UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL PROPERTIES OF NICKEL (II) COMPLEXES WITH DERIVATIVES OF TESTOSTERONE THIOSEMICARBAZONE

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By

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

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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL PROPERTIES OF NICKEL (II) COMPLEXES WITH DERIVATIVES OF TESTOSTERONE THIOSEMICARBAZONE.

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

The side effects of cisplatin such as toxicities are mainly due to the lack of selectivity of this chemotherapeutic agent. In order to increase selectivity of an anticancer agent, hormone molecule that targets a specific receptor may be utilized. The notorious side effects of cisplatin and the potential of hormone molecule have generated a research problem: can a cytotoxic compound with better selectivity and/or specificity made of ligand containing a hormone molecule be prepared? The aim of this study is to prepare cytotoxic nickel complexes containing Schiff base ligands of testosterone and thiosemicarbazide, which are selective towards cancerous cells. Besides, their ability as DNA binders and topoisomerase I inhibitors were tested as well. Three Schiff base ligands that are made of testosterone and three derivatives of thiosemicarbazide (**TT**, **TE**, and **TP**) and their nickel (II) complexes (**NT**, **NE**, and **NP**) were synthesized. Characterizations of these compounds were done by means of FTIR, CHN, ^{1}H-NMR, and X-ray crystallography. Mononuclear complexes **NT**, **NE**, and **NP** adopt the distorted square planar geometry, with two molecules of Schiff base ligand were coordinated to nickel ion via two imine nitrogens and two tautomericthiol sulfurs. The cytotoxicity of these compounds against several cancerous cell lines (prostate cancer cells PC-3 and LNCaP, and colon cancer cell HCT 116) was investigated via MTT assay, with cisplatin as positive reference standard. Preferences towards different cancer cell lines were shown, where parent ligands and their nickel complexes favored different cells. For instance, nickel complex **NT** was shown to be active against PC-3 cells although its Schiff base ligand **TT** was unable to inhibit the growth of the same cell type. On the contrary, the inhibitory strength of both **TE** and **TP** against prostate cancer LNCaP was muted upon complexation with nickel ion. Apart from that, it is noteworthy that all compounds are less toxic

towards human normal colon cell CCD-18Co compared to that of cisplatin, as the IC_{50} values of these compounds were failed to be determined within the tested concentration (0.1 - 30.0 µg/mL). This may be an indication of selectivity towards cancerous cells, which is lacking in cisplatin. Interactions with DNA were evaluated via UV-Vis spectrophotometry and the result suggested non-intercalation binding mode, because batochromic effect and/or isobestic point was absent despite hypochromism was observed. This is further confirmed with the aid of docking simulations (AutoDock 4.2), where all the compounds tested were suggested to interact with the minor groove of DNA. Furthermore, both methods have generated binding constant and estimated binding energy of similar order, with **NE** being the strongest DNA-binding agent. Increased expression of topoisomerase I was observed in numerous neoplastic tissues, particularly due to its importance in replication of DNA and ultimately the proliferation of the cells. Despite its importance in cancerous cells (such as colon cancer), topoisomerase I, the common target in cancer treatment (especially colon cancer), is not inhibited by any of the synthesized compounds. In conclusion, the results suggested the compounds synthesized, which are DNA binders, exert their cytotoxic effects against the prostate and colon cancer cells tested in a topoisomerase I-independent manner.

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

SINTESIS, PENCIRIAN, DAN SIFAT-SIFAT BIOLOGI KOMPLEKS NICKEL (II) DENGAN DERIVATIF TESTOSTERON THIOSEMICARBAZONE.

Oleh

HENG MOK PIEW

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Kesan sampingan dadah chemotherapeutic cisplatin adalah disebabkan oleh kekurangan keupayaan molekul tersebut dalam pemilihan terhadap sel kanser. Untuk meningkatkan keupayaan dalam pemilihian terhadap sel kanser, molekul hormon yang menyasarkan reseptor yang tertentu mungkin boleh digunakan. Kesan sampingan cisplatin bersama potensi melekul hormon telah menjanakan satu masalah kajian, iaitu: bolehkah satu kompaun mengandungi molekul hormon yang sitotosik dan lebih memilih terhadap sel kanser disediakan? Tujuan kajian ini dijalankan ialah untuk menyediakan kompleks nickel mengandungi bes Schiff dengan hormon testosteron dan thiosemicarbazide dan sitotosik dan mempunyai kecenderungan terhadap sel kanser. Tiga bes Schiff telah disintesis melalui kondensasi antara testosteron dengan tiga derivatif thiosemicarbazide bagi menghasilkan bes Schiff **TT**, **TE**, dan **TP**. Tindak balas antara bes Schiff dengan garam Ni(II) dalam etanol menghasilkan kompleks masing-masing (**NT**, **NE**, dan **NP**). Bes Schiff yang dihasilkan telah dicirikan dengan kaedah spektroskopi seperti FT-IR, ^{1}H-NMR, CHN, dan UV. Kompleks-kompleks yang terhasil pula dicirikan dengan kaedah yang sama kecuali^{1}H-NMR. Selain itu, struktur hablur bagi**TT**, **NT**, **NE**, dan **NP** telah ditentukan dengan kaedah kristalografi sinar-X. Data yang diperoleh daripada kaedah kristalografi menunjukkan bahawa nisbah logam/ligan untuk semua komplex (**NT**, **NE**, dan **NP**) adalah 1:2, dimana dua bes Schiff bertindak sebagai ligan dengan atom penderma N dan S membentuk kompleks nickel. Disamping itu, aktiviti perencatan topoisomerase I, penambatan pada DNA (dengan cara UV-Vis spektroskopi dan dok molekul), dan aktiviti sitotosik bagi semua sebatian terhasil telah diuji. Semua sebatian menunjukkan aktiviti sitotoksik apabila diuji dengan sel kanser (kanser kolon dan kanser prostat). Kompleks-kompleks terhasil menunjukkan kecenderungan kepada jenis kanser yang berlainan dengan bes Shiff masing-masing. Contohnya, kompleks **NT**

adalah sitotosik kepada kanser prostat PC-3 walaupun bes Shiff-nya **TT** adalah tidak sitotosik kepada jenis sel tersebut. Disamping itu, **TE** dan **TP** yang sitotosik kepada sel LNCaP telah menjadi tidak aktif apabila kompleks masing-masing (**NE** dan **NP**) dihasilkan. Selain itu, kaedah MTT menunjukkan bahawa semua sebatian adalah tidak toksik kepada sel bukan kanser (CCD-18Co) apabila kepekatan sebatian tersebut tidak melebihi 30 µg/mL. Ini menunjukkan kecenderungan sebatian yang disediakan terhadap sel kanser apabila dibandingkan dengan cisplatin yang aktif terhadap semua jenis sel yang telah diuji dalam kajian ini (kanser dan bukan kanser). Semua sebatian mampu menambat pada CT-DNA melalui ikatan bukan interkalasi, seperti yang dicadangkan oleh keputusan UV and simulasi dok (AutoDock 4.2). Ikatan interkalasi dikecualikan sebab tiada titik isobestik diperhatikan daripada spektra UV yang terhasil (bagi semua sebatian yang diuji). Selain daripada itu, keputusan UV dan simulasi dok menunjukkan kekuatan ikatan sebatian kepada DNA yang sama. Peningkatan aktiviti enzim topoisomerase I telah dilaporkan dalam banyak jenis sel kanser atas sebab kepentingan enzim ini dalam replikasi DNA dan percambahan sel kanser. Walaupun penting dalam percambahan sel kanser seperti kanser kolon, semua sebatian gagal merencatkan enzim ini. Keputusan daripada kajian ini menunjukkan walaupun semua sebatian yang disediakan tidak dapat merencatkan topoisomerase I, semua sebatian berupaya menambat pada DNA dan sitotosik kepada kanser kolon dan kanser prostat yang diuji.

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I certify that a Thesis Examination Committee has met on 16 December 2015 to conduct the final examination ofHengMokPiewon his thesis entitled "Synthesis, Characterization, and Biological Properties of Nickel (II) complexes with Derivatives of Testosterone Thiosemicarbazone" 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 Master of Science.

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

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LIST OF ABBREVIATIONS

°C	Degree celsius
µL	Microliter
µM	Micromolar
Å	Angstrom
BSA	Bovine serum albumin
cm	Centimeter
CT-DNA	Calf-thymus DNA
DMF	N,N-dimethylformamide
DNA	Deoxyribonucleic acid
E. coli	*Escherichia coli*
g	Gram
h	Hour
IC_{50}	Median inhibition concentration
IR	Infrared
K_b	Intrinsic binding constant
M	Molar
min	Minute
ml	Milliliter
mmol	Millimole
nm	Nanometer
NMR	Nuclear magnetic resonance
PDB	Protein data bank
ppm	Parts per million
Topo	Topoisomerase
UV-Vis	Ultraviolet-visible
V	Volt

CHAPTER 1

INTRODUCTION

The serendipitous discovery of the antiproliferative property of cisplatin and its subsequent approval by the FDA has turned this platinum complex into one of the leading anticancer agent in the market (Flohe, Brigelius-Flohe, Saliou, Traber, & Packer, 1997; Sanchez-Cano & Hannon, 2009a). It is estimated that approximately 50-70% of cancer patients are treated with the platinum drug, with the exception of prostate and breast tumors (Hannon, 2007). Unfortunately, the clinical usefulness of cisplatin is limited due to some major drawbacks such as drug resistance, and severe toxic side effects including hepatotoxicity, nephrotoxicity, and neurotoxicity (Bruijnincx & Sadler, 2008; Chang, Nishikawa, Sato, Utsumi, & Inoue, 2002; Fuertes, Alonso, & Perez, 2003; Ott & Gust, 2007; Ruiz, Rodriguez, Cutillas, Espinosa, & Hannon, 2011b).

The success of cisplatin in cancer treatment has inspired scientists around the world to explore the use of coordination complexes, particularly transition metal complexes, in antitumor therapy (Sanchez-Cano & Hannon, 2009a). This is not surprising because several transition metals are essential for the normal functioning of living organisms. These metal ions function as important modulators for biological system where nearly one-third of enzyme-mediated processes required metal ion cofactors for activity (Maxwell & Bates, 2009; Sissi & Palumbo, 2009). Meanwhile, the unwanted side effects and drug resistance against cisplatin further prompted researchers to develop new compounds based on different metals and aimed at different targets that exhibit high cytotoxicity along with reduced side effects and no cross-resistance (Bruijnincx & Sadler, 2008; Gao, Vera, Matta, & Melendez, 2010). As a result, the anticancer properties of a wide range of metal complexes including platinum (Biersack et al., 2011; Huxley et al., 2010; J. Ruiz et al., 2012; Sanchez-Cano et al., 2010), copper (Chen et al., 2008; Daniel, Gupta, Harbach, Guida, & Dou, 2004; Varadarajan Uma, Castineiras, & Nair, 2007; Varadarjan Uma, Kanthimathi, Weyhermuller, & Nair, 2005), zinc (Kikuta, Koike, & Kimura, 2000; Tan et al., 2012; Uzzo et al., 2002), nickel (Afrasiabi et al., 2005; Kamalakannan & Venkappayya, 2002; Prabhakaran et al., 2011), ruthenium (Ruiz, et al., 2011b; Schobert et al., 2011; Simeone et al., 2012), selenium (Freitas, Alves, Sarmento-Ribeiro, & Mota-Pinto, 2011; Kong et al., 2011), and several other transition metals (Asiri & Khan, 2010; Che et al., 2003; Gao, et al., 2010; Manosroi et al., 2010; Osella et al., 2002) were reported.

Targeting the drugs to a specific organ or tumor type is highly desirable in order to maximize the delivery of the anticancer agent into the cell and onto the DNA (Heffeter et al., 2008; Huxley, et al., 2010; Ruiz, Rodriguez, Cutillas, Espinosa, & Hannon, 2011a; Ruiz, et al., 2012). This can be achieved by applying drug carrier strategy instead of free drug solution. In fact, by conjugating to

biomolecules that target a specific organ or receptor, the carriers used may be able to direct the drug towards the specified organ/receptor (Sanchez-Cano & Hannon, 2009b). Besides, drug carrier systems are able to protect the cytotoxic agents against elimination and *in vivo* degradation and thereby transporting the drugs to the target while minimizing toxicity to healthy cells (Laine & Passirani, 2012). Therefore, different organometallic and coordination units have been attached to natural and synthetic estrogens and androgens in order to target the steroidal receptors or as target-specific anticancer drugs for hormone-dependent cancers (Gao, et al., 2010; Ruiz, et al., 2011b).

Androgens (e.g., testosterone) are sex hormones that are required for normal growth and functional activities of the human prostate. These hormones are capable of interacting with the androgen receptors and form a stable receptor-ligand complex (Debes & Tindall, 2002; Manosroi, et al., 2010; Szyczewski, Hołderna-Natkaniec, & Natkaniec, 2004). Antiproliferative effect of several organometallic steroidal complexes containing ferrocenyl on hormone-independent prostate cancer cells PC-3 were tested by Top *et. al.* (2009) and the reported activity of these complexes is stronger compared to the ferrocenyl derivative of nonsteroidalantiandrogennilutamide(Top et al., 2009). By conjugating to a cytotoxic component, androgen may be able to act as a vector and directs the molecule towards androgen receptors, thereby improve the selectivity and specificity of the cytotoxic molecule (Zamora et al., 2013). This strategy may improve the delivery of an anticancer agent to androgen receptor positive cells such as prostate, breast, or even colon cells, since expression of these receptors on the membrane of human colon cell lines were reported (Gu et al., 2009).

On the other hand, metal complexes of thiosemicarbazones have demonstrated a wide array of biological activities including antibacterial, antitumor, antifungal, antileukemic, and cytotoxic properties (Khan, Kumar, Joshi, Iqbal, & Saleem, 2008; Khan & Yusuf, 2009; Prabhakaran, et al., 2011). Thiosemicarbazones, which are a type of Schiff base, are a class of versatile ligands and they can be synthesized through the condensation of thiosemicarbazide and a carbonyl compound. This process will results in the formation of C=N bond at the expense of a water molecule (Kovala-Demertzi et al., 2002). Interestingly, the diversity of certain biological properties are increased by steroidal thiosemicarbazones(Khan, et al., 2008). A ligand containing testosterone acetate and thiosemicarbazone, and the copper and platinum complexes of this steroid derivative were synthesized by Murugkar*et al.* (1999) and comparable cytotoxicity (against human breast cancer cell line MCF-7) at identical concentration as cisplatin was reported for these compounds (Murugkar et al., 1999). Moreover, cellular delivery of a range of non-conventional platinum (II) complexes was proven to be enhanced upon conjugation of androgen, and their cytotoxicity were inproved compared with nonsteroidal compounds as reported by some researchers (Huxley, et al., 2010). Ability of these testosterone-based complexes to cause the DNA helix to undergo unwinding and bending was reported as well, which is similar to those induced by cisplatin on DNA structure (Sanchez-Cano, et al., 2010). Furthermore, a Schiff base of testosterone thiosemicarbazone was prepared by Al-Bayati*et al.* (2010; in the absence of crystal structure) and the antimicrobial

property of this compound was reported (Al-Bayati, Amier, Al-Amiery, & Al-Majedy, 2010).

The notorious side effects have generated a research problem: can a cytotoxic metal complex with better specificity and/selectivity made of ligand containing a hormone molecule be prepared? For instance, can a cytotoxic compound be more selective towards cancerous cells (such as androgen receptors positive prostate cancer cells LNCaP) when it is conjugated to a testosterone molecule?

In order to answer the research problem, this study was performed with the following objectives:

- To synthesize and characterize three Schiff base ligands containing testosterone and three derivatives of thiosemicarbazide (**TT**, **TE**, and **TP**) and their nickel (II) complexes (**NT**, **NE**, and **NP**).
- To evaluate their cytotoxicity against several cancer cell lines, which are two prostate (LNCaP and PC-3) and a colon (HCT 116) cancer cells, alongside a normal human colon cell line (CCD-18Co), since expressions of membrane androgen receptors were reported on these cells.
- To investigate the ability of these compounds to interact with DNA and to inhibit the activity of topoisomerase I.

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