UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, STRUCTURAL CHARACTERISATION AND CYTOTOXIC STUDY OF MULTIDENTATE DITHIOCARBAZATE SCHIFF BASES AND THEIR DIVALENT Cu, Ni, AND Zn COMPLEXES

ENIS NADIA BINTI MD YUSOF

FS 2014 57

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By

ENIS NADIA BINTI MD YUSOF

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

December 2014

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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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December 2014

Chairman: Thahira Begum, PhD

Faculty: Science

Three series of dithiocarbazate Schiff bases derived from S-benzyldithiocarbazate (SBDTC), S-2-methylbenzyldithiocarbazate (S2MBDTC) and S-4-methylbenzyldithiocarbazate (S4MBDTC) were synthesized using 2-hydroxy-3-methoxybenzaldehyde (OVa), 2-methoxybenzaldehyde (2MB), 3-methoxybenzaldehyde (3MB) and 2-furaldehyde (Fu) *via* condensation. The Schiff bases were then complexed with the respective metal salts to produce transition metal complexes. The metal complexes formed are expected to have a general formula of $[M(ONS).H_2O]$ and $[M(NS)_2]$ where M = Cu^{2+}, Ni^{2+}, and Zn^{2+}. These compounds were characterized by elemental analysis, molar conductivity, magnetic susceptibility and various spectroscopic techniques including 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 agreement with the proposed molecular formulae of Schiff bases and metal complexes. The complexes are non-electrolytes in DMSO solution, where anionic ligands are bonded covalently to the metal ions. The FTIR spectra of the dithiocarbazate Schiff bases displayed a sharp band which corresponded to *ν*(C=N), that shifted to lower wavenumbers and a *ν*(N-H) band which disappeared in all of the metal complexes suggesting the protonation of the Schiff bases that occurred upon complexation to the metal ions. The magnetic susceptibility measurements and spectral results support the coordination geometry in which the Schiff bases behave as tridentate ONS or bidentate NS donor ligand coordinating *via* the azomethine nitrogen, thiolo sulphur, and oxygen atoms (where applicable). Single crystal X-ray crystallographic analysis of seven new Schiff bases, one copper(II) complex, $[Cu(S2MOVa).H_2O].H_2O$, and one nickel (II) complex, $Ni(SB3MB)_2$ were obtained. The Schiff bases and their metal complexes have been evaluated for their biological activities against an estrogen receptor positive breast cancer cell line (MCF-7) and an estrogen receptor negative breast cancer cell line (MDA-MB-231). All of the Cu(II) complexes showed marked cytotoxicity against cell lines while the other complexes were found to be inactive. The preliminary binding

interaction of the copper(II) complexes with calf thymus DNA (CT-DNA) was also investigated and the binding constant (10^4-10^5 M^{-1}) obtained indicate that the copper (II) complexes have a good binding affinity to the CT-DNA , in agreement with the cytotoxic data.

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

SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BAGI BES SCHIFF DITIOKARBAZAT MULTIDENTAT DAN KOMPLEKS LIGAN

Oleh

ENIS NADIA BINTI MD YUSOF

Disember 2014

Pengerusi: Thahira Begum, PhD

Fakulti: Sains

Tiga siri bes Schiff dithiokarbazat yang diterbitkan daripada S-benzilditiokarbazat (SBDTC), S-2-metilbenzilditiokarbazat (S2MBDTC) dan S-4-metilbenzilbitiokarbazat telah disintesis menggunakan 2-hidroksi-3-metoksibenzaldehid (OVa), 2-metoksibenzaldehid (2MB), 3-metoksibenzaldehid (3MB), dan 2-furaldehid (Fu) melalui tindakbalas kondensasi. Seterusnya bes Schiff telah dikomplekkan dengan garam logam masing-masing untuk menghasilkan logam peralihan kompleks. Logam kompleks yang dihasilkan adalah dianggarkan mempunyai formula umum $[M(ONS).H_2O]$ dan $[M(NS)_2]$ dimana M = Cu^{2+}, Ni^{2+}, and Zn^{2+}. Sebatian-sebatian itu dicirikan dengan analisis unsur, kekonduksian molar, kerentanan magnetik dan pelbagai teknik-teknik spektroskopi termasuklah analisis spektroskopi Transformasi Fourier Inframerah (FTIR), Resonans Magnetik Nuklear (NMR), Mass spektroskopi (MS), Ultra Lembayung/Boleh Nampak (UV/Vis) dan Spektroskopi Pancaran Pasangan Plasma-Atom secara Induktif (ICP-AES). Analisis unsur yang diperolehi sejajar dengan formula molekul yang dicadangkan bagi bes Schiff dan logam komplek. Komplek-komplek adalah bukan elektrolit dalam larutan DMSO, dimana ligan anionik berhubung secara kovalen terhadap ion logam. Spektra FTIR Bes Schiff dithiokarbazat menunjukkan regangan tajam yang mana berpadanan dengan *ν*(C=N), regangan ini beralih kepada number gelombang rendah dan kehilangan regangan *ν*(N-H) dalam semua komplek metal mencadangkan bahawa pemprotonan bes Schiff berlaku setelah komplekasi dengan ion logam. Ukuran kerentenan magnetik dan keputusan spektra meyokong geometri berkoordinat yang mana bes Schiff berkelakuan sebagai ligan penderma tridentat ONS atau bidentat NS yang berkoordinat melalui atom-atom nitrogen azomethin, sulfur tiolo, dan oksigen atau atom-atom nitrogen azomethin dan sulfur tiolo. Analisis kristalografi hablur tunggal sinar X bagi tujuh bes Schiff, satu komplek kuprum(II), $[Cu(S2MOVa).H_2O].H_2O$, dan satu nickel(II) komples, $Ni(SB3MB)_2$ telah diperoleh. Bes Schiff dan kompleks-kompleks logamnya telah dinilai untuk aktiviti biologi mereka terhadap sel kanser payudara dengan reseptor estrogen positif (MCF-7) dan sel kanser payudara dengan reseptor estrogen negatif (MDA-MB-231). Kesemua kompleks kuprum(II) menunjukkan tanda posotif sitotosik terhadap sel-sel kanser tersebut manakala kompleks-kompleks lain telah ditemui tidak aktif. Pra interaksi

mengikat kuprum(II) kompleks dengan DNA timus anak lembu (CT-DNA) telah disiasat dan pemalar ikatan (10^4-10^5 M^{-1}) menunjukkan bahawa kuprum(II) kompleks mempunyai pertalian baik yang mengikat kepada CT-DNA, disokong oleh data sitotoksik.

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Lastly, I offer my best wishes to all who supported me in any way during the completion of this research.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee are as follows:

Thahira Begum, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Mohamed Ibrahim Mohamed Tahir, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Abhimanyu Veerakumarasivam, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences, Perdana University
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

SBDTC	S-benzyldithiocarabazate
S2MBDTC	S-2-methyldithiocarbazate
S4MBDTC	S-2-methyldithiocarbazate
FT-IR	Fourier-Transform Infrared
NMR	Nuclear Magnetic Resonance
B.M	Bohr Magneton
LMCT	Ligand to metal charge transfer
IC_{50}	Inhibitory concentration at 50%
MCF-7	Estrogen receptor positive human breast cancer cell line
MDA-MB-231	Estrogen receptor negative human breast cancer cell line
CT-DNA	Calf thymus DNA
m/z	Mass to charge ratio
SBOVa	S-benzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylene dithiocarbazate
SB2MB	S-benzyl-β-N-(2-methoxybenzyl)methylenedithiocarbazate
SB3MB	S-benzyl-β-N-(3-methoxybenzyl)methylenedithiocarbazate
SBFu	S-benzyl-β-N-(2-furyl)methylenedithiocarbazate
S2MOVa	S-2-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylene dithiocarbazate
S2M2MB	S-2-methylbenzyl-β-N-(2-methoxybenzyl)methylene dithiocarbazate
S2M3MB	S-2-methylbenzyl-β-N-(3-methoxybenzyl)methylene dithiocarbazate
S2MFu	S-2-methylbenzyl-β-N-(2-furyl)methylenedithiocarbazate
S4MOVa	S-4-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylene dithiocarbazate

S4M2MB	S-4-methylbenzyl-β-N-(2-methoxybenzyl)methylene dithiocarbazate
S4M3MB	S-4-methylbenzyl-β-N-(3-methoxybenzyl)methylene dithiocarbazate
S4MFu	S-4-methylbenzyl-β-N-(2-furyl)methylenedithiocarbazate
$[Cu(SBOVa)_2]$	Copper(II) complex of S-benzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylene dithiocarbazate
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$[Cu(SB3MB)_2]$	Copper(II) complex of S-benzyl-β-N-(3-methoxybenzyl) methylenedithiocarbazate
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$[Cu(SBFu)_2]$	Copper(II) complex of S-benzyl-β-N-(2-furyl)methylene dithiocarbazate
$[Ni(SBFu)_2]$	Nickel(II) complex of S-benzyl-β-N-(2-furyl)methylene dithiocarbazate
$[Zn(SBFu)_2]$	Zinc(II) complex of S-benzyl-β-N-(2-furyl)methylene dithiocarbazate
$[Cu(S2MOVa)H_2O].H_2O$	Copper(II) complex of S-2-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylenedithiocarbazate
$[Ni(S2MOVa)_2]$	Nickel(II) complex of S-2-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylenedithiocarbazate

$[Zn(S2MOVa)H_2O]$	Zinc(II) complex of S-2-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzyl)methylenedithiocarbazate
$[Cu(S2M2MB)_2]$	Copper(II) complex of S-2-methylbenzyl-β-N-(2-methoxybenzyl) methylenedithiocarbazate
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$[Zn(S2M2MB)_2]$	Zinc(II) complex of S-2-methylbenzyl-β-N-(2-methoxybenzyl) methylenedithiocarbazate
$[Cu(S2M3MB)_2]$	Copper(II) complex of S-2-methylbenzyl-β-N-(3-methoxybenzyl) methylenedithiocarbazate
$[Ni(S2M3MB)_2]$	Nickel(II) complex of S-2-methylbenzyl-β-N-(3-methoxybenzyl) methylenedithiocarbazate
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$[Cu(S4M2MB)_2]$	Copper(II) complex of S-4-methylbenzyl-β-N-(2-methoxybenzyl) methylenedithiocarbazate
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CHAPTER I

INTRODUCTION

Cancer is one of the most common diseases in Malaysia. Based on the 2013 health facts released by Ministry of Health (MoH) Malaysia, cancer is the one of the top ten diseases that causes hospitalisation and one of the top five causes of death in Malaysia. Based on statistics from National Cancer Registry Report 2007, the five most common cancers are breast (18.1%), head and neck (13.2%) colorectal (12.3%), trachea, bronchus, lung (10.2%) and cervix uteri (4.6%) cancers. In Malaysia, the incidence of cancer increased from 32000 new cases in 2008 to about 37000 in 2012 and the number of deaths also increased from 20100 (2008) to 21700 (2012) deaths. The major factors have been identified as lifestyle behaviours, such as the fact that more than 50% of Malaysian Malay men smoke, more than 30% Malaysian are obese, yet they still did not change their behaviour to prevent this incidence from happening.

Peyron (1944) was responsible for the first discovery of an anticancer compound, *cis*-diamminedichloridoplatinum(II) (*cis*-$[PtCl_2(NH_3)_2]$) also known as cisplatin.

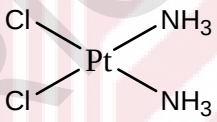


Figure 1: Structure of *cis*-diamminedichloridoplatinum(II) (cisplatin)

The cisplatin drug and its subsequent clinical success generated interest in researchers with regards to the use of metal complexes as anticancer drugs (Rosenberg, 1971; Guo and Sadler, 1999). Cisplatin still plays a great role in treating over 90% of testicular cancer cases and is now one of the most successful anticancer drugs available in the market (Hambley, 1997; Weiss and Christian, 1997; Wong, 1999). Cisplatin generally interacts with DNA by inducing programmed cell death (apoptosis) as shown in Figure 2.

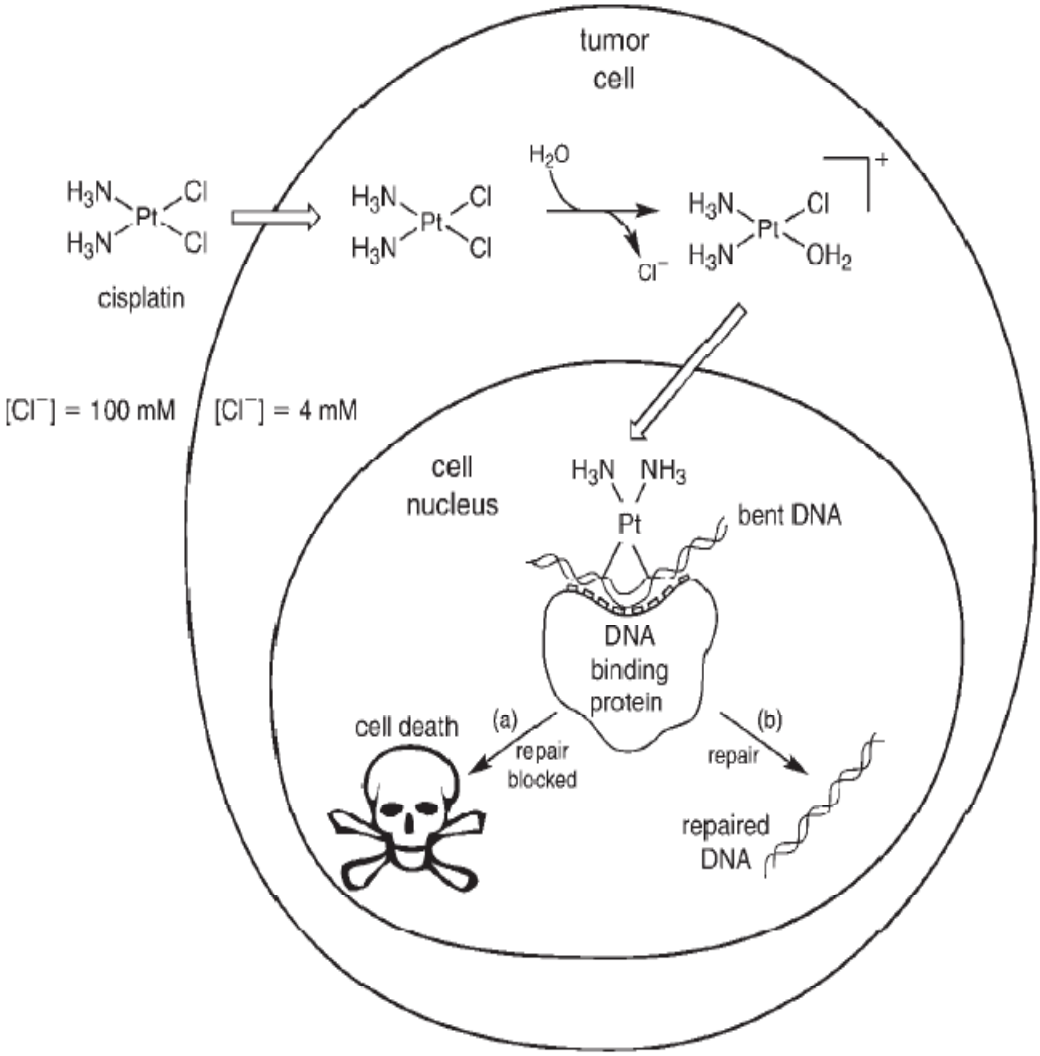


Figure 2: Schematic diagram showing the cytotoxic pathway for cisplatin. After entering the tumour cells, cisplatin is equated, then binds to cellular DNA. If the DNA lesion is not repaired by the cell, then cell death, can occur (Alderden *et al.*, 2006)

Although cisplatin is used in cancer treatment there are side effects that developed after administration of the treatment such as anemia, diarrhea, alopecia, petechia, fatigue, nephrotoxicity, emetogenesis, ototoxicity, and neurotoxicity (Subbaraj *et al.*, 2014) . This then opened up research areas in developing new metal-based anticancer drugs with minimal side effects and maximal curative potential for the cancer phenotype.

Dithiocarbazate derivatives

Dithiocarbazate and its organic substituted compounds remain of interest to researchers since 1974 and have received much attention recently because:

i. they can be easily modified by introducing different types of organic substituents, thus can create variation in ultimate donor properties,
ii. the formation of metal complexes based on the interaction of the donor atom with the metal ions give complexes of different geometries and properties,
iii. they have good potential as biologically active agents

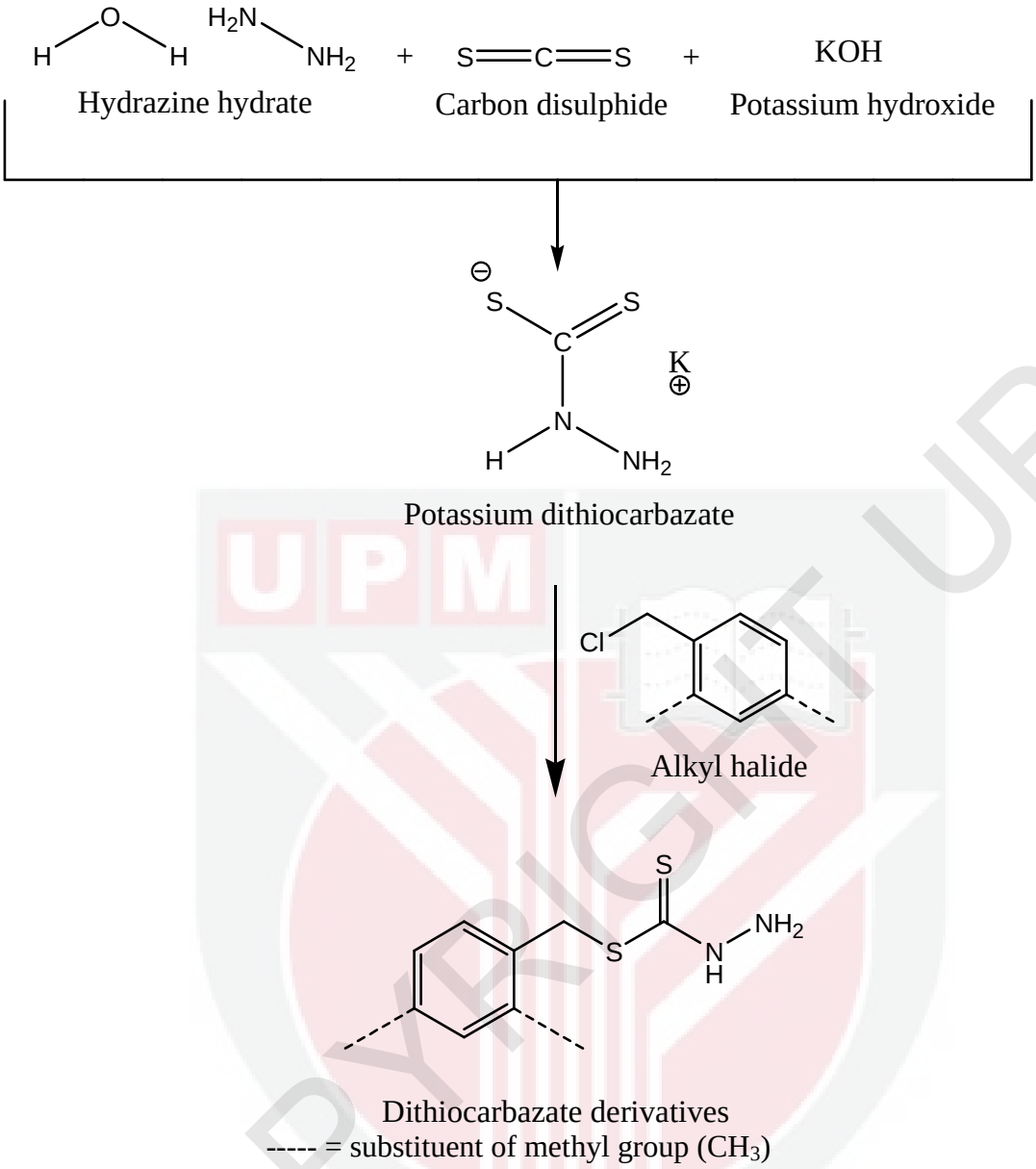
Dithiocarbazate derivatives can exist as thiol and thione tautomers. Dithiocarbazate adopted the thione form in solid and it can exist in an equilibrium mixture of tautomers in solution (Ali and Livingstone, 1974; Bose and Ali, 1980). For S-benzyldithiocarbazate (SBDTC) (Fig. 5), in the solution form, the thione tautomer of dithiocarbazate is unstable and is converted to the stable thiolo forms by enethiolization (Ali and Tarafder, 1977). Both tautomers have been confirmed by ^{1}H NMR analysis.

Thione form Thiol form

(R' indicates the presence of various different organic substituents)

Figure 3: Tautomerism in dithiocarbazate ligands

The tetrahedral dipolar intermediate compounds are formed from the reaction of hydrazine hydrate (NH_2NH_2) and carbon disulphide (CS_2), which is converted to the potassium dithiocarbazate in base solution (Scheme 1). Potassium dithiocarbazate undergoes nucleophilic substitution during the addition of an organic halide such as benzylchloride, 2-methylbenzylchloride, and 4-methybenzylchloride in this work.

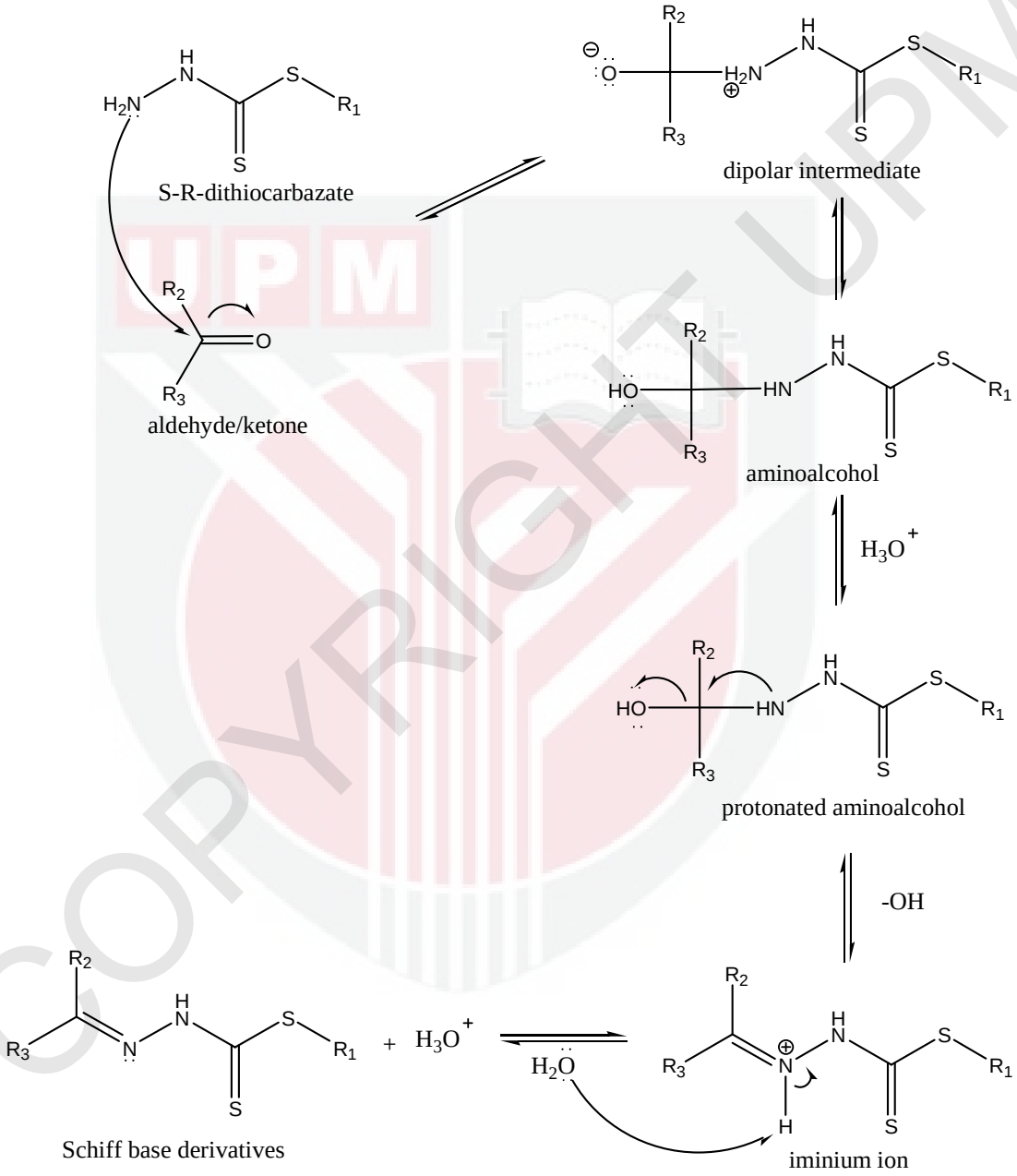


Scheme 1: Reaction pathway for the synthesis of dithiocarbazate derivatives

Formation of bidentate and tridentate Schiff bases derived from dithiocarbazate derivatives

Amine group, NH_2 from dithiocarbazate derivatives can undergo nucleophilic addition with aldehydes or ketones to form Schiff bases. The fundamental step involves the formation of iminium ion by the removal of water molecules from protonated aminoalcohol. The reaction starts with the migration of proton from nitrogen atom to the oxygen atom to form the aminoalcohol. The protonation of oxygen produces a good leaving group,-OH and the elimination of water molecules yields Schiff bases with the appearance of azomethine group, C=N. A schematic illustration of the formation of Schiff bases is shown in Figure 1.2. Bidentate Schiff bases are much more stable and can frequently be deprotonated or oxidised while still bound to the metal compared to the monodentate Schiff bases.

IR spectra is routinely used as an evidence to confirm the formation of Schiff bases. A strong and sharp signal for a carbonyl group, v(C=O) found in the spectra of aldehydes or ketones and a sharp peak attributed to the free amine group, v(NH_2) found in the spectra of dithiocarbazate derivatives disappear in the IR of the Schiff bases.



Scheme 2: Reaction pathway for the formation of Schiff bases

Formation of metal complexes

The formation of metal complexes is preliminarily determined by the IR spectra. Bidentate Schiff bases coordinate to the metal ions through the sulphur and β-nitrogen atoms while tridentate Schiff bases coordinate to the metal ions through sulphur, β-nitrogen, and other donor atoms. The ν(NH) band found in the free ligand disappeared in the metal complexes, indicating an *in situ* deprotonation of the ligand to form the thiol tautomers for the formation of metal complexes to take place. The disappearance of ν(C=S) band in the metal complexes supports the suggestion of coordination through the sulphur atom. In addition, the sharp bands that indicate the presence ν(C=N) and ν(N-N) in the spectrum of Schiff bases which are shifted to lower frequencies indicates the coordination of the azomethine nitrogen to the central metal ions (Ali *et al*., 1995; Koji, 1977). The splitting of ν(CSS) bands in the complexes indicate that the thiolate sulphur coordinates to the metal ions (Ali *et al*., 2004). Further analyses such as ICP-AES and CHNS for the metal complexes can be carried out to confirm the formation of the metal complexes.

Properties and applications of dithiocarbazate ligands, their Schiff bases and metal complexes

Inorganic molecules have a long history in both biology and medicine due to the role and functionality of the compounds. Electronic, chemical, and photophysical properties are particularly useful for various applications. A summary of chemical properties that affect the biological activity, DNA binding, and viscosity of the compound is given below (Lippard *et al*., 1978).

- **Charge**

The charge of metal complexes can be cationic, anionic, and neutral depending on the coordination mode

- **Interactions with ligands**

Schiff bases bind to a metal ion via strong and selective interactions and the functionality can be modified depending on the donor atoms of the metal complex

- **Structure and bonding**

Metal—ligand complexes have range of coordination geometries that give them unique shapes compared to organic molecules. The bond lengths, bond angles, and number of coordination sites can vary depending on the metal and its oxidation state. Based on Ligand Field Stabilization Energy (LFSE), the arrangement series of the complex stabilities for the first-row metal ion are $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$. The stability of the complex increases with the decreasing ionic radius across the series, but Zn^{2+} shows lower LFSE due to the full-filled d-shell orbital. Copper(II) complexes have higher stability compared to other first-row transition metal indicating an inherent challenge in designing chelating agents that are selective for Cu^{2+}.

- **Lewis acid character**

Metal ions with high electron affinity can significantly polarize groups that are coordinated to them, and hence facilitate hydrolysis reactions.

- **Partially filled d-shell**

The metal complexes shows interesting electronic and magnetic properties due to variable number of electrons in d-shell orbital for first row d-block transition metals.

- **Redox activity**

The variability of electrons in d-shell orbital undergo 1-electron oxidation and reduction reactions. Metal to the ligand bonding is significant in its reversibility.

Cytotoxic activity

Most of the researchers report that the chelating metal complexes are active against cancer cell lines compared to Schiff bases. As reported by Livingstone and Mihkelson (1970) and Akbar Ali and Livingstone (1974), only platinum(II), palladium(II), and copper(II) complexes were found to be active against lymphocytic leukaemia cancer cell lines (P388). The presence of sulphur donor atoms chelated to the metal ions enhanced the killing effect of the cancer cell lines. Sulphur donor chelating agents coordinate more strongly to the metals ion compared to oxygen donor chelating agents. The metals ions are very easily polarisable and have greater affinity for sulphur ions.

The biological activities are influenced by the position of attachment of methyl group to the aromatic ring. The attachment of methyl group to the aromatic ring increases size and lipophilicity of the compound hence reducing the solubility of the compound (Ravoof *et al*., 2011). The presence of methyl ($-CH_3$) group either in an ortho, para, or meta position has greats effects on its biological activity. Ravoof *et. al*. (2010) reported that the complexes having electron donating groups at the meta and para positions of the aromatic ring were significantly more active than those complexes having a methyl group in the ortho position. For instance, 2-methylbenzyl-2-(dipyridin-2-ylmethylene)hydrazinecarbodithioate (dpyS2M) Schiff base (Fig. 4) was inactive against two breast cancer cell lines [MCF-7 (Human Breast carcinoma with positive estrogen receptor) and MDA-MB-231 (Human Breast carcinoma with negative estrogen receptor)] due to the presence of steric interferences and interactions between methyl group and carbon at the aromatic ring. Methyl groups also block metabolic hydroxylation reactions resulting in metal complexes that are less active towards microbes and cancer cells (Thomas, 2000).

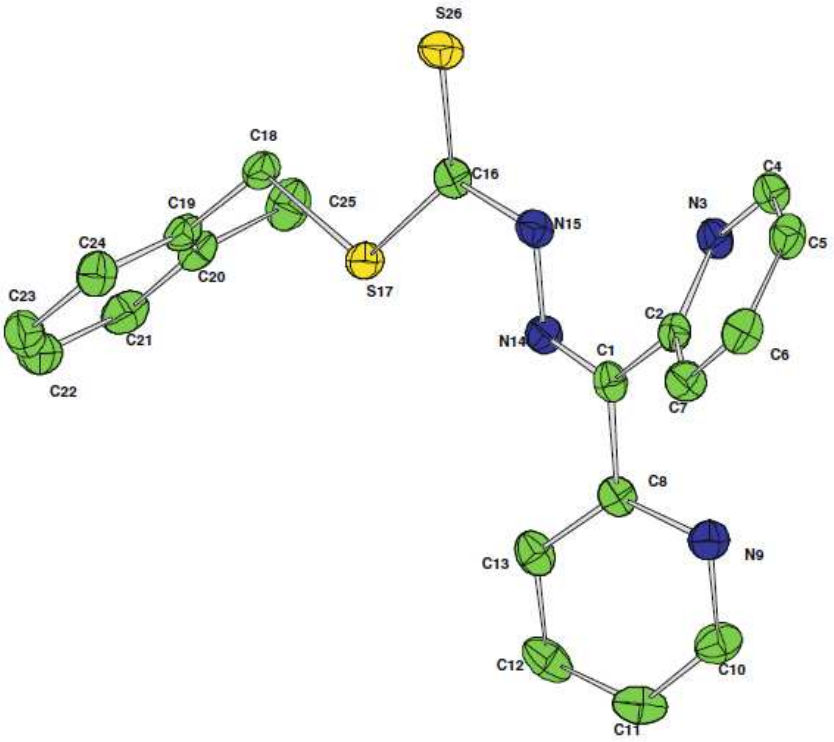


Figure 4: ORTEP diagram of the dpyS2M Schiff base

DNA binding activity

DNA binding studies is initiated to explore the interaction of metal complexes to the DNA. DNA binding is a critical step for DNA activity and it is a better way to design effective chemotherapeutic agents and anticancer drugs.

Barton and co-workers reported that the variety in shape and functionalities of DNA major grooves allow for only specific geometries of metal complexes that can intercalate to the DNA double-helix sequences. Intercalation is a DNA binding mode in which the planar metal complexes inserts and π-π stacking occurs between the metal complexes and DNA sequences through non-covalent interactions. Howegrant *et. al.* (1976) reported one of the earliest research on intercalation and they stated that the square planar platinum complex intercalated with DNA sequences and produced strong interactions between the platinum complex and DNA sequences.

Electronic absorption spectroscopy is widely used to determine the DNA binding mode of metal complexes. The increasing addition of calf thymus DNA does not affect any intense d-d transitions of metal complexes. But the intense absorption ($\pi \rightarrow \pi^*$ and LMCT) bands are used to monitor the interaction of metal complexes with CT DNA. Complexes bound to the DNA through intercalation in which it involves a strong stacking interaction of the planar aromatic rings of the ligand with double-helix strand of DNA base pairs is recorded in the electronic spectra as a $\pi \rightarrow \pi^*$ absorption (Tomoya *et al.,* 2004). Complexes with the absence of methyl group show greater binding to CT DNA that complexes having methyl group (Foong,

2008). The steric effect imposed by methyl groups reduce the binding ability of the heterocyclic base to the CT DNA. Shanta *et al.* (2003) reported the DNA cleavage activity of the complexes has been studied under different reaction conditions. The complexes were found to be nuclease inactive in the absence of any reducing agent when the reactions are carried out in a dark chamber (Shanta *et al.*, 2003).

In light of the various studies on metal complexes of substituted dithiocarbazate ligands, it is hoped that this study would find the way to produce metal-based drugs for cancer treatment.

OBJECTIVES

The objectives of this project were:

1. To synthesis and structural characterisation Schiff bases derived from S-substituted dithiocarbazate and their divalent Cu, Ni, and Zn complexes

2. To study the cytotoxic activities of Schiff bases ligand and their metal complexes against two breast cancer cell lines (breast cancer cell lines with positive estrogen receptor, MCF-7 and negative estrogen receptor, MDA-MB-231)

3. To carry out a preliminary study of the binding properties of selected metal complexes towards calf thymus DNA (CT-DNA)

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