

ห้องสมุดงานวิจัย สำนักงานคณะกรรมการการวิจัยแห่งชาติ



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CHEMICAL CONSTITUENTS AND BIOACTIVE SUBSTANCES
FROM FUNGI *CHAETOMIUM ELATUM* AND
CHAETOMIUM LUCKNOWENSE

MR. SANTI TECHINUNG

A THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
KHON KAEN UNIVERSITY

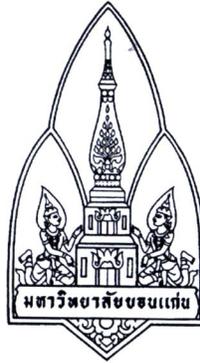
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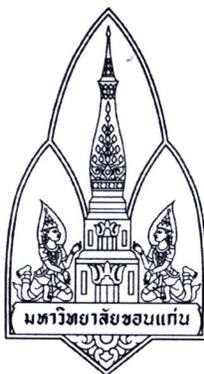
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*CHAETOMIUM LUCKNOWENSE***

MR. SANTI THOHINUNG

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY
GRADUATE SCHOOL KHON KAEN UNIVERSITY**

2010



THESIS APPROVAL
KHON KAEN UNIVERSITY
FOR
DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

Thesis Title: Chemical Constituents and Bioactive Substances from Fungi
Chaetomium elatum and *Chaetomium lucknowense*

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สันติ โถหินัง. 2553. การศึกษาองค์ประกอบทางเคมีและสารออกฤทธิ์จากรา *Chaetomium elatum* และ *Chaetomium lucknowense*. วิทยานิพนธ์ปริญญาปรัชญาดุษฎีบัณฑิต สาขาวิชาเคมีอินทรีย์ บัณฑิตวิทยาลัย มหาวิทยาลัยขอนแก่น.

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บทคัดย่อ

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จากการสกัดเส้นใยแห้งรา *Chaetomium elatum* (210 กรัม) และ *C. lucknowense* (282 กรัม) ด้วยตัวทำละลายเฮกเซน เอทิลอะซิเตต และเมทานอล ได้ส่วนสกัดหยาบ 3 ส่วน จากรา *C. elatum* คือ ส่วนสกัดหยาบเฮกเซน 8.4 กรัม ส่วนสกัดหยาบเอทิลอะซิเตต 21.7 กรัม และส่วนสกัดหยาบเมทานอล 28.5 กรัม และ 3 ส่วนจากรา *C. lucknowense* คือ ส่วนสกัดหยาบ เฮกเซน 8.4 กรัม ส่วนสกัดหยาบเอทิลอะซิเตต 18.0 กรัม และส่วนสกัดหยาบเมทานอล 45.3 กรัม

จากการแยกส่วนสกัดหยาบของรา *C. elatum* ด้วยวิธีทางโครมาโทกราฟีได้สาร 12 สาร เป็นสารใหม่ 1 สาร คือ chaetoglobosin V (XI) และสารที่ทราบโครงสร้างแล้ว 11 สาร คือ ergosterol (I), 24(R)-5 α ,8 α -epidioxyergosta-6-22-diene-3 β -ol (II), chaetoglobosin C (III), isochaetoglobosin D (IV), chaetoglobosin F (V), chaetoglobosin G (VI), chaetoglobosin B (VII), chaetoglobosin D (VIII), prochaetoglobosin III (IX), prochaetoglobosin IIIed (X) และ D-mannitol (XIX) สำหรับการแยกส่วนสกัดหยาบของรา *C. lucknowense* ด้วยวิธีทางโครมาโทกราฟีได้สาร 10 สาร เป็นสารใหม่ 1 สาร คือ XVIII และสารที่ทราบโครงสร้างแล้ว 9 สาร คือ ergosterol (I), 24(R)-5 α ,8 α -epidioxyergosta-6-22-diene-3 β -ol (II), chrysophanol (XII), emodin (XIII), chaetoviridin A (XIV), cochliodone D (XV), xanthoquinodin A1 (XVI), xanthoquinodin B2 (XVII) และ D-mannitol (XIX) การพิสูจน์โครงสร้างของสารเหล่านี้ด้วยเทคนิคทางสเปกโทรสโกปี (UV, IR, MS, ¹H NMR, ¹³C NMR, DEPT และ 2D NMR) จากการแยกองค์ประกอบจากราทั้งสองพบว่าได้สารเหมือนกัน 3 สาร คือสาร I, II และ XIX นอกจากนี้ยังเป็นการพบสารในกลุ่ม cytochalasan ในรา *C. elatum* และกลุ่ม xanthoquinodin ในรา *C. lucknowense* เป็นครั้งแรก

จากการทดสอบฤทธิ์ทางชีวภาพ พบว่าสาร XI, XVI, XVII และ XVIII มีฤทธิ์ยับยั้งเชื้อ *Plasmodium falciparum* สาเหตุของไข้มาลาเรีย โดยมีค่า IC₅₀ เท่ากับ 2.40, 1.43, 1.70 และ 3.2 μ g/mL ตามลำดับ รวมทั้งมีฤทธิ์ยับยั้งเชื้อ *Mycobacterium tuberculosis* สาเหตุของวัณโรค โดยมีค่า MIC เท่ากับ 50, 12.50, 25 และ 25 μ g/mL ตามลำดับ และสารดังกล่าวยังมีความเป็นพิษต่อ

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เซลล์มะเร็งชนิด KB ด้วยค่า IC_{50} เท่ากับ 2.28, 2.77, 4.01 และ 9.6 $\mu\text{g/mL}$ ตามลำดับ สาร XI, XVI และ XVII มีความเป็นพิษต่อเซลล์มะเร็งชนิด NCI-H187 ด้วยค่า IC_{50} เท่ากับ 11.57, 0.456 และ 1.03 $\mu\text{g/mL}$ ตามลำดับ สาร III-XI และ XVI-XVIII มีความเป็นพิษต่อเซลล์มะเร็งชนิด BC1 ด้วยค่า IC_{50} อยู่ในช่วง 1.29-25.23 $\mu\text{g/mL}$ นอกจากนี้สาร III-XI แสดงการยับยั้งเซลล์มะเร็งชนิด cholangiocarcinoma 2 ชนิด โดยให้ค่า IC_{50} อยู่ในช่วง 1.8-46.8 $\mu\text{g/mL}$

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Thesis Advisors: Assoc. Prof. Dr. Somdej Kanokmedhakul,
Assoc. Prof. Dr. Kwanjai Kanokmedhakul

ABSTRACT

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Air-dried mycelial mat of *Chaetomium elatum* (210 g) and *C. lucknowense* (282 g) were successively extracted with hexane, EtOAc and MeOH to give six crude extracts. Three were from *C. elatum*, crude hexane (8.4 g), EtOAc (21.7 g), and MeOH (28.5 g) extracts, while the other three from *C. lucknowense*, crude hexane (8.4 g), EtOAc (18.0 g), and MeOH (45.3 g) extracts, respectively.

Chromatographic separation of the crude extracts from *C. elatum* led to the isolation of twelve compounds. There were a new compound; chaetoglobosin V (**XI**) together with eleven known compounds; ergosterol (**I**), 24(*R*)-5 α ,8 α -epidioxyergosta-6-22-diene-3 β -ol (**II**), chaetoglobosin C (**III**), isochaetoglobosin D (**IV**), chaetoglobosin F (**V**), chaetoglobosin G (**VI**), chaetoglobosin B (**VII**), chaetoglobosin D (**VIII**), prochaetoglobosin III (**IX**), prochaetoglobosin IIIed (**X**), and D-mannitol (**XIX**). The chromatographic separation of the crude extracts from *C. lucknowense* yielded ten compounds. There were a new compound: **XVIII** along with nine known compounds; ergosterol (**I**), 24(*R*)-5 α ,8 α -epidioxyergosta-6-22-diene-3 β -ol (**II**), chrysophanol (**XII**), emodin (**XIII**), chaetoviridin A (**XIV**), cochliodone D (**XV**), xanthoquinodin A1 (**XVI**), xanthoquinodin B2 (**XVII**), and D-mannitol (**XIX**). Their structures were elucidated on the basis of spectroscopic analysis (UV, IR, MS, ^1H NMR, ^{13}C NMR, DEPT and 2D NMR). Among the isolation compounds, **I**, **II**, and **XIX** were produced from both fungi. In addition, this is the first report for the isolation of cytochalasan and xanthoquinodin analogs from *C. elatum* and *C. lucknowense*, respectively

The bioactivity assays revealed that compounds **XI**, **XVI**, **XVII**, and **XVIII** displayed antimalarial activity against *Plasmodium falciparum* with IC_{50} values of

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2.40, 1.43, 1.70, and 3.2 $\mu\text{g/mL}$, respectively and antimycobacterial activity against *Mycobacterium tuberculosis* with MIC values of 50, 12.50, 25, and 25 $\mu\text{g/mL}$, respectively. Compounds **XI**, **XVI**, and **XVII** showed cytotoxicity against NCI-H187 cancer cell line with IC_{50} values of 11.57, 0.456, and 1.03 $\mu\text{g/mL}$, respectively. Compounds **XI**, **XVI**, **XVII**, and **XVIII** showed cytotoxicity against KB cancer cell line with IC_{50} of 2.28, 2.77, 4.01, and 9.6 $\mu\text{g/mL}$, respectively. Compounds **III-XI** and **XVI-XVIII** exhibited cytotoxicity against BC1 cancer cell line with IC_{50} values ranging 1.29-25.23 $\mu\text{g/mL}$. In addition, Compound **III-XI** exhibited cytotoxicity against two cholangiocarcinoma cell lines with IC_{50} values ranging 1.8-46.8 $\mu\text{g/mL}$.

**The good aspects of the present thesis are dedicated to
my parents and the entire teaching staff.**

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Santi Thohinung

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LIST OF ABBREVIATIONS

1°	primary
2°	secondary
1D NMR	one-dimensional Nuclear Magnetic Resonance
2D NMR	two-dimensional Nuclear Magnetic Resonance
¹ H NMR	Proton Nuclear Magnetic Resonance
¹³ C NMR	Carbon Nuclear Magnetic Resonance
%	percent
δ	chemical shift
δ _C	chemical shift of carbon
δ _H	chemical shift of proton
λ	wavelength
ν	wavenumber
°C	degree Celsius
μg	microgram
[α] _D	specific optical rotation
anti-TB	antituberculosis
BC1	Human breast cancer cells
br	broad (IR spectra)
bd	broad doublet
bs	broad singlet
<i>c</i>	concentration (%v/v)
calcd	calculated
CC	Column Chromatography
CCA	cholangiocarcinoma
CDCl ₃	chloroform- <i>d</i>
CD ₃ OD	methanol- <i>d</i> ₄
CHCl ₃	chloroform

LIST OF ABBREVIATIONS (Cont.)

CH ₂ Cl ₂	dichloromethane
cm ⁻¹	per centimeter
COSY	Homonuclear Correlation Spectroscopy
d	doublet
D ₂ O	deuterium oxide
dd	doublet of doublet
ddd	double doublet of doublet
ddt	double doublet of triplet
dt	doublet of triplet
DEPT	Distortionless Enhancement by Polarization Transfer
EtOAc	ethyl acetate
FCC	Flash Column Chromatography
g	gram
HMBC	Heteronuclear Multiple Bond Correlation
HRESITOFMS	High Resolution Electrospray Ionization-Time Of Flight Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IC ₅₀	Half Maximal Inhibitory Concentration
IR	Infrared Spectrum
<i>J</i>	coupling constant
KB	Human epidermoid carcinoma in the mouth
KBr	potassium bromide
L	liter
m	multiplet (¹ H NMR spectra)
m	medium (IR spectra)
MeOH	methanol
mg	milligram

LIST OF ABBREVIATIONS (Cont.)

MHz	Megahertz
MIC	Minimum Inhibitory Concentration
mL	milliliter
mp	melting point
MS	Mass Spectrum
NIC-H187	Human small lung cancer cells
Na	sodium metal
nm	nanometre
NOESY	Nuclear Overhauser Enhanced Spectroscopy
PDB	Potato Dextrose Broth
PLC	preparative Thin Layer Chromatography
ppm	parts per million
q	quartet
quint	quintet
recryst.	recrystallization
R_f	Retardation factor
s	singlet (^1H NMR spectra)
s	strong (IR spectra)
t	triplet
TLC	Thin Layer Chromatography
TMS	tetramethylsilane
UV	Ultraviolet
vw	very weak
w	weak