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CHEMISTRY AND BIOACTIVITY ON P19 NEURON-LIKE CELLS OF GELDANAMYCINS

Miss Sarin Tadtong

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for the Degree of Doctor of Philosophy Program in Pharmaceutical Chemistry and Natural Products

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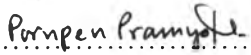
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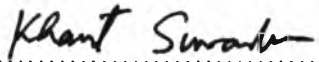
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สาร geldanamycin (1) เป็นสารต้านมะเร็งและต้านเชื้อราในกลุ่ม ansamycin ที่แยกได้จากน้ำหมักเชื้อ *Streptomyces hygroscopicus* var. *geldanus* และต่อมาสามารถแยกได้จากน้ำหมักเชื้อ *Streptomyces* sp. TRA-9875-2 จากป่าชายเลนบริเวณฝั่งทะเลอันดามัน ในจังหวัดตรัง ประเทศไทย จึงได้ทำการดัดแปลงสูตรโครงสร้างทางเคมีในบางตำแหน่งโดยเฉพาะที่ quinone ring ของ 1 เพื่อศึกษาฤทธิ์ทางชีวภาพของอนุพันธ์ต่างๆ ต่อเซลล์พีลิปแก์ และเซลล์คล้ายเซลล์ประสาทพีลิปแก์ โดยสามารถเตรียมอนุพันธ์ได้ทั้งหมด 18 ชนิด การพิสูจน์สูตรโครงสร้างทางเคมีของสารเหล่านี้ ทำได้โดยการวิเคราะห์ข้อมูลทางสเปกโตรสโคปีจาก NMR, MS, และ UV ร่วมกับการเปรียบเทียบข้อมูลกับ 1 และข้อมูลของสารกลุ่มนี้ที่เคยมีรายงานมาก่อน จากการศึกษาฤทธิ์ทางชีวภาพพบว่า ที่ความเข้มข้น 1 นาโนโมลาร์ มีเพียงเฉพาะสาร 1, 17-O-ethyl-17-O-demethylgeldanamycin (6), 17-O-n-propyl-17-O-demethylgeldanamycin (8), 17-O-benzyl-17-O-demethylgeldanamycin (9), และ 19-O-methylgeldanamycin (18) ไม่มีความเป็นพิษต่อเซลล์พีลิปแก์ แต่สามารถทำให้เซลล์คล้ายเซลล์ประสาทพีลิปแก์มีเส้นประสาทที่ยาวและแตกแขนงเพิ่มขึ้น และยังสามารถป้องกันเซลล์คล้ายเซลล์ประสาทพีลิปแก์จากความเป็นพิษต่อเซลล์ประสาทของสารต้านมะเร็ง taxol ที่ความเข้มข้น IC_{50} 0.65 ไมโครโมลาร์ ได้อีกด้วย แต่เมื่อทดสอบที่ความเข้มข้นสูงถึง 10 ไมโครโมลาร์ พบว่าสาร 18 ชนิดเดียวเท่านั้น ที่ไม่แสดงความเป็นพิษต่อเซลล์พีลิปแก์และเซลล์คล้ายเซลล์ประสาทพีลิปแก์ ในขณะที่สาร 1, 6, 8, และ 9 แสดงความเป็นพิษต่อเซลล์พีลิปแก์และเซลล์คล้ายเซลล์ประสาทพีลิปแก์ที่ IC_{50} 0.1 และ 2.0 ไมโครโมลาร์, 0.1 และ 1.6 ไมโครโมลาร์, 0.2 และ 6.7 ไมโครโมลาร์, และ 0.5 และ >10 ไมโครโมลาร์ ตามลำดับ

สาขาวิชา เกษตรเคมีและผลิตภัณฑ์ธรรมชาติ
ปีการศึกษา 2548

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ลายมือชื่ออาจารย์ที่ปรึกษา.....
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ABBREVIATIONS

ACN	=	acetonitril
ADP	=	adenosine diphosphate
α -MEM	=	alpha minimal essential medium
Ara-C	=	Cytosine-1- β -D-arabinoside
Asn	=	asparagine
Asp	=	aspartic acid
ATCC	=	American Type Culture Collection, Maryland, U.S.A.
ATP	=	adenosine triphosphate
br s	=	broad singlet
c	=	concentration
calcd	=	calculated
cm	=	centimeter
^{13}C -NMR	=	carbon-13 nuclear magnetic resonance
CNS	=	central nervous system
COSY	=	correlation spectroscopy
Cys	=	cysteine
δ	=	chemical shift
d	=	doublet
dd	=	doublet of doublet
DMF	=	dimethyl formamide
DMSO	=	dimethyl sulfoxide
ϵ	=	molar absorptivity
EC ₅₀	=	50% effective concentration
ED	=	effective dose
ED ₅₀	=	50% effective dose
ESI-Q-TOFMS	=	electrospray ion source qaudrupole time of flight mass spectrometry
FBS	=	fetal bovine serum
Glu	=	glutamic acid
Gly	=	glycine
h	=	hour

HMBC	=	¹ H-detected heteronuclear multiple bond correlation
¹ H-NMR	=	proton nuclear magnetic resonance
HRFABMS	=	high resolution fast atom bombardment mass spectrometry
Hz	=	hertz
IC ₅₀	=	50% inhibitory concentration
<i>J</i>	=	coupling constant
kDa	=	kilo-Dalton
λ _{max}	=	wavelength at maximum absorption
L	=	liter
Leu	=	leucine
Lys	=	lysine
M	=	molar
m	=	multiplet
MHz	=	megahertz
min	=	minute
μL	=	microliter
mL	=	milliliter
μm	=	micrometer
μM	=	micromolar
mm	=	millimeter
<i>m/z</i>	=	mass to charge ratio
NCS	=	newborn calf serum
nm	=	nanometer
nM	=	nanomolar
NMR	=	nuclear magnetic resonance
P19GM	=	P19 growth medium
P19IM	=	P19 induction medium
P19NLC	=	P19 neuron-like cell
P19SM	=	P19 supplement medium
PBS	=	Phosphate buffer saline solution
pg	=	picogram
Phe	=	phenylalanine
PLC	=	preparative thin layer chromatography

pM	=	picomolar
ppm	=	part per million
q	=	quartet
RA	=	all- <i>trans</i> -retinoic acid
Rb	=	Retinoblastoma protein
rt	=	room temperature
s	=	singlet
SEM	=	standard error of the mean
sp.	=	species
t	=	triplet
Thr	=	threonine
TLC	=	thin layer chromatography
UV	=	ultraviolet