SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF Ag(I) COMPLEXES WITH MIXED THIAZOLIDINE AND MONO-, BI-DENTATE PHOSPHINE LIGANDS

NUR RAHIMAH FITRAH BINTI MOHD SOFYAN

FACULTY OF SCIENCE
UNIVERSITY OF MALAYA
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NUR RAHIMAH FITRAH BINTI MOHD SOFYAN

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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF Ag(I) COMPLEXES WITH MIXED THIAZOLIDINE AND MONO-, BI-DENTATE PHOSPHINE LIGANDS

ABSTRACT

Five silver(I) complexes containing mixed ligand system of phosphine and thiazolidine were successfully synthesized. The structural information of the complexes was assembled using various spectroscopic techniques such as CHN elemental analysis, Fourier Transformed Infrared (FTIR) spectroscopy, ^{1}H, ^{13}C, and $^{31}P\{^{1}H\}$ NMR spectroscopy and thermogravimetric analysis (TGA). A bindetate phosphine ligand acted as chelating agent which bond to the Ag in 1:2 molar ratios. Meanwhile, thiazolidine was attached to the Ag in a 1:1 molar ratio. The antiplasmodial properties of all synthesized complexes were investigated on chloroquine resistant *P. falciparum* parasite via HRP2 assays and cytotoxicity tests on MDBK cells. Of all the synthesized complexes, complex **2** showed the highest SI value (> 12.279) followed by complex **5** (5.218). The potent properties of compounds **2** and **5** were also noted in the *in vitro* antiproliferative assays involving MDA-MB-231 and MCF-7 breast cancer cell lines as well as HT-29 colon cancer cell line. Complex **2** was selective for MDA-MB-231 cells (GI_{50} = 1.957 ± 0.347 μM), while complex **5** acted predominantly on breast carcinoma cells (GI_{50} MDA-MB-231 = 9.328 ± 2.162 μM; MCF-7 = 5.784 ± 1.821 μM) instead of colon carcinoma (HT29) cells (GI_{50} = 30.220 ± 3.744 μM).

Keywords: thiazolidine, silver complexes, antimalarial, anticancer, phosphine

SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BAGI KOMPLEKS Ag(I) BERSAMA CAMPURAN LIGAN TIAZOLIDINA DAN MONO-, DWI-DENTAT FOSFINA

ABSTRAK

Lima kompleks Ag(I) yang mengandungi campuran ligan fosfina dan tiazolidina telah berjaya disintesis. Pelbagai teknik spektroskopik digunakan untuk mengumpul informasi mengenai struktur kompleks seperti analisis unsur CHN, spektroskopi Inframerah Fourier Transformasi (FTIR), ^{1}H, ^{13}C, dan $^{31}P\{^{1}H\}$ spektroskopi NMR dan Analisis Termogravimetrik (TGA). Ligan dwi-dentat fosfina bertindak sebagai kelat yang terikat pada logam Ag dengan nisbah 1:2 manakala tiazolidina bercantum pada logam Ag dengan nisbah 1:1. Kesemua ligan tiazolidina dan kompleksnya telah diuji keupayaan biologinya sebagai antiplasmodial menentang klorokuina terhadap parasit P. *falciparum*; cerakin HRP2 serta ujian kesitotoksikan pada sel MDBK. Di antara kesemua kompleks yang telah disintesis, kompleks **2** mempunyai nilai indeks selektif yang terbaik (>12.279) diikuti kompleks **5** (5.128). Selain itu, potensi keberkesanan asai antiproliferatif *in vitro* bagi kompleks **2** dan **5** juga dinilai dengan menggunakan sel kanser payudara MDA-MB-231 dan MCF-7 beserta sel kanser kolon HT-29. Kompleks **2** memilih untuk merencat pertumbuhan sel MDA-MB-231 (GI_{50} = 1.957 ± 0.347 μM) manakala kompleks **5** lebih kuat merencat pertumbuhan karsinoma payudara (GI_{50}: MDA-MB-231 = 9.328 ± 2.162 μM; MCF-7 = 5.784 ± 1.821 μM) berbanding karsinoma kolon, (HT29) sel (GI_{50} = 30.220 ± 3.744 μM).

Kata kunci: tiazolidina, kompleks argentum, antimalarial, antikanser, fosfina

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Thank you so much.

"O my Lord, increases me in knowledge." [Taha: 114]

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LIST OF SYMBOLS AND ABBREVIATIONS

Anal.Calc	:	Analytical calculation
CC_{50}	:	Cytotoxic concentration of the extract to cause death
dppe	:	1,2-bis(diphenylphosphino)ethane
dppf	:	1,1-bis(diphenylphosphino)ferrocene
dppm	:	1,2-bis(diphenylphosphino)methane
EC_{50}	:	Concentration of a drug achieve that desire effect
EDX	:	Energy-dispersive X-ray spectroscopy
FTIR	:	Fourier Transformed Infrared
GI_{50}	:	Growth inhibition of compound on cancer cell
IC_{50}	:	Concentration of an inhibitor
m.p.	:	Melting point
NMR	:	Nuclear Magnetic Resonance
O.D.	:	Optical density
PPh_3	:	Triphenylphosphine
RBC	:	Red blood cell
TGA	:	Thermogravimetric Analysis

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CHAPTER 1: INTRODUCTION

1.1 Research background

Thiazolidine is one of the compounds which show a good potential in various biological activities (Tunçbilek & Altanlar, 1999; Verma & Saraf, 2008). Based on the analysis and database from National Cancer Institute (NCI, USA), approximately about 42,247 compounds which consist of 734 non-fused and 146 fused thiazolidine derivatives are active in three tumor cell line assay. Adding to that, five-membered heterocyclic ring systems such as thiazolidin-4-one (Rojas Ruiz et al., 2011), thiazole (Karade et al., 2008), 1,3,4-thiadiazole (Foroumadi et al., 2005) and pyrazoline (Insuasty et al., 2013) also reported to have beneficial biological activities against malaria.

Malaria is a parasitic disease that has favorable condition particularly in the tropical country. In 2010, over one million deaths were reported because of malaria (Sullivan et al., 2015). However, the rise of a few critical issues on combating malaria such as lack of effective vector control and vaccines (White, 2004), the limitations and toxicity of the commercially available antimalarial drugs (Fidock et al., 2004) and the spread of an antimalarial drug-resistant cases (Noedl et al., 2002) had encouraging the development of more effective and less toxic new antimalarial drugs with perhaps possessing a different mechanism of action.

On a different awareness, cancer is also reported as one of the uncontrolled and speedy pathological proliferation of abnormal cell diseases that causes around 550,000 deaths per year around the globe (Nepali et al., 2014; Noolvi et al., 2012) which can invade, spread and growth in any part of the body (Sung et al., 2011). The failure to control the disease may appear as one of the most eminent reason for its lethality since until now the cure for cancer is almost none discovered or reported (Gupta et al., 2013).

Therefore, there is a critical needs to explore and develop a new classes of substances with selective action against cancer cells to at least offer solutions for the prominent problems (Varmus, 2006).

Since thiazolidine ligands are heterocyclic, a lot of researches have shown that the heterocyclic substituent in organometallic and coordination chemistry where the biocompatibility of the adjoined system greatly assists in enhancing biological activities. For example, pure silver metal is biologically inactive, meanwhile imidazole that is another class of nitro-heterocyclic without the *S*-donor atom as compared to thiazolidine ligand portrayed a good activity against pathogenic microorganisms; and interestingly, the activity was enhanced with the presence of silver ions (Kalinowska-Lis et al., 2015). Due to this, it is worth noting that metals play a role in improving the efficiency and enhancing the potential between organic and metal drugs based on the ligand-metal bonding.

Hence, the resurgence on the research and application of silver(I) complexes has greatly been reviewed as a leading candidate in fighting various infectious diseases (Carter et al., 2010; Kascatan-Nebioglu et al., 2007). The growth of a new metallotherapeutic drug by using silver coordination compound gives many benefits to human body because of its low toxicity (Ahmad Khan et al., 2014). Although cisplatin had such a high success rate, the uses of cisplatin were limited due to some side effects and toxicity (Florea & Büsselberg, 2011; Jamieson & Lippard, 1999). In the approach to find the new compound, the presence of silver(I) complexes with ligands that contain various types of donor atom such as nitrogen, phosphorus and sulphur were believed to be significant in anticancer activities (Banti & Hadjikakou, 2013). On the other hand, the commercial antimalarial drug, chloroquine did show ineffectiveness due to parasite resistance (Hemmert et al., 2013). Consequently, to overcome the limitations of

cisplatin and CQ, we investigated another form of metal-based drugs which are less harmless and more effective by using silver complexes with bioactive thiazolidine and phosphine ligand.

Even though malaria and cancer are totally different diseases with different symptoms, surprisingly; it is possible to cure both diseases using the same drug since it shares a similar mechanism of action for their manifestation and the mechanistic pathway for the treatment (Hooft van Huijsduijnen et al., 2014; Kundu et al., 2015). From recent research, there are also a number of anticancer drugs that display potent antimalarial properties (Nzila et al., 2010). Hence, we attempt to discover drugs that can apply and act as both, an agent for anticancer and antimalarial.

In this research, we report the preparation of the silver(I) complexes with thiazolidine and different phosphine ligands along with its *in vitro* antiplasmodial and antiproliferative activities, in five chapters. Chapter **1** gives the overview, objectives and problem statement of the research; Chapter **2** cover the literature study and careful discussion on the research development in the stated field such as ligands and metal complexes in biological applications, Chapter **3** involves experimental procedures to synthesizing ligand and metal complexes, instrumental technique to characterize ligands and complexes and also biological procedures for antimalarial and anticancer meanwhile Chapter **4** outline the outcome of our works and discuss the results in details. The overall summary and suggestions for future work will be concluded in chapter **5**.

1.2 Objective and scopes of research

In sight of our attention in the growth of coordination chemistry of silver(I) nitrate, we have studied complexes with phosphine and heterocyclic ligands, namely, thiazolidine. Thus, in this research, our main attention is to study the structural chemistry and application of silver complexes with thiazolidine along with mono- and

di-phosphine ligands. Furthermore, the synthesized were tested against selected cell in order to examine its properties of antimalarial and anticancer. It is very remarkable to explore on the interaction of the molecular structures of Ag(I) complexes with a mixture of N, S, and P donor ligands and the development of their variation in physical designation, chemical properties and biological aspects.

1.3 Problem statement

A significant researches about metal complexes as drug agents have been widely exposed. However, despite recent advances in treatment modalities like medicine, surgery or chemotherapy, there are still insufficient treatments for antimalarial and anticancer disease. The determination for the improvement of new metallotherapeutic agents was rising given that, the high rate of existence and mortality of disease; the reduced bioavailability of some drugs agents; and the increased of resistance against many conventional drugs. In order to overcome the limitations, we focus to design another form of multi targeted metal-based drugs depends on several factors like simpler method, safer compounds, more efficacy and selectivity complexes with bioactive ligands towards malaria and cancer disease.

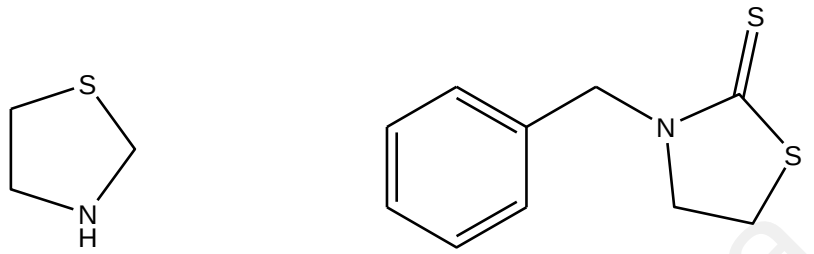
CHAPTER 2: LITERATURE REVIEW

2.1 Thiazolidine

Carbenes are unstable and reactive molecule that contains a divalent carbon atom bearing two valence electrons. It can be stabilized by the presence of single or a couple π-donors neighboring atom for example, nitrogen into the empty orbital of the carbene carbon atom (Kovac et al., 2015). Over the past twenty years, a great effort has been given to study the properties and applications of N-heterocyclic carbenes (NHCs) and their metal complexes which exhibit different electronic or steric properties (Lin & Vasam, 2007). From research, the N-heterocyclic carbenes (NHC) such as free, stable and crystalline carbine of imidazoline-2-ylidene have become high affinity classes of ligands in the chemistry of transition metals complexes due to the versatility of electron density and sterics effects (Hollóczki et al., 2011; Muñoz et al., 2012; Schumacher & Goldfuss, 2015)

Heterocyclic compounds are one of the fundamental parts in organic chemistry and establishing in modern research field that currently being hunted by many researchers (Lobana et al., 2013). Since N-heterocyclic ligands play an important role in chemical reactions, it is interesting to investigate a combination of NHC-based ligands featuring the thione functionality (Slivarichova et al., 2011). Thiones compound have widely being used as ligands when synthesizing metal complexes because it is one of the most interesting heterocyclic ligand connecting the chemically active groups of –N(H)-C(=S)-, -N=C(-SH)-, N(H)-C(=S)-N(H)- or –N=C(-SH)-N(H)- (Aulakh et al., 2018; Lobana et al., 2008). These heterocyclic thio-ligands moiety were reportedly to have biochemical significance and uses in medicinal chemistry or pharmaceutical field such as anticancer, antifungal, and antibacterial (Aneja et al., 2011; Mentese et al., 2009; Qiu et al., 2010).

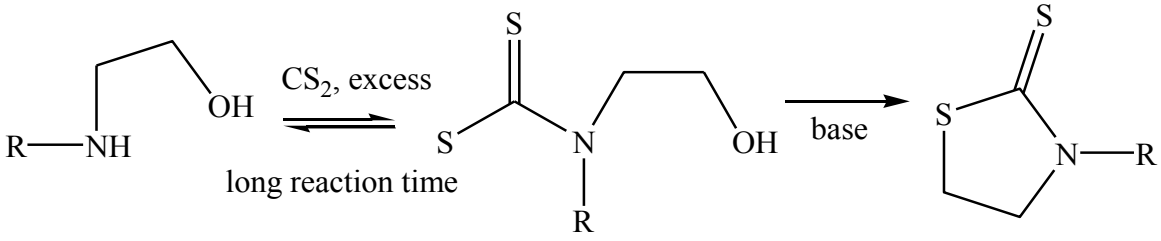
Thiazolidine (**Figure 2.1(a)**) is a five-membered heterocyclic organic compound that consists of thioether and amine in 1 and 3 position; in this research 3-benzyl-1,3-thiazolidine-2-thione is used as a ligand as shown in Figure **2.1(b)**.



(a) Thiazolidine (b) 3-benzyl-1,3-thiazolidine-2-thione

Figure 2.1: Type of heterocyclic ligands

Five-membered heterocyclic thiazolidine-2-thione rings constitute an essential class of organic compounds. The thiazolidine-2-thiones can be acquired from an alcohol, a primary amine and hydrogen sulfide or from a *β*-amino alcohol precursor by condensation with thiophosgene or carbon disulfide (Delaunay et al., 1995; Medini et al., 2015). In the latter method, dire conditions are required such as excess of CS_2, basic media and heating over extended period of time as shown in Scheme **2.1**. In recent times, amino acids have become popular chiral auxiliaries in asymmetric synthesis since they can be either identical or even more effective chiral inductors predominantly after the chiral transformation has been attained that represent as a major aspect of cyclic system particularly five-membered rings (Ager et al., 1996; Panzariu et al., 2016).



Scheme 2.1: General procedures of synthesizing thiazolidine-2-thiones

The miscellany in the biological response of the heterocyclic thiazolidine derivatives had enticed the attention of many multi-field researchers for a thorough exploration of their potential. For instance, thiazolidine-2-thiones are also applied in the synthesis of substituted taurines (Chen et al., 2009). Thiazolidine ring was identified as a crucial innovation for enhancing drug mechanism such as penincilin, a β-lactam antibiotic group on the inhibition of the bacterial cell wall synthesis (Frere et al., 1976; Sheehan & Panetta, 1973). Besides, thiazolidine derivatives such as thiazolidinones gain wide attention from researcher as promising anticancer agents (Romagnoli et al., 2013). Other than that, the commanding structural behaviour that comprise in the heterocyclic thiazolidine has also attracted attention to explore its potential as antimalarial agent (Solomon et al., 2005).

2.2 Silver complexes with NHC and phosphine ligand

Some metals are applicable in catalytic and polymerization purposes and also show remarkably applications in metal-based drugs such as silver. Recently, it has been a great interest in transition metal complexes which can modify DNA by intercalation, groove binding and external static electronic effects and lead to have possible application as biological tools and cancer therapeutic agents (Morshedi & Hadadzadeh, 2013; Vranec et al., 2014). Most agents inhibit the growth cancer cells by direct damage to DNA and disrupting the flow of the genetic information (Parveen et al., 2014; Wu et al., 2015)

A lot of research has proven that, metals can affect the pharmacological properties of organic-based drugs through coordination complexes which depend on the function of the metal and ligands moieties itself (Oehninger et al., 2013). This metal-based can be divided into a few categories; a ligand is biologically active, the metal complexes is active in its inert and reactive form, some of the fragment in the complex and the

product is active or the compound contains a radioactive metal and the metal act as enhancer in radiation (Hambley, 2007). Besides, silver is not classified as an endogenous metal towards human body; hence, silver is recognized for being valuable probes in biological systems such as antimicrobial agents since it demonstrate relatively low toxicity (Melaiye et al., 2004; Melaiye et al., 2005; Ray et al., 2007).

Silver(I) complexes are chosen to be versatile components because of its metal coordination number allowing the different kind of geometry ranging from linear, square planar, tetrahedral or octahedral (Steel & Fitchett, 2008; Zhou et al., 2008). Designing and synthesizing these distinct metal complexes node has been challenging especially when metal that act as centre with ligands that consist of nitrogen, sulfur and phosphorus, since Ag(I) possesses high affinity towards these donor atoms (Kole et al., 2013).

To our concern, metal complexes with heterocyclic ligands are commonly used in catalysis but additionally it is also studied for medicinal significance in antimicrobial, antimalarial as well as anticancer (Coetzee et al., 2011; Hindi et al., 2009; Patil et al., 2010). Current reports have portrayed the potential mode of action of metal group-NHC based drug-like candidates as the metal centers emerge positive results in DNA replication, condensation, fragmentation and also altering migration of the cell (Kehua & Enjun, 2014; Pages et al., 2015). Ag(I)-NHC complexes have presented significance role in this field compared to other NHC metals complexes (Budagumpi et al., 2013).

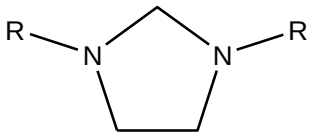
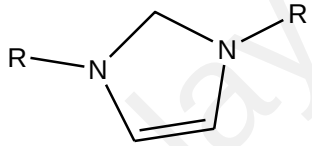
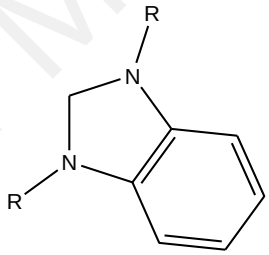
Variety of silver-NHC complexes can be divided into two categories which are functionalized and non-functionalized (Lorber & Vendier, 2009; Saha et al., 2012). It is believed that functionalized NHC salts are more stable due to chelating, steric, and electronic properties by manipulating the substituent as yearning depends on the σ-

donation from the NHC ligand to the silver center and the extent of back bonding from the silver center to the empty p-orbital of the NHC ligand (Ghdhayeb et al., 2017)

Many syntheses of platinum based complexes have been biologically evaluated such as cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin and heptaplatin (Boulikas et al., 2007). However, the efficiency of these platinum cancer drugs is hampered due to some unwelcome negative side effects such as neurotoxicity, ototoxicity, anemia and nausea (Arany & Safirstein, 2003; Hamers et al., 1991; Yorgason et al., 2006). Therefore, it is expected that many researchers are concern to produce non-platinum complexes to overcome this impediments. Thus, one of the ways is by using silver compound that was proven as anticancer drug candidates with much lower toxicity and fewer side effects against cancer cell lines (Human et al., 2015; Medvetz et al., 2008).

Imidazolidin-2-ylidene, imidazole-2-ylidene and benzimidazol-2-ylidene as shown in Table **2.1** are imidazole-based and types of NHC structures used as the ligands in silver complexes.

Table 2.1: Types of imidazole-based

Types	Structures
Imidazolidin-2-ylidene	
Imidazole-2-ylidene	
Benzimidazol-2-ylidene	

Strangely, even if free imidazole ligands showed movement against pathogenic microorganisms, their action is additionally enhanced when react with silver ions. The mechanisms of the silver(I) compound presumably act synergistically in this situation (Jin et al., 2009; Kalinowska-Lis et al., 2015). It is known that, the slower the rate time of silver ions bind and interact with bacteria to damage the cell, the better the activities (Haziz et al., 2016). Since N-heterocyclic carbenes (NHCs) are strong σ-donating and weak π-accepting ligands, and Ag(I)–NHC complexes were proved to have ability to release silver ion slower compared to other current silver antitumor agent, thus this complexes can be used to overcome this problem (Liu & Gust, 2013).

With that approach, various Ag(I)–NHC complexes were synthesized and their various other biological activities have been investigated by the researchers. Heterocyclic thioamides can found in thioketo which referred as thiones and its corresponding anions as thionates. The thiones can bind with silver metals through their exocyclic S-atom (S_{exo}) due to their versatility in adopting monodentate, bridging and chelating modes of coordination (Garcia-Vazquez et al., 2000; Zhang et al., 2003).

Silver(I)-NHC complexes can be produce productively because they show exceptionally steady to air and moisture (Lin et al., 2009). Past findings have built up to three common approaches to synthesize silver(I)-NHC complexes. In the first method, treatment of free NHCs with appropriate silver sources, normally at liquid nitrogen temperature, yields desired complexes. The second way utilizes treatment of silver bases, such as Ag_2O, AgOAc, and Ag_2CO_3, among others, with azolium salts at ambient/high temperature. In this classical method, silver oxide act as base and metal source in aprotic solvents with stable reactants and produce high yield products in minimum reaction times (Hayes et al., 2007). However, this method is quite challenging and difficult to prepare $[Ag(NHC)_2]^+$ complexes with non-coordinating counter ions since NHC ligands might be as heteropletic or homoleptic complexes which depends on certain conditions that applied for conventional or functionalized types of NHC ligands (Beillard et al., 2016). Thus, other alternative ways to tackle this problem is by using $AgNO_3$ as the silver source and resulting heteroleptic complexes with a good yields. Lastly, the third technique involves treatment of silver salts with azolium salts under basic phase-transfer conditions (Visbal et al., 2013)

In addition, NHC ligands are also often applied together with phosphine-based ligands. However, NHC ligands are commonly believed as better σ-donors and weaker π-acceptors compared phosphine ligands as for electronic purposes (Swor et al., 2011).

Since NHC have abilities to act as donor electron which are more stronger than phosphine ligands, thus relation between both ligands can create excellent combination ligands to stabilize complexes such as silver-NHC(I) as monomeric drugs candidates (Browne et al., 2014; Sharkey et al., 2012).

In recent years, a huge number of data with the structural and kinetic features of Ag(I)-phosphine complexes have been published (Burgoyne et al., 2010; Meijboom et al., 2009). Based on Hard Soft Acid Base (HSAB) concept, Ag(I) can coordinate to S donor atom because the Ag(I) is categorized as soft acid meanwhile S is soft bases character (Pearson, 1995). 'Soft' refers to species which have low charge states and strong polarized while 'hard' is vice versa. In summary, soft acids react faster and form stronger bond with soft bases. Hence, various heterometallic or bimetallic coordination containing Ag(I) have been successfully synthesized exhibit a variety structural motifs (Fan et al., 2011; Schoedel et al., 2011).

Numerous mono- and di-phosphine derived ligands plays an important key role of compound because of their coordination behaviour with silver and other transition-metal ions produce different structural geometries and tend to have lipophilic properties (Tharmaraj et al., 2009). It is important to choose the right phosphine ligands to bind with metal because phosphine ligands are soft bases, posses as a strong σ-donors and their steric capabilities and the coordination mode are different depends on the substituent bonded to the phosphorus. For example, diphosphine ligands are well-known for their good chelating capabilities with transition metals, which could tailor the stability and reactivity of the complexes (Horak et al., 2015). A subclass of these is small bite-angle diphosphines in which the two phosphorus centers are separated only by a single atom linker unit, example bis(diphenylphosphino)methane (dppm).

First silver-phosphine (Ag:P) complexes were reported in 1937 and commonly the reactions are between silver salt and phosphine ligands with suitable amount of ratios, for example 1:1, 1:2 or 1:3 (Mann et al., 1937; Teo & Calabrese, 1976). In general, silver-phosphine complexes can form 4 coordination numbers but it may changes depending on the type and bulkiness of the phosphine ligand. Ag-P compounds also were tested in *in vitro* activity against multiple cell lines such as breast carcinoma, breast adenocarcinoma, or colon carcinoma (Potgieter et al., 2016). According to McKeage, Ag-P complexes were capable to break cisplatin-resistant cell lines and were claimed to be active anticancer agents besides cisplatin (Liu et al., 2008).

An extra preferred standpoint of utilizing silver coordination complexes in the advancement of new metallotherapeutic drugs is their low harmfulness to people. In any case, this component additionally brings up the issue of whether such complexes, when the best possible ligands are available which affect the thermodynamic, kinetic stability plus influencing its solubility and lipophilicity. Nonetheless, many articles that concentrates on silver(I) complex containing different kinds of ligands, such as amino acids, carboxylic acids, nitrogen, phosphorus or sulfur ligands which had shown specific impacts against a wide range of tumor cells (Md Yusof et al., 2015).

A vast literature study towards metallodrugs in the past few years have demonstrate how eager researchers in this stimulating area. Inspired by the promising potentials in metallodrugs applications, numerous structures of Ag(I) complexes have been produced due to multifarious coordination designs and easy preparation in inorganic procedure compare to organic synthesis which usually involve in more steps.

2.3 Antimalarial

Malaria is a parasitic disease which constitutes major impacts on health that leads to severe illness and death (Jain et al., 2002). Eventhough the number of cases was

reduced as reported in 2015, malaria still a highly prevalent disease in some countries like sub-Sahara Africa, Latin America and Asia (Alba et al., 2003; Rai et al., 2017) .

The discovery of designing new novel drug to tackle malaria diseases is somehow a bit complicated due to the requirement to meet certain criteria such as; the targeted process must be absent or slightly different between the parasite and host cell, the targeted process must be essential for parasite growth *in vivo*, the presence of antigen or receptors on the surface of the parasite, the total in sequence about receptors that present on the infected cells and can reach targeted organ, tissue or cells (Ridley, 1997; Ziegler et al., 2001). Thus, the availability for safety, affectivity and essential biochemical targets must be identified.

Malaria is primarily caused by four species of the protozoan parasites belonging to the *Plasmodium* genus (*P. falciparum, P. vivax, P. malariae,* and *P. ovale*) which are transmitted through female *Anopheles* mosquitoes bite (Kumar et al., 2014; Walker et al., 2018). Out of the four species of parasites, P. *falciparum* is the predominant species which responsible for causing human population's death (Jain et al., 2004).

The malaria parasite has a complex life cycle consists of three general stages. The malarial infection begins with an insertion of *Plasmodium* sp. into human body by mosquitoes during a blood meal and then contaminates the bite site with saliva containing malaria sporozoites (Winzeler, 2005). After the infection, the parasites were carried by the circulatory system to the liver (hepatic stage) and rapidly reproduce for approximately 48 to 72 hours (Gazzinelli et al., 2014). The parasites then burst from the liver, enter the bloodstream, and within minutes it will invade the host's erythrocytes (merozoite/intraerythrocytic stage), where they grow and divide passing through several morphological changes (ring stage, trophozoite stage, and schizont stage) (Bousema et al., 2014).

Furthemore, the merozoites were transformed into schizonts in the red blood cells, then mature into merozoites, lyse the red blood cell, and released into the circulation (the erythrocytic cycle). After that, the rupture red blood cells dispersing more parasites in the merozoite stage along with waste products and toxins into the bloodstream (Kerlin & Gatton, 2013).

Nonetheless, in every cycle, not all merozoites will reinfect the erythrocytes to form schizonts; some of the invading parasites tend to develop into gametocytes, male or female (sexual forms) that are subsequently ingested by uninfected mosquitoes wherein the parasites reproduce (Kumar et al., 2018). These parasites then will make their way to the salivary glands of the mosquito, ready to move into another animal host with the next biting. The stages happen in continuation to other blood cells, re-launching the cycle repetitively (Yang & Boddey, 2017).

Since the infection of malaria disease results in an extensive variety of symptoms, ranging from absent or mild symptoms to severe illness or even death, therefore, new medicines is urgently design where the drugs need to be active, efficient, relatively cheap, speedily efficacious, and safe in all age groups. Hence, in this research work, we aim to develop new potential drugs from Ag-NHC-Phosphines complexes that resistance against parasite compare to conventional antimalarial drugs like chloroquine, mefloquine and other frontline drugs for the treatment and prevention of malaria.

2.4 Anticancer

Cancer can refer as a disease affecting any cells and tissues in human body (Edwards et al., 2005). Particularly, the biological process for the transformation of normal cells into malignant cancer cells has become one of vital research endeavors in the biomedical sciences (Kerru et al., 2017).

Most cancers are recognized by the uncontrolled growth and spread of abnormal cells due to the deregulation of vital enzymes and protein cell division and proliferation (Mareel & Leroy, 2003; Wesche et al., 2011). There are six unique characteristic traits for a cell to become cancerous which are i) the ability to generate their own growth signals or respond to weak growth signals that are ignored by healthy cells; ii) insensitivity to antiproliferative signals; iii) resistance to cellular suicide mechanisms that normally cause aberrant cells to die by apoptosis; iv) the capacity for limitless replication; v) the ability to stimulate new blood vessel development in order to allow for tumors growth; and vi) the capacity to invade tissues at the beginning and later to spread or metastasize throughout the body (Hanahan & Weinberg, 2011).

Cancer can be categorized as a versatile and multi-mechanistic disease where require unique treatment by using multi-target therapy as an alternative approach to overcome the problem. Studies show that metal complexes such as silver(I) complexes can react with various kind of donating atoms with its ligands for antitumor activities (Hadjikakou et al., 2008; Movahedi & Rezvani, 2018). They show selectivity towards DNA strand and act as a sensitive chemical probes for the structure of DNA (Barton, 1986; Tabassum et al., 2012). Other than that, in some cases, silver have shown more stable DNA-Ag complexes (DNA binding constants) in *invitro* antiproliferative action compared to cisplatin (Banti et al., 2012). Considering this, silver complexes stand out as good candidates for antitumor agents.

Other than that, N-heterocyclic ligand creates anticancer impacts in various sorts of tumor through apoptosis or restraining cell development and acceptance of cell separation (Akhtar et al., 2017). The compounds which consist of heteroatoms, for example, nitrogen, sulfur or oxygen can enhance the quality of the complex by forming hydrogen bonds with DNA. Furthermore, intercalating chromophore possesses a

polarized character and an optimal interaction take place if one or more nitrogen heteroatoms appeared on the structure (Özkay et al., 2010). Hence, Ag-NHC complexes show a promising biological activity to extent various selective cancer cell death such as human renal (Patil et al., 2011), colon/colocteral (Haque et al., 2013) and breast cancers (Chie-Hong et al., 2011).

In this aspect, depth study is require on structural characteristic of the complex such as the charges, shapes and trend of binding to nucleic acid interaction mode of complexes with DNA (Mathur & Tabassum, 2008). Since DNA interacts with small molecules is the primary intercellular target, thus it is a good probe for designing potential reagents for site-specific drugs. Thus, silver and thiazolidine might be reliable choice for incorporation into new anticancer drugs.

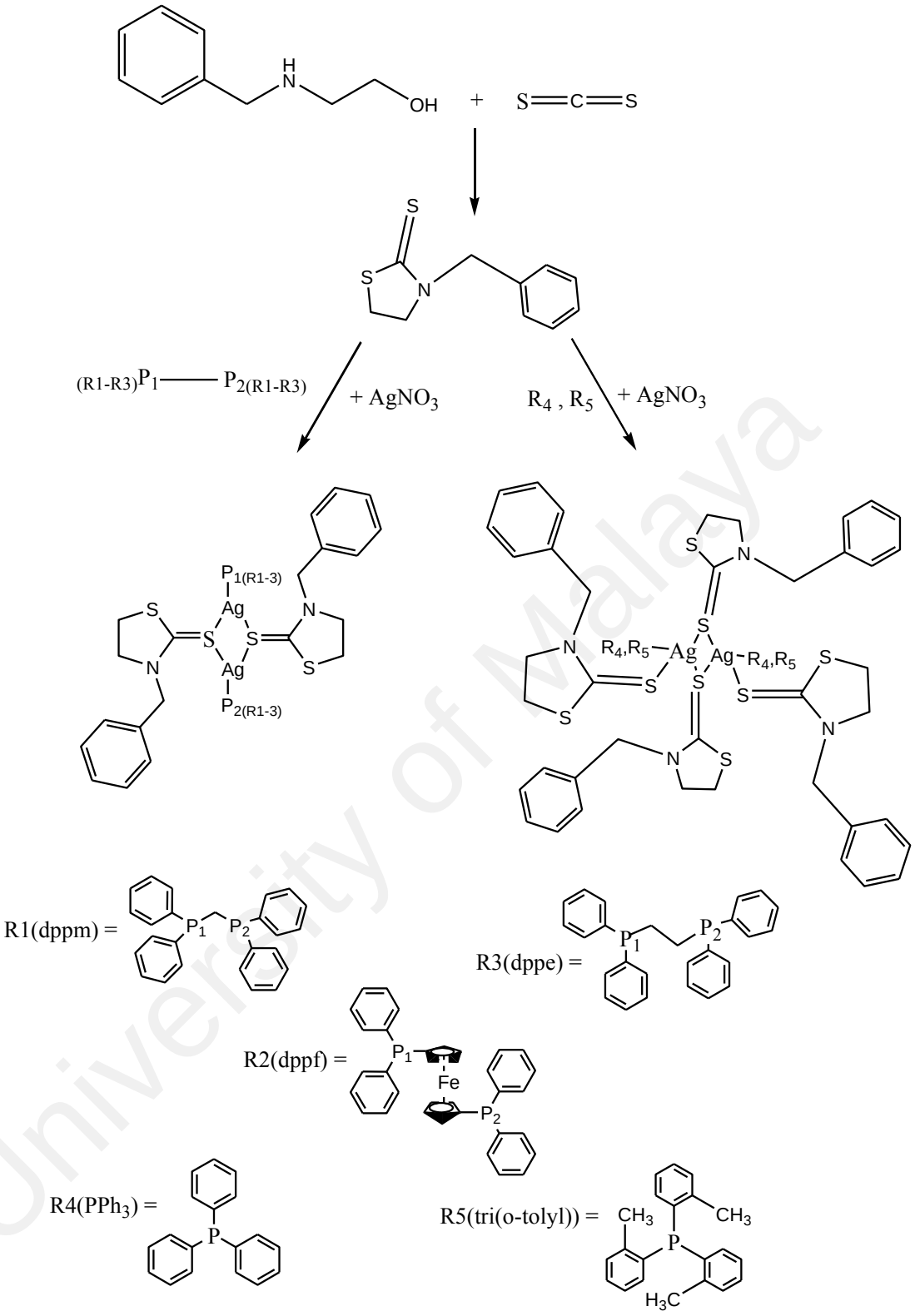
Despite major progress of conventional anticancer therapies such as chemotherapy or radiotherapy in the cancer treatment, the efficacy is determined by their direct or indirect effects on cancer cells between the host immune system which still remains as a challenge. Cytotoxic treatment regimens elicit several changes in immune-related parameters including the composition, phenotype, and function of immune cells (Coffelt & de Visser, 2015).

Herein, the development of various investigations focusing on the role of Ag–NHC-phosphine as metal-complexes as new class of anticancer drugs that lack toxicity compare conventional chemotherapeutic agents and are unaffected by common mechanisms of chemo-resistance would be a major advance in cancer treatment.

CHAPTER 3: METHODOLOGY

3.1 General preparation of ligand and silver complexes

The synthesis of silver complexes in this research was done in at least two steps of reaction. First, the 3-benzyl-1,3-thiazolidine-2-thione ligand was synthesized from benzylaminoethanol and carbon disulphide. Then, it was introduced to the silver that was pre-complexes with either mono-, or bidentate phosphine ligand. An overview of the overall procedure was shown in Scheme **3.1**. The experimental details are discussed further in this chapter.



Scheme 3.1: An overview procedures of synthesizing the ligand and complexes

3.2 Materials and instruments

All solvents and reagents were analytical grade and purchased commercially from Sigma Aldrich Ltd. The silver nitrate, 1,2-bis(diphenylphosphino)methane (dppm), 1,1-bis(diphenylphosphino)ethane (dppe), 1,1-bis(diphenylphosphino)ferrocene (dppf), triphenylphosphine (PPh_3), tri(o-tolyl)phosphine, ethanol, methanol and acetonitrile were used without further purification unless stated otherwise. The CHN analyses were obtained using Perkin Elmer CHNS/O 2400 Series II. The UV-visible spectra for solutions of the complexes were recorded with an Agilent Technologies Cary60 UV-VIS spectrophotometer in the region of 270-900nm using acetonitrile as solvent. The infra-red (IR) spectra were recorded on Perkin Elmer Spectrum One FT-IR spectrophotometer (ATR) within the frequency range of 450-4000cm^{-1}. The Nuclear Magnetic Resonance (NMR) spectra of ^{1}H, ^{13}C, $^{31}P\{^{1}H\}$ were obtained using JEOL FT-NMR ECX 400 (ECX 400) at 400 MHz in deuterated solvents without any internal reference used. The presence of silver metal and other elements were detected by Energy-dispersive X-ray spectroscopy (EDX). The thermogravimetric analyses were also carried out on a Perkin Elmer TGA 4000 Thermogravitmetic Analyzer at heating rate of 10°C/min.

3.3 Synthesis of 3-benzyl-1,3-thiazolidine-2-thione (L)

The thiazolidine ligand was synthesized according to a method reported in the literature with slight modifications (Alhamadsheh et al., 2007). Generally, benzylaminoethanol (10 mmol, 1.4 mL) was added dropwise into a solution of potassium hydroxide (50 mmol, 2.81 mg) in ethanol (50 mL). A clear solution was formed. Carbon disulfide (50 mmol, 3 mL) was added dropwise to the reaction mixture then refluxed (90 °C) for 18h. An orange precipitate was formed. The resulting precipitate was filtered off and left in the oven for overnight. The ligand was identified by elemental analysis and by their IR and NMR.

Yield, 88%, m.p. 132-133 °C. *Anal*. Calc. for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69; S, 30.64. Found: C, 56.86; H, 4.80; N, 6.34; S, 30.61. IR: ν(C-N) 1149, ν(C=S) 1242. ^{1}H NMR (ppm, CD_3CN): 7.37-7.25 (m, 5.41H, H-Ar); 4.93 (s, 2.07H, Ar-H_2-N); 3.95 (t, 2.01H, H_2-N); 3.23 (t, 2H, H_2-S). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 196.9 (C=S); 135-127 (C-Ar); 56.3 (C-N); 51.9 (N-C-Ar); 26.8 (C-S).

3.4 Synthesis of silver complexes

The complexes were prepared according to the following general procedure with slight modifications (Aslanidis et al., 2004). Two different molar ratios were used which are 2:1:2 and 1:1:2 (Ag: phosphine: thiazolidine).

For bidentate phosphine, a suspension of silver nitrate (2.00 mmol, 0.17 mg) and bis-(diphenylphosphino)methane [**R1**] (1.00 mmol, 0.19 mg), 1,1-bis(diphenylphosphino)ferrocene [**R2**] (1.00 mmol, 0.50 mg) or 1,2-bis(diphenylphosphino)ethane [**R3**] (1.00 mmol, 0.20 mg) in acetonitrile (10 mL) was stirred at 40 °C. A solution of 3-benzyl-thiazolidine-2-thione (2 mmol, 0.21 mg) in methanol (10 mL) was then added and the suspension changes colors. The resulting solution was filtered off and the clear filtrate solution was reduced to dryness.

While for monodentate phosphine (Sultana et al., 2010), a solution of silver nitrate (0.14 mmol, 0.02 mg) in acetonirile (10 mL) was added to a solution of 3-benzyl-thiazolidine-2-thione (0.28 mmol, 0.06 mg) in methanol (10 mL) followed by stirring at room temperature for a few hours. Then a solution of triphenylphosphine [**R4**] (0.14 mmol, 0.04 mg) or tri(o-tolyl)phosphine [**R5**] (0.14 mmol, 0.04 mg) in acetonitrile (5 mL) and methanol (5 mL) was added. The resulting solution was filtered off and was reduced to dryness.

3.4.1 (Ag_2 [R1] [3-benzyl-1,3-thiazolidine-2-thione]$_2$).(NO_3)$_2$ [1]

Yield, 67%, m.p. 165-166 °C. *Anal*. Calc: C, 53.05; H, 4.35; N, 2.75, and S; 12.59 Found: C, 52.64; H, 3.88; N, 2.30, and S; 12.12. IR data (cm^{-1}): ν(NO_3^-) 1310, ν(C-N) 1223, ν(C=S) 1152, ν(P-C_{ph}) 1094. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): 7.50-7.18 (m, 30H, H-Ar); 4.89 (s, 4.00H, Ar-H_2-N); 3.91 (t, 4.36H, *J* = 8 Hz, H_2-N); 3.67 (s, 2.09H, P-H_2-P); 3.13 (t, 4.24H, *J* = 8 Hz, H_2-S). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 196.7 (C=S); 136-128 (C-Ar); 56.6 (C-N); 52.3 (N-C-Ar); 26.8 (C-S); 25 (P-C-P). ^{31}P{^{1}H} NMR (400 MHz, CD_3CN, δ ppm): 5.2, 8.0 (s)

3.4.2 (Ag_2 [R2] [3-benzyl-1,3-thiazolidine-2-thione]$_2$).(NO_3)$_2$ [2]

Yield, 54%, m.p. 190-191 °C. *Anal*. Calc: C, 54.56; H, 4.24; N, 2.36, and S; 10.79 Found: C, 54.24; H, 3.92; N, 2.24, and S; 10.43.. IR data (cm^{-1}): ν(NO_3^-) 1307, ν(C-N) 1223, ν(C=S) 1163, ν(P-C_{ph}) 1095. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): 7.50-7.28 (m, 30H, H-Ar); 4.93 (s, 4.37H, Ar-H_2-N); 4.35 (s, 4H, H_α(cyclopentadiene)-Fe); 4.17 (s, 4.28H, H_β(cyclopentadiene)-Fe); 3.95 (t, 4H, *J* = 8 Hz, H_2-N); 3.11 (t, 4.32H, *J* = 8 Hz, H_2-S). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 197.1 (C=S); 135-127 (C-Ar); 74 (C_5H_4Fe); 72 (C-P-Ph); 57.1 (C-N); 52.5 (N-C-Ar); 27.3 (C-S). ^{31}P{^{1}H} NMR (400 MHz, CD_3CN, δ ppm): -1.4 (s)

3.4.3 (Ag_2 [R3] [3-benzyl-1,3-thiazolidine-2-thione]$_2$).(NO_3)$_2$ [3]

Yield, 55%, m.p. 156-157 °C. *Anal*. Calc: C, 53.49; H, 4.49; N, 2.70, and S; 12.42 Found: C, 52.98; H, 3.98; N, 2.61, and S; 11.89. IR data (cm^{-1}): ν(NO_3^-) 1307, ν(C-N) 1223, ν(C=S) 1153, ν(P-C_{ph}) 1097. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): 7.42-7.22 (m, 30H, H-Ar); 4.88 (s, 4.01H, Ar-H_2-N); 3.92 (t, 4H, *J* = 8 Hz, H_2-N); 3.12 (t, 4.12H, *J* = 8 Hz, H_2-S); 2.46 (s, 4.15H, P-H_2-H_2-P). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 196.9 (C=S); 135-127 (C-Ar); 56.9 (C-N); 52.4 (N-C-Ar); 27.3 (C-S); 24 (P-C-C-P). ^{31}P{^{1}H} NMR (400 MHz, CD_3CN, δ ppm): 4.3 (s)

3.4.4 (Ag_2 [R4]$_2$ [3-benzyl-1,3-thiazolidine-2-thione]$_4$).(NO_3)$_2$ [4]

Yield, 54%, m.p. 135-136 °C. *Anal*. Calc: C, 57.86; H, 4.73; N, 3.55, and S; 16.26 Found: C, 57.45; H, 4.46; N, 3.10, and S; 15.73. IR data (cm^{-1}): ν(NO_3^-) 1314, ν(C-N) 1223, ν(C=S) 1154, ν(P-C_{ph}) 1092. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): 7.33-7.15 (m, 50.37H, H-Ar); 4.91 (s, 7.80H, Ar-H_2-N); 3.94 (t, 8H, *J* = 8 Hz, H_2-N); 3.18 (t, 7.88H, *J* = 8 Hz, H_2-S). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 196.9 (C=S); 136-127 (C-Ar); 56.4 (C-N); 52.1 (N-C-Ar); 26.9 (C-S). ^{31}P{^{1}H} NMR (400 MHz, CD_3CN, δ ppm): 8.3(s)

3.4.5 (Ag_2 [R5]$_2$ [3-benzyl-1,3-thiazolidine-2-thione]$_4$).(NO_3)$_2$ [5]

Yield, 37%, m.p. 144-145 °C. *Anal*. Calc: C, 59.27; H, 5.22; N, 3.37, and S; 15.54 Found: C, 58.83; H, 4.97; N, 2.94, and S; 14.97. IR data (cm^{-1}): ν(NO_3^-) 1315, ν(C-N) 1266, ν(C=S) 1160, ν(P-C_{ph}) 1129. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): 7.40-6.62 (m, 44.24H, H-Ar); 4.92 (s, 8H, Ar-H_2-N); 3.95 (t, 7.52H, *J* = 8 Hz, H_2-N); 3.21 (t, 8.35H, *J*= 8 Hz, H_2-S); 2.31 (s, 17.86H, H_3-Ar-P). ^{13}C NMR (400 MHz, CD_3CN, δ ppm): 197.1 (C=S); 143-126 (C-Ar); 56.4 (C-N); 52.1 (N-C-Ar); 26.9 (C-S), 20.5 (CH_3-Ar-P). ^{31}P{^{1}H} NMR (400 MHz, CD_3CN, δ ppm): -27.8, 37 (s)

3.5 Biological procedures

There are two tests for biological activities which are antiplasmodial and antiproliferative done by our research collaborator. Antimalarial assay were carried out at the Bioassay Unit, Herbal Medicine Research Centre, Institute for Medical Research by Dr. Mohd Ridzuan Mohd Abd Razak while for anticancer assay were carried out at the Faculty of Health Sciences, Universiti Kebangsaan Malaysia by Mrs. Fariza Juliana Nordin. The detail procedures of both biological activities are as described below.

3.5.1 *In vitro* culture and synchronization of P. *falciparum*

The CQ resistant P. *falciparum* were grown in 5% CO_2 incubator. The culture was set up in a 25 cm^3 culture flask with filtered vent and maintained in a complete RPMI 1640 culture medium (Invitrogen, USA). The *P. falciparum* was grown in an 'O' type fresh red blood cells (RBC) with the initial culture started with 1% parasitemia at 2.5% hematocrit. The parasite density was monitored daily by making a thin blood smears stained with 10% Giemsa solution and observed under the microscope at 1000 times magnification. The parasites were synchronized using a 5% sorbitol (Lambros & Vanderberg, 1979) and cultured for one complete cycle prior for the *in vitro* usage of *P. falciparum* HRP2 assay once the parasitemia of the parasite culture reached approximately 5 to 7%.

3.5.2 P. *falciparum* HRP2 assay

The HRP2 assay was carried out according to previous reported procedure (Mohd Abd Razak et al., 2014; Noedl et al., 2005), with some modifications. Briefly, the substance was solubilized in a 100% dimethyl sulfoxide (DMSO) to get 50 µM stock solutions. For each compound stock plate, the compounds (50 µM) were serially diluted (2-fold dilution) to 8-point concentrations (ranging from 25 µM to 0.39 µM) in DMSO from well A1 to A7 in a 96 well plate. A 15 µL each of the serially diluted stock were transferred correspondingly into watery plates containing 225 µL of sterile H_2O. An aliquot of the watery plates was used in the HRP2 assay.

Ring-infected RBCs with 5% parasitemia were adjusted to 0.05% parasitemia and 1.5% hematocrit. A total of 190 µL parasitized RBCs at 1.5% hematocrit were added into each well of the test plates. A total of 10 µL of serially diluted compounds from the pre-prepared watery plates were transferred into the test plates containing parasitized RBCs and incubated in a candle jar at 37 $^{\circ}$C for 72 hours and final concentration of the

compounds ranging from 0.156 µM to 0.002 µM with the concentration of DMSO being 0.3%.

Chloroquine (Sigma, USA), quinine (Q) (Sigma, USA), mefloquine (Mef) (Sigma, USA) and artemisinin (Art) (Sigma, USA) were used as standard control to validate the test. The range of the standards concentration was from 1772.6-27.7 nM for CQ, 3495-54.6 nM for Q, 601.3-9.4 nM for Mef and 51.2-0.8 nM for Art. The negative control used was the infected RBC without tested compounds or with sterile H_2O only.

After 72 hours of incubation, the test plates were kept at -80 °C overnight. A 100 µL of the *P. falciparum* infected RBC lysates (freeze thawed at room temperature beforehand) were then transferred from the test plates into ELISA plates coated with of immunoglobulin M (IgM) capture antibody (MPFM-55A, ICL, Inc, Newberg, OR, USA) specific for *P. falciparum* HRP2 (1 µg/mL in phosphate-buffered saline (PBS)) and incubated in humidity chamber for 1 hour at room temperature. The ELISA plates were washed three times with 0.05% PBS-Tween 20 (PBST). A 100 µL of the detector antibody (MPFG-55P, ICL, Inc, Newberg, OR, USA) conjugated with horseradish peroxidase (0.2 µg/mL in PBS) were added to each well then incubated in humid chamber for 1 hour at room temperature. A subsequent washing step similar to the above was followed with 100 µL of 3,3', 5,5;-tetramethylbenzidine (TMB) chromogen (Zymed Lab., Inc., San Francisco, CA, USA) added to each well then incubated for 10 min with the absence of light, followed by the addition of 50 µL of 1M sulphuric acid. The absorbance was determined by using ELISA plate reader at a wavelength of 450 nm (FLUOstar Omega, Germany). Finally, the collected data were transferred to HN-nonLin software (malaria.farch.net) to get a 50% Inhibitory Concentration (IC_{50}) value directly from the graph.

3.5.3 *In vitro* cytotoxicity assay

The MDBK cells were maintained in complete DMEM culture medium containing 25 mM HEPES, 0.4% sodium bicarbonate ($NaHCO_3$), 100U of Penstrep (100U penicillin and 100U streptomycin) supplemented with 10% fetal bovine serum (FBS). The cytotoxicity of the synthesized compounds were measured by 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay (Mosmann, 1983). Prior to the day of the testing, the stock plates were prepared by serially diluting (2-fold dilution) the compounds (50 µM) to 7-point concentrations (ranging from 25 µM to 0.39 µM) with DMSO.

Then, a 6 µL of serially diluted stocks were transferred into a 96-well plate containing 294 µL of complete DMEM media (medium plates). Subsequently, a 100 µL of the compounds taken from the medium plate (as prepared) were added to the test plate containing 1×10^3 MDBK cells accordingly with a range of concentrations between 0.25 µM to 0.004 µM. The final concentration of DMSO in all tests was less than 1%. All tests were performed in duplicate.

The positive control for the cell growth is the cell suspension without test substance while the negative control is the cell suspension with 0.05% Triton × 100. The culture was incubated at 37 $^{\circ}$C in 5% CO_2 incubator for 72 hours. A 50 µL of the MTT solution (5 mg MTT in 1 mL PBS and 2.5 mL DMEM media) were added to each well then further incubated for 4 hours at 37 $^{\circ}$C in 5% CO_2 incubator. The medium was removed and replaced with 200 µL of DMSO to solubilize the MTT formazan product. The solution was mixed for 15 min and once for 30 sec before measuring the absorbance at 540 nm with a micro plate reader (FLUOstar Omega, Germany). The percentage of growth inhibition and the IC_{50} were estimated from a dose response curve. A selectivity

index (SI), corresponding to the ratio between the antiplasmodial and cytotoxic activities was calculated according to the following formula:

$$SI_{Plasmodium} = \frac{IC_{50\ normal\ cell\ lines}}{IC_{50\ Plasmodium}}$$

3.5.4 Antiproliferative assay

Sulforhodamine B (SRB) assay was carried out to determine the 50% Growth Inhibition (GI_{50}) of all compounds as described in previous studies (Holbeck et al., 2010). Briefly, cells were seeded in 96-well plates at 1×10^5 cells/ml (MCF-7) or 2×10^5 cells/ml (MDA-MB-231 and HT-29) and incubated overnight to allow the cells adhered to the bottom of the plate. The next day, some of the plates were processed to determine the time zero (t_0) density. According to the National Cancer Institute (NCI), the use of the t_0 control allows the determination of cell kills as well as net growth inhibition (Holbeck et al., 2010). The cells in the remaining plates were treated with each of the compounds at concentrations ranged from (0.383-12.269 µM) (0.378-12.103 µM), (0.657-21.031 µM), (0.496-15.846 µM), or (1.881-60.176 µM) for **1**, **2**, **3**, **4**, or **5**, respectively.

After 48 hours, the cells were fixed in the plate with 50 µL of 50% (w/v) trichloroacetic acid (TCA) solution and further incubated at 4 °C for an hour. Then, the plates were washed five times with tap water and air dried. The cells were stained with 100 µL of 0.4% (w/v) SRB staining solution and further incubated for 10 minutes at room temperature. Subsequently, the plates were washed three times with 1% (v/v) acetic acid to remove unbound stains and air dried. Following that, a 200 µL of 10 mM Trizma base was added into the wells and shake well for 10 minutes.

Thenceforth, measure the absorbance by using a microplate reader at λ = 490 nm. All experiments were carried out in triplicates. The GI_{50} were calculated based on the formula:

$$GI_{50} = \frac{OD_{sample} - OD_{t_0}}{OD_{control} - OD_{t_0}} \times 100$$

OD_{sample} : Optical density of compound/complex treated cell

OD_{to} : Optical density at time zero

$OD_{control}$: Optical density of solvent treated cell

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Mechanism of reaction

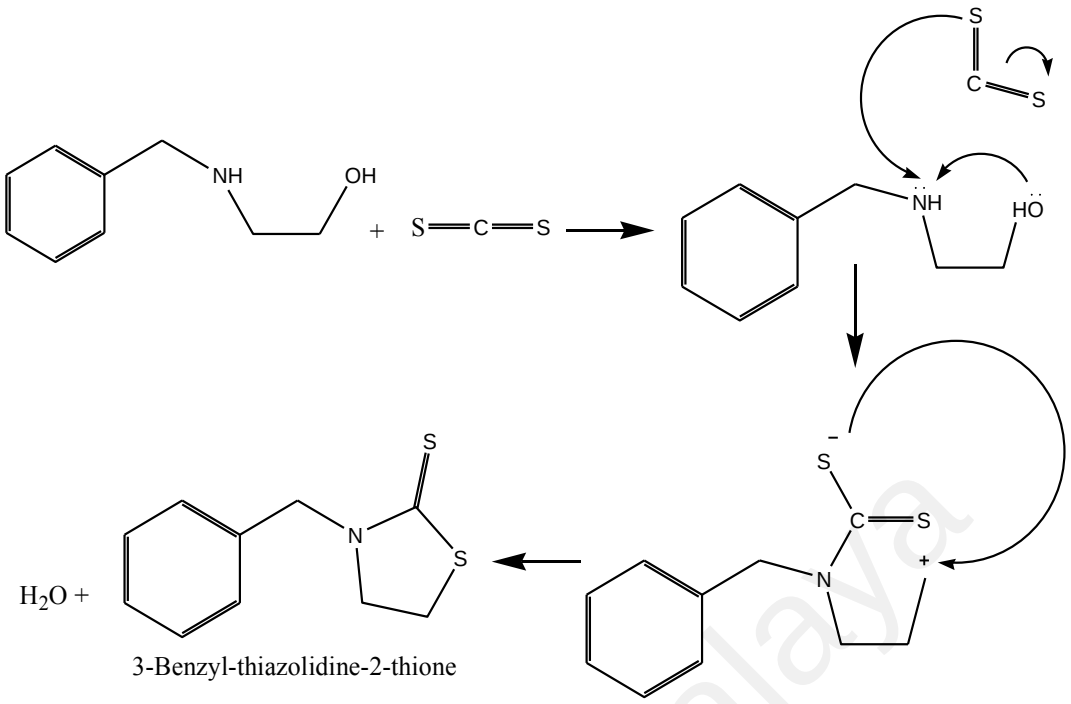
A 3-benzyl-1,3-thiazolidine-2-thione ligand with a total of 5 complexes were tested in antimalarial and anticancer activities. All compounds were structurally elucidated by CHN, UV-Vis, FT-IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, EDX and TGA.

There were two stages involved when designing these complexes. The first stages was the preparation of 3-benzyl-1,3-thiazolidine-2-thione ligand while second stages was to synthesize the silver complexes with the synthesized thiazolidine, monodentate or bidentate phosphine ligand via one-pot reaction.

The thiazolidine was reacted with silver nitrate and with either 1,2-bis(diphenylphosphino)methane (**R1**, dppm), 1,1-bis(diphenylphosphino)ferrocene (**R2**, dppf) or 1,1-bis(diphenylphosphino)ethane (**R3**, dppe) in the molar ratio of 2:1:2 (Ag:P:S) while with triphenylphosphine (**R4**, PPh_3) and tri(*o*-tolyl)phosphine (**R5**) in the molar ratio of 1:1:2 (Ag:P:S) using acetonitrile/methanol as solvent. Based on the reaction, complexes **1, 3, 4** and **5** produced clear black solution while complex **2** produced clear orange solution and all the complexes were soluble in acetonitrile.

4.1.1 3-benzyl-1,3-thiazolidine-2-thione

3-benzyl-1,3-thiazolidine-2-thione was synthesized during a long reaction time in a very alkaline medium with an excess of carbon disulphide. The mechanism of reaction (Scheme **4.1**) involves initial attack by sulphur atom from carbon disulphide that act as nucleophile to the thiocarbonyl group of amino alcohol resulting in intermolecular cyclization. The formation of thiazolidine was then involves with an inversion configuration of the carbon bearing the oxygen and ejection of water to yield the complexes. The removal of water in the final step was apparently believed to be the rate determining step and considered as critical to obtain the ligand in high yield.



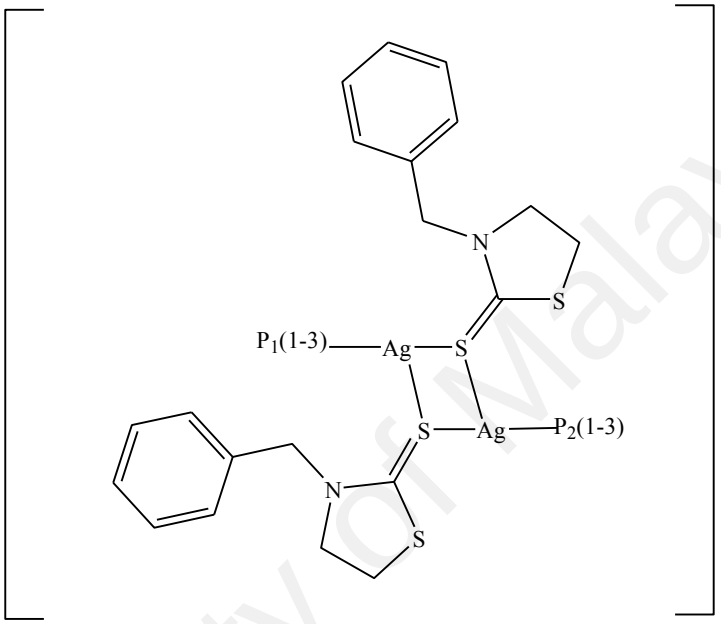
Scheme 4.1: Reaction mechanism of 3-benzyl-1,3-thiazolidine-2-thione synthesis

4.1.2 Silver complexes

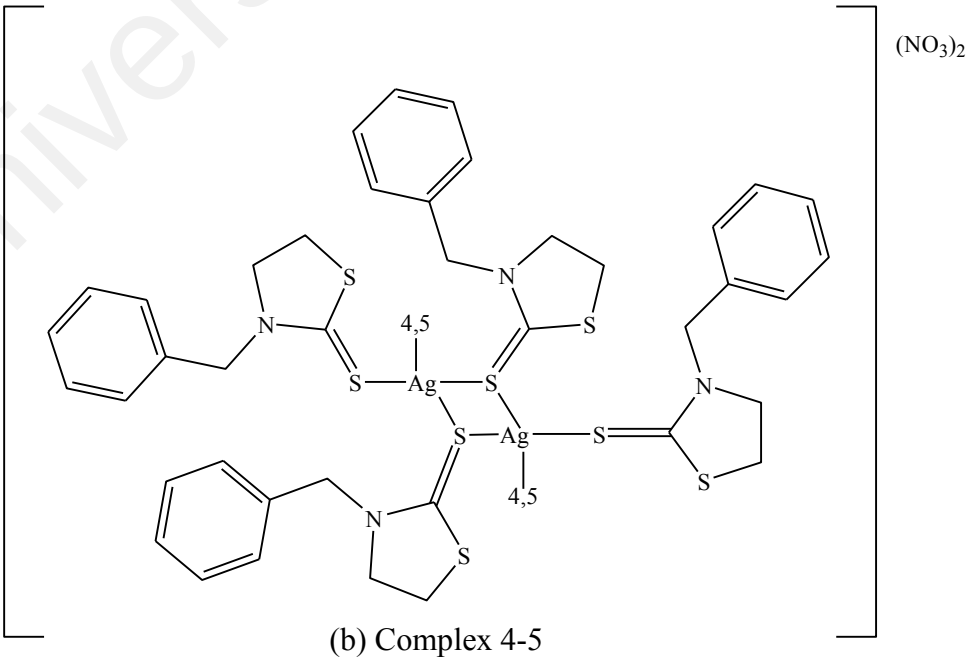
Complexes that produce in this research consist of two ligands which are thiazolidine and phosphine. Despite the high number dominated by bridging sulfur donor ligand, there is increasing interest to explore bridging phosphorus-donor ligands in coordination chemistry field of molecular materials. -PR_3 can act as σ donor; π acceptor while –S act as σ donor; π donor and in term of bond strength, the σ bond is much important than π bond (donor/acceptor). The coordination number for silver(I) are ranging from 2 to 4 and as might be expected, principle factors in the reactivity of thiazolidine complexes occurs due to the availability of electron density in sulphur atom (electrophile attack) while for diphosphine ligands may involve in several different coordination (chelate vs bridge, *syn* v*s anti* conformation when bridging). Thus, there are a lot of potential for many structural types in the formation of silver complexes.

The expected structures of complex **1-3** as showed in **Scheme 4.2(a)** and for complex **4-5** in **Scheme 4.2(b)** respectively. There are several limitations of valence

bond theory such as difficulties to predict the hybridization of the metal in five *d*-orbitals, cannot provide particular geometry for the preference, no strong explanation for inner or outer orbital complexes and many more. Thus, in general, the formation of complexes occurred when silver act as a metal centre and receive lone pair from sulphur and phosphine donor atom (bonded by chelating ligands).



(a) Complex 1-3



(b) Complex 4-5

Scheme 4.2: Expected structures for complexes **1-5**

4.2 CHN elemental analyses

Table **4.1** shows the physical properties and elemental analysis of 3-benzyl-1,3-thiazolidine-2-thione ligand and silver(I) complexes. The experimental data for elemental analyses was found to be in a good agreement with the calculated value of proposed formulae.

$$\%\ \text{Element (calculated)} = \frac{\text{Molar mass of the element in the compound}}{\text{Molecular mass of the entire compound}} \times 100\ \%$$

Table 4.1: Analytical data and physical properties of ligand and silver(I) complexes

Compound	Colour	Yield (%)	Calculated (%) Found (%)			
			C	H	N	S
L	Yellow	88	57.38 56.86	5.30 4.80	6.69 6.34	30.64 30.61
1	Black	67	53.05 52.64	4.35 3.88	2.75 2.30	12.59 12.12
2	Orange	54	54.56 54.24	4.24 3.92	2.36 2.24	10.79 10.43
3	Black	55	53.49 52.98	4.49 3.98	2.70 2.61	12.42 11.89
4	Black	54	57.86 57.45	4.73 4.46	3.55 3.10	16.26 15.73
5	Black	37	59.27 58.83	5.22 4.97	3.37 2.94	15.54 14.97

The table shows that the percentage yield for complex **5** was low as compared to others. It might be due to experimental errors such as filtering or purification steps for the desired complex. Other than that, any inconsistency value between theoretical and experimental results perhaps because of the reaction was still incomplete, the equilibrium reactions may not lie completely on the side of the products or the products still contains solvent and not completely dry.

The solubility of the synthesised silver(I) complexes was good in some organic solvents such as acetonitrile, dimethyl sulfoxide, diethyl ether or dimethylformamide. However, reported in pharmaceutical and medicinal research, there is potential active silver(I) compounds that contain nitrogen and sulfur as ligands are hard to crystallize because this type of compound perhaps appeared as polymeric (Altaf et al., 2013; Kasuga et al., 2004; Kasuga et al., 2006).

From the spectroscopic evidences, the silver atoms of complexes **1** until **3** were found to be connected to the bidentate phosphine ligand which acts as chelating or either bridging ligand (Gao et al., 2014). In addition, heterocyclic thione ligands having both sulfur and nitrogen atoms were acting as donor atoms which potentially available for coordination (Aslanidis et al., 1997). Other than that, thiazolidine-2-thione with silver nitrate was assumed to form tetrahedral and mononuclear complexes for **4** and **5** in the presence of equivalents phosphine ligand with respect to the thione ligand.

4.3 UV-Vis spectra data

The electronic absorption spectrum of the 3-benzyl-1,3-thiazolidine-2-thione ligands and their Ag(I) complexes were recorded at 270-770 nm in acetonitrile (refer appendix A).

In UV-Vis, most molecules that absorb ultraviolet or visible radiations undergo electronic transitions. The absorption in the visible ranges for transition metals will directly forming colored complexes. It occurs when sufficient amount of energy of photon, from visible range of the electromagnetic spectrum to excite electrons from its ground state to a higher state of energy orbital. The value of this absorbed energy at a certain wavelength generates absorption bands which can be studied thoroughly by UV-Visible spectroscopy. There are four possible types of electronic transition for ligands which are $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, $\sigma \rightarrow \sigma^*$, and $\pi \rightarrow \pi^*$. While for complexes, there are two types of electronic absorption transition which are *d-d* transition and charge transfer transition. The *d-d* electronic transition involves with the electronic transitions within the *d*-orbitals from lower energy to higher energy.

Meanwhile charge transfer occurs when a change in electron distribution between the metal and a ligand when performing ultraviolet-visible. Since electron can jump from the orbitals of metal and ligands, it is possible ligand-to-metal charge transfer (LMCT) may occur from the filled ligand molecular orbitals to an empty or partially filled metal *d*-orbitals (reduction of the metal).

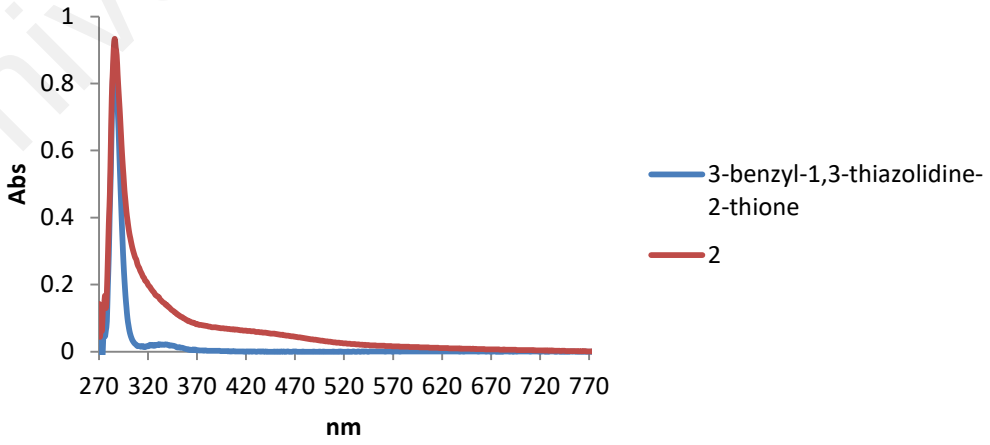


Figure 4.1: UV-Vis spectra of complex **2**

In general, quantitative analysis for *d-d* transition is not applicable because the sensitivity was relatively poor due to its very low ε max values. Based on the data, silver complexes (for example complex **2**), a graph features was unstructured and unclear broad emission band around 370- 470 nm (Figure **4.1**) since there are no *d-d* transitions of d^{10} complexes because the d-orbital are completely filled. Thus, UV-Vis absorption bands were not observed. To overcome this problem, the complexes were analyzed in other instrument such as Energy-dispersive X-ray (EDX) to support the existence of silver metals.

4.4 FTIR spectra data

The IR spectra of the compounds reported in the range of wavelength 450-4000cm^{-1} were mainly characterized by vibrational absorptions of coordinated functional group of ligands and complexes. The important stretching and bending frequencies of ligand and complexes were tabulated in Table **4.2**.

Table 4.2: Selected IR Spectral data of ligand and silver(I) complexes

Compound	Wavenumber (cm^{-1})			
	C=S	C-N	P-C_{ph}	NO_3^-
L	1242	1149	-	-
1	1152	1223	1094	1310
2	1163	1223	1095	1307
3	1153	1223	1097	1307
4	1154	1223	1092	1314
5	1160	1266	1129	1315

The 3-benzyl-1,3-thiazolidine-2-thione ligand offers three types of donor atoms which are thiocarbonyl sulfur atom, the nitrogen atom, and the endocyclic sulfur atom.

The nitrogen and sulfur within the ring that contained electron pairs should be in resonance with the thiocarbonyl group, thus causes to higher delocalization of electrons and lowering the ability of coordination (Chaves et al., 2014). A ν(C=S) in complexes **1, 2, 3, 4** and **5** were assigned at 1275-1030 cm^{-1} that were shifted to a lower energy as compared to the free 3-benzyl-1,3-thiazolidine-2-thione ligand. At 1360-1180 cm^{-1} observed in the spectra of ν(C-N) vibration complexes that shifted due to the higher energy than its free ligand. Besides, the displacement to low energy of the thioamide band shows the coordination to silver metal through the C=S sulfur atom. Other than that, the presence of phosphine was shown by its characteristic ν(P-C_{ph}) band in the range of 1130-1090 cm^{-1}. From IR data, it may be concluding that the silver metal ion is coordinated to sulfur atom of the thiazolidine ligand.

From IR table, it shows that value of P-C_{ph} wavenumber for complex **5** was very different compared to other complexes. This is apparently the existence of alkyl group (electron donating groups) in phosphorus ligand which able to activate the aromatic ring by the electron density on the ring through an inductive donating effect.

Other than that, the present of a broad peak in thiazolidine ligand (3600-3200 cm^{-1}) was presumably the OH- group due to the excess from solvent used which is KOH. Since each molecule was determined by the exact environment, the OH- will appear broad in a high range frequency because H atom vibrates really fast and form hydrogen bonding with O atom.

4.5 NMR spectra data

From the observation that monitored using ^{1}H NMR spectroscopy over the period of time, the silver(I) complexes synthesised were found to be non-hygroscopic and thus can be stored over a long period of time (at least one year) without decomposition.

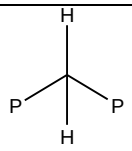
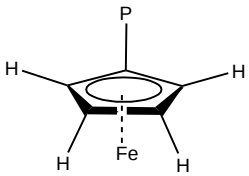
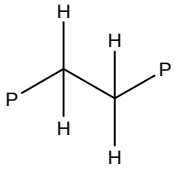
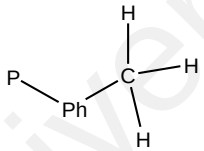
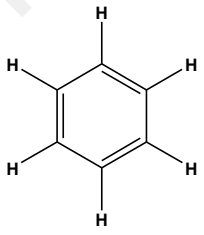
4.5.1 ^{1}H NMR

The ^{1}H NMR spectrum of thiazolidine ligand and its Ag(I) complexes were dissolved in acetonitrile (ACN) as deuterated solvent. In the ^{1}H NMR spectra of thiazolidine ligand (Table **4.3**), there were signals observed in the δ 7.25 – δ 7.37 ppm region corresponding to aromatic proton while for the complexes, the additional aromatic protons observed at the region of δ 6.62 – 7.50 ppm indicating the existence of the phosphine ligand. The peaks for Ar-H_2-N, H_2-N and H_2-S signals in all complexes showed slightly shifted upfield relative to its free thiazolidine ligand.

In addition, there were new signals appeared in all complexes that proved the existence of mono- or bidentate phosphine ligands. A singlet signal was observed at δ 3.67 ppm for **1** due to the –H_2C protons in dppm ligands. A singlet signal also appeared at δ 2.46 ppm for **3** corresponding to the -H_2CH_2C proton in dppe ligand and complex **5**, there was a singlet signal at δ 2.31 ppm due to the –H_3C-P protons in the ortho position of the tri(*o*-tolyl) ligands.

Two broad signals presence at δ 4.35 ppm and δ 4.17 ppm at **2** corresponding to the cyclopentadienyl protons in dppf ligand. The broad spectrum appeared in the complex compared sharp signal in free ligand presumably because of fluxionality effects since dppf ligand has unique ability to modify and adapt different geometric obligation of the metal center (Cauzzi et al., 1999; Díez et al., 1999).

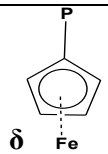
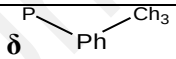
Table 4.3: ^{1}H NMR spectra of thiazolidine ligand and Ag(I) complexes

Compound	**L**	**1**	**2**	**3**	**4**	**5**
δ Ar-H_2-N	4.93	4.89	4.93	4.88	4.91	4.92
δH_2CN	3.95	3.91	3.95	3.92	3.94	3.95
δH_2CS	3.23	3.13	3.11	3.12	3.18	3.21
	-	3.67	-	-	-	-
	-	-	4.35 4.17	-	-	-
	-	-	-	2.46	-	-
	-	-	-	-	-	2.31
	7.37- 7.25	7.50- 7.18	7.50- 7.28	7.42- 7.22	7.33- 7.15	7.40- 6.62

4.5.2 ^{13}C NMR

In all data of complexes as shows in Table **4.4**, the coordination between thiazolidine ligand and silver centre via thione sulfur influenced the C=S signal in ^{13}C NMR spectra which observed by a small shifted of a chemical shift value by δ 0.2 ppm as compared to its free ligand which in agreement with the previous study (Chaves et al., 2014). Furthermore, there were additional carbon peak appeared in the spectra at δ25.3 ppm for complex **1,** δ74.8 ppm and δ72.8 ppm for **2,** δ24.4 ppm for **3,** and δ20.5 ppm for **5** indicating carbon from phosphine ligands.

Table 4.4: ^{13}C NMR spectra of thiazolidine ligand and Ag(I) complexes

Compound	L	1	2	3	4	5
δC=S	196.9	196.7	197.1	196.9	196.9	197.1
δC-N	56.3	56.6	57.1	56.9	56.4	56.4
δN-C-Ar	51.9	52.3	52.5	52.4	52.1	52.1
δC-S	26.8	26.8	27.3	27.3	26.9	26.9
δCH_2-P	-	25.0	-	-	-	-
	-	-	74.0 72.0	-	-	-
δCH_2CH_2-P	-	24.0	-	-	-	-
	-	-	-	-	-	20.5
	127.3,127.9,128.8,135.7	128.1,128.7,128.8,128.9,131.1,131.2,133.1,135.3	128.1,128.2,128.9,129.0,130.6,133.4,133.5,135.1	128.1,128.2,128.9,129.2,130.7,132.4,132.7,135.1	128.0,128.8,129.1,130.6,131.8,132.1,133.6,135.5	126.4,127.9,128.8,129.3,130.4,132.9,133.5,135.6,142.5,142.7

4.5.3 ^{31}P NMR

Phosphorus NMR data are crucial for studies of metal involving phosphorus ligands because it is very sensitive to the electron density that surrounding the phosphorus atom. Coupling constants and chemical shifts can guide the confirmation of bonding and structure of the research molecule since it has been discovered that phosphorus NMR spectroscopy is a suitable way for metal-phosphorus complexes studies.

It was observed that in comparison to free phosphine ligands, the ^{31}P $\{^{1}H\}$ NMR resonances in all the complexes were shifted downfield in light of the formation of σ bonds between P and Ag. As per the $^{31}P\{^{1}H\}$ NMR data of complexes **2**, **3,** and **4**, the singlet peaks can be ascribed to two chemically-equivalent P atoms each in dppf and dppe, as well as one in triphenylphosphine.

However, the spectrum of compound **1** surprisingly showed two different singlet peaks at δ 5.2 and δ 8.0 ppm as shows in Figure **4.2**. In contrast, its corresponding free dppm ligand had only one singlet peak. This phenomenon could presumably be attributed to the fact that there were non-equivalent P atoms in the complex probably due to ^{31}P-$^{109/107}Ag$ coupling (Lobana et al., 2007; Nawaz et al., 2011; Pettinari et al., 2009).

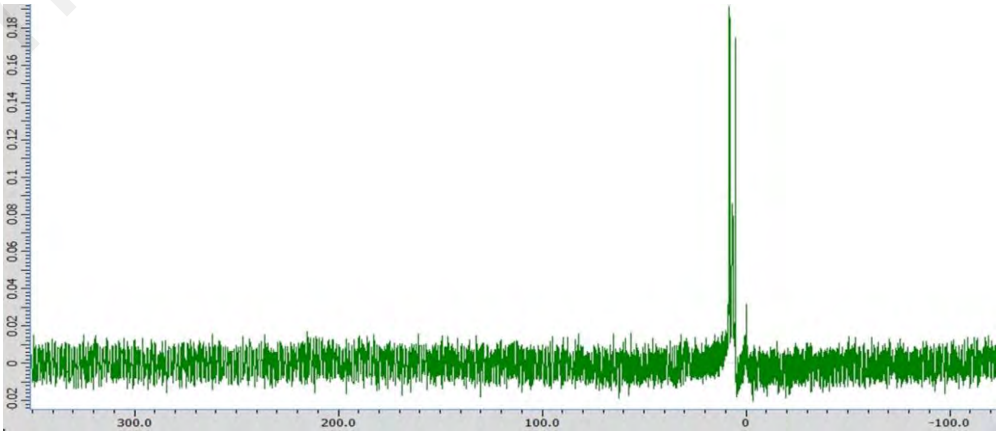


Figure 4.2: ^{31}P NMR spectrum for complex **1**

For complex **5**, the $^{31}P\{^{1}H\}$ NMR spectrum revealed two singlet peaks at δ -27.8 and δ 38 ppm as shows in Figure **4.3**. The former peak, which was at an unusually low frequency, was also reported by Rizatto et al. It indicated the formation of an unexpected product in the presence of an uncoordinated P atom from the tri(*o*-tolyl)phosphine ligand (Caldwell et al., 2007; Pregosin, 2008). Nonetheless, it is suggested that the two signals appeared most likely due to the high steric effect from the bulky arrangements of phosphine ligand (Zartilas et al., 2009). Since we are yet to obtain data from X-ray crystallography, it is worth noting that the structure of complex **5** structures is still uncertain.

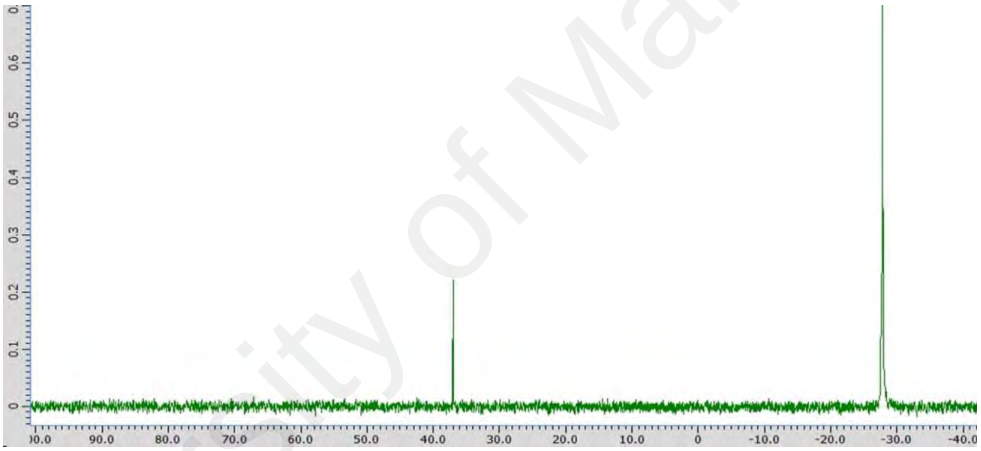


Figure 4.3: ^{31}P NMR spectrum for complex **5**

4.6 Energy-dispersive X-ray spectroscopy

The obtained complexes were subjected to EDX analysis (refer appendix D) to confirm the presence of silver metal in each compound. For example for complex **5** (Figure **4.4**), the analysis of the complexes showed the presence of silver metal as well as all other components such as phosphorus, sulfur and carbon that expected to be present.

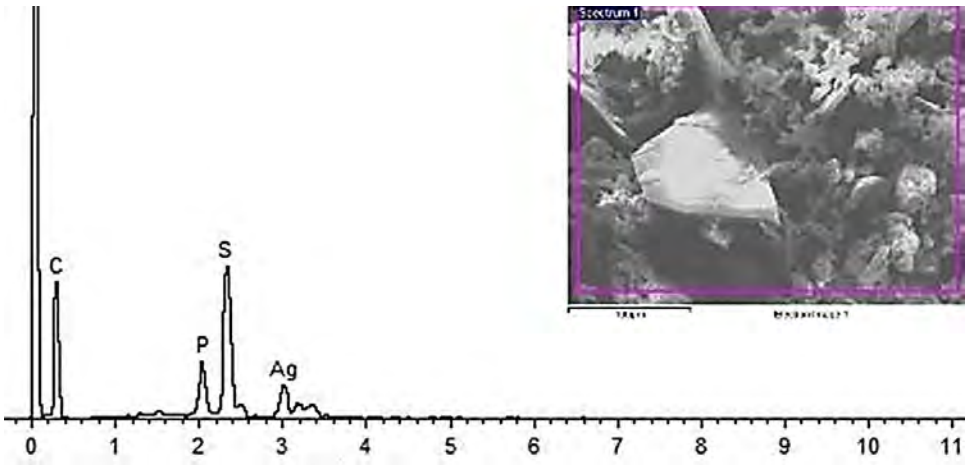


Figure 4.4: EDX analysis for complex **5**

4.7 Thermal decomposition

The thermal decompositions of complexes **1-5** were examined (refer appendix E). The TGA graph showed that all of the complexes decomposed in a few stages. Percentages of residues in final stages for each complex are calculated by using this formula;

$$\% \text{ of complex} = \frac{\text{Molecular weight of residue}}{\text{Molecular weight of complex}} \times 100\ \%$$

In final stages, complex **1** showed the decomposition of the silver metal to Ag_2O and the phosphine molecules to its oxide form which was 34.99% (theoretical: 35%) starting from 450 °C to 900 °C and for complex **3** was 32.41% (theoretical: 34.54%) starting from 490 °C to 900 °C. Other than that, the decomposition of silver, phosphine and iron molecules as the oxide forms for complex **2** was 40.16% (theoretical: 39.32%) starting from 710 °C to 886 °C as shows in Figure **4.4**.

While for complex **4** the Ag was observed 25.73% (theoretical: 29.38%) to be decomposed from 500 °C to 880 °C and complex **5** was 25.27% (theoretical: 27.89%) from 300 °C to 900 °C. Thus, from the data, it was shown that the theoretical and experimental mass losses were in agreement to each other.

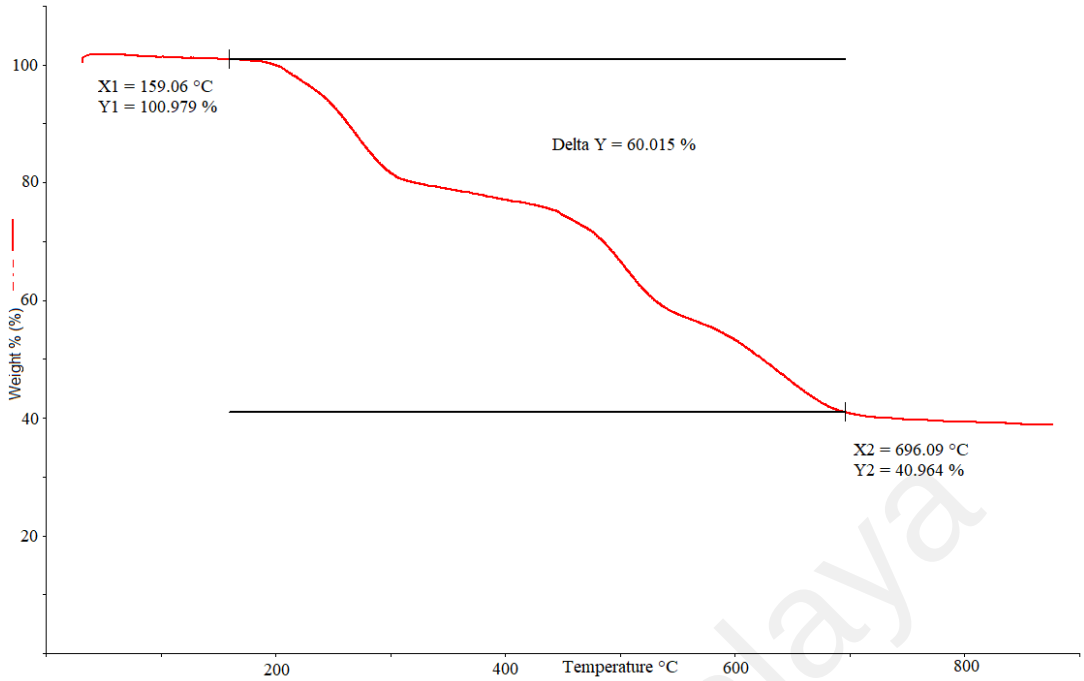


Figure 4.5: TGA result for complex **2**

4.8 Biological applications

4.8.1 Antiplasmodial activity

Thiazolidine derivatives have been extensively studied for their antimicrobial activity against pathogenic bacteria, fungi, anti-HIV and *P. falciparum* (Mital et al., 2015; Pandey et al., 2011). In addition, the introduction of amide bond with heterocyclic ring system (4-thiazolidine) on lateral side chain of 4-aminoquinoline, an antimalarial agent, has been shown to improve the antimalarial activity of this compound (Solomon et al., 2013). In the present study, five silver complexes with thiazolidine ligand showed a promising antiplasmodial activity against the chloroquine resistant *P. falciparum* parasite K1 strain *in vitro*. The EC_{50} values of five thiazolidine ligand complexes fall within the acceptable cut-off values more than 1-5 µM for further *in vivo* preclinical antimalarial study (Fidock et al., 2004; Katsuno et al., 2015). The cytotoxic effect of each complex on VERO cells was assessed for determination of selectivity index or ratio of cytotoxicity to biological activity (SI). The antiplasmodial activity of complexes was considered specific and safe when the SI is more than 10 (Katsuno et al., 2015;

Weniger et al., 2001). Out of 5 silver complexes, **2** exhibited higher SI followed by complex **5** as shown in Table **4.5**.

Table 4.5: Antiplasmodial and cytotoxicity activities of silver(I) complexes

Complexes	***P. falciparum* K1**	**VERO cell line**	**SI**
	EC_{50} (μM)	CC_{50} (μM)	
1	2.597	2.782	1.071
2	2.036	>25	>12.279
3	1.538	5.485	3.566
4	1.639	2.528	1.542
5	2.984	15.570	5.218

4.8.2 Antiproliferative activity

Breast and colon cancer are the most common cancer worldwide (Deen et al., 2016; Ferlay et al., 2010). According to the National Cancer Registry 2007 of Malaysia, breast and colorectal cancer also are the most common cancer in Malaysian (Omar & Tamin, 2011). One of the main treatments for cancer is chemotherapy (Matsuda et al., 2018; Redden & Fuhrman, 2013), however, the development of drug resistance (Alfarouk et al., 2015; Crawford, 2013) and drug toxicity (Han et al., 2017) result in significant relapse as well as decreased overall survival rates in cancer patients (Morris et al., 2007). Thus, searching for potential drug with high efficacy and low drug toxicity remains a huge challenge in the anticancer drug discovery research and development.

Clinical success of cisplatin, carboplatin and oxiplatin resulted in the use of metal complexes in the treatment of malignant tumours (Desoize, 2004). Development of anticancer drugs based on coinage metals such as silver is currently a very active field (Tan et al., 2010). Previous studies suggested that silver mixed ligands complexes has

antiproliferation activity (Shukla & Mishra, 2013). Thus, the antiproliferative potential of our newly synthesized silver complexes with thiazolidine and phosphine ligand was verified on different human carcinomas.

The evaluation of new anticancer drug agents through preclinical testing using cell culture is important to eliminate unsuitable candidates before pursuing into clinical research. In the present study, sulforhodamine B (SRB) was used to evaluate the anticancer properties of our drug candidates. Although MTT has been the gold standard for cytotoxicity assays, it showed interactions with many compounds thus may yield inaccurate results (Wang et al., 2011; Wang et al., 2015). On the other hand, SRB assay is highly reproducible and this assay is dependent on the protein content thus test compound interference can be avoided (van Tonder et al., 2015).

Antiproliferation activity was evaluated on three human cancer cell lines including metastatic breast carcinoma, MDA-MB-231, breast adenocarcinoma, MCF-7, and colon carcinoma, HT-29. Dose-response curve was constructed to calculate the GI_{50} (μM) value which correspond to the concentration required to inhibit 50% of cell growth. Table **4.6** showed the GI_{50} values of the synthesized compounds against the tested human carcinomas.

The selectivity of Ag complexes towards the tumor cells was ligand-dependent, which could probably be attributable to the stability and hydrophilicity-lipophilicity of the complexes formed by the type of the ligand (Kalinowska-Lis et al., 2016). Interestingly, compound **2** was selective to inhibit the 50% of MDA-MB-231 cell growth (GI_{50} = 1.9 ± 0.3 μM) while compound **5** acted more potent to inhibit breast carcinoma growth (GI_{50}: MDA-MB-231 = 4.7 ± 1.1 μM; MCF-7 = 2.9 ± 0.9 μM) instead of colon carcinoma, HT29 (GI_{50} = 15.1 ± 1.9 μM). Fichtner et al. (2012) reported that silver-carbene complexes were a potent cytotoxic and resistant-breaking

anticancer agent but unfortunately their efficacy was at the expense of high toxic effect and low selectivity in *in vivo* setting (Iduna et al., 2012). However, the type of ligands that attached to the metal can contribute to its anticancer properties as they can be involved in target recognition and interfere in biochemical pathways (Pingyu & Sadler, 2017). The presence of phosphine ligands increases the lipophilicity and membrane permeability of metal-based complexes that make them active (Keter et al., 2014). On the other hand, thiazolidine was known to exert anticancer activity mainly via PPARγ-independent mechanism of actions (Asati et al., 2014; El-Gaby et al., 2009). Our synthesized Ag complexes with bioactive thiazolidine and phosphine ligands were able to halt the proliferation of breast and colon cancer cells thus warrant further investigations for its mechanism of action *in vivo*.

Table 4.6: GI_{50} (μM) of compounds on different cancer cell lines

Complexes	**GI_{50} ± SD (μM)**		
	MDA-MB-231	MCF-7	HT-29
1	1.709 ± 1.284	0.508 ± 0.167	1.598 ± 0.651
2	1.957 ± 0.347	>21.03	>21.03
3	0.411 ± 0.572	0.200 ± 0.062	0.250 ± 0.280
4	2.956 ± 0.565	2.342 ± 0.411	3.063 ± 1.762
5	9.328 ± 2.162	5.784 ± 1.821	30.220 ± 3.744

CHAPTER 5: CONCLUSION

5.1 Conclusion

A series of five silver(I) complexes with either monodentate or bidentate phosphines and 3-benzyl-1,3-thiazolidine-2-thione ligand were successfully prepared and characterized by spectroscopic methods. The discussions were as outlined in chapter **4**, indicating that complexes **1**, **2** and **3** were coordinated with bidentate phosphine ligand that act as chelating substance, formed in the molar ratio of 2:1:2 (Ag: P: S) while complexes **4** and **5** consisted of monodentate phosphine ligand were arranged in the molar ratio of 1:1:2 (Ag: P: S). Other than that, from the $^{31}P\{^{1}H\}$ NMR data, compound **1** and **5** showed two different singlet peaks due the ^{31}P-$^{109/107}Ag$ coupling or non-equivalent phosphorus atom respectively.

All complexes were tested for their properties as antimalarial and anticancer. For anti proliferative, all compounds demonstrate a good potential as metallotherapeutic agents. While for antimalarial, the five silver complexes displayed promising antiplasmodial activity against the chloroquine resistant *P. falciparum* parasite K1 strain *in vitro* because the EC_{50} values of the complexes fall within the acceptable cut-off values which is more than 1-5 μM for further *in vivo* preclinical antimalarial study. Besides, it was found out that both complex **2** and **5** had exhibit promising results for further investigation towards developing antimalarial and anti cancer agents. Thus, we have discovered potential candidates that have the ability to act as dual-proposed drug either for antiplasmodial or anti proliferative activities.

5.2 Suggestions for future work

The research had gives us preliminary insight on the structural properties of the synthesized Ag(I) complexes. However, there are a lot of advancement work can be carried out. For future plan, we will attempt to grow crystal for further confirmation

about its structural geometric arrangement, coordination and designation of the structure for each complex. In addition, two synthetic chemical compounds (complex **2** and **5**) have showed good results for both biological applications in antimalarial and anticancer and these warrants for further in-depth study on its molecular mechanism of action.

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Research Article

New Silver Complexes with Mixed Thiazolidine and Phosphine Ligands as Highly Potent Antimalarial and Anticancer Agents

Nur Rahimah Fitrah Mohd Sofyan,[1] Fariza Juliana Nordin,[2] Mohd Ridzuan Mohd Abd Razak,[3] Syahrina Nur 'Ain Abdul Halim,[1] Nur Adila Fatin Mohd Khir,[1] Amirrudin Muhammad,[3] Nor Fadilah Rajab,[2] and Rozie Sarip[1]

[1]*Department of Chemistry, Faculty of Science, University of Malaya, Lembah Pantai, 50603 Kuala Lumpur, Malaysia*
[2]*Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur Campus, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia*
[3]*Bioassay Unit, Herbal Medicine Research Centre, Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia*

Correspondence should be addressed to Rozie Sarip; rozie@um.edu.my

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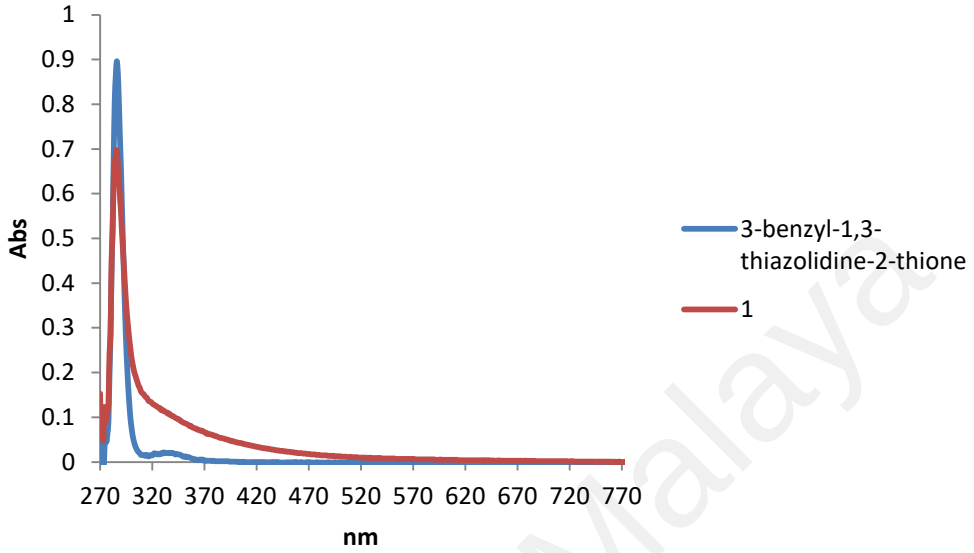
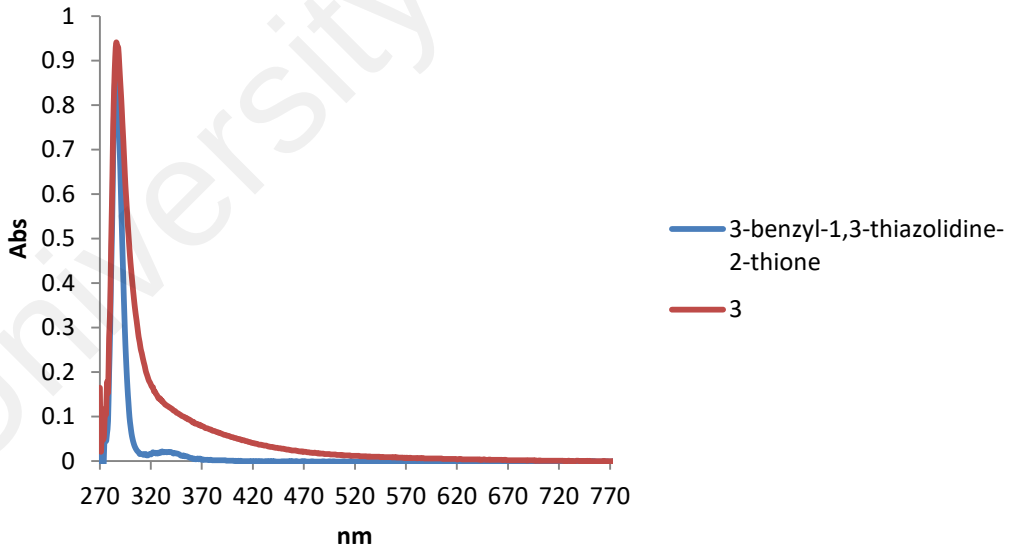
Five silver(I) complexes containing a mixed ligand system of phosphine and thiazolidine were successfully synthesized. .e structural information of the complexes was assembled using various spectroscopic techniques such as CHN elemental analysis, Fourier transformed infrared (FTIR), ^{1}H, ^{13}C, and $^{31}P\{^{1}H\}$ NMR spectroscopy, and thermogravimetric analysis (TGA). A bidentate phosphine ligand acted as a chelating agent which bond to the silver in 1 : 2 molar ratios. Meanwhile, thiazolidine was attached to the silver in a 1 : 1 molar ratio. .e antiplasmodial properties of all synthesized complexes were investigated on chloroquine-resistant *P. falciparum* parasite via HRP2 assays and cytotoxicity tests on Vero cells. Of all the synthesized complexes, complex **2** showed the highest SI value (more than 12.4) followed by complex **5** (6.6). .e potent properties of compounds **2** and **5** were also noted in the *in vitro* antiproliferative assays involving MDA-MB-231 and MCF-7 breast cancer cell lines as well as HT-29 colon cancer cell line. Complex **2** was selective for MDA-MB-231 cells (GI_{50} = 1.9 ±0.3 μM), while complex **5** acted predominantly on breast carcinoma cells (GI_{50} MDA-MB-231 = 4.7 ±1.1 μM; MCF-7 = 2.9 ±0.9 μM) instead of colon carcinoma (HT-29) cells (GI_{50} = 15.1 ±1.9 μM).

APPENDIX

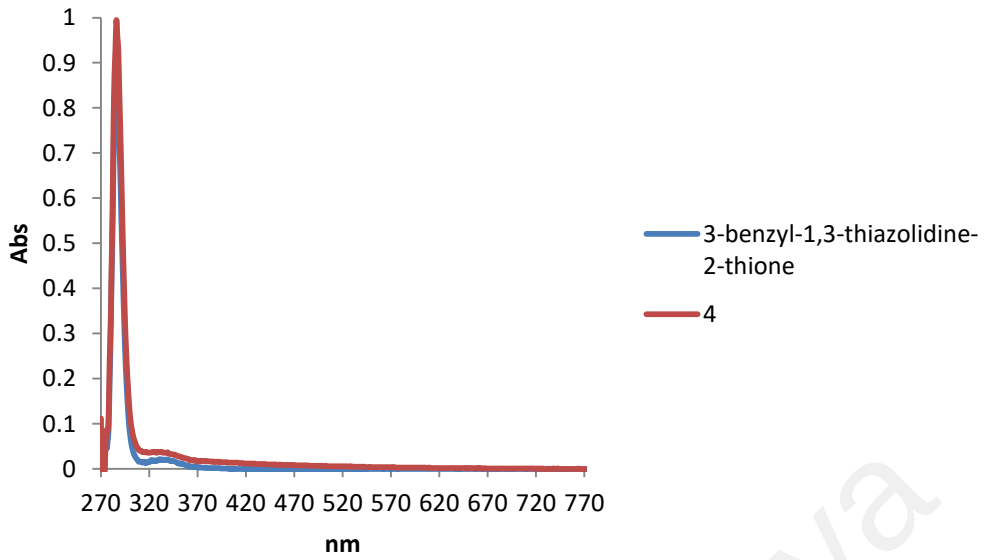
Appendix A: UV-Vis



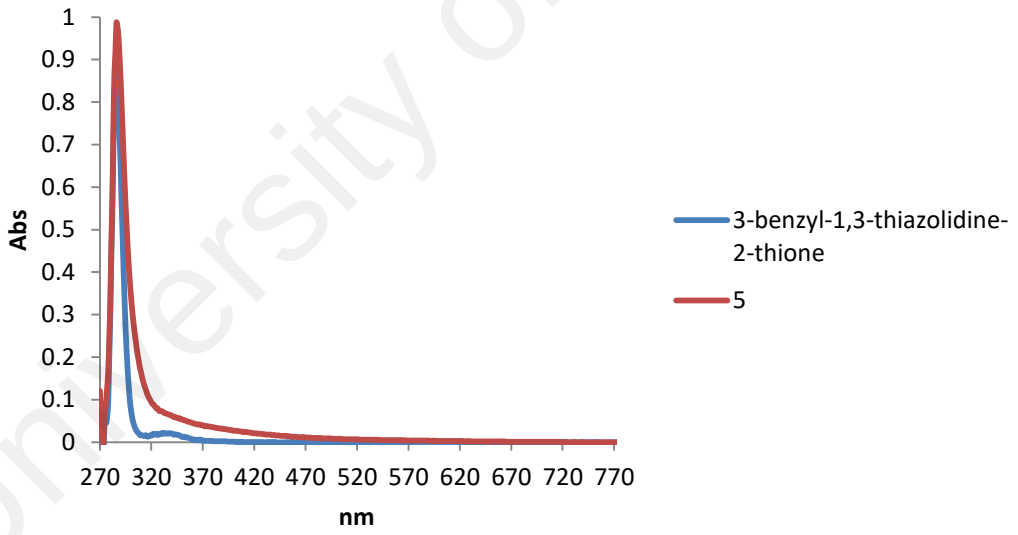
UV-Vis comparison graph data for 3-benzyl-1,3-thiazolidine-2-thione and complex **1**



UV-Vis comparison graph data for 3-benzyl-1,3-thiazolidine-2-thione and complex **3**

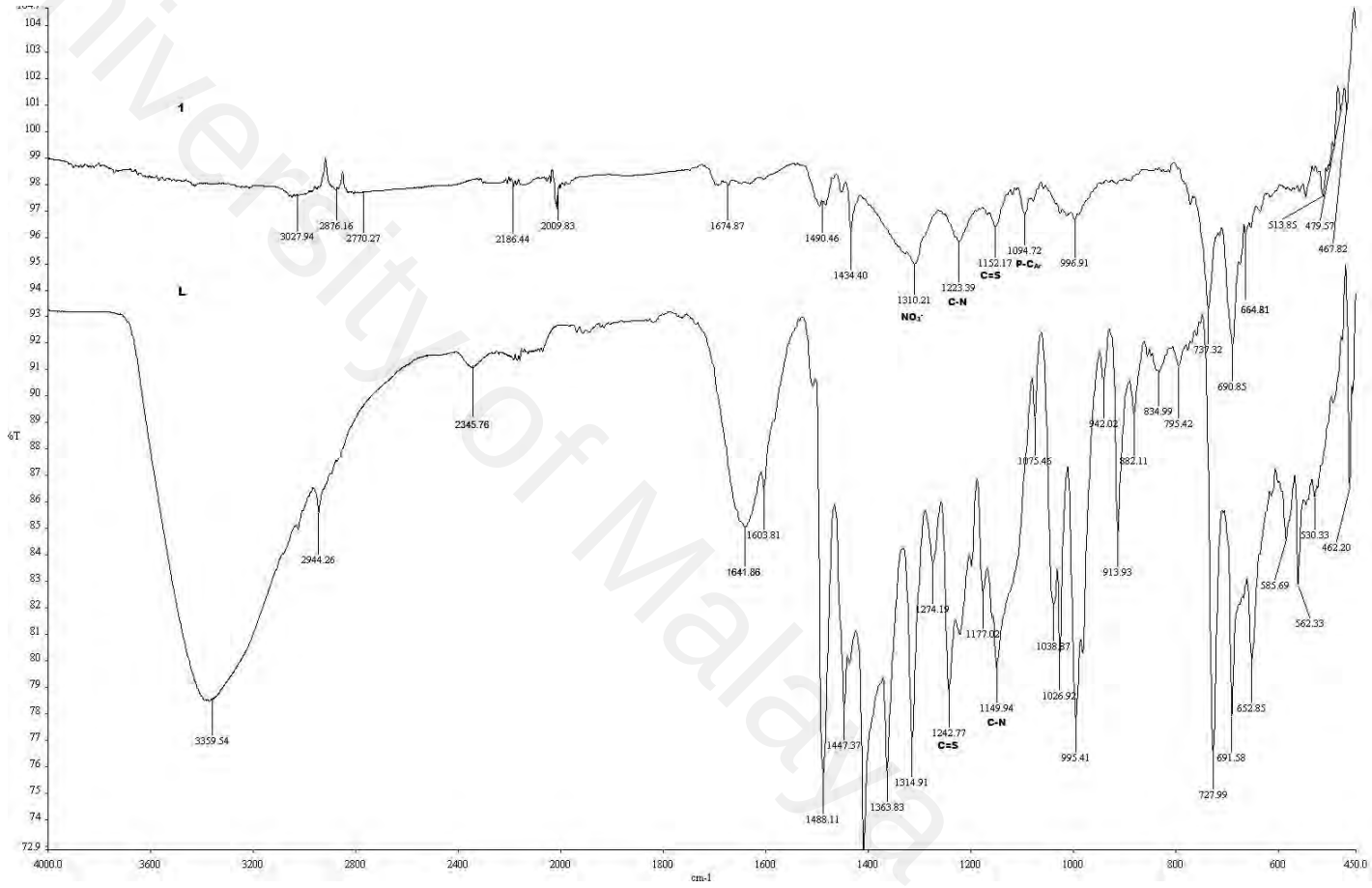


UV-Vis comparison graph data for 3-benzyl-1,3-thiazolidine-2-thione and complex **4**

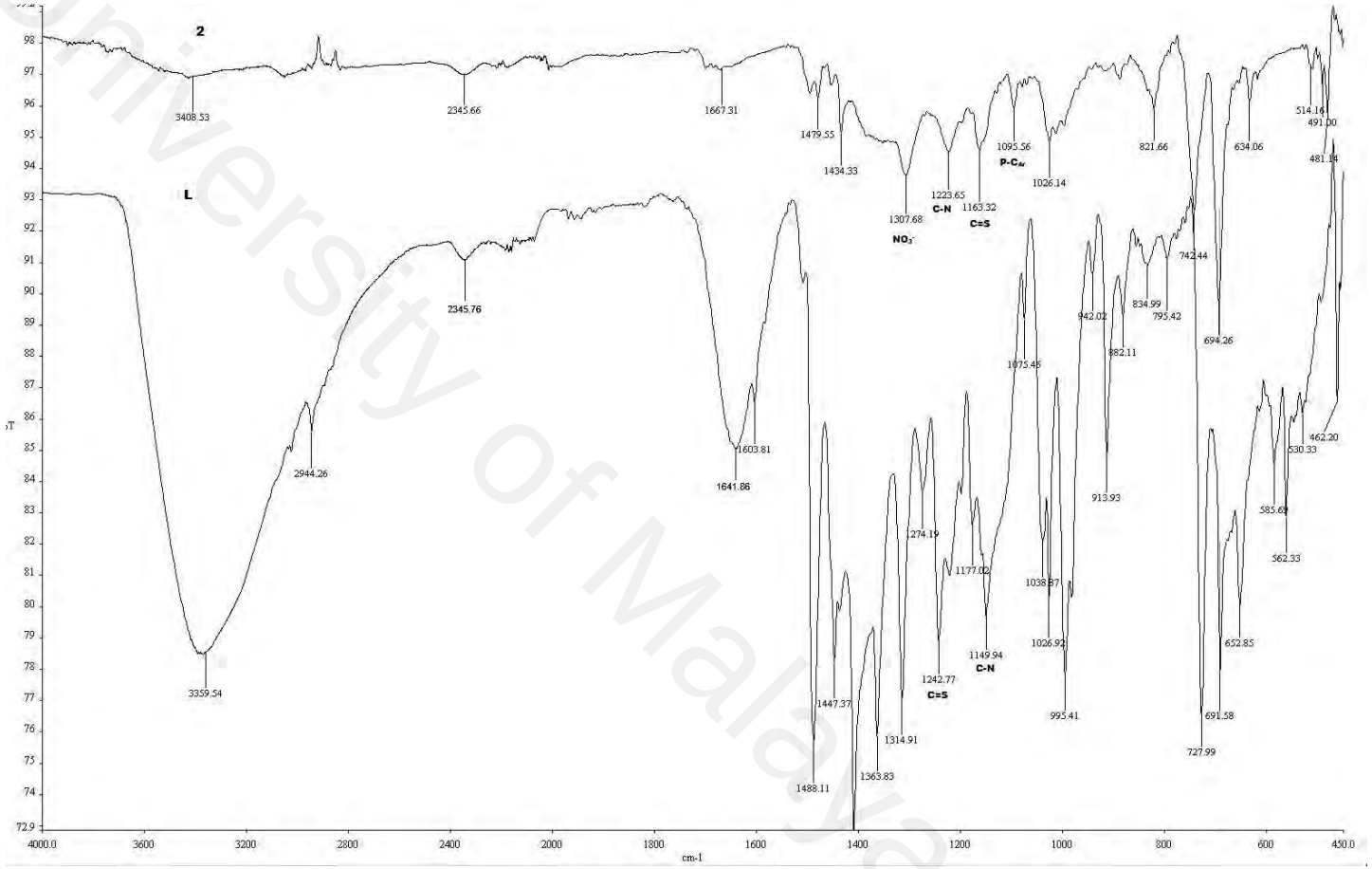


UV-Vis comparison graph data for 3-benzyl-1,3-thiazolidine-2-thione and complex **5**

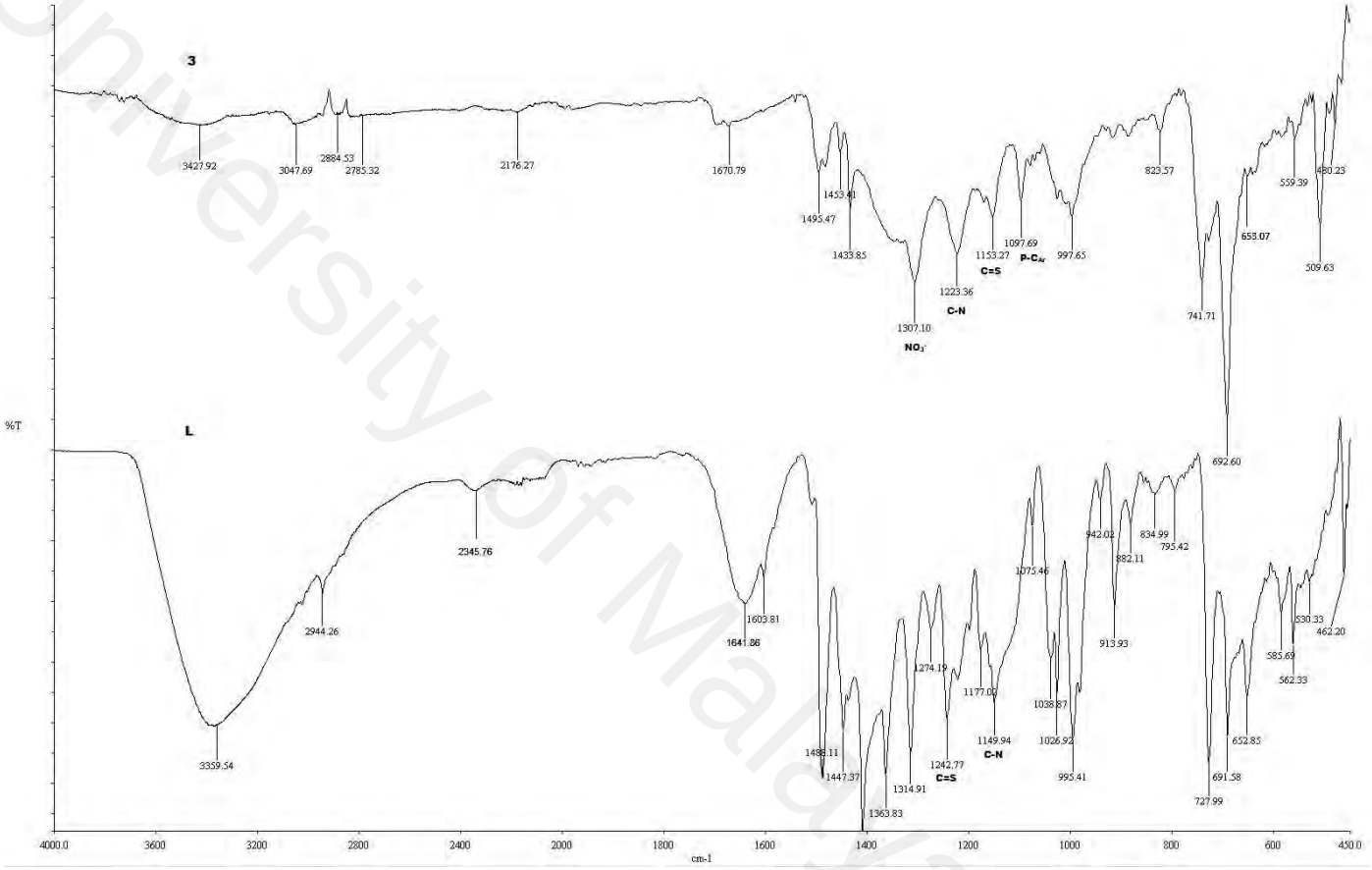
Appendix B: FTIR



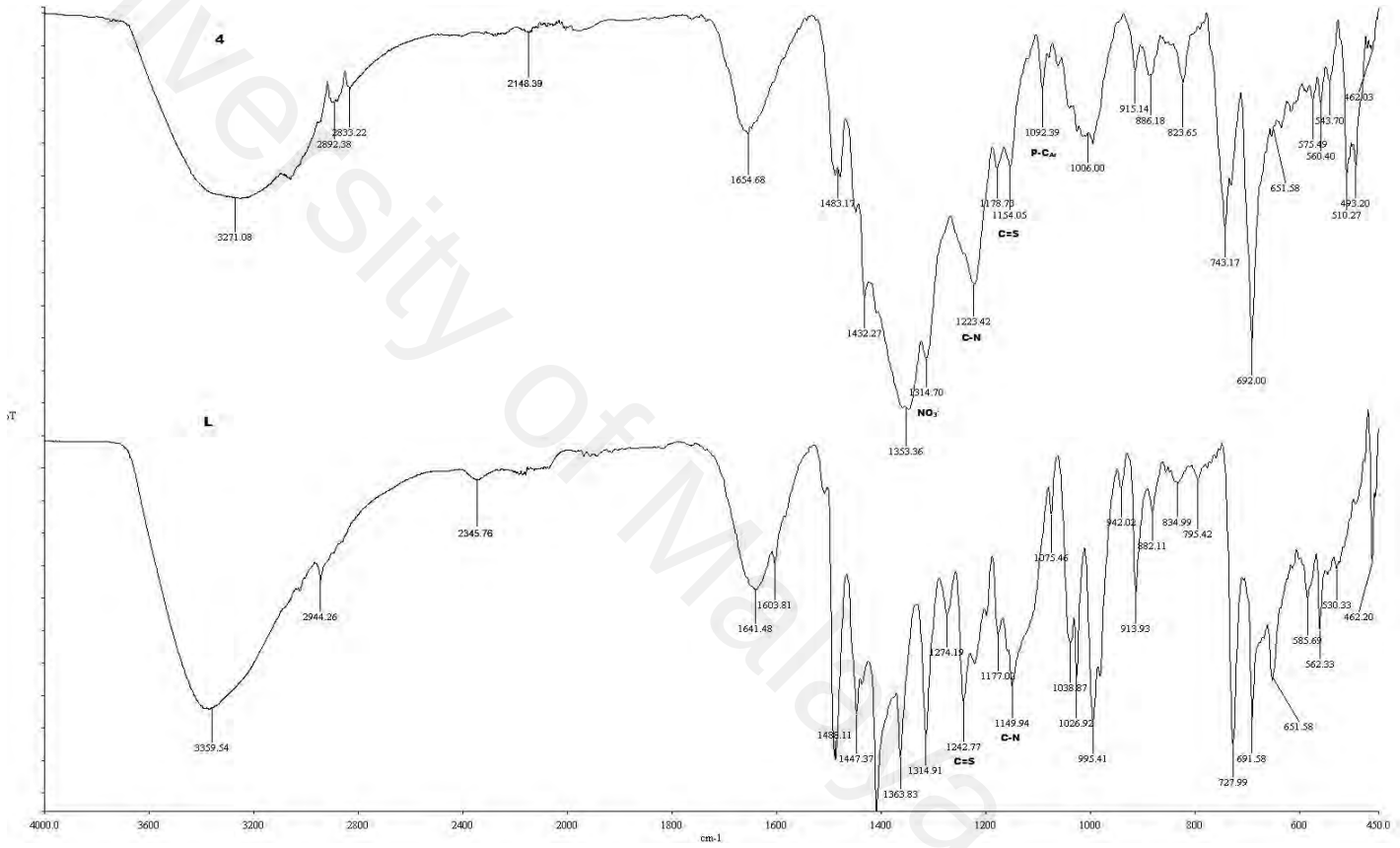
Comparison of the FTIR spectra for 3-benzyl-1,3-thiazolidine-2-thione (**L**) and complex **1**



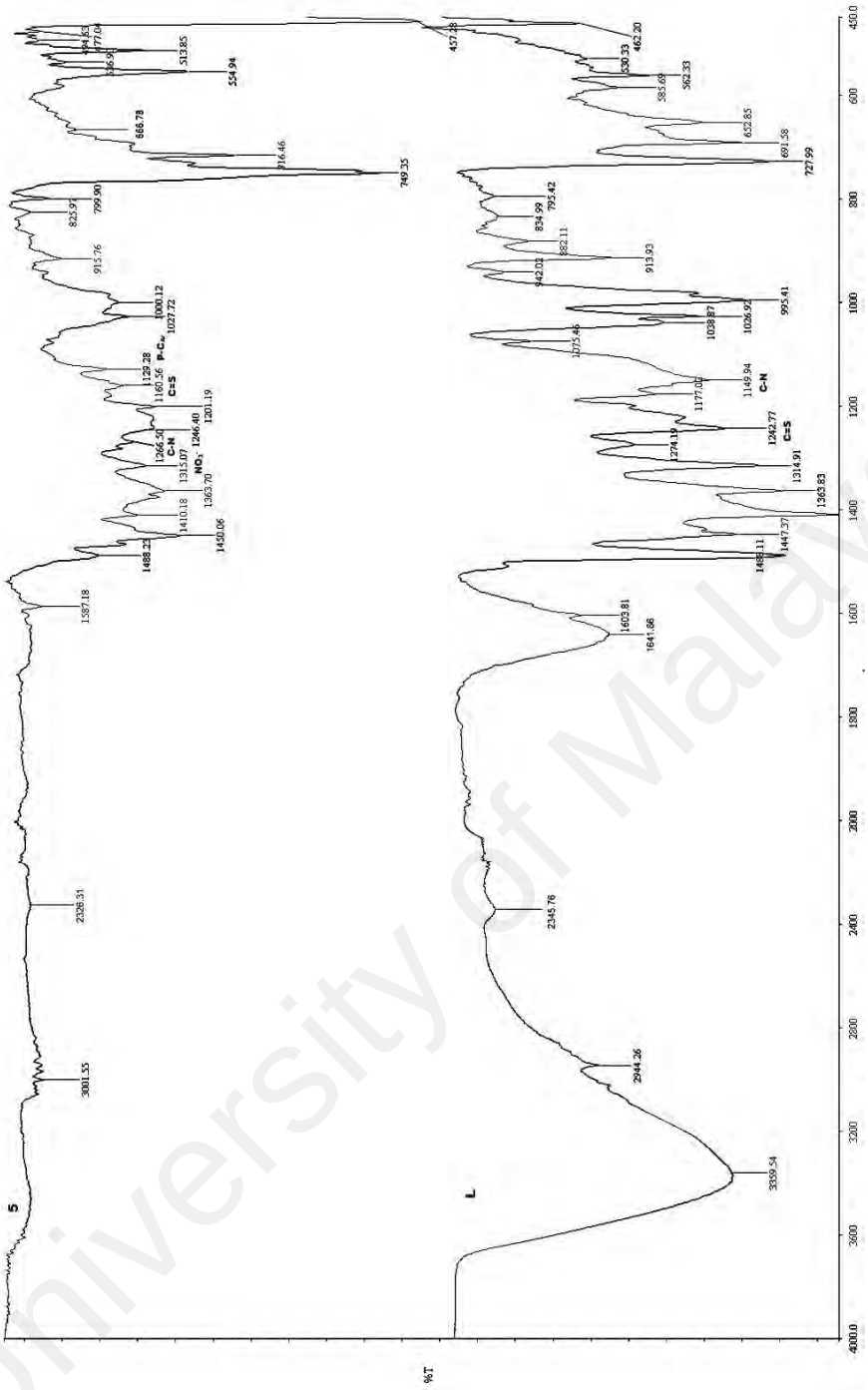
Comparison of the FTIR spectra for 3-benzyl-1,3-thiazolidine-2-thione (**L**) and complex **2**



Comparison of the FTIR spectra for 3-benzyl-1,3-thiazolidine-2-thione (**L**) and complex **3**

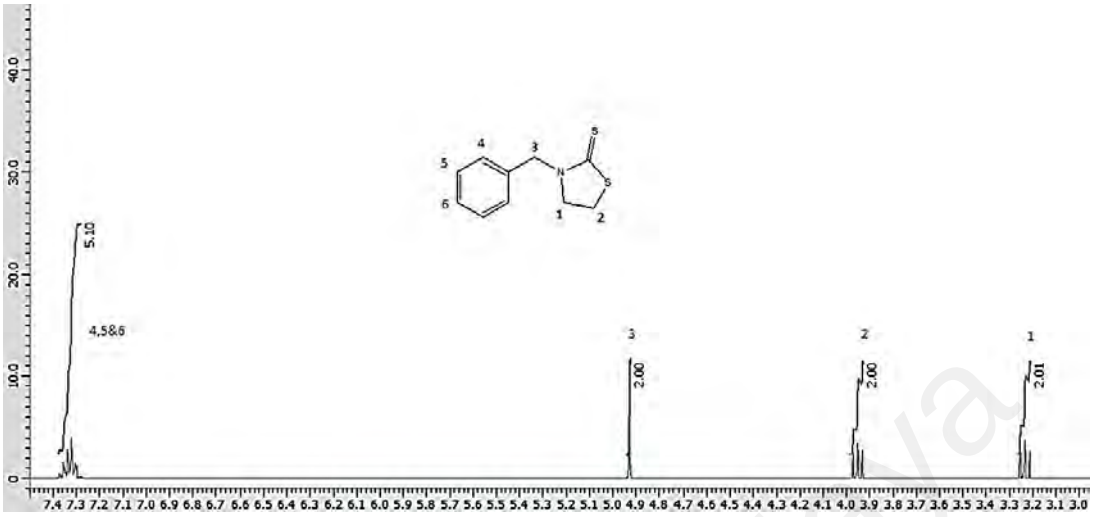


Comparison of the FTIR spectra for 3-benzyl-1,3-thiazolidine-2-thione (**L**) and complex **4**

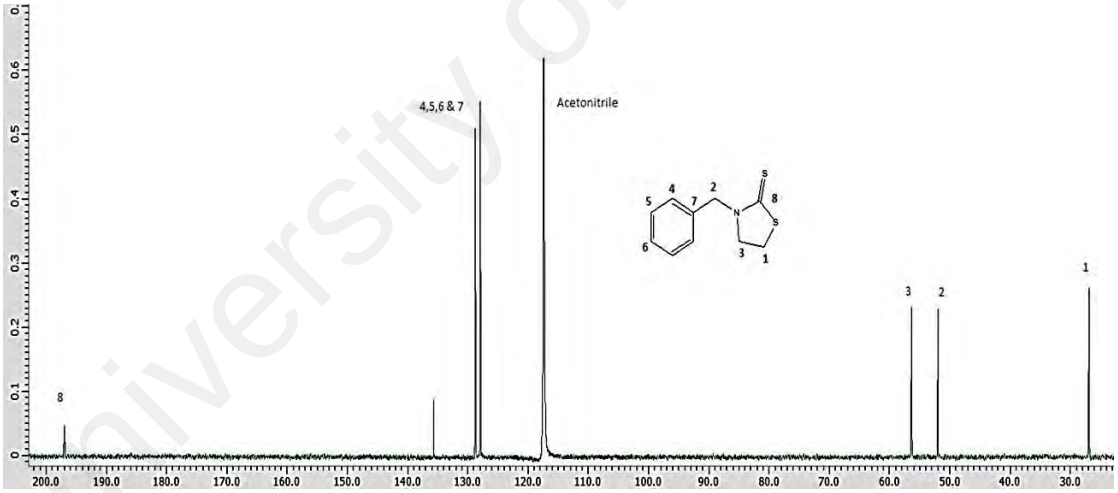


Comparison of the FTIR spectra for 3-benzyl-1,3-thiazolidine-2-thione (**L**) and complex **5**

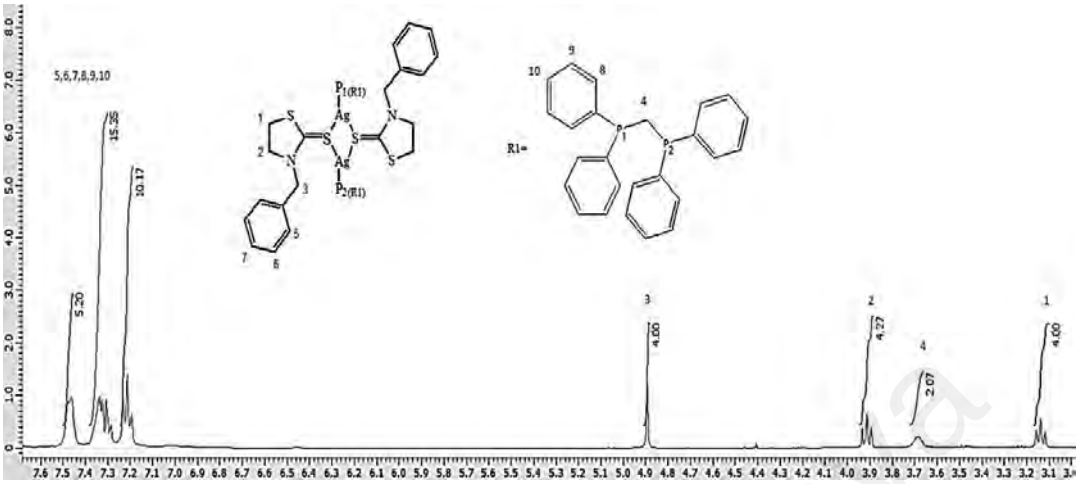
Appendix C: NMR



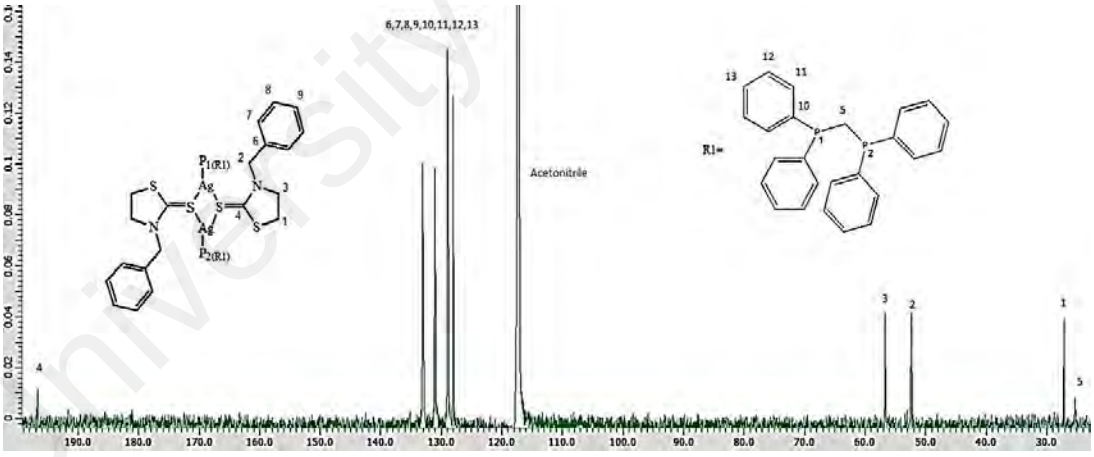
^{1}H NMR spectrum for 3-benzyl-1,3-thiazolidine-2-thione (L)



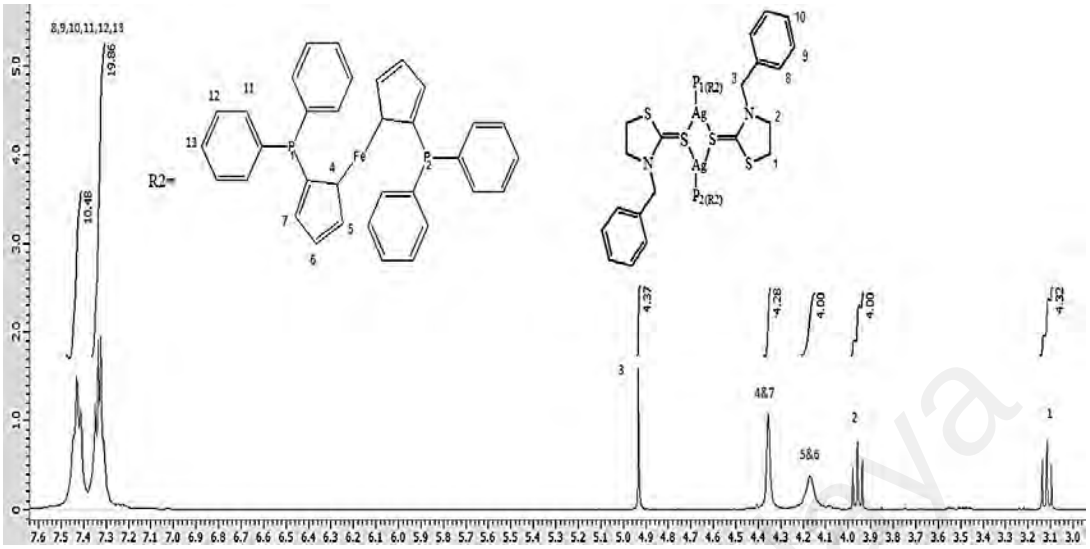
^{13}C NMR spectrum for 3-benzyl-1,3-thiazolidine-2-thione (L)



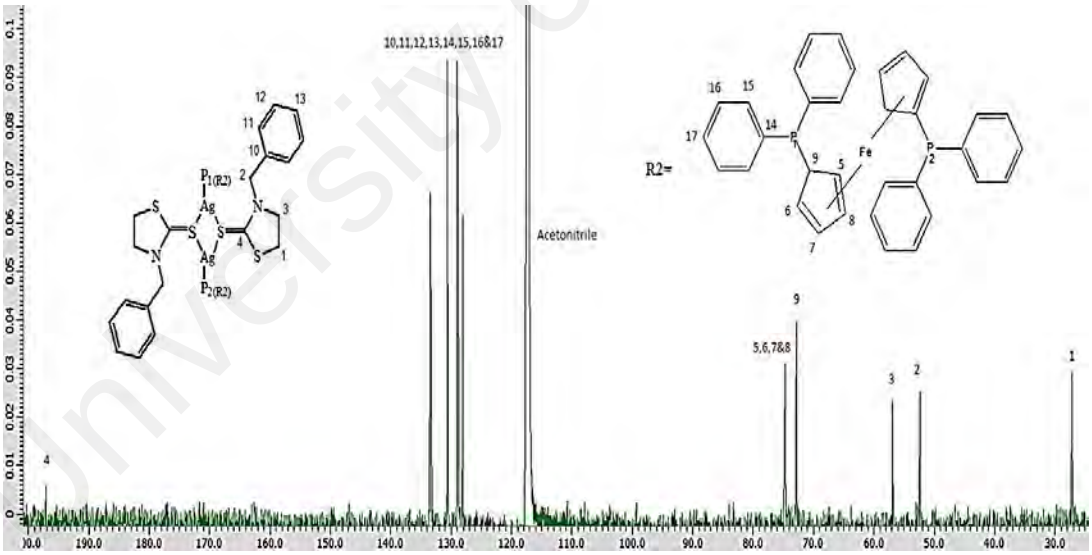
^{1}H NMR spectrum for complex **1**



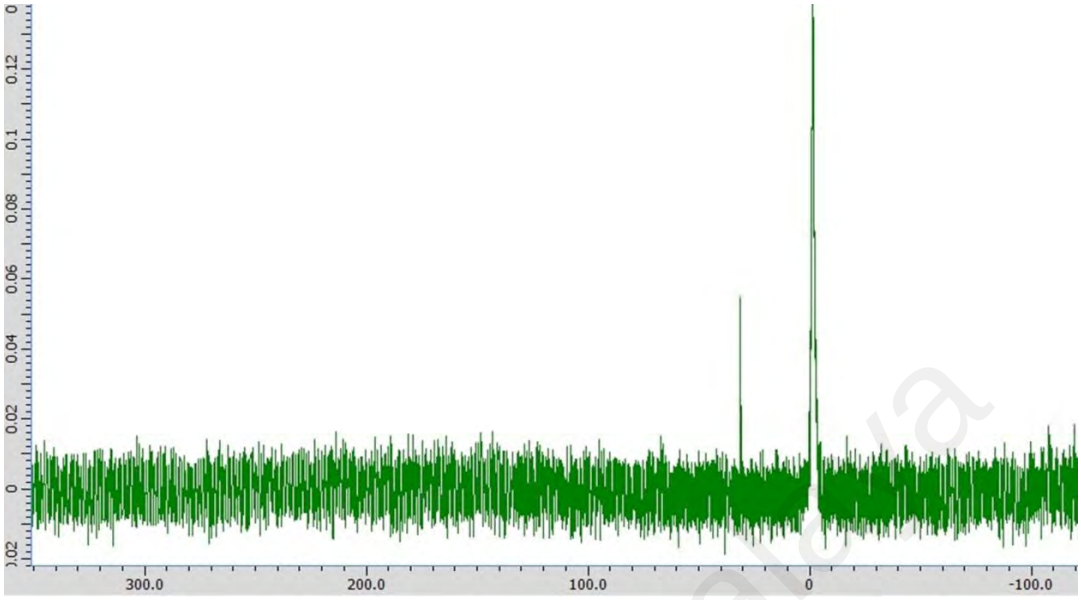
^{13}C NMR spectrum for complex **1**



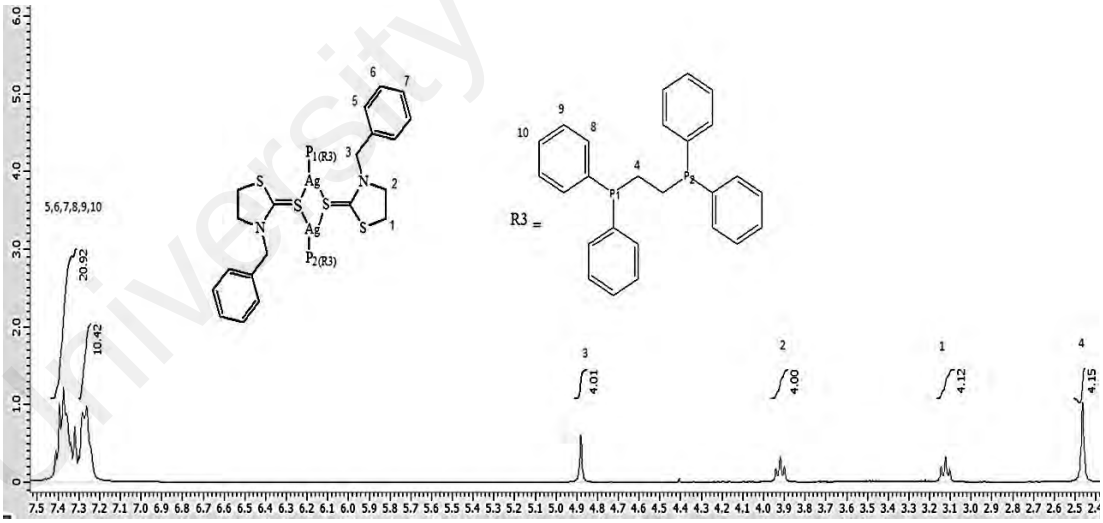
^{1}H NMR spectrum for complex **2**



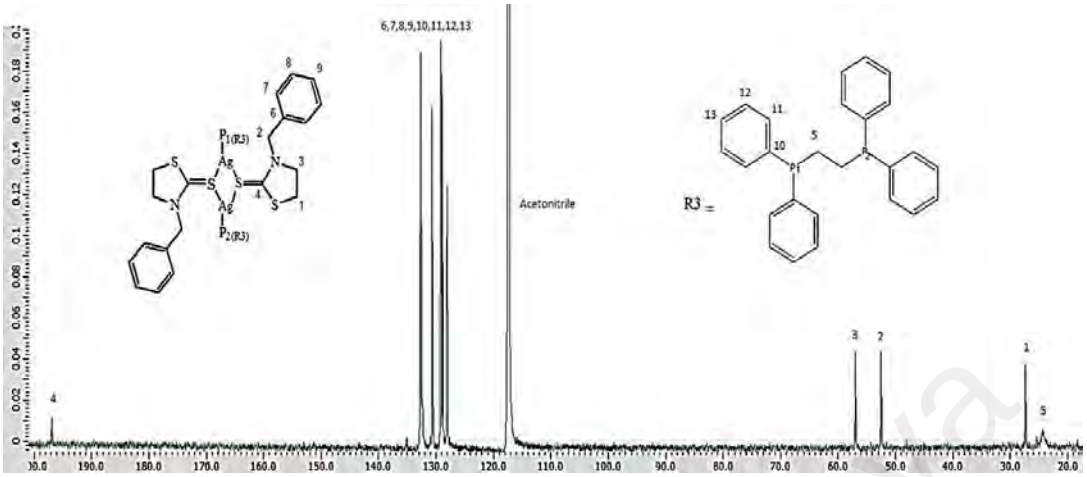
^{13}C NMR spectrum for complex **2**



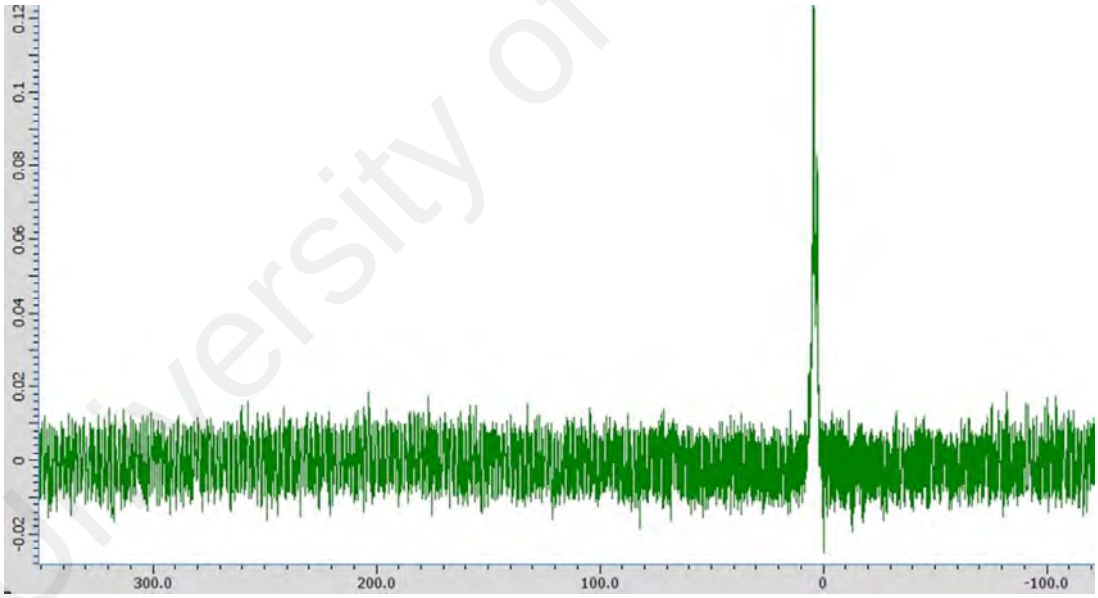
^{31}P NMR spectrum for complex **2**



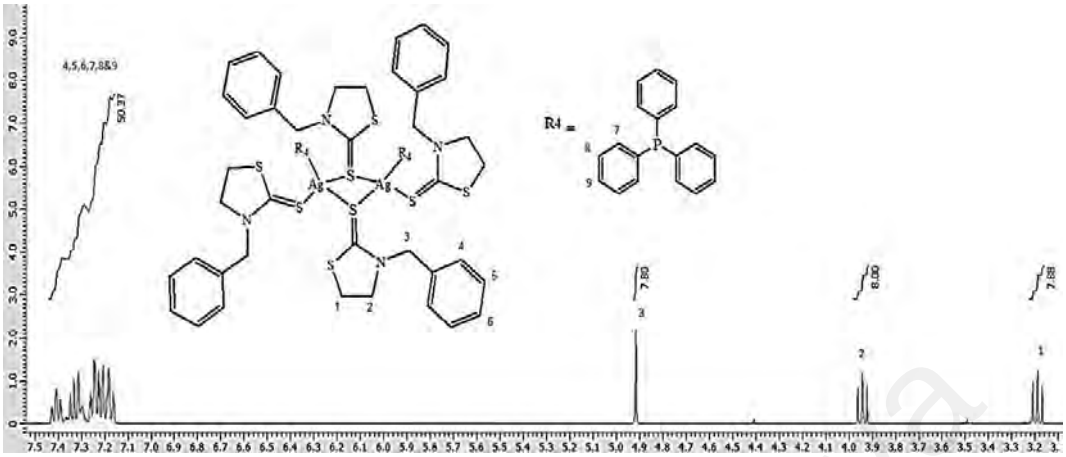
^{1}H NMR spectrum for complex **3**



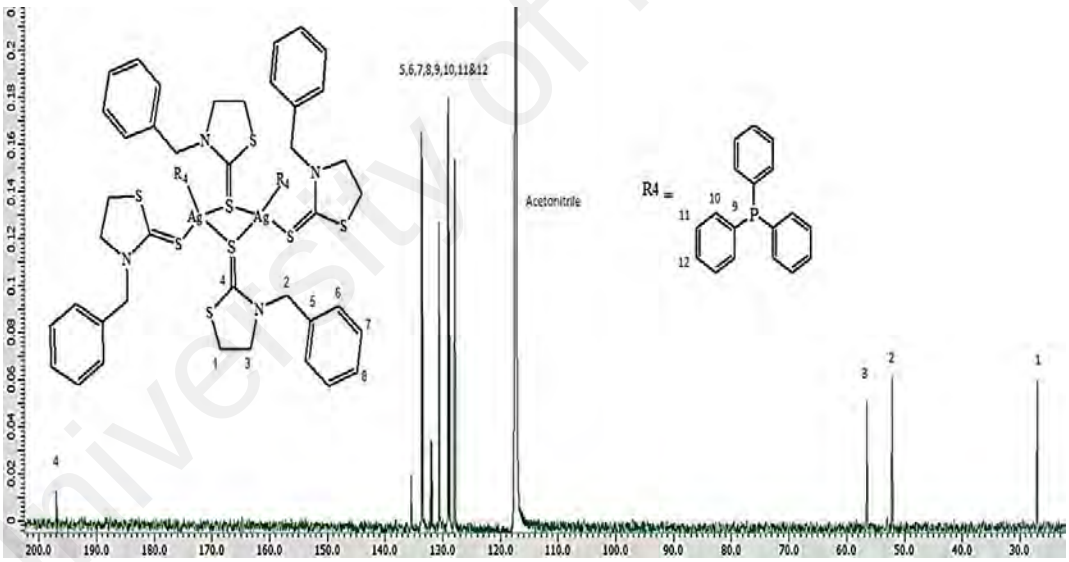
^{13}C NMR spectrum for complex **3**



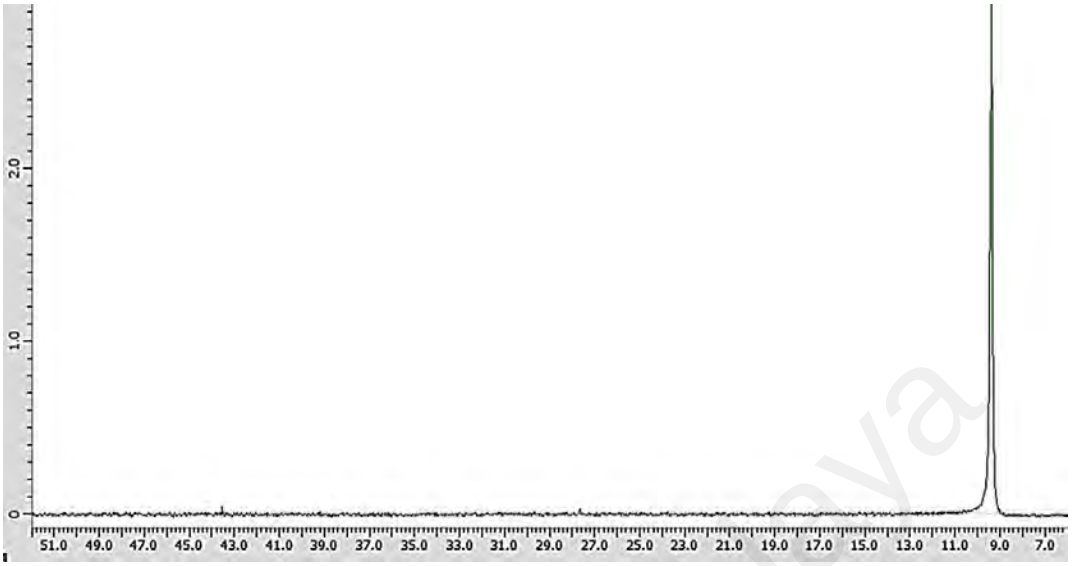
^{31}P NMR spectrum for complex **3**



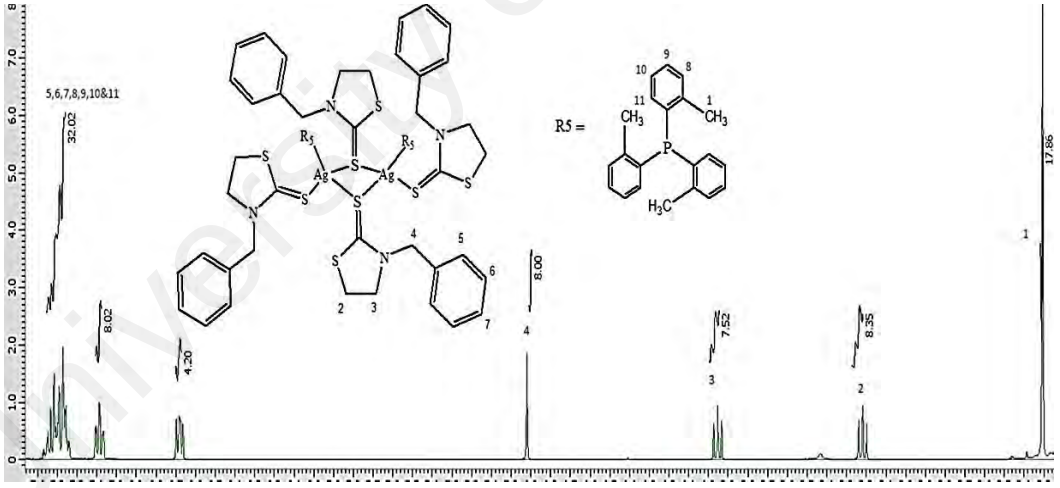
^{1}H NMR spectrum for complex **4**



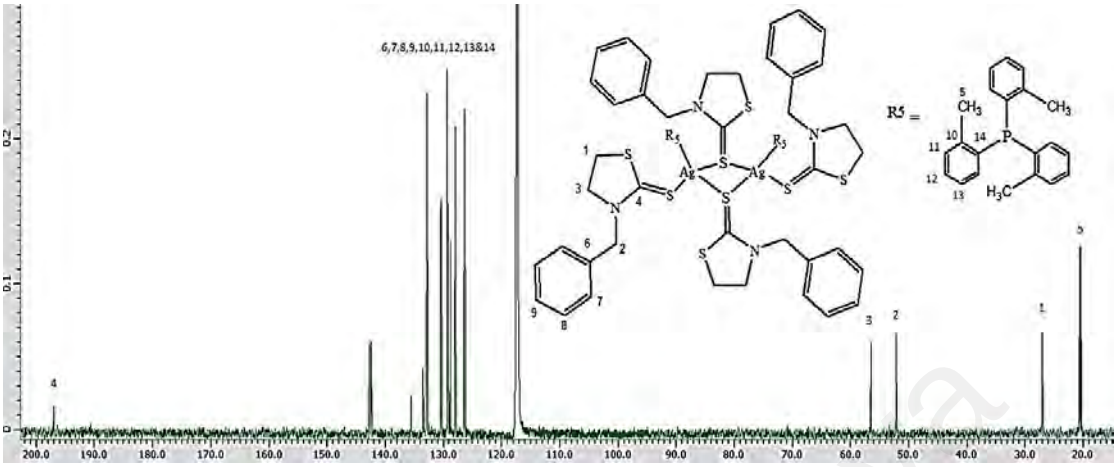
^{13}C NMR spectrum for complex **4**



^{31}P NMR spectrum for complex **4**

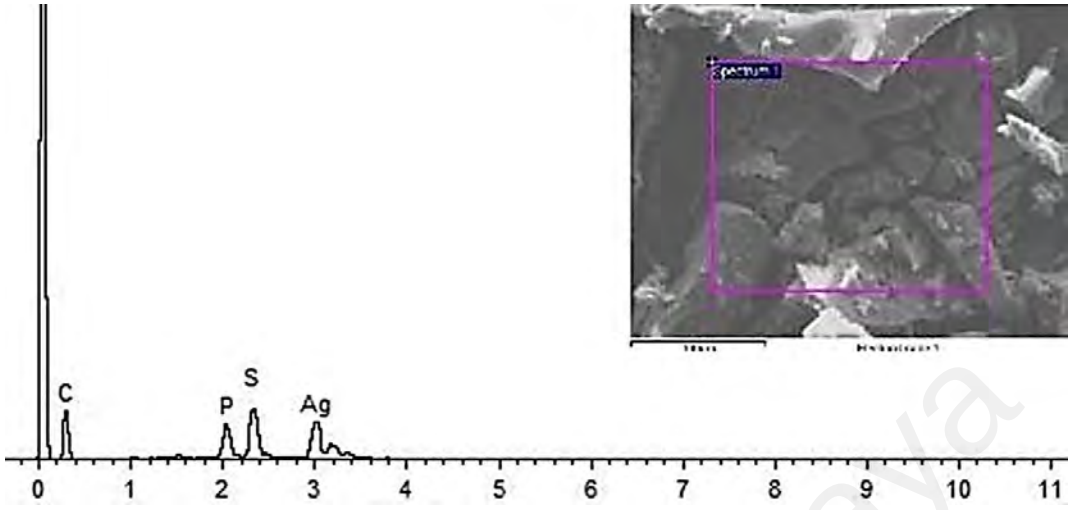


^{1}H NMR spectrum for complex **5**

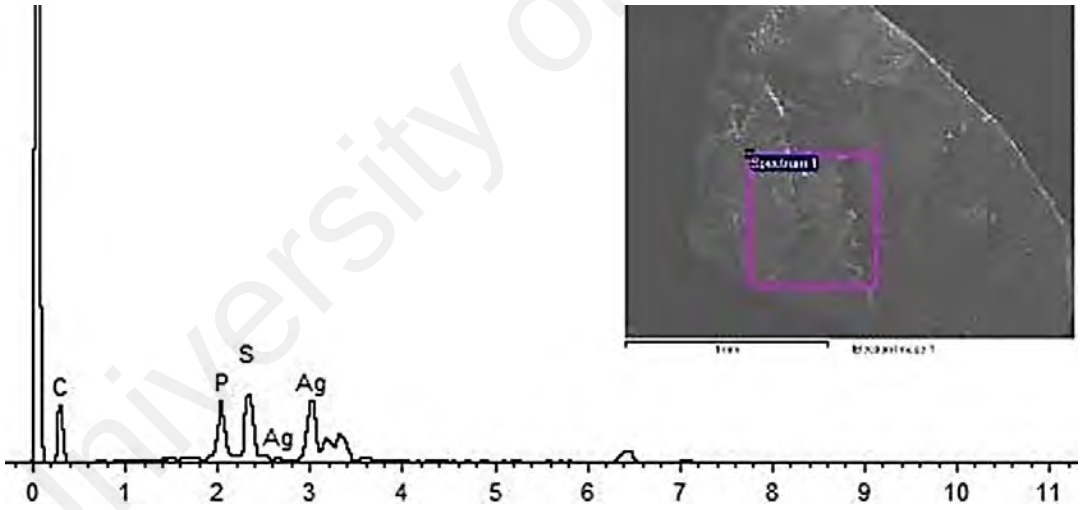


^{13}C NMR spectrum for complex **5**

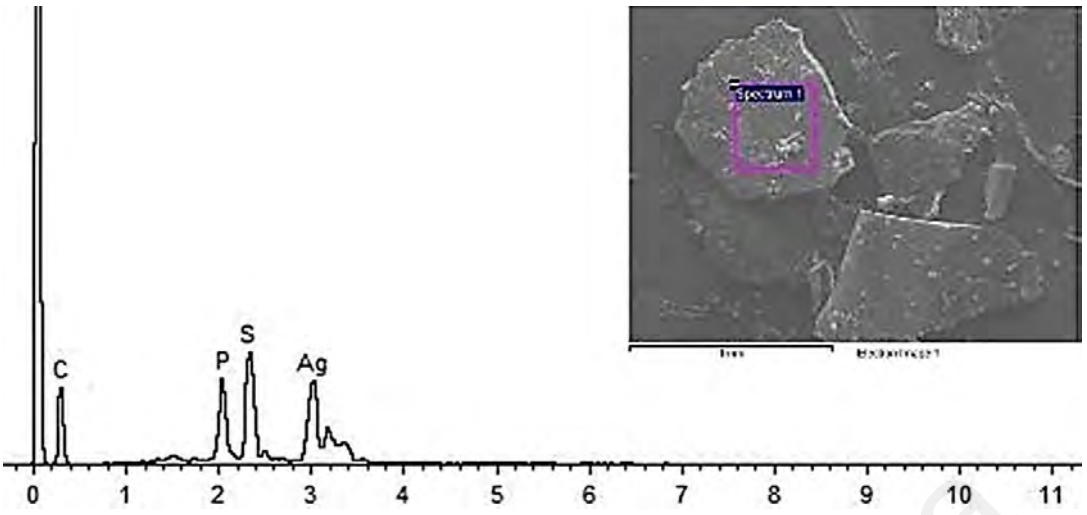
Appendix D: EDX



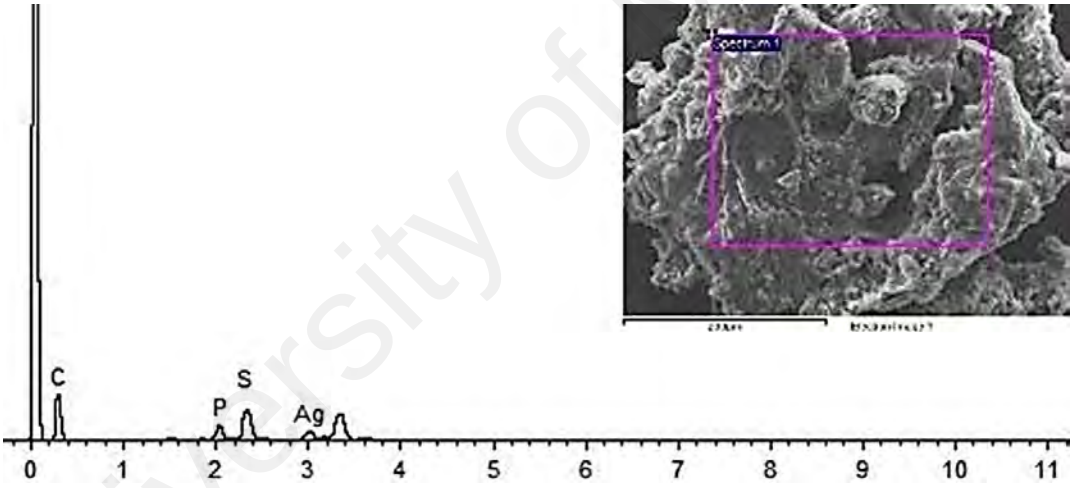
EDX analysis for complex **1**



EDX analysis for complex **2**

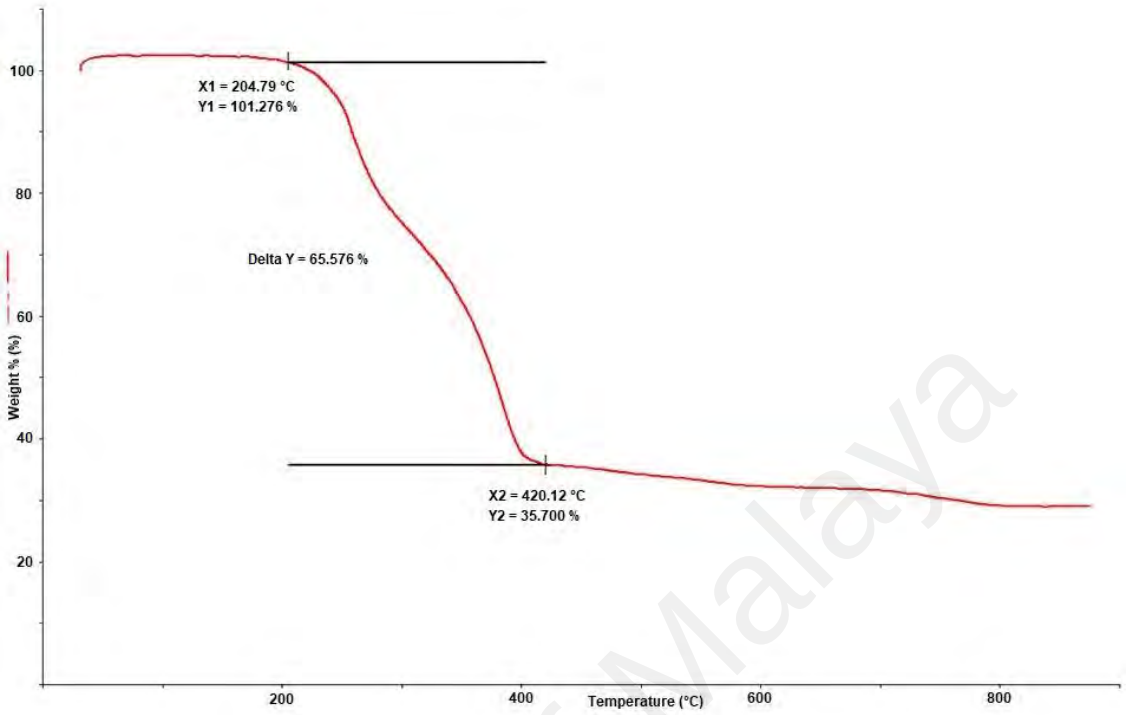


EDX analysis for complex **3**

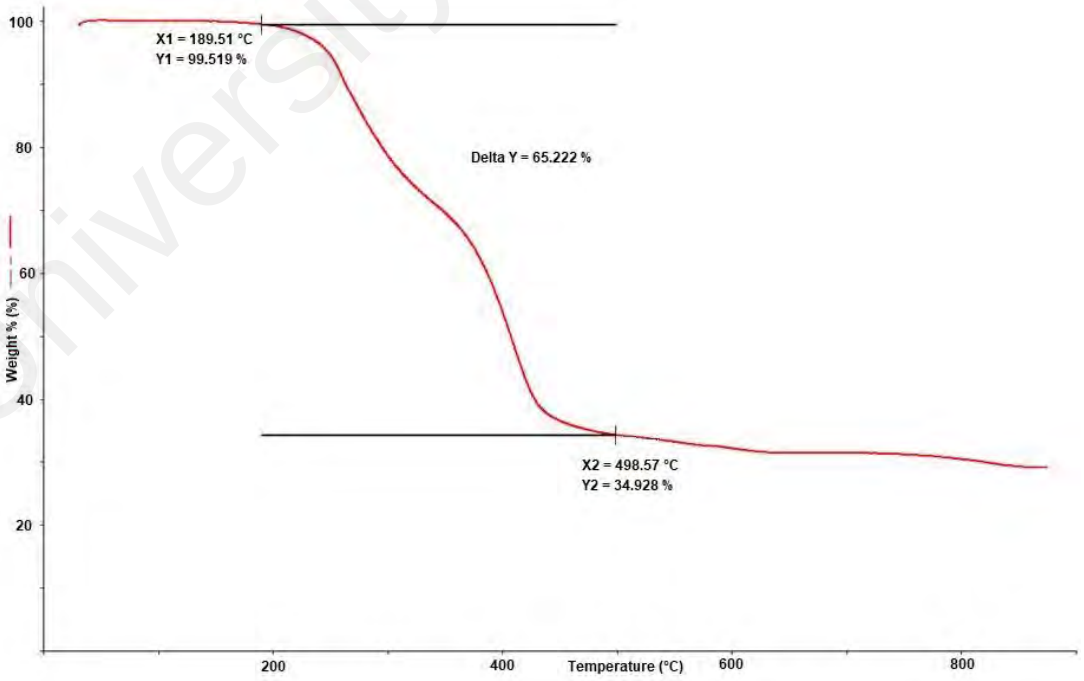


EDX analysis for complex **4**

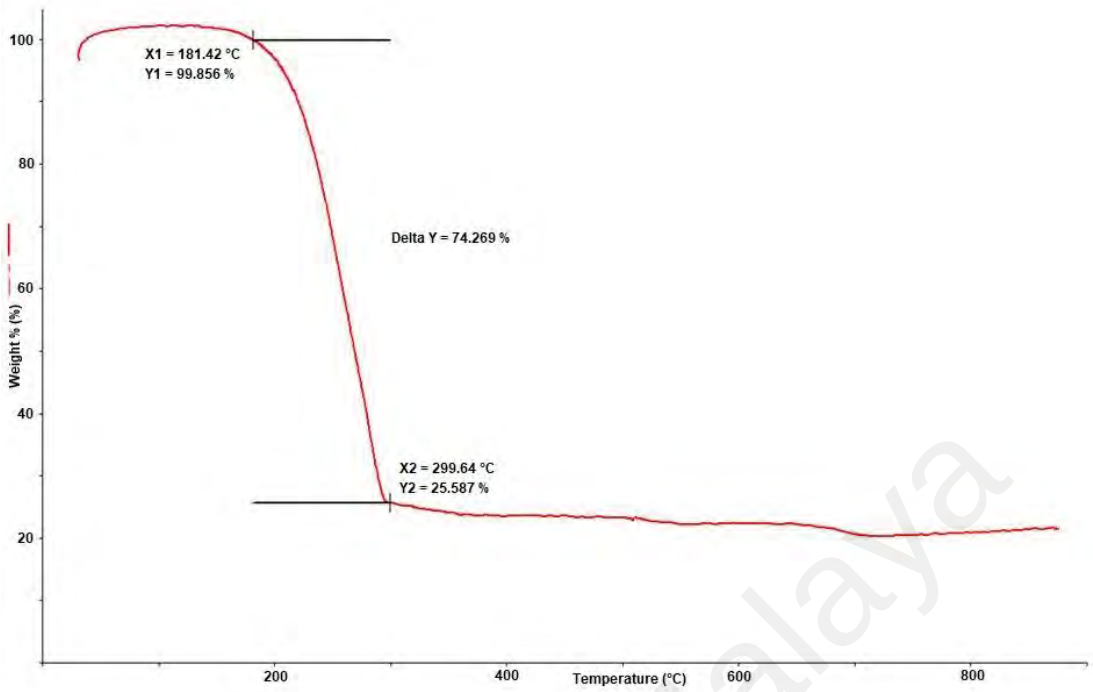
Appendix E: TGA



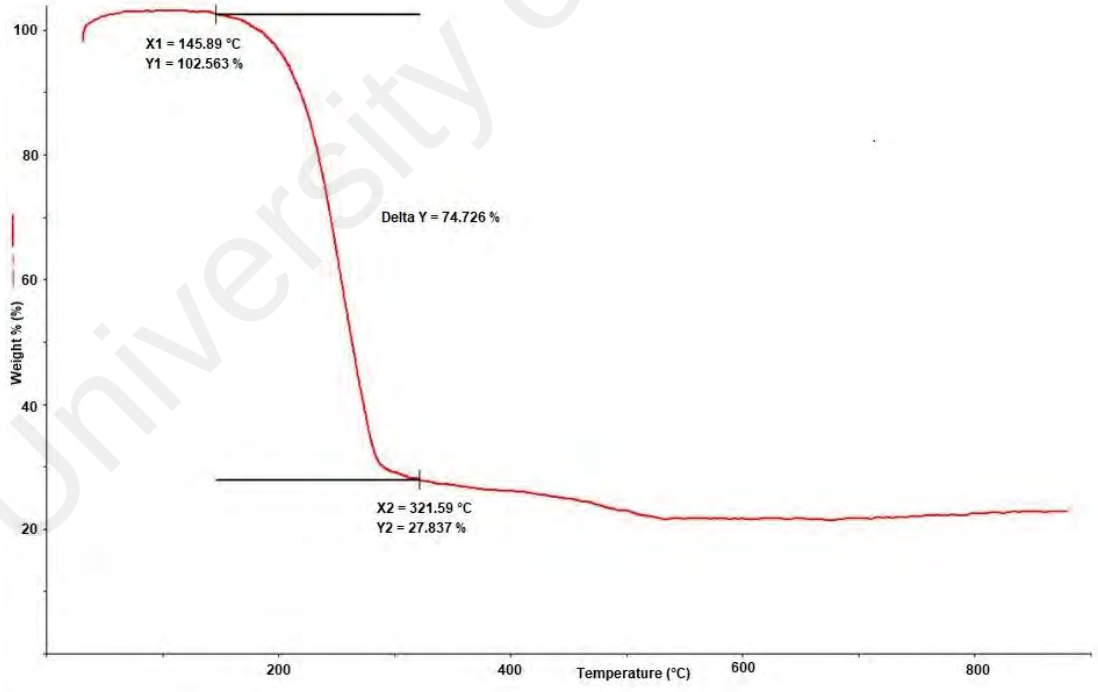
TGA results for complex **1**



TGA result for complex **3**



TGA result for complex **4**



TGA result for complex **5**