



**UNIVERSITI PUTRA MALAYSIA**

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

**FIONA HOW NI FOONG**

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**DOCTOR OF PHILOSOPHY  
UNIVERSITI PUTRA MALAYSIA**

**2008**



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DITHIOCARBAZATE DERIVATIVES**

By

**FIONA HOW NI FOONG**

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

**September 2008**



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

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By

**FIONA HOW NI FOONG**

**September 2008**

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

**Faculty: Science**

Four new substituted dithiocarbazate ligands [*S*-naphthalen-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*-naphthalen-2-yl methyl- $\beta$ -*N*-(2-acetylpyridine)dithiocarbamate (SNM2AP) that coordinated with metal ions *via* the azomethine nitrogen atom, the pyridyl nitrogen atom and the thio 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

**FIONA HOW NI FOONG**

**September 2008**

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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 disintesis 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- $\beta$ -*N*-(2-asetilpiridin)ditiokarbamat (SNM2AP) yang membentuk koordinasi dengan ion logam melalui azometin nitrogen atom, piridin nitrogen atom dan tiolo sulfur (penderma NNS).

Sesetengah sebatian baru yang disintesisakan 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 struktur 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

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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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