
**UNIVERSITI PUTRA MALAYSIA**

***SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF TRIDENTATE ONS SCHIFF BASES AND THEIR MIXED-LIGAND METAL COMPLEXES CONTAINING IMIDAZOLE OR BENZIMIDAZOLE***

**NURUL AIN MAZLAN**

**FS 2014 10**

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF TRIDENTATE ONS SCHIFF BASES AND THEIR MIXED-LIGAND METAL COMPLEXES CONTAINING IMIDAZOLE OR BENZIMIDAZOLE

**By**

**NURUL AIN MAZLAN**

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

**June 2014**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF TRIDENTATE (ONS) SCHIFF BASES AND THEIR MIXED-LIGAND METAL COMPLEXES CONTAINING IMIDAZOLE OR BENZIMIDAZOLE**

By

**NURUL AIN MAZLAN**

**June 2014**

**Chairman: Thahira Begum, PhD**

**Faculty: Science**

Breast cancer is the most common cancer diagnosed and the second leading cause of cancer death among women after lung cancer. This fact had led the researchers to continuously synthesize new drugs to treat breast cancer. Thus, with this aim, new mixed-ligand metal complexes have been synthesized and evaluated for their biological activities in this research. Three series of tridentate Schiff bases derived from 4-methyl-3-thiosemicarbazide, 4-ethyl-3-thiosemicarbazide and 4-phenyl-3-thiosemicarbazide were synthesized using three aldehydes *via* condensation reactions, to form tridentate Oxygen-Nitrogen-Sulphur (ONS) containing ligands. The Schiff bases were then complexed with the imidazole or benzimidazole and Cu(II) and Ni(II) salts to produce new mixed-ligand transition metal complexes. These compounds were characterized by elemental analysis, molar conductivity, magnetic susceptibility and various spectroscopic techniques including Fourier-Transform Infrared (FT-IR), Nuclear Magnetic Resonance (NMR), UltraViolet/Visible (UV/Vis) and Inductively Coupled Plasma – Atomic Emission Spectroscopy (ICP-AES) analyses. The elemental analyses support the proposed formulae for the synthesized compounds while the molar conductance values indicated that the metal complexes were essentially non-electrolytes in DMSO solution. The magnetic susceptibility measurements and spectral results support the four-coordinate (square planar) geometry in which the Schiff bases behave as the tridentate ONS donor ligand coordinating *via* the hydroxyl oxygen, azomethine nitrogen, and thiolo sulphur atom while the imidazole or benzimidazole coordinates as a unidentate N-donor ligand. Single Crystal X-ray crystallographic analysis of five new mixed-ligand Cu(II) and Ni(II) complexes containing imidazole or benzimidazole shows that the complex exhibit a distorted square planar structure. The Schiff bases and their metal complexes have been evaluated for their biological activities against estrogen receptor positive breast cancer cell line (MCF-7) and estrogen receptor negative breast cancer cell line (MDA-MB-231). All of the Cu(II)



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complexes from salicylaldehyde and 3-methoxy salicylaldehyde derivatives with five Ni(II) complexes showed marked cytotoxicity against the cell lines while all except MTSali Schiff bases and most Ni(II) complexes were found to be inactive.



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**SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BAGI BES SCHIFF TRIDENTAT (ONS) DAN KOMPLEKS LOGAM BERLIGAN CAMPURAN YANG MENGANDUNGI IMIDAZOL ATAU BENZIMIDAZOL**

Oleh

**NURUL AIN BINTI MAZLAN**

**Jun 2014**

**Pengerusi: Thahira Begum, PhD**

**Fakulti: Sains**

Kanser payudara merupakan kanser yang biasa dikesan dan penyebab kedua kematian dalam kalangan wanita selepas kancer paru-paru. Fakta ini telah menjadi panduan kepada para penyelidik untuk mensintesis secara berterusan ubat yang baru untuk merawat kanser payudara. Oleh yang demikian, berdasarkan matlamat ini, sintesis kompleks logam berligan campuran yang baru dan penilaian aktiviti-aktiviti biologi telah dijalankan dalam penyelidikan ini. Tiga siri bes Schiff yang diterbitkan daripada 4-metil-3-tiosemikarbazid, 4-etil-3-tiosemikarbazid dan 4-phenil-3-tiosemikarbazid telah disintesis menggunakan beberapa aldehid melalui tindakbalas kondensasi untuk membentuk ligan tridentat mengandungi Oksigen-Nitrogen-Sulfur (ONS). Kemudian, bes Schiff tersebut dikomplekskan dengan imidazol atau benzimidazol dan garam logam Cu(II) dan Ni(II) untuk menghasilkan kompleks logam peralihan berligan campuran yang baru. Sebatian-sebatian itu dicirikan dengan analisis unsur, kekonduksian molar, kerentanan magnetic dan pelbagai teknik-teknik spektroskopi termasuk analisis spektroskopi Transformasi Fourier Inframerah (FT-IR), Resonans Magnetik Nuklear (NMR), Ultra Lembayung/Boleh Nampak (UV/Vis) dan Spektroskopi Pancaran Pasangan Plasma-Atom secara Induktif (ICP-AES). Analisis unsur menyokong formula yang dicadangkan bagi sebatian-sebatian yang disintesis manakala nilai konduksi molar menunjukkan bahawa kompleks-kompleks logam bukan elektrolit dalam larutan DMSO. Ukuran kerentanan magnetik dan data spektrum menyokong geometri berkoordinat empat (segiempat planar) di mana bes Schiff berkelakuan sebagai ligan penderma tridentat ONS melalui atom oksigen hidroksil, nitrogen azomethine dan sulfur tiolo manakala imidazol atau benzimidazol berkoordinat sebagai satu penderma ligan unidantat. Analisis kristalografi hablur tunggal sinar X bagi lima Cu dan Ni kompleks berligan campuran imidazol atau benzimidazole menunjukkan bahawa kompleks berstruktur segiempat planar terherot. Bes Schiff dan semua kompleks-kompleks logam telah dinilai untuk aktiviti biologi mereka terhadap sel kanser payudara dengan reseptor



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estrogen positif (MCF-7) dan sel kancer payudara dengan reseptor estrogen negatif (MDA-MB-231). Semua kompleks-kompleks Cu(II) yang diterbitkan daripada salisilaldehid dan 3-metoksi salisilaldehid dengan lima kompleks-kompleks Ni(II) menunjukkkan ciri sitotosik terhadap sel-sel kanser tersebut manakala semua kecuali bes Schif MTSali dan kebanyakan kompleks-kompleks logam Ni(II) telah didapati tidak aktif.

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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 were 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
Universiti Putra Malaysia
(Member)

_____
**BUJANG BIN KIM HUAT, PhD**
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Im | Imidazole |
| Bz | Benzimidazole |
| EPR | Electron paramagnetic resonance |
| B.M | Bohr Magneton |
| LMCT | Ligand to metal charge transfer |
| CDK | Cyclin Dependent Kinase |
| A549 | Human alveolar epithelial cells line |
| MCF-7 | Estrogen receptor positive human breast cancer cells line |
| MDA-MB-231 | Estrogen receptor negative human breast cancer cells line |
| U937 | Leukemic cancer cell line |
| CEM | Leukemic cancer cell line |
| K562 | Leukemic cancer cell line |
| HT-29 | Human colon adenocarcinoma cells |
| WHC01 | Oesophageal cancer cell lines |
| WHC05 | Oesophageal cancer cell lines |
| WHC06 | Oesophageal cancer cell lines |
| SOD | Superoxide dismutase |
| CT DNA | Calf Thymus DNA |
| SABI | Salicylidene-2-aminobenzimidazole |
| SAA | Salicylidene anthanilic acid |
| HB | Benzylate ligand |
| $PPh_3$ | Triphenylphosphine |
| Py | Pyridine |
| 4-pic | 4-Picoline |
| 2,2’-bipy | 2,2’-bipyridine |



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| | |
|---|---|
| MTSali | Salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MTSali)bz | Copper(II) benzimidazole complex of salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MTSali)im | Copper(II) imidazole complex of salicylaldehyde-4- methyl-3-thiosemicarbazone |
| Ni(MTSali)bz | Nickel(II) benzimidazole complex of salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Ni(MTSali)im | Nickel(II) imidazole complex of salicylaldehyde-4-methyl-3-thiosemicarbazone |
| PTSali | Salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(PTSali)bz | Copper(II) benzimidazole complex of salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(PTSali)im | Copper(II) imidazole complex of salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PTSali)bz | Nickel(II) benzimidazole complex of salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PTSali)im | Nickel(II) imidazole complex of salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| ETSali | Salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Cu(ETSali)bz | Copper(II) benzimidazole complex of salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Cu(ETSali)im | Copper(II) imidazole complex of salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Ni(ETSali)bz | Nickel(II) benzimidazole complex of salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| MToVa | 3-Methoxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MToVa)bz | Copper(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MToVa)im | Copper(II) imidazole complex of 3-methoxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Ni(MToVa)bz | Nickel(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-methyl-3-thiosemicarbazone |



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| | |
|---|---|
| Ni(MToVa)im | Nickel(II) imidazole complex of 3-methoxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| PToVa | 3-Methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(PToVa)bz | Copper(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(PToVa)im | Copper(II) imidazole complex of 3-methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PToVa)bz | Nickel(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PToVa)im | Nickel(II) imidazole complex of 3-methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| EToVa | 3-Methoxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(EToVa)bz | Copper(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Cu(EToVa)im | Copper(II) imidazole complex of 3-methoxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Ni(EToVa)bz | Nickel(II) benzimidazole complex of 3-methoxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Ni(EToVa)im | Nickel(II) imidazole complex of 3-methoxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| MTDiOH | 3-hydroxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MTDiOH)bz | Copper(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Cu(MTDiOH)im | Copper(II) imidazole complex of 3-hydroxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Ni(MTDiOH)bz | Nickel(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| Ni(MTDiOH)im | Nickel(II) imidazole complex of 3-hydroxy salicylaldehyde-4-methyl-3-thiosemicarbazone |
| PTDiOH | 3-hydroxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Cu(PTDiOH)bz | Copper(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |

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| | |
|---|---|
| Cu(PTDiOH)im | Copper(II) imidazole complex of 3-hydroxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PTDiOH)bz | Nickel(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| Ni(PTDiOH)im | Nickel(II) imidazole complex of 3-hydroxy salicylaldehyde-4-phenyl-3-thiosemicarbazone |
| ETDiOH | 3-hydroxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Cu(ETDiOH)bz | Copper(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Cu(ETDiOH)im | Copper(II) imidazole complex of 3-hydroxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Ni(ETDiOH)bz | Nickel(II) benzimidazole complex of 3-hydroxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |
| Ni(ETDiOH)im | Nickel(II) imidazole complex of 3-hydroxy salicylaldehyde-4-ethyl-3-thiosemicarbazone |

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# CHAPTER I

# INTRODUCTION

## 1.1 Imidazole and Benzimidazole – Structure and Historical Background

Imidazole and benzimidazole (numbering system is given in Figure 1.1) are classified as amphoteric compounds in which they are able to accept a proton at N-3 as a strong organic base and are capable of losing a proton from N-1 as a very weak acid. In the neutral condition, they may act as a ligand where coordination with other atoms takes place through the unshared pair of electrons at N-3. Due to the delocalization of electrons throughout the π-system, bonding via N-1 is unfavorable since there is no unshared electron pair at the pyrrole nitrogen. Thus, the activity of imidazole and its derivatives in coordination sphere are mainly related to the basicity and modest electron acceptor behavior (Curini *et al.*, 1990).

Imidazole and benzimidazole are important pharmacophores and find importance in medicinal chemistry (Walia *et al.*, 2011). Imidazole-based compounds are very special since they are a mimic of the histidine moiety and its metal complexes have potential covalent binding abilities towards biomolecules (Heijden *et al.*, 1993). The nitrogen donor atom of imidazole is the primary metal binding site as well as the most common binding site in metalloenzymes. When metal ions react with imidazole, the π-acceptor properties of imidazole ring will produce metal complexes with higher relative stability compared to other most common diamines (Savago *et al.*, 2002). The metal binding ability of the ligands is expected to be enhanced by the existence of the imidazole residue which coordinates *via* the equatorial position.

Although it is well known that reaction between first row transition metal ions with imidazole and benzimidazole would result in a new metal-nitrogen bond, Sundberg *et al.*, (1977) tried to investigate if a carbon-metal bond could form *via* that reaction. There is no evidence that the C(2) proton of the imidazole ring would deprotonate to react with the first-row transition metal ions and the carbon complexation *via* imidazolium ylide species was hence forbidden.

Benzimidazole is also known as benziminazole or benzoglyoxaline. It has been also called as methenyl-*O*-phenylenediamine which is a derivative of *O*-phenylenediamine.

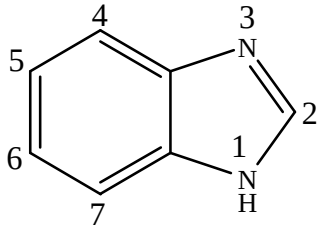


**Figure 1.1: Structure of benzimidazole**

The tautomerism of benzimidazole (Figure 1.2) occurs between the hydrogen atom attached to nitrogen in the 1-position and the unsaturated nitrogen atom at the 3-position (Day, 1950).

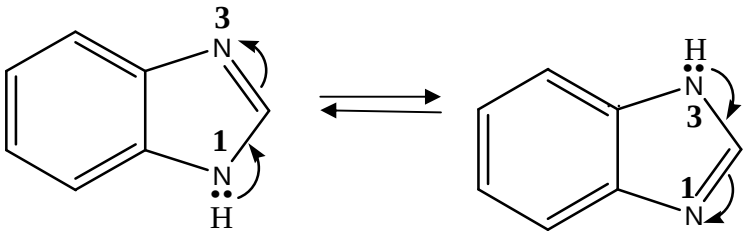


**Figure 1.2: Tautomerism of benzimidazole**

Benzimidazole moiety (in dotted circle) has also known to exist in nature, for example in Vitamin B12 (Figure 1.3). The *N*-ribosyl-dimethylbenzimidazole in Vitamin B12 is coordinated in an axial position which acts as a ligand towards the central cobalt atom.

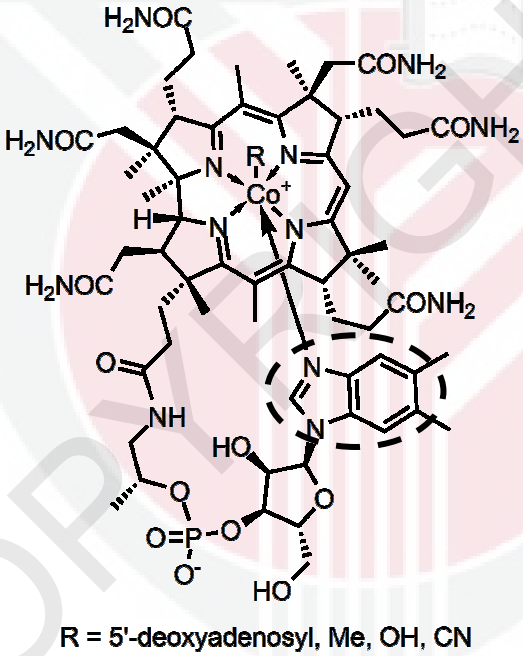


**Figure 1.3: Structure of Vitamin B12 (Hodgkin *et al.*, 1956)**

On the other hand, there are several benzimidazole-based drugs which already in use as proton pump inhibitors, (Figure 1.4a & 1.4b) to treat gastroesophageal reflux disease, gastric and duodenal ulceration (Miner *et al.*, 2003). Antihelminthics drug, mebendazole (Figure 1.5) is also one of the benzimidazole-based drugs which is readily available today (Borgers *et al.*, 1975). Thiabendazole (Figure 1.6) was a chosen drug for the treatment of fungus *Strongyloides stercoralis* which is also derived from benzimidazole (Gann *et al.*, 1994).

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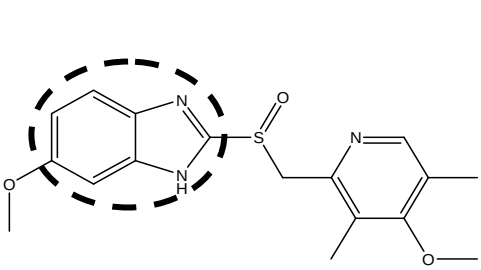
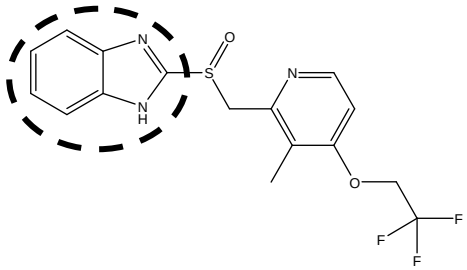



**1.4a: Omeprazole**




**1.4b: Lansoprazole**

**Figure 1.4: Examples of benzimidazole-based proton pump inhibitors**

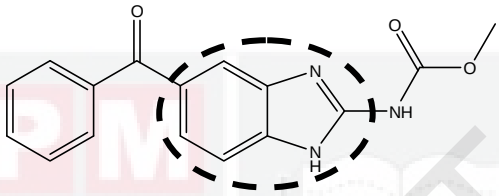



**Figure 1.5: Antihelminthics drug, mebendazole**

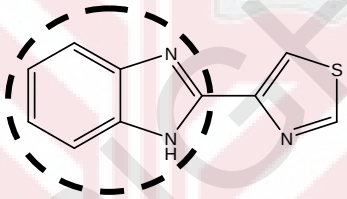



**Figure 1.6: Benzimidazole-based antifungal drug, thiabendazole**

The ability of imidazole and benzimidazole to act as a ligand when coordinating with metal ions has attracted researchers to synthesize many compounds containing imidazole derivatives in to design new drugs with potential biological applications. Besides, several studies on benzimidazole-based compounds has been proven to have significant use in the pharmaceutical industry. Therefore, the use of imidazole and benzimidazole in this research is hoped to produce new mixed-ligand metal complexes containing tridentate ONS Schiff bases with potential biological properties.

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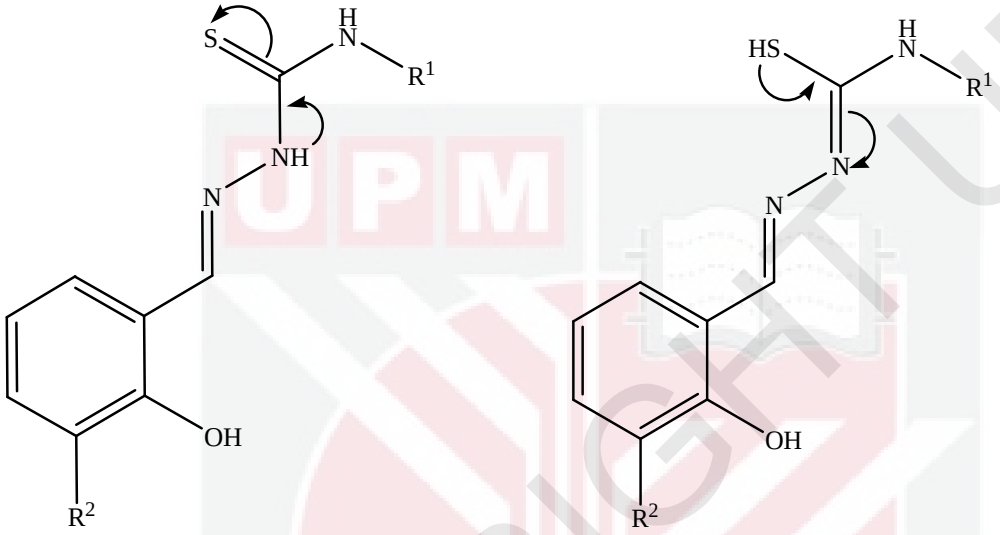
## 1.2 Tautomerisme of the Schiff Bases

The Schiff base compounds make up an important class of ligands which have been extensively studied in coordination chemistry due to their uncomplicated synthesis process and easily modifiable properties (Ispir and Serin, 2008). The Schiff bases derived from thiosemicarbazide are known to have –NH-C(S)NR thioamide functional group which exhibits tautomerism, characteristic of the Schiff bases. The thione-thiol tautomerism of the Schiff bases is illustrated in Figure 4.1.




**Thione form** **Thiol form**

**Figure 1.7: Thione-Thiol Tautomerism of the HONS Schiff Bases**

**$R^1$ = $CH_3$/ $CH_2CH_3$/ $C_6H_5$, $R^2$ = H/ $CH_3$/ $OCH_3$**

Although the Schiff base is expected to exhibit this tautomerism, previous studies of related metal complexes containing HONS Schiff bases (Tarafder *et al.*, 2002) suggested that the thione form of the Schiff base is the major tautomer in solid state. This was evidenced by the disappearance of $\nu$(SH) band at approximately 2570 $cm^{-1}$ in the IR spectra of metal complexes. However, the Schiff bases were quickly converted to the thiolate form when they were dissolved in a solvent to form the metal complexes.

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## 1.3 Problem Statement

Breast cancer is an uncontrolled growth of breast cells. The term “breast cancer” refers to a malignant tumor that has developed from cells in the breast. Breast cancer is the most common cancer diagnosed among women. It is also the second leading cause of cancer death among women after lung cancer. These facts have led researchers to continuously synthesized new drugs formula to treat breast cancer in women, especially older women, who are of higher risk. There has been an increasing interest to synthesized new compounds which can be potentially used as a breast cancer drug.

Previously synthesized complexes derived from thiosemicarbazones have shown good biological activities. In order to contribute to this scope of research, several new mixed-ligand metal complexes derived from tridentate ONS Schiff bases and imidazole or benzimidazole have been synthesized. Thus, it is hoped that these mixed-ligand metal would posses good activities towards breast cancer cell lines.

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## 1.4 OBJECTIVES

The objectives of this project are:

1. To synthesize mixed-ligand metal complexes containing tridentate ONS Schiff bases with imidazole or benzimidazole
2. To characterize the new complexes by physico-chemical techniques, including elemental analysis, magnetic susceptibility and molar conductivity measurements, spectroscopic techniques, and single crystal X-Ray diffraction analysis for crystallized compound
3. To evaluate the cytotoxicity of the synthesized compounds against MCF-7 and MDA-MB-231 breast cancer cell lines

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