



UNIVERSITI PUTRA MALAYSIA

***SYNTHESIS, ELECTROCHEMICAL AND CYTOTOXIC STUDIES OF
BIDENTATE DITHIOCARBAZATE SCHIFF BASES AND THEIR METAL
(NI, CU, AND ZN) COMPLEXES***

SYAHIRAH RAMLI

FS 2016 79



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By

SYAHIRAH BINTI RAMLI

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
in Fulfilment of the Requirements for the Degree of Master of Science**

November 2016

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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November 2016

Chairman : Thahira Begum, PhD
Faculty : Science

Three series of dithiocarbazate Schiff bases derived from S-2-methylbenzylidithiocarbazate, S-3-methylbenzylidithiocarbazate and S-4-methylbenzylidithiocarbazate were synthesised using thiophene-2-carboxaldehyde, methyl-2-thienylketone, 3-methylthiophene-2-carboxaldehyde, and 5-methylthiophene-2-carboxaldehyde via condensation. The Schiff bases were then complexed with respective metal salts to produce transition metal complexes. The metal complexes formed are expected to have general formula of $[M(NS)_2]$, $[M(NS)_2 \cdot H_2O]$, $[M(NS)_2 \cdot 2H_2O]$, and $[M(NS)(H_2O)(OAc^-)]$ where $M = Cu^{2+}$, Ni^{2+} , dan Zn^{2+} . These compounds were characterised by elemental analysis, molar conductivity, magnetic susceptibility and various spectroscopy techniques including Fourier-Transform Infrared (FT-IR), Nuclear Magnetic Resonance (NMR), Mass Spectroscopy (MS), UltraViolet/Visible (UV/Vis) and Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) analyses. The elemental data obtained are in good agreement with the proposed molecular formula of the Schiff bases and metal complexes. The magnetic susceptibility measurements and spectral results support the coordination geometry in which the Schiff bases behave as bidentate NS donor ligand coordinating via azomethine nitrogen and thio sulphur atom. The Schiff bases and metal complexes have been evaluated for their biological activities against two bladder cancer cell lines, RT-112 (non invasive) and EJ-28 (invasive). Only $[Cu(S2T2C)(H_2O)(OAc^-)]$, $[Cu(S2M2TK)_2]$, $[Cu(S4T2C)_2]$, $[Cu(S4MB5MT)_2]$ and $[Ni(S4M2TK)(H_2O)(OAc^-)]$ showed remarkable anticancer properties while the other compounds were inactive against both bladder cancer cell lines. A series of Schiff bases derived from S-4-methylbenzylidithiocarbazate were developed as self assembled monolayers (SAMs) and were tested for the detection of Zn^{2+} ion in water. All the Schiff base modified electrodes showed better response for the detection of Zn^{2+} ion compared with the conventional electrode, indium tin oxide.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

**SINTESIS, ELEKTRO DAN SITOTOSIK BAGI BES SCHIFF
DITIOKARBAZAT MULTIDENTAT DAN LOGAM (Ni, Cu, DAN Zn)
KOMPLEKS**

Oleh

SYAHIRAH BINTI RAMLI

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Tiga siri Schiff bes yang diterbitkan daripada S-2-metilbenzildithiokarbazat (S2MBDTC), S-3-metilbenzildithiokarbazat (S3MBDTC) and S-4-metilbenzildithiokarbazat (S4MBDTC) telah disintesis menggunakan thiofin-2-karboksaldehid, metil-2-thienilketon, 3-metil-thiofin-karboksaldehid dan 5-metil-thiofin-karboksaldehid melalui tindak balas kondensasi. Seterusnya bes Schiff telah dikomplekkan dengan garam logam masing-masing untuk menghasilkan kompleks logam peralihan. Kompleks logam yang dihasilkan adalah dianggarkan mempunyai formula umum $[M(NS)_2]$, $[M(NS)_2.H_2O]$, $[M(NS)(H_2O)(OAc^-)]$ dimana $M = Cu^{2+}$, Ni^{2+} , dan Zn^{2+} . Sebatian-sebatian itu dicirikan dengan analisis unsur, kekonduksian molar, kerentanan magnetic dan pelbagai teknik-teknik spektroskopi termasuklah analisis spektroskopi Transformasi Fourier Inframerah (FT-IR), Resonans Magnetik Nuklear (NMR), Mass spektroskopi (MS), Ultra Lembayung/Boleh Nampak (UV/Vis) dan Spektroskopi Pancaran Pasangan Plasma-Atom secara Induktif (ICP-AES). Analisis menunjukkan unsur yang diperolehi sejajar dengan formula molekul yang dicadangkan bagi bes Schiff dan kompleks logam. Ukuran kerentanan magnetic dan keputusan analisis spectra menyokong geometri berkoordinat yang mana bes Schiff bertindak sebagai ligan penderma bidentat NS yang berkoordinat melalui atom-atom nitrogen azomethin dan sulfur tiolo. Bes Schiff dan logam kompleksnya telah dinilai untuk aktiviti biologi mereka terhadap sel pundi kencing, RT-112 dan EJ-28. Hanya kompleks $[Cu(S2T2C)(H_2O)(OAc^-)]$, $[Cu(S2M2TK)_2]$, $[Cu(S4T2C)_2]$, $[Cu(S4MB5MT)_2]$ and $[Ni(S4M2TK)(H_2O)(OAc^-)]$ menunjukkan potensi sebagai agen antikanser manakala bes-bes Schiff dan kompleks yang lain tidak aktif terhadap kedua-dua sel. Satu siri bes Schiff daripada S-4-metilbenzildithiokarbazat diaplikasikan sebagai bahan pengubah suai untuk elektrod tercetak terpakai buang yang diaplikasi ke untuk mengesan ion zink.. Semua elektro terubah suai bes Schiff menunjukkan sifat selektiviti dan sensitiviti yang tinggi untuk pengesanan Zn^{2+} ion berbanding elektrod yang konvensional, indium tin oksida. berat.

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I certify that a Thesis Examination Committee has met on 9 November 2016 to conduct the final examination of Syahirah binti Ramli on her thesis entitled "Synthesis, Electrochemical and Cytotoxic Studies of Bidentate Dithiocarbazate Schiff Bases and their Metal (Ni, Cu and Zn) Complexes" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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TABLE OF CONTENTS

	Page
ABSTRACT	i
ASBTRAK	ii
ACKNOWLEDGEMENTS	iii
APPROVAL	iv
DECLARATION	vi
LIST OF FIGURES	xi
LIST OF TABLES	xiii
LIST OF SCHEMES	xiv
LIST OF ABBREVIATIONS	xv
CHAPTER	
1 INTRODUCTION	1
1.1 Dithiocarbazate Derivatives and their Schiff bases	1
1.2 Thiophene Derivatives	3
1.3 Properties of ligand with nitrogen and sulfur donor atom	3
1.4 Transition metal complexes of heterocyclic thiones	4
1.5 Schiff bases and metal complexes in chemistry	4
1.6 Zinc toxicity	5
1.7 Schiff base for detection of heavy metal ion	6
1.7.1 Self assembled monolayers	6
1.8 Gold nanoparticles (AuNPs) containing functional thiol ligand in self assembled monolayer	8
1.9 Problem statements	9
1.9.1 Objectives	9
2 LITERATURE REVIEW	10
2.1 Thiophene based drug and metal complexes and their biological activities	10
2.2 Coordination chemistry and biological of dithiocarbazate Schiff bases and their metal complexes Schiff bases and their metal complexes.	13
2.3 Self Assembled monolayers and its applications	19
2.3.1 Schiff bases for heavy metal ions detection	19
2.3.2 Application of Schiff bases and their metal complexes in electroanalysis	20
3 METHODOLOGY	24
3.1 Chemicals	24
3.2 Synthesis of substituted dithiocarbazate derivatives	24
3.3 General method for the synthesis of Schiff bases	24
3.4 General method for the synthesis of Metal Complexes	25
3.5 Physical-chemico Analysis	25
3.5.1 Melting Point Determination	25
3.5.2 Elemental (CHNS) analysis	25
3.5.3 Metal Content Determination	25

3.5.4	Conductivity Measurement	26
3.5.5	Magnetic Susceptibility Measurement	26
3.5.6	Fourier Transform Infrared Spectrophotometer	26
3.5.7	Gas Chromatography-Mass Spectrometry (GC-MS) Analysis	26
3.5.8	Nuclear Magnetic Resonance (NMR) Analysis	27
3.5.9	Ultraviolet / Visible (UV-Vis) Spectroscopy Analysis	27
3.5.10	Single Crystal Structure Determination	27
3.5.11	Cytotoxicity Assay Schiff bases based self assembled monolayers for detection of Heavy metal ion	27
3.6	Chemicals	28
3.7	Characterization	28
3.8	Methodology	28
3.8.1	Preparation of modified electrode (Schiff base modified electrode)	29
3.9	Preparation of working solution	30
3.10	Electrochemical measurements	30
4	RESULTS AND DISCUSSION	31
4.1	Microanalytical Data of the Schiff Bases and Their metal Complexes	33
4.2	Molar Conductivity and Magnetic Susceptibility of the Metal Complexes.	40
4.3	Electronic Spectral Data of the Schiff Bases and Metal Complexes	42
4.4	Fourier-Transform Infrared Data for the Schiff bases and their metal complexes	44
4.5	Nuclear Magnetic Resonance (NMR) spectrometric analysis	48
4.6	Mass Spectral Data of Schiff Bases	51
4.7	X-ray Crystallographic Analysis of the [S4M2TK]	61
4.8	Cytotoxicity Analysis	64
4.9	Schiff base based self assembled Monolayers for the detection of heavy metal ion	68
4.9.1	Contact angle analysis	68
4.9.2	X-Ray Photoelectron Spectroscopy (XPS) Analysis	69
4.9.3	Cyclic voltammetry (CV) analysis	73
4.9.4	Effect of the Number of Cycles on the Electrochemical Response	74
4.9.5	Effect of Scan Rates on the Electrochemical Response on the Schiff Base Modified Electrodes	75
4.9.6	Effect of the immersion time of the Schiff Base modified Electrode for Zn ²⁺ ion detection.	76
4.9.7	Effect of pH on the electrochemical response of the Schiff Base modified Electrode for Zn ²⁺ ion detection.	78
4.9.8	Electrochemical Characterization of the Modified for Zn ²⁺ ion detection	81

5	CONCLUSION	83
	BIBLIOGRAPHY	85
	APPENDICES	94
	BIODATA OF STUDENT	162



LIST OF FIGURES

Figure	Page
1.1 General molecular structure of dithiocarbazate with potential donor atoms	1
1.2 Structure of Thiophene	3
1.3 Structure of Piroxicam	3
1.4 Structure of Lornoxicam	3
1.5 General Structure of Self Assembled Monolayers (SAMs)	7
1.6 Schematic diagram of formation of self-assembled monolayer	8
2.1 Molecular structure of Tienilic acid	10
2.2 General molecular structure of HL	11
2.3 Propose molecular structure for metal complexes where, M = Cu, Fe	12
2.4 (a) Structure of pyrrole-2-aldehyde Schiff base of S benzylthiocarbazate (b) Structure of pyrrole-2-aldehyde Schiff base of S-methylthiocarbazate.	13
2.5 Structure of NS Schiff base	14
2.6 Structure of NS' Schiff base	14
2.7 The thione and thiol form of SB2AT and SB3AT	15
2.8 ORTEP diagram of Ni(SB2AT) ₂	15
2.9 Tautomeric form of S-allyl-3-(2-pyridyl-methylene)dithiocarbazate	16
2.10 ORTEP drawing of (C ₁₀ H ₁₀ N ₃ S ₂) ₂ Mn	16
2.11 ORTEP drawing of one of the two crystallographically independent units of (C ₁₀ H ₁₀ N ₃ S ₂) ₂ Co	17
2.12 ORTEP drawing of allyl-2-(4-benzyloxyphenylmethylene)hydrazine Carbodithioate	18
2.13 ORTEP drawing of Ni(II) of allyl 2-(1H-pyrrol-2-ylmethylidene)-1-hydrazinecarbodithioate	18
2.14 Schiff base 2-{(E)-[(8-aminonaphthalen-1-yl)imino]methyl}phenol	19
2.15 Schematic diagram of construction of functional monolayer films via the self-assembly approach	21

2.16	Structure of $[\text{Ni}(\text{SC}_6\text{H}_4\text{NC}(\text{H})\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{SMe})(5\text{-C}_5\text{H}_5)]_2$.	21
2.17	General molecular structure of SB1	23
4.1	Expected Structure for metal complexes	31
4.2	General molecular structure of the Schiff base	32
4.3	FT-IR spectra of S2M2TK and its metal complexes	45
4.4	General molecular structure of Dithiocarbazate Schiff bases derived from S-2,S-3 and S4MBDTC	60
4.5	ORTEP diagram of S4M2TK	62
4.6	Structure of S4M2TK Schiff base	62
4.7	XPS Analysis of (a) S4M2TK modified Electrode	69
4.7	XPS Analysis of (b) MPA-ITO modified Electrode	70
4.8	High resolution scan of S (sulphur) for ITO – MPA electrode	71
4.9	Carbon hybridization analysis by XPS. Deconvolution of the C1s core level spectra	72
4.10	High resolution scan of N1s for the S4M2TK modified electrode	72
4.11	Cyclic voltammetry spectra of different modification stemodified Schiff bases electrode	73
4.12	Cyclic voltammetry spectra of S4T2C modified electrode at different number of cycle	74
4.13	Cyclic voltammetry of S4T2C modified electrode at different scan rates.	75
4.14	Effect of immersing time on the peak current of Zn^{2+}	78
4.15	Plot of the effect of pH on the peak current of Zn^{2+}	79
4.16	Electrochemical characterization of modified electrode for detection of Zn^{2+} ion	81

LIST OF TABLES

Table		Page
4.1	Microanalytical Data for dithiocarbazate Schiff bases and their metal 35 complexes	34
4.2	Molar Conductivity Data for Metal Complexes of Schiff Bases	41
4.3	Electronic Spectral Data for Dithiocarbazate Schiff Bases and Their Metal Complexes	43
4.4	Infrared Data of Dithiocarbazate Schiff Bases and Their Metal Complexes	46
4.5	¹³ C NMR Spectral Data for all the Schiff bases	49
4.6	¹ H NMR Spectral Data for all the Schiff bases	49
4.7	Suggested ion fragmentation for S2T2C, S2M2TK, S2MB3MT and S2MB5MT	51
4.8	Suggested ion fragmentation for S3T2C, S3MB3MT and S3MB5MT	54
4.9	Suggested ion fragmentation for S4T2C, S4M2TK, S4MB3MT and S4MB5MT	57
4.10	Crystallography data and structure refinement detail of the S4M2TK	62
4.11	Selected bond length (Å) and bond angles (°) for S4M2TK Schiff Bases	63
4.12	Cytotoxic Activities of dithiocarbazate Schiff Bases and Their Metal Complexes	67
4.13	Contact Angle Analysis Data for bare ITO and MPA modified ITO	69

LIST OF SCHEMES

Scheme	Page
1. Formation of dithiocarbazate ion	1
2. Suggested mechanism of self-assembled monolayer	29
3. Proposed fragmentation pattern for S2-, S3- and S4MBDTC	60



LIST OF ABBREVIATIONS

S2MBDTC	S-2-methylbenzyldithiocarbazate
S3MBDTC	S-3-methylbenzyldithiocarbazate
S4MBDTC	S-3-methylbenzyldithiocarbazate
FT-IR	Fourier-Transform Infrared
NMR	Nuclear Magnetic Resonance
B.M	Bohr Magnetron
LMCT	Ligand to metal charge transfer
MLCT	Metal to ligand charge transfer
RT-112	Non invasive bladder cancer cell line
EJ-28	Invasive bladder cancer cell line
SAM	Self assembled Monolayer
ITO	Indium Tin Oxide
MPA	3-mercaptopropionic acid
S2T2C	S-2-methylbenzyl- β -N-(2-thiophenyl) methylene dithiocarbazate
S2M2TK	S-2-methylbenzyl- β -N-(2-thiophenyl) ethylene dithiocarbazate
S2MB3MT	S-2-methylbenzyl- β -N-(3-methyl-2-thiophenyl) methylene dithiocarbazate
S2MB5MT	S-2-methylbenzyl- β -N-(5-methyl-2-thiophenyl) methylene dithiocarbazate
S3T2C	S-3-methylbenzyl- β -N-(2-thiophenyl) methylene dithiocarbazate
S3MB3MT	S-3-methylbenzyl- β -N-(3-methyl-2-thiophenyl) methylene dithiocarbazate
S3MB5MT	S-3-methylbenzyl- β -N-(5-methyl-2-thiophenyl) methylene dithiocarbazate
S4T2C	S-4-methylbenzyl- β -N-(2-thiophenyl) methylene dithiocarbazate
S4M2TK	S-4-methylbenzyl- β -N-(2-thiophenyl) ethylene dithiocarbazate

S4MB3MT	S-4-methylbenzyl- β -N-(3-methyl-2-thiophenyl)methylene dithiocarbazate
S4MB5MT	S-4-methylbenzyl- β -N-(5-methyl-2-thiophenyl)methylene dithiocarbazate
Cu(S2T2C)(H ₂ O)(AOC ⁻)	Cu(II) complex of S-2-methylbenzyl- β -(2-thiophenyl)methylene dithiocarbazate
Ni(S2T2C) ₂	Ni(II) complex of S-2-methylbenzyl- β -N-(2-thiophenyl)methylene dithiocarbazate
Zn(S2T2C) ₂	Zn(II) complex of S-2-methylbenzyl- β -N-(2-thiophenyl)methylene dithiocarbazate
Cu(S2M2TK) ₂	Cu(II) complex of S-2-methylbenzyl- β -N-(2-thiophenyl)ethylene dithiocarbazate
Ni(S2M2TK) ₂	Ni(II) complex of S-2-methylbenzyl- β -N-(2-thiophenyl)ethylene dithiocarbazate
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Cu(S2MB3MT) ₂	Cu(II) complex of S-2-methylbenzyl- β -N-(3-methyl-2-thiophenyl)methylene dithiocarbazate
Ni(S2MB3MT) ₂	Ni(II) complex of S-2-methylbenzyl- β -N-(3-methyl-2-thiophenyl)methylene dithiocarbazate
Zn(S3MB3MT) ₂	Zn(II) complex of S-2-methylbenzyl- β -N-(3-methyl-2-thiophenyl)methylene dithiocarbazate
Cu(S2MB5MT) ₂	Cu(II) complex of S-2-methylbenzyl- β -N-(5-methyl-2-thiophenyl)methylene dithiocarbazate
Ni(S2MB5MT) ₂	Ni(II) complex of S-2-methylbenzyl- β -N-(5-methyl-2-thiophenyl)methylene dithiocarbazate
Zn(S2MB5MT) ₂	Zn(II) complex of S-2-methylbenzyl- β -N-(5-methyl-2-thiophenyl)methylene dithiocarbazate
Cu(S3T2C) ₂ 2(H ₂ O)	Cu(II) complex of S-3-methylbenzyl- β -N-(2-thiophenyl)methylene dithiocarbazate
Ni(S3T2C) ₂	Ni(II) complex of S-3-methylbenzyl- β -N-(2-thiophenyl)methylene dithiocarbazate

Zn(S3T2C) ₂	Zn(II) complex of S-3-methylbenzyl-β-N-(2-thiophenyl)methylene dithiocarbazate
Cu(S3MB3MT) ₂	Cu(II) complex of S-3-methylbenzyl-β-N-(3-methyl-2-thiophenyl) methylene dithiocarbazate
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Ni(S4M2TK) (H ₂ O)(OAc ⁻)	Ni(II) complex of S-4-methylbenzyl-β-N-(2-thiophenyl)ethylene dithiocarbazate
Zn(S4M2TK) ₂	Zn(II) complex of S-4-methylbenzyl-β-N-(2-thiophenyl)ethylene dithiocarbazate
Cu(S4MB3MT) (H ₂ O)(OAc ⁻)	Cu(II) complex of S-4-methylbenzyl-β-N-(3-methyl-2-thiophenyl) methylene dithiocarbazate
Ni(S4MB3MT) (H ₂ O)(OAc ⁻)	Ni(II) complex of S-4-methylbenzyl-β-N-(3-methyl-2-thiophenyl) methylene dithiocarbazate

$\text{Zn}(\text{S4MB3MT})_2$	Zn(II) complex of S-4-methybenzyl- β -N-(3-methyl-2-thiophenyl) methylene dithiocarbazate
$\text{Cu}(\text{S4MB5MT})_2$	Cu(II) complex of S-4-methybenzyl- β -N-(5-methyl-2-thiophenyl) methylene dithiocarbazate
$\text{Ni}(\text{S4MB5MT})_2$	Ni(II) complex of S-4-methybenzyl- β -N-(5-methyl-2-thiophenyl) methylene dithiocarbazate
$\text{Zn}(\text{S4MB5MT})_2$	Zn(II) complex of S-4-methybenzyl- β -N-(5-methyl-2-thiophenyl) methylene dithiocarbazate



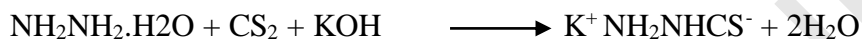
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CHAPTER 1

INTRODUCTION

1.1 Dithiocarbazate derivatives and their Schiff bases.

Dithiocarbazic acid is a primary amine that is synthesised by the reaction of hydrazine hydrate and carbon disulphide in the presence of potassium hydroxide.



Scheme 1: Formation of dithiocarbazate ion

Dithiocarbazate derivatives can chelate to metals through the sulfur and nitrogen atom and generally behave as bidentate ligands with sulfur and nitrogen donor atoms that react with the metal ion (Ameram *et al.*, 2013). A wide series of dithiocarbazate derivatives with interesting chemical properties and biological activities can be derived by substituting the -R group with alkyl or aryl substituents (Ameram *et al.*, 2013).

Dithiocarbazate actually has four potential donor atoms, which of two are sterically available at a time to bind with metal ions. Normally, dithiocarbazic esters with NS donor atoms would form five membered chelate rings (Rakha *et al.*, 2000 and Bera *et al.*, 2008) while SS chelate complexes are feasible with four membered ring complexes (Rakha *et al.*, 2000).

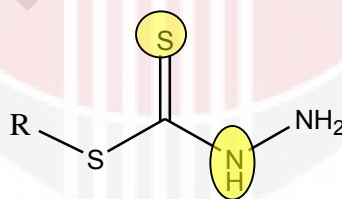
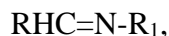


Figure 1.1: General Structure of dithiocarbazate with potential donor atoms

However, a modification of the dithiocarbazic moiety with change of suitable groups, gives rise to complexes with different coordination geometries (Ravoof *et al.*, 2007).

The condensation of primary amines with aldehydes or ketones will form Schiff bases. Schiff bases are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group (Bera *et al.*, 2008). The common structural feature of these compounds is the azomethine group with the general formula,



where R and R₁ are alkyl, aryl, cyclo alkyl or heterocyclic groups.

Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized compared to alkyl substituents. Aromatic Schiff bases are stable due to the conjugation effect of the cyclic compound while Schiff bases synthesized by the condensation of amine and aliphatic aldehydes are relatively unstable and easily undergoes polymerization. The formation of a Schiff base is favourable in the presence of acid or base or upon heating. The reaction is reversible and in some cases, Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines (Rakha *et al.*, 2000)

Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities (Kumar *et al.*, 2009). The azomethine linkage may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes. Schiff bases appear to be important intermediates in a number of enzymatic reactions involving the interaction of an enzyme with an amino or a carbonyl group of the substrate (Amanullah *et al.*, 2011)

Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom. Schiff bases with oxygen, nitrogen and sulfur donors and their complexes have been used as drugs and are important medicinal and chemotherapeutic agents that have been reported to possess a wide variety of biological activities against bacteria, fungi and cancer cells (Golcu *et al.*, 2005). Besides, Schiff bases are some of the most widely used organic compounds. They are used as pigment and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers (Gaertner *et al.*, 2011).

The presence of sp² hybridized orbital of nitrogen atom of on the azomethine makes it easier for a Schiff base to react by covalent bonding with hard nitrogen and soft sulphur atom nature and able to form a variety of metal complexes with unique properties (Etorki *et al.*, 2013).

There are many industrial and biologically active compounds that have been prepared and derived from Schiff bases like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions (Chen *et al.*, 2009).

1.2 Thiophene Derivatives.

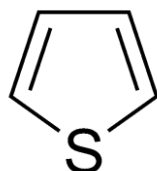
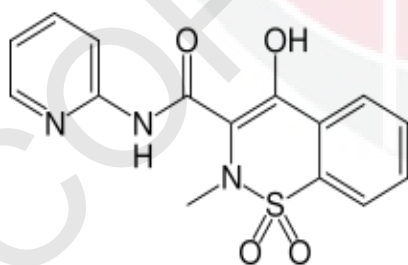


Figure1.2: Structure of Thiophene

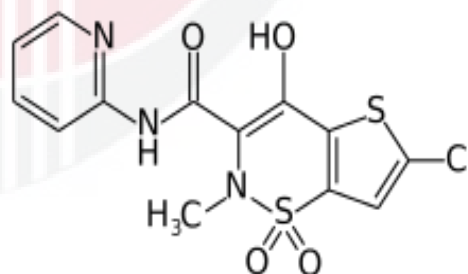
Thiophenes are a class of heterocyclic compounds also commonly called thiacyclopentadiene with the general formula C_4H_4S . Thiophene is a sulphur containing heterocycle that has been used as a therapeutic agents in medicinal chemistry (Mishra *et al.*, 2011) especially thiazolidinone, trizolo and imidazo moieties.

Thiophenes are widely used as building blocks in many agrochemicals. Thiophene possesses antimicrobial, analgesic and antiinflammatory, antihypertensive, antidiabetic, gonadotropin releasing hormone antagonist, cholesterol inhibition, antiallergic and, antitumor properties (Mishra *et al.*, 2011). Thiophene based compounds have been used in modern drug design due to their biologically active properties. Ketones of a thiophene series containing a nitro group possess the ability to suppress the growth of *Staphylococcus Aureus* and *Escherichia Coli*. It has been observed that the thienyl ring mimics the phenyl group of phenylalanine and is a peptidomimetic in many drugs (Spherry *et al.*, 2005).

The benzene ring of biologically active compounds may be replaced with thiophene without loss of its activity like the NSAID Lornoxicam which is the thiophene analog of piroxicam as anticancer agents.



(a) Figure 1.3: Piroxicam



(b) Figure 1.4: Lornoxicam

Thiophenes also have applications as metal complexing agents and in the development of insecticides (Mishra *et al.*, 2011).

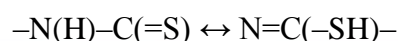
1.3 Properties of ligands with nitrogen-sulfur donor atoms.

Nitrogen and sulfur have the nucleophilic character and have particular bonding properties and coordination modes. They can behave as monodentate or bidentate chelates or bridging species and they can be used as chiral auxiliary reagents. The presence of sulphur in the ligand molecules with the π orbital does improve the

activity of the ligand to react with another molecule. Similarly heterocyclic-N donor ligands are deficient molecules. The ligands of sp^2 - π -donor and σ hybrid N-donor centers stem from their acceptor properties, their versatile coordination behaviour, easy synthesis, photophysical, photochemical and catalytic activity (Afanas'ev *et al.*, 1989)

1.4 Transition metal complexes of heterocyclic thiones

The coordination chemistry of heterocyclic thione derivatives containing



- (a) mimic cysteine sulphur coordination in metalloenzymes (Shalini *et al.*, 2010.)
- (b) show electronic and structural properties of the active sites in copper blue proteins involving S,N-coordination and (Vessières *et al.*, 2006)
- (c) comprise purine and pyrimidine bases (Akrivos *et al.*, 2001).

It is evident that thione-thiol equilibrium is dependent on environmental factors with the thiol form favored in the gas phase and non-polar solvents, and the thione form favored in the solid state and polar solvents (Al Zoubi *et al.*, 2013).

N and S donor atoms of heterocyclic thiones will coordinate to metal ions and chelate by short strong metal-nitrogen bonds, relatively long metal-sulphur bonds, small chelating angles and normally behave as bidentate ligands and form square planar complexes. In the absence of extraneous structural effects, the metal-sulphur bonds formed by S,N-chelating heterocyclic thionates are invariably slightly longer than those formed by the monodentate ligands (Chen *et al.*, 2009).

So in this context, it can be concluded that the design of ligands with the thioether-S donor centre in a chelated environment with additional heterocyclic-N donor backbone i.e, N,S donor environment are interesting and have unique properties.

1.5 Schiff Bases and Metal Complexes in Medicinal Chemistry

Metal compounds have been used as medicine for many diseases since ancient times. In traditional Chinese medicine, arsenic drugs, like arsenic trioxide (ATO), were used as antiseptic agents or in the treatment of rheumatoid diseases, syphilis, and psoriasis (Chen *et al.*, 2011). Inorganic elements like metal complexes play an important role in biological and medical processes, and it is evident that many organic compounds used in medicine do not have a purely organic mode of action, some are activated or bio-transformed by metal ion metabolism (Chen *et al.*, 2009).

Metal ions can modify electron flow in a substrate or enzyme, thus effectively controlling an enzyme catalyzed reaction (Fricker *et al.*, 2007).

Metal complexes can interact in the body by binding to DNA, affecting cellular equilibrium and inhibiting protein function. Besides, transition metal complexes can alter cellular equilibrium involving reactive oxygen species (ROS) and can act as protein kinase inhibitors (Gianferrara *et al.*, 2009).

The discovery of the antiproliferative effects of *cis*-diamine-dichloro-platinum(II) (cisplatin) in 1965 by Rosenberg and coworkers, has interested researchers to develop new metal-based drugs as radiation therapeutic, diagnostic and imaging agents, and as small molecule drugs with less toxicity and better activity (Gianferrara *et al.*, 2009).

The biological activities of metal complexes are affected by the molecular structure and stereochemistry of metal complexes. The presence of different functional groups will also affect the biological activities of metal complexes. Metal complexes have been known to accelerate drug action. It was reported that the efficiency of metal complexes as therapeutic agents could often be enhanced upon coordination with a metal ion and biological activity depended on the identity of the metal ions (Vessières *et al.*, 2006).

1.6 Zinc toxicity

Heavy metals are elements that persist in the environment (waters and soils), that cannot be degraded and come from anthropic activities like mining, smelting or different kind of wastes (Roesijadi *et al.*, 1996). Although these elements are necessary for life, (iron, selenium, cobalt, copper, manganese, molybdenum, zinc) the abundance and excess of these elements from mining or industrial waste can come environmental pollution and health problems to society.

Zn(II) is a main component in the production of synthetic fibres. Industrial wastewaters containing Zn(II) ions are the most toxic of all that are developed in this process (Nghah *et al.*, 2008). According to World Health Organization, a daily dietary requirement of zinc is 0.3 mg/kg of body weight and a provisional maximum tolerable daily intake of 1.0 mg/kg of body weight. The daily requirement for adult humans is 15–22 mg/day. The disposal of Zn to rivers can cause abdominal pain, nausea, vomiting, and diarrhea and serious disease in humans with high intake of the river water (Pereira *et al.*, 2010).

Drinking water containing zinc at levels above 3 mg/litre tends to be opalescent, develops a greasy film when boiled, and has an undesirable astringent taste. There are many analytical methods had been reported on the determination of zinc content

in water. The detection limit zinc by Atomic Absorption Spectrophotometry (AAS) of the direct air–acetylene flame method is 50 µg/litre (Geneva *et al.*, 1986). Low concentrations can be measured by chelating zinc with ammonium pyrrolidine dithiocarbamate and extracting it with methylisobutyl ketone (detection limit 0.5–1 µg/litre)(Haase *et al.*, 1954).

This project investigates the use of cyclic voltammetry techniques and the development of Schiff bases as self assembled monolayers on modified ITO as well as the detection of Zn²⁺ ion by electrochemical methods.

1.7 Schiff Bases for the detection of Heavy Metal Ions.

Schiff bases can accommodate different metal centres involving various coordination modes thereby allowing successful synthesis of homo- and heterometallic complexes with varied stereochemistry (Silva *et al.*, 2011). Transition metal complexes with oxygen and nitrogen donor Schiff base ligands are of particular interest because of their ability to possess unusual configuration, being structurally labile and their sensitivity to the molecular environment (Golcu *et al.*, 2005). Generally, pyrrole, –OH, –NH₂, urea, thiourea, –CONH centers etc., act as binding sites for cations.

There has been much research related to Schiff bases and their applications in biological studies but few have reported the development of Schiff bases as electrocatalytic sensors.

Electrochemical detection is one of the most selective and sensitive methods compared to other detection methods as this method has short time duration, is cost effective, has low detection limits and is easy to handle (Janata *et al.*, 2002).

1.7.1 Self Assembled Monolayers (SAMs).

A self assembled monolayer (SAM) is formed by arrangement of molecules or atoms adsorbed on solid surface by intermolecular forces, that forms from solution or vapour phase. Formation of SAMs involves a spontaneous reaction between an interface and an electron donor functional group (Politi *et al.*, 2007) that organise spontaneously into crystalline(or semicrystalline) structures.

Self assembled monolayers constitute building blocks that can be divided into three different parts: the headgroup (linking group), the backbone (main chain), and the specific terminal (active) group. The headgroup guides the self-assembly process on each type of substrate, linking the hydrocarbon chain (of variable length) to the substrate through a strong bond.

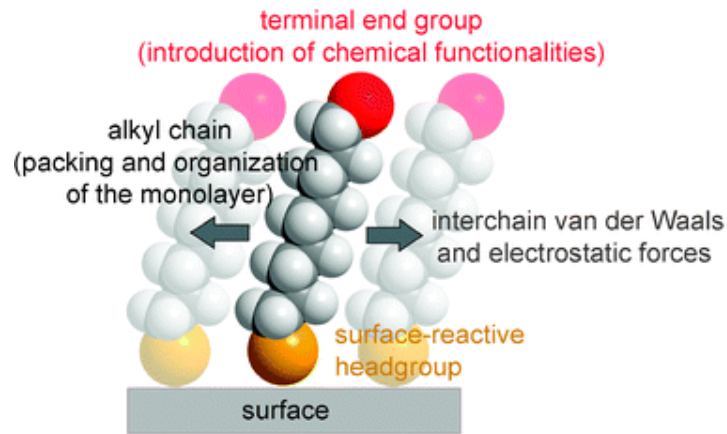


Figure 1.5: General structure of self assembled monolayer (SAM)
(Love *et al.*, 2005)

The molecules or ligands that form SAMs have a chemical functionality or “headgroup”, with a specific affinity for a substrate; in many cases, the headgroup has a high affinity for the surface and displaces adsorbed organic materials from the surface (Love *et al.*, 2005).

Generally, a self assembled monolayer would consist of important functional groups like thiols, disulfides and sulfides on gold (Chidsey *et al.*, 1990), silanes on silicon dioxides, fatty acids on metal oxide surfaces, phosphonates on phosphonate surfaces, and isocyanides on platinum (Ticha *et al.*, 2007) that adsorb on the surface of the substrate.

There are two types of self-assembled monolayers that are commonly used which is the adsorption of organosulfur compounds on noble metals such as gold, silver and reaction of alkyltrichlorosilanes with silicon or glass. These type of SAMs have been well known for providing an organic surface with a uniform chemical structure (Hickman *et al.*, 1989 and Allara *et al.*, 1985)

Sulfur-based compounds like alkanethiols have the affinity to bind strongly to different metal surfaces such as iron, silver, gold, copper and a diverse range of nanomaterials such as gold and carbon nanoparticles (Tien *et al.*, 1997 and Tachibana *et al.*, 2002)

Short-chain alkanethiols are preferred in biosensor development because they have fewer cohesive interactions between adsorbed species, resulting in a less packed surface (Poirier *et al.*, 1997 and Rowe *et al.*, 1994) thus inducing less stress and improving the formation of high ordered monolayers (Pathrima *et al.*, 2005).

The three dimensional self-assembled monolayers (SAMs) constructed on various nanostructures by chemisorption of bifunctional organic compounds have emerged as versatile tools of surface modification (Jadhav *et al.*, 2012) to perform electrochemical study and direct measurement.

SAMs can be prepared by immersing a desired substrate in a dilute solution of alkanethiol (mM) at ambient temperature followed by washing with the same solvent and drying with gas such argon or nitrogen to remove impurities.. The formation of the monolayer can be affected by several factors such as nature and roughness of substrate, solvent used, nature of the adsorbate, temperature and concentration of adsorbate.

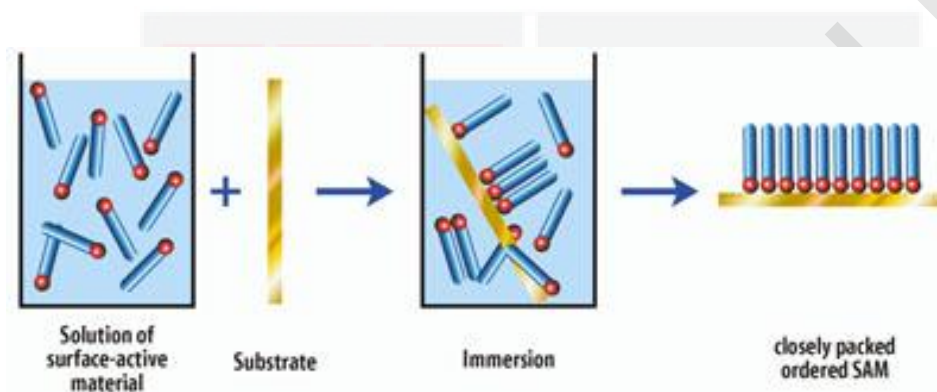


Figure 1.6: Schematic diagram showing preparation of Monolayer (Tien *et al.*, 1997)

1.8 Gold nanoparticles (AuNPs) containing functional thiol ligands in a self assembled monolayers (SAMs).

Gold nanoparticles are the most stable metal for nanomaterials and have been used for self assembled monolayer construction. Gold nanoparticles (AuNPs) have attracted substantial attention for their potent application in drug delivery (Ruan *et al.*, 2015) magnetic resonance imaging (MRI) (Debouttière *et al.*, 2006), X-ray computed tomography (X-ray CT) (Qian *et al.*, 2015), catalysis (Wu *et al.*, 2015), biosensing (Mohammed *et al.*, 2014) and so forth because their size, shape, and surface functionalization are easily controlled through the ligands and corresponding metal complexes. Nowadays, AuNPs have been widely used for colorimetric detection of metal ions in the environment as well as in physiological systems due to its excellent optical properties, such as high extinction coefficients and distance-dependent plasmonic absorption (Daniel and Astruc, 2004) (Burda *et al.*, 2005). Covalent binding between thiol ligands with gold makes the monolayer more stable and they can be repeatedly dried and redispersed in solvents. There are several studies on sulphur donor atoms – gold that have had significant sensor applications. Therefore, the use of Schiff bases that contain sulphur donor atom as in this work, is hoped to produce new self assembled monolayers (SAMs) with potential sensing properties.

1.9 Problem Statements

Most natural drugs isolated from wild-growing materials causes a shortened the life span of nature and thus need to be changed to more potent materials. Nowadays, microbial resistance to antibiotics is of much attention, leading to finding of novel active compounds against new targets. Many of the crude drugs, which are sources of medicinal preparations, still originate from wild-growing material. Transition metals are expected to be highly toxic and unstable in aqueous media. However, since the discovery of the antiproliferative effects of *cis*-diamine-dichloro-platinum(II) (cisplatin) in 1965 by Rosenberg and coworkers, a new field of research emerged. Since then, transition metal complexes have been used for medicinal applications like radiation therapeutics, diagnostics and imaging agents, and as small molecule drugs.

On the other hand, the development of heavy metal ions detection and quantification in the environment is crucial to our present society. There is an increasing need for analytical systems that deliver fast and reliable data in the development of novel sensors.

The monolayer self- assembly technique could yield a very simple, and yet highly versatile, controllable and stable approach for tailoring electrode surfaces (Ding *et al.*, 2002).The Self assembled monolayers have already been proven to be extremely useful for development of highly sensitive and more sophisticated sensors and biosensors for trace analysis studying (Zohreh *et al.*, 2013)

The interesting properties of Schiff bases that provide binding sites for the interaction for metal ions and form stable metal complexes gave a wide spectrum of promising activities in coordination chemistry and analytical chemistry for the detection of heavy metal ions. Furthermore, it was reported that transition metal complexes of bidentate NS Schiff bases derived from dithiocarbazate have shown promising activity as anticancer agents. Thus, it is hoped that these Schiff bases and their metal complexes would possess promising activity against bladder cancer cell lines and have a good potential as a new sensor for detection of heavy metal ions.

1.9.1 Objectives

The objectives of this project were:

1. To synthesis and characterise Schiff bases derived from S-substituted dithiocarbazates and their divalent Cu, Ni and Zn complexes.
2. To study the cytotoxicity of the Schiff bases and their metal complexes against two bladder cancer cell lines, RT-112 and EJ-28.
3. To develop new Schiff base based self assembled monolayers (SAMs) using selected Schiff bases for the detection of Zn²⁺ ion.

BIBLIOGRAPHY

- Afanas' ev, I. B., Dcrozko, A. I., Brodskii, A. V., Kostyuk, V. A., & Potapovitch, A. I. (1989). Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. *Biochemical pharmacology*, 38(11), 1763-1769.
- Akrivos, P. D. (2001). Recent studies in the coordination chemistry of heterocyclic thiones and thionates. *Coordination Chemistry Reviews*, 213(1), 181-210.
- Al-Amiery, A. A., Kadhun, A. A. H., & Mohamad, A. B. (2012). Antifungal activities of new coumarins. *Molecules*, 17(5), 5713-5723.
- Allara, D. L., & Nuzzo, R. G. (1985). Spontaneously organized molecular assemblies. 1. Formation, dynamics, and physical properties of n-alkanoic acids adsorbed from solution on an oxidized aluminum surface. *Langmuir*, 1(1), 45-52.
- Al Zoubi, W. (2013). Biological activities of Schiff bases and their complexes: a review of recent works. *International Journal of Organic Chemistry*, 2013.
- Ameram, N., & Othman, U. (2013). Synthesis And Characterization Of Co (Ii), Cu (Ii), Cd (Ii), Zn (Ii) And Ni (Ii) Complexes Of Schiff Base Ligand Derived From S-Benzylidithiocarbazate (Sbdtc) And Acetophenone With Their Biological Activity Studies. *Synthesis*, 3(8).
- Amanullah, M.; Sadozai, S.K.; Rehman, W.; Hassan, Z.;Rauf, A.; Iqbal, M. *African J. Biotech.* 2011,**10**,209.
- Anand, P., Patil, V. M., Sharma, V. K., Khosa, R. L., & Masand, N. (2012). Schiff bases: a review on biological insights. *International Journal of Drug Design and Discovery*, 3(3).
- Atilla-Gokcumen, G. E., Williams, D. S., Bregman, H., Pagano, N., & Meggers, E. (2006). Organometallic compounds with biological activity: a very selective and highly potent cellular inhibitor for glycogen synthase kinase 3. *ChemBioChem*, 7(9), 1443-1450.
- Bain, C. D., Biebuyck, H. A., & Whitesides, G. M. (1989). Comparison of self-assembled monolayers on gold: coadsorption of thiols and disulfides. *Langmuir*, 5(3), 723-727.3568.
- Bain, C. D., Troughton, E. B., Tao, Y. T., Evall, J., Whitesides, G. M., & Nuzzo, R. G. (1989). Formation of monolayer films by the spontaneous assembly of organic thiols from solution onto gold. *Journal of the American Chemical Society*, 111(1), 321-335.
- Bader, N. R. (2010). Applications of Schiffs Bases Chelates in Quantitative Analysis A Review. *RASAYAN j. Chem*, 3(4), 660-670.

- Ballarin, B., Cassani, M. C., Scavetta, E., & Tonelli, D. (2008). Self-assembled gold nanoparticles modified ITO electrodes: The monolayer binder molecule effect. *Electrochimica Acta*, 53(27), 8034-8044.
- Bella, S.D., Fragala, I., Leonardi, N., Sortino, S. (2004). Self-assembled monolayers of bis(salicylaldiminato)nickel(II) Schiff-base complexes: synthesis and structure. *Inorganica Chimica Acta* 357 (2004) 3865–3870.
- Bera, P., Kim, C. H., & Seok, S. I. (2008). Synthesis, spectroscopic characterization and thermal behavior of cadmium (II) complexes of S-methyldithiocarbazate (SMDTC) and S-benzylthiocarbazate (SBDTC): X-ray crystal structure of [Cd (SMDTC) 3]· 2NO 3. *Polyhedron*, 27(17), 3433-3438.
- Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K., & Watkin, D. J. (2003). CRYSTALS version 12: software for guided crystal structure analysis. *Journal of Applied Crystallography*, 36(6), 1487-1487.
- Chan, M. H. E., Crouse, K. A., Tahir, M. I. M., Rosli, R., Umar-Tsafe, N., & Cowley, A. R. (2008). Synthesis and characterization of cobalt (II), nickel (II), copper (II), zinc (II) and cadmium (II) complexes of benzyl N-[1-(thiophen-2-yl) ethylidene] hydrazine carbodithioate and benzyl N-[1-(thiophen-3-yl) ethylidene] hydrazine carbodithioate and the X-ray crystal structure of bis {benzyl N-[1-(thiophen-2-yl) ethylidene] hydrazine carbodithioate} nickel (II). *Polyhedron*, 27(4), 1141-1149.
- Chaki, N. K., Aslam, M., Sharma, J., & Vijayamohanan, K. (2001). Applications of self-assembled monolayers in materials chemistry. *Journal of Chemical Sciences*, 113(5-6), 659-670
- Chavain, N., & Biot, C. (2010). Organometallic complexes: new tools for chemotherapy. *Current medicinal chemistry*, 17(25), 2729-2745.
- 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.
- Chen, S., & Murray, R. W. (1999). Arenethiolate monolayer-protected gold clusters. *Langmuir*, 15(3), 682-689.
- Chen, Z. F., Mao, L., Liu, L. M., Liu, Y. C., Peng, Y., Hong, X., & Liang, H. (2011). Potential new inorganic antitumour agents from combining the anticancer traditional Chinese medicine (TCM) matrine with Ga (III), Au (III), Sn (IV) ions, and DNA binding studies. *Journal of inorganic biochemistry*, 105(2), 171-180.
- Chew, K. B., Tarafder, M. T. H., Crouse, K. A., Ali, A. M., Yamin, B. M., & Fun, H. K. (2004). Synthesis, characterization and bio-activity of metal complexes of bidentate N–S isomeric Schiff bases derived from S-methyldithiocarbazate (SMDTC) and the X-ray structure of the bis [S-methyl-β-N-(2-furyl-methylketone) dithiocarbazato] cadmium (II) complex. *Polyhedron*, 23(8), 1385-1392.

- Chidsey, C. E., & Loiacono, D. N. (1990). Chemical functionality in self-assembled monolayers: structural and electrochemical properties. *Langmuir*, 6(3), 682-691.
- Cras, J. J., Rowe-Taitt, C. A., Nivens, D. A., & Ligler, F. S. (1999). Comparison of chemical cleaning methods of glass in preparation for silanization. *Biosensors and Bioelectronics*, 14(8), 683-688
- Di Bella, S., Fragalà, I., Leonardi, N., & Sortino, S. (2004). Self-assembled monolayers of bis (salicylaldehyde) nickel (II) Schiff-base complexes: synthesis and structure. *Inorganica chimica acta*, 357(13), 3865-3870.
- Dimitra, K. D., & Miller, J. R. (1999). Palladium (II) and platinum (II) complexes of pyridin-2-carbaldehyde thiosemicarbazone with potential biological activity. Synthesis, structure and spectral properties. *Polyhedron*, 18(7), 1005-1013.
- Dmg, K., Wang, Q., Jia, Z., Tian, N., Wang, N., Tong, R., & Shao, H. (2002). Electrochemical Study of Schiff Bases by Means of Self-Assembled Monolayers. *Journal of the Chinese Chemical Society*, 49(2), 185-190.
- Etorki, A., Ben-Saber, S., El-ajaily, M., & Maihub, A. (2013). Metal Ions Uptake Using Schiff Bases Derived from Salicylaldehyde and Appropriate Amino Compounds. *Journal of Chemistry and Chemical Engineering*, 7(3), 193.
- Evaluation of Certain Food Additives and Contaminants: Seventy-seventh Report of the Joint FAO/WHO Expert Committee on Food Additives (Vol. 77)*. World Health Organization.
- Fricker, S. P. (2007). Metal based drugs: from serendipity to design. *Dalton Transactions*, (43), 4903-4917.
- GAERTNER, D. J. (2011). A. Anesthetics. *Anesthesia and Analgesia in Laboratory Animals*, pp.277. Academic Press.
- Gianferrara, T., Bratsos, I., & Alessio, E. (2009). A categorization of metal anticancer compounds based on their mode of action. *Dalton Transactions*, (37), 7588-7598.
- Golcu, A., Tumer, M., Demirelli, H., & Wheatley, R. A. (2005). Cd (II) and Cu (II) complexes of polydentate Schiff base ligands: synthesis, characterization, properties and biological activity. *Inorganica Chimica Acta*, 358(6), 1785-1797.
- Golcu, A., Tumer, M., Demirelli, H., & Wheatley, R. A. (2005). Cd (II) and Cu (II) complexes of polydentate Schiff base ligands: synthesis, characterization, properties and biological activity. *Inorganica Chimica Acta*, 358(6), 1785-1797.
- Gyepi-Garbrah, S. H., & Šilerová, R. (2002). The first direct comparison of self-assembly and Langmuir–Blodgett deposition techniques: Two routes to highly organized monolayers. *Physical Chemistry Chemical Physics*, 4(14), 3436-3442.

- Hickman, J. J., Zou, C., Ofer, D., Harvey, P. D., Wrighton, M. S., Laibinis, P. E., ... & Whitesides, G. M. (1989). Combining spontaneous molecular assembly with microfabrication to pattern surfaces: Selective binding of isonitriles to platinum microwires and characterization by electrochemistry and surface spectroscopy. *Journal of the American Chemical Society*, 111(18), 7271-7272.
- Hostetler, M. J., Green, S. J., Stokes, J. J., & Murray, R. W. (1996). Monolayers in three dimensions: synthesis and electrochemistry of ω -functionalized alkanethiolate-stabilized gold cluster compounds. *Journal of the American Chemical Society*, 118(17), 4212-4213.
- Humphrey, J., & Copsey, M. (2007). Dalton Discussion 10: applications of metals in medicine and healthcare. *Dalton Transactions*, (43), 4883-4883.
- Hartinger, C. G. (2008). Dalton Discussion 10: Applications of Metals in Medicine and Healthcare. *Platinum Metals Review*, 52(2), 96.
- Jadhav, S. A. (2012). Functional self-assembled monolayers (SAMs) of organic compounds on gold nanoparticles. *J. Mater. Chem.*, 22(13), 5894-5899.
- Jamuna, K., Naik, B.R., Sreenu, B., Sessaiah, K. (2012). Synthesis, characterization and antibacterial activity of Cu(II) and Fe(III) complexes of a new tridentate Schiff base ligand. *Journal of Chemical and Pharmaceutical Research*, 4(9):4275-4282.
- Janata, J. (2002). Electrochemical sensors and their impedances: a tutorial. *Critical reviews in analytical chemistry*, 32(2), 109-120.
- Jimoh, A. A., Helal, A., Shaikh, M. N., Aziz, M. A., Yamani, Z. H., Al-Ahmed, A., & Kim, J. P. (2015). Schiff base ligand coated gold nanoparticles for the chemical sensing of Fe (III) ions. *Journal of Nanomaterials*, 16(1), 190.
- Joseyphus, R. S., & Nair, M. S. (2010). Synthesis, characterization and biological studies of some Co (II), Ni (II) and Cu (II) complexes derived from indole-3-carboxaldehyde and glycylglycine as Schiff base ligand. *Arabian Journal of Chemistry*, 3(4), 195-204.
- Kalinowski, D. S., & Richardson, D. R. (2007). Future of toxicology iron chelators and differing modes of action and toxicity: the changing face of iron chelation therapy. *Chemical research in toxicology*, 20(5), 715-720.
- Kong, D. S., Wan, L. J., Han, M. J., Pan, G. B., Lei, S. B., Bai, C. L., & Chen, S. H. (2002). Self-assembled monolayer of a Schiff base on Au (111) surface: electrochemistry and electrochemical STM study. *Electrochimica acta*, 48(4), 303-309.
- Kumar, S., Dhar, D. N., & Saxena, P. N. (2009). Applications of metal complexes of Schiff bases—a review. *Journal of scientific and industrial research*, 68(3), 181-187.
- Lin, Y. C., Yu, B. Y., Lin, W. C., Chen, Y. Y., & Shyue, J. J. (2008). Site-selective deposition of gold on pPhoto-patterned self-assembled monolayers. *Chemistry of Materials*, 20(21), 6606-6610.

- Li, W. C., & Lee, S. W. (2011). The Characteristic Self-assembly of Gold Nanoparticles over Indium Tin Oxide (ITO) Substrate. *Bulletin of the Korean Chemical Society*, 32(4), 1133-1137.
- Love, J. C., Estroff, L. A., Kriebel, J. K., Nuzzo, R. G., & Whitesides, G. M. (2005). Self-assembled monolayers of thiolates on metals as a form of nanotechnology. *Chemical reviews*, 105(4), 1103-1170.
- Ma, D. L., He, H. Z., Chan, D. S. H., Wong, C. Y., & Leung, C. H. (2014). A colorimetric and luminescent dual-modal assay for Cu (II) ion detection using an iridium (III) complex. *PloS one*, 9(6), e99930.
- March, G., Nguyen, T. D., & Piro, B. (2015). Modified electrodes used for electrochemical detection of metal ions in environmental analysis. *Biosensors*, 5(2), 241-275.
- Masoud, S. A., Johnson, L. B., White, F. F., & Reeck, G. R. (1993). Expression of a cysteine proteinase inhibitor (oryzacystatin-I) in transgenic tobacco plants. *Plant molecular biology*, 21(4), 655-663.
- Maye, M. M., Luo, J., Lin, Y., Engelhard, M. H., Hepel, M., & Zhong, C. J. (2003). X-ray photoelectron spectroscopic study of the activation of molecularly-linked gold nanoparticle catalysts. *Langmuir*, 19(1), 125-131.
- Mazlan, N.A. 2013. Synthesis and characterization of Schiff bases containing inidazole / benzimidazole, their metal complexes and biological acrivities, MSc Thesis. Universiti Putra Malaysia.
- Mishra, R., Jha, K. K., Kumar, S., & Tomer, I. (2011). Synthesis, properties and biological activity of thiophene: A review. *Der Pharma Chemica*, 3(4), 38-54.
- Mishra, N., Poonia, K., & Kumar, D. (2013). An overview of biological aspects of Schiff base metal complexes. *International Journal of Advancements in Research & Technology*, 2(8), 52-66.
- M. M. Singh, R. B. Rastogi, B. N. Upadhyay, and M. Yadav, "Thiosemicarbazide, phenyl isothiocyanate and their condensation product as corrosion inhibitors of copper in aqueous chloride solutions," *Materials Chemistry and Physics*, vol. 80, no. 1, pp. 283–293, 2003.
- Morrin, A., Moutloali, R. M., Killard, A. J., Smyth, M. R., Darkwa, J., & Iwuoha, E. I. (2004). Electrocatalytic sensor devices:(I) cyclopentadienylnickel (II) thiolato Schiff base monolayer self-assembled on gold. *Talanta*, 64(1), 30-38.
- Ngah, W. W., & Hanafiah, M. A. K. M. (2008). Removal of heavy metal ions from wastewater by chemically modified plant wastes as adsorbents: a review. *Bioresource technology*, 99(10), 3935-3948.
- Pattan, S. R., Pawar, S. B., Vetel, S. S., Gharate, U. D., & Bhawar, S. B. (2012). The Scope of Metal Complexes in Drug Design-A Review. *Indian Drugs*, 49(11), 5-12.

- Perepichka, D. F., & Rosei, F. (2007). Metal nanoparticles: From “artificial atoms” to “artificial molecules”. *Angewandte Chemie International Edition*, 46(32), 6006-6008.
- Prathima, N., Harini, M., Rai, N., Chandrashekara, R. H., Ayappa, K. G., Sampath, S., & Biswas, S. K. (2005). Thermal study of accumulation of conformational disorders in the self-assembled monolayers of C8 and C18 alkanethiols on the Au (111) surface. *Langmuir*, 21(6), 2364-2374.
- Pereira, F. V., Gurgel, L. V. A., & Gil, L. F. (2010). Removal of Zn 2+ from aqueous single metal solutions and electroplating wastewater with wood sawdust and sugarcane bagasse modified with EDTA dianhydride (EDTAD). *Journal of Hazardous Materials*, 176(1), 856-863.
- Poirier, G. E., & Pylant, E. D. (1996). The self-assembly mechanism of alkanethiols on Au (111). *Science*, 272(5265), 1145-1148.
- Politi, L., Leone, F., Morini, L., & Poletti, A. (2007). Bioanalytical procedures for determination of conjugates or fatty acid esters of ethanol as markers of ethanol consumption: a review. *Analytical biochemistry*, 368(1), 1-16.
- Porter, M. D., Bright, T. B., Allara, D. L., & Chidsey, C. E. (1987). Spontaneously organized molecular assemblies. 4. Structural characterization of n-alkyl thiol monolayers on gold by optical ellipsometry, infrared spectroscopy, and electrochemistry. *Journal of the American Chemical Society*, 109(12), 3559-3568.
- Pozo-Guisado, E., Alvarez-Barrientos, A., Mulero-Navarro, S., Santiago-Josefat, B., and
 Fernandez-Salguero, P.M. (2002). The antiproliferative activity of resveratrol results in apoptosis in MCF-7 but not in MDA-MB-231 human breast cancer cells: cell-specific alteration of the cell cycle. *Biochemical Pharmacology*. 64: 1375 – 1386.
- Q Memon, S., Memon, N., Mallah, A., Soomro, R., & Y Khuhawar, M. (2014). Schiff Bases as Chelating Reagents for Metal Ions Analysis. *Current Analytical Chemistry*, 10(3), 393-417
- Rakha, T. H., & Bekheit, M. M. (2000). Mononuclear and polynuclear chelates of picolinoyldithiocarbamate. *Chemical and pharmaceutical bulletin*, 48(7), 914-919.
- Raja, D. S., Paramaguru, G., Bhuvanesh, N. S., Reibenspies, J. H., Renganathan, R., & Natarajan, K. (2011). Effect of terminal N-substitution in 2-oxo-1, 2-dihydroquinoline-3-carbaldehyde thiosemicarbazones on the mode of coordination, structure, interaction with protein, radical scavenging and cytotoxic activity of copper (II) complexes. *Dalton Transactions*, 40(17), 4548-4559.
- Ravoof, T. B. S. A., Tahir, M. I. M., & Tiekink, E. R. T. (2015). Crystal structure of 4-methylbenzyl N'-[(thiophen-2-yl) methylidene] hydrazinecarbodithioate.

Acta Crystallographica Section E: Crystallographic Communications, 71(7), o475-o476.

- Ravoof, T. B., Crouse, K. A., Tahir, M. I. M., Rosli, R., Watkin, D. J., & How, F. N. (2011). Synthesis, characterisation and biological activities of 2-methylbenzyl 2-(dipyridin-2-yl methylene) hydrazinecarbodithioate. *Journal of Chemical Crystallography*, 41(4), 491-495.
- Ravoof, T. B., Crouse, K. A., Tahir, M. I. M., Cowley, A. R., & Ali, M. A. (2007). Synthesis, characterization and bioactivity of mixed-ligand Cu (II) complexes containing Schiff bases derived from S-benzylthiocarbamate and saccharinate ligand and the X-ray crystal structure of the copper-saccharinate complex containing S-benzyl- β -N-(acetylpyrid-2-yl) methylenedithiocarbamate. *Polyhedron*, 26(6), 1159-1165.
- R. B. Rastogi, M. M. Singh, M. Yadav, and K. Singh, "Substitutedthiobiurets and their molybdenum and tungsten complexes as corrosion inhibitors for mild steel in 1.0 N N sulphuric acid," *Indian Journal of Engineering and Materials Sciences*, vol. 10, no. 2, pp. 155–160, 2003.
- 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.
- Rowe, G. K., & Creager, S. E. (1994). Chain length and solvent effects on competitive self-assembly of ferrocenylhexanethiol and 1-alkanethiols onto gold. *Langmuir*, 10(4), 1186-1192.
- Samanta, S., Goswami, S., Ramesh, A., & Das, G. (2014). A new fluorogenic probe for solution and intra-cellular sensing of trivalent cations in model human cells. *Sensors and Actuators B: Chemical*, 194, 120-126.
- Shalini, K., Sharma, P. K., & Kumar, N. (2010). Imidazole and its biological activities: A review. *Der Chemica Sinica*, 1(3), 36-47.
- Sekhar, E. V. (2014). Synthesis and characterisation of metal complexes of some novel schiff bases. *In Press*.
- Sekhar, E. V., Jayaveera, K. N., & Srihari, S. Studies on the metal complexes of N⁷-(thiophen-2-yl-methylidene)-pyridine-4-carbohydrazide.
- Shipway, A. N., Katz, E., & Willner, I. (2000). Nanoparticle arrays on surfaces for electronic, optical, and sensor applications. *ChemPhysChem*, 1(1), 18-52.
- da Silva, C. M., da Silva, D. L., Modolo, L. V., Alves, R. B., de Resende, M. A., Martins, C. V., & de Fátima, Â. (2011). Schiff bases: a short review of their antimicrobial activities. *Journal of Advanced research*, 2(1), 1-8.
- Sperry, J. B., & Wright, D. L. (2005). Furans, thiophenes and related heterocycles in drug discovery. *Current opinion in drug discovery & development*, 8(6), 723-740.

- Sun, M., Ding, B., Yu, J., Hsieh, Y. L., & Sun, G. (2012). Self-assembled monolayer of 3-mercaptopropionic acid on electrospun polystyrene membranes for Cu²⁺ detection. *Sensors and Actuators B: Chemical*, 161(1), 322-328.
- Tachibana, M., Yoshizawa, K., Ogawa, A., Fujimoto, H., & Hoffmann, R. (2002). Sulfur-gold orbital interactions which determine the structure of alkanethiolate/Au (111) self-assembled monolayer systems. *The Journal of Physical Chemistry B*, 106(49), 12727-12736.
- Takjoo, R., Centore, R., Hakimi, M., Beyramabadi, S. A., & Morsali, A. (2011). S-allyl-3-(2-pyridyl-methylene) dithiocarbazate ligand and its manganese (II), cobalt (III) and nickel (II) complexes. *Inorganica Chimica Acta*, 371(1), 36-41.
- Teoh, S. G., Ang, S. H., Fun, H. K., & Ong, C. W. (1999). Synthesis, crystal structure and biological activity of thiophene-2-carboxaldehyde thiosemicarbazone and its tin complexes. *Journal of organometallic chemistry*, 580(1), 17-21.
- Thomas, G. 2000. Medicinal chemistry: an introduction. In *Anticancer agents*, pp. 279. New York: Wiley.
- Tien, J., Terfort, A., & Whitesides, G. M. (1997). Microfabrication through electrostatic self-assembly. *Langmuir*, 13(20), 5349-5355.
- Ticha, L. A. (2007). *Development of amperometric biosensor with cyclopentadienylruthenium (II) thiolato schiff base self-assembled monolayer (SAM) on gold* (Doctoral dissertation, University of the Western Cape).
- Vance, A. L., Alcock, N. W., Heppert, J. A., & Busch, D. H. (1998). An octahedral template based on a new molecular turn: synthesis and structure of a model complex and a reactive, diphenolic ligand and its metal complexes. *Inorganic chemistry*, 37(26), 6912-6920.
- Vessières, A., Top, S., Beck, W., Hillard, E., & Jaouen, G. (2006). Metal complex SERMs (selective oestrogen receptor modulators). The influence of different metal units on breast cancer cell antiproliferative effects. *Dalton Transactions*, (4), 529-541.
- Whitesides, G. M., & Laibinis, P. E. (1990). Wet chemical approaches to the characterization of organic surfaces: self-assembled monolayers, wetting, and the physical-organic chemistry of the solid-liquid interface. *Langmuir*, 6(1), 87-96.
- Yadav, M. (2012). Synthesis, Characterization, and Biological Activity of Some Transition Metal Complexes of N-Benzoyl-N'-thiophenethiocarbohydrazide. *International Journal of Inorganic Chemistry*, 2012
- Yang, Y., Wang, Z., Yang, M., Guo, M., Wu, Z., Shen, G., & Yu, R. (2006). Inhibitive determination of mercury ion using a renewable urea biosensor based on self-assembled gold nanoparticles. *Sensors and Actuators B: Chemical*, 114(1), 1-8.

- Yazdanbakhsh, M., Takjoo, R., Frank, W., & Aghaei Kaju, A. (2009). The preparation, spectroscopic characterization and X-ray crystal structures of the pyrrole-2-carboxaldehyde Schiff base of S-allyldithiocarbazate (HL) and its nickel (II) complex ([Ni (L) 2]). *Journal of Coordination Chemistry*, 62(22), 3651-3660.
- Yildirim, H., Guler, E., Yavuz, M., Ozturk, N., Yaman, P. K., Subasi, E., & Timur, S. (2014). Ruthenium (II) complexes of thiosemicarbazone: Synthesis, biosensor applications and evaluation as antimicrobial agents. *Materials Science and Engineering: C*, 44, 1Yildirim, H., Guler, E., Yavuz, M., Ozturk, N., Yaman, P.K., Subasi,
- Yusof, E.N. 2014. *Synthesis and characterization of dithiocarbazate schiff base derived from natural product aldehydes, their metal complexes and biological activities*, MSc Thesis, Unversiti Putra Malaysia.
- Zhang, H., Lu, H., & Hu, N. (2006). Fabrication of electroactive layer-by-layer films of myoglobin with gold nanoparticles of different sizes. *The Journal of Physical Chemistry B*, 110(5), 2171-2179.
- Zohreh, M., Ghoreishi, S. M., Behpour, M., & Mohammadhassan, M. (2012). Applied electrochemical biosensor based on covalently self assembled monolayer at gold surface for determination of epinephrine in the presence of Ascorbic acid. *Arabian Journal of Chemistry*.In Press.

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