UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF DITHIOCARBAZATE NITROGEN SULFUR DONOR LIGANDS AND THEIR METAL COMPLEXES

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By

HIBA HAYDER HAMZA ELHASSAN

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

December 2012

Dedication

I dedicate this work to my son and my hero, Yousif, with love.

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 2012

Chair: Professor Karen A. Crouse, PhD

Faculty: Science

Three new Schiff bases were synthesized from the condensation reaction of *S*-benzyldithiocarbazate (SBDTC) with acetylferrocene, and *S*-4-methylbenzyldithiocarbazate (S4MBDTC) with *S*-camphorquinone and *R*-camphorquinone.

A series of fifteen metal complexes were successfully synthesized from the reaction of the Schiff bases with metal salts of Cobalt(II), Nickel(II), Cadmium(II), Copper(II), and Zinc(II). All the compounds were characterized using various physio-chemical and spectroscopic techniques. Two structures were determined using X-ray diffraction analysis. The crystal structure of Ni(II) complex of camphorquinone and *S*-4-methylbenzyldithiocarbazate showed that the complex exhibited a six coordinate octahedral geometry. The Schiff base acted as a uninegatively charged tridentate ligand

coordinating to the Ni(II) ion *via* the azomethine nitrogen atom, thiolate sulfur atom, and carbonyl oxygen atom. Unfortunately, attempts to grow crystals of the other metal complexes were not successful.

These newly synthesized compounds exhibited significant cytotoxic activities towards MCF-7 (Human breast carcinoma cells with positive estrogen receptors) and MDA-MB-231 (Human breast carcinoma cells with negative estrogen receptors). Schiff bases were found to be more active towards the tested cancer cells than their metal complexes.

Abstrak tesis yang dikemukakan kepada Universiti Putra Malaysia sabagai memenuhi keperluan untuk ijazah Master Sains

SINTESIS, PENCIRIAN DAN AKTIFITI BIOLOGI BAGI LIGAN PENDERMA DAN KOMPLEKS LOGAM NITROGEN SULFUR DITIOKARBAZT

Oleh

HIBA HAYDER HAMZA ELHASSAN

Disember 2012

Pengerusi: Professor Karen A. Crouse, PhD

Fakulti: Sains

Tiga bes Schiff baru telah disintesis melalui tindak balas *S*-benzilditiokarbazat (SBDTC) dengan asitilferosin dan *S*-4-metilbenzilditiokarbazat (S4MBDTC) dengan *S*-kamforkuinon dan *R*-kamforkuinon.

Satu siri 15 kompleks logam telah berjaya disintesis daripada tindak balas bes Schiff dengan garam logam Kobalt(II), Nikel(II), Kadmium(II), Kupum(II), dan Zink(II). Semua sebatian telah dicirikan dengan menggunakan pelbagi teknik kimia-fizik dan spektroskopi.

Dua struktur telah berjaya ditentukan dengan menggunakan teknik kristalografi sinar-X. Struktur kristal kompleks Ni(II) kamforkuinon dan *S*-4-metilbenzilditiokarbazat menunjukkan kompleks bergeometri oktahedron dengan enam koordinatan. Bes Schiff bertindak sebagai ligan tridentat

uninegatif koordinat dengan ion Ni(II) melalui nitrogen azometin, sulfur tiolat, dan oksigen karbonil. Walau bagaimana pun percubaan untuk pembentukan kristal kompleks logam yang lain tidak berjaya.

Sebatian baru yang disintesis ini mempamerkan aktiviti sitotoksik terhadap sel MCF-7 (sel barah manusia dengan penerima estrogen positif) dan sel MDA-MB-231 (sel barah manusia dengan penerima estrogen negatif). Bes Schiff didapati lebih aktif terhadap sel-sel kanser yang diuji berbanding dengan kompleks logam.

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My grandmother, I have always looked up to you. You are not only my grandmother but you are my second mother and you are my role model. Without your prayers, I would be nowhere today. I am proud to have you as a grandmother and hope to make you proud of me one day. I love you.

My best friend Thwiba, in the times when nothing makes sense, you always gave me hope. You are the one who always lifts me up when I am down, and pushes me further and further. When I am in need of positive energy, you are the one I turn to. Thank you for being there for me.

I certify that a Thesis Examination Committee has met on 18.12.2012 to conduct the final examination of Hiba Hayder Hamza Elhassan on her Master of Scince thesis entitled "**Synthesis, Characterization and Biological activities of Dithiocarbazate Nitrogen Sulfur Donor Ligands and Their Metal Complexes**" in accordance with 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…………..

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

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DECLARATION

I declare that the thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously, and is not or concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

HIBA HAYDER HAMZA ELHASSAN

Date: 18 December 2012

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LIST OF ABBREVIATIONS

AF	Acetylferrocene
CHNS	Carbon, Hydrogen, Nitrogen, and Sulfur
CQ	Camphorquinone
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d6	Deuterated–dimethylsulfoxide
DNA	Deoxyribonucleic acid
DTC	Dithiocarbazate
FT-IR	Fourier Transform - Infrared
GC-MS	Gas Chromatography- Mass Spectrometry
IC_{50}	Inhibition Concentration at 50%
ICP-AES	Inductively Coupled Plasma-Atomic Emission Spectroscopy
MCF-7	Human breast carcinoma cells with positive estrogen receptors
MDA-MB-231	Human breast carcinoma cells with negative estrogen receptors
MTT	3-(4,5- Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NMR	Nuclear Magnetic Resonance
NNS	Nitrogen-nitrogen-sulfur
NS	Nitrogen-sulfur
ONS	Oxygen-nitrogen-sulfur
ORTEP	Oak Ridge Thermal Ellipsoid Plot
SBAF	Schiff base of *S*-benzyldithiocarbazate and acetylferrocene
SBDTC	*S*-benzyldithiocarbazate
S4MBRCQ	Schiff base of *S*-4-methlylbenzyldithiocarbazate and *R*-camphorquinone
S4MBSCQ	Schiff base of *S*-4methlylbenzyldithiocarbazate and *S*-camphorquinone
S4MBDTC	*S*-4-methylbenzyldithiocarbazate
UV-Vis	Ultraviolet / visible

CHAPTER 1

INTRODUCTION

1.1 Dithiocarbazate Derivatives

Dithiocarbazate ion ($NH_2NHCS_2^-$) is formed by the reaction of hydrazine hydrate and carbon disulfide in the presence of potassium hydroxide.

$$NH_2NH_2.H_2O + CS_2 + KOH \xrightarrow{EtOH} K^+ \; \underset{\text{Dithiocarbazate Ion}}{NH_2NHCS_2^-} + 2H_2O$$

Scheme 1-1: Formation of Dithiocarbazate Ion

Dithiocarbazate compounds have been shown capable of thione-thiol tautomerism in solution. In the solid state these compounds remain in the thione form, while in solution both thione and thiol forms have been often detected (Ali *et al.*, 2005). The thione tautomer is relatively unstable in the monomeric form and tends to convert to the more stable C-S bond by enethiolization if there is at least one adjacent proton (Ali *et al.*, 1977). Thione-thiol tautomerism is shown in Figure 1-1.

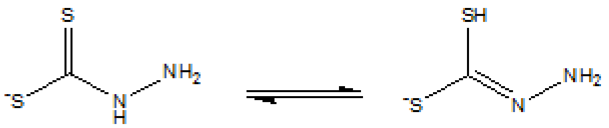

Figure 1-1: Thione-thiol Tautomerism in Dithiocarbazate Ion

Dithiocarbazate derivatives have four potential donor atoms, two nitrogen atoms and two sulfur atoms. The four donor atoms are theoretically available for coordination to metal ions; however, studies showed that dithiocarbazate derivatives generally behave as NS donor ligands. Although in some cases substitution of organic groups on the nitrogen atoms led to SS chelation.

1.2 Schiff Bases

Schiff bases, named after the chemist Hugo Schiff, are compounds containing the functional group carbon – nitrogen double bond, where the nitrogen atom is bonded to an alkyl or an aryl group but not a hydrogen atom. Schiff bases are formed from the reaction of primary amines with aldehydes or ketones. Condensation of carbonyl compounds with various nitrogen bases such as amines, hydroxylamines, and semicarbazones to form Schiff bases have been investigated over the past few decades.

$$R_2C = O + R'NH_2 \rightarrow R_2C = NR' + H_2O$$

Schiff Base

(R=H, alkyl, or aryl, R′= alkyl or aryl)

Scheme 1-2: Formation of a Schiff Base

Some Schiff bases exhibit interesting physico-chemical properties and potentially useful biological activities (Ali *et al.*, 2011) which prompted researchers to conduct different studies involving their preparation and applications. The reaction of these Schiff bases with metal ions results in metal complexes with different molecular structures (How *et al*., 2008).

1.3 Metal Complexes of Dithiocarbazate Schiff Bases

Metal complexes of dithiocarbazate derivatives exhibit unique structural features. Moreover, many studies showed that the coordination to metal ions sometimes afforded compounds with greater biological activity than that of uncomplexed ligands (Afrasiabi *et al*., 2005). This raised considerable interest in metal complexes of dithiocarbazate derivatives (Bouchameni *et al*., 2011). However, in some cases, Schiff bases were found to show more biological and cytotoxic activity than their metal complexes (How *et al*., 2008).

Transition metal complexes of dithiocarbazate ligands containing NNS donor atoms have been the focus of research in recent years, whereas dithiocarbazate ligands with ONS donor atoms have received less attention (Ali *et al*., 2011). However, these complexes have shown interesting physical and chemical properties in the few studies that have been conducted (Latheef *et al*., 2008). Transition metal complexes are of great interest because of their potential for therapeutic use (Crouse *et al*., 2004). Furthermore, these complexes also have applications in skin care, paint manufacturing, catalysis and other fields (Ali *et al*., 1971).

1.4 Properties of Ligands with Nitrogen-Sulfur Donor Atoms

Ali and Livingstone (1974) have summarized the characteristics of ligands with sulfur donor atom as follows:

1. The permanent dipole moment and coordinating ability normally decreases in the order: H_2O > ROH > R_2O, but the reverse order holds for sulfur, i.e. H_2S < RSH < R_2S.

2. The strength of bonding to a metal (considering both electrostatic and covalent models) is in the following order: RO^- > RS^- and R_2O > R_2S. However, sulfur has vacant d orbitals that can be used for d_π – d_π bonding with the later transition metals and the early transition metals in unusually low oxidation states.

3. The polarisabilities of sulfur donors and the number of lone pairs decrease in the order S^{2-} > RS^- > R_2S. Consequently, thiolo ligands are more polarizable but not as effective d_π electron acceptors as thioethers, which is why most ithiocarbazate Schiff bases coordinate in their thiolate forms.

4. Sulfur donors bind more strongly to (b) class metals (metals that form soft cids) than do oxygen donors. [Class (a) metals (metals that form hard acids) ions are small, not very easily polarized and have a greater affinity for F^- than for I^-. Class (b) metal ions are essentially opposite in character].

5. Sulfur ligands occupy a late position in the nephalauxetic series (a measure of the degree of covalent bonding between metal and ligand). The series of donor atoms is F < O < N < Cl < Br < S ≈ I < Se.

6. Sulfur atoms in heterocyclic rings have very poor coordinating ability due to the pseudo-aromatic nature of the ring, which has the two-fold effect of causing the lone pairs on the sulfur atom to be less available for donation and the π–orbitals to be less capable of accepting electrons from the metal.

In general, the properties of sulfur ligands can also apply to sulfur-nitrogen chelating ligands. These ligands appear to give rise to a smaller reduction in the interelectronic repulsion energy than that observed for sulfur-sulfur ligands. In the case of nitrogen-sulfur ligands, it can be stated that the presence of nitrogen is responsible for lowering the solubility of the metal complexes of these ligands in non-polar solvents (Ali and Livingston *et al*., 1974).

1.5 Ferrocene

Ever since its discovery in 1951, ferrocene has played an enormous role in developing knowledge of electronic structures of organometallic compounds. This is due to its high stability, special structure and well established methods for its incorporation into more complex structures (Shi, 2004). Ferrocene has become a starting material for the synthesis of a considerable number of ferrocene derivatives, which have been studied intensively. Some of those compounds displayed significant biological activities (Shi *et al.,* 2004). Ferrocene is known to be a chemically and thermodynamically stable species, which is why it is used in many research areas. It is also known for its different membrane permeation properties. Furthermore, it is widely known that the biological activities of some drugs are improved by addition of ferrocene moiety to their structure; ferr-chloroquine, ferrocene asprin, anticancer drug ferrocifen (Nawaz *et al.*, 2009). The structure of ferrocene is shown in Figure 1-2.

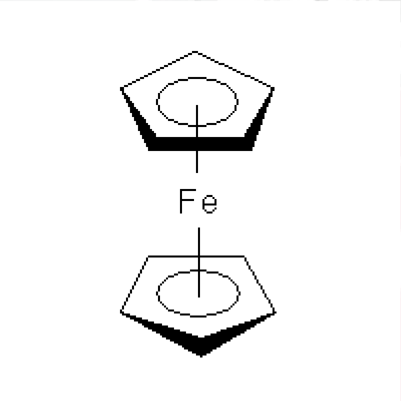

Figure 1-2: Structure of Ferrocene

In this study, a ferrocene derivative, acetylferrocene, is used to form a Schiff base with *S*-benzyldithiocarbazate.

1.6 Biological Activity

Recently attention to synthetic drugs has increased noticeably, especially with the limitation of drugs derived from natural products in the treatment of many diseases. Researchers now focus on the synthesis of drugs for different diseases, and many of these drugs are metal based. One of the main factors that affect the biological activity of a certain compound is the shape of the molecule. Other factors include the ability to chelate to metal ions, lipophilicity, and steric and electronic effects (Gringauz *et al*., 1997). One of the widely spread diseases today that raises international concern is cancer. Cancer is a large group of diseases in which a group of cells displays uncontrolled growth. It is considered one of the leading causes of death in the world today (Vrzal *et al*., 2010).

The discovery of cis-platin and its anticancer properties has marked a changing point in the history of anticancer drugs. Cis-platin is one of the most commonly used drugs in the treatment of human cancers (Pasheva *et al*., 2002). The toxicity of cis-platin originates from its ability to block the DNA replication, by forming covalent adducts with the DNA (Zamble *et al*., 1995). The clinical success of cis-platin as an anticancer drug has prompted the interest of researchers in the field of synthetic anticancer drugs. Like any other drug, cis-platin does have its limitations, which is why efforts at improvement of this drug have also intrigued researchers in the field. Attempts to improve cis-platin in terms of reduced toxicity, increased clinical effectiveness, elimination of side effects as well as selectivity, have been made.

In this study, the synthesized compounds have been investigated for their cytotoxic activities towards two cancer cell lines, MCF-7 (Human breast carcinoma with positive estrogen receptors) and MDA-MB-231 (Human breast carcinoma with negative estrogen receptors).

1.7 Cytotoxicity of Some Sulfur-Nitrogen Ligands and Their Metal Complexes

The following criteria are among those used to predict whether a metal complex is carcinostatically active:

1. The complex should be reasonably labile.

2. The metal chelate should have reasonably high thermodynamic stability.

3. Ligands with sulfur donors are most likely to be effective, since they allow for lipid solubility of the metal complex and form stable complexes with metals (Ali and Livingstone, 1974).

The significant anticancer activity of dithiocarbazate Schiff bases and their metal complexes as mentioned in this introduction, stimulated the interest on the subject, hence this research focuses on the Schiff bases of dithiocarbazate derivatives with acetylferrocene and camphorquinone and their metal complexes, investigating their anticancer activities.

1.8 Objectives

- To synthesize and characterize new dithiocarbazate Schiff bases from *S* benzyldithiocarbazate with acetylferrocene, and *S*-4-methylbenzyldithiocarbazate with camphorquinone isomers.
- To synthesize and characterize metal complexes with the new Schiff bases.
- To evaluate the cytotoxic activities of the Schiff bases and their metal complexes.

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