



UNIVERSITI PUTRA MALAYSIA

***SYNTHESIS AND CYTOTOXICITY OF DITHIOCARBAZATE AND
THIOSEMICARBAZIDE SCHIFF BASES DERIVED FROM CHALCONE
AND PHENYLBUTANONE ANALOGUES AND THEIR Cd(II) AND Zn(II)
COMPLEXES***

TAN MING YUEH

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COMPLEXES**

By

TAN MING YUEH

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in
Fulfilment of the Requirement of the Requirements for the Degree of Doctor of
Philosophy**

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Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

SYNTHESIS AND CYTOTOXICITY OF DITHIOCARBAZATE AND THIOSEMICARBAZIDE SCHIFF BASES DERIVED FROM CHALCONE AND PHENYLBUTANONE ANALOGUES AND THEIR Cd(II) AND Zn(II) COMPLEXES

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September, 2015

Chair: Prof. Emerita Karen Badri, PhD

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Bidentate nitrogen-sulfur (NS) Schiff bases derived from the condensation of *S*-benzyl- (SBDTC) and *S*-methylthiocarbazate (SMDTC) as well as *N*-phenyl- (PT) and *N*-methylthiosemicarbazide (MT) with 4-substituted chalcone (H, Cl, OCH₃ and NO₂), phenylbutanone (H, OH, OCH₃ and CH₃-C(=O)) analogues and zingerone have been prepared. The Schiff bases were characterized using various physico-chemical and spectroscopic methods. The characterized Schiff bases were complexed with cadmium(II) and zinc(II) ions. A total of 50 metal complexes and 35 Schiff base ligands were synthesized and characterized. A total of 30 crystal structures were elucidated throughout this work. The metal complexes adopted either distorted tetrahedral or square planar geometries and coordinated with ligand in 1:2 mol ratios *via* azomethine nitrogen and thio sulphur atoms in four-coordinated geometries. The cytotoxicities of synthesized and characterized Schiff bases and their complexes were evaluated against breast cancer estrogen receptor positive, MCF-7 and breast cancer estrogen receptor negative, MDA-MB-231 cell lines. It was found that Schiff bases which showed the most active cytotoxicity against MCF-7 and MDA-MB-231 were SM4C/TC and SB4C/TC, respectively. The IC₅₀ values for SM4C/TC and SB4C/TC against MCF-7 and MDA-MB-231 were 2.4 μM and 2.8 μM, respectively. Dithiocarbazate Schiff bases condensed with chalcone analogues were generally more active than the phenylbutanone derived thiosemicarbazones.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Falsafah Kedoktoran

**SINTESIS DAN AKTIVITI SITOTOKSIK DITHIOKARBAZAT DAN
TIOSEMIKARBAZAT BES SCHIFF DITERBITKAN DARIPADA KALKON
DAN FENILBUTANON ANALOG SERTA Cd(II) DAN Zn(II) KOMPLEKS
MEREKA**

Oleh

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Bes Schiff bidentat NS hasil kondensasai S-benzildithiokarbazon (SBDTC) dan S-metildithiokarbazon (SMDTC), N-fenilsemikarbazon (PT) dan N-metiltio semikarbazon (MT) dengan kalkon gantian (H, Cl, OCH₃ dan NO₂), fenilbutanon (H, OH, OCH₃ dan CH₃-C(=O)) dan zingeron telah disediakan. Bes Schiff dicirikan dengan pelbagai teknik kimia-fizik dan spektroskopi. Bes Schiff yang dicirikan terkompleks dengan ion kadmium(II) dan zink(II). Sebanyak 35 ligan bes Schiff dan 50 kompleksnya telah disintesis dan dicirikan. Struktur bagi hablur tunggal 30 sebatian telah ditentukan melalui kaedah difraktometri sinar-X. Kompleks didapati terkordinasi dengan nisbah mol logam:ligan 1:2 bergeometri tetrahedron atau empat segi sesatah terkoordinat melalui atom nitrogen azometin dan sulfur tiolo. Aktiviti sitotoksik terhadap sel barah payudara reseptor positif estrogen, MCF-7 dan sel barah payudara reseptor negative estrogen, MDA-MB-231 telah dinilai bagi semua sebatian yang disintesis. Sebatian SM4C/TC dan SB4C/TC menunjukkan aktiviti sitotoksik yang tertinggi terhadap kedua-dua jeni sel barah itu. Nilai IC₅₀ bagi SM4C/TC dan SB4C/TC adalah 2.4 μM dan 2.8 μM terhadap MCF-7 dan MDA-MB-231 masing-masing. Pada keseluruhannya bes Schiff dithiokarbazon hasil analog kalkon lebih aktif berbanding bes Schiff tiosemikarbazon hasil analog fenilbutanon.

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I certify that a Thesis Examination Committee has met on 28th October 2015 to conduct the final examination of Tan Ming Yuehon her thesis entitled “Synthesis and Cytotoxicity of Dithiocarbazate and Thiosemicarbazide Schiff bases Derived From Chalcone and Phenylbutanone Analogues and their Cd(II) and Zn(II) 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 degree of Doctor of Philosophy.

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CHAPTER ONE

INTRODUCTION

Cancer is among the leading causes of morbidity and mortality worldwide with 14 million of new cases in year 2012 and it is expected to rise by about 70% (22 million) over the next two decades (Siegel *et al.*, 2014). In Malaysia, more than 10,000 new cancer cases were reported and 38% of new cases among women were breast cancers. About one in 19 women are at risk, compared to one in eight in Europe and the United States. There is an urgent need to discover anti-breast cancer drugs with improved selectivity and activity. Natural products have been a rich source of lead compounds in anticancer drug discovery contributing approximately 74% of anticancer drugs (Newman *et al.*, 2003). In this work, two natural product derived analogues of chalcone and phenylbutanone, were chosen to condense with sulphur-nitrogen chelating agents, *S*-substituted dithiocarbazate and *N*-substituted thiosemicarbazide, to form the Schiff bases. The Schiff bases were then reacted with transition metal ions of cadmium, Cd(II), and zinc, Zn(II), to form the metal complexes with a view to assessing the cytotoxicity of the Schiff bases and the affect of complexation with metals on cytotoxicity towards breast cancer cell lines, MCF-7 and MDA-MB-231.

1.1 Schiff bases derived from *S*-substituted dithiocarbazate and *N*-substituted thiosemicarbazide

Dithiocarbazate, with its $\text{NH}_2\text{NHCS}_2^-$ backbone, is produced by condensation of hydrazine hydrate and carbon disulphide in potassium hydroxide solution. *S*-substituted dithiocarbazate is formed through nucleophilic substitution upon addition of organic halide. The synthetic route is shown in Figure 1.1.

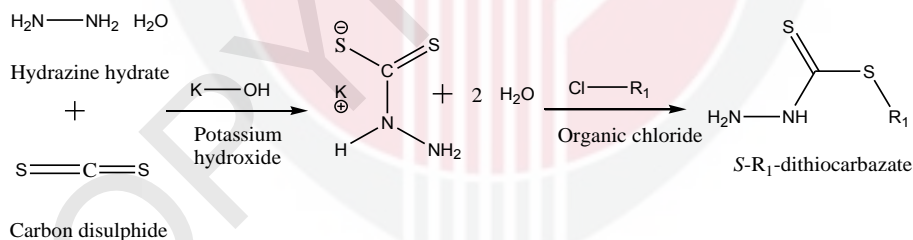


Figure 1.1: Reaction pathway for the synthesis of *S*-substituted dithiocarbazate

S-substituted dithiocarbazate compounds are able to undergo thione-thiol tautomerism because of the presence of thioamide functions, $-\text{HN}(\text{C}=\text{S})$. In the solid state, these ligands have been found exist as thione tautomers. However, in solution, these ligands can exist in both thione and thiol forms in equilibrium (Ali and Livingstone, 1974). *S*-substituted dithiocarbazate ligands, $\text{H}_2\text{N}-\text{HN}-\text{C}(=\text{S})\text{S}-\text{R}_1$ have a free primary amine group, NH_2 , that is susceptible to nucleophilic addition reactions with aldehydes and ketones to form Schiff bases. The reaction scheme is shown in Figure 1.2.

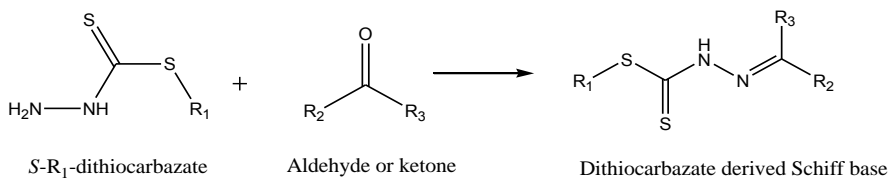


Figure 1.2: Reaction scheme for the synthesis of Schiff bases

Schiff bases derived from dithiocarbazates are a class of Schiff bases that are particularly important due to their interesting physico-chemical and potentially pharmacological properties as well as their intriguing bonding and geometric variations with metal ions (Islam *et al.*, 2011). The flexibility and bioactivity of Schiff bases are proposed to be associated with the presence of both imino (-N=CH-) and thioamino (C(=S)NH-) moieties in the structures. Dithiocarbamate derived Schiff bases form an interesting series of ligands to study because small differences in molecular structures caused by introducing slightly variant organic substituents can greatly modify their properties (Crouse *et al.*, 2004a; Tarafder *et al.*, 2002). Formation of Schiff bases is proved by the appearance of azomethine, $\nu(\text{C}=\text{N})$ and secondary amine, $\nu(\text{N}-\text{H})$ infrared absorptions that fall in the ranges of 1460-1490 cm^{-1} and 3200-3100 cm^{-1} , respectively (Khoo *et al.*, 2014; Omar *et al.*, 2014a). In the ^{13}C NMR analysis, the presence of azomethine, C=N bond is evidenced by the appearance of a C=N resonance at δ 152-154 ppm.

Schiff bases are able to exhibit thione-thiol tautomerism because of the presence of thioamide, -NH-C(S) functions as shown in Figure 1.3.

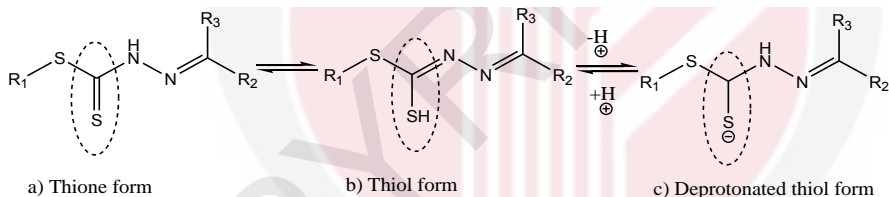


Figure 1.3: The (a) thione, (b) thiol and (c) deprotonated thiolate tautomeric forms of dithiocarbamate derived Schiff bases

In the IR spectra, the existence of either thione or thiol tautomers can be determined through the appearance of $\nu(\text{C}=\text{S})$ and $\nu(\text{C}-\text{S})$ bands that found at regions 1100-1000 cm^{-1} and ~ 2700 cm^{-1} , respectively (Ali and Livingstone, 1974) while in the ^1H NMR spectra, the appearance of singlet peaks due to secondary N-H and S-H protons at regions $\sim \delta$ 12.5 ppm and $\sim \delta$ 4.0 ppm indicate the thione or thiol forms, respectively (Khoo *et al.*, 2014; Taha *et al.*, 2014).

Schiff bases derived from thiosemicarbazide or thiosemicarbazones are obtained by the reaction of thiosemicarbazides or *N*-substituted thiosemicarbazides with aldehydes or ketones as shown in Figure 1.4. Thiosemicarbazones and dithiocarbamate derived Schiff bases share similar thioamide functions, -HN(C=S) as and also able to exhibit thione-thiol tautomerism as shown in Figure 1.3. Thiosemicarbazones have received considerable attention since the Domagk report regarding their anti-tubercular activity (Domagk, 1951). They are one of the important classes of Schiff bases with wide pharmacological activities and their activities are often related to their ability to coordinate with metal centers in enzyme substrates (Seena *et al.*, 2006). Currently, 3-aminopyridine-2-carboxylaldehyde thiosemicarbazone, Triapine, is being evaluated in

human phase II trials as cancer chemotherapeutic agent (Feng *et al.*, 2014). They also react as chelating ligands to trace metals qualitatively and quantitatively (Jagadeesh *et al.*, 2015). Thiosemicarbazones usually coordinate with metal ions through thioamide sulfur and azomethine nitrogen atoms. However, the number of coordination sites can be increased by the suitable substitution on the thiosemicarbazone framework to form coordination polymers with multiple dimensions and various topologies (Li *et al.*, 2010).

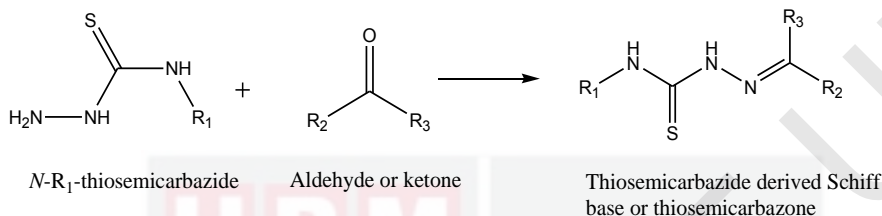


Figure 1.4: Reaction scheme of the synthesis of thiosemicarbazone

1.2 Chalcone and phenylbutanone analogues

Both chalcone and phenylbutanone analogues are characteristic constituents in many edible plants, including vegetables, fruits and spices. Chalcones, or 1,3-diaryl-2-propen-1-ones, belong to the flavonoid family and consist of two aromatic rings joined by a three-carbon α , β -unsaturated carbonyl system (Nowakowska, 2007b). Naturally occurring and synthetic chalcone analogues have been reported to be non-toxic to normal cells while possessing widespread of biological activities, including antimicrobial, antifungal, antioxidant, anti-inflammatory, cytotoxic, antitumor and anticancer activities (Nowakowska, 2007a). They have the potential to serve as lead compounds for the discovery of new pharmacological agents with reduced side effects and improved efficacy (Mai *et al.*, 2014). The presence of an α , β -unsaturated carbonyl system is reported to be critical for biological activity (Sahu *et al.*, 2012). Phenylbutanones are phenolic alkanones containing vanilloid groups in their 4-phenyl-2-butanone structures (Koeduka *et al.*, 2011). Naturally occurring and synthetic phenylbutanone analogues exhibit chemopreventive properties both *in vitro* and *in vivo* by suppressing the transformative, hyperproliferative, and inflammatory activities that initiate carcinogenesis as well as angiogenesis and metastasis in the later steps of carcinogenesis (Shukla and Singh, 2007).

In this study, a total of nine chalcone and phenylbutanone analogues are used to condense with *S*-substituted dithiocarbazates and *N*-substituted thiosemicarbazides to form 45 Schiff bases. Chalcone and three 4-substituted chalcone analogues substituted with the electron-donating methoxy, OCH₃, group and electron-withdrawing chloride (Cl) and nitro (NO₂) groups are used in preliminary exploration of structure activity relationships. Three phenylbutanone analogues with electron donating hydroxy (OH) and methoxy (OCH₃) substituent groups or the electron-withdrawing acetoxy (C=O(O)CH₃) and zingerone (or vanillylacetone) group are used as shown in Figure 1.5. The cytotoxicity of Schiff bases derived from chalcones are compared with phenylbutanones derived Schiff bases to explore the importance of α , β -unsaturated systems in biological activity.

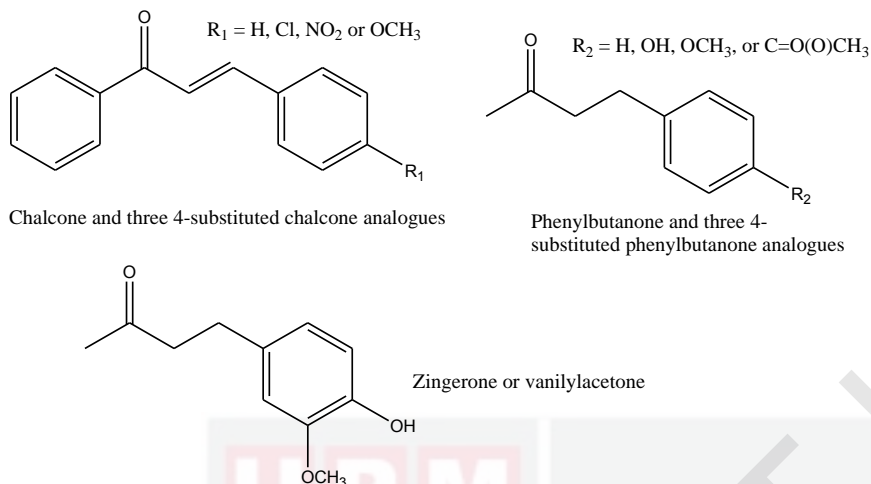


Figure 1.5: Chalcone and phenylbutanone analogues used in this study

1.3 Transition metal complexes

Dithiocarbamate and thiosemicarbazide derived Schiff bases are among the most widely studied chelating agents (Mayer *et al.*, 2009). The presence of both soft sulphur and hard nitrogen donor atoms allows coordination with a broad range of transition and non-transition metal ions yielding stable metal complexes with interesting structural, physico-chemical properties and pronounced biological activities. Ali and Livingstone first reviewed the chemistry of nitrogen-sulfur (NS) chelating ligands in 1974. Since then, much work has been published about these compounds and their metal complexes.

These Schiff bases generally behave as bidentate (*N, S*) ligands forming five-membered chelate rings; however the presence of additional donor atoms in suitable position can increase the coordination ability of the ligand resulting in neutral and cationic complexes. Transition metal ions are good candidates for ligation because they possess vacancies in *d* and *f* orbitals that facilitate the coordination with ligands. The presence of an additional donor atom in a suitable position of ligand can raise the coordination ability of the ligand and increase denticity from monodentate to hexadentate giving rise to different coordination geometries and architectures with potentially beneficial applications in material science, such as molecular-based magnet, catalysis, zeolite-like porous materials, and luminescence (Morshedi *et al.*, 2009).

Schiff bases can coordinate with metal ions as either mono(ligand) or bis(ligands) which could result in open chain and macrocyclic metal complexes. Schiff base condensations between diamines and dicarbonyls are among the simplest and most popular methods for synthesis of macrocyclic ligands (Keypour *et al.*, 2008).

There are also reports of mixed-ligand complexes containing saccharin (Omar *et al.*, 2014; Ravoof *et al.*, 2007a), substituted salicylaldehyde (Devi and Batra, 2015), and heterocyclic nitrogen bases such as pyridine, bis(pyridine), imidazole, and 1,10-phenanthroline (Babu *et al.*, 2007; Jia *et al.*, 2013) as the co-ligands. Mixed-ligand complexes are reported to exhibit good nucleolytic cleavage activity, enzyme activation, as well as the storage and transportation of active material through membrane (Devi and Batra, 2015).

Transition metals, such as manganese, cobalt, nickel and copper have been intensively studied because they have variable oxidation states, coordination numbers and the ability to bind to a variety of ligands through O, S, N, P, C and halides donor groups (Sujarani and Ramu, 2014; van Rijt and Sadler, 2009). Metal complexation arranges the coordinating ligands into three dimensional spaces going beyond structures that are accessible with purely organic compounds giving shape- and functional group complementarity with targeted protein pocket (Meggers, 2007). Metal compounds, especially those of second and third row transition metals, are sufficiently thermodynamically stable to enable the organic ligands to remain bound to the metal at the targeted site.

Some metal complexes also act as inert drug derivatives or “prodrugs” converting to active forms and binding to biologically targeted molecules through ligand substitution, redox activation or photoactivation (Lainé and Passirani, 2012). To release the ligands to the targeted molecules, the metal-to-ligand coordination should be hydrolytically and kinetically stable to allow ligation or de-ligation reaction *in vivo* (van Rijt and Sadler, 2009).

Metal compounds have a range of accessible redox states and the activation is triggered by ligand release. For instance, the cisplatin prodrug reduces the inert platinum (IV)–cisplatin to labile platinum (II) and releases cisplatin in the targeted active site in a dose-limiting approach (Lainé and Passirani, 2012). In short, the wide range of coordination modes, accessible redox states, tunable thermodynamic and kinetic properties, and intrinsic properties of cationic metal ions allow metal complexes to exhibit advantages over organic agents alone (van Rijt and Sadler, 2009). In recent years, Schiff base metal complexes have played a prominent role in the discovery of metal coordination complexes with pronounced biological activities.

1.4 Cadmium (Cd) and Zinc (Zn)

The International Agency for Research on Cancer (IARC) and the USA National Toxicology Program have classified cadmium as a carcinogen of category 1. However, at very low concentrations down to 1 μM , it enhances DNA synthesis and cell proliferation (von Zglinicki *et al.*, 1992). Cadmium(II), Cd(II) ion has been found to serve as catalytic centre in a newly discovered carbonic anhydrase from the marine diatom phytoplankton, *Thalassiosira weissflogii* (Lane *et al.*, 2005). The Cd(II) ion has also been found to induce metallothionein synthesis in many organs, including the liver and kidney. Metallothionein is an important transportation and storage protein for cadmium and other metal ions. The binding of intracellular cadmium to metallothionein in tissue protects against from the toxicity of cadmium (Thomas, 2011).

Zinc is the second most prominent trace intracellular metal in the human body after iron and plays wide range of essential cellular processes, including cell proliferation, reproduction, immune function and defense against free radicals (Salgueiro *et al.*, 2000). It is a component of more than 3000 zinc-associated transcription factors involving in gene expression to maintain structural integrity and binding to DNA and more than 300 enzymes of DNA replication and transcription as well as DNA repair (Ho, 2004). Thus, zinc has a significant impact on DNA replication and transcription as well as DNA repair. Zinc plays an essential role in the development and progression of

maglinancy in prostate cancer with three proposed mechanism as: intermediary metabolism and bioenergetics effects; mobility and invasive effects; growth and proliferation effects (Franklin and Costello, 2007). Zinc deficiency may increase the risk for cancer by increasing sensitivity to oxidative stress which cause DNA damage or by impairing DNA damage repair response (Song *et al.*, 2010).



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