



UNIVERSITI PUTRA MALAYSIA

***BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR
PHOSPHANEGOLD(I) DITHIOCARBAMATES***

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**BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR
PHOSPHANEGOLD(I) DITHIOCARBAMATES**

By

CHEN BAO JING

**Thesis Submitted to the School of Graduate Studies, Universiti Putra
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Philosophy**

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

BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

By

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December 2017

Chair: Associate Professor Cheah Yoke Kqueen, PhD
Faculty: Medicine and Health Sciences

The notable achievement of medicinal inorganic chemistry in particular transition metal and the development of medicinal metal complexes is extended beyond platinum class. Gold complexes aims to solve chemoresistance and toxic side effects of platinum have inspired the idea of synthesizing mononuclear phosphanegold(I) dithiocarbamate complexes series, $R_3PAu[S_2CN(CH_2CH_2OH)_2]$, R = phenyl (Ph) (1a), cyclohexyl (Cy) (1b) and ethyl (Et) groups (2a and 3a). Antibacterial screening of the four complexes by antimicrobial susceptibility tests encompasses disc diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determination and time kills assay allowed the identification of antibacterial properties against 24 Gram-positive and Gram-negative pathogens. The antibacterial activity of the complexes was found to differ among each other, either broad range or specific and bacteriostatic or bactericidal. Anticancer properties of the complexes was demonstrated in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and flow-cytometry, showed to be effective against breast, lung and colorectal cancer cell lines with identified IC_{50} in μM over 24 hours interaction. The anticancer activity also found to be associated with the ability to inhibit breast cancer invasion and migration through BioCoat™ Matrigel™ Invasion Chamber and scratch assay. Investigation of the cell death mode induced by the four complexes through acridine orange (AO)/ propidium iodide (PI) double staining and DNA fragmentation, indicated the apoptosis event was occurring with the observation of apoptotic morphological features and fragmented DNA. Complexes 1a, 1b, 2a, and 3a resulted apoptosis were further assessed with fluorescent detection. Translocation of phosphatidylserine (PS), cell cycle arrest, and increase caspases expressions provided the hint of increase mitochondrial membrane potential related to intrinsic and extrinsic pathways. Data was then supported by RT² Profiler™ PCR array which involve the study of 84 apoptotic genes, exhibited the upregulation of p53/p73 and higher expression of pro-apoptotic genes over anti-apoptotic genes. Toxicity of the complexes were determined through *in vivo* survival assay on *Caenorhabditis elegans* and *in vitro* MTT assay on human embryonic kidney cell (HEK293) and rat myocardium cell (H9C2). Result showed the complexes at low dosage showed generally not effect on lifespan but high dosage cause lifespan reduction. However, all four complexes displayed

low toxicity on HEK293 and H9C2 with higher IC_{50} than cancer cells. Apart from that, mutagenicity of the complexes were evaluated through Ames test and showed lack of mutagenic potential. Based on *in vitro* antibacterial and anticancer potency, all four complexes were arranged in the descending order $2a > 3a > 1a > 1b$. However, the four complexes exhibited toxicity in the descending order $1b > 1a > 2a > 3a$. Complex 2a represented the complex with greatest antibacterial and anticancer activities and lower toxic than complex 3a. As a conclusion, mononuclear phosphane-gold(I) dithiocarbamates have excellent antibacterial and anticancer activities which induce both mitochondria and death receptors apoptotic pathways with generally low toxicity and not mutagenic.



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

PEMERIKSAAN SIFAT BIOPERUBATAN MONONUKLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

Oleh

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Disember 2017

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Pencapaian yang penting dari perubatan mengenai kimia tidak organik, terutamanya logam peralihan, pembangunan kompleks logam perubatan telah dilanjutkan kepada kelas selain daripada platinum. Kompleks emas yang bertujuan untuk menyelesaikan masalah rintangan kemoterapi dan kesan sampingan platinum telah menginspirasi idea untuk menghasilkan siri kompleks mononuklear phosphanegold(I) dithiocarbamates, $R_3PAu[S_2CN(CH_2CH_2OH)_2]$, R = phenyl (Ph) (1a), cyclohexyl (Cy) (1b) dan ethyl (Et) (2a dan 3a). Pemeriksaan anti-bakteria keempat-empat kompleks dengan ujian antimikrob kecenderungan merangkumi disc diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determination dan time kills assay membenarkan untuk mengenal pasti aktiviti anti-bakteria terhadap 24 Gram-positive dan Gram-negative patogens. Sifat anti-bakteria keempat-empat kompleks itu didapati berbeza antara sama satu lain, sama ada kesan yang luas atau tertentu dan bakteriostatik atau bactericidal. Sifat anti-kanser keempat-empat kompleks telah didemotrasikan melalui 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay dan sitometri aliran, menunjukkan keberkesanan terhadap kanser payudara, paru-paru dan kolorektal dengan IC₅₀ dalam unit μM selepas 24 jam interaksi. Aktiviti anti-kanser tersebut juga didapati berkaitan dengan keupayaan untuk menghalang kanser payudara pencerobohan dan penghijrahan melalui BioCoat™ Matrigel™ Invasion Chamber dan eksperimen pemulihan luka. Penyiasatan mod kematian sel yang disebabkan oleh empat kompleks melalui pewarnaan Akridina Jingga (AO)/ Propidium iodida (PI) dan ujian fragmentasi DNA, menunjukkan aktiviti apoptosis telah berlaku dengan pemerhatian morfologi apoptotik dan pembentukan fragmentasi DNA. Kompleks 1a, 1b, 2a, dan 3a yang menyebabkan apoptosis telah lanjut dinilai dengan pengesanan pendarfluor. Translokasi Phosphatidylserine (PS), perencatan kitaran sel, dan peningkatan caspases ungkapan memberikan tanda-tanda bahawa peningkatan mitokondria membran berpotensi yang berkaitan dengan jalur intrinsik dan ekstrinsik. Data adalah seterusnya disokong oleh RT² Profiler™ PCR yang melibatkan kajian 84 gen apoptotic, mempamerkan peningkatan p53/p73 dan ungkapan yang lebih tinggi oleh gen pro-apoptotic daripada gen anti-apoptotic. Kesan toksik daripada keempat-empat kompleks yang diuji telah ditentukan melalui ujian jangka hayat pada *Caenorhabditis elegans in vivo* dan MTT assay pada sel manusia embrio

buah pinggang (HEK293) dan sel tikus miokardium (H9C2) *in vitro*. Keputusan menunjukkan kompleks pada sukatan yang rendah menunjukkan secara amnya tidak kesan ke atas jangka hayat tetapi dos tinggi mengurangkan jangka hayat. Walau bagaimanapun, keempat-empat kompleks yang diuji telah memaparkan toksik rendah pada HEK293 dan H9C2 dengan nilai IC_{50} lebih tinggi daripada sel-sel kanser. Selain itu, mutagen kompleks telah dinilai melalui ujian Ames dan menunjukkan kekurangan potensi mutagen. Berdasarkan potensi aktiviti-aktiviti antibakteria and anticancer, keempat-empat kompleks adalah disusun mengikut giliran menurun $2a > 3a > 1a > 1b$. Sebaliknya, kesan toksik keempat-empat kompleks adalah disusun mengikut giliran menurun $1b > 1a > 2a > 3a$. Kompleks 2a mewakili sebagai kompleks yang mempunyai aktiviti antibakteria dan antikanser yang terkuat dan toksisiti yang rendah daripada kompleks 3a. Kesimpulannya, kompleks mononuklear phosphanegold(I) dithiocarbamates mempunyai aktiviti antibakteria dan anti-kanser yang sangat baik dengan kedua-dua mitokondria dan reseptor kematian jalur apoptotik dan keracunan seluruhnya rendah dan tidak mutagen.

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I certify that a Thesis Examination Committee has met on 15 December 2017 to conduct the final examination of Chen Bao Jing on her thesis entitled "Biomedical Properties of Novel Mononuclear Phosphane-gold(I) Dithiocarbamates" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

ABC	Adenosine triphosphate-binding cassette
AJ	Adherens junctions
ARID1A	AT-rich interactive domain 1A
ASK1	Apoptosis signal-regulating kinase 1
ATM	Ataxia telangiectasia-mutated
ATP	Adenosine triphosphate
Au	Gold
BER	Base excision repair
BL1 and BL2	Basal-like 1 and 2
CARD	Caspase recruitment domain
CDC	Centers for Disease Control and Prevention
C elegans	Caenorhabditis elegans
CIN	Chromosomal instability
Cy	Cyclohexyl
DCIS	Ductal carcinoma in situ
DHPS	Dihydropteroate synthetase
DHFR	Dihydropteroate reductase
DISC	Death-inducing signaling complex
DNA	Deoxyribonucleic acid
DSBR	DNA double strand break repair
EGF	Epidermal growth factor
ER	Estrogen receptor
ERK	Extracellular signal-regulated protein kinase
Et	Ethyl
FADH2	Flavin adenine dinucleotide
FGF-2	Fibroblast growth factor-2
GDF15	Growth differentiation factor 15
GJ	Gap junctions
HER2	Human epidermal receptor 2
IGF	Insulin-like growth factor
IDC	Infiltrating ductal carcinomas
IL	Interleukin
ILC	Invasive lobular carcinoma
IM	Immunomodulatory
JNK	C-Jun N-terminal kinase
KLF5	Krüppel-like factor 5
LAR	Luminal androgen receptor
LCIS	Lobular carcinoma in situ
M	Mesenchymal
MAPK	Mitogen-activated protein kinase
MATE	Multidrug and toxic compound extrusion
MBC	Minimum bactericidal concentration
MFS	Major facilitator superfamily
MIC	Minimum inhibition concentration
MMR	Mismatch repair
MOMP	Membrane outer membrane permeability
MSI or MIN	Microsatellite instability

MSL	Mesenchymal stem-like
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADH	Nicotinamide adenine dinucleotide
NHC	N-heterocyclic carbine
NER	Nucleotide excision repair
NF- κ B	Nuclear factor-kappaB
NK	Natural killer
NST	Invasive carcinoma of no special type
OECD	Organisation for Economic Cooperation and Development
PBP	Penicillin binding protein
PDGF	Platelet derived growth factor
PEt3	Triethylphosphine
Ph	Phenyl
PIGF	Placental growth factor
PPh3	Triphenylphosphine
PR	Progesterone receptor
PS	Phosphatidylserine
PTEN	Phosphatase and tensin homolog
rRNA	Ribosomal ribonucleic acid
RND	Resistance-nodulation-division
ROS	Reactive oxygen species
SMR	Mall multidrug resistance
Stat3	Signal transducer activator of transcription-3
TAM	Tumor-associated macrophages
tBid	Truncated Bid
TGF- β	Transforming growth factor-beta
TJ	Tight junctions
TMP	Trimethoprim
TNBC	Triple negative breast cancer
TNF	Tumour necrosis factor
TP53	Tumor protein 53
TRAIL	TNF-related apoptosis-inducing ligand
Trx	Thioredoxin
VEGF	Vascular endothelial growth factor
WHO	World health organisation
Wnt	Wingless and Integrase-1
XIAP	X-linked inhibitor of apoptosis protein

CHAPTER 1

INTRODUCTION

Urbanization, modernization and industrialization that occurred rapidly since 1950, leads to increase health burden not only in low income countries, but also in developing and developed countries. The epidemiological transition fuelled by growing aging population and shifting towards chronic diseases and injuries has impacted on worldwide mortality by changing the lifestyle and socioeconomic. Communicable and non-communicable diseases are two major etiologies contribute to most of mortality cases and global burden. Communicable diseases refer to those contagious illness transmitted from animal or human. On the other hands, non-communicable diseases are those non-infectious or non-transmissible resulted from chronic exposure to environmental factors or those carry with inherited genes. Bacterial infections are example of communicable diseases, while cancers are under non-communicable diseases. Bacterial infection and cancer are interconnected where bacterial infections can cause cancer, while cancer patients who are immunocompromised have greater risk of bacterial infections (Samaras et al., 2010; Steele, 2012). Hence, antibacterial and anticancer are two important aspects in pharmaceutical research and development.

Metallopharmaceutical involves the application of metal in the treatment of various illnesses and highlights the importance of metal coordination geometry in medicinal inorganic chemistry field (Gielen and Tiekink, 2005). Metal was widely utilized as treatment regime in many diseases since thousand years ago. For example, gold complex was used in the treatment of rheumatoid arthritis, bismuth was applied in the gastric lymphoma and arsenic trioxide for acute promyelocytic leukemia. The importance of the metals with interesting medical values in various clinical diseases is undisputed, as can be determined as treatment of various diseases (Desoize, 2004). Albeit metal was first reported as chemotherapy for cancer and leukemia started from sixteenth century, the research into metal-based drugs was began in the early 1900s. In mid-1870, first metal compound synthesizing work was started by Sophus Jorgensen and followed by Alfred Werner who was awarded the Nobel Prize in 1913 for his work on synthesizing of a series of metal based compounds (Rafique et al., 2010).

Besides as coinage metal, gold metal is also found to have great medicinal potential. Gold has been well-documented with anti-arthritic (Youn et al., 2006; Shoeib et al., 2010), anti-inflammatory (Trávníček et al., 2012; Hošek et al., 2013), anticancer (Iii, 1999; Che and Sun, 2011), antimicrobial (Novelli et al., 1999) including antibacterial (Fernández et al., 2014; Glišić and Djuran, 2014), antiviral (Fonteh et al., 2010), and anti-parasitic activities (Navarro et al., 2001; Navarro et al., 2004; Navarro, 2009). Auranofin, an orally administered gold based disease modifying anti-rheumatic drug (DMARD), is a relatively late comer in the treatment of rheumatoid arthritis (Kean and Kean, 2008; Corti and Holliday, 2009) and is recently listed as “drug repurposing/repositioning” attribute to its applications against other diseases (Pessetto et al., 2013). Indeed, auranofin® displays anticancer potential (Roder and Thomson, 2015)

and antimicrobial applications (Cassetta et al., 2014). Following that, a numbers of gold (I) complexes are coupled with phosphine-type and dithiocarbamate ligands were extensively studied their biological activities including the determination of biological targets and mechanisms of cell death (Jamaludin et al., 2013; Keter et al., 2014; Altaf et al., 2015).

Given the emerging interest in the metallopharmaceutical and the ideas of phosphane, dithiocarbamates and auranofin, two series of phosphane-gold(I) dithiocarbamates, namely $R_3PAu[S_2CN(iPr)CH_2CH_2OH]$ for R= ethyl (Et), cyclohexyl (Cy) and phenyl (Ph), were investigated for antibacterial and anticancer activities, as well as determine their toxicities.

1.1 Problem statement and justification

Raising cost in research and development and declining productivity are challenges in pharmaceutical industry (Khanna, 2012). From 2013 to 2015, 218 clinical trial failures were reported. Oncology and infectious diseases are two therapeutic areas in which the failure was commonly detected. The failure was due to lack of therapeutic index owing to reduced drug efficacy and safety (Harrison, 2016). Multidrug resistance greatly reduces drug efficacy in current treatments of communicable and non-communicable diseases (Tanwar et al., 2014). In addition, there is lack of biological characteristics assessment of novel mononuclear phosphane-gold(I) dithiocarbamate complexes. Therefore, it is necessary to determine effectiveness and toxicity of mononuclear phosphane-gold(I) dithiocarbamate complexes.

1.2 Hypothesis

Mononuclear phosphane-gold(I) dithiocarbamates is expected to exhibit antibacterial and apoptosis related antiproliferative activities with low toxicity and less mutagenic than cisplatin.

1.3 Objectives

1.3.1 General Objectives

The general objective for this study is to investigate the *in vitro* antibacterial, anticancer properties, mutagenicity and toxicity of four mononuclear phosphane-gold(I) dithiocarbamates and *in vivo* toxicity assessment in *Caenorhabditis elegans*.

1.3.2 Specific Objectives

- To determine the antibacterial activity of four mononuclear phosphane-gold(I) dithiocarbamates (Chapter 3)
- To evaluate *in vitro* anticancer properties of four mononuclear phosphane-gold(I) dithiocarbamates on breast, colon and lung cancer cell lines. (Chapter 4)

- c) To determine the apoptosis pathway induced by the four mononuclear phosphanegold(I) dithiocarbamates (Chapter 5)
- d) To profile *in vivo*, *in vitro* toxicity and mutagenic characteristics of the four mononuclear phosphanegold(I) dithiocarbamates. (Chapter 6)

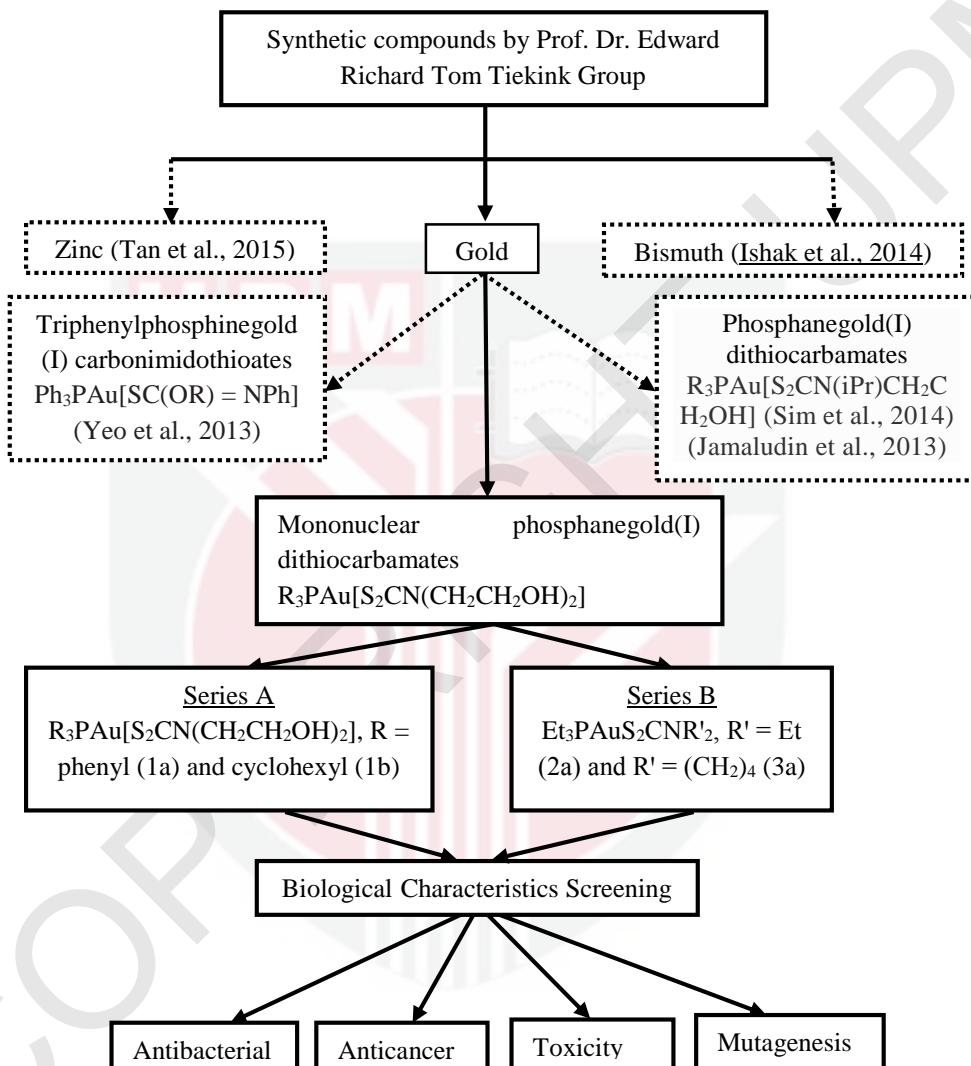


Figure 1.1: Conceptual framework illustrates the workflow of antibacterial, anticancer, toxicity and mutagenicity determination of mononuclear phosphanegold(I) dithiocarbamates. Bold line indicates for relevant part to be discussed in this study. Dotted line indicates for irrelevant parts which conducted by others, but under same project.

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