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Andrew Giltrap

Total Synthesis of Natural Products with Antimicrobial Activity

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Total Synthesis of Natural Products with Antimicrobial Activity

Doctoral Thesis accepted by
The University of Sydney, Sydney, Australia

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Supervisor's Foreword

Natural products represent a unique source of biologically active molecules that have revolutionised modern medicine. One particularly significant class of natural products is nonribosomal peptides which include a number of clinically essential antibiotics such as penicillin and vancomycin. The ability to synthesise these peptide natural products represents the first step in the development of analogues and is essential in order to improve biological activity and medicinal chemical properties. The development of novel antibiotics with new mechanisms of action is desperately needed as bacteria are rapidly developing resistance to the currently used therapies.

The work described in this thesis represents the first total synthesis of two classes of important bioactive peptide natural products: teixobactin and the skyllamycins. The isolation and structure of teixobactin were first reported in 2015 and possess potent activity against a number of clinically relevant pathogenic bacteria, including methicillin-resistant *Staphylococcus aureus*. Using a solid-phase peptide synthesis approach, the total synthesis of teixobactin was successfully accomplished. Importantly, the synthetic natural product possessed potent activity against a number of gram-positive bacteria. This represented an important breakthrough in how to access teixobactin synthetically, and the technology developed is currently being applied to the generation of analogues.

The second part of this thesis involves the synthetic efforts towards the skyllamycins, a family of modified nonribosomal peptides with bacterial biofilm inhibitory activity. These natural products are highly complex and contain a number of synthetic challenges, including the unusual α-hydroxyglycine moiety. While these natural products were first reported in 2001 no total synthesis had been reported. This work describes the synthesis of four simplified analogues as well as the first total synthesis of a family of skyllamycin natural products. The final step of the total synthesis involved the concomitant cyclisation and formation of the unusual

α-hydroxyglycine. This work has laid the foundation for further synthetic and biosynthetic investigations into this unusual class of natural products, as well as the development of analogues with improved biological activity.

January 2018 Prof. Richard Payne

Abstract

Natural products are an essential source of many modern medicines. Examples of important natural products include the antibiotic penicillin, the anticancer drug taxol, the immunosuppressant cyclosporine and the antimalarial quinine. One significant class of bioactive natural products is nonribosomal peptides (NRPs), and two prototypical members of this class are the extremely important antibiotics, penicillin and vancomycin. Currently, bacterial resistance to antibiotics, including penicillin and vancomycin, is one of the most pressing global health issues. The need for new antibiotics with novel mechanisms of action is paramount. This thesis describes the total synthesis of the recently isolated antimicrobial NRPs teixobactin and skyllamycins A–C. Chapter 2 of this thesis describes the first total synthesis of teixobactin, a novel cyclic NRP antibiotic isolated in 2015. This was carried out *via* a solid-phase peptide synthesis (SPPS) strategy with a late-stage cyclisation reaction. The synthetic natural product possessed potent activity against a number of clinically relevant gram-positive bacterial pathogens. Chapters 3 and 4 describe investigations towards the total synthesis of skyllamycins A–C, a family of structurally complex cyclic NRPs. These natural products inhibit the growth of bacterial biofilms, a mechanism by which bacteria evade antibiotics. The most unusual feature of these natural products is the presence of an α-OH-glycine (Gly) moiety, which to date has only been found in one other linear peptide natural product. Chapter 3 details the synthesis of the non-proteinogenic amino acids present in the natural products and their incorporation into the synthesis of four skyllamycin analogues that omit the unusual α-OH-Gly residue. These analogues were analysed for their biofilm growth inhibition activity. Chapter 4 describes the completion of the first total synthesis of skyllamycins A–C. This was achieved through a SPPS strategy followed by a late-stage cyclisation and concomitant formation of the unusual α-OH-Gly residue in one step.

Parts of this thesis have been published in the following journal articles:

Giltrap, A. M.; Dowman, L. J.; Nagalingam, G.; Ochoa, J. L.; Linington, R. G.; Britton, W. J.; Payne, R. J. *Org. Lett.* **2016**, *18*, 2788–2791.

Giltrap, A. M.; Haeckl, F. P J.; Kurita, K. L.; Linington, R. G.; Payne, R. J. *Chem. Eur. J.* **2017**, *23*, 15046–15049.

In addition to the statement above, in cases where I am not the corresponding author of the published item, permission to include the published material has been granted by the corresponding author.

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