UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITY SCREENING OF SCHIFF BASE LIGANDS CONTAINING ISATIN AND THEIR METAL COMPLEXES

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By

MOHD ABDUL FATAH BIN ABDUL MANAN

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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APRIL 2008

Chair: Mohamed Ibrahim Mohamed Tahir, PhD

Faculty: Science

Six new Schiff bases formed from the condensation reaction of *S*-benzyldithiocarbazate (SBDTC) and *S*-methyldithiocarbazate (SMDTC) with selected diketones containing isatin derivatives namely isatin, 5-fluroisatin, 5-chloroisatin, 5-bromoisatin and methylisatin have been synthesised. Complexes of cobalt(II), nickel(II), copper(II), zinc(II) and cadmium(II) with these Schiff bases were prepared. These compounds were characterised by elemental analyses and various physico-chemical techniques. Single crystal X-ray analyses were carried out on five different compounds. X-ray crystallographic study of SB5ClISA and SB5BrISA Schiff bases proved that the condensation reaction between *S*-benzyldithiocarbazate with the isatin derivatives occur at the carbonyl position number 3 in the isatin ring. Crystal structure analyses of Co(II) and Ni(II) complexes showed that $[Ni(SMISA)_2]\cdot MeCN$ and $[Co(SMISA)_2]\cdot MeCN$ are six-coordinate and have a distorted octahedral structure with the ligands coordinated to the metal ions as uninegatively charged tridentate chelating agents *via* the azomethine nitrogen, thiolate sulphur atom and carbonylic oxygen atoms of the isatin moiety. Crystal structure of the $Cu(SMISA)_2$ complex

exhibited distorted square planar geometry with the ligands coordinated to the metal ion as uninegatively charged bidentate ions through the azomethine nitrogen and thiolate sulphur atoms. Unfortunately, none of the Zn(II) and Cd(II) complexes produced single crystals but, it is proposed, that they are also four-coordinated with a tetrahedral geometry. The Schiff bases and their metal complexes were evaluated for cytotoxic and antimicrobial activity. Cytotoxic screening was carried out against human breast cancer cells with positive estrogen receptor (MCF-7) and human breast cancer cells with negative estrogen receptor (MDA-MB-231). Some of the Schiff bases and metal complexes were found to be very active against these breast cancer cell lines with a CD_{50} values lower than Tamoxifen. Antimicrobial screening was carried out against four bacteria and three fungi. All compounds were found to have low or no activity against the selected bacteria and fungal strains.

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

SINTESIS, PENCIRIAN DAN SARINGAN AKTIVITI BIOLOGI TERHADAP LIGAN BES SCHIFF YANG MENGANDUNGI ISATIN DAN KOMPLEK LOGAM MASING-MASING

Oleh

MOHD ABDUL FATAH BIN ABDUL MANAN

APRIL 2008

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Enam bes Schiff baru telah berjaya disintesiskan daripada tindak balas kondensasi di antara *S*-benzilditiokarbazat (SBDTC) dan *S*-metilditiokarbazat (SMDTC) dengan diketon terpilih yang terdiri daripada terbitan isatin iaitu isatin, 5-floroisatin, 5-kloroisatin, 5-bromoisatin dan metilisatin Pelbagai kompleks logam kobalt(II), nikel(II), kuprum(II), zink(II) dan kadmium(II) telah berjaya disintesis dengan menggunakan bes Schiff tersebut. Semua sampel telah dicirikan dengan menggunakan pelbagai teknik kimia-fizik. Analisis sinar-X telah berjaya dilakukan terhadap lima hablur tunggal. Analisis sinar-X untuk hablur tunggal bes Schiff SB5ClISA dan SB5BrISA telah membuktikan bahawa tindak balas kondensasi antara *S*-benzilditiokarbazat dan terbitan isatin berlaku pada kedudukan kumpulan karbonil nombor 3 dalam gelang isatin. Analisis hablur tunggal kompleks logam Co(II) dan Ni(II) menunjukkan bahawa kompleks $[Co(SMISA)_2]\cdot MeCN$ dan $[Ni(SMISA)_2]\cdot MeCN$ adalah berkoordinat enam dan mempunyai geometri oktahedron terherot di mana ligan itu mengkoordinat pada ion logam melalui nitrogen azometin, sulfur tiolat dan oksigen karbonilik daripada isatin. Analisis sinar-X ke atas hablur tunggal kompleks logam $Cu(SMISA)_2$ pula menunjukkan geometri empat segi satah

terherot dengan ligan mengkoordinat pada ion logam melalui atom nitrogen azometin dan sulfur tiolat. Tiada hablur tunggal dapat dihasilkan daripada Zn(II) dan Cd(II) tetapi adalah dicadangkan bahawa kompleks logam ini adalah berkoordinasi empat dan mempunyai geometri tetrahedron. Bes Schiff dan kompleks logam masing-masing telah diuji untuk menilai aktiviti antimikrob dan sitotoksik. Analisis sitotoksik telah dilakukan ke atas dua jenis sel barah iaitu sel barah payu dara manusia dengan penerima estrogen positif (MCF-7) dan sel barah payu dara manusia dengan penerima estrogen negatif (MDA-MB-231). Terdapat beberapa bes Schiff dan kompleks logam yang sangat aktif terhadap sel barah payu dara ini dengan nilai CD_{50} nya adalah lebih rendah berbanding dengan piawai yang digunakan iaitu *Tamoxifen*. Saringan kereaktifan mikrob telah dilakukan terhadap empat jenis bakteria dan tiga jenis kulat. Semua sebatian yang disintesis didapati tidak aktif atau hanya menunjukkan aktiviti yang sederhana terhadap bakteria dan kulat yang diuji.

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I certify that an Examination Committee has met on **14 April 2008** to conduct the final examination of **Mohd Abdul Fatah Bin Abdul Manan** on his **Master of Science** thesis entitled "**Synthesis, characterisation and biological activities of Schiff base ligands containing isatin and their metal complexes**" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the Master of Science.

Members of the Examination Committee were as follows:

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Date:

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 are as follows:

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Date: 12 June 2008

DECLARATION

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

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MOHD ABDUL FATAH BIN ABDUL MANAN

Date:

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LIST OF ABBREVIATIONS

δ	Chemical shift in ppm
μM	Micro molar
$3CL^{pro}$	3C-like proteinase
3D	3 dimensional
A.alternata	*Alternaria alternata*
A.ochraceous	*Aspergillus ochraceous* (398)
AIDS	Acquired immune deficiency syndrome
Ar	Aromatic hydrophobic unit
B.Subtilis	*Bacillus subtilis*- wild type (B29)
C.A	*Candida albicans*
C.geniculata	*Curvularia geniculata*
$Cd(SB5BrISA)_2$	Bis[*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazato]cadmium(II) complex
$Cd(SB5ClISA)_2$	Bis[*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazato]cadmium(II) complex
$Cd(SB5FISA)_2$	Bis[*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazato]cadmium(II) complex
$Cd(SBISA)_2$	Bis[*S*-benzyl-β-*N*-(isatin-3)dithiocarbazato]cadmium(II) complex
$Cd(SBMeISA)_2$	Bis[*S*-benzyl-β-*N*-(1-methylisatin-3)dithiocarbazato]cadmium(II) complex
$Cd(SMISA)_2$	Bis[*S*-methyl-β-*N*-(isatin-3)dithiocarbazato]cadmium(II) complex
CD_{50}	Cytotoxic dose at 50%
CEM-SS	Human cell T-lymphoblastic leukemia
cfu	Colony forming units
CGM	Completed growth medium

CHNS	Carbon, Hydrogen, Nitrogen, Sulphur
CNS	Central nervous system
$Co(SB5BrISA)_2$	Bis[*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazato]cobalt(II) complex
$Co(SB5ClISA)_2$	Bis[*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazato]cobalt(II) complex
$Co(SB5FISA)_2$	Bis[*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazato]cobalt(II) complex
$Co(SBISA)_2$	Bis[*S*-benzyl-β-*N*-(isatin-3)dithiocarbazato]cobalt(II) complex
$Co(SBMeISA)_2$	Bis[*S*-benzyl-β-*N*-(1-methylisatin-3)dithiocarbazato]cobalt(II) complex
$Co(SMISA)_2$	Bis[*S*-methyl-β-*N*-(isatin-3)dithiocarbazato]cobalt(II) complex
$Cu(SB5BrISA)_2$	Bis[*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazato]copper(II) complex
$Cu(SB5ClISA)_2$	Bis[*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazato]copper(II) complex
$Cu(SB5FISA)_2$	Bis[*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazato]copper(II) complex
$Cu(SBISA)_2$	Bis[*S*-benzyl-β-*N*-(isatin-3)dithiocarbazato]copper(II) complex
$Cu(SBMeISA)_2$	Bis[*S*-benzyl-β-*N*-(1-methylisatin-3)dithiocarbazato]copper(II) complex
$Cu(SMISA)_2$	Bis[*S*-methyl-β-*N*-(isatin-3)dithiocarbazato]copper(II) complex
D	Electron donor
DI-MS	Direct Injection-Mass Spectroscopic
DMEM	Dullbecco's Modified Eagle's Medium
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
F.Palidoroseum	*Fusarium Palidoroseum*

FBS	Foetal Bovine Serum
FT-IR	Fourier Transform-Infrared
GC-MS	Gas Chromatography- Mass Spectrometer
HBD	Hydrogen bonding domain
HCV	Hepatitis C virus
HELA	Cervical cancer cells
HIV	Human immunodeficiency virus
HT-29	Human colon adenocarcinoma cells
IC_{50}	Half maximal inhibitory concentration
ICP-AES	Inductive Coupled Plasma-Atomic Emission Spectroscopy
ISA	Isatin
KBr	Potassium bromide
K-DTCA	Potassium dithiocarbazate
LMCT	Ligand to metal charge transfer
MAO	Mono amino-oxidase
MCF-7	Human breast cancer cells with positive estrogen receptor
MDA-MB-231	Human breast cancer cells with negative estrogen receptor
MeCN	Acetonitrile
MRSA	Methicillin resistant *Staphylococcus*
NA	Nutrient agar
$Ni(SB5BrISA)_2$	Bis[*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazato]nickel(II) complex
$Ni(SB5ClISA)_2$	Bis[*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazato]nickel(II) complex
$Ni(SB5FISA)_2$	Bis[*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazato]nickel(II) complex
$Ni(SBISA)_2$	Bis[*S*-benzyl-β-*N*-(isatin-3)dithiocarbazato]nickel(II) complex

$Ni(SBMeISA)_2$	Bis[*S*-benzyl-β-*N*-(1-methylisatin-3)dithiocarbazato]nickel(II) complex
$Ni(SMISA)_2$	Bis[*S*-methyl-β-*N*-(isatin-3)dithiocarbazato]nickel(II) complex
NMR	Nuclear Magnetic Resonance
NNRTI's	Non-nucleoside reverse transcriptase inhibitors
NNS	Nitrogen, nitrogen, sulphur donor ligands
NS	Nitrogen, sulphur donor ligands
OIs	Opportunistic infections
ONS	Oxygen, nitrogen, sulphur donor ligands
ORTEP	Oak Ridge Thermal Ellipsoid Plot (from the program for Crystal Structure Illustration)
P.aeruginosa	*Candida albicans* (C.A)
PBS	Phosphate-buffered Saline
PDA	Potato dextrose agar
ppm	Part per million
R	Hydrophobic unit
RPMI-1640	Roswell Park Memorial Institute Medium
RT	reverse transcriptase
S.aureus	*Staphylococcus aureus*
S.cerivisiae	*Saccharomyces cerivisiae* (20341)
S.choleraesuis	*Salmonella choleraesuis*
S2PDTC	*S*-2-picolyldithiocarbazate
SARS	Severe acute respiratory syndrome
SARS CoV	SARS Coronavirus
SB5BrISA	*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazate
SB5ClISA	*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazate

SB5FISA	*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazate
SBDTC	*S*-benzyldithiocarbazate
SBISA	*S*-benzyl-β-*N*-(isatin-3)dithiocarbazate
SBMeISA	*S*-benzyl-β-*N*-(1-methylisatin-3)dithiocarbazate
SMDTC	*S*-methyldithiocarbazate
SMISA	*S*-methyl-β-*N*-(isatin-3)dithiocarbazate
SS	Sulphur, sulphur donor ligands
SU11248	*N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol 3-ylidine)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide
UKM	Universiti Kebangsaan Malaysia
US FDA	United States Food and Drug Administration
UV-Vis	Ultraviolet Visible Spectroscopy
$Zn(SB5BrISA)_2$	Bis[*S*-benzyl-β-*N*-(5-bromoisatin-3)dithiocarbazato]zinc(II) complex
$Zn(SB5ClISA)_2$	Bis[*S*-benzyl-β-*N*-(5-chloroisatin-3)dithiocarbazato]zinc(II) complex
$Zn(SB5FISA)_2$	Bis[*S*-benzyl-β-*N*-(5-fluoroisatin-3)dithiocarbazato]zinc(II) complex
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