UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION, AND BIOACTIVITIES OF DITHIOCARBAZATE-SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES

LOW MAY LEE

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SYNTHESIS, CHARACTERIZATION, AND BIOACTIVITIES OF DITHIOCARBAZATE-SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES

By

LOW MAY LEE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia and École Doctorale 406 Chimie Moléculaire of Université Pierre et Marie Curie in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July 2014

Abstract of thesis presented to the Senate of Universiti Putra Malaysia and École Doctorale 406 Chimie Moléculaire Université Pierre et Marie Curie in fulfilment of the requirement for the degree of Doctor of Philosophy

SYNTHESIS, CHARACTERIZATION, AND BIOACTIVITIES OF DITHIOCARBAZATE-SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES

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Chair: Karen Ann Crouse, PhD
Faculty: Science

There is an urgent need to discover new drugs with novel mechanisms of action, higher activity and improved selectivity to address the severe challenge of multi-drug resistance in treating bacterial infections and cancer. In view of this, Schiff bases derived from S-substituted dithiocarbazate and their corresponding metal complexes with a plethora of potentially exciting biological activities and coordination chemistry are attractive candidates for consideration.

Macroacyclic and open chain metal complexes with their respective tetradentate and bidentate nitrogen-sulphur (NS) Schiff base ligands derived from the condensation of S-benzyldithiocarbazate (SBDTC) and S-methyldithiocarbazate (SMDTC) with 2,5-hexanedione, methyl levulinate, levulinic acid, 4-carboxybenzaldehyde and 3-acetylcoumarin have been prepared. The compounds were fully characterized with various physico-chemical and spectroscopic methods. A total of 11 crystal structures were determined throughout this work. In order to provide more insight into the behaviour of the complexes in solution, electron paramagnetic resonance (EPR) and cyclic voltammetry (CV) experiments were performed.

Conjugation of the most promising antimicrobial compound (Schiff base of SBDTC with 4-carboxybenzaldehyde) to various vectors (polyarginine, oligoethylene glycol (OEG) and phenylalanine-arginine-β-napthylamide (PAβN)) was achieved using either standard solid phase or solution synthetic methodologies to prepare improved therapeutic agents. Among the conjugates, the nonaarginine (R9) derivatives showed the most encouraging synergistic effect upon conjugation and complexation to copper ion with enhanced water solubility, bacteria cell membrane permeability and bioactivity. The Cu(II) R9 derivatives possess remarkable antibacterial activity against a wide spectrum of bacteria and in particular, highly efficacious against *Staphylococcus aureus* with MIC values up to 1-0.5 µM when tested against nine strains of Gram-positive and Gram-negative bacteria. This appears to be the pioneer study to show that the conjugation of polyarginine to dithiocarbazate compounds can greatly influence their therapeutic potential.

Cytotoxic assay was also carried out for selected non-conjugated compounds. All the selected Cu(II) complexes assayed against breast cancer cells lines (MCF-7 and MDA-MB-231) exhibited good cytotoxicity with lower IC_{50} values (0.71-8.31 µM) in comparison to their respective ligands.

This work highlights the relevance of metal complexation strategy to stabilize the ligands and improve their bioactivity. The structure-activity relationships of the compounds are discussed.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia dan École Doctorale 406 Chimie Moléculaire Université Pierre et Marie Curie sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

SINTESIS, PENCIRIAN, DAN AKTIVITI BIOLOGI LIGAN DITIOKARBAZAT-BES SCHIFF DAN KOMPLEKS LOGAM

Oleh

LOW MAY LEE

Julai 2014

Pengerusi: Karen Ann Crouse, PhD
Fakulti: Sains

Terdapat keperluan segera untuk menemui ubat-ubatan baru dengan mekanisme baru, aktiviti yang lebih tinggi dan tindakan yang lebih khusus bagi menangani cabaran yang serius iaitu rintangan terhadap pelbagai ubat-ubatan dalam rawatan jangkitan bakteria dan kanser. Bes Schiff dan kompleks logam yang berasal daripada S-gantian ditiokarbazat yang mempunyai pelbagai potensi aktiviti biologi dan kimia koordinatan menarik merupakan calon-calon yang baik untuk pertimbangan dalam menghasilkan farmaseutik baru.

Kompleks logam bersistem makro-bukan-kitaran dan rantaian-terbuka masing-masing dengan ligan nitrogen-sulfur (NS) tetradentat dan bidentat bes Schiff yang berasal daripada kondensasi S-benzilditiokarbazat (SBDTC) dan S-metilditiokarbazat (SMDTC) dengan 2,5-heksanadion, metil levulinat, asid levulinik, 4-karboksibenzaldehid dan 3-asetilkoumarin telah disediakan. Semua sebatian tersebut telah dicirikan sepenuhnya dengan pelbagai kaedah fiziko-kimia dan spektroskopi. Sebanyak 11 struktur hablur tunggal telah ditentukan sepanjang kajian ini. Untuk memberi gambaran yang lebih jelas terhadap sifat-sifat kompleks dalam larutan, eksperimen resonans paramagnet electron (EPR) dan voltammetri berkitar (CV) telah dijalankan.

Konjugasi sebatian yang paling berpotensi sebagai antimikrob (bes Schiff SBDTC dengan 4-karboksibenzaldehid) dengan pelbagai vektor (poliarginina, oligoetilena glikol (OEG) dan fenilalanina-arginina-β-naptilamida (PAβN)) telah berjaya dicapai sama ada melalui metodologi sintetik standard peptida fasa pepejal atau larutan bagi penyediaan agen terapeutik yang lebih baik. Antara sebatian yang dikonjugasi, terbitan nonaarginina (R9) menunjukkan kesan sinergi yang paling menggalakkan melalui konjugasi dan juga pembentukan kompleks dengan ion kuprum yang turut membawa kepada peningkatan kelarutan dalam air, ketelapan terhadap membran sel bakteria dan bioaktiviti sebatian. Terbitan Cu(II) R9 memiliki aktiviti antibakteria yang terbaik terhadap spektrum bakteria yang luas dan khususnya, sangat berkesan terhadap *Staphylococcus aureus* dengan nilai MIC sehingga 1-0.5 μM apabila diuji terhadap sembilan jenis bakteria Gram-positif dan Gram-negatif. Ini merupakan kajian perintis yang menunjukkan konjugasi antara polyarginina dengan sebatian ditiokarbazat boleh mempengaruhi potensi terapeutik mereka.

Kajian sitotoksik juga dijalankan untuk segelintir sebatian yang tidak dikonjugasi. Semua Cu(II) kompleks yang diuji terhadap sel-sel kanser payudara (MCF-7 dan MDA-MB-231) menunjukkan sifat sitotoksik yang baik dengan nilai-nilai IC_{50} (0.71-8.31 µM) yang lebih rendah berbanding dengan ligan asal.

Kajian ini menunjukkkan kesesuaian strategi pembentukan kompleks dengan ion logam untuk menstabilkan ligan dan meningkatkan bioaktiviti mereka. Perhubungan di antara struktur dan aktiviti sebatian juga dibincang.

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Dans la vie, rien n'est à craindre, tout est à comprendre.
Nothing in life is to be feared, it is only to be understood.
- Marie Curie

I certify that a Thesis Examination Committee has met on 9 July 2014 to conduct the final examination of Low May Lee on her thesis entitled "Synthesis, Characterization, and Bioactivities of Dithiocarbazate-Schiff Base Ligands and Their 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 degree of Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Mahiran binti Basri, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Nor Azah binti Yusof, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Yang Farina binti Abdul Aziz, PhD
Professor
Universiti Kebangsaan Malaysia
(External Examiner)

Bernold Hasenknopf, PhD
Professor
Université Pierre et Marie Curie - Paris 6
France
(External Examiner)

NORITAH OMAR, PhD
Associate Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 21 July 2014

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

Karen Ann Crouse, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Clotilde Policar, PhD
Professor
Laboratoire des BioMolécules (UMR 7203)
Université Pierre et Marie Curie
(Member)

Nicolas Delsuc, PhD
Chargé de Recherche CNRS
Laboratoire des BioMolécules (UMR 7203)
Université Pierre et Marie Curie
(Member)

Mohamed Ibrahim Mohamed Tahir, D.Phil
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Thahira B.S.A Ravoof, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Rozita Rosli, PhD
Professor
Faculty of Medical and Health Science
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

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Declaration by graduate student

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Name and Matric No: Low May Lee (GS26866)

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LABORATOIRE DES BIOMOLECULES
UMR 7203
ENS - Université Pierre et Marie Curie - CNRS
ENS - Département de chimie
24, rue Lhomond - 75231 PARIS CEDEX 05

Signature: _____
Name of Chairman of Supervisory Committee: Karen Ann Crouse, PhD

Signature: _____
Name of Member of Supervisory Committee: Clotilde Policar, PhD

Signature: _____
Name of Member of Supervisory Committee: Mohamed Ibrahim Mohamed Tahir, D.Phil

Signature: _____
Name of Member of Supervisory Committee: Nicolas Delsuc, PhD

Signature: _____
Name of Member of Supervisory Committee: Thahira B.S.A Ravoof, PhD

Signature: _____
Name of Member of Supervisory Committee: Rozita Rosli, PhD

PROF. DR. ROZITA ROSLI
Ketua
Laboratori Penyelidikan Kanser UPM-MAKNA
Institut Biosains
Universiti Putra Malaysia
43400 UPM, Serdang
Selangor.

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LIST OF ABBREVIATIONS

A. baumannii	*Acinetobacter baumannii*
A. fumigates	*Aspergillus fumigatus*
A. niger	*Aspergillus niger*
A. ochraceous	*Aspergillus ochraceus*
ABC	ATP binding cassette
Abs.	Absorbance
ACN	Acetonitrile
ΔH	Enthalpy of the reactions
AMPs	Antimicrobial peptides
ABC	ATP binding cassette
Arg	Arginine
a.u.	Arbitrary unit
B. cereus	*Bacillus cereus*
B. subtilis	*Bacillus subtilis*
BAM	Biologically active molecule
BBN	Bombesin
BHT	Buthylatedhydroxytoluene
Boc	Tert-butyloxycarbonyl
C. lusitaniae	*Candida lusitaniae*
C. albicans	*Candida albicans*
C. lypolytica	*Candida lypolytica*
Caov-3	Human ovarian cancer
Cb4PDTC	S4PDTC with 4-carboxybenzaldehyde
CD3OD	Deuterated methanol

CEM-SS	T-lymphoblastic leukemia
CHCA	Alpha-cyano-4-hydroxycinnamic acid
CHNS	Carbon, hydrogen, nitrogen, sulphur
CH_3CN	Acetonitrile
CH_3OH	Methanol
CI	Chemical ionization
CPPs	Cell penetrating peptides
$Cu(OAc)_2.H_2O$	Copper(II) acetate monohydrate
CV	Cyclic voltammetry
DCM	Dichloromethane
DFO	Desferrioxamine B
DFT	Density functional theory
DIEA	N,N-Diisopropylethylamine
DiSC3(5)	3,3′-Dipropylthiadicarbocyanine iodide
DMEM	Dulbecco's modified Eagle's medium
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d6	Deuterated dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dpq	Dipyrido[3,2-d:2′,3′-f]quinoxaline
dppz	Dipyrido[3,2-a:2′,3′-c]phenazine
DTC	Dithiocarbazate
E. aerogenes	*Enterobacter aerogenes*
E. coli	*Escherichia coli*
E. histolytica	*Entamoeba histolytica*

E_p	Peak potentials
$E_{1/2}$	Half-wave potentials
EPIs	Efflux pump inhibitors
EPR	Electron paramagnetic resonance
ER	Estrogen receptor
ESI-MS	Electrospray ionization-mass spectroscopy
EtOH	Ethanol
F	Phenylalanine
F. oxysporum	*Fusarium oxysporum*
FAB	Fast atom bombardment
FBS	Fetal bovine serum
FDA	Food and Drug Administration
Fmoc	Fluorenlymethyloxycarbonyl
Fmoc-AEEA-OH	[2-[2-(Fmoc-amino)ethoxy]ethoxy]acetic acid
FT-IR	Fourier transform infrared spectroscopy
FTSC	2-Formylpyridine thiosemicarbazone
GRP	Gastrin-releasing peptide
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBTU	N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uraniumhexafluorophosphate, O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HELA	Cervical cancer cells
HEPES	2-[4-(2-Hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
HF	Hydrofluoric acid
HIV-TAT	Human immunodeficiency virus - trans-activator of transcription

HL-60	Human promyelocytic leukemia cells
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HR-MS	High resolution mass spectroscopy
HT-29	Colon cancer cells
HTS	High throughput screening
IC_{50}	Inhibition concentration at 50%
INT	Iodonitrotetrazolium
i_{pa}	Anodic current
i_{pc}	Cathodic current
ITC	Isothermal titration calorimetry
K562	Human acute myelocytic leukemia cell line
KAN^R	Resistance to kanamycin
K_{ass}	Association constant
K. pneumonia	*Klebsiella pneumonia*
LC-MS	Liquid chromatography-mass spectrometry
LMCT	Ligand-to-metal charge-transfer
LPS	Lipopolysaccharide
M. tuberculosis	*Mycobacterium tuberculosis*
MATE	Multidrug and toxic compound extrusion
MALDI-TOF-MS	Matrix-assisted laser desorption/ionization-time-of-flight-mass spectroscopy
MBHA	4-Methylbenzhydrylamine
MCF-7	Human breast carcinoma cells expressing nuclear estrogen receptors

MDA-MB-231	Human breast carcinoma cells not expressing nuclear estrogen receptors
MDCK	Madin-Darby canine kidney
MDR	Multi-drug resistance
MeOH	Methanol
Me_2S	Dimethysulfide
MFS	Major facilitator superfamily
MHB	Mueller-Hinton broth
MIC	Minimum inhibitory concentration
m/*z*	Mass-to-charge ratio
MOPS	3-(N-Morpholino)propanesulfonic acid
MPA	3-Mercaptopropionic acid
MRSA	Methicillin-resistant *Staphylococcus aureus*
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
n	Stoichiometry
NHE	Normal hydrogen electrode
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NS	Nitrogen-sulphur
OEG	Oligoethylene glycol
OPNG	Ortho-nitrophenyl-β-D-galactopyranoside
ORTEP	Oak Ridge thermal ellipsoid plot
$^1O_2$	Singlet oxygen
P. aeruginosa	*Pseudomonas aeruginosa*
PAβN	Phenylalanine-arginine-β-napthylamide

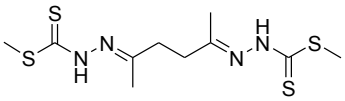
PBS	Phosphate buffered saline
Pc4PDTC	S4PDTC with pyridine-2-carboxaldehyde
PEG	Polyethylene glycol
phen	1,10-phenanthroline
PMB	Polymyxin B
PMBN	Polymyxin B nonapeptide
PNAs	Polynucleic acids
Pro	Proline
pyta	4-(2-Pyridyl)-1,2,3-triazole
QSAR	Quantitative structure-activity relationship
R	Arginine
RND	Resistance-nodulation-division
RP-HPLC	Reversed phase-high performance liquid chromatography
RPM	Revolutions per minute
r.t.	Room temperature
R_T	Retention time
S. aureus	*Staphylococcus aureus*
S. ceciricaee	*Saccaromyces ceciricaee*
sac	Saccharinate anion
S2PDTC	S-2-picolyldithiocarbazate
S4PDTC	S-4-picolyldithiocarbazate
SB2ATP	SBDTC-2-acetylthiophene
SB3ATP	SBDTC-3-acetylthiophene
SB4CB	4-(Benzylsulfanylthiocarbonyl-hydrazonomethyl)-benzoic acid

SBCM	N'-[1-(2-Oxo-2H-chromen-3-yl)-ethylidene]-hydrazinecarbodithioic acid benzyl ester
SBDTC	S-benzyldithiocarbazate
SBEL	4-(Benzylsulfanylthiocarbonyl-hydrazono)-pentanoic acid ethyl ester
SBHD	N'-[4-(Benzylsulfanylthiocarbonyl-hydrazono)-1-methyl-pentylidene]-hydrazinecarbodithioic acid benzyl ester
SBLA	4-(Benzylsulfanylthiocarbonyl-hydrazono)-pentanoic acid
SBML	4-(Benzylsulfanylthiocarbonyl-hydrazono)-pentanoic acid methyl ester
SBPY	(2,5-Dimethyl-pyrrol-1-yl)-dithiocarbamic acid benzyl ester
SCE	Saturated calomel electrode
SCXRD	Single crystal X-ray diffraction
S. enterica	*Salmonella enterica*
SM4CB	4-(Methylsulfanylthiocarbonyl-hydrazonomethyl)-benzoic acid
SMDB	S-methyl-β-N-(2-acetylfuran)dithiocarbazate
SMDTC	S-methyldithiocarbazate
SMHD	N'-[1-Methyl-4-(methylsulfanylthiocarbonyl-hydrazono)-pentylidene]-hydrazinecarbodithioic acid methyl ester
SMISA	S-methyldithiocarbazate with isatin
SMLA	4-(Methylsulfanylthiocarbonyl-hydrazono)-pentanoic acid
SMML	4-(Methylsulfanylthiocarbonyl-hydrazono)-pentanoic acid methyl ester
SMR	Small multidrug resistance
SOD	Superoxide dismutase
SPPS	Solid-phase peptide synthesis
STSC	Salicylaldehyde thiosemicarbazone
TFA	Trifluoroacetic acid

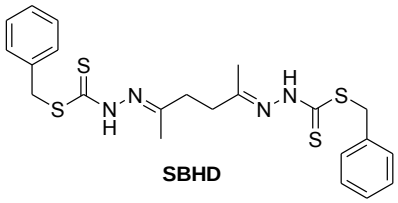
TIS	Triisopropylsilane
TRIS	2-Amino-2-hydroxymethyl-propane-1,3-diol
Trp	Tryptophan
%T	Percentage of transmission
UV-Vis	Ultraviolet-visible
W	Tryptophan
WT	Wild type
XO	Xanthine oxidase
e	Extinction coefficient
α^2	Molecular orbital coefficient α^2
$A_{Ý}$, $g_{Ý}$, $g_{Ù}$	EPR parameters

LIST OF COMPOUNDS IN THIS WORK

(a) Macroacyclic Cu(II) system with tetradentate NNSS ligands.



SMHD



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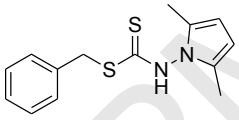
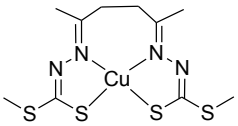
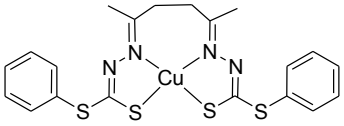


SBPY

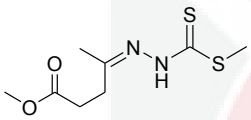


CuSMHD

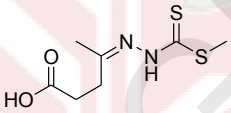


CuSBHD

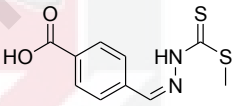
(b) Open chain Cu(II) system with bidentate NS ligands with acid or ester functionality.



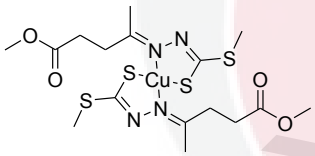
SMML



SMLA



SM4CB



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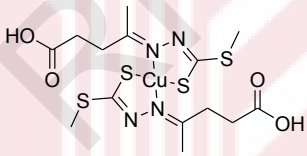

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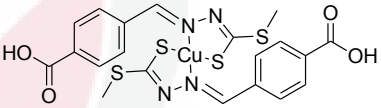

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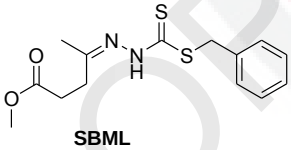

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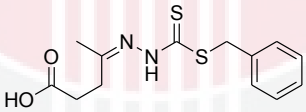

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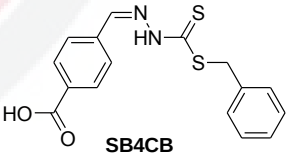

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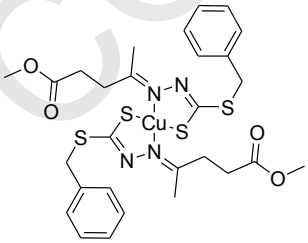

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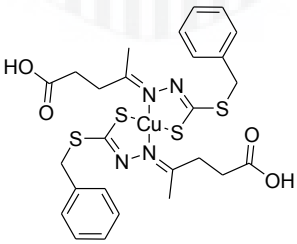

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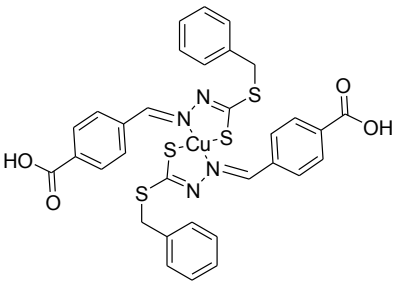

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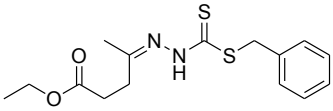
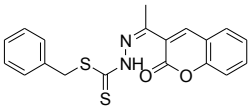
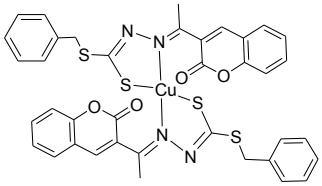


SBEL

(c) Open chain metal system with bidentate NS ligands with natural ketone moiety.



SBCM



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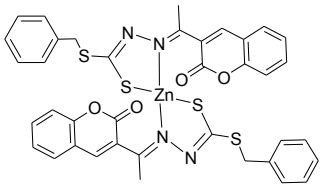
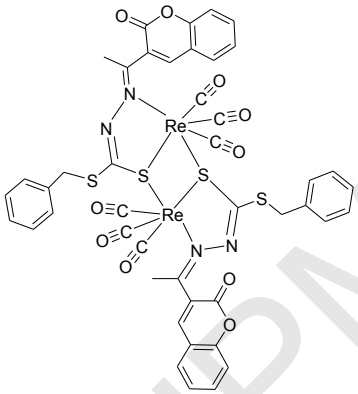
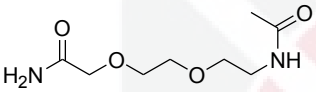


Zn(SBCM)$_2$

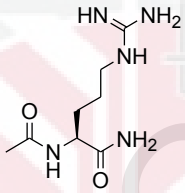


Re$_2$(SBCM)$_2$

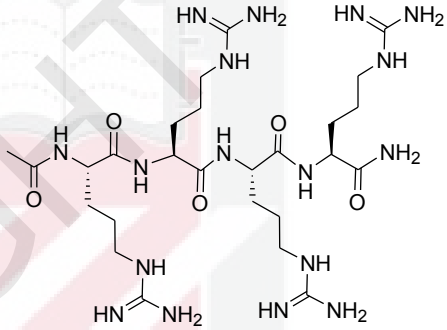
(c) Acetylated vectors.



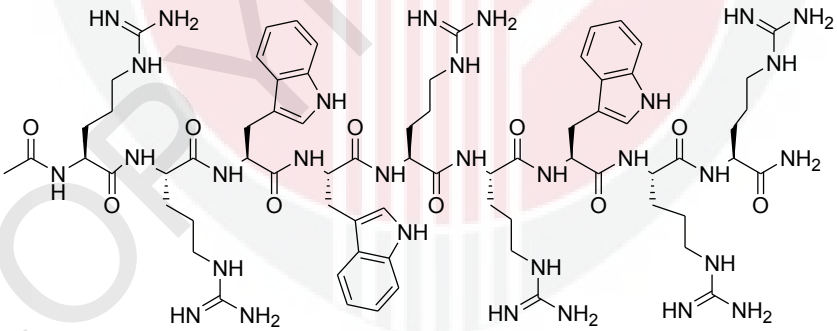
OEGAC



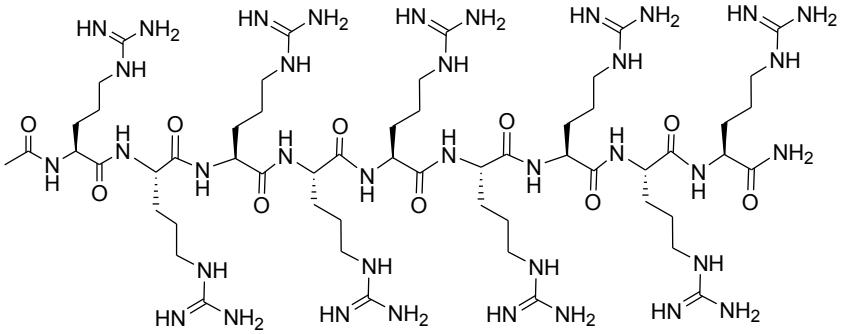
R1AC



R4AC

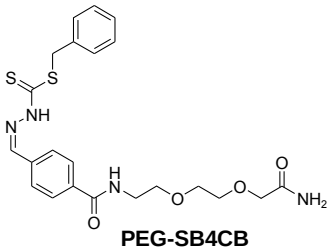


RW9AC

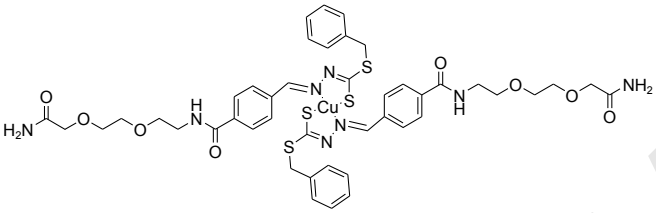


R9AC

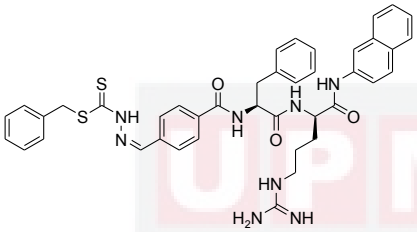
(d) Functionalized compounds.



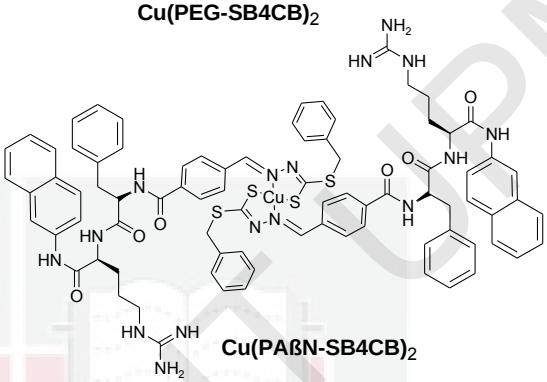
PEG-SB4CB



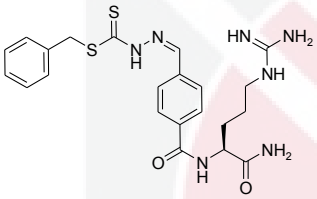
Cu(PEG-SB4CB)$_2$



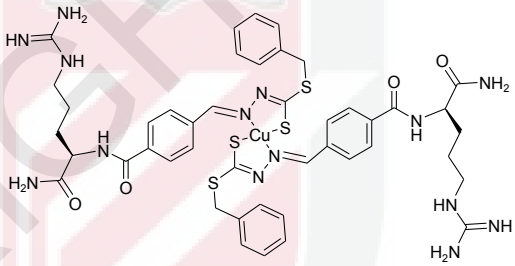
PAßN-SB4CB



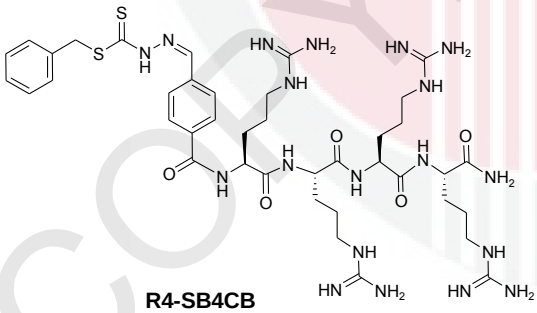
Cu(PAßN-SB4CB)$_2$



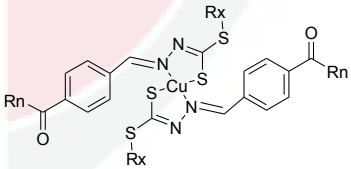
R1-SB4CB



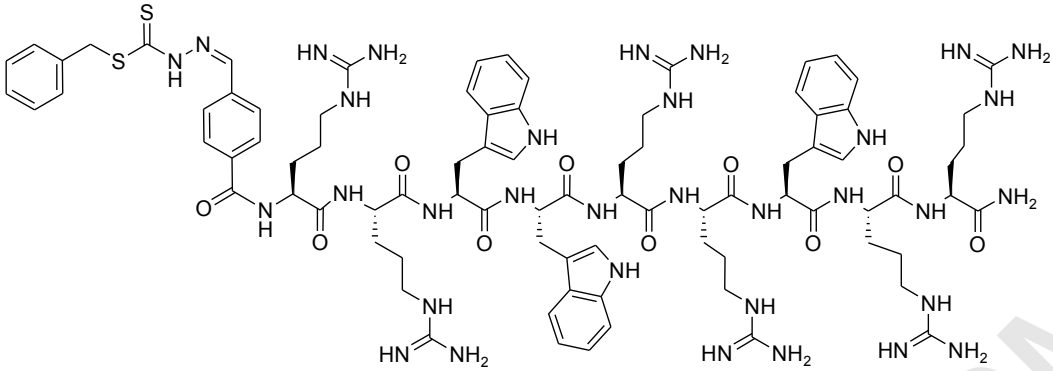
Cu(R1-SB4CB)$_2$



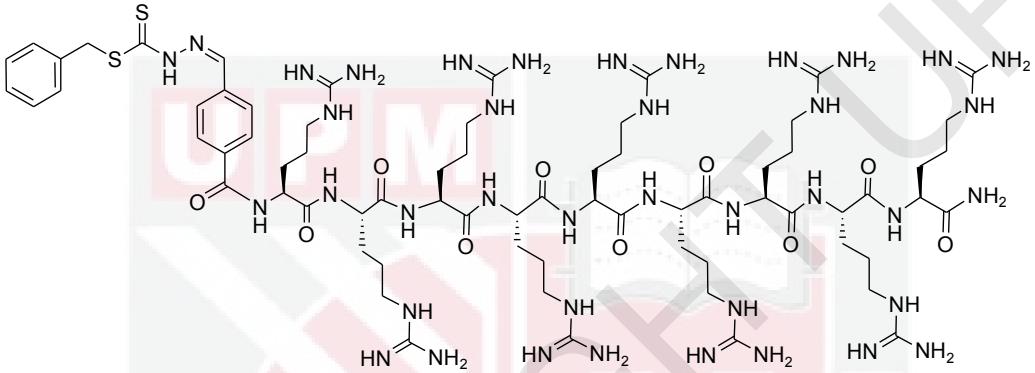
R4-SB4CB



Cu(R4-SB4CB)2 : Rx=CH_2Ph, Rn=R4
Cu(RW9-SB4CB)2 : Rx=CH_2Ph, Rn=RW9
Cu(R9-SB4CB)2 : Rx=CH_2Ph, Rn=R9
Cu(RW9-SM4CB)2 : Rx=CH_3, Rn=RW9
Cu(R9-SM4CB)2 : Rx=CH_3, Rn=R9



RW9-SB4CB



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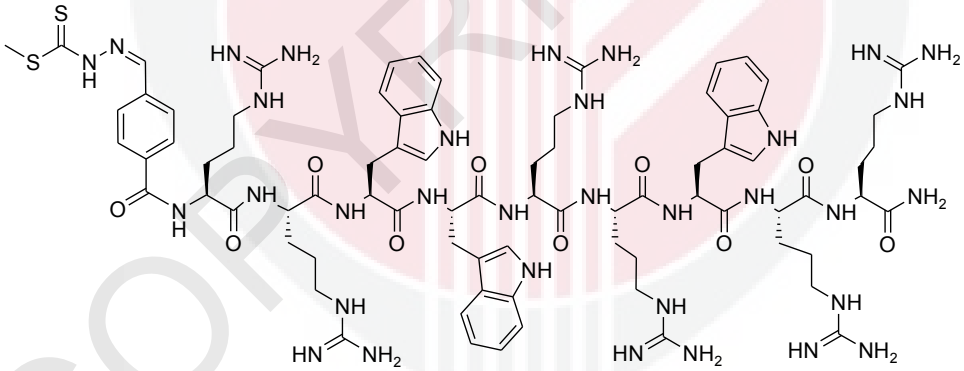

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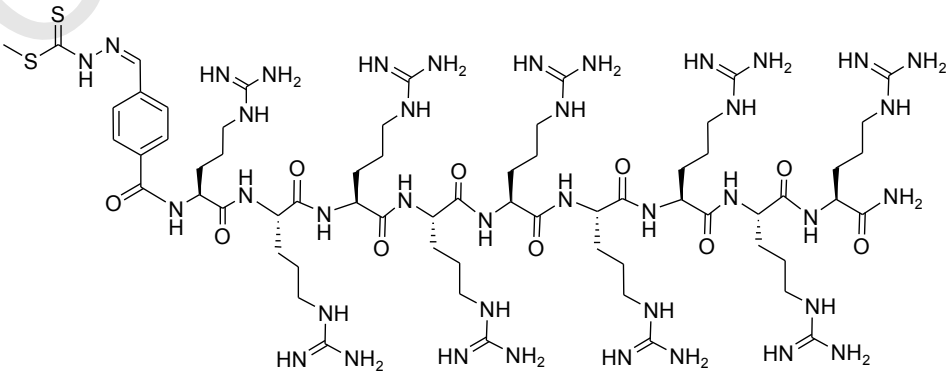

R9-SM4CB

CHAPTER 1

INTRODUCTION

1.1 General

The use of QRYHOH[RWLFRULJLQDOFRPSRXQGVIURPQDWXUH¶VFKHVWWRWUHDW has been a quest of mankind since ancient time (Li and Vederas, 2009). Although natural products have historically been a rich source of lead therapeutic molecules, +DUYH\ S SRLQWHG RXW WKDW ¹WKH GLIILFXOWLHV LQ DFFHVV DQG VXSSO\ complexities of natural product chemistry and inherent slowness of working with WKHPKDYHFRQWULEXWHG WR WKH GH emphasis of natural products programs in industry over the years. It is foreseeable that developments in the field of synthesis will only continue as synthetic compounds hold the upper hand in meeting the demand of the highly competitive pharmaceutical industry to adapt to the current state-of-the-art advancement in science and technology (Li and Vederas, 2009).

In terms of metal-containing drugs, the platinum drug cisplatin introduced clinically in 1971 and approved by Food and Drug Administration (FDA) in late 1978, has been the most e¡ ective metal-based anticancer drug in the market (Hoeschele, 2009; Swarts et al., 2008). In general, ³cisplatin is believed to kill cancer cells by binding to DNA and interfering with the cell's repair mechanism which eventually leads to programmed cell death´ called apoptosis (Trzaska, 2005, p. 52 and Goodsell, 2006). The resounding therapeutic success of cisplatin and its analogues has triggered tremendous effort in search of alternative metal-based chemotherapeutic agents in the past few decades (Ronconi and Fregona, 2009; Jakupec et al., 2008). The rationale for these studies is that metal centers other than platinum might open up new avenues in the development of clinically useful drug (Ronconi et al., 2006). Furthermore, there is an urgency to discover and characterize new drugs with enhanced activity, selectivity, bioavailability and fewer side-effects than conventional drugs to treat current diseases. Figure 1.1 highlights the steady decrease in not only the commercialization but also the discovery for new antibiotics after the 1980s while the serious threat of antimicrobial resistance continues to prevail as reflected in the increasing occurrence of Methicillin-resistant *Staphylococcus aureus* (MRSA) over the same period (Bandow and Metzler-Nolte, 2009; Patra et al., 2012b). In addition, parallel concern over acquired drug resistance and serious side-effects of current anti-cancer drugs in the midst of the rise of cancer, in particular breast cancer as one of the leading causes of death worldwide, also drives the need to develop better alternatives (Ahmad et al., 2013; Yang et al., 2013; Ronconi and Fregona, 2009).

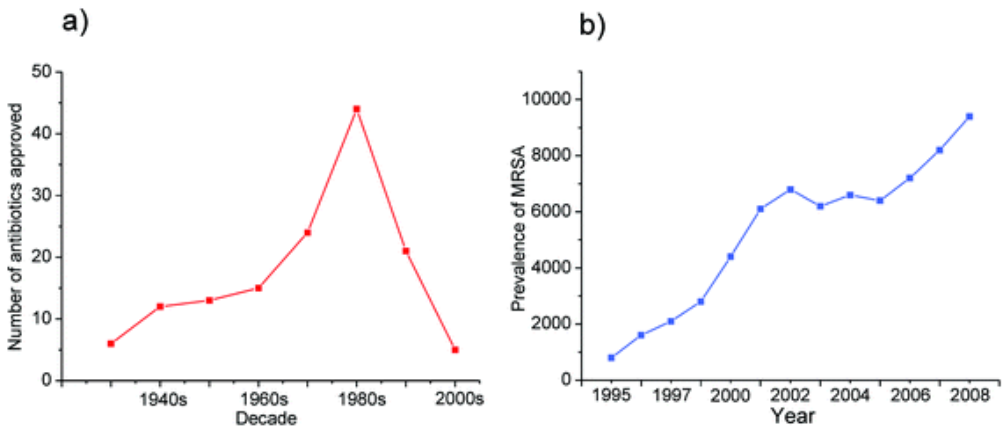

Figure 1.1. (a) Decade-wise approval of new antibiotics and (b) prevalence of MRSA. (Source: Patra et al., 2012b)

Many publications have highlighted the rich diversity and potential of metal complexes for the design of novel therapeutic agents (Fricker, 2007; Haas and Franz, 2009; Ronconi and Sadler, 2007; Hambley, 2007; Thompson and Orvig, 2006; Meggers, 2009). The intrinsic nature of metal centers, characteristic coordination modes, accessible redox states and tuneable thermodynamic and kinetic properties allow metal complexes to offer potential advantages over organic agents alone (Rijt and Sadler, 2009). In addition, Sadler (2009, p. 10647 VWDWHG WKDW ³WKH ligands not only control the reactivity of the metal but also play critical roles in determining the nature of interactions involved in the recognition of biological target sites such as deoxyribonucleic acid (DNA), enzymes and protHLQUHFHSWRUV´

The great expansion of research in the coordination chemistry of nitrogen- and sulphur-containing ligands such as Schiff bases derived from thiosemicarbazones and dithiocarbazates has taken place during recent years (Pelosi, 2010; Beraldo and Gambinob, 2004; Ali and Livingstone, 1974). Schi¡ base metal complexes have played a prominent role in the development of coordination chemistry. This area of research has a wide spectrum, ranging from synthesis to application in many diverse fields. According to IUPAC, Schiff bases are ³imines bearing a hydrocarbyl group on the nitrogen atom $R_2C=NR'$ (R' • H)´. Hydrocarbyl groups are ³univalent groups formed by removing a hydrogen atom from a hydrocarbon, e.g. ethyl, phenyl´. Nonetheless, this term has been broadly used in many publications for any compound that includes an azomethine group formed from the condensation of primary amines with aldehydes or ketones. Schiff bases have often been used as chelating ligands for preparation of complex compounds which are useful as catalysts, in various biological systems, polymers and dyes besides some uses as antifertility and enzymatic agents (Kumar et al., 2009; Soliman and Linert, 2007). Since this class of ligands possess both hard nitrogen and soft sulphur donor atoms, they are capable to act as good chelating agents for various metal ions (Mohamed et al., 2009). The flexibility and bioactivity of nitrogen and sulphur containing Schiff bases have also been associated with the presence of both imino (-N=CH-) and thioamino (-(C=S)-NH-) moieties in their structures (Tarafder et al., 2008). Coordination of such compounds with metal ions often enhances their activities

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