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Natural Products from New Zealand

*Latrunculia* Species Sponges

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A thesis submitted in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy in Chemistry  
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## 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

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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.

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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 <sup>-1</sup> | Wave numbers  |
| CoA              | Co-enzyme A   |
| COSY             | Gradient correlation spectroscopy ( <sup>1</sup> H- <sup>1</sup> H) |
| CPP32            | Caspase-3   |
| C <sub>18</sub>  | Octadecyl-derivatized silica  |
| C <sub>8</sub>   | 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 <sub>50</sub> | 50% Effective dose  |
| EI               | Electron impact   |
| E <sub>1/2</sub> | Half-wave reduction potential                                       |
| E <sub>7</sub>   | One electron reduction potential                                    |

|                  |  |
|------------------|--|
| FAB              | Fast atom bombardment  |
| GC               | Gas chromatography   |
| GI <sub>50</sub> | 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 <sub>50</sub> | 50% Inhibitory concentration                                   |
| IDO              | Indoleamine-2,3-dioxygenase                                    |
| IR               | Infrared   |
| <i>J</i>         | Coupling constant  |
| <i>J</i> -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             | $\alpha$ -Methoxy- $\alpha$ -trifluoromethylphenyl-acetic acid |
| Mult             | Multiplicity   |
| <i>m/z</i>       | 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) <i>bis</i> -(trifluoroacetate)     |
| P388                        | Murine leukemia cell line                            |
| ROESY                       | Rotating frame Overhauser enhancement spectroscopy   |
| R <sub>T</sub>              | Retention time                                       |
| s                           | Singlet  |
| Sp.                         | Species  |
| Spp.                        | Species (plural)                                     |
| t                           | Triplet  |
| TCEP                        | Tris(2-carboxyethyl)phosphine                        |
| TDDFT                       | Time dependant density functional theory             |
| TFA                         | Trifluoroacetic 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                      |
| [ $\alpha$ ] <sub>D</sub>   | Optical rotation at 589 nm                           |
| [ $\alpha$ ] <sub>578</sub> | Optical rotation at 578 nm                           |
| [ $\alpha$ ] <sub>546</sub> | Optical rotation at 546 nm                           |
| $\beta$ -CD                 | $\beta$ -Cyclodextrin                                |
| $\delta$                    | ppm of the applied magnetic field                    |
| $\tau_{\text{mix}}$         | Mixing time  |

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