Semisynthetic glycopeptide antibiotics

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List of abbreviations

ABS	absorbance
ADD	antibiotic-induced diarrhea
Ala	alanine
AMR	antimicrobial resistance
API-TOF	Atmospheric pressure interface time-of-flight
Asn	asparagine
Asp	aspartic acid
ATP	adenosine triphosphate
AUC	area under the curve
BBO	broadband observe
BLD	below limit of detection
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BPO	benzoyl peroxide
BSA	bovine serum albumin
$C_{55}P$	undecaprenyl pyrophosphate
CAMHB	cation-adjusted Mueller Hinton broth
CAS	Chrome azerol S
CBP	4-chloro-1,1'-biphenylmethyl
CC_{50}	50% cytotoxic concentration
CDC	Centers for Disease Control and Prevention
CFU	colony forming unit
ciPTECs	conditionally immortalized proximal tubule epithelial cells
CLSI	Clinical & Laboratory Standards Institute
CuAAC	copper-click azido-alkyne catalysis
d	doublet
Dab	diaminobutyric acid
DBCO	dibenzocyclooctyne
DCM	dichloromethane
DIPEA	N,N-Diisopropylethylamine
$diSC_3(5)$	dipropylthiadicarbocyanine iodide
DMEM	Dulbecco's Modified Eagle Medium
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DOPC	dioleoylphosphatidylcholine
DPA	dipicolylamine
EC_{50}	50% effective dose
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
eq	equivalent
ESI	electrospray ionization
EtOAc	ethyl acetate
far	farnesyl
FBS	fetal bovine serum
FDA	Food and Drug Administration
FIC	fractional inhibitory concentration
GC	growth control
ger	geranyl
GFP	green fluorescent protein
Glu	glutamic acid
Gly	glycine

h	hours
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HBSS	Hank's Balanced Salt Solution
HBTU	Hexafluorophosphate Benzotriazole Tetramethyl Uronium
HEPA	high-efficiency particulate air
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSA	human serum albumin
Hz	Hertz
IE	infective endocarditis
IM	inner membrane
ITC	isothermal titration calorimetry
IV	intravenous
K_D	association constant
Lac	lactate
LB	Lysogeny broth
LCMS	liquid chromatography mass spectrometry
LD_{50}	50% lethal dose
LI	lipid I
LII	lipid II
LOD	limit of detection
LPS	lipopolysaccharide
LUMC	Leiden University Medical Center
LUVs	large unilateral vesicles
m	multiplet
MAC	membrane attack complex
MBEC	minimal biofilm eradication concentration
MBIC	minimal biofilm inhibitory concentration
MBTE	methyl-tert-butylether
MDR	multi-drug resistance
MES	2-(N-morpholino)ethanesulfonic acid
MHB	Mueller Hinton Broth
MIC	minimum inhibitory concentration
min	minutes
MRSA	methicillin-resistant *S. aureus*
MSSA	methicillin-sensitive *S. aureus*
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NARSA	Network on Antimicrobial Resistance in *S. aureus*
nb	no binding
NC	negative control
NCA	non-compartmental analysis
NDM	New Delhi metallo-β-lactamase
NHS	*N*-hydroxysuccinimide
NMR	nuclear magnetic resonance
NP	nanoparticle
ns	non-significant
OD	optical density
OM	outer membrane
orn	ornithine
p80	polysorbate 80
PBP	penicillin binding protein
PBS	phosphate buffered saline

PC	positive control
PE	petroleum ether
PEG	polyethylene glycol
PI	propidium iodide
PK	pharmacokinetics
PMBN	polymyxin B nonapeptide
PMEN	polymyxin E nonapeptide
ppm	parts per million
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
q	dosing interval
QTOF	quadrupole time-of-flight
RP-HPLC	reverse phase high performance liquid chromatography
rpm	rounds per minute
RT	room temperature
s	singlet
S.P.	*Streptococcus pneumoniae*
SC	subcutaneous
SD	standard deviation
Ser	serine
SFI	saline for injection
SSSI	skin and skin structure infections
t	triplet
TC_{50}	50% toxic concentration
TCD	Tricyclo[3.3.1.1^{3,7}]decane or adamantane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THPTA	tris(3-hydroxypropyltriazolylmethyl)amine
TIPS	triisopropyl silane
TLC	thin layer chromatography
TSB	tryptic soy broth
UDP-MurNAc-pp	UDP-N-acetylmuramic acid pentapeptide
UK	United Kingdom
UMCU	University Medical Center Utrecht
US(A)	United States (of America)
UV	ultraviolet
Vc	vancomycin C-terminus
VISA	vancomycin-intermediate *S. aureus*
Vn	vancomycin N-terminus
Vr	vancomycin resorcinol
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant *S. aureus*
VSE	vancomycin-sensitive enterococci
Vv	vancomycin vancosamine
WFI	water for injection
WHO	World Health Organization
WT	wildtype

List of publications

Patents during doctoral research

- 2019 Dutch Patent application filing, 2021 granted; Title: "Antibacterial Compounds"; Inventors: Martin, N.I.; **van Groesen, E.**; Tehrani, K.H.M.E.; Wade, N. Priority date: September 24, 2019; Application no. N2023883

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- **van Groesen, E.**,* Slingerland, C. J.,* Innocenti, P., Mihajlovic, M., Masereeuw, R. & Martin, N. I. Vancomyxins: Vancomycin-Polymyxin Nonapeptide Conjugates That Retain Anti-Gram-Positive Activity with Enhanced Potency against Gram-Negative Strains. *ACS Infect. Dis.* 7, 2746–2754 (2021).

- **van Groesen, E.**, Innocenti P., Martin, N.I. Recent advances in the development of semisynthetic glycopeptide antibiotics (2014-2022). *ACS Infect. Dis.* (accepted)

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Curriculum vitae

Emma van Groesen was born on 14 January 1994 in Goirle, The Netherlands. After graduating high school at the Sint Odulphuslyceum in Tilburg in 2012, she started the honors bachelor College of Pharmaceutical Sciences at Utrecht University, where she joined the group of Prof. Dr. Nathaniel Martin for 6 months to work on the development of novel semisynthetic nisin antibiotics. After she graduated *cum laude* in 2015, Emma initiated her masters Drug Innovation at Utrecht University. Here, she first spend 9 months on the development of a novel controlled drug delivery system for DNA/RNA therapeutics in the lab of Prof. dr. Tina Vermonden. Subsequently, Emma moved to Oxford for 7 months to study lysine carbamylation and substrate/inhibitor binding of antimicrobial resistance enzyme OXA-48 using NMR in the lab of Prof. dr. Christopher Schofield at the University of Oxford. In 2017, she obtained her Masters of Science with judicium *cum laude*. October 2017, Emma started her PhD research in the group of Prof. dr. Nathaniel Martin, initially at Utrecht University and subsequently at Leiden University. Here, Emma worked on the development and assessment of novel semisynthetic glycopeptide antibiotics to tackle drug-resistant infections. As of June 2022, Emma works as Scientist in the Non-Clinical Bioanalytical Science team at Genmab in Utrecht.