A SYNOPSIS

of the thesis

"Synthesis, Characterization and Biological Property of Amine Functionalized Ligand Precursors and Their Metal Dithiocarbamate Derivatives"

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

DOCTOR OF PHILOSOPHY

in
Chemistry

By
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Under the supervision of
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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: Savani Chirag

Title of the Thesis: "Synthesis, Characterization and Biological Property of Amine Functionalized Ligand Precursors and Their Metal Dithiocarbamate Derivatives"

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Registration No.: FOS/2060

Date of Registration: 31st July 2017

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

Chapter 1: Introduction

Chapter 2: Ferrocene Functionalized Achiral Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Chapter 3: Ferrocene Functionalized Chiral Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Chapter 4: Use of Ferrocene Functionalized Amines in the Development of Novel Ni^{+2}dithiocarbamates complexes

Chapter 5: Benzyl Functionalized Chiral 2^0 and 3^0 Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Chapter 6: Use of Benzyl Functionalized Chiral Amines in the Development of Novel Cu^{+2} and Ni^{+2} dithiocarbamates complexes

Chapter 7: Naphthoquinone Functionalized Chiral and Achiral 2^0 Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Chapter 8: Novel metallomacrocyclic 1,1-dithio complexes of Cu^{+2} Ni^{+2} and Zn^{+2} complexes holding pendent amido groups: Synthesis, characterization and DFT study.

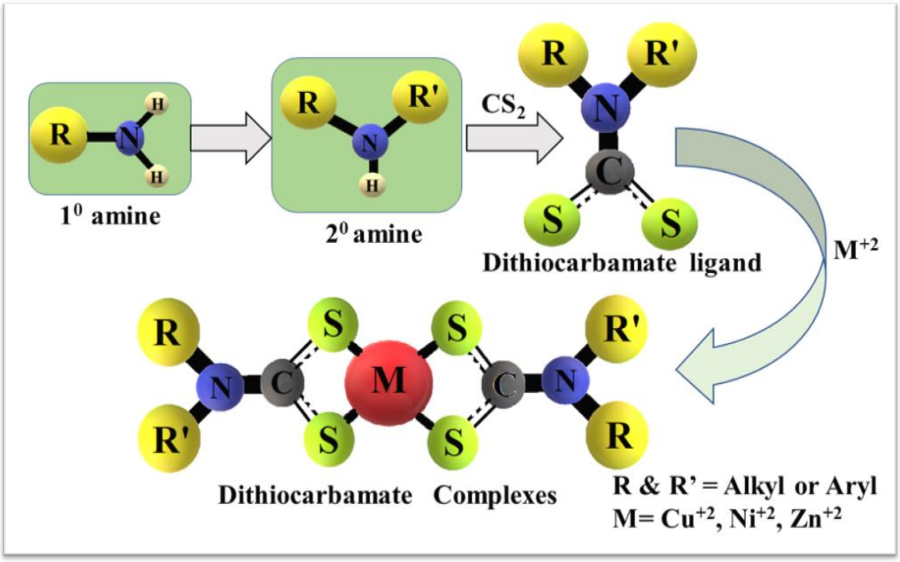
Chapter: 1

Introduction

What is dithiocarbamate complexes?

Transition metal dithiocarbamate complexes are coordination complexes containing one or more dithiocarbamate ligand, which are typically abbreviated R_2dtc^-. Many complexes are known.

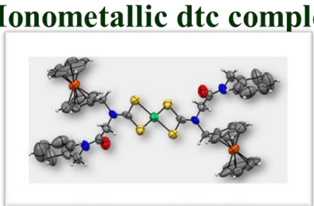
This is general synthesis of Dithiocarbamate complexes

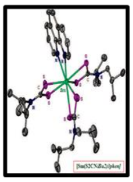


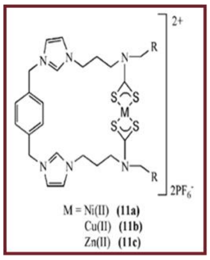
classification of self-assembled structures

-Based on the number of metal centers in the self-assembled structures

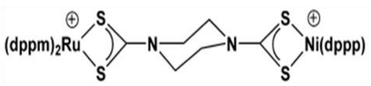
✓ **Monometallic dtc complexes**





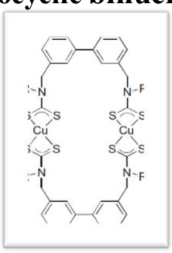


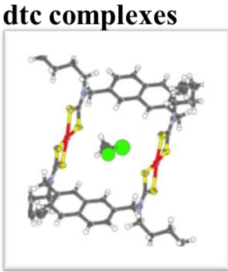
✓ **Linear Bimetallic dtc complexes**



Macrocyclic transition metal dithiocarbamate imidazolium receptors with xylene spacer group

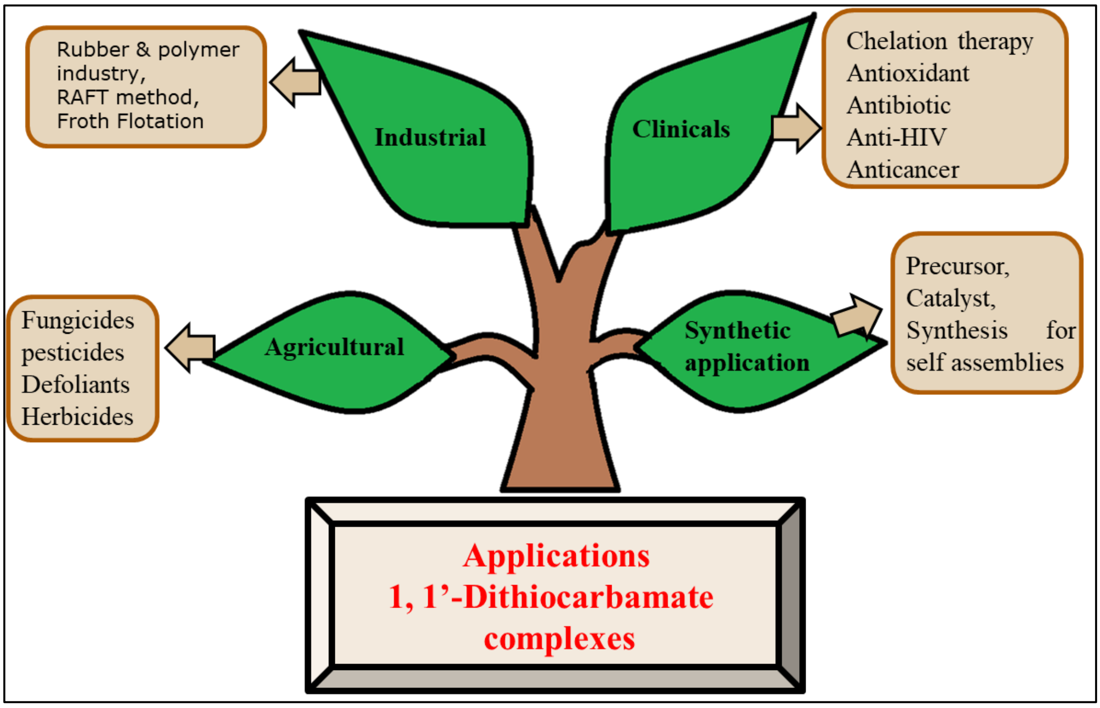
✓**Macrocyclic binuclear dtc complexes**





Inorg. Chem., **2008**, 47, 1512-1523
J. Chem. Soc. Dalton Trans., **1996**, 4135
Dalton Trans., **2010**, 39, 2667–2675
ChemistrySelect 2019, 4, 8689 –8699

Application of dithiocarbamate Complexes



Electrical conductivity, Molecular magnetism, Electrochemical responses, Biological properties. As a single source precursor for the synthesis of metal-sulfide nanoparticles

We are interested to derive new transition metal complexes with 1,1-dithio ligands such as dithiocarbamate bearing pendent functional groups viz. -CONH-, -C=N-, $-NO_2$, -OMe *etc* in the molecular framework.

Aim and Objectives

- ✓ Design and synthesize novel amine functionalized precursors and to explore their reactivity towards CS2 and transition metal ions to obtained various organic and organometallic dithiocarbonate compounds.
- ✓ Characterization of new compounds by standard spectroscopic techniques such as NMR, IR, UV-Visible, Mass, Fluorescence.
- ✓ Investigation of thermal behavior of the newly synthesized compounds by using thermogravimetric technique.
- ✓ Determination of molecular structure of the compounds by means of Single Crystal X-ray Diffraction studies.
- ✓ Screening of the newly synthesized compounds for their possible biological applications.
- ✓ Performing in-silico study to reinforce the experimental outcomes.

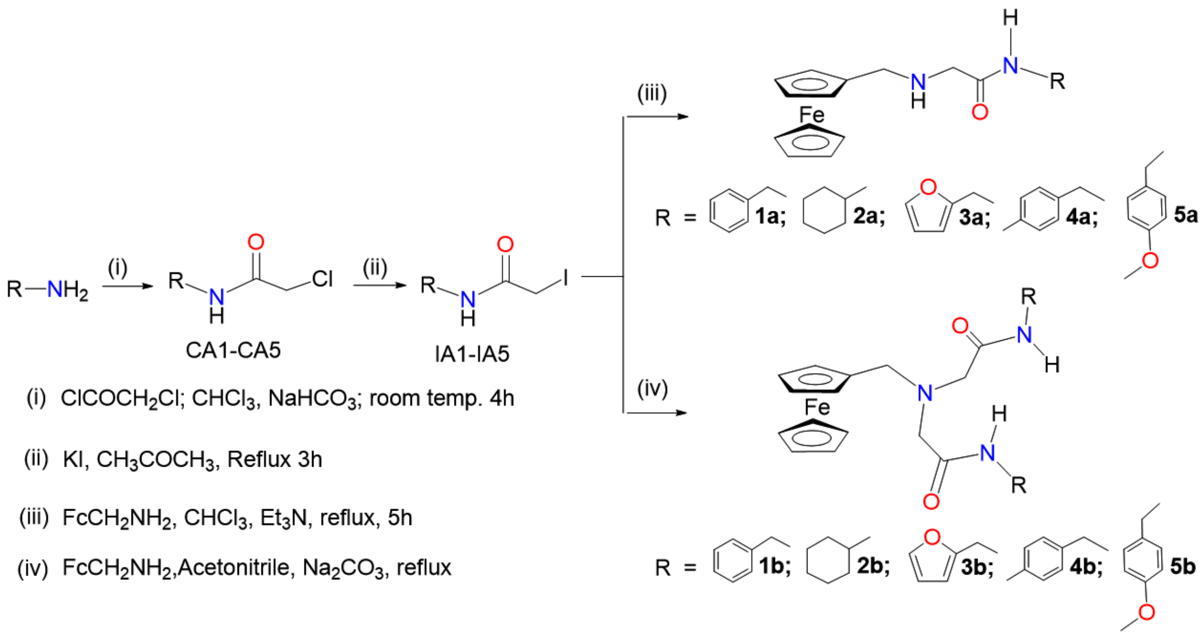
Chapter: 2

Ferrocene Functionalized Achiral Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

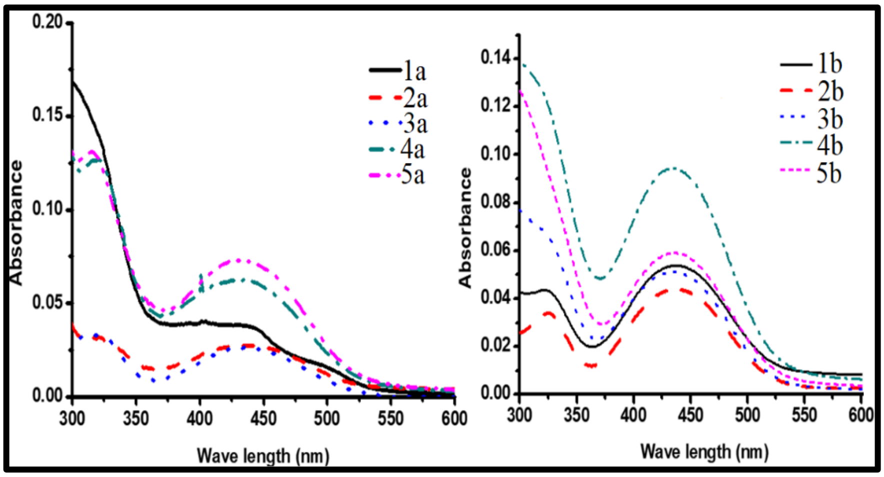
Introduction

Since the discovery of ferrocene there is a substantial growth in the chemistry utilizing the ferrocene typically because of its lipophilic character, ease of chemical modification and accessible one-electron-oxidation potential.[1] In spite of the nontoxic nature of ferrocene, its stability in aqueous and aerobic media and biological inertness, many ferrocenyl derivatives exhibit significant anticancer, antibacterial, antiparasitic, antifungal, and other biological activities. [1-4]The interest in the ferrocene and its new derivatives have been continued due to their many of technological applications. The intriguing redox properties of ferrocenes led to applications in coordination chemistry, inorganic materials, molecular wires, sensors, macrocages, clusters growth, catalysis and in medicinal research.[5-8] The development of new molecules that induce apoptosis and DNA fragmentation is crucial for the discovery and development of novel anticancer agents.[9] Reports suggest that incorporating amino groups into the molecular framework helps in an active transport process via the formation of organic cation transporters and is responsible for the improved biological activity. We anticipate that the combination of the ferrocenyl group with biologically relevant pharmacophore dithiocarbamtes could be a successful method to discover new promising antimicrobial candidates.[10]

Scheme: General synthetic strategies adopted for 2-(ferrocenylmethylamino)-N-alkylacetamide(1a-5a) and 2, 2'-(ferrocenylmethylazanediyl)-bis-(*N*-alkylacetamide) (1b-5b).



UV-visible study:

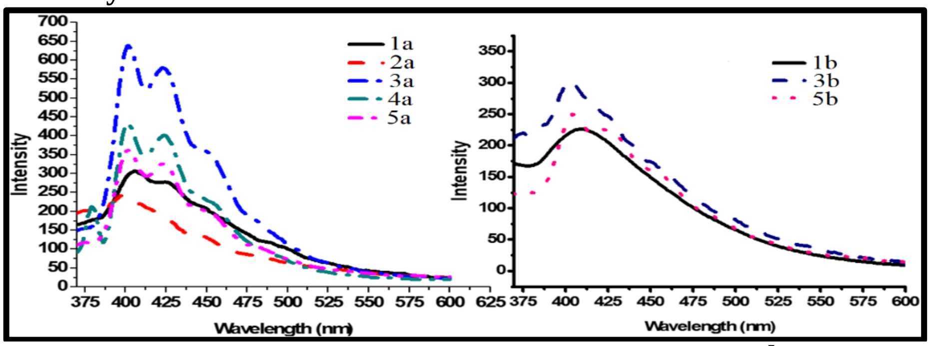


UV-visible absorption spectrum of the compounds under investigation at room temperature in 10-5 M CH3CN

The UV-visible spectral spectrum of all compounds gives a high intensity absorption bands in the region of 300-324 nm which is mainly attributed to the locally excited n→ π* transitions.

A broad, low intensity band observed in the 430-439 nm region attributable to metal (LMCT) charge transfer transitions, a characteristic feature of attached ferrocene moiety

Fluorescence study:



Fluorescence spectrum of compounds under investigation at room temperature in 10^{-5}M CH_3CN solution

The majority of the compound's fluorescence in the visible region of upon excitation in the ultraviolet region with a concomitant Stokes shift of 60-100 nm

Biological activity

	Ligand	IC$_{50}$ values (μM)			
		MCF 7	**IMR 32**	**L132**	**HepG2**
1	1a	41.45±0.22	35.45±0.11	91.80±0.07	13.19±0.17
2	1b	23.63±0.12	52.11±0.11	22.37±0.13	7.25±0.11
3	2a	15.54±0.54	53.20±0.15	43.74±0.08	25.38±0.21
4	2b	10.49±0.37	31.96±0.20	71.68±0.01	14.60±0.08
5	3a	50.42±0.43	30.35±0.07	94.30±0.14	33.84±0.37
6	3b	12.89±0.33	19.14±0.20	93.79±0.12	13.74±0.05
7	4a	29.07±0.09	16.17±0.19	13.77±0.01	24.14±0.22
8	4b	11.49±0.07	10.39±0.30	19.10±0.12	25.25±0.08
9	5a	15.60±0.19	17.55±0.19	18.74±0.24	16.83±0.09
10	5b	2.10±0.41	16.95±0.15	13.56±0.07	8.66±0.21
11	Cisplatin	32.41±1.5	29.6±1.26	21.4±2.2	24.3±1.7

Values are represented as Mean ± SEM.

The cytotoxic potential of these compounds against selected cell lines is presented in Table. he obtained IC_{50} values for herein studied ferrocene containing compounds (except some) are more effective than cisplatin on different human cancer cell line. Bis-amide inhibitors 1b-5b show improved cytotoxicity profile as compared to mono-amide inhibitors 1a-5a

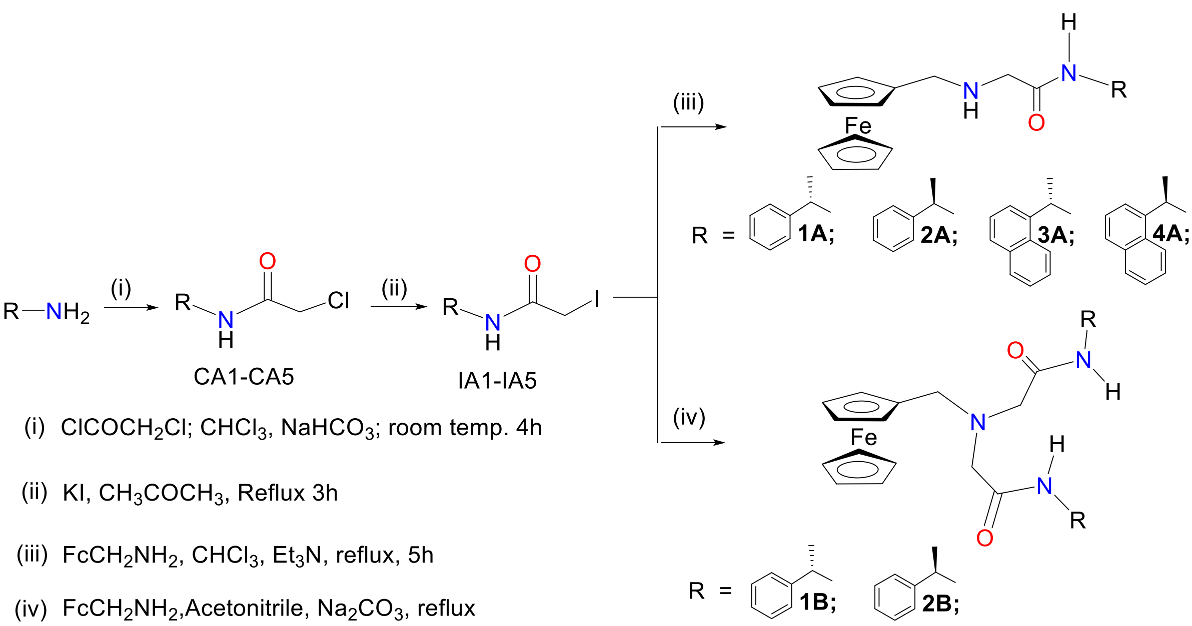
Chapter 3

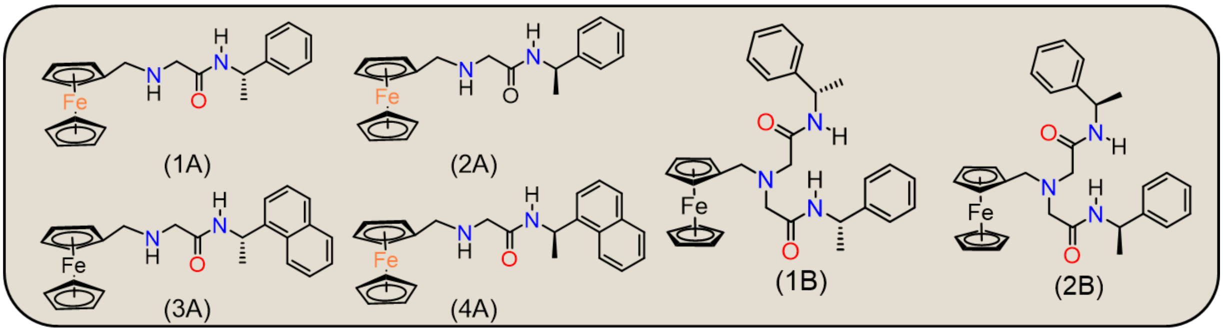
Ferrocene Functionalized Chiral Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Introduction

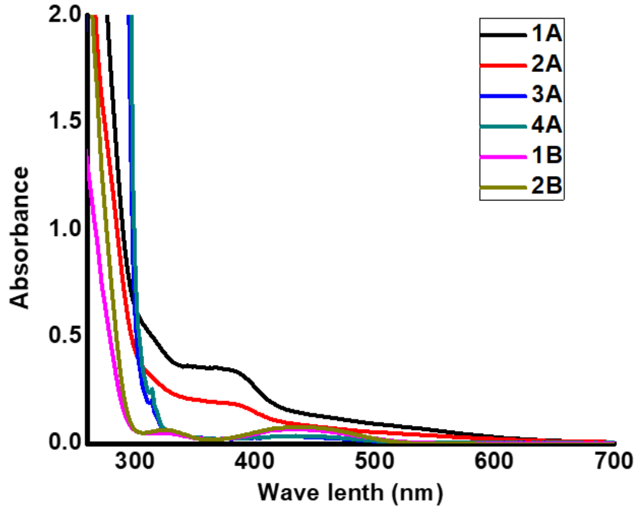
The interest in developing novel organic,[11] inorganic[12] and organometallic[13] compounds as antitumor agents has been continued because cancer has become the second leading cause of death globally and this burden continues to increase day by day. An estimated 9.6 million deaths have been recorded due to cancer in the year 2018.[14] This has created a growing interest to explore chiral metal-based drugs with their unique properties and potential selectivity toward nucleic acids and protein based chiral biomolecules.[15] In this direction, chirality has become an important tool in modern drug development because one of the enantiomers may be beneficial, while other may be harmful and thus their therapeutic activity can differ severely in terms of toxicity and pharmacokinetics[16] ferrocene containing compounds have been emerged as a novel class of anticancer drugs. To attain better medicinal properties, biologically relevant groups have been methodically attached into the cyclo-pentadienyl ring of ferrocene,[17-19] which may offer chirality into the molecule, or chemotherapeutic agents were attached to the ferrocene moiety.[20]

Scheme: Ferrocene Functionalized Chiral Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents.





UV-visible Study

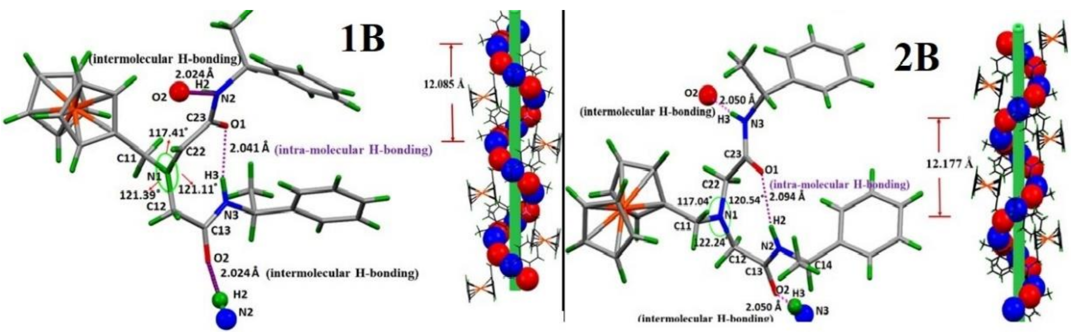


The UV-visible spectrum of all compounds shown in Figure gives three absorption bands in the region of 243-253 nm, 300-400 nm and 400-500 nm, mainly attributed to the locally excited intra-ligand π→ π*, n→ π* and ligand to metal (LMCT) charge transfer transitions.

Cytotoxicity (µM) of ferrocene functionalized enantiomers S,S-(-)-1, R,R-(+)-2

	Ligand	IC$_{50}$ values (µM)[a]			
		MCF 7	IMR 32	L132	HepG2
1	1B	63.91±0.08	101.10±0.12	97.98±0.13	65.96±0.12
2	2B	48.16±0.20	31.91±0.08	11.08±0.20	6.35±0.19
3	Cisplatin[b]	32.41±1.5	29.6±1.26	21.4±2.2	24.3±1.7

Analysis of Crystal Packing



The results showed that optically pure ferrocene functionalized tertiary amine enantiomer 2B forming the right-handed helical motif at supramolecular level, displayed stronger inhibition against all the investigated cell lines MCF 7, IMR 32, HepG2, and immortal L132 cell lines of human origin as compared to enantiomer 1B. The biological characterization of these compounds provides convincing sign to recommend that 2B is more potent than cisplatin and other structural analogues and pointing toward the potential of this compound for further development as anticancer agent with high efficacy against multiple cancer types.

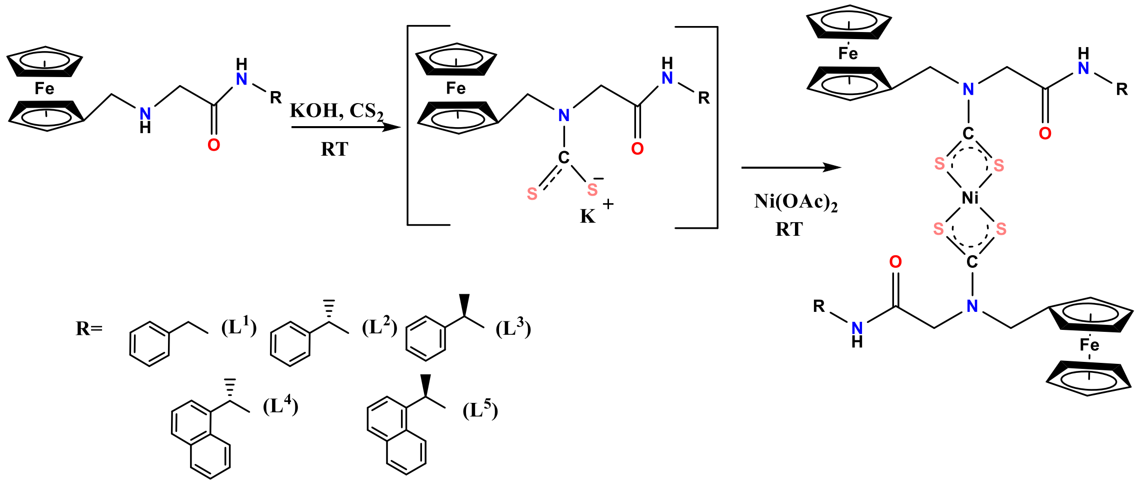
Chapter 4

Use of Ferrocene Functionalized Amines in the Development of Novel Ni^{+2}dithiocarbamates complexes

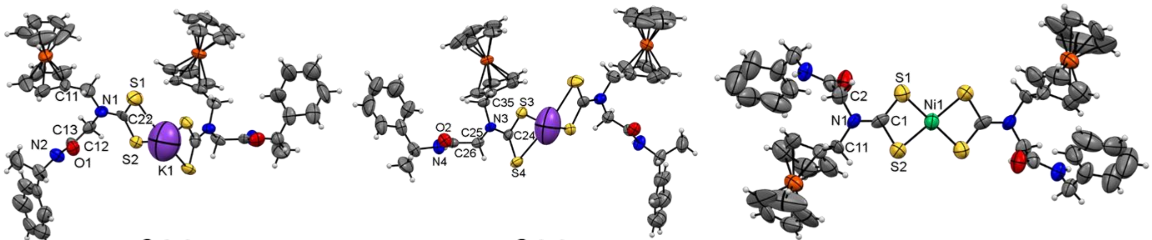
Introduction

Metal dithiocarbamate complexes have myriad applications that range over a variety of fields such as medicine [21-23], vulcanization accelerators [24,25] and catalysis. [26-28] In addition, they are suitable single source precursors for the preparation of corresponding metal sulfides,[29-31] which form semiconductor nanocrystals [32], nanotubes, [33] nanofibers [34] and thinfilms [35,36]. Ni^{2+} complexes, both heteroleptic and homoleptic comprising dithiocarbamate ligands are of interest because of their importance in determination of pollutants [37], sensing humidity, biological [38-40] and catalytic activities. Since intermolecular interactions modify the physical properties of the complexes, for many of the presently known and structurally characterized homoleptic and heteroleptic Ni^{2+} complexes containing dithiocarbamates [41], the important role of secondary bonds in their supramolecular self-organization has been established.
The metal complexes show enhanced biological activities such as antibacterial, antimalarial, and fungicidal activities compared to free ligands due to drop in polarity of metals after complexation. Dithiocarbamate from nickel group that is of Pt^{+2} and Pd^{+2}, as well as of isoelectronic Au^{+3}, showed remarkable antitumor properties.[42]

Scheme: Synthesis of Novel Ferrocene functionalized Ni^{+2}dithiocarbamates complexes



X-ray crystallographic study



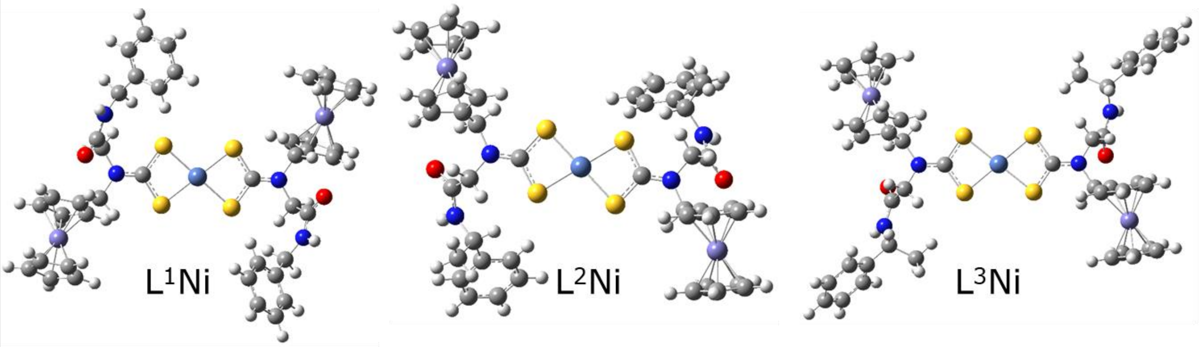
L^2CS_2 K L^3CS_2 K   1

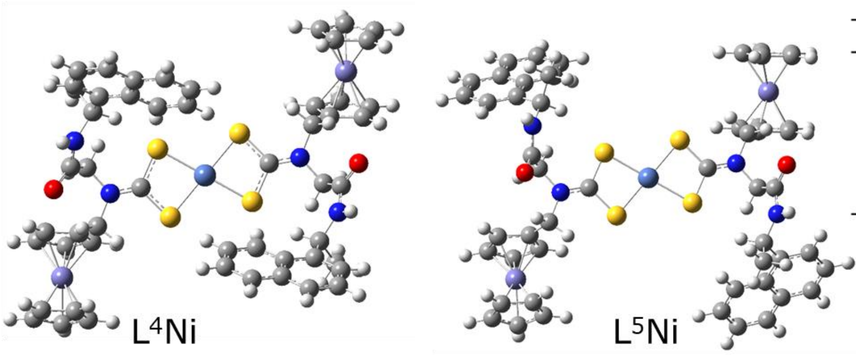
The ORTEP diagram with partial atom numbering showing 50 % probability ellipsoid.

Code	L^2CS_2K	L^3CS_2K	L^1Ni
Empirical formula	$C_{44}H_{46}Fe_2N_4KO_2S_4$	$C_{44}H_{46}Fe_2KN_4O_2S_4$	$C_{21}H_{21}FeN_2Ni_{0.5}OS_2$
Formula weight	971.24	941.89	466.72
Crystal system	Monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1/c$
a/Å	12.1513(13)	12.1704(6)	16.739(6)
b/Å	9.7103(12)	9.7304(6)	12.493(5)
c/Å	19.361(2)	19.2861(11)	9.781(3)
α/°	90	90	90
β/°	103.222(11)	103.206(5)	98.98(3)
γ/°	90	90	90

Crystallographic parameters

Computational investigations





Code	Energy
L^1Ni	-2451.59
L^2Ni	-2530.21
L^3Ni	-2530.21
L^4Ni	-2837.44
L^5Ni	-2837.45

An optimized geometry for the minimum energy conformation of compounds L^1Ni-L^5Ni at B3LYP/LanL2DZ level

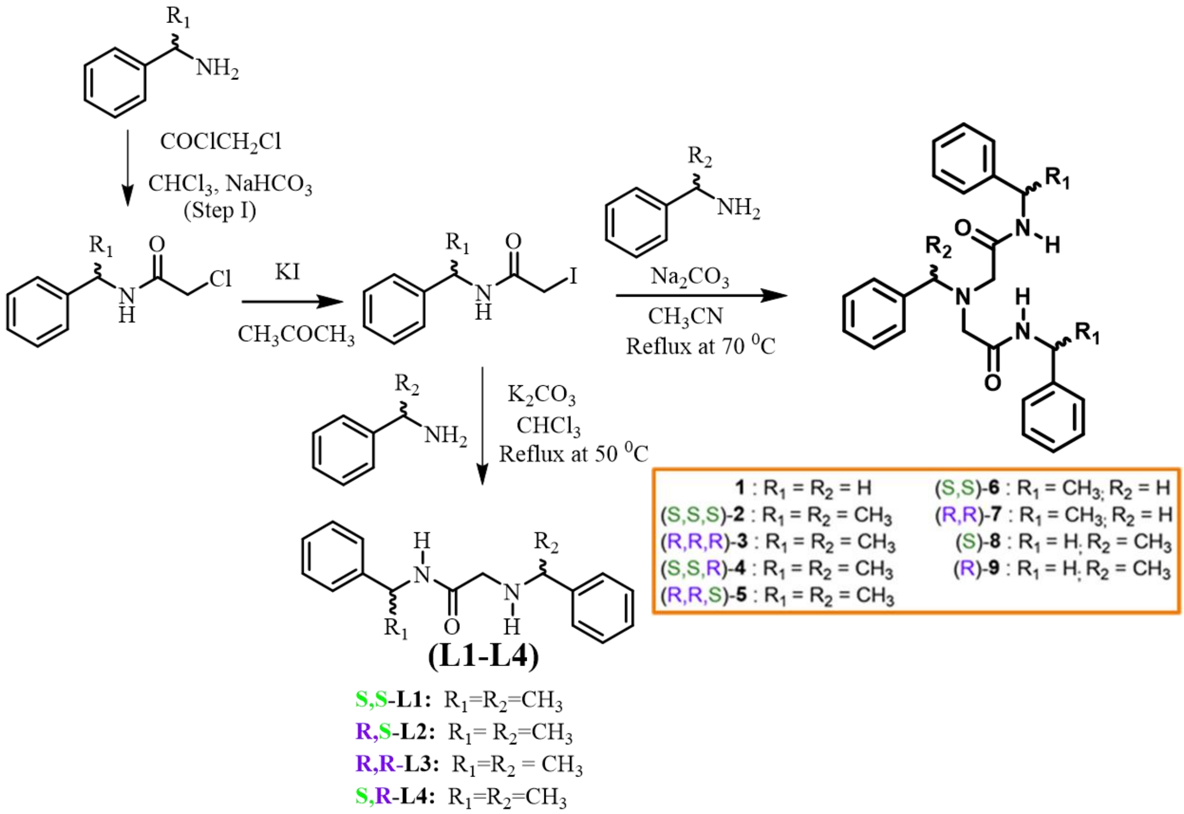
Chapter 5

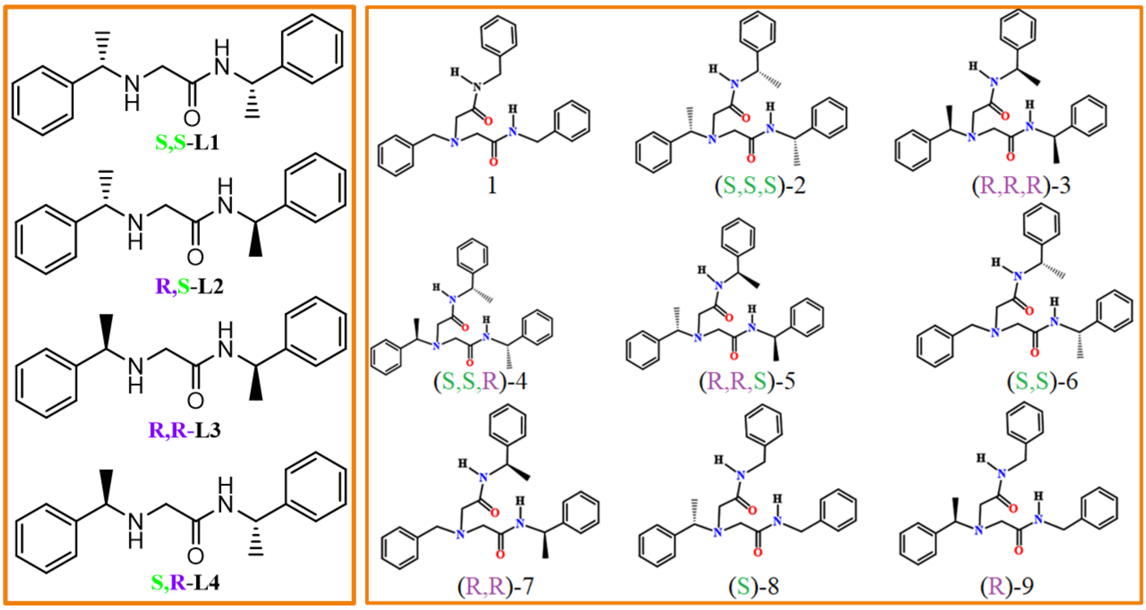
Benzyl Functionalized Chiral 2^0 and 3^0 Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Introduction

Chiral amines play an important role as the building blocks of many life-saving drugs and other industrially important chemicals, such as agrochemicals.[43−46] It has been estimated that ~40% of the currently used pharmaceuticals contain chiral amine functional groups in their structure.[47,48]Therefore, various enzymatic methods have been developed that provide sustainable synthetic alternatives toward a range of chiral amines.[49−51] Chiral amines are importance in various industries, progress in the field of the enzymatic synthesis of functionalized chiral amines, especially using transaminases, has been reviewed in the past few years.[52−56] The current review endeavors to describe advances in the discovery, recent developments and current perspectives in the applications of four important enzymes for the synthesis of chiral amines Secondary amine are also use in synthesis of dithiocarbamate complexes

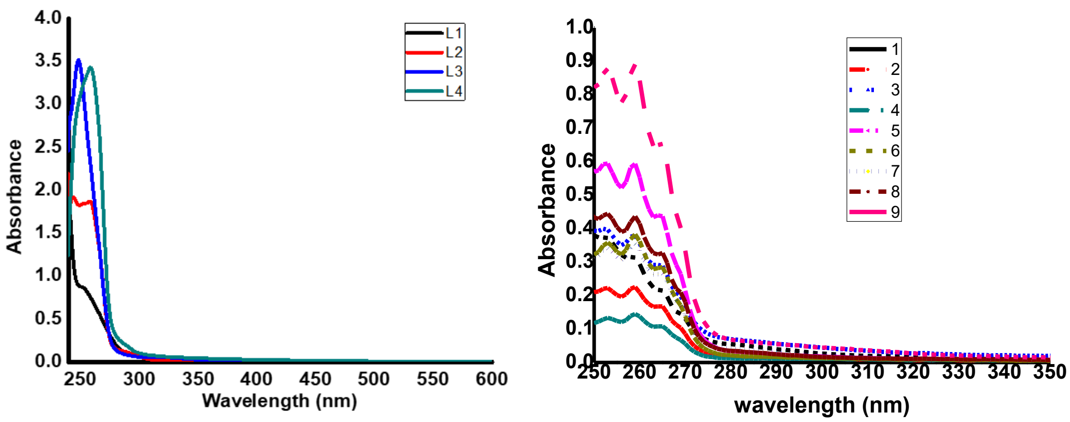
Scheme: General synthetic strategies adopted for chiral amide functionalize 2° amines (L^1-L^4) and 3° amines (1-9).





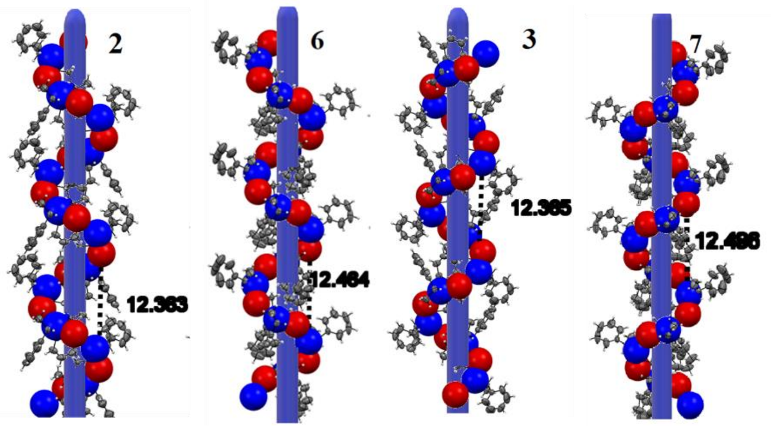
List of compounds which we had synthesized

UV-visible study



UV-visible absorption spectrum of the compounds (1-9) and L1-L4 under investigation at room temperature in 10^{-4} M CH_3CN

X-ray crystallographic study



The presence of chirality at the amidic N-substituent is found to be crucial for formation of diverse helical motifs. For example, The S, S-chirality leads to the formation of M-helix whereas R, R-chirality leads to the formation of P-type of helical arrangement.

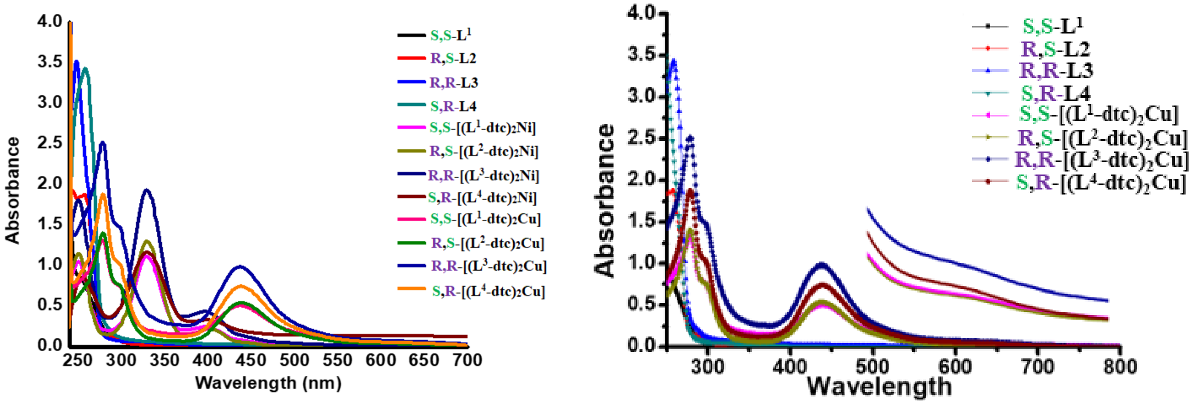
Chapter 6

Use of Benzyl Functionalized Chiral Amines in the Development of Novel Cu^{+2} and Ni^{+2} dithiocarbamates complexes

Introduction

Over the decades, transition metal complexes derived from sulphur rich ligands have received a great deal of attention because of their conducting properties, molecular magnetism, electrochemical, optoelectronic properties and biological applications.Metal dithiocarbamate for instance has received much attention in developing anticancer agents [57-59]. In addition to their stable bonding configuration and various structural arrangement in solid state due to delocalized lone pair of electrons on carbon -nitrogen and carbon-sulphur ($NCSS^-$) backbone of the thioureide moiety[60].Metal dithiocarbamate of various transition elements such as copper, Nickel and zinc, are potential sources for effective anticancer agents [61, 62].They have shown various degrees of DNA binding affinity and potential cytotoxic and antiproliferative activity [63-65].They have been used to platinum drug resistance and toxicity. [66, 67] In view of these potential properties of metal dithiocarbamate and the growing interest to synthesized new chiral dithiocarbamate complexes

UV-visible study



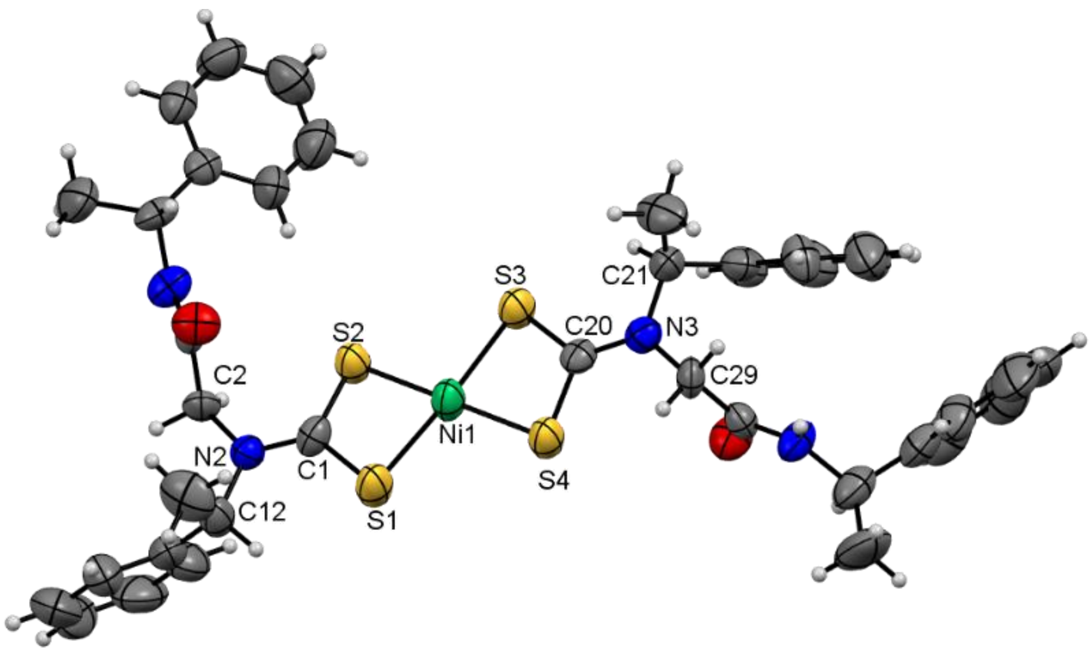
UV-visible absorption spectrum of the L1-L4 and all complexes under investigation at room temperature in 10^{-3} M CH_3CN

Entry	λ_{max} nm (10^{-4}M, ε L Mol^{-1} cm^{-1})	Magnetic Moment µeff (BM)
S,S-L^1	255 (10850) $\pi\rightarrow\pi^*$	-
R,S-L2	259 (18429) $\pi\rightarrow\pi^*$	-
R,R-L3	256 (34421) $\pi\rightarrow\pi^*$	-
S,R-L4	267 (31834) $\pi\rightarrow\pi^*$	-
S,S-[(L^1-dtc)$_2$Ni]	252 (10400) $\pi\rightarrow\pi^*$, 330(11600) $n\rightarrow\pi^*$, 404(1948)chargetransfer	**dia**

R,S-[(L^2-dtc)$_2$Ni]	253 (11217) π→ π*, 329(13018) n→π*,402(2183)charge transfer	**dia**
R,R-[(L^3-dtc)$_2$Ni]	255 (8500) π→ π*, 329(11630) n→π*,400(03290) Charge transfer	**dia**
S,R-[(L^4-dtc)$_2$Ni]	256 (10200) π→ π*, 328(23110) n→π*,395(4332) charge transfer	**dia**
S,S-[(L^1-dtc)$_2$Cu]	278 (13123) π→ π*, 298 (7351) n→ π*, 436(5016) LMCT, 637(1179) d-d transition.	**1.73**
R,S-[(L^2-dtc)$_2$Cu]	278(14004) π→ π*, 297(7646) n→ π*, 437(5216) LMCT, 637(1198) d-d transition.	**1.73**
R,R-[(L^3-dtc)$_2$Cu]	278(15101)π→ π*, 298(7715) n→ π*, 438(5311) LMCT, 638(1234) d-d transition.	**1.73**
S,R-[(L^4-dtc)$_2$Cu]	278(13264)π→ π*, 298(7454) n→ π*, 437(5165) LMCT, 637(1146) d-d transition.	**1.73**

The UV-visible spectral spectrum of all compounds gives a high intensity absorption bands in the region of 250-260 nm which is mainly attributed to the locally excited π → π* transitions.A low intensity absorption bands in the region of 320-340 nm which is mainly attributed to the locally excited n → π* transitions.A broad, very low intensity band observed in the 430-439 nm region attributable to metal (LMCT) charge transfer transitions, and in case of Cu^{+2} complexes a band is observed in the region of 630-640 nm which is mainly attributed d-d transition.

X-ray crystallographic study



The ORTEP diagram of complex 2 with partial atom numbering showing 50 % probability ellipsoid.

Chapter 7

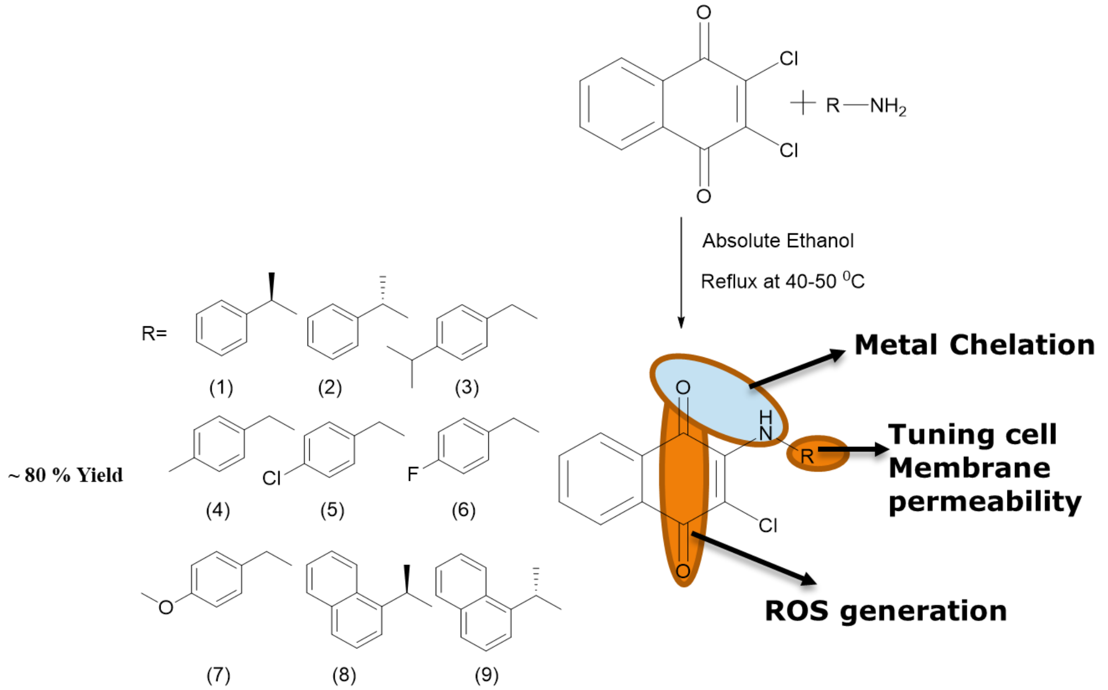
Naphthoquinone Functionalized Chiral and Achiral 2^0 Amines: Synthesis, Characterization, *In-silico* study and Evaluation of as Cytotoxic Agents

Introduction

Natural naphthoquinone derivatives have been widely identified as functional metabolites from various plants, microbes, and marine organisms.Naphthoquinone derivatives have significant pharmacological properties. They are cytotoxic, they have ignificant antibacterial, antifungal, antiviral, insecticidal, anti-inflammatory, and antipyretic properties.[68-72] Plants with naphthoquinone content are widely used in China and the countries of South America, where they are used to treat malignant and parasitic diseases.Apart from this, considerable attention has been paid to the functionalization of naphthoquinone derivatives and evaluation of their biological properties[73] mainly due to their involvement in intermolecular interactions during multiple biological oxidative processes,[74] and thus they have a great impact on the biological systems[75].Important cellular biological and pharmacological properties of natural naphthoquinones are recognized by numerous studies; for instance, the plant and intestinal bacteria sourced vitamin K1 and K2 are the vital factors in the blood clotting response, lacking of which dramatically increases the risk of coagulopathy

A number of naphthoquinone analogues have been designed and evaluated for their pharmacological profile, along with those natural naphthoquinones. On this basis, mechanism research has been conducted to reveal the molecular biological roles of both naturally occurring and synthetic naphthoquinones in exposed cells

Scheme: Synthesis of naphthoquinone containing Secondary amines



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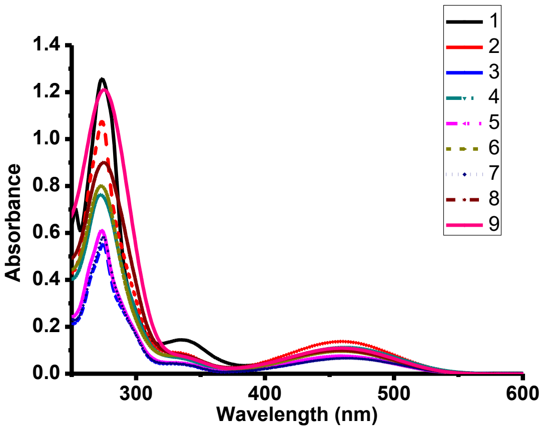
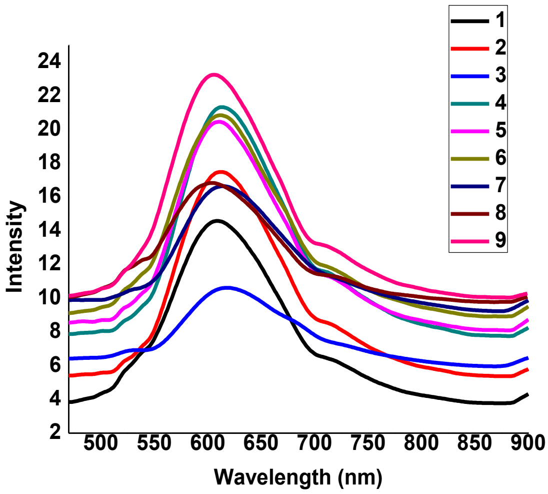
UV-visible and fluorescence study:

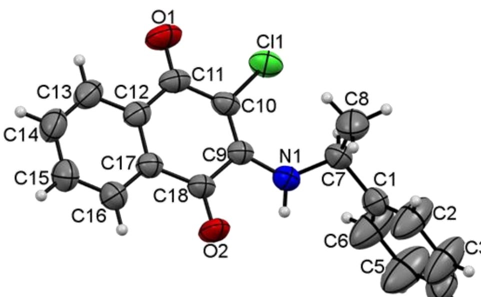




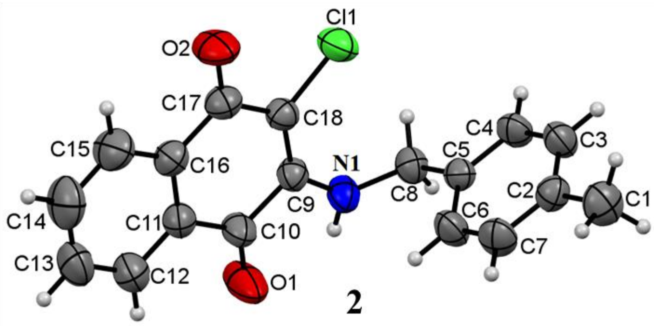
The UV-visible spectral spectrum of all compounds gives a high intensity absorption bands in the region of ~250 nm (Figure) which is mainly attributed to the locally excited π → π* transitions.A broad, low intensity band observed in the ~350 nm region attributable to n → π* and very low intensity band observed in the ~450 nm region attributable to charge transfer transitions, a characteristic feature of attached napthoquinone moiety

The majority of the compounds fluoresces in the visible region of upon excitation in the ultraviolet region with a concomitant Stokes shift of ~150 nm

X-ray crystallographic study



1



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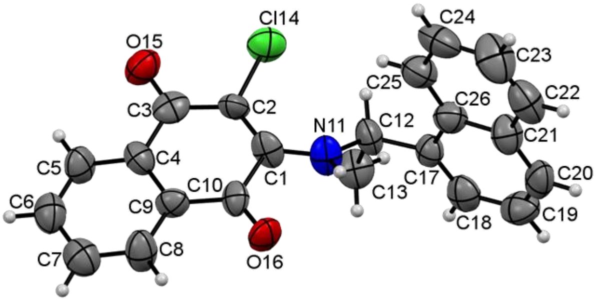
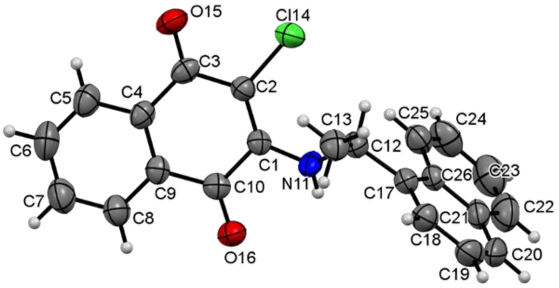


8

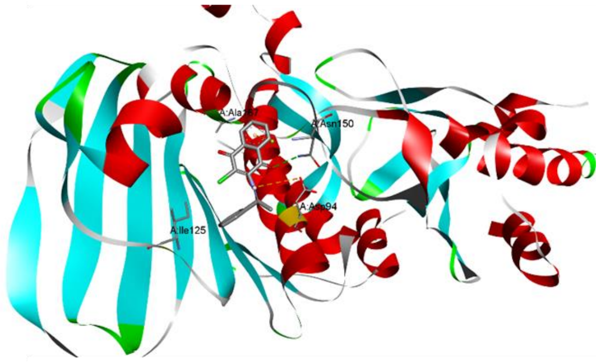


9

The ORTEP diagram of compounds **1,2, 8** and **9** with partial atom numbering showing 50 % probability ellipsoid

Docking study

1



2

Chapter 8

Novel metallomacrocyclic 1,1-dithio complexes of Cu^{+2} Ni^{+2} and Zn^{+2} complexes holding pendent amido groups: Synthesis, characterization and DFT study.

Introduction

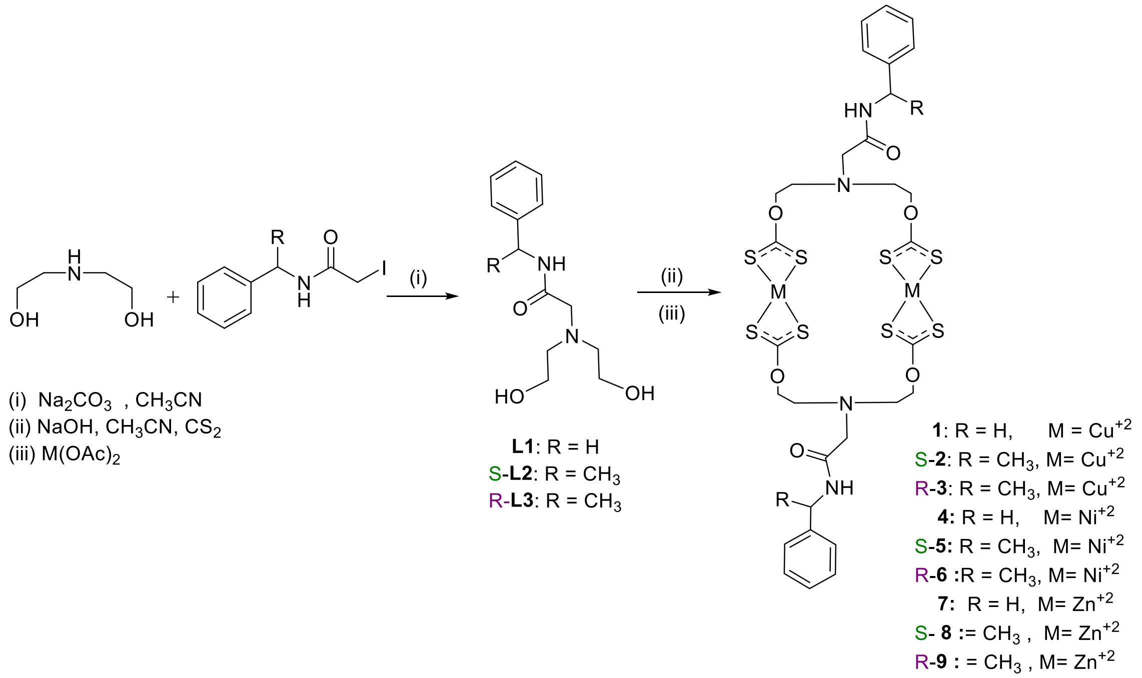
As a result of high degree of potency and selectivity shown by a wide range of natural products bearing macrocyclic motifs[76-78] in medicinal chemistry. synthetic chemists are enthused to discover a broader use of macrocyclic frameworks in therapeutic uses.

In recent times, our lab has examined in vitro cytotoxic activity of a number of 1,1-dithio based metallomacrocyclic complexes and some of these complexes evidently showed remarkable activity against human hepatoma and neuroblastoma cell lines.[79,80]

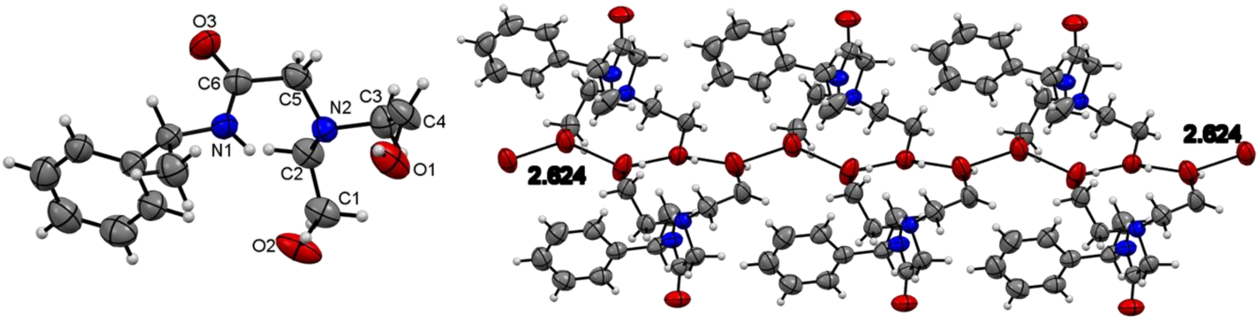
The sulfur atoms in molecule as donor sites reportedly play various role viz. as chemoprotectants in platinum-based chemotherapy, to modulate Cisplatin nephrotoxicity and in transporting the molecule to the targets as well as protect against untimely reaction with biomolecules.[80-83] In spite of appreciated efficacy of macrocyclic compounds and sulphur donor ligands in biological processes (vide supra), the metallomacrocyclic dithiocarbamates complexes are surprisingly far less studied from medicinal perspectives.[84]

Applications of the transition metal macrocyclic complexes (TMMC) can be divided in to several sections such as antibacterial drugs, catalysts, MRI scanning agents, antioxidants, ion transporters, radiopharmaceuticals etc, according to the way they use.

Scheme: Binuclear xanthate Cu Ni and Zn complexes of bearing amide functionalized linkers: Synthesis, characterization and DFT study.

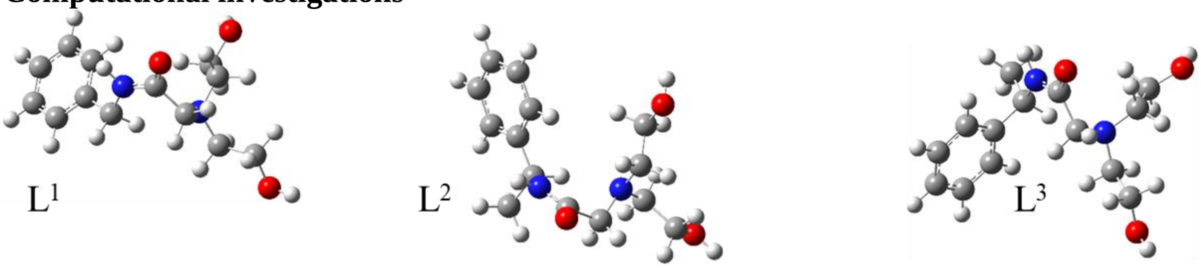


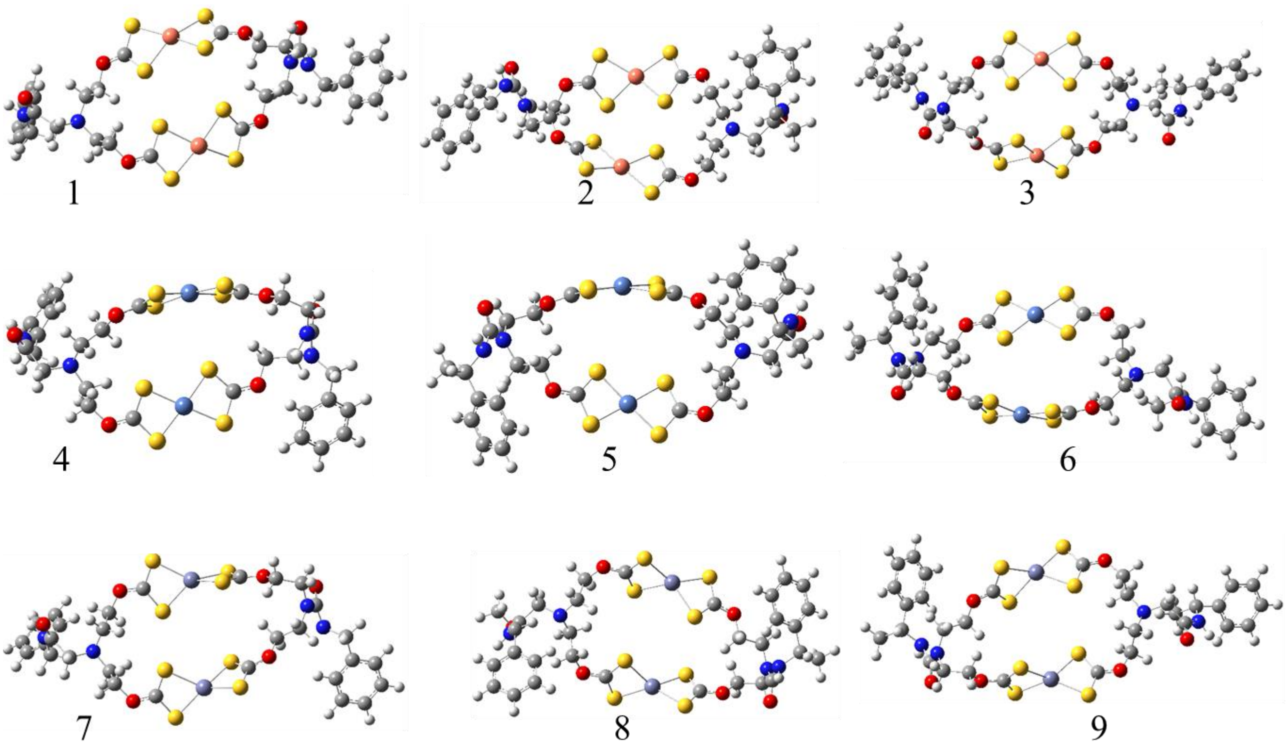
X-ray crystallographic study



The ORTEP diagram of L^3 with partial atom numbering showing 50 % probability ellipsoid. Inter molecular hydrogen bonding involving oxygen atom in L^3 bond length ~2.6 Å.

Computational investigations

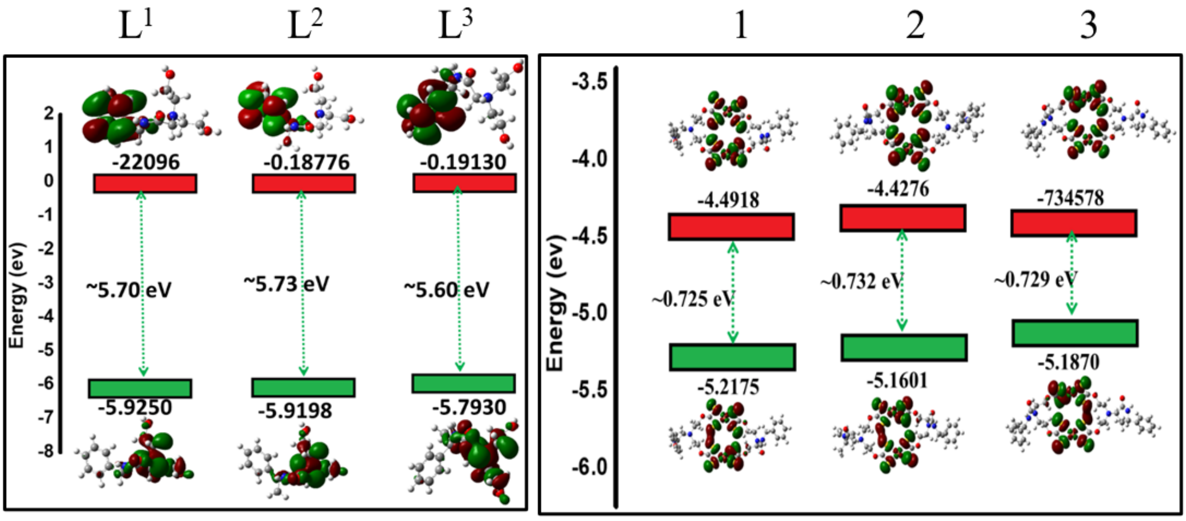


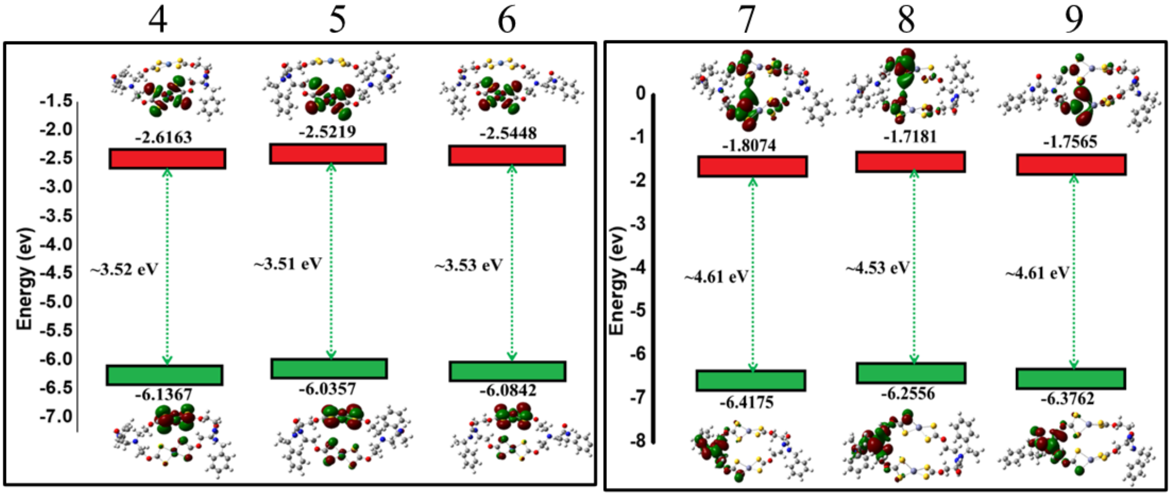


An optimized geometry for the minimum energy conformation of Ligand (L^1-L^3) and complexes 1-9 at B3LYP/LanL2DZ level

We carried out a full geometry optimization of all compounds using DFT with B3LYP/LanL2DZ basic set.Electrical structureal parameters are found to be consistent with X-ray data

Frontier molecular orbital analysis





The calculated energy of the HOMO- LUMO and corresponding energy gaps (ΔE_{H-L}) (Isovalue= 0.02) for L^1–L^3 and complexes 1-9

All the copper(II) complexes 1-3 gives HOMO-LUMO energy gaps in the range of 0.725 eV which suggest their semiconducting nature.

Conclusion:

- We have synthesized a new series of amide functionalized chiral secondary and tertiary amine and complexes of Cu^{+2} Ni^{+2} and Zn^{+2} complexes holding pendent amido groups.
- All these compounds were structurally characterized by FT-IR, ^{1}H, ^{13}C, NMR spectroscopy, UV-visible, fluorescence spectrophotometers, single crystal XRD, circular dichroism spectroscopy analysis.
- To shed more on the experimental outcomes, a DFT calculations have been performed
- Further, chirality in the molecular structure at the atomic level has guided the self-assembly, to give the chirality at supramolecular level, in a similar way as the proteins we observe in living organisms.
- The influence of redox behavior and chirality in the molecules on their cytotoxicity has been established by means of electrochemical and SCXRD investigations.
- MTT assay was carried out on bisamide to explore for their in vitro cytotoxic activity against cancer cell line.

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