UNIVERSITI PUTRA MALAYSIA

CYTOTOXIC PROPERTIES OF PHOSPHINEGOLD (I) DITHIOCARBAMATES ON BREAST CARCINOMA CELL LINE MCF-7

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By

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Chairman : Associate Professor Cheah Yoke Kqueen, PhD
Faculty : Medicine and Health Science

Statistical report by World Health Organization showed an increase of 20.5% in total number of cancer caused deaths from year 2000 to year 2011 with the total number of cancer caused deaths in year 2011 hitting 11.39% of the total number of deaths. Development of drug resistance of cancer and severe side effects of anti-cancer drug has been the reasons known to the increase in total number of cancer caused deaths. And this situation has call upon development of anticancer drug with better selectivity, enhanced therapeutic index, minimal side effects and is able to overcome the resistance phenomena. In this study, cytotoxic property of three phosphinegold(I) dithiocarbamates, $R_3PAu[S_2CN(iPr)CH_2CH_2OH]$, for R = Ph (1), Cy (2) and Et (3) was studied against breast cancer cell line, MCF-7. Cell cytotoxicity was tested using methylthiazolyldiphenyl-tetrazolium bromide (MTT) cell viability assay, present of apoptosis was tested using apoptotic assay using acridine orange / propidium iodide (AO/PI) staining, further validation using DNA fragmentation test. Gene expression study employed human apoptosis PCR array analysis and protein detection was done by caspase activity assays. Based on MTT cell viability assay, cytotoxicity of 1, 2, and 3 against MCF-7 is confirmed with 1, 2, and 3 exhibiting greater cytotoxicity than commercial drug cisplatin. Besides that, acridine orange / propidium iodide (AO/PI) cell apoptotic assay and DNA fragmentation test showed that MCF-7 cells treated with 1, 2 and 3 underwent apoptosis, at the same time cells treated with 2 and 3 also underwent necrosis. On the other hand, human apoptosis PCR-array analysis on MCF-7 cells treated with 1, 2 and 3 exhibited up regulation of CASP7, CASP8, CASP9 and CASP10 outlining the evidence of apoptosis which has occured in MCF-7 cells treated with 1, 2 and 3. The result is further supported by detection of caspases activities of caspase-7, caspase-8, caspase-9 and caspase-10. Induction of both intrinsic and extrinsic apoptosis by 1, 2 and 3 were demonstrated in the human apoptosis PCR-array analysis and the detection of caspases activities of caspase-7, caspase-8, caspase-9 and caspase-10 detection. Result of human apoptosis PCR-array analysis on MCF-7 also suggested that compound 1 has activated TP53 gene, has compound 2 activated only

the TP73 gene, whereas compound 3 has activated both the TP53 and TP73 genes. The mechanism of death induced by compound 1 is apoptosis while compound 2 and compound 3 induced both apoptosis and necrosis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

SIFAT SITOTOKSIK PHOSPHINEGOLD (I) DITHIOCARBAMATES KE ATAS SEL KARSINOMA PAYUDARA MCF-7

Oleh

GOH ZHENG JIE

Mac 2017

Pengerusi : Profesor Madya Cheah Yoke Kqueen, PhD
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Lapor statistik dari Pertubuhan Kesihatan Sedunia menyatakan bahawa kes kematian yang disebabkan oleh kanser telah meningkat sebanyak 20.5% dari tahun 2000 sehingga tahun 2011, dimana 11.39% dari jumlah kes kematian dalam tahun 2011 adalah diakibatkan oleh kanser. Antara faktor kepada peningkatan kes kematian akibat kanser adalah kesan sampingan ubatan anti kanser yang mudarat serta peningkatan kes kanser yang melibatkan rintangan kepada ubatan anti kanser. Situasi ini perlu diselesaikann dengan inovasi untuk mencipta ubatan anti kanser yang mempunyai pemilihan yang lebih sensitif, dengan index therapatik yang lebih kuat, minima kesan sampingan dan keupayaan untuk mengatasi fenomena rintangan terhadap ubatan anti kanser. Kajian ini melibatkan penyiasatan sifat sitotoksik Phosphanegold(I) dithiocarbamates, $R_3PAu[S_2CN(iPr)CH_2CH_2OH]$, di mana R = Ph (1), Cy (2) dan Et (3) ke atas warisan sel kanser , MCF-7. Sifat sitotoksik sel telah diuji dengan methylthiazolyldiphenyl-tetrazolium bromide (MTT) ujian daya hidup sel, kehadiran apoptosis telah diuji dengan ujian apoptosis dengan akridin oren / propidium iodida (AO/PI) perwarnaan, pengesahan selanjutnya menggunakan ujian fragmentasi DNA. Kajian ekspresi menggunakan analisa PCR-array apoptosis manusia dan pengesanan protein telah dijalankan dengan ujian aktiviti caspase. Bedasarkan keputusan yang diperolehi dari methylthiazolyldiphenyl-tetrazolium bromide (MTT) ujian daya hidup sel, telah disahkan bahawa 1, 2 dan 3 mempamerkan lebih sitotoksik potensi daripada ubatan komersial cisplatin. Selain itu, akridin oren / propidium iodida (AO/PI) analisa apoptosis sel dan analisa fragmentasi DNA menunjukkan sel MCF-7 yang dirawat dengan 1, 2 dan 3 telah menjalani apoptosis. Pada masa yang sama, sel MCF-7 yang dirawat dengan 2 dan 3 juga telah menjalani nekrosis. Selain itu, analisa PCR-array apoptosis manusia ke atas sel MCF-7 yang telah dirawat dengan 1, 2, dan 3 menunjukkan peningkatan regulasi gen CASP7, CASP8, CASP9 dan CASP10 merupakan bukti bahawa apoptosis berlaku ke atas sel MCF-7 yang telah dirawat dengan 1, 2, dan 3. Keputusan ini juga disokong oleh pengesanan aktiviti caspase-7, aktiviti caspase-8, aktiviti caspase-9 dan aktiviti caspase-10. Induksi apoptosis intrinsik dan ekstrinsik oleh 1, 2 dan 3 juga terbukti dengan merujuk kepada keputusan

analisa kepelbagaian-PCR apoptosis manusia dimana pengesanan aktiviti CASP7, CASP8, CASP9 dan CASP10 adalah positif. Keputusan analisa PCR-array apoptosis manusia terhadap MCF-7 mencadangkan bahawa kompaun 1 telah mengaktifkan gen TP53, kompaun 2 telah mengaktifkan gen TP73, dan kompaun 3 telah mengaktifkan kedua-dua gen TP53 dan gen TP73. Mekanisme kematian sel yang disebabkan oleh kompaun 1 adalah apoptosis, dari segi kompaun 2 dan kompaun 3 pula adalah kedua-dua apoptosos dan nekrosi.

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I certify that a Thesis Examination Committee has met on 20 March 2017 to conduct the final examination of Goh Zheng Jie on his thesis entitled "Cytotoxic Properties of Phosphinegold (I) Dithiocarbamates on Breast Carcinoma Cell Line MCF-7" 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 Master of Science.

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ABL1	ABL proto-oncogene 1, non-receptor tyrosine kinase gene
AKT1	v-akt murine thymoma viral oncogene homolog 1 gene
AO	acridine orange
APAF1	apoptotic peptidase activating factor 1
ATP	adenosine triphosphate
BAD	BCL2 associated agonist of cell death gene
BAG3	BCL2 associated athanogene 3 gene
BAG4	BCL2 associated athanogene 4 gene
BAK/BAK1	BCL2 antagonist/killer 1 gene
BAX	BCL2-associated X protein gene
BCL10	B-cell CLL/lymphoma 10 gene
BCL2	B-cell CLL/lymphoma 2 gene
BCL2A1	BCL2 related protein A1 gene
BCL2L1	BCL2 like 1 gene
BCL2L10	BCL2 like 10 gene
BCL2L11	BCL2 like 11 gene
BCL2L2	BCL2 like 2 gene
BCLAF1	BCL2 associated transcription factor 1 gene
BFAR	bifunctional apoptosis regulator gene
BH	BCL2 homology domain
BH1	BCL2 homology 1 domain
BH2	BCL2 homology 2 domain
BH3	BCL2 homology 3 domain
BID	BH3 interacting domain death agonist gene
BIK	BCL2-interacting killer
BIM	BCL2 like 11 gene
BIRC2	baculoviral IAP repeat containing 2
BIRC3	baculoviral IAP repeat containing 3
BIRC6	baculoviral IAP repeat containing 6
BIRC8	baculoviral IAP repeat containing 8
BNIP1	BCL2/adenovirus E1B 19kDa interacting protein 1
BNIP2	BCL2/adenovirus E1B 19kDa interacting protein 2
BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
CARD6	caspase recruitment domain family member 6
CARD8	caspase recruitment domain family member 8
CASP1	caspase 1
CASP10	caspase 10
CASP14	caspase 14
CASP2	caspase 2
CASP3	caspase 3
CASP5	caspase 5
CASP6	caspase 6
CASP7	caspase 7

CASP8	caspase 8
CASP9	caspase 9
CD27	CD27 molecule
CD40	CD40
CD40LG	CD40 ligand
CD70	CD70 molecule
CFLAR	CASP8 and FADD like apoptosis regulator
CIDEA	cell death-inducing DFFA-like effector a
CIDEB	cell death-inducing DFFA-like effector b
CRADD	CASP2 and RIPK1 domain containing adaptor with death domain
Cy	Cyclohexyl
DAPK1	death associated protein kinase 1
DFFA	DNA fragmentation factor subunit alpha
DFFB	DNA fragmentation factor subunit beta
DISC	death-inducing signalling complex
EDTA	ethylenediaminetetraacetic acid
Et	Ethyl
FADD	Fas associated death domain
FAS	Fas cell surface death receptor
FASL/FALG	Fas ligand gene
GADD45A	growth arrest and DNA damage inducible alpha
HRK	harakiri, BCL2 interacting protein gene
HRT	hormone replacement therapy
IC_{50}	half maximal inhibitory concentration
IGF1R	insulin like growth factor 1 receptor
IGFBP2	insulin like growth factor binding protein 2 gene
IGFBP4	insulin like growth factor binding protein 4 gene
IGFBP5	insulin like growth factor binding protein 5 gene
IL-1β	interleukin 1 beta
LTA	lymphotoxin alpha
LTBR	lymphotoxin beta receptor
MBD2	methyl-CpG binding domain protein 2 gene
MCF-7	Michigan Cancer Foundation-7 cell line
MCL1	myeloid cell leukemia 1 gene
MDR	multiple-drug resistance
MGMT	O-6-methylguanine-DNA methyltransferase gene
MHT	menopause hormone therapy
MTT	methylthiazolyldiphenyl-tetrazolium bromide
NAIP	NLR family, apoptosis inhibitory protein
NOD1	nucleotide binding oligomerization domain containing 1
NOL3	nucleolar protein 3
p53	p53 protein
PBS	phosphate saline buffer
P-gp	P-glycoprotein
Ph	Phenyl
PI	propidium iodide
PS	Phosphatidylserine
PTP	Permeability transition pore
PYCARD	PYD and CARD domain containing
RAD21	RAD21 cohesin complex component gene

RIPK2	receptor interacting serine/threonine kinase 2
RPAP1	RNA polymerase II associated protein 1 gene
SMAC	diablo IAP-binding mitochondrial protein
SNP	single nucleotide polymorphism
tBID	truncated BID protein
TNF	tumor necrosis factor gene
TNFRS	tumour necrosis factor receptor superfamily
TNFRSF10A	tumor necrosis factor receptor superfamily member 10a
TNFRSF10B	tumor necrosis factor receptor superfamily member 10b
TNFRSF11A	tumor necrosis factor receptor superfamily member 11a
TNFRSF1A	tumor necrosis factor receptor superfamily member 1a
TNFRSF21	tumor necrosis factor receptor superfamily member 21
TNFRSF25	tumor necrosis factor receptor superfamily member 25
TNFRSF9	tumor necrosis factor receptor superfamily member 9
TNFSF10	tumor necrosis factor superfamily member 10
TNFSF8	tumor necrosis factor superfamily member 8
TP53	tumour protein p53 gene
TP53BP2	tumor protein p53 binding protein 2
TP73	tumor protein p73
TRADD	TNFRSF1A-associated via death domain
TRAF	TNF receptor-associated factor
TRAF2	TNF receptor associated factor 2
TRAF3	TNF receptor associated factor 3
WNT7B	wingless-type MMTV integration site family member 7B gene
XIAP	X-linked inhibitor of apoptosis gene

CHAPTER 1

INTRODUCTION

Cancer has been one of the leading causes of death around the globe. According to World Health Organization (2014), there were 14.09 million diagnosed cases of cancer in year 2012, whereby cancer alone had caused 8.2 million deaths in the same year. The most common fatal cases of cancer were caused by lung cancer, liver cancer, stomach cancer, colorectal cancer, breast cancer and esophageal cancer. Cancer can be caused naturally either by ageing, or by carcinogen, such as infections, radiations and chemicals. Treatment has been bountiful since the invention of cisplatin in 1978, to platinum based anticancer drugs development, and recently into other metal based anticancer drugs development. In a nutshell, the main objective is to develop an anticancer drug with better selectivity, enhanced therapeutic index, minimal side effects and is able to overcome the resistance phenomena (Enyedy *et al.*, 2013). There were countless attempts to invent anticancer drugs, yet few can pass the clinical testing (Retzios, 2009; Amiri-Kordestani, 2012). Constant effort is needed to invent new anticancer drugs with the hope that one of them can put into good use, or we look into the mechanism of how these existing drugs works in attempt to improve the synthesized compound.

In this study, the cytotoxicity properties of three synthetic crystals phosphinegold(I) dithiocarbamates, triphenylphosphinegold(I) dithiocarbamate ($Ph_3PAu[SC(=S)N((i)Pr)CH_2CH_2OH]$), tricyclohexylphosphinegold(I) dithiocarbamate ($Cy_3PAu[SC(=S)N((i)Pr)CH_2CH_2OH]$) and triethylphosphinegold(I) dithiocarbamate ($Et_3PAu[SC(=S)N((i)Pr)CH_2CH_2OH]$ against breast cancer carcinoma cell line, MCF-7 cells were carried out. Phosphinegold compound has been well known for its antiarthritic activity (Gandin *et al.*, 2010). All compounds used in this study were based on the property that phosphinegold(I) dithiocarbamate has anticancer activity and potential to induce cell death (Horvath *et al.*, 2012). Dithiocarbamate was incorporated into the phosphinegold(I) structure to enhance increase the stability of the compound. With the combined effect of the phosphinegold(I) and dithiocarbamate, the phosphinegold(I) dithiocarbamate compounds used in this study were expected to present cytotoxic effect against breast carcinoma cell line (MCF-7). The cytotoxic event caused by phosphinegold(I) dithiocarbamates was studied to check if the compounds were able to cause apoptotic cell death. This was performed through cell viability testing using Methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay. On the other hand, the mode of cell death was further investigated by using Acridine Orange / Propidium Iodide (AO/PI) cells staining and DNA fragmentation test. Subsequently, apoptotic real-time polymerase chain reaction (PCR) array profiler was conducted to study the effect of the phosphinegold(I) dithiocarbamates compounds on the apoptotic gene regulation of MCF-7 cell lines. Finally, the detection of the apoptotic related proteins, Caspase 3, Caspase 7, Caspase 8, Caspase 9 and Caspase 10 was performed.

The problem statement for this study is that there is a lack of effective anti-cancer drug that is able to deliver higher cytotoxic effect and milder side effect. Hypothesis of this study is stated hereby as the three chemically synthesized phosphinegold(I) dithiocarbamate compounds, triphenylphosphinegold(I) dithiocarbamate (compound 1), tricyclohexylphosphinegold(I) dithiocarbamate (compound 2) and triethylphosphinegold(I) dithiocarbamate (compound 3) are cytotoxic to breast carcinoma cell line, MCF-7.

The general objective of this study is to investigate the cytotoxic properties of compound 1, compound 2 and compound 3 against MCF-7 cell lines by cell viability testing, cell staining, DNA integrity test, gene expression of MCF-7 cell lines and protein activity confirmation.

First specific objective is to investigate cytotoxic property of compound 1, compound 2 and compound 3 against MCF-7 cell lines and look for evidence of apoptosis. Second specific objective is to study apoptotic gene expression of each of the compound 1, compound 2 and compound 3 treated MCF-7 cells by employing real-time polymerase chain reaction (PCR) array. Finally, the third objective is to validate the result of apoptotic gene expression by studying the protein activity of caspase 7, caspase 8, caspase 9 and caspase 10 against compound 1, compound 2 and compound 3 treated MCF-7 cells.

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