

ห้องสมุดงานวิจัย สำนักงานคณะกรรมการวิจัยแห่งชาติ



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CHEMICAL CONSTITUENTS AND BIOACTIVE SUBSTANCES  
FROM FUNGI *CHAETOMIUM* SPP.

MISS PRIMMALA KHUMKOMKHET

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

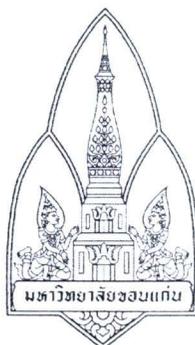
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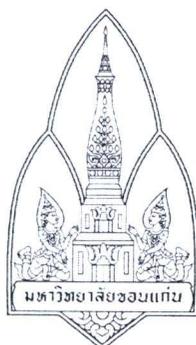
**2010**

**CHEMICAL CONSTITUENTS AND BIOACTIVE SUBSTANCES  
FROM FUNGI *CHAETOMIUM* SPP.**

**MISS PRIMMALA KHUMKOMKHET**

**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**



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**KHON KAEN UNIVERSITY**  
**FOR**  
**DOCTOR OF PHILOSOPHY**  
**IN ORGANIC CHEMISTRY**

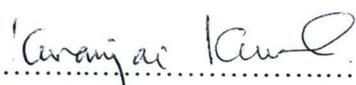
**Thesis Title:** Chemical Constituents and Bioactive Substances from Fungi  
*Chaetomium* spp.

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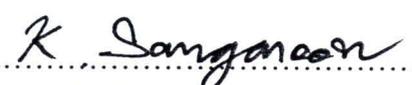
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## บทคัดย่อ

**E47237**

จากการสกัดเส้นใยแห้งของรา *Chaetomium brasiliense* (300 กรัม) *Chaetomium bostrychodes* (119 กรัม) และ *Chaetomium siamense* (135 กรัม) ด้วยตัวทำละลายเฮกเซน เอทิลอะซิเตต และเมทานอล ได้ส่วนสกัดหยาบ 9 ส่วน คือส่วนสกัดหยาบเฮกเซน 6.8 กรัม ส่วนสกัดหยาบเอทิลอะซิเตต 17.8 กรัม และส่วนสกัดหยาบเมทานอล 20.6 กรัม จาก *C. brasiliense* ส่วนสกัดหยาบเฮกเซน 1.5 กรัม ส่วนสกัดหยาบเอทิลอะซิเตต 2.1 กรัม และส่วนสกัดหยาบเมทานอล 4.5 กรัม จาก *C. bostrychodes* และส่วนสกัดหยาบเฮกเซน 3.6 กรัม ส่วนสกัดหยาบเอทิลอะซิเตต 4.9 กรัม และส่วนสกัดหยาบเมทานอล 7.6 กรัม จาก *C. siamense*

จากการแยกส่วนสกัดหยาบของ *C. brasiliense* ด้วยวิธีทางโครมาโทกราฟีได้สาร 12 สาร เป็นสารใหม่ 4 สาร ได้แก่ mollicellin K (1.5), mollicellin L (1.6), mollicellin M (1.7) และ mollicellin N (1.11) และสารที่ทราบโครงสร้างแล้ว 8 สาร ได้แก่ ergosterol (1.1), 24(R)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (1.2), mollicellin H (1.3), mollicellin J (1.4), mollicellin B (1.8), mollicellin C (1.9), mollicellin E (1.10) และ mollicellin F (1.12) การแยกส่วนสกัดหยาบของ *C. bostrychodes* ด้วยวิธีทางโครมาโทกราฟีได้สารที่ทราบโครงสร้างแล้ว 7 สาร ได้แก่ ergosterol (2.1), 24(R)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (2.2), ergosterylplamitate (2.3), chaetoviridin A (2.4), chaetoviridin F (2.5), chrysophanol (2.6) และ emodin (2.7) และจากการแยกส่วนสกัดหยาบของ *C. siamense* ด้วยวิธีทางโครมาโทกราฟีได้สารที่ทราบโครงสร้างแล้ว 8 สาร ได้แก่ ergosterol (3.1), 24(R)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (3.2), ergosterylplamitate (3.3), cochliodone D (3.4), chaetoviridin A (3.5), chaetoviridin F (3.6), chaetoviridin G (3.7) และ chrysophanol (3.8) การพิสูจน์โครงสร้างของสารเหล่านี้อาศัยเทคนิคทางสเปกโทรสโกปี (UV, IR, MS, <sup>1</sup>H NMR, <sup>13</sup>C NMR, DEPT และ 2D NMR) จากการแยกครั้งนี้ยังพบว่าราทั้งสามผลิตสารเหมือนกัน 2 สาร ได้แก่สาร ergosterol (1.1, 2.1 หรือ 3.1) และ 24(R)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (1.2, 2.2 หรือ 3.2)

จากการทดสอบฤทธิ์ทางชีวภาพ พบว่าสาร 1.4-1.10 มีฤทธิ์ยับยั้งเชื้อ *Plasmodium falciparum* สาเหตุของไข้มาลาเรีย โดยมีค่า IC<sub>50</sub> เท่ากับ 4.9, 1.2, 3.4, 2.9, 4.7, 9.1 และ 3.2  $\mu$ g/mL ตามลำดับ มีเพียงสาร 1.5 ที่มีฤทธิ์ยับยั้งเชื้อ *Mycobacterium tuberculosis* สาเหตุของวัณโรค โดยมีค่า MIC เท่ากับ 12.5  $\mu$ g/mL พบว่า สาร 1.5, 1.9 และ

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1.10 มีฤทธิ์ยับยั้งเชื้อ *Candida albicans* ซึ่งเป็นสาเหตุของเชื้อราโรคผิวหนัง IC<sub>50</sub> เท่ากับ 1.2, 49.9 และ 39.7 µg/mL ตามลำดับ นอกจากนี้ สาร **1.3-1.6, 1.9** และ **1.10** มีความเป็นพิษต่อเซลล์มะเร็งชนิด KB ด้วยค่า IC<sub>50</sub> เท่ากับ 16.6, 29.1, 1.9, 33.9, 37.1, 46.3, 25.9 และ 37.9 µg/mL ตามลำดับ มีเพียงสาร **1.5** ที่มีพิษต่อเซลล์มะเร็งชนิด BC1 ด้วยค่า IC<sub>50</sub> เท่ากับ 6.8 µg/mL นอกจากนี้ยังพบว่า สารทุกตัวมีความเป็นพิษต่อเซลล์มะเร็ง NCI-H187 และมะเร็งท่อน้ำดี 5 เซลล์ มีค่า IC<sub>50</sub> เท่ากับ 2.5 ถึง 15.7 µg/mL โดยพบว่าความเป็นพิษสำหรับเซลล์ K KU-100 ค่า IC<sub>50</sub> เท่ากับ 4.5 ถึง 6.5 µg/mL และพบว่ามีความเป็นพิษต่อเซลล์มากกว่ายา ellipticine

Primmala Khumkomkhet. 2010. **Chemical Constituents and Bioactive Substances from Fungi *Chaetomium* spp.** Doctor of Philosophy Thesis in Organic Chemistry, Graduate School, Khon Kaen University.

**Thesis Advisors:** Assoc. Prof. Dr. Kwanjai Kanokmedhakul,  
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## ABSTRACT

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Extraction of air-dried mycelial mats of *Chaetomium brasiliense* (300 g), *C. bostrychodes* (119 g) and *C. siamense* (135 g) were successively extracted with hexane, EtOAc and MeOH gave nine crude extracts. *C. brasiliense* gave crude hexane 6.8 g, crude EtOAc 17.8 g, and crude MeOH 20.6 g. *C. bostrychodes* gave crude hexane 1.5 g, crude EtOAc 2.1 g, and crude MeOH 4.5 g. *C. siamense* gave crude hexane 3.6 g, crude EtOAc 4.9 g, and crude MeOH 7.6 g.

The chromatographic separation of crude extracts from *C. brasiliense* led to the isolation of twelve compounds. They were four new compounds: mollicellin K (**1.5**), mollicellin L (**1.6**), mollicellin M (**1.7**) and mollicellin N (**1.11**) together with eight known compounds: ergosterol (**1.1**), 24(*R*)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (**1.2**), mollicellin H (**1.3**), mollicellin J (**1.4**), mollicellin B (**1.8**), mollicellin C (**1.9**), mollicellin E (**1.10**) and mollicellin F (**1.12**). The chromatographic isolation of crude extracts from *C. bostrychodes* yielded seven compounds. They were known compounds: ergosterol (**2.1**), 24(*R*)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (**2.2**), ergosterylplamitate (**2.3**), chaetoviridin A (**2.4**), chaetoviridin F (**2.5**), chrysophanol (**2.6**) and emodin (**2.7**). While, the chromatographic isolation of crude extracts from *C. siamense* yielded eight compounds. They were known compounds ergosterol (**3.1**), 24(*R*)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (**3.2**), ergosterylplamitate (**3.3**), cochliodone D (**3.4**), chaetoviridin A (**3.5**), chaetoviridin F (**3.6**), chaetoviridin G (**3.7**) and chrysophanol (**3.8**). These structures were elucidated on the basis of spectroscopic analysis (UV, IR, MS, <sup>1</sup>H NMR, <sup>13</sup>C NMR, DEPT, and 2D NMR). Among isolated compounds, ergosterol (**1.1**, **2.1** or **3.1**) and 24(*R*)-5 $\alpha$ ,8 $\alpha$ -epidioxyergosta-6-22-diene-3 $\beta$ -ol (**1.2**, **2.2** or **3.2**) were produced from all three fungi.

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The bioactivity assays revealed that compounds **1.4-1.10** showed antimalarial activity against *Plasmodium falciparum* with IC<sub>50</sub> values of 4.9, 1.2, 3.4, 2.9, 4.7, 9.1 and 3.2 µg/mL, respectively. Only **1.5** exhibited antimycobacterial activity against *Mycobacterium tuberculosis* with MIC values of 12.5 µg/mL. Compounds **1.5, 1.9** and **1.10** showed antifungal activity against *Candida albicans* with IC<sub>50</sub> values of 1.2, 49.9 and 49.7 µg/mL, respectively. Compounds **1.3-1.6, 1.9, and 1.10** showed cytotoxicity against KB cancer cell line with IC<sub>50</sub> values of 16.6, 29.1, 1.9, 33.9, 37.1, 46.3, 25.9 and 37.9 µg/mL, respectively. Only **1.5** showed cytotoxicity against BC1 cancer cell lines with IC<sub>50</sub> values of 6.8 µg/mL. In addition, all of them displayed cytotoxicity against NCI-H187, and five cholangiocarcinoma cell lines with IC<sub>50</sub> values ranging from 2.5 to 15.7 µg/mL. It should be noted that all compounds exhibited IC<sub>50</sub> values against KKU-100 ranging from 4.5 to 6.5 µg/mL and were more cytotoxic than the control drug ellipticine.

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

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Primmala Khumkomkhet

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## LIST OF ABBREVIATIONS

%	percent
$\delta$	chemical shift
$\lambda$	wavelength
$\nu$	wavenumber
$^{\circ}\text{C}$	degree Celsius
$\mu\text{g}$	microgram
$[\alpha]_{\text{D}}$	specific optical rotation
$^{13}\text{C}$ NMR	Carbon Nuclear Magnetic Resonance
$^1\text{H}$ NMR	Proton Nuclear Magnetic Resonance
2D NMR	two-dimensional Nuclear Magnetic Resonance
antiTB	antituberculosis
aq.	aqueous
BC1	Human breast cancer cells
Br	broad
Br	broad (IR spectra)
Brd	broad doublet
Brs	broad singlet
BuOH	butanol
C	concentration (%v/v)
Calcd	calculated
CC	Column Chromatography
$\text{CD}_3\text{OD}$	methanol- $d_4$
$\text{CDCl}_3$	chloroform- $d$
$\text{CH}_2\text{Cl}_2$	dichloromethane
$\text{CHCl}_3$	chloroform
$\text{cm}^{-1}$	per centimeter
COSY	Homonuclear Correlation Spectroscopy

**LIST OF ABBREVIATIONS (Cont.)**

D	doublet
D <sub>2</sub> O	deuterium oxide
Dd	doublet of doublet
DEPT	Distortionless Enhancement by Polarization Transfer
DMSO- <i>d</i> <sub>6</sub>	dimethylsulfoxide- <i>d</i> <sub>6</sub>
EtOAc	ethyl acetate
FCC	Flash Column Chromatography
G	gram
H	hours
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
HPLC	High Pressure Liquid Chromatography
HRESITOFMS	High Resolution Electrospray Ionization-Time Of Flight Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IC <sub>50</sub>	Half Maximal Inhibitory Concentration
IR	Infrared Spectrum
<i>J</i>	coupling constant
KB	Human epidermoid carcinoma in the mouth
KBr	Potassium Bromide
lit.	literature
M	multiplet ( <sup>1</sup> H NMR spectra)
M	medium (IR spectra)
MeOH	methanol
Mg	milligram
MHz	Megahertz
MIC	Minimum Inhibitory Concentration

**LIST OF ABBREVIATIONS (Cont.)**

Min	minute
mL	milliliter
Mp	melting point
MS	Mass Spectrum
NCI-H187	Human small lung cancer cells
Nm	nanometre
NOESY	Nuclear Overhauser Enhanced Spectroscopy
PDB	Potato Dextrose Broth
PLC	preparative Thin Layer Chromatography
Ppm	parts per million
Recryst.	recrystallization
$R_f$	Retardation factor
S	singlet ( $^1\text{H}$ NMR spectra)
S	strong (IR spectra)
T	triplet
Sext	sextet
Sept	septet
Quint	quintet
TLC	Thin Layer Chromatography
TMS	tetramethylsilane
UV	Ultraviolet
W	Weak