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# Design and Synthesis of Novel Cationic Peptide Antibiotics

A thesis submitted in fulfilment of the
requirements for the award of the degree

DOCTOR OF PHILOSOPHY

from

**THE UNIVERSITY OF WOLLONGONG**

by

**Timothy P. Boyle, B. Med. Chem. (Hons)**

**DEPARTMENT OF CHEMISTRY**
**SEPTEMBER 2004**

*For Mum and Dad*

# Certification

I, Timothy P. Boyle, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Timothy P. Boyle

September 2004

# Patents and Publications

- Bremner, John; Pyne, Stephen; Keller, Paul; Coghlan, Dan; Garas, Adel; Witchard, Helen; Boyle, Tim; Coates, Jonathan. Preparation of peptoid compounds for treatment of bacterial infections. PCT Int. Appl. (2003), 102 pp. CODEN: PIXXD2 WO 2003002545 A1 2003010 CAN 138:90077 AN 2003:22860 CAPLUS

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*Finally I would like to thank Gill, for helping me realise that it is impossible to solve all life's problems on my own.*

# Abbreviations

| | |
|---|---|
| °C | degrees Celsius |
| μM | micromolar |
| +ve | positive |
| δ | chemical shift in parts per million downfield from TMS |
| μ | micro |
| 1D | one dimensional |
| 2D | two dimensional |
| 3D | three dimensional |
| Ala | alanine |
| Arg | arginine |
| Boc | *tert*-butoxycarbonyl |
| br | broad (spectral) |
| $CaCO_3$ | calcium carbonate |
| Calcd | calculated |
| $CDCl_3$ | deuterated chloroform |
| $CD_3OD$ | deuterated methanol |
| $CH_3CN$ | acetonitrile |
| CI | chemical ionisation (in mass spectrometry) |
| COSY | correlation spectroscopy |
| d | doublet (spectral) |
| Da | Dalton |
| DCC | *N*,*N*-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DCU | *N*,*N*-dicyclohexylurea |
| DEPT | distortionless enhancement by polarisation transfer |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| EDCI | 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride |
| EI | electron impact (in mass spectrometry) |
| ES | electrospray |
| Et | ethyl |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| Fmoc | 9-fluorenylmethoxycarbonyl |
| g | grams |
| gHMBC | gradient heteronuclear multiple bond correlation |
| gHSQC | gradient heteronuclear single quantum correlation |
| HRMS | high resolution mass spectroscopy |
| Grubbs' Ru catalyst | benzylidene bis(tricyclohexylphosphine)dichlororuthenium |
| h | hours |
| HCl | hydrochloric acid |
| HOBt | 1-hydroxy-1*H*-benzotriazole |
| HRMS | high-resolution mass spectrometry |

| | |
|---|---|
| Hz | Hertz |
| $IC_{50}$ | inhibitory concentration (50%) |
| *J* | coupling constant (in NMR) |
| $K_2CO_3$ | potassium carbonate |
| $K_i$ | binding affinity |
| KOH | potassium hydroxide |
| L | litre |
| Lac | lactate |
| Lys | lysine |
| m | multiplet (spectral), milli |
| M | molar |
| max. | maximum |
| Me | methyl |
| MeOH | methanol |
| mg | milligram |
| $MgSO_4$ | magnesium sulfate |
| MHz | megahertz |
| MIC | minimum inhibitory concentration |
| min | minute(s) |
| mL | millilitre |
| mmol | millimole |
| mol | mole |
| Mp | melting point |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| MS | mass spectrum (spectrometry) |
| MW | molecular weight |
| *m/z* | mass/charge ratio |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear overhauser effect spectroscopy |
| Orn | ornithine |
| PBP | penicillin binding proteins |
| Pd/C | palladium-on-carbon catalyst |
| Pmc | 2,2,5,7,8-pentamethylchroman-6-sulfonyl |
| ppm | parts per million |
| q | quartet (spectral) |
| RCM | ring closing metathesis |
| RT | room temperature |
| s | singlet (spectral) |
| SAR | structure activity relationship |
| Ser | serine |
| $S_N2$ | bimolecular nucleophilic substitution |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| Tyr | tyrosine |
| TMS | trimethylsilane |
| VRE | vancomycin-resistant enterococci |

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# Abstract

The results of the research on the development of novel cationic peptoids as potential new antibacterial agents is presented in this thesis. The series of macrocyclic peptoids prepared in this study arises from a previously identified lead which was designed to act as a vancomycin mimic, and possessed many of the features believed to be necessary for antibacterial activity. Chapters 2 and 4 describe the design and synthesis of a number of structurally different cyclised and linear peptoids, which were produced from a multi-step synthetic pathway. The basic strategy involved the synthesis of a hydrophobic scaffold, to which a cationic peptide was attached. Compounds described in Chapter 2 contained two remote allyl substituents which were utilized in the reliable ring-closing metathesis reaction to produce the desired macrocycles. Subsequent removal of the amino acid residue protecting groups yielded the desired targets for antibacterial testing. A total of 163 compounds were synthesized, including 146 new compounds.

In Chapters 3 and 5, the results from the antibacterial testing assays against *Staphylococcus aureus* (Chapters 3 and 5) and several vancomycin-resistant enterococci (VRE) strains (Chapter 5), are discussed and structure-activity trends are highlighted. It was found that for antibacterial activity against both *Staphylococcus aureus* and VRE strains, a (*S*)-1,1'-binaphthyl hydrophobic scaffold must be present (MIC 3.9 μg/mL against *Staphylococcus aureus* and 15.6 μg/mL against the VRE for one such derivative).

Chapter 6 reports the screening of several peptoids against the HIV integrase enzyme. From the screening, key structure activity trends were observed and a preliminary computational model indicating the mechanism of binding and inhibition is proposed. Four target compounds were prepared to justify the preliminary model.