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## **New cationic amphiphilic compounds as potential antibacterial agents**

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# **New Cationic Amphiphilic Compounds as Potential Antibacterial Agents**

## **PROEFSCHRIFT**

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van de Rector Magnificus Dr. D.D. Breimer,  
hoogleraar aan de faculteit der Wiskunde en  
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volgens het besluit van het College voor Promoties  
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te klokke 16:15 uur

door

**Peter Christian de Visser**

geboren te Delft in 1977

## Promotiecommissie

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in memoriam prof. dr. Jacques H. van Boom

If we knew what it was we were doing, it would not be called research, would it?  
- *Albert Einstein (1879-1955)*

*Voor Ilse*

## Table of Contents

<b>List of Abbreviations</b>	6
<b>General Introduction</b>	9
<b>Chapter 1</b>	45
<i>Biological Evaluation of Stabilized Drosocin Analogues</i>	
<b>Chapter 2</b>	57
<i>Safety-Catch Synthesis &amp; Biological Evaluation of Polymyxin B1 and Analogues</i>	
<b>Chapter 3</b>	75
<i>Acyl Migration in Polymyxin Synthesis</i>	
<b>Chapter 4</b>	89
<i>Design, Synthesis &amp; Biological Evaluation of PMBN/CAP Conjugates</i>	
<b>Chapter 5</b>	103
<i>Antimicrobial Gels Based on Quaternary Ammonium Salts</i>	

<b>Chapter 6</b>	117
<i>Fluorous Techniques in Solid-Phase Peptide Synthesis</i>	
<b>Chapter 7</b>	131
<i>Summary &amp; Future Prospects</i>	
<b>General Materials &amp; Methods</b>	143
<b>Samenvatting</b>	145
<i>Summary in Dutch</i>	
<b>List of Publications</b>	149
<b>Curriculum Vitae</b>	151
<b>Nawoord</b>	152

## List of Abbreviations

a	C-terminal amide	CPMBN	Cys-polymyxin B nonapeptide
AA	amino acid residue <sup>1</sup>	CTAB	cetyltrimethylammonium bromide
Abu	$\gamma$ -aminobutyric acid		
Ac	acetyl	Cys (C)	cysteine
ACPC	<i>trans</i> -2-aminocyclopentane carboxylic acid	Dab (X)	$\alpha,\gamma$ -diaminobutyric acid <sup>2</sup>
		dansyl	5-dimethylamino-1-naphthalenesulfonyl
Ada	1-adamantaneacetyl		
ADP	adenosine 5'-diphosphate	DAST	diethylaminosulfurtrifluoride
Ala (A)	alanine	DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
AM	aminomethyl	DCE	1,2-dichloroethane
anh.	anhydrous	Dde	1-(4,4-dimethyl-2,6-dioxo-cyclohex-1-ylidene)ethyl
aq.	aqueous		
Ar	aromatic	Dhb (U)	$\alpha$ -aminodehydrobutyric acid
Arg (R)	arginine	DIAD	diisopropyl azodicarboxylate
Asn (N)	asparagine	DiBAL-H	diisobutylaluminum hydride
Asp (D)	aspartic acid	DIC	<i>N,N'</i> -diisopropylcarbodiimide
AP	alkaline phosphatase	DiPEA	<i>N,N</i> -diisopropylethylamine
ATCC	American type culture collection	DMAP	4-dimethylaminopyridine
		DMF	<i>N,N</i> -dimethylformamide
Ava	$\delta$ -aminovaleric acid <sup>2</sup>	DMSO	dimethylsulfoxide
$\beta$ Ala	$\beta$ -alanine	DNA	deoxyribonucleic acid
BF2	buforin II	DOSPER	1,3-dioleyloxy-2-(6-carboxy-spermidyl)propylamide
BHI	brain/heart infusion		
bm	broad multiplet	DPPA	diphenylphosphoryl azide
Bn	benzyl	DPX	dansylated polymyxin B
Boc	<i>tert.</i> -butoxycarbonyl	DRC	(S7T)-drosocin
BOP	(benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate	DTT	dithiothreitol
		EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
Bu	butyl	EDTA	ethylenediaminetetraacetate
<i>c</i> (prefix)	cyclo	ESI	electrospray interface
C <sub>x</sub>	<i>n</i> -alkyl chain containing <i>x</i> carbon atoms	Et	ethyl
		eq.	equivalent(s)
CAP	cationic antimicrobial peptide	<i>E</i> -gel	gel containing ethylene glycol
Capro	( <i>S</i> )-3-amino-1-carboxymethyl caprolactame	F (prefix)	fluorous
		FA or fa	fatty acyl
CD	circular dichroism	FDA	(United States) Federal Drug Administration
CFU	colony-forming units		
Clt	(2-chlorotriphenyl)methyl	FITC	fluoresceinyl isothiocyanate
CMP	cytidine 5'-monophosphate	Fmoc	9-fluorenylmethoxycarbonyl
Cmpi	<i>N</i> -carboxymethylpiperazine	Gal	galactose
COSY	correlated spectroscopy	G <sup>-</sup>	Gram-negative
CPC	cetylpyridinium chloride	G <sup>+</sup>	Gram-positive
		Glc	glucose
		Gln (Q)	glutamine
		Glu (E)	glutamic acid
		Gly (G)	glycine
		GRAVY	grand average of hydrophathy

<sup>1</sup> Where applicable, amino acid residues are of the L-configuration unless otherwise stated.

<sup>2</sup> Due to shortage of unique one-letter codes, Ava is denoted with X in Chapter 4 and Tmd(Phe) with Z in Chapter 7.

G-gel		gel containing glycerol	MIC	minimal inhibitory concentration, <i>i.e.</i> the lowest concentration at which no bacterial growth can be detected by spectroscopic analysis after incubation for a specified time, compared with a positive control (Triton X-100).
HATU		<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate		
hBD		human $\beta$ -defensin		
HCTU		<i>O</i> -(6-chlorobenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate		
Hep		<i>L-glycero-D-manno</i> -heptose		
HEPES		<i>N</i> -(2-hydroxyethyl)piperazine- <i>N'</i> -(2-ethanesulfonic acid)	MIM	<i>N</i> -methyl- <i>N'</i> -alkyl imidazolium
His	(H)	histidine	MMT	(4-methoxytriphenyl)methyl
HMDS		hexamethyldisilazane	MOA	( <i>S</i> )-6-methyloctanoyl, -oic acid
HOAt		1-hydroxy-7-azabenzotriazole	Mpa	3-maleimidopropionyl
HOBt		1-hydroxybenzotriazole	MPD	<i>N</i> -methyl- <i>N</i> -alkyl-pyrrolidinium
HPLC		high-performance liquid chromatography		mass spectrometry
HRMS		high-resolution mass spectrometry	MS/MS	tandem mass spectrometry
HSer	( $\beta$ S)	$\beta^3$ -homoserine	Msc	methylsulfonylethoxycarbonyl
HTyr	( $\beta$ Y)	$\beta^3$ -homotyrosine	Mtt	(4-methyltriphenyl)methyl
IBX		triacetoxyiodobenzoic acid	MW	microwave (oven)
IL		interleukin	<i>n</i> ( <i>prefix</i> )	natural
Ile	(I)	isoleucine	<i>n</i> -	normal (linear)
IM		inner (cytoplasmic) membrane	<i>n/a</i>	not applicable
IR		infrared	<i>n/d</i>	not determined
ISB		iso-sensitest broth	NBE	nutrient broth E
ISO		International Organization for Standardization	NCL	native chemical ligation
ivDde		1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl	<i>n</i> G	not glycosylated
Kdo		3-deoxy- <i>D-manno</i> -oct-2-ulosonic acid	NMP	<i>N</i> -methylpyrrolidone
KFF		KFF peptide (KFF) <sub>3</sub> K	NMR	nuclear magnetic resonance
LB		Luria-Bertani (broth)	NOE	nuclear Overhauser effect
LBP		LPS-binding protein	NOESY	nuclear Overhauser effect spectroscopy
LC		liquid chromatography	Orn	(O) ornithine
LCMS		liquid chromatography/mass spectrometry	Pamb	<i>p</i> -(aminomethyl)benzoic acid
Leu	(L)	leucine	PAMP	pathogen-associated molecular pattern
LPS		lipopolysaccharide	PBS	phosphate-buffered saline
Lys	(K)	lysine	PE	petroleum ether 40/60
OM		outer membrane	PEG	polyethyleneglycol
Orn	(O)	ornithine	Ph	phenyl
Mamb		<i>m</i> -(aminomethyl)benzoic acid	Phe	(F) phenylalanine
MALDI		matrix-assisted laser desorption/ionisation	PhPip	4-phenyl-4-carboxymethyl-piperidine
Me		methyl	PMB	polymyxin B
<sup>Me</sup> Arg	( <sup>Me</sup> R)	<i>N</i> <sup>α</sup> -methylarginine	PMBN	polymyxin B nonapeptide
<sup>Me</sup> Ser	( <sup>Me</sup> S)	<i>N</i> -methylserine	PNT	pentamidine (derivative)
Met	(M)	methionine	Pro	(P) proline
MHC		minimal hemolytic concentration	PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate



## List of Abbreviations

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PyBroP	bromotripyrrolidino-phosphonium hexafluorophosphate	TCEP	tris(carboxyethyl)phosphine
		TES	triethylsilane
		TFA	trifluoroacetic acid
QAC	quaternary ammonium compound	TFE	2,2,2-trifluoroethanol
RBC	red blood cell	THF	tetrahydrofuran
Ref.	reference	THP	tetrahydropyran
R <sub>f</sub>	retardation factor	Thr	(T) threonine
RNA	ribonucleic acid	TIC	total ion count
ROESY	rotating frame NOESY	TIS	triisopropylsilane
RP	reversed phase	Tmd	3-(trifluoromethyl)-3H-diazirin-3-yl
Rt	retention time	TMS	trimethylsilyl
RT	room temperature	TNBS	2,4,6-trinitrobenzenesulfonic acid
RTD	rhesus $\theta$ -defensin		
s ( <i>prefix</i> )	synthetic	TNF	tumor necrosis factor
SAA	sugar amino acid	TLC	thin-layer chromatography
Sar	sarcosine	TLR	Toll-like receptor
sat.	saturated	TOCSY	total correlation spectroscopy
SCL	3-carboxypropanesulfonamide	TOF	time-of-flight
Ser	(S) serine	Tr	triphenylmethyl
SIC	streptococcal inhibitor of complement	Tran	tranexamic acid
SPE	solid-phase extraction	Trp	(W) tryptophane
SPPS	solid-phase peptide synthesis	TTC	tripticin
SPy	2-pyridylsulfenyl	Tyr	(Y) tyrosine
SS	disulfide linkage	UDP	uridine 5'-diphosphate
StBu	<i>tert.</i> butylsulfenyl	UV	ultraviolet
Su	succinimidyl	Val	(V) valine
tBu	<i>tert.</i> butyl	W-gel	gel containing water
TCA	trichloroacetic acid	Z	benzyloxycarbonyl <sup>2</sup>

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# General Introduction

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