

**SUPRAMOLECULAR PROPERTIES OF METAL COMPLEXES
FABRICATED FROM FUNCTIONALIZED NITROGEN-DONOR
LIGANDS: SYNTHESIS, CHARACTERIZATION, THEORETICAL
STUDIES, CATALYTIC PROPERTIES, AND BIOLOGICAL
ACTIVITIES**

By

AFZAL HUSSAIN SHEIKH



Submitted to

NAGALAND UNIVERSITY

In Partial Fulfillment of the Requirements for Award of the Degree

of

DOCTOR OF PHILOSOPHY IN CHEMISTRY

**DEPARTMENT OF CHEMISTRY
NAGALAND UNIVERSITY
LUMAMI-798627
NAGALAND, INDIA**

2025

THESIS

IS

DEDICATED TO

My

LATE FATHER

JABAN ALI SHEIKH

Who always taught me “Honesty is the best Policy”

NAGALAND



UNIVERSITY

(A Central University Estd. By the Act of Parliament No. 35 of 1989)

DEPARTMENT OF CHEMISTRY

Headquarters: LUMAMI, ZUNHEBOTO DISTRICT-798627, NAGALAND, INDIA

DECLARATION

I, **Mr. Afzal Hussain Sheikh**, bearing Registration No. **Ph.D/CHE/00222** with effect from 30/08/2018, hereby declare that the contents of the thesis entitled “**SUPRAMOLECULAR PROPERTIES OF METAL COMPLEXES FABRICATED FROM FUNCTIONALIZED NITROGEN-DONOR LIGANDS: SYNTHESIS, CHARACTERIZATION, THEORETICAL STUDIES, CATALYTIC PROPERTIES, AND BIOLOGICAL ACTIVITIES**” is the result of my research on the subject. I also declare that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other university/institute.

This is being submitted to Nagaland University for the degree of Doctor of Philosophy in Chemistry.

Afzal Hussain Sheikh
Afzal Hussain Sheikh

Upasana
Head
Department of Chemistry
Nagaland University
Head
Department of Chemistry
Nagaland University

Nurul A. Choudhury
Supervisor
Dr. Nurul A. Choudhury
Assistant Professor
Department of Chemistry
Nagaland University
Head Quarters-Lumami

Suman Adhikari
Co-Supervisor
Dr. Suman Adhikari
Associate Professor
Department of Chemistry
Govt. Degree College
Dharmanagar, North Tripura



NAGALAND

UNIVERSITY

(A Central University Estd. By the Act of Parliament No. 35 of 1989)

DEPARTMENT OF CHEMISTRY

Headquarters: LUMAMI, ZUNHEBOTO DISTRICT-798627, NAGALAND, INDIA

CERTIFICATE

This is to certify that **Mr. Afzal Hussain Sheikh** Registered as a Research Scholar for Ph.D. (Science) degree in Chemistry in Nagaland University and has been working under our guidance and supervision. His thesis entitled “**SUPRAMOLECULAR PROPERTIES OF METAL COMPLEXES FABRICATED FROM FUNCTIONALIZED NITROGEN-DONOR LIGANDS: SYNTHESIS, CHARACTERIZATION, THEORETICAL STUDIES, CATALYTIC PROPERTIES, AND BIOLOGICAL ACTIVITIES**” is being forwarded for submission for the Ph.D. (Science) Degree of this university. It is certified that he has fulfilled all the requirements according to the rules of this University regarding investigation embodied in his thesis and the work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other University.


(Nurul Alam Choudhury)

Supervisor

Dr. Nurul A. Choudhury
Assistant Professor
Department of Chemistry
Nagaland University
Head Quarters-Lumami


(Suman Adhikari)

Co-Supervisor

Dr. Suman Adhikari
Associate Professor
Department of Chemistry
Govt. Degree College
Dharmanagar, North Tripura

NAGALAND UNIVERSITY



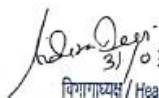
HEAD QUARTERS : LUMAMI

Ph. D COURSE WORK EXAMINATION

This is to certify that Mr/Ms Afzal Hussain Sheikh

of Nagaland University bearing Roll No. 2018-19/Ph.D. Chem/1 is qualified in the Ph.D Course Work Examination

in the Department of Chemistry Nagaland University held in the Year 2018.....


31/07/19
विभागाध्यक्ष / Head
Head of Department
नागालैण्ड विश्वविद्यालय / Nagaland University


Dean
Dean
School of ~~Sciences~~ School of Sciences
Nagaland University
Lumami Nagaland

ACKNOWLEDGEMENTS

I express my deep sense of gratitude to **Dr. Nurul Alam Choudhury, Department of Chemistry, Nagaland University, Nagaland**, my supervisor, for giving me the opportunity to conduct my research work under his supervision. He has always been supportive and approachable. He helped me discover my potential and encouraged me to develop my research skills.

I express my profound gratitude to **Dr. Suman Adhikari, Department of Chemistry, Govt. Degree College, Dharmanagar, Tripura**, my co-supervisor, for his immense love, guidance, availability and support throughout the research investigation and preparation of the thesis. His profound knowledge, constant encouragement and valuable input helped me succeed in all stages of my research and achieve greater heights in my life.

I extend my sincere gratitude to all the teaching faculties of the **Chemistry Department, Nagaland University: Prof. Upasana Bora Sinha (HOD), Prof. M. Indira Devi, Prof. Dipak Sinha, Prof. Ambrish Singh, Dr. Tavishe Phucho, Dr. M. Prabhakar, and Dr. Seram Dushila Devi**, for their extended help and encouragement throughout my research period.

I want to acknowledge **Dr. Surajit Chakraborty, Department of Chemistry, Iswar Chandra Vidyasagar College, Belonia, Tripura**, for his cooperation and encouragement from the beginning of my Ph.D. work.

My heartfelt gratitude goes to **Dr. Mehnaz Mazumdar** for her motivation during my Ph.D. work. My heartfelt thankfulness also goes to **Dr. Folguni Laskar Adhikari, Department of Botany, Govt. Degree College, Dharmanagar, Tripura**, for her motivation during my Ph.D. work.

I am also grateful to **Dr. Ghodrat Mahmoudi**, Department of Chemistry, Faculty of Science, University of Maragheh, Maragheh, Iran, **Dr. Akalesh Kumar Verma**, Department of Zoology, Cell & Biochemical Technology Laboratory, Cotton University, Guwahati-781001, India, **Prof. Stefan Bernhard**, Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213, USA, and **Dr. Nabajyoti Baidya**, Department of Chemistry, Milki High School, Milki, Malda-732209, India, for their valuable supports during my research period.

My sincere gratitude to **Nagaland University, Nagaland**, for providing the basic facilities to conduct my research work. I also extend my sincere gratitude to **Govt. Degree College, Dharmanagar, Tripura**, for providing the basic facilities to conduct my research work.

My gratitude and thanks to the non-teaching staff, **Mr. S. Bendangtemsu, Ms. Sunepjungla, Ms. Temsuienla Amer, Mr. Vekhuroh, and Ms. Lovi, Department of Chemistry, Nagaland University, Nagaland**, for their kind help and assistance throughout my research period. I also express my thanks to the non-teaching staff, **Mr. Benu Suklabadhya, Department of Chemistry, Govt. Degree College Dharmanagar, Tripura**, for his kind help and assistance throughout my research period.

I owe my deepest gratitude to my Lab mates, **Mr. Duangailung Kamei, Mr. Dipankar Hazarika, Ms. Marjo A Kichu, Mr. Nuphizo Shijoh, and Ms. Rizwana Begum Choudhury** for their continual love and support. I also owe my deepest gratitude to my Lab mate **Mr. Sourav Nath** for his continual love and support.

Special thanks to Research Scholars from other laboratories and departments for their wonderful friendship and encouragement. I am especially thankful to **Ms. Nungshisangla Jamir, Ms. Tsathrongla Sangtam, Mr. Shisak Sharma, and Ms. Betokali K. Zhimomi** for their valuable help in spectroscopic characterizations of my samples during research work.

My heartfelt thankfulness goes to **Dr. Atiqur Rahman Laskar, Mr. Nizam Uddin Laskar, Dr. Dipak Dutta, Dr. Golam Mohiuddin, and Mr. Sumit Bhattacharjee** for their continual love and support.

On a personal note, I take this opportunity to express my profound regards to my beloved Mother **Minara Khanam Sheikh** and love to my brothers who have shared the joys and sorrows during my Ph.D. period and other family members who gave me the courage and continuous inspiration to stride into the realm of higher studies.

Last but not least, I humbly convey all praises and honour to my **Late Father, Jaban Ali Sheikh**, for showering me with his unfailing love, blessings and abundant grace.

Afzal Hussain Sheikh.
Afzal Hussain Sheikh

ABBREVIATIONS AND TERMINOLOGIES

DNA = deoxyribonucleic acid

2D = two dimensional

3D = three dimensional

EDTA = ethylene diamine tetraacetic acid

MOMs = metal-organic materials

MOFs = metal-organic frameworks

SCCs = supramolecular coordination complexes

PCPs = porous coordination polymers

c = concentration

CDCl_3 = deuterated chloroform

HS = Hirshfeld surface

$\text{K}_2i\text{-mnt}$ = 1, 1-dicyano-2, 2-ethylenedithiolate di-potassium salt

DFT = density functional theory

DMF = dimethyl formamide

DMSO = dimethyl sulphoxide

tetraen = tris-(2-aminoethyl) amine

MPPA = magnesium monoperoxyphthalic acid

salen = bis-(salicylidene) ethylenediamine

MeOH = methanol

EtOH = ethanol

Et_3N = triethyl amine

H^+ = weak acid

Me = methyl

Et = ethyl

CSD= Cambridge Structural Database

MCF-7 = human breast cancer cell line named after Michigan Cancer Foundation

UV = ultraviolet

FT-IR = Fourier Transform Infrared

UV-Vis = Ultraviolet-visible

^1H NMR = proton nuclear magnetic resonance

ESI-MS= Electrospray ionisation mass spectrometry, analyses a sample by creating ions from it and separating them by mass-to-charge ratio

MS = mass spectrum

HPLC = High-performance liquid chromatography

ν = Stretching frequency

m/z = mass to charge ratio

M^+ = molecular ion

δ = chemical shift

s = singlet

m = multiplet

MHz = megahertz

Min = minute (s)

mmol = millimole (s)

mL = milliliter (s)

FP = Finger print

qPCR = quantitative polymerase chain reaction

MTT = 3-(4, 5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide method

V_H = Hirshfeld volumes

A_H =Hirshfeld surface areas

G = globularity

Ω = asphericity

2D FP = two dimensional finger print

IC₅₀ =Half-maximal inhibitory concentration, is a measure of how much of a compound or drug is needed to inhibit a biological process by 50%

HUH7 = hepatocellular carcinoma cell line

A549 = non-small lung carcinoma cell line

HCT116 = colon carcinoma cells line

Ploxal-S = a brand name for the drug oxaliplatin

PCR = Polymerase Chain Reaction used to amplify DNA

p21 = a protein that regulates cell cycle, apoptosis and transcription after DNA damage

p53 = a protein that prevents cancer formation by binding to DNA and regulating gene expression

mRNA = messenger ribonucleic acid

qPCR = quantitative Polymerase Chain Reaction

mp = melting point

μM = micromolar

PET = photo-induced electron transfer

Ph = phenyl

rt = room temperature

S = Shape index

C = Curvedness

d_i = Distance between the Hirshfeld surface point and the closest interior atom

d_e = Distance between the Hirshfeld surface point and the closest exterior atom

vd_w = van der Waals radii of atoms

RPMI = Roswell Park Memorial Institute

RPMI 1640 = a medium used for cell and tissue culture

FBS = fetal bovine serum, a blood derived supplement used in cell culture to support cell growth.

PBS = Phosphate buffer saline, a isotonic solution used to prevent the rupture of cells due to osmosis during cell culture

rRNA = ribosomal ribonucleic acid

18S rRNA = a part of ribosomal ribonucleic acid where S of 18S denoted the Svedberg units

$\Delta\Delta\text{CT}$ = a convenient way to analyze the relative changes in gene expression during PCR experiment

96-well plate = a typical microplate of 8×12 well used to perform different phytochemical tests.

SYBR Green mix = a double-stranded DNA binding dye that detects any double-stranded DNA generated during PCR experiment

cDNA = complementary DNA

NIH = National institute of health

AMR = Antimicrobial resistance

COVID-19 = “Coronavirus disease 2019” is the official name given by the World Health Organization (WHO) to the disease caused by SARS-CoV-2 virus

in vitro = a process performed or taking place in a test tube, culture dish or elsewhere outside a living organism

in vivo = a process performed or taking place in a living organism

CO-ADD = Community for Open Antimicrobial Drug Discovery

ESKAPE = An acronym consisting of the Scientific names of six highly virulent and antibiotic resistant bacteria including *Enterococcus faecium*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Enterobacter* spp and *Pseudomonas aeruginosa*

PDT = photodynamic treatment

ROS = reactive oxygen species

FDA = U.S. Food and Drug Administration

UTIs = urinary tract infections

en = ethylene diamine

DACH = 1, 2-dimethylcyclohexane

in silico = In biology or in other experimental sciences, an *in silico* experiment is one, performed on computer or via computer simulation software

DL = Dalton's lymphoma

PBMC = peripheral blood mononuclear cell

r.m.s deviation = root mean square deviation

S.D = Standard deviation

D = Debye

TNF = Tumor necrosis factor

TNFR-2 = Tumor necrosis factor receptor-2

2TNF = Resolution structure of mouse tumor necrosis factor

LD₅₀ = Lethal dose that causes death of half of the particular cancer cells

TD-DFT = time-dependent density functional theory

AutoDock = molecular modeling simulation software

TON = turnover number

HER = hydrogen evolution reaction

PS = photosensitisers

SED = sacrificial electron donors

dmgH₂ = Dimethyl glyoxime

SMMs = single-molecule magnets

χ_m = molar magnetic susceptibility

$\chi_{||}$ = parallel component of the magnetic susceptibility

$\chi_{\perp}$ = perpendicular component of the magnetic susceptibility

T = Temperature

S = spin-state (total spin quantum number)

M = molar magnetization

μ_B = Bohr magneton

D = axial zero-field splitting parameter

Z = number of closest neighbours surrounding a certain magnetic species in the crystal system

g = average Landé factor

J = interaction parameter between two closest neighbour magnetic species (exchange coupling constant) which determines whether the interaction is ferromagnetic ($J > 0$) or antiferromagnetic ($J < 0$)

H = External magnetic field

$\hat{H}$ = Hamiltonian operator

$\hat{S}$ = spin operator

$\hat{S}_z$ = z-component of spin operator

$\hat{S}_1$ and $\hat{S}_2$ = spin operators of two interacting spins (magnetic species)

N = number of magnetic species

B = Bohr magneton

k = Boltzmann constant

SHE = standard hydrogen electrode

CV = cyclic voltammogram

WRC = water reduction catalyst

HOMO = highest occupied molecular orbital

LUMO = lowest unoccupied molecular orbital

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

XRD = X-ray Diffraction

$RdRp$ = RNA-Dependent RNA polymerase protein

$ACE2$ = Angiotensin-converting enzyme 2

K_i = Inhibition constant

TABLE OF CONTENTS

CONTENTS	PAGE NO.
CHAPTER 1: Introduction	1-26
1.1 Introduction	2
1.2 Division of supramolecular chemistry	5
1.3 Types of supramolecular interactions	6
1.3.1 Ionic and dipolar interactions	6
1.3.2 Hydrogen bonding	7
1.3.3 π –interaction	8
1.3.4 CH- π interactions	9
1.3.5 van der Waals interactions	9
1.3.6 Hydrophobic interactions	10
1.4 Host-guest assembly	12
1.4.1 Complementarity	12
1.4.2 Co-operativity	13
1.4.3 Preorganization	14
1.5 Metal-based supramolecular architectures	14
1.6 Supramolecular areas of coordination chemistry	15
1.7 Techniques for development of supramolecular coordination complexes	16
1.8 Supramolecular chirality	17
1.9 Importance of supramolecular chemistry	17
1.10 Aim and scope of work	18
1.11 References	20-26
 CHAPTER 2: Design and synthesis of an unsymmetrical Schiff base ligand <i>N</i>-2-(6 methylpyridyl)-2-hydroxy-1-naphthaldimine and its metal complexes	 27-30
2.1 Importance of Schiff base and its metal complexes	28

CHAPTER 2A: Synthesis, Crystal structures, Theoretical studies, and Anticancer properties of an unsymmetrical Schiff base ligand	
<i>N</i>-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex	31-80
2A.1 Anticancer properties of metal complexes	32
2A.2 Present work	34
2A.2.1 Reaction schemes for the synthesis of the unsymmetrical pyridyl Schiff base ligand <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 and its Ni(II) complex Bis[<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) 2	35
2A.2.2 FT-IR and NMR spectral characterization of 1 and 2	35
2A.2.3 Description of structures of 1 and 2	39
2A.2.4 DFT Simulations of 1 and 2	53
2A.2.5 Hirshfeld surface analysis of 1 and 2	54
2A.2.6 Anticancer activities of 1 and 2	62
2A.3 Experimental	68-72
2A.3.1 Synthesis of pyridyl Schiff base ligand 1 and its Ni (II) metal complex 2	69
2A.3.2 Crystallographic data collection and refinement of 1 and 2	70
2A.3.3 Hirshfeld Surface Analysis of 1 and 2	70
2A.3.4 Cells and cell culture of 1 and 2	71
2A.3.5 Cytotoxicity assay of 1 and 2	71
2A.3.6 Apoptosis assay of 1 and 2	71
2A.3.7 Quantitative polymerase chain reaction (qPCR) of 1 and 2	72
2A.3.8 Colony forming assay of 1 and 2	72
2A.4 References	73-80
CHAPTER 2B: Synthesis, Characterization, Antimicrobial activities of Co(III) and Cd(II) complexes derived from an unsymmetrical pyridyl Schiff base ligand	
<i>N</i>-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine	81-108
2B.1 Antimicrobial properties of metal-based complexes	82
2B.2 Present work	86
2B.2.1 Reaction schemes for the synthesis of Co(III) complex 3 and Cd(II) complex	

4 derived from an unsymmetrical pyridyl Schiff base ligand <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1	86
2B.2.2 Synthesis, FT-IR, NMR, and ESI-MS spectral characterization of 3 and 4	87
2B.2.3 Thermogravimetric Analysis of 3 and 4	92
2B.2.4 Description of structures of 3 and 4	94
2B.2.5 Anti-bacterial activity of 3 and 4	95
2B.3 Experimental	100-102
2B.3.1 Synthesis of pyridyl Schiff base ligand 1 and its Co(III) complex 3 and Cd(II) complex 4	100
2B.3.2 Bacterial culture and antibacterial assays of 3 and 4	101
2B.4 References	103-108

CHAPTER 3: Antiproliferative Evaluation and Supramolecular Properties of a Pd(II) complex Harvested from Benzil bis(pyridyl hydrazone) Ligand: Combined Experimental and Theoretical Studies **109-158**

3.1 Anticancer properties Pd- based complexes	110
3.2 Most important factors affecting their anticancer activity of Pd- based complexes	112
3.3 Importance of Benzil bis (pyridyl hydrazones)	113
3.4 Present work	114
3.4.1 Reaction schemes for the synthesis of benzil bis(pyridyl hydrazone) ligand (H ₂ L) 5 and its Pd(II) complex 6	115
3.4.2 FT-IR and NMR spectral characterization of 5 and 6	116
3.4.3 UV-Visible absorption spectra of 5 and 6	120
3.4.4 Description of structure of 6	120
3.4.5 Theoretical Study of 6	131
3.4.6 Hirshfeld Surface Analysis of 6	132
3.4.7 Cytotoxicity and apoptosis assays of 5 and 6	135
3.4.8 Survivability study	138
3.4.9 Molecular docking of 6	140
3.5 Experimental	142-145
3.5.1 Synthesis of benzil bis(pyridyl hydrazone) ligand (H ₂ L) 5 and its Pd(II) complex 6	142
3.5.2 X-ray Crystal Structure Determination of 6	143

3.5.3 Cytotoxicity and apoptosis assays of 5 and 6	143
3.5.4 Survivability study	144
3.5.5 Theoretical methodology of 6	145
3.6 References	146-158

CHAPTER 4: Supramolecular Co(II) Complexes Based on Dithiolate and Dicarboxylate Ligands: Crystal structures, Theoretical studies, Magnetic Properties, and Catalytic Activity Studies in Photocatalytic

Hydrogen Evolution 159-208

4.1 Photocatalytic evolution of hydrogen with cobalt-based complexes	160
4.2 Magnetic properties of cobalt-based complexes	163
4.3 Importance of dithiolate and dicarboxylate-based ligands in coordination compounds	164

4.4 Present work 165

4.4.1 Reaction schemes for the synthesis of the Co(II) complexes 8 and 9 from 1, 1-dicyano-2,2-ethylenedithiolate (<i>i-mnt</i> ²⁻) 7 and pyridine-2,6-dicarboxylic acid ligands respectively	166
4.4.2 FT-IR spectral characterization of 7 and Co(II) complexes 8 and 9	167
4.4.3 Crystal structure description of complex 8	169
4.4.4 Crystal structure description of complex 9	173
4.4.5 Hirshfeld surface analysis of 8 and 9	178
4.4.6 Magnetic Susceptibility Measurements of 8 and 9	182
4.4.7 DFT Study of 8 and 9	190
4.4.8 Electrochemical analysis of 8 and 9	191
4.4.9 Photocatalytic Hydrogen Evolution of 8 and 9	193

4.5. Experimental 196-198

4.5.1 Synthesis of the metal complex 8	196
4.5.2 Crystallographic data collection and refinement of 8 and 9	197
4.5.3 Hirshfeld surface analysis of 8 and 9	198
4.5.4 Theoretical Studies of 8 and 9	198
4.5.5 Magnetic Susceptibility Measurements of 8 and 9	198

4.5.6 Photocatalytic Hydrogen Evolution of 8 and 9	198
4.6 References	199-208

CHAPTER 5: Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound	209-225
5.1 Biological importance of Benzimidazoles	210
5.2 Present work	211
5.2.1 Synthesis of 2, 6-Bis (2-benzimidazolyl) pyridine 10	211
5.2.2 FT-IR and NMR spectral characterization of 2, 6-Bis (2-benzimidazolyl) pyridine 10	211
5.2.3 Description of the crystal structure of 10	212
5.2.4 Hirshfeld Surface Analysis of 10	216
5.2.5 DFT optimization of 10	218
5.2.6 Molecular docking studies of 10	219
5.3. Experimental	
5.3.1 Synthesis of 2, 6-Bis (2-benzimidazolyl) pyridine 10	222
5.3.2 Crystallographic data collection and refinement of 10	222
5.4. References	223-225

LIST OF FIGURES

CHAPTER 1

Fig.1.1 Comparison between the scope of molecular and supramolecular chemistry according to Lehn.	3
Fig.1.2 The development of a supramolecular system from molecular building blocks: (a) host guest complexation: (b) lattice inclusion; (c) self assembly between complementary molecules.	6
Fig.1.3 Examples of electrostatic interactions: (a) ion- ion interaction in tetra butyl ammonium chloride; (b) ion-dipole interaction in the sodium complex of [15]crown-5; (c) dipole-dipole interaction in acetone.	7
Fig.1.4 (a) A carbonyl accepting a hydrogen bond from a secondary amine donor; (b) the standard way of expressing donor and acceptor atoms (D, donor atom; A, acceptor atom).	8
Fig.1.5 (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base-pairs in DNA and (b) A schematic representation.	8
Fig.1.6 Example of cation- π interactions.	9
Fig.1.7 Two types of π - interactions: (a) face-to-face; (b) edge-to-face.	9
Fig.1.8 van der Waals interaction between two argon atoms.	10
Fig.1.9 Hydrophobic interactions: (a) Displacement of water molecules from hydrophobic cavity due to enthalpic hydrophobic interaction; (b) two organic molecules creating a hole within an aqueous phase, giving rise to hydrophobic effects.	11
Fig.1.10 (a) Rigid lock and key and (b) induced fit models of enzyme–substrate binding.	13
Fig.1.11 Different types of metal bonded assemblies (examples): Coordination polymers or networks formed by divergent (left) and discrete supramolecular complexes formed by convergent combination of nodes and organic linkers (right).	17

CHAPTER 2

CHAPTER 2A	32-67
Fig. 2A.1 Clinically approved platinum-based anticancer drugs.	32
Fig. 2A.2 FT-IR spectrum of pyridyl Schiff base ligand 1 .	36

Fig. 2A.3 FT-IR spectrum of Ni(II) complex 2 .	37
Fig. 2A.4 ^1H NMR Spectrum of pyridyl Schiff base ligand 1 in CDCl_3 .	37
Fig. 2A.5 ^1H NMR Spectrum of Ni(II) complex 2 in CDCl_3 .	38
Fig. 2A.6 Mass spectrum of pyridyl Schiff base ligand 1 .	38
Fig. 2A.7 Mass spectrum of Ni(II) complex 2 .	39
Fig. 2A. 8 Molecular structure of pyridyl Schiff base ligand <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 .	40
Fig. 2A.9 Partial view of 3D stacked dimeric columns along <i>ac</i> plane (left) and dimer formation by $\text{N1-H1N}\cdots\text{O1}$ and $\text{C13-H13A}\cdots\text{O1}^i$ hydrogen bonds (right) [Symmetry code (i) $-x+1, -y, -z+1$].	41
Fig. 2A.10 $\text{C-H}\cdots\text{O}$ and $\text{N-H}\cdots\text{O}$ type hydrogen bonds creating ring geometries of graph-set-motifs $\text{S}(6)$ and $\text{R}_4^2(12)$ in <i>N</i> -2-(6-methylpyridyl) -2-hydroxy-1-naphthaldimine 1 . Symmetry code: (i) $-x+1, -y, -z+1$.	41
Fig. 2A.11 Crystal structure of 2 with atom labelling scheme at 50% probability ellipsoids (left) and distorted octahedron around Ni^{+2} (right). Symmetry code: (i) $-x+1/2, y, -z+1$.	50
Fig. 2A.12 Partial view of $\text{C-H}\cdots\text{O}$ type hydrogen bonds in 2 . [Symmetry codes: (i) $-x+1/2, y, -z+1$; (ii) $-x, -y+1, -z+1$; (iii) $x-1/2, -y+1, z$].	50
Fig. 2A.13 View of weak $\text{C-H}\cdots\pi$ interactions between C10-H10 and naphthyl moiety in 2 .	51
Fig. 2A.14 View of weak $\pi\text{-}\pi$ interactions in 2 .	51
Fig. 2A.15 $\text{C-H}\cdots\text{O}$ hydrogen bonds creating rings and infinite chain geometries of graph-set-motifs $2\text{R}_2^1(7)$, $\text{R}_2^1(10)$ and $\text{C}(5)$ in bis[<i>N</i> -2-(6-methylpyridyl) -2-oxo-1-naphthaldimnato- $\text{k}^3\text{N}^{\wedge}\text{N}^{\wedge}\text{O}$] nickel(II) 2 . Symmetry codes: (i) $-x+1/2, y, -z+1$; (ii) $x-1/2, -y+1, z$.	52
Fig. 2A.16 Projection of stacked chain type 3D supramolecular architecture in 2 along <i>bc</i> plane (left). Crystal packing arrangement as 3D right handed helix (right).	52
Fig. 2A.17 Geometry-optimized structure of the pyridyl Schiff base ligand 1 in two possible canonical forms together with the energy difference (ΔE) of 2.4 kJ mol^{-1} indicated. The geometry-optimized version of the solid-state structure (ketone form) is the lowest energy conformation.	54
Fig. 2A.18 Geometry-optimized structures of square planar and octahedral forms of the Ni(II) complex 2 together with their respective ΔE (kJ mol^{-1}). The geometry	

-optimized square planar conformation is the lowest energy reference for the ΔE calculation.	54
Fig. 2A.19 View of Hirshfeld surfaces mapped over d_{norm} (left), shape index (middle) and curvedness (right) for 1 and 2 .	56
Fig. 2A.20 View of HS showing two deep circular red depressions in <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 due to strong $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ contacts.	57
Fig. 2A.21 View of HS (space fill presentation) showing three $\text{O1}\cdots\text{H10}$, $\text{O1}\cdots\text{H1}$ and $\text{O1}\cdots\text{H13}$ contacts in bis[<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $\kappa^3\text{N}^{\wedge}\text{N}^{\wedge}\text{O}$] nickel(II) 2 .	57
Fig. 2A.22 View of Hirshfeld surfaces mapped on d_{norm} (left), SI (middle) and C (right) showing $\text{C}-\text{H}\cdots\pi$ (top) and $\pi-\pi$ interactions (bottom) in 2 .	58
Fig. 2A.23 View of HS (Shape index) in <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 showing $\text{C}-\text{H}\cdots\pi$ type interaction between C8–H8A donor and c.g acceptor as concave (-0.6596) red patches (around C7) and convex (0.6528) deep blue region (around H8A).	58
Fig. 2A .24 2D fingerprint plots for 1 (top) and 2 (bottom).	60
Fig. 2A.25 2D Pie bar diagram illustrating the relative distribution (% scale) of non-covalent interactions from HS analysis of 1 (left) and 2 (right).	60
Fig. 2A.26 View of atomic HS study (top) at Ni^{+2} -center mapped on d_{norm} (left), SI (middle), C (right) and corresponding 2D FP plots (bottom) showing $\text{Ni}\cdots\text{N}$, $\text{Ni}\cdots\text{O}$, $\text{Ni}\cdots\text{H}$ interactions.	61
Fig. 2A.27 View of Hirshfeld surface (atomic level) in bis[<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $\kappa^3\text{N}^{\wedge}\text{N}^{\wedge}\text{O}$] nickel(II) 2 showing $\text{Ni}\cdots\text{H}$ interactions.	61
Fig. 2A.28 Partial view of atomic Hirshfeld surface (d_{norm}) showing asymmetric units of 2 linked by weak $\text{Ni}\cdots\text{H}$ interactions (non-bonded H-atoms omitted for clarity).	62
Fig. 2A.29 Cytotoxic effects of 1 (blue) and 2 (red) on the HUH7, HCT116, A549 cancer cells and Beas-2B normal lung cells. Cell viability assay was performed via a MTT protocol at concentrations of 0, 0.3, 1, 3, 10, 30, 100 and 300 μM for 24 h. Graphs show the best curve fit of non-linear regression analysis. Calculated IC_{50} values are given in Table.	64

Fig. 2A.30 Colony formation assay, performed in the HUH7 and HCT116 cells exposed to 1 and 2 , and DMSO as a control, at two different concentrations. Cells were allowed to grow for two weeks before staining with methylene blue solution.	65
Fig. 2A.31 Apoptotic cell rates in the HUH7, HCT116 and A549 cells treated with 1 , 2 and equal amount of DMSO with 1 and 2 as a control. Apoptosis ratio was measured by flow cytometry. The upper (late) and lower (early) right quadrants show the apoptotic cells of the population.	66
Fig. 2A.32 HCT116 and A549 cells incubated with 1 and 2 for 4 h, and qPCR, performed after mRNA isolation to evaluate expression levels of apoptosis and cell cycle related genes p21 and p53. Fold differences of mRNA levels of the compound-treated samples were normalized to DMSO-treated samples.	67

CHAPTER 2B

Fig. 2B.1 Metal compounds (a) and (b) under clinical trial and (c) clinically approved antimicrobials.	84
Fig. 2B.2 FT-IR spectrum of Co(III) complex 3 .	89
Fig. 2B.3 Comparison of FT-IR spectra of the pyridyl Schiff base ligand 1 and Co (III) complex 3 .	89
Fig. 2B.4 FT-IR spectrum of Cd(II) complex 4 .	90
Fig. 2B.5 Comparison of FT-IR spectra of the pyridyl Schiff base ligand 1 and Cd (II) complex 4 .	90
Fig. 2B.6 ¹ H NMR Spectrum of Co(III) complex 3 in CDCl ₃ .	91
Fig. 2B.7 ¹ H NMR Spectrum of Cd(II) complex 4 in CDCl ₃ .	91
Fig. 2B.8 Mass spectrum of Co(III) complex 3 .	92
Fig. 2B.9 Mass spectrum of Cd(II) complex 4 .	92
Fig. 2B.10 Thermogravimetric analysis curve of Co(III) complex 3 .	93
Fig. 2B.11 Thermogravimetric analysis curve of Cd(II) complex 4 .	93
Fig. 2B.12. Crystal structure of pyridyl Schiff base ligand 1 with Ni(II) ions.	94
Fig. 2B.13. Probable structure of pyridyl Schiff base ligand 1 with Co(III) and Cd(II) ions.	95
Fig. 2B.14 Agar well diffusion assay with varying doses of pyridyl Schiff base ligand 1 shown in <i>Escherichia coli</i> . (Fig. 14a), <i>Salmonella typhi</i> (Fig. 14b), <i>Shigella sonnei</i> (Fig. 14c). The zones of inhibition are depicted for varying concentrations of Schiff base ligand 1 (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria.	

(1) Denotes treatment with 1 μM of Schiff base ligand **1**; (2) Denotes treatment with 10 μM of Schiff base ligand **1**; (3) Denotes treatment with 100 μM of Schiff base ligand **1**; (4) Denotes treatment with 500 μM of Schiff base ligand **1**; (5) Denotes the treatment with positive control (Gentamicin).

97

Fig. 2B.15 Disc well diffusion assay with varying doses of pyridyl Schiff base ligand **1** shown in *Escherichia coli*. (**Fig 15a**), *Salmonella typhi* (**Fig 15b**), *Shigella sonnei* (**Fig 15c**). The zones of inhibition are depicted for varying concentrations of pyridyl Schiff base ligand **1** (1 μM , 10 μM , 100 μM , 500 μM) in various strains of bacteria.

(1) Denotes treatment with 1 μM of pyridyl Schiff base ligand **1**; (2) Denotes treatment with 10 μM of pyridyl Schiff base ligand **1**; (3) Denotes treatment with 100 μM of pyridyl Schiff base ligand **1**; (4) Denotes treatment with 500 μM of pyridyl Schiff base ligand **1**; (5) Denotes the treatment with positive control (Gentamicin).

97

Fig. 2B.16 Agar well diffusion assay with varying doses of Co(III) complex **3** shown in *Escherichia coli*. (Fig. 16a), *Salmonella typhi* (Fig. 16b), *Shigella sonnei* (Fig. 16c). The zones of inhibition are depicted for varying concentrations of Co(III) complex **3** (1 μM , 10 μM , 100 μM , 500 μM). (1) Denotes treatment with 1 μM of Co(III) complex **3**; (2) Denotes treatment with 10 μM of Co(III) complex **3**; (3) Denotes treatment with 100 μM of Co(II) complex **3**; (4) Denotes treatment with 500 μM of Co(II) complex **3**; (5) Denotes the treatment with positive control (Gentamicin).

98

Fig. 2B.17. Disc well diffusion assay with varying doses of Co(III) complex **3** shown in *Escherichia coli*. (**Fig. 17a**), *Salmonella typhi* (**Fig. 17b**), *Shigella sonnei* (**Fig. 17c**). The zones of inhibition are depicted for varying concentrations of Co(III) complex **2** (1 μM , 10 μM , 100 μM , 500 μM).

(1) Denotes treatment with 1 μM of Co(III) complex **3**; (2) Denotes treatment with 10 μM of Co(III) complex **3**; (3) Denotes treatment with 100 μM of Co(III) complex **3**; (4) Denotes treatment with 500 μM of Co(II) complex **3**; (5) Denotes the treatment with positive control (Gentamicin).

98

Fig. 2B.18 Agar well diffusion assay with varying doses of Cd(II) complex **4** shown in *Escherichia coli*. (**Fig. 18a**), *Salmonella typhi* (**Fig. 18b**), *Shigella sonnei* (**Fig. 18c**). The zones of inhibition are depicted for varying concentrations of Cd(II) complex **4** (1 μM , 10 μM , 100 μM , 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Cd(II) complex **4**; (2) Denotes treatment with 10 μM of Cd(II) complex **4**; (3) Denotes treatment with 100 μM of Cd(II) complex **4**; (4) Denotes

treatment with 500 μM of Cd(II) complex **4** (5); Denotes the treatment with positive control (Gentamicin). 99

Fig. 2B.19 Disc well diffusion assay with varying doses of Cd(II) complex **4** shown in *Escherichia coli*. (**Fig. 19a**), *Salmonella typhi* (**Fig. 19b**), *Shigella sonnei* (**Fig. 19c**). The zones of inhibition are depicted for varying concentrations of Cd(II) complex **4** (1 μM , 10 μM , 100 μM , 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Cd(II) complex **4**; (2) Denotes treatment with 10 μM of Cd(II) complex **4**; (3) Denotes treatment with 100 μM of Cd(II) complex **4**; (4) Denotes treatment with 500 μM of Cd(II) complex **4**; (5) Denotes the treatment with positive control (Gentamicin). 99

CHAPTER 3

Fig. 3.1 FT-IR spectrum of benzil bis(pyridyl hydrazone) ligand **5**. 117

Fig. 3.2 FT-IR spectrum of Pd(II) complex **6**. 118

Fig. 3.3 ^1H NMR Spectrum of benzil bis(pyridyl hydrazone) ligand **5** in CDCl_3 . 118

Fig. 3.4 ^1H NMR Spectrum of Pd(II) complex **6**. 119

Fig. 3.5 ^{13}C NMR Spectrum of Pd(II) complex **6**. 119

Fig. 3.6 UV-Visible spectra of the benzil bis(pyridyl hydrazone) ligand ($c = 2.06 \times 10^{-5} \text{ M}$) **5** and its Pd(II) complex **6** ($c = 2.06 \times 10^{-5} \text{ M}$) in CHCl_3 . 120

Fig. 3.7 Molecular aggregation in the crystal structure of the Pd(II) complex **6**. 122

Fig. 3.8 Molecular structure of Pd(II) complex **6**. Only ipso carbons of the PPh_3 ligand are shown for clarity. Ellipsoids are drawn at 50% probability. 122

Fig. 3.9 (a) Optimized geometry of Pd-complex **6**, (b) Reduced density gradient of Pd-complex, (c) HOMO to LUMO electronic transition for Pd-complex with respective band gap, and (d) theoretical UV-Vis. spectrum of Pd-complex in CHCl_3 . 132

Fig. 3.10 Hirshfeld surface analysis: (a) surface mapped on d -norm N-H interactions shown in red, H-H interactions shown in green, and Pd-C, Pd-H interactions shown in magenta; (b) Intermolecular interactions in the d -norm Hirshfeld surface including; (c) surface mapped on curvedness; and (d) surface mapped on shape index. 134

Fig. 3.11 2D fingerprint plots of the main intermolecular interactions and contacts in the crystal structure of the Pd(II) complex **6**. 135

Fig. 3.12 Upper panel show cell cytotoxicity using trypan blue assay. Blue-stained cells reflect dead cells and non-stained cells reflect live cells. The morphological

properties of viable (green) and apoptotic (red) cells were studied using fluorescence microscopy. 137

Fig. 3.13 Percentage cell cytotoxicity (left) induced by benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** in DL cells after exposure with various test concentrations. Cisplatin was used as a positive (reference drug) control. Data are mean $\pm$ S.D., n=3). Percentage of apoptotic cells (right) in the DL cell line after treatment with benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6**. The data represent the mean standard deviation, n=3. 137

Fig. 3.14 The dosage response curves of benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** shown in order to determine the IC₅₀ values in DL and PBMC cell lines. 138

Fig. 3.15 Graphs showing the survival pattern of tumor-bearing mice after treatment with the most potent dose of benzil bis(pyridyl hydrazone) ligand and corresponding Pd(II) complex **6** (20mg/kg body weight) and standard reference drug, cisplatin (2mg/kg body weight). Results are mean of 5 independent experimental data sets. 139

Fig. 3.16 Graphs showing changes in the body weight and tumor volume of the mice treated with cisplatin (2mg/kg body weight), benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** (20mg/kg body weight). Results are mean $\pm$ S.D., n=5. 140

Fig. 3.17 (a) Docked structure between 2tnf and Pd(II) complex **6**, (b) hydrophobic (red) and hydrophilic (blue) interaction between 2TNF and Pd(II) complex **6**. 141

CHAPTER 4 167-195

Fig. 4.1 FT-IR spectrum of *K₂i-mnt.H₂O* **7**. 167

Fig. 4.2 FT-IR spectrum of **8**. 168

Fig. 4.3 FT-IR spectrum of **9**. 168

Fig. 4.4 The content of the asymmetric unit of **8**. Thermal displacement ellipsoids are shown at their 50% probability levels. 170

Fig. 4.5 A view of crystal packing of **8** along *a*-axis direction. (Co1: Purple, Co2: Yellow, Co3: Blue, and Co4: Green). 170

Fig. 4.6 A partial view of crystal packing of **8** showing hydrogen bonds. (Co1: Purple, Co2: Yellow, Co3: Blue, and Co4: Green). 171

Fig. 4.7 Molecular structure of complex **9** with the displacement ellipsoids drawn at 50% probability level. 175

Fig. 4.8 A partial view of the crystal packing for complex 9 . The dashed lines denote the intermolecular O–H···O hydrogen bonds parallel to <i>bc</i> plane.	175
Fig. 4.9 Hirshfeld surfaces and fingerprints of 8 mapped with d_{norm} .	179
Fig. 4.10 Intermolecular interactions and their percentages for molecules A, B, C and D in 8 .	180
Fig. 4.11 Hirshfeld surfaces of 9 , mapped with d_{norm} , d_i , d_e , and shape index.	181
Fig. 4.12 Hirshfeld surface analyses of 9 , mapped with d_{norm} showing O–H···O hydrogen-bonded contacts.	181
Fig. 4.13 Intermolecular interactions and their percentage contributions for 9 .	182
Fig. 4.14 Temperature dependence of experimental $\chi_m T$ ($\circ$) (χ_m per Co ^{II} unit) for 8 and $\chi_m T$ ($\square$) (χ_m per Co ₂ unit) for 9 . The solid lines are the calculated curves obtained from equations (2-5) for 9 and equations (6-7) for 9 .	187
Fig. 4.15 Field dependences of the magnetization (M per Co ^{II} ion) for 8 . The solid line is the Brillouin function curve for the system of one uncoupled spin with $S = 3/2$ and $g = 2.0$ in the absence of zero-field splitting.	187
Fig. 4.16 Field dependence of the magnetization (M per Co ₂ unit) for 9 . The solid line is the Brillouin function curve for the system of two unpaired spins with $S = 3/2$ and $g = 2.0$ in the absence of zero-field splitting.	188
Fig. 4.17 Thermogravimetric analysis curve of complex 8 .	188
Fig. 4.18 Thermogravimetric analysis curve of complex 9 .	189
Fig. 4.19 Powder XRD pattern of complex 8 .	189
Fig. 4.20 Powder XRD pattern of complex 9 .	190
Fig. 4.21 (A) Optimized geometry of 8 , (B) Molecular Electrostatic Potential of A, (C) HOMO to LUMO transition for A, (D) Optimized geometry of complex 9 , (E) Molecular Electrostatic Potential of B, and (F) HOMO to LUMO transition for D.	191
Fig. 4.22 Cyclic voltammograms recorded in dry DMSO for both the compounds corrected by the introduction of an internal standard.	192
Fig. 4.23 Cyclic voltammograms recorded in dry ACN for both the compounds corrected by the introduction of an internal standard. Experimental conditions are the same as those described in the body of the manuscript.	193
Fig. 4.24 TON per Co atom for the production of hydrogen in photocatalytic water reduction presented for various PS and WRC concentration combinations.	194
Fig. 4.25 TON per Co atom for the production of hydrogen in photocatalytic water reduction presented for three cobalt complexes, CoCl ₂ , controls, and an internal	

standard at varying PS and WRC concentrations. 194

Fig. 4.26 Images of reaction solutions for the production of hydrogen in photocatalytic water reduction are presented for three cobalt complexes, CoCl₂, controls, and an internal standard with no irradiation and after 30 minutes of irradiation. 195

CHAPTER 5

Fig. 5.1 Molecular structure of 2, 6-Bis (2-benzimidazolyl) pyridine compound **10**. 210

Fig. 5.2 FT-IR spectrum of the compound 2, 6-Bis (2-benzimidazolyl) pyridine **10**. 211

Fig. 5.3 ¹H NMR Spectrum of 2, 6-Bis (2-benzimidazolyl) pyridine **10** in DMSO-*d*₆. 212

Fig. 5.4 The solid-state structure and the atom-numbering scheme of compound **10**. 213

Fig. 5.5 Arrangement in the packing demonstrates the involvement of the inter and intramolecular interactions in hydrogen bonding along the [110] axis of compound **10**. 215

Fig. 5.6 The Hirshfeld surface plots mapped across *d*_{norm}, shape-index, and curvedness maps The Hirshfeld surface plots mapped across *d*_{norm}, shape-index, and curvedness maps drawn over compound **10**. 217

Fig. 5.7 2D Fingerprint plots of the compound **10**. 218

Fig. 5.8 (a) Optimized geometry of 2, 6-Bis (2-benzimidazolyl) pyridine **10**,
(b) Electrostatic potential surface of 2, 6-Bis (2-benzimidazolyl) pyridine **10**,
(c) HOMO to LUMO electronic transition for 2, 6-Bis (2-benzimidazolyl) pyridine **10**, and (d) Chemical parameters for 2, 6-Bis (2-benzimidazolyl) pyridine **10**. 219

LIST OF TABLES

CHAPTER 1

Table 1.1 Summary of different types of noncovalent interactions.	11
--	----

CHAPTER 2A

Table 2A.1 Summary of intermolecular interactions in 1 and 2 .	43
Table 2A.2 Crystal data and structure refinement for 1 and 2 .	44
Table 2A.3 Bond lengths (Å) of <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 and bis [<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) 2 .	45
Table 2A.4 Bond angles ($^{\circ}$) of <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 and bis [<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) 2 .	46
Table 2A.5 Torsion angles ($^{\circ}$) of <i>N</i> -2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine 1 and bis [<i>N</i> -2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) 2 .	48
Table 2A.6 Quantitative data from HS of 1 and 2 .	62

CHAPTER 2B

Contains no tables.

CHAPTER 3

Table 3.1 Short intermolecular contacts of the Pd(II) complex 6 (Å, $^{\circ}$).	123
Table 3.2 Crystal data and structure refinement for Pd(II) complex 6 .	123
Table 3.3 Bond lengths [Å] and angles [$^{\circ}$] for Pd(II) complex 6 .	124
Table 3.4 Torsion angles [$^{\circ}$] for for Pd(II) complex 6 .	128
Table 3.5 Percentage contributions of intermolecular contacts on the Hirshfeld surface calculated for the Pd(II) complex 6 .	135
Table 3.6 IC ₅₀ value of ligand and its Pd (II) complex 6 in DL and PBMC cell lines.	138

CHAPTER 4

Table 4.1 Hydrogen bond geometry for 8 .	171
Table 4.2 Some selected geometric parameters for 8 .	172
Table 4.3 Hydrogen bond geometry for 9 .	176
Table 4.4 Some selected geometric parameters for 9 .	176

Table 4.5 Experimental details for crystal structures of 8 and 9 .	177
---	-----

CHAPTER 5

Table 5.1 Refinement parameters and crystallographic information for the 2, 6-Bis (2-benzimidazolyl) pyridine 10 .	213
Table 5.2 Selected bond lengths (Å) and angles (°) for 2, 6-Bis (2-benzimidazolyl) pyridine 10 .	214
Table 5.3 Hydrogen-bond geometries (Å, °) for 2, 6-Bis (2-benzimidazolyl) pyridine 10 .	216
Table 5.4 Docking score with docking cavity of 10 .	220



A general introduction to Supramolecular Chemistry

Outline

This chapter describes the introductory part of supramolecular chemistry. Supramolecular chemistry is one of the most popular and fastest growing areas of chemistry. This interdisciplinary area of research deals with different intermolecular forces to assemble chemical structures and thus offers a new and subtle approach to the synthesis of supramolecules with potential applications in various domains. This introductory chapter thus highlights some general aspects of supramolecular chemistry utilizing examples from the literature. This survey is by no means comprehensive, for which there are existing review articles.

Chapter 1

1.1 Introduction

Supramolecular chemistry is one of the recent branches of chemistry which deals with the physical, chemical, and biological characteristics of chemical entities that are governed *via* noncovalent interactions. It is an interdisciplinary branch of study that explains the properties of chemical species at higher levels of complexity on physical, biological, and chemical aspects [1]. This comparatively new field has developed quickly into a well-defined and well-thought-out research area. Another well-known term used for supramolecular chemistry is “Chemistry beyond the molecule” where a chemical entity called supramolecule is formed by noncovalent interactions between two or more covalent species [2]. This field emerged in 1967 after Nobel Laureate Charles J. Pedersen accidentally synthesized dibenzo[18]crown-6 as a byproduct [3, 4], though early examples of supramolecules had come into focus at the start of today’s chemistry. Supramolecular chemistry can be alternatively referred to as “lego chemistry”, where “lego brick” is a molecular building unit that is joined to create a supramolecular aggregate by reversible intermolecular interactions [5]. This intermolecular contact consists of electrostatic interactions, dispersion interaction, hydrophobic effects, hydrogen bonds, halogen bonds, C-H... π , π ... π stacking, lone pair... π , cation... π , anion... π interactions, host-guest interactions, charge-transfer interactions, hydrophilic interactions, dipole-dipole interactions, etc. Hence, supramolecular chemistry is broadly termed as the study of a system consisting of species, which may be either the aggregation of molecules or ions bound together by noncovalent interactions. These noncovalent interactions are very effective for developing supramolecular assemblies/architectures [6-12]. Long before the field of supramolecular chemistry emerged, there was a field of research known as molecular recognition chemistry where various host molecules were proposed to show molecular recognition. Molecular recognition is fundamental to supramolecular chemistry because the construction of any supramolecular system involves selective molecular combinations. There are various examples in which specific molecules recognize other molecules in efficient and selective ways. Host molecules recognize guest molecules during molecular recognition. Therefore, molecular recognition chemistry is sometimes called host-guest chemistry [13], and so molecular compatibility is the foundation for molecular recognition in supermolecules created by receptor-substrate interaction [14]. Traditional chemistry deals with covalent interactions while supramolecular chemistry deals with noncovalent interactions [15, 16]. This multidisciplinary field influences many other fields, including physical chemistry studies the characteristics of the supramolecular systems, computational chemistry aids in comprehending complex supramolecular activity, and the traditional areas of organic and inorganic chemistry which are

Chapter 1

necessary to prepare the precursors for a supramolecule and hence the broad and multidisciplinary subject of supramolecular concept has been always at the front of contemporary study, drawing ever-increasing interest from researchers. A comparison between the scope of molecular and supramolecular chemistry was summarized by Lehn [6] (**Fig. 1.1**).

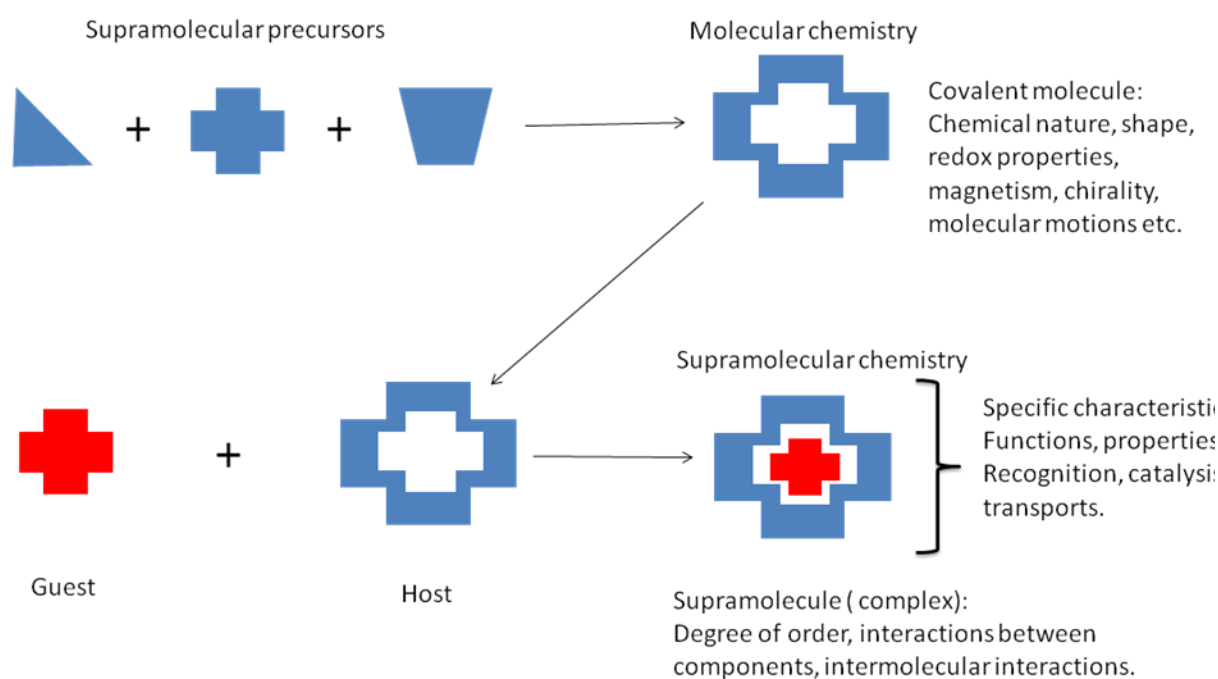


Fig. 1.1. Comparison between the scope of molecular and supramolecular chemistry according to Lehn [6].

The noncovalent interactions deliver plenty of benefits over covalent interactions. Initially, noncovalent interactions offer simple and straightforward methods for constructing supramolecular structures, potentially saving time and money by reducing the need for several synthesis steps and complicated purification procedures during fabrication [17]. For example, a single self-complementary zwitterionic building unit consisting of guanidinium and amino moieties is obtained through the combination of H-bonding, ionic, and π -stacking motifs in an “all-in-one” design approach [18, 19]. It has been demonstrated that self-assembling vesicles featuring bilayer membranes were formed by this basic molecule. The latter is made of linear dimers stacking in an anti-parallel manner to encourage more π -stacking interactions between the aromatic residues and greater interactions of oppositely charged groups [20]. Nano containers that can react to stimuli can be developed by pH-dependent reversible disassembly

Chapter 1

of the vesicles [21]. The zwitterion-based systems show how different kinds of interactions within a single molecule work together to produce a well-defined assembly. Thus, self-complementarity is introduced as an effective design technique by simple zwitterion molecules, which generate a higher order of supramolecular aggregation. Particular benefits can arise from multivalent electrostatic interactions between organic and inorganic molecules. Covalent interactions among the donor atoms/groups of ligands and the metal centers dominate the primary coordination sphere whereas the noncovalent contacts regulate the secondary coordination sphere. Many features of coordination compounds for example shape of the complex, selectivity and rate of metal-assisted catalytic reactions are impacted by these noncovalent interactions [20, 22]. Charge-transfer interactions stabilize the interesting self-aggregations among coordination compounds/complexes in addition to other noncovalent interactions. The complicated role of complementary noncovalent interactions governs and controls the selective bindings among the coordination compounds to form supramolecular aggregations/assemblies [22-26]. Therefore, it is necessary to understand cooperatively effects deeply for planning and fabricating innovative supramolecular motifs having multiple components which have inferences for designing and synthesizing solid-state structures/crystals with desired geometry and applications in medicinal chemistry and material science [27-37].

Supramolecular techniques are frequently economical and environmentally harmless because intrinsic self-assembly can generate supramolecular structures by combining the building components in solution at room temperature without the use of external factors [38- 40]. So, any material with components linked by noncovalent interactions that undergo a self-assembly or disassembly process without the aid of external agencies is considered a supramolecular material [17]. The reversible and dynamic nature of supramolecular materials arises because of the noncovalent interactions making the supramolecular entities enable easy destruction and reformation at the cost of low energy. As a result, the supramolecular materials can self-repair after suffering mechanical damage from the outside. Moreover, it is capable of responding to outside stimuli that can cause supramolecular materials to change concerning structure by reorganizing their morphologies or structures, to respond to the outside's stimuli, leading to the lowest energy states due to the reduction of Gibb's free energy [38]. So, for the design and preparation of stimuli-responsive active materials, the responding capacities of supramolecular materials can be used [17].

Chapter 1

1.2 Division of supramolecular chemistry

Supramolecular chemistry can be categorized into two subcategories: (i) self-assembly (the spontaneous and reversible aggregation of two more components to produce a bigger noncovalently bonded assembly) and (ii) host-guest assembly (study of large host molecules that can wrap smaller guest molecules through noncovalent contacts is known as host-guest chemistry). The guest molecule is generally the smaller molecule which is encapsulated by the host molecule which is noticeably bigger than the guest molecule and hence, the host molecule can wrap around the guest molecule (**Fig. 1.2a**) [6]. A definition of hosts and guests was provided by Nobel laureate Donald Cram. The host component is defined as an organic molecule or ion whose binding sites converge in the complex. The guest component is any molecule or ion whose binding sites diverge in the complex [41, 42]. A portion of the host or guest which has the ideal size, shape and chemical composition for interaction with the other chemical species is called a binding site [43]. Enzyme and their substrates are examples of host-guest complexes in the biological system where the substrates are the guests and the enzymes are the hosts [44]. In coordination chemistry metal-ligand complexes are viewed as a host-guest entity, in which ligands serve as hosts for metal ions [45]. Solid-state inclusion compounds behave as crystalline solids when they are host-guest because the guest is confined inside a cavity created by a hole in the guest lattice's packing. These substances are commonly known as clathrates which mean the "bars" (**Fig. 1.2b**) [46]. Self-assembly is known as the equilibrium condition existing between two or more chemical species to obtain an assembly whose arrangement depends exclusively on the information found in the chemical building units. Although it is spontaneous, this self-assembly process can be impacted by templation, solvation or in the case of solids, the same process is impacted by nucleation and crystallization processes (**Fig. 1.2c**) [47- 49].

Chapter 1

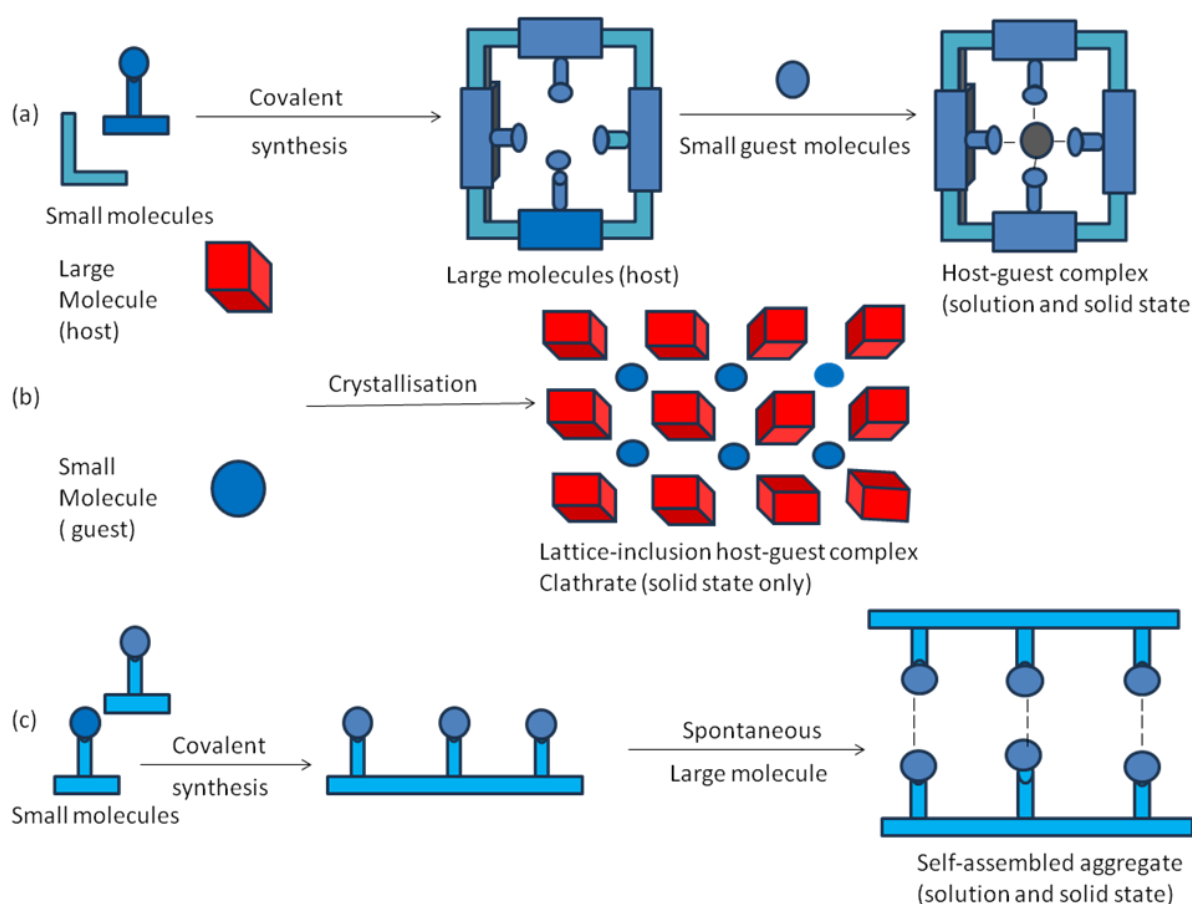


Fig. 1.2. The development of a supramolecular system from molecular building blocks: (a) host-guest complexation; (b) lattice inclusion; and (c) self-assembly between complementary molecules [47].

1.3 Types of supramolecular interactions

Different types of supramolecular interactions (noncovalent interactions) for stabilizing supramolecules are described below:

1.3.1 Ionic and dipolar interactions: Ionic and dipolar interactions are classified into three classes based on columbic interaction between oppositely charged species: (i) Ion-ion interactions, (ii) Dipole-dipole interactions, and (iii) Ion-dipole interactions [50]. The strongest interaction is the ion-ion interaction among these, comparable to the covalent bond (**Fig. 1.3a**) [51]. Ion-ion interaction can take place in any direction as such interaction is flexible/ non-directional by nature. However, there are orientations-dependent components to ion-dipole (**Fig. 1.3b**) and dipole-dipole (**Fig. 1.3c**) interactions, which need two entities to be aligned in the ideal direction for the

Chapter 1

interactions to occur. Directional interactions can only form aggregates between the species that are mutually complimentary due to their relative rigidity compared to non-directional interactions which can stabilize a large number of molecular pairings [51]. Depending on the species involved, these directed interactions can vary in strength. Compared to dipoles, ions have a larger charge density, which makes ion-dipole interactions stronger [52].

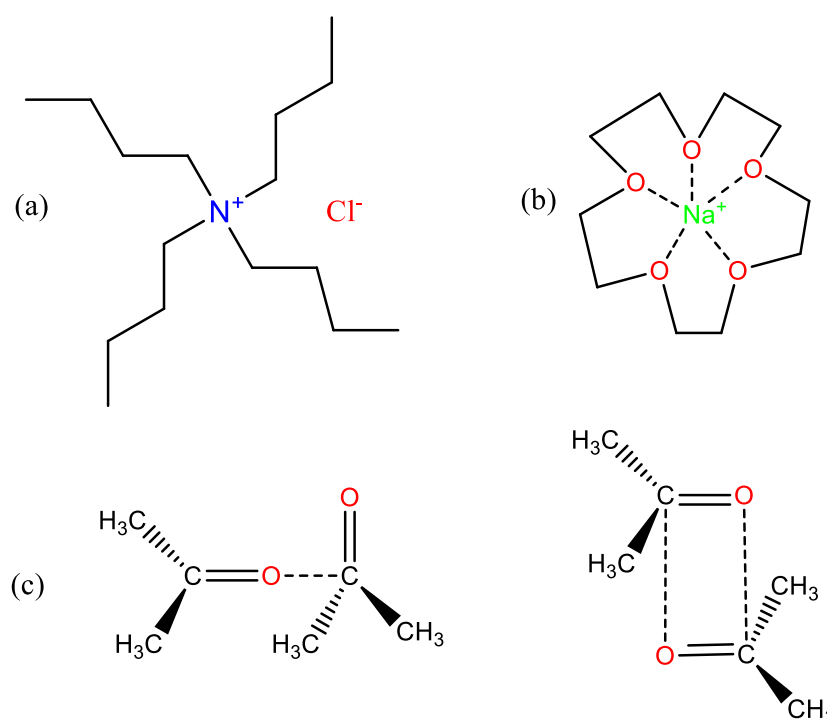


Fig. 1.3. Examples of electrostatic interactions: (a) ion-ion interaction in tetra butyl ammonium chloride; (b) ion-dipole interaction in the sodium complex of [15] crown-5; (c) dipole-dipole interaction in acetone [6].

1.3.2 Hydrogen bonding: Hydrogen bonding is a type of noncovalent interaction and has a high degree of directionality [53]. Hydrogen bonding is perhaps the most significant factor in the construction of supramolecular structures [51]. A special kind of dipole-dipole interaction between donors of protons (D) and an acceptor of protons (A) is provided by hydrogen bonding. A few examples of naturally occurring building units which are a rich source of hydrogen bond donors and acceptors are amino acids, carbohydrates and nucleobases. Groups, where a hydrogen atom is joined to an electronegative atom (like oxygen or nitrogen) to form a dipole with the hydrogen atom containing a small positive charge, are called donors of hydrogen bonds. Dipoles containing electron-withdrawing elements, with which positively charged hydrogen atoms interact, such as carbonyl moieties, are known as hydrogen bond acceptors

Chapter 1

shown in **Fig. 1.4** and **Fig. 1.5**. The strength of hydrogen bonding varies from 4 to 120 KJ mol⁻¹ [54].

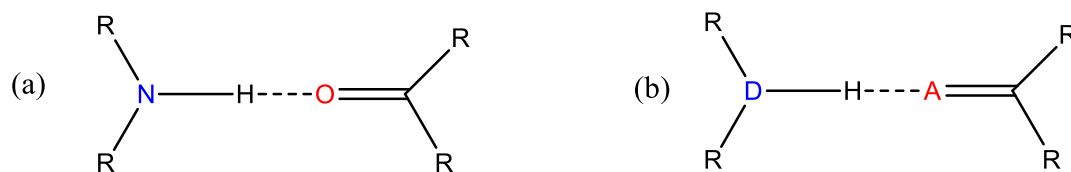


Fig. 1.4. (a) A carbonyl accepting a hydrogen bond from a secondary amine donor; (b) the standard way of expressing donor and acceptor atoms (D, donor atom; A, acceptor atom)

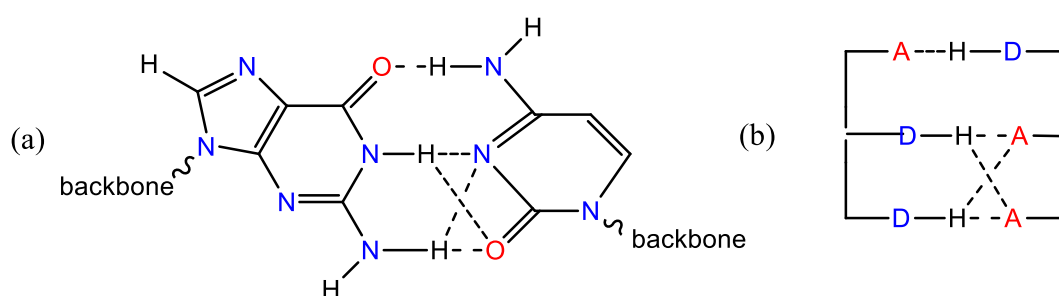


Fig. 1.5. (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base-pairs in DNA and (b) A schematic representation [6, 35].

1.3.3 π -interaction: Three primary types of π -interactions are found in supramolecular systems viz (a) cation- π interactions (b) π - π interactions (c) anion- π interactions [51]. In the field of organometallic chemistry, cation- π interactions are widely recognized, where olefinic moieties are held to metal centres of transition elements, for example, ferrocene and Zeise's salt, K⁺ in benzene shown in **Fig. 1.6** [55, 56]. The anion- π interaction happens due to the attractive nature of an anion to a π -system that is highly electrophilic. Such type of interaction has been known from computation for a long time but developed the interest of the researchers because of some well-organized supramolecular aggregations due to which the study of such kind of interaction is possible [47, 57, 58]. π - π interactions are of two types, one is edge-to-face (**Fig. 1.7a**) where a hydrogen atom from one ring interacts perpendicularly with the centre of another ring and another one is face-to-face or slip-stacked (**Fig. 1.7b**), in which parallel ring systems apart by approximately of 3.5 Å, are offset and the interaction occurs between the corner of one ring and the centre of another ring [47]. These π - π interactions result from the attraction between neighbouring molecules's positively

Chapter 1

charged σ framework and the negatively charged π -electron cloud of one conjugated system [55, 56]. In nature, interactions involving π -systems occur, for instance, the weak face-to-face interactions between base pairs are found in the double helical form of DNA [59].

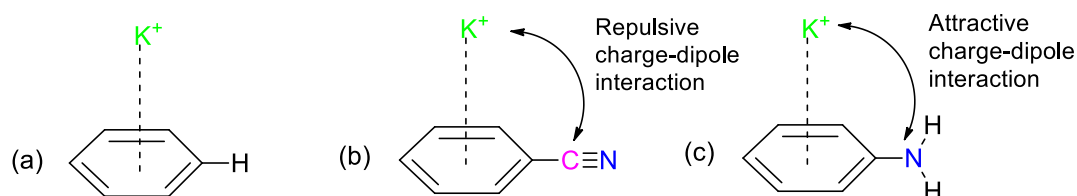


Fig. 1. 6. Examples of cation- π interactions: (b) weaker cation- π interaction (c) stronger cation- π interaction

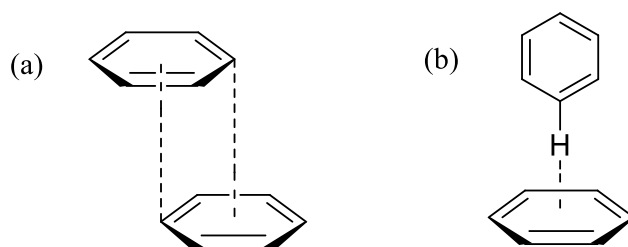


Fig. 1.7. The two types of π -interactions: (a) face-to-face; and (b) edge-to-face [47].

1.3.4 CH- π interaction: The CH- π interaction in supramolecular chemistry has a contribution concerning the selectivity of organic reactions and to specify substrate of biologically important macromolecules [60-62]. The foundation of weak attractive interaction has been considered as a type of hydrogen bond between positively charged CHs in an alkyl group or aromatic group and an electron cloud of the π -system. The CH- π interaction is characteristic of a relatively large contribution from delocalization and dispersive interaction compared to normal hydrogen bonding. Unlike hydrogen bonding, CH- π interaction is exhibited in polar and non-polar solvents. Enthalpy for a one-unit CH- π interaction is small, around 1 kcal/mol [63]. Such weak CH- π interaction is thus quite important in understanding the structures and behaviours of biomolecules such as protein, haemoglobin, lysozyme, D-xylose isomerase, Immunoglobulin McPC603 etc. [62, 63].

1.3.5 van der Waals interactions: Such non-directional attractions are not very prominent in supramolecular architecture. van der Waals force of interaction results from

Chapter 1

variations in the distribution of the electrons between nearby molecules. Within a molecule, an instantaneous dipole is created as the electron cloud travels around its transient location. There will be an attraction between the partial positive charge of one species with the partial negative charge of the other species because of the oscillation of the distributed electron cloud or dipoles between the adjacent species (**Fig. 1.8**). Such type of attractive interaction between two instantaneous dipoles results in London forces of attraction. A van der Waals interaction is a relatively weak interaction ranging from 0.5 to 1 kcal/mol and is nonionic [64].

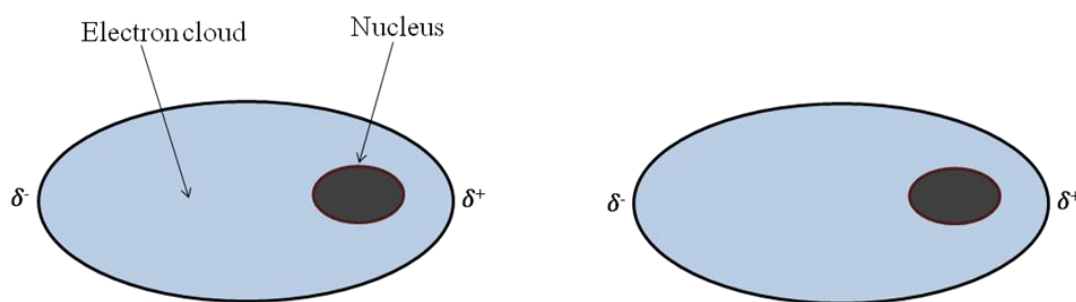


Fig. 1.8. van der Waals interaction between two argon atoms.

1.3.6 Hydrophobic interactions: When non-polar molecules or groups are excluded or partitioned from an aqueous solution, hydrophobic effects result [51]. Anslyn and Dougherty described that the hydrophobic effect is the “single most important component in biological molecular recognition” [50]. Water molecules preferentially interact with other dipoles as well as with themselves making the situation more energetically beneficial. Certain self-assembly processes for example attraction of organic molecules in water within cyclophanes and cyclodextrins depend heavily on hydrophobic interactions. Hydrophobic interaction can be divided into two energy components which are enthalpic hydrophobic effect and entropic hydrophobic effect. The enthalpic hydrophobic effect in a cavity occurs when a guest displaces the water [65]. This phenomenon happens relatively easily because of the high energy of the system and weak interaction between the water and hydrophobic cavity of the host species. The binding between the water as guest and the solvent outside the cavity

Chapter 1

lowers the energy as soon as water is displaced by a guest shown in **Fig. 1.8**. This process also involves an entropic component because the water which was initially ordered inside the voids becomes disordered as it exists freely. The process becomes more favourable when entropy rises [66].

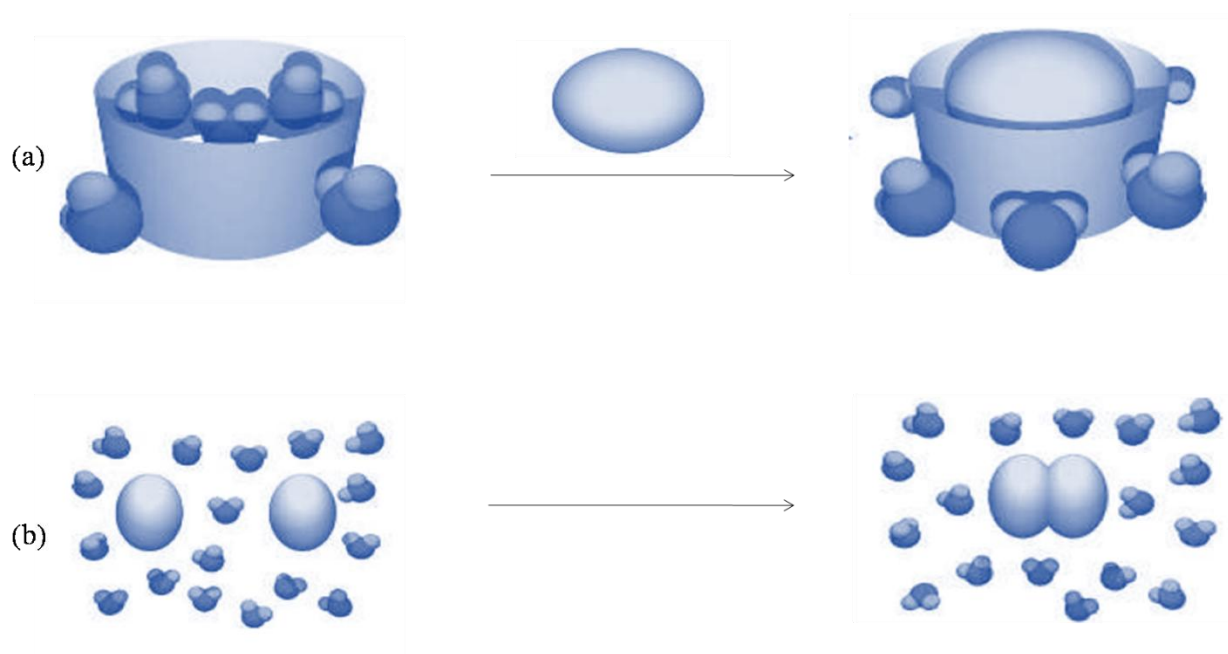


Fig. 1.9. Hydrophobic interactions: (a) Displacement of water molecules from hydrophobic cavity due to enthalpic hydrophobic interaction; (b) two organic molecules creating a hole within an aqueous phase, giving rise to hydrophobic effects [47].

Table 1.1. Summary of different types of noncovalent interactions:

Types of interactions	Binding energy (kJ/mol)	Examples	References
Ion-ion interactions	100-350	Tetrabutylammonium chloride	6, 50
Ion-dipole interactions	50-200	Sodium crown [15] ether	6
Dipole-dipole interactions	5-50	Acetone	47
Hydrogen bonding	4-120	Hydrogen bonding between base pairs of DNA	54

Chapter 1

π - π interactions	0-5	Benzene and graphite	6
Cation- π interactions	5-80	K ⁺ in benzene, ferrocene, Zeise's salt	6, 55, 56
Anion- π interactions	Comparable to Cation- π interactions	Interaction of Ag(I) complexes with -acidic aromatic rings	47, 57
CH- π interactions	2.27-5	Methane/benzene binary system, acetylene dimer, methane/ethylene supramolecular system	61
van der Waal's interactions	< 5 KJ/mol	Packing of argon atoms in molecular crystal	6
Hydrophobic interactions	Dependent on the energy of solvent-solvent interaction	Cyclodextrin inclusion compounds	6

1.4 Host-guest assembly

One of the most significant concepts in supramolecular chemistry is host-guest chemistry, which defines the creation of distinct structural complexes by non-covalent interactions between two or more molecules or ions [67]. The selectivity of the host molecule, or the preference shown by the host molecule for the guest molecule, essentially allows the host-guest attraction to occur when the host species has the right bonding sites for the guest species [6]. Numerous factors including complementarity between the binding sites of the host and guest molecules, pre-organization of the shape of the host or cooperativeness of the binding sites, can contribute to this selectivity.

1.4.1 Complementarity: Complementarity of the binding sites (according to the lock and key and induced-fit models) of host and guest molecules both geometrically and electrically is the necessary condition for the generation of supramolecule [68, 47]. In biological and supramolecular systems complementarity is a crucial process like enzyme activity [69]. The

Chapter 1

total structure of an enzyme is typically much greater than that of its substrate. The 3D structure of an enzyme folds in such a way that it arranges its binding sites into a pocket that is functionally suitable with the substrate and somewhat complementary in size and shape. This similarity in size and shape allows the enzyme and the substrate to identify one another. The two are allowed to bind within the pocket due to the presence of complementary binding sites. Generally speaking, strong, selective binding requires chemically complementary binding sites for both the enzyme and the substrate in addition to the complementary size and shape of both the host and guest [70].

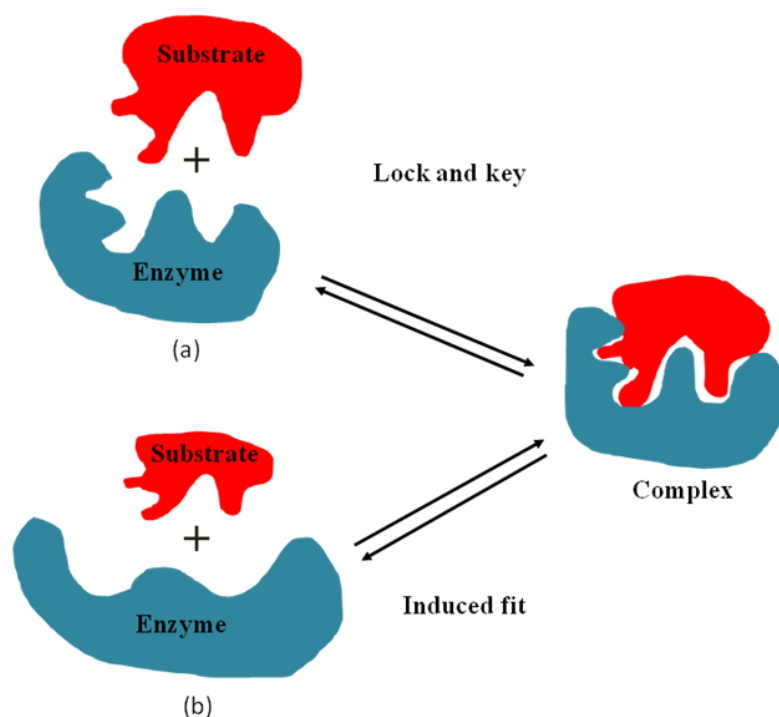


Fig. 1.10. (a) Rigid lock and key and (b) induced fit models of enzyme-substrate binding.

1.4.2 Co-operativity: A combined interaction that results from two or more binding sites acts better compared to their activities. A host species having a multiple number of binding sites generates a more stable host-guest complex compared to a similar system containing sites working independently of one another. This inter-site co-operativity is a consequence of coordination chemistry's chelate effect. For instance, one metal ion coupled with the three bidentate ligands (ethylene diamine) and another with six unidentate ligands (ammonia) [71]. Using nitrogen atom lone pairs, the ligand-metal dative bond in both situations is about the same. However, the complex with ethylenediamine is 100 times more stable than the hexamine complex. A common chelating ligand called ethylene diamine tetraacetic acid (EDTA) can

Chapter 1

bind through coordination mode with a variety of metals in a hexadentate manner applying two nitrogen lone pairs and four deprotonated acid groups. The six interaction sites of EDTA⁴⁻ undergo self-organisation to produce an octahedral structure keeping the central metal atom at the center. The resulting complex is extremely stable because only one EDTA⁴⁻ completely satisfies both the primary and the secondary valencies of the central metal ion [72].

1.4.3 Preorganization: If the host molecule is preorganised then the stability of the host-guest complex relationship further increases due to the co-operative effect [73]. A set of well-defined arrangements of binding sites and complementary shapes within its structure are found in a preorganised host molecule. This signifies that the host species can interact with a guest most stably without undergoing a large conformational change. This can be accomplished by creating a rigid host with prepared cavities that already have the suitable size and proper binding location set up to accommodate the possible guest molecule and. Use of a host which has one or more rings or macrocycles inside its structure is the most common way to achieve this arrangement. These rings have relatively little conformational mobility or rigidity. Host complexes with ring residue are more stable due to the macrocyclic effect in comparison to their acyclic analogues [68].

1.5 Metal-based supramolecular architectures

In supramolecular chemistry, metal ions are widely employed because of their unique capacity to arrange the chemical species (molecules/atoms) in certain geometry [74]. The coordination of metal centers with the organic ligands/linkers in the supramolecular system greatly influences the modification of the shape/structure/functions of the synthesized supramolecular systems and the regulation of self-assembly. Different metal ions differ in size, coordination geometry, charge density, coordination number and binding affinity and so metal ions with binding ligands determine the features of the metal-coordinated supramolecular architectures [75]. Self-assembly based on coordination bonds has served as the basic/foundation for numerous advancements in a variety of chemistry-related subdisciplines, to conduct basic investigations on the synthesis of novel supramolecular architectures defining practical applications [76]. These efforts are largely motivated by the finding that the extremely simple non-covalent weak forces such as hydrogen bonding, hydrophobic interactions, hydrophilic, and dipole-dipole interactions among the molecular building blocks subunits are the source of complexity in natural systems. Even though individual interactions may be observed as straightforward, where unprecedentedly diverse designs can be developed when numerous

Chapter 1

interactions work together [77]. It is essential to assume the chemical and physical forces of interaction of various strengths as well as the several diverse degrees of geometrical preferences. In supramolecular chemistry, metal-mediated architectures refer to the self-organized assembly of coordination bonds between metal ions/nodes and organic ligands/linkers. The strength of coordination bonds between metal ions and organic linkers ranges from noncovalent to covalent contacts. So, self-assembly exhibits both a stable and dynamic nature in complex environments. The fundamental features of metal-based supramolecular structures at the time of self-organized are their ability to adjust for designing according to necessary and their logical coordination combinations between the metal ion and ligand for particular applications, due to which they can be set for numerous applications [75]. In recent decades numerous types of supramolecular frameworks based on metal have been developed as inspired by many self-assemblies found in nature. As a result, in addition to the carefully planned and regulated aggregation of multi-component species, the system with metal can be developed with a wide range of extra capabilities. The majority of such supramolecular systems are composed of heteroatom-metal centers/Lewis acids and multidentate ligands/Lewis bases. The structure of the resulting materials is known as metal-organic materials (MOMs) [78]. Coordination geometries of both the metal ions or clusters and multidentate organic ligands determine the structures of the MOMs [79, 80].

1.6 Supramolecular areas of coordination chemistry

Two distinct areas of coordination chemistry have developed (**Fig. 1.11**) in the last few decades which are (a) Metal-organic frameworks (MOFs) and (b) supramolecular coordination complexes (SCCs). MOFs are networks of metal center or inorganic clusters connected with basic organic linkers (ligands) *via* coordination bonds between the metal and ligand or infinite coordination compounds called polymers [78]. SCCs comprise discrete systems where ligands with multiple binding sites ordered with a specified angularity undergo self-assembly with carefully chosen metal centers to form a finite supramolecular complex [15]. Supramolecular coordination complexes (SCCs) are 2D or 3D structures which are formed if the combination of geometries allows a convergent array of metal centers (nodes) and linkers/ligands [78]. Fundamentally, metal nodes connected by organic ligands are a common feature of both SCCs and MOFs and these structures are included to as metal-organic materials (MOMs) [15]. Morphologically speaking, supramolecular coordination complexes (SCCs) fall into three primary categories which are metallacycles, metallacages and helicates. The cavity-like structure of the metallacycles and metallacages is their characteristic feature. In metallacycles

Chapter 1

coordination with a ring form limits the void simply in 2D. When it comes to metallacages, the vertices, faces and edges around the cavity are defined by the combination of metal centers and ligands, limiting the cavity to 3D. The structure of helicates (non-porous materials) on the other hand is sturdy and compact with well-defined faces having binding capacities for many guest/target molecules [81]. In order to develop bigger structures known as metal-organic materials (MOMs), nodes used are transition metal elements connected by organic ligands called “linkers” [79, 80]. For example, Pd(II) and Pt(II) supramolecular coordination complexes, two coordination binding sites are left open for the complexation with multidentate ligands to produce discrete structures of supramolecular coordination complexes. The complexes thus obtained adopt the square planar shape around the metal center. The metal precursors used in these examples are *cis*-capped [78]. Metal-organic frameworks (MOFs) are constructed by inorganic nodes (metal ions/clusters) with organic connectors (linkers) also known as porous coordination polymers (PCPs)/supramolecular assembly. PCPs act as significant/promising types of substances with multiple unique characteristics, including high porosity, tunable pore structure, diverse composition and versatile functionalities [82].

1.7 Techniques for the development of SCCs

The edge and face-directed techniques are the two synthetic strategies that are frequently used to develop SCCs [11]. The latter is also known as “paneling method” and it was created by Fujita in the late 1990s. Planar multidentate ligand molecules are used to build up SCCs. Such ligand molecules coordinate to empty binding sites of the nodes (metals) to construct surfaces/faces of polyhedra or polygons which are the result of supramolecular aggregation [78]. To generate the edges of SCCs, the edge-directed approaches which were first introduced by Stang et al. [83, 84] primarily used bidentate ligands containing pyridyl residue of banana type in combination with the nodes of palladium(II) and platinum(II). Fujita and his colleagues synthesized and described a set of trigonal prisms by treating Pd(II) nodes (*cis*-capped) with the ligands triphenyl-triazine (planar) and bipyridyl pillar (linear). The length of the pillar ligands can be changed to vary the size of the hydrophobic cavity. Prisms with larger cavities can encapsulate pairs or triples of some metal complexes which are flat in structure. This thing happens due to the combined effects of d-d coupling between metal nodes/centres, π - π interactions between the ligands and hydrophobic effects [85]. These two approaches of synthetic strategies of SCCs were greatly advanced by Raymond et al., who expanded the research to include dynamic behaviour [86].

Chapter 1

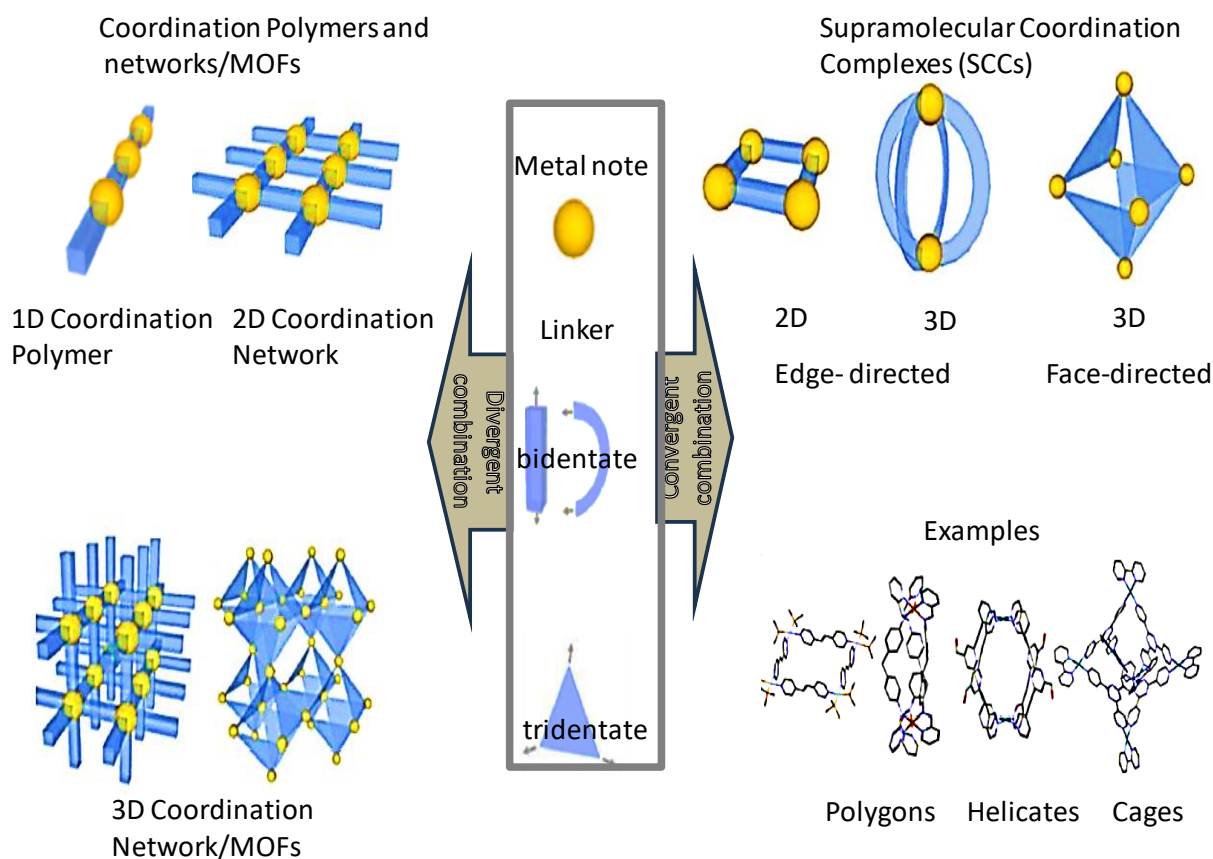


Fig. 1.11. Different types of metal bonded assemblies (examples): Coordination polymers or networks formed by divergent (left) and discrete supramolecular complexes formed by convergent combination of nodes and organic linkers (right) [78].

1.8 Supramolecular chirality

Assembly based on supramolecular interactions yields supramolecular chirality. The focus is on ensembles that are composed only of achiral building blocks; and consist of asymmetric ligand arrangements or metal coordination geometries to produce chirality through supramolecular interactions. Assemblies having chiral cavities that may be used as nano-reaction containers for identification, storage and encapsulation of guests are of special interest [87].

1.9 Importance of supramolecular chemistry

The majority of the chemistry in the previous century was related to covalent bonding, whereas noncovalent interaction is the focus of chemistry in the current century. With the help of precise interactions between pre-organized bonding centers, supramolecular chemistry has started to accomplish complicated operations in highly ordered molecular systems [16, 88]. Chemists, biologists and material scientists have been interested in the idea of supramolecular chemistry

Chapter 1

with non-dynamic covalent interactions to describe systems ranging from simple to complex. Many supramolecular systems have been developed and their potential uses as functional materials, catalysis, electronics, nanomaterials, sensors and other fields have been extensively researched during the last few decades [20]. The objective of supramolecular aggregation is to take advantage of the weak attractive forces among the species as a basis to control chemical kinetics and reactivity [89], which involves the spontaneous self-assembly process. Artificial supramolecular assembly can provide a unique reactivity to an encapsulated guest. Synthesized host molecules which are developed can bring about complicated chemical reactions inside their voids. The assembly of pre-organized building blocks is thermodynamically stable. So, to develop a final supramolecular structure that frequently possesses features different from any of the individual building blocks or subunits, the additive behaviour of the weak and non-covalent forces is very crucial. Such structures can facilitate both stoichiometric and catalytic reactions [90]. Research on supramolecular motifs that are developed as building blocks for future nano-machine technologies by noncovalent interactions of their constituent parts *via* self-assembly is architecturally crucial [41]. A flexible area for the creation of innovative self-assemblies (supramolecular systems) is offered by recent developments for chemical reactions in supramolecular architectural areas. The supramolecular self-assemblies impact the selectivity, stability and dynamic nature of certain chemical compounds or phenomena. Supramolecular self-assemblies significantly have been involved in both catalytic properties and biological activities [91].

1.10 Aim and scope of present work

Design and synthesis of hydrogen-bonded supramolecular assembly with other various additional noncovalent interactions with significant biological properties (anticancer, antiviral and antibacterial agent), and magnetic and catalytic properties are the interesting aspects in the research of supramolecular chemistry. In recent days, Hirshfeld surface (HS) analyses decode the different types of noncovalent interactions, which play important roles in supramolecular aggregation and stabilizing the crystal structures. Furthermore, theoretical investigations based on the DFT calculations have also been applied to investigate the electronic properties of complexes. During our work on supramolecular chemistry, we were interested in synthesizing novel compounds that can show different kinds of supramolecular aggregations and potential applications in different fields of science. Thus, we framed our objectives as below.

Chapter 1

- (i) The design, synthesis, supramolecular properties, and pharmacological properties of the Schiff-base ligand, *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its hitherto unknown Ni(II), Co(III) and Cd(II) complexes.
- (ii) The design and synthesis of Pd(II) complex fabricated from Schiff base benzil bis(pyridyl hydrazone), and study of its supramolecular aggregation and anticancer properties.
- (iii) The design and synthesis of mixed ligand complex of Co(II) complexes harvested from ligands 1,1-dicyano-2,2-ethylenedithiolate di-potassium salt (*K₂i-mnt*) and tris- (2-aminoethyl) amine (tetraen) and pyridine-2, 6-dicarboxylic, and exploring the supramolecular properties, magnetic properties, and photocatalytic hydrogen evolution.
- (iv) Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound.

Chapter 1

1.11 References

- [1] Lehn, J. M. (1993). Supramolecular chemistry. *Science*, 260(5115), 1762-1763.
- [2] Ariga, K. (2016). Supramolecules. In *Biomaterials Nanoarchitectonics* (pp. 25-40). William Andrew Publishing.
- [3] Adhikari, S., Datta, A., Saha, I., & Ghosh, K. (2024). Synthetic receptors for urea and barbiturates: An overview. *Coordination Chemistry Reviews*, 517, 215989.
- [4] Pedersen, C. J. (1967). Cyclic polyethers and their complexes with metal salts. *Journal of the American Chemical Society*, 89(26), 7017-7036.
- [5] Pawełczyk, A., Sowa-Kasprzak, K., Olender, D., & Zaprutko, L. (2018). Molecular consortia—Various structural and synthetic concepts for more effective therapeutics synthesis. *International journal of molecular sciences*, 19(4), 1104.
- [6] Steed, J. W., Turner, D. R., & Wallace, K. J. (2007). Core concepts in supramolecular chemistry and nanochemistry. John Wiley & Sons.
- [7] Huang, Z., & Ma, X. (2020). Tailoring tunable luminescence via supramolecular assembly strategies. *Cell Reports Physical Science*, 1(8).
- [8] Sánchez-Fernández, J. A., Cue-Sampedro, R., & Saade, H. (2024). Supramolecular Systems Linked to Metal-Organic Frameworks.
- [9] Matsuoka, R., & Nabeshima, T. (2018). Functional supramolecular architectures of dipyrin complexes. *Frontiers in chemistry*, 6, 349.
- [10] Tesfaye, D., Linert, W., Gebrezgiabher, M., Bayeh, Y., Elemo, F., Sani, T., ... & Thomas, M. (2023). Iron (II) mediated supramolecular architectures with schiff bases and their spin-crossover properties. *Molecules*, 28(3), 1012.
- [11] Cook, T. R., & Stang, P. J. (2015). Recent developments in the preparation and chemistry of metallocycles and metallocages via coordination. *Chemical reviews*, 115(15), 7001-7045.
- [12] Basak, T., Frontera, A., & Chattopadhyay, S. (2021). Insight into non-covalent interactions in two triamine-based mononuclear iron (iii) Schiff base complexes with special emphasis on the formation of Br... π halogen bonding. *CrystEngComm*, 23(7), 1578-1587.
- [13] Ariga, K., & Kunitake, T. (2006). The Chemistry of Molecular Recognition—Host Molecules and Guest Molecules. *Supramolecular Chemistry—Fundamentals and Applications: Advanced Textbook*, 7-44.
- [14] Lehn, J. M. (1988). Struct. Bonding (Berlin), 1973, 16, 1á CAS á; JM Lehn. *Angew. Chem., Int. Ed. Engl*, 27.

Chapter 1

- [15] Cook, T. R., Zheng, Y. R., & Stang, P. J. (2013). Metal–organic frameworks and self-assembled supramolecular coordination complexes: comparing and contrasting the design, synthesis, and functionality of metal–organic materials. *Chemical reviews*, 113(1), 734-777.
- [16] Schneider, H. J. (2009). Binding mechanisms in supramolecular complexes. *Angewandte Chemie International Edition*, 48(22), 3924-3977.
- [17] Ma, Xing, and Yanli Zhao. "Biomedical applications of supramolecular systems based on host–guest interactions." *Chemical reviews* 115.15 (2015): 7794-7839.
- [18] Schmuck, C., & Wienand, W. (2003). Highly stable self-assembly in water: ion pair driven dimerization of a guanidiniocarbonyl pyrrole carboxylate zwitterion. *Journal of the American Chemical Society*, 125(2), 452-459.
- [19] Rehm, T., & Schmuck, C. (2008). How to achieve self-assembly in polar solvents based on specific interactions? Some general guidelines. *Chemical communications*, (7), 801-813.
- [20] Rybtchinski, B. (2011). Adaptive supramolecular nanomaterials based on strong noncovalent interactions. *ACS nano*, 5(9), 6791-6818.
- [21] Rodler, F., Linders, J., Fenske, T., Rehm, T., Mayer, C., & Schmuck, C. (2010). pH-Switchable Vesicles from a Serine-Derived Guanidiniocarbonyl Pyrrole Carboxylate Zwitterion in DMSO. *Angewandte Chemie International Edition*, 49(46), 8747-8750.
- [22] Mahmudov, K. T., Kopylovich, M. N., da Silva, M. F. C. G., & Pombeiro, A. J. (2017). Non-covalent interactions in the synthesis of coordination compounds: Recent advances. *Coordination Chemistry Reviews*, 345, 54-72.
- [23] Fujita, M. (2000). Molecular paneling through metal-directed self-assembly. *Molecular Self-Assembly Organic Versus Inorganic Approaches*, 177-201.
- [24] Philp, D. (1996). Supramolecular chemistry: Concepts and perspectives. By J.-M. Lehn, VCH, Weinheim 1995, x, 271 pp., softcover, DM 58.00, ISBN 3-527-2931 1-6.
- [25] Dutta, D., Sharma, P., Frontera, A., Gogoi, A., Verma, A. K., Dutta, D., ... & Bhattacharyya, M. K. (2020). Oxalato bridged coordination polymer of manganese (iii) involving unconventional O... π -hole (nitrile) and antiparallel nitrile... nitrile contacts: antiproliferative evaluation and theoretical studies. *New Journal of Chemistry*, 44(46), 20021-20038.
- [26] Ghosh, K., & Adhikari, S. (2008). A quinoline-based tripodal fluororeceptor for citric acid. *Tetrahedron Letters*, 49(4), 658-663.
- [27] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Acharya, S., ... & Frontera, A. (2018). Mixed-ligand complexes of zinc (II) with 1, 1-dicyanoethylene-2, 2-dithiolate and

Chapter 1

N-donor ligands: A combined experimental and theoretical study. *Journal of Molecular Structure*, 1164, 334-343.

[28] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Butcher, R. J., ... & Das, A. (2017). A new cadmium (II) complex with bridging dithiolate ligand: Synthesis, crystal structure and antifungal activity study. *Journal of Molecular Structure*, 1139, 395-399.

[29] S. Adhikari, trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study, *Inorg. Chim. Acta*.

[30] Adhikari, S., Bhattacharjee, T., Butcher, R. J., Porchia, M., De Franco, M., Marzano, C., ... & Tisato, F. (2019). Synthesis and characterization of mixed-ligand Zn (II) and Cu (II) complexes including polyamines and dicyano-dithiolate (2-): In vitro cytotoxic activity of Cu (II) compounds. *Inorganica Chimica Acta*, 498, 119098.

[31] Adhikari, S., Bhattacharjee, T., Das, A., Roy, S., Daniliuc, C. G., Zaręba, J. K., ... & Frontera, A. (2020). On the supramolecular properties of neutral, anionic and cationic cadmium complexes harvested from dithiolate–polyamine binary ligand systems. *CrystEngComm*, 22(46), 8023-8035.

[32] Bhattacharjee, T., Adhikari, S., & Butcher, R. J. (2022). Supramolecular Properties Directed by Weak Interactions in a Copper (II) Complex Based on 8-Hydroxy Quinoline-Pyridine Binary Ligand Systems: Crystal Structure and Hirshfeld Surface Analyses. *Journal of Chemical Crystallography*, 1-12.

[33] Bhattacharjee, T., Adhikari, S., Datta, A., Daniliuc, C. G., Montazerzohori, M., Naghiha, R., & Hayati, P. (2022). Cadmium (II) coordination polymer based on flexible dithiolate-polyamine binary ligands system: crystal structure, Hirshfeld surface analysis, antimicrobial, and DNA cleavage potential. *Polyhedron*, 211, 115544.

[34] Bhattacharjee, T., Adhikari, S., Bhattacharjee, S., Debnath, S., Das, A., Daniliuc, C. G., ... & Frontera, A. (2022). Exploring dithiolate-amine binary ligand systems for the supramolecular assemblies of Ni (II) coordination compounds: Crystal structures, theoretical studies, cytotoxicity studies, and molecular docking studies. *Inorganica Chimica Acta*, 543, 121157.

[35] Bhattacharjee, T., Adhikari, S., Sheikh, A. H., Mahmoudi, G., Mlowe, S., Akerman, M. P., ... & Saygideger, Y. (2022). Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine and its Ni (II) complex. *Journal of Molecular Structure*, 1269, 133717.

[36] S. Kandir, Handbook of Animal Models and its Uses in Cancer Research, (2022).

Chapter 1

- [37] Adhikari, S., Bhattacharjee, T., Nath, P., Das, A., Jasinski, J. P., Butcher, R. J., & Maiti, D. (2020). Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study. *Inorganica Chimica Acta*, 512, 119877.
- [38] Liu, K., Kang, Y., Wang, Z., & Zhang, X. (2013). 25th anniversary article: Reversible and adaptive functional supramolecular materials: “Noncovalent interaction” matters. *Advanced Materials*, 25(39), 5530-5548.
- [39] Wagner, B. D. (2020). *Host–Guest Chemistry: Supramolecular Inclusion in Solution*. Walter de Gruyter GmbH & Co KG.
- [40] Oshovsky, G. V., Reinhoudt, D. N., & Verboom, W. (2007). Supramolecular chemistry in water. *Angewandte Chemie International Edition*, 46(14), 2366-2393.
- [41] Yoshida, N., Oshio, H., & Ito, T. (2001). Supramolecular motifs in metal complexes of Schiff bases. Part 6. 1 Topology of two types of self-assembly of bis-N, O-bidentate Schiff base ligands by copper (II) ions. *Journal of the Chemical Society, Perkin Transactions 2*, (9), 1674-1678.
- [42] Cram, D. J. (1988). The design of molecular hosts, guests, and their complexes (Nobel lecture). *Angewandte Chemie International Edition in English*, 27(8), 1009-1020.
- [43] Hardianto, A., Yusuf, M., Liu, F., & Ranganathan, S. (2019). Structure-based drug design workflow.
- [44] Cram, D. J., & Cram, J. M. (1978). Design of complexes between synthetic hosts and organic guests. *Accounts of Chemical Research*, 11(1), 8-14.
- [45] Gasperov, V., Gloe, K., Lindoy, L. F., & Mahinay, M. S. (2004). Host–guest assembly of ligand
- [46] Muller, P. (1994). Glossary of terms used in physical organic chemistry (IUPAC Recommendations 1994). *Pure and Applied Chemistry*, 66(5), 1077-1184.
- [47] Steed, J. W., & Atwood, J. L. (2022). *Supramolecular chemistry*. John Wiley & Sons.
- [48] An, M., Feng, Y., Liu, Y., & Yang, H. (2023). External power-driven micro/nanorobots: Design, fabrication, and functionalization for tumor diagnosis and therapy. *Progress in Materials Science*, 101204.
- [49] Nyande, B. W., Gao, Y., & Lakerveld, R. (2019). A dynamic model for automated control of directed self-assembly of colloidal particles at low densities. In *Computer Aided Chemical Engineering* (Vol. 46, pp. 1783-1788). Elsevier.
- [50] Anslyn, E. V., & Dougherty, D. A. (2006). *Modern physical organic chemistry*. University science books.

Chapter 1

- [51] Daze, K., & Hof, F. (2016). Molecular interaction and recognition. *Encyclopedia of physical organic chemistry*, 1-51.
- [52] Lower, S. K. (2000). A Chem1 Reference Text. Online at: www.chem1.com/acad/webtext/pdf/c3carb.pdf.
- [53] Steiner, T. (2002). The hydrogen bond in the solid state. *Angewandte Chemie International Edition*, 41(1), 48-76.
- [54] Jeffrey, G. A., & Jeffrey, G. A. (1997). An introduction to hydrogen bonding (Vol. 12, p. 228). New York: Oxford university press.
- [55] Ma, J. C., & Dougherty, D. A. (1997). The cation- π interaction. *Chemical reviews*, 97(5), 1303-1324.
- [56] An, Y., & Wheeler, S. E. (2015). Cation- π Interactions. *The Lightest Metals: Science and Technology from Lithium to Calcium*, 173.
- [57] Garau, C., Frontera, A., Quiñonero, D., Ballester, P., Costa, A., & Deyà, P. M. (2004). Cation- π versus anion- π interactions: energetic, charge transfer, and aromatic aspects. *The Journal of Physical Chemistry A*, 108(43), 9423-9427.
- [58] Berryman, O. B., Bryantsev, V. S., Stay, D. P., Johnson, D. W., & Hay, B. P. (2007). Structural criteria for the design of anion receptors: the interaction of halides with electron-deficient arenes. *Journal of the American Chemical Society*, 129(1), 48-58.
- [59] Hunter, C. A., Lawson, K. R., Perkins, J., & Urch, C. J. (2001). Aromatic interactions. *Journal of the Chemical Society, Perkin Transactions 2*, (5), 651-669.
- [60] Nishio, M., & Hirota, M. (1989). CH/ π interaction: Implications in organic chemistry. *Tetrahedron*, 45(23), 7201-7245;
- [61] Meyer, E. A., Castellano, R. K., & Diederich, F. (2003). Interactions with aromatic rings in chemical and biological recognition. *Angewandte Chemie International Edition*, 42(11), 1210-1250.
- [62] Nishio, M., Umezawa, Y., Fantini, J., Weiss, M. S., & Chakrabarti, P. (2014). CH- π hydrogen bonds in biological macromolecules. *Physical Chemistry Chemical Physics*, 16(25), 12648-12683.
- [63] Nishio, M., Umezawa, Y., Hirota, M., & Takeuchi, Y. (1995). The CH/ π interaction: significance in molecular recognition. *Tetrahedron*, 51(32), 8665-8701.
- [64] Roy, K., Kar, S., & Das, R. N. (2015). *Understanding the basics of QSAR for applications in pharmaceutical sciences and risk assessment*. Academic press.

Chapter 1

- [65] Smithrud, D. B., Sanford, E. M., Chao, I., Ferguson, S. B., Carcanague, D. R., Evanseck, J. D., ... & Diederich, F. (1990). Solvent effects in molecular recognition. *Pure and applied chemistry*, 62(12), 2227-2236.
- [66] Southall, N. T., Dill, K. A., & Haymet, A. D. J. (2002). A view of the hydrophobic effect. *The Journal of Physical Chemistry B*, 106(3), 521-533.
- [67] Teyssandier, J., De Feyter, S., & Mali, K. S. (2016). Host–guest chemistry in two-dimensional supramolecular networks. *Chemical Communications*, 52(77), 11465-11487.
- [68] Cram, D. J. (1986). Preorganization—from solvents to spherands. *Angewandte Chemie International Edition in English*, 25(12), 1039-1057.
- [69] Wittenberg, J. B., & Isaacs, L. (2012). Complementarity and preorganization. *Supramolecular Chemistry: From Molecules to Nanomaterials*.
- [70] Behr, J. P. (1995). The Lock-and-Key Principle. *Trends in Pharmacological Sciences*, 16(1), 322-322.
- [71] Hancock, R. D. (1992). Chelate ring size and metal ion selection. The basis of selectivity for metal ions in open-chain ligands and macrocycles. *Journal of chemical education*, 69(8), 615.
- [72] Ercolani, G. (2003). Assessment of cooperativity in self-assembly. *Journal of the American Chemical Society*, 125(51), 16097-16103.
- [73] von Krbek, L. K., Achazi, A. J., Schoder, S., Gaedke, M., Biberger, T., Paulus, B., & Schalley, C. A. (2017). The delicate balance of preorganisation and adaptability in multiply bonded host–guest complexes. *Chemistry—A European Journal*, 23(12), 2877-2883.
- [74] He, C., Liu, D., & Lin, W. (2015). Nanomedicine applications of hybrid nanomaterials built from metal–ligand coordination bonds: nanoscale metal–organic frameworks and nanoscale coordination polymers. *Chemical reviews*, 115(19), 11079-11108.
- [75] Tesfaye, D., Linert, W., Gebrezgiabher, M., Bayeh, Y., Elemo, F., Sani, T., ... & Thomas, M. (2023). Iron (II) mediated supramolecular architectures with schiff bases and their spin-crossover properties. *Molecules*, 28(3), 1012.
- [76] Olson, A. J., Hu, Y. H., & Keinan, E. (2007). Chemical mimicry of viral capsid self-assembly. *Proceedings of the National Academy of Sciences*, 104(52), 20731-20736.
- [77] Cook, T. R., & Stang, P. J. (2015). Recent developments in the preparation and chemistry of metallocycles and metallocages via coordination. *Chemical reviews*, 115(15), 7001-7045.
- [78] Pöthig, A., & Casini, A. (2019). Recent developments of supramolecular metal-based structures for applications in cancer therapy and imaging. *Theranostics*, 9(11), 3150.

Chapter 1

- [79] Cook, T. R., Zheng, Y. R., & Stang, P. J. (2013). Metal–organic frameworks and self-assembled supramolecular coordination complexes: comparing and contrasting the design, synthesis, and functionality of metal–organic materials. *Chemical reviews*, 113(1), 734-777.
- [80] Biological Applications of Supramolecular Coordination Complexes Chung-Hang Leung, Tian-Shu Kang, and Chao Yang, Ka-Ho Leung and Dik-Lung Ma.
- [81] Moreno-Alcántar, G., & Casini, A. (2023). Bioinorganic supramolecular coordination complexes and their biomedical applications. *FEBS letters*, 597(1), 191-202.
- [82] Chen, L., & Xu, Q. (2019). Metal-organic framework composites for catalysis. *Matter*, 1(1), 57-89.
- [83] Chakrabarty, R., Mukherjee, P. S., & Stang, P. J. (2011). Supramolecular coordination: self-assembly of finite two-and three-dimensional ensembles. *Chemical reviews*, 111(11), 6810-6918.
- [84] Seidel, S. R., & Stang, P. J. (2002). High-symmetry coordination cages via self-assembly. *Accounts of chemical research*, 35(11), 972-983.
- [85] Han, M., Engelhard, D. M., & Clever, G. H. (2014). Self-assembled coordination cages based on banana-shaped ligands. *Chemical Society Reviews*, 43(6), 1848-1860.
- [86] Davis, A. V., Yeh, R. M., & Raymond, K. N. (2002). Supramolecular assembly dynamics. *Proceedings of the National Academy of Sciences*, 99(8), 4793-4796.
- [87] Seeber, G., Tiedemann, B. E., & Raymond, K. N. (2006). Supramolecular chirality in coordination chemistry. *Supramolecular chirality*, 147-183.
- [88] Biedermann, F., & Schneider, H. J. (2016). Experimental binding energies in supramolecular complexes. *Chemical reviews*, 116(9), 5216-5300..
- [89] Brown, C. J., Toste, F. D., Bergman, R. G., & Raymond, K. N. (2015). Supramolecular catalysis in metal–ligand cluster hosts. *Chemical reviews*, 115(9), 3012-3035.
- [90] Pluth, M. D., Bergman, R. G., & Raymond, K. N. (2009). Proton-mediated chemistry and catalysis in a self-assembled supramolecular host. *Accounts of chemical research*, 42(10), 1650-1659.
- [91] Alcázar Jiménez, J. J., Geue, N., Valladares, V., Cañete, A., Pérez, E. G., García-Río, L., ... & Aliaga, M. E. (2022). Supramolecular Control of Reactivity toward Hydrolysis of 7-Diethylaminocoumarin Schiff Bases by Cucurbit [7] uril Encapsulation.



Design and synthesis of an unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its metal complexes

Outline

This chapter describes the present work, related to the design and synthesis of an unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its metal complexes. The unsymmetrical pyridyl Schiff base ligand and metal (II) complexes are characterized by spectral techniques (IR, ¹H NMR and Mass) and single-crystal X-ray diffraction methods. The supramolecular properties of the metal (II) complexes derived from the unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine have been explored. The pharmacological properties of the metal (II) complexes such as anticancer and antimicrobial properties have also been explored. The related review on the Schiff base and its metal (II) complexes is also cited.

Chapter 2

Present work

This Chapter mainly highlights the following important points

- (a) Synthesis, Crystal structures, Theoretical studies, and Anticancer properties of an unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex.
- (b) Synthesis, Characterization, Antimicrobial activities of Co(III) and Cd(II) complexes derived from an unsymmetrical pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine

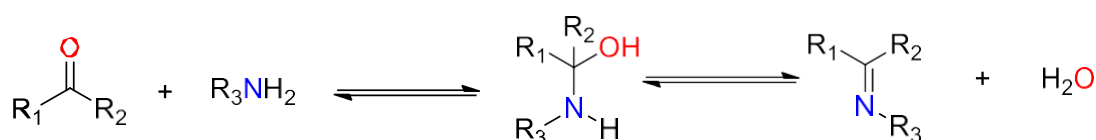
2.1. Importance of Schiff base and its metal complexes

Schiff bases are organic molecules which can be best used as a ligand, named after Hugo Schiff and are produced due to the condensation carbonyl groups (aldehyde/ketones) of organic compounds with primary amine groups of either aliphatic or aromatic compounds. Due to the presence of imine or azomethine functional groups Schiff bases exhibit special pharmacological properties. From a structural perspective, imine or azomethine ($-\text{HC}=\text{N}-$) functionality is developed due to the condensation of the carbonyl groups with the primary amine groups [1]. Schiff bases are considered “privileged ligands” due to their special characteristic of forming compounds of higher stability with the major part of metals. Hence, they become significant in the field of coordination chemistry [2-4]. Schiff base forms very stable complexes because of the chelation phenomenon.

In coordination chemistry, the chelation enhances stability due to the circulation of electrons within the ring and varies the complex's physiological nature. The stability of the coordination compounds is enhanced significantly when the chelate ring consists of five or six members. Schiff base-metal complexes have valuable applications in various fields. Schiff bases are traditionally used for the complexation with the p, d and f block metal ions that contribute to the fundamental and practical advancement of coordination chemistry. Such ligands have a significant contribution towards the formation of supramolecular species through several noncovalent interactions. The preparation of a broad range of Schiff base ligands with flexibility, chelating capacities, chirality or size can be facilitated by simple reaction conditions, which make a popular choice for designing and building supramolecular architecture for precise uses. Furthermore, macrocyclic species like helicate, meso-helicate, grid, spiral, square, cage or cube having imine/azomethine groups can also form the architecture of a supramolecule through the cyclization reaction. Such a process depends on

Chapter 2

the shape of the starting compounds and the metal-ion template has a remarkable role in carrying out cyclization reactions of macrocyclic species [5]. The research on the Schiff bases and their related metal-organic framework has attracted constant interest due to their chelating capacity, steric and electronic properties, and simplicity of tremendously modular synthesis, that permits jurisdiction type of denticity [3, 6- 9]. The general synthesis of Schiff bases is shown in **Scheme 1**.



Scheme 1. General preparation of Schiff base.

Complexes of transition metals based on Schiff bases are now important chemical entities for the creation of supramolecular aggregations *via* hydrogen bonds, coordination bonds and other various types of intermolecular interactions, leading to the development of an extensive variety of supramolecular architectures, including high dimensional frameworks. Fascinating ligands with heterocyclic rings having various binding atoms inside the ring, provide architectural beauty to these coordination complexes and weak intermolecular bonds such as hydrogen bonds, π - π stacking interactions, C-H... π chalcogen bonds, halogen bonds, and other weak intermolecular bonds have attracted researchers' curiosity in the last 20 years because of their guidance and regulation of the supramolecular framework in crystalline solids [10-18]. The aim of recent research on supramolecular chemistry and crystal engineering is to find more evidence for novel weak intermolecular interactions. The π -electron cloud often offers geometrical restrictions in the Schiff base resulting in a desirable supramolecular architecture [19-21]. Schiff base compounds and their complexes can mimic the active parts of biomolecules and hence are used in several biological fields [21, 22]. The metal ions can bind with the azomethine nitrogen atom and other active parts of the Schiff bases *via* coordinate bonds and hence provide a wide range of pharmacological activities to the complexes. Due to the pyridine ring nitrogen atom, Schiff bases containing pyridyl moiety have gained a lot of attention in coordination chemistry because of their structural modification properties. Furthermore, due to their novel electronic characteristics as well as their capacity to modify the interaction of DNA

Chapter 2

and cleaving ability, metal complexes based on Schiff bases containing pyridyl moieties have currently generated interest in the domain of pharmacological research as well as the progress of novel therapeutic medicine [24-28].



Synthesis, Crystal structures, Theoretical studies, and Anticancer properties of an unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex.

Chapter 2A

2A.1. Anticancer properties of metal-based complexes

Pt(II) derivatives have garnered significant attention in the area of anticancer therapeutic research after the cytotoxic characteristics of cisplatin were discovered. M. Peyrone prepared cisplatin for the first time in 1845, and B. Rosenberg and associates unintentionally found its anticancer activities in 1965 [29]. Because of its broad-spectrum effectiveness against numerous cancer types, including ovarian, cervix, testis, breast, bladder, rectum, head, colon, lung, and neck cancers, cisplatin is known as “the penicillin of cancer drugs” [30]. It remains among the top-selling anticancer medications worldwide after more than 50 years of use. However, cisplatin and its related platinum-based compounds have also been shown to cause severe toxicity [31]. Because of the alkylating agent cisplatin disrupts transcription and replication by creating intra and interstrand interactions which distorts the double helical structure of DNA. Platinum-based drugs are, however, non-selective and have serious toxicity. Various long-term side effects like vomiting, nephrotoxicity, ototoxicity, nausea, myelosuppression and drug resistance are found in the patients receiving cisplatin [32]. Due to the above-mentioned well-known limitations of cisplatin and its analogues, pharmaceutical chemists are working to create novel anticancer medications which are extremely effective and have minimum toxicity as well as particular selectivity.

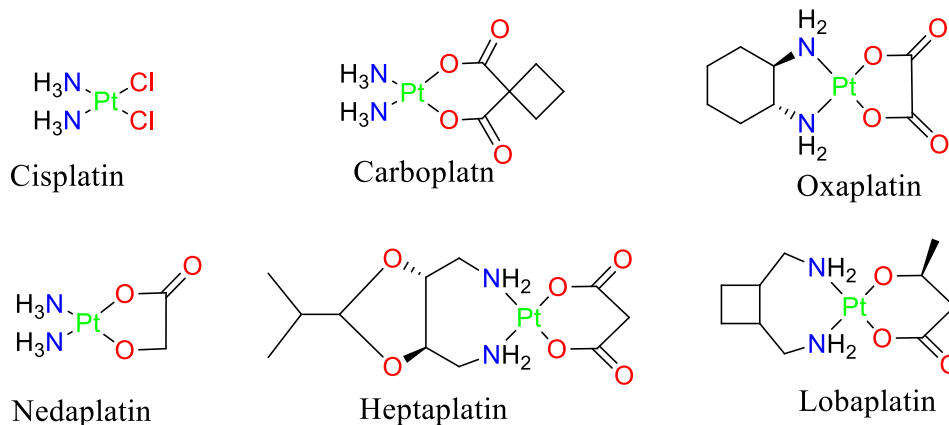


Fig. 2A.1. Clinically approved platinum-based anticancer drugs.

Recently, more active non-platinum metal-based anticancer complexes with less toxicity have been explored. Significant anticancer activity was demonstrated by metal complexes based on nickel, copper, gold, palladium, ruthenium etc exhibiting strong antitumour activity [33]. Various Schiff bases and their complexes were reported to possess potent antitumour activities [34, 35]. It is found that the metal complexes demonstrate more effectiveness compared to unbound Schiff bases, which can be best understood by Tweed’s theory (1964). According to this restricted neutralization of the metal’s positive charge with the ligand’s donor atoms and

Chapter 2A

delocalization of π electron inside the entire chelating ring make the chelation process increase the lipophilicity of the metal fundamentally and due to the penetration of the metal atom through the lipid layer of the becomes easy. The metal ions's size, the presence of bulkier organic moieties, and the high solubility of the complexes under investigation play a significant role in explaining their increased activity. The mode of action may also include the hydrogen bond formation of azomethine nitrogen atom with active parts of the cell components hence interfering with the usual cell process. Additionally, it has been shown that when the protic ligand was bonded with the specific metal ions through coordinate bonds, the anticancer potency increased. Because of the positive charge of the metal ions, the bonded protic ligands become more acidic, which in turn creates stronger hydrogen bonds with cancer cells's DNA, due to which metal chelates show greater cytotoxicity [36]. The chemistry of nickel complexes based on Schiff base ligands is important for redox enzyme systems and bioinorganic chemistry [37-40]. Morrow and associates reported that in the presence of either iodosulbenzene or magnesium monoperoxyphthalic acid (MPPA), a nickel-salen [bis-(salicylidene) ethylenediamine] complex with square planar geometry cleaves plasmid DNA. [41]. El-Metwaly and colleagues have created Schiff base complexes of Ni(II) ions that exhibit encouraging anticancer properties against the MCF-7 cancer cells *in vitro* [42]. Several Schiff base Ni(II) complexes have been published in the literature to exhibit anticancer properties against different cancer cells [43, 44].

The survey of various reports and reviews reveals that Schiff bases and their metal complexes have seen tremendous advancements in design and synthesis, but their anticancer properties are less explored. The use of pyridine-based moiety, which is a well-known motif for metal binding, has been reported less in number in the literature in designing pyridyl-incorporated unsymmetrical Schiff base ligands for metal complexation. From consideration of all the above points, we report here the preparation and characterization of an unsymmetrical pyridyl Schiff base ligand **1** and its Ni(II) complex **2** to examine the various non-covalent interactions pertaining to the supramolecular array and their applications as anticancer agents.

Chapter 2A

2A.2. Present work

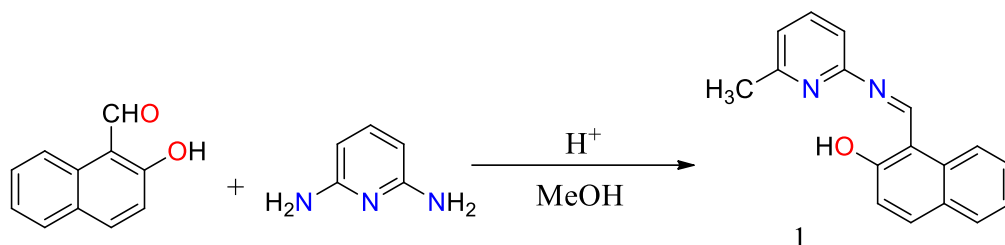
Synthesis, Crystal structures, Theoretical studies, and Anticancer properties of an unsymmetrical Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex

Section 2A describes the present work, related to the design, synthesis, supramolecular properties, DFT studies, Hirshfeld Surface analysis, and anticancer activity of the Schiff-base ligand, *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** and its hitherto unknown chelate from Ni(II) salt, bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k³N[^]N[^]O] nickel(II) **2**. The compounds are characterized by spectral techniques (IR, ¹H NMR, Mass) and single-crystal X-ray diffraction methods. Solid state structures and non-covalent interactions persisting in **1** and **2** are studied by Density Functional Theory (DFT) optimizations and Hirshfeld Surface (HS) analysis at molecular and atomic levels respectively. X-ray diffraction study shows zwitter ionic keto-amine tautomer form of planar Schiff base **1** that crystallizes in orthorhombic crystal system (space group *Pbca*) and exists as stacked column of dimeric segments in 3D formed by C13–H13A···O1ⁱ [(i) -x+1, -y, -z+1] hydrogen bonds where each dimer has a ring geometry of $R_4^2(12)$ graph-set-motif. While the chelate **2** crystallizes in monoclinic crystal system, (space group *I2/a*) and the NiN₄O₂ coordination kernel adopts distorted octahedral geometry around the Ni⁺² center. In 3D, stacked chain like supramolecular assembly is observed and overall crystal structure stability may be credited to weak C–H··· π , π ··· π stacking, van der Waals interactions and C–H···O type intermolecular hydrogen bonds that generate interesting ring/chain geometries of $2R_2^1(7)$, $R_2^1(10)$, C(5) graph-set-motifs. HS study and 2D Finger Print (FP) plots for **1-2** corroborates well with X-ray data and shows prominent O···H/H···O spikes ($2.2 \text{ \AA} < d_e + d_i < 2.3 \text{ \AA}$) and C···H/H···C ($2.5 \text{ \AA} < d_e + d_i < 2.6 \text{ \AA}$) spikes that arise from C–H···O type H-bonds and C–H··· π interactions respectively along with significant C···C interactions ($d_e + d_i \sim 3.3 \text{ \AA}$) due to π ··· π stacking **2**. HS at atomic level shows Ni–N (54.3%) and Ni–O (37.1%) coordination as spikes at $d_e + d_i \approx 1.9 \text{ \AA}$ and $d_e + d_i \approx 2 \text{ \AA}$ respectively. The anticancer activity of **1** and **2** has been investigated using cytotoxicity measure (MTT assay), apoptosis assay, quantitative polymerase chain reaction (qPCR), and colony formation assays. The Ni(II) metal complex **2**, demonstrated dose-dependent cytotoxicity *in vitro*, killing A549 lung cancer cells *via* an apoptotic pathway.

Chapter 2A

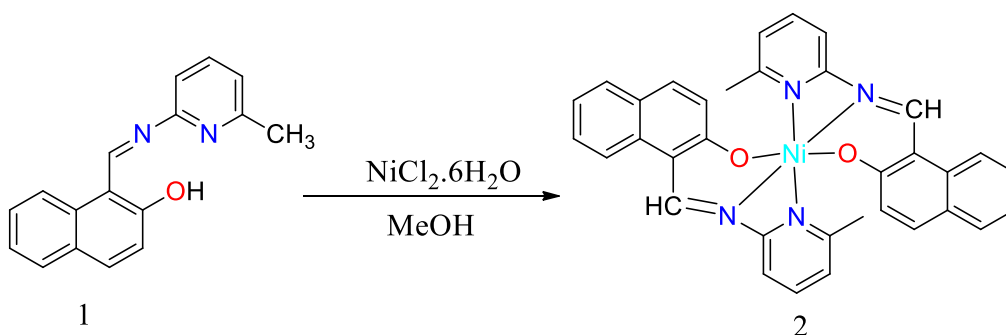
2A.2.1 Reaction schemes for the synthesis of the unsymmetrical pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** and its Ni(II) complex bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**

The compound **1** was synthesized in good yields from 2-Hydroxy-1-naphthaldehyde and 2-amino-6-methyl pyridine following **Scheme 2**.



Scheme 2. Synthesis of pyridyl Schiff base ligand **1**.

Compound **2** was synthesized from pyridyl Schiff base ligand **1** following **Scheme 3**.



Scheme 3. Synthesis of Ni(II) complex **2**.

2A.2.2 FT-IR and NMR spectral characterization of **1** and **2**

To better understand the nature of coordination modes of the pyridyl Schiff base ligand **1** to the Ni(II) metal centre, the IR spectra of **1** and **2** were carefully investigated (**Fig. 2A.2** and **Fig. 2A.3**). In the experimental section, selected vibrational spectroscopy data of the pyridyl Schiff base ligand **1** and complex **2** are presented. The presence of an intense absorption band at 1624 cm^{-1} which is due to $\nu(\text{C}=\text{N})$ of azomethine group ($-\text{CH}=\text{N}-$) in the spectra of ligand confirms the formation of pyridyl Schiff base ligand **1**. The intense absorption band at 1614 cm^{-1} in the spectra of **2** is ascribed to the imine stretching frequency of the azomethine scaffold of the ligand. The shift of the band to a lower frequency, compared to free ligand **1** (1624 cm^{-1}), signifies that the coordination interaction persists between the imine nitrogen atom to the Ni(II) metal centre. This appears to be due to the electron density shifting from the nitrogen

Chapter 2A

atom to Ni(II), which decreases the stretching frequency and weakens the C=N bond. The ligand stretching frequency at 3053 cm^{-1} in the spectra of **1** was ascribed to $\nu(\text{C-H})$ of the aromatic group. The peaks at 3031 cm^{-1} and 2920 cm^{-1} were assigned $\nu(\text{C-H})$ of olefinic and aliphatic groups in **2** respectively. The downward shift of $\nu(\text{C-O})$ band from 1304 cm^{-1} - 1134 cm^{-1} in **1** to 1254 cm^{-1} - 1089 cm^{-1} in **2** corroborates the involvement of deprotonated phenolic oxygen in the coordination with Ni(II) metal centre. The ligand coordination to the nickel ion is also confirmed by the appearance of new noticeable bands at 655 cm^{-1} and 490 cm^{-1} which can be attributed to $\nu(\text{Ni-N})$ and $\nu(\text{Ni-O})$ stretching vibrations respectively.

In addition to the IR data, a comprehensive examination of the ^1H NMR of **1** and **2** gave additional evidence to support the complex formation (**Fig. 2A.4** and **Fig. 2A.5**). The Schiff base ligand's phenolic proton (-OH) displays a doublet at most down field at δ 15.43 ppm, which is conspicuously absent in **2** that confirms the complex formation. The azomethine proton displays a doublet at δ 9.95 ppm in the free ligand **1**, while the same shows a triplet at δ 11.41 ppm in **2**. The downfield shift of the azomethine proton further corroborates the formation of **2**. The other aromatic protons in both the free ligand and Ni(II) complex are found at their suitable positions.

Overall, the structure of the synthesized Ni(II) complex in the solution state seems to be similar to that of the solid-state, according to FT-IR and ^1H NMR data.

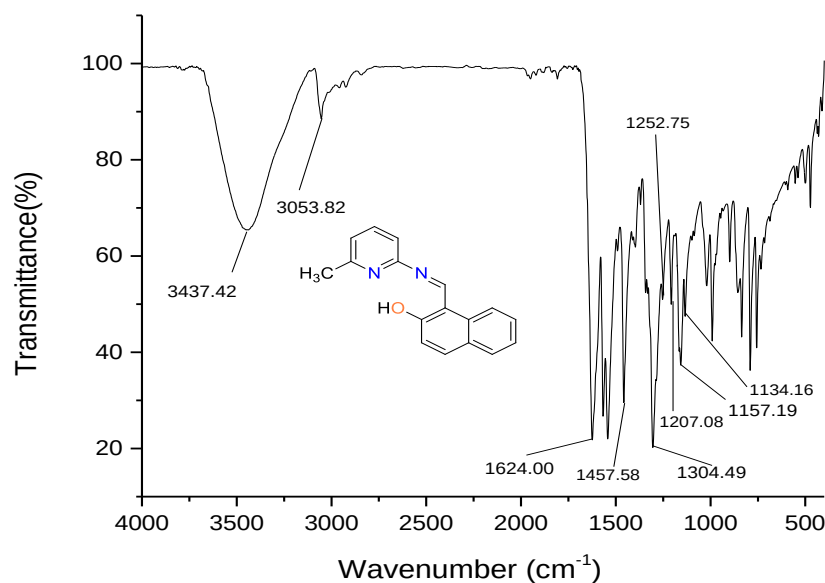


Fig. 2A.2. FT-IR spectrum of pyridyl Schiff base ligand **1**.

Chapter 2A

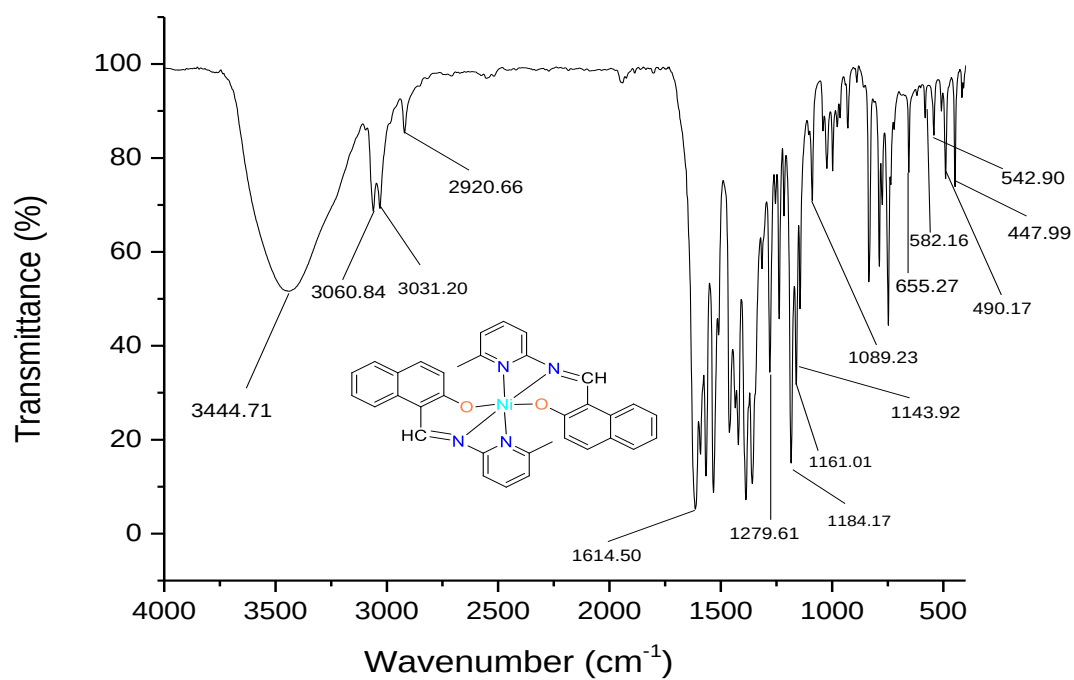


Fig. 2A.3. FT-IR spectrum of Ni(II) complex **2**.

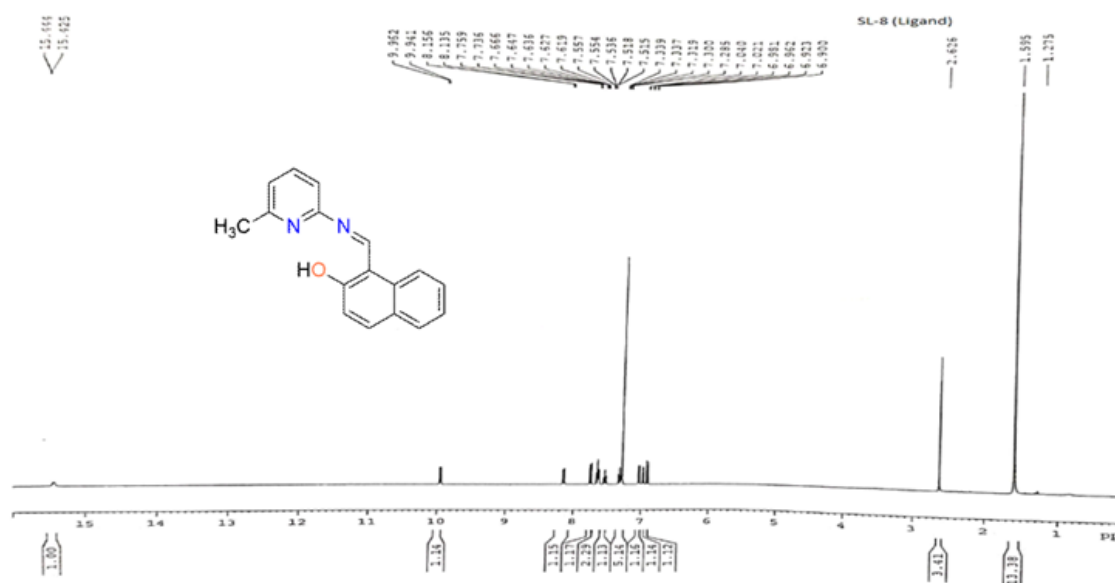


Fig. 2A.4. ^1H NMR spectrum of pyridyl Schiff base ligand **1** in CDCl_3 .

Chapter 2A

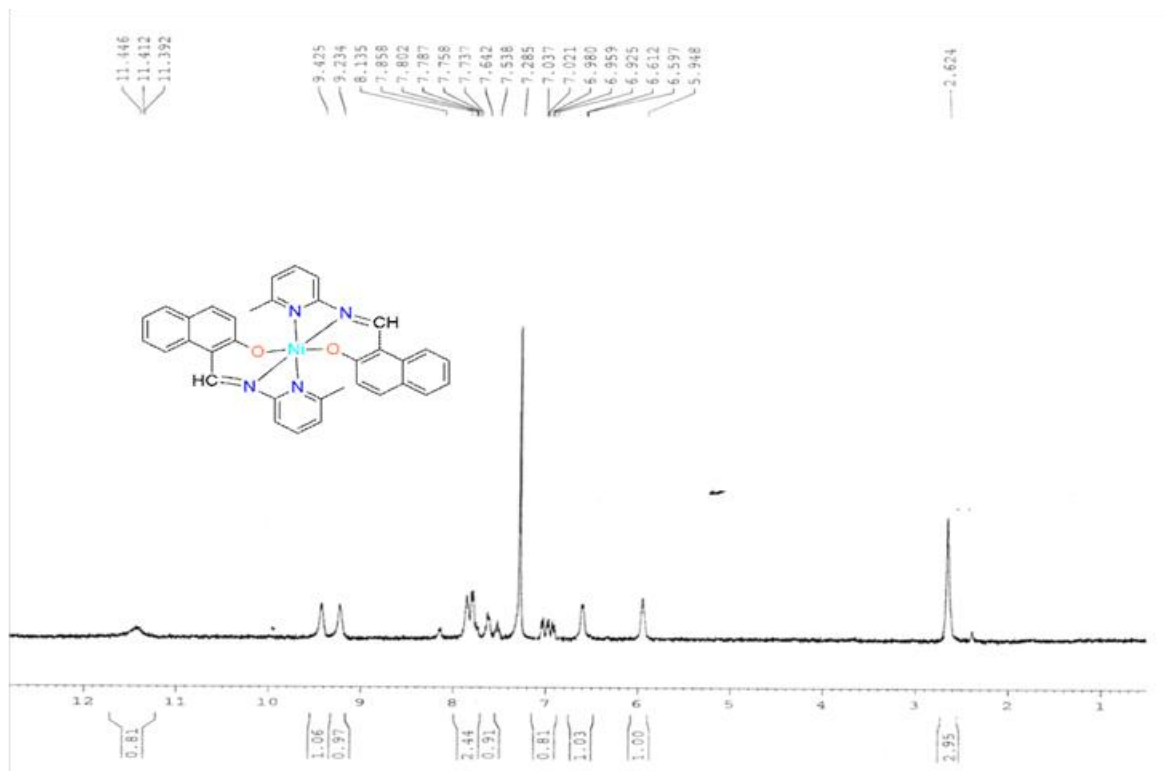


Fig. 2A.5. ¹H NMR spectrum of Ni(II) complex **2** in CDCl₃.

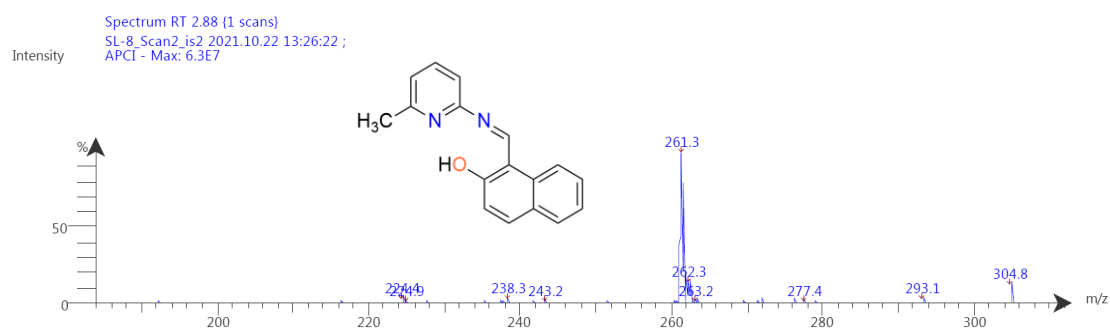


Fig. 2A.6. Mass spectrum of pyridyl Schiff base ligand **1**.

Chapter 2A

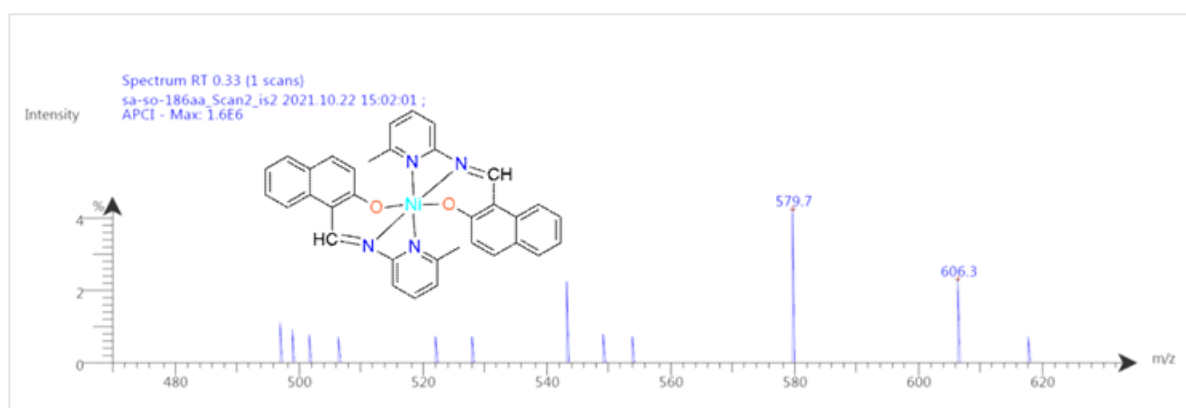


Fig. 2A.7. Mass spectrum of Ni(II) complex **2**.

2A.2.3. Description of structures of **1** and **2**

Crystallographic study of pyridyl Schiff base ligands of the class *N*-2-(*R*-pyridyl)-2-hydroxy-1-naphthalimine (*R*: H, 4-CH₃, 6-CH₃) and corresponding metal chelates remain unexplored till date with a mere twelve examples of free ligands and metal chelates [45, 46-56] were reported so far in Cambridge Structural Database (CSD). These pyridyl Schiff base ligands generally remain either as enol-imino tautomer or as keto-amine tautomer (zwitter ions) [46, 49]. The zwitter ionic structure adaptation arises due to para substitution of electron withdrawing or electron donating moieties [47, 48] at the pyridine ring. The relative energies of these keto-enol tautomer forms are further explored by DFT methods in the present study; vide infra. The pyridyl Schiff base ligand architecture generally favours bidentate coordination to metal ions through oxo and imine ends yielding a six-membered chelate ring [50-56]. In principle, the pyridyl N-atom could also participate in coordinating to metal center rendering the ligand tridentate but no such structures reported so far in CSD. Thus, we intend to investigate the possibility of tridentate coordination mode in *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalimine towards Ni²⁺ metal center which might form a new solid chelate with fascinating crystal structure and supramolecular array. In this section, crystal structures of free ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalimine **1** and its complex with Ni(II) salt, bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthalimnato-k3N[^]N[^]O] nickel(II) **2** are presented.

Chapter 2A

N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1**

The pyridyl Schiff base ligand **1** was previously reported [57], but its crystal structure remained hitherto unexamined. The crystals of **1**, are orthorhombic having *Pbca* space group with a single un-fragmented molecule in the asymmetric unit having *Z* = 8 as shown in **Fig. 2A.8**. It adopts an *E*-conformation at the imine double bond and extended π -conjugation favours a planar geometry which is evident from dihedral angles of $1.41(9)^\circ$ between naphthyl and pyridyl rings [fold angle $1.40(10)^\circ$]. The ligand **1** appears as zwitter ion in a solid state confirming its keto-amine tautomer form which is further evident from the C1–O1 [1.269(4) Å] bond length. In the optimization section, the relative energy of keto/enol forms in **1** is extensively probed using DFT methods (*vide infra*). The elongation of N1–C11 [1.323(4) Å] bond compared to a typical C=N imine (*ca.* 1.28 Å) highlights the existence of the keto-amine form of **1**. The strong N1–H1N $\cdots$ O1 intramolecular hydrogen bond characteristics of the class *N*-2-(*R*-pyridyl)-2-hydroxy-1-naphthaldimine, exist between ketonic acceptor O1 and amine donor N1–H1N that forms six membered intra rings of graph-set-motifs S(6) that stabilize the molecular geometry and crystal packing array along with nonspecific, non-directional van der Waals interactions. Crystal structure is further stabilized by intermolecular C13–H13A $\cdots$ O1ⁱ [(i) -x+1, -y, -z+1] H-bond (**Table 2A.1**) resulting in the formation of a dimer where a twelve-membered ring of graph-set-motif $R_4^2(12)$ is prominent as shown in **Fig. 2A.9** and **Fig. 2A.10** when extended in three dimensions (3D), stacked columns of independent dimers are observed along [010] axis (**Fig. 2A.9**).

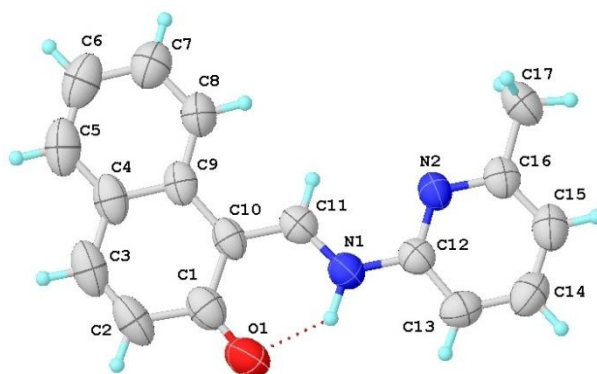


Fig. 2A.8. Molecular structure of *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine [Displacement ellipsoids at 50% probability level].

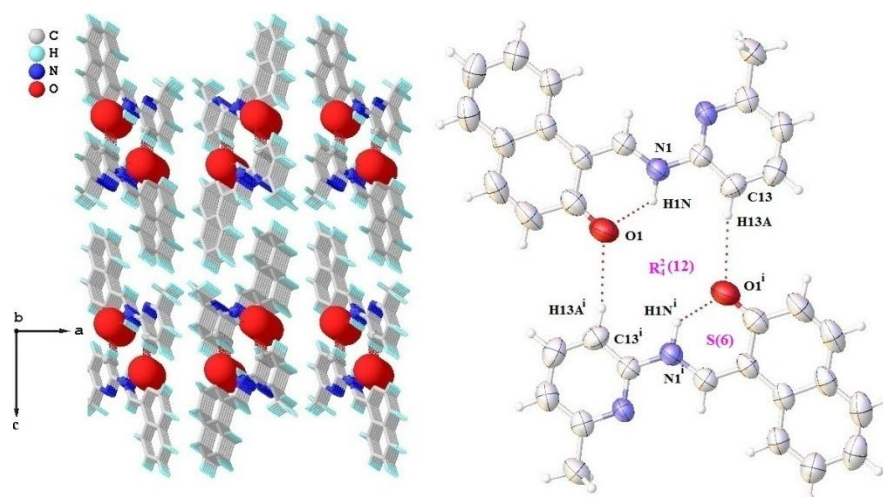


Fig. 2A.9. Partial view of 3D stacked dimeric columns along *ac* plane (left) and dimer formation by N1-H1N...O1 and C13-H13A...O1ⁱ hydrogen bonds (right) [Symmetri code (i) -x+1, -y, -z+1].

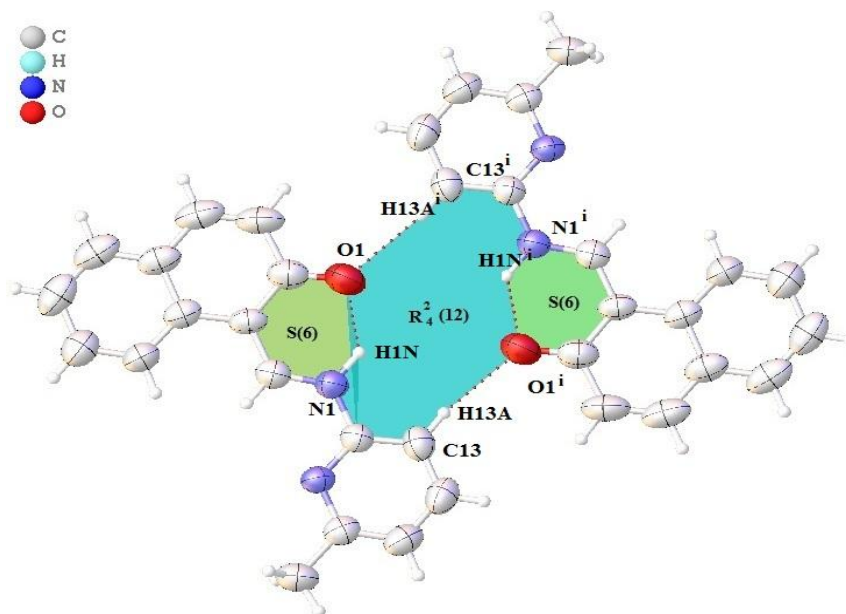


Fig. 2A.10. C-H...O and N-H...O type hydrogen bonds creating ring geometries of graph-set-motifs S(6) and R₄²(12) in *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1**. Symmetry code: (i) -x+1, -y, -z+1.

Chapter 2A

Bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**

The neutral mononuclear chelate bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2** has monoclinic crystal system, space group *I2/a* and the asymmetric unit contains half a molecule that is one Ni^{+2} ion and one *N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimine de-protonated ligand **L** and the metal center experiences hexa-coordination with NiN_4O_2 coordination environment. **Fig. 2A.11** shows that each de-protonated ligand molecule **L** coordinated to Ni^{+2} in a bischelated mode (tridentate) through imine N-atom (N1), pyridyl N-atom (N2) and oxo O-atom (O1) forming a distorted octahedral coordination kernel around metal center bearing N1, $N1^i$, O1, N2 atoms [(i) $-x+1/2, y, -z+1$] occupying corners of the equatorial basal plane, axial sites having $O1^i, N2^i$ atoms [(i) $-x+1/2, y, -z+1$] and Ni^{+2} resides marginally below the plane by a distance of 0.1683(8) Å [0.3794(7) Å from the centroid of the basal plane]. The deviation from ideal octahedral geometry apparently observed from the trans angles $163.04(10)^\circ$ [N1–Ni1–N1ⁱ], $148.20(5)^\circ$ [O1ⁱ–Ni1–N2ⁱ and O1–Ni1–N2], and chelate bite angles varying in the range $60.77(6)^\circ$ to $106.41(6)^\circ$. The observed deviation of chelate bite angles (axial-metal-equatorial) from 90° [$60.77(6)^\circ$ (N1ⁱ–Ni1–N2ⁱ), $87.64(5)^\circ$ (N1ⁱ–Ni1–O1ⁱ)] is due to the unusual coordination from non-flexible **1** to Ni^{+2} and that also contributes in the octahedral distortion, in fact, the two **L** molecules in **2** are almost perpendicular to each other with normal, twist and fold angles $89.22(4)^\circ$, $88.76(4)^\circ$ and $14.19(7)^\circ$ respectively permitting the close proximity of 2° - imine N-atoms (N1, N1ⁱ) to metal center as evident from shorter Ni–N_{imine} bonds [1.9746(13) Å (Ni1–N1 and Ni1–N1ⁱ)] compared to Ni–N_{pyridyl} bonds [2.3818(16) Å (Ni1–N2 and Ni1–N2ⁱ)] leading to relatively weaker coordination through the later. The factor of longer equatorial Ni1–N2 bonds also influences octahedral distortion and the equatorial and axial Ni–O bond distances are found to be 2.0033(13) Å [Ni1–O1 and Ni1–O1ⁱ]. Mean triangle twist angle of $42.17(6)^\circ$ between trigonal planes [plane N1N2O1ⁱ and plane N1ⁱN2ⁱO1, (i) $-x+1/2, y, -z+1$] and 1.14 s/h ratio (s = average length of the sides of the trigonal faces of the polygon, h = distance between the trigonal faces) unambiguously prove the octahedral geometry with distortions in **2**, rather than trigonal prism geometry [For ideal octahedron s/h 1.22 and twist angle 60° (staggered)]. Contrary to **2**, the pyridyl Schiff base ligand **1** favours tetrahedral geometry in reported Schiff base complexes of Cu(II) and Zn(II) [45,56]. Interestingly complex **2** is found to be the first ever octahedral Ni^{+2} based chelate harvested from *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine in Cambridge Structural Database (CSD). The large Ni....Ni distances [6.2716(2) Å– 12.2347(10) Å] between neighbouring asymmetric units nullifying the possibility of Ni(II)....Ni(II) metallophilic interaction [57].

Chapter 2A

In **2**, each ligand moiety forms three C–H···O type intermolecular hydrogen bonds with oxo O-atoms of perpendicular **L** moieties in nearby asymmetric units that undoubtedly contribute to supramolecular crystal architecture (**Table 2A.1**, **Fig. 2A.12**). These C–H···O hydrogen bonds and other existing interactions (van der Waals) are responsible for imparting stability to crystal structure. Apart from C–H···O type H-bonds, weak interactions arising from C–H··· π and π ··· π stacking also contribute to crystal stability. The weak C–H··· π interactions exist between naphthyl C10–H10 of **2** and cg that is naphthyl ring of adjacent **2** with a distance of 2.235(2) Å [H10 to cg centroid distance 3.3885(7) Å] along *ac* plane (**Fig. 2A.13**). Whereas the parallel naphthyl and pyridyl rings in crystal packing array favour the π ··· π stacking with the cg···cg distance of 3.6800(10) Å (**Fig. 2A.14**). The cg···cg twist angle is 12.00(15)° [1.522(3) Å {plane shift angle}, 0.12(6)° {fold angle}]. Close observations lead to the fact that these C–H···O connectors create intermolecular seven membered [ring O1ⁱH1C1N1C12C13H13 (i: x-½, -y+1, z)], ten membered ring geometries [ring H10C10C11C2C1N1C12C13H13O1ⁱ (i: x-½, -y+1, z)] and infinite chain geometries having five membered repeating units (chain bearing atoms H1, C1, N1, Ni1, O1) of graph-set-motifs 2R₂¹(7), R₂¹(10) and C(5) respectively (**Fig. 2A.15**). In two dimensions (2D) these H-bonds are found to link the molecules in the formation of independent parallel infinite chains, and each chain consists of parallel moieties of **L** flanked by consecutive perpendicular pair of **L** moieties (**Fig. 2A.16**). Further extending the connectivity through these C–H···O H-bonds in crystal packing forms a three-dimensional (3D) stacked chain like array along *bc* plane (**Fig. 2A.16**). The crystal packing pattern as 3D right handed helix shows consecutive perpendicular and parallel pairs of **L** moieties in a chain assuming the imaginary axis passing through Ni⁺² ions of each complex molecule (**Fig. 2A.16**) where parallel naphthyl and pyridyl rings are linked presumably by weak π ··· π interactions.

Table 2A.1. Summary of intermolecular interactions in **1** and **2**.

D–H···A	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	<(D–H···A) (°)
1				
N1–H1N···O1	0.99(4)	1.81(3)	2.577(4)	132(3)
C13–H13A···O1 ⁱ	0.93	2.423(3)	3.328(4)	164.4(2)
2				
C1–H1···O1 ⁱⁱ	0.98(2)	2.58(2)	3.435(19)	147(16)
C10–H10···O1 ⁱⁱ	0.95	2.5474(12)	3.443(2)	157.21(12)

Chapter 2A

C13–H13···O1ⁱⁱ 0.95 2.3899(13) 3.250(2) 150.48(11)

symmetry operation: (i) $-x+1, -y, -z+1$; (ii) $x-\frac{1}{2}, -y+1, z$.

Table 2A.2. Crystal data and structure refinement for **1** and **2**.

Parameters	1	2
Empirical formula	C ₁₇ H ₁₄ N ₂ O	C ₃₄ H ₂₆ N ₄ NiO ₂
Formula weight	262.30	581.30
Temperature (K)	296(2) K	100(2) K
Crystal system	Orthorhombic	Monoclinic
Space group	P b c a	I 2/a
a (Å)	16.2423(11)	12.2347(1)
b (Å)	5.6367(4)	9.4157(1)
c (Å)	29.285(2)	23.5556(3)
α (°)	90	90
β (°)	90	91.696(1)
γ (°)	90	90
V (Å ³)	2681.2(3)	2712.38(5)
Z	8	4
D _{cal} (gcm ⁻³)	1.300	1.423
μ (mm ⁻¹)	0.082	1.347
F(000)	1104	1208
θ range for data collection (°)	1.872 to 30.725	3.755 to 71.228
Index ranges	-22 ≤ h ≤ 16, -7 ≤ k ≤ 8, -41 ≤ l ≤ 33	-13 ≤ h ≤ 15, -11 ≤ k ≤ 11, -28 ≤ l ≤ 28
Reflections collected	44797	11926
Independent reflections	4050 [R(int) = 0.1316]	2623 [R(int) = 0.0190]
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max and min transmission	1.00000 and 0.80969	1.00000 and 0.04306
Data/restraints/parameters	4050/0/186	2623/0/191
Goodness-of-fit on F ²	1.013	1.089
Final R indices [$I > 2\sigma(I)$]	R ₁ = 0.1002, wR ₂ = 0.1395	R ₁ = 0.0361, wR ₂ = 0.0957
Final R indices [all data]	R ₁ = 0.2952, wR ₂ = 0.1880	R ₁ = 0.0390, wR ₂ = 0.0973
Largest difference in peak and hole (e Å ⁻³)	0.169 and -0.132	
CCDC	2077047	2150126

Chapter 2A

Table 2A.3. Bond lengths (Å) of *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** and bis [*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**.

Bond lengths					
Compound 1					
O1—C1	1.269 (4)	C1—C10	1.440 (4)	C4—C5	1.396 (5)
C7—C8	1.363 (4)	C11—H11A	0.9300	C15—C16	1.378 (4)
N1—C11	1.323 (4)	C1—C2	1.451 (5)	C4—C9	1.403 (4)
C7—H7A	0.9300	C12—C13	1.373 (4)	C15—H15A	0.9300
N1—C12	1.413 (4)	C2—C3	1.336 (5)	C5—C6	1.357 (5)
C8—C9	1.400 (4)	C13—C14	1.374 (4)	C16—C17	1.508 (4)
N1—H1N	0.99 (4)	C2—H2A	0.9300	C5—H5A	0.9300
C8—H8A	0.9300	C13—H13A	0.9300	C17—H17A	0.9600
N2—C12	1.331 (4)	C3—C4	1.426 (5)	C6—C7	1.392 (5)
C9—C10	1.458 (4)	C14—C15	1.377 (4)	C17—H17B	0.9600
N2—C16	1.341 (4)	C3—H3A	0.9300	C6—H6A	0.9300
C10—C11	1.392 (4)	C14—H14A	0.9300	C17—H17C	0.9600
Complex 2					
Ni1—Ni1i	1.9746 (13)	N1—C1	1.300 (2)	C2—C11	1.459 (2)
C6—C7	1.414 (2)	C10—C11	1.417 (2)	C15—C16	1.393 (3)
Ni1—N1	1.9746 (13)	N1—C12	1.398 (2)	C3—C4	1.437 (3)
C7—C8	1.370 (3)	C10—H10	0.9500	C15—H15	0.9500
Ni1—O1i	2.0033 (13)	N2—C16	1.335 (3)	C4—C5	1.351 (3)
C7—H7	0.9500	C12—C13	1.393 (2)	C16—C17	1.503 (3)
Ni1—O1	2.0034 (13)	N2—C12	1.350 (2)	C4—H4	0.9500
C8—C9	1.396 (3)	C13—C14	1.381 (3)	C17—H17A	0.9800
Ni1—N2i	2.3818 (16)	C1—C2	1.418 (3)	C5—C6	1.430 (3)
C8—H8	0.9500	C13—H13	0.9500	C17—H17B	0.9800
Ni1—N2	2.3818 (16)	C1—H1	0.98 (2)	C5—H5	0.9500
C9—C10	1.377 (3)	C14—C15	1.386 (3)	C17—H17C	0.9800
O1—C3	1.291 (2)	C2—C3	1.436 (2)	C6—C11	1.411 (3)
C9—H9	0.9500	C14—H14	0.9500		

Chapter 2A

Table 2A.4. Bond angles ($^{\circ}$) of *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** and bis [*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**

Bond angles					
Compound 1					
C11—N1—C12	124.5 (3)	C2—C3—C4	123.1 (4)	C5—C6—H6A	120.5
C8—C9—C10	123.8 (3)	C13—C12—N1	118.8 (3)	N2—C16—C15	122.7 (3)
C11—N1—H1N	117 (2)	C2—C3—H3A	118.5	C7—C6—H6A	120.5
C4—C9—C10	118.7 (3)	C12—C13—C14	117.5 (3)	N2—C16—C17	116.3 (3)
C12—N1—H1N	119 (2)	C4—C3—H3A	118.5	C8—C7—C6	120.7 (4)
C11—C10—C1	119.3 (3)	C12—C13— H13A	121.3	C15—C16—C17	121.0 (3)
C12—N2—C16	116.7 (3)	C5—C4—C9	120.0 (4)	C8—C7—H7A	119.7
C11—C10—C9	120.3 (3)	C14—C13— H13A	121.3	C16—C17— H17A	109.5
O1—C1—C10	122.1 (3)	C5—C4—C3	120.6 (4)	C6—C7—H7A	119.7
C1—C10—C9	120.4 (3)	C13—C14—C15	119.4 (3)	C16—C17—H17B	109.5
O1—C1—C2	120.5 (4)	C9—C4—C3	119.4 (4)	C7—C8—C9	121.5 (3)
N1—C11—C10	124.5 (3)	C13—C14— H14A	120.3	H17A—C17— H17B	109.5
C10—C1—C2	117.4 (4)	C6—C5—C4	121.3 (4)	C7—C8—H8A	119.3
N1—C11— H11A	117.8	C15—C14— H14A	120.3	C16—C17—H17C	109.5
C3—C2—C1	120.9 (4)	C6—C5—H5A	119.3	C9—C8—H8A	119.3
C10—C11— H11A	117.8	C14—C15—C16	118.9 (3)	H17A—C17— H17C	109.5
C3—C2—H2A	119.5	C4—C5—H5A	119.3	C8—C9—C4	117.4 (3)
N2—C12—C13	124.8 (3)	C14—C15— H15A	120.5	H17B—C17— H17C	109.5
C1—C2—H2A	119.5	C5—C6—C7	119.1 (4)		
N2—C12—N1	116.5 (3)	C16—C15— H15A	120.5		

Chapter 2A

Complex 2

N1i—Ni1—N1	163.04 (10)	O1—Ni1—N2	148.20 (5)	C1—C2—C11	119.33 (15)
C11—C6—C5	119.05 (16)	C11—C10—H10	119.3	C14—C15—C16	119.23 (18)
N1i—Ni1—O1i	87.64 (5)	N2i—Ni1—N2	91.50 (7)	C3—C2—C11	119.08 (16)
C7—C6—C5	120.38 (18)	C6—C11—C10	116.91 (16)	C14—C15—H15	120.4
N1—Ni1—O1i	103.70 (5)	C3—O1—Ni1	129.07 (11)	O1—C3—C2	125.96 (17)
C8—C7—C6	120.9 (2)	C6—C11—C2	120.18 (15)	C16—C15—H15	120.4
N1i—Ni1—O1	103.70 (5)	C1—N1—C12	124.68 (15)	O1—C3—C4	116.30 (15)
C8—C7—H7	119.6	C10—C11—C2	122.91 (17)	N2—C16—C15	121.16 (17)
N1—Ni1—O1	87.64 (5)	C1—N1—Ni1	131.58 (12)	C2—C3—C4	117.73 (15)
C6—C7—H7	119.6	N2—C12—C13	122.89 (17)	N2—C16—C17	116.63 (19)
O1i—Ni1—O1	96.90 (8)	C12—N1—Ni1	103.63 (10)	C5—C4—C3	122.78 (17)
C7—C8—C9	119.18 (18)	N2—C12—N1	108.60 (15)	C15—C16—C17	122.22 (19)
N1i—Ni1—N2i	60.77 (6)	C16—N2—C12	119.27 (16)	C5—C4—H4	118.6
C7—C8—H8	120.4	C13—C12—N1	128.50 (16)	C16—C17—H17A	109.5
N1—Ni1—N2i	106.41 (6)	C16—N2—Ni1	153.65 (13)	C3—C4—H4	118.6
C9—C8—H8	120.4	C14—C13—C12	117.33 (17)	C16—C17—H17B	109.5
O1i—Ni1—N2i	148.20 (5)	C12—N2—Ni1	86.95 (11)	C4—C5—C6	121.05 (18)
C10—C9—C8	120.96 (19)	C14—C13—H13	121.3	H17A—C17— H17B	109.5
O1—Ni1—N2i	94.35 (5)	N1—C1—C2	124.11 (15)	C4—C5—H5	119.5
C10—C9—H9	119.5	C12—C13—H13	121.3	C16—C17—H17C	109.5
N1i—Ni1—N2	106.41 (6)	N1—C1—H1	117.8 (12)	C6—C5—H5	119.5
C8—C9—H9	119.5	C13—C14—C15	120.12 (18)	H17A—C17— H17C	109.5
N1—Ni1—N2	60.77 (6)	C2—C1—H1	118.0 (12)	C11—C6—C7	120.56 (17)
C9—C10—C11	121.41 (19)	C13—C14—H14	119.9	H17B—C17— H17C	109.5

Chapter 2A

O1i—Ni1—N2	94.35 (5)	C1—C2—C3	121.59 (15)
C9—C10—H10	119.3	C15—C14—H14	119.9

Table 2A.5. Torsion angles ($^{\circ}$) of *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** and bis [*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**

Torsion angles			
Compound 1			
O1—C1—C2—C3	177.6 (4)	C7—C8—C9—C4	0.6 (5)
C8—C9—C10—C11	1.7 (5)	C11—N1—C12—C13	179.7 (3)
C10—C1—C2—C3	−1.9 (5)	C7—C8—C9—C10	−178.6 (3)
C4—C9—C10—C11	−177.5 (3)	N2—C12—C13—C14	−3.8 (5)
C1—C2—C3—C4	2.2 (6)	C5—C4—C9—C8	−1.0 (5)
C8—C9—C10—C1	−178.9 (3)	N1—C12—C13—C14	176.0 (3)
C2—C3—C4—C5	179.6 (4)	C3—C4—C9—C8	179.0 (3)
C4—C9—C10—C1	1.9 (4)	C12—C13—C14—C15	1.9 (5)
C2—C3—C4—C9	−0.4 (5)	C5—C4—C9—C10	178.3 (3)
C12—N1—C11—C10	−177.7 (3)	C13—C14—C15—C16	0.5 (5)
C9—C4—C5—C6	1.2 (5)	C3—C4—C9—C10	−1.7 (5)
C1—C10—C11—N1	−2.4 (5)	C12—N2—C16—C15	−0.2 (5)
C3—C4—C5—C6	−178.8 (3)	O1—C1—C10—C11	−0.2 (5)
C9—C10—C11—N1	177.1 (3)	C12—N2—C16—C17	−178.6 (3)
C4—C5—C6—C7	−1.0 (6)	C2—C1—C10—C11	179.3 (3)
C16—N2—C12—C13	3.0 (5)	C14—C15—C16—N2	−1.5 (5)

Chapter 2A

C5—C6—C7—C8	0.7 (6)	O1—C1—C10—C9	−179.7 (3)
C16—N2—C12—N1	−176.8 (3)	C14—C15—C16—C17	176.9 (3)
C6—C7—C8—C9	−0.5 (5)	C2—C1—C10—C9	−0.1 (5)
C11—N1—C12—N2	−0.4 (4)		

Complex 2

C12—N1—C1—C2	177.69 (16)	C3—C4—C5—C6	−1.1 (3)
C9—C10—C11—C6	−3.8 (3)	C1—N1—C12—C13	6.7 (3)
Ni1—N1—C1—C2	2.2 (3)	C4—C5—C6—C11	−2.4 (3)
C9—C10—C11—C2	176.82 (18)	Ni1—N1—C12—C13	−176.76 (16)
N1—C1—C2—C3	−0.9 (3)	C4—C5—C6—C7	178.84 (19)
C1—C2—C11—C6	177.35 (16)	N2—C12—C13—C14	0.1 (3)
N1—C1—C2—C11	179.40 (16)	C11—C6—C7—C8	−0.7 (3)
C3—C2—C11—C6	−2.4 (3)	N1—C12—C13—C14	178.95 (17)
Ni1—O1—C3—C2	1.8 (3)	C5—C6—C7—C8	178.0 (2)
C1—C2—C11—C10	−3.3 (3)	C12—C13—C14—C15	−0.3 (3)
Ni1—O1—C3—C4	−178.57 (12)	C6—C7—C8—C9	−1.8 (4)

C3—C2—C11—C10	177.00 (16)	C13—C14—C15—C16	0.3 (3)
C1—C2—C3—O1	−1.1 (3)	C7—C8—C9—C10	1.5 (4)
C16—N2—C12—C13	0.0 (3)	C12—N2—C16—C15	0.0 (3)
C11—C2—C3—O1	178.57 (16)	C8—C9—C10—C11	1.4 (3)
Ni1—N2—C12—C13	177.26 (16)	Ni1—N2—C16—C15	−173.79 (19)
C1—C2—C3—C4	179.28 (16)	C7—C6—C11—C10	3.4 (3)
C16—N2—C12—N1	−179.03 (15)	C12—N2—C16—C17	179.65 (17)
C11—C2—C3—C4	−1.0 (2)	C5—C6—C11—C10	−175.33 (17)
Ni1—N2—C12—N1	−1.77 (12)	Ni1—N2—C16—C17	5.8 (4)

Chapter 2A

O1—C3—C4—C5	−176.83 (18)	C7—C6—C11—C2	−177.17 (17)
C1—N1—C12—N2	−174.37 (16)	C14—C15—C16—N2	−0.2 (3)
C2—C3—C4—C5	2.8 (3)	C5—C6—C11—C2	4.1 (3)
Ni1—N1—C12—N2	2.19 (15)	C14—C15—C16—C17	−179.80 (19)

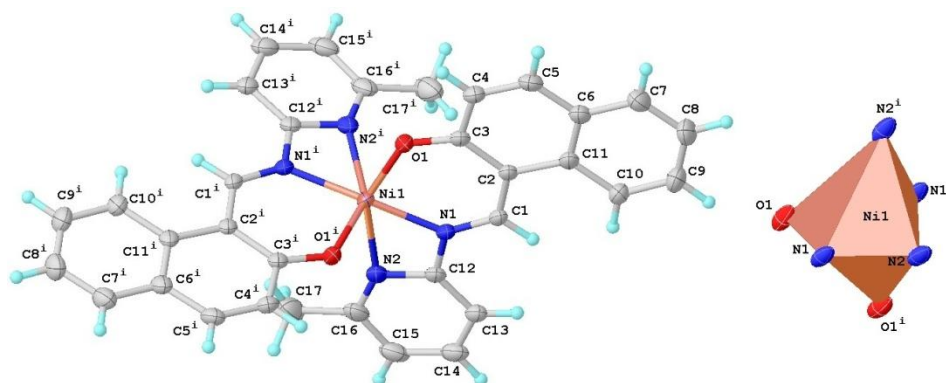


Fig. 2A.11. Crystal structure of **2** with atom labelling scheme at 50% probability ellipsoids (left) and distorted octahedron around Ni^{+2} (right). Symmetry code: (i) $-x+1/2, y, -z+1$.

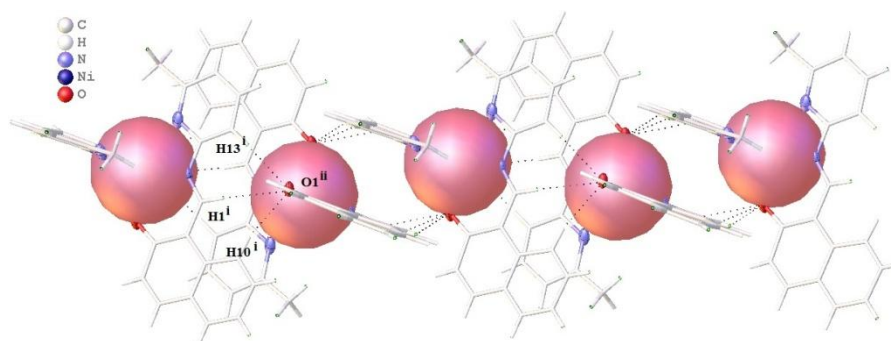


Fig. 2A.12. Partial view of C—H $\cdots$ O type hydrogen bonds in **2**. [Symmetru codes: (i) $-x+1/2, y, -z+1$; (i) $-x, -y+1, -z+1$; (iii) $x-1/2, -y+1, z$.].

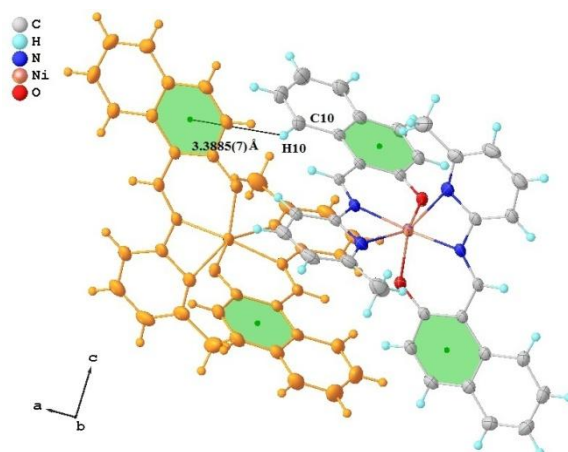


Fig. 2A.13. View of weak C-H... π interactions between C10–H10 and naphthyl moiety in 2.

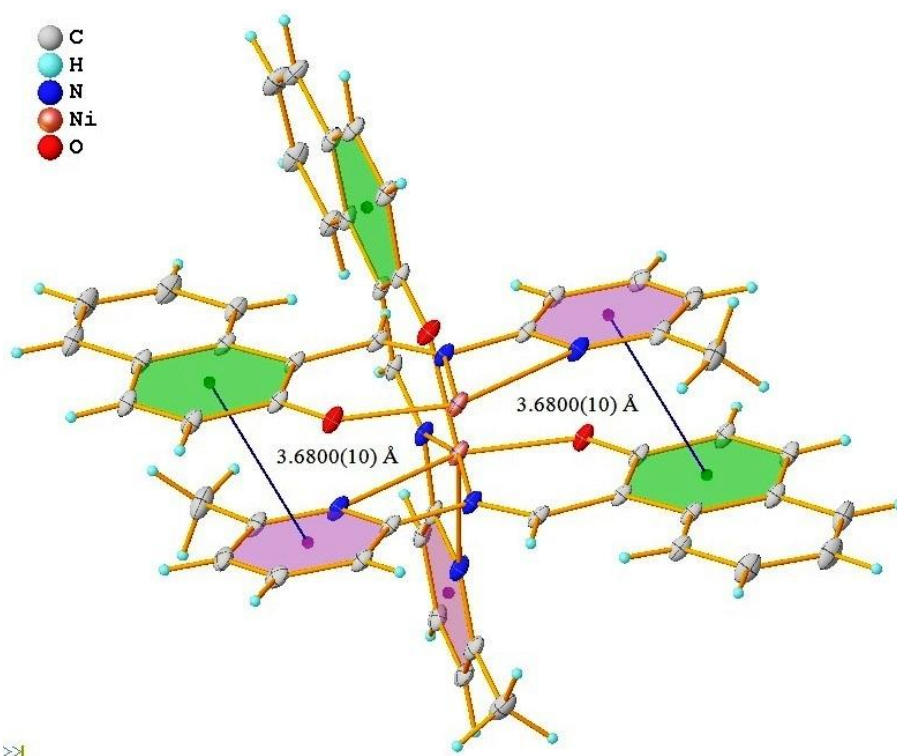


Fig. 2A.14. View of weak π - π interactions in 2.

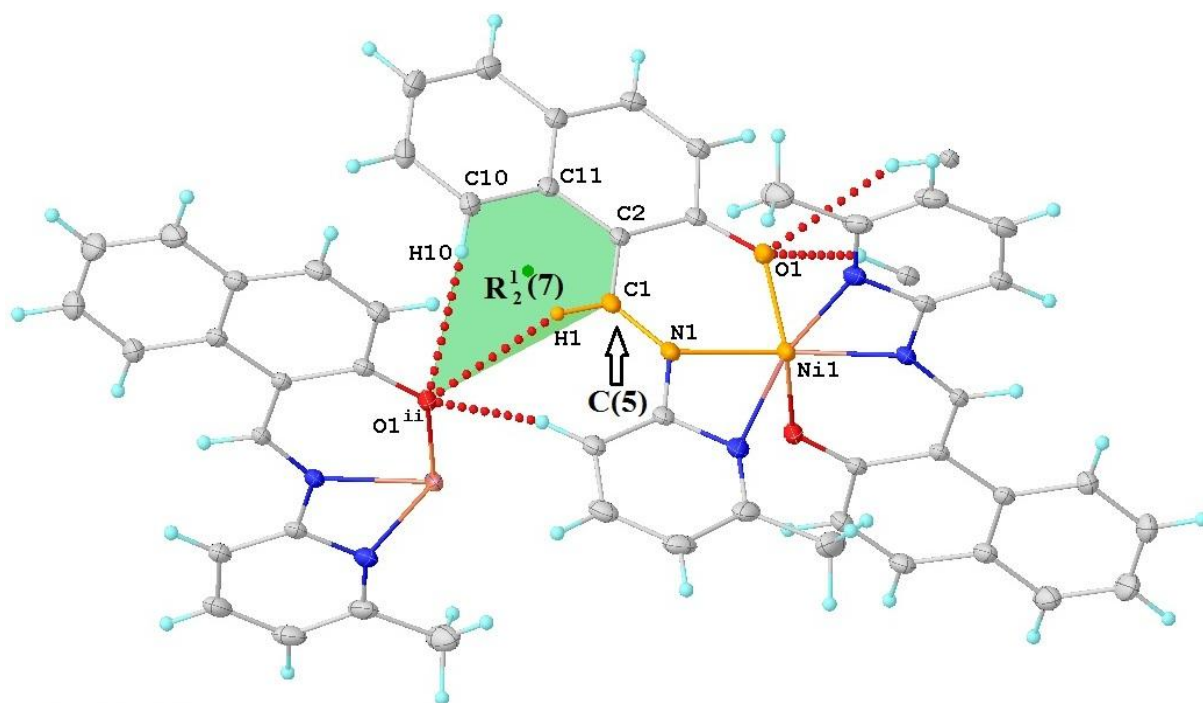


Fig. 2A.15. C–H···O hydrogen bonds creating rings and infinite chain geometries of graph-set-motifs $2R_2^1(7)$, $R_2^1(10)$ and $C(5)$ in bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2**. Symmetry codes: (i) $-x+1/2, y, -z+1$; (ii) $x-1/2, -y+1, z$.

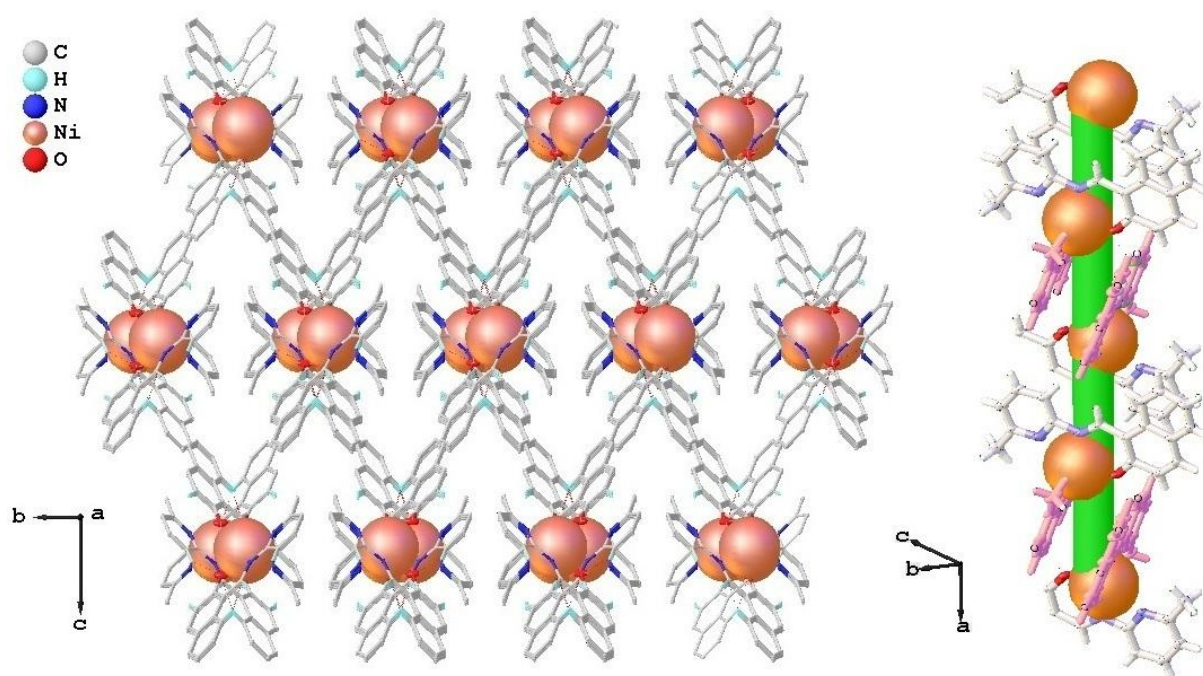


Fig. 2A.16. Projection of stacked chain type 3D supramolecular architecture in **2** along *bc* plane (left). Crystal packing arrangement as 3D right-handed helix (right).

Chapter 2A

2A.2.4. DFT Simulations of **1** and **2**

Given the unusual geometry of the metal chelate and the number of stabilizing intermolecular interactions in the pyridyl Schiff base ligand **1** structure, density functional theory (DFT) simulations were used to further understand the solid-state structures of both the free ligand and metal chelate. In the case of the free ligand **1**, the relative energies of the zwitterionic and neutral tautomers were analyzed to explain why they have both been observed experimentally in the CSD. The nickel(II) chelate **2** is a unique example of an octahedral bis(imino-methyl-2-naphthoate) chelate, the first reported in the CSD, to the best of our knowledge. The relative stabilities of the square planar and octahedral bis(imino-methyl-2-naphthoate) chelates are thus relevant. The simulations were performed using Gaussian 09W [58] at the CAM-B3LYP/6-311G level of theory. Single first polarization functions (d, p) were added to the basis set to increase the accuracy of the simulations. The X-ray coordinates were used for the input structures. The input files were prepared using Gauss View 5.0 [59]; the same program was used to analyze the output files. Geometry optimization and frequency calculations were executed for all structures studied by DFT methods using the above-mentioned level of theory. The absence of negative frequency eigen values (except where indicated in the text) suggests that the geometry-optimized structures are true minima on the global potential energy surface.

Analysis of the solid-state structures of this class of pyridyl Schiff base ligands reported in the CSD shows that both zwitterionic and neutral tautomers are known. In the present study, the zwitterionic form was noted. Simulations show that the zwitterion is a modest 2.4 kJ mol^{-1} lower in energy than the neutral form (**Fig. 2A.17**). This low energy barrier could explain why both forms have been reported in the solid state. It is also interesting to note that in both forms, the frequency eigen values are all positive. This suggests that both structures are stable in the gas phase. The intramolecular hydrogen bond is ubiquitous in all closely related pyridyl Schiff base ligand structures reported in the CSD. Simulations at the above level of theory show that the intramolecular hydrogen bond stabilizes the ligand by 74.5 kJ mol^{-1} . The enol form without a hydrogen bond also has a negative frequency eigen value, indicating that it is a saddle point on the potential energy surface.

The energetics of the tridentate versus bidentate coordination modes of the pyridyl Schiff base ligand **1** were evaluated using the above level of theory (**Fig. 2A.18**). These simulations show that an octahedral geometry with two ligands coordinated in a tridentate mode (as was experimentally observed herein) is significantly less stable, by 82.4 kJ mol^{-1} , than the square planar geometry resulting from a bidentate coordination mode. This large energy barrier is a

Chapter 2A

plausible explanation for the exclusively square planar and tetrahedral bis(imino-methyl-2-naphthoate) metal chelates reported in the CSD. In this work, the crystals were grown by a less common branched tube-sealed apparatus above room temperature. It is possible that growing the crystals at an elevated temperature might have supplied the energy required to form the octahedral species.

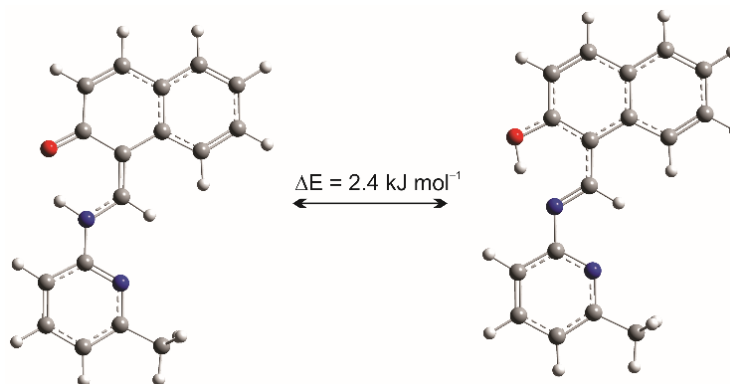


Fig. 2A.17. Geometry-optimized structure of the pyridyl Schiff base ligand **1** in two possible canonical forms together with the energy difference (ΔE) of 2.4 kJ mol^{-1} indicated. The geometry-optimized version of the solid-state structure (ketone form) is the lowest energy conformation.

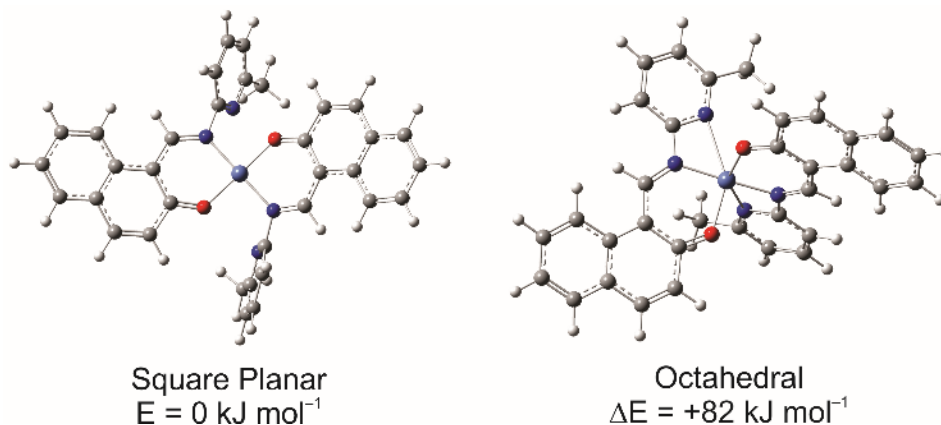


Fig. 2A.18. Geometry-optimized structures of square planar and octahedral forms of the bis(imino methyl-2-naphthoate) nickel(II) chelates **2** together with their respective ΔE (kJ mol^{-1}). The geometry-optimized square planar conformation is the lowest energy reference for the ΔE calculation.

2A.2.5 Hirshfeld surface analysis of **1** and **2**

The 3D Hirshfeld surface (HS) [60, 61] and 2D fingerprint (FP) plots are now a days extensively used as optimization tools for analysing multicomponent crystal structures [62],

Chapter 2A

unveiling the proximal surroundings of a molecule and quantifying all non-covalent intermolecular interactions, thereby aiding the systematic study of related crystal structures [63, 64].

Fig. 2A.19 shows the 3D HS_{molecular} mapped with d_{norm} , SI and C for **1** and **2**. While optimization, resolution was set at standard (high) and after the generation of HSs, the surface transparency option enabled to study of all non-covalent interactions *via* the mapped surfaces. HS quantitative properties like molecular volume (V_H), surface area (A_H), globularity (G), and asphericity (Ω) for **1** and **2** are mentioned in **Table 2A.6**. Because of its compact form, **2** has greater Hirshfeld volumes (V_H) and surface areas (A_H) compared to Schiff base **1**. The globularity [65] values for **1** and **2** are less than one, indicating that the asymmetric units have well-defined 3D surfaces where HS of **1** is more convex in nature. The pyridyl Schiff base ligand **1** has higher anisotropy properties and can be referred to as an oblate object compared to **2** (**Table 2A.6**) as the latter has a lower asphericity [66] value.

Two deep circular red depressions on HS (d_{norm}) in **1** (**Fig. 2A.20**) indicate strong O $\cdots$ H/H $\cdots$ O contacts (optimized O $\cdots$ H distance 2.276 Å) resulting from C13–H13A $\cdots$ O1 hydrogen bond (**Table 2A.1**), while in case of **2**, three intense deep red depressions of varied sizes around each hydroxy O atom are observed that indicate strong O $\cdots$ H non-covalent interactions with optimized distances 2.425 Å (O1 $\cdots$ H10), 2.486 Å (O1 $\cdots$ H1) and 2.275 Å (O1 $\cdots$ H13) (**Fig. 2A.21**) that well corroborates with C–H $\cdots$ O type H-bonds (**Table 2A.1**). The same optimized data were also found for H $\cdots$ O contacts that appeared as six bright red depressions around C10–H10, C1–H1 and C13–H13 donor moieties (**Fig. 2A.19**). Rest of the faded red depressions on HS in **1**, indicate weak C $\cdots$ H/H $\cdots$ C contacts with optimized distances of 2.763 Å (C11 $\cdots$ H17C) and 2.719 Å (C7 $\cdots$ H8A) where the later specifically can be assigned for C–H $\cdots$ π type interactions between C8–H8A donor and c.g acceptor (ring C4C5C6C7C8C9) (**Fig. 2A.22** and **Fig. 2A.23**). The existence of C–H $\cdots$ π interaction is further proven from the appearance of characteristic concave (-0.6596) red patches around C7 and convex (0.6528) deep blue region around H8A on the shape index mapped HS. Similarly for **2**, faded red regions around each naphthyl ring (C3, C10, H7) appeared that indicate C $\cdots$ H/H $\cdots$ C contacts, out of which the red depression around C10–H10 moiety can be assigned for the weak C–H $\cdots$ π interactions between C10–H10 donor and c.g. acceptor (ring C1C2C3C4C5C6) with an optimized H $\cdots$ π distance of 2.576 Å (**Fig. 2A.22**). The C–H $\cdots$ π interaction is further confirmed as blue patches appeared on shape index mapped HS (deep red region on d_i). The ligand

Chapter 2A

has no π - π interaction in crystal packing arrangement as no characteristic flat green surfaces (curvedness) and red-blue triangles (shape index) on the HS. On the contrary for **2**, HS (d_{norm}) has a faded white region around the pyridyl ring (ring N2C12C13C14C15C16) which indicates the possibility of weak π - π interaction between parallel pyridyl and naphthyl rings (ring C2C3C4C5C6C11) with a minimum C-C optimized distance of 3.363 Å between c.gs. Characteristic red-blue triangles (bow-tie pattern) on the shape index mapped HS and prominent flat green surfaces around c.gs on the curvedness mapped HS infer further the existence of π - π interaction (**Fig. 2A.22**). Very weak N $\cdots$ H/H $\cdots$ N contacts appeared as faded white spots on HS of **1** and **2**. The H $\cdots$ H contacts appeared as scattered white regions on HS (d_{norm}) and no interaction zone appeared as blue regions.

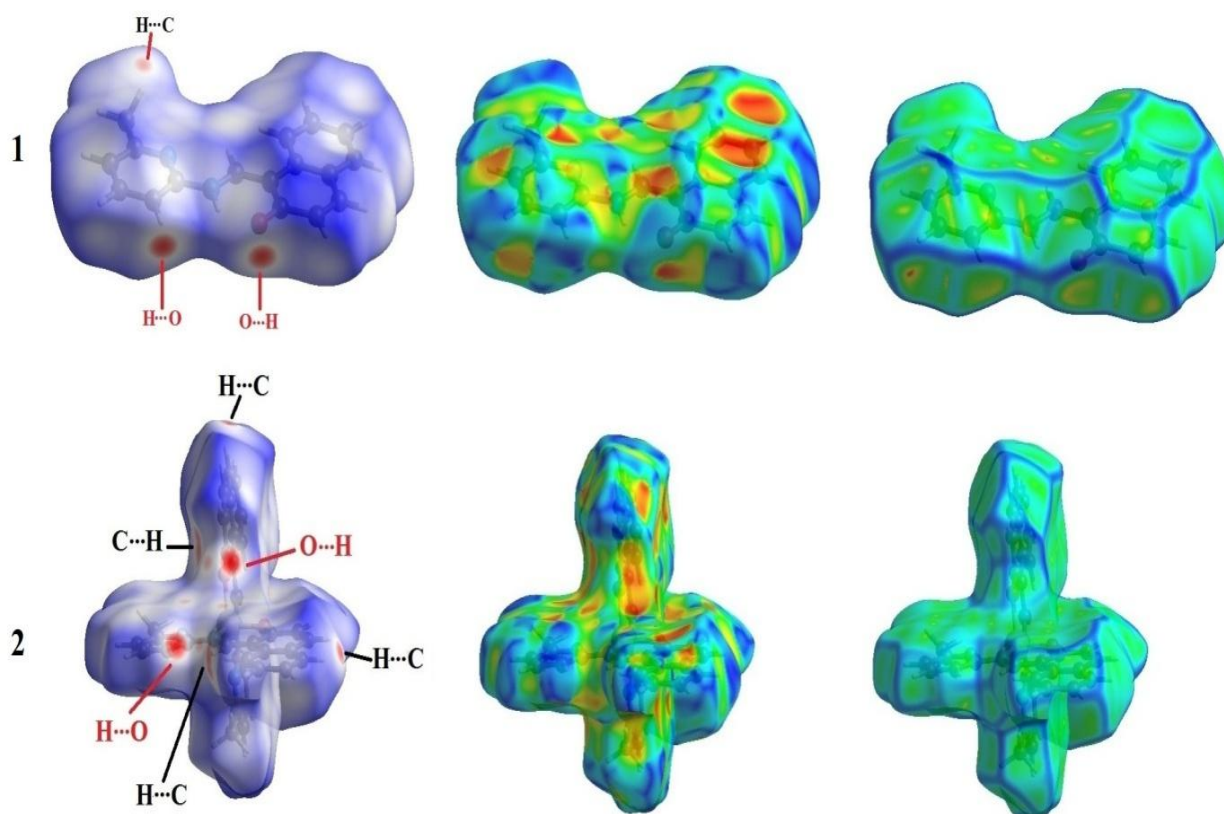


Fig. 2A.19. View of Hirshfeld surfaces mapped over d_{norm} (left), shape index (middle) and curvedness (right) for **1** and **2**.

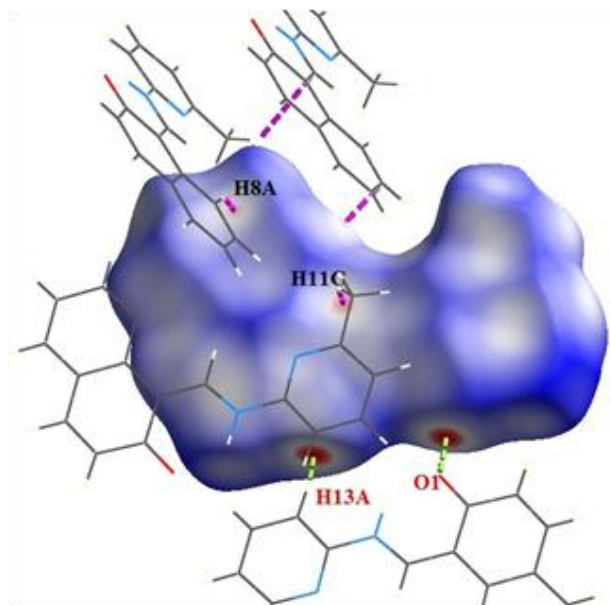


Fig. 2A.20. View of HS showing two deep circular red depressions in *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine **1** due to strong O $\cdots$ H/H $\cdots$ O contacts.

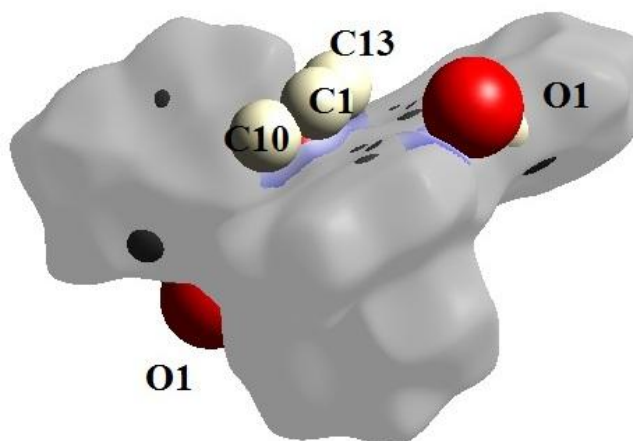


Fig. 2A.21. View of HS (space fill presentation) showing three O1 $\cdots$ H10, O1 $\cdots$ H1 and O1 $\cdots$ H13 contacts in bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthalaldimnato- $k^3N^N^O$]nickel(II) **2**.

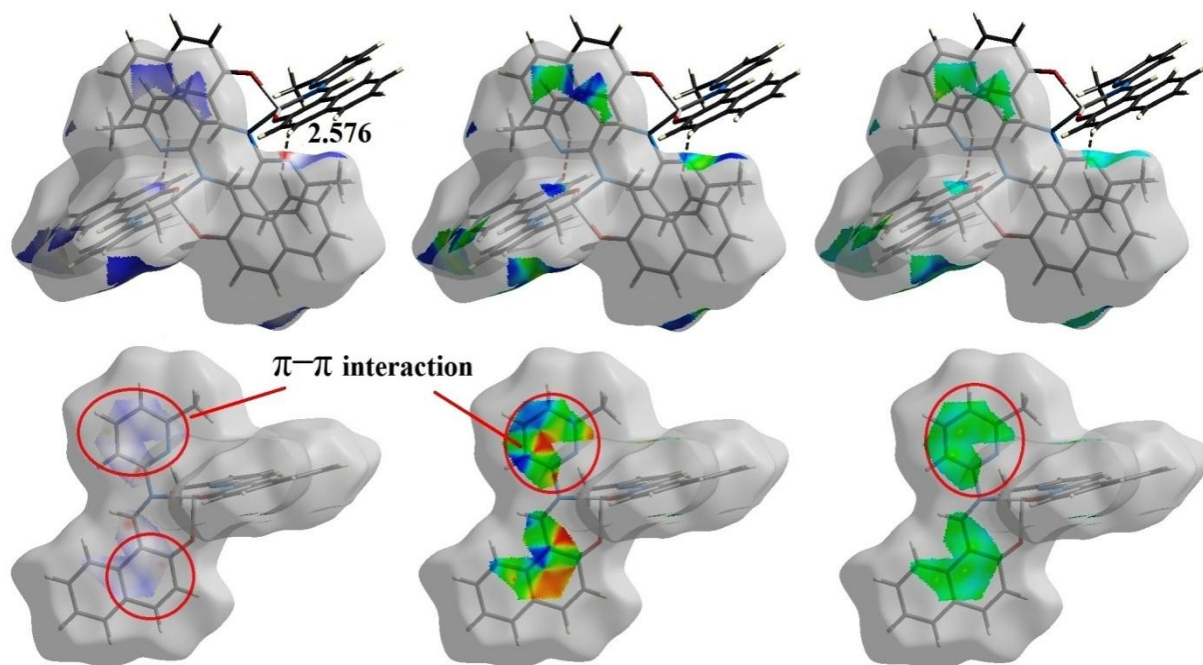


Fig. 2A.22. View of Hirshfeld surfaces mapped on d_{norm} (left), SI (middle) and C (right) showing C-H... π (top) and π - π interactions (bottom) in **2**.

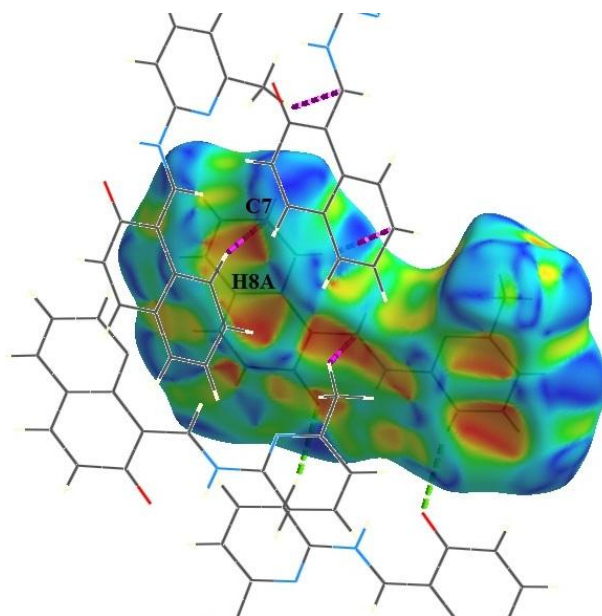


Fig. 2A.23. View of HS (Shape index) in *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine **1** showing C-H... π type interaction between C8-H8A donor and c.g acceptor as concave (-0.6596) red patches (around C7) and convex (0.6528) deep blue region (around H8A).

Chapter 2A

The 2D FP plots (translated range) (**Fig. 2A.24**) for **1** and **2** appeared as prominent donor (upper) and acceptor (lower) spikes representing $O\cdots H/H\cdots O$ contacts around $2.2 \text{ \AA} < d_e + d_i < 2.3 \text{ \AA}$, $C\cdots H/H\cdots C$ contacts around $2.5 \text{ \AA} < d_e + d_i < 2.6 \text{ \AA}$ and the $C\cdots C$ contacts (for **2**) (π - π interactions) around $d_e + d_i \sim 3.3 \text{ \AA}$. The $H\cdots H$ weak interactions manifested as scattered points that expand up to $d_i = d_e = 2.4 \text{ \AA}$ in **1** and $d_i = d_e = 2.5 \text{ \AA}$ in **2** which is responsible for crystalline lattice strength. It is found that $H\cdots C/C\cdots H$ interactions [39.1% (**1**), 27.5% (**2**)] and $H\cdots H$ interactions [43.8% (**1**), 52.7% (**2**)] dominate interaction contribution chart. The $O\cdots H/H\cdots O$ contacts [8.1% (**1**), 7.4% (**2**)] and $C\cdots C$ contacts [8.7% (**2**)] have small contributions but play a vital role in supramolecular crystal packing. Some minor weak interactions such as $O\cdots N/N\cdots O$ (0.5%), $O\cdots C/C\cdots O$ (1.3%), $N\cdots C/C\cdots N$ (1.9%), $C\cdots C$ (0.5%) in **1** and $N\cdots N$ (0.2%), $N\cdots C/C\cdots N$ (0.7%) in **2** have also been observed in 2D FP plots. The comparative distribution of all non-covalent interactions is shown as 2D pie diagram in **Fig. 2A.25**.

The HS analysis [67] at the atomic level (nickel center) was performed to observe the coordination impact of N,O-atoms of **1** at Ni^{2+} as minimal changes in coordination direction resulted in abrupt significant depressions on HS so changes in the inherent HS properties like volume, globularity etc [67] are inevitable as shown in **Table 2A.6**. Interestingly asphericity value suggests that HS surface at Ni^{+2} center is close to isotropic nature ($\Omega=0$ for isotropic object). The Ni-N coordination bonds appeared as circular bright-red depressions perpendicular to the Ni-N bond direction on HS (d_{norm}). The strength of Ni-N bonds manifests as rectangular shaped orange spots and green flat patches on HS (S) and HS (C), respectively (**Fig. 2A.26**). For Ni-O bonds, similar characteristic coloured depressions observed on HS mapped with d_{norm} , S and C. Due to differences in Ni-N optimized bond lengths [Ni-N1 (1.975 Å), Ni-N2 (2.053 Å)] irregular concave orange depressions appeared which are surrounded by yellow coloured regions on S mapped HS (**Fig. 2A.26**). All the Ni-N coordination seems to be through regions that reside outside the orange patches on HS [shape index] and that might be due to deviation of Ni-N bonds. These Ni-N coordination manifested as a prominent sharp red upper spike at $d_e + d_i \approx 1.9 \text{ \AA}$ in the 2D FP plots (translated range) and a similar red spike at $d_e + d_i \approx 2 \text{ \AA}$ observed for Ni-O bonds (**Fig. 2A.26**). At higher d_i (2.3 Å), d_e (1.9 Å) values in 2D FP plot, chunk of blue abrupt dots appears symbolizing weak $Ni\cdots H$ interactions (**Fig. 2A.26**) that are associated with the edges of the HS metal surface. These $Ni\cdots H$ interactions originates from intramolecular $Ni\cdots H17A$ interaction (3.573 Å) and intermolecular $Ni\cdots H13$ interactions (3.484 Å). This type of weak $Ni\cdots H13$ interactions link neighbouring asymmetric units of **2** (**Fig. 2A.27**) and thereby contributes in crystal packing stabilization along with other

Chapter 2A

hydrogen bonds. Overall contributions of Ni–N, Ni–O coordination and Ni···H contacts are in the order of 54.3%, 37.1% and 8.6% respectively in the 2D FP plots.

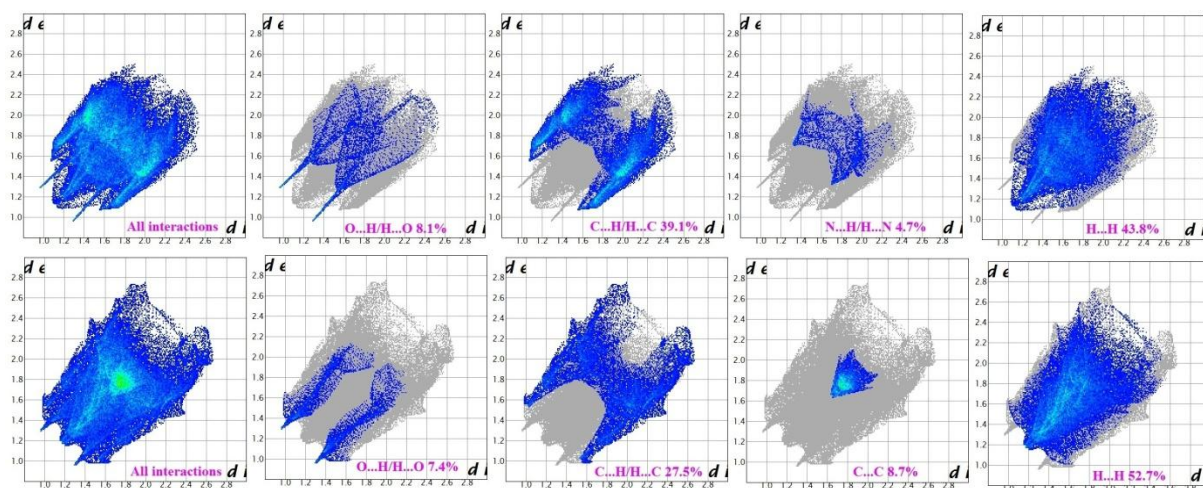


Fig. 2A.24. 2D fingerprint plots for **1** (top) and **2** (bottom).

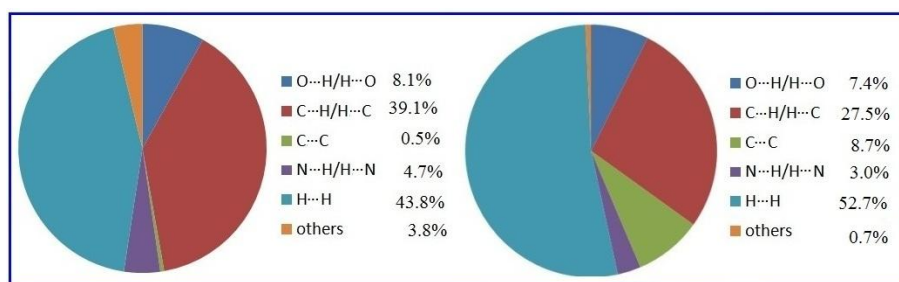


Fig. 2A.25. 2D Pie bar diagram illustrating the relative distribution (%) of non-covalent interactions from HS analysis of **1** (left) and **2** (right).

Chapter 2A

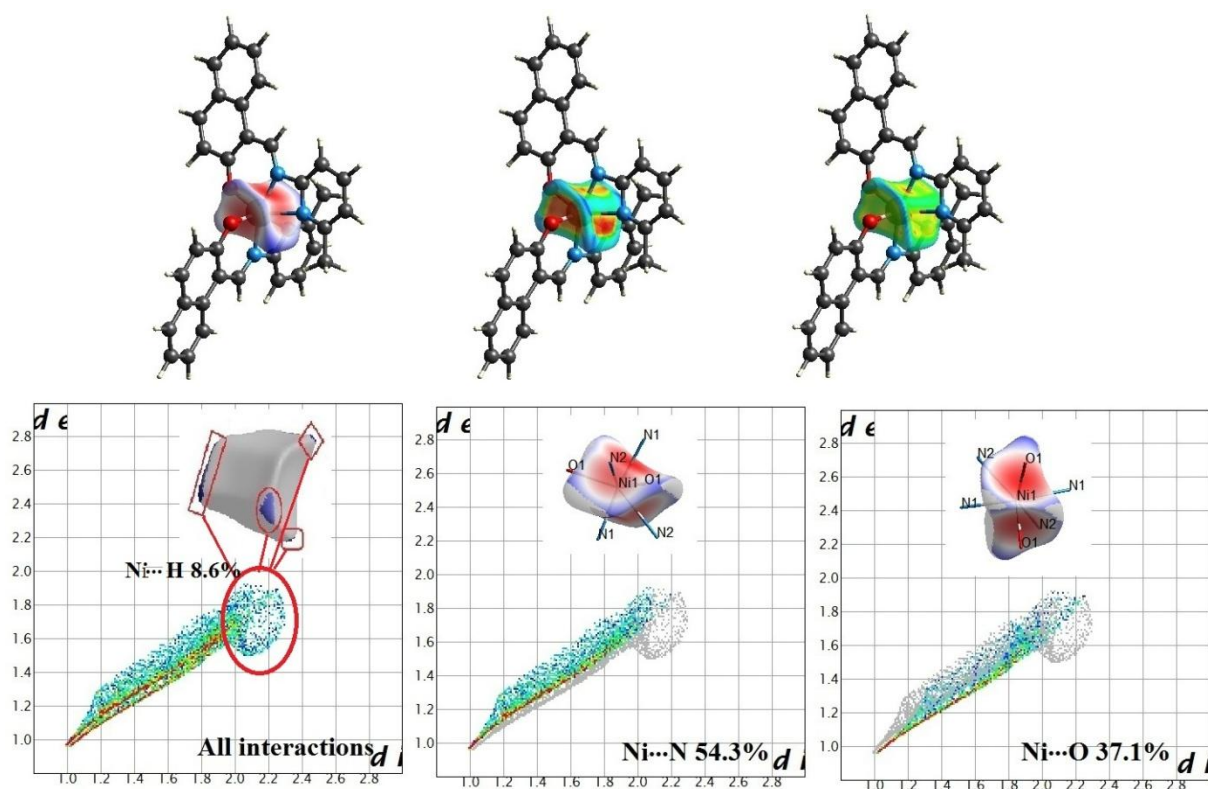


Fig. 2A.26. View of atomic HS study (top) at Ni^{+2} -center mapped on d_{norm} (left), SI (middle), C (right) and corresponding 2D FP plots (bottom) showing $\text{Ni} \cdots \text{N}$, $\text{Ni} \cdots \text{O}$, $\text{Ni} \cdots \text{H}$ interactions.

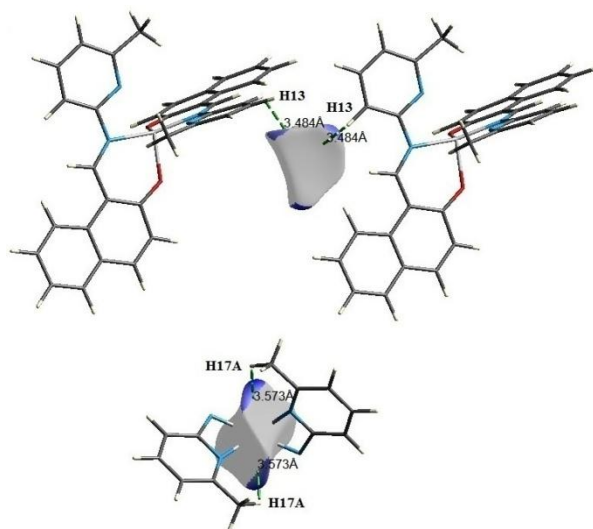


Fig. 2A.27. View of Hirshfeld surface (atomic level) in bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato- $k^3\text{N}^{\wedge}\text{N}^{\wedge}\text{O}$] nickel(II) 2 showing $\text{Ni} \cdots \text{H}$ interactions.

Chapter 2A

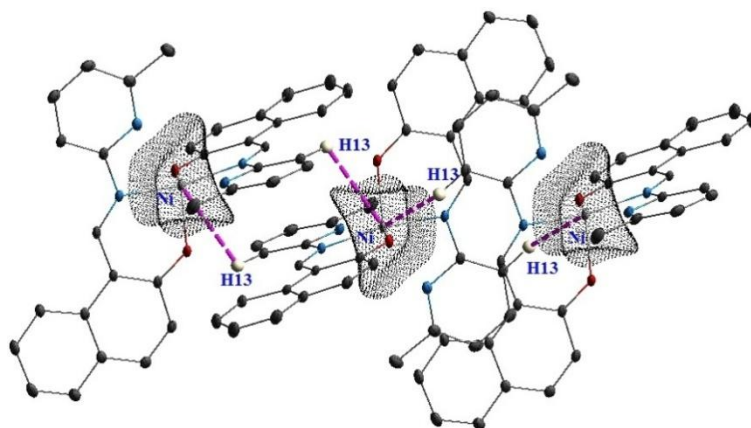


Fig. 2A.28. Partial view of atomic Hirshfeld surface (d_{norm}) showing asymmetric units of **2** linked by weak Ni...H interactions (non-bonded H-atoms omitted for clarity).

Table 2A.6. Quantitative data from HS of **1** and **2**.

compound	$V_H (\text{\AA}^3)$	$A_H (\text{\AA}^2)$	G	Ω
1	328.38	310.33	0.742	0.256
2	667.54	564.90	0.654	0.102
2*	13.81	37.18	0.749	0.023

* Atomic Hirshfeld surface analysis at the Ni^{+2} metal center of **2**.

2A.2.6 Anticancer activities of **1** and **2**

According to the results of the MTT assay performed to evaluate the cytotoxic activities of free pyridyl Schiff base ligand **1** and Ni(II) complex **2**, **1** showed an IC_{50} value of $154.7 \mu\text{M}$ in HUH7 cells, $88.32 \mu\text{M}$ in A549 cells, and $47.80 \mu\text{M}$ in HCT116 cells. The IC_{50} values for **2** were calculated as $86.82 \mu\text{M}$ in HUH7 cell, $24.85 \mu\text{M}$ in A549 cells, and $56.02 \mu\text{M}$ in HCT116 cells. **2** showed a toxic effect at high concentrations in Beas-2B cells, while **1** showed almost the same cytotoxic effect ($\text{IC}_{50}=85.72 \mu\text{M}$) compared to A549 cells (**Fig. 2A.29**). Therefore, it cannot be said that **1** has cancer cell-specific cytotoxic effect. However, for **2** to have a toxic effect on normal lung cells, higher concentrations must be applied, which is promising in terms of specificity for cancer cells. A similar study showed that a Ni(II) complex showed a better cytotoxic effects in A549 lung cancer cells with a lower IC_{50} value than Ag(I) and Pd(II) of the same ligand and compared to Ploxal-S and 5-fluorouracil used as reference drugs revealed in

Chapter 2A

the study [43]. It is seen that **1** and **2** show moderate cytotoxic activity in other cell lines, while **2** shows good cytotoxic effect in A549 cells. It can be said that this new Ni(II) Schiff base complex **2** has a specific impact on the A549 cells.

The ability of the HUH7 and HCT116 cells to form colonies in two weeks in the presence of **1**, **2** and equal concentrations of DMSO as controls were tested. The percentage of colonies formed by HUH7 and HCT116 cells treated with **1** after two weeks was calculated as 32% and 42%, respectively, based on DMSO. The percentage of colonization of the HUH7 cell treated with **2** was 3% and the HCT116 cell 28%. **2** inhibited colonization in both cells more than **1** (**Fig. 2A.30**). Both compounds were able to affect the proliferation and growth rate of cells at different doses. Whether **1** and **2** affect the apoptotic pathway was investigated by Flow cytometry. **Fig. 2A.31** shows Annexin V/PI diagrams showing the ratio of viable and apoptotic cells. Apoptosis rates of all cells incubated with IC₅₀ concentrations of **1** for 48h did not differ significantly from control (DMSO). Incubation of HCT116 cell with IC₅₀ dose of **2** for 48 hours resulted in 45.73% of apoptotic cells. **2** also resulted in 23.63% apoptotic cells in the A549 cell. These results are significantly different from the control (DMSO). **2** did not show apoptotic activity in HUH7 cells. These findings can be supported by different studies proving the effectiveness of Schiff base Ni(II) complexes in the apoptotic pathway [44, 68].

According to the PCR results, **1** and **2** slightly increased p53 expression in A549 cells. This could mean minor DNA damage. However, neither **1** nor **2** increased p21 expression in A549 cells, so cell cycle arrest was not induced. In HCT116 cells **1** and **2** significantly increased the expressions of both p21 and p53. This shows that **1** and **2** both cause DNA damage and affect the cell cycle in the HCT116 cell (**Fig. 2A.32**).

In this study, **2** showed much better efficacy than **1** in terms of cytotoxicity, inducing apoptosis or preventing colonization. That is, it is clear that the anticancer activity of **1**, a Schiff base ligand, increases with the incorporation of Ni(II). Many anticancer studies with nickel complexes have shown that Ni(II), like other transition elements can bind to DNA and various oncoproteins, and can act as an antitumoral agent by affecting cell proliferation, cell cycle steps and many more processes [69-71]. The 3D structure of the ligand, its electronic properties and ligand-metal interactions are of great importance as well as metal in antitumoral activity. In many studies, it has been shown that there are significant differences in anticancer activity between subclasses of Schiff base compounds (Quinazolines, pyrazole-naphthalene derivatives, azosal, sulfonamides, indoles, porphyrins, and chitosan derivatives, etc.), as well as between Schiff base ligands and their metal complexes. In addition, it has been proven that

Chapter 2A

all Schiff bases in general have the potential to interact with many proteins and DNA, thanks to their flexible bond structure and unique π - π interactions [72].

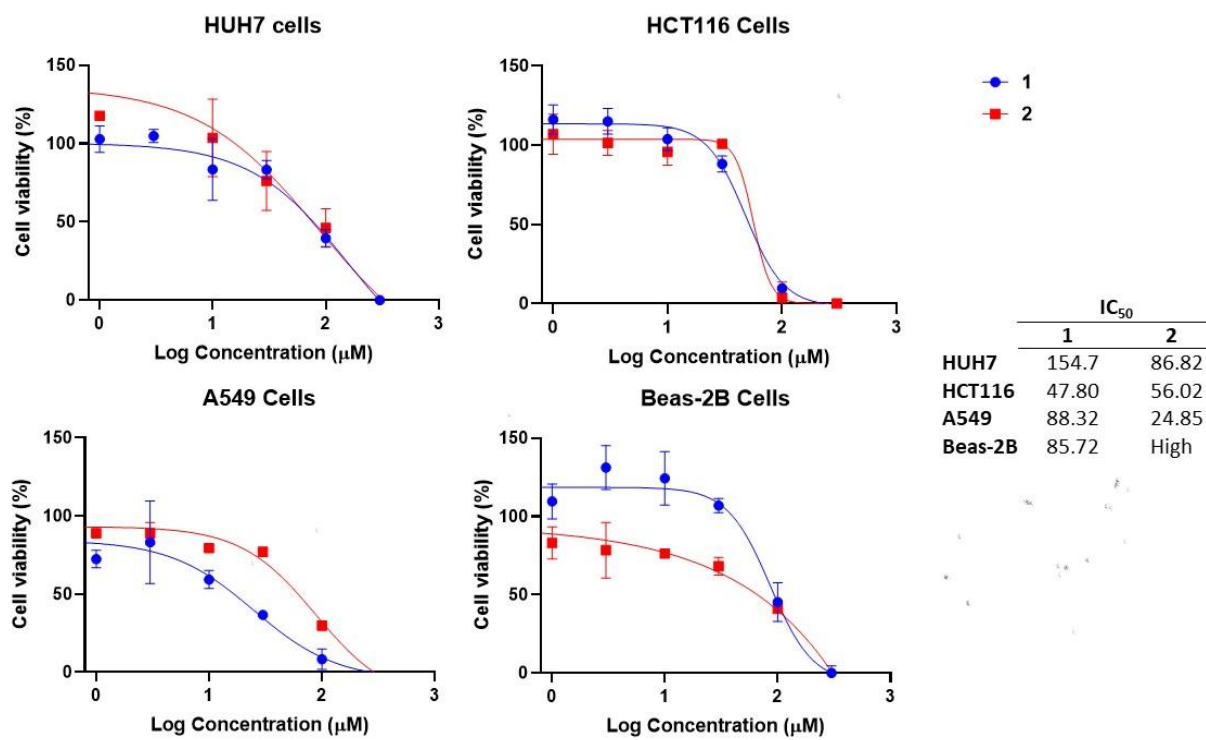


Fig. 2A.29. Cytotoxic effects of **1** (blue) and **2** (red) on the HUH7, HCT116, A549 cancer cells and Beas-2B normal lung cells. Cell viability assay was performed *via* an MTT protocol at concentrations of 0, 0.3, 1, 3, 10, 30, 100 and 300 μ M for 24 h. Graphs show the best curve fit of non-linear regression analysis. Calculated IC_{50} values are given in Table.

Chapter 2A

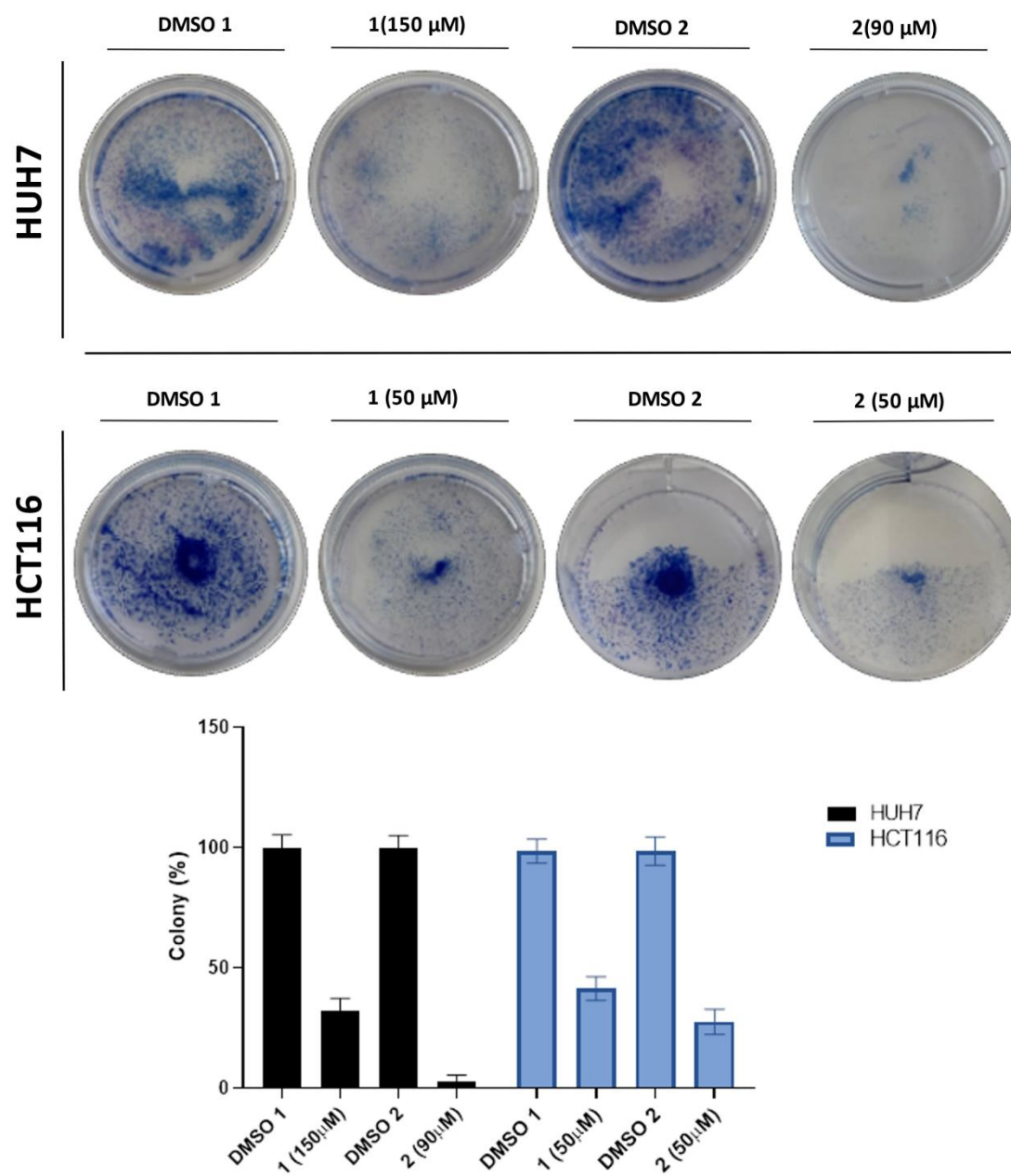


Fig. 2A.30. Colony formation assay, performed in the HUH7 and HCT116 cells exposed to **1** and **2**, and DMSO as a control, at two different concentrations. Cells were allowed to grow for two weeks before staining with methylene blue solution.

Chapter 2A

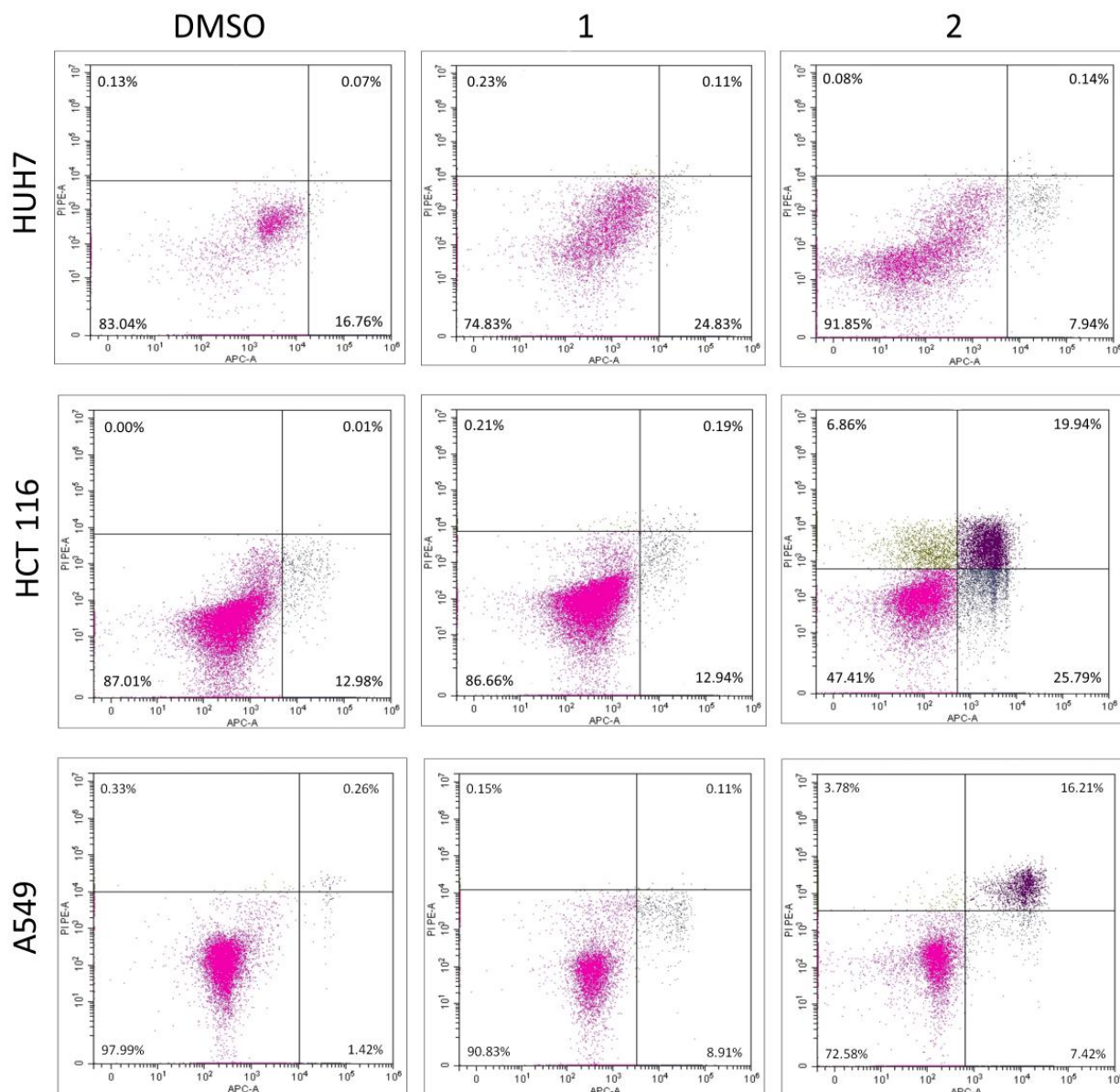


Fig. 2A.31. Apoptotic cell rates in the HUH7, HCT116 and A549 cells treated with **1**, **2** and an equal amount of DMSO with **1** and **2** as a control. The apoptosis ratio was measured by flow cytometry. The upper (late) and lower (early) right quadrants show the apoptotic cells of the population.

Chapter 2A

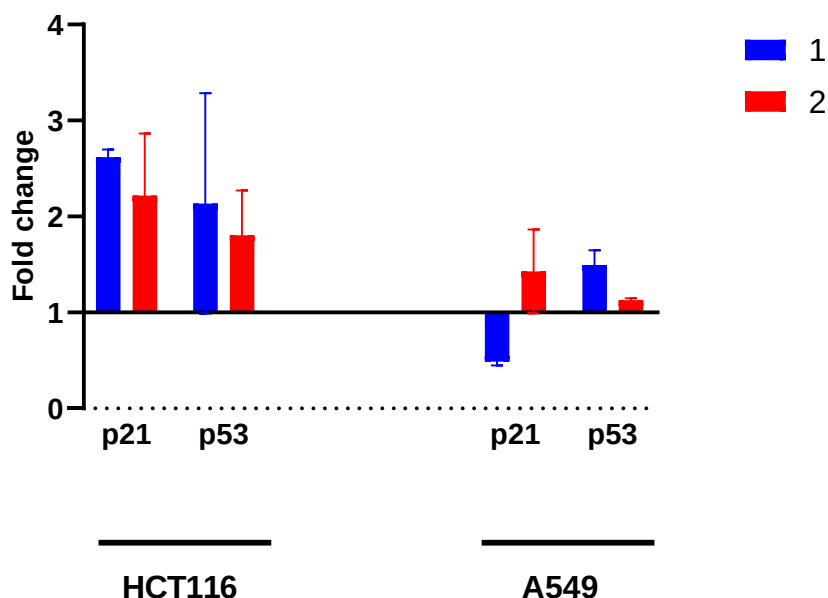


Fig. 2A.32. HCT116 and A549 cells incubated with **1** and **2** for 4 h, and qPCR, performed after mRNA isolation to evaluate expression levels of apoptosis and cell cycle related genes p21 and p53. Fold differences in mRNA levels of the compound-treated samples were normalized to DMSO-treated samples.

Conclusion

The Schiff-base ligand, *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine **1** and its novel chelate bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthalaldimnato- $k^3N^{\wedge}N^{\wedge}O$] nickel(II) **2** have been synthesized and well characterized by IR, ^1H NMR, Mass, X-ray diffraction. X-ray diffraction study reveals that **1** has a zwitter ionic structure due to the prevalence of keto-amine tautomer form and the $C13-H13A \cdots O1^i$ [(i) $-x+1, -y, -z+1$] intermolecular hydrogen bonds succour the existence of dimeric form in **1**. Complex **2** has NiN_4O_2 coordination kernel which attains distorted octahedral geometry around Ni^{+2} center and overall crystal stability is contributed by $C-H \cdots O$ type intermolecular hydrogen bonds, weak $C-H \cdots \pi$, and $\pi \cdots \pi$ stacking interactions. These non-covalent interactions in **1-2** are well reflected in HS study at molecular level with the appearance of $O \cdots H/H \cdots O$ and $C \cdots H/H \cdots C$ interactions as coloured depressions on d_{norm} mapped HS having spikes in 2D FP at $2.2 \text{ \AA} < d_e + d_i < 2.3 \text{ \AA}$ and $2.5 \text{ \AA} < d_e + d_i < 2.6 \text{ \AA}$ respectively where the later invokes for $C-H \cdots \pi$ interactions and specific $C \cdots C$ interactions ($d_e + d_i \sim 3.3 \text{ \AA}$) in **2** signifies $\pi \cdots \pi$ stacking pattern. The effect of ligand coordination on Ni^{+2} center and related interactions are also evaluated by HS study at the atomic level and the surprising revelation is the $Ni \cdots H$ interactions [$3.573 \text{ \AA}$ ($Ni \cdots H17A$)],

Chapter 2A

3.484 Å (Ni...H13)] that connects the neighbouring asymmetric units of **2**. Overall contributions of Ni–N, Ni–O coordination and Ni...H contacts are in the order of 54.3%, 37.1% and 8.6% respectively as apparent in the 2D FP plots. The solid-state structures of **1** and **2** are optimized by density functional theory (DFT) using a basis set CAM-B3LYP/6-311G. The ligand **1** attains the lowest energy conformation (2.4 kJ mol⁻¹) in keto-amine tautomeric form and the intramolecular hydrogen bond stabilizes **1** by 74.5 kJ mol⁻¹ in the formation of a dimer. The octahedral geometry vis-à-vis tridentate coordination of ligand **1** is less favoured towards Ni⁺² center having high energy reference (82.4 kJ mol⁻¹) but still it exists in the present scenario and that might be possible due to requisite energy transfer by crystallization technique in a sealed tube at elevated temperature. MTT assay results direct to the fact that at higher concentrations **2** showed a toxic effect in Beas-2B cells, while **1** showed an almost similar cytotoxic effect (IC₅₀=85.72 µM) compared to A549 cells. On the A549 lung cancer cell line, the novel Ni(II) complex **2** has a good cytotoxic effect and causes apoptotic cell death. Colony forming assay study reveals that both **1** and **2** affect the proliferation and growth rate of cells at different doses, in fact, **2** inhibited colonization in HUH7 and HCT116 cells more than **1**. Flow cytometry shows the effectiveness of **2** in the apoptotic pathway by the generation of 45.73% and 23.63% apoptotic cells when incubated with HCT116 cell, IC₅₀ dose and A549 cell, IC₅₀ dose respectively. The PCR results show that **1** and **2** have slightly increased p53 expression in A549 cells and both cause DNA damage. Thus, we can conclude that anticancer activity of **2** is higher than **1**.

2A.3 Experimental

Materials and physical measurements:

All chemicals were reagent grade obtained from commercial sources and used without purification. The solvents were purified by standard procedures. Infrared spectra were measured on a Perkin-Elmer FT-IR spectrometer with KBr pellets in the range of 4000–500 cm⁻¹. NMR spectra were recorded on Bruker Advance II (400MHz) spectrometer using the residual protic solvent resonance as the internal standard and chemical shifts were expressed in ppm. Mass spectra of **1** and **2** were recorded on inkarp instruments (Expression-S). Elemental analysis was carried out in PerkinElmer 2500 series II elemental analyzer.

Chapter 2A

2A.3.1 Synthesis of pyridyl Schiff base ligand 1 and its Ni(II) metal complex 2

Synthesis of pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine 1 (LH)

The pyridyl Schiff base ligand **1** was synthesized according to an earlier published method with little modifications [45]. 2-Hydroxy-1-naphthaldehyde (1g, 5.81mmol) was dissolved in 20 mL of HPLC grade methanol with continuous stirring for 15 min. After that, 2-3 drops of concentrated acetic acid were added and stirred for 10 min. An equimolar amount of 2-amino-6-methyl pyridine (0.628g, 5.81 mmol) was added to this reaction mixture. The resulting solution was then refluxed for 8 h and color changed to yellow. The solvent was evaporated to 50% in vacuo, and the solution was left to crystallize by gradual evaporation of the solvent at room temperature. The crystals were filtered out and washed with methanol three times. The yellow crystals of the ligand **1** were dried in air for 24 h.

Pyridyl Schiff base ligand **1**: Yield: 84%, ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 15.43 (d, 1H, -OH), 9.95 (d, 1H, -CH=N-), 8.14 (d, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.63 (m, 2H, Ar-H), 7.53 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 6.97 (d, 1H, Ar-H), 6.91 (d, 1H, Ar-H), 2.62 (s, 3H, -CH₃). FT-IR (ν cm⁻¹, KBr): 3437 (ν O-H), 3053 (ν C-H), 1624 (ν C=N), 1566 (ν C=C), and 1304-1134 (ν C-O). ESI-MS m/z = 261.3 [$\text{M} - \text{H}^+$], 262.3 [M^+]; Anal. Calc. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$: C, 48.92; H, 5.05; N, 14.63%. Found: C, 48.88; H, 5.03; N, 14.60%.

Synthesis of bis[*N*-2-(6-methylpyridyl)-2-oxo-1-naphthalaldimnato- $\kappa^3\text{N}^{\wedge}\text{N}^{\wedge}\text{O}$] nickel(II) **2**

Two equivalents of the pyridyl Schiff base ligand **1**, (0.13g, 0.5 mmol) and one equivalent of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.06g, 0.252 mmol) were dissolved in 10 mL and 5mL of HPLC grade methanol respectively and both the solutions were placed in main arm of a branched tube. The extra amount of methanol was cautiously added to fill up the arms. The tube was sealed and placed in an oil bath at 60 °C, while the branched arm was left at room temperature. After 2 days light brown crystals of the nickel complex formed in the cooler arm. The solvent was evaporated and the crystals were collected.

Complex **2**: Yield: 79%, ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 11.41 (t, 1H, -CH=N-), 9.42 (s, 1H, Ar-H), 9.23 (s, 1H, Ar-H), 7.78 (m, 3H, Ar-H), 7.59 (m, 1H, Ar-H), 6.99 (m, 1H, Ar-H), 6.60 (d, 1H, Ar-H), 5.95 (s, 1H, Ar-H), 2.62 (s, 3H, -CH₃). FT-IR (ν cm⁻¹, KBr): 3337-3272 IR(KBr cm⁻¹): 3060, 3031, 2920 (ν C-H), 1614 (ν C=N), 1591, 1566 (ν C=C), 1254-1089

Chapter 2A

(ν C-O), 655 (ν Ni-O), and 490 (ν Ni-N). ESI-MS m/z = 579.7 [$M - 2H^+$]; Anal. Calc. for $C_{34}H_{26}N_4NiO_2$: C, 56.98; H, 4.85; N, 12.74%. Found: C, 56.94; H, 4.82; N, 12.70%.

2A.3.2 Crystallographic data collection and refinement of **1** and **2**

Single-crystal X-ray diffraction data for the pyridyl Schiff base ligand **1** were collected using a Rigaku XtaLAB Mini II diffractometer equipped with a fine-focus sealed X-ray tube using $MoK\alpha$ radiation ($\lambda=0.71073$ Å) operating at 296(2) K. Data for the nickel(II) complex **2** were recorded using ω scans $CuK\alpha$ radiation ($\lambda=1.54184$ Å) on a Rigaku Diffraction Synergy-spectrometer fitted with a micro-source tube at 100(2) K. The Olex2 software [73] was used extensively for producing asymmetric units and other materials for publication. The structure was solved, refined and molecular graphics were managed using SHELXT [74], SHELXL [75] and Bruker SHELXTL [76] program packages respectively. An empirical absorption correction was done by multiscan method (SADABS) [77]. All the available non-hydrogen atoms were refined anisotropically. The amine N-H was located in the difference density map and refined isotropically. The positions of hydrogen atoms were calculated geometrically and the riding model was used for refinement. All e.s.d.'s are estimated using the full covariance matrix. The crystallographic data and structure refinement details are mentioned in **Table 2A.2**. Bond lengths, bond angles, and torsion angles are listed in **Table 2A.2-2A.5**.

2A.3.3 Hirshfeld Surface Analysis of **1** and **2**

Non-covalent interactions in **1** and **2** are investigated by generating 3D Hirshfeld surfaces (HS) and associated 2D fingerprint (FP) plots [60,61,78,79] using Crystal Explorer 17.5 [80]. The HS is generated based on d_{norm} , shape index (S) and curvedness (C) [61]. The surface parameter d_{norm} [21] is defined as

$$d_{norm} = \frac{(d_i - r_i^{vdW})}{r_i^{vdW}} + \frac{(d_e - r_e^{vdW})}{r_e^{vdW}}$$

where d_i , d_e and vdW provide information about the distance between the surface point to the closest interior atom, the surface point to the closest exterior atom and the van der Waals radii of atoms respectively. Shorter contacts, longer contacts and contacts in or beyond the range of van der Waals separation are observed as red, white and blue depressions on d_{norm} mapped HSs respectively.

Chapter 2A

2A.3.4 Cells and cell culture

To assess the anticancer activity of pyridyl Schiff base ligand **1** and its Ni(II) metal complex **2**, three distinct cancer cell lines were used: hepatocellular carcinoma cell line (HUH7), colon carcinoma cell line (HCT116), and non-small cell lung carcinoma cell line (A549). Additionally, to determine the cytotoxic activity of **1** and **2**, the Beas-2B normal lung cell line was used as a control. BG İzmir provided HUH7 and HCT116, while the University of Gaziantep provided A549 and Beas-2B. All cell lines were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) (HyClone Cat. No: SV30160.03) and 1% antibiotics (HyClone Cat. No: SV30079.01) in a CO₂ incubator (Thermo Sci.) at a CO₂ concentration of 5% CO₂ and 21% O₂. Cells were harvested with Trypsin (HyClone Cat. No. SH30042.01) and washed with PBS 1X (HyClone Cat. No. SH30256.01) when necessary. The compounds were dissolved in DMSO at a stock concentration of 10 mM and diluted further in the cell culture media during the experiments.

2A.3.5 Cytotoxicity assay of **1** and **2**

The cytotoxicity of compounds **1** and **2** dissolved in DMSO was determined using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide method (MTT) against HUH7, HCT116, and A549 cells [81]. In brief, 1.0×10^4 cells per well were cultured overnight at 37 °C in 5% CO₂ in RPMI medium containing 10% FBS and 1% antibiotics in a 96-well plate. After 24 hours, the old medium was removed and the cells were incubated for 24 hours with compounds at increasing concentrations (0, 0.3, 1, 3, 10, 30, 100, and 300 µM). Under the same conditions, cells treated with 0.1 percent DMSO (vehicle control) were incubated. At the conclusion of the incubation time, the MTT solution was added to each well at a final concentration of 0.5 mg mL⁻¹, and the cells were further incubated for 4 hours to allow viable cells to metabolize the MTT. After removing the supernatant, 50 L of 96 percent ethanol was added to each well to dissolve the purple crystals, which are a byproduct of living cells' metabolism. The absorbance at 570 nm was determined using a microplate reader (Biochrom EZ Read 400).

2A.3.6 Apoptosis assay of **1** and **2**

Annexin-V/propidium iodide (PI) fluorescein isothiocyanate (FITC) staining was performed according to the protocol of the Biolegend apoptosis detection kit [82]. For quantitative analysis, approximately IC₅₀ concentrations of the compounds were tested on HUH7, HCT116, and A549 cells. A cancer cell (10^5 cells per 1 mL) suspension in a serum-free medium was

Chapter 2A

incubated with the respective compound in 6-well plates in a CO₂ incubator. After treatment with compounds for 48 h, the cancer cells were harvested and incubated with APC-Annexin V and propidium iodide (PI). The fluorescence emission of APC-Annexin-V stained cells was measured at 633 nm (red laser) in a flow cytometer (Beckman Coulter/CytoFLEX, United States). Dots represent cells as follows: bottom left quadrant – living cells (APC–/PI–); bottom right quadrant – early apoptotic cells (APC+/PI–); top left quadrant – necrotic cells (APC–/PI+); top right quadrant – late apoptotic cells (APC+/PI+).

2A.3.7 Quantitative polymerase chain reaction (qPCR) of 1 and 2

Total RNA was extracted from HCT116 and A549 cells incubated for **1** and **2** to 6 hours at concentrations half the IC₅₀ doses using an RNA assay kit (Macherey-Nagel) and reverse transcribed using cDNA reverse transcription kit (Thermo Fisher) according to manufacturer's protocols. Quantitative PCR was done on an Eppendorf Mastercycler using SYBR Green mix (Sigma Aldrich). Reactions were performed in triplicate in a 96-well plate (Bio-rad iCycler). Gene expressions were normalized to 18S rRNA, and fold differences were calculated using the comparative CT method: $2^{-(\Delta\Delta CT)}$, where $\Delta\Delta CT$ refers to (normalized control sample) – (normalized treated sample). Primer pairs were as follows; 18S rRNA: sense: 5'-cttagagggacaagtggcg-3', antisense: 5'-acgctgagccagtcagtga-3'; p21: sense: 5'-cgaggcacaagggtacaaga -3', antisense: 5'-cccgtgagccatggact-3'; p53: sense: 5'-cctggtagtagcggtagaagt -3', antisense: 5'-agggatgtttgggagatgtaag -3'.

2A.3.8 Colony forming assay of 1 and 2

Colony forming assay was performed in a 6-well plate. The cells were seeded at a density of 200 cells per well for HCT116 and HUH7 in a 3 mL complete culture medium. Two different concentrations of **1** and **2** were applied to the cells. After 24 h. the old medium was removed and a new fresh medium was added to the cells. The medium was changed with a new one twice per week. After two weeks, the colonies formed were dyed with methylene blue solution including 50% methanol, 50% distilled water and 0.4 g methylene blue. The colonies were counted using the ImageJ 1.53a software (NIH, USA). Differences between the groups were analyzed with Prism V8 (GraphPad Software, Inc, CA, USA).

Chapter 2A

2A.4. References

- [1] Qin, W., Long, S., Panunzio, M., & Biondi, S. (2013). Schiff bases: A short survey on an evergreen chemistry tool. *Molecules*, 18(10), 12264-12289.
- [2] Liu, X., & Hamon, J. R. (2019). Recent developments in penta-, hexa-and heptadentate Schiff base ligands and their metal complexes. *Coordination Chemistry Reviews*, 389, 94-118.
- [3] Pervaiz, M., Sadiq, S., Sadiq, A., Younas, U., Ashraf, A., Saeed, Z., ... & Adnan, A. (2021). Azo-Schiff base derivatives of transition metal complexes as antimicrobial agents. *Coordination Chemistry Reviews*, 447, 214128.
- [4] Zhang, J., Xu, L., & Wong, W. Y. (2018). Energy materials based on metal Schiff base complexes. *Coordination Chemistry Reviews*, 355, 180-198.
- [5] Tesfaye, D., Linert, W., Gebrezgiabher, M., Bayeh, Y., Elemo, F., Sani, T., ... & Thomas, M. (2023). Iron (II) mediated supramolecular architectures with schiff bases and their spin-crossover properties. *Molecules*, 28(3), 1012.
- [6] Kaur, M., Kumar, S., Yusuf, M., Lee, J., Brown, R. J., Kim, K. H., & Malik, A. K. (2021). Post-synthetic modification of luminescent metal-organic frameworks using schiff base complexes for biological and chemical sensing. *Coordination Chemistry Reviews*, 449, 214214.
- [7] Omidi, S., & Kakanejadifard, A. (2020). A review on biological activities of Schiff base, hydrazone, and oxime derivatives of curcumin. *RSC advances*, 10(50), 30186-30202.
- [8] Shekhar, S., Khan, A. M., Sharma, S., Sharma, B., & Sarkar, A. (2022). Schiff base metallodrugs in antimicrobial and anticancer chemotherapy applications: a comprehensive review. *Emergent Materials*, 5(2), 279-293.
- [9] Malik, M. A., Dar, O. A., Gull, P., Wani, M. Y., & Hashmi, A. A. (2018). Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. *MedChemComm*, 9(3), 409-436.
- [10] J. -M. Lehn, *Suprmol Chem.*, VCH, Weinheim, 1995.
- [11] Fujita, M. (Ed.). (2003). *Molecular self-assembly: organic versus inorganic approaches* (Vol. 96). Springer.
- [12] Adhikari, S., Kar, D., Fröhlich, R., & Ghosh, K. (2019). Pyridine-Based Macrocyclic and Open Receptors for Urea. *ChemistrySelect*, 4(44), 12825-12831.
- [13] Park, I. W., Yoo, J., Adhikari, S., Park, J. S., Sessler, J. L., & Lee, C. H. (2012). Calix [4] pyrrole-based heteroditopic ion-pair receptor that displays anion-modulated, cation-binding behavior. *Chemistry–A European Journal*, 18(47), 15073-15078.

Chapter 2A

- [14] Ghosh, K., Adhikari, S., Fröhlich, R., Petsalakis, I. D., & Theodorakopoulos, G. (2011). Experimental and theoretical anion binding studies on coumarin linked thiourea and urea molecules. *Journal of Molecular Structure*, 1004(1-3), 193-203.
- [15] Ghosh, K., Adhikari, S., & Fröhlich, R. (2008). A pyridine-based macrocyclic host for urea and acetone. *Tetrahedron Letters*, 49(34), 5063-5066.
- [16] Ghosh, K., & Adhikari, S. (2006). Fluorescence sensing of tartaric acid: a case of excimer emission caused by hydrogen bond-mediated complexation. *Tetrahedron letters*, 47(21), 3577-3581.
- [17] Park, I. W., Yoo, J., Kim, B., Adhikari, S., Kim, S. K., Yeon, Y., ... & Lee, C. H. (2012). Oligoether-Strapped Calix [4] pyrrole: An Ion-Pair Receptor Displaying Cation-Dependent Chloride Anion Transport. *Chemistry—A European Journal*, 18(9), 2514-2523.
- [18] Ghosh, K., Adhikari, S., Chattopadhyay, A. P., & Chowdhury, P. R. (2008). Quinoline based receptor in fluorometric discrimination of carboxylic acids. *Beilstein Journal of Organic Chemistry*, 4(1), 52.
- [19] Mahmudov, K. T., Gurbanov, A. V., Guseinov, F. I., & da Silva, M. F. C. G. (2019). Noncovalent interactions in metal complex catalysis. *Coordination Chemistry Reviews*, 387, 32-46.
- [20] Alkorta, I., Elguero, J., & Frontera, A. (2020). Not only hydrogen bonds: Other noncovalent interactions. *Crystals*, 10(3), 180.
- [21] Politzer, P., & Murray, J. S. (2019). An overview of strengths and directionalities of noncovalent interactions: σ -holes and π -holes. *Crystals*, 9(3), 165.
- [22] Majid, S. A., Mir, J. M., Paul, S., Akhter, M., Parray, H., Ayoub, R., & Shalla, A. H. (2019). Experimental and molecular topology-based biological implications of Schiff base complexes: a concise review. *Reviews in Inorganic Chemistry*, 39(2), 113-128.
- [23] Sakthivel, A., Jeyasubramanian, K., Thangagiri, B., & Raja, J. D. (2020). Recent advances in Schiff base metal complexes derived from 4-aminoantipyrine derivatives and their potential applications. *Journal of Molecular Structure*, 1222, 128885.
- [24] Abd El-halim, H. F., Omar, M. M., & Mohamed, G. G. (2011). Synthesis, structural, thermal studies and biological activity of a tridentate Schiff base ligand and their transition metal complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 78(1), 36-44.

Chapter 2A

- [25] Al Zoubi, W., Al-Hamdani, A. A. S., & Kaseem, M. (2016). Synthesis and antioxidant activities of Schiff bases and their complexes: a review. *Applied Organometallic Chemistry*, 30(10), 810-817.
- [26] Catalano, A., Sinicropi, M. S., Iacopetta, D., Ceramella, J., Mariconda, A., Rosano, C., ... & Longo, P. (2021). A review on the advancements in the field of metal complexes with Schiff bases as antiproliferative agents. *Applied Sciences*, 11(13), 6027.
- [27] Carreño, A., Rodríguez, L., Páez-Hernández, D., Martín-Trasanco, R., Zúñiga, C., Oyarzún, D. P., ... & Fuentes, J. A. (2018). Two new fluorinated phenol derivatives pyridine Schiff bases: synthesis, spectral, theoretical characterization, Inclusion in epichlorohydrin- β -cyclodextrin polymer, and antifungal effect. *Frontiers in chemistry*, 6, 312.
- [28] Chen, S., Liu, X., Ge, X., Wang, Q., Xie, Y., Hao, Y., ... & Liu, Z. (2020). Lysosome-targeted iridium (III) compounds with pyridine-triphenylamine Schiff base ligands: Syntheses, antitumor applications and mechanisms. *Inorganic Chemistry Frontiers*, 7(1), 91-100.
- [29] Dasari, S., & Tchounwou, P. B. (2014). Cisplatin in cancer therapy: molecular mechanisms of action. *European journal of pharmacology*, 740, 364-378.
- [30] Ghosh, S. (2019). Cisplatin: The first metal based anticancer drug. *Bioorganic chemistry*, 88, 102925.
- [31] Rabik, C. A., & Dolan, M. E. (2007). Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer treatment reviews*, 33(1), 9-23.
- [32] Kar, K., Ghosh, D., Kabi, B., & Chandra, A. (2022). A concise review on cobalt Schiff base complexes as anticancer agents. *Polyhedron*, 222, 115890.
- [33] Yu, H., Zhang, W., Yu, Q., Huang, F. P., Bian, H. D., & Liang, H. (2017). Ni (II) complexes with Schiff base ligands: preparation, characterization, DNA/protein interaction and cytotoxicity studies. *Molecules*, 22(10), 1772.
- [34] Prashanthi, Y., Kiranmai, K., Ira, K. S. K., Chityala, V. K., & Shivaraj. (2012). Spectroscopic Characterization and Biological Activity of Mixed Ligand Complexes of Ni (II) with 1, 10-Phenanthroline and Heterocyclic Schiff Bases. *Bioinorganic chemistry and applications*, 2012(1), 948534.
- [35] Raman, N., Utthra, P. P., & Chellapandi, T. (2020). Insight into the in vitro anticancer screening, molecular docking and biological efficiency of pyridine-based transition metal (II) complexes. *Journal of Coordination Chemistry*, 73(1), 103-119.
- [36] Fekri, R., Salehi, M., Asadi, A., & Kubicki, M. (2019). Synthesis, characterization, anticancer and antibacterial evaluation of Schiff base ligands derived from hydrazone and their transition metal complexes. *Inorganica Chimica Acta*, 484, 245-254.

Chapter 2A

- [37] Kolodziej, A. F. (1994). The chemistry of nickel-containing enzymes. *Progress in Inorganic Chemistry*, 493-597.
- [38] West, D. X., Gebremedhin, H., Butcher, R. J., Jasinski, J. P., & Liberta, A. E. (1993). Structures of nickel (II) and copper (II) complexes of 2-acetylpyridine azacyclothiosemicarbazones. *Polyhedron*, 12(20), 2489-2497.
- [39] Ghosh, A. K., Mitra, M., Fathima, A., Yadav, H., Choudhury, A. R., Nair, B. U., & Ghosh, R. (2016). Antibacterial and catecholase activities of Co (III) and Ni (II) Schiff base complexes. *Polyhedron*, 107, 1-8.
- [40] Bahron, H., Khaidir, S. S., Tajuddin, A. M., Ramasamy, K., & Yamin, B. M. (2019). Synthesis, characterization and anticancer activity of mono-and dinuclear Ni (II) and Co (II) complexes of a Schiff base derived from o-vanillin. *Polyhedron*, 161, 84-92.
- [41] Morrow, J. R., & Kolasa, K. A. (1992). Cleavage of DNA by nickel complexes. *Inorganica chimica acta*, 195(2), 245-248.
- [42] Abumelha, H. M., Al-Fahemi, J. H., Althagafi, I., Bayazeed, A. A., Al-Ahmed, Z. A., Khedr, A. M., & El-Metwaly, N. (2020). Deliberate-characterization for Ni (II)-Schiff base complexes: promising in-vitro anticancer feature that matched MOE docking-approach. *Journal of Inorganic and Organometallic Polymers and Materials*, 30, 3277-3293.
- [43] Aslan, H. G., Akkoç, S., & Kökbudak, Z. (2020). Anticancer activities of various new metal complexes prepared from a Schiff base on A549 cell line. *Inorganic Chemistry Communications*, 111, 107645.
- [44] Li, Y., Dong, J., Zhao, P., Hu, P., Yang, D., Gao, L., & Li, L. (2020). Synthesis of amino acid Schiff base nickel (II) complexes as potential anticancer drugs in vitro. *Bioinorganic chemistry and applications*, 2020(1), 8834859.
- [45] Enamullah, M., Islam, M. A., Joy, B. A., & Reiss, G. J. (2016). Bis [N-2-(R-pyridyl)-2-oxo-1-naphthaldiminato- $\kappa^2 N^{\wedge} O$] copper (II)(R= H, 4/6-CH₃): Combined studies on syntheses, spectroscopy, cyclic voltammetry, thermal analyses, crystal structure and DFT/TDDFT. *Inorganica Chimica Acta*, 453, 202-209.
- [46] Liu, X. Y., Fan, Y. H., Wang, Q., Bi, C. F., & Wang, Y. F. (2010). 1-[(Z)-(5-Methyl-2-pyridyl) iminiomethyl]-2-naphtholate. *Acta Crystallographica Section E: Structure Reports Online*, 66(2), o309-o309.
- [47] Abdel-Rahman, L. H., Abu-Dief, A. M., Newair, E. F., & Hamdan, S. K. (2016). Some new nano-sized Cr (III), Fe (II), Co (II), and Ni (II) complexes incorporating 2-((E)-(pyridine-2-ylimino) methyl) naphthalen-1-ol ligand: Structural characterization, electrochemical,

Chapter 2A

antioxidant, antimicrobial, antiviral assessment and DNA interaction. *Journal of Photochemistry and Photobiology B: Biology*, 160, 18-31.

[48] Nazır, H., Yıldız, M., Yılmaz, H., Tahir, M. N., & Ülkü, D. (2000). Intramolecular hydrogen bonding and tautomerism in Schiff bases. Structure of N-(2-pyridil)-2-oxo-1-naphthylidenemethylamine. *Journal of Molecular Structure*, 524(1-3), 241-250.

[49] Tskhovrebov, A. G., Novikov, A. S., & Khrustalev, V. N. (2021). identification of supramolecular dimers in the crystal structure of (z)-1-(((5-fluoropyridin-2-yl) amino) methylene) naphthalen-2 (1h)-one via c (sp 2)-h... f hydrogen bonding: a combined experimental and theoretical study. *Journal of Structural Chemistry*, 62, 460-466.

[50] Sedaghat, T., Habibi, R., Motamedi, H., & Khavasi, H. R. (2012). Synthesis, structural characterization and antibacterial activity of diorganotin (IV) complexes with ONO tridentate Schiff bases containing pyridine ring. *Chinese Chemical Letters*, 23(12), 1355-1358.

[51] Chang, F., Zhang, D., Xu, G., Yang, H., Li, J., Song, H., & Sun, W. H. (2004). Synthesis and characterization of new bis (1-aryliminomethylenylnaphthalen-2-oxy) nickel complexes and their catalytic behavior for vinyl polymerization of norbornene. *Journal of organometallic chemistry*, 689(5), 936-946.

[52] Sagar, S., Mongal, B. N., Dutta, A., Mondal, P., Lewis, W., Saba, N., & Naskar, S. (2016). Complexation study of Schiff base ligand: pyridin-2-ylimino methyl naphthanol with Co²⁺, Mn²⁺ and Ni²⁺ ions in solid and solution phase. *Journal of Coordination Chemistry*, 69(15), 2364-2376.

[53] M.-Y. Lan, H. Liang, X.-C Lu, J.-Q. Deng, X. Cheng, J.-X. Chen, Z.-C. Zhang, *JiegouHuaxue* . 34 (2015) 447.

[54] Hökelek, T., Kılıç, Z., Isıklan, M., & Toy, M. (2000). Intramolecular hydrogen bonding and tautomerism in Schiff bases. Part II. Structures of 1-[N-(2-pyridyl) aminomethylidene}-2 (1H)-naphthalenone (1) and bis [2-hydroxy-κO-N-(2-pyridyl)-1-naphthaldiminato-κN] zinc (II)(2). *Journal of Molecular Structure*, 523(1-3), 61-69.

[55] Jing②, X. I. A. N. G., & Ya, L. (2014). A Novel Layer Cadmium Coordination Polymer Containing Tetranuclear [Cd₄ (tpt)₂ (Cl)₄]₄ as a Secondary Building Unit (SBU) Bridged by Pyridine 2, 4-Dicarboxylic Acid ①. *结构化学 (JIEGOU HUAXUE)*, 33(3).

[56] Enamullah, M., Islam, M. A., Joy, B. A., Dittrich, B., Reiss, G. J., & Janiak, C. (2018). π-π interaction leading to an inversion-symmetric complex pair of Λ- and Δ-bis [N-2-(R-pyridyl)-2-oxo-1-naphthaldiminato-κ²N, O] zinc (II). *Inorganica Chimica Acta*, 482, 935-942.

Chapter 2A

- [57] Das, S., Hung, C. H., & Goswami, S. (2003). Syntheses and structures of zwitterionic indium (III) and di-zinc compounds of an extended nitrogenous ligand. Examples of unusually long wavelength transitions in d10-metal complexes. *Inorganic chemistry*, 42(17), 5153-5157.
- [58] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. B. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Gaussian, Inc.: Wallingford, CT, USA, 2009.
- [59] Dennington, R., Keith, T., & Millam, J. (2009). GaussView; Semichem Inc. *Shawnee Mission, KS*.
- [60] Spackman, M. A., & Byrom, P. G. (1997). A novel definition of a molecule in a crystal. *Chemical physics letters*, 267(3-4), 215-220.
- [61] McKinnon, J. J., Spackman, M. A., & Mitchell, A. S. (2004). Novel tools for visualizing and exploring intermolecular interactions in molecular crystals. *Acta Crystallographica Section B: Structural Science*, 60(6), 627-668.
- [62] Castiñeiras, A., García-Santos, I., González-Pérez, J. M., Bauzá, A., Zareba, J. K., Niclós-Gutiérrez, J., ... & Frontera, A. (2018). Multicomponent supramolecular assemblies of melamine and α -hydroxycarboxylic acids: understanding the hydrogen bonding patterns and their physicochemical consequences. *Crystal Growth & Design*, 18(11), 6786-6800.
- [63] Mahmoudi, G., Zaręba, J. K., Bauzá, A., Kubicki, M., Bartyzel, A., Keramidas, A. D., ... & Frontera, A. (2018). Recurrent supramolecular motifs in discrete complexes and coordination polymers based on mercury halides: prevalence of chelate ring stacking and substituent effects. *CrystEngComm*, 20(8), 1065-1076.
- [64] Banik, R., Roy, S., Kirillov, A. M., Bauza, A., Frontera, A., Rodriguez-Dieguez, A., ... & Das, S. (2016). Two mixed-ligand cadmium (ii) compounds bearing 5-nitrosopyrimidine and N-donor aromatic blocks: self-assembly generation, structural and topological features, DFT studies, and Hirshfeld surface analysis. *CrystEngComm*, 18(30), 5647-5657.

Chapter 2A

- [65] Mahmoudi, G., Zaręba, J. K., Gurbanov, A. V., Bauzá, A., Zubkov, F. I., Kubicki, M., ... & Frontera, A. (2017). Benzyl dihydrazone versus thiosemicarbazone Schiff base: Effects on the supramolecular arrangement of cobalt thiocyanate complexes and the generation of CoN6 and CoN4S2 coordination spheres. *European Journal of Inorganic Chemistry*, 2017(40), 4763-4772. [66] Meyer, A. Y. (1986). Molecular mechanics and molecular shape. III. Surface area and cross-sectional areas of organic molecules. *Journal of computational chemistry*, 7(2), 144-152. [67] Rudnick, J., & Gaspari, G. (1986). The asphericity of random walks. *Journal of Physics A: Mathematical and General*, 19(4), L191.
- [68] Fekri, R., Salehi, M., Asadi, A., & Kubicki, M. (2019). Synthesis, characterization, anticancer and antibacterial evaluation of Schiff base ligands derived from hydrazone and their transition metal complexes. *Inorganica Chimica Acta*, 484, 245-254.
- [69] Haribabu, J., Jeyalakshmi, K., Arun, Y., Bhuvanesh, N. S., Perumal, P. T., & Karvembu, R. (2015). Synthesis, DNA/protein binding, molecular docking, DNA cleavage and in vitro anticancer activity of nickel (II) bis (thiosemicarbazone) complexes. *RSC Advances*, 5(57), 46031-46049.
- [70] Banaspati, A., Raza, M. K., & Goswami, T. K. (2020). Ni (II) curcumin complexes for cellular imaging and photo-triggered in vitro anticancer activity. *European Journal of Medicinal Chemistry*, 204, 112632.
- [71] Göktürk, T., Topkaya, C., Sakallı Çetin, E., & Güp, R. (2022). New trinuclear nickel (II) complexes as potential topoisomerase I/II α inhibitors: in vitro DNA binding, cleavage and cytotoxicity against human cancer cell lines. *Chemical Papers*, 76(4), 2093-2109.
- [72] Tadele, K. T., & Tsega, T. W. (2019). Schiff bases and their metal complexes as potential anticancer candidates: a review of recent works. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, 19(15), 1786-1795.
- [73] Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A., & Puschmann, H. (2009). OLEX2: a complete structure solution, refinement and analysis program. *Journal of applied crystallography*, 42(2), 339-341.
- [74] Sheldrick, G. M. (2015). SHELXT—Integrated space-group and crystal-structure determination. *Acta Crystallographica Section A: Foundations and Advances*, 71(1), 3-8.
- [75] Sheldrick, G. M. (2015). Crystal structure refinement with SHELXL. *Acta Crystallographica Section C: Structural Chemistry*, 71(1), 3-8.
- [76] Sheldrick, G. M. (2008). A short history of SHELX. *Acta Crystallographica Section A: Foundations of Crystallography*, 64(1), 112-122.
- [77] B. SMART, SAINT & SADABS. Bruker AXS, Inc., Madison, WI, USA (2007).

Chapter 2A

- [78] McKinnon, J. J., Jayatilaka, D., & Spackman, M. A. (2007). Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces. *Chemical Communications*, (37), 3814-3816.
- [79] Spackman, M. A., & Jayatilaka, D. (2009). Hirshfeld surface analysis. *CrystEngComm*, 11(1), 19-32.
- [80] Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Spackman, P. R., Jayatilaka, D., & Spackman, M. A. (2017). CrystalExplorer17 (2017). *University of Western Australia*, 8.
- [81] Saygideger, Y., Demir, B. S., Tok, T. T., Avcı, A., Toprak, O. B., Sezan, A., & Özyılmaz, E. (2021). Antitumoral effects of Santolina chameacyparissus on non-small cell lung cancer cells. *Journal of Experimental and Clinical Medicine*, 38(3), 294-300.
- [82] <https://www.biolegend.com/nl-be/products/apc-annexin-v-apoptosis-detection-kit-with-pi-9788>.



Synthesis, Characterization,
Antimicrobial activities of Co(III) and
Cd(II) complexes derived from an
unsymmetrical pyridyl Schiff base
ligand *N*-2-(6-methylpyridyl)-2-
hydroxy-1-naphthaldimine

Chapter 2B

2B.1 Antimicrobial properties of metal-based complexes

Antimicrobial resistance (AMR) is a worldwide public health threat that occurs when microbes including viruses, bacteria, parasites, fungi etc change over time and become resistant to the medicine used to treat them. In the upcoming decades, AMR is expected to overtake all other causes of death globally. In 2019 approximately 4.95 million AMR-related deaths occurred, out of which 1.3 million deaths were directly related to resistance infection [1]. If action is not taken earlier, the figure is supposed to increase to 10 million fatalities globally in a year by 2050 [2] because of the widespread overprescription of antibiotics during the last few years to patients suffering from COVID-19 disease [3]. New strategies are thus urgently required to generate the next generation of antibiotics [4]. Antibacterial potentials of metal compounds had been recognized before the development of current inorganic pharmaceutical chemistry. For instance, in 1952, it was found that simple ruthenium compounds have antibacterial characteristics [5]. The antiproliferative attributes of platinum compounds were first shown by *E. coli* bacteria, which paved the way for the development of anticancer medication cisplatin in 1965 [6]. Since then, data on the antibacterial activities of metal complexes have been accumulating slowly but noticeably over the past ten years. However, most data provide *in vitro* measures against a few numbers of species of bacteria without going into great detail about how they work or whether they could be developed into possible antibiotic drug candidates. Furthermore, in *in vivo* animal models, only a small number of metalloantibiotics have been tested [7-10]. The capability of metal complexes to inhibit bacterial growth was assessed by the Community for Open Antimicrobial Drug Discovery (CO-ADD) Initiative, utilizing a wide variety of metal complexes [11]. It has been found that the hit rate of the metal compounds against important ESKAPE pathogens is ten times higher than that of other organic compounds in the database of CO-ADD. Crucially, a comparison of frequencies of hemolysis for human red blood cells and cytotoxicity for mammalian cell lines for the two groups of compounds (organic and metal-based) revealed no noticeable variation in either toxicity measure. This work not only shows how powerful metal complexes may be as antimicrobial agents but also refutes the false belief that metal complexes are intrinsically more harmful compared to organic compounds [12]. The mechanism through which metal complexes produce their antibacterial activities has become more crucial since their promise as the next generation of antimicrobials has been demonstrated. Certain kinds of metal compounds exhibiting antimicrobial properties can be activated by external stimuli, like the light in photodynamic treatment (PDT), in addition to internal stimulation from bacteria called photo-activated antimicrobial metal complexes. Two essential elements are needed for PDT: a

Chapter 2B

photosensitizer and a light source. After absorbing photons from the light source, the photosensitizer is excited to react directly with surroundings such as cellular constituents and either destroys them or changes the neighbouring molecules for example oxygen and water to reactive oxygen species (ROS) which in turn can kill bacteria [13-15]. Transition metal complexes have extensive biological properties. In metal complexes, the metal center is bonded with a variety of ligands via coordination bonds, which have become more significant in pharmaceutical chemistry because they can stabilize the metal center and change its both chemical and medicinal characteristics [16]. Inhibiting microbial activity without causing any side effects is the primary aim of any antimicrobial agent. Following are the factors which affect the antimicrobial activity of complexes based on metal: (a) The chelate action of the ligand (b) The donor sites of ligands (c) Characteristics of the counterions which balance the charge of metal ions (d) The complex's geometry (e) Characteristics of metal ions [17]. The lipid solubility of the coordination compounds is thought to be key element regulating antimicrobial action. Because of the overlapping of orbitals of the ligands with the empty metal orbital and partial neutralization of the ions's positive charge, the lipophilicity of the metal ions is increased at the time of chelation. Additionally, the delocalization of the electron cloud through the ring structure is increased due to the chelation process, which in turn improves the lipophilicity of the complex. Because of their higher lipophilic character, the complexes gain more capability of penetrating lipid membranes and obstructing the binding areas of metal on the enzymes and hence inhibit the survival of the microorganisms. The respiration of the cell is also prevented by such complexes, which inhibit the creation of new proteins and stop the ability of the microbes to grow. The metal-based complexes are more effective antimicrobials compared to their corresponding ligands and metal salts from which they are derived. The difference in microbe ribosomes or the impermeability of microbe cells determines how differently several compounds function against different organisms. The findings of the antibacterial screening showed a noticeable increase in activity against the test bacterial strains when combined with the metal ions. Additionally, the enzymes that depend on these groups for their activity are particularly liable to be deactivated by the metal ions during chelation. The synthesis of enzymes can be suppressed if the ligands contain oxygen and nitrogen as donor atoms [18]. Some metal chelates can have greater and some others have lower antimicrobial activity compared to their corresponding parent ligands. So, their antimicrobial activities can be enhanced by introducing oxygen and nitrogen as donors in the chelating ligands. Therefore, the synergistic effect between the ligand and the metal ions of the complexes increases the bioactivity of the metal coordination compounds [19]. In Schiff base ligands, the hydrogen

Chapter 2B

bond formation between the azomethine functionalities of Schiff base ligands and the active sites of cell constituents is the mechanism of antimicrobial activity. This interferes with the regular cell activity of microbes. These findings may open the door for the creation of therapeutically useful next-generation antibiotics [20]. The incorporation of electron-withdrawing groups to the chelating ligands also makes metal chelates more lipophilic, which facilitates their penetration into the lipid layers of the cells of the microbes [21]. Metal complexes consisting of Schiff base ligands exhibit numerous biological functions, having antioxidant, antimicrobial, anti-inflammatory, antimalarial and antitumor [16] antidepressants, antimicrobial, antitumor, antiphlogistic, nematocide, [22, 23] antiviral, antibiotic, analgesic, anti-inflammatory, antifungal, etc. [24]. In reality, microorganisms have developed resistance to several of the existing antimicrobials because of regular utilization of antibiotics. So, chemists have been compelled to develop a wider range of medications. Studies have demonstrated that the Schiff base metal complexes can broaden the range of medications [25].

Several metal-based complexes are approved for treating various infectious diseases are under clinical trials [26]. Iron-based therapeutic ferroquine has gained significant attention after re-entry into second-phase clinical trials in order to cure malaria. Another illustration is auranofin, a gold metallodrug that was first developed to treat rheumatoid arthritis but is currently being researched to treat parasitic and bacterial infections. In 2020, pravibismane, a bismuth-based medication, received FDA approval to treat infected bone sites [27].

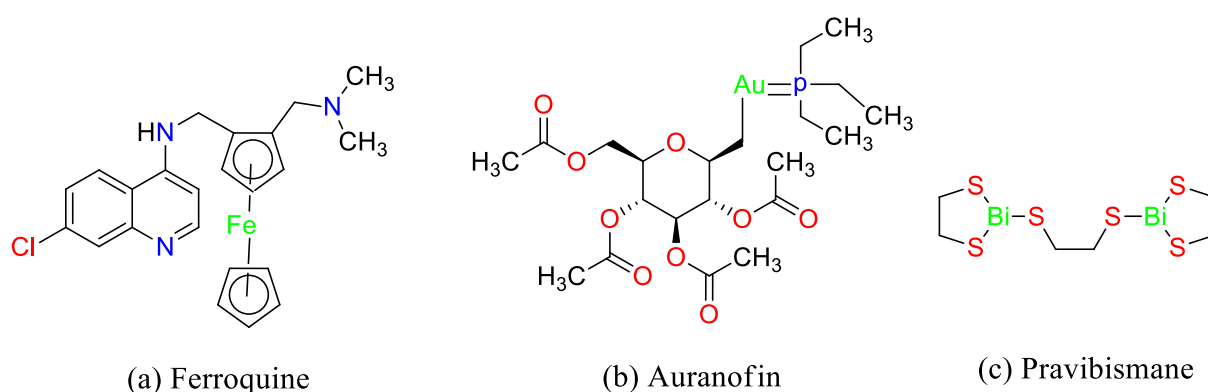


Fig. 2B.1. Metal-based compounds (a) and (b) under clinical trial and (c) clinically approved antimicrobials drugs.

Chapter 2B

In the human body, cobalt is a trace metal that is essential for various biologically noteworthy processes [28]. It is mostly present in vitamin B₁₂, also known as cobalamine. Cobalamine displays a significant role concerning the catabolism of fatty acids of mitochondria and the metabolism of amino acids of cytoplasm in human bodies [29]. Humans have therefore evolved unique methods for managing the body's excess cobalt. Cobalt is present in a broad variety of synthetic and natural compounds in the typical oxidation states of Co(II) and Co(III) [30, 31]. Cobalt complexes of Schiff base ligands are classified as oxygen carriers and have been investigated as potential models for the cobalamine (B₁₂) coenzymes [32]. Numerous structurally established cobalt Schiff base complexes with antibacterial, anti-inflammatory, antiviral, bactericidal, and fungicidal properties have been the subject of investigation [33]. Earlier studies have demonstrated that the oxidation of Co(II) compounds to Co(III) derivatives is influenced by the nature of the compartmental ligand, with simple air oxidation being sufficient to convert Co(II) halides into Co(III) complexes in certain cases. [34, 35]. Numerous functional Cd(II) complexes with intriguing pharmacological properties have been investigated because of their greater radius, broad area of coordination numbers and coordination potentials, as well as their capability to coordinate with Schiff base ligands [36]. The development of novel Cd(II) coordination compounds has been spurred by interesting biological features of cadmium compounds, especially those complexes of Schiff base ligands [37]. Several stable Cd(II) complexes with bioactive ligands that exhibited interesting supramolecular properties and antimicrobial activities have been reported [38-44].

In recent times, bacterial infections caused by gram-negative bacteria have become more prevalent. Due to growing instances of developing antimicrobial resistance among gram-negative bacteria, there is a need for emergent treatment options to manage the rapid spread of antimicrobial drug resistance mechanisms [45]. The use of antibiotics to control bacterial disease caused by *Escherichia coli*, *Salmonella typhi*, and *Shigella sonnei* has led to the growing of antibiotic-resistant microbes. The pathogenic strains of *Enterobacteriaceae* cause infections like urinary tract infections (UTIs), typhoid fever, and shigellosis. Henceforth, the need for alternative medicines is required [46-51]. Inspired by the interesting pharmacological properties of pyridine-based Schiff base and its coordination compounds, herein we report the synthesis, characterization, and antimicrobial properties of pyridyl Schiff base *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Co(III) and Cd(II) complexes. The structure of the novel Co(III) and Cd(II) complexes have been characterized by FT-IR, ¹H NMR, and Mass spectroscopy.

Chapter 2B

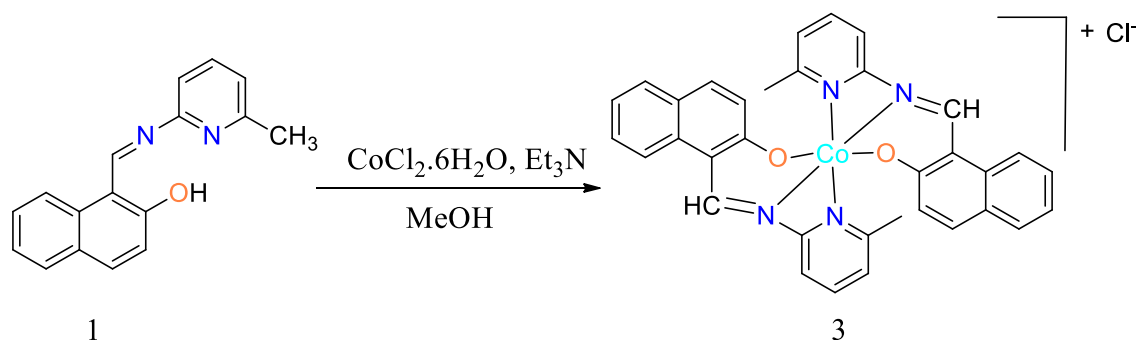
2B.2 Present work

Synthesis, Characterization, Antimicrobial activities of Co(III) and Cd(II) complexes derived from an unsymmetrical pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine

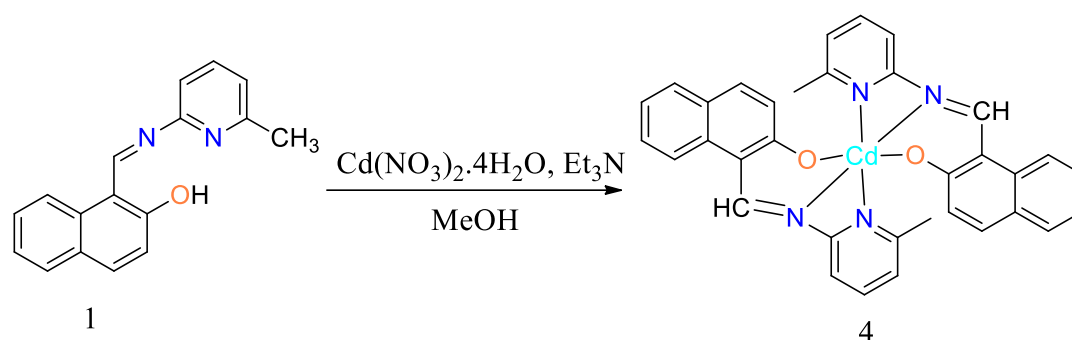
Section 2B deals with the design, synthesis, and antibacterial studies of Co(III) complex **3** and Cd(II) complex **4** using the same Schiff base ligand **1** synthesized in section 2A. The compounds are characterized by FT-IR, ^1H NMR and Mass spectroscopy. The spectral data indicated the coordination of metal ions by the pyridyl Schiff base ligand in a tridentate N, N, O mode. The complexes were assumed to adopt octahedral geometry. In complex **3**, an uncoordinated Cl^- anion is present, thereby balancing the charge of the complex. The antimicrobial activities of the pyridyl Schiff base ligand **1** and synthesized Co(III) complex **3** and Cd(II) complex **4** were studied against gram-negative bacteria. The *in-vitro* antimicrobial study of Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4** in *Escherichia coli* (ATCC 25922), *Salmonella typhi* (ATCC 6539), and *Shigella sonnei* (ATCC 25931) bacterial strains were investigated by performing the Kirby-Bauer disk-diffusion and well diffusion assays. Results indicated that the Cd(II) complex **4** shows better antibacterial activity against *Salmonella typhi*. Before entering into the present work, a general introduction to the antimicrobial activities of metal complexes taking suitable examples related to Co(II)/(III) and Cd(II) from the literature, have been presented.

2B.2.1. Reaction schemes for the synthesis of Co(III) complex **3** and Cd(II) complex **4**

Compounds **3** and **4** were synthesized in good yields from **1**, following **Scheme 1** and **Scheme 2** respectively.



Scheme 1. Synthesis of Co(III) complex **3**.



Scheme 2. Synthesis of Cd(II) complex **4**.

2B.2.2. Synthesis, FT-IR, NMR, and ESI-MS spectral characterization of **3** and **4**

Coordination of ligand **1** with $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ produced complexes **3** and **4**, respectively, both of which are diamagnetic. During the synthesis of complex **3**, an initially formed Co(II) complex was likely oxidized by air. Although X-ray diffraction data are unavailable, the oxidation is evident from the ^1H NMR spectrum of **3**, confirming the formation of a diamagnetic cobalt(III) complex. The ESI mass spectrum of **3** exhibits a peak corresponding to a stable cation with an appropriate m/z for $[\text{Co}(\text{deprotonated ligand})_2]^+$. Efforts to exclude air during the reaction and crystallization still resulted in the formation of cobalt(III) complex **3**. Additionally, the molar conductance value in methanol indicates that complex **3** behaves as a 1:1 electrolyte, consistent with literature [52].

IR spectroscopy provides valuable information regarding the nature of functional groups present in both free ligands as well as in the metal complex, which were recorded in the region $4000\text{--}400\text{ cm}^{-1}$. The presence of an intense absorption band at 1624 cm^{-1} due to $\nu(\text{C}=\text{N})$ of the azomethine group ($-\text{CH}=\text{N}-$) in the spectra confirms the formation of the Schiff base ligand. The formation of unsymmetrical pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine **1** was also confirmed by X-ray analysis, which we have reported in our earlier publication [53]. The intense absorption band at 1616 cm^{-1} and 1615 cm^{-1} in the spectra of the complexes cobalt (III) complex **3** and cadmium (II) complex **4**, respectively is assigned to the imine stretching frequency of the azomethine group of the ligand. The shift of the band to a lower frequency, compared to the free Schiff base ligand (1624 cm^{-1}) indicates the coordination of the imine nitrogen atom to the Co^{III} and Cd^{II} ions (**Fig. 2B.2** and **Fig. 2B.4**). This seems to be due to the shift of the electron density from the nitrogen atom to the Co^{III} and Cd^{II} ions, which lowers the stretching frequency and weakens the $\text{C}=\text{N}$ bond [53]. The peaks at $3046, 2923\text{ cm}^{-1}$ and $3056, 3034, 2916\text{ cm}^{-1}$ are assigned for $\nu(\text{C}-\text{H})$ of olefinic and aliphatic (methyl) groups in the Co(III) complex **3** and Cd(II) complex **4** respectively. The downward

Chapter 2B

shift of $\nu(\text{C-O})$ phenolic band from $1304\text{--}1134\text{ cm}^{-1}$ in the ligand to $1249\text{--}1092\text{ cm}^{-1}$ and $1271\text{--}1089\text{ cm}^{-1}$ in the complexes **3** and **4** respectively confirms the participation of deprotonated phenolic oxygen in the coordination with Co^{III} and Cd^{II} ions. The Schiff-base coordination to the cobalt ion is confirmed by prominent bands at 452 cm^{-1} and 551 cm^{-1} which can be attributed to $\nu(\text{Co-N})$ and $\nu(\text{Co-O})$ respectively [31]. The Schiff-base coordination to the cadmium ion is also confirmed by prominent bands at 476 cm^{-1} , and 579 cm^{-1} which can be attributed to $\nu(\text{Cd-N})$ and $\nu(\text{Cd-O})$ respectively [36]. Thus, the comparison of the IR spectra of pyridyl Schiff base ligand **1** and Co(III) complex **3** and Cd(II) complex **4** indicate the formation of the complexes. In addition to the IR data, a comprehensive examination of the ^1H NMR of pyridyl Schiff base ligand **1**, Co(III) complex **3** and Cd(II) complex **4** gave additional evidence to support the complex formation (**Fig. 2B.6** and **Fig. 2B.7**). The phenolic proton ($-\text{OH}$) of the free pyridyl Schiff base ligand **1** shows a doublet at most downfield at δ 15.44 ppm which is absent in the complexes and confirms the formation of complexes. The azomethine proton shows a doublet at δ 9.95 ppm in the free Schiff base ligand, while the same appeared as a doublet at δ 9.93 ppm in both the Co(III) complex **3** and Cd(II) complex **4** [53]. The up-field shift of the azomethine group further confirms the formation of the complexes and coordination of the imine nitrogen atom to the Co^{II} and Cd^{II} ions. The pyridyl ring protons of free ligand Schiff base ligand **1** were found as a doublet at δ 6.91, 6.97, and 7.03 ppm while in Co(III) complex **3** and Cd(II) complex **4** it shifted to upfield (δ 6.89, 6.95, 7.00 ppm) and (δ 6.89, 6.95, 7.00 ppm). This up-field shifting indicates that pyridyl ring nitrogen is involved in the metal coordination [53]. The other aromatic protons of both free ligands and complex compounds are found at their suitable positions. In the ^1H NMR spectra of the ligand, the methyl protons appear as a singlet at δ 2.63 ppm, which shift to upfield upon coordination to the metal ion at δ 2.60 ppm for both Co(III) complex **3** and Cd(II) complex **4**. Mass spectra of both the pyridyl Schiff base ligand **1** and its complexes with Co (III) and Cd (II) also provide further confirmation for the binding of the Schiff base ligand **1** with the metal ions (**Fig. 2B.8** and **Fig. 2B.9**). The mass spectra of the compounds Schiff base ligand **1**, Co(III) complex **3** and Cd(II) complex **4** displayed prominent peaks corresponding to molecular ion fragments which were at $m/z = 261.3 [\text{M} - \text{H}^+]$, $262.3 [\text{M}^+]$ for Schiff base ligand **1**, $m/z = 583.8 [\text{M} + 2\text{H}^+]$ for Co (III) complex **3** and $m/z = 635.6 [\text{M} + 2\text{H}^+]$ for Cd(II) complex **4**. The molecular formulae and structures assigned to these complexes are further supported by ESI-MS studies. Overall, the formation of the Co(III) complex **3** and Cd(II) complex **4** from the pyridyl Schiff base ligand **1** is confirmed by the spectral analysis of FT-IR, ^1H NMR, and ESI-MS data.

Chapter 2B

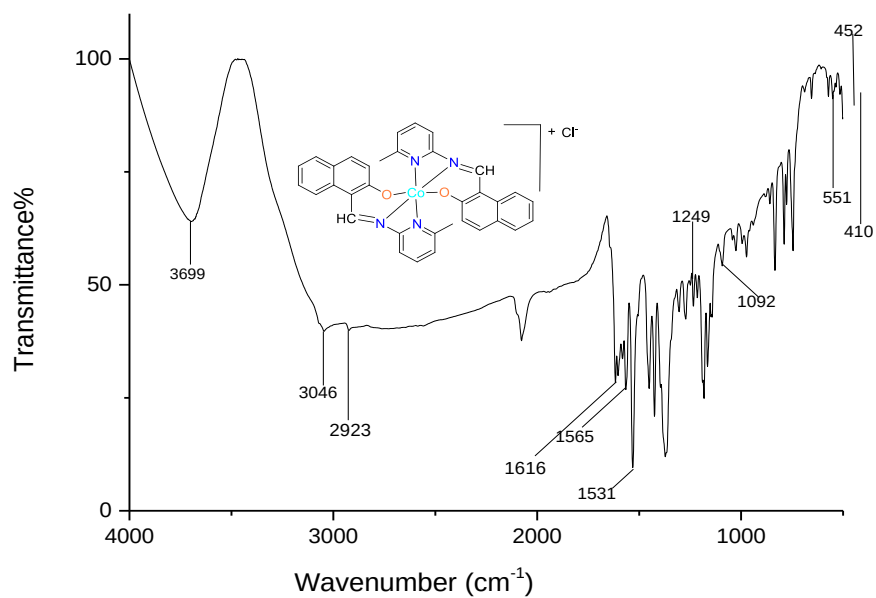


Fig. 2B.2. FT-IR spectrum of Co(III) complex 3.

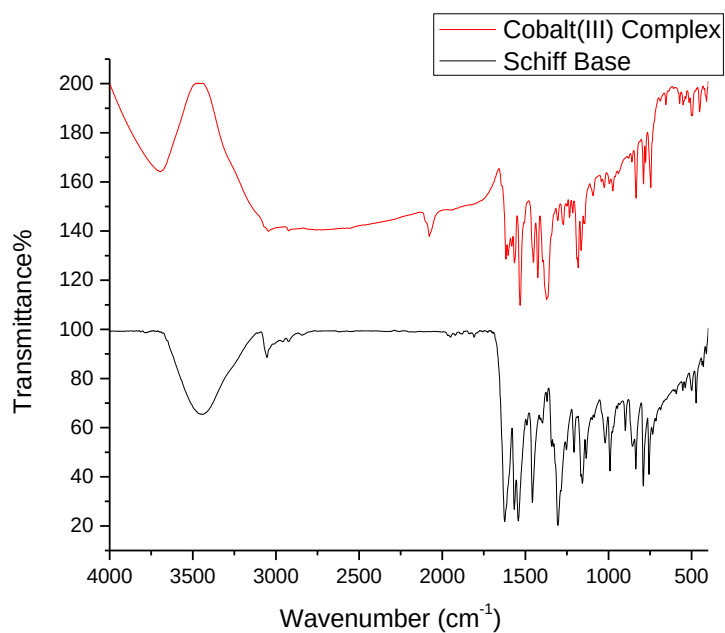


Fig. 2B.3. Comparison of FT-IR spectra of the pyridyl Schiff base ligand 1 and Co (III) complex 3.

Chapter 2B

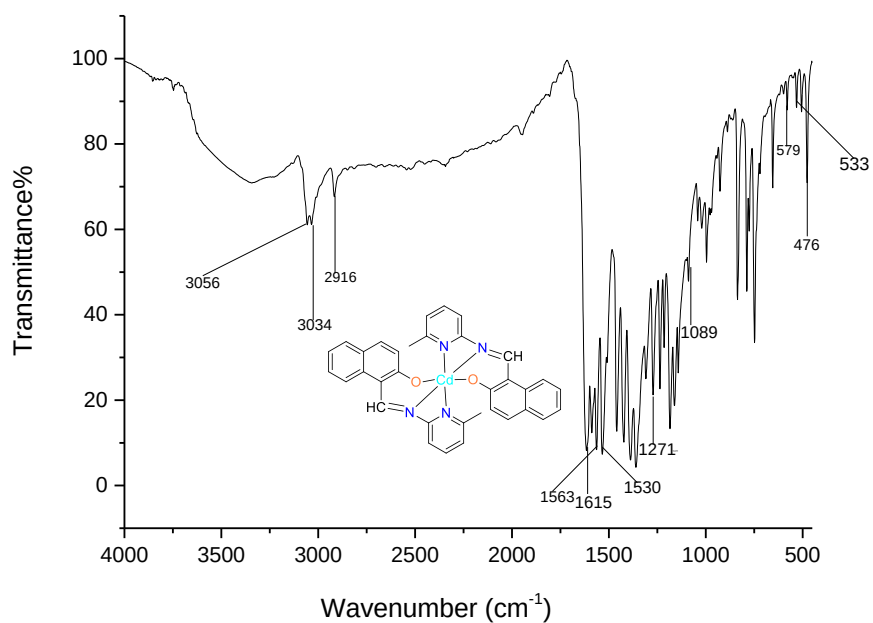


Fig. 2B.4. FT-IR spectrum of Cd(II) complex 4.

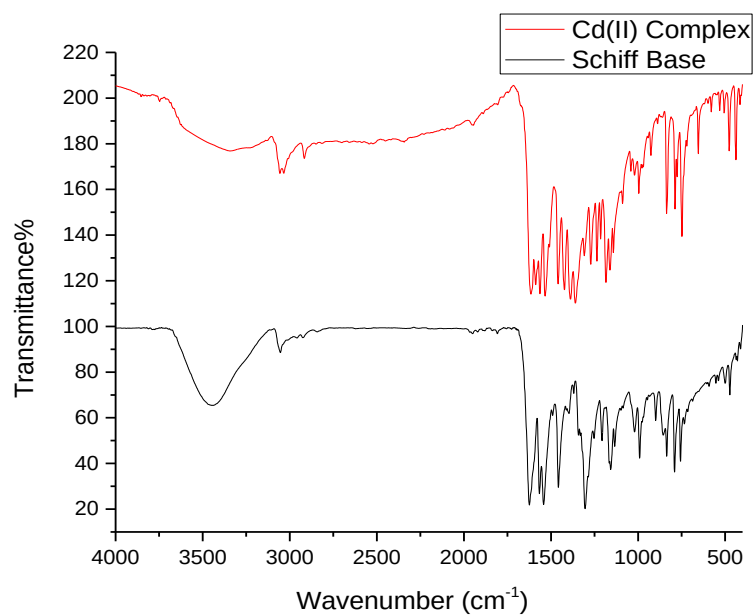


Fig. 2B.5. Comparison of FT-IR spectra of the pyridyl Schiff base ligand 1 and Cd(II) complex 4.

Chapter 2B

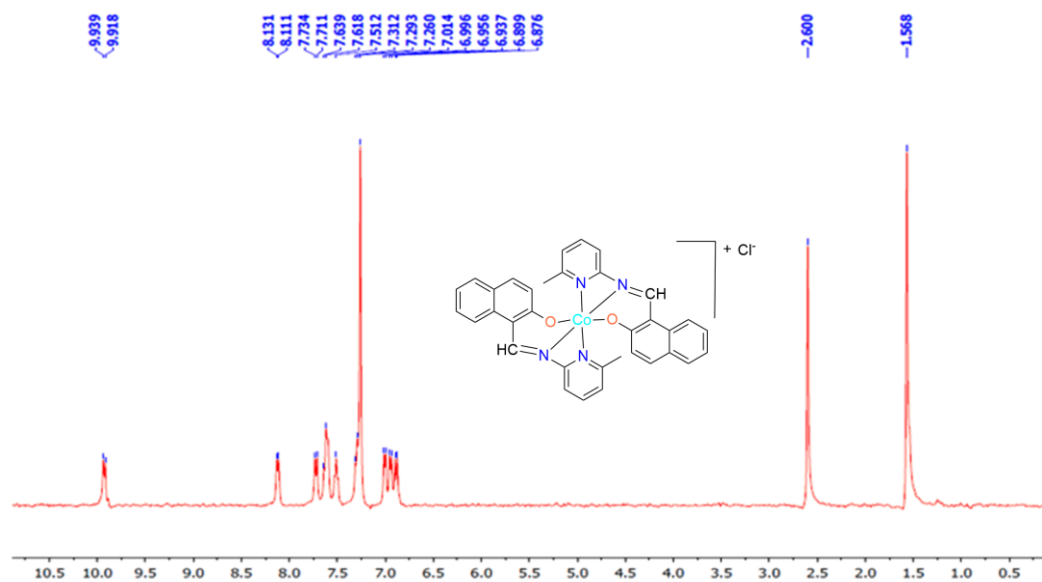


Fig. 2B.6. ^1H NMR Spectrum of Co(III) complex **3** in CDCl_3 .

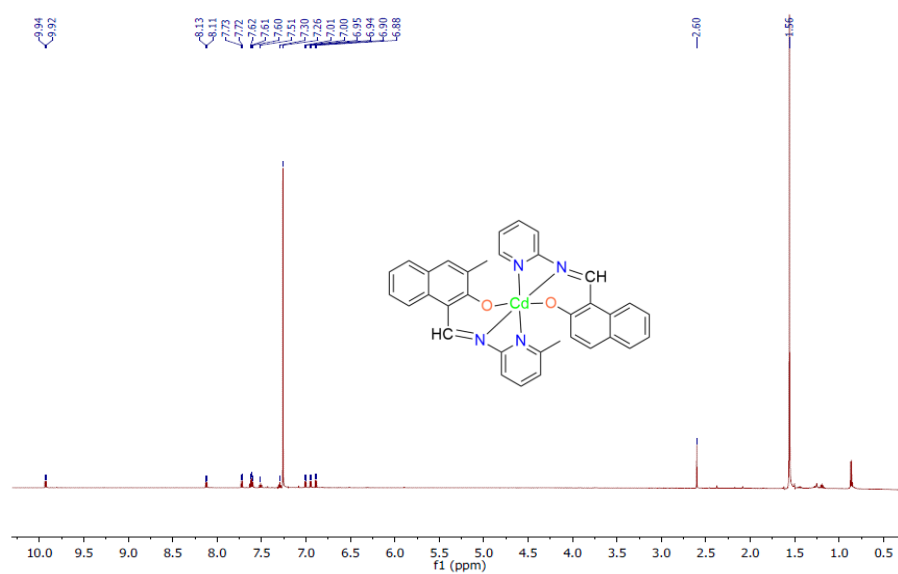


Fig. 2B.7. ^1H NMR Spectrum of Cd(II) complex **4** in CDCl_3 .

Chapter 2B

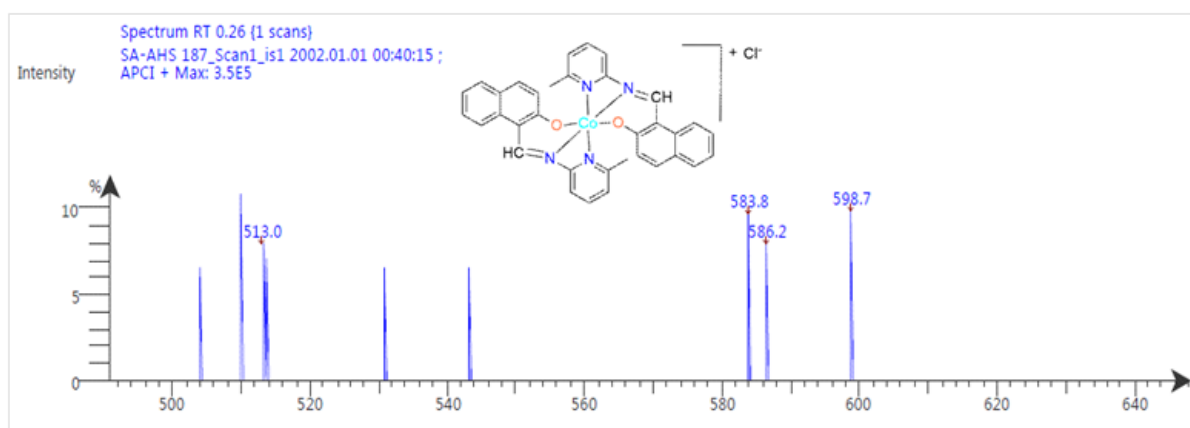


Fig. 2B.8. Mass spectrum of Co(III) complex 3.

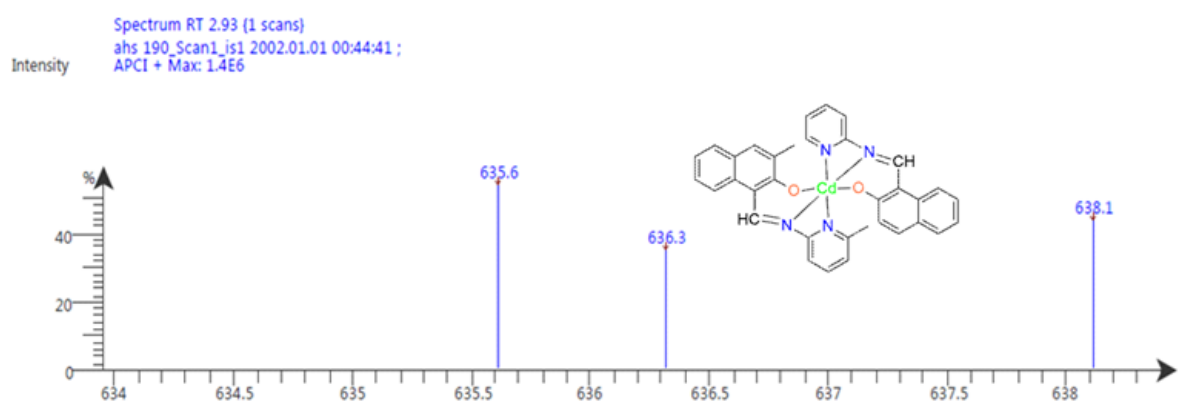


Fig. 2B.9. Mass spectrum of Cd(II) complex 4.

2B.2.3 Thermogravimetric Analysis OF 3 and 4

Figs. 10 and **11** represent the thermogravimetric analysis of Co(III) complex **3** and Cd(II) complex **4**. Complexes **3** and **4** exhibit thermal stability up to 165°C and 270°C, respectively, with no noticeable decomposition near 100°C in the TGA curves, suggesting the absence of solvate molecules in their structures. Subsequently, both complexes undergo decomposition in two distinct steps, likely corresponding to the loss of pyridyl Schiff base ligand **1** moiety. The residual mass observed is 12.52% (calculated 11.84%) for Co(III) oxide in complex **3** and 18.28% (calculated 18.98%) for CdO in complex **4**.

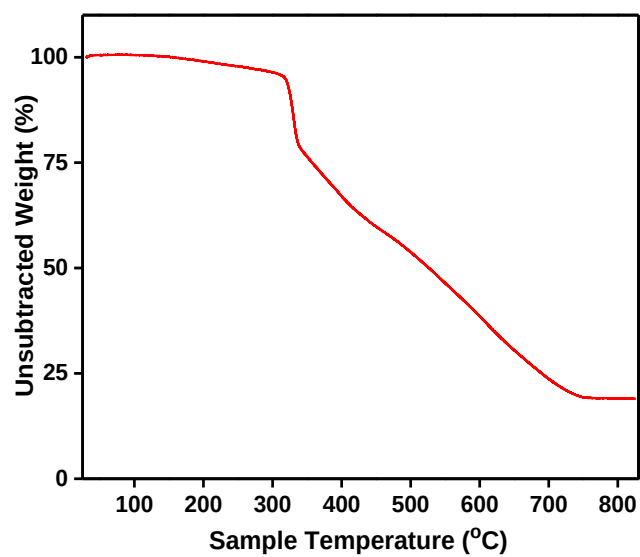


Fig. 2B.10. Thermogravimetric analysis curve of Co(III) complex **3**.

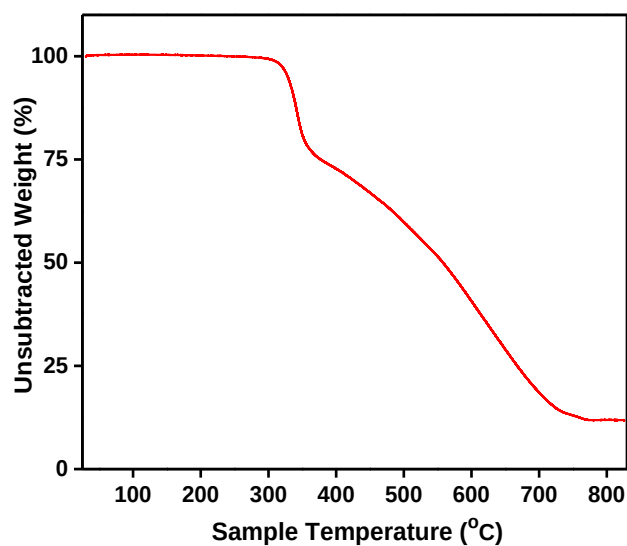
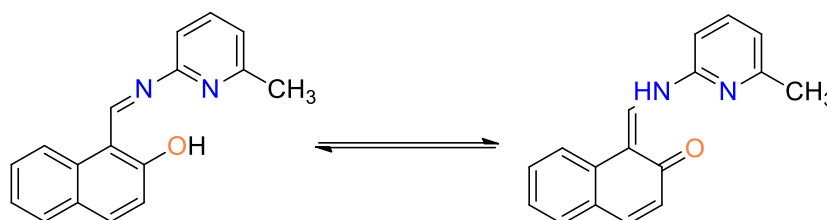


Fig. 2B.11. Thermogravimetric analysis curve of Cd(II) complex **4**.

Chapter 2B

2B.2.4. Description of structures of 3 and 4

Pyridyl Schiff base types of ligands typically persist as either keto-amine tautomers (zwitter ions) or enol-imino tautomers (**Scheme 3**). The zwitter ionic forms result from the para-substitution of moieties at the pyridine ring that either donate or withdraw electrons. In our earlier communication, we reported the solid-state structure of pyridyl Schiff base ligand **1** which established the zwitter ion form in the solid state further confirming its keto-amine tautomeric form [53].



Scheme 3. Schematic representation of the tautomeric structure of the pyridyl Schiff base ligand **1**.

The pyridyl Schiff base ligand can coordinate with metal ions through the oxo and imine ends, resulting in a six-membered chelate ring. The pyridyl ring nitrogen atom can also participate in metal coordination interpreting the ligand tridentate coordination mode. Earlier we reported the X-ray crystal structure of pyridyl Schiff base ligand **1** with Ni(II) ions [53]. Each deprotonated pyridyl Schiff base ligand **1** is coordinated to Ni⁺² in a bis-chelated mode (tridentate) *via* imine N-atom, pyridyl N-atom, and oxo O-atom, generating a distorted octahedral coordination, and the Ni(II) ions experience hexa-coordination, NiN₄O₂ (**Fig. 2B.3**).

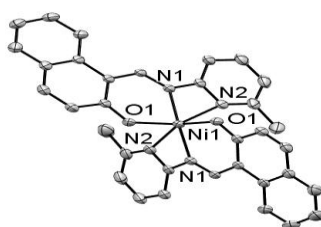


Fig. 2B.12. Crystal structure of pyridyl Schiff base ligand **1** with Ni(II) ions [53].

Chapter 2B

Despite our best efforts to obtain the crystals for Co(III) complex **3** and Cd(II) complex **4** we were unable to get suitable crystals for X-ray analysis for both complexes. But the FT-IR, NMR, and Mass spectra indicate the tridentate mode of binding of the Co^{III} and Cd^{II} ions by pyridyl Schiff base ligand **1** through the imine N-atom, pyridyl N-atom, and oxo O-atom, producing an octahedral geometry of the complexes (**Fig. 2B.13**). For complex **3**, an uncoordinated Cl⁻ anion is required to balance the charge of the complex. Structurally similar octahedral [Co^{III}(L)₂]Cl complexes, where L is an NNO-tridentate chelating ligand, may be referenced for comparison [34, 54-56].

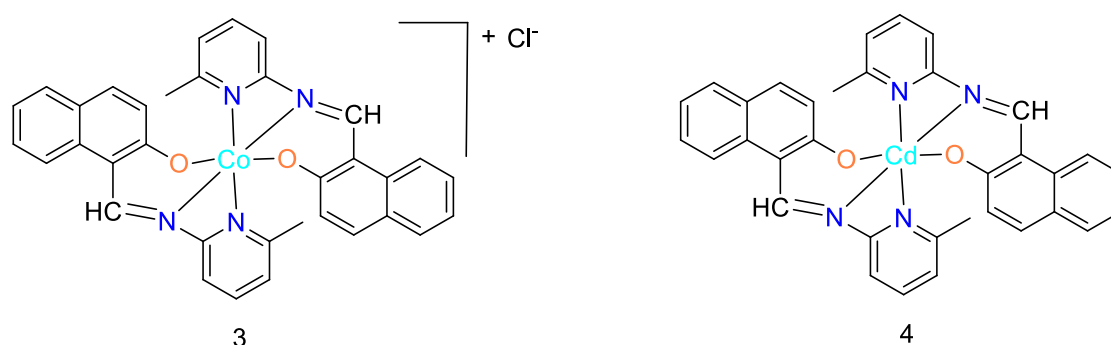


Fig. 2B.13. Probable structure of pyridyl Schiff base ligand **1** with Co(III) and Cd(II) ions.

2B.2.5. Anti-bacterial activity of **3** and **4**

Anti-bacterial assays were carried out with three compounds namely Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4**, against three gram-negative bacteria including *Escherichia coli* (ATCC 25922), *Salmonella typhi* (ATCC 6539), and *Shigella sonnei* (ATCC 25931). Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4** were dissolved in dimethyl sulfoxide (DMSO) in varying concentrations of 500 μ M, 100 μ M, 10 μ M, and 1 μ M. The antibiotic Gentamicin (2mM) was taken as a positive control for all bacteria.

Metal-based complexes are a good choice for the development of novel antimicrobial medications due to their distinct mechanisms of action and a broad range of 3D geometries. In the present investigation, Schiff base ligand **1** did not show antibacterial activity against the tested bacteria but Co(III) complex **3** and Cd(II) complex **4** exhibited antimicrobial properties. In the well diffusion assay Cd(II) complex **4** at doses 100 μ M and 500 μ M displayed a larger zone of inhibition against *Salmonella typhi* in contrast, Co(III) complex **3** displayed a moderate zone of inhibition for *Salmonella typhi* (in 1 μ M dose). The synthesized Co(III) complex **3** and

Chapter 2B

Cd(II) complex **4** demonstrated better anti-microbial activity against *Salmonella typhi* when compared to other gram-negative bacteria (*Escherichia coli* and *Shigella sonnei*) (**Figs. 2B.14-Fig. 2B.19**). A literature survey revealed that an organic ligand's antibacterial capabilities are typically enhanced when it is coordinated with metal centres [57]. Lipo-solubility of the complexes relative to the free ligand appears to be enhanced by overlapping of the ligand and metal ion orbitals, which appears to improve the resonance of π electrons on the compound structure. This enhancement of the antimicrobial activity may be attributed to an increase in lipophilicity character and improved diffusion in the microbial membrane [58]. Furthermore, metal complexes induce many forms of microbial cell damage through oxidative stress, dysfunctional proteins, and membrane disintegration [59]. The aforementioned reason explains the enhanced antibacterial activity of Co(III) complex **3** and Cd(II) complex **4** in comparison to free Schiff base ligand **1**.

The antibiotic gentamicin was utilized as a positive control that significantly suppressed the growth of all three gram-negative bacteria. The results of our investigation show that when compared to all three compounds, Cd(II) complex **4** exhibited better antimicrobial activity. Based on the highest concentration employed here, the Cd(II) complex **4** shows a better antibacterial trend against the following bacteria: *Salmonella typhi* exhibited better antibacterial activity than *Escherichia coli*, whereas no antibacterial activity was shown in *Shigella sonnei* after the treatments with Co(III) complex **3** and Cd(II) complex **4**. In conclusion, disc diffusion and well diffusion assays demonstrated better anti-bacterial activity of compounds Co(III) complex **3** and Cd(II) complex **4** at different doses compared to free Schiff base ligand **1**.

Chapter 2B



Fig. 2B.14a. *Escherichia coli* **Fig. 2B.14b.** *Salmonella typhi* **Fig. 2B.14c.** *Shigella sonnei*

Fig. 2B.14. Agar well diffusion assay with varying doses of pyridyl Schiff base ligand **1** shown in *Escherichia coli*. (**Fig. 2B.14a**), *Salmonella typhi* (**Fig. 2B.14b**), *Shigella sonnei* (**Fig. 2B.14c**). The zones of inhibition are depicted for varying concentrations of Schiff base ligand **1** (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Schiff base ligand **1**; (2) Denotes treatment with 10 μM of Schiff base ligand **1**; (3) Denotes treatment with 100 μM of Schiff base ligand **1**; (4) Denotes treatment with 500 μM of Schiff base ligand **1**; (5) Denotes the treatment with positive control (Gentamicin).



Fig. 2B.15a. *Escherichia coli* **Fig. 2B.15b.** *Salmonella typhi* **Fig. 2B.15c.** *Shigella sonnei*

Fig. 2B.15. Disc well diffusion assay with varying doses of pyridyl Schiff base ligand **1** shown in *Escherichia coli*. (**Fig 2B.15a**), *Salmonella typhi* (**Fig 2B.15b**), *Shigella sonnei* (**Fig 2B.15c**). The zones of inhibition are depicted for varying concentrations of Schiff base ligand **1** (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Schiff base ligand **1**; (2) Denotes treatment with 10 μM of Schiff base ligand **1**; (3) Denotes treatment with 100 μM of Schiff base ligand **1**; (4) Denotes treatment with 500 μM of Schiff base ligand **1**; (5) Denotes the treatment with positive control (Gentamicin).

Chapter 2B



Fig. 2B.16a. *Escherichia coli* **Fig. 2B.16b.** *Salmonella typhi* **Fig. 2B.16c.** *Shigella sonnei*

Fig. 2B.16. Agar well diffusion assay with varying doses of Co(III) complex 3 shown in *Escherichia coli*. (**Fig 2B.16a**), *Salmonella typhi* (**Fig 2B.16b**), *Shigella sonnei* (**Fig 2B.16c**). The zones of inhibition are depicted for varying concentrations of Co(III) complex 3 (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Co(III) complex 3; (2) Denotes treatment with 10 μM of Schiff base ligand 1; (3) Denotes treatment with 100 μM of Schiff base ligand 1; (4) Denotes treatment with 500 μM of Co(III) complex 3; (5) Denotes the treatment with positive control (Gentamicin).

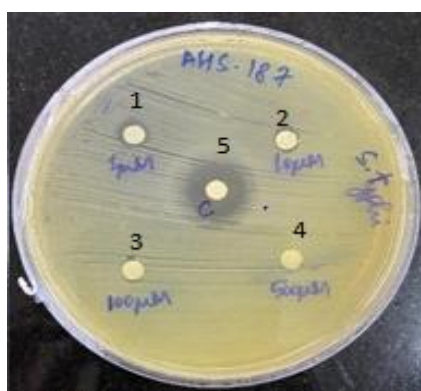


Fig. 2B.17a. *Escherichia coli* **Fig. 2B.17b.** *Salmonella typhi* **Fig. 2B.17c.** *Shigella sonnei*

Fig. 2B.17. Disc well diffusion assay with varying doses of Co(III) complex 3 shown in *Escherichia coli*. (**Fig. 2B.17a**), *Salmonella typhi* (**Fig. 2B.17b**), *Shigella sonnei* (**Fig. 2B.17c**). The zones of inhibition are depicted for varying concentrations of Co(III) complex 2 (1 μM, 10 μM, 100 μM, 500 μM). (1) Denotes treatment with 1 μM of Co(III) complex 3; (2) Denotes treatment with 10 μM of Co(III) complex 3; (3) Denotes treatment with 100 μM of Co(III) complex 3; (4) Denotes treatment with 500 μM of Co(III) complex 3; (5) Denotes the treatment with positive control (Gentamicin).

Chapter 2B



Fig. 2B.18a. *Escherichia coli*

Fig. 2B.18b. *Salmonella typhi*

Fig. 2B.18c. *Shigella sonnei*

Fig. 2B.18. Agar well diffusion assay with varying doses of Cd(II) complex **4** shown in *Escherichia coli*. (**Fig. 2B.18a**), *Salmonella typhi* (**Fig. 2B.18b**), *Shigella sonnei* (**Fig. 2B.18c**). The zones of inhibition are depicted for varying concentrations of Cd(II) complex **4** (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Cd(II) complex **4**; (2) Denotes treatment with 10 μM of Cd(II) complex **4**; (3) Denotes treatment with 100 μM of Cd(II) complex **4**; (4) Denotes treatment with 500 μM of Cd(II) complex **4** (5); Denotes the treatment with positive control (Gentamicin).

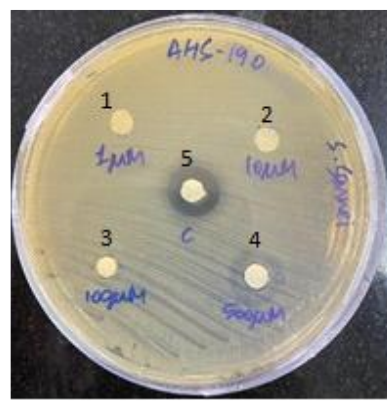
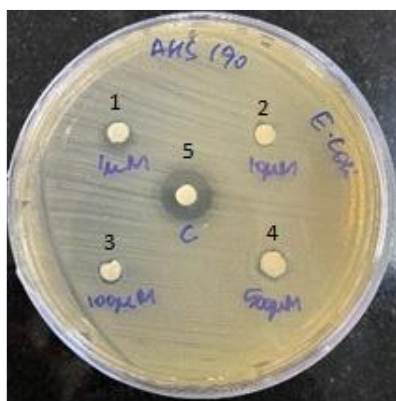


Fig. 2B.19a. *Escherichia coli*

Fig. 2B.19b. *Salmonella typhi*

Fig. 2B.19c. *Shigella sonnei*

Fig. 2B.19. Disc well diffusion assay with varying doses of Cd(II) complex **4** shown in *Escherichia coli*. (**Fig. 2B.19a**), *Salmonella typhi* (**Fig. 2B.19b**), *Shigella sonnei* (**Fig. 2B.19c**). The zones of inhibition are depicted for varying concentrations of Cd(II) complex **4** (1 μM, 10 μM, 100 μM, 500 μM) in various strains of bacteria. (1) Denotes treatment with 1 μM of Cd(II) complex **4**; (2) Denotes treatment with 10 μM of Cd(II) complex **4**; (3) Denotes treatment with 100 μM of Cd(II) complex **4**; (4) Denotes treatment with 500 μM of Cd(II) complex **4**; (5) Denotes the treatment with positive control (Gentamicin).

Chapter 2B

Conclusion

This work focuses on the synthesis and structural characterization of Co(III) and Cd(II) complexes prepared from unsymmetrical pyridyl Schiff base ligand *N*-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine. The shifting of azomethine imine stretching frequency of the pyridyl Schiff base ligand in the IR spectroscopy and the up-field shift of the azomethine proton in the NMR spectroscopy confirmed the formation of the complexes and coordination of the imine nitrogen atom to the metal ions. The FT-IR, ^1H NMR and Mass spectroscopy indicated the coordination of metal ion by the pyridyl Schiff base ligand in a tridentate mode by the imine N-atom, pyridyl N-atom, and O-atom, forming an octahedral geometry of the complexes. The theoretical investigation also revealed that both complexes have octahedral geometry. The antibacterial activity demonstrated that in comparison to parent Schiff base ligand **1**, Co(III) complex **3** and Cd (II) complex **4** exhibited better antibacterial activity. Co (III) complex **3** and Cd (II) complex **4** showed antibacterial activity as evident from the Kirby Bauer method of disc diffusion and well diffusion assay in *Escherichia coli* and *Salmonella typhi*. Our findings indicated that due to the inherent toxicity of cadmium ion, Cd(II) complex **4** has superior antibacterial activity over the other tested compounds, and Schiff base **1** did not exhibit antibacterial properties.

2B.3 Experimental

Materials and physical measurements

All chemicals were reagent grade obtained from commercial sources and used without purification. The solvents were purified according to standard procedures. Infrared spectra were measured using a Perkin-Elmer FT-IR spectrometer with KBr pellets in the range of $4000\text{--}400\text{ cm}^{-1}$. NMR spectra were recorded on Bruker Advance II (400MHz) spectrometer using the residual protic solvent resonance as the internal standard and chemical shifts were expressed in ppm. Mass spectra were recorded on inkarp instruments (Expression-S).

2B.3.1. Synthesis of Co(III) complex **3** and Cd(II) complex **4** from pyridyl Schiff base ligand **1**

Synthesis of cobalt(III) complex **3**

Two equivalents of the pyridyl Schiff base ligand **1**, (0.1 g, 0.38 mmol) and one equivalent of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.045 g, 0.2 mmol) were dissolved in 30 mL methanol (**Scheme 1**). To this reaction mixture, 3 drops of triethyl amine were added and refluxed for 4 hours at $60\text{ }^\circ\text{C}$. The

Chapter 2B

resultant reddish-yellow precipitate of Co(III) complex **3** was collected by filtration, washed with methanol, and dried under vacuum.

Complex **3**: Yield: 81%, ^1H NMR(400 MHz, CDCl_3 , δ in ppm): 9.93 (d, 2H, $-\text{CH}=\text{N}-$), 8.12 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.64-7.51 (m, 6H, Ar-H), 7.30 (d, 2H, Ar-H), 7.00 (d, 2H, Ar-H), 6.95 (d, 2H, Ar-H), 6.89 (d, 2H, Ar-H), 2.60 (s, 6H, $-\text{CH}_3$). FT IR (ν cm^{-1} , KBr): 3699 [$\nu(\text{N}-\text{H})$ asymmetric and symmetric stretching modes], 3046, 2923 ($\nu\text{C}-\text{H}$), 1616 ($\nu\text{C}=\text{N}$), 1565 ($\nu\text{C}=\text{C}$), 1249-1092 ($\nu\text{C}-\text{O}$), 551 ($\nu\text{Co}-\text{O}$), and 452 ($\nu\text{Co}-\text{N}$). ESI-MS m/z = 583.8 [$\text{M} + 2\text{H}^+$].

Synthesis of cadmium(II) complex **4**

Two equivalents of the pyridyl Schiff base ligand **1**, (0.134 g, 0.5 mmol) and one equivalent of $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (0.08 g, 0.26 mmol) were dissolved in 30 mL methanol (**Scheme 2**). To this reaction mixture, 3 drops of triethyl amine were added and refluxed for 5 hours at 60 °C. The resultant brown precipitate of Cd(II) complex **4** was collected by filtration, washed with methanol, and dried under a vacuum.

Cd(II) complex : Yield: 79%, ^1H NMR(400 MHz, CDCl_3 , δ in ppm): 9.93 (d, 2H, $-\text{CH}=\text{N}-$), 8.12 (d, 2H, Ar-H), 7.73 (d, 2H, Ar-H), 7.61 (t, 6H, Ar-H), 7.30 (d, 2H, Ar-H), 7.00 (d, 2H, Ar-H), 6.95 (d, 2H, Ar-H), 6.89 (d, 2H, Ar-H), 2.60 (s, 3H, $-\text{CH}_3$). FT IR (ν cm^{-1} , KBr): 3337-3272 [$\nu(\text{N}-\text{H})$ asymmetric and symmetric stretching modes], 3056, 3034, 2916 ($\nu\text{C}-\text{H}$), 1615 ($\nu\text{C}=\text{N}$), 1563 ($\nu\text{C}=\text{C}$), 1271-1089 ($\nu\text{C}-\text{O}$), 579 ($\nu\text{Cd}-\text{O}$), and 476 ($\nu\text{Cd}-\text{N}$). ESI-MS m/z = 635.6 [$\text{M} + 2\text{H}^+$].

2B.3.2. Bacterial culture and antibacterial assays of **3** and **4**

For the antibacterial assays, different bacterial strains viz., *Escherichia coli* (ATCC 25922), *Salmonella typhi* (ATCC 6539), and *Shigella sonnei* (ATCC 25931) were selected. The bacterial strains were cultured and maintained in suitable culture conditions with appropriate growth media. The bacteria were streaked onto a 90mm petri plate with nutrient agar, which was incubated for 24 hours before being stored at -4°C and utilized for further experiments. The antibacterial effects of the Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4** were verified by performing Kirby-Bauer disk diffusion and well diffusion assays using Mueller Hinton Agar. 50 μl of bacterial culture was inoculated onto the Mueller Hinton agar plates, and the bacteria were evenly distributed using a sterile cotton swab. For the disc diffusion assay, sterilized paper discs of 6 mm were placed using sterile forceps in the agar

Chapter 2B

plates, and each disc was infused with 20 μL of varying concentrations of the 3 compounds namely Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4**. For the well diffusion assay, wells from agar plates were punctured using sterile pipette tips, and the various concentrations of the 3 compounds namely Schiff base ligand **1**, Co(III) complex **3**, and Cd(II) complex **4** were carefully infused inside the well. Antibiotic gentamicin (2 mM) was employed as a positive control. The Mueller Hinton agar plates were carefully sealed using parafilm and kept inside the incubator at 37°C for 24 hours. The following day, the zone of inhibition was measured [48].

Chapter 2B

2B.4 References

- [1] Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., ... & Tasak, N. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The lancet*, 399(10325), 629-655.
- [2] O'Neill, J. (2016). Tackling drug-resistant infections globally: final report and recommendations.
- [3] Cong, W., Poudel, A. N., Alhusein, N., Wang, H., Yao, G., & Lambert, H. (2021). Antimicrobial use in COVID-19 patients in the first phase of the SARS-CoV-2 pandemic: a scoping review. *Antibiotics*, 10(6), 745.
- [4] Butler, M. S., Gigante, V., Sati, H., Paulin, S., Al-Sulaiman, L., Rex, J. H., ... & Beyer, P. (2022). Analysis of the clinical pipeline of treatments for drug-resistant bacterial infections: despite progress, more action is needed. *Antimicrobial agents and chemotherapy*, 66(3), e01991-21.
- [5] Dwyer, F. P., Gyarfas, E. C., Rogers, W. P., & Koch, J. H. (1952). Biological activity of complex ions. *Nature*, 170(4318), 190-191.
- [6] Rosenberg, B., Van Camp, L., & Krigas, T. (1965). Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature*, 205(4972), 698-699.
- [7] Smitten, K. L., Thick, E. J., Southam, H. M., de la Serna, J. B., Foster, S. J., & Thomas, J. A. (2020). Mononuclear ruthenium (ii) theranostic complexes that function as broad-spectrum antimicrobials in therapeutically resistant pathogens through interaction with DNA. *Chemical science*, 11(33), 8828-8838.
- [8] Sovari, S. N., Vojnovic, S., Bogojevic, S. S., Crochet, A., Pavic, A., Nikodinovic-Runic, J., & Zobi, F. (2020). Design, synthesis and in vivo evaluation of 3-arylcoumarin derivatives of rhenium (I) tricarbonyl complexes as potent antibacterial agents against methicillin-resistant *Staphylococcus aureus* (MRSA). *European journal of medicinal chemistry*, 205, 112533.
- [9] Sovari, S. N., Radakovic, N., Roch, P., Crochet, A., Pavic, A., & Zobi, F. (2021). Combatting AMR: A molecular approach to the discovery of potent and non-toxic rhenium complexes active against *C. albicans*-MRSA co-infection. *European Journal of Medicinal Chemistry*, 226, 113858.
- [10] Güntzel, P., Nagel, C., Weigelt, J., Betts, J. W., Patrick, C. A., Southam, H. M., ... & Schatzschneider, U. (2019). Biological activity of manganese (i) tricarbonyl complexes on

Chapter 2B

multidrug-resistant Gram-negative bacteria: From functional studies to in vivo activity in *Galleria mellonella*. *Metallomics*, 11(12), 2033-2042.

[11] Frei, A., Zuegg, J., Elliott, A. G., Baker, M., Braese, S., Brown, C., ... & Blaskovich, M. A. (2020). Metal complexes as a promising source for new antibiotics. *Chemical science*, 11(10), 2627-2639.

[12] Trimble, M. J., Mlynářčik, P., Kolář, M., & Hancock, R. E. (2016). Polymyxin: alternative mechanisms of action and resistance. *Cold Spring Harbor perspectives in medicine*, 6(10), a025288.

[13] Castano, A. P., Mroz, P., & Hamblin, M. R. (2006). Photodynamic therapy and anti-tumour immunity. *Nature Reviews Cancer*, 6(7), 535-545.

[14] Dolmans, D. E., Fukumura, D., & Jain, R. K. (2003). Photodynamic therapy for cancer. *Nature reviews cancer*, 3(5), 380-387.

[15] Frei, A., Verderosa, A. D., Elliott, A. G., Zuegg, J., & Blaskovich, M. A. (2023). Metals to combat antimicrobial resistance. *Nature Reviews Chemistry*, 7(3), 202-224.

[16] Catalano, A., Sinicropi, M. S., Iacopetta, D., Ceramella, J., Mariconda, A., Rosano, C., ... & Longo, P. (2021). A review on the advancements in the field of metal complexes with Schiff bases as antiproliferative agents. *Applied Sciences*, 11(13), 6027.

[17] Abdel-Rahman, L. H., Abdelhamid, A. A., Abu-Dief, A. M., Shehata, M. R., & Bakheet, M. A. (2020). Facile synthesis, X-Ray structure of new multi-substituted aryl imidazole ligand, biological screening and DNA binding of its Cr (III), Fe (III) and Cu (II) coordination compounds as potential antibiotic and anticancer drugs. *Journal of Molecular Structure*, 1200, 127034.

[18] Avaji, P. G., Kumar, C. V., Patil, S. A., Shivananda, K. N., & Nagaraju, C. (2009). Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclic bis hydrazone. *European Journal of medicinal chemistry*, 44(9), 3552-3559.

[19] Abd El-Halim, H. F., Mohamed, G. G., El-Dessouky, M. M., & Mahmoud, W. H. (2011). Ligational behaviour of lomefloxacin drug towards Cr (III), Mn (II), Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Th (IV) and UO₂ (VI) ions: Synthesis, structural characterization and biological activity studies. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 82(1), 8-19.

[20] John, L., Joseyphus, R. S., & Joe, I. H. (2020). Biomedical application studies of Schiff base metal complexes containing pyridine moiety: molecular docking and a DFT approach. *SN Applied Sciences*, 2, 1-14.

Chapter 2B

- [21] AlZamil, N. O. (2020). Synthesis, DFT calculation, DNA-binding, antimicrobial, cytotoxic and molecular docking studies on new complexes VO (II), Fe (III), Co (II), Ni (II) and Cu (II) of pyridine Schiff base ligand. *Materials Research Express*, 7(6), 065401.
- [22] Montazerozohori, M., Joohari, S., & Musavi, S. A. (2009). Synthesis and spectroscopic studies of some cadmium (II) and mercury (II) complexes of an asymmetrical bidentate Schiff base ligand. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 73(2), 231-237.
- [23] Mondal, b. (2020). synthesis, characterization and dna interaction of lead (ii) complex of schiff base derived from 2-(methylthio) aniline. *journal of advanced scientific research*, 11(03), 246-251.
- [24] Chaudhary, N. K., Guragain, B., Chaudhary, S. K., & Mishra, P. (2021). Schiff base metal complex as a potential therapeutic drug in medical science: A critical review. *Bibechana*, 18(1), 214-230.
- [25] Rani, A., Kumar, M., Tuli, H. S., Abbas, Z., & Prakash, V. (2020). *Synthesis and spectral studies of 4, 4'-(hydrazine-1, 2-diylidenedimethylylidene)-bis-(2-methoxyphenol) and its transition metal complexes with promising biological activities Asian J. Chem.* 2020.
- [26] Liang, J., Sun, D., Yang, Y., Li, M., Li, H., & Chen, L. (2021). Discovery of metal-based complexes as promising antimicrobial agents. *European Journal of Medicinal Chemistry*, 224, 113696.
- [27] Waters, J. E., Stevens-Cullinane, L., Siebenmann, L., & Hess, J. (2023). Recent advances in the development of metal complexes as antibacterial agents with metal-specific modes of action. *Current Opinion in Microbiology*, 75, 102347.
- [28] Czarnek, K., Terpiłowska, S., & Siwicki, A. K. (2015). Selected aspects of the action of cobalt ions in the human body. *Central European Journal of Immunology*, 40(2), 236-242.
- [29] Kräutler, B. (2012). Biochemistry of B12-cofactors in human metabolism. *Water Soluble Vitamins: Clinical Research and Future Application*, 323-346.
- [30] Adhikari, S., Sheikh, A. H., Kansız, S., Dege, N., Baildya, N., Mahmoudi, G., ... & Kłak, J. (2023). Supramolecular Co (II) complexes based on dithiolate and dicarboxylate ligands: Crystal structures, theoretical studies, magnetic properties, and catalytic activity studies in photocatalytic hydrogen evolution. *Journal of Molecular Structure*, 1285, 135481.
- [31] Biswas, S., Parsutkar, M. M., Jing, S. M., Pagar, V. V., Herbort, J. H., & RajanBabu, T. V. (2021). A new paradigm in enantioselective cobalt catalysis: Cationic cobalt (I) catalysts for heterodimerization, cycloaddition, and hydrofunctionalization reactions of olefins. *Accounts of chemical research*, 54(24), 4545-4564.

Chapter 2B

- [32] Tiné, M. R. (2012). Cobalt complexes in aqueous solutions as dioxygen carriers. *Coordination Chemistry Reviews*, 256(1-2), 316-327.
- [33] Frei, A., King, A. P., Lowe, G. J., Cain, A. K., Short, F. L., Dinh, H., ... & Blaskovich, M. A. (2021). Nontoxic Cobalt (III) Schiff Base Complexes with Broad-Spectrum Antifungal Activity. *Chemistry—A European Journal*, 27(6), 2021-2029.
- [34] Gupta, S. K., Hitchcock, P. B., Kushwah, Y. S., & Argal, G. S. (2007). Synthesis, structure and DNA binding studies of a mononuclear cobalt (III) complex with a NNO donor Schiff base derived from 4-methyl-2, 6-dibenzoylphenol and ethane-1, 2-diamine. *Inorganica chimica acta*, 360(6), 2145-2152.
- [35] De, R. L., Samanta, K., Maiti, K., & Keller, E. (2001). Metal specific variable binding modes in Schiff base complexes—facile synthesis and crystal structure of anionic bis-N-(2-oxyethyl-5-bromosalicylal-diminato) cobalt (III). *Inorganica Chimica Acta*, 316(1-2), 113-116.
- [36] Borsari, M. (2011). Cadmium: coordination chemistry. *Encyclopedia of Inorganic and Bioinorganic Chemistry*, 1-16.
- [37] More, M. S., Joshi, P. G., Mishra, Y. K., & Khanna, P. K. (2019). Metal complexes driven from Schiff bases and semicarbazones for biomedical and allied applications: a review. *Materials Today Chemistry*, 14, 100195.
- [38] Adhikari, S., Bhattacharjee, T., Nath, P., Das, A., Jasinski, J. P., Butcher, R. J., & Maiti, D. (2020). Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study. *Inorganica Chimica Acta*, 512, 119877.
- [39] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Butcher, R. J., ... & Das, A. (2017). A new cadmium (II) complex with bridging dithiolate ligand: Synthesis, crystal structure and antifungal activity study. *Journal of Molecular Structure*, 1139, 395-399.
- [40] Bhattacharjee, T., Adhikari, S., Datta, A., Daniliuc, C. G., Montazerozohori, M., Naghiha, R., & Hayati, P. (2022). Cadmium (II) coordination polymer based on flexible dithiolate-polyamine binary ligands system: crystal structure, Hirshfeld surface analysis, antimicrobial, and DNA cleavage potential. *Polyhedron*, 211, 115544.
- [41] Adhikari, S., Bhattacharjee, T., Das, A., Roy, S., Daniliuc, C. G., Zaręba, J. K., ... & Frontera, A. (2020). On the supramolecular properties of neutral, anionic and cationic cadmium complexes harvested from dithiolate–polyamine binary ligand systems. *CrystEngComm*, 22(46), 8023-8035.

Chapter 2B

- [42] Adhikari, S., Bhattacharjee, T., Gupta, R., Daniliuc, C. G., Montazerzohori, M., Naghiha, R., & Masoudiasl, A. (2020). Coordination framework of cadmium (II), harvested from dithiolate-imidazole binary ligand systems: Crystal structure, Hirshfeld surface analysis, antibacterial, and DNA cleavage potential. *Polyhedron*, 192, 114838.
- [43] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Butcher, R. J., Acharya, S., & Das, A. (2016). Six-coordinate cadmium (II) complex containing a bridging dithiolate ligand: synthesis, crystal structure and antifungal activity study. *Journal of Coordination Chemistry*, 69(1), 168-175.
- [44] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Butcher, R. J., Acharya, S., & Das, A. (2015). Cd (II) complexation with 1, 1-dithiolate and nitrogen donors: synthesis, luminescence, crystal structure, and antifungal activity study. *Journal of Coordination Chemistry*, 68(8), 1423-1432.
- [45] Kaye, K. S., & Pogue, J. M. (2015). Infections caused by resistant gram-negative bacteria: epidemiology and management. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 35(10), 949-962.
- [46] Lemire, J. A., Harrison, J. J., & Turner, R. J. (2013). Antimicrobial activity of metals: mechanisms, molecular targets and applications. *Nature Reviews Microbiology*, 11(6), 371-384.
- [47] Mittapally, S., Taranum, R., & Parveen, S. (2018). Metal ions as antibacterial agents. *Journal of Drug Delivery and Therapeutics*, 8(6-s), 411-419.
- [48] Lam, P. L., Lu, G. L., Choi, K. H., Lin, Z., Kok, S. H. L., Lee, K. K. H., ... & Chui, C. H. (2016). Antimicrobial and toxicological evaluations of binuclear mercury (II) bis (alkynyl) complexes containing oligothiophenes and bithiazoles. *RSC advances*, 6(20), 16736-16744.
- [49] Malekhoseini, A., Montazerzohori, M., Naghiha, R., Panahi Kokhdan, E., & Joohari, S. (2023). Antimicrobial/antioxidant and cytotoxicity activities of some new mercury (II) complexes. *Chemical Review and Letters*, 6(2), 166-182.
- [50] Ceramella, J., Iacopetta, D., Catalano, A., Cirillo, F., Lappano, R., & Sinicropi, M. S. (2022). A review on the antimicrobial activity of Schiff bases: Data collection and recent studies. *Antibiotics*, 11(2), 191.
- [51] Sieberi, B. M., Omwenga, G. I., Wambua, R. K., Samoei, J. C., & Ngugi, M. P. (2020). Screening of the Dichloromethane: Methanolic Extract of *Centella asiatica* for Antibacterial Activities against *Salmonella typhi*, *Escherichia coli*, *Shigella sonnei*, *Bacillus subtilis*, and *Staphylococcus aureus*. *The Scientific World Journal*, 2020(1), 6378712.

Chapter 2B

- [52] Geary, W. J. (1971). The use of conductivity measurements in organic solvents for the characterisation of coordination compounds. *Coordination Chemistry Reviews*, 7(1), 81-122.
- [53] Bhattacharjee, T., Adhikari, S., Sheikh, A. H., Mahmoudi, G., Mlowe, S., Akerman, M. P., ... & Saygideger, Y. (2022). Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni (II) complex. *Journal of Molecular Structure*, 1269, 133717.
- [54] Salem, N. M., Rashad, A. R., El Sayed, L., Haase, W., & Iskander, M. F. (2014). Synthesis, characterization, molecular structure and self-assembly of some cobalt (III) complexes derived from diacetyl-and benzil bisaroylhydrazones. *Polyhedron*, 68, 164-171.
- [55] Cao, W., Liu, Y., Zhang, T., & Jia, J. (2018). Synthesis, characterization, theoretical and antimicrobial studies of tridentate hydrazone metal complexes of Zn (II), Cd (II), Cu (II) and Co (III). *Polyhedron*, 147, 62-68.
- [56] Taylor, R. A., Bonanno, N. M., Mirza, D., Lough, A. J., & Lemaire, M. T. (2017). A trivalent cobalt complex with the new redox-active ligand 10-(8-quinolylazo)-9-phenanthrol (qapl). *Polyhedron*, 131, 34-39.
- [57] Montazerozohori, M., Zahedi, S., Nasr-Esfahani, M., & Naghiha, A. (2014). Some new cadmium complexes: Antibacterial/antifungal activity and thermal behavior. *Journal of Industrial and Engineering Chemistry*, 20(4), 2463-2470.
- [58] Sharma, B., Shukla, S., Rattan, R., Fatima, M., Goel, M., Bhat, M., ... & Sharma, M. (2022). Antimicrobial agents based on metal complexes: Present situation and future prospects. *International Journal of Biomaterials*, 2022(1), 6819080.
- [59] Claudel, M., Schwarte, J. V., & Fromm, K. M. (2020). New antimicrobial strategies based on metal complexes. *Chemistry*, 2(4), 849-899.



Antiproliferative Evaluation and Supramolecular Properties of a Pd(II) complex Harvested from Benzil bis(pyridyl hydrazone) Ligand: Combined Experimental and Theoretical Studies

Outline

This chapter describes the present work, related to the design, and synthesis of a new Pd(II) coordination compound, $[Pd(L)(PPh_3)_2]$ using ligand benzil bis (pyridyl hydrazone) (H_2L). The newly synthesised $[Pd(L)(PPh_3)_2]$ complex was characterized by using spectroscopic (FT-IR, electronic, and NMR) and single-crystal X-ray diffraction analysis. The supramolecular properties of the Pd(II) complex have been explored. The *in vitro* and *in vivo* anticancer properties of the Pd(II) complex have also been studied. The related review on anticancer properties of Pd(II)-based complexes and significant coordinating features of benzil bis (pyridyl hydrazone) (H_2L) ligand are also discussed.

Chapter 3

3.1. Anticancer properties of Pd(II)-based complexes

Cancer ranks as the second most common cause of death even in developed nations [1-4]. Chemotherapy is the backbone of the treatment of cancer, and physicians have been using it more and more in recent years [5]. Despite the numerous treatment options that are currently available, cancer is still regarded as a terrible disease that kills almost 10 million people globally each year [6]. According to a history of chemotherapy, renowned German chemist Paul Ehrlich began developing medications to treat infectious diseases in the early 1900s. The use of chemicals to cure disease is what he called "chemotherapy". Combination chemotherapy was found to be effective in curing several advanced cancers. Achieving the greatest therapeutic efficacy against tumor cells at the lowest possible medication concentration is the primary objective of cancer treatment [7, 8]. Many metals are present in the environment, and some are necessary for biological functions. Clinically platinum-based complexes are utilized mostly to induce the death of cancer cells. One of the most effective chemotherapy medications, cisplatin (also known as *cis*-Pt(NH₃)Cl₂), is frequently used to treat cancers [9, 10], including ovarian, testicular, lung, bladder, and head and neck cancers [9-15]. In 1960, a new era in the treatment of cancers began with the discovery of cisplatin as an anticancer medication [9, 10, 15, 16]. Although cisplatin is a key component of cancer treatment [24, 26] and one of the most utilized antitumor agents [22, 23], it has a number of limitations including undesirable effects like damage to renal tubular epithelial cells [4, 12, 26, 27], nausea, vomiting, loss of hearing [28, 29], the toxicity of gastrointestinal [30, 31], neurotoxicity, nephrotoxicity, ototoxicity, high blood pressure etc. [10, 11, 32-36]. Over the years cancer cells have developed resistance to cisplatin, which significantly reduces the drug's ability to kill cancer cells through several methods, including (a) the irreversible reaction with biomolecules that contain nucleophilic sulfur groups lowers the concentration of the drug inside the cell; (b) DNA's structural changes; and (c) the apoptotic mechanism of cancer cell death is inactivated [14]. It was also found that enzymes having thiol groups of kidneys can be deactivated through the interaction of complexes based on platinum, causing detrimental effects on the kidney [37]. Cisplatin also has a limited spectrum of treating cancer cells [38, 39] and low solubility in aqueous media [34, 40]. These disadvantages impose dose-limiting and require more clinical trials of cisplatin [40]. Therefore, there is potential for the development of novel anticancer drugs having negligible toxicity, improved clinical efficacy, a wider range of action, minimum adverse effects, improved solubility, and the capacity to combine cisplatin with other medications [41, 42]. By altering the nature of the core metal ion, novel anticancer drugs similar to cisplatin with improved efficacy can also be designed [14]. Due to structural resemblances

Chapter 3

and considerable overlap in coordination chemistry between the two metals palladium and platinum, complexes based on palladium and their platinum analogues are closely related [43-45]. Pd(II) complexes such as *cis*-Pd(DACH)₂Cl₂ and *cis*-Pd(en)₂Cl₂ had been employed first in clinical trials for anticancer treatments due to the similar coordination chemistry of Pd(II) with Pt(II) where en = ethylene diamine and DACH = 1,2-diaminocyclohexane [46]. Das and Livinstone described that Pd(II) chelates with inert ligands with nitrogen and sulfur as donor atoms are more effective anti-tumor agents than those of the other metals as they have the right ability to transport and bind the metal to the target DNA [47]. The latest advancements in antitumour drugs based on palladium have aimed at the fabrication of derivatives of palladium with a slower rate of hydrolysis, which can be achieved through careful selection of organic ligands. *In vivo* and *in vitro* a number of palladium-based complexes have demonstrated significant antiproliferative properties in several cisplatin-sensitive as well as cisplatin-resistant cancers and few of them have considerably different modes of action compared to the Pt-based complexes [48, 49]. The first complex of palladium, which received approval for clinical usage, is padeliporfin (TOOKAD[®]) in 2017. This Pd(II)-substituted bacteriochlorophyll molecule which is applied in photodynamic therapy for the treatment of patients suffering from prostate cancer, demonstrates a significant potential of palladium anticancer medications for therapeutic applications, especially cisplatin-resistant cancers [50]. Several Pd(II) complexes containing amine ligands were synthesized in the 1980s by several research groups, and have demonstrated encouraging anticancer activity [51]. These complexes show low nephrotoxicity, good water solubility, and promise as future medications to treat gastrointestinal cancers. Furthermore, it has been demonstrated that Pd(II) complexes containing neutral ligands such as pyrimidine, pyridine, and aryl groups have antiproliferative and/or anticancer properties [52, 53]. Remarkably, dithiocarbamate-amine compounds of Pd(II) that have anticancer activity similar to that of cisplatin can overcome cisplatin cross-resistance [53]. Due to the intense research into anticancer drugs, several palladium complexes with favourable *in vivo* or *in vitro* properties have been identified. Both covalent and non-covalent Pd(II) complexes have been shown to bind with DNA, which is the cause of their biological activity [51]. Palladium complexes are thought to be less toxic renally compared to cisplatin as kidney tubule proteins cannot substitute a sulfhydryl group for the strongly bonded chelate ligands of Pd(II) [54]. However, it is very difficult to synthesize Pd(II) complexes with potent anticancer properties. Pd(II) complexes are generally less stable compared to Pt(II) complexes in terms of kinetics and thermodynamics [23, 36, 55]. Ligand exchange capabilities of Pd(II) analogues is 10⁴-10⁵ times greater compared to that of Pt(II). This fast exchange

Chapter 3

hinders the complexes of Pd(II) ions from maintaining their structural features in biotic fluids for sufficient time to reach pharmacological targets [23, 55, 56]. Palladium complexes of N,S-chelating ligands, aromatic N and N, N-containing ligands have demonstrated very encouraging antitumor properties [57]. DNA is the principal intracellular target for platinum-based anticancer medicines. DNA-interacting investigation of palladium-based metal complexes demonstrated that the environment of the ligands around Pd(II) centers can influence the reactivity of the complexes [41]. Palladium complexes have therefore demonstrated superior anti-tumor efficacy in a number of cases compared to their platinum analogs (cisplatin, carboplatin, etc.). It has been found that *trans*-palladium complexes have higher cytotoxicity values than those for *cis*-palladium complexes [58]. In 1991, Tusek-Bozic and colleagues presented one of the first evidence of the enhanced antitumor activity of the *trans*-palladium complex [59]. One of these complexes' characteristics was the incorporation of diethylphosphonate and monoethylphosphonate moieties into the quinolmethyl moiety, which improved the complexes' solubility. The diethylphosphonate moiety performed better than its monoethylphosphonate counterpart, according to a comparative analysis. The easier dissociation of the chloride ligand from the palladium center was one of the hypotheses for improved activity, although this assertion has not been confirmed. This established the basis for additional research on the use of palladium complexes as antitumor agents [43]. Numerous research findings showed that DNA's structure changed when Pd bound to it, but it was unable to establish a relationship between the structure and the manner of interaction [60].

3.2. Most important factors affecting the anticancer activity of Pd(II)-based complexes

Following are the factors which affect the anticancer activity of Pd(II)-based complexes:

For intercalative binding with biomolecules, the square-planar coordination topology is ideal; additionally, by employing suitable ligands or substituents in the structures of ligands, electronic and steric characteristics can be adjusted [41]. The square planar complex's auxiliary ligands having a *cis*-position geometry were found to increase the complex's activity and is more accessible to interactions with DNA components [61, 62]. Conversely, the *trans*-isomers create bifunctional adducts *via* 1, 3-intrastrand and interstrand by forming strong associations with DNA through wide-range cross-linkings. The resultant adducts can alter the structure of DNA in the same manner as 1, 2-interstrand cross linkings of cisplatin. It should be noted that, however, large ligands can be utilized to activate the *trans* geometry. For instance, using two large, planar ligands to activate the *trans* geometry has increased the cytotoxic activity of the complex [63]. Furthermore, the activity of the Pd(II) complexes is significantly influenced by

Chapter 3

the bulkiness and electronic characteristics of the ligand substituents [58, 64]. The electron-donating group of ligands strengthened the bond lengths of the Pd-ligand bond and kept the palladium complex integrated; increasing the probability that it would reach the targeted DNA [2]. The palladium (II) complexes' activity sharply decreases when the substituent's electron-donating properties increase [65]. Increased lipophilicity may let drug molecules passively move across lipid cell membranes, increasing the medications' cytotoxicity [35]. Compared to cisplatin, the complexes comprising propyl, tert-butyl, and cyclohexyl are more cytotoxic. However, there may be a connection between Pd complexes' solubility and activity [66]. Compared to other metal chelates, sulfur-containing ligands are probably more effective at preventing cancer, particularly when combined with bidentate sulfur-nitrogen chelating agents. *In vitro* and *in vivo*, sulfur-containing ligands may enhance the cytotoxicity of anticancer complexes [35, 67, 68]. The introduction of a dithiocarbamate group to the Pd(II) complexes is likely to play an important role in enhancing the antiproliferative qualities of the complexes [41]. Increased solubility and lipophilicity brought on by binuclear complexes may make transport across cellular membranes easier and make the drugs more effective.

Because of their reported interesting anticancer activities, compounds of palladium have recently been at the forefront of research attempts to develop novel anticancer medication with the highest efficiency and minimum side effects.

3.3. Importance of Benzil bis (pyridyl hydrazones)

To develop novel compounds with intriguing topologies, and superior pharmacological and physical properties, the design of supramolecular frameworks and the rational synthesis of coordination complexes typically rely on the wise selection of organic ligands with multidentate binding sites and various modes of metal ion binding [69-74]. Benzil bis(pyridyl hydrazones) are unique, multidimensional Schiff base ligands and a versatile class of building blocks with a variety of flexible donor sets that can construct supramolecular architectures and a variety of molecular topologies by coordinating to the metal *via* carbonyl oxygen or pyridyl nitrogen and one of the hydrazinic nitrogen atoms (N1 or N2) [75-77]. They are commonly prepared in high yields using the one-pot Schiff base condensation procedure. This along with the ability of the ligand geometries to exert a noteworthy impact on the structural features of coordination compounds makes them an interesting research topic [78-80]. By typically coordinating through oxygen and nitrogen atoms, hydrazone ligands create an environment resembling that seen in biological systems. Consequently, the development of stable chelates with metals, which increase the activity, may be responsible for the hydrazones' biological

Chapter 3

action. Because of their uses as antifungal, antibacterial, antiviral, and anticancer agents, there is currently a growing interest in the design and synthesis of benzil bis (pyridyl hydrazone) and their metal complexes [81-83]. The versatility of coordination modes, pharmacological efficacies, and expected fascinating supramolecular motifs, make research on benzil bis(pyridyl hydrazone) ligands-based coordination chemistry highly appealing. This type of ligand can exist in both iminol and amido forms at room temperature. Due to their intriguing amido-iminol tautomerism, the ligands can act as a tetradentate N_2O_2 -donor (**Scheme 1**). The geometries of terminal pyridine moiety along with the bulkiness of the ligand, on the other hand, can alter the topology and dimensionality of metal-organic frameworks constructed with benzil bis(pyridyl hydrazone)-based building blocks. Behera and coworkers recently reported a distorted pentagonal bipyramidal dioxouranium (VI) complex with the benzil bis(pyridyl hydrazone) ligand, in which the ONNO-tetradentate binding cleft of the deprotonated ligand generated an equatorial coordination plane [76]. Designing and tuning novel multi-component supramolecular motifs that have ramifications in crystal engineering and application in medical as well as material sciences, therefore, require a profound understanding of cooperativity effects. In continuation of our ongoing endeavors to investigate the supramolecular properties in metal complexes along with pharmacological and material science properties of coordination complexes [84-94], herein we report the synthesis, characterization, theoretical study, and antitumor properties of a novel Pd(II) complex **6** prepared from benzil bis(pyridyl hydrazone) ligand **5**.

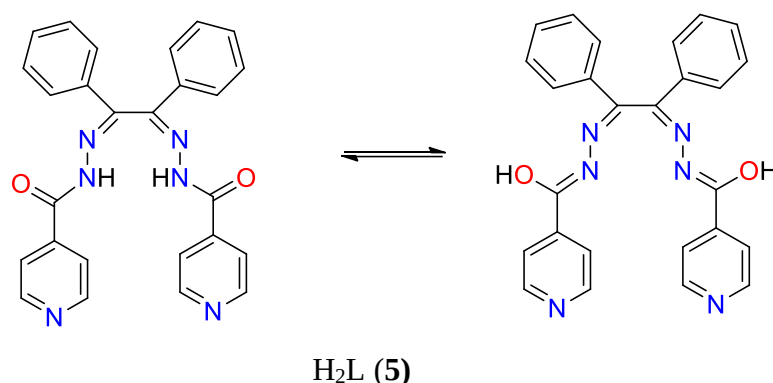
3.4. Present work

Antiproliferative Evaluation and Supramolecular Properties of a Pd(II) complex Harvested from Benzil bis(pyridyl hydrazone) Ligand: Combined Experimental and Theoretical Studies.

This chapter describes the present work, related to the design and synthesis of a new Pd(II) coordination compound, $[Pd(L)(PPh_3)_2]$ **6** where H_2L = benzil bis(pyridyl hydrazone) **5**. The supramolecular properties, Hirshfeld Surface analysis and anticancer activity (both *in vitro* and *in vivo*) of newly synthesized Pd(II) coordination compound **6** has been studied thoroughly. The Pd(II) coordination compound has been characterized by using spectroscopic (FT-IR, electronic, and NMR) and single-crystal X-ray diffraction analysis. The Pd(II) coordination compound **6** preferred a distorted square planar geometry. In the crystal structure of **6**,

Chapter 3

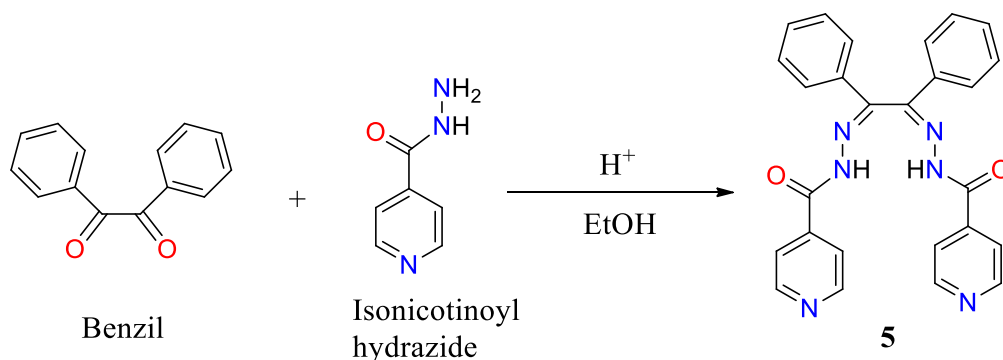
supramolecular networks have been developed by involving the association of C–H $\cdots\pi$, intermolecular C–H $\cdots$ N interactions, C–O $\cdots$ H, and $\pi\cdots\pi$ interactions. Theoretical investigations have been carried out to understand the interactions within **6**. Molecular docking study confirms strong hydrophilic interactions of **6** with the polar moiety of the amino acids in **6**. The antitumor activities of Pd(II) complex **6** and the ligand were studied *in vitro* and *in vivo* using Dalton's lymphoma malignant cancer model. Pd(II) complex **6** induced concentration-dependent cytotoxicity and apoptotic cell death leading to a decrease in cell viability, body weight, and tumor volume in mice. Mice treated with **6** showed an increase in life span with a mean survival period of 25 days. Furthermore, an *in silico* molecular interaction study supports the wet lab results.



Scheme 1. Schematic representation of the tautomeric structure of the benzil bis(pyridyl hydrazone) ligand (H₂L) **5**.

3.4.1 Reaction schemes for the synthesis of benzil bis(pyridyl hydrazone) ligand (H₂L) **5** and its Pd(II) complex **6**

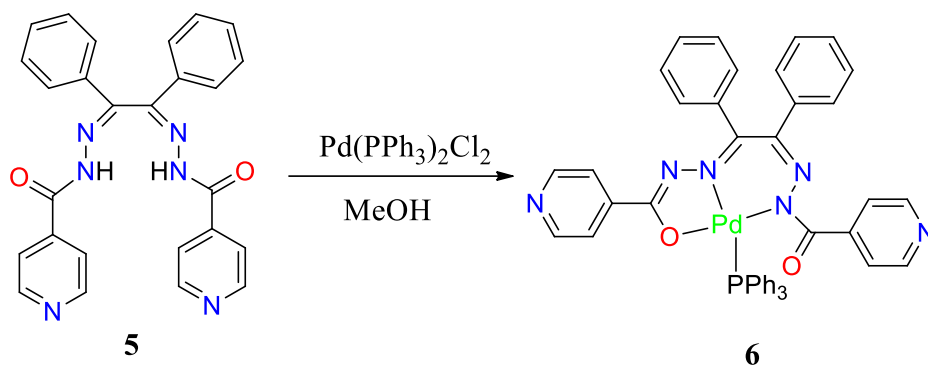
The compound **5** was synthesized in good yields from benzil and isonicotinoyl hydrazide, following **Scheme 3**.



Scheme 2. Synthesis of benzil bis(pyridyl hydrazone) ligand (H₂L) (**5**).

Chapter 3

The compound **6** was synthesized from benzil bis (pyridyl hydrazone) **5** ligand, following **Scheme 3**.



Scheme 3. Synthesis of compound **6**.

3.4.2. FT-IR and NMR spectral characterization:

By comparing the FT-IR spectra of the free benzil bis(pyridyl hydrazone) ligand (H_2L) (**5**) and its Pd(II) complex **6**, the coordination of the ligand with Pd(II) was confirmed (**Fig. 3.1** and **Fig. 3.2**). The coordination of ligand can be easily recognized by looking at the band position of the ligand that changes to either a lower or higher energy after complexation. When, the ligand complexed with palladium cation, the $\nu(N-H)$ stretching vibrations appearing at 3247 and 3176 cm^{-1} , shifted to a lower frequency range of 3244 cm^{-1} and 3172 cm^{-1} respectively, in the FT-IR spectra of the complex **6**. This confirmed the coordination of the nitrogen atom of the amide group of the ligand to the Pd metal centre. A strong absorption band attributed to $\nu(C=O)$ of the amide group of the ligand appears at 1688 cm^{-1} for the free ligand and at 1684 cm^{-1} for the coordinated ligand. This shift of the band to a lower frequency implies the coordination of the ketonic oxygen atom to the Pd(II) metal centre. This appears to be a result of the electron density shifting from oxygen to Pd(II), which reduces the stretching frequency and weakens the C=O bond. After complexation, the appearance of a distinctive peak at 1662 cm^{-1} , which is attributed to $\nu(C=N)$ in the free ligand, was seen to experience a small downward shift in frequency and emerged at 1658 cm^{-1} . This result shows that the role of the C=N stretching mode has been diminished as the electron pair on the N atom is engaged in the formation of a bond with the palladium metal ion. The appearance of a new band at 1097 cm^{-1} due to $\nu(C-O)$ suggested that the oxygen had been coordinated after keto enolization and deprotonation. Additionally, the FT-IR spectra of the Pd(II) complex contain three strong bands, appearing near 746, 691, and 520 cm^{-1} , which are indicative of coordinated triphenylphosphine. The ligand coordination to the palladium ion is further confirmed by

Chapter 3

prominent bands at 520 and 506 cm^{-1} that can be attributed to $\nu(\text{Pd-N})$ and $\nu(\text{Pd-O})$, respectively.

The ^1H NMR spectra of the free ligand and Pd(II) complex **6** have been recorded in CDCl_3 solution (**Fig. 3.3** and **Fig. 3.4**). In the spectra of the Pd(II) complex **6**, signals for the coordinated triphenylphosphines are observed as broad peaks within 7.38–7.46 ppm range. Most of the predictable signals from the aryl moiety of the coordinated benzil bis(pyridyl hydrazone) ligand are noticeably observed in the aromatic region, but a few could not be distinguished due to overlap with other signals. The ^1H NMR spectrum of the Pd(II) complex is found to be qualitatively comparable to that of free benzil bis(pyridyl ligand hydrazone), despite the hydrazinic NH signal being no longer present.

The FT-IR and ^1H NMR spectral data of the Pd (II) complex **6** are, therefore, consistent with its composition.

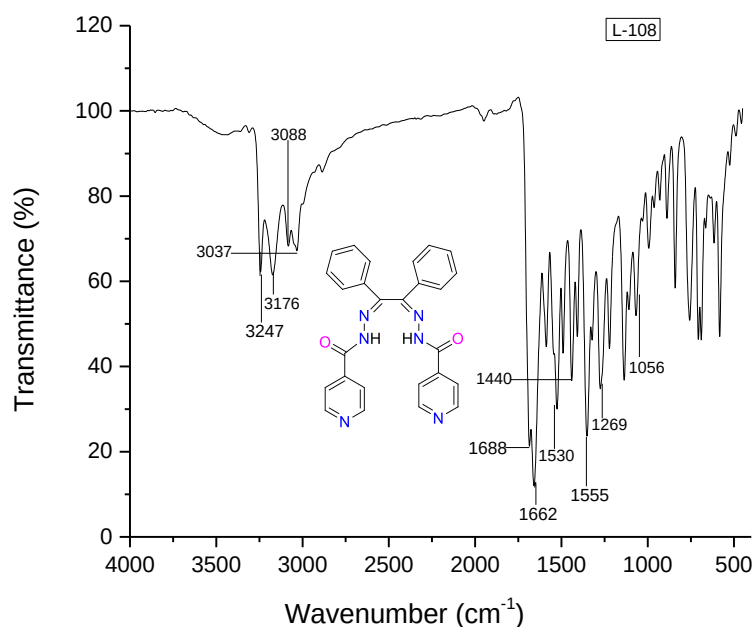


Fig. 3.1. FT-IR spectrum of benzil bis(pyridyl hydrazone) ligand **5**.

Chapter 3

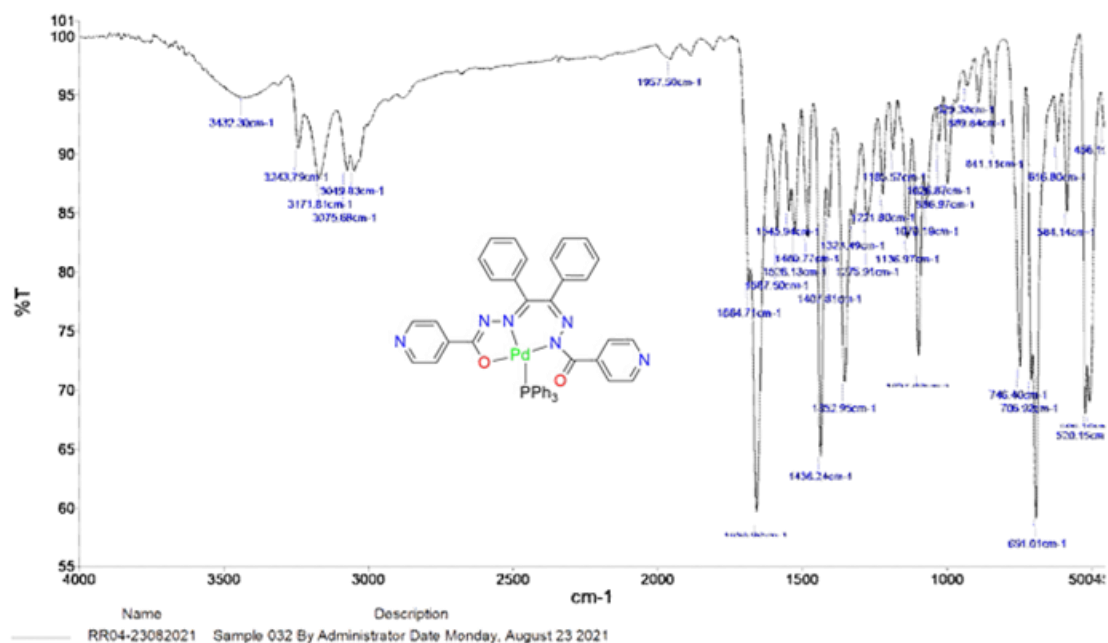


Fig. 3.2. FT-IR spectrum of Pd(II) complex 6.

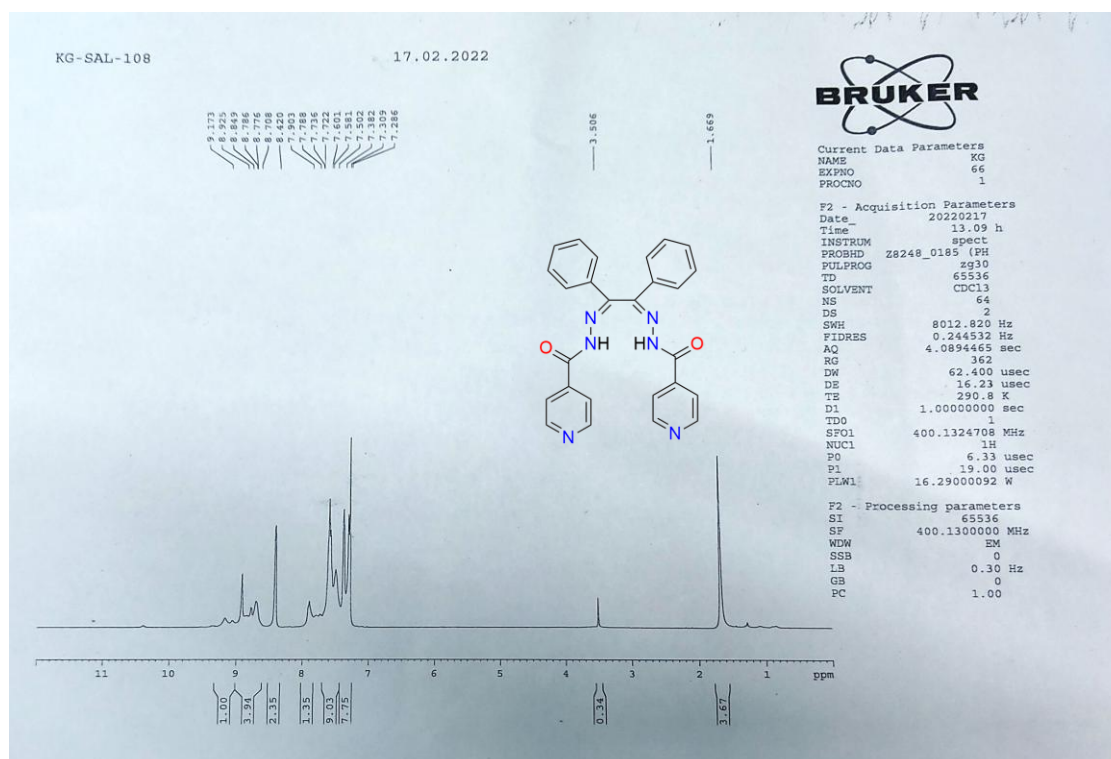


Fig. 3.3. ¹H NMR Spectrum of benzil bis(pyridyl hydrazone) ligand 5 in CDCl₃.

5A-S2

29.11.2021

1.614

7.52
7.48
7.45
7.42
7.38
7.35
7.32
7.28
7.25
7.22
7.18
7.15
7.12

1.00
1.00
1.00

1.37

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

c1ccc(cc1)C2=NC(=C(N2C(=O)c3cccnc3)C(=O)c4cccnc4)C5=CC=CC=C5

Chemical structure of the complex: c1ccc(cc1)P(c2ccccc2)c3ccccc3Pd(c4ccccc4)c5ccccc5C(=O)Nc6ccccc6

¹³C NMR spectrum (CDCl₃) showing peaks at: 149.467, 135.120, 135.059, 134.997, 134.777, 130.543, 130.393, 129.840, 129.761, 129.717, 129.595, 129.350, 128.487, 128.138, 128.086, 128.033, 123.675, 77.358, 77.041, 76.722 ppm.

Scale bar: 0.022 ppm

119

Chapter 3

3.4.3. UV-Visible absorption spectra of 5 and 6

To examine the solution state behaviour of the ligand and its Pd(II) complex **6**, UV-Visible absorption spectra of Pd(II) complex and free ligand were recorded in chloroform solution, and are shown in **Fig. 3.6**. At ~ 305 nm, the free ligand demonstrated a significant absorption band, ascribed to $\pi\text{--}\pi^*$ transition attributable to the π -system of phenyl, carbonyl, pyridyl, and azomethine scaffolds. After complexation with Pd metal, the band owing to the ligand shifted towards the red region in the spectra of complex **6**. The strong band at 343 nm could probably be ascribed to the $M \leftarrow L$ and $n \rightarrow \pi^*$ transitions.

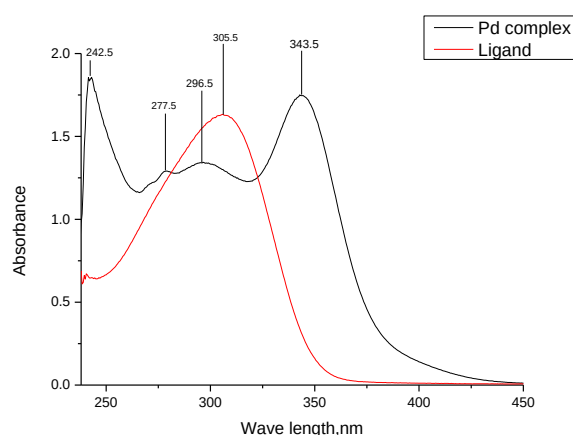


Fig. 3.6. UV-Visible spectra of the benzil bis(pyridyl hydrazone) ligand **5** ($c = 2.06 \times 10^{-5}$ M) and its Pd(II) complex **6** ($c = 2.06 \times 10^{-5}$ M) in CHCl_3 .

3.4.4. Description of structure of 6

The X-ray crystal structure analysis of the Pd(II) complex **6** shows that the compound crystallised in the triclinic crystal system and $P\bar{1}$ space group. The molecular structure of the compound shows a distorted square planar geometry with two nitrogen atoms occupying two adjacent positions and the remaining two positions in the slightly distorted square plane occupied by an oxygen atom and a phosphorus atom of the triphenylphosphine ligand. The r.m.s. deviation of the resulting NNPO donor set is $0.007\text{\AA}$, and the palladium ion lies $0.041\text{\AA}$ out of the square plane. The adjacent pyridyl groups deviate from the metallacyclic ring by dihedral angles of 6° and 76.39° . The cis angles in the square plane range from an acute $80(5)^\circ$ for O-Pd-N chelate angle to a wide $97.90(4)^\circ$ for the angle subtended at the phosphorus (P1) and N(5) donor atoms. The trans angles P1-Pd1-N3 and O1-Pd- N3 deviate from the ideal 180°

Chapter 3

by approximately 10° . The metallocyclic ring shows the central palladium ion coordinating with the ligand in a tridentate fashion to form two palladacyclic rings. The five-membered Pd1-O1-C1-N2-N2-Pd chelate ring involving palladium ion coordinating to an oxygen atom and a nitrogen atom is slightly puckered to an r.m.s. deviation of 0.036 Å, while the six-membered chelate ring Pd1-N3-C13-C20-N6-N5-Pd where Pd ion coordinates to two nitrogen donor atoms, is twice more puckered to an r.m.s. deviation of 0.076 Å. The N3-N2 (1.389(0) Å) azomethine bond is slightly longer than the corresponding N5-N6 bond (1.345(0) Å). The metallocyclic C-N bonds in the molecule are similar, ranging from a shorter C20-N6 (1.299 Å) to a slightly longer C1-N2 (1.309 Å). These bond lengths are similar to those reported for the nickel complex of the ligand [77]. There is obvious electron delocalization within the two chelate rings formed around the four-coordinate Palladium center. The C1-O1 and N2-N3 bonds around the chelate rings are shorter than the corresponding bonds in the ligand reported elsewhere [77].

The two chelate ring arrangement in this compound is different from the three five-membered chelate ring arrangements previously reported for similar ligands involving the coordination of two oxygen atoms of the ligand [75, 95]. The reason for this structural difference is probably due to the presence of the bulky triphenylphosphine ligand in the present complex, resulting in the steric hindrance of the second oxygen atom from coordinating to the palladium metal centre to give the usual three 5-membered ring geometry.

The crystal structure of **6** does not contain any conventional hydrogen bonding interactions. However, molecular aggregation in the crystal structure of the complex shows the presence of some sort of intermolecular contacts. The four molecules' aggregate structure seen in **Fig. 3.7** shows the presence of phenyl-C-H $\cdots$ N(pyridyl) and phenyl-C-H $\cdots$ O interactions linking the individual molecules in the crystal lattice and are shown as blue and red dotted lines. **Table 3.1** shows the geometric parameters for C25-H25 $\cdots$ N1 and C31-H31 $\cdots$ O2 intermolecular short contacts in the crystal lattice. The packing structure of the compound does not show any π - π stacking interactions despite the presence of a number of phenyl rings in the structure. There are, however, a few intermolecular CH $\cdots$ π and π $\cdots$ CH interactions stabilizing the crystal structure in the crystal lattice.

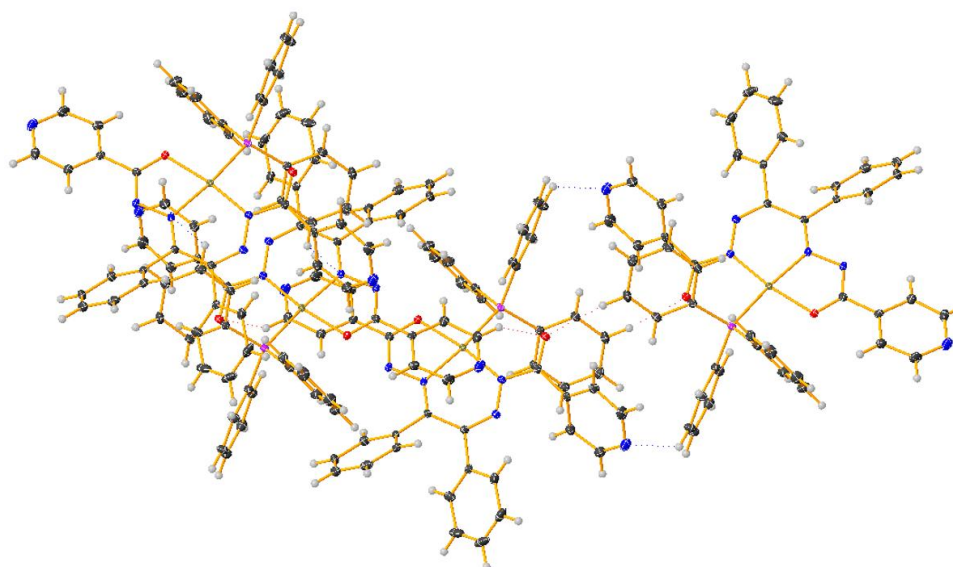


Fig. 3.7. Molecular aggregation in the crystal structure of the Pd(II) complex **6**.

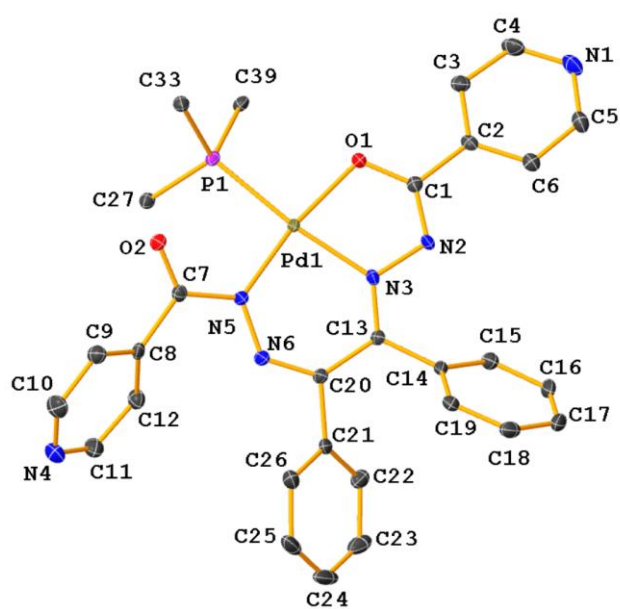


Fig. 3.8. Molecular structure of Pd(II) complex **6**. Only ipso carbons of the PPh₃ ligand are shown for clarity. Ellipsoids are drawn at 50% probability.

Chapter 3

Table 3.1. Short intermolecular contacts of the Pd(II) complex **6** (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C25–H25 $\cdots$ N1	0.95	2.58	3.330(3)	136
C31–H31 $\cdots$ O2	0.95	2.39	3.335(2)	173

Table 3.2. Crystal data and structure refinement for Pd(II) complex **6**.

Empirical formula	C ₄₄ H ₃₃ N ₆ O ₂ PPd
Formula weight	815.13
Temperature/K	100.15
Crystal system	triclinic
Space group	P-1
a/Å	11.0673(7)
b/Å	13.5220(9)
c/Å	13.7285(9)
α /°	68.130(3)
β /°	89.881(3)
γ /°	75.995(3)
Volume/Å ³	1841.1(2)
Z	2
$\rho_{\text{calc}}/\text{cm}^3$	1.470
μ/mm^{-1}	0.595
F(000)	832.0
Crystal size/mm ³	0.45 × 0.08 × 0.03
Radiation	MoK α (λ = 0.71073)
2 Θ range for data collection/°	3.212 to 56.74
Index ranges	-14 ≤ h ≤ 14, -18 ≤ k ≤ 17, -18 ≤ l ≤ 18
Reflections collected	18136
Independent reflections	9160 [R_{int} = 0.0280, R_{sigma} = 0.0385]
Data/restraints/parameters	9160/0/487
Goodness-of-fit on F ²	1.023
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0264, wR_2 = 0.0562
Final R indexes [all data]	R_1 = 0.0346, wR_2 = 0.0599
Largest diff. peak/hole / e Å ⁻³	0.48/-0.58
CCDC	2201603

Chapter 3

Table 3.3. Bond lengths [Å] and angles [°] for Pd(II) complex **6**.

Bond lengths		Bond angles	
C(1)-O(1)	1.297(2)	O(1)-C(1)-N(2)	126.82(15)
C(1)-N(2)	1.309(2)	O(1)-C(1)-C(2)	116.76(14)
C(1)-C(2)	1.483(2)	N(2)-C(1)-C(2)	116.37(14)
C(2)-C(3)	1.385(2)	C(3)-C(2)-C(6)	118.17(15)
C(2)-C(6)	1.394(2)	C(3)-C(2)-C(1)	120.32(15)
C(3)-C(4)	1.386(2)	C(6)-C(2)-C(1)	121.48(15)
C(3)-H(3)	0.9500	C(2)-C(3)-C(4)	118.59(17)
C(4)-N(1)	1.333(3)	C(2)-C(3)-H(3)	120.7
C(4)-H(4)	0.9500	C(4)-C(3)-H(3)	120.7
C(5)-N(1)	1.338(2)	N(1)-C(4)-C(3)	124.21(17)
C(5)-C(6)	1.384(2)	N(1)-C(4)-H(4)	117.9
C(5)-H(5)	0.9500	C(3)-C(4)-H(4)	117.9
C(6)-H(6)	0.9500	N(1)-C(5)-C(6)	124.02(17)
C(7)-O(2)	1.221(2)	N(1)-C(5)-H(5)	118.0
C(7)-N(5)	1.388(2)	C(6)-C(5)-H(5)	118.0
C(7)-C(8)	1.508(2)	C(5)-C(6)-C(2)	118.54(16)
C(8)-C(9)	1.383(2)	C(5)-C(6)-H(6)	120.7
C(8)-C(12)	1.392(2)	C(2)-C(6)-H(6)	120.7
C(9)-C(10)	1.386(2)	O(2)-C(7)-N(5)	120.38(15)
C(9)-H(9)	0.9500	O(2)-C(7)-C(8)	119.33(15)
C(10)-N(4)	1.326(3)	N(5)-C(7)-C(8)	120.29(14)
C(10)-H(10)	0.9500	C(9)-C(8)-C(12)	117.72(16)
C(11)-N(4)	1.343(2)	C(9)-C(8)-C(7)	117.60(16)
C(11)-C(12)	1.380(2)	C(12)-C(8)-C(7)	124.52(15)
C(11)-H(11)	0.9500	C(8)-C(9)-C(10)	118.89(17)
C(12)-H(12)	0.9500	C(8)-C(9)-H(9)	120.6
C(13)-N(3)	1.302(2)	C(10)-C(9)-H(9)	120.6
C(13)-C(20)	1.467(2)	N(4)-C(10)-C(9)	124.42(18)
C(13)-C(14)	1.496(2)	N(4)-C(10)-H(10)	117.8
C(14)-C(19)	1.390(2)	C(9)-C(10)-H(10)	117.8
C(14)-C(15)	1.398(2)	N(4)-C(11)-C(12)	124.19(18)
C(15)-C(16)	1.388(2)	N(4)-C(11)-H(11)	117.9
C(15)-H(15)	0.9500	C(12)-C(11)-H(11)	117.9
C(16)-C(17)	1.384(3)	C(11)-C(12)-C(8)	118.72(17)

Chapter 3

C(16)-H(16)	0.9500	C(11)-C(12)-H(12)	120.6
C(17)-C(18)	1.386(3)	C(8)-C(12)-H(12)	120.6
C(17)-H(17)	0.9500	N(3)-C(13)-C(20)	119.18(14)
C(18)-C(19)	1.390(2)	N(3)-C(13)-C(14)	121.38(14)
C(18)-H(18)	0.9500	C(20)-C(13)-C(14)	119.39(14)
C(19)-H(19)	0.9500	C(19)-C(14)-C(15)	119.02(15)
C(20)-N(6)	1.299(2)	C(19)-C(14)-C(13)	119.72(15)
C(20)-C(21)	1.493(2)	C(15)-C(14)-C(13)	121.26(15)
C(21)-C(26)	1.391(2)	C(16)-C(15)-C(14)	120.02(17)
C(21)-C(22)	1.393(3)	C(16)-C(15)-H(15)	120.0
C(22)-C(23)	1.389(3)	C(14)-C(15)-H(15)	120.0
C(22)-H(22)	0.9500	C(17)-C(16)-C(15)	120.67(17)
C(23)-C(24)	1.383(3)	C(17)-C(16)-H(16)	119.7
C(23)-H(23)	0.9500	C(15)-C(16)-H(16)	119.7
C(24)-C(25)	1.375(3)	C(16)-C(17)-C(18)	119.53(17)
C(24)-H(24)	0.9500	C(16)-C(17)-H(17)	120.2
C(25)-C(26)	1.387(3)	C(18)-C(17)-H(17)	120.2
C(25)-H(25)	0.9500	C(17)-C(18)-C(19)	120.18(17)
C(26)-H(26)	0.9500	C(17)-C(18)-H(18)	119.9
C(27)-C(32)	1.394(2)	C(19)-C(18)-H(18)	119.9
C(27)-C(28)	1.396(2)	C(18)-C(19)-C(14)	120.55(17)
C(27)-P(1)	1.8162(17)	C(18)-C(19)-H(19)	119.7
C(28)-C(29)	1.385(2)	C(14)-C(19)-H(19)	119.7
C(28)-H(28)	0.9500	N(6)-C(20)-C(13)	129.03(15)
C(29)-C(30)	1.386(2)	N(6)-C(20)-C(21)	111.40(14)
C(29)-H(29)	0.9500	C(13)-C(20)-C(21)	119.56(14)
C(30)-C(31)	1.385(3)	C(26)-C(21)-C(22)	119.39(16)
C(30)-H(30)	0.9500	C(26)-C(21)-C(20)	118.66(16)
C(31)-C(32)	1.389(2)	C(22)-C(21)-C(20)	121.75(15)
C(31)-H(31)	0.9500	C(23)-C(22)-C(21)	119.58(18)
C(32)-H(32)	0.9500	C(23)-C(22)-H(22)	120.2
C(33)-C(34)	1.390(2)	C(21)-C(22)-H(22)	120.2
C(33)-C(38)	1.396(2)	C(24)-C(23)-C(22)	120.5(2)
C(33)-P(1)	1.8180(17)	C(24)-C(23)-H(23)	119.8
C(34)-C(35)	1.388(2)	C(22)-C(23)-H(23)	119.8
C(34)-H(34)	0.9500	C(25)-C(24)-C(23)	120.22(18)
C(35)-C(36)	1.387(3)	C(25)-C(24)-H(24)	119.9
C(35)-H(35)	0.9500	C(23)-C(24)-H(24)	119.9

Chapter 3

C(36)-C(37)	1.388(3)	C(24)-C(25)-C(26)	119.80(19)
C(36)-H(36)	0.9500	C(24)-C(25)-H(25)	120.1
C(37)-C(38)	1.383(2)	C(26)-C(25)-H(25)	120.1
C(37)-H(37)	0.9500	C(25)-C(26)-C(21)	120.55(19)
C(38)-H(38)	0.9500	C(25)-C(26)-H(26)	119.7
C(39)-C(40)	1.392(2)	C(21)-C(26)-H(26)	119.7
C(39)-C(44)	1.400(2)	C(32)-C(27)-C(28)	118.71(15)
C(39)-P(1)	1.8277(17)	C(32)-C(27)-P(1)	123.48(13)
C(40)-C(41)	1.392(3)	C(28)-C(27)-P(1)	117.49(12)
C(40)-H(40)	0.9500	C(29)-C(28)-C(27)	120.66(16)
C(41)-C(42)	1.383(3)	C(29)-C(28)-H(28)	119.7
C(41)-H(41)	0.9500	C(27)-C(28)-H(28)	119.7
C(42)-C(43)	1.388(3)	C(28)-C(29)-C(30)	120.13(17)
C(42)-H(42)	0.9500	C(28)-C(29)-H(29)	119.9
C(43)-C(44)	1.381(2)	C(30)-C(29)-H(29)	119.9
C(43)-H(43)	0.9500	C(31)-C(30)-C(29)	119.77(16)
C(44)-H(44)	0.9500	C(31)-C(30)-H(30)	120.1
O(1)-Pd(1)	2.0079(11)	C(29)-C(30)-H(30)	120.1
P(1)-Pd(1)	2.3022(5)	C(30)-C(31)-C(32)	120.24(16)
Pd(1)-N(5)	1.9806(13)	C(30)-C(31)-H(31)	119.9
Pd(1)-N(3)	2.0179(14)	C(32)-C(31)-H(31)	119.9
N(2)-N(3)	1.3892(18)	C(31)-C(32)-C(27)	120.42(16)
N(5)-N(6)	1.3447(19)	C(31)-C(32)-H(32)	119.8
		C(27)-C(32)-H(32)	119.8
		C(34)-C(33)-C(38)	119.14(16)
		C(34)-C(33)-P(1)	120.82(13)
		C(38)-C(33)-P(1)	119.99(13)
		C(35)-C(34)-C(33)	120.46(16)
		C(35)-C(34)-H(34)	119.8
		C(33)-C(34)-H(34)	119.8
		C(36)-C(35)-C(34)	119.94(17)
		C(36)-C(35)-H(35)	120.0
		C(34)-C(35)-H(35)	120.0
		C(35)-C(36)-C(37)	119.94(17)
		C(35)-C(36)-H(36)	120.0
		C(37)-C(36)-H(36)	120.0
		C(38)-C(37)-C(36)	120.09(17)
		C(38)-C(37)-H(37)	120.0

Chapter 3

	C(36)-C(37)-H(37)	120.0
	C(37)-C(38)-C(33)	120.41(17)
	C(37)-C(38)-H(38)	119.8
	C(33)-C(38)-H(38)	119.8
	C(40)-C(39)-C(44)	119.14(16)
	C(40)-C(39)-P(1)	123.13(13)
	C(44)-C(39)-P(1)	117.72(13)
	C(39)-C(40)-C(41)	120.18(17)
	C(39)-C(40)-H(40)	119.9
	C(41)-C(40)-H(40)	119.9
	C(42)-C(41)-C(40)	120.16(18)
	C(42)-C(41)-H(41)	119.9
	C(40)-C(41)-H(41)	119.9
	C(41)-C(42)-C(43)	119.97(17)
	C(41)-C(42)-H(42)	120.0
	C(43)-C(42)-H(42)	120.0
	C(44)-C(43)-C(42)	120.19(17)
	C(44)-C(43)-H(43)	119.9
	C(42)-C(43)-H(43)	119.9
	C(43)-C(44)-C(39)	120.35(17)
	C(43)-C(44)-H(44)	119.8
	C(39)-C(44)-H(44)	119.8
	C(1)-O(1)-Pd(1)	108.96(10)
	C(27)-P(1)-C(33)	108.26(8)
	C(27)-P(1)-C(39)	105.76(8)
	C(33)-P(1)-C(39)	100.95(8)
	C(27)-P(1)-Pd(1)	111.78(6)
	C(33)-P(1)-Pd(1)	119.42(6)
	C(39)-P(1)-Pd(1)	109.38(5)
	N(5)-Pd(1)-O(1)	170.35(5)
	N(5)-Pd(1)-N(3)	90.55(5)
	O(1)-Pd(1)-N(3)	80.00(5)
	N(5)-Pd(1)-P(1)	97.90(4)
	O(1)-Pd(1)-P(1)	91.71(3)
	N(3)-Pd(1)-P(1)	169.25(4)
	C(4)-N(1)-C(5)	116.46(15)
	C(1)-N(2)-N(3)	110.54(13)
	C(13)-N(3)-N(2)	118.26(13)

Chapter 3

	C(13)-N(3)-Pd(1)	128.58(11)
	N(2)-N(3)-Pd(1)	113.16(10)
	C(10)-N(4)-C(11)	115.96(16)
	N(6)-N(5)-C(7)	111.32(13)
	N(6)-N(5)-Pd(1)	124.24(10)
	C(7)-N(5)-Pd(1)	124.34(11)
	C(20)-N(6)-N(5)	126.04(14)

Symmetry transformations used to generate equivalent atoms:

Table 3.4. Torsion angles [°] for Pd(II) complex **6**.

O(1)-C(1)-C(2)-C(3)	-6.0(2)
N(2)-C(1)-C(2)-C(3)	171.69(16)
O(1)-C(1)-C(2)-C(6)	176.04(15)
N(2)-C(1)-C(2)-C(6)	-6.3(2)
C(6)-C(2)-C(3)-C(4)	0.2(3)
C(1)-C(2)-C(3)-C(4)	-177.85(16)
C(2)-C(3)-C(4)-N(1)	0.3(3)
N(1)-C(5)-C(6)-C(2)	0.2(3)
C(3)-C(2)-C(6)-C(5)	-0.5(3)
C(1)-C(2)-C(6)-C(5)	177.57(16)
O(2)-C(7)-C(8)-C(9)	-35.6(2)
N(5)-C(7)-C(8)-C(9)	143.64(17)
O(2)-C(7)-C(8)-C(12)	139.82(18)
N(5)-C(7)-C(8)-C(12)	-41.0(2)
C(12)-C(8)-C(9)-C(10)	2.7(3)
C(7)-C(8)-C(9)-C(10)	178.39(16)
C(8)-C(9)-C(10)-N(4)	-2.2(3)
N(4)-C(11)-C(12)-C(8)	-2.1(3)
C(9)-C(8)-C(12)-C(11)	-0.7(3)
C(7)-C(8)-C(12)-C(11)	-176.10(16)
N(3)-C(13)-C(14)-C(19)	125.27(18)
C(20)-C(13)-C(14)-C(19)	-52.2(2)
N(3)-C(13)-C(14)-C(15)	-54.2(2)
C(20)-C(13)-C(14)-C(15)	128.29(17)

Chapter 3

C(19)-C(14)-C(15)-C(16)	-1.0(3)
C(13)-C(14)-C(15)-C(16)	178.54(16)
C(14)-C(15)-C(16)-C(17)	-0.7(3)
C(15)-C(16)-C(17)-C(18)	1.3(3)
C(16)-C(17)-C(18)-C(19)	-0.2(3)
C(17)-C(18)-C(19)-C(14)	-1.5(3)
C(15)-C(14)-C(19)-C(18)	2.1(2)
C(13)-C(14)-C(19)-C(18)	-177.44(15)
N(3)-C(13)-C(20)-N(6)	-11.1(3)
C(14)-C(13)-C(20)-N(6)	166.44(17)
N(3)-C(13)-C(20)-C(21)	169.45(15)
C(14)-C(13)-C(20)-C(21)	-13.0(2)
N(6)-C(20)-C(21)-C(26)	-46.1(2)
C(13)-C(20)-C(21)-C(26)	133.44(17)
N(6)-C(20)-C(21)-C(22)	128.74(17)
C(13)-C(20)-C(21)-C(22)	-51.7(2)
C(26)-C(21)-C(22)-C(23)	-0.3(3)
C(20)-C(21)-C(22)-C(23)	-175.09(16)
C(21)-C(22)-C(23)-C(24)	-0.4(3)
C(22)-C(23)-C(24)-C(25)	0.7(3)
C(23)-C(24)-C(25)-C(26)	-0.3(3)
C(24)-C(25)-C(26)-C(21)	-0.3(3)
C(22)-C(21)-C(26)-C(25)	0.6(3)
C(20)-C(21)-C(26)-C(25)	175.61(16)
C(32)-C(27)-C(28)-C(29)	-2.3(3)
P(1)-C(27)-C(28)-C(29)	171.46(14)
C(27)-C(28)-C(29)-C(30)	0.0(3)
C(28)-C(29)-C(30)-C(31)	2.1(3)
C(29)-C(30)-C(31)-C(32)	-1.9(3)
C(30)-C(31)-C(32)-C(27)	-0.5(3)
C(28)-C(27)-C(32)-C(31)	2.5(3)
P(1)-C(27)-C(32)-C(31)	-170.82(13)
C(38)-C(33)-C(34)-C(35)	0.2(2)
P(1)-C(33)-C(34)-C(35)	177.34(13)
C(33)-C(34)-C(35)-C(36)	0.6(3)
C(34)-C(35)-C(36)-C(37)	-0.6(3)
C(35)-C(36)-C(37)-C(38)	-0.3(3)
C(36)-C(37)-C(38)-C(33)	1.1(3)

Chapter 3

C(34)-C(33)-C(38)-C(37)	-1.1(3)
P(1)-C(33)-C(38)-C(37)	-178.25(13)
C(44)-C(39)-C(40)-C(41)	-0.3(3)
P(1)-C(39)-C(40)-C(41)	179.76(14)
C(39)-C(40)-C(41)-C(42)	0.4(3)
C(40)-C(41)-C(42)-C(43)	-0.3(3)
C(41)-C(42)-C(43)-C(44)	0.1(3)
C(42)-C(43)-C(44)-C(39)	0.0(3)
C(40)-C(39)-C(44)-C(43)	0.1(3)
P(1)-C(39)-C(44)-C(43)	-179.94(14)
N(2)-C(1)-O(1)-Pd(1)	3.3(2)
C(2)-C(1)-O(1)-Pd(1)	-179.31(11)
C(32)-C(27)-P(1)-C(33)	2.61(17)
C(28)-C(27)-P(1)-C(33)	-170.81(13)
C(32)-C(27)-P(1)-C(39)	-104.90(15)
C(28)-C(27)-P(1)-C(39)	81.68(15)
C(32)-C(27)-P(1)-Pd(1)	136.14(13)
C(28)-C(27)-P(1)-Pd(1)	-37.28(15)
C(34)-C(33)-P(1)-C(27)	116.47(14)
C(38)-C(33)-P(1)-C(27)	-66.45(15)
C(34)-C(33)-P(1)-C(39)	-132.73(14)
C(38)-C(33)-P(1)-C(39)	44.36(15)
C(34)-C(33)-P(1)-Pd(1)	-12.92(16)
C(38)-C(33)-P(1)-Pd(1)	164.16(12)
C(40)-C(39)-P(1)-C(27)	-14.35(17)
C(44)-C(39)-P(1)-C(27)	165.67(13)
C(40)-C(39)-P(1)-C(33)	-127.06(15)
C(44)-C(39)-P(1)-C(33)	52.96(15)
C(40)-C(39)-P(1)-Pd(1)	106.19(14)
C(44)-C(39)-P(1)-Pd(1)	-73.79(14)
C(3)-C(4)-N(1)-C(5)	-0.6(3)
C(6)-C(5)-N(1)-C(4)	0.3(3)
O(1)-C(1)-N(2)-N(3)	2.2(2)
C(2)-C(1)-N(2)-N(3)	-175.18(13)
C(20)-C(13)-N(3)-N(2)	-178.25(14)
C(14)-C(13)-N(3)-N(2)	4.3(2)
C(20)-C(13)-N(3)-Pd(1)	1.3(2)
C(14)-C(13)-N(3)-Pd(1)	-176.16(12)

Chapter 3

C(1)-N(2)-N(3)-C(13)	173.03(15)
C(1)-N(2)-N(3)-Pd(1)	-6.60(17)
C(9)-C(10)-N(4)-C(11)	-0.5(3)
C(12)-C(11)-N(4)-C(10)	2.6(3)
O(2)-C(7)-N(5)-N(6)	161.54(15)
C(8)-C(7)-N(5)-N(6)	-17.6(2)
O(2)-C(7)-N(5)-Pd(1)	-15.0(2)
C(8)-C(7)-N(5)-Pd(1)	165.86(12)
C(13)-C(20)-N(6)-N(5)	3.8(3)
C(21)-C(20)-N(6)-N(5)	-176.74(15)
C(7)-N(5)-N(6)-C(20)	-164.13(16)
Pd(1)-N(5)-N(6)-C(20)	12.4(2)

Symmetry transformations used to generate equivalent atoms:

3.4.5. Theoretical Study of 6

The optimized geometry of Pd(II) complex **6** is shown in **Fig. 3.9a-3.9d** and presents the theoretical UV-Vis plot of Pd(II) complex **6**, which shows that the electronic transition corresponding to H→L transition is at $\lambda_{\text{max}} = 345\text{ nm}$ and is in good agreement with experimental λ_{max} at 343.5 nm. Other inner electronic transitions were observed at 290 and 261 nm, which also agree with experimental λ_{max} at 296.5 and 277.5 nm, respectively. The HOMO-LUMO plot as presented in **Fig. 3.9c** shows that charge is transferred from receptor to Pd metal, which makes the formation of complex more feasible. Again, to study the interaction within the Pd-complex, a reduced density gradient plot (RDG) is shown in **Fig. 3.9b**. Here, the green dots represent attractive forces while the red dots represent the repulsive interactions. The scattered green dots in **Fig. 3.9b** represent that there is strong van der Waals type of interactions between the receptor and the Pd atom which makes the complex formation easier.

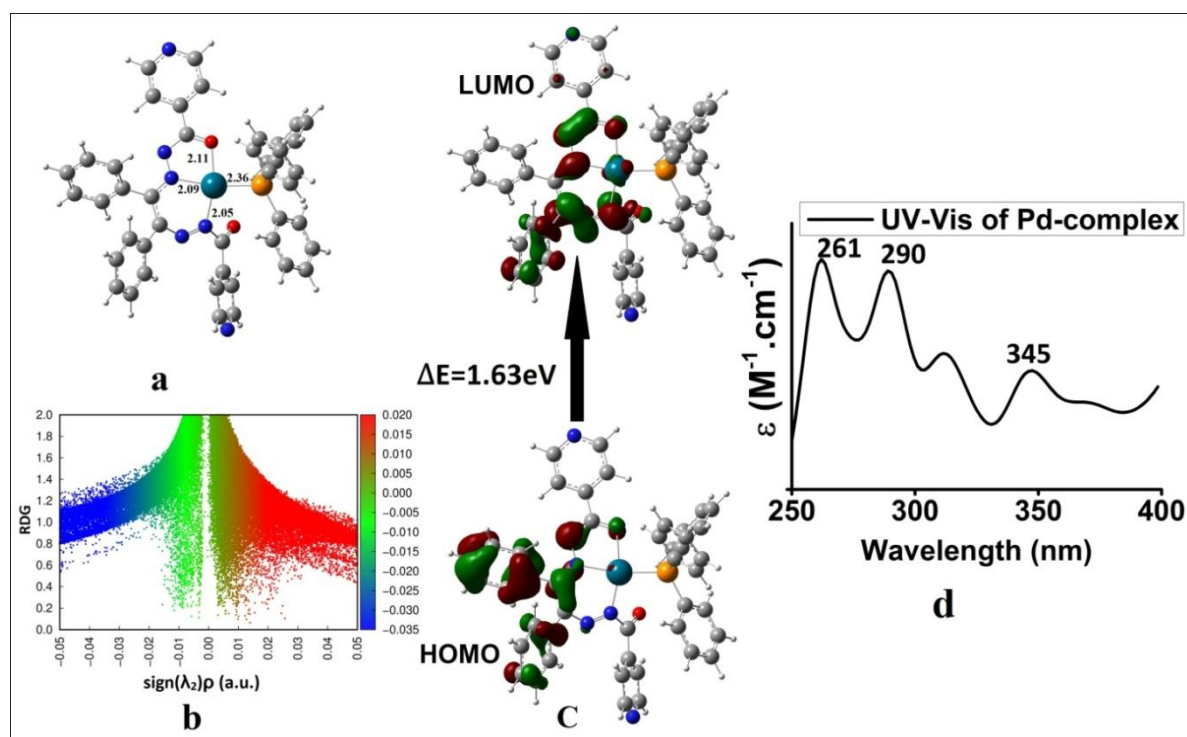


Fig. 3.9. (a) Optimized geometry of Pd-complex **6**, (b) Reduced density gradient of Pd-complex, (c) HOMO to LUMO electronic transition for Pd-complex with respective band gap, and (d) theoretical UV-Vis spectrum of Pd-complex in CHCl_3 .

3.4.6. Hirshfeld Surface Analysis of **6**

To analyse the intermolecular contacts and supramolecular self-assemblies in molecules, the Hirshfeld surface and their 2-D fingerprint plots are used [96, 97]. In the region known as the Hirshfeld surface, the electron density of a given molecule is higher than that of all its neighbours [98]. The Hirshfeld surface of the Pd(II) complex **6** mapped on the d -norm surface demonstrated a three-color scheme. The blue regions denote longer intermolecular contacts, the white regions denote intermediate intermolecular contacts, and the red regions denote close intermolecular contacts with distances shorter than the sum of their respective van der Waals radii [99]. The deep red regions on the d -norm surface of the Pd(II) complex **6** shown in **Fig. 3.10** correspond to the intermolecular phenyl-C-H $\cdots$ N (Pyridyl) contacts, represented as red dotted lines in **Fig. 3.11**, while the slight red regions correspond to the Pd $\cdots$ H and Pd $\cdots$ C contacts shown as magenta-colored dotted lines. The more ubiquitous blue regions corresponded to the H $\cdots$ H contacts in the molecule and are depicted as green-coloured dotted lines in **Fig. 3.10**. The Pd(II) complex **6** was also mapped on the Hirshfeld surface over the

Chapter 3

curvedness and shape index surfaces (**Fig. 3.10c** & **Fig. 3.10d**) to analyze the C–H $\cdots\pi$ contacts in the complex. The blue and red regions around the participating atoms represent the donors and acceptors of intermolecular C–H $\cdots\pi$ interactions [100, 101]. The C $\cdots$ H/H $\cdots$ C contacts are accountable for the molecular packing in the supramolecular assembly of the Pd(II) complex **6** [102]. In the compound, these interactions show up as bulging blue spots (C–H $\cdots\pi$) and hollow orange areas (π –H $\cdots$ C). The complex's phenyl ring shows $\pi\cdots\pi$ stacking interactions in the little blue regions that surround a brilliant orange point. The flat areas surrounding the phenyl and pyridyl rings on the Hirshfeld surface that are mapped over curvedness in **Fig. 3.10c** are also proof that there are $\pi\cdots\pi$ interactions.

The distance from the Hirshfeld surface to the closest nucleus inside and outside the surface is related to the 2D fingerprint plots [103]. To quantify the close interactions in the compound, the two-dimensional global fingerprint plots for the Pd complex were generated. The intermolecular O–H/H–O interactions are thought to be the cause of a pair of symmetric spikes that appear in the compound's overall fingerprint plot but only in the individual plot for those contacts. The O–H/H–O isosurface spikes of a similar nature have been observed in other compounds [103-106]. The percentage contributions of the surface contacts in the 2D fingerprint plots presented in **Table 3.5** indicate that the H $\cdots$ H (54.4%) contribute the greatest percentage of the surface contacts with more than half of the entire intermolecular isosurface interactions attributed to it. The other interactions contributing to the surface contacts include the C $\cdots$ H/H $\cdots$ C (26.8%), H $\cdots$ N/N $\cdots$ H (9.0%), O $\cdots$ H/H $\cdots$ O (3.1%), and C $\cdots$ C (1.8%). The 2D fingerprint plots confirmed that the dominant contacts in the crystal structure of the Pd(II) complex **6** include van der Waal, C–H $\cdots\pi$, and intermolecular C–H $\cdots$ N interactions, while the C–O $\cdots$ H and $\pi\cdots\pi$ interactions contribute only a small percentage of the total contributions.

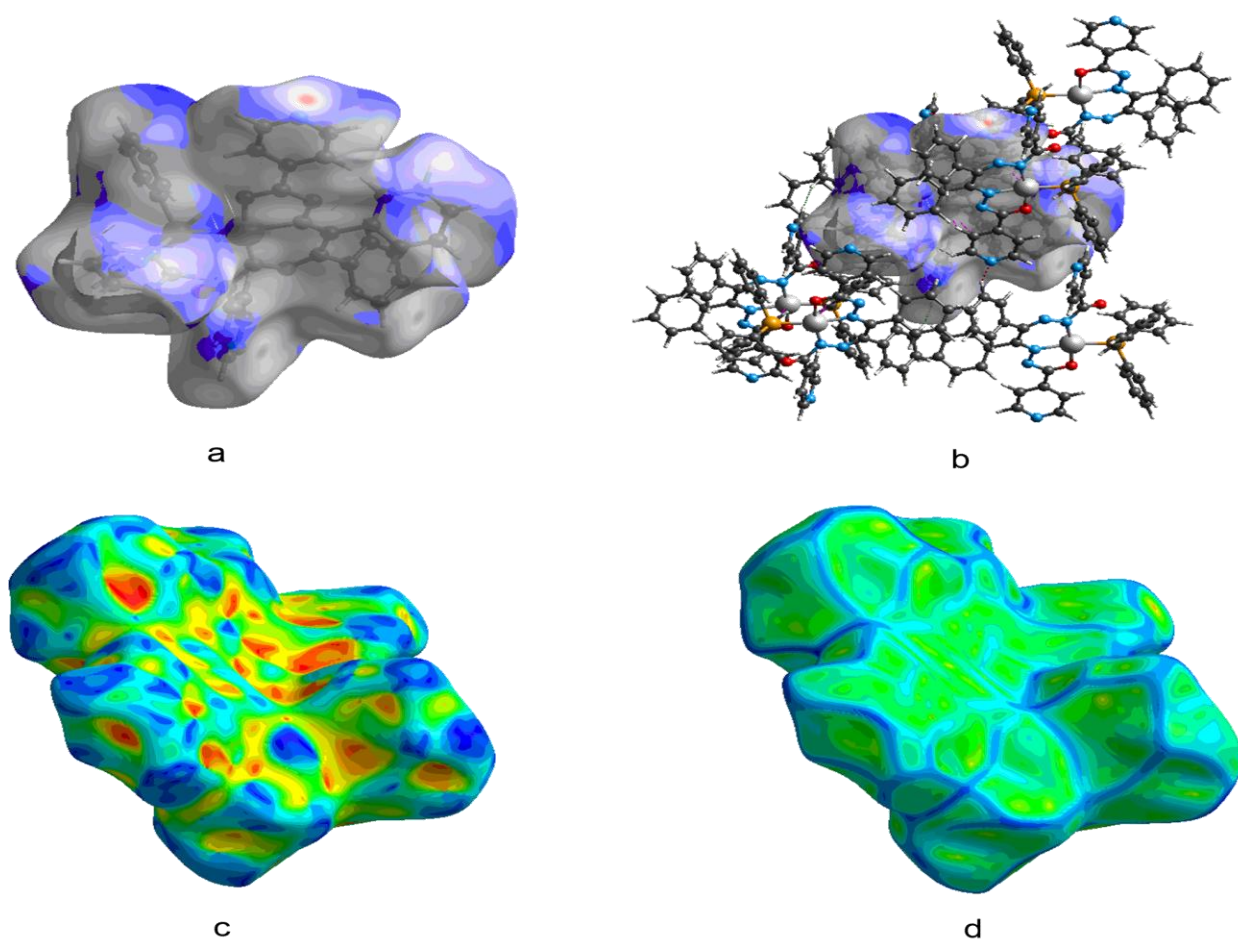


Fig. 3.10. Hirshfeld surface analysis: (a) surface mapped on *d*-norm N-H interactions shown in red, H-H interactions shown in green, and Pd-C, Pd-H interactions shown in magenta; (b) Intermolecular interactions in the *d*-norm Hirshfeld surface including; (c) surface mapped on curvedness; and (d) surface mapped on shape index.

Chapter 3

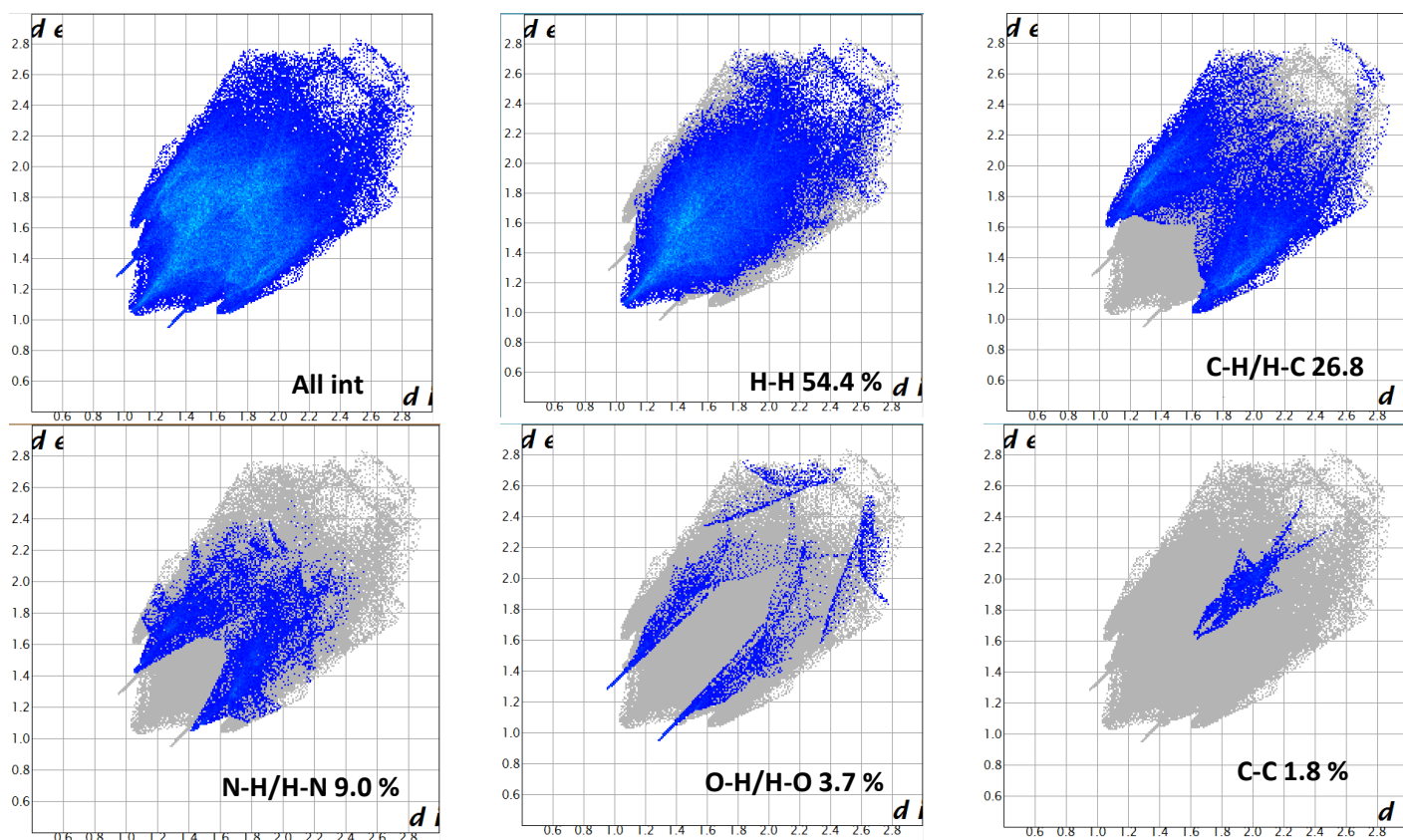


Fig. 3.11. 2D fingerprint plots of the main intermolecular interactions and contacts in the crystal structure of the Pd(II) complex **6**.

Table 3.5. Percentage contributions of intermolecular contacts on the Hirshfeld surface calculated for the Pd(II) complex **6**.

Interaction Type	Percentage (%)
H-H	54.4
C-H /H-C	26.8.
N-H/H-N	9.0
O-H/H-O	3.7
C-C	1.8

3.4.7 Cytotoxicity and apoptosis assays of **5** and **6**

The cytotoxicity assay is based on the principle that polar dyes, such as trypan blue, are impermeable to normal cells; however, due to a compromised membrane structure, they can easily penetrate and colour dead cells [107]. The percentage of blue-stained cells represents the

Chapter 3

percentage of dead cells in the overall population [108]. The cytotoxicity study in DL cell line revealed that benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** induced concentration-dependent cytotoxicity, which led to a decrease in cell viability (**Fig. 3.12** and **Fig. 3.13**). The Pd(II) complex **6** induced higher cytotoxicity (**Fig. 3.13**) at higher concentrations as compared to benzil bis(pyridyl hydrazone) ligand **5**. Healthy (PBMC) cell line exhibited much less cytotoxicity (~8-10%) in parallel experiment (**Fig. 3.13**). The benzil bis(pyridyl hydrazone) ligand **6** and Pd(II) complex **6** induced typical apoptotic features in malignant DL cells (**Fig. 3.12** and **Fig. 3.13**) as reflected by red/orange nucleus; the result is well corroborated with the cytotoxicity assay (trypan blue exclusion method). Because of its ability to interact with DNA, RNA, and protein, cisplatin was chosen as the positive control. Cisplatin-induced apoptosis appears to be the primary cause of cytotoxicity with DNA inter- and intrastrand crosslinks in most cancer types [109]. Apoptotic cells exhibit a number of cytological characteristics, such as membrane blebbing, chromatin condensation, membrane permeability, nuclear fragmentation, phosphatidylserine exposure, caspase activation, and DNA fragmentation [110].

The half-maximal inhibitory concentration (IC_{50}) is typically used to evaluate the preclinical efficacy of newly synthesised compounds for potential as a drug. IC_{50} is a measure of the ability of a substance to inhibit biological response by half [111]. **Fig. 3.14** presents the dose-response data and IC_{50} values for the benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** in the DL and PBMC cell lines (**Table 3.6**). The Pd(II) complex **6** has shown a low IC_{50} value (22.01 μ M) as compared to that of benzil bis(pyridyl hydrazone) ligand (180.71 μ M) in the DL cell line after 48 h of treatment (**Fig. 3.14**). The IC_{50} value of reference drug, cisplatin, ranges from 0.5-0.6 μ M in the same experimental setup.

Chapter 3

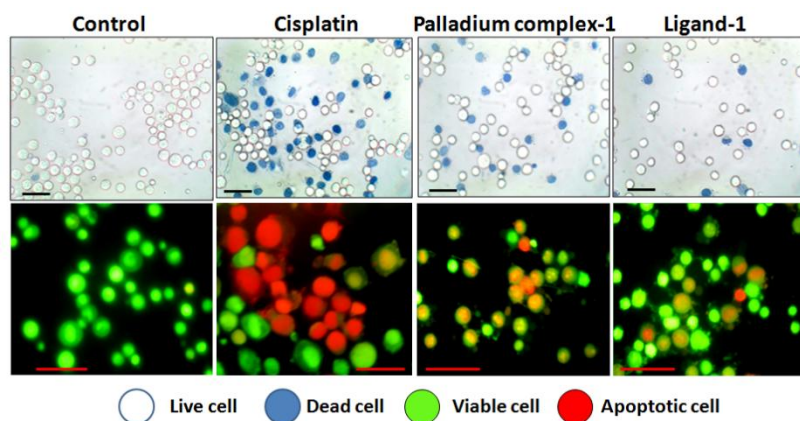


Fig. 3.12. Upper panel show cell cytotoxicity using trypan blue assay. Blue-stained cells reflect dead cells and non-stained cells reflect live cells. The morphological properties of viable (green) and apoptotic (red) cells were studied using fluorescence microscopy.

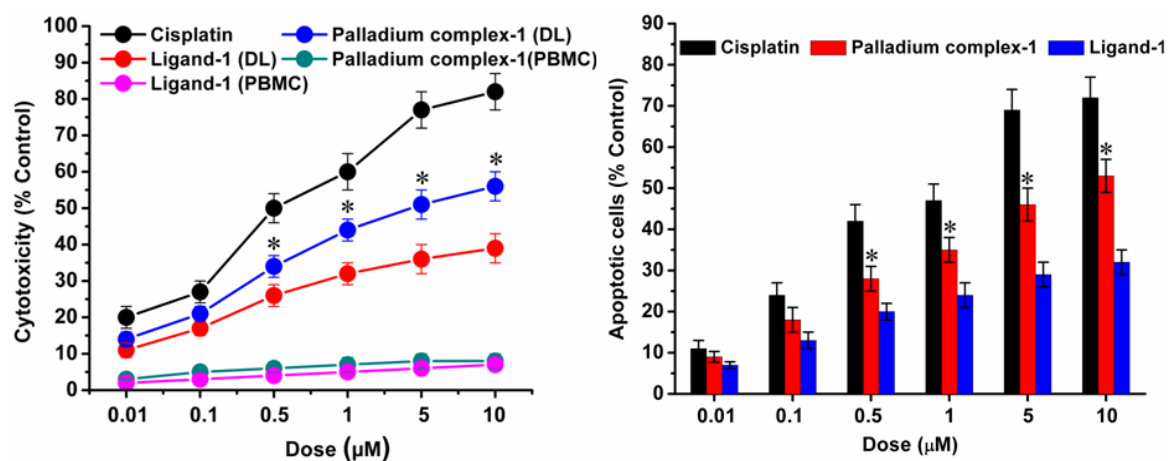


Fig. 3.13. Percentage cell cytotoxicity (left) induced by benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** in DL cells after exposure to various test concentrations. Cisplatin was used as a positive (reference drug) control. Data are mean $\pm$ S.D., $n=3$). Percentage of apoptotic cells (right) in the DL cell line after treatment with benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6**. The data represent the mean standard deviation, $n=3$.

Chapter 3

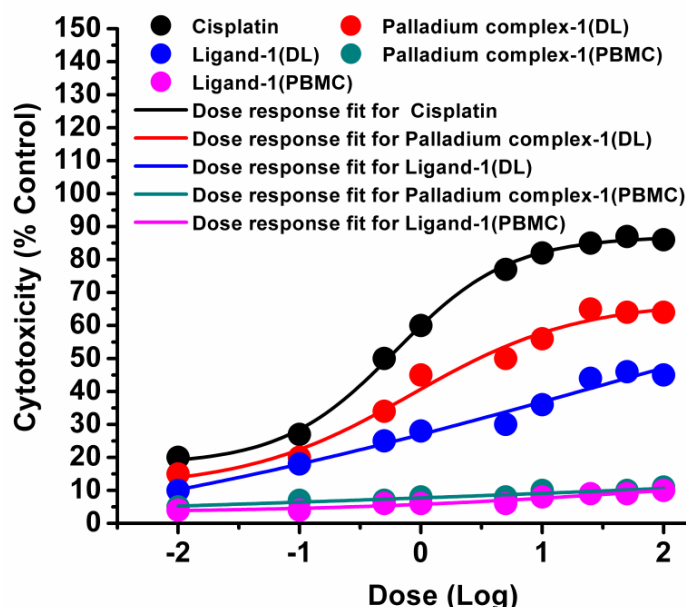


Fig. 3.14. The dosage response curves of benzil bis(pyridyl hydrazone) ligand **5** and its Pd(II) complex **6** are shown in order to determine the IC₅₀ values in DL and PBMC cell lines.

Table 3.6. IC₅₀ value of ligand and its Pd(II) complex **6** in DL and PBMC cell lines.

Sl. Nos.	Drug candidates	Cell lines	Nature of cell lines	IC ₅₀	Error (S.E.)
1.	Cisplatin (Reference)	DL	Malignant cancer	0.52	0.024
2.	Benzil bis(pyridyl hydrazone) ligand 5	DL	Malignant cancer	180.71	0.041
3.	Pd(II) complex 6	DL	Malignant cancer	22.01	0.023
4.	Benzil bis(pyridyl hydrazone) ligand 5	PBMC	Normal cell	520.13	0.049
5.	Pd(II) complex 6	PBMC	Normal cell	490.22	0.042

3.4.8 Survivability study

Mouse models are irreplaceable tools for the study of carcinogenesis, and antitumor activity of unknown compounds/drugs. The availability of rodent models has enabled rational screening of drugs [112]. To evaluate *in vivo* anticancer activity, an increase in the lifespan of tumour-bearing mice along with changes in body weight and tumor volume is the most commonly used method. After treatment with benzil bis(pyridyl hydrazone) ligand **5** and its Pd(II) complex **6** in DL bearing mice model, the survival analysis was performed using the Kaplan-Meier

Chapter 3

survival analysis (**Fig. 3.15**). The control mice had a mean survival day of 18 days. In contrast, the benzil bis(pyridyl hydrazone) ligand and its Pd(II) complex **6** treated mice showed an increase in life span with a mean survival day of 19 and 25 days, respectively. Benzil bis (pyridyl hydrazone) ligand has no significant influence on the increase in the lifespan of treated mice. In the case of the reference drug, cisplatin, the mean survival day was found to be 29 days (**Fig. 3.15**). To corroborate the increase in lifespan of treated mice, changes in body weight and tumor volume were recorded till the death of all mice from each experimental group. The results showed that the treatment with Pd(II) complex **6** significantly reduced the body weight and tumour volume (**Fig. 3.15**), which indicates antitumour potential of the said complex. Further detailed study is required to establish the molecular mode of action of Pd(II) complex **6** using advanced molecular tools and techniques.

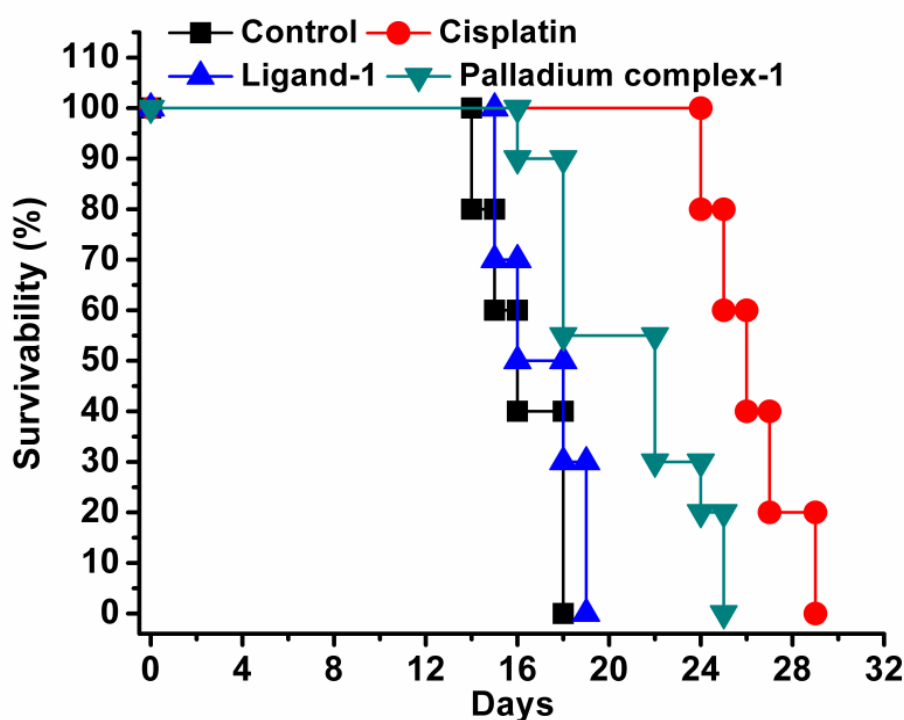


Fig. 3.15. Graphs showing the survival pattern of tumor-bearing mice after treatment with the most potent dose of benzil bis(pyridyl hydrazone) ligand **5** and corresponding Pd(II) complex **6** (20 mg/kg body weight) and standard reference drug, cisplatin (2 mg/kg body weight). Results are mean of 5 independent experimental data sets.

Chapter 3

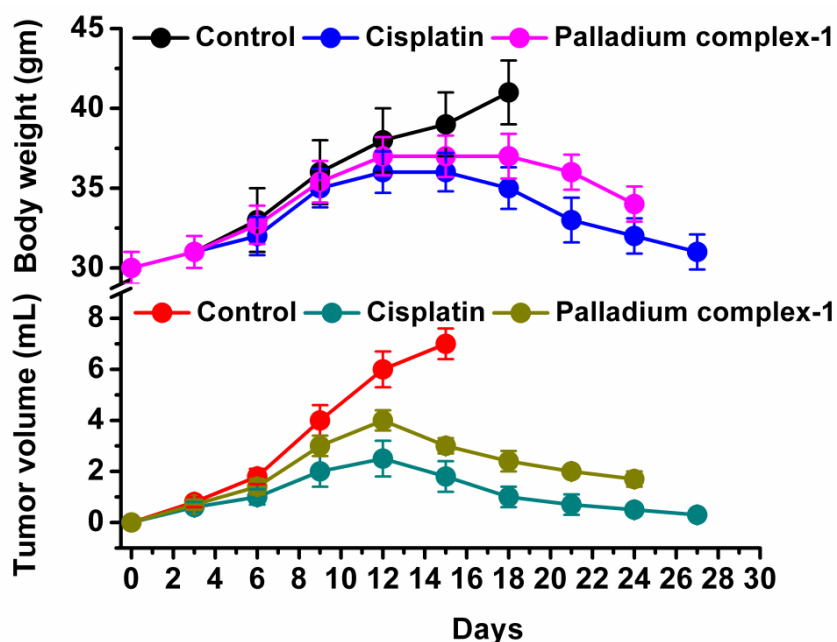


Fig. 3.16. Graphs showing changes in the body weight and tumor volume of the mice treated with cisplatin (2mg/kg body weight), benzil bis(pyridyl hydrazone) ligand **5** and its Pd(II) complex **6** (20mg/kg body weight). Results are mean $\pm$ S.D., $n=5$.

3.4.9 Molecular docking study of **6**

Fig. 3.17a represents the docked conformation of Pd(II) complex **6** with mouse tumour necrosis factor (PDB ID: 2TNF) with corresponding nearest residues. The high docking score of -7.18 kcal/mol without unbound energy indicates perfect fitting of the Pd(II) complex **6** within the cavity of the receptor. To provide a clear look at binding interactions, hydrophobic and hydrophilic interactions between Pd(II) complex **6** and the tumour cell are shown in **Fig. 3.17b**. As the complex is highly polar (Dipole moment = 7.89D), it will have high hydrophilic interactions with the polar part of the amino acids. From **Fig. 3.17b**, it is clear that there are strong hydrophilic interactions (blue) between the Pd-complex and TNF, which makes a favourable binding of the complex with the target receptor. Tumour necrosis factor (TNF) is a multifunctional cytokine involved in a variety of biological activities including cell survival, proliferation, differentiation, and death. TNF, a pro-inflammatory cytokine, is released by inflammatory cells and is reported to be involved in inflammation-mediated carcinogenesis [113]. TNF is also considered a two-edged sword that can be pro- or anti-tumorigenic. In mice with pancreatic tumours, inhibiting TNF using the monoclonal antibody infliximab or recombinant human soluble TNFR-2 had a substantial antitumoral impact [114]. Infliximab and etanercept both produced sustained disease stabilisation in patients with metastatic breast

Chapter 3

cancer, recurrent ovarian cancer, or immunotherapy-resistant or refractory renal cell carcinoma in phase I and II clinical trials [115, 116]. In addition, TNF neutralisation dramatically reduced the development of malignant pleural effusion in mice [117].

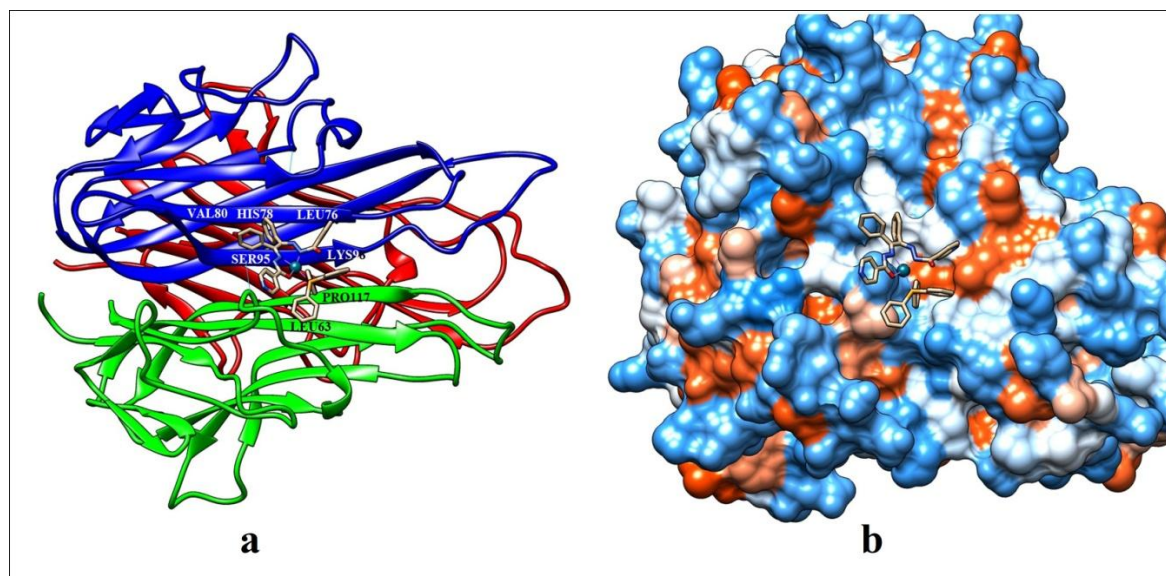


Fig. 3.17. (a) Docked structure between 2tnf and Pd(II) complex **6**, (b) hydrophobic (red) and hydrophilic (blue) interaction between 2TNF and Pd(II) complex **6**.

Conclusions

A novel Pd(II) coordination compound **6** was synthesized from the benzil bis(pyridyl hydrazone) ligand **5** and was fully characterized. Single-crystal X-ray diffraction analysis disclosed that the Pd(II) complex **6** adopted a distorted square planar geometry with two nitrogen atoms occupying two adjacent positions and the remaining two positions in the slightly distorted square plane occupied by oxygen and phosphorus atom of a triphenylphosphine ligand and the central palladium ion coordinating with the ligand in a tridentate fashion to form two palladacyclic rings. The crystal structure of **6** is linked by C–H $\cdots$ N and C–H $\cdots$ O intermolecular interactions and stabilized by C–H $\cdots$ π van der Waals interactions, divulging a fascinating supramolecular architecture in the crystal lattice. Hirshfeld surface analysis and 2D fingerprint plots reveal H $\cdots$ H (54.4 %) as contributing more than half of the total interactions on the Hirshfeld surface. The Pd(II) complex **6** induced cell cytotoxicity in DL cells through apoptotic cell death as revealed by the fluorescence-based dual staining method. The corresponding decrease in body weight, as well as tumour volume and simultaneous increase

Chapter 3

in a life span of tumor-bearing mice, further support the anticancer activity of said complex in a murine model. Interestingly, the *in silico* docking study reflects the interaction of the Pd(II) complex **6** with the TNF proteins, which further confirms their possible inhibition leading to apoptotic cell death.

3.5 Experimental

Materials and physical measurements

All chemicals were reagent grade, obtained from commercial sources, and used without purification. The solvents were purified by standard procedures. Benzil bis(pyridyl hydrazone) ligand **5** was prepared according to the procedure reported earlier [75, 76]. Fourier Transform Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer with KBr pellets in the range of 4000–500 cm^{-1} . NMR spectra were recorded on a Bruker Advance II spectrometer using the residual protic solvent resonance as the internal standard, and chemical shifts were expressed in ppm. Elemental analysis was carried out in a Perkin Elmer 2500 series II elemental analyzer. UV-Vis spectra were recorded on a Perkin Elmer model Lambda [78].

3.5.1. Synthesis of Benzil bis (pyridyl hydrazone) ligand **5** and Pd(II) complex **6**

Synthesis of the ligand **5**

A solution of benzil (1.1 g, 5 mmol) in 15 ml in ethanol was added to 20 mL of ethanolic solution of isonicotinoyl hydrazide (1.4 g, 10 mmol) along with the addition of a few drops of conc. HCl. The resulting yellow-coloured solution was stirred for 1 hour and then refluxed for a further 4 hours. When cooled to room temperature, a colourless precipitate was formed. The resultant product was filtered off and washed with ethanol (20 mL $\times$ 3) and chloroform (20 mL $\times$ 3), dried and collected. Yield: 1.6 g, 72%,

Synthesis of the Pd(II) complex **6**

A colourless solution of the ligand H_2L (0.3 mmol) dissolved in 10 mL CH_3OH was added dropwise to an orange-red coloured solution of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.3 mmol) in CH_3OH (10 mL) with stirring. After that, the reaction mixture was refluxed for 4 hours. The reddish-yellow reaction mixture was then stirred for an additional two hours at room temperature. The resultant yellow product was filtered off, washed with 5 mL of methanol, and dried in air. The Pd(II)

Chapter 3

complex was then dissolved in a saturated solution of methanol, and slow evaporation of the methanol solution yielded single crystals of **6**, suitable for X-ray diffraction analysis.

Complex 6: Yield: 78%, ^1H NMR (CDCl_3 , δ in ppm): 7.71-7.75 (m, 14H), 7.38-7.46 (m, 24H). ^{13}C NMR (CDCl_3 , δ in ppm): 123.67, 128.03, 128.08, 128.14, 128.48, 129.35, 129.59, 129.72, 129.78, 129.84, 130.39, 130.54, 134.77, 134.99, 135.05, 135.12, 149.46. FT IR (ν cm^{-1} , KBr): 3244 and 3172 [$\nu(\text{N-H})$ asymmetric and symmetric stretching modes], 3075-3049 ($\nu\text{C-H}$ stretching), 1684 [$\nu(\text{C=O})$ stretching], 1658 ($\nu\text{N-H}$ bending scissoring vibration), 1097 [$\nu(\text{C-O})$ absorption band], 520 [$\nu(\text{Pd-N})$ band], 506 [$\nu(\text{Pd-O})$ band]. *Anal.* Calc. for $\text{C}_{44}\text{H}_{33}\text{N}_6\text{O}_2\text{PPd}$: C, 64.83; H, 4.08; N, 10.31. Found: C, 64.81; H, 4.05; N, 10.33 %.

3.5.2. X-ray Crystal Structure Determination of 6

A bright yellow single crystal of the Pd(II) complex, $\text{C}_{44}\text{H}_{33}\text{N}_6\text{O}_2\text{PPd}$ **6**, suitable for X-ray diffraction analysis was selected, and the data were collected on a Bruker APEX-II diffractometer. The crystal was kept at 100(2) K during data collection. The molecular structure diagrams were generated with Olex2 Draw [118] with displacement ellipsoids at 50% probabilities **Fig.3.8** The structure was solved with ShelXT [119] employing the dual space method and refined with the SHELXL [120] using Least Squares minimization. The crystal refinement parameters are presented in **Table 3.6**. Hirshfeld surfaces (HSs) mapped over d -norm, shape index, and curvedness, 2-D fingerprint plots were used to analyse the non-covalent interactions in the molecule [121, 122].

3.5.3. Cytotoxicity and apoptosis assays of 5 and 6

To evaluate the antiproliferative and cytotoxic potential of benzil bis(pyridyl hydrazone) ligand **5** and Pd(II) complex **6**, Trypan blue exclusion experiment was carried out in DL cancer cell line [123]. Various concentrations (0, 0.01, 0.1, 0.5, 1, 5, and 10 M) were used to study potential cytotoxicity on 96 cell culture plates (Thermo Scientific, Cat. No: 265301). After 48 h of *in vitro* treatment in suitable culture media, the IC_{50} value was determined using the dose-response non-linear curve fitting approach [124]. The non-linear curve fitting function used to get the IC_{50} (50% inhibition) was as follows:

$$y = A1 + (A2-A1)/(1 + 10^{((\text{LOG}x_0-x)*p)})$$

(Where, A1 = bottom asymptote, A2 = top asymptote, $\text{LOG}x_0$ = center and p = hill slope).

Chapter 3

To further support the cytotoxicity results, an apoptosis assay was conducted after 48 hours of *in vitro* treatment. To differentiate between viable and apoptotic cells, the treated cell populations were stained with AO/EB (Sigma, St. Louis, MO, USA) for 3 minutes in the ambient condition. Apoptotic cells appear red/orange under a fluorescence microscope. However, healthy cells appear green [125]. Finally, 1000 cells were counted considering multiple view fields from each experimental group ($n=3$) to assess the percentage of apoptotic cells.

3.5.4. Survivability study

DL cells were maintained *in vivo* in Swiss albino mice by intraperitoneal administration. When transferring the tumour cells to the grouped animals, the DL cells were aspirated from the peritoneal cavity of the mice by using saline. The cells were counted and further diluted so that the total cells would be 1×10^6 /mouse. This dilution was given intraperitoneally. The study was conducted after obtaining clearance from the Institutional Animal Ethical Committee, Cotton University (Protocol. No. CU/IAEC/AKV/21/2012). The mice were segregated based on their gender and acclimatized for 15 days before the commencement of the experiment.

The animals were divided into four groups ($n = 10$). All the groups received 0.1 mL cell suspension of the DL tumor cell line (1×10^6 cells/mouse, i.p.). This was considered as day '0'.. The first group served as a control, which received drug vehicle 0.1mL (i.p.). The second group served as the DL tumour cell line positive control received and standard drug cisplatin (2 mg/kg body weight, i.p.). The third group received the benzil bis(pyridyl hydrazone) ligand **5** (20 mg/kg body weight, i.p.). The fourth group received Pd(II) complex **6** (20 mg/kg body weight, i.p.). All the treatment was given for five consecutive days. The doses of synthesized compounds were selected based on the LD50 value (data not shown). After treatment, the animals of each group were kept with food and water *ad libitum*, to check for an increase in lifespan of the mice [126]. The effects of benzil bis(pyridyl hydrazone) ligand **5** and its Pd(II) complex **6** on tumour growth was assessed by observation of body weight, tumour volume, and percent increase in lifespan.

Percentage increase in lifespan (ILS) was calculated by the formula:

$$\% \text{ ILS} = (\text{Lifespan of treated group})/(\text{Lifespan of control group}) - 1 \times 100.$$

Chapter 3

3.5.5 Theoretical methodology of 6

Geometry optimization of Pd(II)-complex **6** was performed using Gaussian 09 package [127], based on density functional theory (DFT). B3LYP hybrid functional with 6-31G(d) basis set for the non-metals (C,N, P,O, and H) and LANL2DZ basis set with effective core potential was used for metal, Pd. To understand the solvent effect, Polarizable Continuum Model (PCM) [128, 129] with implicit solvent effect (chloroform) were applied during geometry optimization and also the time-dependent density functional theory (TD-DFT) calculations were performed by considering 30 singlet excitations. To further corroborate the cytotoxicity (in vitro) and antitumor study (in vivo), an in silico molecular interactions study was performed between Pd(II)-complex **6** and Mouse Tumor Necrosis Factor (PDB ID: 2TNF) using AutoDock4 [130] software following Lamarkian Genetic algorithm. Tumor necrosis factor (TNF) is a multifunctional cytokine involved in a variety of biological activities including cell survival, proliferation, differentiation, and death. TNF, a pro-inflammatory cytokine, is released by inflammatory cells and is reported to be involved in inflammation-mediated carcinogenesis [131]. TNF is also considered a two-edged sword that can be pro- or anti-tumorigenic. In mice with pancreatic tumours, inhibiting TNF using the monoclonal antibody infliximab or recombinant human soluble TNFR-2 had a substantial antitumoral impact [114]. Infliximab and etanercept both produced sustained disease stabilization in patients with metastatic breast cancer, recurrent ovarian cancer, or immunotherapy-resistant or refractory renal cell carcinoma in phase I and II clinical trials [115, 132]. In addition, TNF neutralization dramatically reduced the development of malignant pleural effusion in mice.

Chapter 3

3.6 References

- [1] Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 74(3), 229-263.
- [2] Filho, A. M., Laversanne, M., Ferlay, J., Colombet, M., Piñeros, M., Znaor, A., ... & Bray, F. (2024). The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. *International Journal of Cancer*.
- [3] Cao, W., Qin, K., Li, F., & Chen, W. (2024). Comparative study of cancer profiles between 2020 and 2022 using global cancer statistics (GLOBOCAN). *Journal of the National Cancer Center*.
- [4] Bizuayehu, H. M., Dadi, A. F., Ahmed, K. Y., Tegegne, T. K., Hassen, T. A., Kibret, G. D., ... & Belachew, S. A. (2024). Burden of 30 cancers among men: Global statistics in 2022 and projections for 2050 using population-based estimates. *Cancer*.
- [5] Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., ... & de la Lastra, J. M. P. (2023). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases*, 10(4), 1367-1401.
- [6] W.H. Organization, Latest global cancer data: cancer burden rises to 19.3 million new cases and 10.0 million cancer deaths in 2020, Questions and Answers (Q&A). Available online: <https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa/> (accessed on 12 December 2021), (2020).
- [7] DeVita Jr, V. T., & Chu, E. (2008). A history of cancer chemotherapy. *Cancer research*, 68(21), 8643-8653
- [8] Kumar, R. S., Arunachalam, S., Periasamy, V. S., Preethy, C. P., Riyasdeen, A., & Akbarsha, M. A. (2009). Surfactant–cobalt (III) complexes: synthesis, critical micelle concentration (CMC) determination, DNA binding, antimicrobial and cytotoxicity studies. *Journal of Inorganic Biochemistry*, 103(1), 117-127.
- [9] Zhang, C., Xu, C., Gao, X., & Yao, Q. (2022). Platinum-based drugs for cancer therapy and anti-tumor strategies. *Theranostics*, 12(5), 2115.
- [10] Florea, A. M., & Büsselberg, D. (2011). Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers*, 3(1), 1351-1371.
- .
- [11] Shah, N., & Dizon, D. S. (2009). New-generation platinum agents for solid tumors. *Future Oncology*, 5(1), 33-42.

Chapter 3

- [12] Zhang, Q., Zhong, W., Xing, B., Tang, W., & Chen, Y. (1998). Binding properties and stoichiometries of a palladium (II) complex to metallothioneins in vivo and in vitro. *Journal of inorganic biochemistry*, 72(3-4), 195-200.
- [13] Kasparkova, J., Zehnulova, J., Farrell, N., & Brabec, V. (2002). DNA interstrand cross-links of the novel antitumor trinuclear platinum complex BBR3464: conformation, recognition by high mobility group domain proteins, and nucleotide excision repair. *Journal of Biological Chemistry*, 277(50), 48076-48086.
- [14] Mansouri-Torshizi, H., Saeidifar, M., Divsalar, A., & Saboury, A. A. (2011). Binding studies of a novel antitumor palladium (II) complex to calf thymus DNA. *Nucleosides, Nucleotides and Nucleic Acids*, 30(6), 405-422.
- [15] Chen, D., Milacic, V., Frezza, M., & Dou, Q. P. (2009). Metal complexes, their cellular targets and potential for cancer therapy. *Current pharmaceutical design*, 15(7), 777-791.
- [16] Alderden, R. A., Hall, M. D., & Hambley, T. W. (2006). The discovery and development of cisplatin. *Journal of chemical education*, 83(5), 728.
- [17] Spiro, T. G. (1980). Nucleic acid-metal ion interactions. (*No Title*).
- [18] Chen, D., Milacic, V., Frezza, M., & Dou, Q. P. (2009). Metal complexes, their cellular targets and potential for cancer therapy. *Current pharmaceutical design*, 15(7), 777-791.
- [19] Lebwohl, D., & Canetta, R. (1998). Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. *European journal of cancer*, 34(10), 1522-1534.
- [20] Olszewski, U., & Hamilton, G. (2010). A better platinum-based anticancer drug yet to come?. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, 10(4), 293-301.
- [21] Divsalar, A., Saboury, A. A., Mansoori-Torshizi, H., & Ahmad, F. (2010). Design, synthesis, and biological evaluation of a new palladium (II) complex: β -lactoglobulin and K562 as targets. *The journal of physical chemistry B*, 114(10), 3639-3647.
- [22] Lippert, B. (Ed.). (1999). *Cisplatin: chemistry and biochemistry of a leading anticancer drug*. John Wiley & Sons.
- [23] Rocha, F. V., Barra, C. V., Netto, A. V. D. G., Mauro, A. E., Carlos, I. Z., Frem, R. C. G., ... & da Rocha, M. (2010). 3, 5-Dimethyl-1-thiocarbamoylpyrazole and its Pd (II) complexes: synthesis, spectral studies and antitumor activity. *European journal of medicinal chemistry*, 45(5), 1698-1702.
- [24] Wang, D., & Lippard, S. J. (2005). Cellular processing of platinum anticancer drugs. *Nature reviews Drug discovery*, 4(4), 307-320.

Chapter 3

- [25] Tummala, R., Diegelman, P., Fiuza, S. M., Batista de Carvalho, L. A., Marques, M. P. M., Kramer, D. L., ... & Pendyala, L. (2010). Characterization of Pt-, Pd-spermine complexes for their effect on polyamine pathway and cisplatin resistance in A2780 ovarian carcinoma cells. *Oncology reports*, 24(1), 15-24.
- [26] Divsalar, A., Saboury, A. A., Yousefi, R., Moosavi-Movahedi, A. A., & Mansoori-Torshizi, H. (2007). Spectroscopic and cytotoxic studies of the novel designed palladium (II) complexes: β -Lactoglobulin and K562 as the targets. *International Journal of Biological Macromolecules*, 40(4), 381-386.
- [27] Divsalar, A., Bagheri, M. J., Saboury, A. A., Mansoori-Torshizi, H., & Amani, M. (2009). Investigation on the interaction of newly designed anticancer Pd (II) complexes with different aliphatic tails and human serum albumin. *The journal of physical chemistry B*, 113(42), 14035-14042.
- [28] Kostova, I. (2006). Platinum complexes as anticancer agents. *Recent patents on anti-cancer drug discovery*, 1(1), 1-22.
- [29] Ghani, N. T. A., & Mansour, A. M. (2011). Novel Pd (II) and Pt (II) complexes of N, N-donor benzimidazole ligand: Synthesis, spectral, electrochemical, DFT studies and evaluation of biological activity. *Inorganica Chimica Acta*, 373(1), 249-258.
- [30] Dorr, R. T. (1996). A review of the modulation of cisplatin toxicities by chemoprotectants. *Platinum and other metal coordination compounds in cancer chemotherapy* 2, 131-154.
- [31] Mansouri-Torshizi, H., Moghaddam, M. I., Divsalar, A., & Saboury, A. A. (2009). Diimine platinum (II) and palladium (II) complexes of dithiocarbamate derivative as potential antitumor agents: synthesis, characterization, cytotoxicity, and detail DNA-binding studies. *Journal of Biomolecular Structure and Dynamics*, 26(5), 575-586.
- [32] Tsang, R. Y., Al-Fayea, T., & Au, H. J. (2009). Cisplatin overdose: toxicities and management. *Drug safety*, 32, 1109-1122.
- [33] Budzisz, E., Krajewska, U., Rozalski, M., Szulawska, A., Czyz, M., & Nawrot, B. (2004). Biological evaluation of novel Pt (II) and Pd (II) complexes with pyrazole-containing ligands. *European journal of pharmacology*, 502(1-2), 59-65.
- [34] Brudzińska, I., Mikata, Y., Obata, M., Ohtsuki, C., & Yano, S. (2004). Synthesis, structural characterization, and antitumor activity of palladium (II) complexes containing a sugar unit. *Bioorganic & medicinal chemistry letters*, 14(10), 2533-2536.

Chapter 3

- [35] Yan, L., Wang, X., Wang, Y., Zhang, Y., Li, Y., & Guo, Z. (2012). Cytotoxic palladium (II) complexes of 8-aminoquinoline derivatives and the interaction with human serum albumin. *Journal of inorganic biochemistry*, 106(1), 46-51.
- [36] Moro, A. C., Mauro, A. E., Netto, A. V., Ananias, S. R., Quilles, M. B., Carlos, I. Z., ... & Hörner, M. (2009). Antitumor and antimycobacterial activities of cyclopalladated complexes: X-ray structure of [Pd (C2, N-dmba)(Br)(tu)](dmba= N, N-dimethylbenzylamine, tu= thiourea). *European Journal of Medicinal Chemistry*, 44(11), 4611-4615.
- [37] Divsalar, A., Saboury, A. A., Mansoori-Torshizi, H., Moghaddam, M. I., Ahmad, F., & Hakimelahi, G. H. (2009). Comparative studies on the interaction between bovine β -lactoglobulin type a and B and a new designed Pd (II) complex with anti-tumor activity at different temperatures. *Journal of Biomolecular Structure and Dynamics*, 26(5), 587-597.
- [38] Ahmad, S., Isab, A. A., & Ali, S. (2006). Structural and mechanistic aspects of platinum anticancer agents. *Transition Metal Chemistry*, 31(8), 1003-1016.
- [39] Ahmad, S. (2010). Platinum–DNA interactions and subsequent cellular processes controlling sensitivity to anticancer platinum complexes. *Chemistry & biodiversity*, 7(3), 543-566.
- [40] Wong, E., & Giandomenico, C. M. (1999). Current status of platinum-based antitumor drugs. *Chemical reviews*, 99(9), 2451-2466.
- [41] Jahromi, E. Z., Divsalar, A., Saboury, A. A., Khaleghizadeh, S., Mansouri-Torshizi, H., & Kostova, I. (2016). Palladium complexes: new candidates for anti-cancer drugs. *Journal of the Iranian Chemical Society*, 13, 967-989.
- [42] Ghani, N. T. A., & Mansour, A. M. (2011). Novel Pd (II) and Pt (II) complexes of N, N-donor benzimidazole ligand: Synthesis, spectral, electrochemical, DFT studies and evaluation of biological activity. *Inorganica Chimica Acta*, 373(1), 249-258.
- [43] Kapdi, A. R., & Fairlamb, I. J. (2014). Anti-cancer palladium complexes: a focus on PdX₂L₂, palladacycles and related complexes. *Chemical Society Reviews*, 43(13), 4751-4777.
- [44] Czarnomysy, R., Radomska, D., Szewczyk, O. K., Roszczenko, P., & Bielawski, K. (2021). Platinum and palladium complexes as promising sources for antitumor treatments. *International journal of molecular sciences*, 22(15), 8271.
- [45] Lazarević, T., Rilak, A., & Bugarčić, Ž. D. (2017). Platinum, palladium, gold and ruthenium complexes as anticancer agents: Current clinical uses, cytotoxicity studies and future perspectives. *European journal of medicinal chemistry*, 142, 8-31.
- [46] Butour, J. L., Wimmer, S., Wimmer, F., & Castan, P. (1997). Palladium (II) compounds with potential antitumour properties and their platinum analogues: a comparative study of the

Chapter 3

reaction of some orotic acid derivatives with DNA in vitro. *Chemico-Biological Interactions*, 104(2-3), 165-178.

[47] Das, M., & Livingstone, S. E. (1978). Cytotoxic action of some transition metal chelates of Schiff bases derived from S-methyldithiocarbamate. *British journal of cancer*, 37(3), 466.

[48] Carneiro, T. J., Martins, A. S., Marques, M. P. M., & Gil, A. M. (2020). Metabolic aspects of palladium (II) potential anti-cancer drugs. *Frontiers in oncology*, 10, 590970.

[49] Vojtek, M., Marques, M. P., Ferreira, I. M., Mota-Filipe, H., & Diniz, C. (2019). Anticancer activity of palladium-based complexes against triple-negative breast cancer. *Drug Discovery Today*, 24(4), 1044-1058.

[50] Tookad, European Medicines Agency. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/tookad>., European Medicines Agency. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/tookad>.

[51] Gao, E., Liu, C., Zhu, M., Lin, H., Wu, Q., & Liu, L. (2009). Current development of Pd (II) complexes as potential antitumor agents. *Anti-Cancer Agents in Medicinal Chemistry (Formerly current medicinal chemistry-anti-cancer agents)*, 9(3), 356-368.

[52] Kuduk-Jaworska, J., Puszko, A., Kubiak, M., & Pełczyńska, M. (2004). Synthesis, structural, physico-chemical and biological properties of new palladium (II) complexes with 2, 6-dimethyl-4-nitropyridine. *Journal of inorganic biochemistry*, 98(8), 1447-1456.

[53] Messere, A., Fabbri, E., Borgatti, M., Gambari, R., Di Blasio, B., Pedone, C., & Romanelli, A. (2007). Antiproliferative activity of Pt (II) and Pd (II) phosphine complexes with thymine and thymidine. *Journal of inorganic biochemistry*, 101(2), 254-260.

[54] Saeidfar, M., Masouri-Torshizi, H., Behbehani, G. R., Divsalar, A., & Saboury, A. A. (2009). A thermodynamic study of new designed complex of ethylenediamine 8-hydroxyquinolinato palladium (II) chloride with calf thymus DNA. *Bulletin of the Korean Chemical Society*, 30(9), 1951-1955.

[55] Nadeem, S., Bolte, M., Ahmad, S., Fazeelat, T., Tirmizi, S. A., Rauf, M. K., ... & Haider, S. Z. (2010). Synthesis, crystal structures and, antibacterial and antiproliferative activities in vitro of palladium (II) complexes of triphenylphosphine and thioamides. *Inorganica Chimica Acta*, 363(13), 3261-3269.

[56] Tušek-Božić, L., Juribašić, M., Traldi, P., Scarcia, V., & Furlani, A. (2008). Synthesis, characterization and antitumor activity of palladium (II) complexes of monoethyl 8-quinolylmethylphosphonate. *Polyhedron*, 27(4), 1317-1328.

[57] Juribašić, M., Molčanov, K., Kojić-Prodić, B., Bellotto, L., Kralj, M., Zani, F., & Tušek-Božić, L. (2011). Palladium (II) complexes of quinolinyaminophosphonates: Synthesis,

Chapter 3

structural characterization, antitumor and antimicrobial activity. *Journal of inorganic biochemistry*, 105(6), 867-879.

[58] Abu-Surrah, A. S., Al-Sa'doni, H. H., & Abdalla, M. Y. (2008). Palladium-based chemotherapeutic agents: Routes toward complexes with good antitumor activity. *Cancer Ther*, 6(1), 1-10.

[59] Tušek-Božić, L., Matijašić, I., Bocelli, G., Calestani, G., Furlani, A., Scarcia, V., & Papaioannou, A. (1991). Preparation, characterization and activity of palladium (II) halide complexes with diethyl 2-quinolylmethylphosphonate (2-dqmp). X-ray crystal structures of trans-[Pd (2-dqmp) 2X₂](X= Cl or Br). *Journal of the Chemical Society, Dalton Transactions*, (2), 195-201.

[60] Onoa, G. B., Cervantes, G., Moreno, V., & Prieto, M. J. (1998). Study of the interaction of DNA with cisplatin and other Pd (II) and Pt (II) complexes by atomic force microscopy. *Nucleic Acids Research*, 26(6), 1473-1480.

[61] Johnstone, T. C., Suntharalingam, K., & Lippard, S. J. (2016). The next generation of platinum drugs: targeted Pt (II) agents, nanoparticle delivery, and Pt (IV) prodrugs. *Chemical reviews*, 116(5), 3436-3486.

[62] El-Boraey, H. A. (2012). Coordination behavior of tetraaza [N₄] ligand towards Co (II), Ni (II), Cu (II), Cu (I) and Pd (II) complexes: synthesis, spectroscopic characterization and anticancer activity. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 97, 255-262.

[63] Al-Noaimi, M., Abu-Surrah, A. S., & Tahtamouni, L. (2016). Palladium (II) complexes incorporating phenylazo arylmethine ancillary ligands: Synthesis, spectral and antitumor activity. *Arabian Journal of Chemistry*, 9, S1503-S1509.

[64] Kurpik, G., Walczak, A., Gołdyn, M., Harrowfield, J., & Stefankiewicz, A. R. (2022). Pd (II) complexes with pyridine ligands: substituent effects on the NMR data, crystal structures, and catalytic activity. *Inorganic Chemistry*, 61(35), 14019-14029.

[65] Zhao, G., Lin, H., Ping, Y., Sun, H., Zhu, S., Xuncheng, S., & Chen, Y. (1999). Ethylenediamine-palladium (II) complexes with pyridine and its derivatives: synthesis, molecular structure and initial antitumor studies. *Journal of inorganic biochemistry*, 73(3), 145-149.

[66] Karami, K., Sadeghi-Aliabadi, H., Lipkowski, J., & Mirian, M. (2013). Dinuclear bridged biphosphinic and mononuclear cyclopalladated complexes of benzylamines: Synthesis, structural characterization and antitumor activity. *Polyhedron*, 50(1), 187-192.

Chapter 3

- [67] Ali, M. A., Mirza, A. H., Butcher, R. J., Tarafder, M. T. H., Keat, T. B., & Ali, A. M. (2002). Biological activity of palladium (II) and platinum (II) complexes of the acetone Schiff bases of S-methyl-and S-benzylthiocarbamate and the X-ray crystal structure of the [Pd (asme)₂](asme= anionic form of the acetone Schiff base of S-methylthiocarbamate) complex. *Journal of Inorganic Biochemistry*, 92(3-4), 141-148.
- [68] Ghani, N. T. A., & Mansour, A. M. (2012). Novel palladium (II) and platinum (II) complexes with 1H-benzimidazol-2-ylmethyl-N-(4-bromo-phenyl)-amine: Structural studies and anticancer activity. *European journal of medicinal chemistry*, 47, 399-411.
- [69] Adhikari, S., Kar, D., Fröhlich, R., & Ghosh, K. (2019). Pyridine-Based Macrocyclic and Open Receptors for Urea. *ChemistrySelect*, 4(44), 12825-12831.
- [70] Park, I. W., Yoo, J., Adhikari, S., Park, J. S., Sessler, J. L., & Lee, C. H. (2012). Calix [4] pyrrole-based heteroditopic ion-pair receptor that displays anion-modulated, cation-binding behavior. *Chemistry—A European Journal*, 18(47), 15073-15078.
- [71] Ghosh, K., Adhikari, S., Fröhlich, R., Petsalakis, I. D., & Theodorakopoulos, G. (2011). Experimental and theoretical anion binding studies on coumarin linked thiourea and urea molecules. *Journal of Molecular Structure*, 1004(1-3), 193-203.
- [72] Ghosh, K., & Adhikari, S. (2006). Fluorescence sensing of tartaric acid: a case of excimer emission caused by hydrogen bond-mediated complexation. *Tetrahedron letters*, 47(21), 3577-3581.
- [73] Park, I. W., Yoo, J., Kim, B., Adhikari, S., Kim, S. K., Yeon, Y., ... & Lee, C. H. (2012). Oligoether-Strapped Calix [4] pyrrole: An Ion-Pair Receptor Displaying Cation-Dependent Chloride Anion Transport. *Chemistry—A European Journal*, 18(9), 2514-2523.
- [74] Ghosh, K., Adhikari, S., Chattopadhyay, A. P., & Chowdhury, P. R. (2008). Quinoline based receptor in fluorometric discrimination of carboxylic acids. *Beilstein Journal of Organic Chemistry*, 4(1), 52.
- [75] Hassanien, M. M., Mortada, W. I., & Kenawy, I. M. (2015). Selective separation of palladium from synthetic highly active liquid waste by cloud point extraction using benzil mono-(2-pyridyl) hydrazone and Triton X-114. *Journal of Radioanalytical and Nuclear Chemistry*, 303, 261-269.
- [76] Sethi, S., Panigrahi, R., Paul, A. K., Mallik, B. S., Parhi, P., Das, P. K., & Behera, N. (2020). Detailed characterization of dioxouranium (vi) complexes with a symmetrical tetradentate N₂O₂-benzil bis (isonicotinoyl hydrazone) ligand. *Dalton Transactions*, 49(30), 10603-10612.

Chapter 3

- [77] López-Torres, E., & Mendiola, M. A. (2009). Structural diversity of benzil bis (benzoylhydrazone): Mononuclear, binuclear and trinuclear complexes. *Dalton Transactions*, (37), 7639-7647.
- [78] Karmakar, T. K., Chandra, S. K., Ribas, J., Mostafa, G., Lu, T. H., & Ghosh, B. K. (2002). Synthesis, structure and magnetism of a new dicubane-like ferromagnetic tetranuclear nickel cluster containing versatile azido-only bridges and a bis (bidentate) Schiff base blocker. *Chemical communications*, (20), 2364-2365.
- [79] Naskar, S., Mishra, D., Chattopadhyay, S. K., Corbella, M., & Blake, A. J. (2005). Versatility of 2, 6-diacetylpyridine (dap) hydrazones in stabilizing uncommon coordination geometries of Mn (II): synthesis, spectroscopic, magnetic and structural characterization. *Dalton Transactions*, (14), 2428-2435.
- [80] Mukherjee, A., Dutta, A., Jana, A. D., & Patra, G. K. (2013). Copper (I) and silver (I) coordination assemblies of imino-pyridyl and azino-pyridyl ligands: Syntheses, crystal structures, spectroscopic and photophysical properties. *Inorganica Chimica Acta*, 404, 131-143.
- [81] Shakhdofo, M. M., Shtaiwi, M. H., Morsy, N., & Abdel-rassel, T. (2014). Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review. *Main Group Chemistry*, 13(3), 187-218.
- [82] Subarkhan, M. K. M., Ren, L., Xie, B., Chen, C., Wang, Y., & Wang, H. (2019). Novel tetranuclear ruthenium (II) arene complexes showing potent cytotoxic and antimetastatic activity as well as low toxicity in vivo. *European journal of medicinal chemistry*, 179, 246-256.
- [83] Kasim, M. S. M., Sundar, S., & Rengan, R. (2018). Synthesis and structure of new binuclear ruthenium (II) arene benzil bis (benzoylhydrazone) complexes: investigation on antiproliferative activity and apoptosis induction. *Inorganic chemistry frontiers*, 5(3), 585-596.
- [84] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Acharya, S., ... & Frontera, A. (2018). Mixed-ligand complexes of zinc (II) with 1, 1-dicyanoethylene-2, 2-dithiolate and N-donor ligands: A combined experimental and theoretical study. *Journal of Molecular Structure*, 1164, 334-343.
- [85] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Butcher, R. J., ... & Das, A. (2017). A new cadmium (II) complex with bridging dithiolate ligand: Synthesis, crystal structure and antifungal activity study. *Journal of Molecular Structure*, 1139, 395-399.
- [86] Adhikari, S., Bhattacharjee, T., Nath, P., Das, A., Jasinski, J. P., Butcher, R. J., & Maiti, D. (2020). Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-

Chapter 3

dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study. *Inorganica Chimica Acta*, 512, 119877.

[87] Adhikari, S., Bhattacharjee, T., Butcher, R. J., Porchia, M., De Franco, M., Marzano, C., ... & Tisato, F. (2019). Synthesis and characterization of mixed-ligand Zn (II) and Cu (II) complexes including polyamines and dicyano-dithiolate (2-): In vitro cytotoxic activity of Cu (II) compounds. *Inorganica Chimica Acta*, 498, 119098.

[88] Adhikari, S., Bhattacharjee, T., Das, A., Roy, S., Daniliuc, C. G., Zaręba, J. K., ... & Frontera, A. (2020). On the supramolecular properties of neutral, anionic and cationic cadmium complexes harvested from dithiolate–polyamine binary ligand systems. *CrystEngComm*, 22(46), 8023-8035.

[89] Bhattacharjee, T., Adhikari, S., & Butcher, R. J. (2022). Supramolecular Properties Directed by Weak Interactions in a Copper (II) Complex Based on 8-Hydroxy Quinoline-Pyridine Binary Ligand Systems: Crystal Structure and Hirshfeld Surface Analyses. *Journal of Chemical Crystallography*, 422-433.

[90] Bhattacharjee, T., Adhikari, S., Datta, A., Daniliuc, C. G., Montazerzohori, M., Naghiha, R., & Hayati, P. (2022). Cadmium (II) coordination polymer based on flexible dithiolate-polyamine binary ligands system: crystal structure, Hirshfeld surface analysis, antimicrobial, and DNA cleavage potential. *Polyhedron*, 211, 115544.

[91] Bhattacharjee, T., Adhikari, S., Bhattacharjee, S., Debnath, S., Das, A., Daniliuc, C. G., ... & Frontera, A. (2022). Exploring dithiolate-amine binary ligand systems for the supramolecular assemblies of Ni (II) coordination compounds: Crystal structures, theoretical studies, cytotoxicity studies, and molecular docking studies. *Inorganica Chimica Acta*, 543, 121157.

[92] Bhattacharjee, T., Adhikari, S., Sheikh, A. H., Mahmoudi, G., Mlowe, S., Akerman, M. P., ... & Saygideger, Y. (2022). Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthalimine and its Ni (II) complex. *Journal of Molecular Structure*, 1269, 133717.

[93] S. Kandır, Handbook of Animal Models and its Uses in Cancer Research, (2022).

[94] Adhikari, S., Bhattacharjee, T., Nath, P., Das, A., Jasinski, J. P., Butcher, R. J., & Maiti, D. (2020). Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study. *Inorganica Chimica Acta*, 512, 119877.

Chapter 3

- [95] De, S., Chowdhury, S., Tocher, D. A., & Datta, D. (2006). Molecular and supramolecular structures of benzil dihydrazone, an organic helical molecule. Comparison with diacetyl dihydrazone. *CrystEngComm*, 8(9), 670-673.
- [96] El-Adel, L., Ouasri, A., Zouihri, H., & Rhandour, A. (2019). Crystal structure, DSC, TGA, Hirshfeld and infrared study at ambient temperature of phenylammonium hexachlorobismuthate trihydrate $[C_6H_5NH_3] \cdot 3BiCl_6 \cdot 3H_2O$. *Journal of Molecular Structure*, 1188, 110-120.
- [97] Kumar, S., Kumar, B. C. V., & Revanasiddappa, H. D. (2019). Crystal structure, Hirshfeld analysis and HSA interaction studies of N'-[(E)-(5-bromothiophen-2-yl) methylidene]-3-hydroxynaphthalene-2-carbohydrazide. *Journal of Molecular Structure*, 1189, 343-351.
- [98] Yousuf, I., Usman, M., Ahmad, M., Tabassum, S., & Arjmand, F. (2018). Single X-ray crystal structure, DFT studies and topoisomerase I inhibition activity of a tailored ionic Ag (I) nalidixic acid–piperazinium drug entity specific for pancreatic cancer cells. *New Journal of Chemistry*, 42(1), 506-519.
- [99] Asegbeloyin, J. N., Ifeanyieze, K. J., Okpareke, O. C., Oyeka, E. E., & Groutso, T. V. (2019). Crystal structure and Hirshfeld surface analysis of a new dithioglycoluril: 1, 4-bis (4-methoxyphenyl)-3a-methyltetrahydroimidazo [4, 5-d] imidazole-2, 5 (1H, 3H)-dithione. *Acta Crystallographica Section E: Crystallographic Communications*, 75(9), 1297-1300.
- [100] Spackman, M. A., & Jayatilaka, D. (2009). Hirshfeld surface analysis. *CrystEngComm*, 11(1), 19-32
- [101] Tan, S. L., Jotani, M. M., & Tiekink, E. R. (2019). Utilizing Hirshfeld surface calculations, non-covalent interaction (NCI) plots and the calculation of interaction energies in the analysis of molecular packing. *Acta Crystallographica Section E: Crystallographic Communications*, 75(3), 308-318.
- [102] Tan, S. L., & Tiekink, E. R. (2020). Crystal structure, Hirshfeld surface analysis and computational study of the 1: 2 co-crystal formed between N, N'-bis (pyridin-4-ylmethyl) ethanediamide and 4-chlorobenzoic acid. *Acta Crystallographica Section E: Crystallographic Communications*, 76(2), 245-253.
- [103] Izuogu, D. C., Asegbeloyin, J. N., Jotani, M. M., & Tiekink, E. R. (2020). 2-[(2, 4, 6-Trimethylbenzene) sulfonyl] phthalazin-1 (2H)-one: crystal structure, Hirshfeld surface analysis and computational study. *Acta Crystallographica Section E: Crystallographic Communications*, 76(5), 697-702.
- [104] Ozochukwu, I. S., Okpareke, O. C., Izuogu, D. C., Ibezim, A., Ujam, O. T., & Asegbeloyin, J. N. (2021). N'-(Pyridin-3-ylmethylene) benzenesulfonohydrazide: Crystal

Chapter 3

structure, DFT, Hirshfeld surface and in silico anticancer studies. *European Journal of Chemistry*, 12(3), 256-264.

[105] Ifeanyieze, K. J., Ayiya, B. B., Okpareke, O. C., Groutso, T. V., & Asegbeloyin, J. N. (2022). Crystal structure, Hirshfeld surface and computational study of 1-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-3-propanoylthiourea. *Acta Crystallographica Section E: Crystallographic Communications*, 78(4), 439-444.

[106] Ekowo, L. C., Eze, S. I., Ezeorah, J. C., Groutso, T., Atiga, S., Lane, J. R., ... & Okparaeke, O. C. (2020). Synthesis, structure, Hirshfeld surface, DFT and in silico studies of 4-[(E)-(2, 5-dimethoxybenzylidene) amino]-1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one (DMAP) and its metal complexes. *Journal of Molecular Structure*, 1210, 127994.

[107] Tennant, J. R. (1964). Evaluation of the trypan blue technique for determination of cell viability. *Transplantation*, 2(6), 685-694.

[108] Altman, S. A., Randers, L., & Rao, G. (1993). Comparison of trypan blue dye exclusion and fluorometric assays for mammalian cell viability determinations. *Biotechnology progress*, 9(6), 671-674.

[109] Dijt, F. J., Fichtinger-Schepman, A. M. J., Berends, F., & Reedijk, J. (1988). Formation and repair of cisplatin-induced adducts to DNA in cultured normal and repair-deficient human fibroblasts. *Cancer research*, 48(21), 6058-6062.

[110] Prasad, S. B., & Verma, A. K. (2013). Cantharidin-mediated ultrastructural and biochemical changes in mitochondria lead to apoptosis and necrosis in murine Dalton's lymphoma. *Microscopy and microanalysis*, 19(6), 1377-1394.

[111] Das, A., Sharma, P., Gomila, R. M., Frontera, A., Verma, A. K., Sarma, B., & Bhattacharyya, M. K. (2022). Synthesis, structural topologies and anticancer evaluation of phenanthroline-based 2, 6-pyridinedicarboxylato Cu (II) and Ni (II) compounds. *Polyhedron*, 213, 115632.

[112] Koiri, R. K., Mehrotra, A., & Trigun, S. K. (2017). Dalton's lymphoma as a murine model for understanding the progression and development of t-cell lymphoma and its role in drug discovery. *Int j immunother cancer res*, 3(1), 1-6.

[113] Wang, X., & Lin, Y. (2008). Tumor necrosis factor and cancer, buddies or foes? 1. *Acta Pharmacologica Sinica*, 29(11), 1275-1288.

[114] Egberts, J. H., Cloosters, V., Noack, A., Schniewind, B., Thon, L., Klose, S., ... & Trauzold, A. (2008). Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis. *Cancer research*, 68(5), 1443-1450.

Chapter 3

- [115] Madhusudan, S., Foster, M., Muthuramalingam, S. R., Braybrooke, J. P., Wilner, S., Kaur, K., ... & Harris, A. L. (2004). A phase II study of etanercept (Enbrel), a tumor necrosis factor α inhibitor in patients with metastatic breast cancer. *Clinical Cancer Research*, 10(19), 6528-6534.
- [116] Harrison, M. L., DeWitte, M., Ahern, R., Li, N. F., Eisen, T., Chao, D., ... & Timotheadou, E. (2007). *Tumor necrosis factor alpha as a new target for renal cell carcinoma* (No. RefW-23-23955). Aristotle University of Thessaloniki.
- [117] Stathopoulos, G. T., Kollintza, A., Moschos, C., Psallidas, I., Sherrill, T. P., Pitsinos, E. N., ... & Kalomenidis, I. (2007). Tumor necrosis factor- α promotes malignant pleural effusion. *Cancer research*, 67(20), 9825-9834.
- [118] Sheldrick, G. M. (2009). SHELXL, University of Göttingen, Germany, 2014;(d) OV Dolomanov, LJ Bourhis, RJ Gildea, JAK Howard and H. Puschmann. *J. Appl. Crystallogr*, 42, 339-341.
- [119] Bourhis, L. J., Dolomanov, O. V., Gildea, R. J., Howard, J. A., & Puschmann, H. (2015). The anatomy of a comprehensive constrained, restrained refinement program for the modern computing environment—Olex2 dissected. *Acta Crystallographica Section A: Foundations and Advances*, 71(1), 59-75.
- [120] Sheldrick, G. M. (2013). SHELX2013, Programs for Crystal Structure Analysis. *Structure Determination (SHELXS) and ii. Refinement (SHELXL-2013)*, University of Göttingen, Germany.(b) Sheldrick, G. M. (2015). *Acta Crystallogr., Sect. A. Struct. Chem.*, 71, 3.
- [121] Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Spackman, P. R., Jayatilaka, D., & Spackman, M. A. (2017). *CrystalExplorer17*, University of Western Australia, 2017.
- [122] Tan, S. L., & Tiekink, E. R. (2019). A 1: 2 co-crystal of 2, 2'-dithiodibenzoic acid and benzoic acid: crystal structure, Hirshfeld surface analysis and computational study. *Acta Crystallographica Section E: Crystallographic Communications*, 75(1), 1-7.
- [123] Van Meerloo, J., Kaspers, G. J., & Cloos, J. (2011). Cell sensitivity assays: the MTT assay. *Cancer cell culture: methods and protocols*, 237-245.
- [124] Sharma, P., Baishya, T., Gomila, R. M., Frontera, A., Barcelo-Oliver, M., Verma, A. K., ... & Bhattacharyya, M. K. (2022). Structural topologies involving energetically significant antiparallel π -stacking and unconventional N (nitrile) $\cdots \pi$ (fumarate) contacts in dinuclear Zn (ii) and polymeric Mn (ii) compounds: antiproliferative evaluation and theoretical studies. *New Journal of Chemistry*, 46(11), 5296-5311.

Chapter 3

- [125] Verma, A. K., & Singh, S. (2020). Phytochemical analysis and in vitro cytostatic potential of ethnopharmacological important medicinal plants. *Toxicology Reports*, 7, 443-452.
- [126] Thavamani, B. S., Mathew, M., & Dhanabal, S. P. (2014). Anticancer activity of cissampelos pareira against dalton's lymphoma ascites bearing mice. *Pharmacognosy magazine*, 10(39), 200.
- [127] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., ... & Nakatsuji, H. (2009). Uranyl extraction by N, N-dialkylamide ligands studied by static and dynamic DFT simulations. In *Gaussian 09*. Gaussian Inc Wallingford.
- [128] Hartnett, P. E., Mauck, C. M., Harris, M. A., Young, R. M., Wu, Y. L., Marks, T. J., & Wasielewski, M. R. (2017). Influence of anion delocalization on electron transfer in a covalent porphyrin donor–perylene diimide dimer acceptor system. *Journal of the American Chemical Society*, 139(2), 749-756.
- [129] Tomasi, J., Mennucci, B., & Cammi, R. (2005). Quantum mechanical continuum solvation models. *Chemical reviews*, 105(8), 2999-3094.
- [130] Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, 30(16), 2785-2791.
- [131] Wang, X., & Lin, Y. (2008). Tumor necrosis factor and cancer, buddies or foes? 1. *Acta Pharmacologica Sinica*, 29(11), 1275-1288.
- [132] Harrison, M. L., Obermueller, E., Maisey, N. R., Hoare, S., Edmonds, K., Li, N. F., ... & Gore, M. (2007). Tumor necrosis factor α as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard and high dose. *Journal of Clinical Oncology*, 25(29), 4542-4549.



Supramolecular Co(II) Complexes Based on Dithiolate and Dicarboxylate Ligands: Crystal structures, Theoretical studies, Magnetic Properties, and Catalytic Activity Studies in Photocatalytic Hydrogen Evolution

Outline

This chapter describes the present work, related to the synthesis of two Co(II) coordination compounds based on dithiolate and dicarboxylate ligands. One novel compound consisting of two ([tris (2-aminoethyl) amine Co] 1,1-dicyano-2,2-ethylenedithiolate)⁺ per thiosulphate ion linked through intermolecular hydrogen bonds is synthesized. Another compound is (pyridine-2,6-dicarboxylate)₂Co·5H₂O·Co).2H₂O. Both of the compounds have been characterized by using FT-IR spectroscopy and single-crystal X-ray diffraction analysis. The supramolecular properties of both Co(II) complexes have been explored. Magnetic susceptibility measurements are carried out on both Co(II) complexes. The photocatalytic properties for the evolution of molecular hydrogen of both Co(II) complexes are also explored.

Chapter 4

4.1 Photocatalytic hydrogen evolution with cobalt-based complexes

The rapid rise of industrialization, urbanization, and the usage of carbon-based fuels has garnered much attention, due to energy shortages and environmental pollution from poisonous and dangerous chemical pollutants [1]. Fossil fuels have become an essential part of the global energy supply for generations because most of the world's electricity and transportation are provided by fossil fuels. This situation led to concerns about the greenhouse effect getting worse as a result of the atmosphere's rising of CO₂, which has caused several environmental issues [2-4]. Solar power must be converted into a system that can be stored, transported and consumed at a scale that minimizes global energy crises. The development of environmentally friendly and renewable energy sources that can take the place of conventional non-renewable ones has drawn a lot of interest from both academic and commercial purposes [5]. Hydrogen is considered a pollution-free energy source with a high energy density of 143kJg⁻¹ with high promise [6]. Furthermore, no secondary pollution is produced by it [7]. Therefore, hydrogen is considered a source of future energy that is a carbon-free, renewable, and environmentally friendly energy source [8]. Burning hydrogen, which produces the largest amount of energy per unit mass, produces water as waste. However, because of the absence of free form of hydrogen molecules in the atmosphere, the production of hydrogen needs a large input of energy [9]. Since molecular hydrogen burns virtually pollution-free, it is typically regarded as the perfect energy transporter [10-12]. Applying the transition metals of the first row of the periodic table that are sustainable and earth-abundant in place of precious noble metals to produce molecular systems with high turnover numbers (which implies the system's stability) as well as high turnover frequencies (which implies catalyst's efficient) is a key objective in the research arena of hydrogen production using sunlight. The development of an effective solar-powered hydrogen-generating device is now considered the "Holy Grail" of splitting water with solar power [13, 14]. Water splitting is very desirable since it stores 4.92 eV when two H₂O molecules split into 2H₂ + O₂. However, the reaction is difficult to conduct. It includes two different multi-electron redox processes: a 2-electron reduction and a 4-electron oxidation. Since successive electron or hole transfers directly to H₂O result in high-energy intermediates, catalysts that prevent the production of these species are necessary for an energy-efficient process. In certain situations, coordination with metals can stabilize these energetic intermediates, lessening the barriers to the development of hydrogen [36].

Three primary methods exist for producing H₂: The evolution of H₂ from water splitting, biofuels, and fossil fuels [15]. The most common methods of H₂ evolution from fossil fuels

Chapter 4

include coal vaporization, natural gas pyrolysis, heavy oil partial oxidation, and methane reforming. Methane reforming is a popular and economically feasible method for H₂ evolution. It does, however, utilize a lot of energy, and the CO₂ that is ultimately produced could have a greenhouse impact and cause health issues [16]. In biological H₂ evolution, organic matter is fermented, photosynthetic bacteria break down organic matter, biomass is pyrolyzed or gasified etc [17, 18]. The procedure has few negative environmental effects and is renewable. However, this method is expensive for producing H₂ on a large scale. Water splitting is an environmentally beneficial method that uses wastewater as the source of H₂. Photocatalytic and photoelectrocatalytic evolution of hydrogen are the two primary methods for the evolution of molecular hydrogen *via* photochemical reactions, depending on the reaction mechanism. Traditionally, turnover number (TON) is used to express the activity of the photocatalytic reactions, which compare the concentration of photosensitizers to the amount of molecular hydrogen generated throughout the experiment. Treatments with radiation of light as well as usage of photocatalysts as electrodes are employed by the photoelectrocatalytic approach. The photocatalytic evolution of molecular hydrogen is widely used because of its high efficiency.

In contrast, when solar energy is used in the photocatalytic process to split water molecules into molecular hydrogen using either a two- or four-electron mechanism, it can successfully prevent contamination of the environment and the need for additional energy [7]. There have been very few reports of completely noble-metal-free molecular devices that are efficient at producing H₂ when exposed to light [19]. Photocatalysts based on noble metal are expensive because of their low abundance in nature and thus have limited practical applications in the splitting of water. But photocatalysts based on non-noble metals such as cobalt and nickel are low-priced and highly effective and hence, they are highly attractive in the evolution of hydrogen *via* the splitting of water molecules. Furthermore, photocatalysts based on platinum which is also known as noble-metal-based photocatalysts, exhibit deactivation of platinum metal in the presence of chloride ions whereas the photocatalysts based on non-noble metals show high stability and thus do not exhibit any kind of deactivation in any particular environment. So, by applying the photocatalysts based on noble metals, water can be converted into molecular hydrogen. There are not many reports related to the evolution of molecular hydrogen *via* photocatalytic reactions using non-noble metal-based photocatalysts though they have several advantages [7]. Therefore, the aim of numerous significant scientific works is an attempt to split water molecules into molecular hydrogen and oxygen photocatalytically. Utilizing [CoCl(pyr)(dmgH)₂], (pyr = pyridine and dmgH = dimethylglyoximate anion) as photocatalyst with Eosin Y as the photosensitizer, in a system that was created and investigated

Chapter 4

after the first investigations of the cobalt-based complexes as a photocatalytic production of molecular hydrogen [20]. The system was significant since it showed more effectiveness compared to the earlier reports related to this catalyst and contained no elements of platinum group metals in its constituent parts. However, the overall system longevity was poor for H₂ generation, which stopped within 10 hours and may be extended with the addition of a dmgH ligand [21, 22]. The first-generation non-noble metal catalysts for the evolution of molecular hydrogen are [Co(bpy)₃]²⁺ and other compounds of cobalt with glyoximate ligands or its derivatives. It was suggested that the two essential processes for the synthesis of molecular hydrogen involve the creation of intermediates, Co(I) and Co(III)-H respectively [22]. The first square planar cobalt dimethylglyoxime complexes were developed by Schrauzer and Kohnle, with cyanide and pyridine groups occupying the axial coordination sites [23]. Wagner and Bernheimer developed a cobalt-alkyl derivative that mimicked the core of vitamin B₁₂ by substituting a Grignard reagent for the axial cyanide group [24]. The cobalt dimethylglyoxime [Co(dmgH)₂] molecule was later referred to as "cobaloxime." Though the cobaloxime complex was initially discovered to mimic the vitamin B₁₂, it achieved recognition because of its inherent capability to catalyze the production of molecular hydrogen. One special kind of catalyst that works well for investigating both homogeneous and heterogeneous catalytic conditions is cobaloxime [25]. Several cobaloxime compounds were effective initial catalysts, but their activity was very limited and found to undergo ligand exchange when light-driven H₂ production was present [22]. Three separate components usually work together to govern the photocatalytic hydrogen evolution reaction (HER) activity: (i) photocatalysts (ii) photosensitisers (PS) and (iii) sacrificial electron donors (SED). Photosensitizers (PS) have been divided into four categories based on their nature: (i) inorganic PS based on noble metals, (ii) inorganic PS based on non-noble metals (iii) organic PS and (iv) PS consisting of nanomaterials. The cobaloxime core's chemical properties, tuneability, synthetic flexibility, and robustness made it a popular candidate for screening a variety of PS's photocatalytic performance across a broad chemical space. Cobaloximes can be activated for the evolution of molecular hydrogen photocatalytically by the addition of the proper electron supplements from a light-driven source [25].

The structure of cobalt-based complexes has a major role in determining the catalytic efficiency. The environments around the ligands that are directly attached to the cobalt metal ion, have a significant impact on the structure. Furthermore, supramolecular interactions also play a significant role in determining the catalytic efficiency. Therefore, knowledge of the complex's catalytic characteristics requires an understanding of its supramolecular properties

Chapter 4

[12, 26]. The presence of the axial ligands stabilizes the cobalt-core in vitamin B₁₂ [27]. In search of stable cobaloxime [XCo(dmghH₂)₂Y] where X and Y are axial ligands, several ligands such as monoanions, alkyl-phosphines, halides and even solvent molecules are screened. The network of internal hydrogen bonding (-N-OH...O-N-) of oxime was further difluoroborylated to produce the derivative [XCo(dmghBF₂)₂Y] of [XCo(dmghH₂)₂Y]. The barrier of energy for the catalytic reduction process by the cobaloxime is reduced by the introduction of this BF₂ functionality which is electron-withdrawing in nature [25, 28]. This thermodynamic advantage was exploited by Espenson et al., who found that [XCo(dmghBF₂)₂Y] or Co(dmghBF₂)₂ produced H₂ in molecular form from hydrochloric acid [29]. However poor turnover frequencies of these cobaloximes, lack of catalytic ability in acidic medium and instability in water medium have created doubt about their suitability for widespread use [25, 30-32]. Coordination of pyridyl groups of several PS with Co(II) centers of the cobaloxime creates the 1st supramolecular aggregation for photocatalysis that has been reported [23]. Modifying cobalt compounds with efficient catalytic activities *via* the creative fabrication of ligands is one of the interesting research fields. An effective method for creating efficient electron and proton transport routes is the supramolecular approach. The initial synthesis of supramolecular catalysts based on cobaloxime needs the binding of photosensitizers having pyridyl functional groups to the Co(II) centers of the macrocyclic cobaloximes [33]. A small number of photocatalytic supramolecular complexes with an active site made of cobaloxime have recently been reported [34, 35]. Although much effort has been put into the development of novel Co(II)-based supramolecular complexes for photocatalytic hydrogen evolution, the number of molecular systems available, particularly with crystallographic evidence is still inadequate.

4.2 Magnetic properties of cobalt-based complexes

Given the well-known importance of cobalt in molecular magnetism and catalysis, cobalt-based supramolecular assemblies, among all the transition-metal compounds, are particularly alluring due to their potential to influence the innovative fields of advanced functional materials [37-39]. Following the invention of single-molecule magnets (SMMs) based on lanthanide complexes, a number of complexes with 3d-series metals, such as Cr, Mn, Fe, Co, Ni, and Cu, have been investigated [40, 41]. Cobalt(II) complexes have attracted a lot of research interest owing to their high magnetic anisotropy, a wide range of geometry and coordination numbers, robust first-order spin-orbit coupling, and non-integer ground spin state. The non-integer ground spin state may diminish the possibility of a quantum tunnelling mechanism for the

Chapter 4

relaxation of the magnetization [42, 43]. Despite significant advancements in Co(II)-based SMMs in recent years, it is still difficult to rationally develop desired magnetic materials based on cobalt complexes.

4.3 Importance of dithiolate and dicarboxylate-based ligands in coordination chemistry

Supramolecular assemblies fabricated from metal complexes containing dithiolate and dicarboxylate-based multifunctional ligands have advanced significantly during the past few decades owing to their exciting applications in magnetism, catalysis, material science, and biochemistry [44-46]. In view of the extremely high strengths of metal-sulphur as well as metal-oxygen bonds and their significant roles in a variety of biological processes, the research attention being devoted to metal complexes containing dithiolate and dicarboxylate-based multifunctional ligands remains exceptionally high. Such research efforts have received further momentum due to the natural ability of the functionalized dithiolate and dicarboxylate ligands to demonstrate adaptable coordination modes during complexation, thereby resulting in their utilization in constructing fascinating supramolecular frameworks. The structural chemistry of functionalized dithiolate and dicarboxylate ligands is astoundingly distinct and has a considerable edge over that of other organic ligands. Depending on the nature of metal ions, the dithiolate and dicarboxylate ligands can chelate and also bridge with various metal centres to create supramolecular architectures [4, 5]. The coordination complexes comprising dithiolate and dicarboxylate-based ligands have been extensively studied and the advancement of research work done in this field has been published in several research papers and review articles [49-61]. The catalytic activities, magnetic properties, and biological activities of metal complexes harvested from functionalized dithiolate and dicarboxylate-based ligands have stirred a lot of research interest in the arena of inorganic supramolecular chemistry [46, 62, 63].

We are particularly interested in the dithiolate and dicarboxylate-based multifunctional ligands because of their ability to interact with a broad range of metals and produce complexes with vastly different binding constants. In addition, they can be functionalized rather easily, allowing them to be incorporated into desired architectures. While substantial progress has been made on multifunctional dithiolate and dicarboxylate-based ligands, the versatility of substituents on the ligand backbones is yet to be explored. The said exploration may lead to more complex supramolecular structures with interesting magnetic and catalytic properties.

Given these considerations and in light of our general interest in exploring various dithiolate and dicarboxylate building blocks for the development of diverse functional metal

Chapter 4

compounds, the salient aims of the current work include: (i) expanding the usages of dithiolate and dicarboxylate ligands for the preparation of supramolecular Co(II) compounds, (ii) recognizing their structural and non-covalent interactions features, and (iii) examining their magnetic behaviour and photocatalytic activity towards hydrogen generation.

In pursuit of developing supramolecular aggregates for self-assembly, efficient photocatalysts for the evolution of molecular hydrogen, and exploring the magnetic properties, we synthesized Co(II) metal complexes **8** and **9**.

4.4 Present work

Supramolecular Co(II) Complexes Based on Dithiolate and Dicarboxylate Ligands: Crystal structures, Theoretical studies, Magnetic Properties, and Catalytic Activity Studies in Photocatalytic Hydrogen Evolution

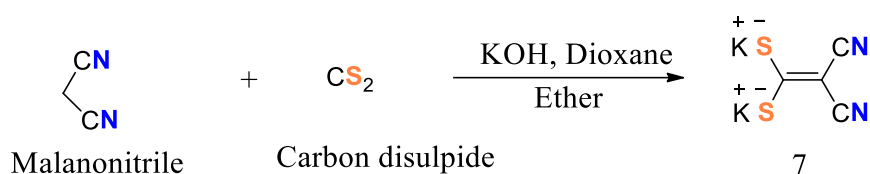
This chapter describes the present work, related to the discussion of two Co(II) complexes based on dithiolate and dicarboxylate ligands. Supramolecular properties, Hirshfeld Surface analysis, magnetic properties, and photocatalytic hydrogen evolution activity of the synthesized compounds have been studied. One compound/salt **8** consisting of two ([tris (2-aminoethyl) amine Co] 1, 1-dicyano-2, 2-ethylenedithiolate)⁺ per thiosulphate ion linked through intermolecular hydrogen bonds is designed and synthesized during our present work. They have been structurally characterized by FT-IR, elemental analysis, and single-crystal X-ray diffraction. Compound **9**, (pyridine-2, 6-dicarboxylate)₂ Co·5H₂O·Co).2H₂O, is stabilized by intramolecular O–H···O hydrogen bonds, building ribbons that propagate along the [100] direction in the crystals. From HS analysis, it is observed that the major non-covalent interactions present in **8** are C–H···O, N–H···N, N–H···S, and N–H···O hydrogen bonds, which play an important role in stabilizing the crystal structure. In **9**, out of all the non-covalent interactions, O···H/H···O interactions have major contributions to stabilize the crystal structure. Theoretical investigation of the molecular structures of the crystals also revealed that the major stabilizing factor for **8** is H-bonding along with π - π stacking while that for **9** is the coordinate bond between water and cobalt(II) ion. Direct current variable-temperature magnetic susceptibility measurements carried out on polycrystalline samples of **8** and **9** in the temperature range of 1.8-300 K show the presence of magnetic anisotropy of the cobalt(II) ion in **8** and weak intermolecular exchange in **9**. Further, both compounds **8** and **9** are found to be highly efficient water reduction catalysts in terms of per Co turn-over-numbers at lower

Chapter 4

concentrations. Before entering into the present work, a general introduction to supramolecular architectures of the complexes based on dithiolate and dicarboxylate ligands, catalytic properties, magnetic properties and photocatalytic properties for evolution of molecular hydrogen of cobalt and Co(II) complexes from literature, have been presented.

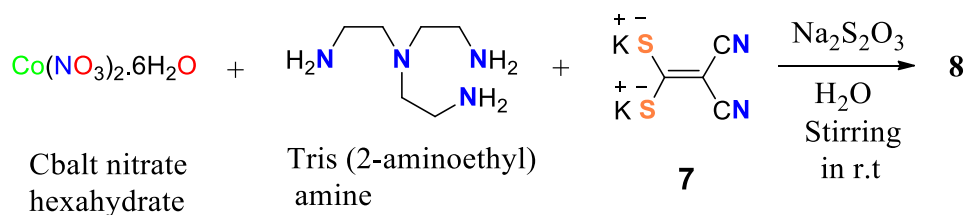
4.4.1 Reaction schemes for the synthesis of 1, 1-dicyano-2, 2-ethylenedithiolate (*i-mnt*²⁻) ligand 7 and Co(II) complexes 8 and 9

The ligand 7 was synthesized from malononitrile and carbon disulphide, following **Scheme 1**



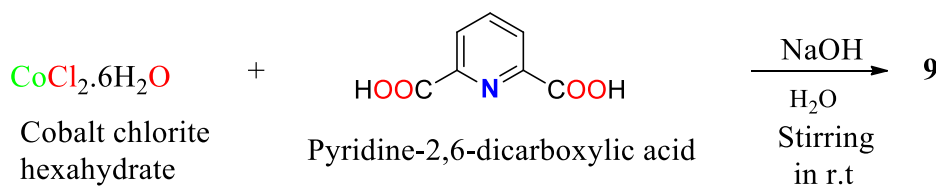
Scheme 1. Synthesis of 1, 1-dicyano-2, 2-ethylenedithiolate (*i-mnt*²⁻) ligand 7.

The complex 8 was synthesized in good yields, following **Scheme 2**.



Scheme 2. Synthesis of complex 8.

The complex 9 was synthesized from pyridine-2, 6-dicarboxylic acid according to reported procedure [64], following **Scheme 3**.



Scheme 3. Synthesis of complex 9.

Chapter 4

4.4.2 FT-IR spectral characterization of **8** and **9**

To comprehend the coordination modes of two ligands (tetraen and $i\text{-mnt}^{2-}$) to the Co(II) metal centre, the FT-IR spectra of Co(II) complex **8** as well as those of the free ligands were thoroughly investigated. The pertinent data are shown in **Fig. 4.1** and **Fig. 4.2**. The broad bands observed in the $3428\text{--}3120\text{ cm}^{-1}$ region of the spectrum of **8** are ascribed to $\nu(\text{N-H})$ (asymmetric and symmetric) stretching modes of the amino nitrogen of tetraen ligand. The $\nu(\text{C-H})$ stretching band for **8** can be found at 2930 cm^{-1} . The IR spectrum of **8** shows a strong absorption band at 2201 cm^{-1} , which is attributed to the $\nu(\text{C}\equiv\text{N})$ stretching frequencies of the coordinated $i\text{-mnt}^{2-}$ ligand. This confirms the formation of a mixed ligand complex. The $\nu(\text{N-H})$ bending (scissoring) vibration for **8** is detected at 1612 cm^{-1} , which is lower than that for the free tetraen ligand (1636 cm^{-1}). The observed shift to a lower frequency advocate that the amino nitrogen atoms of tetraen are coordinated to the cobalt metal center. The stretching frequency of $\nu(\text{C}=\text{C})$ in **8** is observed at 1384 cm^{-1} , while the same for free ligand $K_2i\text{-mnt}$ is observed at 1365 cm^{-1} . The increased value of $\nu(\text{C}=\text{C})$ stretching frequency indicates the delocalization of π electrons, which also confirms the formation of the mixed ligand complex **8**. Absorption bands at 1030 and 945 cm^{-1} are due to $=\text{CS}_2$ group. The $\nu(\text{C-S})$ band appearing at 870 cm^{-1} in the spectrum of free ligand $i\text{-mnt}^{2-}$, appears at 899 and 889 cm^{-1} in the spectrum of **8**, signifying symmetrical bonding of both the S atoms to the cobalt ion. The band at 747 cm^{-1} is ascribed to Co-S vibration. The weak bands at 521 and 479 cm^{-1} are ascribed to Co-N vibration. **Fig. 4.3** represents the FT-IR spectra of complex **9**.

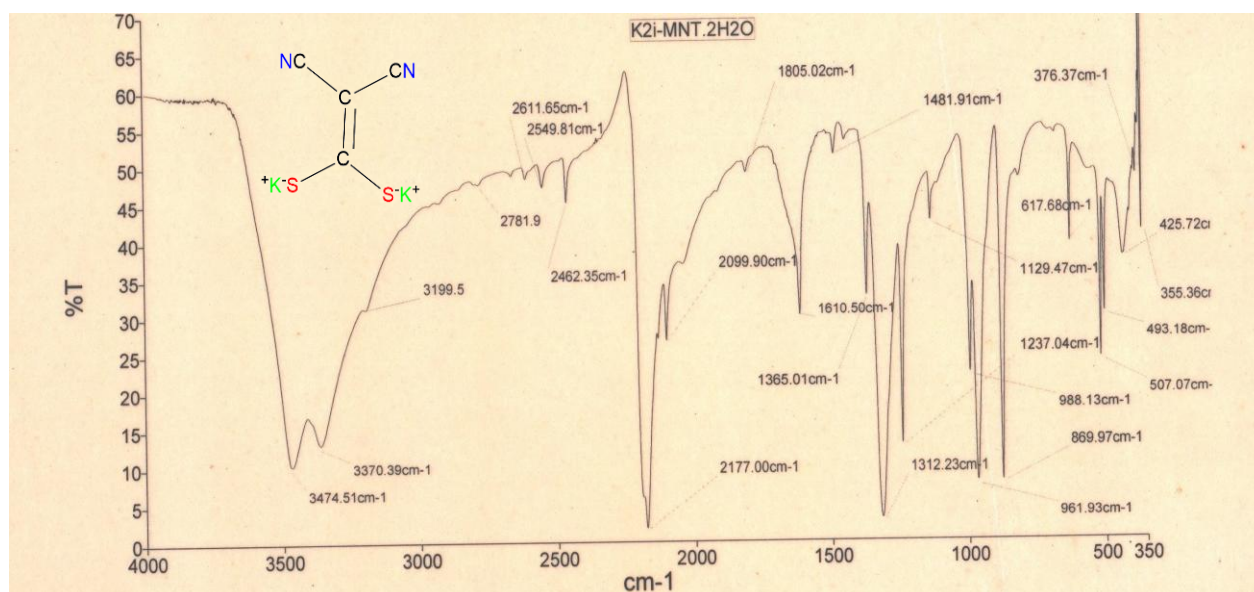


Fig. 4.1. FT-IR spectrum of $K_2i\text{-mnt}\cdot\text{H}_2\text{O}$.

Chapter 4

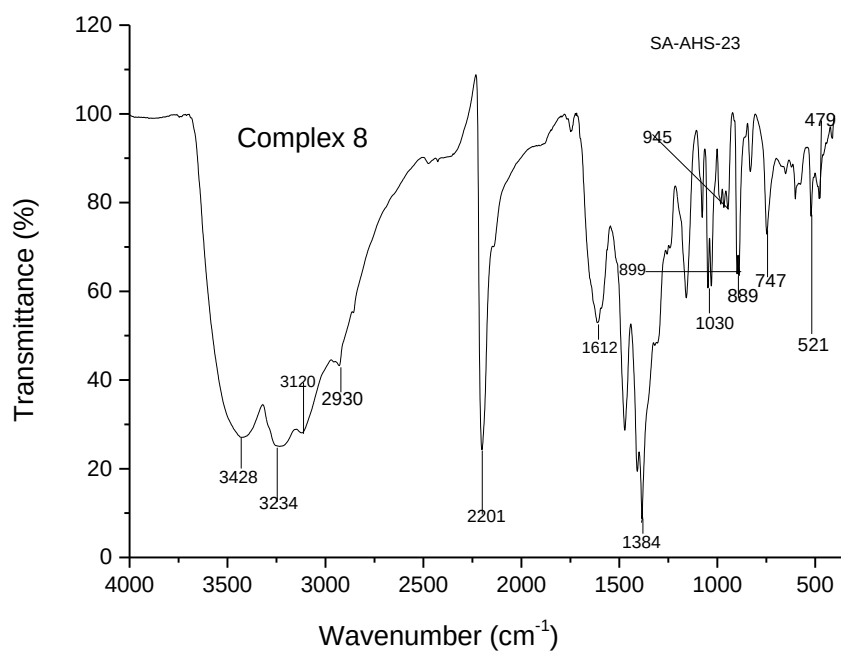


Fig. 4.2. FT-IR spectrum of **8**.

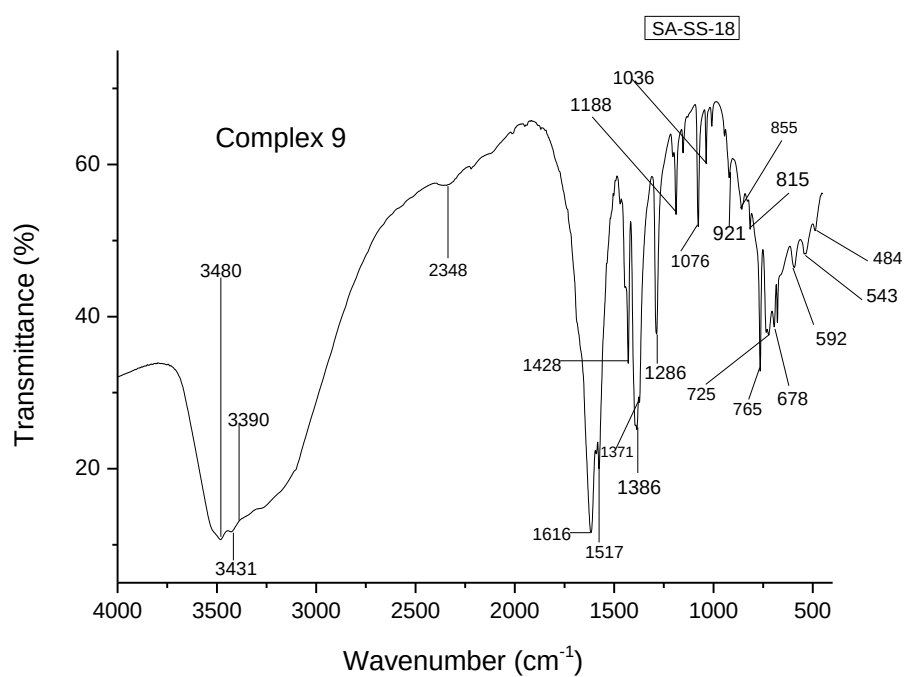


Fig. 4.3. FT-IR spectrum of **9**.

Chapter 4

4.4.3 Crystal structure description of complex **8**

Fig. 4.4 depicts the asymmetric unit of **8**, which consists of two thiosulphate ions and four cobalt ions. The six-coordinate Co1 center, existing in a distorted octahedral environment, is bonded to four enamine nitrogens (N1, N2, N3, and N4) of tris (2-aminoethyl) amine (tetraen) ligand and two sulfur atoms (S1 and S2) of *i-mnt*²⁻ ligand. The coordination geometries of Co2, Co3, and Co4 ions are distorted octahedral, similar to that of Co1 center. The cobalt (II) ions and the two thiosulphate ion ligands are linked to one another *via* intramolecular N3–H3C···N11, N9–H9A···N5, N14–H14C···S12, N15–H15D···O6, and C22–H22B···O6 hydrogen bonds (**Table 4.1**). The molecules are linked by several intermolecular C–H···O, C–H···S, C–H···N, N–H···S, N–H···N, and N–H···O hydrogen bonds in the crystal structure, forming a 3D supramolecular framework (**Fig. 4.5** and **Fig. 4.6**). The Co–S and Co–N bond distances are in 2.245–2.305 Å and 1.945–1.981 Å ranges, respectively. Compared to Co–S bonds, the Co–N bonds are shorter. Although the Co–N bond distances are comparable with the same bond distances in reported cobalt compounds, the values reported herein are slightly shorter than the previously reported values [65, 66]. While the shortest bond length, between two metal centers (Co1–Co2), is 6.948 Å, the longest distance is between Co1–Co4 with a value of 15.321 Å. The S1–Co1–S2, S3–Co2–S4, S5–Co3–S6, and S7–Co4–S8 bond angles have almost identical values (**Table 4.2**). Similarly, the N–Co–N bond angles are nearly identical. The bond angles around Co1 metal center, namely S1–Co1–S2, S1–Co1–N3, S2–Co1–N4, N1–Co1–N2, N1–Co1–N4, and N2–Co1–N3 are 76.88(6)°, 92.8(2)°, 88.5(2)°, 86.9(2)°, 85.0(2)°, and 90.4(2)°, respectively, which exhibit a distorted octahedral geometry. These prominent angle values are similarly observed around Co2, Co3, and Co4 metal centers. The S9–S10, S11–S12, S9–O1, S9–O2, S9–O3, S11–O4, S11–O5, and S11–O6 bond distances are 1.995(2), 2.023(2), 1.471(4), 1.469(4), 1.471(4), 1.480(4), 1.487(4), and 1.470(4) Å, respectively. These S–S and S–O bond lengths of thiosulphate ions are in good agreement and comparable with reported thiosulphate compounds [67, 68].

Chapter 4

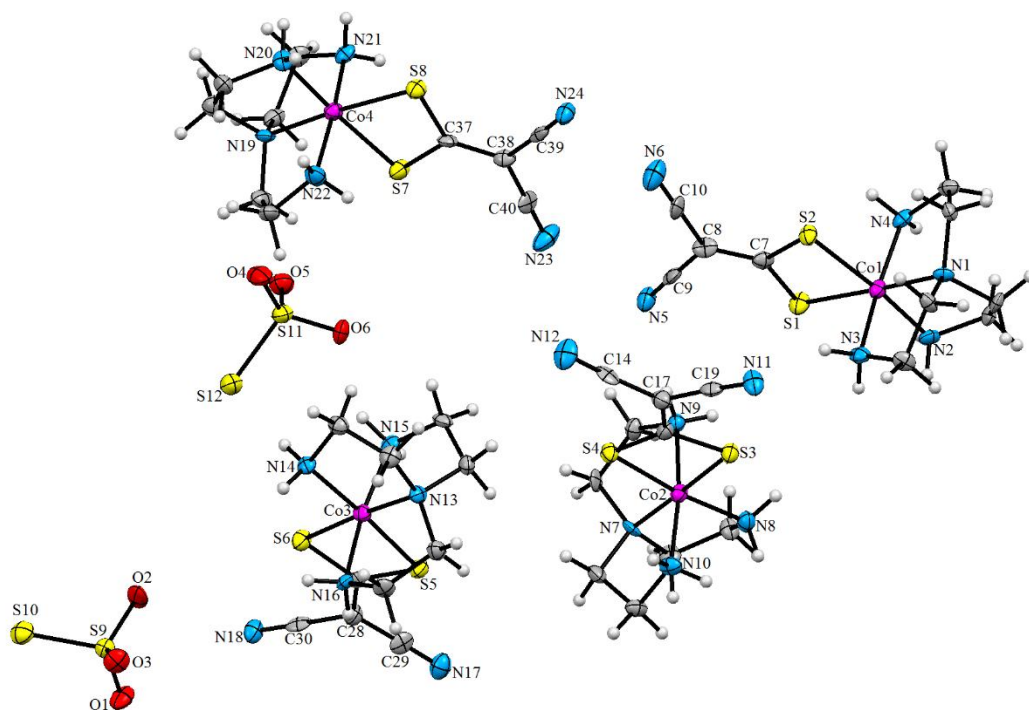


Fig. 4.4. The content of the asymmetric unit of **8**. Thermal displacement ellipsoids are shown at their 50% probability levels.

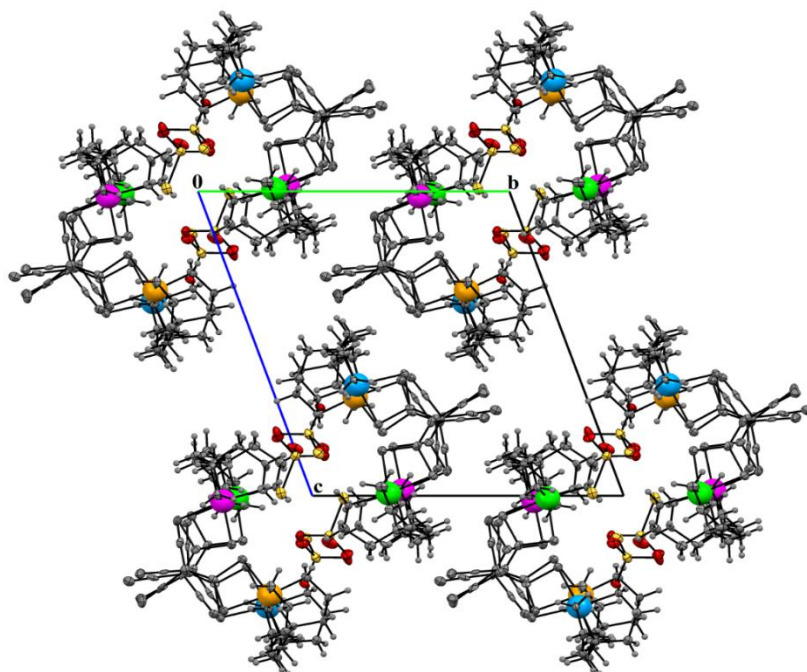


Fig. 4.5. A view of the crystal packing of **8** along *a*-axis direction. (Co1: Purple, Co2: Yellow, Co3: Blue, and Co4: Green).

Chapter 4

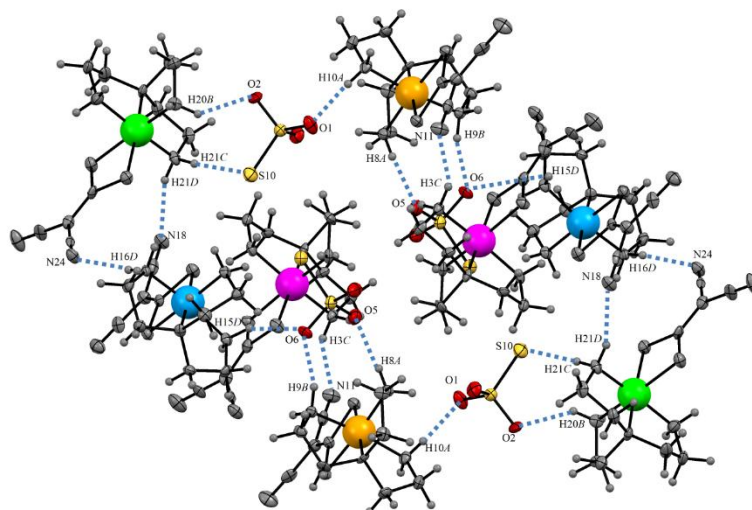


Fig. 4.6. A partial view of the crystal packing of **8** showing hydrogen bonds. (Co1: Purple, Co2: Yellow, Co3: Blue, and Co4: Green).

Table 4.1. Hydrogen bond geometry for **8**.

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>	Symmetry codes
C22—H22B...O6	0.99	2.62	3.493(7)	146	
N3—H3C...N11	0.91	2.21	3.031(7)	150	
N9—H9A...N5	0.91	2.27	3.136(7)	159	
N14—H14C...S12	0.91	2.53	3.435(5)	175	
N15—H15D...O6	0.91	2.05	2.863(6)	147	
C1—H1B...O4 ⁱ	0.99	2.35	3.173(7)	140	<i>x</i> , <i>y</i> +1, <i>z</i> −1
C2—H2A...S9 ⁱⁱ	0.99	2.99	3.846(6)	146	<i>x</i> +1, <i>y</i> +1, <i>z</i> −1
C2—H2A...S10 ⁱⁱ	0.99	2.84	3.790(6)	161	<i>x</i> +1, <i>y</i> +1, <i>z</i> −1
C2—H2A...O3 ⁱⁱ	0.99	2.47	3.168(7)	127	<i>x</i> +1, <i>y</i> +1, <i>z</i> −1
C2—H2B...O5 ⁱ	0.99	2.47	3.358(7)	150	<i>x</i> , <i>y</i> +1, <i>z</i> −1
C3—H3A...N18 ⁱⁱⁱ	0.99	2.57	3.494(8)	155	<i>x</i> +1, <i>y</i> , <i>z</i> −1
C4—H4A...O4 ⁱ	0.99	2.57	3.540(7)	166	<i>x</i> , <i>y</i> +1, <i>z</i> −1
C6—H6A...N18 ^{iv}	0.99	2.47	3.233(8)	134	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
C13—H13A...N5 ^{iv}	0.99	2.68	3.624(8)	159	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
C24—H24A...O5 ^{iv}	0.99	2.60	3.342(7)	132	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
C33—H33B...N11 ^v	0.99	2.66	3.630(8)	167	<i>x</i> , <i>y</i> , <i>z</i> +1
C34—H34A...N6 ^v	0.99	2.61	3.317(7)	128	<i>x</i> , <i>y</i> , <i>z</i> +1
N2—H2D...S12 ^{iv}	0.91	2.49	3.403(5)	177	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
N4—H4C...S10 ⁱⁱ	0.91	2.61	3.388(2)	144	<i>x</i> +1, <i>y</i> +1, <i>z</i> −1
N4—H4D...N18 ^{iv}	0.91	2.56	3.234(7)	131	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
N8—H8A...O5 ^{iv}	0.91	2.10	3.000(6)	173	− <i>x</i> +1, − <i>y</i> +1, − <i>z</i> +1
N8—H8A...O1 ^v	0.91	2.45	3.254(6)	148	− <i>x</i> , − <i>y</i> +1, − <i>z</i> +1

Chapter 4

N8—H8B $\cdots$ O3 ^v	0.91	2.31	3.134(6)	151	$-x, -y+1, -z+1$
N9—H9B $\cdots$ O6 ^{iv}	0.91	2.11	2.992(6)	162	$-x+1, -y+1, -z+1$
N10—H10A $\cdots$ O1 ^v	0.91	2.01	2.915(6)	174	$-x, -y+1, -z+1$
N15—H15C $\cdots$ N5 ^{iv}	0.91	2.57	3.276(7)	135	$-x+1, -y+1, -z+1$
N16—H16D $\cdots$ N24 ^{vi}	0.91	2.19	3.029(6)	153	$x-1, y, z$
N20—H20A $\cdots$ O1 ^{vii}	0.91	2.38	3.197(6)	150	$x+1, y, z$
N20—H20B $\cdots$ O2 ^{viii}	0.91	2.23	2.995(6)	141	$-x+1, -y, -z+2$
N21—H21C $\cdots$ S10 ^{viii}	0.91	2.42	3.325(5)	174	$-x+1, -y, -z+2$
N21—H21D $\cdots$ N18 ^{vii}	0.91	2.22	3.074(7)	157	$x+1, y, z$
N22—H22D $\cdots$ O1 ^{vii}	0.91	2.34	3.112(6)	142	$x+1, y, z$

Table 4.2. Some selected geometric parameters for **8**.

Bond length	Value (Å)	Bond angle	Value (°)
Co1—S1	2.253 (2)	S1—Co1—S2	76.88 (6)
Co1—S2	2.305 (2)	S1—Co1—N3	92.8 (2)
Co1—N1	1.970 (4)	S2—Co1—N4	88.5 (2)
Co1—N2	1.967 (4)	N1—Co1—N2	86.9 (2)
Co1—N3	1.956 (4)	N1—Co1—N4	85.0 (2)
Co1—N4	1.973 (4)	N2—Co1—N3	90.4 (2)
Co2—S3	2.247 (2)	S3—Co2—S4	76.92 (6)
Co2—S4	2.301 (2)	S3—Co2—N8	95.7 (2)
Co2—N7	1.979 (4)	S4—Co2—N7	100.9 (2)
Co2—N8	1.974 (4)	N7—Co2—N10	86.7 (2)
Co2—N9	1.975 (4)	N8—Co2—N10	92.5 (2)
Co2—N10	1.958 (4)	N9—Co2—N8	90.7 (2)
Co3—S5	2.293 (2)	S5—Co3—S6	77.26 (6)
Co3—S6	2.245 (2)	S5—Co3—N13	99.6 (2)
Co3—N13	1.968 (4)	S6—Co3—N14	96.3 (2)
Co3—N14	1.981 (4)	N14—Co3—N15	90.2 (2)

Chapter 4

Co3—N15	1.957 (4)	N15—Co3—N13	86.3 (2)
Co3—N16	1.963 (4)	N16—Co3—N13	85.9 (2)
Co4—S7	2.293 (2)	S7—Co4—S8	76.93 (6)
Co4—S8	2.259 (2)	S8—Co4—N21	93.3 (2)
Co4—N19	1.960 (4)	S7—Co4—N22	88.6 (2)
Co4—N20	1.961 (4)	N20—Co4—N21	92.6 (2)
Co4—N21	1.945 (4)	N19—Co4—N20	87.3 (2)
Co4—N22	1.973 (5)	N19—Co4—N22	85.8 (2)
S9—S10	1.995 (2)	S1—C7—S2	110.9 (4)
S11—S12	2.023 (2)	S3—C17—S4	110.3 (3)
S9—O1	1.471 (4)	S5—C27—S6	110.8 (3)
S9—O2	1.469 (4)	S7—C37—S8	111.2 (4)
S9—O3	1.471 (4)		
S11—O4	1.480 (4)		
S11—O5	1.487 (4)		
S11—O6	1.470 (4)		

4.4.4 Crystal structure description of complex **9**

Even though the crystal structure of compound **9** has already been reported [64], we have chosen to gather the data once again to check for any substantial structural variations. The structure is much the same, but there are a few differences that merit reporting. The molecular structure of **9** with pyridine-2,6-dicarboxylate or dipicolinate (*dpc*) is shown in **Fig. 4.7**. As shown in **Fig. 4.7**, the asymmetric unit of **9** contains one of the cobalt(II)-cobalt(II) compounds [including $\text{Co}(\text{dpc})_2\text{--O--Co--}(\text{H}_2\text{O})_5$] and two additional water molecules. The Co1 ion has a distorted octahedral geometry with four oxygen and two nitrogen atoms from two *dpc* ligands, while the Co2 is octahedrally coordinated by five oxygen atoms of five water molecules and one oxygen atom of a carboxyl group. In **9**, the *dpc* acts as a tridentate ligand. The two cobalt(II) ions are linked to one another by the carboxyl groups, so the carboxyl group (O1—C1—O2) is in a bridging position. The complex is non-planar with two pyridine rings inclined to one

Chapter 4

another by making a dihedral angle of nearly $89.51(3)^\circ$. The cobalt(II)-cobalt(II) complex and two aqua molecules are linked to one another by intramolecular $O5W-H5W1\cdots O1$, $O1W-H1W1\cdots O6W$, and strong $O4W-H4W1\cdots O7W$ hydrogen bonds. The molecules are linked by several intermolecular $O-H\cdots O$ and $C-H\cdots O$ type-hydrogen bonds in the crystal structure of **9**, forming a 3D supramolecular framework (**Fig. 4.8** and **Table 4.3**). In the previous study, as stated by Qi et al. [64], all water molecules also participate in hydrogen bonding. Extensive intermolecular hydrogen bonds are formed in the crystal using the five coordinated water molecules (OW1, OW2, OW3, OW4, and OW5) and two crystal water molecules (OW6 and OW7). There are also weak $\pi\cdots\pi$ contacts between the two pyridine rings of *dpc* [$Cg5\cdots Cg5^i = 3.724(2) \text{ \AA}$; here, $Cg5$ is center of the N1/C2–C6 ring and symmetry code (i); $-x+1, -y, -z+1$].

The $Co-O_{dpc}$ bonds are, on average, longer than the $Co-O_{water}$ bonds (**Table 4.4**). The $Co-O$ bond distances vary from $2.0808(8)$ to $2.2117(8) \text{ \AA}$ with an average of $2.108 \text{ \AA}$, which is comparable to that reported for Co(II) complexes [69]. In a previous study, $Co-O$ distances were found in the range of $2.1160(19)$ to $2.2184(18) \text{ \AA}$, and the average bond length was $2.1728 \text{ \AA}$, which is consistent with the values here [64]. $Co1-N1$ and $Co1-N2$ bond distances are $2.0248(8)$ and $2.0207(9) \text{ \AA}$, respectively, and the $Co-N$ distances in the previous study were $2.015(2)$ and $2.022(2) \text{ \AA}$ [64]. These lengths are close to $2.012(2)$ and $2.005(2) \text{ \AA}$, as reported by Chkirate and co-workers [70]. $C2-N1$, $C6-N1$, $C9-N2$, and $C13-N2$ bond lengths are $1.3326(12)$, $1.3341(12)$, $1.3324(12)$, and $1.3300(12) \text{ \AA}$, respectively. These $C-N$ bond distances within pyridine rings are in good agreement with the corresponding bond lengths reported for pyridine compounds [71, 72]. In the cobalt(II)-cobalt(II) complex, the carboxyl group distances are unremarkable with an average $C-O$ bond distance of $1.258 \text{ \AA}$, which is comparable to that reported for carboxylic compounds [73, 74].

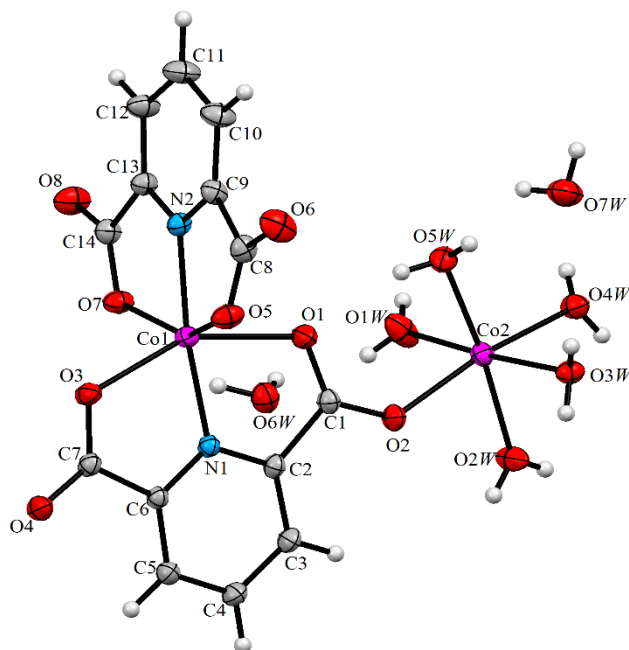


Fig. 4.7. Molecular structure of complex **9** with the displacement ellipsoids drawn at 50% probability level.

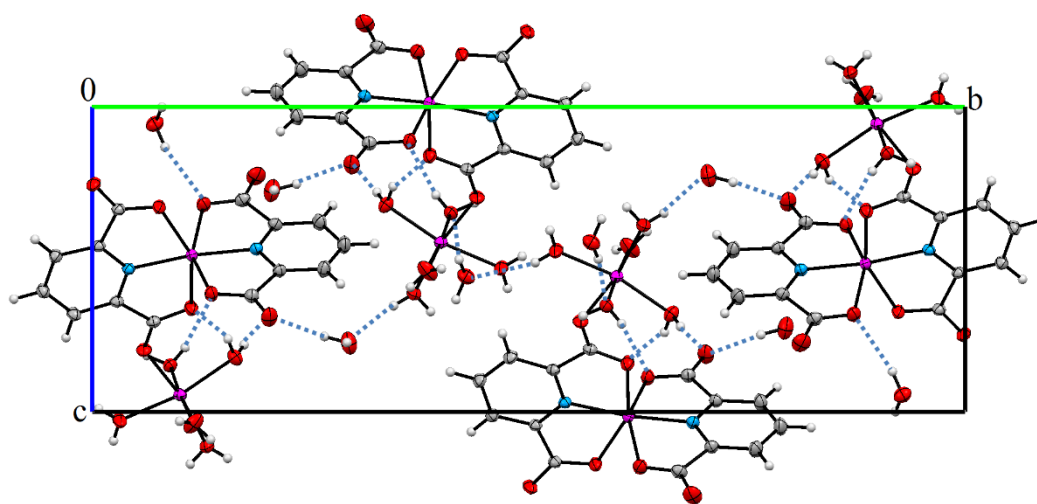


Fig. 4.8. A partial view of the crystal packing for complex **9**. The dashed lines denote the intermolecular O-H...O hydrogen bonds parallel to *bc* plane.

Chapter 4

Table 4.3. Hydrogen bond geometry for **9**.

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>	Symmetry codes
O5 <i>W</i> —H5W1...O1	0.81 (2)	2.04 (2)	2.8122 (12)	159 (2)	
O1 <i>W</i> —H1W1...O6 <i>W</i>	0.73 (2)	2.11 (2)	2.8138 (12)	161 (2)	
O4 <i>W</i> —H4W1...O7 <i>W</i>	0.80 (2)	1.87 (2)	2.6517 (12)	169 (2)	
O1 <i>W</i> —H1W2...O6 ⁱ	0.75 (2)	1.96 (2)	2.7102 (13)	178 (2)	<i>x</i> , <i>y</i> , <i>z</i> +1
O2 <i>W</i> —H2W1...O6 <i>W</i> ⁱⁱ	0.77 (2)	2.21 (2)	2.9403 (12)	160 (2)	− <i>x</i> +1, − <i>y</i> +1
O2 <i>W</i> —H2W2...O4 ⁱⁱⁱ	0.74 (2)	1.89 (2)	2.6337 (11)	175 (3)	<i>x</i> +1, <i>y</i> , <i>z</i> +1
O3 <i>W</i> —H3W1...O4 ^{iv}	0.80 (2)	1.88 (2)	2.6704 (11)	173.3 (18)	− <i>x</i> +1, − <i>y</i> +1
O3 <i>W</i> —H3W2...O7 ^v	0.77 (2)	2.03 (2)	2.7815 (11)	166 (2)	<i>x</i> +1, <i>y</i> , <i>z</i>
O4 <i>W</i> —H4W2...O3 ⁱⁱⁱ	0.80 (2)	1.96 (2)	2.7538 (11)	170 (2)	<i>x</i> +1, <i>y</i> , <i>z</i> +1
O5 <i>W</i> —H5W2...O8 ^v	0.79 (2)	1.91 (2)	2.6946 (11)	176 (2)	<i>x</i> +1, <i>y</i> , <i>z</i>
C5—H5A...O7 ^{vi}	0.95	2.58	3.4775 (13)	157	− <i>x</i> , − <i>y</i> +1
O6 <i>W</i> —H6W1...O3 ⁱ	0.79 (2)	2.59 (2)	3.1907 (12)	134.4 (19)	<i>x</i> , <i>y</i> , <i>z</i> +1
O6 <i>W</i> —H6W1...O5 ⁱ	0.79 (2)	2.28 (2)	3.0086 (12)	152 (2)	<i>x</i> , <i>y</i> , <i>z</i> +1
O6 <i>W</i> —H6W2...O3 <i>W</i> ^{vii}	0.86 (2)	2.05 (2)	2.8973 (12)	170 (2)	<i>x</i> −1, <i>y</i> , <i>z</i>
O7 <i>W</i> —H7W1...O6 ⁱ	0.74 (3)	2.07 (3)	2.7638 (14)	156 (3)	<i>x</i> , <i>y</i> , <i>z</i> +1
O7 <i>W</i> —H7W2...O8 ^{viii}	0.85 (2)	1.92 (2)	2.7649 (13)	175 (2)	<i>x</i> +1, − <i>y</i> +1/2, <i>z</i> +1/2

Table 4.4. Some selected geometric parameters for **9**.

Bond length	Value (Å)	Bond angle	Value (°)	Dihedral angle	Value (°)
Co1—O1	2.2117(8)	N1—Co1—O1	76.23(3)	Co2—O2—C1—C2	168.18(7)
Co1—O3	2.1764(8)	O1—Co1—O5	97.41(3)	Co1—O1—C1—C2	1.71(11)
Co1—O5	2.1127(8)	N2—Co1—O5	76.64(3)	Co1—N1—C2—C1	5.91(11)
Co1—O7	2.1692(8)	N2—Co1—O7	75.76(3)	O2—C1—C2—N1	173.59(9)
Co1—N1	2.0248(8)	O3—Co1—O7	94.54(3)	O1—C1—C2—C3	176.62(9)
Co1—N2	2.0207(9)	N1—Co1—O3	75.64(3)	Co1—O5—C8—C9	12.93(12)
Co2—O1 <i>W</i>	2.0521(9)	O1—Co1—O3	151.47(3)	Co1—N2—C9—C10	173.69(8)
Co2—O2 <i>W</i>	2.0533(9)	N1—Co1—N2	171.86(3)	O6—C8—C9—N2	179.29(9)
Co2—O3 <i>W</i>	2.1641(8)	O5—Co1—O7	149.99(3)	O5—C8—C9—C10	174.05(11)
Co2—O4 <i>W</i>	2.0869(8)	O2—Co2—O2 <i>W</i>	79.82(3)	Co1—N2—C9—C8	−9.04(11)
Co2—O5 <i>W</i>	2.0808(8)	O2—Co2—O1 <i>W</i>	87.23(4)	Co1—N2—C13—C12	−175.46(8)
Co2—O2	2.0849(8)	O2 <i>W</i> —Co2—O3 <i>W</i>	86.15(4)		
C1—O1	1.2691(12)	O3 <i>W</i> —Co2—O4 <i>W</i>	85.86(3)		
C1—O2	1.2473(12)	O2 <i>W</i> —Co2—O5 <i>W</i>	168.67(4)		
C7—O3	1.2675(12)	O4 <i>W</i> —Co2—O5 <i>W</i>	99.26(3)		
C7—O4	1.2470(12)	O1 <i>W</i> —Co2—O5 <i>W</i>	96.56(4)		
C8—O6	1.2461(12)	C2—N1—C6	120.60(8)		
C14—O8	1.2430(12)	C9—N2—C13	121.49(9)		
C2—N1	1.3326(12)	O1—C1—O2	126.93(9)		
C6—N1	1.3341(12)	O3—C7—O4	125.73(9)		
C9—N2	1.3324(12)	O5—C8—O6	125.89(9)		
C13—N2	1.3300(12)	O7—C14—O8	125.35(9)		

Chapter 4

Table 4.5. Experimental details for crystal structures of **8** and **9**.

Crystal Data	Complex 8	Complex 9
Chemical Formula	$2(\text{C}_{10}\text{H}_{18}\text{CoN}_6\text{S}_2) \cdot \text{O}_3\text{S}_2$	$\text{C}_{14}\text{H}_{16}\text{Co}_2\text{N}_2\text{O}_{13} \cdot 2(\text{H}_2\text{O})$
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
Temperature (K)	100 (2)	100 (2)
Formula weight (a.k.b.)	802.83	574.18
a, b, c (Å)	16.1221 (6), 16.8450 (7), 17.3907 (8)	8.3476 (3), 27.1461 (8), 9.5826 (3)
α, β, γ (°)	63.710 (2), 69.397 (3), 59.872 (2)	90, 98.115 (1), 90
Crystal size (mm)	$0.19 \times 0.06 \times 0.03$	$0.48 \times 0.18 \times 0.16$
Volume, V (Å ³)	3610.9 (3)	2149.72 (12)
Calculated density (Mg/m ³)	1.477	1.774
F ₀₀₀	1656	1168
μ (mm ⁻¹)	1.31	1.62
Z	4	4
Diffractometer	Bruker APEX-II CCD	Bruker APEX-II CCD
θ range (°)	$2.2 \leq \theta \leq 26.0$	$2.3 \leq \theta \leq 36.4$
Wavelength (Å)	0.71073	0.71073
Measurement method	ω scan	ω scan
Absorption correction	Multi-scan	Multi-scan
$h_{\min}, h_{\max}$	−19, 19	−13, 10
$k_{\min}, k_{\max}$	−20, 20	−45, 44
$l_{\min}, l_{\max}$	−21, 20	−15, 15
T _{min} , T _{max}	0.471, 0.747	0.471, 0.747
R _{int}	0.124	0.028
Reflections collected	25499	34360
Independent reflections	13460	10359
Observed reflections [$I > 2\sigma(I)$]	6084	9517
Refinement method	SHELXL18/3	SHELXL18/3
Parameters	775	355
$R[F^2 > 2\sigma(F^2)]$	0.056	0.029
$wR(F^2)$	0.123	0.072
GooF = S	0.87	1.10
$\Delta\rho_{\min}, \Delta\rho_{\max}$ (e/Å ³)	−0.61, 0.63	−0.78, 0.74
CCDC	2221761	2146827

Chapter 4

4.4.5. Hirshfeld surface analysis of 8 and 9

Intermolecular interactions are important for the crystal stability of crystalline compounds. Hirshfeld calculations have been frequently used in recent years to investigate different intermolecular interactions in the crystal structures [71, 73, 75-77]. The Hirshfeld surfaces were visualized with the 3D d_{norm} mapped over fixed color scales of -0.410 to 2.782 Å (Molecule A), -0.392 to 2.271 Å (Molecule B), -0.538 to 2.803 Å (Molecule C), and -0.491 to 2.785 Å (Molecule D) (**Fig. 4.9**). The red circles on the d_{norm} surface of molecules A, B, C, and D represent the C–H $\cdots$ O, N–H $\cdots$ N, N–H $\cdots$ S, and N–H $\cdots$ O interactions, respectively (**Fig. 4.9**). The major contacts of the compound are N $\cdots$ H (33%), H $\cdots$ H (22%), S $\cdots$ H (16%), and O $\cdots$ H (11%) for molecule A; N $\cdots$ H (34%), H $\cdots$ H (18%), S $\cdots$ H (16%), and O $\cdots$ H (12%) for molecule B; N $\cdots$ H (33%), H $\cdots$ H (29%), O $\cdots$ H (13%), and S $\cdots$ H (8%) for molecule C; and N $\cdots$ H (34%), H $\cdots$ H (31%), S $\cdots$ H (11%), and O $\cdots$ H (6%) for molecule D (**Fig. 4.10**). The results show that the structure is stabilized by C–H $\cdots$ O, N–H $\cdots$ N, N–H $\cdots$ S, and N–H $\cdots$ O hydrogen bonds. Some other interactions that contribute to a lesser extent are also present.

Chapter 4

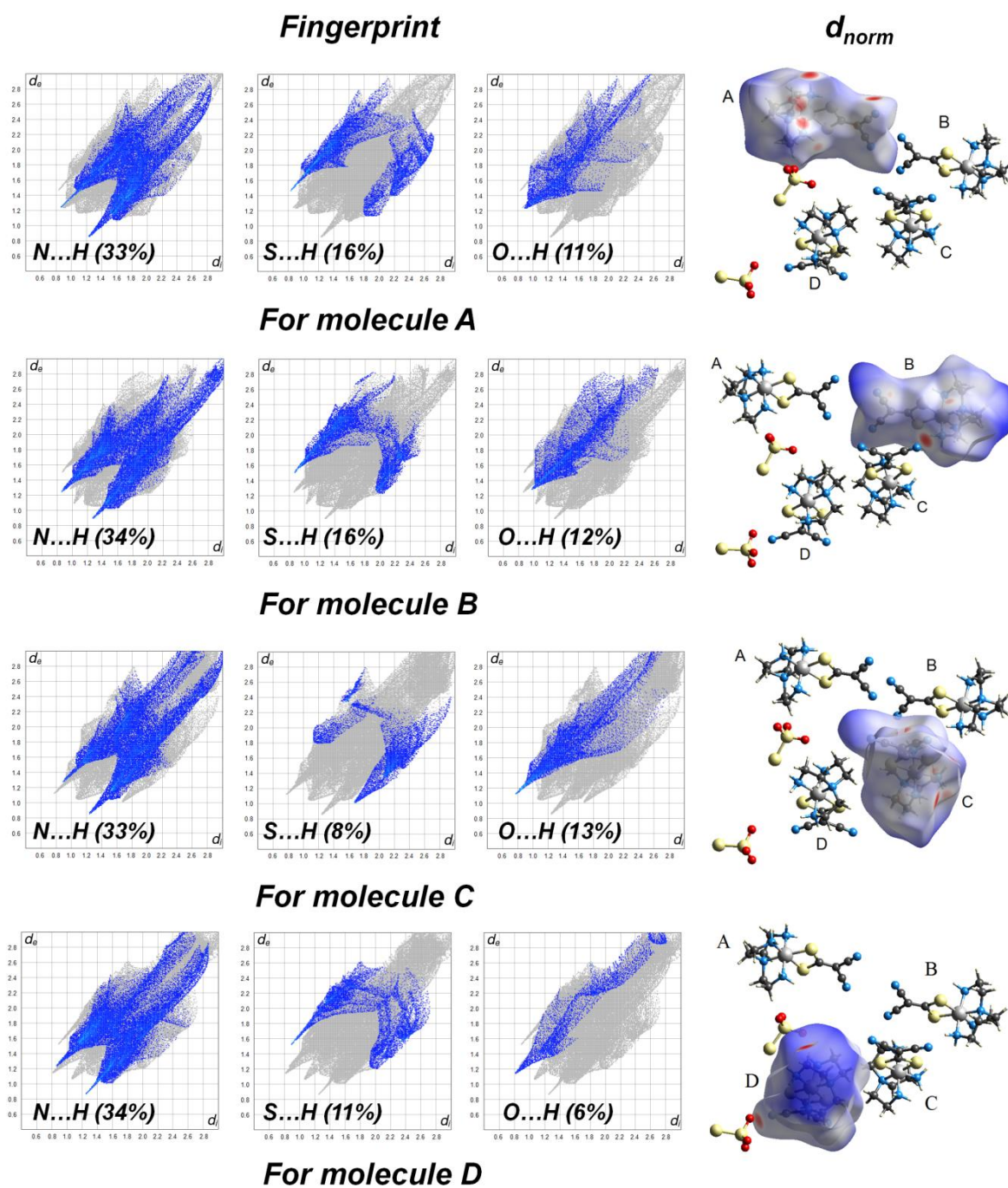


Fig. 4.9. Hirshfeld surfaces and fingerprints of **8** mapped with d_{norm} .

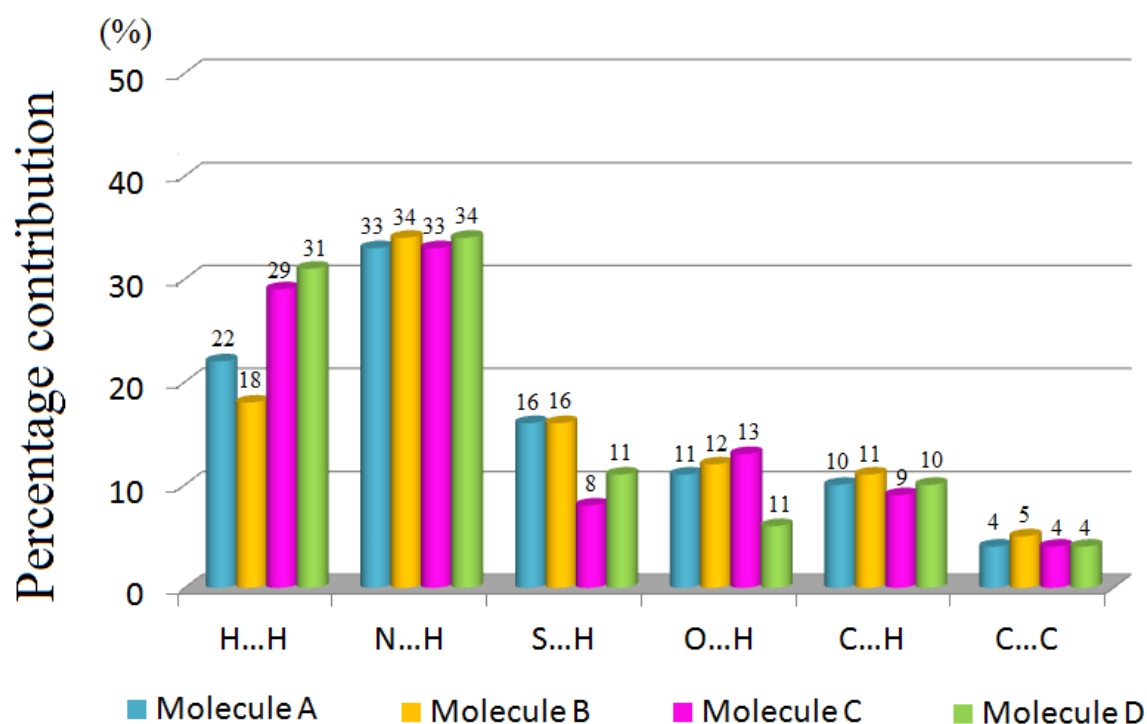


Fig. 4.10. Intermolecular interactions and their percentages for molecules A, B, C, and D in **8**.

In **Fig. 4.11**, the interactions are visualized by a 3D view of the molecular Hirshfeld surface mapped over d_{norm} , d_i , d_e , and shape index of complex **9**. On the d_{norm} Hirshfeld surface, bright red areas indicate H-bond interaction sites, represented by red dots (**Fig. 4.10**); the Hirshfeld surface mapped on d_{norm} ranges from 0.0783 to 1.0981 a.u. The red regions on the d_{norm} surface are located on the oxygen and hydrogen atoms, which contribute to non-covalent contacts, as established by the interactions in **Fig. 4.11**. The results of fingerprint analyses are given in **Fig. 4.12**. The interactions with a contribution of less than 1% are not included in the visualization. **Fig. 4.13** summarizes the contributions of all the interactions. With a value of 49%, the contribution of $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ contacts has the largest share in the crystal packing of **9**, wherein the heteronuclear contacts appear as spikes. The $\text{H}\cdots\text{H}$ contact has a smaller share with a contribution of 30% and $\text{C}\cdots\text{H}/\text{H}\cdots\text{C}$ contacts with a contribution of 8%.

Chapter 4

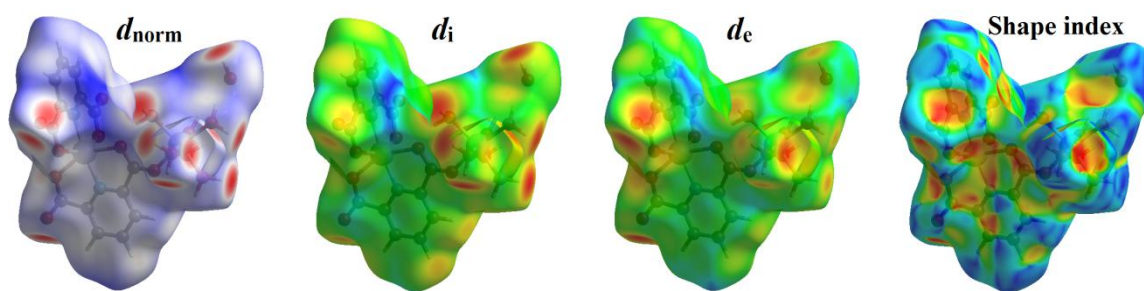


Fig. 4.11. Hirshfeld surfaces of **9**, mapped with d_{norm} , d_i , d_e , and shape index.

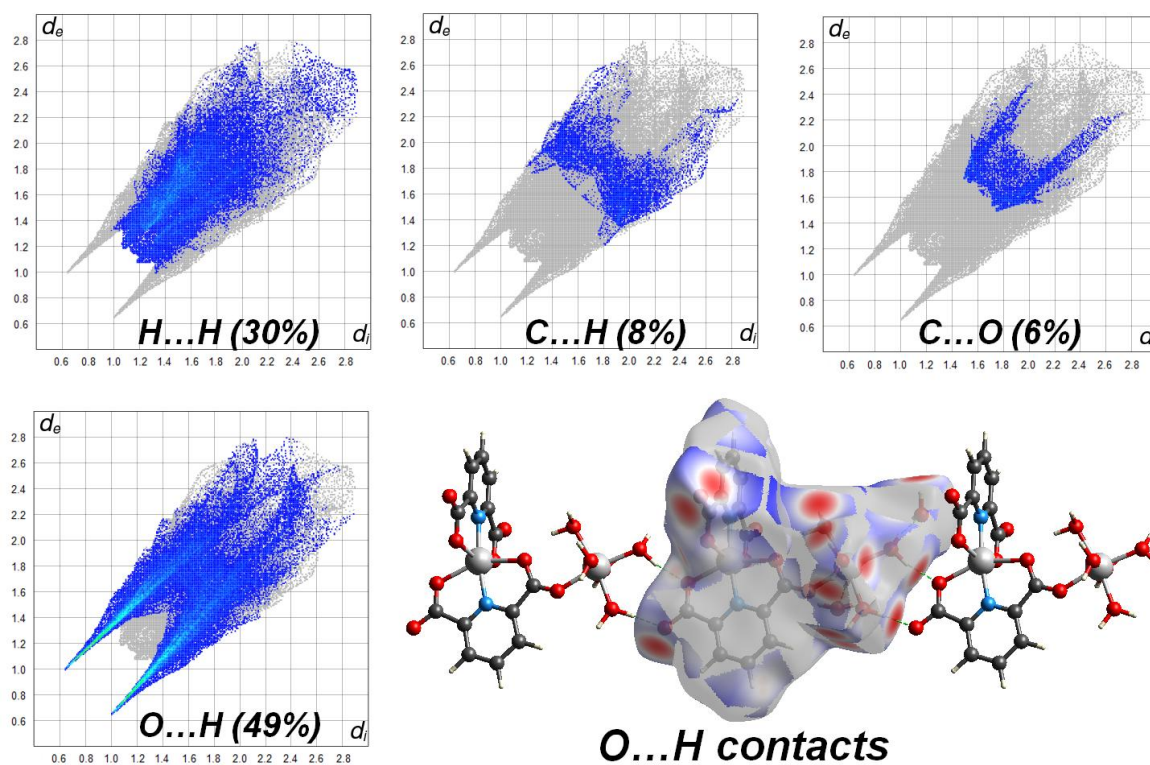


Fig. 4.12. Hirshfeld surface analyses of **9**, mapped with d_{norm} showing O–H $\cdots$ O hydrogen-bonded contacts.

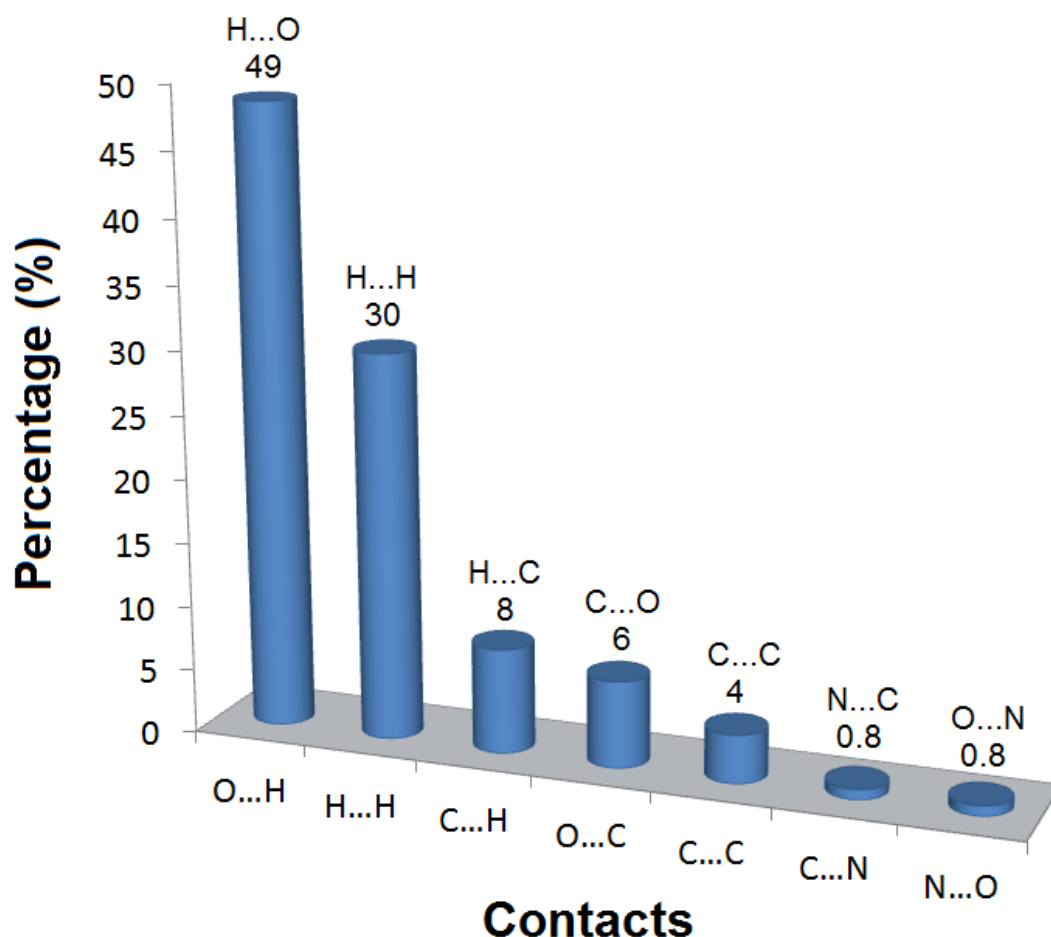


Fig. 4.13. Intermolecular interactions and their percentage contributions for **9**.

4.4.6 Magnetic Susceptibility Measurements of **8** and **9**

The ground state of high-spin octahedral Co(II) is ${}^4T_{1g}$. As the angular orbital momentum is largely quenched, it is difficult to interpret the magnetic moments of compounds with T ground state terms that frequently exhibit significant temperature dependence [78-82]. These types of systems display significant zero-field splitting, which results in considerable magnetic anisotropy because of the enormous spin-orbit coupling.

The magnetic characteristics of **8** were evaluated in the temperature range of 1.8-300 K. The magnetic susceptibility ($\chi_m T$) vs. Temperature plot (T) (where χ_m is the molar magnetic susceptibility per Co(II) unit) is displayed in **Fig. 4.14**. The value of $\chi_m T$ at room temperature is $2.50 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$, which is more than that anticipated for a spin quartet ($\chi_m T = 1.87 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$, for $S = 3/2$ with $g = 2.0$). However, it matches with the values observed for octahedral Co(II) compounds having a strong first-order contribution of the orbital magnetic moment, typical of the ${}^4T_{1g}$ ground state [82-85]. The $\chi_m T$ values for **8** remain constant at about 20 K and considerably decrease at lower temperatures, reaching $1.45 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ at about 1.8 K. The

Chapter 4

decrease of $\chi_m T$ at lower temperatures could be due to the intermolecular antiferromagnetic exchange interaction as well as the depopulation of higher-energy spin-orbit coupling levels of the six coordinated Co(II) metal centers [86, 87]. Furthermore, for **8**, at low temperatures, there is no maximum molar susceptibility. In the solid state, strong antiferromagnetic interactions can, therefore, be ruled out. Both in the presence and absence of applied static fields, there were no alternating current magnetic susceptibility signals.

The Curie and Weiss constant values were calculated using the relationship $\chi_m^{-1} = f(T)$. The calculated Curie constant value for **8** is $2.38 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$. The negative Weiss temperature is comparatively small ($\theta = -1.3 \text{ K}$). The result of non-zero Curie–Weiss temperature, being reported herein, probably replicates the decrease of $\chi_m T$ with decreasing temperature that is attributable to the spin–orbit coupling instead of the frail antiferromagnetic interaction [82].

To investigate the ground state of **8**, we looked into how the magnetization, M , varied with the applied magnetic field at temperatures of 2, 4, 6, and 8 K. The outcomes are displayed in **Fig. 4.15**, where the molar magnetization M (per Co^{II} unit) is represented in μ_B units. In the chosen range of applied fields, the complex does not attain saturation, and the magnetization at 7 T (2 K) is around $2.7\mu_B$. For one uncoupled Co(II) ion in the $S = 3/2$ ground state with $g = 2$ and no zero-field splitting, the shape of the experimental plot for **8** does not obey the Brillouin function. This type of behaviour may be a result of the Co^{II} ions' magnetic anisotropy and/or the weak intermolecular antiferromagnetic interaction at low temperatures.

The $S = 3/2$ state is divided into two Kramer's doublets ($M_s = \pm 1/2$ and $\pm 3/2$) due to spin-orbit coupling, with a distance of $2D$ between them, where D is the axial zero-field splitting parameter. Under the influence of the spin Hamiltonian (eq. 1), the magnetic properties may be viewed as an $S = 3/2$ spin-state, appropriate for depicting magnetic anisotropy [88]:

$$\hat{H} = D \left[\hat{S}_z^2 - \frac{1}{3} S(S+1) \right] + g\beta H \hat{S} \quad (1)$$

Equations (2-4) display the magnetic susceptibility for a magnetically isolated Co(II) ion resulting from this Hamiltonian [88]:

$$\chi_m = \frac{\chi_{||} + 2\chi_{\perp}}{3} \quad (2)$$

$$\chi_{||} = \frac{N\beta^2 g_{||}^2}{4kT} \cdot \frac{1 + 9 \exp\left(-\frac{2D}{kT}\right)}{1 + \exp\left(-\frac{2D}{kT}\right)} \quad (3)$$

Chapter 4

$$\chi_{\perp} = \frac{N\beta^2 g_{\perp}^2}{4kT} \cdot \frac{4 + 3 \frac{kT}{D} \left[1 - \exp\left(-\frac{2D}{kT}\right) \right]}{1 + \exp\left(-\frac{2D}{kT}\right)} \quad (4)$$

Taking into account the possibility of the presence of weak intermolecular magnetic interaction, eq. 2 must be redefined by involving a molecular field rectification term zJ' [79]. This yields the equation (eq.5):

$$\chi_m^{corr} = \frac{\chi_m}{1 - \frac{2zJ'}{N\beta^2 g^2} \chi_m} \quad (5)$$

Here, z is the number of closest neighbours surrounding a certain magnetic species in the crystal system and J' is the interaction parameter between two closest neighbour magnetic species. To avoid over-parameterization, we ignored the rhombic zero-field splitting components and took into account $g_{\parallel} = g_{\perp} = g$ (average Landé factor) during the fitting process. The values obtained from the best fit are: $|D| = 25.5(1) \text{ cm}^{-1}$ (the sign of D cannot be inferred from the data on powder magnetic susceptibility), $zJ' = -0.21(2) \text{ cm}^{-1}$ and $g = 2.31(1)$ for **8**. The best fit was determined by using the criterion $R = \Sigma(\chi_{\text{exp}}T - \chi_{\text{calc}}T)^2 / \Sigma(\chi_{\text{exp}}T)^2$ ($R = 4.42 \times 10^{-4}$), which is based on diminishing the sum of squares of the deviation. In the entire temperature range, the computed curve for **8** (solid line in **Fig. 4.14**) closely fits the experimental data. The value of D falls in the range of similar magneto-structurally studied Co(II) compounds that have been reported [89-91]. Due to the relatively large distance between the paramagnetic Co^{II} ions in the crystal structure (average Co...Co distances are 5.95 Å), the value of zJ' in **8** is very low, which indicates that there are very few intermolecular magnetic interactions. The computed D parameter, however, indicates that in **8**, large magnetic anisotropy is dominating because of its substantially larger value as compared to zJ' .

In contrast to compound **8**, compound **9** is a dinuclear cobalt(II) complex. The magnetic characteristics of **9** are depicted in **Fig. 4.14** as a $\chi_m T$ against T plot (χ_m is the magnetic susceptibility per two Co^{II} ions). The measured $\chi_m T$ value at 300 K is $4.63 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$, which is higher than the spin-only value of $3.75 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ for two uncoupled $S = 3/2$ spins ($g = 2.0$). This is explained by the unquenched orbital angular momentum caused by the cobalt(II) ion's $^4T_{1g}$ ground state [92]. Upon cooling, the $\chi_m T$ value decreases very slowly in the temperature range of 300–50 K but does so sharply in the temperature range of 50–1.8 K to attain the lowest

Chapter 4

value of $3.35\text{cm}^3\text{mol}^{-1}\text{K}$ at 1.8 K. The decrease of magnetic moment with the lowering of temperature can be explained on the basis of three factors, viz.: (i) orbital angular momentum contribution, (ii) a two-cobalt(II) intramolecular antiferromagnetic coupling, and (iii) an antiferromagnetic intermolecular coupling. Since the dinuclear cobalt(II) ions entities are far apart from one another, the intermolecular interactions may be neglected. A fit of χ_m^{-1} , at temperature values higher than 50 K, to the Curie–Weiss law yields a Curie constant (C) value of $4.65\text{cm}^3\text{Kmol}^{-1}$ and a Weiss temperature (θ) value of -1.9K . A weak antiferromagnetic interaction inside the Co(II)–Co(II) dinuclear unit is further indicated by the negative value of the Weiss temperature. As no maximum is observed in the χ_m vs. T plot until 1.8 K, the thermal dependence of χ_m is indicative of a weak antiferromagnetic interaction. Similar to **8**, there are no signs of magnetic susceptibility for alternating current in the case of **9**.

Magnetization studies in the temperature range of 2–8 K confirmed the ground state nature of **9** (Fig. 4.16). With a magnetization value of $\sim 3.6\mu_B$ at 7 T at 2 K, the compound does not reach saturation in the M vs. H measurements. Even at 7 T and 2 K, the magnetization is less than what is expected for two uncoupled $S = 3/2$ systems (with $g = 2$) due to the absence of zero-field splitting. The experimental data do not precisely obey the Brillouin formula for **9**. The experimental data at intermediate magnetic field values are well below the theoretical curve, indicating a weak antiferromagnetic interaction.

As the orbital angular momentum contribution is absent in the ground state term, the spin-only method may be appropriate for this system when considering the distorted octahedral geometry of the high-spin cobalt(II) cations in **9** [86, 87, 93, 94]. The decrease of $\chi_m T$ in the temperature region of 300–1.8K implies the presence of intramolecular antiferromagnetic interactions and in such a case, the Heisenberg–Van Vleck spin Hamiltonian (eq. 6) for an $S = 3/2$ dimer can be used as a simplification [86, 87]:

$$\hat{H} = -2J\hat{S}_1 \cdot \hat{S}_2 \quad (6)$$

Equation (7) was used to fit the magnetic data [86–88].

$$\chi_m = \frac{2N\beta^2 g^2}{kT} \cdot \frac{14 \exp\left(-\frac{12J}{kT}\right) + 5 \exp\left(-\frac{6J}{kT}\right) + \exp\left(-\frac{2J}{kT}\right)}{7 \exp\left(-\frac{12J}{kT}\right) + 5 \exp\left(-\frac{6J}{kT}\right) + 3 \exp\left(-\frac{3J}{kT}\right) + 1} \quad (7)$$

Chapter 4

Here, J is the intradimer interaction parameter (exchange coupling constant) between Co^{II} ions. The best fit of the data utilising the above-mentioned equation for **2** results in $J = -1.21(2) \text{ cm}^{-1}$ and $g = 2.35(1)$ ($R = 8.37 \times 10^{-4}$), as demonstrated by the solid curve in **Fig. 4.14**. In the entire temperature range, the experimental results are reproducible. The Co_2 unit exhibits weak antiferromagnetic interaction, as indicated by the negative J value. Other structurally significant dinuclear cobalt(II) complexes have also exhibited antiferromagnetic coupling interactions, and the observed J values for such complexes have magnitudes close to that reported for **9**. As mentioned previously, the kind of bridging mode, the $\text{Cu} \cdots \text{Cu}$ separations, the coordination arrangement of $\text{Cu}(\text{II})$ centers, and the bond angles of bridging ions, all affect the magnitude and sign of J in carboxylato-based $\text{Cu}(\text{II})$ complexes [95, 96]. Because of the complexities arising from the orbital angular momentum contributions, which are highly reliant on the coordination geometry as well as the ligand field surrounding the metal centre, the magneto-structural correlation for the cobalt(II) complexes is still unclear [97, 98]. However, taking into account that the Co1-O-C-O-Co2 backbone in **9** deviates from planarity, the overlap among the magnetic orbitals of both cobalt (II) ions *via* the *syn-anti* carboxylate linkage is appreciably frail and results in weak antiferromagnetic interactions.

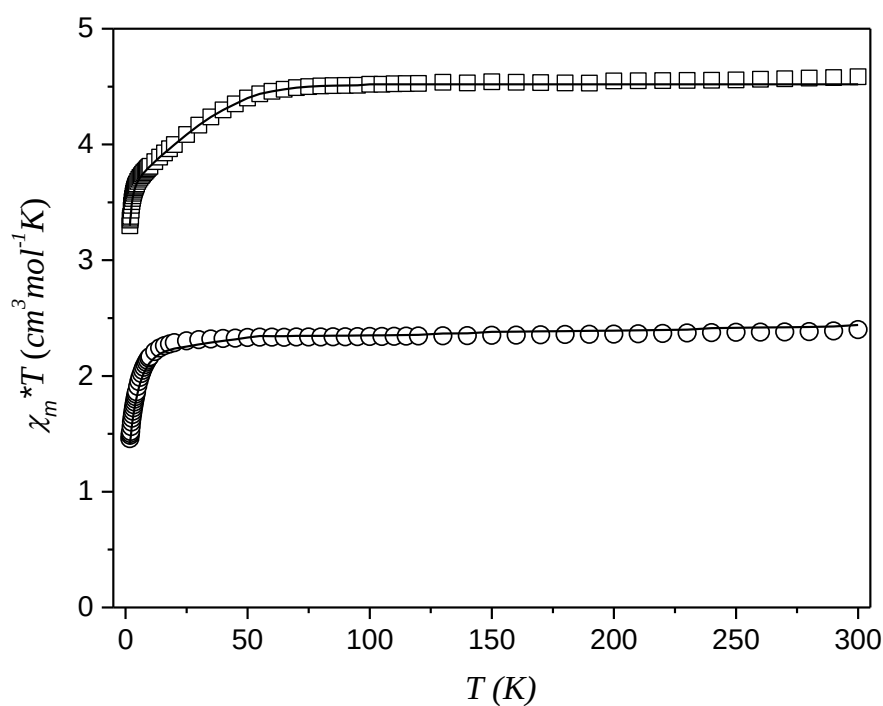


Fig. 4.14. Temperature dependence of experimental $\chi_m T$ ($\circ$) (χ_m per Co^{II} unit) for **8** and $\chi_m T$ ($\square$) (χ_m per Co_2 unit) for **9**. The solid lines are the calculated curves obtained from equations (2-5) for **9** and equations (6-7) for **9**.

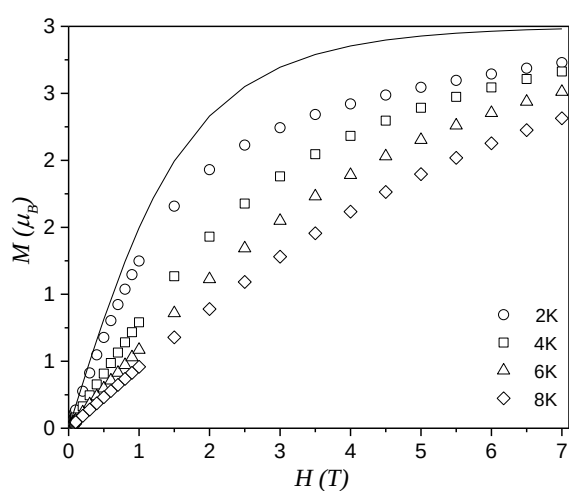


Fig. 4.15. Field dependences of the magnetization (M per Co^{II} ion) for **8**. The solid line is the Brillouin function curve for the system of one uncoupled spin with $S = 3/2$ and $g = 2.0$ in the absence of zero-field splitting.

Chapter 4

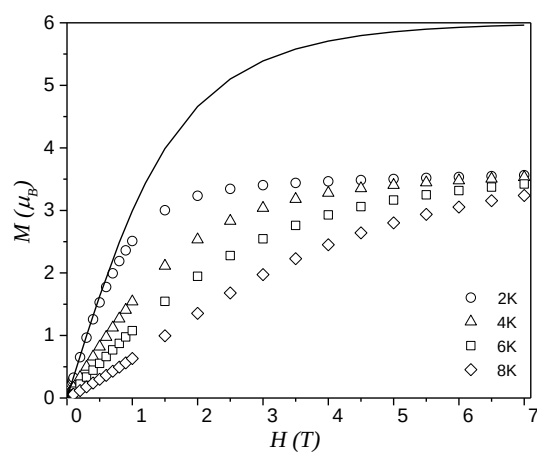


Fig. 4.16. Field dependence of the magnetization (M per Co_2 unit) for **9**. The solid line is the Brillouin function curve for the system of two unpaired spins with $S = 3/2$ and $g = 2.0$ in the absence of zero-field splitting.

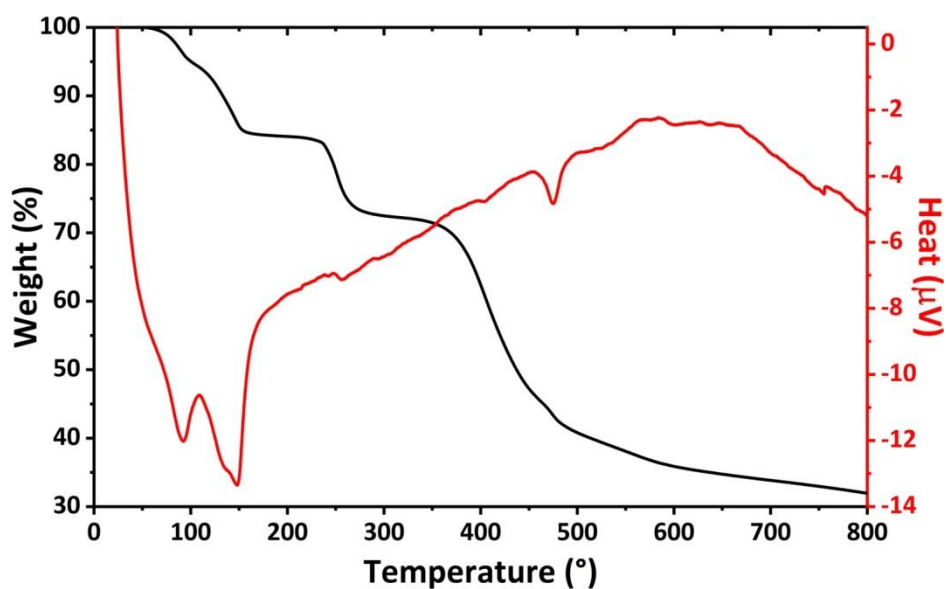


Fig. 4.17. Thermogravimetric analysis curve of complex **8**.

Chapter 4

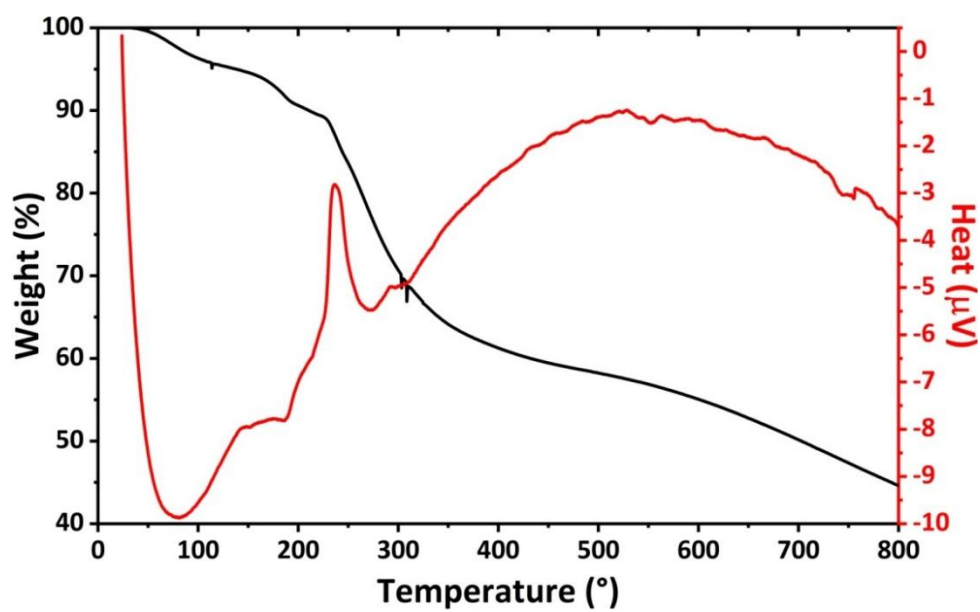


Fig. 4.18. Thermogravimetric analysis curve of complex 9.

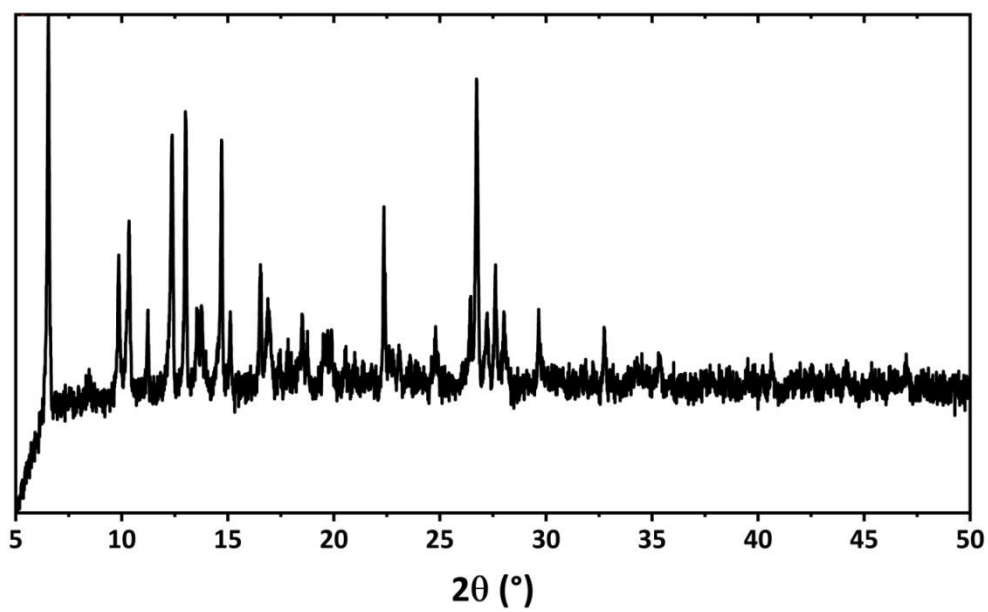


Fig. 4.19. Powder XRD pattern of complex 8.

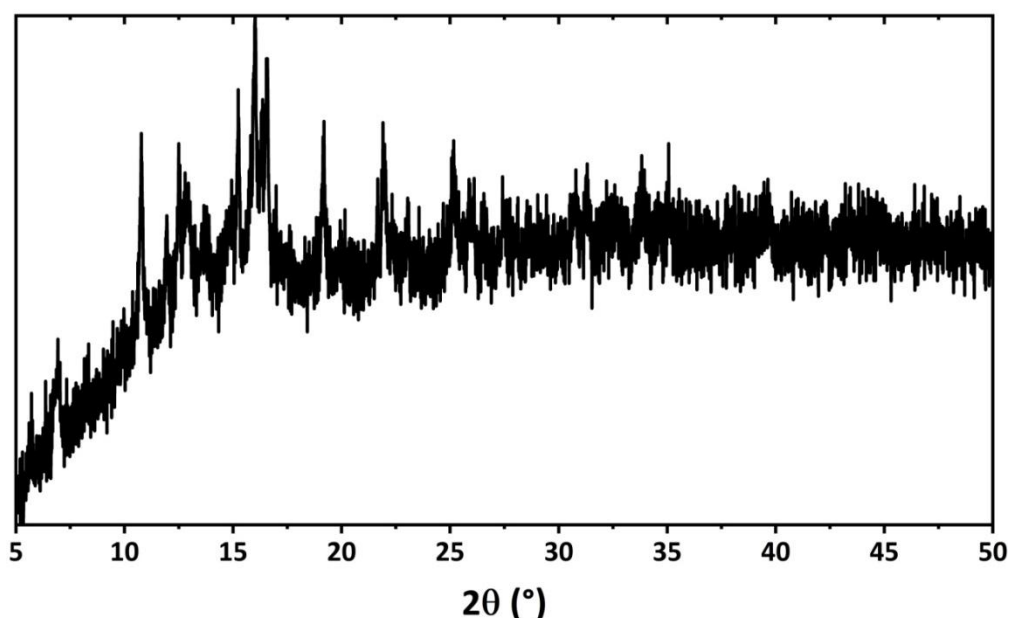


Fig. 4.20. Powder XRD pattern of complex **9**.

4.4.7 DFT Study of **8** and **9**

Fig. 4.21A represents the optimized geometry of **8**. The two $C_{10}H_{18}CoN_6S_2$ units are held together by $S_2O_3^{2-}$ group *via* H-bond formation with a distance of 1.70 to 1.93 Å between them and by $\pi \cdots \pi$ stacking with a distance of 3.56 Å between the units with a Co-Co distance of 5.95 Å. **Fig. 4.21B** represents the molecular electrostatic potential (MEP) of **8**. From **Fig. 4.21B**, it is clear that stacking occurs *via* two cyanide groups indicated by red regions. The electronic transition from HOMO to LUMO is shown in **Fig. 4.21C** with a band gap of 2.37 eV. The charge is transferred from $S_2O_3^{2-}$ to metal, suggesting strong chelation. **Fig. 4.21D** represents the optimized geometry of **9**. Here, water molecules are coordinated to cobalt (II) to satisfy the valency of the latter and also to stabilize the crystal with a Co-Co distance of 4.78 Å. MEP plot for **9**, shown in **Fig. 4.21E**, suggests that H-bonding interactions are the only stabilizing factor for the crystal. Electronic transition with a band gap of 1.90 eV has been shown in **Fig. 4.21F**. The charge-transfer occurs from oxygen to metal, which reveals the donor-acceptor HOMO-LUMO modeling for the prediction of crystal formation. Low magnetic moment values of 0.55 and 0.52 BM per atom for **8** and **9**, respectively, were found. Magnetic susceptibility values of -63.82 and -19.36 au were observed for **8** and **9**, respectively, which indicate their antiferromagnetic behaviour; these findings are in concordance with the experimental results.

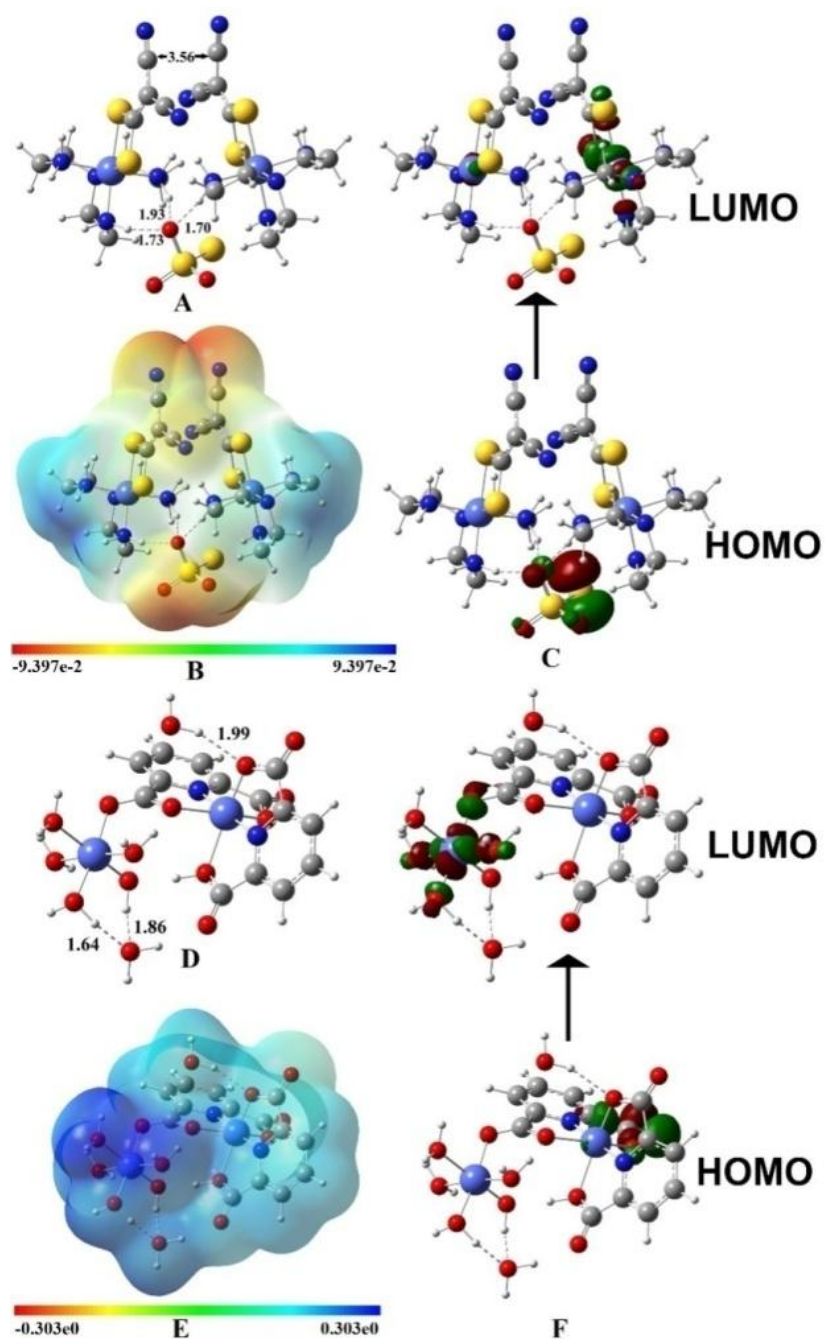


Fig. 4.21. (A) Optimized geometry of **8**, (B) Molecular Electrostatic Potential of A, (C) HOMO to LUMO transition for A, (D) Optimized geometry of complex **9**, (E) Molecular Electrostatic Potential of B, and (F) HOMO to LUMO transition for D.

4.4.8 Electrochemical analysis of **8** and **9**

Cyclic voltammetry was performed on a CH-Instruments Electrochemical Analyzer 600C potentiostat, equipped with three electrodes: glassy carbon as working, platinum as counter,

Chapter 4

and silver (Ag/AgCl) as reference. Solutions of both compounds were prepared in dry DMSO to a concentration of 1 mM, with 0.1 M tetrabutylammonium hexafluorophosphate as the electrolyte. Cyclic voltammetric scans were recorded in a potential range of -2.0 to +0.9 V and were adjusted to the standard hydrogen electrode (SHE) by the introduction of an internal standard, ferrocene. Compound **8** revealed a non-reversible reduction peak at -1.42 V. In comparison **9** revealed two non-reversible reduction peaks at -1.35 and -1.78 V (**Fig. 4.22**). Moving to acetonitrile as an electrolyte solvent documented that **8** does not undergo solvent exchange under these conditions and the CVs show only minor changes. Compound **9**, on the other hand, exhibits a current response that was diminished by a factor of 2 and some of the peaks disappeared, indicating the susceptibility of this compound to solvent exchange.

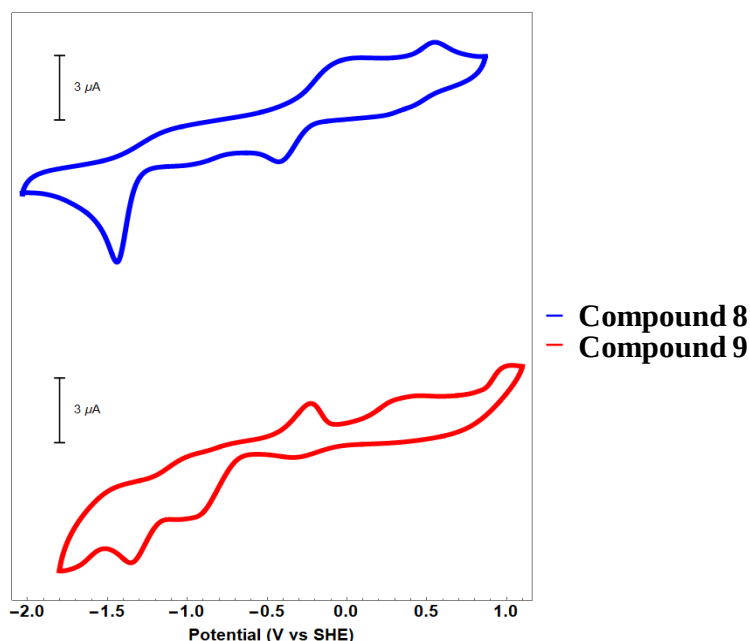


Fig. 4.22. Cyclic voltammograms recorded in dry DMSO for both compounds were corrected by the introduction of an internal standard.

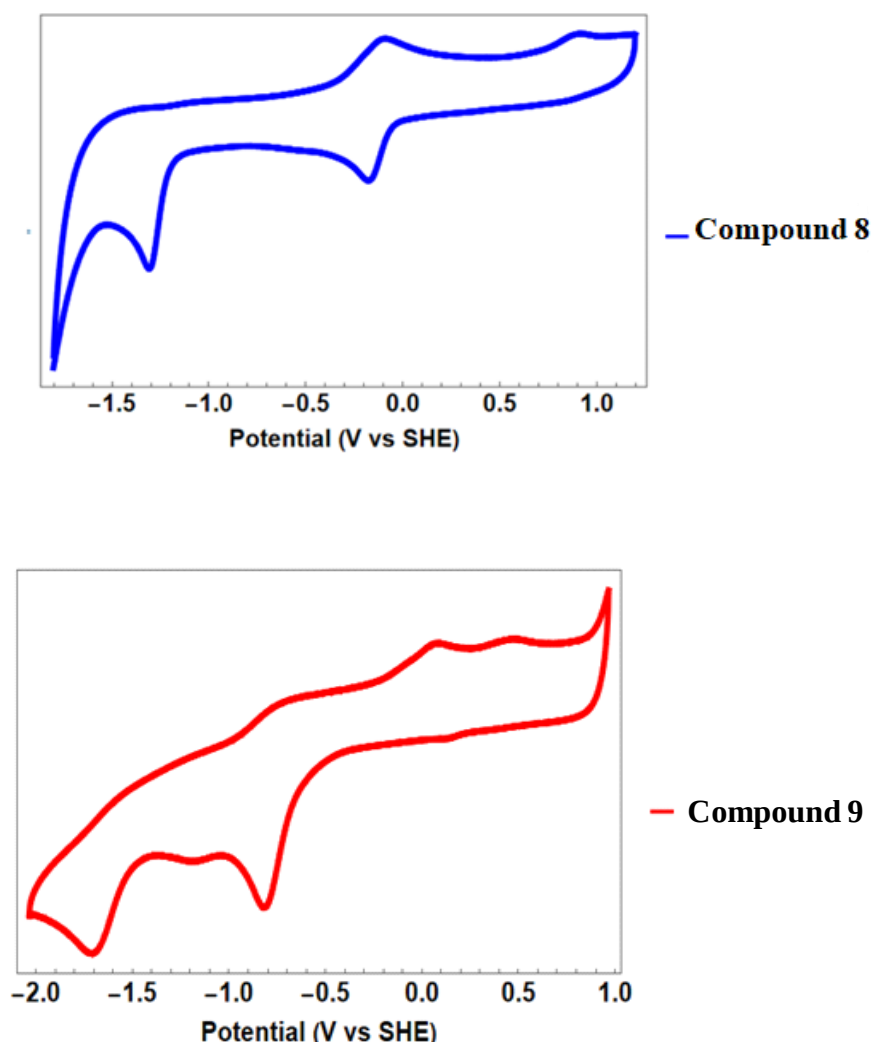


Fig. 4.23. Cyclic voltammograms recorded in dry CH_3CN for both the compounds were corrected by the introduction of an internal standard. Experimental conditions are the same as those described in the body of the manuscript.

4.4.8 Photocatalytic Hydrogen Evolution of 8 and 9

Using the high throughput photoreactor, the two compounds were tested for their water reduction capabilities. Concentration was gradated in two dimensions, by variation of PS and WRC concentrations by either column or row, respectively (**Fig. 4.24**). The results demonstrate that the catalysts are highly efficient in terms of turn-over-numbers (TON) per Co when they are at lower concentration with higher concentration of PS. A comparison of rates of light-driven hydrogen evolution of the two compounds against standard cobalt-containing systems can be found in the Supporting Information (**Fig. 4.25** and **Fig. 4.26**).

Chapter 4

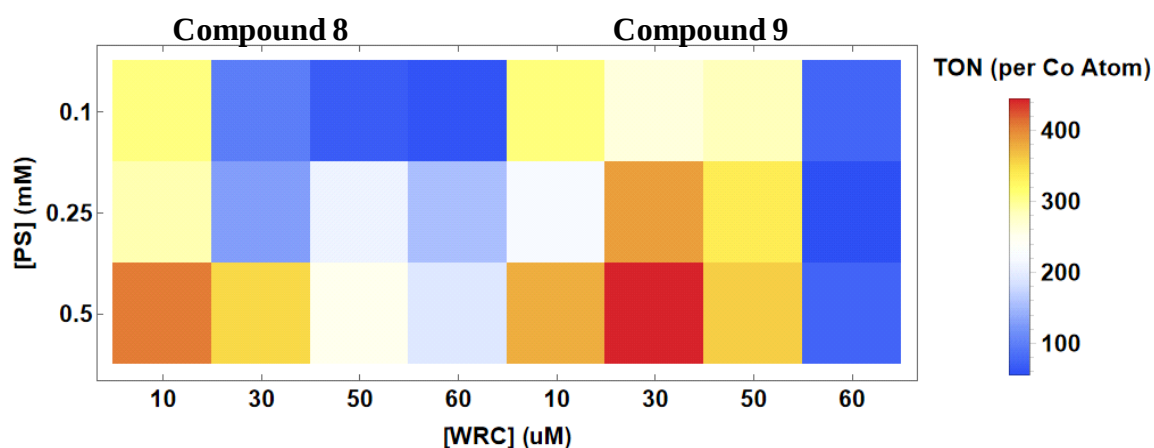


Fig. 4.24. TON per Co atom for the production of hydrogen in photocatalytic water reduction presented for various PS and WRC concentration combinations.

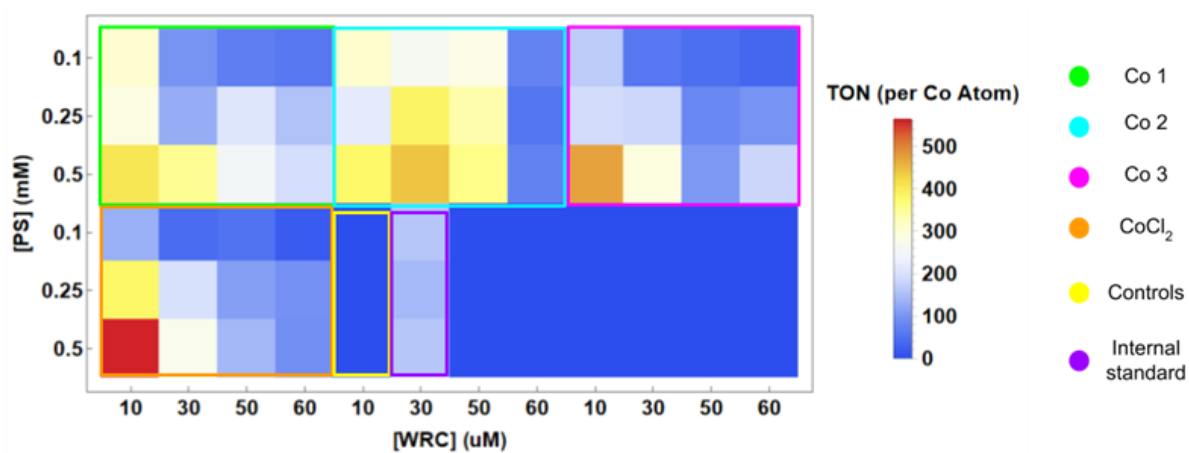


Fig. 4.25. TON per Co atom for the production of hydrogen in photocatalytic water reduction presented for three cobalt complexes, CoCl₂, controls, and an internal standard at varying PS and WRC concentrations.

Chapter 4

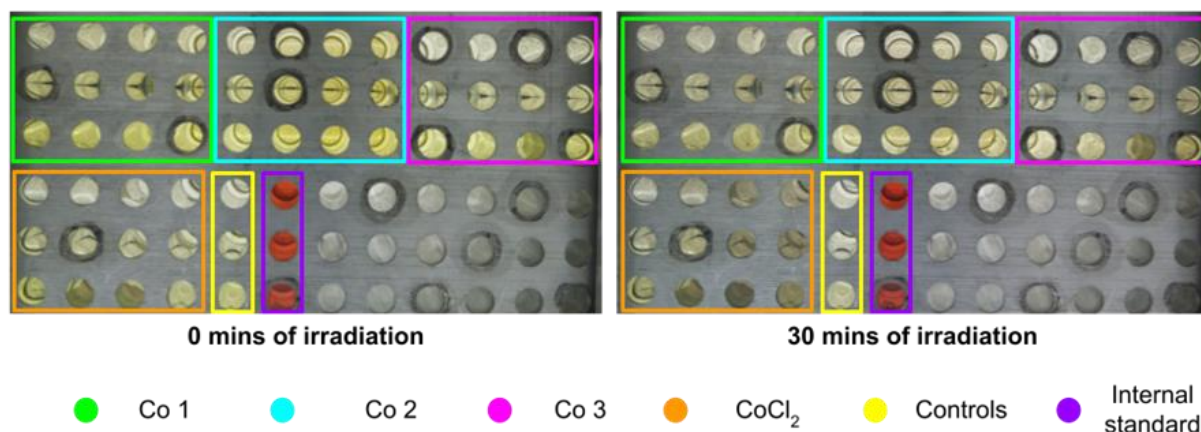


Fig. 4.26. Images of reaction solutions for the production of hydrogen in photocatalytic water reduction are presented for three cobalt complexes, CoCl₂, controls, and an internal standard with no irradiation and after 30 minutes of irradiation.

Conclusions

In this work, we have successfully synthesized two cobalt (II)-based coordination complexes **8** and **9**, which exhibit supramolecular assemblies. In **8**, the X-ray structure analysis discloses the coordination of Co1 ion to four enamine nitrogen atoms of ligand *tetraen* and two sulfur atoms of *i-mnt*²⁻ ligand, creating a distorted octahedral geometry. The Co2, Co3, and Co4 atoms have similar geometries. The thiosulphate ions act as a connector between two cobalt(II) centers. The two thiosulphate ions and Co(II) ions are connected *via* intermolecular hydrogen bonding. In compound **9**, the dicarboxylate ligand acts as a tetradentate ligand and the two Co (II) centers are joined by a carboxylate bridging ligand. HS analyses decoded the different types of noncovalent interactions, which play important roles in stabilizing the crystal structures of both coordination compounds. For **8**, the most significant contributions to the Hirshfeld surface are N···H, H···H, S···H, and O···H interactions. In the case of **9**, the outcome of the investigation shows that the O···H (49%) contacts are the most prominent ones, whereas H···H (30%) and C···H (8%) contacts are less noteworthy. Magnetic susceptibility measurement results for **8** suggest that the effect of zero-field splitting of Co^{II} ion is mainly responsible for the decrease of magnetic moment at low temperatures. The magnetic studies of **9** point out the presence of weak intermolecular exchange interactions. The HOMO-LUMO donor-acceptor modeling revealed from the DFT study also supports for prediction of crystal formation. Cyclic voltammetry confirmed non-reversible reduction peaks beyond -1 V (vs. SHE) for both complexes. Furthermore, photocatalytic hydrogen evolution testing resulted in the conclusion

Chapter 4

that both the complexes perform highly efficiently at lower concentrations resulting in TON per Co Atom of up to 325.

4.5. Experimental

Materials and physical measurements

All chemicals were reagent grade, procured from commercial sources, and used without purification. The solvents were purified by standard procedures. The 1,1-dicyano-2,2-ethylenedithiolate di-potassium salt ($K_2i\text{-mnt}$) **7** was synthesized according to a procedure reported previously [99]. Fourier-Transform Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer with KBr pellets in the range of 4000–400 cm^{-1} . Elemental analysis was carried out in Perkin-Elmer 2500 Series II elemental analyzer. Cyclic voltammetry was performed on a CH-Instruments Electrochemical Analyzer-600C Potentiostat at a scan rate of 0.1 V s^{-1} using negative scan polarity in a three-electrode system configuration.

4.5.1 Synthesis of the 1, 1-dicyano-2, 2-ethylenedithiolate ($i\text{-mnt}^{2-}$) ligand **7** and Co(II) complex **8** and **9**

Synthesis of ligand **7**

Pulverized potassium hydroxide (0.2 mol) was suspended in dioxane (100 mL) and a solution of malononitrile (0.1 mol) and carbon disulphide (0.1 mol) in dioxane (50 mL) was added with stirring and cooling to maintain a temperature of 15–20 $^{\circ}\text{C}$. After the addition, the suspension was stirred for another 20 mins and diluted with 250 mL of ether. The yellow precipitate was filtered, washed with dioxane-ether (1:1) and dried in vacuo over sodium hydroxide and phosphorous pentoxide. Yield is nearly 100%.

Synthesis of Co(II) complex **8**

To a stirred solution of $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (1.03 mmol) in 20 mL of HPLC-grade methanol, a solution of tris (2-aminoethyl) amine (*tetraen*) ligand (3.09 mmol) dissolved in 15 mL of HPLC-grade methanol was added slowly with constant stirring at room temperature. After 30 mins of stirring, $K_2i\text{-mnt} \cdot \text{H}_2\text{O}$ (1.03 mmol) ligand dissolved in 15 mL HPLC-grade methanol and sodium thiosulphate (1.03 mmol) dissolved in 10 mL of distilled water were slowly added to the reaction mixture, resulting in the immediate formation of a deep brown precipitate. The stirring was continued for 3 h. The compound was collected through filtration, washed a few

Chapter 4

times with methanol and ether, and dried. Single crystals of **8**, suitable for X-ray analysis were grown from a solution of Dimethyl Sulphoxide (DMSO).

Complex 8: Yield: 72%, FTIR (ν cm⁻¹, KBr): 3428-3120 [ν (N-H) symmetric and asymmetric stretching modes], 2930 (ν C-H stretching), 2201 (ν C $\equiv$ N stretching), 1612 (ν N-H bending scissoring vibration), 1384 [ν (C=C) absorption band], 1030 and 945 [ν (=CS₂) group], 899 and 889 [ν (C-S) band], 747 (ν Co-S band), 521 and 479 (ν Co-N band). *Anal.* Calc. for C₂₀H₃₆Co₂N₁₂S₆O₃: C, 29.92; H, 4.52; N, 20.94. Found: C, 29.90; H, 4.51; N, 20.92 %.

Synthesis of Co(II) complex 9

Complex 9 was synthesized according to a previously described method [64].

A solution of CoCl₂.6H₂O (0.24 g, 1 mmol) in 15 mL of water was added slowly to a solution of pyridine-2, 6 dicarboxylic acid (0.34 g, 2 mmol) in 15 ml of water. The P^H of the resultant solution was adjusted to 7.5 by the addition of NaOH solution and the reaction mixture stirred for 6 hours. Rose coloured single crystals of **9**, suitable for X-ray analysis were obtained after 5 days.

Complex 9: Yield: 68%, FTIR (ν cm⁻¹, KBr): 3480-3390 [ν (O-H) symmetric and asymmetric stretching modes], 1616 (ν C-O stretching), 1386 (ν (C=C) absorption band), 592 (ν Co-O band), 543 and 484 (ν Co-N band). *Anal.* Calc. for C₁₄H₂₀Co₂N₂O₁₅: C, 29.29; H, 3.51; N, 4.88. Found: C, 29.31; H, 3.50; N, 4.86 %.

4.5.2 Crystallographic data collection and refinement of 8 and 9

For recording the X-ray diffraction data for **8**, an inclusion-free red prism was chosen, whereas a clear purple needle was chosen for **9**. The said data were collected with graphite-monochromatized Mo-K α radiation (λ = 0.71073 Å) on a Bruker APEX-II CCD (100 (2) K) diffractometer [100]. The structures were solved using SHELXT [101], a refinement was done using SHELXL-2018 with least-squares minimization versus F^2 [103]. Multi-scan absorption correction was applied (SADABS) [103]. All H atoms were initially located in a different Fourier map and were refined using a riding model. The H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C—H distances in the range of 0.95–1.00 Å. The related experimental details for **8** and **9** are summarized in **Table 4.5**.

Chapter 4

4.5.3 Hirshfeld surface analysis of **8** and **9**

Hirshfeld surface analysis [104] and fingerprint plots were generated with the *CrystalExplorer21* program [105] to investigate the different interactions in the crystal structures of **8** and **9**.

4.5.4 Theoretical Studies of **8** and **9**

Ground-state geometry optimization of crystal systems **8** and **9** was performed with the help of Density Functional Theory using Gaussian 09 [106]. To determine the precise geometry of the crystals, B3LYP hybrid function was used [107]. For the non-metal elements, the 6-31G(d) basis function was used while for cobalt, the pseudopotential-based LANL2DZ basis set was employed.

4.5.5 Magnetic Susceptibility Measurements of **8** and **9**

A Quantum Design SQUID magnetometer (type MPMS-3) was used to assess magnetic susceptibility and magnetization. Polycrystalline samples of **8** and **9** were subjected to direct current magnetic measurements in the temperature range of 1.8-300 K with an externally imposed magnetic field of 0.5 T. Corrections were made by subtracting the sample-holder signal and contribution χ_D estimated from Pascal's constants [108].

4.5.6 Photocatalytic Hydrogen Evolution of **8** and **9**

Compounds **8** and **9** were tested as water reduction catalysts (WRC) in a photocatalytic water reduction system using $[\text{Ir}(\text{Fmppy})_2 \text{ dtbbpy}]\text{PF}_6$ (where Fmppy = 4'-fluoro-2-phenyl-5-methylpyridine, and dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) as the photosensitizer (PS), and triethanolamine (Alfa Aesar L04486) as the sacrificial donor (SD). Each test sample contained 750 μL of a total solution comprising 600 μL of PS and WRC solutions in DMSO (J.T. Baker JT 9224) and 150 μL of 30% w/w aqueous solution of SD. The reactions were conducted at a PS concentration range of 0.1 to 0.5 mM and a WRC concentration range of 0.01 to 0.1 mM. Hydrogen evolution was measured on a parallel high-throughput photoreactor using colorimetric chemo-sensitive H_2 detector (DetecTape Hydrogen Detection Tape – Midsun Specialty Products, Item DT-H210015-PF4) as described previously [109, 110].

Chapter 4

4.6 References

- [1] Voumik, L. C., & Sultana, T. (2022). Impact of urbanization, industrialization, electrification and renewable energy on the environment in BRICS: fresh evidence from novel CS-ARDL model. *Heliyon*, 8(11).
- [2] Alagoz, E., & Alghaw1, Y. (2023). The Future of Fossil Fuels: Challenges and Opportunities in a Low-Carbon. *International Journal of Earth Sciences Knowledge and Applications*, 5(3), 381-388.
- [3] Sousa, S. F., Souza, B. L., Barros, C. L., & Patrocinio, A. O. T. (2019). Inorganic photochemistry and solar energy harvesting: Current developments and challenges to solar fuel production. *International Journal of Photoenergy*, 2019(1), 9624092.
- [4] Armaroli, N., & Balzani, V. (2007). The future of energy supply: challenges and opportunities. *Angewandte Chemie International Edition*, 46(1-2), 52-66.
- [5] Sivula, K. (2015). Toward economically feasible direct solar-to-fuel energy conversion. *The Journal of Physical Chemistry Letters*, 6(6), 975-976.
- [6] Xu, You, and Rong Xu. "Nickel-based cocatalysts for photocatalytic hydrogen production." *Applied Surface Science* 351 (2015): 779-793.
- [7] Zhao, W., Chen, Z., Yang, X., Qian, X., Liu, C., Zhou, D., ... & Ok, Y. S. (2020). Recent advances in photocatalytic hydrogen evolution with high-performance catalysts without precious metals. *Renewable and Sustainable Energy Reviews*, 132, 110040.
- [8] Turner, J. A. (2004). Sustainable hydrogen production. *Science*, 305(5686), 972-974.
- [9] Haryanto, A., Fernando, S., Murali, N., & Adhikari, S. (2005). Current status of hydrogen production techniques by steam reforming of ethanol: a review. *Energy & Fuels*, 19(5), 2098-2106.
- [10] Lewis, N. S., & Nocera, D. G. (2006). Powering the planet: Chemical challenges in solar energy utilization. *Proceedings of the National Academy of Sciences*, 103(43), 15729-15735.
- [11] Cook, T. R., Dogutan, D. K., Reece, S. Y., Surendranath, Y., Teets, T. S., & Nocera, D. G. (2010). Solar energy supply and storage for the legacy and nonlegacy worlds. *Chemical reviews*, 110(11), 6474-6502.
- [12] Niklas, J., Mardis, K. L., Rakhimov, R. R., Mulfort, K. L., Tiede, D. M., & Poluektov, O. G. (2012). The hydrogen catalyst cobaloxime: A multifrequency EPR and DFT study of cobaloxime's electronic structure. *The Journal of Physical Chemistry B*, 116(9), 2943-2957
- [13] Dempsey, J. L., Brunschwig, B. S., Winkler, J. R., & Gray, H. B. (2009). Hydrogen evolution catalyzed by cobaloximes. *Accounts of chemical research*, 42(12), 1995-2004.

Chapter 4

- [14] Chouhan, N., Liu, R. S., & Zhang, J. (2017). *Photochemical water splitting: materials and applications*. CRC Press.
- [15] Balat, M. (2008). Possible methods for hydrogen production. *Energy Sources, Part A: Recovery, Utilization, and Environmental Effects*, 31(1), 39-50.
- [16] Fang, S., & Hu, Y. H. (2019). Recent progress in photocatalysts for overall water splitting. *International Journal of Energy Research*, 43(3), 1082-1098.
- [17] Ren, N., Cao, G., Wang, A., Lee, D. J., Guo, W., & Zhu, Y. (2008). Dark fermentation of xylose and glucose mix using isolated *Thermoanaerobacterium thermosaccharolyticum* W16. *International Journal of Hydrogen Energy*, 33(21), 6124-6132.
- [18] Khetkorn, W., Rastogi, R. P., Incharoensakdi, A., Lindblad, P., Madamwar, D., Pandey, A., & Larroche, C. (2017). Microalgal hydrogen production—a review. *Bioresource technology*, 243, 1194-1206.
- [19] Zhang, P., Wang, M., Li, C., Li, X., Dong, J., & Sun, L. (2010). Photochemical H₂ production with noble-metal-free molecular devices comprising a porphyrin photosensitizer and a cobaloxime catalyst. *Chemical communications*, 46(46), 8806-8808.
- [20] Hogue, R. W., Schott, O., Hanan, G. S., & Brooker, S. (2018). A smorgasbord of 17 cobalt complexes active for photocatalytic hydrogen evolution. *Chemistry—A European Journal*, 24(39), 9820-9832.
- [21] Lazarides, T., McCormick, T., Du, P., Luo, G., Lindley, B., & Eisenberg, R. (2009). Making hydrogen from water using a homogeneous system without noble metals. *Journal of the American Chemical Society*, 131(26), 9192-9194.
- [22] Han, Z., & Eisenberg, R. (2014). Fuel from water: the photochemical generation of hydrogen from water. *Accounts of chemical research*, 47(8), 2537-2544.
- [23] Schrauzer, G. N., & Kohnle, J. (1964). Coenzym B₁₂-Modelle. *Chemische Berichte*, 97(11), 3056-3064.
- [24] Wagner, F., & Bernhauer, K. (1964). New aspects of the structure of corrinoid coenzymes. *Annals of the New York Academy of Sciences*, 112(2), 580-589.
- [25] Dolui, D., Khandelwal, S., Majumder, P., & Dutta, A. (2020). The odyssey of cobaloximes for catalytic H₂ production and their recent revival with enzyme-inspired design. *Chemical Communications*, 56(59), 8166-8181.
- [26] Mulfort, K. L., & Tiede, D. M. (2010). Supramolecular Cobaloxime Assemblies for H₂ Photocatalysis: An Initial Solution State Structure– Function Analysis. *The Journal of Physical Chemistry B*, 114(45), 14572-14581.

Chapter 4

- [27] Ragsdale, S. W., Lindahl, P. A., & Münck, E. (1987). Mössbauer, EPR, and optical studies of the corrinoid/iron-sulfur protein involved in the synthesis of acetyl coenzyme A by *Clostridium thermoaceticum*. *Journal of Biological Chemistry*, 262(29), 14289-14297.
- [28] Bakac, A., & Espenson, J. H. (1984). Unimolecular and bimolecular homolytic reactions of organochromium and organocobalt complexes. Kinetics and equilibria. *Journal of the American Chemical Society*, 106(18), 5197-5202.
- [29] Connolly, P., & Espenson, J. H. (1986). Cobalt-catalyzed evolution of molecular hydrogen. *Inorganic Chemistry*, 25(16), 2684-2688.
- [30] Razavet, M., Artero, V., & Fontecave, M. (2005). Proton electroreduction catalyzed by cobaloximes: Functional models for hydrogenases. *Inorganic chemistry*, 44(13), 4786-4795.
- [31] Hu, X., Cossairt, B. M., Brunschwig, B. S., Lewis, N. S., & Peters, J. C. (2005). Electrocatalytic hydrogen evolution by cobalt difluoroboryl-diglyoximate complexes. *Chemical communications*, (37), 4723-4725.
- [32] Lakadamyali, F., Kato, M., Muresan, N. M., & Reisner, E. (2012). Selective reduction of aqueous protons to hydrogen with a synthetic cobaloxime catalyst in the presence of atmospheric oxygen. *Angewandte Chemie International Edition*, 37(51), 9381-9384.
- [33] Mulfort, K. L., & Tiede, D. M. (2010). Supramolecular Cobaloxime Assemblies for H₂ Photocatalysis: An Initial Solution State Structure–Function Analysis. *The Journal of Physical Chemistry B*, 114(45), 14572-14581.
- [34] Fihri, A., Artero, V., Razavet, M., Baffert, C., Leibl, W., & Fontecave, M. (2008). Cobaloxime-based photocatalytic devices for hydrogen production. *Angewandte Chemie*, 120(3), 574.
- [35] Li, C., Wang, M., Pan, J., Zhang, P., Zhang, R., & Sun, L. (2009). Photochemical hydrogen production catalyzed by polypyridyl ruthenium–cobaloxime heterobinuclear complexes with different bridges. *Journal of Organometallic Chemistry*, 694(17), 2814-2819.
- [36] Hawecker, J., Lehn, J. M., & Ziessel, R. (1983). Efficient homogeneous photochemical hydrogen generation and water reduction mediated by cobaloxime or macrocyclic cobalt complexes. *Nouv. J. Chim.; (France)*, 7(5).
- [37] S. Vela, M. Deumal, J. Ribas-Arino, J.J. Novoa, Tracing the sources of the different magnetic behavior in the two phases of the bistable (BDTA) ₂ [Co (mnt) ₂] compound, *Inorganic Chemistry* 51(16) (2012) 8646-8648.
- [38] A.K. Mondal, A. Mondal, B. Dey, S. Konar, Influence of the coordination environment on easy-plane magnetic anisotropy of pentagonal bipyramidal cobalt (II) complexes, *Inorganic Chemistry* 57(16) (2018) 9999-10008.

Chapter 4

- [39] J.W. Shin, A.R. Jeong, S.Y. Lee, C. Kim, S. Hayami, K.S. Min, Trinuclear nickel and cobalt complexes containing unsymmetrical tripodal tetradentate ligands: syntheses, structural, magnetic, and catalytic properties, *Dalton Transactions* 45(36) (2016) 14089-14100.
- [40] D. Maniaki, E. Pilichos, S.P. Perlepes, Coordination clusters of 3d-metals that behave as single-molecule magnets (SMMs): synthetic routes and strategies, *Frontiers in Chemistry* 6 (2018) 461.
- [41] J.-H. Wang, Z.-Y. Li, M. Yamashita, X.-H. Bu, Recent progress on cyano-bridged transition-metal-based single-molecule magnets and single-chain magnets, *Coordination Chemistry Reviews* 428 (2021) 213617.
- [42] S. Ghosh, S. Kamilya, M. Das, S. Mehta, M.-E. Boulon, I. Nemec, M. Rouziers, R. Herchel, A. Mondal, Effect of Coordination Geometry on Magnetic Properties in a Series of Cobalt (II) Complexes and Structural Transformation in Mother Liquor, *Inorganic Chemistry* 59(10) (2020) 7067-7081.
- [43] J. Wang, J.-N. Li, S.-L. Zhang, X.-H. Zhao, D. Shao, X.-Y. Wang, Syntheses and magnetic properties of a pyrimidyl-substituted nitronyl nitroxide radical and its cobalt (II) complexes, *Chemical Communications* 52(28) (2016) 5033-5036.
- [44] S.-J. Bao, Z.-M. Xu, Y. Ju, Y.-L. Song, H. Wang, Z. Niu, X. Li, P. Braunstein, J.-P. Lang, The covalent and coordination co-driven assembly of supramolecular octahedral cages with controllable degree of distortion, *Journal of the American Chemical Society* 142(31) (2020) 13356-13361.
- [45] H.A. Nkabyo, I. Barnard, K.R. Koch, R.C. Luckay, Recent advances in the coordination and supramolecular chemistry of monopodal and bipodal acylthiourea-based ligands, *Coordination Chemistry Reviews* 427 (2021) 213588.
- [46] G.E. Decker, G.R. Loring, M.M. Deegan, E.D. Bloch, MOF-mimetic molecules: Carboxylate-based supramolecular complexes as molecular metal-organic framework analogues, *Journal of Materials Chemistry A* 8(8) (2020) 4217-4229.
- [47] J. Gu, M. Wen, X. Liang, Z. Shi, M.V. Kirillova, A.M. Kirillov, Multifunctional aromatic carboxylic acids as versatile building blocks for hydrothermal design of coordination polymers, *Crystals* 8(2) (2018) 83.
- [48] G. Moreno-Alcántar, L. Turcio-García, J.M. Guevara-Vela, E. Romero-Montalvo, T. Rocha-Rinza, Á.M. Pendás, M. Flores-Álamo, H. Torrens, Directing the crystal packing in triphenylphosphine gold (I) thiolates by ligand fluorination, *Inorganic chemistry* 59(13) (2020) 8667-8677.

Chapter 4

- [49] M.R. Carlson, D.L. Gray, C.P. Richers, W. Wang, P.-H. Zhao, T.B. Rauchfuss, V. Pelmeshnikov, C.C. Pham, L.B. Gee, H. Wang, Sterically stabilized terminal hydride of a diiron dithiolate, *Inorganic chemistry* 57(4) (2018) 1988-2001.
- [50] G. Li, M.F. Mark, H. Lv, D.W. McCamant, R. Eisenberg, Rhodamine-platinum diimine dithiolate complex dyads as efficient and robust photosensitizers for light-driven aqueous proton reduction to hydrogen, *Journal of the American Chemical Society* 140(7) (2018) 2575-2586.
- [51] D. Coucouvanis, The chemistry of the dithioacid and 1, 1-dithiolate complexes, 1968–1977, *Progress in Inorganic Chemistry* (1979) 301-469.
- [52] G. Hogarth, K. Karlin, In *Prog. Inorg. Chem*, Wiley Hoboken, NJ, 2005.
- [53] S. Naeem, L. Delaude, A.J. White, J.D. Wilton-Ely, The use of imidazolium-2-dithiocarboxylates in the formation of gold (I) complexes and gold nanoparticles, *Inorganic chemistry* 49(4) (2010) 1784-1793.
- [54] M.K. Singh, S. Sutradhar, B. Paul, S. Adhikari, F. Laskar, R.J. Butcher, S. Acharya, A. Das, A new cadmium (II) complex with bridging dithiolate ligand: Synthesis, crystal structure and antifungal activity study, *Journal of Molecular Structure* 1139 (2017) 395-399.
- [55] M.K. Singh, S. Sutradhar, B. Paul, S. Adhikari, F. Laskar, S. Acharya, D. Chakraborty, S. Biswas, A. Das, S. Roy, Mixed-ligand complexes of zinc (II) with 1, 1-dicyanoethylene-2, 2-dithiolate and N-donor ligands: A combined experimental and theoretical study, *Journal of Molecular Structure* 1164 (2018) 334-343.
- [56] S. Adhikari, T. Bhattacharjee, R.J. Butcher, M. Porchia, M. De Franco, C. Marzano, V. Gandin, F. Tisato, Synthesis and characterization of mixed-ligand Zn (II) and Cu (II) complexes including polyamines and dicyano-dithiolate (2-): In vitro cytotoxic activity of Cu (II) compounds, *Inorganica Chimica Acta* 498 (2019) 119098.
- [57] S. Adhikari, T. Bhattacharjee, P. Nath, A. Das, J.P. Jasinski, R.J. Butcher, D. Maiti, Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study, *Inorg. Chim. Acta* (512) (2020).
- [58] S. Adhikari, T. Bhattacharjee, A. Das, S. Roy, C.G. Daniliuc, J.K. Zaręba, A. Bauza, A. Frontera, On the supramolecular properties of neutral, anionic and cationic cadmium complexes harvested from dithiolate–polyamine binary ligand systems, *CrystEngComm* 22(46) (2020) 8023-8035.
- [59] T. Bhattacharjee, S. Adhikari, R.J. Butcher, Supramolecular Properties Directed by Weak Interactions in a Copper (II) Complex Based on 8-Hydroxy Quinoline-Pyridine Binary Ligand

Chapter 4

Systems: Crystal Structure and Hirshfeld Surface Analyses, *Journal of Chemical Crystallography* (2021) 1-12.

[60] T. Bhattacharjee, S. Adhikari, A. Datta, C.-G. Daniliuc, M. Montazeri, R. Naghiha, P. Hayati, Cadmium (II) coordination polymer based on flexible dithiolate-polyamine binary ligands system: Crystal structure, Hirshfeld surface analysis, antimicrobial, and DNA cleavage potential, *Polyhedron* 211 (2022) 115544.

[61] T. Bhattacharjee, S. Adhikari, A.H. Sheikh, G. Mahmoudi, S. Mlowe, M.P. Akerman, N.A. Choudhury, S. Chakraborty, R.J. Butcher, A.R. Kennedy, Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthalaldimine and its Ni (II) complex, *Journal of Molecular Structure* 1269 (2022) 133717.

[62] S.C. Zacharias, G. Ramon, S.A. Bourne, Supramolecular metallogels constructed from carboxylate gelators, *Soft Matter* 14(22) (2018) 4505-4519.

[63] Q. Wang, S.-L. Dong, D.-D. Tao, Z. Li, Y.-B. Jiang, Ag (I)-thiolate coordination polymers: Synthesis, structures and applications as emerging sensory ensembles, *Coordination Chemistry Reviews* 432 (2021) 213717.

[64]. Qi, Y. Wang, H. Fan, M. Cao, L. Mao, C. Hu, E. Wang, N. Hu, H. Jia, Structure characterization and physical properties of a complex with supramolecular architectures Co₂ (2, 6-DPC) 2Co (H₂O) 5· 2H₂O Y (DPC = 2, 6-pyridinedicarboxylate), *Journal of molecular structure* 694(1-3) (2004) 73-78.

[65] D. Avcı, S. Altürk, F. Sönmez, Ö. Tamer, A. Başoğlu, Y. Atalay, B.Z. Kurt, N. Dege, Novel Cu (II), Co (II) and Zn (II) metal complexes with mixed-ligand: Synthesis, crystal structure, α -glucosidase inhibition, DFT calculations, and molecular docking, *Journal of Molecular Structure* 1197 (2019) 645-655.

[66] S. Altürk, D. Avcı, B.Z. Kurt, Ö. Tamer, A. Başoğlu, F. Sönmez, Y. Atalay, N. Dege, Two new Co (II) complexes of picolinate: synthesis, crystal structure, spectral characterization, α -glucosidase inhibition and TD/DFT study, *Journal of Inorganic and Organometallic Polymers and Materials* 29(4) (2019) 1265-1279.

[67] A.J. Fischmann, A.C. Warden, J. Black, L. Spiccia, Synthesis, Characterization, and Structures of Copper (II)- Thiosulfate Complexes Incorporating Tripodal Tetraamine Ligands, *Inorganic chemistry* 43(21) (2004) 6568-6578.

[68] E.Z. Dalton, W.R. Blomberg, E.M. Villa, Syntheses and Structures of the First Lanthanide-Thiosulfate Complexes and the Subsequent Formation of Mixed Thiosulfate-Sulfite Compounds, *Crystal Growth & Design* 21(5) (2021) 3071-3081.

Chapter 4

- [69] A. Kufelnicki, S.V. Tomy, V. Vitske, J. Jaciubek-Rosińska, M. Haukka, I.O. Fritsky, Synthesis, solid state and solution studies of cobalt (II) complexes with 2-hydroxyiminopropanoic acid, *Polyhedron* 56 (2013) 144-151.
- [70] K. Chkirate, K. Karrouchi, N. Dege, N.K. Sebbar, A. Ejjoumany, S. Radi, N. Adarsh, A. Talbaoui, M. Ferbinteanu, E.M. Essassi, Co (ii) and Zn (ii) pyrazolyl-benzimidazole complexes with remarkable antibacterial activity, *New Journal of Chemistry* 44(6) (2020) 2210-2221.
- [71] D.M. Al-thamili, A.I. Almansour, N. Arumugam, S. Kansız, N. Dege, S.M. Soliman, M. Azam, R.S. Kumar, Highly functionalized N-1-(2-pyridinylmethyl)-3, 5-bis [(E)-arylmethylidene] tetrahydro-4 (1H)-pyridinones: Synthesis, characterization, crystal structure and DFT studies, *Journal of Molecular Structure* 1222 (2020) 128940.
- [72] K. Karrouchi, S. Fettach, Ö. Tamer, D. Avci, A. Başoğlu, Y. Atalay, Z. Ayaz, S. Radi, H.A. Ghabbour, Y.N. Mabkhot, Synthesis, crystal structure, spectroscopic characterization, α -glucosidase inhibition and computational studies of (E)-5-methyl-N'-(pyridin-2-ylmethylene)-1H-pyrazole-3-carbohydrazide, *Journal of Molecular Structure* 1248 (2022) 131506.
- [73] A.J.M. Al-Karawi, A.-A.B. OmarAli, N. Dege, S. Kansız, Formation of a new CuII-triazole ester complex from 1, 2-cyclohexanedione-bis (p-bromobenzohydrazone) compound as a consequence of copper (II)-catalyzed click reaction, *Chemical Papers* 75(8) (2021) 3901-3914.
- [74] A.J.M. Al-Karawi, A.-A.B. OmarAli, S. Mangelsen, N. Dege, S. Kansız, P. Breuninger, C. Baydere, O.B. OmarAli, An unprecedented formation of new copper (II) complexes as bioactive materials based on copper-catalyzed click reaction, *Polyhedron* 198 (2021) 115084.
- [75] M. Azam, P.K. Sahoo, R.K. Mohapatra, M. Kumar, A. Ansari, I.S. Moon, A. Chutia, S.I. Al-Resayes, S.K. Biswal, Structural investigations, Hirshfeld surface analyses, and molecular docking studies of a phenoxo-bridged binuclear Zinc (II) complex, *Journal of Molecular Structure* 1251 (2022) 132039.
- [76] M. Morales-Toyo, S. Kansız, N. Dege, C. Glidewell, A. Fuenmayor-Zafra, N. Cubillán, Polymorphs of 2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetic acid (Diclofenac): Differences from crystallography, Hirshfeld surface, QTAIM and NCIPLOTS, *Chemical Physics* 544 (2021) 111119.
- [77] N.K. Yağcı, S. Kansız, E. Özcandan, Synthesis, crystal structure, DFT studies, Hirshfeld surface analysis and drug delivery performance of bis (2-chloro-4, 6-diaminopyrimidine) copper (II)-dichloride, *Journal of Molecular Structure* 1246 (2021) 131142.

Chapter 4

- [78] L.J. Daumann, P. Comba, J.A. Larrabee, G. Schenk, R. Stranger, G. Cavigliasso, L.R. Gahan, Synthesis, magnetic properties, and phosphoesterase activity of dinuclear cobalt (II) complexes, *Inorganic Chemistry* 52(4) (2013) 2029-2043.
- [79] H. Sakiyama, Amendment to “Magnetic susceptibility equation for dinuclear high-spin cobalt (II) complexes considering the exchange interaction between two axially distorted octahedral cobalt (II) ions”[*Inorg. Chim. Acta* 359 (2006) 2097–2100], *Inorganica Chimica Acta* 2(360) (2007) 715-716.
- [80] F. Lloret, M. Julve, J. Cano, R. Ruiz-García, E. Pardo, Magnetic properties of six-coordinated high-spin cobalt (II) complexes: Theoretical background and its application, *Inorganica Chimica Acta* 361(12-13) (2008) 3432-3445.
- [81] S.Y. Lin, G.F. Xu, L. Zhao, J. Tang, G.X. Liu, Structure and Magnetic Properties of A μ -Phenoxido-bridged Dinuclear Cobalt (II) Complex, Wiley Online Library, 2011.
- [82] Y.-H. Zhou, Z.-Y. Wang, Four coordination polymers based on flexible carboxylic acid and bis (pyridyl) mixed ligands: synthesis, structures, fluorescent and magnetic properties, *Transition Metal Chemistry* 40(1) (2015) 89-98.
- [83] C.Y. Sun, X.J. Zheng, S. Gao, L.C. Li, L.P. Jin, Multiple regulated assembly, crystal structures and magnetic properties of porous coordination polymers with flexible ligands, Wiley Online Library, 2005.
- [84] B.N. Figgis, J. Lewis, Etd. by FA Cotton, *Prog. Inorg. Chem* 6 (1964) 37.
- [85] F.E. Mabbs, D.J. Machin, Magnetism and transition metal complexes, Courier Corporation 2008.
- [86] O. Kahn, Molecular magnetism, VCH, Publishers Inc., New York (1993) 167-174.
- [87] O. Kahn, J. Larionova, J. Yakhmi, Molecular magnetic sponges, *Chemistry—A European Journal* 5(12) (1999) 3443-3449.
- [88] O. Kahn, Magnetism of the heteropolymetallic systems, *Theoretical Approaches* (1987) 89-167.
- [89] R. Rabelo, A.K. Valdo, C. Robertson, J.A. Thomas, H.O. Stumpf, F.T. Martins, E.F. Pedroso, M. Julve, F. Lloret, D. Cangussu, Synthesis, crystal structure and magnetic properties of $[\text{Co}(\text{bpcam})_2]\text{ClO}_4 \cdot \text{dmsO} \cdot \text{H}_2\text{O}$, $[\text{Co}(\text{bpcam})_2]_2[\text{Co}(\text{NCS})_4] \cdot \text{dmsO} \cdot \text{H}_2\text{O}$ and $[\text{Ni}(\text{bpcam})_2] \cdot \text{H}_2\text{O}$ [Hbpcam= bis (2-pyrimidylcarbonyl) amide], *New Journal of Chemistry* 41(14) (2017) 6911-6921.
- [90] Y.-Y. Zhu, F. Liu, J.-J. Liu, Y.-S. Meng, S.-D. Jiang, A.-L. Barra, W. Wernsdorfer, S. Gao, Slow Magnetic Relaxation in Weak Easy-Plane Anisotropy: the Case of a Combined Magnetic and HFEPR Study, *Inorganic Chemistry* 56(2) (2017) 697-700.

Chapter 4

- [91] M. Rathnam, A. Kumar, I. Verma, J. Kłak, J. Cano, A.J. Mota, A. Rajput, H. Arora, Discrete unusual mixed-bridged trinuclear Co III 2 Co II and pentanuclear Ni II coordination complexes supported by a phenolate-based ligand: theoretical and experimental magneto-structural study, *New Journal of Chemistry* 45(13) (2021) 6053-6066.
- [92] B. Ay, G. Mahmoudi, A.A. Khandar, F.A. Afkhami, A. Toprak, F.I. Zubkov, J. White, J. Kłak, D.A. Safin, A novel paramagnetic coordination polymer, fabricated from Co (NCS) 2 and 2-pyridinecarbaldehyde isonicotinoylhydrazone, *Inorganica Chimica Acta* 522 (2021) 120335.
- [93] S.-Q. Bai, E.-Q. Gao, Z. He, C.-J. Fang, C.-H. Yan, Crystal structures and magnetic behaviour of three new azido-bridged dinuclear cobalt (II) and copper (II) complexes, *New Journal of Chemistry* 29(7) (2005) 935-941.
- [94] M.-H. Zeng, S. Gao, X.-M. Chen, A novel 3D coordination polymer containing pentacoordinate cobalt (II) dimers with antiferromagnetic ordering, *Inorganic Chemistry Communications* 7(7) (2004) 864-867.
- [95] S. Youngme, C. Chailuecha, G.A. van Albada, C. Pakawatchai, N. Chaichit, J. Reedijk, Dinuclear triply-bridged copper (II) compounds containing carboxylato bridges and di-2-pyridylamine as a ligand: synthesis, crystal structure, spectroscopic and magnetic properties, *Inorganica chimica acta* 358(4) (2005) 1068-1078.
- [96] S. Youngme, J. Phatchimkun, N. Wannarit, N. Chaichit, S. Meejoo, G.A. van Albada, J. Reedijk, New ferromagnetic dinuclear triply-bridged copper (II) compounds containing carboxylato bridges: Synthesis, X-ray structure and magnetic properties, *Polyhedron* 27(1) (2008) 304-318.
- [97] G.A. Seisenbaeva, M. Kritikos, V.G. Kessler, Synthesis, X-ray single crystal and magnetic study of new heteroleptic late transition metal alkoxides with tetranuclear square planar metal core, Co₄Cl₂ (OC₂H₄OEt) 6, Co₄ (OMe) 2 (acac) 6 (MeOH) 2 and Zn₄ (OMe) 2 (acac) 6 (C₇H₈), *Polyhedron* 22(18) (2003) 2581-2586.
- [98] G.A. Seisenbaeva, T. Mallah, V.G. Kessler, Highly symmetric organic ligand-capped Lindqvist structures derived from 3d-elements, *Dalton Transactions* 39(33) (2010) 7774-7779.
- [99] K. Jensen, L. Henriksen, Studies of thioacids and their derivatives, *Acta Chemica Scandinavica* 22 (1968) 1107-1128.
- [100] Bruker, APEX3 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA (2017).
- [101] G. Sheldrick, Using phases to determine the space group, *Acta Crystallogr. A* 74 (2018) a353.

Chapter 4

- [102] G.M. Sheldrick, Crystal structure refinement with SHELXL, *Acta Crystallographica Section C: Structural Chemistry* 71(1) (2015) 3-8.
- [103] L. Krause, R. Herbst-Irmer, G.M. Sheldrick, D. Stalke, Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination, *Journal of applied crystallography* 48(1) (2015) 3-10.
- [104] M.A. Spackman, D. Jayatilaka, Hirshfeld surface analysis, *CrystEngComm* 11(1) (2009) 19-32.
- [105] M. Turner, J. McKinnon, S. Wolff, D. Grimwood, P. Spackman, D. Jayatilaka, M. Spackman, *CrystalExplorer (Version 17.5)*, University of Western Australia: Crawley, Australia (2017).
- [106] M. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. Petersson, Gaussian 09, revision D. 01, Gaussian, Inc., Wallingford CT, 2009.
- [107] X. Qian, Y.-Z. Zhu, J. Song, X.-P. Gao, J.-Y. Zheng, New donor- π -acceptor type triazatruxene derivatives for highly efficient dye-sensitized solar cells, *Organic letters* 15(23) (2013) 6034-6037.
- [108] G. Bain, J. Berry, *J. Chem. Educ.* (2008).
- [109] E.M. Lopato, E.A. Eikey, Z.C. Simon, S. Back, K. Tran, J. Lewis, J.F. Kowalewski, S. Yazdi, J.R. Kitchin, Z.W. Ulissi, Parallelized screening of characterized and DFT-modeled bimetallic colloidal cocatalysts for photocatalytic hydrogen evolution, *ACS Catalysis* 10(7) (2020) 4244-4252.
- [110] W. Song, E.M. Lopato, S. Bernhard, P.A. Salvador, G.S. Rohrer, High-throughput measurement of the influence of pH on hydrogen production from BaTiO₃/TiO₂ core/shell photocatalysts, *Applied Catalysis B: Environmental* 269 (2020) 118750.



Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound

Outline

This chapter explores the present work, related to the discussion of supramolecular properties and potency against SARS-CoV-2 proteins of a benzimidazole-pyridine hybrid 2, 6-Bis (2-benzimidazolyl) pyridine 10. Supramolecular properties directed by intra and intermolecular hydrogen bonding interactions were explored. Numerous intermolecular interactions that stabilize the crystal structure of the 2, 6-Bis (2-benzimidazolyl) pyridine 10 were also investigated. Moreover, Hirshfeld surface analysis was used to support supramolecular assembly in the solid-state structure. According to this analysis, the interactions that have the largest influences on the crystal packing are those between $H\cdots H/H\cdots H$, $C\cdots H/H\cdots C$, $N\cdots H/H\cdots N$, and $C\cdots H/H\cdots C$. Furthermore, Density functional approach has been applied to 2, 6-Bis (2-benzimidazolyl) pyridine 10 to determine the reactivity parameters. Finally, molecular docking study has been performed to understand the potency of 2, 6-Bis (2-benzimidazolyl) pyridine 10 against SARS-CoV-2 proteins. Before entering into the present work, a general introduction regarding various pharmacological properties of benzimidazole and its derivative from literature, has been described.

Chapter 5

5.1. Biological importance of Benzimidazoles

Benzimidazoles, an integral part of vitamin B₁₂, are versatile pharmacophores that have revolutionized medicinal chemistry with their various pharmacological properties, which enable them to function as a useful scaffold and act through a variety of pathways to cure numerous diseases [1]. Owing to its correlation with numerous biological functions, benzimidazole is considered as a "privileged structure" in the field of heterocyclic chemistry [2]. Numerous benzimidazole derivatives have received clinical approval, including omeprazole, lansoprazole, pantoprazole, and albendazole, which are used as antihelmintics; cilexetil and telmisartan, which are used as antihypertensives; astemizole, which is used as an antihistaminic; and envirodine, which is used as an antiviral drug. On the other hand, pyridine and its derivatives are core scaffolds extensively found in many classes of natural and synthetic drugs, exhibiting various fascinating pharmacological properties [3]. Moreover, it has recently been found that derivatives of benzimidazole and pyridine are potentially effective for COVID-19 treatments [4-6]. Thus, it would be desirable to integrate the benzimidazole and pyridine fragments into a single compound to develop a potential influence to constrain the proteins of the severe acute respiratory syndrome-correlated coronavirus 2 (SARS-CoV-2).

In continuation of our ongoing endeavours to explore the supramolecular properties of biologically active compounds, herein we report the investigation of the role of vital interactions in guiding supramolecular framework in the benzimidazole-pyridine hybrid 2, 6-Bis (2-benzimidazolyl) pyridine **10** compound. The significant aspects of undertaking this work are: (i) to investigate the influence of cooperative action of numerous non-covalent interactions present in the 2, 6-Bis (2-benzimidazolyl) pyridine **10** and (ii) to study the potency of 2, 6-Bis (2-benzimidazolyl) pyridine **10** against SARS-CoV-2 proteins.

In pursuit of exploring supramolecular properties, self-assembly and antiviral activities, compound 2, 6-Bis(2-benzimidazolyl)pyridine **10** was selected.

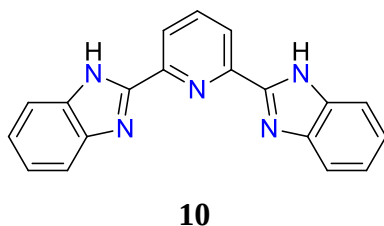


Fig. 5.1. Molecular structure of 2, 6-Bis (2-benzimidazolyl) pyridine compound **10**.

Chapter 5

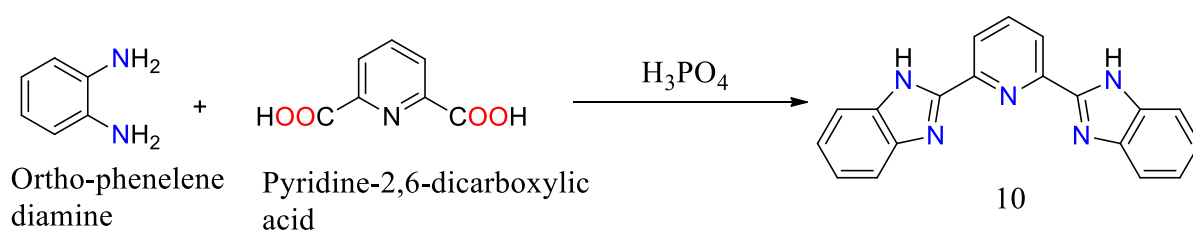
5.2. Present work

Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound

This chapter explores the supramolecular properties found in 2, 6-Bis (2-benzimidazolyl) pyridine **10** and also, it was found that 2, 6-Bis (2-benzimidazolyl) pyridine **10** was active against a number of the SARS-CoV-2 proteins.

5.2.1 Synthesis of the compound **10**

The compound was synthesized from *o*-phenylenediamine and syrupy phosphoric acid according to **Scheme 1** [7].



Scheme 1. Synthesis of 2, 6-Bis (2-benzimidazolyl) pyridine compound **10**.

5.2.2 FT-IR and NMR spectral characterization of **10**

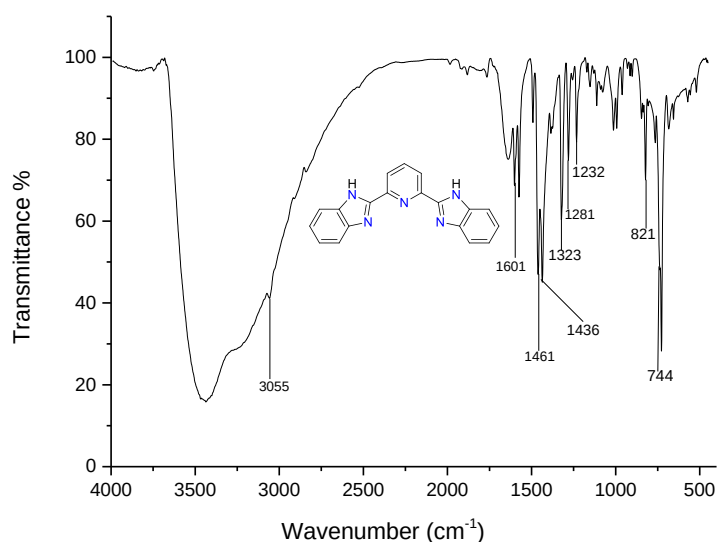


Fig. 5.2. FT-IR spectrum of 2, 6-Bis (2-benzimidazolyl) pyridine compound **10**.

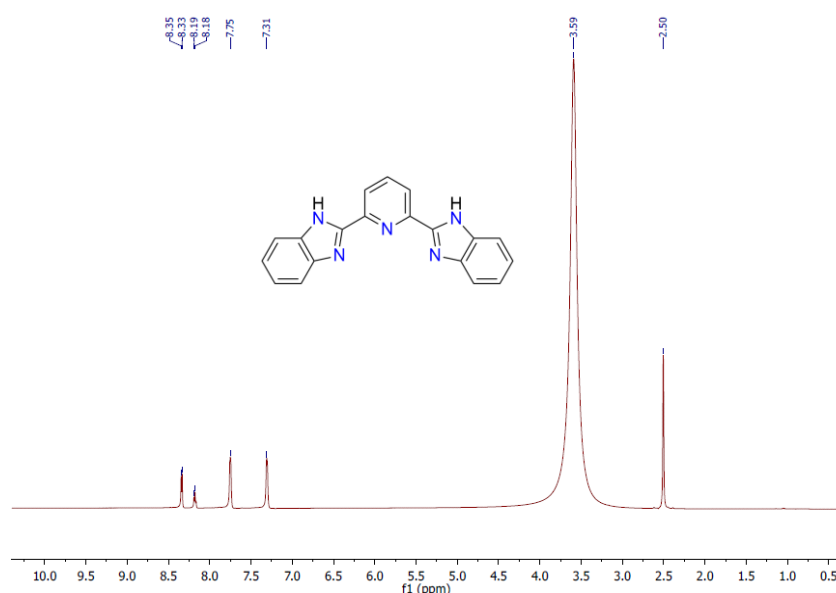


Fig. 5.3. ¹H NMR Spectrum of 2, 6-Bis (2-benzimidazolyl) pyridine compound **10** in DMSO-*d*₆.

5.2.3 Description of the crystal structure of **10**

The crystal structure of the 2, 6-Bis (2-benzimidazolyl) pyridine **10** has already been reported [8], but we decided to collect the data yet again to look for any significant structural changes. There are a few characteristic features that are worth mentioning, despite the framework being largely the same. The RMSD values of the two benzimidazole rings are 0.0125 Å and 0.0048 Å, respectively, in the planar form. Pyridine, which has a torsion angle of 9.961°, bridges the two benzimidazole rings. At the same time, the water molecules in the compound contribute to intramolecular binding as shown in **Fig. 5.4**. The C–N and C–C bond lengths of the pyridine rings, as indicated in **Table 5.2** for compound **10**, are in good accord with substituted pyridine derivatives in the literature [9-12].

Chapter 5

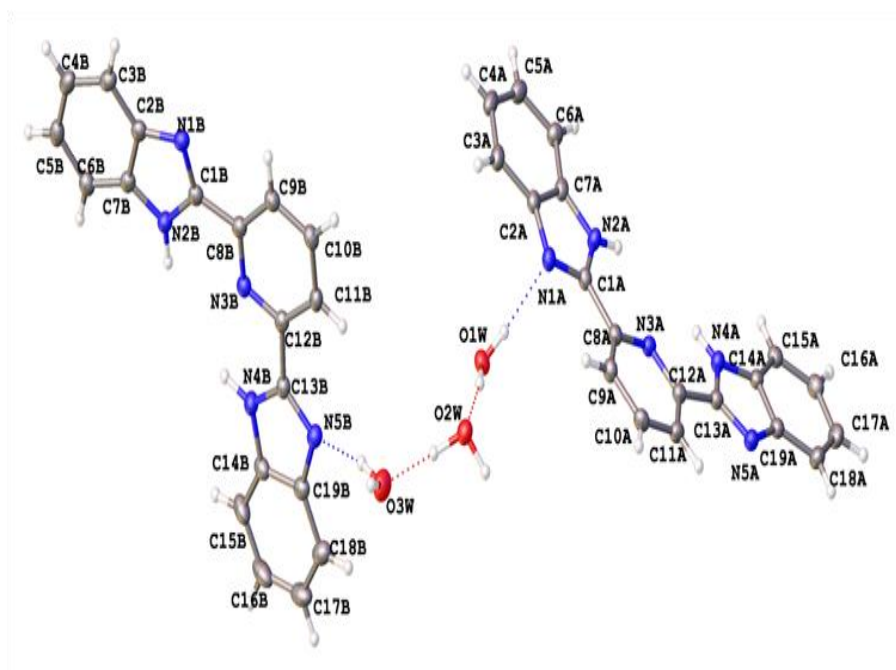


Fig. 5.4. The solid-state structure and the atom-numbering scheme of compound **10**.

Table 5.1. Refinement parameters and crystallographic information for the 2, 6-Bis (2-benzimidazolyl) pyridine **10**.

Crystal data

Chemical formula	C ₃₈ H ₃₂ N ₁₀ O ₃
Mr	676.73
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁ / <i>c</i>
Temperature (K)	100
a, b, c (Å)	18.5736 (7), 18.4141 (7), 10.2322 (3)
β (°)	104.946 (2)
V (Å ³)	3381.2 (2)
Z	4
Radiation type	Mo K α
μ (mm ⁻¹)	0.09
Crystal size (mm)	0.33 × 0.26 × 0.14

Data collection

Diffractometer	Bruker APEX-II CCD
Absorption correction	Multi-scan
Tmin, Tmax	0.464, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	57359, 8380, 5872
R _{int}	0.153
(sin θ/λ) _{max} (Å ⁻¹)	0.667

Chapter 5

Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.056, 0.152, 1.02
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.43, -0.29
CCDC	2310174

Table 5.2. Selected bond lengths (Å) and angles (°) for 2, 6-Bis (2-benzimidazolyl) pyridine **10**.

Bond lengths (Å)			
N1A—C1A	1.322 (2)	N1B—C1B	1.325 (2)
N1A—C2A	1.388 (2)	N1B—C2B	1.383 (2)
N2A—C1A	1.358 (2)	N2B—C1B	1.363 (2)
N2A—C7A	1.380 (2)	N2B—C7B	1.381 (2)
N2A—H2A	0.91 (2)	N3B—C12B	1.340 (2)
N3A—C12A	1.339 (2)	N3B—C8B	1.345 (2)
N3A—C8A	1.342 (2)	N4B—C13B	1.358 (2)
N4A—C13A	1.361 (2)	N4B—C14B	1.381 (2)
N4A—C14A	1.383 (2)	N5B—C13B	1.326 (2)
N5A—C13A	1.325 (2)	N5B—C19B	1.386 (2)
N5A—C19A	1.396 (2)		
Bond angles (°)			
H1WA—O1W—H1WB	109 (2)	C1B—N1B—C2B	104.86 (15)
H2WA—O2W—H2WB	108 (3)	C1B—N2B—C7B	106.92 (15)
H3WA—O3W—H3WB	108 (3)	C12B—N3B—C8B	117.31 (15)
C1A—N1A—C2A	104.13 (14)	C13B—N4B—C14B	106.79 (15)
C1A—N2A—C7A	106.84 (15)	C13B—N5B—C19B	104.63 (16)
C12A—N3A—C8A	117.46 (15)	N1B—C1B—N2B	113.10 (16)
C13A—N4A—C14A	107.11 (15)	N1A—C1A—C8A	125.89 (16)
C13A—N5A—C19A	104.48 (15)	N2A—C1A—C8A	120.25 (15)
N1A—C1A—N2A	113.78 (16)	N1A—C2A—C3A	130.13 (17)
Torsion angles (°)			
C2A—N1A—C1A—N2A	-0.9 (2)	N1B—C2B—C7B—N2B	-0.21 (19)
C7A—N2A—C1A—N1A	0.4 (2)	N1B—C1B—C8B—N3B	174.25 (16)
N1A—C2A—C7A—N2A	-1.0 (2)	N2B—C1B—C8B—N3B	-4.1 (2)
N1A—C1A—C8A—N3A	178.11 (16)	N3A—C12A—C13A—N5A	176.82 (16)
N2A—C1A—C8A—N3A	-5.4 (2)	N3A—C12A—C13A—N4A	-2.5 (2)
N4A—C14A—C19A—N5A	-0.18 (19)		

Chapter 5

H-bonding influences the supramolecular structure of compound **10**. **Fig. 5.5** shows that H-bonding is also accountable for the consistency of the intermolecular packing in the compound. The hydrogen atom combines with two other atoms having high electronegativity and small atomic radii to create $X-H\cdots Y$ hydrogen bonds. The hydrogen atoms are the primary sources of the bonding force in a hydrogen-bonded supramolecular architecture. The $O1W-H1WA\cdots N1A$, $O1W-H1WB\cdots O2W$, $O2W-H2WB\cdots O3W$, and $O3W-H3WA\cdots N5B$ intramolecular hydrogen bonds join each other to create chains that connect two rings of the compound **10** in the asymmetric unit as depicted in **Fig. 5.4** and **Table 5.3** [13-16]. The crystal lattice of the compound is stabilized through a large number of intermolecular contacts: (i) the nitrogen $N1B$ of the benzimidazole ring is H-bonded with the oxygen $O2W$ of the water molecule with an $O2W-H2WA\cdots N1B^i$ distance of 2.792 (2) and the other $O3W$ atom of the water molecule is linked to the neighboring oxygen atom $O2W$ of the water in the compound **10** having an $O3W-H3WB\cdots O2W^{ii}$ distance of 2.885 (2) Å; (ii) the nitrogen $N2A$ atom of symmetric benzimidazole ring in the compound is H bonded through $N2A-H2A\cdots N5A^{iii}$ and $N2A-H4A\cdots N5A^{iii}$ linkages; (iii) the carbon $C11A$ and the nitrogen $N3A$ of a neighboring pyridine ring are weakly H-bonded through the $C11A-H11A\cdots N3A^{iv}$ linkage; and (iv) the oxygen atom $O1W$ of the water molecule is constituted bifurcated H-bond with the nitrogen $N2B$ and $H4B$ atoms in the same molecule *via* an eight-membered ring ($R_2^2(10)$) supramolecular structure[17] as seen in **Fig. 5.5**.

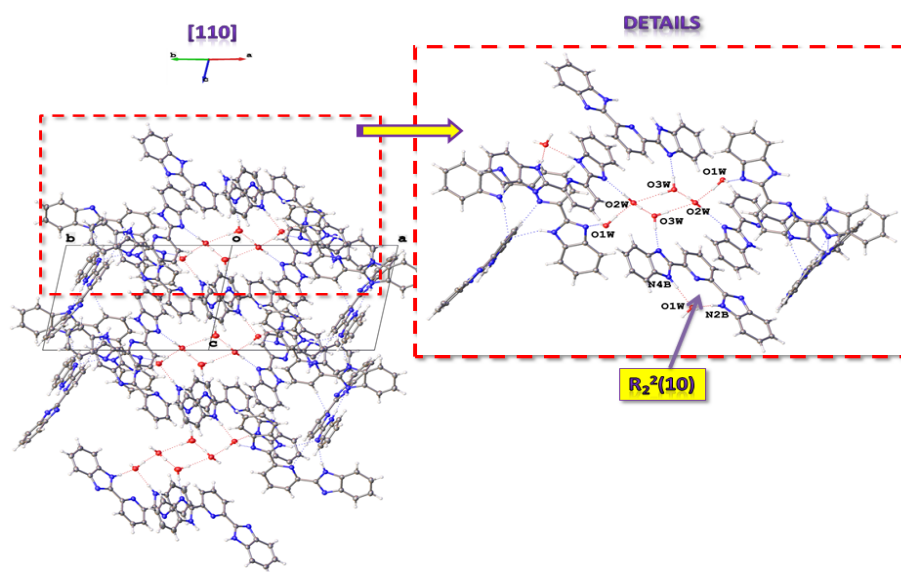


Fig. 5.5. Arrangement in the packing demonstrates the involvement of the inter and intramolecular interactions in hydrogen bonding along the [110] axis.

Chapter 5

Table 5.3. Hydrogen-bond geometries (Å) for 2, 6-Bis (2-benzimidazolyl) pyridine **10**.

<i>D</i> — <i>H</i> ··· <i>A</i>	<i>D</i> — <i>H</i>	<i>H</i> ··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> — <i>H</i> ··· <i>A</i>
O1W—H1WA···N1A	0.88 (3)	2.05 (3)	2.898 (2)	161 (3)
O1W—H1WB···O2W	0.98 (3)	1.77 (3)	2.737 (2)	167 (2)
O2W—H2WA···N1B ⁱ	0.98 (3)	1.82 (3)	2.792 (2)	172 (3)
O2W—H2WB···O3W	1.04 (4)	1.70 (4)	2.728 (2)	175 (4)
O3W—H3WA···N5B	0.96 (3)	1.84 (3)	2.787 (2)	168 (2)
O3W—H3WB···O2W ⁱⁱ	0.89 (3)	2.01 (3)	2.885 (2)	165 (3)
N2A—H2A···N5A ⁱⁱⁱ	0.91 (2)	2.17 (2)	3.009 (2)	153.0 (19)
N2A—H4A···N5A ⁱⁱⁱ	0.90 (2)	2.44 (2)	3.321 (2)	168 (2)
C11A—H11A···N3A ^{iv}	0.95	2.62	3.572 (2)	177
N2B—H2B···O1W ^v	0.96 (3)	1.95 (3)	2.907 (2)	173 (2)
N4B—H4B···O1W ^v	0.96 (2)	1.92 (3)	2.870 (2)	169 (2)

Symmetry codes: (i) $-x+1, y-1/2, -z+3/2$; (ii) $-x+1, -y+1, -z+2$; (iii) $x, -y+1/2, z-1/2$; (iv) $x, -y+1/2, z+1/2$; (v) $-x+1, -y+1, -z+1$.

5.2.4 Hirshfeld Surface analysis of **10**

Quantitative graphical representations of intermolecular forces or interactions together with their nature, surface properties, and molecular space occupied in crystal packing were evaluated using 3D-Hirschfeld surface analysis [18] and its corresponding 2D-fingerprint plots [19], which were generated by importing a cif file into Crystal Explorer17 [20]. The interactions between molecules in the crystal structure of **10** have been evaluated using d_{norm} , shape index, and curvedness and are presented in **Fig. 5.6**. Here, d_{norm} represents the distance from two atoms across the surface to their respective atomic radii, and the blue, white, and red color conventions in the d_{norm} represent the interatomic interactions as longer at van der Waals separations, and short interatomic contacts, respectively [21-24]. Curvedness is a function defined as the root mean square curvature of the surface. The distinctive packing modes and stacking configurations of the molecules are displayed with the shape index. Red and blue are complimentary color schemes used in this mapping. The acceptor atoms are surrounded by a red-colored concave region on the shape index, whereas the surface around the donor atoms is emphasized by blue-colored bumps. In the concave region of the shape index, bright red circles indicate the existence of intramolecular H-bonding interactions, supporting the results indicated in **Fig. 5.6**.

The 2D fingerprint plots presented in **Fig. 5.7** are advantageous because they give the relative contribution of different intermolecular interactions. Non-classical H···H/H···H interactions account for approximately 43.7% of the total HS contribution due to the presence

Chapter 5

of a huge number of hydrogen atoms. Nevertheless, the C $\cdots$ H/H $\cdots$ C interactions are one of the principal interactions accountable for the stability of crystal structure with a contribution of 27.8% for the HS area in compound **10**. Concurrently, the molecule exhibits noteworthy levels of N $\cdots$ H/H $\cdots$ N interactions with a 12.5% percentage contribution. In **Fig. 5.7**, symmetrical spikes indicate interactions between N–H and O–H intermolecular hydrogen bonds. All other significant contributions are from C–C (6.3%), O–H (5.7%), and N–C (3.7%). Consequently, these results corroborate XRD results.

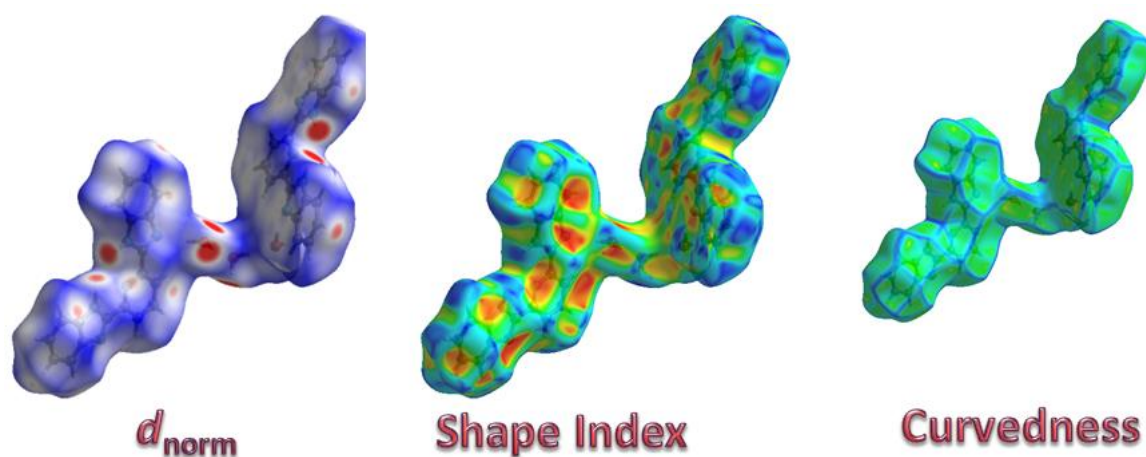


Fig. 5.6. The Hirshfeld surface plots mapped across d_{norm} , shape-index, and curvedness maps were drawn over compound **10**.

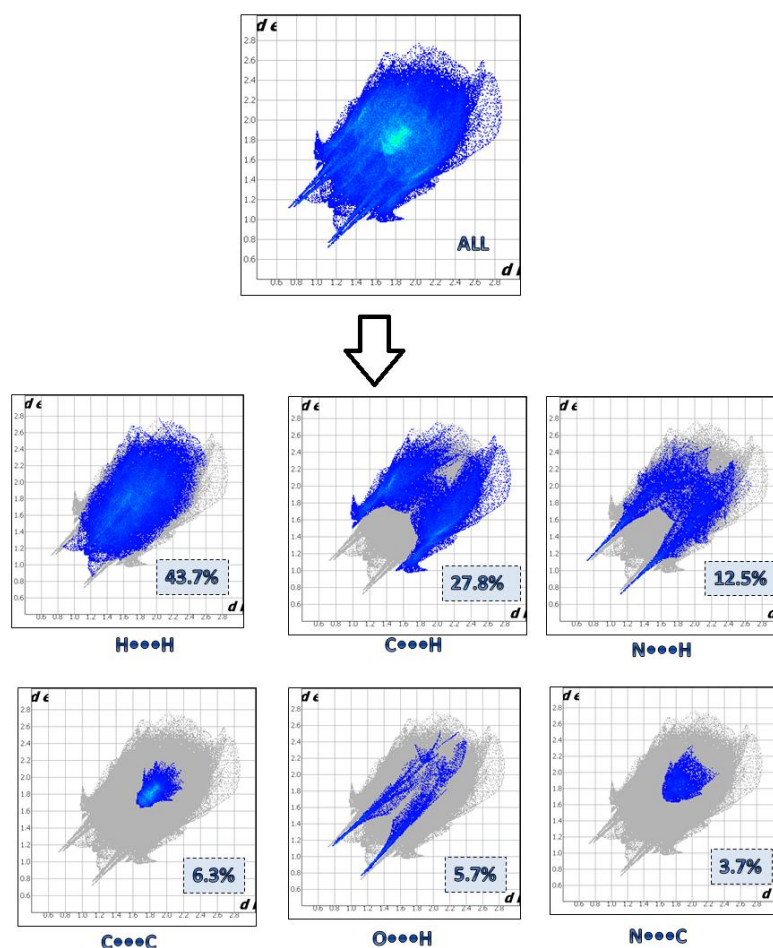


Fig. 5.7. 2D Fingerprint plots of the compound **10**.

5.2.5 DFT optimization of **10**

With the help of DFT, ground state geometry optimization of 2, 6-Bis (2-benzimidazolyl) pyridine **10** was performed using the Gaussian 09 package [25]. To offer the precise geometry of **10** in molecular form, B3LYP hybrid functional [26] with 6-31+G(d) basis function was used. The molecular docking study of the SARS-CoV-2 Main protease (PDB ID: 6LU7), ACE-2 receptor (PDB ID: 6LZG), RdRp (PDB ID: 6W9C) and PL-Pro (PDB ID: 6M71) against 2, 6-Bis (2-benzimidazolyl) pyridine **10** were performed using Autodock Vina [27] by employing Lamarckian Genetic algorithm. Autodock Tools was used to prepare the necessary files for this study. For the generation and visualization of the docked cavity and nearby residues, LigPlot was used [28]. **Fig. 5.8a** represents the optimized geometry of 2, 6-Bis (2-benzimidazolyl) pyridine **10**. **Fig. 5.8b** represents the ESP plot of 2, 6-Bis (2-benzimidazolyl) pyridine **10**, which indicates the active sites of the compound. The electronic transition from HOMO to LUMO has been shown in **Fig. 5.8c** with an energy gap of 4.25 eV. The electronic parameters

Chapter 5

of 2, 6-Bis (2-benzimidazolyl) pyridine **10** are given in **Fig. 5.8d**. From **Fig. 5.8d**, it is clear that the compound is sufficiently electronegative to bind with other molecules. The high electrophilicity index also.

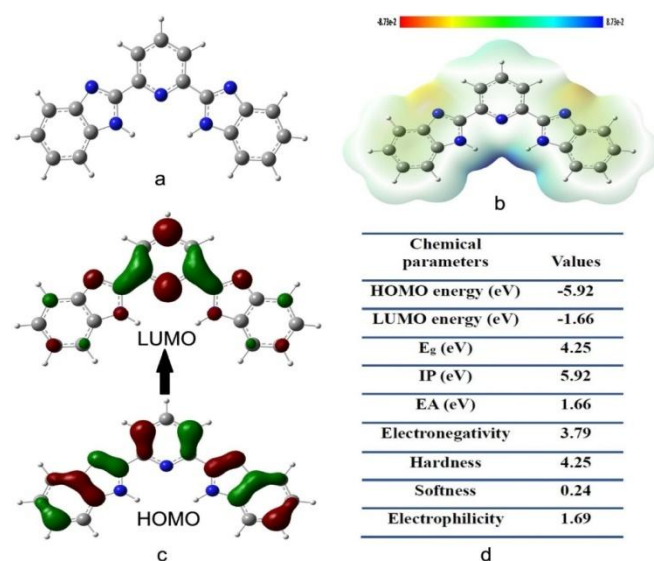


Fig. 5.8. (a) Optimized geometry of 2, 6-Bis (2-benzimidazolyl) pyridine **10**, (b) Electrostatic potential surface of 2, 6-Bis (2-benzimidazolyl) pyridine **10**, (c) HOMO to LUMO electronic transition for 2, 6-Bis (2-benzimidazolyl) pyridine **10**, and (d) Chemical parameters for 2, 6-Bis (2-benzimidazolyl) pyridine **10**

5.2.6 Molecular docking studies

Furthermore, we explored 2, 6-Bis (2-benzimidazolyl) pyridine **10** to determine its possible efficacy against a few COVID-19 proteins. Table 4 represents the docking score as well as the binding cavity of compound **10**. A high docking score with COVID-19 protease arises due to high EA, high electrophilicity, and planar structure of the molecule. Amongst the four different COVID-19 proteins (*Mpro*, *ACE2*, *RdRp*, and *PL-pro*), 2, 6-Bis (2-benzimidazolyl) pyridine **10** showed the maximum binding affinity against ACE2. The PDB files of the SARS-CoV-2 proteins were downloaded from the protein data bank. The corresponding binding cavity of the protease is also given in Table 4. It is clear from Table 4 that in all cases, 2, 6-Bis (2-benzimidazolyl) pyridine **10** is strongly bonded to the cavity of the proteins with the help of H-bonding with a distance ranging from 2.79 Å to 3.28 Å. The lower inhibition constant values indicate stronger binding against the protein. In all the cases, the inhibition constants are very small indicating a good fitting of 2, 6-Bis (2-benzimidazolyl) pyridine **10** into the binding cavity [29,30]. The nearest residue of **10** with the docked main protease is *Glu166* having an H-bonding distance of 3.28 Å. The H-bonding distance of the nearest residue *Gly205* with

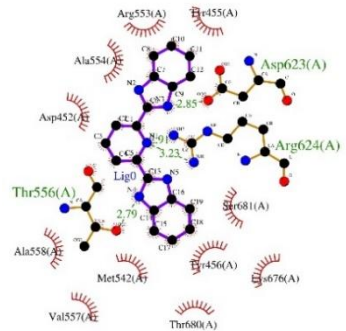
Chapter 5

ACE2 receptor is 3.02 Å. In the case of *RdRp* protein, the H-bonding distance is between 2.80 and 3.06 Å for the residues *Ser278* and *Gly256*, respectively. For *Pl-pro*, the H-bonding distances are 2.79, 2.85, and 3.23 Å corresponding to *Thr556*, *Asp623*, and *Arg624*, respectively. Docking score as well as inhibition constant values revealed the order of binding affinity as *ACE2* > *PL-pro* > *Main protease* > *RdRp*.

Table 5.4. Docking score of **10** with docking cavity.

Protein name	PDB ID	Docking score (kcal/mol)	Inhibition constant (K _i μM)	Docked cavity
Main Protease	6LU7	-7.9	1.53	
ACE2	6LZG	-9.6	0.08	
RdRp	6W9C	-7.4	3.58	

Chapter 5

PL-pro	6M71	-8.8	0.33	
--------	------	------	------	---

Conclusions

In this work, we have explored the supramolecular features of 2, 6-Bis (2-benzimidazolyl) pyridine **10** and also unveiled its potency against SARS-CoV-2 proteins. The unique supramolecular properties have been described by using single-crystal X-ray diffraction, Hirshfeld surface analysis, and DFT calculations of stabilization energies. The efficiency of intermolecular packing and the supramolecular structure compound **10** is influenced by both intra and intermolecular hydrogen bonding. The nitrogen atoms (N2B and N4B) in the same molecule, and the oxygen atom of the water molecule form a bifurcated H-bond through an eight-membered ring (R22(10)) supramolecular structure. The Hirshfeld surface analysis indicated that the interactions between H $\cdots$ H/H $\cdots$ H (43.7%), C $\cdots$ H/H $\cdots$ C (27.8%), N $\cdots$ H/H $\cdots$ N (12.5%), and C $\cdots$ H/H $\cdots$ C (6.5%) contributed substantially to the crystal packing and stabilization of the supramolecular networks. Furthermore, the reactive nature of 2, 6-Bis (2-benzimidazolyl) pyridine **10** is clearly revealed from the DFT calculations, which showed the electronic separation between the HOMO and LUMO level along with the high electrophilicity index and electronegativity. The high binding affinity of **10** against the SARS-CoV-2 proteins revealed from the molecular docking study is in concordance with the chemical parameters derived from DFT calculations. Moreover, based on the results of molecular docking, it was found that the 2, 6-Bis (2-benzimidazolyl) pyridine **10** exhibited the best activity against ACE2 and are within the acceptable levels for a Hit.

Chapter 5

5.3. Experimental

Materials and physical measurements

All chemicals were reagent grade, obtained from commercial sources, and used without purification. The solvents were purified by standard procedures. Fourier Transform Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer with KBr pellets in the 4000-500 cm^{-1} range. NMR spectra were recorded on a Bruker Advance II spectrometer using the residual protic solvent resonance as the internal standard, and chemical shifts were expressed in ppm.

5.3.1 Synthesis of 2, 6-Bis (2-benzimidazolyl) pyridine **10**

o-phenylenediamine (2.16 g, 22 mmol) was mixed with pyridine-2, 6-dicarboxylic acid (1.67 g, 10 mmol) in 20 mL of syrupy phosphoric acid. The homogeneous mixture was stirred for 4 hrs with the maintenance of temperature at 230 °C. After that the reaction mixture was poured into 500 mL of vigorously stirred cooled water. After cooling, a bulky blue-green coloured precipitate was obtained and collected by filtration, then slurred with 150 mL of hot 10% aqueous sodium carbonate solution. The resulting solid was filtered off and recrystallised from DMSO.

The FT-IR and ^1H NMR spectral data of 2, 6-Bis (2-benzimidazolyl) pyridine **10** agreed with published spectral data.

2, 6-Bis (2-benzimidazolyl) pyridine **10:** Yield: 92%, FT-IR (ν cm^{-1} , KBr): 3490, 1601, 1574, 1461, 1436, 1323, 1281, 1232, 821, 744. ^1H NMR(400 MHz,DMSO- d_6 , δ in ppm): 8.34 (d, 3H), 8.19 (d, 2H), 7.75 (s, 4H), 7.31 (s, 4H).

5.3.2 Crystallographic data collection and refinement of **10**

Using a Bruker APEX-II CCD diffractometer, intensities data were obtained at 100 K using graphite monochromated MoK_α radiation ($\lambda=0.71073\text{\AA}$) after a suitable single crystal was placed on a glass fiber. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 of data using SHELXTL software [31]. The software of WinGX [32] and PLATON [33] was used to compute the geometrical computations. The atom-numbering scheme of the solid-state and packing diagrams were generated by OLEX-2 [34]. **Table 5.1** provides a summary of the refining parameters used to collect the data.

Chapter 5

5.4. References

- [1] Bansal, Y., & Silakari, O. (2012). The therapeutic journey of benzimidazoles: A review. *Bioorganic & medicinal chemistry*, 20(21), 6208-6236.
- [2] Brishty, S. R., Hossain, M. J., Khandaker, M. U., Faruque, M. R. I., Osman, H., & Rahman, S. A. (2021). A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. *Frontiers in pharmacology*, 12, 762807.
- [3] Ling, Y., Hao, Z. Y., Liang, D., Zhang, C. L., Liu, Y. F., & Wang, Y. (2021). The expanding role of pyridine and dihydropyridine scaffolds in drug design. *Drug design, development and therapy*, 4289-4338.
- [4] Alghamdi, A., Abouzied, A. S., Alamri, A., Anwar, S., Ansari, M., Khadra, I., ... & Gomha, S. M. (2023). Synthesis, molecular docking, and dynamic simulation targeting main protease (Mpro) of new, Thiazole clubbed pyridine scaffolds as potential COVID-19 inhibitors. *Current Issues in Molecular Biology*, 45(2), 1422-1442.
- [5] Marinescu, M. (2023). Benzimidazole-triazole hybrids as antimicrobial and antiviral agents: A systematic review. *Antibiotics*, 12(7), 1220.
- [6] Deodato, D., Asad, N., & Dore, T. M. (2022). Discovery of 2-thiobenzimidazoles as noncovalent inhibitors of SARS-CoV-2 main protease. *Bioorganic & Medicinal Chemistry Letters*, 72, 128867.
- [7] Addison, A. W., & Burke, P. J. (1981). Synthesis of some imidazole-and pyrazole-derived chelating agents. *Journal of Heterocyclic Chemistry*, 18(4), 803-805.
- [8] Freire, E., Baggio, S., Muñoz, J. C., & Baggio, R. (2003). Two hydrates of 2, 6-bis (1H-benzimidazol-2-yl) pyridine. *Acta Crystallographica Section C: Crystal Structure Communications*, 59(5), o259-o262.
- [9] Adhikari, S., Sheikh, A. H., Kansız, S., Dege, N., Baildya, N., Mahmoudi, G., ... & Kłak, J. (2023). Supramolecular Co (II) complexes based on dithiolate and dicarboxylate ligands: Crystal structures, theoretical studies, magnetic properties, and catalytic activity studies in photocatalytic hydrogen evolution. *Journal of Molecular Structure*, 1285, 135481.
- [10] Iskenderov, T. S., Golenya, I. A., Gumienna-Kontecka, E., Fritsky, I. O., & Prisyazhnaya, E. V. (2009). (2RS)-3-Hydroxy-2-methyl-2-(2-pyridyl) imidazolidine-4-one. *Acta Crystallographica Section E: Structure Reports Online*, 65(9), o2123-o2124.
- [11] Golenya, I. A., Gumienna-Kontecka, E., Boyko, A. N., Haukka, M., & Fritsky, I. O. (2012). Collapsed Cu (II)-hydroxamate metallacrowns. *Inorganic Chemistry*, 51(11), 6221-6227.

Chapter 5

- [12] Kanmazalp, S. D., Qadir, A., & Dege, N. (2023). Synthesis and crystal structure of the copper (II) carboxylate with 2, 2-bipyridine, [Cu (4-mba) 2 (bipy)(H₂O)]. *European Journal of Chemistry*, 14(1), 109-113.
- [13] Kanmazalp, S. D., Sagher, M., Dege, N., & İçbudak, H. (2023). Synthesis, Hirshfeld Surface, FTIR Analysis and Single Crystal X-Ray Structure of 2-Amino-3-Hydroxypyridinium Saccharinate. *Journal of Structural Chemistry*, 64(6), 1137-1146.
- [14] Bhattacharjee, T., Adhikari, S., Datta, A., Daniliuc, C. G., Montazerzohori, M., Naghiha, R., & Hayati, P. (2022). Cadmium (II) coordination polymer based on flexible dithiolate-polyamine binary ligands system: crystal structure, Hirshfeld surface analysis, antimicrobial, and DNA cleavage potential. *Polyhedron*, 211, 115544.
- [15] Singh, M. K., Sutradhar, S., Paul, B., Adhikari, S., Laskar, F., Acharya, S., ... & Frontera, A. (2018). Mixed-ligand complexes of zinc (II) with 1, 1-dicyanoethylene-2, 2-dithiolate and N-donor ligands: A combined experimental and theoretical study. *Journal of Molecular Structure*, 1164, 334-343.
- [16] Adhikari, S., Bhattacharjee, T., Nath, P., Das, A., Jasinski, J. P., Butcher, R. J., & Maiti, D. (2020). Bimetallic and trimetallic Cd (II) and Hg (II) mixed-ligand complexes with 1, 1-dicyanoethylene-2, 2-dithiolate and polyamines: Synthesis, crystal structure, Hirshfeld surface analysis, and antimicrobial study. *Inorganica Chimica Acta*, 512, 119877.
- [17] Bell, C. C. W., Aruldas, D., Balachandran, S., Joe, I. H., & Masand, V. V. (2020). Structural, spectroscopic and O–H... O hydrogen bonding interaction on monomer and dimer form of hydroxy phenoxy acetic acid derivatives by experimental and computational techniques. *Journal of Molecular Structure*, 1204, 127471.
- [18] Spackman, M. A., & Jayatilaka, D. (2009). Hirshfeld surface analysis. *CrystEngComm*, 11(1), 19-32.
- [19] Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Spackman, P. R., Jayatilaka, D., & Spackman, M. A. (2017). CrystalExplorer17, University of Western Australia, 2017.
- [20] Kanmazalp, S. D., Dege, N., İlhan, I. O., & Akin, N. (2020). Crystal structure and Hirshfeld surface analysis of 3, 5-bis (4-methoxyphenyl)-4, 5-dihydro-1 H-pyrazole-1-carbothioamide. *Journal of Structural Chemistry*, 61, 126-132.
- [21] Merabet, L., Setifi, Z., Ferjani, H., Geiger, D. K., Glidewell, C., Kanmazalp, S. D., ... & Kaboub, L. (2023). Dinuclear azide-bridged copper (II) polymer with azido... π (pyridyl) interaction: Synthesis, crystal structure and Hirshfeld surface analysis. *Journal of Chemical Crystallography*, 53(2), 209-216.

Chapter 5

- [22] Demir Kanmazalp, S., Başaran, E., & Karaküçük-Iyidoğan, A. (2023). A Research into Chiral Thiosemicarbazide Compound: XRD Analysis, Hirshfeld Surface Analysis, and Energy Framework. *Journal of Structural Chemistry*, 64(8), 1482-1491.
- [23] Bhattacharjee, T., Nath, S., Baildya, N., Das, A., Pathak, S., Molins, E., ... & Adhikari, S. (2024). Supramolecular assemblies of Zn (II) complex based on dithiolate-amine binary ligands: Synthesis, crystal structure, Hirshfeld surface, DFT, molecular docking, and anticancer studies. *Inorganic Chemistry Communications*, 167, 112762.
- [24] Adhikari, S., Bhattacharjee, T., Gupta, R., Daniliuc, C. G., Montazerzohori, M., Naghiha, R., & Masoudiasl, A. (2020). Coordination framework of cadmium (II), harvested from dithiolate-imidazole binary ligand systems: Crystal structure, Hirshfeld surface analysis, antibacterial, and DNA cleavage potential. *Polyhedron*, 192, 114838.
- [25] Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., ... & Fox, D. J. (2009). Gaussian 09, revision a. 02. gaussian. Inc.: Wallingford, CT, 2009.
- [26] Perdew, J. P., Burke, K., & Ernzerhof, M. (1996). Generalized gradient approximation made simple. *Physical review letters*, 77(18), 3865.
- [27] Trott, O., & Olson, A. (2009). Software news and update AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function. *Effic. Optim. Multithreading*, 31, 455-461.
- [28] Wallace, A. C., Laskowski, R. A., & Thornton, J. M. (1995). LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein engineering, design and selection*, 8(2), 127-134.
- [29] Adhikari, S., Nath, S., Sen, T., Raza, R., Sahin, O., Eftekhari-Sis, B., ... & Safin, D. A. (2025). A novel tetrazole–1, 8-naphthyridine–amide hybrid: First structurally characterized tetrazolo [1, 5-a]-derivative of naphthyridines with a luminescence activity, potency against COVID-19, and anticancer activity. *Journal of Molecular Structure*, 1321, 139803.
- [30] Kanmazalp, S. D., Dege, N., Baildya, N., & Adhikari, S. (2024). Exploring the Supramolecular Features, Computational Studies, and Molecular Docking Studies of a Carbamate Schiff Base. *Letters in Organic Chemistry*, 21(7), 568-574.
- [31] G.M. Sheldrick. SHELXTL (Version 6.12), Bruker Analytical X-ray Systems, Madison, WI (2001).
- [32] Farrugia, L. J. (1999). WinGX suite for small-molecule single-crystal crystallography. *journal of Applied Crystallography*, 32(4), 837-838.
- [33] Spek, A. L. (2003). Single-crystal structure validation with the program PLATON. *Journal of applied crystallography*, 36(1), 7-13.

Chapter 5

[34] Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A., & Puschmann, H. (2009). OLEX2: a complete structure solution, refinement and analysis program. *Journal of applied crystallography*, 42(2), 339-341.

APPENDIX-I

PLAGIARISM REPORT



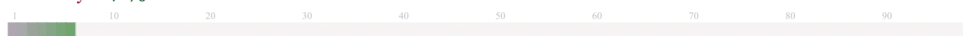
The Report is Generated by DrillBit Plagiarism Detection Software

Submission Information

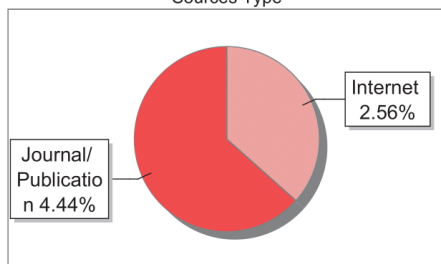
Author Name	Afzal Hussain Sheikh
Title	SUPRAMOLECULAR PROPERTIES OF METAL COMPLEXES FABRICATED FROM FUNCTIONALIZED NITROGEN-DONOR LIGANDS: SYNTHESIS, CHARACTERIZATION, THEORETICAL STUDIES, CATALYTIC PROPERTIES, AND BIOLOGICAL ACTIVITIES
Paper/Submission ID	3327159
Submitted by	nachoudhury@nagalanduniversity.ac.in
Submission Date	2025-02-12 15:15:16
Total Pages, Total Words	260, 64461
Document type	Thesis

Result Information

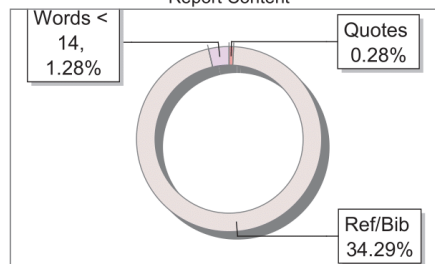
Similarity **7 %**



Sources Type



Report Content



Exclude Information

Quotes	Not Excluded	Language	English
References/Bibliography	Excluded	Student Papers	No
Source: Excluded < 14 Words	Not Excluded	Journals & publishers	Yes
Excluded Source	0 %	Internet or Web	Yes
Excluded Phrases	Not Excluded	Institution Repository	Yes

Database Selection

A Unique QR Code use to View/Download/Share Pdf File





NAGALAND UNIVERSITY
(A Central University Estd. By the Act of Parliament No. 35 of 1989)

DEPARTMENT OF CHEMISTRY
Headquarters: LUMAMI, ZUNHEBOTO DISTRICT-798627, NAGALAND, INDIA

Ph.D Thesis Certificate on Plagiarism check

Name of the Research Scholar	Mr. AFZAL HUSSAIN SHEIKH
Ph.D Registration Number	Ph.D/CHE/00222 with effect from 30/08/2018
Title of Ph.D thesis	SUPRAMOLECULAR PROPERTIES OF METAL COMPLEXES FABRICATED FROM FUNCTIONALIZED NITROGEN-DONOR LIGANDS: SYNTHESIS, CHARACTERIZATION, THEORETICAL STUDIES, CATALYTIC PROPERTIES, AND BIOLOGICAL ACTIVITIES
Name and institutional address of the supervisor	Dr. Nurul Alam Choudhury Department of Chemistry Nagaland University, Lumami
Name of the department and school	Department of Chemistry, School of Sciences
Date of plagiarism check	12-02-2025
Percentage of similarity detected by the DRILLBIT software	7%

I hereby declare that/certify that the Ph.D thesis submitted by me is complete in respect as per the guidelines of Nagaland University (NU) for this purpose. I also certify that the thesis (soft copy) has been checked for plagiarism using **DRILLBIT** similarity check software. It is also certified that the contents of the electronic version of the thesis are the same as the final hard copy of the thesis. Copy of the report generated by the **DRILLBIT** software is also enclosed.

Place: Lumami
Date: 12/02/2025

Afzal Hussain Sheikh
Mr. Afzal Hussain Sheikh
(Scholar)

Name & signature of the Supervisor:

Dr. Nurul Alam Choudhury
N A Choudhury
Dr. Nurul A. Choudhury
Assistant Professor
Department of Chemistry
Nagaland University
Head Quarters-Lumami

APPENDIX-II

CURRICULUM VITAE

CURRICULUM VITAE

PERSONAL DETAILS

Name in Full

AFZAL HUSSAIN SHEIKH

Date of Birth

01/06/1980

Address of Correspondence

Department of Chemistry
Nagaland University
Lumami Campus-798627
Zunheboto, Nagaland

Email Address

afzalhussain4658@gmail.com

ACADEMIC QUALIFICATIONS

Exam Passed	Board/university	Year of Passing	Division/Class	Percentage of marks	Subjects
HSLC	SEBA	1997	First Division	61	English, Bengali, Mathematics, General Science, Social Studies and Hindi
HS	AHSEC	1999	Third Division	43	English, Bengali, Physics, Chemistry and Mathematics
BSc	Assam University	2006	Second Division	50	English, Physics, Chemistry, Mathematics and FCES
MSc	Assam University	2009	First Class	62	Chemistry
PhD	Nagaland University	2025	Thesis submitted		

AREAS OF RESEARCH INTEREST

1. Design and synthesis of coordination compounds exhibiting hydrogen-bonded supramolecular assembly with other various additional noncovalent interactions.
2. Crystallographic study of the novel synthesized compounds.
3. Biological study of the synthesis compounds including anticancer properties, anti-microbial properties and molecular docking.
4. Analysis of catalytic and magnetic properties of the synthesized compounds.

LIST OF PUBLICATIONS

1. Chakrabarty, S., Bhattacharjee, S., **Sheikh, A. H.**, Ahmed, A., Pal, S., & Sarkhel, P. (2016). Synthesis and Characterization of Some Dimeric Platinum Metal Complexes with N, N, N', N'-Tetrakis (2-pyridylmethyl) benzene-1, 4-diamine. *Asian Journal of Chemistry*, 28(3), 622. **(Published)**
2. Chakrabarty, S., Bhattacharjee, S., Rahmani, R., **Sheikh, A. H.**, Chouaih, A., & Hamzaoui, F (2019). Synthesis, characterization and DFT studies of a palladium (ii) complex with bidentate Schiff base ligands. *International Journal of Advanced Chemistry*, 7 (1) 67-72. **(Published)**
3. Bhattacharjee, T., Adhikari, S., **Sheikh, A. H.**, Mahmoudi, G., Mlowe, S., Akerman, M. P., ... & Saygideger, Y. (2022). Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni (II) complex. *Journal of Molecular Structure*, 1269, 133717. **(Published)**
4. Adhikari, S., **Sheikh, A. H.**, Kansız, S., Dege, N., Baildya, N., Mahmoudi, G., ... & Kłak, J. (2023). Supramolecular Co (II) complexes based on dithiolate and dicarboxylate ligands: Crystal structures, theoretical studies, magnetic properties, and catalytic activity studies in photocatalytic hydrogen evolution. *Journal of Molecular Structure*, 1285, 135481. **(Published)**
5. Adhikari, S., **Sheikh, A. H.**, Baildya, N., Mahmoudi, G., Choudhury, N. A., Okpareke, O., ... & Kaminsky, W. (2023). Antiproliferative evaluation and supramolecular properties of a Pd (II) complex harvested from benzil bis (pyridyl hydrazone) ligand: Combined experimental and theoretical studies. *Inorganic Chemistry Communications*, 152, 110646. **(Published)**

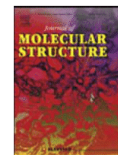
6. **Sheikh, A. H.**, Baildya, N., Butcherd, R. J., Choudhury, N. A.*, Kanmazalpe, S. D., Adhikari, S.* (2025). Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound, *Russian journal of organic chemistry*. **(Accepted)**
7. **Sheikh, A. H.**, Farhana, A., Nethaji, K., Baildya, N., Madhu, N. R., Choudhury, N. A.*, Shanmugam, P., Pathak, S., Banerjee, A., *, Adhikari, S.* (2025). Synthesis, Characterization, Antimicrobial activities of Co(II) and Cd(II) complexes derived from an unsymmetrical pyridyl Schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine,. *journal of coordination chemistry*. **(Under minor revision)**

SEMINARS AND WORKSHOPS ATTENDED

1. An oral presentation on “***Synthesis and Characterization of Complexes of Ruthenium with N-donor Ligands***” at National Seminar on Chemistry in interdisciplinary research (NSIR-2018) Organised by Department of chemistry, Nagaland University held on 9th-10th November, 2018.
2. An oral presentation on “***Synthesis, Crystal structure and Hirshfeld Surface Analysis of a novel Ni (II) complex with a unsymmetrical Schiff ligand***” at National Conference on Natural sustainability Through Advancement In Science, Technology And Women Empowerment, organized by growing Seed, NTDP And ISCA; during 19-20 February 2022.
3. Paper presentation on “***Anticancer properties of a novel Pd(II) Complex generated from Benzil Bis (pyridyl hydrazone)***” in the national Webinar on “ROLE OF MATERIAL SCIENCE IN HEALTH AND MEDICINE” Organised by Department of physics, Department of Human Physiology, Department of Chemistry in association with Health Care Centre Govt. Degree College, Dharmanagar, North Tripura, Pin-799253 held on 8th August, 2021
4. Paper presentation on “***Supramolecular Co(II) complexes Based on Dithiolate and Dicarboxylate ligands: Crystal Structures, Theoretical Studies, Magnetic properties and catalytic activity studies in photocatalytic hydrogen evolution***” in “One-Day

National Seminar on Application on Chemical Science for Sustainable Solution of Energy, Health and Environment” held in hybrid mode on 19th December 2024 at Moinul Hoque Choudhury Memorial Science College, Algapur, Hailakandi (Assam).

5. A three-day workshop on “***Capacity Building Workshop in Social Science Research***” organized by the Institute in association with Government Degree College, Dharmanagar, during 21-23 January, 2019.



Syntheses, crystal structures, theoretical studies, and anticancer properties of an unsymmetrical schiff base ligand N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex

Tirtha Bhattacharjee^a, Suman Adhikari^{b,i,*}, Afzal Hussain Sheikh^c, Ghodrat Mahmoudi^{d,\$}, Sixberth Mlowe^e, Matthew P Akerman^f, Nurul Alam Choudhury^c, Surajit Chakraborty^b, Raymond J. Butcher^g, Alan R. Kennedy^h, Burcu Saygıdeğer Demirⁱ, Aylin Örs^j, Yasemin Saygıdeğer^{i,j,k}

^a Department of Chemistry, Bineswar Brahma Engineering College, Kokrajhar-783370, Assam, India

^b Department of Chemistry, Govt. Degree College, Dharmanagar, Tripura(N)-799253, India

^c Department of Chemistry, Nagaland University, Lumami, 798627, Nagaland, India

^d Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran

^e Department of Chemistry, University of Dar es Salaam, Dar es Salaam, Tanzania

^f School of Chemistry and Physics, University of KwaZulu-Natal, Private Bag X01, Scottsville, Pietermaritzburg, 3209, South Africa

^g Department of Inorganic and Structural Chemistry, Howard University, Washington DC 20059, USA

^h Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland, UK

ⁱ Department of Biotechnology, Institute of Natural and Applied Sciences, Çukurova University, 01330, Adana, Turkey

^j Department of Pulmonary, School of Medicine, Çukurova University, 01330, Adana, Turkey

^k Department of Translational Medicine, Institute of Health Sciences, Çukurova University, 01330, Adana, Turkey

^l Itanagar Regional Centre, Indira Gandhi National University, Itanagar-791113, Arunachal Pradesh, India

ARTICLE INFO

Article history:

Received 12 May 2022

Revised 26 June 2022

Accepted 12 July 2022

Available online 14 July 2022

Keywords:

Schiff base

Hydrogen bond

Supramolecular architecture

Hirshfeld surface

DFT

Anticancer

ABSTRACT

In this work, syntheses of Schiff-base ligand, N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (**1**) and its hitherto unknown chelate with a Ni(II) salt, bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimino-k³N·N'O]nickel(II) (**2**) have been reported and characterized by spectral techniques (IR, ¹H NMR, Mass). Solid state structures and non-covalent interactions persisting in **1** and **2** are studied by Density Functional Theory (DFT) optimizations and Hirshfeld Surface (HS) analysis. X-ray diffraction (XRD) study shows zwitter ionic keto-amine tautomer form of planar Schiff base **1** that exists as dimer formed by C13–H13A...O1ⁱ [(i) -x+1, -y, -z+1] hydrogen bonds and distorted octahedral geometry around Ni²⁺ center in chelate **2**, where overall crystal structure stability may be attributed to weak C–H...π, π...π stacking, van der Waals interactions, and C–H...O type intermolecular hydrogen bonds. The HS study and 2D Finger Print (FP) plots corroborate well with XRD data and show prominent O...H/H...O spikes (2.2 Å < d_e+d_i < 2.3 Å) and C...H/H...C (2.5 Å < d_e+d_i < 2.6 Å) spikes that arise from C–H...O type H-bonds and C–H...π interactions respectively, along with significant C...C interactions (d_e+d_i ~ 3.3 Å) due to π...π stacking (**2**). The anticancer activity has been investigated by using cytotoxicity measure (MTT assay), apoptosis assay, quantitative polymerase chain reaction (qPCR), and colony formation assays. The Ni(II) metal complex demonstrates dose-dependent cytotoxicity *in vitro*, killing A549 lung cancer cells via an apoptotic pathway.

© 2022 Elsevier B.V. All rights reserved.

* Corresponding author address: S. Adhikari, Department of Chemistry, Govt. Degree College, Dharmanagar, Tripura (N)-799253, India.

\$ Corresponding author address: G. Mahmoudi, Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran.

E-mail addresses: sumanadhi@gmail.com (S. Adhikari), ghodratmahmoudi@gmail.com (G. Mahmoudi).



Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Short communication



Antiproliferative evaluation and supramolecular properties of a Pd(II) complex harvested from benzil bis(pyridyl hydrazone) ligand: Combined experimental and theoretical studies

Suman Adhikari^{a,*}, Afzal Hussain Sheikh^b, Nabajyoti Baildya^c, Ghodrat Mahmoudi^{d,e,*}, Nurul Alam Choudhury^b, Obinna Okpareke^f, Tanushree Sen^g, Akalesh Kumar Verma^{h,*}, Rohit Kumar Singh^h, Surajit Pathakⁱ, Werner Kaminsky^j^a Department of Chemistry, Govt. Degree College, Dharmanagar, Tripura(N) 799253, India^b Department of Chemistry, Nagaland University, Lumami 798627, Nagaland, India^c Department of Chemistry, Milki High School, Milki, Malda 732209, India^d Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran^e Samara State Technical University, Molodogvardeyskaya Str 244, Samara 443100, Russian Federation^f Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria^g Department of Chemistry, Jagannath Kishore College, Purulia, West Bengal 723101, India^h Department of Zoology, Cell & Biochemical Technology Laboratory, Cotton University, Guwahati 781001, Indiaⁱ Department of Medical Biotechnology, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Chettinad Hospital and Research Institute, Kelambakkam, Chennai, Tamil Nadu 603103, India^j Department of Chemistry, University of Washington, Seattle, WA 98195, United States

ARTICLE INFO

Keywords:

Supramolecular properties

Pd(II) complex

Crystal structure

Hirshfeld Surface analysis

Cytotoxicity

Docking study

ABSTRACT

A new Pd(II) coordination compound, [Pd(L)(PPh₃)₂] (1) (H₂L = benzil bis(pyridyl hydrazone)) has been synthesized and characterized by using spectroscopic (FT-IR, electronic, and NMR) and single crystal X-ray diffraction confirming that Pd(II) coordination compound (1) preferred a distorted square planar geometry. In the crystal structure of 1, supramolecular networks have been developed by involving the association of C—H... π , intermolecular C—H...N interactions, C—O...H, and π ... π interactions. Theoretical investigations have been carried out to understand the interactions within 1. Molecular docking study confirms strong hydrophilic interactions of 1 with the polar moiety of the amino acids in 1. The antitumor activities of Pd(II) complex (1) and the ligand were studied *in vitro* and *in vivo* using Dalton's lymphoma malignant cancer model. Pd(II) complex (1) induced concentration-dependent cytotoxicity and apoptotic cell death leading to a decrease in cell viability, body weight, and tumor volume in mice. Mice treated with 1 showed an increase in life span with a mean survival period of 25 days. Furthermore, an *in silico* molecular interaction study supports the wet lab results.

1. Introduction

Despite the various therapy modalities currently available, cancer is considered to be a dreadful disease that results in ~10 million annual deaths worldwide [1]. Chemoradiotherapy is used to treat around half of cancer patients, and most regimens call for using platinum-based anticancer drugs [2]. Cisplatin and its second or third-generation derivatives are popular chemotherapeutic agents used to treat a variety of human tumors; however, they have several side effects, including limited solubility in water, ototoxicity, nephrotoxicity, and peripheral

neuropathy [3,4]. Drug design and development of next generation antineoplastic metalodrugs based on metals other than Pt with superior pharmacological qualities and fewer side effects have become a focus of contemporary inorganic medicinal chemistry research in recent years [5–9]. Due to similar chemical characteristics and generally high stability under physiological conditions, Pd(II) appears to be a viable replacement for Pt(II) in potential alternative anticancer drugs [10,11]. Pd(II) derivatives have greater solubilities than those of Pt(II) compounds and have aquation as well as ligand-exchange rates that are approximately 10⁵ times faster as compared to Pt(II) complexes [10].

* Corresponding authors at: Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran (G. Mahmoudi).

E-mail addresses: sumanadhi@gmail.com (S. Adhikari), ghodratmahmoudi@gmail.com (G. Mahmoudi), akhilesh@cottonuniversity.ac.in (A. Kumar Verma).<https://doi.org/10.1016/j.inoche.2023.110646>

Received 9 February 2023; Received in revised form 19 March 2023; Accepted 22 March 2023

Available online 28 March 2023

1387-7003/© 2023 Elsevier B.V. All rights reserved.



Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Short communication



Antiproliferative evaluation and supramolecular properties of a Pd(II) complex harvested from benzil bis(pyridyl hydrazone) ligand: Combined experimental and theoretical studies

Suman Adhikari^{a,*}, Afzal Hussain Sheikh^b, Nabajyoti Baildya^c, Ghodrat Mahmoudi^{d,e,*},
Nurul Alam Choudhury^b, Obinna Okpareke^f, Tanushree Sen^g, Akalesh Kumar Verma^{h,*},
Rohit Kumar Singh^h, Surajit Pathakⁱ, Werner Kaminsky^j

^a Department of Chemistry, Govt. Degree College, Dharmanagar, Tripura(N) 799253, India^b Department of Chemistry, Nagaland University, Lumami 798627, Nagaland, India^c Department of Chemistry, Milki High School, Milki, Malda 732209, India^d Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran^e Samara State Technical University, Molodogvardeyskaya Str 244, Samara 443100, Russian Federation^f Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria^g Department of Chemistry, Jagannath Kishore College, Purulia, West Bengal 723101, India^h Department of Zoology, Cell & Biochemical Technology Laboratory, Cotton University, Guwahati 781001, Indiaⁱ Department of Medical Biotechnology, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Chettinad Hospital and Research Institute, Kelambakkam, Chennai, Tamil Nadu 603103, India^j Department of Chemistry, University of Washington, Seattle, WA 98195, United States

ARTICLE INFO

Keywords:

Supramolecular properties
Pd(II) complex
Crystal structure
Hirshfeld Surface analysis
Cytotoxicity
Docking study

ABSTRACT

A new Pd(II) coordination compound, [Pd(L)(PPh₃)₂] (**1**) [H₂L = benzil bis(pyridyl hydrazone)] has been synthesized and characterized by using spectroscopic (FT-IR, electronic, and NMR) and single crystal X-ray diffraction confirming that Pd(II) coordination compound (**1**) preferred a distorted square planar geometry. In the crystal structure of **1**, supramolecular networks have been developed by involving the association of C—H... π , intermolecular C—H...N interactions, C—O...H, and π ... π interactions. Theoretical investigations have been carried out to understand the interactions within **1**. Molecular docking study confirms strong hydrophilic interactions of **1** with the polar moiety of the amino acids in **1**. The antitumor activities of Pd(II) complex (**1**) and the ligand were studied *in vitro* and *in vivo* using Dalton's lymphoma malignant cancer model. Pd(II) complex (**1**) induced concentration-dependent cytotoxicity and apoptotic cell death leading to a decrease in cell viability, body weight, and tumor volume in mice. Mice treated with **1** showed an increase in life span with a mean survival period of 25 days. Furthermore, an *in silico* molecular interaction study supports the wet lab results.

1. Introduction

Despite the various therapy modalities currently available, cancer is considered to be a dreadful disease that results in ~10 million annual deaths worldwide [1]. Chemoradiotherapy is used to treat around half of cancer patients, and most regimens call for using platinum-based anticancer drugs [2]. Cisplatin and its second or third-generation derivatives are popular chemotherapeutic agents used to treat a variety of human tumors; however, they have several side effects, including limited solubility in water, ototoxicity, nephrotoxicity, and peripheral

neuropathy [3,4]. Drug design and development of next generation antineoplastic metalodrugs based on metals other than Pt with superior pharmacological qualities and fewer side effects have become a focus of contemporary inorganic medicinal chemistry research in recent years [5–9]. Due to similar chemical characteristics and generally high stability under physiological conditions, Pd(II) appears to be a viable replacement for Pt(II) in potential alternative anticancer drugs [10,11]. Pd(II) derivatives have greater solubilities than those of Pt(II) compounds and have aquation as well as ligand-exchange rates that are approximately 10⁵ times faster as compared to Pt(II) complexes [10].

* Corresponding authors at: Department of Chemistry, Faculty of Science, University of Maragheh, P.O. Box 55181-83111, Maragheh, Iran (G. Mahmoudi).
E-mail addresses: sumanadhi@gmail.com (S. Adhikari), ghodratmahmoudi@gmail.com (G. Mahmoudi), akhilesh@cottonuniversity.ac.in (A. Kumar Verma).

<https://doi.org/10.1016/j.inoche.2023.110646>

Received 9 February 2023; Received in revised form 19 March 2023; Accepted 22 March 2023

Available online 28 March 2023

1387-7003/© 2023 Elsevier B.V. All rights reserved.

Unveiling the supramolecular properties, DFT optimization, and molecular docking studies against SARS-CoV-2 proteins of a 2, 6-Bis (2-benzimidazolyl) pyridine compound

Afzal Hussain Sheikh^{a,b}, Nabajyoti Baildya^c, Raymond J. Butcher^d, Nurul Alam Choudhury^{b,*}, Sibel Demir Kanmazalp^{e,*}, Suman Adhikari^{a,*}

^aDepartment of Chemistry, Nagaland University, Lumami, Nagaland –798627, India.

^bDepartment of Chemistry, Govt. Degree College, Dharmanagar, Tripura(N)-799253, India.

^cDepartment of Chemistry, Milki High School, Milki, Malda-732209, India.

^dDepartment of Inorganic and Structural Chemistry, Howard University, Washington DC20059

^eNaci Topçuoğlu Vocational School, Biomedical Device Technology Program, Gaziantep University, Gaziantep, Turkey

*e-mail addresses: sumanadhi@gmail.com, (S. Adhikari); sibeld@gantep.edu.tr (S.Demir Kanmazalp); nachoudhury@gmail.com (N.A. Choudhury).

Abstract—In this work, supramolecular properties and potency against SARS-CoV-2 proteins of a benzimidazole-pyridine hybrid 2, 6-Bis (2-benzimidazolyl) pyridine (**1**) has been explored. Supramolecular properties directed by intra and intermolecular hydrogen bonding interactions were explored. Numerous intermolecular interactions that stabilize the crystal structure of the 2, 6-Bis (2-benzimidazolyl) pyridine (**1**) were also investigated. Moreover, Hirshfeld surface analysis was used to support supramolecular assembly in the solid-state structure. According to this analysis, the interactions that have the largest influences on the crystal packing are those between H···H/H···H, C···H/H···C, N···H/H···N, and C···H/H···C. Furthermore, density functional approach has been applied to 2, 6-Bis (2-benzimidazolyl) pyridine (**1**) to determine the reactivity parameters. Finally, molecular docking study has been performed to understand the potency of 2, 6-Bis (2-benzimidazolyl) pyridine (**1**) against SARS-CoV-2 proteins.

Keywords: Crystal structure, supramolecular features, Hirshfeld surface analysis, DFT study, SARS-CoV-2 proteins.

INTRODUCTION

Supramolecular chemistry is currently one of the most prevalent and rapidly expanding disciplines in the arena of chemical, biological, and material science [1-3]. Supramolecular chemistry is governed by weak non-covalent interactions, viz. hydrogen bonding, van der Waals interactions, π - π contacts, electrostatic forces, and metal-ligand coordination. This is contrary to the conventional covalent bond, which is based on strong chemical bonds [4, 5]. These interactions are crucial for the development and modification of supramolecular structures, which are dynamic, reversible, and sensitive to changes in the surrounding environment [6-8]. Furthermore, supramolecular architecture is determined by external environmental factors, such as solvent, temperature, concentration, and the synthetic procedure, all of which have a substantial influence on non-covalent interactions [9, 10].

Molecular self-assembly is one of the most crucial and essential aspects of supramolecular architecture [11, 12]. Molecular self-assembly is an unmanaged system where molecules or sections of molecules spontaneously create organized groupings [13]. The molecular structure dictates the structure of the



Synthesis and Characterization of Some Dimeric Platinum Metal Complexes with N,N,N',N'-Tetrakis(2-pyridylmethyl)benzene-1,4-diamine

SURAJIT CHAKRABARTY^{1,*}, SHOUMIK BHATTACHARJEE², AFZAL HUSSAIN SHEIKH³,
AZIZ AHMED⁴, SUBRATA PAL⁵ and PRASHANTA SARKHEL⁶

¹Department of Chemistry, Government Degree College, Dharmanagar, Tripura North-799 250, India

²Department of Chemistry, Ledrai Dewan Class XII School, Machmara, Kumarghat, Tripura, India

³Department of Chemistry, N.C. College, Badarpur, Karimgang, India

⁴Department of Chemistry, Indian Institute of Technology, Patna-18, India

⁵OSD, District School Education Office, Dharmanagar, North Tripura, India

⁶Department of Chemistry, St. Edmunds College, Shillong-793 022, India

*Corresponding author: E-mail: surajit_chakrabarty@yahoo.co.in

(Received: ; Accepted:) AJC-0000

Dinuclear platinum metal complexes $[M_2(1,4\text{-tpbd})Cl_2]Cl_2$ (where, $M = Pd$ or Pt and $1,4\text{-tpbd} = N,N,N',N'\text{-tetrakis(2-pyridylmethyl)benzene-1,4-diamine}$), $[Ru_2(1,4\text{-tpbd})(DMSO)_2Cl_4]$ and $[Rh_2(1,4\text{-tpbd})(PPh_3)_2Cl_2]$ were synthesized from their precursors $PdCl_2$, K_2PtCl_4 , $[Ru(DMSO)_4Cl_2]$ and $[Rh(PPh_3)_3Cl_2]$ respectively. The composition and the expected structures of the complexes have been discussed in view of their data obtained from various analytical, magnetic moment, molar conductance, UV-visible, FT-IR and ^1H NMR spectroscopic studies. $[M_2(1,4\text{-tpbd})Cl_2]Cl_2$ (where, $M = Pd$ or Pt) complexes were expected to have distorted square-planar geometries, in which the coordination of the ligand $1,4\text{-tpbd}$ to the metal ions occurs through all the N atoms in a *bis*-tridentate bridging fashion. The complex $[Rh_2(1,4\text{-tpbd})(PPh_3)_2Cl_2]$, a square-planar geometry was proposed, in which the ligand $1,4\text{-tpbd}$ bonded through two N-atoms of the picolyl group, one chlorine atom and one triphenylphosphine group per rhodium atom. An octahedral structure was proposed to the complex $[Ru_2(1,4\text{-tpbd})(DMSO)_2Cl_4]$. The electronic spectra of all the complexes were dominated by strong charge transfer bands indicative of binding of $1,4\text{-tpbd}$ ligand in a bridging manner to the metal centers. For the $[Rh_2(1,4\text{-tpbd})(PPh_3)_2Cl_2]$ complex in dichloromethane, a reversible peak at $E_{1/2} = 0.39$ V and $\Delta E_p = 80$ mV was observed, which may be assigned to two electrons Rh^I/Rh^{III} oxidation couple.

Keywords: Dimeric, N,N,N',N'-Tetrakis(2-pyridylmethyl)benzene-1,4-diamine, UV-visible, ^1H NMR, Cyclic voltammetry.

INTRODUCTION

Complexes containing polypyridyl chelating ligands have been extensively studied in the recent past [1-5]. The rich photo-physical and redox properties make them potentially useful in areas as diverse as light harvesting, electron transfer, non-linear optics, photo-voltaics, self-assembly and probes for biologically relevant molecules such as DNA [6-10]. The chemistry of metal complexes with *bis*-tridentate ligand *e.g.* N,N,N',N'-tetrakis(2-pyridylmethyl)benzene-1,4-diamine (1,4-tpbd) (Fig. 1) has received attention after its discovery by Buchen *et al.* [11] and introduced it to build up defined polynuclear coordination-systems [10]. Beside some mononuclear complexes of 3d transition metals and one polynuclear Pd-containing complex [11-14] only four multinuclear complexes have been reported by McKenzie *et al.* [14(a)-(d)]. In all these complexes $1,4\text{-tpbd}$ acts either as a tridentate ligand or a bridging *bis*-tridentate ligand between two metal centres.

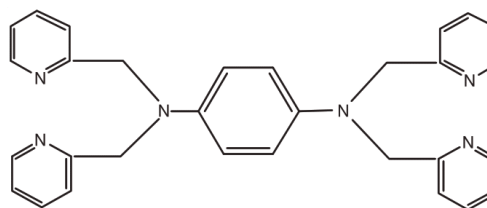


Fig. 1. Structure of N,N,N',N'-tetrakis(2-pyridylmethyl)benzene-1,4-diamine (1,4-tpbd)

In view of the above importance of the platinum metal complexes with $1,4\text{-tpbd}$ ligand, the present work describes the synthesis, characterization and structure elucidation of some dinuclear platinum metal complexes with the $1,4\text{-tpbd}$ ligand which is bonded either in a bridged *bis*-tridentate or *bis*-bidentate fashion to the metal centers. Here in, we report

Synthesis, characterization and DFT studies of a palladium (ii) complex with bidentate Schiff base ligands

Surajit Chakrabarty ^{1*}, Shoumik Bhattacharjee ², Rachida Rahmani ³, Afzal Hussain Sheikh ⁴, Abdelkader Chouaih ^{3*}, Fodil Hamzaoui ⁵

¹ Department of Chemistry, Government Degree College, Dharmanagar, North Tripura - 799250, India

² Department of Chemistry, Ledrai Dewan Class XII School, Machmara, Unakoti, Tripura-799263, India

³ LTPS Laboratory, Abdelhamid Ibn Badis University of Mostaganem, 27000 Mostaganem, Algeria

⁴ Department of Chemistry, N. C College, Badarpur, Karimgang, Assam-788806, India

⁵ LPFM Académie de Montpellier – France

*Corresponding author E-mail: achouaih@gmail.com

Abstract

The N-donor bidentate complexes of Palladium (II) of the type [PdL1Cl2] and [PdL2Cl2] {where L1 = N, N'-bis(napthanidal)-1,4-diacetyldihydiimine and L2= N, N'-bis(napthanidal)-1,2-ethylenediimine} were synthesized by refluxing of PdCl2 in acetonitrile with ligand L1 and L2. Complexes have been characterized by elemental analysis, conductivity measurement, IR, UV-Vis and 1H-NMR spectroscopy. Full geometry optimization of the ground state of the complex [PdL1Cl2] was carried out using Density Functional Theory (DFT) at B3LYP functional with 6-311G(d, p) basis set for C, N, Cl, H and LANL2DZ basis set for Pd atoms in gas and solvent (DMSO) phases. The calculated geometric and spectral results reproduced the experimental data with well agreement. Theo-retical calculated molecular orbitals (HOMO–LUMO) and their energies have been calculated that suggest charge transfer occurs within the complexes. The HOMO-LUMO energy gap was found 2.6210 eV. The electrophilic and nucleophilic sites are theoretically evaluated by molecular electrostatic potential.

Keywords: Pd (II); Bidentate; IR; UV-Vis; 1H-NMR; DFT.

1. Introduction

The Chemistry of metal complexes with Schiff base ligands has vital role in the biological field due to their well known antifungal and antibacterial activity (Garoufis et al. 2009, Mukherjee et al. 2011, Abdel Ghani et al. 2001). Considerable interest has been given to transition metal complexes with Schiff base ligands on account of their structural diversity, stability, ease of preparation and variety of applications (Pal et al. 2000, De et al. 2011, Tong et al. 2014). The coordination chemistry of square planner Pd(II) with N-donor Schiff base ligands and their DFT studies have gain importance due to their antitumor, anticancer and catalytic activities (Akbari et al. 2013, Sönmez et al. 2010, Mocanu et al. 2010, Anan et al. 2011, Petrović et al. 2015). In view of diverse chemistry possessed by the Pd (II) Schiff base complexes, we under took the synthesis and characterization of Pd (II) complexes containing bidentate N-donor ligands L1 and L2. Structural elucidation of [PdL1Cl2] was carried out using Density Functional Theory (DFT) which exhibit slightly distorted square planar arrangement around the Pd (II) metal center ((Ruike et al. 1996, Akbari et al. 2013). Schiff base bidentate N-donor ligands viz. N, N'-bis(napthanidal)-1,4-diacetyldihydiimine (L1) and L2= N, N'-bis(napthanidal)-1,2-ethylenediimine (L2) (Fig. 1) were prepared according to or similar to the reported methods earlier (Busch et al. 1956, Bariz et al. 1986, Hauer et al. 1987, Kesslen et al. 1995, Pal et al. 2000, Chowdhury et al. 2003).

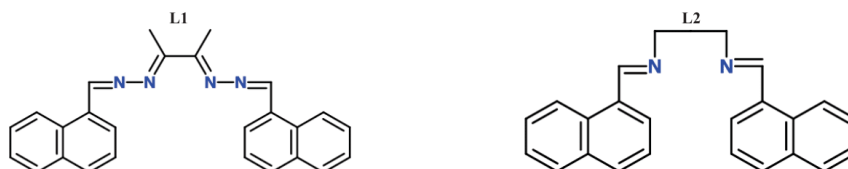


Fig. 1: Structure of Bidentate N-Donor Ligands L1 & L2, Where L1= N, N'-Bis (Napthanidal)-1,4-Diacetyldihydiimine and L2= N, N'-Bis (Napthanidal)-1, 2-Ethylenediimine.

2. Experimental

All chemicals used were of AR or chemically pure grade. Solvents were purified prior to use by standard methods. Diacetely (2,4-butanedione), 1-Naphthaldehyde ethylenediamine and PdCl2 were purchased from Merck. Molar conductivity measurements of millimolar dimethylsulphoxide (DMSO)



Copyright © Surajit Chakrabarty et al. This is an open access article distributed under the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.