



Universiteit
Leiden
The Netherlands

Towards peptide based therapeutics-applications in celiac disease and infectious diseases

Kapoerchan, V.V.

Citation

Kapoerchan, V. V. (2009, December 22). *Towards peptide based therapeutics-applications in celiac disease and infectious diseases*. Retrieved from <https://hdl.handle.net/1887/14542>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/14542>

Note: To cite this publication please use the final published version (if applicable).

Towards peptide-based therapeutics- Applications in celiac disease and infectious diseases

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden
op gezag van de Rector Magnificus, prof. mr. P. F. Van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 22 december 2009
klokke 15.00 uur

door

Vanita Varsha Kapoerchan
geboren te Den Haag in 1982

Promotiecommissie

Promotor : Prof. dr. F. Koning

Promotor : Prof. dr. H. S. Overkleeft

Co-promotor : Dr. ing. M. Overhand

Overige leden : Prof. dr. J. Brouwer

Dr. J.W. Drijfhout

Dr. G. M. Grotenbreg

Prof. dr. G. A. Van der Marel

Prof. dr. E. J. H. J. Wiertz

Part of the research described in this Thesis was supported by the Celiac Disease Consortium., an Innovative Cluster approved by the Netherlands Genomics Initiative.

This thesis was printed by Ridderprint Offsetdrukkerij BV (Ridderkerk, the Netherlands).

Voor mijn ouders

Table of Contents

List of abbreviations	6
Chapter 1 General Introduction	9
Chapter 2 From a Natural Gluten Peptide to a HLA-DQ2 Blocker	41
Chapter 3 Design, Synthesis and Biological Evaluation of High Affinity HLA-DQ2 Binding Compounds	65
Chapter 4 Modification of a High Affinity HLA-DQ2 binding peptide	99
Chapter 5 Adamantyl Amino Acid Modified Gramicidin S Analogs Combine more Potent And Broader Bactericidal Activity with Reduced Hemolytic Activity in Comparison with Natural Gramicidin S	111

Chapter 6	135
Turn-Modified Gramicidin S Analogs Containing Morpholine Amino Acids	
Chapter 7	153
Summary and Future Prospects	
Nederlandse samenvatting (Summary in Dutch)	167
List of publications	170
Curriculum Vitae	171
Nawoord	173
Appendix	175

List of Abbreviations

4-DAPA	N α -Fmoc-N β -(4-N,N $^{\prime}$ -dimethyl-aminophthalimidoyl)-L-diamino-propionic acid	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
6-DMNA	N α -Fmoc-N β -(6-N,N $^{\prime}$ -dimethyl-aminonaphtalimidoyl)-L-diamino-propionic acid	EDTA	ethylenediaminetetraacetic acid
A	L-alanine	eq	equivalents
Å	Ångstrom	ESI	electrospray ionization
aa	amino acid	EtOAc	ethyl acetate
Ala	L-alanine	F	L-phenylalanine
APC	antigen presenting cell	Fmoc	9-fluorenylmethoxycarbonyl
Asp	L-aspartic acid	Fmoc-OSu	N-(9-fluorenylmethoxy-carbonyloxy)succinimide
Asn	L-asparagine	g	gram(s)
BAIB	iodobenzene diacetate	G	glycine
BHA	benzhydramine	GFD	gluten-free diet
Boc	<i>t</i> -butyloxycarbonyl	Gln	L-glutamine
BSA	bovine serum albumin	Glu	L-glutamic acid
Cbz	benzyloxycarbonyl	Gly	glycine
CD	celiac disease	GS	gramicidin S (Soviet)
CDI	1,1'-carbonyl diimidazole	GTP	guanidine triphosphate
Chg	cyclohexyl-L-glycine	h	hour(s)
Cha	cyclohexyl-L-alanine	HBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate
C $_q$	quaternary carbon	HCTU	2-(6-chloro-1-H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate
Cys	L-cysteine	HFiP	hexafluoroisopropanol
d	doublet	His	L-histidine
D	L-aspartic acid	HLA	human leukocyte antigen
DCM	dichloromethane	HMPB	4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid
dd	doublet of doublets	HOBt	N-hydroxybenzotriazole
ddd	doublet of doublet of doublets	HPLC	high performance liquid chromatography
DIAD	diisopropyl azodicarboxylate	HRMS	high resolution mass spectrometry
DIC	N,N'-diisopropylcarbodiimide	Hz	hertz
DIPEA	N,N'-diisopropylethylamine	I	L-isoleucine
DMAP	N,N'-dimethylaminopyridine	IC $_{50}$	concentration at which 50% inhibition occurs
DMF	N,N-dimethylformamide		
DMSO	dimethyl sulfoxide		
DON	6-diazo-5-oxo-norleucine		
Dpr	L-2,3-diaminopropionic acid		
dt	double triplet		
E	L-glutamic acid		

IR	infrared spectroscopy	PIFA	bis(trifluoroacetoxy)-iodobenzene
<i>J</i>	coupling constant	PPII	polyproline type II
K	L-lysine	Pro	L-proline
kD	kilodalton	PyBOP	benzotriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate
L	L-leucine	Pyr	L-pyroglutamic acid
LC-MS	liquid chromatography mass spectrometry	q	quartet
Leu	L-leucine	Q	glutamine
Lys	L-lysine	R	L-arginine
m	multiplet	RCM	ring-closing metathesis
M	molar	RP	reversed phase
MAA	morpholine amino acid	S	L-serine
MBHA	4-methylbenzhydrylamine	s	singlet
Me	methyl	SAA	sugar amino acid
MeCN	acetonitrile	Ser	L-serine
MeOH	methanol	SPPS	solid phase peptide synthesis
MHC	major histocompatibility complex	t	triplet
MIC	minimal inhibitory concentration	TBAF	tetrabutylammonium fluoride
min	minute(s)	<i>t</i> Bu	<i>tert</i> -butyl
ml	milliliter(s)	TCR	T cell receptor
mM	millimolar	td	triple doublet
mmol	millimole(s)	TEMPO	2,2,6,6-tetramethylpiperidinoxy
MRSA	methicillin resistant <i>Staphylococcus Aureus</i>	TFA	trifluoroacetic acid
MS	mass spectrometry	TG2	tissue transglutaminase
μ M	micromolar	THF	tetrahydrofuran
m/z	mass over charge ratio	TIS	triisopropylsilane
NMR	nuclear magnetic resonance	TLC	thin layer chromatography
nM	nanomolar	Tmd	trifluoromethyldiazirine
NMM	N-methylmorpholine	TMS	trimethylsilyl
NMP	N-methyl-2-pyrrolidone	Trt	trityl
NOE	nuclear Overhauser effect	Ts	toluenesulfonyl
Orn	L-ornithine	<i>t</i> TG	tissue transglutaminase
P	L-proline	UV	ultraviolet
PBS	phosphate buffered saline	V	L-valine
PEP	prolyl endopeptidase	Val	L-valine
Phe	L-phenylalanine	W	L-tryptophan
		Y	L-tyrosine

