

การสังเคราะห์และฤทธิ์ทางชีวภาพของออกพคัลลีแอคทีฟ 4,6-ไดอะมิโน-1,2-ไดไฮโดร-
1,3,5-ไตรอะซีน

นางสาววนิดา วิริยะวารี



วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

สาขาวิชาเคมี ภาควิชาเคมี

คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ปีการศึกษา 2543

ISBN 974-13-0975-9

ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF OPTICALLY ACTIVE 4,6-
DIAMINO-1,2-DIHYDRO-1,3,5-TRIAZINE

Miss Wanida Wiriyawaree

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Chemistry

Department of Chemistry

Faculty of Science

Chulalongkorn University

Academic Year 2000

ISBN 974-13-0975-9

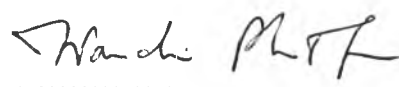
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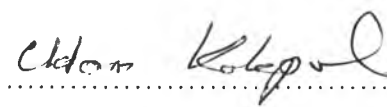
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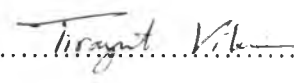
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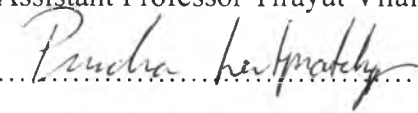
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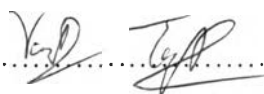

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วนิดา วิริยะวารี : การสังเคราะห์และฤทธิ์ทางชีวภาพของออปติคัลลิแอกทีฟ 4,6-ไดอะมิโน-1,2-ไดไฮโดร-1,3,5-ไตรอาซีน : (SYNTHESIS AND BIOLOGICAL ACTIVITIES OF OPTICALLY ACTIVE 4,6-DIAMINO-1,2-DIHYDRO-1,3,5-TRIAZINE) อาจารย์ที่ปรึกษา : ศศ. คร. ชีรยุทธ วิไลวัลย์ ; 203 หน้า. ISBN 974-13-0975-9

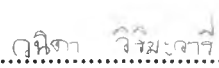
สามารถแยกอิแนนทิโอเมอร์ของสารประกอบ 4,6-ไดอะมิโน-1,2-ไดไฮโดรไตรอาซีนบางชนิดได้โดยเทคนิคโครมาโตกราฟีรีเวอร์สเฟส HPLC อิแนนทิโอเมอร์ที่แยกออกมาแสดงค่าคงที่การจับยึดกับเอนไซม์ไดไฮโดรโฟเลตรีดักเทส (DHFR) จากพลาสมิดเทียมพาลซิพารัมทั้งในแบบธรรมชาติและมิวแตนท์ (mutant) A16VS108T ที่แตกต่างกันแต่ไม่สามารถระบุคอนฟิกูเรชันของแต่ละอิแนนทิโอเมอร์ที่แยกจากกันได้เนื่องจากสารที่แยกได้มีปริมาณจำกัดและเกิดการราซีไมซ์ได้ง่าย นอกจากนี้ยังสังเคราะห์ออปติคัลลิแอกทีฟไดไฮโดรไตรอาซีนที่เป็นไดอะสเตอร์ริโอไอโซเมอร์ได้โดยวิธีการสังเคราะห์แบบอะซิมเมตริก (asymmetric synthesis) โดยทราบเอบโซลูตคอนฟิกูเรชันที่แน่นอน แต่ไดอะสเตอร์ริโอเมอร์ที่สังเคราะห์ได้ทุกตัวแสดงการจับยึดกับเอนไซม์ทั้งแบบธรรมชาติและแบบมิวแตนท์ได้ไม่คี่ ดังนั้น จากผลการทดลองยังไม่สามารถยืนยันแบบจำลองของโมเลกุลที่ทำนายรูปแบบของการจัดยึดกันระหว่างสารประกอบชนิดนี้กับเอนไซม์ได้ อย่างไรก็ตามผลการทดลองเบื้องต้นเสนอแนะว่าวิธีอะซิมเมตริก ทรานสฟอร์มเมชัน (asymmetric transformation) อาจนำไปสู่ความสำเร็จในการเตรียมออปติคัลลิแอกทีฟไดไฮโดรไตรอาซีนในปริมาณมากพอที่จะศึกษาคอนฟิกูเรชันและฤทธิ์ทางชีวภาพต่อไป

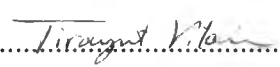
ภาควิชา.....เคมี.....ลายมือชื่อนิสิต.....วนิดา วิริยะวารี.....
 สาขาวิชา.....เคมี.....ลายมือชื่ออาจารย์ที่ปรึกษา.....ศศ. คร. ชีรยุทธ วิไลวัลย์.....
 ปีการศึกษา.....2543.....ลายมืออาจารย์ที่ปรึกษาร่วม.....

4172429723 : MAJOR CHEMISTRY

KEY WORD: OPTICAL RESOLUTION / 4,6-DIAMINO-1,2-DIHYDRO-1,3,5-TRIAZINE / CYCLO-GUANIL / DIHYDROFOLATE REDUCTASE : SYNTHESIS AND BIOLOGICAL ACTIVITIES OF OPTICALLY ACTIVE 4,6-DIAMINO-1,2-DIHYDRO-1,3,5-TRIAZINE. THESIS ADVISOR : ASSISTANT PROFESSOR TIRAYUT VILAIVAN, D. Phil, 203 pp. ISBN 974-13-0975-9

Enantiomers of 4,6-diamino-1,2-dihydrotriazine have been successfully resolved by chiral HPLC. The enantiomers exhibited different binding constants to dihydrofolate reductase (DHFR) enzymes from *Plasmodium falciparum* both wild type and A16VS108T mutant. The absolute configuration, however, could not be determined due to the small amounts of materials available and racemization of the enantiomers. Another series of optically active diastereoisomers dihydrotriazines with known absolute configuration at C₂ were synthesized by asymmetric synthesis. These compounds showed very poor binding affinity to both wild type and mutant DHFR. No significant difference in binding constant between each diastereomer was observed. The model of binding of dihydrotriazine to DHFR has therefore not yet been successfully validated. However, preliminary studies suggested that asymmetric transformation could be a possible route to prepare optically active dihydrotriazines in sufficient quantities for determination of structural configuration and further biological study in the future.

Department.....Chemistry.....Student's signature.....

Field of studyChemistry.....Advisor's signature.....

Academic year.....2000.....Co-Advisor's signature.....



ACKNOWLEDGEMENT

I wish to thank and express my deepest gratitude to Assistant Professor Dr. Tirayut Vilaivan, my thesis advisor, for his kindness, guidance, suggestions and assistance throughout the course of this research; Professor Dr. Udom Kokpol, Assistant professor Dr. Preecha Lertpratchya and Dr. Varawut Tangpasuthadol, thesis examiners, for their valuable comments and suggestions.

I would like to thank of Department of Chemistry, The Thailand Research Funds and The Graduate School, Chulalongkorn University for financial support to this research, Prof Yodhathai Thebtaranonth and Miss Chavanee Sirichaiwat (Mahidol University/NSTDA) for providing the chiral column and HPLC in crystallization of the diastereomeric salts, Dr. Sumalee Kamchonwongpaisan and Ms. Duenpen Japroong (National Science and Technology Development Agency (NSTDA)) for analyses of anti-DHFR (wild-type and mutant A₁₆VS₁₀₈T type) activities of all samples; Assistant Professor Dr. Palangpol Kongsaree (Mahidol University) for X-ray analysis; Assistant Chuchat Thamcharoen for his kind suggestion on kinetic studies; Dr. Khanit Suwanborirux and Mr. Amnut Pakdeeto (Faculty of Pharmacy, Chulalongkorn University) for the use of CD spectrometer and polarimeter; Ms. Amporn Ungpakornkaew and Ms. Wanwimon Thabdee (Chulalongkorn Research Equipment Centre) for elemental and NOE analysis; Ms. Nanthiga Panchan (the Institute for Genetic Engineering and Biotechnology) for MALDI-TOF mass spectrometry; Department of Chemistry, Chulalongkorn University for the use of facilities, equipment, glassware, and chemicals. I am also grateful to Dr. Roderick W. Bates, Assistant Professor Warinthorn Chavasiri and Assistant Professor Worawan Bhanthumnawin for chemicals and glasswares.

I wish to express my special thank to my best friends, Miss Neungruthai Saesaengseerung and Miss Netnapa Charoensetakul, for all of their kindness and hearty help involving HPLC, NMR and MASS and other in experiments. Thanks go towards everyone who has contributed suggestions and support throughout this work. Finally, I would like to pay respect to my family who had mormally supported and encouraged me during the studies

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LIST OF ABBREVIATIONS

i) Nomenclature and abbreviations of nucleic acids, enzymes and other biochemical

DHFR	dihydrofolate reductase
DHFR-TS	dihydrofolate reductase-thymidylate synthase
FH ₄	tetrahydrofolate
GTP	guanosine triphosphate
pfDHFR	<i>Plasmodium falciparum</i> dihydrofolate reductase
A	Alanine
S	Serine
T	Threonine
V	Valine

ii) Miscellaneous

abs.	absolute
Anal.	Analytical
br	broad
°C	degree celcius
Calcd.	calculated
CDCl ₃	deuterated chloroform
conc.	concentrated
Cyc	cycloguanil
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DIAD	diisopropylazodicarboxylate
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
hr	hour
Hz	hertz
<i>J</i>	coupling constant
k	rate of reaction constant
K _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
TLC	thin layer chromatography
wt.	wild-type
δ	chemical shift