UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND ELUCIDATION OF THE STRUCTURE–ACTIVITY RELATIONSHIP OF HETEROATOM DONOR LIGANDS AND THEIR COMPLEXES DERIVED FROM SUBSTITUTED DITHIOCARBAZATE DERIVATIVES

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DOCTOR OF PHILOSOPHY
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By

FIONA HOW NI FOONG

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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

SYNTHESIS, CHARACTERIZATION AND ELUCIDATION OF THE STRUCTURE–ACTIVITY RELATIONSHIP OF HETEROATOM DONOR LIGANDS AND THEIR COMPLEXES DERIVED FROM SUBSTITUTED DITHIOCARBAZATE DERIVATIVES

By

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September 2008

Chairman: **Professor Karen A. Crouse, PhD**

Faculty: **Science**

Four new substituted dithiocarbazate ligands [*S*-napthalen-2-ylmethyl-dithiocarbazate (SNMDTC), *S*-quinolin-2-ylmethyl-dithiocarbazate (SQ2MDTC), S-benzyl-*N*-benzyldithiocarbazate (SBNBDTC) and S-methyl-*N*-benzyldithiocarbazate (SMNBDTC)], eight series of isomeric Schiff bases derived from different types of *S*-substituted dithiocarbazate and their metal complexes were successfully synthesized and characterized. Eighteen structures were determined using single crystal X-ray diffraction analysis. These newly synthesized compounds were systematically designed to form structurally heterogeneous compounds for QSAR study.

Schiff bases were derived from condensation of isomeric aldehydes and ketones, 3- and 4-methylacetophenone and 2-, 3- and 4-acetylpyridine with different substituted dithiocarbazate compounds. Upon complexation, all Schiff bases formed bis-

chelated (NS donor) complexes except for the uninegative tridentate, *S*-napthalen-2yl methyl-β-*N*-(2-acetylpyridine)dithiocarbazate (SNM2AP) that coordinated with metal ions *via* the azomethine nitrogen atom, the pyridyl nitrogen atom and the thiolo sulfur (NNS donor)

Some of these newly synthesized compounds exhibited significant activities towards selective strains of pathogens and marked cytotoxicity when assayed against breast cancer estrogen receptor positive, MCF-7 and breast cancer estrogen receptor negative, MDA-MB-231 cell lines. The biological activities of the isomeric Schiff bases and their complexes were investigated. Most of the complexes exhibited higher activity compared to their parent ligands upon complexation with metal ions.

The cytotoxicity data for all the compounds were used to construct QSAR model in an attempt to elucidate the relationship between structure and bioactivity. Satisfactory QSAR models were developed focusing on a few of the informative descriptors based on a wide set of relatively heterogeneous compounds as evidenced with value r^2>0.6 and r^2_{CV}> 0.5.

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

SINTESIS, PENCIRIAN DAN ILUSIDASI PERHUBUNGAN STRUKTURAL–AKTIVITI TERHADAP LIGAN HETEROATOM DAN KOMPLEKNYA DARIPADA TERBITAN DITIOKARBAZAT

Oleh

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Empat dithiokarbazat ligan yang baru [*S*-naftalen-2-ylmetilditiokarbazat (SNMDTC), *S*-kuinolin-2-ylmetil-ditiokarbazat (SQ2MDTC), *S*-benzil-*N*-benzilditiokarbazat (SBNBDTC) and *S*-metil-*N*-benzilditiokarbazat (SMNBDTC)], lapan siri bes Schiff yang berisomer berasal daripada berbagai *S*-gantian dithiokarbazat dengan kompleks logam telah berjaya disintesis dan dicirikan. Lapan belas struktur telah ditentukan dengan menggunakan pembelauan sinar-X. Sebatian baru telah direka secara sistematik sebelum disintesiskan bagi tujuan menghasilkan sebilangan sebatian yang berstruktur hetero-jenis untuk diaplikasikan dalam pengajian QSAR.

Bes Schiff yang berasal daripada proses kondensasi dengan aldehid dan keton yang berisomer seperti, 3- dan 4-metilasetofenon dan 2-, 3- and 4-asetilpiridin dengan berbagai jenis sebatian gantian ditiokarbazat. Apabila pengkompleksan berlaku, semua bes Schiff membentuk bis-kelat (penderma NS) kompleks kecuali uninegatif

tridentat *S*-naftalin-2ylmetil-β-*N*-(2-asetilpiridin)ditiokarbazat (SNM2AP) yang membentuk koordinasi dengan ion logam melalui azometin nitrogen atom, piridin nitrogen atom dan tiolo sulfur (penderma NNS).

Sesetengah sebatian baru yang disintesiskan mempamerkan aktiviti yang signifikan terhadap patogen tertentu dan sitotoksik terhadap dua jenis sel barah payudara, sel barah payudara reseptor positif estrogen, MCF-7 dan sel barah payudara reseptor positif estrogen, MDA-MB-231. Aktiviti biologi untuk bes Schiff dan kompleksnya dinilai untuk menyiasat aktiviti paten. Kebanyakan kompleks telah dinilai lebih aktif berbanding dengan ligan asalnya selepas pengkomplekan dengan ion logam.

Kesemua data sitotoksik sebatian telah dikumpulkan untuk membina model QSAR dengan harapan untuk mengilusidasi perhubungan di antara sturktur dan bioaktiviti. QSAR model yang memuaskan telah dibina yang memfokuskan beberapa diskriptor yang berinformasi berdasarkan kepada set yang mengandungi struktur hetero-jenis secara meluas berdasarkan nilai r^2>0.6 dan r^2_{CV}> 0.5.

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APPROVAL

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

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I certify that an Examination Committee has met on 25th September 2008 to conduct the final examination of Fiona How Ni Foong on her Doctor of Philosophy thesis entitled "Synthesis, Characterization and Elucidation of the Structure-Activity Relationship of Heteroatom Donor Ligands and Their Complexes Derived from Substituted Dithiocarbazate Derivatives" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the student be awarded the degree of Doctor of philosophy.

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DECLARATION

I declare that the thesis is my original work except for the quotations and citations, which have been duly acknowledged. I also declare that this it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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FIONA HOW NI FOONG

Date: 25 September 2008

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