UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, AND PHYSICO-CHEMICAL AND BIOLOGICAL CHARATERIZATION OF NEW SCHIFF BASES DERIVED FROM THIOPHENE AND THEIR TRANSITION METAL COMPLEXES

MD.UWAISULQARNI OSMAN

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By

MD.UWAISULQARNI OSMAN

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

April 2007

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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April 2007

Chairman: **Mohamed Ibrahim Mohamed Tahir, PhD**

Faculty: **Science**

Several new Schiff bases formed from *S*-benzyldithiocarbazate (SBDTC) and *S*-methyldithiocarbazate (SMDTC) with selected aldehyde/ketones containing a thiophene ring namely, 1-(2-thienyl)-1-propanone and thiophene-2-carbaldehyde in 95 % of ethanol have been synthesized. Complexes of Cobalt(III), Nickel(II), Copper(II), Zinc(II) and Cadmium(II) with these Schiff bases were prepared. These compounds were characterized by elemental analyses and various physico-chemical techniques. Their thermal behaviour was also investigated. Single crystal X-ray analysis was carried out on nine single crystals. The Co(III) complexes are six-coordinated whereas, Ni(II), Zn(II) and Cd(II) complexes are four-coordinated. Unfortunately, none of the Cu(II) complexes produced single crystals but, it is proposed, that they are also four-coordinated. The Schiff bases and their metal complexes were evaluated for their cytotoxic and antimicrobial activities. Cytotoxic screening was carried out against Human ovarian cancer cells (CaOV-3), Human breast carcinoma cells with negative estrogen receptor (MDA-MB-231) and Human liver carcinoma cells (HEP-G2). Antimicrobial screening

was carried out against four bacteria and three fungi. All compounds were found to have low or no activity except for $Cu(SBT2P)_2$. H_2O which is active against *Bacillus subtilis*-wild type (B29).

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

SINTESIS, DAN FIZIKAL-KIMIA SERTA KAJIAN SECARA BIOLOGI TERHADAP BES SCHIFF TERBITAN DARIPADA THIOPHENE DAN KOMPLEK LOGAM PERALIHAN MASING-MASING

Oleh

MD.UWAISULQARNI BIN OSMAN

April 2007

Pengerusi: **Mohamed Ibrahim Mohamed Tahir, PhD**

Fakulti: **Sains**

Beberapa bes Schiff baru telah berjaya disintesiskan daripada *S*-benzildithiokarbazat (SBDTC) dan *S*-metildithiokarbazat (SMDTC) yang bertindak balas dengan aldehid/keton terpilih yang ia mengandungi gelang thiophen iaitu, 1-(2-thienil)-1-propanon and thiophen-2-carbaldehid dengan menggunakan pelarut etanol (95 %). Pelbagai komplex Cobalt(III), Nikel(II), Kuprum(II), Zink(II) dan Cadmium(II) juga berjaya disediakankan dengan menggunakan bes Schiff tersebut. Kesemua sampel telah dicirikan dengan menggunakan pelbagai teknik kimia-fizik. Kajian terhadap sifat termanya juga telah dijalankan. Analisis sinar-X telah dijalankan terhadap sembilan hablur tunggal. Didapati bahawa komplek Co(II) berkoordinasi enam manakala, Ni(II), Zn(II) dan Cd(II) adalah berkoordinasi empat. Malangnya, tiada hablur tunggal dapat dihasilkan daripada Cu(II) tetapi adalah dicadangkan ia mempunyai struktur empat koordinasi berdasarkan maklumat yang diperolehi. Bes Shiff dan komplek logamnya telah diuji untuk menilai aktiviti antimikrob dan sitotoksik. Saringan sitotoksik telah dijalankan dengan menggunakan CaOV-3 (Sel kanser ovari manusia), MDA-MB-231

(Sel barah payu dara dengan penerima estrogen negatif) and HEP-G2 (Sel barah hati Manusia). Saringan antimikrob telah dijalankan terhadap empat bakteria dan fungi terpilih. Ujian biologi telah menunjukkan bahawa kesemua sampel yang disintesiskan tidak memberi sebarang aktiviti kecuali $Cu(SBT2P)_2$. H_2O, di mana ia aktif menentang *Bacillus subtilis*-wild type (B29).

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

Mohamed Ibrahim Mohamed Tahir, D.Phil
Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Karen Badri Anne Crouse, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

_____
AINI IDERIS, PhD
Profesor/Dean
School of Graduate Studies,
Universiti Putra Malysia

Date: 14 JUNE 2007

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Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

AINI IDERIS, PhD
Profesor/Dean
School of Graduate Studies
Universiti Putra Malysia

Date:14 JUNE 2007

DECLARATION

I hereby declare that the thesis is based on my original work except for the quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at UPM or other institutions.

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MD.UWAISULQARNI BIN OSMAN

Date: 4 MAY 2007

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LIST OF REACTION SCHEMES

LIST OF ABBREVIATIONS

A.ochraceous	*Aspergillus ochraceous* (398)
B.Subtilis	*Bacillus subtilis*- wild type (B29)
C.albicans	*Candida albicans* (C.A)
CaOV-3	Human Ovarian Cancer cell
CD_{50}	Cytotoxic dose at 50%
CEM-SS	Human cell T-lymphoblastic leukemia

CGCs	cerebella granule cells
CHNS	Carbon, Hydrogen, Nitrogen and Sulfur analyses
DMF	Dimethylformamide
DMSO-d_6	Deuterited -dimethylsulphoxide
DNA	Deoxyribonucleic acid
dsDNA	doubly stranded Deoxyribonucleic acid
DTG	Derivative Thermogravimetric
FT-IR	Fourier Transform-Infrared
GC-MS	Gas Chromatography- Mass Spectrometer
HEP-G2	Human Liver carcinoma cells
HL60	Human Tlymphoblastic leukemic cells
HT-29	Human colon adenocarcinoma cells
ICP-AES	Inductively coupled plasma-atomic emission spectroscopy
MDA-MB-231	Human breast carcinoma cells with negative estrogen receptor
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus Aureus*
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Program
P.aeruginosa	*Pseudomonas aeruginosa* (60690)
S.cerivisiae	*Saccharomyces cerivisiae* (20341)
S.typhimurium	*Salmonella typhimurium*
SBDTC	*S*-benzyldithiocarbazate
SBT2C	*N'*-Thiophen-2-ylmethyl-hydrazinecarbodithioic acid phenyl ester

SBT2P	*N*'-(1-Thiophen-2-yl-propyl)-hydrazine carbodithioic acid phenyl ester
SMDTC	*S*-methyldithiocarbazate
SMT2C	*N*'-Thiophen-2-ylmethyl-hydrazinecarbodithioic acid methyl ester
SMT2P	*N*'-(1-Thiophen-2-yl-propyl)-hydrazine carbodithioic acid methyl ester
TGA	Thermogravimetric analysis
UV-Vis	Ultraviolet/Visible

CHAPTER I

INTRODUCTION

In recent years, considerable attention has been paid to the metal complexes due to the importance in understanding the effect of metal complexes in biological activity. Modification of the structure of the metal complexes by coordinating with different organic compounds has been carried out to enhance the potential use as drugs. However, studies related to drug design are limited and knowledge of the physico-chemical characteristics of potentially active compounds are required. Considering the wide scope of the subject, present research is restricted to the thiophene derivatives of dithiocarbazate with five transition metals, namely, cobalt(III), nickel(II), copper(II), zinc(II) and cadmium(II) and their biological activities.

Structure of the Thiophene ring

The structure of thiophene ring itself has been determined by previous reports **[1]** and is as shown in the figure below:

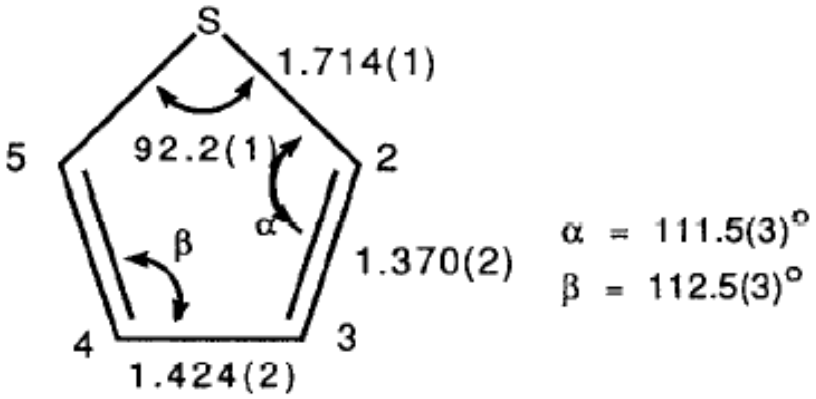


Figure 1: Bond lengths (Å) and angles (°) in of thiophene ring.

History of thiophene compounds

The history of thiophene has been documented **[2]** and is summarized as follows:

In 1844, Laurent synthesized thionessal (tetraphenylthiophene) but the structure of that compound was not able to be determined until Victor Meyer understood the properties of the 'unknown' compound.

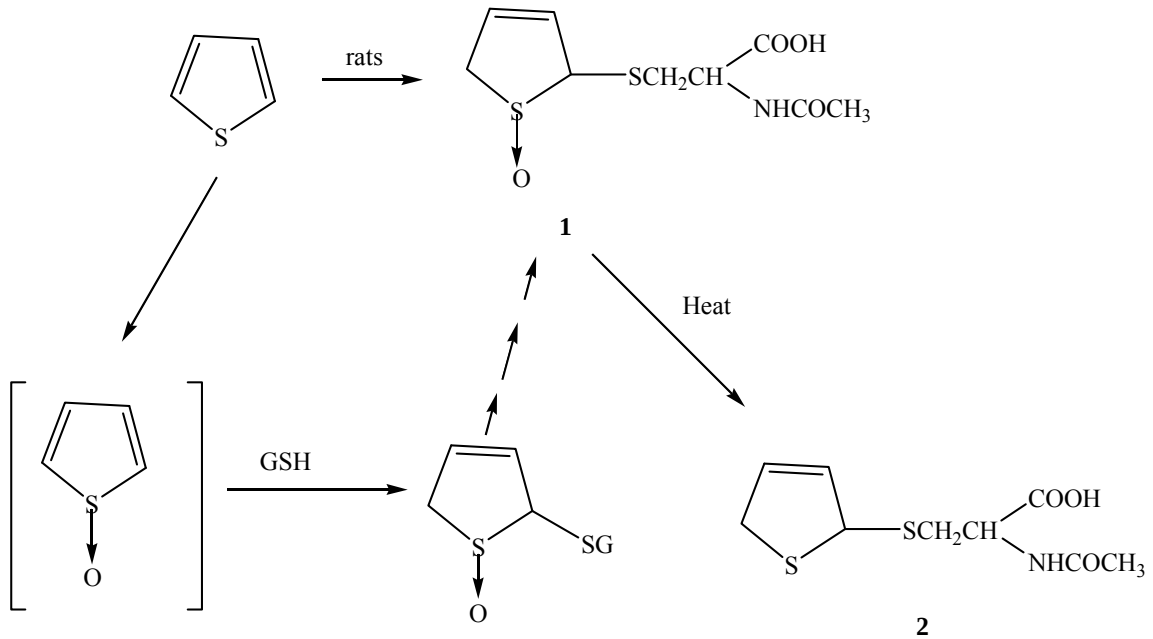
Victor Meyer used 250L of benzene with 25L of concentrated sulfuric acid. The "black-acid" produced by this process was converted into the lead salt and dry distillation of this salt with ammonium chloride gave a "crude thiophene". The thiophene formed from this treatment, 140g from a 2660g portion of the lead salt, was found to boil at 84^{o}C and contain about 28% sulphur (the sample was about 70% thiophene and 30% benzene). A portion, 70g was brominated and a dibromo derivative, which was found to be $C_4H_2Br_2S$, was obtained. Victor Meyer then could surmise that the original material, before bromination, was C_4H_4S. The dibromothiophene resisted dehydrobromination in boiling alcoholic potassium hydroxide and the bromo groups could not be removed by reduction. Its properties were similar to those of the bromobenzenes and Victor Meyer quickly grasped its aromatic nature.

The history of the naming the C_4H_4S compound was described by Thorpe. Firstly, Meyer suggested the name *thianthren*, then *thiophan,* next *thiol* and finally *thiophene*, meaning that it was a sulphur-containing compound giving derivatives to those of the phenyl series.

Biological studies of the thiophene ring system

As certain physical and chemical properties of benzene and thiophene were similar, researchers studied biological activity of the thiophene ring, based on the activity of the benzene ring. Some research was also carried out on furan rings, analogues of the thiophene ring, the only difference being the substitution of the sulphur by the oxygen atom **[3, 4]**.

In 1992 **[5]**, the initial research on biological activity of the thiophene ring was reported and that thiophene-*S*-oxides were formed intermediately *in vivo* and acted as reactive metabolites. A mechanism was proposed as follows:



GSH = glutathione

1 = dihydrothiophene sulfoxide mercapturate

2 = *N*-acetyl-*S*-(2-thienyl)-*L*-cysteine

Scheme 1: Formation of thiophene-*S*-oxide as a primary reactive metabolite

From the scheme above, it was found that the metabolite **1** was present in urine of rats after treatment with thiophene. It was also suggested that metabolite **1** was derived from the reactive thiophene sulfoxide intermediate and reacted with glutathione. Finally, transformation of **2** from **1** was through a dehydration reaction, a reaction well known for hydrothiophene sulfoxide.

Remarkably, research has revealed that thiophene itself can cause death of cerebella granule cells (CGCs) in presence of rat liver postmitochondrial (S9) fraction as a source of biotransformation enzyme **[6]**. It was believed that the metabolism of thiophene was the same as reported previously, where thiophene was converted to reactive thiophene-*S*-oxide through oxidation **[5]**. However, damage due to interaction between doubly stranded deoxyribonucleic acid (dsDNA) with thiophene-*S*-oxide can be detected by using an electrochemical DNA-biosensor **[7]**.

Dithiocarbazate Derivatives

In metal complexes containing Schiff bases, the environment at the coordination center can be modified by attaching different substituents to the ligand for the fine-tuning of structure and reactivity **[8, 9, 10, 11, 12]**. Research has shown that different ligands show different biological properties even with slight modifications in their molecular structure.

Dithiocarbazates, $NH_2NHCS_2^-$, react with aldehydes or ketones *via* a condensation reaction to produce a dithiocarbazate Schiff base. The Schiff bases are reacted with

transition metal salts, bonding through the mercaptide sulphur and azomethine nitrogen atoms to form a bidentate ligand (Figure 2) **[13]**, although in some cases they can behave as multidentate ligands (Figure 3), bonding through the sulphur and two nitrogen atoms, depending on the nature of the aldehyde or ketone used **[9]**.

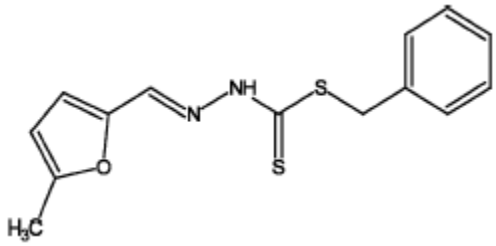


Figure 2: Structure of bidendate ligand

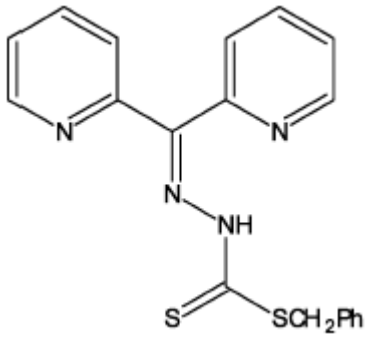


Figure 3: Structure of multidendate ligand

Dithiocarbazates, such as *S*-benzyldithiocarbazate, SBDTC (Figure 4) **[14]**, *S*-methyldithiocarbazate, SMDTC (Figure 5) **[15]** and their Schiff bases have potential as antimicrobial and anticancer agents. Furthermore, the activity of these compounds is sometimes enhanced by the presence of coordinated transition metal ions.

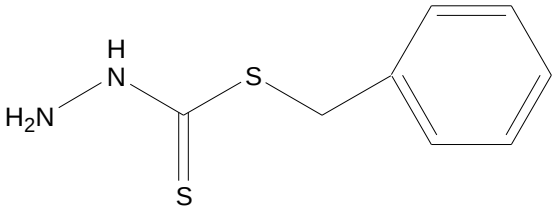


Figure 4: Structure of *S*-benzyldithiocarbazate (SBDTC)

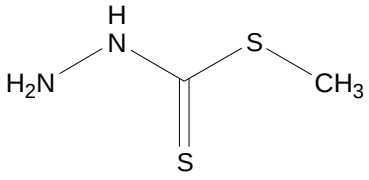


Figure 5: Structure of *S*-methyldithiocarbazate (SMDTC)