

การสังเคราะห์และฤทธิ์ทางชีวภาพของสารยับยั้งไดไฮโดรโฟเลตรีดักเตสของเชื้อมาลาเรีย
ชนิดขึ้นสมอง *Plasmodium falciparum*

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF DIHYDROFOLATE
REDUCTASE INHIBITORS OF *Plasmodium falciparum*

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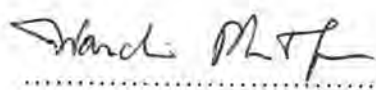
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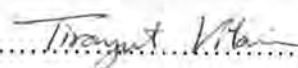
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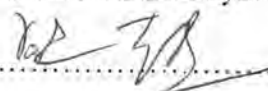
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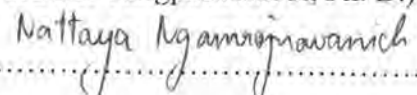
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เนตรนภา เจริญเศรษฐกุล : การสังเคราะห์และฤทธิ์ทางชีวภาพของสารยับยั้งไดไฮโดรโฟเลตรีดักเตสของเชื้อมาลาเรียชนิดขึ้นสมอง *Plasmodium falciparum* (SYNTHESIS AND BIOLOGICAL ACTIVITIES OF DIHYDROFOLATE REDUCTASE INHIBITORS OF *Plasmodium falciparum*) อ.ที่ปรึกษา : ผศ. ดร. ชีรยุทธ วิไลวัลย์ ; 244 หน้า.

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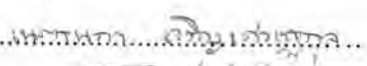
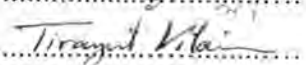
ได้สังเคราะห์อนุพันธ์ของ 4,6-ไดอะมิโน-1,2-ไดไฮโดรไตรอาซีน 137 ชนิด ที่มีหมู่แทนที่ที่ตำแหน่ง N-1 และ C-2 แตกต่างกัน และทดสอบค่าคงที่การยับยั้งเอนไซม์ (K_i) กับเอนไซม์ไดไฮโดรโฟเลตรีดักเตสจากเชื้อมาลาเรียชนิด *Plasmodium falciparum* ทั้งชนิดธรรมชาติและชนิดมิวแทนต์ที่คือต่อยาไซโคลกัวนิล (A16V+S108T) ข้อมูลที่ได้ทำให้เข้าใจถึงความสัมพันธ์ระหว่างโครงสร้างและฤทธิ์ทางชีวภาพ และนำไปสู่การออกแบบสารยับยั้งที่มีประสิทธิภาพต่อทั้งเอนไซม์ชนิดธรรมชาติและชนิดมิวแทนต์ ได้พบสารหลายชนิดเป็นสารยับยั้งคั่นแบบที่มีศักยภาพสูงในการพัฒนาต่อไปเป็นยาด้านมาลาเรีย

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One hundred and thirty-seven 4,6-diamino-1,2-dihydrotriazine derivatives bearing different N-1 and C-2 substituents have been synthesized and their inhibition constants (K_i) against wild-type and cycloguanil resistant (A16V+S108T) Dihydrofolate Reductase Enzyme from *Plasmodium falciparum*. The data revealed the structure-activity relationship and lead to the design of novel inhibitors, which are effective to both wild-type and mutant enzyme. A number of compounds of 4,6-diamino-1,2-dihydrotriazine derivatives were found to be potential lead compound to be developed into antimalarial agents.

Department.....Chemistry.....Student's signature..........
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LIST OF ABBREVIATIONS

i) Nomenclature and abbreviations of amino acids, enzymes and other biochemicals

DHFR	dihydrofolate reductase
DHFR-TS	dihydrofolate reductase-thymidylate synthase
DNA	deoxyribonucleic acids
FH ₄	tetrahydrofolate
GTP	guanosine triphosphate
pfDHFR	<i>Plasmodium falciparum</i> dihydrofolate reductase
A	alanine
S	serine
T	threonine
V	valine

ii) Miscellaneous

Anal.	Analytical
br	broad
°C	degree celcius
Calcd.	calculated
CDCl ₃	deuterated chloroform
Cyc	cycloguanil
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DMF	<i>N,N'</i> -dimethylformamide
DMSO-d ₆	deuterated dimethyl sulfoxide
D ₂ O	deuterium oxide
eq	equivalents

Et ₂ O	diethyl ether
g	gram
h	hour
Hz	hertz
<i>J</i>	coupling constant
<i>K_i</i>	inhibition constant
m	multiplet
MALDI-TOF	matrix-assisted laser desorption/ionization-time of flight
MHz	megahertz
mg	milligram
min	minute
mL	milliliter
mmol	millimole
mp.	Melting point
mut.	Mutant
<i>m/z</i>	mass pre charge ration
nM	nanomolar
NMR	nuclear magnetic resonance
ppm	part per million
Pyr	pyrimethamine
q	quartet
s	singlet
t	triplet
td	triplet of doublet
TLC	thin layer chromatography
ν_{\max}	the eavelength at maximum absorption
wt.	wild-type
δ	chemical shift