UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF TRIDENTATE NNS SCHIFF BASES AND THEIR COPPER(II) COMPLEXES CONTAINING SACCHARIN

SITI AMINAH OMAR

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By

SITI AMINAH OMAR

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

May 2014

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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May 2014

Chairman: Thahira Begum, PhD

Faculty: Science

New tridentate NNS Schiff bases derived from dithiocarbazate and thiosemicarbazide and their corresponding mixed-ligand copper(II) saccharinate complexes were synthesized. The Schiff bases as well as the copper(II) saccharinate complexes were characterized by elemental analysis, ^{1}H and ^{13}C NMR, mass spectrometry, conductance, magnetic susceptibility, IR, UV-Vis analysis and X-Ray diffraction analysis where appropriate. The spectral, mass spectrometry, ^{1}H and ^{13}C NMR analysis supported the formation of the Schiff bases. The structure of four of the Schiff bases and one of the complexes were further confirmed by X-Ray diffraction analysis. These include SB-4, S4M-4, S4M-5, 4M3T-4 and [Cu-4M3T5(sac)(H_2O)]·Hsac. The copper(II) saccharinate complexes adopted either four or five coordinate geometry as suggested by magnetic and spectral analysis. The [Cu-4M3T5(sac)(H_2O)]·Hsac complex was confirmed by X-Ray diffraction analysis to adopt a distorted square-pyramidal structure in which the Schiff bases coordinated to the copper(II) ion as tridentate NNS chelating agent *via* its azomethine nitrogen atom, thione sulphur atom and the pyridine nitrogen atom while the saccharinate anion coordinated as a unidentate N-donor ligand. The fifth coordination site is occupied by a water ligand. Interestingly, an un-coordinated saccharin was present outside of the coordination sphere. The Schiff bases and the complexes were tested for their cytotoxic properties towards MCF-7 (Estrogen receptor positive human breast carcinoma cells) and MDA-MB-231 (Estrogen receptor negative human breast carcinoma cells). The position of methyl group of the benzene ring was found to have an effect to the cytotoxic properties of the Schiff bases. All of the Schiff bases containing methyl group at the *ortho* position of the benzene ring were found to be inactive towards MDA-MB-231 cells, while having a methyl group at the *para* position increased the cytotoxicity of the Schiff bases. All of the copper(II) saccharinate complexes were moderately to highly cytotoxic towards both cell lines.

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

SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BAGI LIGAND TIGA BERKOORDINATAN BES SCHIFF NNS SERTA KOMPLEKS KUPRUM(II) YANG MENGANDUNGI SAKARIN

Oleh

SITI AMINAH OMAR

Mei 2014

Pengerusi: Thahira Begum, PhD

Fakulti: Sains

Bes Schiff NNS yang terhasil daripada dithiocarbazate dan thiosemicarbazide serta kompleks kuprum(II) sakarinat yang baru telah berjaya dihasilkan. Bes Schiff dan kompleks ini telah dicirikan melalui analisis unsur, spektral, ^{1}H dan ^{13}C NMR, spektrometri jisim, konduktiviti dan kerentanan magnetik, pengukuran spektroskopi elektronik serta analisis struktur hablur sinar X mengikut kesesuaian. Analisis spektral, spektroskopi jisim dan ^{1}H and ^{13}C NMR menyokong penghasilan bes Schiff. Analisis struktur hablur sinar bagi empat daripada bes Schiff dan satu kompleks membuktikan penghasilan bes Schiff. Antaranya ialah SB-4, S4M-4, S4M-5, 4M3T-4 and [Cu-4M3T5(sac)(H_2O)]·Hsac. Kompleks kupum(II) sakarinat didapati berkoordinatan empat atau lima berdasarkan analisa spektral dan kerentanan magnetik. Analisis struktur hablur sinar X menunjukkan kompleks [Cu-4M3T5(sac)(H_2O)]·Hsac berstruktur piramid segiempat terherot dengan bes Schiff terkoordinat kepada ion kuprum sebagai agen kelat tridentate NNS melalui atom nitrogen azometin, atom sulphur tione dan atom nitrogen piridin manakala ion sakarinat terkoordinat melalui nitrogen imino. Ligan yang kelima ialah air. Terdapat satu sakarin yang tidak terkoordinat. Bes Schiff dan kompleks diuji untuk menilai keaktifan sitotoksik terhadap dua jenis sel kanser, MCF-7 (Sel kanser payudara dengan reseptor estrogen positif) dan MDA-MB-231 (Sel kanser payudara dengan reseptor estrogen negatif). Kedudukan kumpulan metil gelang benzena didapati mempunyai kaitan ke atas keaktifan sitotoksik. Bes Schiff yang mengandungi kumpulan metil pada kedudukan *orto* didapati tidak aktif ke atas sel MDA-MB-231, manakala kumpulan metil pada kedudukan *para* meningkatkan keaktifan sitotoksik bes Schiff. Kesemua kompleks kupum(II) sakarinat adalah sederhana aktif hingga sangat aktif terhadap kedua-dua sel.

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I would also like to thank my parents, for always being there for me. Last but not least, thank you to my siblings too.

I certify that a Thesis Examination Committee has met on 23 May 2014 to conduct the final examination of Siti Aminah Omar on her thesis entitled "Synthesis, Characterization and Biological Properties of Tridentate NNS Schiff Bases and Their Cu(II) Complexes Containing Saccharin" 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 Master of Science.

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sac	Saccharinate anion
FT-IR	Fourier-transform Infrared
B.M	Bohr magneton
LMCT	Ligand to metal charge transfer
DMSO	Dimethylsulphoxide
HLE	human leukocyte elastase
SOD	superoxide dismutase
DMEM	Dulbecco's Modified Eagle Medium
CD_{50}	Cytotoxic dose at 50%
IC_{50}	Cytotoxic dose at 50%
MCF-7	Estrogen receptor positive human breast cancer cells
MDA-MB-231	Estrogen receptor negative human breast cancer cells
CHN	Carbon, Hydrogen and Nitrogen
NNS	Nitrogen-nitrogen-sulphur
UV/Vis	Ultraviolet/Visible Spectroscopy
SBDTC	S-benzyldithiocarbazate
S2MBDTC	S-2-Methylbenzyldithiocarbazate
S3MBDTC	S-3-Methylbenzyldithiocarbazate
S4MBDTC	S-4-Methylbenzyldithiocarbazate
4M3T	4-Methyl-3-thiosemicarbazide
SB-4	S-benzyl-β-*N*-*(*4-methylpyrid-2-yl)methylenedithiocarbazate
SB-5	S-benzyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
SB-Pz	S-benzyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate

S2M-4	S-benzyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
S2M-5	S-benzyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
S2M-Pz	S-benzyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
S3M-4	S-3-methyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
S2M-5	S-3-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
S3M-5	S-3-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
S3M-Pz	S-3-methyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
S4M-4	S-4-methyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
S4M-5	S-4-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
S4M-Pz	S-4-methyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
4M3T-4	(*E*)-*N*-methyl-2-(1-(4-methylpyridin-2-yl)ethylidene)hydrazinecarbothio amide
4M3T-5	(*E*)-*N*-methyl-2-(1-(5-methylpyridin-2-yl)ethylidene)hydrazinecarbothio amide
4M3T-Pz	(*E*)-*N*-methyl-2-(1-(Pyrazine-2-yl)ethylidene)hydrazinecarbothio amide
[Cu-SB4(sac)]	Copper(II) Saccharinate Complex of S-benzyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-SB5(sac)]	Copper(II)Saccharinate Complex of S-benzyl-β-*N*-(5- methylpyrid-2-yl)methylenedithiocarbazate
[Cu-SBPz(sac)]	Copper(II) Saccharinate Complex of S-benzyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
[Cu-S2M4(sac)]	Copper(II) Saccharinate Complex of S-2-methyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-S2M5(sac)·H_2O]·Hsac	Copper(II) Saccharinate Complex of S-2-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-S2MPz(sac)]	Copper(II) Saccharinate Complex of S-2-methyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
[Cu-S3M4(sac)]	Copper(II) Saccharinate Complex of S-3-methyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate

[Cu-S3M5(sac)]	Copper(II) Saccharinate Complex of S-3-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-S3MPz(sac)]	Copper(II) Saccharinate Complex of S-3-methyl-β-*N*-(Pyrazin-2-yl)methylenedithiocarbazate
[Cu-S4M4(sac)]	Copper(II) Saccharinate Complex of S-4-methyl-β-*N*-(4-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-S4M5(sac)]	Copper(II) Saccharinate Complex of S-4-methyl-β-*N*-(5-methylpyrid-2-yl)methylenedithiocarbazate
[Cu-S4MPz(sac)]	Copper(II) Saccharinate Complex of S-4-methyl-β-*N*(Pyrazin-2-yl)methylenedithiocarbazate
[Cu-4M3T4(sac)]	Copper(II) Saccharinate Complex of (*E*)-*N*-methyl-2-(1-(4-methylpyridin -2-yl)ethylidene)
[Cu-4M3T5(sac)·H_2O]·Hsac	Copper(II) Saccharinate Complex of (*E*)-*N*-methyl-2-(1-(4-methylpyridin -2-yl)ethylidene)
[Cu-4M3TPz(sac)]	Copper(II) Saccharinate Complex of (*E*)-*N*-methyl-2-(1-(Pyrazine-2-yl)ethylidene)hydrazinecarbothio amide

CHAPTER 1

INTRODUCTION

1.1 Saccharin

Saccharin (Figure 1) has been widely used as an artificial sweetening agent since 1885 (Gençer *et al.,* 2012). The history of saccharin can be traced back from as early as 17th century. The synthesis of saccharin was found merely from accidental work done by Constantin Fahlberg in 1879 while working at Professor Ira Ramsen's laboratory at Johns Hopkins University during the investigation of the oxidation of toluene derivatives (Sardesai and Waldshan, 1991). He experienced inordinary sweet taste of his bread due to contact from his unwashed hand. He later attributed the compound as 1,2-benzisothiazoline-3-(2H)one 1,1-dioxide or 'saccharin' (Oser, 1985).

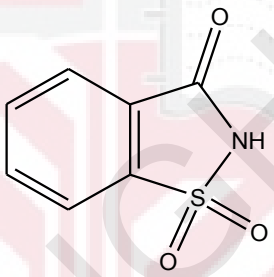


Figure 1: Structure of Saccharin

Soon after its discovery, saccharin was produced on an industrial scale as synthetic sweetening agent in the production of candies, beverages and bakery products (Sardesai and Waldshan, 1991). Even until today, saccharin continues to play a major role in the industry as the demand for dietary products keep increasing (Ravoof *et al.,* 2004). One of the special characteristics of saccharin is that it has zero-calorie which makes it a good option as a sugar substitute to reduce calories taken in by those on a diet (Ferrer *et al.,* 2010).

The physiological and biochemical activity of saccharin and its compounds have been thoroughly studied particularly because of its suspected carcinogenicity (Jovanovski, 2000). Preliminary findings showed that saccharin implanted into the bladders of mice caused urinary bladder carcinomas in second-generation male rats fed with high doses of saccharin (Sardesai and Waldshan, 1991). It was after years of extensive investigation that saccharin is now considered safe at human level of consumption (Price *et al.,* 1970; Gerland *et al.,* 1989; Celik *et al.,* 2012). One of the reasons that support the safety of saccharin is that sodium saccharin differs from classical carcinogens as it is not metabolized to a reactive electrophile, it does not react with DNA, and it is not mutagenic in a variety of *in vitro* and short-term assays (Gerland *et al.,* 1989).

Apart from its major function as artificial sweetening agent, saccharin also finds use as electroplating-bath brightener (Jovanovski, 2000) and inhibitor for certain enzyme reactions (Groutas *et al.,* 1996). Saccharinate complexes with amine derivatives have also

been reported useful antidote for metal poisoning (Yerli *et al.*, 2003) as well as DNA-alerting ability (Azza and Wolfgang, 2009). In addition, a saccharin-based inhibitor was found to have potent human leukocyte elastase (HLE) inhibitory effects (Groutas *et al.*, 1996).

It was also found that metal complexes of saccharin exhibited superoxide dismutase (SOD) mimetic activity (Ferrer *et al.*, 2010). Superoxide dismutase is a diverse group of metalloenzymes that catalyze the dismutation of superoxide radical anion to molecular oxygen and hydrogen peroxide (J. Lin *et al.*, 2003). A series of divalent metal-aqua-saccharinato complexes of the type $[M(sac)_2(H_2O)_4]\cdot 2H_2O$ (with M= Mn, Fe, Co, Ni, Cu and Zn) have been investigated for their superoxide-dismutase like activity using the nitrobluetetrazolium/superoxide reduction assay (Apella *et al.*, 1993). The findings showed positive result for all of the complexes to dismute the superoxide anion generated in the xanthine/xanthine oxidase system. Of all the metal complexes tested, the corresponding copper complexes were found to exhibit the greatest activity. It was also found that the presence of coordination sites belonging to nitrogen heteroaromatic rings such as imidazole, pyridine and pyrazole are important for high SOD activity (Bienvenue *et al.*, 1995).

Another important biological properties showed by saccharinate complexes is the ability to inhibit carbonic anhydrase. Carbonic anhydrase is a type of enzyme that catalayze the reversible hydration of carbon dioxide into bicarbonate and protons: $CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$ (Bertucci *et al.*, 2009). As such, these enzymes are involved in many physiological processes such as pH and CO_2 homeostasis, bone resorption and calcification (Supuran *et al.*, 2003). The inhibition profile of saccharin against a panel of different carbonic anhydrase isoenzymes has been analyzed and the result indicated that saccharin inhibits some members of this carbonic anhydrase at nanomolar level (Khalifah, 1971). Saccharin was also found to show remarkable selectivity discrimination among the different isoforms compared with classical and well-established carbonic anhydrase inhibitors namely acetazolamide and other sulfonamides such as furosemide, hydrochlorothiazide and topiramate (Kohler *et al.*, 2007).

1.2 Dithiocarbazate and thiosemicarbazide

Dithiocarbazate and thiosemicarbazide (Figure 2) are a group of compounds containing nitrogen sulphur donor atoms. Interest in this group remain high as studies showed that they possess many significant biological properties such as anticancer, antibacterial, antimalarial, antitumor and antiviral (Hossain *et al.*, 1996(b); Das and Livingston, 1978; Chew *et al.*, 2004). Condensation reaction of these compounds with various ketones and aldehydes yielded the corresponding Schiff bases which is commonly enhanced in their biological activity. In fact, a related thiosemicarbazone drug, 3-aminopyridinecarbaldehyde thiosemicarbazone (Triapine) is currently undergoing clinical phase I evaluation, where it showed promising activity against advanced leukemia (Karp *et al.*, 2008). Studies also showed that the properties of these compounds can be greatly modified by introducing different organic substituents. Different ligands show different biological properties, although they may differ only slightly in their molecular structures (Ali *et al.*, 1977; Tarafder *et al.*, 2002; Tarafder *et al.*, 2001). It is also known that complexation with metal ions increase the activity of the compound (Ali *et al*., 1996).

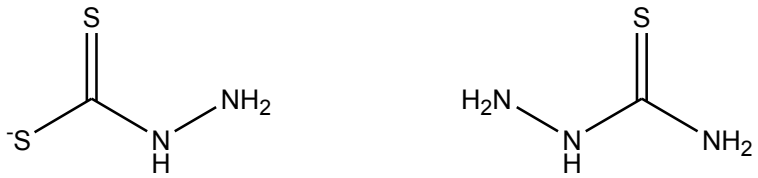


Figure 2: Structure of dithiocarbazate and thiosemicarbazide

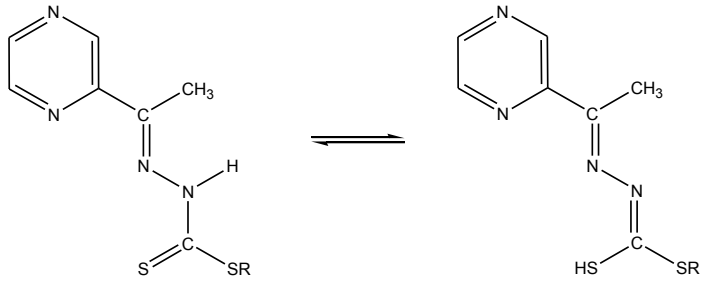
1.2.1 Thione-thiol Tautomerization

Schiff bases derived from dithiocarbazate and thiosemicarbazide having the thioamide function (-HN-C(S)SR) are capable of showing thione-thiol tautomerization (Ali *et al.*, 1998; Ali *et al.*, 2005). Consequently, they can remain as thione form (-N=C=S), thiol form (-N=C-SH) or as a mixture of both forms (Ali *et al.*, 2011).

Ali *et al.*, (1977) had synthesized Schiff base derived from dithiocarbazate by reacting *S*-benzyldithiocarbazate with pyridine-2-aldehyde. The IR spectra of the Schiff base did not show any peak at *ν*(S-H) at *ca.* 2570 cm^{-1} which indicated that it remained in the thione form in solid form. In solution, both thione and thiol tautomer are possible, in which the Schiff base under study was greatly deprotonated, due to the stabilization of the deprotonated form by the conjugation of the –C=N-N=C- group (Ali *et al.*, 1977).

Hamid *et al.*, (2009) synthesized the 2-acetylpyrazine Schiff bases of S-methyl- (Hapsme) and S-benzyldithiocarbazate (Hapsbz) which was capable of showing thione-thiol tautomerization (Figure 3). Both Schiff bases were found to exist in thione form as evident from the IR and NMR spectra. IR spectra for both of the Schiff bases did not show *ν*(S-H) band at 2600 cm^{-1} but displayed a *ν*(N-H) band which belong to the thioamide NH group in the range 3078-3085 cm^{-1}, which proved that they exist only as the thione tautomer. In addition, ^{1}H NMR signal did not show any peaks attributable to the –SH proton at ~4.00 ppm which further supported the finding that the Schiff bases remained in thione form.

Although the Schiff bases exist in thione form, they may convert to thiol form (Fig 3b) in solution with the concomitant formation of the complexes of empirical formula [Cu(NNS)X] (NNS = deprotonated form of the Schiff base; X = Cl, Br, NCS, NO_3). Deprotonation of the Schiff bases derived from S-alkyl/aryl dithiocarbazates while coordinating with metal ions have always been observed (Ali *et al.*, 2003). The same case is observed in this Schiff base as evident from the C(1)—S(1) bond length of 1.73(2) Å as seen in $[Cu(apsbz)(NO_3)]_\infty$, and in other metal complexes of structurally similar Schiff bases (Hossein *et al.*, 1996(a); Hossein *et al.*, 1996(b)). This will consequently lead to complexes of deprotonated thiolate forms of the ligands (Hamid *et al.*, 2009).



(a) (b)

Figure 3: The thione (a) and thiol (b) forms of Hapsme (R = Me) and Hapsbz (R = Bz).

Thiosemicarbazones' on the other hand, have been reported to coordinate to metal ions in both protonated and deprotonated forms. An interesting example is the bis-ligand copper(II) complex of 2-acetylpyridinethiosemicarbazone (Figure 4) in which the protonated as well as the deprotonated forms of the Schiff base were present in the same complex (Souza *et al.*, 1996; Ali *et al.*, 2001(a)). The complex consist of $[Cu(HL)L]^+$ cation and NCS^- anion as a result of transmetallation reaction which crystallized as distorted octahedron with non-equivalent Schiff base as one side had lost the N proton (deprotonated) while the other one was in neutral form.

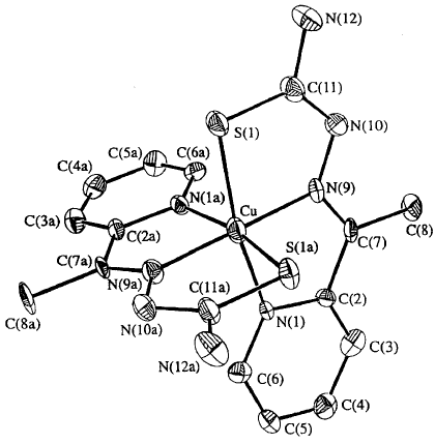


Figure 4: ORTEP diagram of the complex [Cu(HL)L]NCS (Souza *et al.*, 1996)

1.3 Copper: Chemistry and biology

Copper is an essential metallic element in our body. It is involved in several enzymatic and protein functions in metabolism (Linder, 2001). A normal adult contains about 80 – 120 mg of copper in his body (Marzano *et al.*, 2009). Plants and animals contain a variety of copper-containing metalloenzymes which is pivotal in regulating many important functions such as electron transfer, oxygenation reaction and oxygen transport. These

include azurin, plastocyanin, tyrosinase, ascorbate oxidase and haemocyanin (Tisato *et al.*, 2010).

Copper is the 29th chemical element of the Periodic Table. It belongs to the first row of the Group 11 metals with electronic configurations of $3d^{10}4s^{1}$. In complexes, copper may exist in Cu(I), Cu(II) and Cu(III) forms. Of the three different forms, Cu(III) is the least common. Cu(I) has a complete d^{10} configuration, hence it is diamagnetic and colourless. Cu(I) complexes have been reported to exist as linear, trigonal and tetrahedral in geometry, with the most occurrences having a tetrahedral geometry (Marzano *et al.*, 2009). Cu(I) is a soft metal ion, thus it prefers ligands having soft donor atoms such as sulphur, phosphorus and aromatic amines (Marzano *et al.*, 2009).

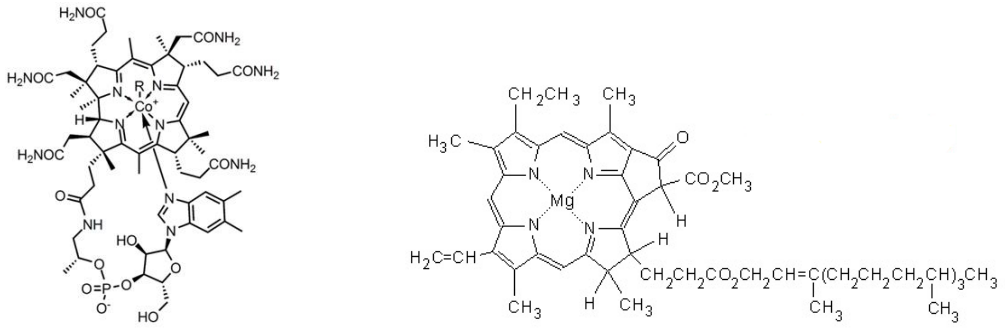
Cu(II) usually forms 4, 5 and 6 coordination complexes (Hathaway and Billing, 1970). This will lead to complexes having octahedral (sixth-coordinate), square-pyramidal, trigonal bipyramidal (fifth-coordinate) and tetrahedral (four-coordinate) geometry. Distortion from ideal arrangement usually results in tetragonal distortions (Marzano *et al.*, 2009). Cu(II) complexes are mostly in blue or green colour due to the presence of *d-d* transition bands at wavelengths around 600-900 nm. Cu(II) being a hard metal ion prefer nitrogen containing ligands. However, copper enzymes involved in redox reactions usually have both types of the ligands, allowing the Cu ion to exist in either oxidation state (Tisato *et al.*, 2010).

Copper is required to sustain life. Indeed, copper in trace quantities is required to maintain proper cellular functions. Several copper complexes have been reported to have effective anti-inflammatory, antirheumatic and anticancer activities, which is often associated with their superoxide dismutase-like activity (Eduardo *et al.*, 2011). As mentioned previously, copper is part of the redox active metalloenzymes which consists of cytochrome c oxidase, tyrosinase or Cu,Zn-superoxide (Buchtík *et al.*, 2012).

Altered level of copper concentration in the body resulted in several diseases such as Menkes disease, Wilson disease, Alzheimer disease, rheumatoid arthritis, gastrointestinal ulcers, epilepsy, diabetes and cancer (Marzano *et al.*, 2009).

1.4 Mixed-ligand Complexes

Mixed-ligand complexes are those complexes in which the metal ion binds to two different ligand moieties. Mixed-ligand metal complexes have been extensively studied as they play important roles in biological processes such as galactose oxidase, vitamin B12, chlorophyll and haemoglobin (Ahmad *et al.*, 2012). Figure 5 shows some of the structures of these mixed-ligand complexes. Of these naturally occurring mixed-ligand complexes of Cu, Co, Fe and Mg, they consist of at least 2 different ligand moieties or two or more different kinds of donor sets of atoms in case the ligand is a single macromolecule. They also find use in activation of enzymes and also storage and transport of active substances (El-Sherif and Jeragh, 2007).



(a) **(b)**

Figure 5: Structure of (a) Vitamin B12 and (b) chlorophyll

Studies on this subject have also been motivated by the finding that mixed-ligand complexes are more active than their constituting ligands or the corresponding homoligated biscomplexes. Mixed-ligand complexes also find use in industrial reactions such as hydrogenation, hydroformation and oxidative hydrolysis of olefins and carboxylation of methanol where the mixed-ligand complexes act as active catalysts in those reactions (Kamini *et al.*, 2012).

Based on the discussion in this chapter, it is worthwhile to synthesize the Schiff bases derived from dithiocarbazate and thiosemicarbazide as well as their respective copper(II) complexes containing saccharin as co-ligand. The characterization and the biological studies of the Schiff bases and the mixed-ligand copper(II) complexes shall add additional info and value on the chemistry and biology of the compounds studied.

1.5 Problem Statements

Cancer is one of the leading causes of death globally. In Malaysia alone, cancer has overtaken heart disease as the number one killer. The Malaysia National Registry Report 2007 showed that breast cancer was the leading top five cancers among the general population of Malaysia.

Cisplatin is a popular metal-based anti-cancer drug. Its effectiveness has been proven in treating various types of cancers. Despite that, the usage of cisplatin was found to exhibit high general toxicity which leads to several side effects (Zhang and Lippard, 2003). Hence, it is hoped that the research done on on this projects will help in the discovery for a better drug to treat cancer, especially breast cancer, with improved pharmacological properties.

1.6 Objectives

The objectives of this project are:

(I) To synthesize new tridentate NNS Schiff bases derived from dithiocarbazate and thiosemicarbazide and their respective mixed-ligand copper(II) complexes containing saccharin.

(II) To characterize the new Schiff bases as well as the mixed-ligand copper(II) complexes by using various physico-chemical techniques, including elemental analysis, magnetic susceptibilities, molar conductance, spectroscopic techniques and X-ray diffraction analysis where possible.

(III) To study the cytotoxicity of the Schiff bases and the mixed-ligand copper(IIcomplexes against MCF-7 (Estrogen receptor positive human breast carcinoma cells) and MDA-MB-231 (Estrogen receptor negative human breast carcinoma cells) breast cancer cell lines.

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