

สารกลุ่มเรเนียร์รามัยซินจากทากเปลือย *JORUNNA FUNEBRIS* และการเปลี่ยนแปลง
โครงสร้างทางเคมีของสารเรเนียร์รามัยซินเอ็มที่เป็นพิษต่อเซลล์จากฟองน้ำ
XESTOSPONGIA SP.

นางสาว กรวิกา จารุพันธ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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RENIERAMYCINS FROM THE NUDIBRANCH *JORUNNA FUNEBRIS* AND
CHEMICAL MODIFICATIONS OF CYTOTOXIC RENIERAMYCIN M
FROM THE SPONGE *XESTOSPONGIA* SP.

Miss Kornvika Charupant

A Dissertation Submitted in Partial Fulfillment of the Requirements
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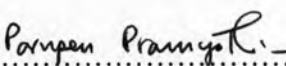
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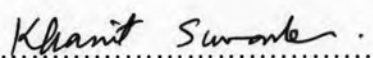
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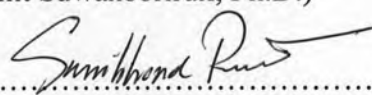
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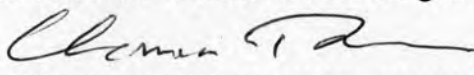

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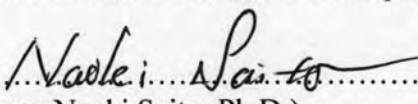
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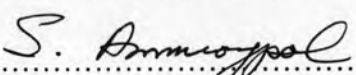

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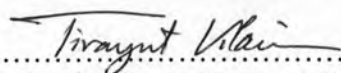

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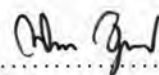
รายงานการแยกสารใหม่ 3 ชนิดที่มีโครงสร้างหลักเป็น bistetrahydroisoquinolines เหมือนสารแอลคาลอยด์กลุ่ม renieramycins คือ jorunnamycins A, B, และ C แยกได้จาก แมนเดิลอวัยวะภายใน และ ไข่ ของทากเปลือย *Jorunna funebris* ที่มีการเติมสารโปแตสเซียมไซยาไนด์ก่อนการสกัด นอกจากนี้ยังสามารถแยกสารที่เคยพบมาก่อนแล้ว 5 ชนิดคือ renieramycins M, N, O, และ Q และ mimosamycin โดยได้ทำการพิสูจน์สูตรโครงสร้าง และสเตอริโอเคมีของสารที่แยกได้นี้ด้วยข้อมูลทางสเปกโทรสโคปีและเปรียบเทียบกับข้อมูลที่มีรายงานมาก่อน

เพื่อศึกษาความสัมพันธ์ของโครงสร้างต่อการออกฤทธิ์ความเป็นพิษต่อเซลล์ของสารกลุ่ม renieramycins ได้ทำการสังเคราะห์อนุพันธ์ renieramycins ใหม่ 21 ชนิดจาก renieramycin M ที่แยกได้จากฟองน้ำ *Xestospongia* sp. โดยทำปฏิกิริยาระหว่างสาร deangeloylrenieramycin M กับสาร acid anhydrides หรือ acid chlorides ได้เป็นอนุพันธ์ที่ตำแหน่ง C-22 เป็น acyclic, alicyclic, และ aromatic acyl ในปริมาณ 25-85%

เมื่อทำการทดสอบฤทธิ์ความเป็นพิษของอนุพันธ์ renieramycins ต่างๆ ต่อเซลล์มะเร็ง 4 ชนิด ได้แก่ มะเร็งลำไส้ มะเร็งปอด มะเร็งต่อมลูกหมาก และ มะเร็งเต้านม พบว่า หมู่ cyano หรือ hydroxyl ที่ C-21 และหมู่ ester ที่ C-22 จำเป็นต่อความแรงของฤทธิ์ความเป็นพิษต่อเซลล์ การแทนที่หมู่ angelate ที่ C-22 ด้วยหมู่ aliphatic ขนาดเล็ก เช่น acetate หรือ propionate ทำให้ฤทธิ์ความเป็นพิษต่อเซลล์สูงขึ้น ในขณะที่หมู่ขนาดใหญ่มากกว่า 5 คาร์บอน ทำให้ฤทธิ์ความเป็นพิษต่อเซลล์ลดลงอย่างมาก และการแทนที่ด้วย oxygen ที่ C-14 ทำให้ฤทธิ์ความเป็นพิษต่อเซลล์ลดลงเช่นเดียวกัน นอกจากนี้ยังพบว่า aliphatic ester ขนาดเล็กที่มี α, β unsaturated carbonyl รวมทั้ง aromatic และ heteroaromatic esters ยังคงทำให้สารมีฤทธิ์ความเป็นพิษต่อเซลล์ที่แรง ในการศึกษาข้อมูลเกี่ยวกับผลของสาร renieramycin M และ jorunnamycin C ต่อการแสดงออกของยีน พบว่า สารทั้งสองมีผลเด่นในการกดการทำงานของยีน และพบว่ายีน PTPRK เป็นตัวบ่งชี้ทางชีวภาพตัวหนึ่งสำหรับการแสดงผลความเป็นพิษต่อเซลล์มะเร็งของสารทั้งสอง

สาขาวิชา เกษตรเขต
ปีการศึกษา 2549

ลายมือชื่อนิติ.....
ลายมือชื่ออาจารย์ที่ปรึกษา.....




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KORNIKA CHARUPANT : RENIERAMYCINS FROM THE NUDIBRANCH *JORUNNA FUNEBRIS* AND CHEMICAL MODIFICATIONS OF CYTOTOXIC RENIERAMYCIN M FROM THE SPONGE *XESTOSPONGIA* SP. THESIS ADVISOR : KHANIT SUWANBORIRUX, Ph.D. 249 pp.

Three new bistetrahydroisoquinolines similar to renieramycins, including jorunnamycins A, B, and C, were isolated from the mantles, the visceral organs, and the egg ribbons of the nudibranch *Jorunna funebris* pretreated with potassium cyanide. Five known compounds, including renieramycins M, N, O, and Q and mimosamycin were also isolated. Their structures and relative stereochemistries were elucidated on the basis of spectroscopic data and comparison with the literatures.

In order to investigate the structure-activity relationships (SAR), chemical modifications on C-22 of renieramycin M obtained from the sponge *Xestospongia* sp. were performed. New twenty one acyl analogs including acyclic, alicyclic, and aromatic acyl derivatives were prepared by treatment deangeloylrenieramycin M with corresponding acid anhydrides or acid chlorides to provide those derivatives in 25-85 % yields.

The cytotoxicity of the renieramycin analogs against 4 tumor cell lines including HCT116 (human colon carcinoma), QG56 (human lung carcinoma), DU145 (human prostate carcinoma), and MDA-MB-435 (human breast carcinoma) were evaluated. The results revealed that a cyano group or a hydroxyl group at C-21 and an ester side chain at C-22 were essential for high cytotoxicity. Replacement of the angelate at C-22 by relatively small aliphatic substituents such as the acetate or the propionate led to a significant increase in potency whereas more bulky substituents (more than five carbons) resulted in a substantial loss in cytotoxicity. Likewise, the substitution of oxygen at C-14 dramatically reduced cytotoxicity. In addition, the small aliphatic esters incorporating an α , β unsaturated carbonyl, the aromatic, and the heteroaromatic esters at C-22 retained potent cytotoxicity. Interestingly, array-based gene expression monitoring of renieramycin M and jorunnamycin C profiles revealed that both compounds showed predominant down-regulated genes and PTPRK was proposed as one of the candidate biomarkers for their cytotoxicity.

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ABBREVIATIONS

%	=	percent or part per hundred
°C	=	degree Celsius
δ	=	chemical shift
ϵ	=	molar absorptivity
μg	=	microgram
μl	=	microliter
λ_{max}	=	wave length at maximum absorption
ν_{max}	=	wave number at maximum absorption
$[\alpha]_{\text{D}}$	=	specific rotation at sodium D line (589 nm)
A375	=	malignant melanoma cell line
A549	=	lung carcinoma cell line
br s	=	broad singlet
<i>c</i>	=	concentration
CD	=	circular dichroism
cm	=	centimeter
^{13}C NMR	=	carbon-13 nuclear magnetic resonance
d	=	doublet
dd	=	doublet of doublets
ddd	=	doublet of doublets of doublets
DEPT	=	distortionless enhancement by polarization transfer
DLD1	=	human colon carcinoma cell line
DMAP	=	4-dimethylaminopyridine
DMSO	=	dimethylsulfoxide
dq	=	doublet of quartets
dt	=	doublet of triplets
DU145	=	human prostate carcinoma cell line
ESI	=	electrospray ionization
g	=	gram
h	=	hour
^1H - ^1H COSY	=	^1H - ^1H correlation spectroscopy
HCT116	=	human colon carcinoma cell line

HMBC	=	¹ H-detected heteronuclear multiple bond correlation
HMQC	=	¹ H-detected heteronuclear multiple quantum coherence
¹ H NMR	=	proton nuclear magnetic resonance
HR-MS	=	high resolution mass spectrum
Hz	=	hertz
IC ₅₀	=	50% inhibition concentration
IR	=	infrared
<i>J</i>	=	coupling constant
Kg	=	kilogram
L, l	=	liter
L1210	=	leukemia cell line
m	=	multiplet
M	=	molar
M ⁺	=	molecular ion
[M+H] ⁺	=	protonated molecular ion
M.F.	=	molecular formula
MDA-MB-435	=	human breast carcinoma cell line
mg	=	milligram
MHz	=	megahertz
min	=	minute
ml	=	milliliter
mmol	=	milimol
MTT	=	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
M.W.	=	molecular weight
<i>m/z</i>	=	mass to charge ratio
NCI-H460	=	human lung carcinoma cell line
NMR	=	nuclear magnetic resonance
nm	=	nanometer
nM	=	nanomolar
NOESY	=	nuclear overhauser effect correlation spectroscopy
PC-3	=	prostate carcinoma cell line
PTPRK	=	protein tyrosine phosphate, receptor type K
ppm	=	part per million

q	=	quartet
QG56	=	human lung carcinoma cell line
s	=	singlet
sp.	=	species
t	=	triplet
TLC	=	thin layer chromatography
UV	=	ultraviolet