



UNIVERSITI PUTRA MALAYSIA

**SYNTHESIS, CHARACTERIZATION AND BIOACTIVITY OF NEW
PHOSPHOROUS CONTAINING SCHIFF BASES PREPARED FROM
DITHIOCARBAZATE DERIVATIVES AND THEIR METAL
COMPLEXES**

ISAM HUSSAIN T. AL-KARKHI

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**DOCTOR OF PHILOSOPHY
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By

ISAM HUSSAIN T. AL-KARKHI

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
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January 2011



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SYNTHESIS, CHARACTERIZATION AND BIOACTIVITY OF NEW PHOSPHOROUS CONTAINING SCHIFF BASES PREPARED FROM DITHIOCARBAZATE DERIVATIVES AND THEIR METAL COMPLEXES

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January 2011

Chairman: Dr. Mohamed Ibrahim Mohamed Tahir (D. Phil.)

Faculty: Science

Twelve novel phosphorous containing Schiff bases derived from the four isomeric dithiocarbazates which are methyl hydrazinecarbodithioate (SMDTC), phenyl hydrazinecarbodithioate (SBDTC), 2-methylbenzyl hydrazinecarbodithioate (S2MBDTC) and 4-methylbenzyl hydrazinecarbodithioate (S4MBDTC) with 2-(diphenylphosphino) benzaldehyde (DPPB), (triphenylphosphanylidene) acetaldehyde (TPPA) and (triphenylphosphanylidene)propan-2-one (TPPP). Metal complexes of Cd(II), Co(III), Cu(II), Ni(II) and Zn(II) were synthesized from these twelve Schiff bases to obtain sixty metal complexes. All these novel compounds have been successfully synthesized and characterized by various physico-chemical and spectroscopic techniques. The structures of nine Schiff bases and two transition metal complexes were successfully determined *via* X-ray crystallographic analysis.



Four novel Schiff bases were coordinated in their metal complexes through nitrogen, sulfur and phosphorous donor atoms (PNS tridentate ligands), while the other eight Schiff bases coordinated through nitrogen and sulfur donor atoms (NS bidentate ligands). The cobalt complexes $\text{Co}(\text{SMDPB})_2 \text{NO}_3 \cdot 3\text{H}_2\text{O}$ had distorted octahedral geometry, coordinating *via* the triphenylphosphine phosphorous, azomethine nitrogen and thiolate sulphur atoms of the Schiff bases. The nickel complex has square planar geometry and coordinated *via* azomethine nitrogen and thiolate sulphur atoms of the Schiff base, while the λ^5 phosphorous do not coordinate.

All the seventy two novel compounds have been evaluated for their biological activities against certain pathogenic microbial and two breast cancer cell lines, MCF-7 (human breast carcinoma cells with positive estrogen receptor) and MDA-MB231 (human breast carcinoma cells with negative estrogen receptor). The complexes were mostly antibacterial, but were less active against the fungal strains tested. The Schiff bases in this study show a weak activity except for S2MBDTPA which shows a moderate activity. Complexation of these Schiff bases with the transition metal ions will enhance and increased the activity significantly. It was also found that the complexes contain λ^5 P shows more activity than λ^3 P. The complexes were generally more active against the MCF-7 cell line as compared to the MDA-MB231 cell line. Most of the metal complexes exhibited higher bioactivity compared to their ligands in the complexes.



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

**SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BES SCHIFF BARU
MENGANDUNGI FOSFORUS YANG DISEDIAKAN DARIPADA
TERBITAN DITHIOKARBAZAT DAN KOMPLEKS-KOMPLEKS
LOGAMNYA**

Oleh

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January 2011

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Dua belas bes Schiff novel yang mengandungi fosforus dan gabungan empat isomerik ditiokarbazat iaitu metilhidrazinkarboditioat (SMDTC), fenilhidrazinkarboditioat (SBDTC), 2-metilbenzilhidrazinkarboditioat (S2MBDTC) dan 4-metilbenzilhidrazinkarboditioat (S4MBDTC) dengan 2-(difenilfosfino)benzaldehyd(DPPB), (trifenilfosfanilidin)asetaldehyd (TPPA) dan (trifenilfosfanilidin)propan-2-on (TPPP). Kompleks logam Cd(II), Co(II), Cu(II), Ni(II) dan Zn(II) telah disintesis daripada duabelas bes Schiff tersebut untuk mendapatkan enam puluh kompleks logam, kesemua sebatian novel telah berjaya disintesis dan dicirikan dengan pelbagai teknik-teknik fisiko-kimia dan spektroskopi. Struktur sembilan bes Schiff dan dua kompleks logam peralihan telah berjaya ditentukan melalui analisis kristalografi sinar-X.



Empat bes Schiff novel terkoordinat didalam kompleks logam mereka melalui atom penderma nitrogen, sulfur dan fosforus (ligan tridentat PNS), sementara lapan bes Schiff yang lair berkoordinat melalui atom perderma nitrogen dan sulfur (ligan bidentat NS). Kompleks kobalt $\text{Co}(\text{SMDPB})_2 \text{NO}_3 \cdot 3\text{H}_2\text{O}$ mempunyai geometri oktahedron terherot, dikoordinat melalui atom fosforus trifenilfosfin, nitrogen azometin dan sulfur tiolat pada bes Schiff. Kompleks nikel mempunyai geometri satah segiempat sama dan berkoordinat melalui atom nitrogen azometin dan sulfur tiolat pada bes Schiff, sementara fosforus λ^5 tidak terkoordinat.

Kesemua tujuh puluh dua sebatian novel tersebut telah dinilai untuk aktiviti biologi terhadap beberapa mikrob patogen dan dua titisan sel kanser payudara MCF-7 (sel karsinoma payudara manusia dengan penerima estrogen positif) dan MDA-MB231 (sel karsinoma payudara penerima estrogen negatif). Kebanyakan kompleks antibakteria tetapi kurang aktif terhadap strain kulat yang diuji. Bes Schiff dalam kajian ini menunjukkan aktiviti yang lemah kecuali S2MBDTPA dimana menunjukkan aktiviti yang moderat. Pengkompleksan bes Schiff ini dengan ion logam peralihan akan meningkatkan aktiviti dengan signifikan lebih dan. Kompleks mengandugi $\lambda^5\text{P}$ menunjukkan aktiviti yang teloh can $\lambda^3\text{P}$. Kompleks secara umumnya lebih aktif terhadap titisan sel MCF-7 jiba dibandingkan dengan titisan sel MDA-MB231. Kebanyakan kompleks logam menunjukkan bioaktiviti yang lebih tinggi berbanding dengan ligan didalamnya.

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I certify that an Examination Committee met on date of viva to conduct the final examination of Isam Hussain T. Al-Karkhi on his Doctor of Philosophy thesis entitled “Synthesis, Characterization and Bioactivity of New Phosphorous Containing Schiff Bases Prepared from Dithiocarbazate Derivatives and Their Transition Metal Complexes” in accordance with 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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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 institutions.

ISAM HUSSAIN T. AL-KARKHI

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LIST OF ABBREVIATIONS

DTC	Dithiocarbazate
K-DTC	Potassiun-Dithiocarbazae
SMDTC	methylhydrazinecarbodithioate
SBDC	benzylhydrazinecarbodithioate
S2MBDTC	2-methylbenzylhydrazinecarbodithioate
S4MBDTC	4-methylbenzylhydrazinecarbodithioate
HIV	Human Immunodeficiency Virus
TQMP4, L	8-[(pyridin-4-yl)methylthio] quinoline
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
NLO	Non-Linear Optical properties
DPPB	2-(diphenylphosphino) benzaldehyde
TPPA	(triphenylphosphoranylidene) acetaldehyde
TPPP	1-(triphenyl phosphoranylidene)-2-propanone
SMDPB	(<i>E</i>)-methyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate
SBDPB	(<i>E</i>)-phenyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate



S2MBDPB	(<i>E</i>)-2-methylbenzyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate
S4MBDPB	(<i>E</i>)-4-methylbenzyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate
SMDTPA	Methyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene) ethylidene]hydrazinecarbodithioate
SBDTPA	Phenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene) ethylidene]hydrazinecarbodithioate
S2MBDTPA	2-methylphenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene) ethylidene]hydrazinecarbodithioate
S4MBDTPA	4-methylphenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene) ethylidene]hydrazinecarbodithioate
SMDTPP	Methyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene) propan-2-ylidene]hydrazinecarbodithioate
SBDTPP	Phenyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene) propan-2-ylidene]hydrazinecarbodithioate
S2MBDTPP	2-methylbenzyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene) propan-2-ylidene]hydrazinecarbodithioate
S4MBDTPP	4-methylbenzyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene) propan-2-ylidene]hydrazinecarbodithioate
TSC	Thiosemicarbazone
HPyTSC	Pyridine-2-aldehyde thiosemicarbazonato
HS(S)PPh ₂	Dithiodiphenylphosphine
MTB	Mycobacterium tuberculosis



REMA	Repetitive Excess Mixed Anhydride
TB	Tubercles Bacillus
IC ₅₀	Inhibition concentration at 50%
MIC	Minimum inhibitory concentration in $\mu\text{g cm}^{-3}$
MTT	3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
ORTEP	Oak Ridge Thermal Ellipsoid Program
QSAR	Quantitative Structure-Activity Relationship
CHNS	Carbon, Hydrogen, Nitrogen, Sulphur
MCF-7	human breast cancer cell line with positive estrogen receptor
MDA-MB-231	Human breast carcinoma cells with negative estrogen receptor
MRSA	Methicillin resistant <i>staphylococcus</i>
B29	<i>Bacillus subtilis</i> wild type
60690	<i>Pseudomonas aeruginosa</i>
S.C	<i>Salmonella choleraesuis</i>
C.A	<i>Candida albicans</i>
398	<i>Aspergillus ochraceous</i>
20341	<i>Saccaromyces cerevisiae</i>

ICP-AES	Inductively Coupled Plasma-Atomic Emission Spectroscopic Analyses
UATR	Universal ATR (Attenuated Total Reflection Spectroscopy)
DMEM	Dulbecco's Modified Eagle Medium
dppm	(diphenylphosphino) methane
dppe	(diphenylphosphino) ethane
PBS	Phosphate buffered saline
FBS	Fetal bovine serum
NA	Nutrient Agar
PDA	Potato Dextrose Agar
HeLA	Cervical Cancer cells
ER	Estrogen
RNR	Ribonucleotide Reductase



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