

การสังเคราะห์และสมบัติของเปปไทด์นิวคลีอิกแอซิดชนิดใหม่ที่มีโซ่ข้างแบบไฮโดรฟิลิก

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SYNTHESIS OF NOVEL PEPTIDE NUCLEIC ACIDS CARRYING HYDROPHILIC
SIDE-CHAIN AND THEIR PROPERTIES

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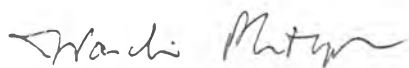
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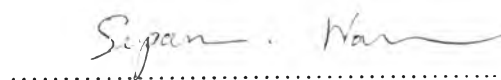

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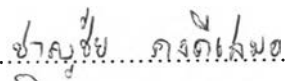


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ได้สังเคราะห์เปปไทด์นิวคลีอิกแอซิดแบบมีคอนฟอร์เมชันที่ถูกจำกัด(ซีพีเอ็นเอ)ที่มี
โครงสร้างต่างกัน 3 แบบ ซีพีเอ็นเอนี้เป็นสารเลียนแบบดีเอ็นเอโดยแทนที่ไดออกซีไรโบสฟอสเฟต
ของดีเอ็นเอทั้งหมด ด้วยไดเปปไทด์โมโนเมอร์ของดีและแอลซีริลโปรลีน หรือไดออกซีไกลซิล
โปรลีนที่เชื่อมต่อกับไทมีนที่เป็นนิวคลีโอเบสที่ตำแหน่งที่ 4 ของวง โครงสร้างที่แข็งแรงของ
ซีพีเอ็นเอได้จากการเชื่อมวงโปรลีนที่มีสเตอริโอเคมีแบบ “ซีส-ดี” หรือ 2R, 4R สลับกับกรดอะมิโน
ซีรีนทั้งชนิดแอลหรือดีหรือหมู่อะมิโนเอธิลด้วยวัตถุประสงค์ที่จะเพิ่มความสามารถในการละลายน้ำ
ของซีพีเอ็นเอ ไดเปปไทด์โมโนเมอร์นี้ถูกสังเคราะห์ขึ้นจาก ซีส-4-ไฮดรอกซี-ดี-โปรลีน ที่ถูกแทนที่
ด้วยไทมีนโดยอาศัยปฏิกิริยามิซูโนบุและจึงนำไปทำปฏิกิริยากู่ควบต่อเข้ากับชิ้นส่วนสเปเซอร์
ในกรณีของซีรีนจะใช้ Fmoc-Ser(O'Bu)-OH ซึ่งสามารถคู่ควบเข้ากับสารมัธยันตร์ได้โดยตรง ในขณะที่
การต่อหมู่ไดออกซีไกลซิลสเปเซอร์ทำได้โดยใช้แอซิริดที่ถูกกระตุ้น การโอลิโกเมอร์ไรซ์ให้
ซีพีเอ็นเอมีความยาว 10 หน่วย ทำได้โดยใช้ยุทธวิธีการคู่ควบแบบชิ้นส่วนโดยใช้การปกป้องแบบ
Fmoc/O'Bu และใช้การกระตุ้นด้วยเพนตะฟลูออโรฟีนิลเอสเทอร์ หรือ HBTU นอกจากนี้ยังได้ศึกษา
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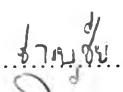
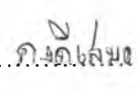
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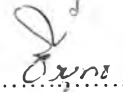
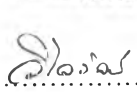
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Three different conformationally constraint peptide nucleic acids (cPNA) have been synthesized. These cPNA are DNA mimics in which the entire deoxyribose phosphate is replaced with L- and D-serylproline or deoxyglycylproline dipeptide units bearing thymine as nucleobase at C-4 position. Their rigid backbones were derived from “*cis*-D” or (2*R*, 4*R*) absolute stereochemistry on proline ring alternating with D or L serine or aminoethyl spacers with the aim to improve water solubility of the resulting cPNA. Dipeptide monomers were synthesized from *cis*-4-hydroxy-D-proline derivatized with thymine by Mitsunobu reaction followed by coupling with the spacer moiety. The serine spacer were introduced as Fmoc-Ser(O^tBu)-OH which could be directly coupled to the intermediate by DCC coupling whereas the deoxyglycyl spacer was introduced by alkylation of the intermediate with activated aziridine. Oligomerization of the cPNA up to 10-mers were achieved by solid phase peptide synthesis methodology employing Fmoc/O^tBu fragment coupling strategy using pentafluorophenyl ester or HBTU activation. Preliminary binding stability of these cPNA toward fluorescence labelled oligoadenylic acid F(dA₁₀) were studied by gel electrophoresis. Lacking of binding of all cPNA oligomers was observed even at high PNA concentration.

ภาควิชา.....เคมี..... ลายมือชื่อนิสิต.....  

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LIST OF ABBREVIATIONS

i) Nomenclature and abbreviations of nucleic acids and their constituents

DNA	deoxyribonucleic acids
RNA	ribonucleic acid
mRNA	messenger ribonucleic acid
A	Adenine
T	Thymine
C	Cytosine
G	Guanine
B	unspecified nucleobase
dA	2'-deoxy adenosine
dT	(2'-deoxy)thymine

ii) Nomenclature and Abbreviations of amino acids

Ala	Alanine
Gly	Glycine
Lys	Lysine
Pro	Proline
Ser	Serine

iii) Miscellaneous

Ac ₂ O	acetic anhydride
Boc	<i>tert</i> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
br	broad
Bz	benzoyl

c	concentration
°C	degree celcius
calcd	calculated
CD	circular dichroism
CDCl ₃	deuterated chloroform
cm ⁻¹	unit of wave number
¹ H- ¹ H COSY	proton-proton correlation spectroscopy
cPNA	chiral or conformationally constraint peptide nucleic acid
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
DC	direct current
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexyl urea
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIEA	<i>N,N'</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N'</i> -dimethylformamide
DMSO- <i>d</i> ₆	deuterated dimethylsulfoxide
Dpm	diphenylmethyl
D ₂ O	deuterium oxide
EDTA	ethylenediamine tetraacetic acid
eq.	equivalent (s)
Fmoc	9-fluorenylmethoxycarbonyl
FmocCl	9-fluorenylmethylchloroformate
g	gram

HBTU	(1- <i>H</i> -benzotriazol-1-yloxy)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAc	acetic acid
HOBt	1 <i>H</i> -hydroxybenzotriazole
HPLC	high performance liquid chromatography
hr	hour
IR	infrared
<i>J</i>	coupling constant
m	multiplet
MALDI-TOF	matrix-assisted laser desorption/ionization-time of flight
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
mp.	melting point
M_r	relative molecular mass
NMR	nuclear magnetic resonance
Ns	nosyl or 4-nitrobenzenesulfonyl
m/z	mass per charge ratio
Pfp	pentafluorophenyl
PfpOH	pentafluorophenol
Ph	phenyl
PNA	peptide nucleic acid or polyamide nucleic acid
ppm	part per million
rpm	round per minute
s	singlet
t	triplet
T ^{Bz}	<i>N</i> ³ -benzoylthymine
TBE	tris-borate EDTA buffer
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
T_m	melting temperature
TEMED	<i>N, N, N', N'</i> -tetramethylethylenediamine
t_R	retention time
UV	ultraviolet
V	volt
ν_{\max}	the wavelength at maximum absorption
μL	microliter
μm	micrometer
μmol	micromol
δ	chemical shift
$[\alpha]_D$	specific rotation