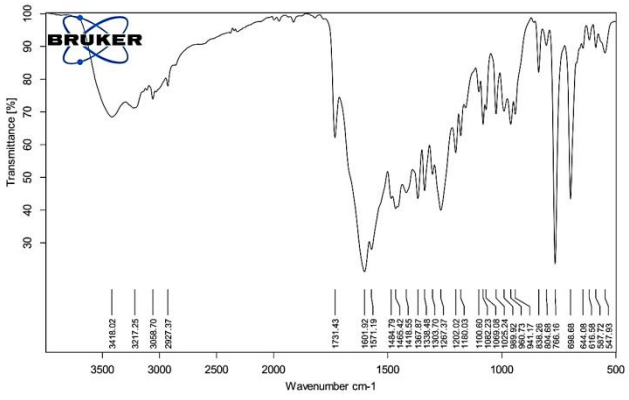
with copper(II) centre. In this complex the Cu(II) centre in an approximate pseudo-tetrahedral geometry is ascertained by the value of τ-index ($\tau_4 = 360^0 - (\alpha + \beta) / 141^0$), where α and β are the two largest angles in four coordinate complexes. The value of τ_4 would range from 1.00 for a perfect tetrahedral geometry to zero for a perfect square planar geometry. For this complex τ_4 is 0.81.Therefore, the geometry of copper ion is approximate tetrahedral. The Cu−N and Cu−O bond distances of this complex are comparable to those some reported four coordinate geometry of Cu(II) complexes.



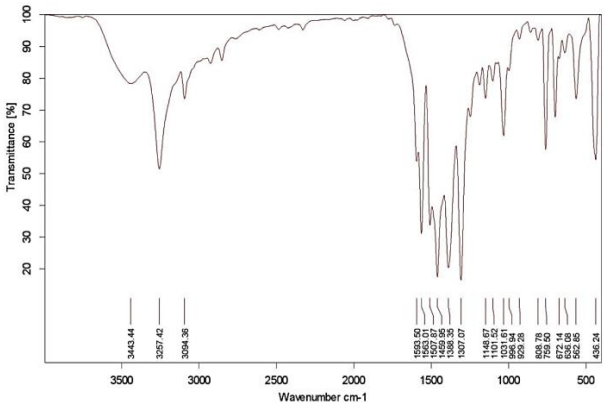
Empirical formula	$C_{12}H_{13}CuN_3O_5$
Formula weight	342.79
Temperature (K)	150(2)
Crystal system	Triclinic
Space group	P -1

IR spectroscopy

The FT-IR spectraof the complex was analyzed in comparison with that of free ligand (HL) in the region 4000-400 cm^{-1}.



Ligand

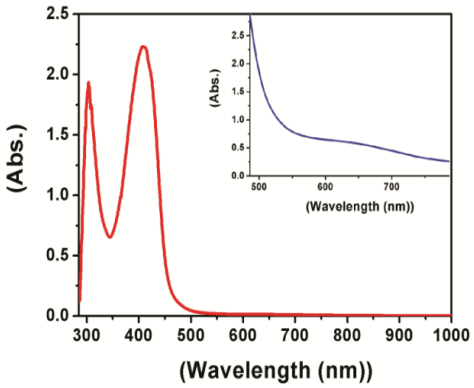


Complex

FTIR spectra of Ligand and Complex

Electronic spectral studies

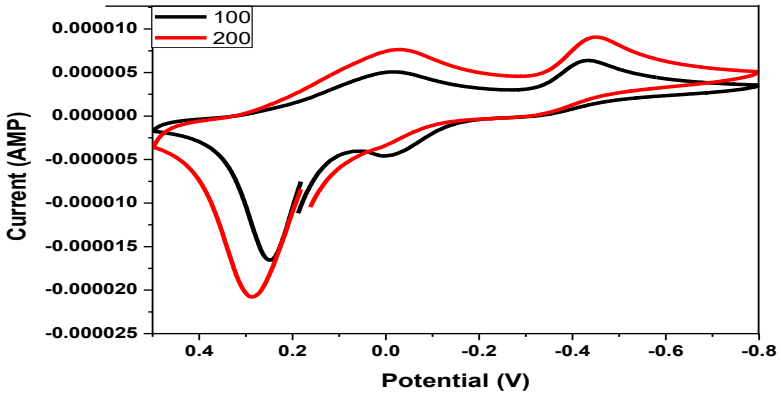
The ligand field absorption spectrum is also measured. The absorption bands of complex in DMSO are shown below.



Absorption spectra of 1×10^{-3} M DMSO solution of complex

Electrochemical studies

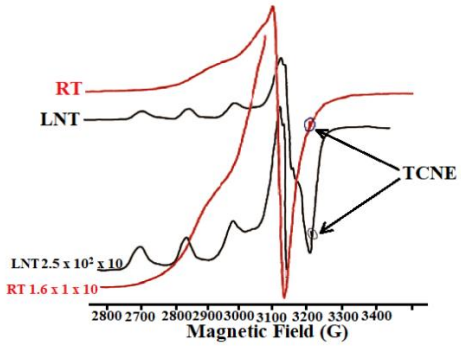
The redox properties of this complex were investigated in DMSO (0.003 ML^{-1}) using cyclic voltammetry. Tetra butyl ammonium perchlorate (TBAP) was used as supporting electrolyte. Cyclic voltammograms were recorded with 100 and 200 mVs^{-1} scan rates vs Ag/AgCl as the reference electrode.



Cyclic voltammogram of complex in DMSO

Epr spectral study

Epr spectra of complex recorded in polycrystalline at room temperature and in DMSO solution at liquid nitrogen temperature (LNT). The polycrystalline spectrum (RT) exhibited a broad absorption at <g> = 2.



Epr spectra of complex

Conclusions

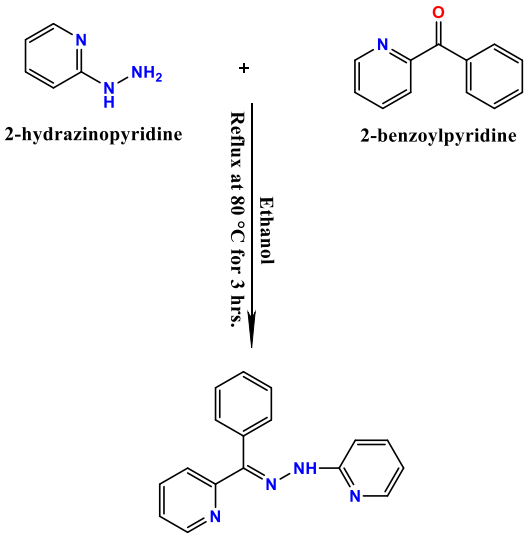
The new mononuclear complex ($Cu(HL)NO_3$) where HL = (N'-[(2E,3Z)-4-hydroxy-4-phenylbut-3-en-2-ylidene]acetohydraziede) was obtained. The Schiff base coordinate through metal ion via two nitrogen and one oxygen atoms. Hence Schiff base behave as a tridentate ligand. The crystallographic data reveal that the metal ion is also coordinated to nitrate ligand forming pseudo-tetrahedral geometry. We have also characterized complex by various spectroscopic techniques. This complex showed good antioxidant SOD properties. The complex also exhibit good anticancer activity prominent anticancer properties in vitro. The antiproliferative of this complex have opened the avenues to design and synthesize new members of the same ligand frame work to investigate better anticancer drug.

Chapter 3

Copper(II) complexes incorporating NNN-tridentate hydrzone as proligand

(A) Synthesis and structural characterization of copper(II) complexes with flexible hydrazone: Structural diversity, Hirshfeld analysis, density functional calculations and biological study

Synthesis of Ligand HL

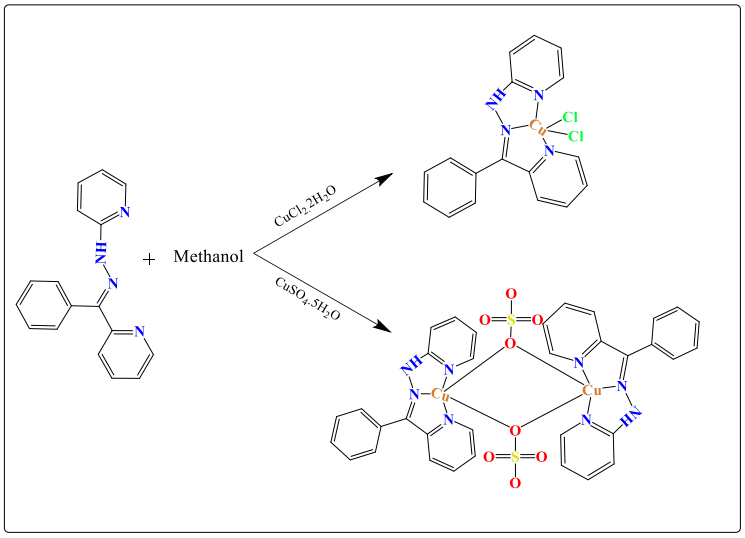


HL = (*E*)-2-(phenyl(2-(pyridin-2-yl)hydrazono)methyl)pyridine

Synthetic route of ligand (HL = (E)-2-(phenyl (2-(pyridine-2-yl) hydrazono) methyl) pyridine.

The part is devoted to the structural, magneto-chemical and quantum chemical (DFT) calculations using (Z)-2-(phenyl(2-(pyridin-2-yl)hydrazone)methyl)pyridine ligand. The extent of deprotonation depends on the used reaction conditions and metal. The hydrazone Schiff bases inspired us to investigate the nature of coordination as well as structural properties of copper(II) complexes with (Z)-2-(phenyl(2-(pyridin-2-yl)hydrazono)methyl)pyridine (HL) viz., $[Cu(Cl)_2(L)]$ **1** and $[Cu_2(\mu\text{-}SO_4)_2(L)_2]$ **2**. The molecular structures of these complexes were determined using single-crystal X-ray analysis. Both complexes were further character using other physicochemical techniques (UV-vis, IR,

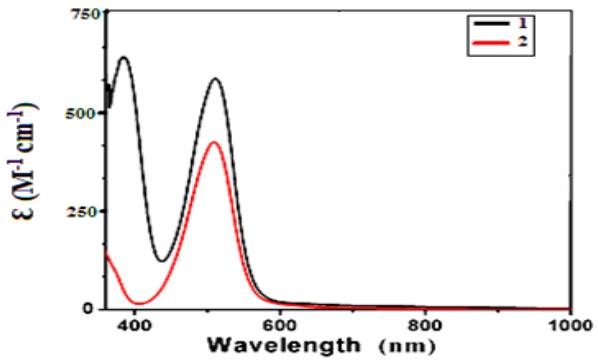
CV and DPV). These two complexes were also studied using electron paramagnetic resonance (Epr) spectroscopy. This technique is widely used for the characterization of paramagnetic species[25-27]. The technique enables important insight into the description of the chemical environment and binding pattern around the center metal. These complexes catalyzing the copper(II) N_3Cl_2/N_3O_2 structural motifs as their inner sphere structure (Scheme 1). The coordination sites available for binding of $O_2^{\cdot-}$ are shown by single-crystal X-ray structures. Besides, antioxidants superoxide dismutase activity data of both complexes were also collected and compared with reported SOD models. The anticancer activities of compounds toward human IMR 32 (neuroblastoma), MCF 7 (breast cancer), HepG2 (hepatocellular carcinoma) and A549 (lung cells) cancer cell lines have been examined in comparison with the cisplatin under identical conditions by using MTT assay.



Synthetic route of metal complexes 1-2.

Electronic spectra

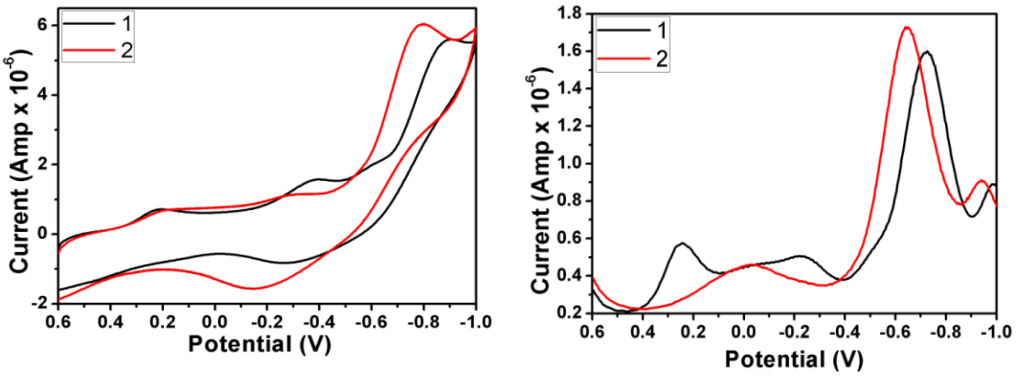
The electronic spectra were recorded using DMSO (3.0×10^{-3} M) solutions of **1** and **2**.



UV-visible spectra of complexes.

Electrochemical studies

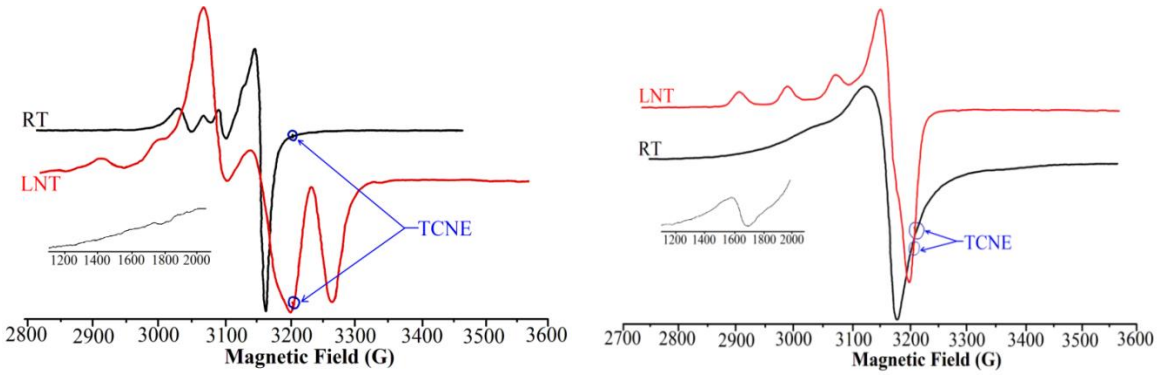
The electrochemical behaviour of both complexes was studied using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. The CV and DPV diagrams are shown. Both complexes display two reduction process.



(a) Cyclic voltammograms of complexes 1and 2 in DMSO at an Ag/AgCl electrode with a scan rate of 300 mV s^{-1} and temperature 20°C. (b) Differential pulse voltammogram of complexes 1 and 2at room temperature using a scan rate of 20 mV s^{-1} in DMSO. The pulse amplitude is 50 mV.

Epr measurements

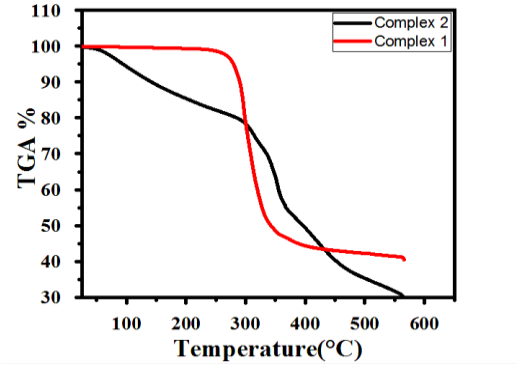
The Epr spectra of complexes **1** and **2**were measured in a Varian E-line Spectrometer working in the X-band at RT of polycrystalline and LNT of frozen solutions. The Epr spectra of these complexes were recorded in polycrystalline samples at RT and in DMSO solution (3×10^{-3} M) at LNT.



X-band EPR spectra of complex 1 and 2 in the polycrystalline state (RT) and DMSO solution at LNT. Inset: EPR spectra showing half-field signals.

Thermal gravimetric analysis

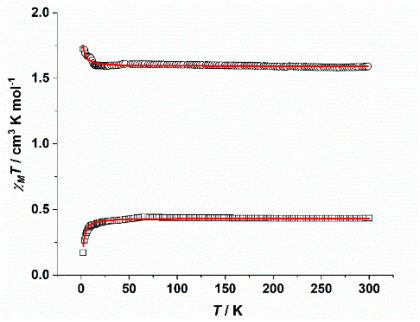
The thermal behaviour of complexeswas studied by thermal gravimetric analysis. The curves of thermo-gravimetric analysis (TG) are displayed in Fig.6.Thermal decomposition of the copper complexes occurs at the temperature range of 100-530 °C showing high thermal stability of the complexes.



TGA curves of Complexes 1 and 2.

Cryomagnetic susceptibility studies

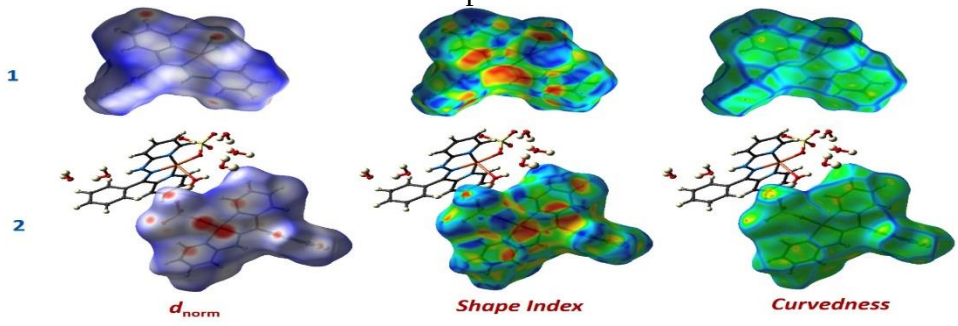
The thermal variation $\chi_M T$ (χ_M = molar magnetic susceptibility) for 1 and 2 in the temperature range 300-2 K is shown in Fig. 7. The value of the$\chi_M T$product obtained at room temperature for complex **1**is 0.43cm^{3}Kmol^{-1}. The$\chi_M T$product of **2**at room temperature is 1.66 cm^{3}Kmol^{-1}.



Temperature dependence of the $\chi_M \cdot T$ product of complexes 1 (squares) and 2 (circles) measured under a magnetic field of 0.5 T. The solid lines represent the fit of the data as described in the text.

Hirshfeld Surface Analysis of Complexes

Molecular Hirshfeld surfaces in the crystal structure were constructed on the basis of the electron distribution calculated as the sum of spherical atom electron densities.



Hirshfeld surfaces mapped with d_{norm}, shape index and curvedness for the complexes 1 and 2

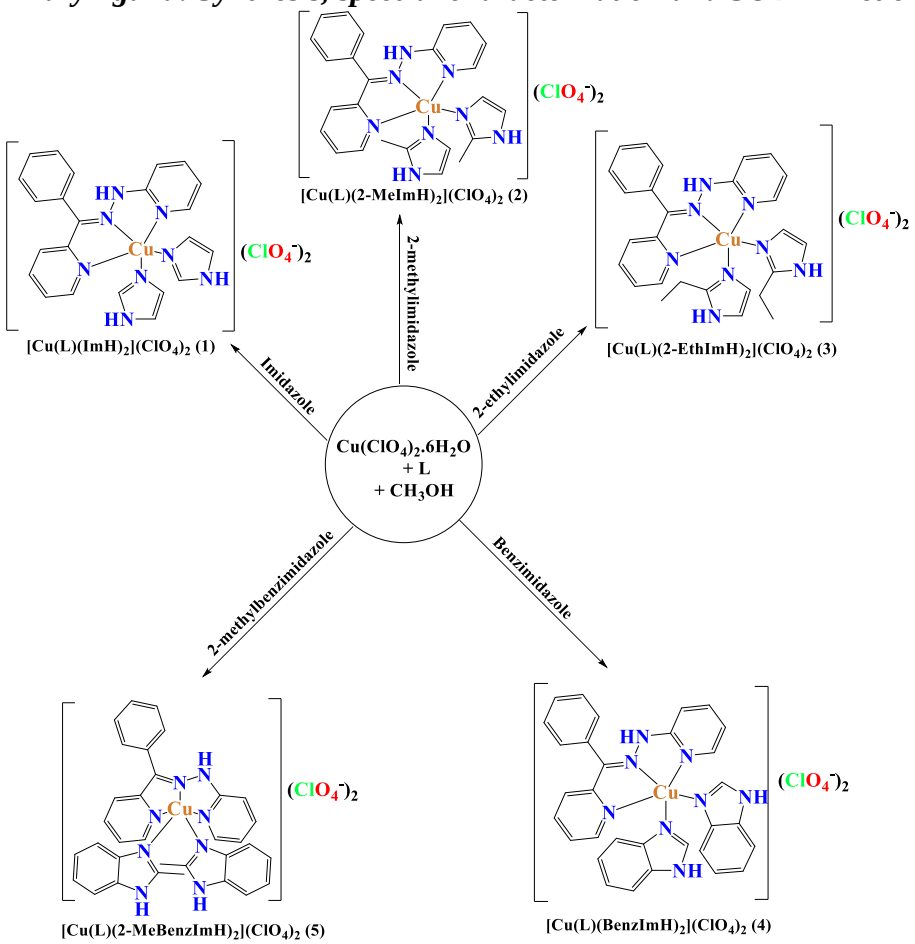
Conclusions

Two new mono and binuclear copper(II) complexes were synthesized by a biomimetic strategy and their structures were solved by single-crystal X-ray and various spectral techniques. All the copper centers in both complexes have pentacoordinate

geometries. This kind of geometry has been observed also some known di- or polynuclear copper(II) complexes. Low-temperature susceptibility measurements revealed that the copper(II) centers in both complexes **1** and **2** are weakly anti-ferromagnetically coupled. Complex **2** is a unique example showing Ferro- and antiferromagnetic couplings. The ferromagnetic coupling in the two symmetric sulphate bridges fully agrees with the previous magneto-structural correlations. Antioxidant SOD activities were also examined. Both complexes are potent SOD mimics. The structures-activity relationship for complexes was studied to support the experimental findings to assess some important parameters, *viz.*, bond length, bond angle, HOMO-LUMO energy gap (ΔE), global reactivity descriptors, dipole moment, second-order perturbation energies and spin density. The antioxidant SOD and antiproliferative properties *in vitro* suggest the encouraging applications of **1** and **2** in biology and pharmaceuticals sciences.

Chapter: 3

(B) Penta-coordinated copper(II) complexes with hydrazido based ligand and imidazole as auxiliary ligand: Synthesis, spectral characterization and SOD mimetic activities



General synthetic route of complexes 1-5.

We have used same ligand to synthesised these five complexes. The molecular formulations of these complexes are as $[Cu(L)(ImH)_2](ClO_4)_2$**(1)**, $[Cu(L)(2\text{-}MeImH)_2](ClO_4)_2$**(2)**,

$[Cu(L)(2\text{-}EthImH)_2](ClO_4)_2$**(3)**, $[Cu(L)(BenzImH)_2](ClO_4)_2$**(4)** and $[Cu(L)(2\text{-}MeBenzImH)_2](ClO_4)_2$**(5)**.The spectral and electrochemical behaviour of these complexes were also studied. The magnetic properties of these complexes are similar from those of previously reported mononuclear copper(II) complexes with Schiff bases and co-ligands. Additionally, in this chapter SOD mimetic activities have been examined and compared with known SOD mimics.

FTIR spectra

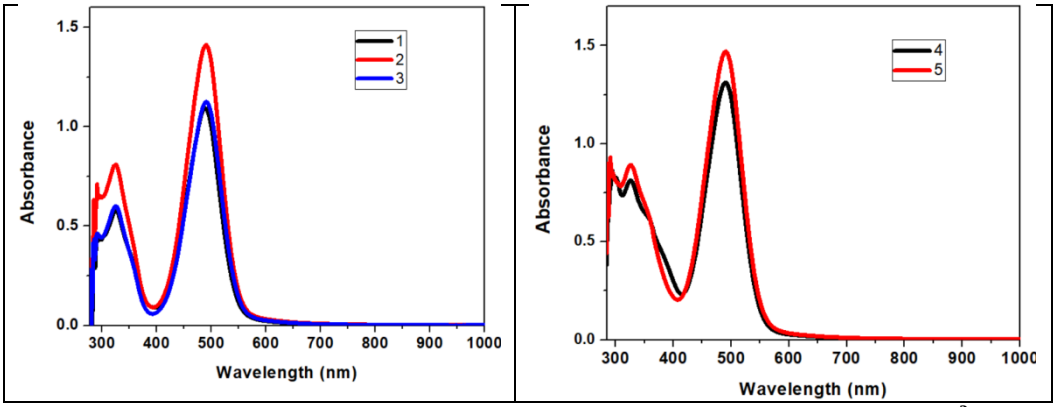
The FTIR spectra of hydrazone ligand (L) as well as complexes **1-5** have been recorded to get a preliminary idea about the binding mode of the ligands.

Table 1. IR spectral band assignments of L and complexes.

Compounds	ν(NH)	ν(>C=N)	ν(N-N)	ν(Cu-O)	ν(Cu-N)
L	**3084**	**1592**	**988**	**-**	**-**
1	**3420**	**1537**	**1086**	**486**	**423**
2	**3396**	**1569**	**1020**	**461**	**421**
3	**3417**	**1572**	**1093**	**461**	**419**
4	**3421**	**1563**	**1018**	**418**	**411**
5	**3421**	**1563**	**1018**	**419**	**411**

Electronic spectra

The electronic spectra of complexes also provide structural information. The most intense absorption bands for complexes 1-5 was indicated in the range of ~ 490-492 nm owing to ligand to metal charge transfer (LMCT). The highest energy band shown in the range of 325-329 in spectra of complexes are due to π→π* transition of aromatic and azomethine groups.

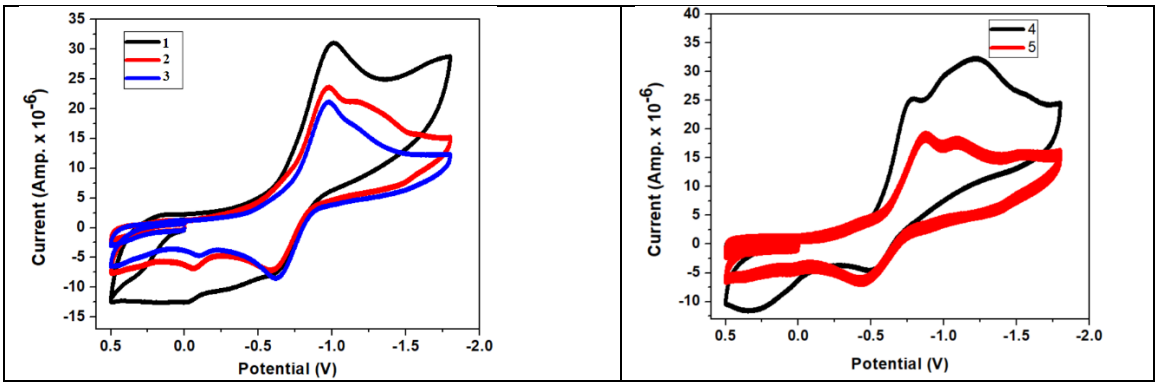


Electronic absorption spectra of all complexes were measured in DMSO (1.0×10^{-3} M) solutions.

Electrochemical studies

The CV of complex **1** shows two reductive and two oxidative responses, while **2** shows two reductive and one oxidative response. One reductive wave of this complex does not have its counterpart in the return scan of CV. This shows that this species is unstable in DMSO solution in the CV time scale. The bound hydrazone ligand to the copper centre makes the reduction of metal centre unfavourable, leading to negative reduction potential. The cathodic

reduction potential in all complexes are within the range of values reported for the reduction (Cu^{II} / Cu^{I}) of hydrazone copper(II) complexes. The extra reduction and oxidation peaks in the complexes are due to ligand centred electron transfer reaction. The effect of auxiliary ligand is obvious on E_{pc}. E_{pc} of complexes become more negative as the molecular weight increases.



Cyclic voltammograms of complexes 1-5 in DMSO at an Ag/AgCl electrode with a scan rate of 300 mV s^{-1} and temperature 20°C.

Epr spectra

The epr spectra of microcrystalline complexes **1-5** were measured at room temperature. The frozen DMSO solution 3.0 × 10^{-3} M were also measured at X-band frequency region.

Epr parameters of copper(II) complexes in polycrystalline state at 298K and in DMSO solution at 77K.

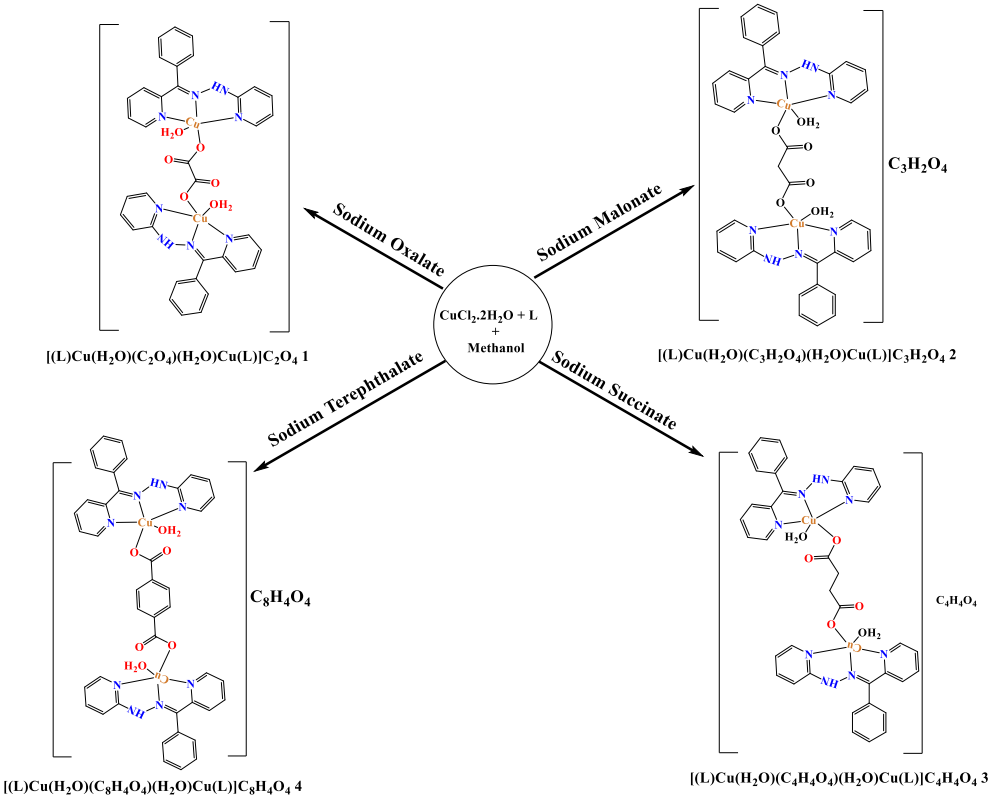
Complex	RT (Polycrystalline)				LNT (Solution) in DMSO (77K)		
	$g_{\parallel}$	$g_{\perp}$	G	D(cm^{-1})	$g_{\parallel}$	$g_{\perp}$	$A_{\parallel}$(G)
1	g_{iso} = 2.084		-	0.018	2.182	2.047	177
2	2.264	2.070	3.866	0.055	2.177	2.048	187
3	2.263	2.069	3.910	0.056	2.177	2.050	175
4	2.237	2.057	4.290	0.052	2.197	2.047	170
5	2.211	2.053	4.110	0.052	2.222	2.049	177

Conclusion

In this chapter we have synthesized five copper complexes using $Cu(ClO_4)_2.6H_2O$ and hydrazone ligand (HL) with using different imidazole series as co-ligand led to the formation of mononuclear complexes. These complexes were isolated in good yield and characterized using UV-vis, FT-IR and epr spectral physico-chemical techniques. Thecopper(II) centre in all complexes are penta-coordinated. The proligand has NNN donor sites viz., two pyridine N and one azomethine N atoms whereas co-ligand coordinates through pyridine N atom forming two five membered chelate rings. Both pro and co-ligands are neutral. Thus geometry around copper(II) ion remain square pyramidal. The τ_5 values of theses complexes are in the range 0.177-0.495. The IC_{50} value of present complexes remains in the range 26-43 µM.

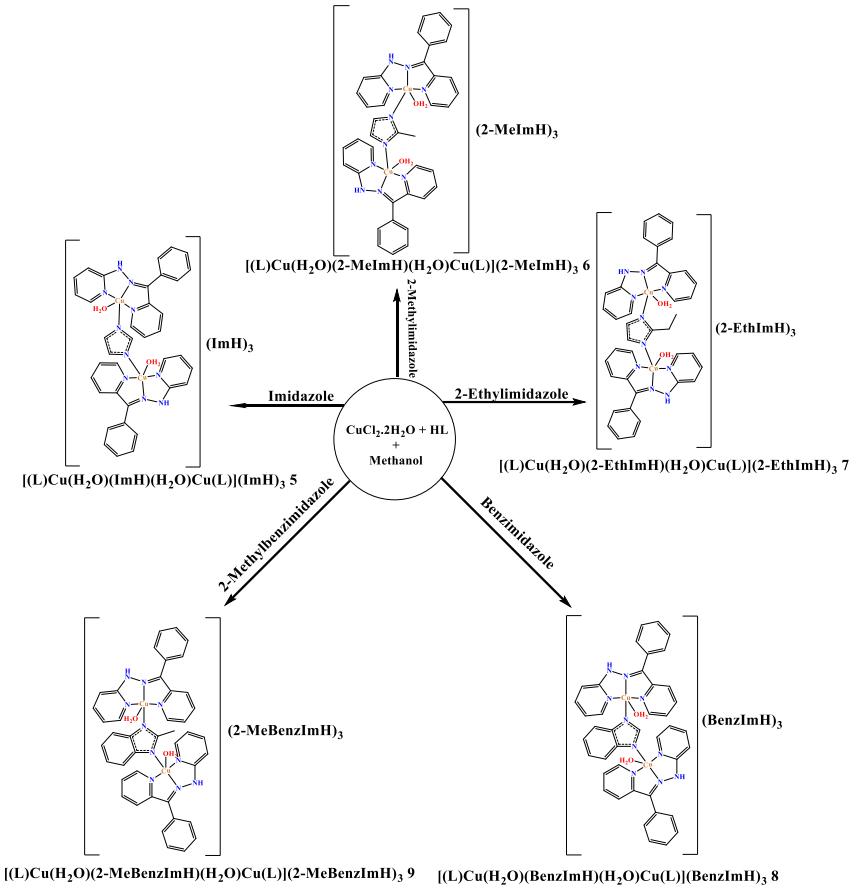
Chapter: 3

(C) Synthesis, spectral characterization and biomimetic activity of homobinuclearcopper(II) 2-[(E)-phenyl(pyridine-2-yl-hydrazone)methyl]pyridine complexes containing inorganic salts



Synthetic route of complexes 1-4

In this part of thesis, homobinuclear copper(II) 2-[(E)-phenyl(pyridine-2-yl-hydrazono)methyl]pyridine (L) complexes containing inorganic salts with compositions, $[(L)Cu(H_2O)(C_2O_4)(H_2O)Cu(L)](C_4O_4)$ (**1**), $[(L)Cu(H_2O)(C_3H_2O_4)(H_2O)Cu(L)](C_3H_2O_4)$ (**2**), $[(L)Cu(H_2O)(C_4H_4O_4)(H_2O)Cu(L)](C_4H_4O_4)$ (**3**),$[(L)Cu(H_2O)(C_8H_4O_4)(H_2O)Cu(L)](C_8H_4O_4)$(**4**), $[(L)Cu(H_2O)(ImH)(H_2O)(Cu(L)](ImH)_3$ (**5**), $[(L)Cu(H_2O)(2\text{-}MeImH)(H_2O)(Cu(L)](2\text{-}MeImH)_3$(**6**),$[(L)Cu(H_2O)(2\text{-}EthImH)(H_2O)(Cu(L)](2\text{-}EthImH)_3$(**7**), $[(L)Cu(H_2O)(BenzImH)(H_2O)(Cu(L)](BenzImH)_3$(**8**) and $[(L)Cu(H_2O)(2\text{-}MeBenzImH)(H_2O)(Cu(L)](BenzImH)_3$(**9**) have been synthesized and characterized for their spectroscopic and redox properties. In addition, SOD mimetic activities of these complexes have also been investigated. We have also done DFT calculation.



Synthetic route of complexes 5-9.

FTIR Analysis

A FTIR spectral study of all nine copper(II) was performed to get a basic idea about the binding mode of anionic co-ligands.

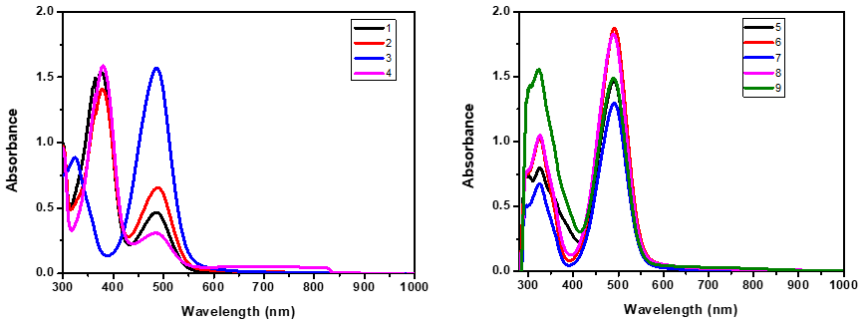
FTIR important bands.

Compounds	ν(NH)	ν(OH)	ν(>C=O)	ν(>C=N)	ν(N-N)	ν(Cu-O)	ν(Cu-N)
HL	3084			1592	988		
1		3289	1613	1578	1068	472	419
2		3233	1625	1533	1089	542	479
3		3107	1603	1580	1026	542	479
4		3061	1612	1545	1108	435	419
5		3424		1564	1003	466	419
6		3442		1564	1004	467	419
7		3425		1564	1002	464	419
8		3408		1563	1001	418	411
9		3421		1563	1002	418	411

Electronic Spectra

The electronic spectra of copper(II) complexes **1-9** were recorded in DMSO (1.0×10^{-3}M). UV visible spectra are shown in the wave length range 300-1000 nm, three main absorptions

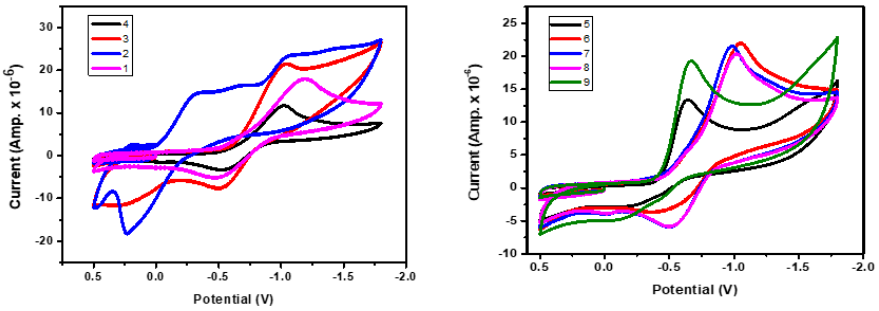
are observed. The electronic data of these complexes are in good agreement with their geometrics.



UV-visible spectra of complexes 1-9.

Electrochemistry

The redox behavior of complexes 1-9 have been explored using cyclic voltammetry (CV) and differential pulse voltammetry (DPV). The cyclic voltammograms of complexes (1.0×10^{-3}M) in DMSO were recorded with tetrabutyl ammoniumperchlorate (TBAP) as the supporting electrolyte in the potential range 0.3 to -1.8 V versus Ag/AgCl.



Electronic spectra of complexes 1-9.

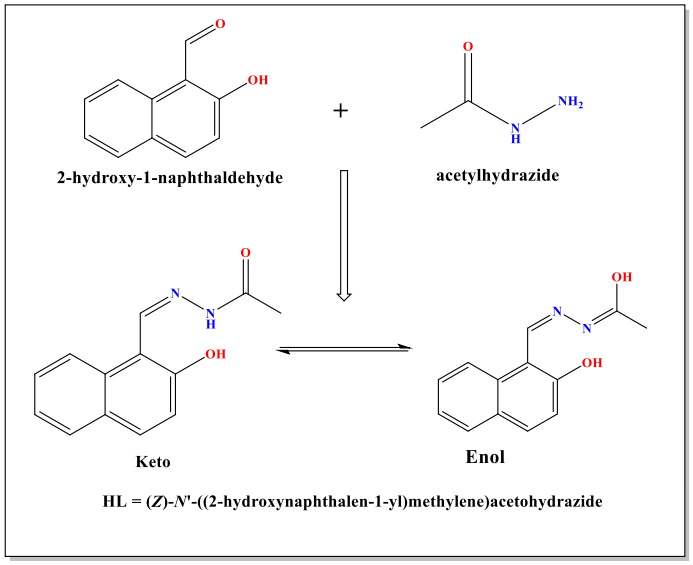
Conclusion

In this chapter we have synthesized ninebinuclear copper complexes using $CuCl_2.2H_2O$ and hydrazone ligand (HL) with using different bridging ligand led to the formation of binuclear complexes.These complexes were isolated in good yield and characterized using UV-vis, FT-IR and epr spectral physico-chemical techniques.The Geometry optimized structures of the complexes **1-9**were carried out using density functional theory calculations at B3LYP/LANL2DZ level. In these binuclear complexes each copper(II) centre has distorted square pyramidal geometry. The equatorial sites around copper(II) centres are occupied by NNN atom of hydrazone ligand and fourth position is occupied by O atom of bridging carboxylate moiety whereas axial position is occupied by O atom of coordinated water molecule.

Chapter: 4

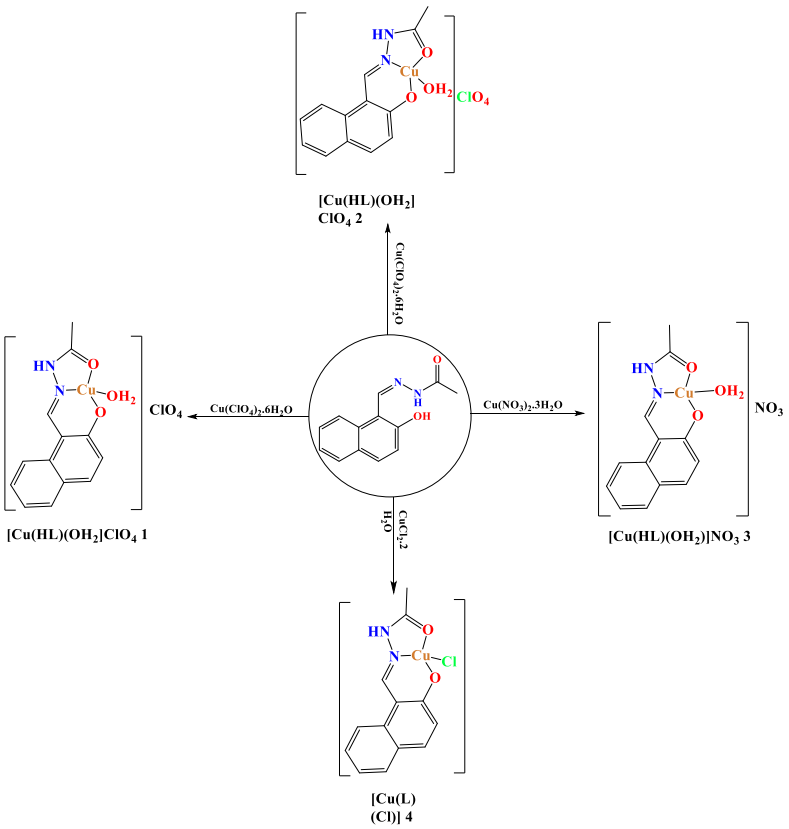
Copper(II) hydrazone complexes with different nuclearties and geometries: Synthesis, structure, spectral properties, electrochemical behaviour, density functional study and *in vitro* catalytic activity

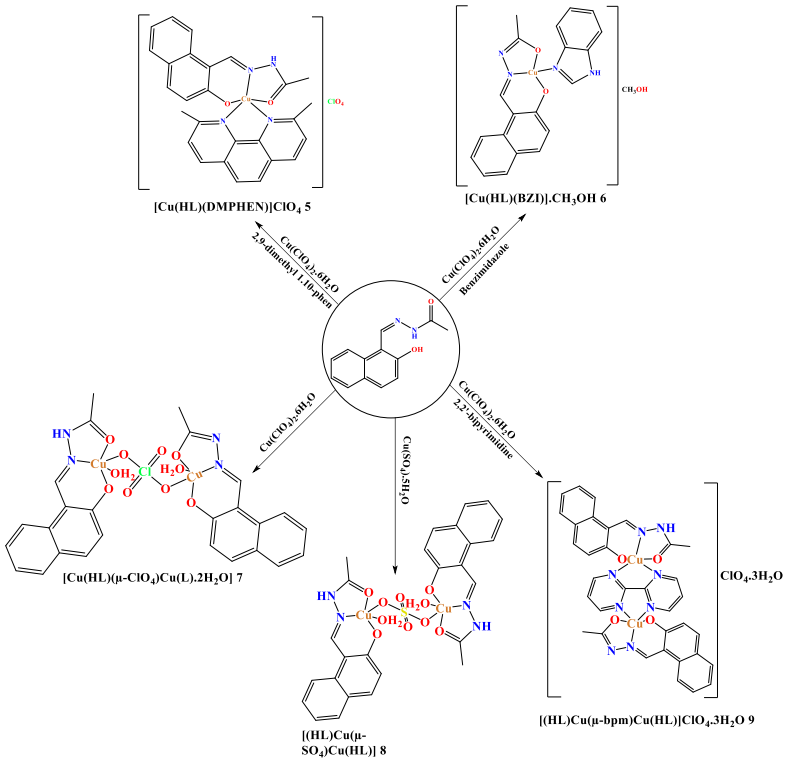
Synthesis of Ligand HL



Synthetic route of ligand (HL =N'-((2-hydroxynaphthalen-1-yl) methylene) acetohydrazide.

Synthesis of Complexes





Synthetic route of complexes 1-9

FTIR Spectra

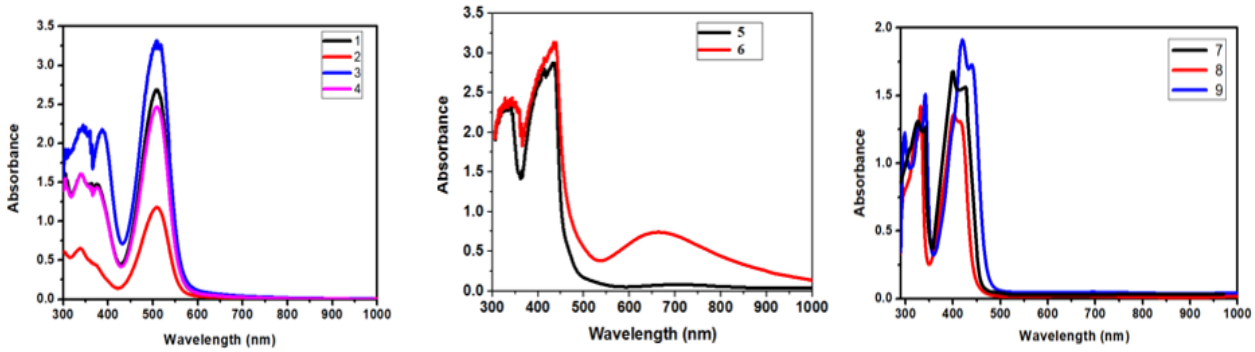
In the IR spectra of ligand and complexes shows several bands appears in the region 400-4000 cm^{-1}. Verification of the structure of metal complexes can be easily achieved by comparing the IR spectra of the free ligand with their metal complexes.

Compounds	ν (C=O)	ν (C=N)	ν (M-O)	ν (M-N)
HL	**1672**	**1643**	**- - -**	**- - -**
1	**1617**	**1598**	**493**	**441**
2	**1618**	**1597**	**492**	**439**
3	**1618**	**1578**	**491**	**447**
4	**1592**	**1516**	**469**	**434**
5	**1616**	**1601**	**476**	**459**
6	**1622**	**1590**	**456**	**437**
7	**1617**	**1599**	**457**	**423**
8	**1618**	**1606**	**456**	**427**
9	**1631**	**1572**	**511**	**477**

Electronic spectral study

In each spectrum of these complexes lower energy absorption in the visible region (λ_{max} = 403-506 nm) and higher energy absorption in the UV-region (λ_{max} = 291-341 nm) are to be

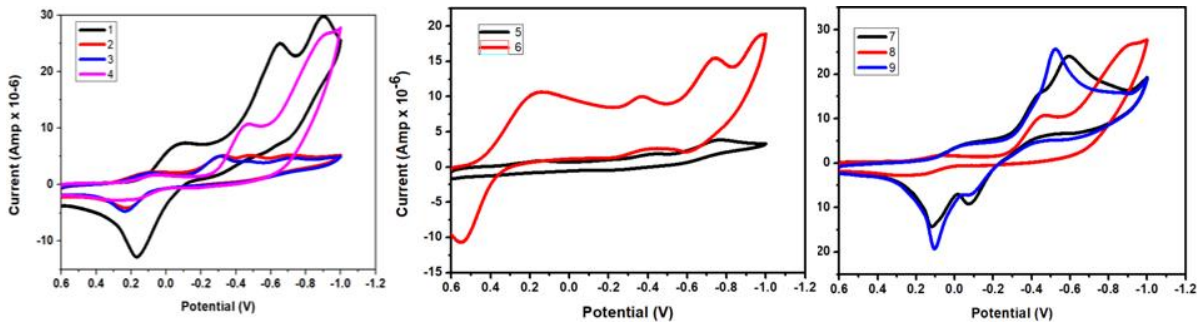
expected due to ligand centre transitions. The higher energy band can be attributed due to the $\pi \rightarrow \pi^*$ transition of the aromatic rings and azomethine group.Electronic spectra of all complexes exhibit a d-d transition in the region 617-731 nm.



The electronic spectra of complexes have been measured in DMSO solution (3.0×10^{-4} M).

Electronic spectra

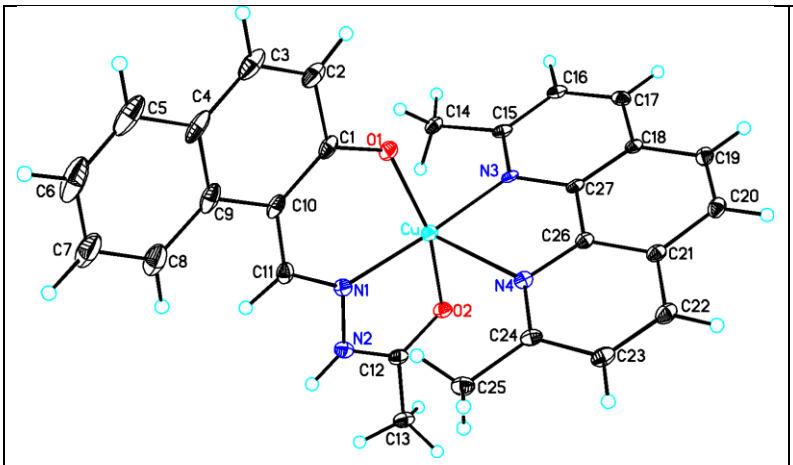
An electrochemical property of present complexes has been explored using cyclic volatammetery (CV).All of the complexes exhibit two reduction waves and one oxidation wave except **9**. This shows two redox waves which are associated with the stepwise reduction of the Cu(II) centre. Were as binuclear complexes **7** and **8** are related with one step reduction of Cu(II) centers.The electrode reactions for mononuclear complexes 1-5 can be associated with the stepwise reduction of the Cu(II) centre.All reduction waves are quasireversible in nature except in complex **5**. Cyclic voltammogram of **5** shows one irreversible reduction wave.



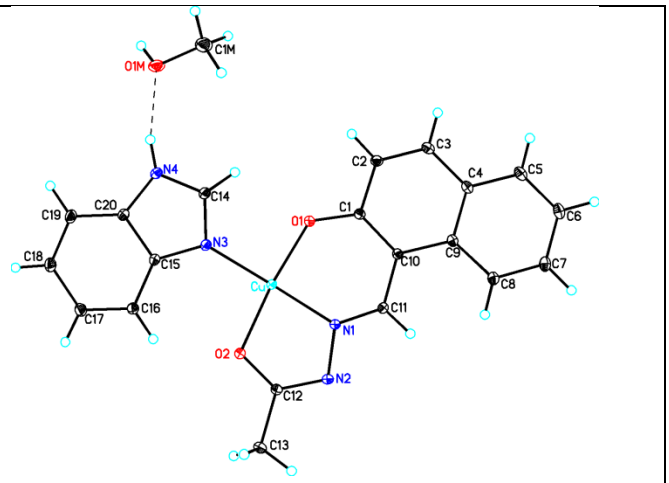
Electronic spectra of complexes 1-9.

Crystal structures of some complexes

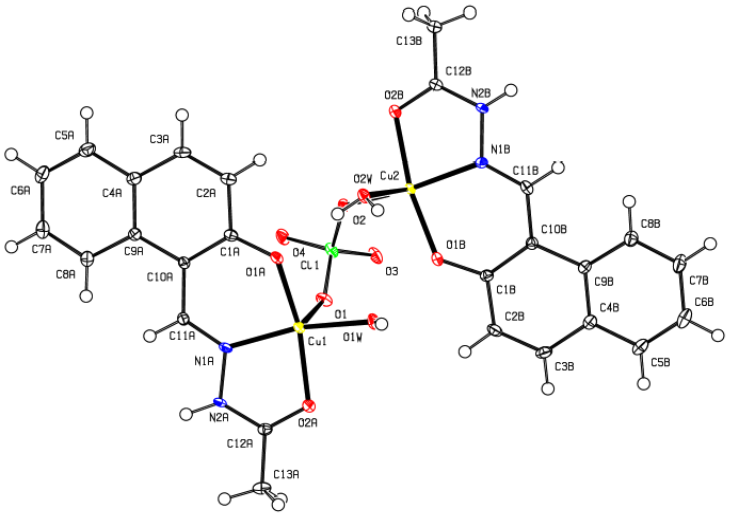
We got the crystal structure of all complexes. Crystal structure of some complexes are shown below.



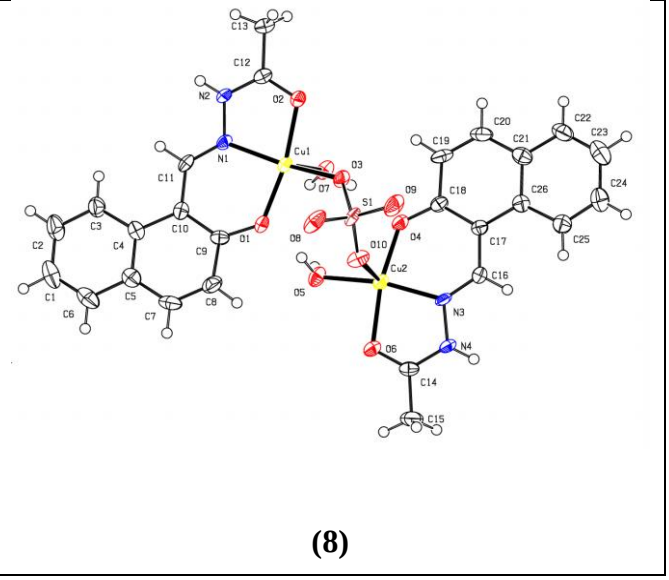
(5)



(6)



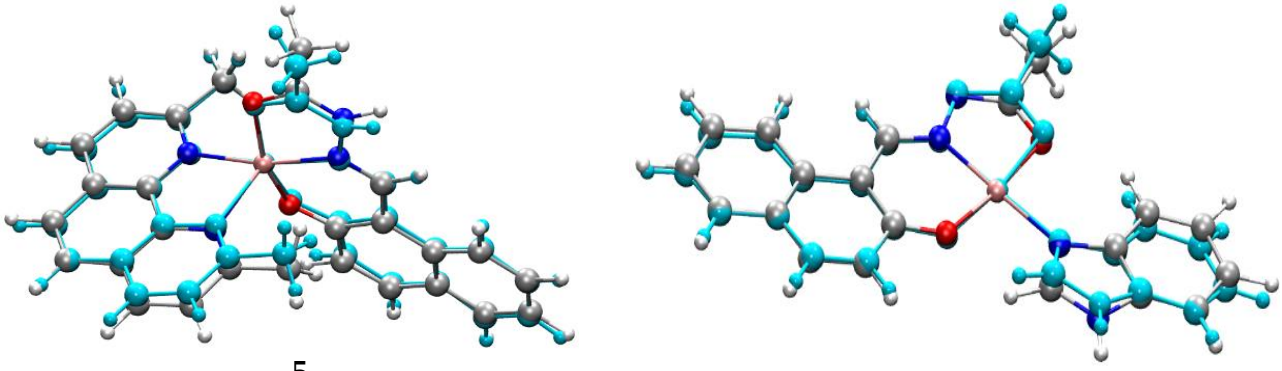
(7)



(8)

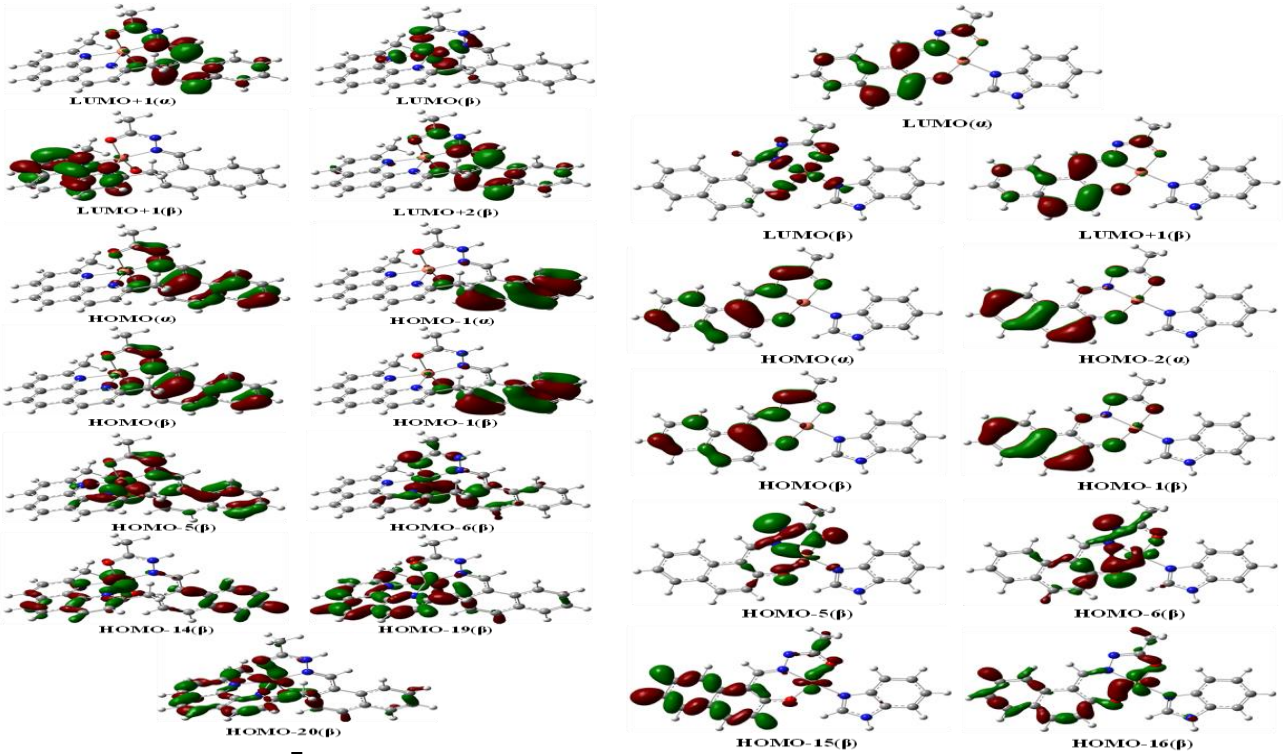
DFT studies

The molecular geometry was optimized by the Gaussian 09 with the level of B3LYP basis set. There are slight differences in bond parameters, owing to the theoretical calculations were carried out on an isolated molecule in gas phase.The geometry of complexes 1-4 and 6 are distorted square planar and for remaining complexes the geometry is five coordinated square pyramidal. On the basis of distortion index, the geometry of 1-4 and 6 is distorted square planar and for rest complexes the geometry around copper centre is distorted square pyramidal. These observations are in the same line of single crystal X-ray analysis. The electronic structures of the complexes 1-9 by characterized by analysing highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbitals (LUMO). The HOMO-LUMO energy gaps (ΔE) furnish information about the reactivity and nature (soft or hard) of a given molecule. These HOMO and LUMO energies are negative for all complexes (1-9), indicating that the complexes are stable. The ΔE also predicts the various reactivity parameters, which additionally reveal the internal charge transfer, susceptibility and stability of molecules.



5 6

Comparison of the PBE0-D3BJ/def2-TZVP optimized geometries (element color) and XRD crystal structures (cyan color) for complexes **5** and **6.**

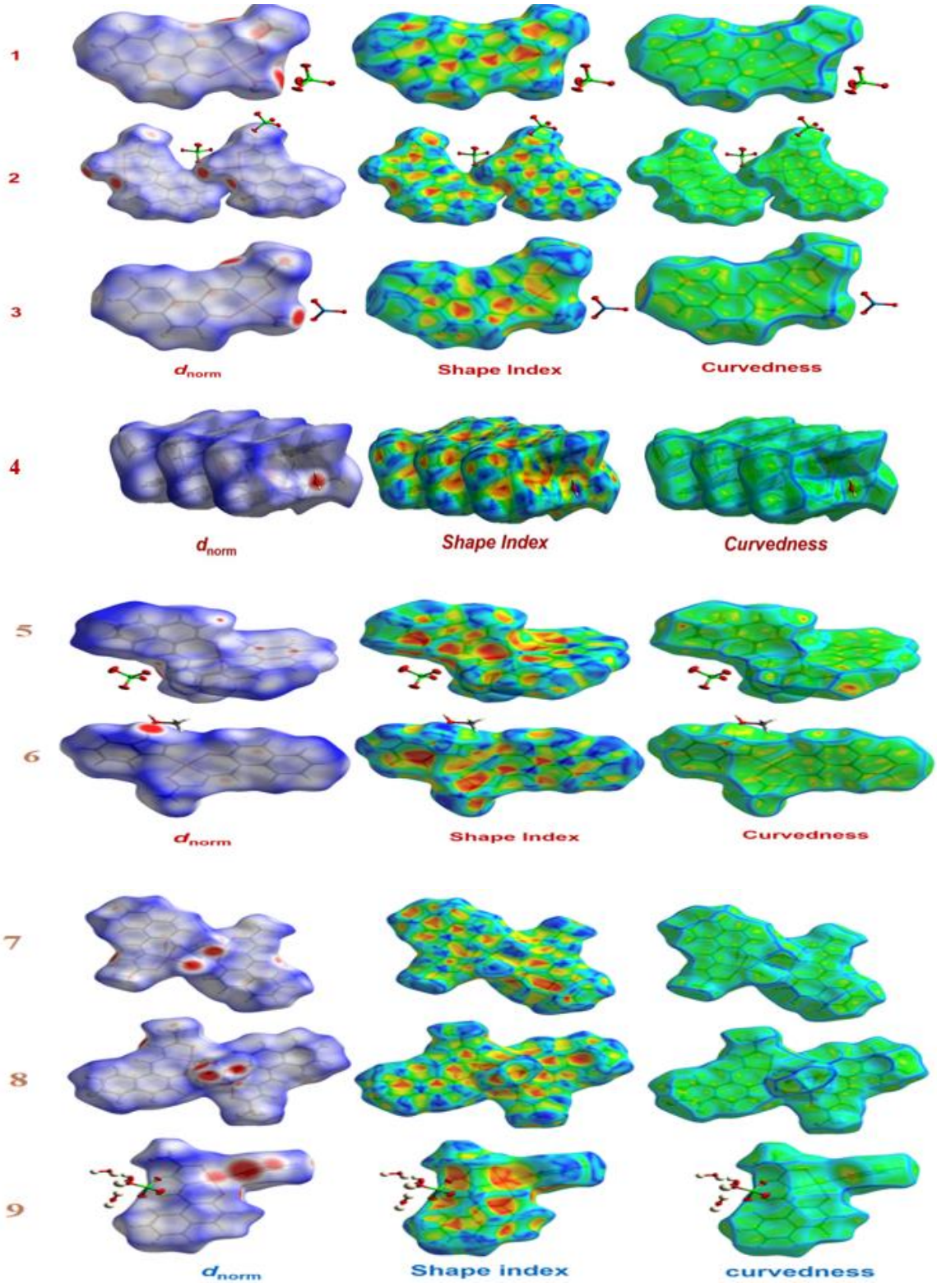


5 **6**

Hirshfeld Surface Analysis (HSA)

The Hirshfeld surfaces are used to associate the average electron density of atoms in a molecule with the entire electron density of crystal, by mapping the spatial contacts between the intermolecular interactions, lattice voids, shape index, surface curvedness, etc. involved in the crystals. Additionally, is useful in demonstrating how the percentage of weak interactions plays a crucial role in developing the crystal geometry in the interstitial spaces in crystals. The white region in the d_{norm}surface illustrating the weak contacts within the van der Waals distance while the red and blue regions dictate the contacts less and more than van der Waals distance respectively. The d_{norm}surface for both the complexes has been mapped between -0.4 to 1.4 Å range and shape index plots are covering the range between -0.9 to 0.9 Å while curvedness plots are constructed between -4.0 to 0.4 Å. The Hirshfeld surfaces for both of the

copper complexes are presented. For better visualization of the molecule, these surfaces are plotted as transparent.



Hirshfeld surfaces mapped with d_{norm}, shape index and curvedness for the complexes.

Superoxide scavenging activity

Compound	IC_{50} (µM)	SOD activity (μM^{-1})	k_{McCF} $(ML)^{-1}s^{-1} \times 10^4$
VC	**852**	**1.17**	**0.39**
$[Cu(Phimp)(H_2O)]_2(ClO_4)_2$	**11.20**	**89.28**	**29.70**
$[Cu(Phimp)(CH_3COO)]$	**8.31**	**120.34**	**40.03**
$[Cu(tnpa)OH]ClO_4$	**11.03**	**90.66**	**30.16**
$[Cu(tapa)OH]ClO_4$	**7.46**	**134.05**	**44.59**
$[Cu(tpa)(H_2O)](ClO_4)_2$	**12.50**	**80.00**	**26.61**
$[(L^1)Cu(\mu\text{-}CH_3COO)_2Cu(L^1)]$	**35.00**	**28.57**	**9.50**
$[(L^1)Cu(\mu\text{-}NO_3)_2Cu(L^1)]$	**26.00**	**38.46**	**12.79**
1	**11.21**	**89.21**	**29.67**
2	**13.67**	**73.15**	**24.33**
3	**11.20**	**89.28**	**29.70**
4	**12.85**	**78.23**	**25.76**
5	**16.72**	**59.81**	**19.89**
6	**18.27**	**54.73**	**18.21**
7	**6.23**	**160.51**	**53.39**
8	**7.35**	**136.05**	**45.26**
9	**11.45**	**87.34**	**29.05**

The scavenging activities of complexes (1-9) are to the value reported other similar complexes. Scavenging activity values indicates that complexes 7 and 8 are potent superoxide dismutase mimics. The SOD scavenging activities of mononuclear complexes are less than those of homobinuclear complexes. Such behaviour is in agreement with results of previously reported IC_{50} values of homo or hetero binuclear complexes.

Conclusion

The copper ions in the mononuclear complexes (**1-4**) have a tetra coordinated structures. Similarly, we have synthesized and characterized two copper(II) complexes with tridentate hydrazone (HL) as pro-ligand and N-donor mono or bidentate compounds as co-ligand in complex **5** and **6**. Complex **5** possesses distorted square pyramidal geometry whereas **6** shows distorted square planar geometry. The Hirshfeld analysis and the fingerprint plots revealed how much the weak CH···π and π ···π non-covalent interactions lead both complexes to build supramolecular architectures.All three binuclear complexes contain two copper atoms in the symmetric unit with molecular formula $[(L)Cu\text{-}(\mu\text{-}ClO_4)Cu(L)]ClO_4$**7**, $[(L)Cu\text{-}(\mu\text{-}SO_4)Cu(L)]$ **8** and $[(L)Cu\text{-}(\mu\text{-}pym)Cu(L)]2ClO_4$**9**.In these binuclear complexes (7-9) each copper atom has a pent coordinated environment thus forming a $[Cu_2(\mu^2\text{-}SO_4/\text{-}ClO_4/\text{-}bpm)]$ core unit. The paramagnetic behaviours of both complexes **5** and **6** has been explored using magnetic and X-band epr spectral study. The electrochemical stability of the metal center was investigated using cyclic and differential pulse voltammetry. Time-Dependent Density functional theory

(TD-DFT) calculations throw light on electronic transitions. Scavenging activity values indicates that complexes **7** and **8** are potent superoxide dismutase mimics.

References:

1. M. E. Weeks, 'Discovery of the Elements', 6th edn., Journal of Chemical Education, Easton, PA, 1960.
2. 'Copper Through the Ages', Copper Development Association, London, 1937.
3. F. J. Owens and C. P. Poole Jr, 'The New Superconductors', Plenum, New York, 1996.
4. J. D. Dow and D. R. Harshman, J. Phys. Chem. Solids, 2002, 63, 2309.
5. K. Uchinokura, J. Phys. Condens. Matter, 2002, 14, R195.

Synopsis

6. C. Klein, and C. S. Hurlbut Jr 'Manual of Mineralogy', 21st edn.; Wiley, New York, 1993.
7. R. R. Moskalyk and A. M. Alfantazi, Miner. Eng., 2003, 16, 893.
8. P. Singer, Semicond. Int., 2002, 46. 10. 2005, http://www.matweb.com/reference/copper-alloys.asp.
9. J. K. Irangu and R. B. Jordan, Inorg. Chem., 2003, 3934.
10. N. J. Curro, J. Phys. Chem. Solids, 2002, 63, 2181.
11. B. Grevin, Y. Berthier, G. Collin, and P. Mendels, ´ Phys. Rev. Lett., 1998, 80, 2405.
12. M. J., O'Neil, ed. 'The Merck Index', 13th edn., Merck, Whitehouse Station, NJ, 2001.
13. R. Ahlrichs, C. E. Anson, D. Fenske, O. Hampe, A. Rothenberger, and M. Sierka, Angew. Chem., Int. Ed. Engl., 2003, 42, 4036.
14. M. E. Padilla-Tosta, O. D. Fox, M. G. B. Drew, and P. D. Beer, Angew. Chem., Int. Ed. Engl., 2001, 40, 4235.
15. M. Melnik, L. Macaskova, and C. E. Holloway, Coord. Chem. Rev., 1993, 126, 71.
16. Holm, R.H.; Kennepohl, P.; Solomon, E.I. Structural and functional aspects of metal sites in biology. Chem. Rev. 1996, 96, 2239–2314.
17. Worrall, J.A.R.; Machczynski, M.C.; Keijser, B.J.F.; di Rocco, G.; Ceola, S.; Ubbink, M.; Vijgenboom, E.; Canters, G.W. Spectroscopic characterization of a high-potential lipo-cupredoxin found in Streptomyces coelicolor. J. Am. Chem. Soc. 2006, 128, 14579–14589.
18. Rosenzweig, A.C. Copper delivery by metallochaperone proteins. Acc. Chem. Res. 2001, 34, 119–128.
19. Conry, R.R. Copper: Inorganic & Coordination Chemistry. In Encyclopedia of Inorganic Chemistry, 2nd ed.; King, R.B., Ed.; Wiley: Hoboken, NJ, USA, 2005; Volume 1, pp. 1–19.
20. Cotton, F.A.; Wilkinson, G. Advanced Inorganic Chemistry, 4th ed.; Wiley: New York, NY, USA, 1980; pp. 79, 798–821.

Abhay Kumar Patel
Research Scholar

Dr. R.N. Jadeja
Research Supervisor

Prof. (Dr.) Anjali Patel
Offg. Head
Department of Chemistry

HEAD
Department of Chemistry
Faculty of Science
The Maharaja Sayajirao University of Baroda
Vadodara- 390002. Gujarat - INDIA