Natural Products from New Zealand *Latrunculia* Species Sponges

Tanja Grkovic

A thesis submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
The University of Auckland, 2008

Abstract

In a survey of the secondary metabolite chemistry profiles of ten New Zealand, one Antarctic and one South African-sourced collections of *Latrunculia* spp. sponges, eighteen discorhabdin alkaloids have been isolated. Four of those, namely discorhabdin K, 3-dihydro discorhabdin A, 1-thiomethyl discorhabdin G*/I, and 16a,17a-dehydro discorhabdin W were fully characterized as new natural products in the series. In addition, for the first time, five enantiomeric pairs and two sets of diastereomers of the naturally-occurring discorhabdin alkaloids were identified. The absolute configuration of all of the chiral compounds isolated, including new natural products, has been established upon comparison of the observed experimental data with the results of time dependant density functional theory calculations of the electronic circular dichroism spectra.

A structure activity relationship study on discorhabdin B, the main natural product of the Wellington-sourced sponges, has identified four reactive centres on the molecule and yielded nine novel semi-synthetic derivatives. Consequently, a new discorhabdin biosynthetic tree was proposed which highlighted discorhabdin B as a crucial precursor to a number of other naturally-occurring analogues. The importance of the iminoquinone moiety and the spirodienone ring with respect to the bioactivity of the compounds in a range of naturally-occurring discorhabdins was demonstrated. A new semi-synthetic derivative, 1-discorhabdyl discorhabdin D, was identified as a potent anti-malarial agent and has opened new possibilities for the therapeutic development of the discorhabdin alkaloids.

Declaration

This is to certify that:

1) This thesis comprises only the authors original work, except where indicated below;

2) Due acknowledgment to all other material used has been made in the main text of the thesis

My overall contribution to the work presented in this thesis is approximately 90%, based on the following:

Chapter 2

95% Time dependent density functional theory calculations of the electronic circular dichroism spectra were the work of Professor Daneel Ferreira, Dr Yuanqing Ding and Dr Xing-Cong Li at Department of Pharmacognosy and National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi.

Chapter 3

95 % One-electron reduction potentials are the work of Associate Professor Robert F. Anderson and Dr. Sujata S. Shinde at Department of Chemistry, The University of Auckland

Acknowledgments

I would like to thank my supervisor, Associate Professor Brent Copp. For the support, guidance and encouragement over the last couple of years. Thank you for believing and for giving me the freedom and confidence to give it a try.

To Dr Norrie Pearce, thank you for teaching me all the lab skills there ever was to know, for looking after all of us and for being the best role model one can have. Thank you for showing me how to be both a good chemist and good person.

Over the last five years, or ten semesters rather, I was fortunate enough to be involved in stage I chemistry teaching labs. Thanks to Dr Judy Brittain for keeping me around, and for exemplifying that no problem is too big or too impossible to handle, as long as you have a good strategy.

A big thank you also goes to all of my lab mates, the “click”, and to all of my friends near and far. Every smile and every single good thought mattered. You guys have made this a great experience.

To my dearest family, mum, dad, Nikola and Christoph. I am never alone and all of you are with me every day. Thank you for believing and making me strong enough. And opinionated (not always in my best interest). This all was possible only because I had the benefit of your support (always in my best interest).

Thank you to our collaborators, Professor Daneel Ferreira, Dr Yuanqing Ding and Dr Xing-Cong Li for the calculations of the electronic circular dichroism spectra that were crucial in securing the stereochemistry of the discorhabdin alkaloids, and to Associate Professor Robert F. Anderson and Dr. Sujata S. Shinde for measuring the one-electron reduction potentials.

I am grateful to Professors John Blunt and Murray Munro at The University of Canterbury, Professor Mike Davies-Coleman at The Rhodes University and Dr Fernando Reyes at PharmaMar for sharing their *Latrunculia* spp. sponge samples and purified discorhabdin compounds used for the stereochemical comparison study in this work. Your collegiality and willingness to help is greatly appreciated.

Thank you to Professor Tom Brittain at the School of Biological Sciences, University of Auckland for the use of his electronic circular dichroism spectrophotometer; to Ms Gill Ellis at The University of Canterbury for P388 and antimicrobial assays; to Dr Marcel Kaiser at The Swiss Tropical Institute for the testing of compounds in their tropical disease assay and to the National Cancer Institute for the 60 human tumor cell line assays.

In my biased opinion not knowing what magic compound you might have dissolved in the NMR tube is the most fun a natural product chemist can ever have. However the task of obtaining good quality and an informative NMR dataset for the same can sometimes be challenging. A very big thank you goes to Mr. Michael Walker and Dr Michael Schmitz for help with NMR data acquisition, and to Mrs. Raisa Imatdieva for obtaining the mass spectral data.

Finally I am grateful to the University of Auckland for a UoA Doctoral Scholarship and the Graduate Research Fund reward.

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List of Abbreviations

Ac	Acetyl
A-549	Human lung adenocarcinoma
BV	Benzyl viologen
br	broad
CaN	Calcineurin
CD	Circular dichroism
CN	Cyanoalkyl-derivatized silica
calcd	Calculated
CI	Chemical impact
cm^{-1}	Wave numbers
CoA	Co-enzyme A
COSY	Gradient correlation spectroscopy (^1H-^1H)
CPP32	Caspase-3
C_{18}	Octadecyl-derivatized silica
C_8	Octyl-derivatized silica
d	Doublet
DCI	Desorption chemical impact
dd	Doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
deg	Degrees
DEPT	Distortionless enhancement by polarisation transfer
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DQ	Duroquinone
DTT	Dithiothreitol
ECD	Electronic circular dichroism
ED_{50}	50% Effective dose
EI	Electron impact
$E_{1/2}$	Half-wave reduction potential
E_7	One electron reduction potential

FAB	Fast atom bombardment
GC	Gas chromatography
GI_{50}	50% Growth Inhibition
GSH	Reduced glutathione
HCT-116	Human colon tumor cell line
HIV-1	Human immunodeficiency virus type 1
HMBC	Gradient heteronuclear multiple-bond correlation
HPLC	High performance liquid chromatography
HR	High resolution
HSQC	Gradient heteronuclear single-quantum correlation
HT-29	Human colon cancer cell line
Hz	Hertz
IC_{50}	50% Inhibitory concentration
IDO	Indoleamine-2,3-dioxygenase
IR	Infrared
J	Coupling constant
J-HMBC	Long-range gradient heteronuclear multiple-bond correlation
KB	Human oral epidermoid cancer cell line
L-1210	Mouse lymphatic leukemia cell line
L-1210/DX	Doxorubicin resistant mouse lymphatic leukemia cell line
m	Multiplet
M	mol/L
MCF-7	Human breast cancer cell line
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MIC	Minimum inhibitory concentration
MS	Mass spectrometry
MTPA	α-Methoxy-α-trifluoromethylphenyl-acetic acid
Mult	Multiplicity
m/*z*	Mass to charge ratio
NADPH	Nicotine adenine dinucleotide phosphate
NCI	National Cancer Institute

NIWA	National Institute of Water and Atmospheric Research
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
ppm	Parts per million
q	Quartet
PANC-1	Human pancreatic cancer cell line
pBR322	Plasmid used as a cloning vector
PIFA	Phenyliodone(III) *bi*s-(trifluoroacetate)
P388	Murine leukemia cell line
ROESY	Rotating frame Overhauser enhancement spectroscopy
R_T	Retention time
s	Singlet
Sp.	Species
Spp.	Species (plural)
t	Triplet
TCEP	Tris(2-carboxyethyl)phosphine
TDDFT	Time dependant density functional theory
TFA	Triflouroacetic acid
TLC	Thin layer chromatography
TMBQ	2,3,5-trimethylbenzoquinone
UV	Ultraviolet
V	Volt
VCD	Vibrational circular dichroism
Vis	Visible
WHCO-1	Human oesophageal cancer cell line
xrs-6	Chinese hamster ovary cell line
$[\alpha]_D$	Optical rotation at 589 nm
$[\alpha]_{578}$	Optical rotation at 578 nm
$[\alpha]_{546}$	Optical rotation at 546 nm
β-CD	*β*-Cyclodextrin
δ	ppm of the applied magnetic field
τ_{mix}	Mixing time

^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon-13 nuclear magnetic resonance spectroscopy
2D NMR	Two dimensional nuclear magnetic resonance spectroscopy