SYNTHESIS OF TRANSITION METAL COMPLEXES CONTAINING SYMMETRICAL CHALCONE-DERIVED SCHIFF BASES AND CYTOTOXIC STUDIES AGAINST BLADDER CANCER CELLS

NABEEL ARIF TAWFEEQ

FS 2019 60

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By

NABEEL ARIF TAWFEEQ

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

May 2019

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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May 2019

Chairman : Mohamed Ibrahim Mohamed Tahir, D.Phil.
Faculty : Science

Dithiocarbazate Schiff bases and their derivatives have drawn considerable attention due to their unique properties and applications. Many dithiocarbazate metal complexes have been synthesised and applied in many applications such as antibacterial, antifungal, antioxidant agents and in catalysis. Dithiocarbazate metal complexes have also shown significant cytotoxicity against many types of cancer cell lines. This study aims to synthesise non-toxic compounds by synthesising para substituted chalcone derivatives and studying the effect of substituted functional group electronegativity on the cytotoxicity of the metal complexes. Nine chalcones were synthesised using base-catalysed Aldol condensation. The chalcones were symmetrical in order to direct the electron density towards the transition metal in the complexes. These symmetrical chalcones were then reacted with S-benzyldithiocarbazate to form nine novel Schiff bases. A total of 45 novel metal complexes were synthesised by reacting these nine Schiff bases with five divalent transition metal acetates which were Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+}. These Schiff bases and their metal complexes were fully characterised using various characterisation techniques including FTIR, UV-Vis, ^{1}H and ^{13}C NMR spectroscopy, mass spectral, elemental analysis, and single crystal X-ray diffraction. The cytotoxic properties of these compounds were also tested against two types of bladder cancer cell lines which were the minimum-invasive human bladder cancer carcinoma cell line (RT112) and the invasive human bladder carcinoma cell line (EJ28).All Schiff bases were inactive against both types of bladder cancer cell. The unsubstituted chalcones and their metal complexes were inactive against both cells which means the substituted group on benzene ring plays an important roles toward the cytotoxicity of metal complexes. Cu(II) complexes of DTASB, DEASB, DIPASB, DCLASB, DBRASB, DNNMASB and DMeOSB showed moderate cytotoxicity against both cell lines with more selectivity toward EJ-28 than RT-112. Less than that, Zn(II) complexes of DTASB, DEASB and DIPASB showed moderate activity against bladder cancer cell line type EJ-28 while they were inactive against RT-112 cell lines.

An Fe(II) complex, FeDMeOSB, showed moderate activity against both cell lines. CuDMeOSB showed highest cytotoxicity against both types of bladder cancer cell lines EJ-28 and RT-112 with IC_{50} values equal to 1.651 and 1.762 μM, respectively. In addition, CuDNNMASB showed more selectivity against RT-112 than EJ-28 with IC_{50} value equal to 1.874 μM.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS KOMPLEKS LOGAM PERALIHAN MENGANDUNGI BES SCHIFF TERBITAN KALKON BERSIMETRI DAN KAJIAN SITOTOKSIK TERHADAP SEL KANSER PUNDI

Oleh

NABEEL ARIF TAWFEEQ

Mei 2019

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Fakulti : Sains

Bes Schiff ditiokarbazat dan terbitannya telah mendapat perhatian yang besar disebabkan oleh sifat dan aplikasi unik mereka. Banyak kompleks logam ditiokarbazat telah disintesis dan digunakan dalam banyak aplikasi seperti antibakteria, antikulat, agen antioksidan dan pemangkinan. Kompleks logam ditiokarbazat juga menunjukkan sitotoksisiti yang ketara terhadap pelbagai jenis sel kanser. Kajian ini bertujuan untuk mensintesis sebatian bukan toksik dengan mensintesis terbitan para kalkon gantian dan mengkaji kesan keelektronegatifan kumpulan fungsi yang digantikan pada kesitotoksikan kompleks logam. Sembilan kalkon telah disintesis dengan menggunakan pemeluwapan Aldol berbes. Kalkon ini kemudiannya bertindak balas dengan S-benzilditiokarbazat untuk membentuk sembilan novel bes Schiff. Empat puluh lima kompleks logam novel telah disintesis dengan bertindak balas terhadap sembilan bes Schiff dengan lima asetat logam peralihan divalen iaitu Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+} dan Cd^{2+}. Bes Schiff dan kompleks logam mereka telah dicirikan sepenuhnya menggunakan teknik pencirian pelbagai termasuk spektroskopi FTIR, UV-Vis, ^{1}H & ^{13}C NMR, spektrum jisim, analisis unsur, dan pembelauan sinar-X hablur tunggal. Sifat sitotoksik sebatian ini juga diuji terhadap dua jenis sel kanser pundi iaitu sel karsinoma kanser pundi manusia yang kurang invasif (RT112) dan sel karsinoma kanser pundi manusia yang invasif (EJ28). Semua bes Schiff tidak aktif terhadap kedua-dua jenis sel kanser pundi. Kalkon yang tiada gantian dan kompleks logam mereka tidak aktif terhadap kedua-dua sel bermaksud kumpulan yang digantikan pada gelang benzena memainkan peranan penting ke arah kesitotoksikan kompleks logam. Kompleks Cu(II) dengan DTASB, DEASB, DIPASB, DCLASB, DBRASB, DNNMASB dan DMeOSB menunjukkan kesitotoksikan sederhana terhadap kedua-dua sel sel dengan lebih selektif ke arah EJ-28 daripada RT-112. Kompleks Zn(II) dengan DTASB, DEASB dan DIPASB menunjukkan aktiviti sederhana terhadap jenis sel kanser pundi jenis EJ-28 sementara mereka tidak aktif terhadap sel RT-112. Kompleks Fe(II), FeDMeOSB, menunjukkan aktiviti sederhana terhadap kedua-dua

sel. CuDMeOSB menunjukkan kesitotoksikan tertinggi terhadap kedua-dua jenis sel kanser pundi EJ-28 dan RT-112 dengan nilai IC_{50} bersamaan dengan 1.651 dan 1.762 μM masing-masing. Di samping itu, CuDNNMASB menunjukkan lebih banyak kepilihan terhadap RT-112 daripada EJ-28 dengan nilai IC_{50} bersamaan dengan 1.874 μM.

ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge and thank my project supervisor, Dr Mohamed Ibrahim Mohamed Tahir, for his supporting, patience, wisdom, encouragements and invaluable guidance during my PhD study. I will forever remember those long talks we had in both academic and personal matters. I would also like to thank Assoc. Prof. Dr Thahira Begum, who has also been there for her advice, encouragement, friendship and guidance. I am also grateful to Assoc. Prof. Dr Abhimanyu for his advice, guidance and using his lab for doing cytotoxicity part in this project. Also I would like to thank Dr Mohd Farid for his guidance and advice.

Special thanks to Prof. Karen A. Crouse for her advice, supporting and motivation. I am also indebted to all lecturers, the laboratory thechnicians and staff in the Faculty of Science and Faculty of Medicine for helping me throughout my PhD study.

I would like to thank my dear labmates: Nadia Enis, Fatiha, Fadila, Chah Chee Keong, Lee Chin, Ali, Idris, Nabihah and Nazirah. We have had a lot of sweet memories together.

Last but not least, I gratefully thank my wife Iqbal and my sons Farooq, Husham, Ahmed and my daughter Haneen for their encouragements, supporting and unconditional love. Special thanks to my father, mother. Also I would like to thank my brothers Kamal, Waleed, Tagreed and Waiel.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

SBDTC	S-benzyldithiocarbazate
DBA	Dibenzalacetone
DCNMA	Dicinnamalacetone
DTA	Di-*p*-tolylacetone
DEA	Di-*p*-ethylbenzalacetone
DIPA	Di-*p*-isopropylbenzalacetone
DCLA	Di-*p*-chlorobenzalacetone
DBRA	Di-*p*-bromobenzalacetone
DMeO	Di-*p*-methoxybenzalacetone
DNNMA	Di-*p*-N,N-dimethylaminobenzalacetone
RPMI	Roswell Park Memorial Institute medium
FBS	Fetal bovine serum
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
PBS	Phosphate-buffered saline
DMSO	Dimethylsulphoxide
FT-IR	Fourier Transform Infrared
NMR	Nuclear Magnetic Resonance
MS	Mass spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
UV-Vis	Ultraviolet-Visible
RT-112	Minimally-invasive human bladder carcinoma cell line
EJ-28	Invasive human bladder carcinoma cell line
IC_{50}	Inhibition concentration at 50%
ELISA	Enzyme-linked immunosorbent assay
XRD	X-ray diffraction
SC-XRD	Single Crystal X-ray Diffraction

CHAPTER 1

INTRODUCTION

1.1 General

Medicinal bioinorganic chemistry field blossoming inspired many worldwide researchers to design and innovate metal-based drugs to be used as anticancer drugs. Therefore, using transition metals has outweigh the organic-based drugs because of transition metals have wide range of oxidation and coordination numbers, redox states, tuneable kinetics and thermodynamics, and structural and geometries diversity of the substituted ligands (van Rijt& Sadler, 2009). The discovery of cisplatin as anticancer, about 45 years ago, has making a breakthrough in medicinal inorganic chemistry field as well as in our understandings to the disease and treatment approaches. The organic ligands which effectively bonded with metal ions enhanced the overall efficiency and also driving the innovation in therapy and disease diagnosis areas. Besides, increasing of therapeutic compounds potency and limiting their side-effects is a common goal in the field of medicinal chemistry (Jones *et al*., 2014). To achieve this goal, compounds are developed to target the disease site or activated by the disease of specific biological process. The metal complexes which containing the targeting functions or bioactive ligands or agents activated by specific enzymes provide a new avenues in drug development (Chiang *et al*., 2012). Nowadays, after more than 30 years from the improvement of using cisplatin as a powerful chemotherapeutic agent, still it is the best-selling anticancer drug in the world. It is used as chemotherapeutic agent to treat many types of cancer such as bladder, ovarian, head and neck, lymphomas and cervical cancers. Over many past decades, cispaltin and its derivatives have been ensured as powerful anticancer agents, while, only two of them (oxaliplatin and carboplatin) have been used clinically worldwide. Unfortunately, there are some obstacles side-effects against current platinum drugs such as (van Rijt & Sadler, 2009):-

- Limited efficiency because they are efficient for limited cancer types.
- Some types of tumors may have acquired or intrinsic resistance.
- They have many side-effects like, kidney toxicity, bone narrow suppression and nausea.

Therefore, there is a big need to discover new compounds to treat many types of cancer with less side-effects better than cisplatin and its derivatives. New anticancer metal based compounds development is important challenge for many inorganic chemists to face the fact that after more than four decades of researches in anticancer field there are few compounds clinically used as anticancer drug. Based on metal-based anticancer action mode, metal anticancer compounds can be categorized into five categories (Gianferrara *et al*., 2009):-

(1) The metal in any compound may has the functional role and bind with the biological target.
(2) The central metal may has structural role and bind through non-covalent bond with the biological target.
(3) The metal may acts as a good carrier for the active ligands which delivered in vivo.
(4) The metal compound may acts like catalyst.
(5) The metal compound may behaves as a photo-sensitizer or photoactive.

It is known that the fourth most common cancer among men is bladder cancer. Recent diagnostic data on this disease showed that men diagnostic four times more than women. Older people are most affected by bladder cancer than young people. 90% of people suffer from bladder cancer are older than 55 years old. The average age of people who diagnosed with bladder cancer is 73 years old (Fosså *et al.* 2008; Jacobs *et al.* 2010; Tiwari & Roy,2012). Recent therapy of bladder cancer are Cisplatin, Methotrexate, Gemcitabine, Mitomycin, Vinblastine, Doxorubicin, Carboplatin, Docetaxel, Paclitaxel, 5-Flurouracil (5-FU) and its derivatives (Edson Pontes, 1994; Galsky& Bajorin,2007; Kaufman *et al*.,2009; Oosterlinck *et al*., 2002). They are general therapy and have many disadvantages such as expensive, difficult to synthesised, only 25% response to the treatment and many side effects of chemotherapy like nausea and vomiting, loss of appetite, hair loss, mouth sores, diarrhea or constipation, increased risk of infections (because of shortage of white blood cells), bleeding or bruising after minor cuts or injuries due to a shortage of blood platelets and fatigue because of a shortage of red blood cells (Dasari& Bernard Tchounwou, 2014; Georg *et al*.,2012; Koya *et al*., 2006).

Metal-containing drugs have been used to treat many diseases. The most famous one is cisplatin, used in late 1978, which is the most effective anticancer drug in the world (Jemal *et al*., 2009; Swarts *et al*., 2008). Cisplatin success has been motivate many researcher in the past few decades to try another transition metals in term of alternative searching in metal-base chemotherapeutic area (Jakupec *et al*., 2008). There is an urgent issue to synthesise new drugs with less side effects and better selectivity, activity and bioavailability to treat different types of cancer diseases. Furthermore, discovering new drugs with non platin metal centre might open new way to develop useful drugs with fewer side effects (Marcon *et al*., 2002; Ronconi *et al*., 2006). There are many articles highlighted and explained in details the effect of metal complexes potential in designing of novel drugs (Fricker, 2007; Haas & Franz, 2009; Hambley, 2007; Meggers, 2009; Ronconi& Sadler, 2007; Thompson & Orvig, 2006).

Metal centre in transition metal complexes has intrinsic nature, accessible redox state, distinctive coordination modes, and tuneable kinetic and thermodynamic properties drive the transition metal complexes to add more potential advantages more than the organic ligand in the complexes (van Rijt& Sadler, 2009). Furthermore, metal reactivity in the complexes not only controlled by ligands but also the ligands play important roles in the biological activity (Gianferrara *et al*.,2009). In the few last decades there were a great expansion researches happened in the field of coordination

chemistry of nitrogen-sulphur containing Schiff bases compounds such as thiosemicarbazides, dithiocarbazates and their organic derivatives (Akbar Ali *et al*.,1974; Beraldo, 2004; Pelosi, 2010).Transition metal complexes derived from Schiff bases have been played an important role to develop coordination chemistry. Furthermore, the synthesis and application of Schiff bases and their metal complexes add more attention on this area. Schiff bases can be synthesized by the condensation reaction between aliphatic or aromatic aldehydes or ketonesand primary amines. The yielded imine (R-C=N-R') can be used as a chelating ligands for the metal complexes preparation which are useful and can be used in many biological and industrial applications (Kumar *et al*.,2009; Soliman *et al*.,2007). This type of Schiff bases possess two types of donor atoms soft nitrogen and hard sulphur. They have the ability to act as a good chelating agent for various transition metals (Mohamed *et al*.,2009). The bioactivity and flexibility of sulphur and nitrogen containing ligands associated with the presence of both thioamino (-(C=S)-NH-) and imino (-HC=N-) in their structures moieties (Stringer *et al*., 2011). Many advantages can be gain from synthesizing these metal complexes such as: chelating of metals with such Schiff bases enhances their biological activity, easy preparation and low coast (Perrin & Chang, 2016).

1.2 Dibenzalacetone Ketones

Aldol condensation reaction like Grignard reaction both are useful carbon-carbon bond-forming organic reaction. Aldol condensation reaction can be used to synthesize unsaturated ketones by reacting aliphatic or aromatic aldehyde with ketone in the presence of mineral acid or alkaline base. This type of reaction is usually used in organic reaction to form bigger ketones with C-C bonds (Carey *et al*., 2008). This type of reaction contains two steps the first step called Aldol reaction while the second step called elimination reaction for both acid and base Aldol condensation (Carey *et al*., 2000). Base catalyzed Aldol condensation can be proceeds by using sodium hydroxide or potassium hydroxide.

Dibenzalacetone is a conjugated symmetric chalcone contains two benzene rings connected by unsaturated aliphatic chain with carbonyl group as shown in Figure1.1.

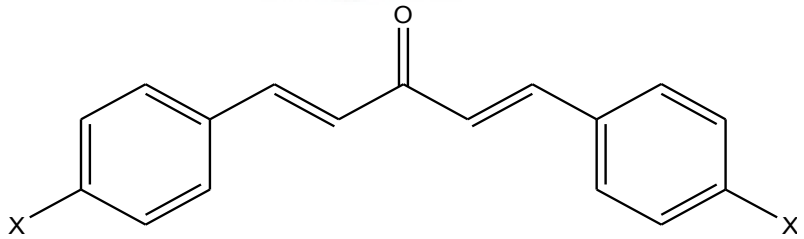


Figure 1.1 : General chemical structure of dibenzalacetone

Table1.1 represents dibenzalacetone derivatives.

Table 1.1 : Dibenzalacetone derivatives used in this study

X	Compound name	Abbreviation	Reference
H	Dibenzalacetone	DBA	(Conard *et al*., 1932)
CH_3	Di-*p*-tolylacetone	DTA	(Arshad*et al*., 2008)
C_2H_5	Di-*p*-ethylbenzalacetone	DEA	New compound
$CH(CH_3)_2$	Di-*p*-isopropylbenzalacetone	DIPA	New compound
Cl	Di-*p*-chlorobenzalacetone	DCLA	(Butcher *et al*., 2007)
Br	Di-*p*-bromobenzalacetone	DBRA	New compound
OCH_3	Di-*p*-methoxybenzalacetone	DMeO	(Handani *et al*., 2008)
$N(CH_3)_2$	Di-*p*-N,N-dimethylbenzalacetone	DNNMA	New compound

Unsymmetrical chalcones, type from flavonoids family, are naturally occurring compounds in many edible plants such as fruits, spices and vegetables which are non-toxic to normal cells. While, symmetrical chalcones like dibenzalacetone and dicinnamalacetone are not naturally occurring compounds. Dibenzalacetone can be synthesized by using Aldol condensation from the reaction between two moles of benzaldehyde or its derivatives and one mole of acetone (Youg *et al*., 2016). Figure 1.2 explains the reaction mechanism of base catalyzed Aldol condensation to synthesized dibenzalacetone ketone in the following main steps (Kim *et al*., 2016; Perrin *et al*., 2016):-

- First step: - Deprotonation of acetone by potassium hydroxide or sodium hydroxide and produce nucleophilic enolate.
- Second step: - The nucleophile attacks thye electrophile which is benzaldehyde or its derivatives to give alkoxide.
- Third step: - Protonation of alkoxide to produce neutral hydroxylketone.
- Fourth step: - Deprotonation again of hydroxyl-ketone to make nucleophilic enolate (hydroxyenolate).
- Fifth step: - Elimination of hydroxide ion to produce benzalacetone (monoaddition).
- Sixth step: - Repeat steps one to five again to produce the final product dibenzalacetone or its derivatives.

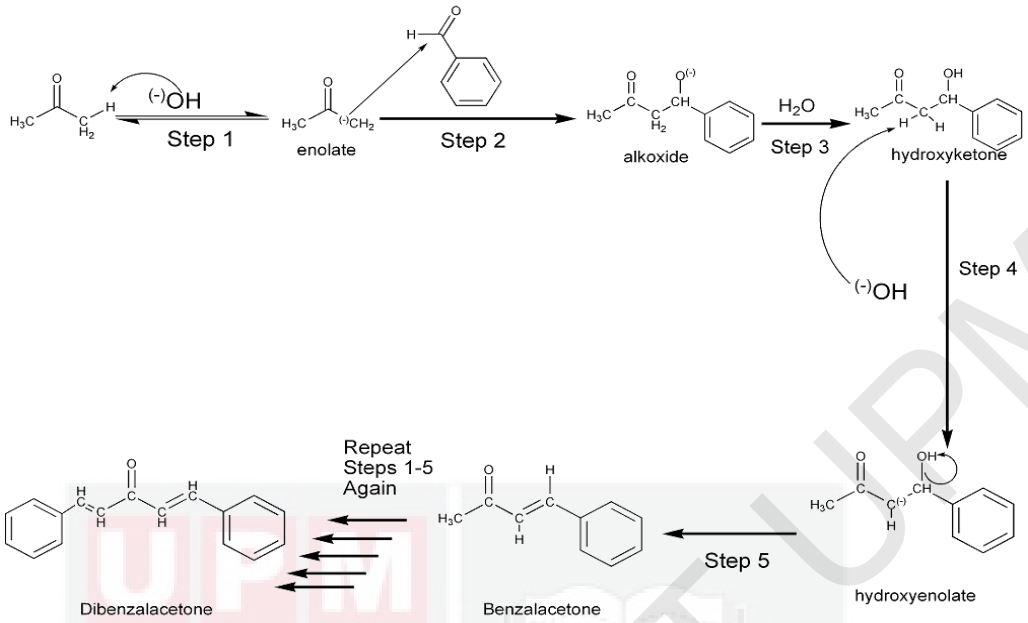


Figure 1.2 : Base catalyzed Aldol condensation mechanism (Kim *et al*., 2016)

Dibenzalacetone derivatives can be synthesized by using benzaldehyde derivatives instead of un-substituted benzaldehyde.Dibenzalacetone or dibenzylideneacteone is used as an ingredient in sunscreen cream and also as a ligand in organometallic chemistry in the synthesis of palladium(0) complexes (Ogasawara *et al*., 2001). Para substituted dibenzalacetone can be synthesized by the following Aldol condensation procedure with para substituted benzaldehyde. In the same manner, dicinnamalacetone (Figure 1.3) can be synthesized by using also base catalyzed Aldol condensation with using cinnamaldehyde instead of benzaldehyde.

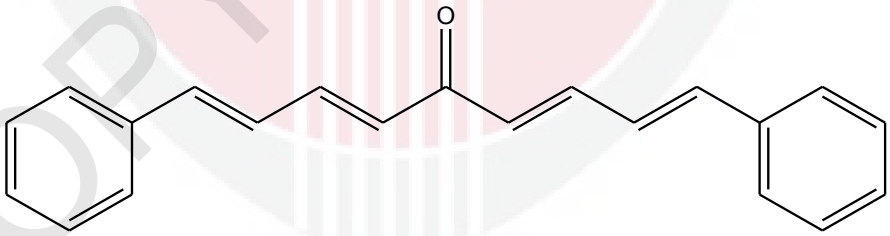


Figure 1.3 : Chemical structure of dicinnamalacetone DCNMA
(da Silva *et al*., 2018)

These ketones have many features:-

- These compounds are symmetrical chalcones.
- These compounds have long double-single bond conjugation system.
- Many types of functional groups can be substituted on the benzene ring.
- By varying the number of substituted group and the type of substituted group on the two benzene rings it is easy to direct the electron density.

1.3 Dithiocarbazate

Dithiocarbazate compounds are sulphur-nitrogen containing compounds which have the structural analogy to semicarbazides, thiosemicarbazides and carbazates as shown in Figure 1.4.

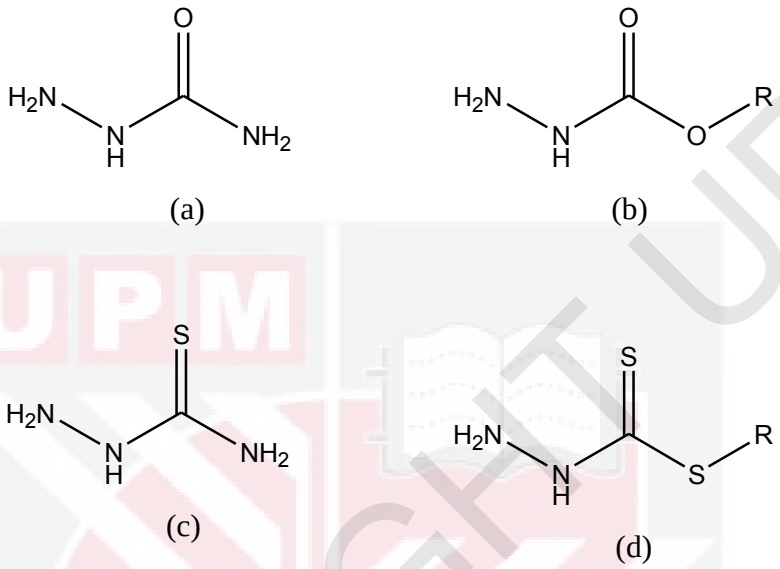


Figure 1.4 : Molecular structure of (a) semicarbazide, (b) carbazate, (c) thiosemicarbazide and (d) dithiocarbazate

The origin of this type of organic compounds is not well-known but the earliest publication on these compounds was made on 1905 (Dunlap, 1905) who synthesized Schiff base derived from phthalic anhydride and phenylsemicarbazide. In 1946 Domagk studied the antitubercular activity of some thiosemicarbazide derivatives (Domagk *et al*., 1946). Another important finding in 1970 it was reported on the cytotoxicity of thiosemicarbazide derivatives which were synthesized from thiosemicarbazide and aminopyridine-2-carboxaldehyde (Meldrum *et al*., 1970). The first publication on dithiocarbazate derivatives was reported in the chemistry of their metal complexes (Ali *et al*., 1972).

Dithiocarbazate is an organic amine containing two nitrogen atoms and two sulphur atoms as shown in Figure1.5. Ali and Livingstone was first toreview on the chemistry of this type of organic compound which was used to synthesize different compounds of Schiff bases (Akbar *et al*., 1974). Since then, many derivatives of dithiocarbazate compounds had been synthesized and applied in different applications.

The researchers in this field mostly focused on S-benzyl and S-methyldithiocarbazate (Ali *et al*., 1978; Rao *et al*., 1965; Tofazzal *et al*., 2000) while the others studied recently (Antony *et al*., 2014; Begum *et al*., 2015a; Begum *et al*., 2015b; Low *et al*., 2016; Mirza *et al*., 2014).

1.4 Schiff bases

Schiff base has the general chemical structure as shown in the Figure1.5. It is manly produce from reacting primary amine with ketone or aldehyde.

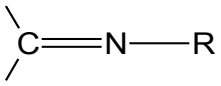


Figure 1.5 : Chemical structure of Schiff base

Many nitrogen-sulphur Schiff bases have been synthesized from the condensation of dithiocarbazate derivatives with aliphatic and aromatic aldehydes and ketones. Dithiocarbazate Schiff bases have tautomeric resonance which is called thione-thiol reseonance as shown in Figure1.6 (Krasowska *et al*., 2010).

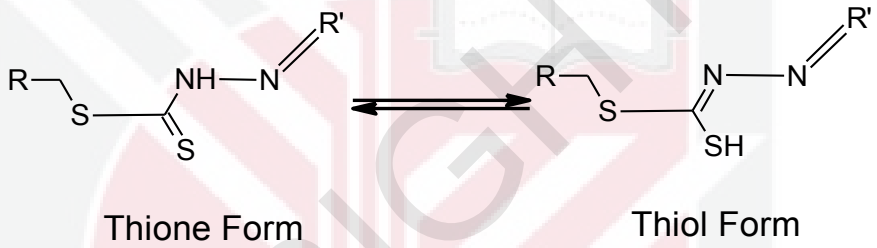
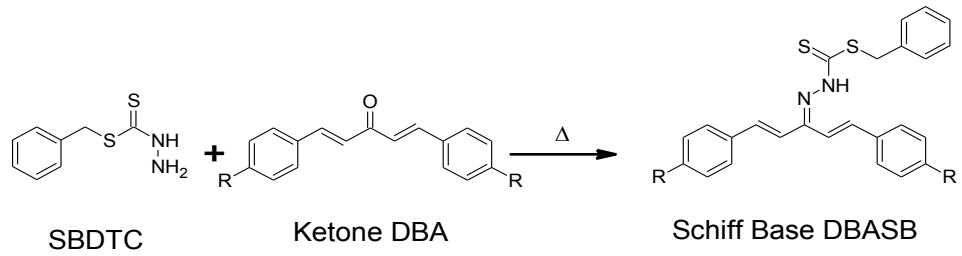
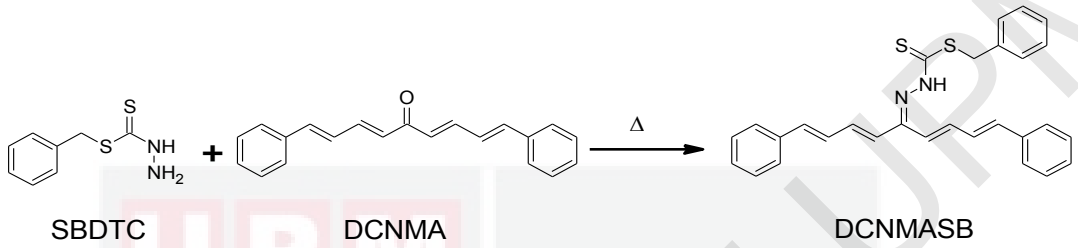


Figure 1.6 : Thione-Thiol tautomerism

Thiosemicarbazide Schiff bases coordinate with transition metal ions in both thione and thiol forms (De Lima *et al*., 1999). In the same manner, dithiosemicarbazide Schiff bases appear in the thione form when coordinate with transition metal complexes (Hossain *et al*., 1996).

In this study, nine Schiff bases have been synthesised from reacting SBDTC with dibenzalacetone, dibenzalacetone derivatives and dicinnamalacetone. The reaction between SBDTC and the synthesised ketones was catalyzed by hydrochloric acid or acetic acid. The reaction scheme illustrated in Figure1.7.





R	Ketone	Schiff Base
- H	Dibenzalacetone (DBA)	DBASB
- CH_3	Di-*p*-tolylacetone (DTA)	DTASB
- C_2H_5	Di-*p*-ethylbenzalacetone (DEA)	DEASB
- $CH(CH_3)_2$	Di-*p*-isopropylbenzalacetone (DIPA)	DEASB
- Cl	Di-*p*-chlorobenzalacetone (DCLA)	DCLASB
- Br	Di-*p*-bromobenzalacetone (DBRA)	DBRASB
- OCH_3	Di-*p*-methoxybenzalacetone (DMeO)	DMeOSB
- $N(CH_3)_2$	Di-*p*-N,N-dimethylaminobenzalacetone (DNNMA)	DNNMASB

Figure 1.7 : Reaction scheme of Schiff bases synthesis and chemical structure of the synthesized Schiff bases

1.5 Metal complexes

It is well known that the drug action can be accelerated by metal complexes and therapeutic efficiency can be enhanced by the coordination with transition metal ions (Navarro *et al*., 2004; Raman *et al*., 2008; Sánchez-Delgado *et al*., 1996). Biological activity of metal complexes highly depends on the transition metal and the donor ligand. The observation from different published articles on metal complexes of NS donor Schiff bases showed that nickel, copper and zinc complexes have good activity against Human T-lymphoblastic leukemia cell (CEM-SS) with low CD_{50} values 2.0-3.4 μg cm^{-3}. While cadmium complexes showed moderate activity against cervical cancer cells (HELA) and CEM-SS cell with CD_{50} values 4.0 and 4.95 μg cm^{-3}, respectively (Tarafder *et al*., 2002a).

To summarize briefly, this thesis aimed to study the effect of aromatic dithiocarbazate (SBDTC), double bond-single bond conjugation system (highly conjugated ketones), vital transition metals and the effect of functional group substituted on para position of both benzene rings on the cytoxicity of these metal complexes against two types of bladder cancer cell lines which are invasive human bladder carcinoma cell line (EJ-

28) and minimally invasive human bladder carcinoma cell line (RT-112). The target metal complexes were synthesized and characterized. The five divalent transition metals were chosen in this study due to their biological lability and inertness (Figure 1.8). While, Cd(II) and Zn(II) were the most labile (Blusch *et al*., 2013; Karlin, 2012). Their vital presence in biological systems and many enzymes, as outlined previously, were also chosen as important aspects in their selection in this study.

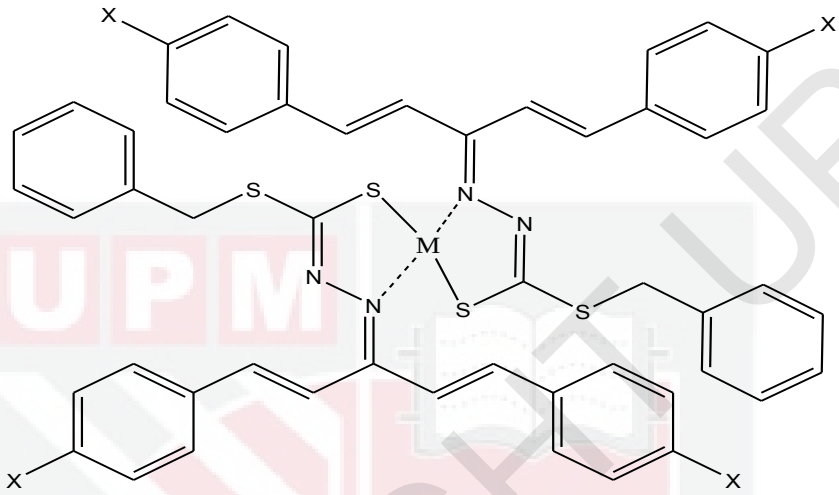


Figure 1.8 : General chemical structure of the transition metal complexes

Table 1.2 shows the metal complexes which have been synthesised in this study.

Table 1.2 : The synthesised transition metal complexes

X	M	Name	X	M	Name
Hydrogen H	Ni(II)	NiDBASB	Methyl CH_3	Ni(II)	NiDTASB
	Cu(II)	CuDBASB		Cu(II)	CuDTASB
	Fe(II)	FeDBASB		Fe(II)	FeDTASB
	Cd(II)	CdDBASB		Cd(II)	CdDTASB
	Zn(II)	ZnDBASB		Zn(II)	ZnDTASB
Ethyl C_2H_5	Ni(II)	NiDEASB	isopropyl $CH(CH_3)_2$	Ni(II)	NiDIPASB
	Cu(II)	CuDEASB		Cu(II)	CuDIPASB
	Fe(II)	FeDEASB		Fe(II)	FeDIPASB
	Cd(II)	CdDEASB		Cd(II)	CdDIPASB
	Zn(II)	ZnDEASB		Zn(II)	ZnDIPASB
Chloro Cl	Ni(II)	NiDCLASB	Bromo Br	Ni(II)	NiDBRASB
	Cu(II)	CuDCLASB		Cu(II)	CuDBRASB
	Fe(II)	FeDCLASB		Fe(II)	FeDBRASB
	Cd(II)	CdDCLASB		Cd(II)	CdDBRASB
	Zn(II)	ZnDCLASB		Zn(II)	ZnDBRASB
Methoxy OCH_3	Ni(II)	NiDMeOSB	N,N-dimethylamino $N(CH_3)_2$	Ni(II)	NiDNNMASB
	Cu(II)	CuDMeOSB		Cu(II)	CuDNNMASB
	Fe(II)	FeDMeOSB		Fe(II)	FeDNNMASB
	Cd(II)	CdDMeOSB		Cd(II)	CdDNNMASB
	Zn(II)	ZnDMeOSB		Zn(II)	ZnDNNMASB

1.6 Cytotoxicity

The biological activity of a chemical species can be explained by experimental and computational methods. There are a lot of theoretical studies about the determination of chemical activity. Generally, quantum chemical descriptors are used to determine the ranking of biological activities (Sayin & Karakas, 2013). The examples of these parameters include the highest occupied molecular orbital energies (HOMO), the lowest unoccupied molecular orbital energies (LUMO), the energy gap between LUMO and HOMO, hardness or softness of the molecules or atoms and the global electronegativity. The biological activities closely depend on the separation of the LUMO and HOMO in a molecule. The bending ability of an inhibitor to the appropriate molecule will increase with the increase of the HOMO and decrease of the LUMO of complex ions. This due to the ability of electrons to transfer to the acceptor molecule and the strong electron accepting ability of the molecules. The smaller the energy gap between HOMO and LUMO, the more active the molecule is in the term of biological properties. This because the electrons are easily excited from the lower energy orbital to higher energy orbital (Zhang *et al.*, 2012). Besides that, soft complexes (complexes in which sulphur atoms act as donor atoms) have a small energy gap between the molecular orbital and can interact easily with biological molecules. Hence, the biological activity is increased with the increase of softness of the complexes. Cytotoxicity of some sulphur-nitrogen ligands and their metal complexes is based on four main criteria. Firstly, the complex should be reasonably labile. Zinc and cadmium complexes are the most labile with d^{10} configurations. Secondly, the metal chelate should have reasonably high thermodynamic stability. The metals used on complexation should be (b) class metals (4d metals), in particular palladium and platinum due to its similarity to cisplatin, a common anticancer drug used in cancer treatment. Complexes or ligands with sulphur acting as donor atoms are the most likely to be effective drugs. This is because they allow for lipid solubility of the stable metal complexes (Ali *et al.*, 2011).

Besides, some studies on the behaviour of bladder cancer cells shown that acidic environments help bladder cancer cells grow. From this point, synthesizing of alkaline or neutral metal complexes may raises pH level and make the body more alkaline and cure or prevent bladder cancer. While, some *in vitro* studies on cancer cells do not represent the complex acidity or basicity nature of how tumors behave *in vivo* or in the human body (Ali & Livingstone, 1974).

1.7 Problem statements

Globally, bladder cancer is the fourth most common type of cancer in men. General therapy such as Cisplatin, Methotrexate, Gemcitabine, Mitomycin, Vinblastine, Doxorubicin, Carboplatin, Docetaxel, Paclitaxel, 5-Flurouracil (5-FU) and its derivatives are still used in the treatment of bladder cancer and also they are used to treat many types of cancer. The side effects of these chemotherapies include nausea, vomiting, loss of appetite, hair loss, mouth sores, diarrhea or constipation, increased risk of infections (because of a shortage of white blood cells), bleeding or bruising

after minor cuts or injuries (due to a shortage of blood platelets), fatigue (because of a shortage of red blood cells) are very severe. Thus there is a need to identify, efficacious anti-cancer drugs that are less toxic. Besides, the electron density can be directed to the complex centre which is transition metal by using symmetrical chalcones better than using unsymmetrical chalcones. Therefore, the cytotoxicity of the synthesized metal complexes solution dissolved in DMSO as a solvent was determined which are non-toxic due to the nontoxicity of dibenzalacetone which are chalcones. The advantage of using these aromatic chalcones is to synthesise chalcones substituted with many functional groups after studying the effect of functional group against bladder cancer cells. The cytotoxicity of dithiocarbazate metal complexes have been studied by many researchers against many types of cancer. Unfortunately, there is a very little research on using dithiocarbazate complexes as an anticancer agents against bladder cancer. The previous works on testing dithiocarbazate complexes against different types of cancer cells showed significant activity. The previous studies showed that the metal complexes of Cu^{2+}, Ni^{2+}, Cd^{2+}, and Zn^{2+} were active compounds against cancer cells. In the same manner, these metal complexes derived from SBDTC and symmetrical dibenzalacetone are expected to show significant activity against bladder cancer cells due to their lipholicity and ability to penetrate lipid permeable membrane of cancer cell. Then, ligands (Schiff base) used to transport and address the compounds to the specific site of cancer cell. This research will not study the toxicity of the synthesised compounds against normal bladder cells because of the slow growth of normal bladder cells and the concentration of the tested compounds is less than the toxic concentration of dithiocarbazate metal complexes which is more than 10 μM.

1.8 Objectives

This study was conducted to synthesizeand fully characterize dithiocarbazate derived from S-benzyldithiocarbazate and highly conjugated ketones and their metal complexes. Besides, this study aimed to test the cytotoxicity activity against two types of bladder cancer cell lines EJ28 & RT112. The toxicity of the synthesised complexes will not tested in this study because normal bladder cells grow at much slower rate in induced conditions compared to cancer cells. Besides, bladder cancer cells mutate and not typically like normal cells and making the test inaccurate. Secondly, normal bladder cells tend to get contaminated and died very easly compared to cancer cells which means sustaining enough cells for analysis is difficult. The main objectives of this study include:

- To synthesise and characterize nine symmetrical ketones with highly conjugated system via base catalysed Aldol condensation.
- To synthesise and characterize nine novel Schiff bases derived from the above symmetrical ketones and S-benzyldithiocarbazate by acid catalised condensation.
- To synthesise and characterize 45 novel metal complexes derived from the above Schiff bases and five divalent transition metals which are Ni(II), Cu(II), Fe(II), Zn(II) and Cd(II).
- To elucidate the cytotoxic activity of the Schiff bases and their metal complexes against two types from bladder cancer cell lines (EJ28 & RT112).

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