Universiteit Leiden
The Netherlands

Cyclophellitol and its derivatives: synthesis and application as beta-glycosidase inhibitors

Li, K.J.

Citation

Li, K. J. (2014, December 11). *Cyclophellitol and its derivatives: synthesis and application as beta-glycosidase inhibitors*. Retrieved from https://hdl.handle.net/1887/30102

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/1887/30102

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

Cyclophellitol and Its Derivatives

Synthesis and Application

as Retaining β-Glycosidase Inhibitors

Proefschrift
Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. dr. C. J. J. M. Stolker
volgens het besluit van het College voor Promoties
te verdediging op donderdag 11 december 2014
klokke 15:00 uur

door

Kah-Jee Li

Geboren te Amsterdam in 1985

Promotiecommissie

Promotores	:	Prof. dr. H.S. Overkleeft Prof. dr. G.A van der Marel
Overige leden	:	Prof. dr. J.M.F.G Aerts (Universiteit van Amsterdam) Prof. dr. S.G. Withers (University of British Columbia) Prof. dr. J. Brouwer Prof. dr. J. Lugtenburg Dr. Martin D. Witte (Universiteit Groningen) Dr. Tom Wennekes (Universiteit Wageningen)

Druk: Ridderprint BV

Cover design: Antonio Ip

Table of Contents

List of Abbreviations

1 **General Introduction and Outline** 9

2 **Activity-Based Retaining β-Exoglucosidases Probes** 27
Their Rational Design and Biological Applications

3 **Synthesis of Cyclophellitol and Cyclophellitol Aziridine** 41

4 **Cyclophellitol Aziridines ABPs** 53
for broad-spectrum profiling of retaining β-exoglucosidases

5 **Cyclophellitol Analogues** 67
as Inhibitors of Human Retaining β-Glucosidases

6 **Synthesis of Cellobiosyl Cyclophellitol and Analogues** as Potential Cellulase Inhibitors and Activity-Based Probes 79

7 **Cellobiosyl Cyclophellitol and 4'-deoxy Cellobiosyl Cyclophellitol Aziridine Derivatives** Synthesis and Evaluation as Inhibitors and Activity-Based Probes of *H. jecorina* Cellulases 101

8 **Synthesis and Biological Evaluation of Exo-*N*-Cyclic Deoxynojirimycin and Derivatives** 115

9 **Summary and Future Prospects** 129

Samenvatting – Summary in Dutch 147

List of Publications 150

Curriculum Vitae 153

List of Abbreviations

4-mu	4-methylumbelliferyl
ABP	activity-based probe
ABPP	activity-based protein profiling
Ac	acetyl
ACN	acetonitrile
Ada	adamantane
AMP	5-(adamantan-1-yl-methoxy)-pentyl
AMP-DNM	*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin
APT	attached proton test
aq.	aqueous
Ar	aromatic
Asp	aspartic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyldicarbonate
BODIPY	boron-dipyrromethane
br	broad
BSA	bovine serum albumin
Bz	benzoyl
Bu	butyl
cald.	calculated
CBE	conduritol β-epoxide
CBH	cellobiohydrolase
COSY	correlation spectroscopy
CMT	chaperone-mediated therapy
C_q	quarternary carbon atom
d	doublet
δ	chemical shift
Da	Dalton
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	double double doublet
ddt	double double triplet
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTF	*N*, *N*-dimethylthioformamide
DNP	2,4-dinitrophenyl
DNPC	2,4-dinitrophenyl-β-cellobioside
dt	double triplet
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EG	endoglucanase
eq	molar equivalents
ERT	enzyme replacement therapy
Et	ethyl
et al.	*et alii* (and others)
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
Gal	D-galactose
GalF	D-galactosyl fluoride
GBA	glucocerebrosidase
GBA2	β-glucosidase 2
GBA3	cytosolic β-glucosidase

GCS	glucosylceramide synthase
Glc	D-glucose
GlcF	D-glucosyl fluoride
Glu	glutamic acid
h	hour (s)
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
J	coupling constant
LC/MS	liquid chromatography/mass spectrometry
LPH	lactase-phlorizin hydrolase
m	multiplet
M	molar (s)
m/z	mass to charge ratio
*m*CBPA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	mega Hertz
min	minute(s)
mL	millilitre(s)
mmol	millimol(s)
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
NaH	sodium hydride
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
PAGE	polyacrylamide gel electrophoresis
Pd/C	palladium on charcoal
Ph	phenyl
ppm	parts per million
*p*TsOH	*para*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet
SRT	substrate reduction therapy
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimetylsilyl
TBTA	*N*,*N*,*N*-tris((1-benzyl-1*H*-1,2,3-triazol-4-yl-methyl)amine
*t*Bu	*tert*-butyl
td	triple doublet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tr	trityl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
WT	wild-type

Note: the one and three letter codes for the amino acids follow the recommendations of IUPAC. *J. Biol. Chem.* **1968**, *243*, 3557-3559 and *J. Biol. Chem.* **1972**, *247*, 977-983