Proceedings of the 36th European Peptide Symposium
Michal Lebl (Editor)
European Peptide Society, 2022 *https://doi.org/10.17952/36EPS.2022.086*

New Generation of Polyethylene Glycol (PEG)-Based Peptidomimetics of Antimicrobial Peptides (AMPs)

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Introduction

Peptidomimetic conversion of Antimicrobial Peptides (AMPs) is one of the main medicinal chemistry approaches currently investigated to improve their therapeutic potential as antibiotic candidates. AMP analogues generated by this approach range from type-1 (*e.g.*, inverso or beta-amino acid peptides and peptoids) to type-3 (*e.g.*, brilacidin) peptidomimetics. Polymer-based mimetics, encompassing functionalised poly(norbornene), poly(acrylic) and nylon-3 backbones, have also been developed [1]. Considering the number of clinically approved polyamide-based biopharmaceuticals including Polyethylene Glycol (PEG) in their structures, we investigated the use of functionalised PEGs as peptidomimetics of AMPs (Figure 1) [2]. These 'pegtides' were produced by co- and post-polymerisation functionalisation of two substituted ethylene oxide monomers, as analogues of cationic and hydrophobic residues in AMPs. This approach has also been independently applied to AMP mimetics produced from three substituted oxirane monomers, allowing the addition of hydrophilic repeating units [3].

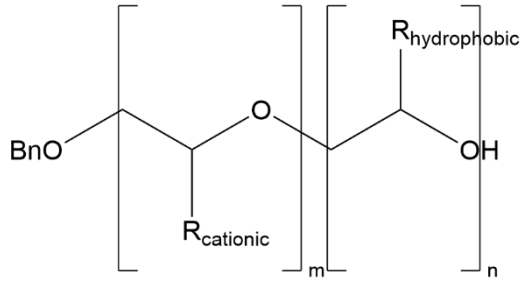

Fig. 1. Structure of the pegtide where $R_{cationic}$ is typically an arginine-like side-chain while $R_{hydrophobic}$ can be, for example, a tryptophan-like or valine-like side-chain.

Preliminary susceptibility and antibiofilm assays performed with the first generation of antimicrobial pegtides, as random copolymers with cationic (guanidyl side-chain) and hydrophobic (n-alkyl/branched/aromatic side-chain) repeating units, showed that the activities of these candidates remained lower than the one of a prototypical AMP ($(Arg\text{-}Trp)_5$ decapeptide), in particular against Gram-negative bacteria. However, the parent peptides of these mimetics were themselves analogues of AMPs, where amino acids commonly found in these amphipathic peptides are replaced by analogous residues (*e.g.*, (2-naphtyl)alanine, in place of tryptophan). To improve the activity of these PEG-based mimetics against both Gram-negative and Gram-positive bacteria, we have developed novel oxirane monomers allowing the preparation of PEG-based copolymers, functionalized with side-chains matching those of amino acids frequently selected in optimised AMP sequences. Their use in the production of novel antimicrobial pegtides is presented here.

Results and Discussion

The monomers were synthesized in a chiral fashion by employing the Sharpless asymmetric dihydroxylation (Figure 2).

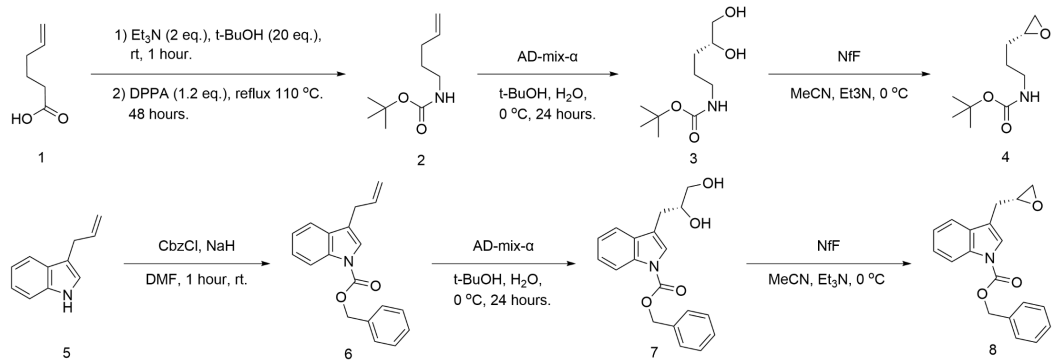

Fig. 2. Reaction schemes for the synthesis of chiral oxirane monomers 4 and 8 bearing protected amino acid side-chain functionalities.

Nonafluorobutanesulfonyl fluoride (NfF) was used to convert the chiral diols to their respective chiral epoxides as standard epoxidation methods could not be employed to compound 6 as the indole ring was extremely susceptible to oxidation. Compound 4 is Boc-deprotected post-polymerization and guanylated to afford the cationic arginine-like residue while compound 8 is complementary Cbz-deprotected by hydrogenation post-polymerization to afford the tryptophan-like residue (Figure 3).

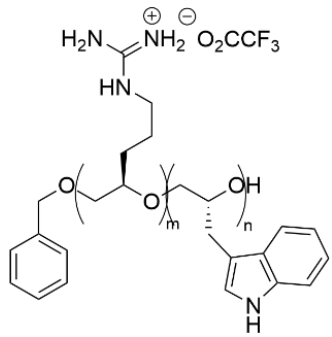

Fig. 3. Structure of the pegtide after post-polymerisation deprotection and guanylation.

Benzyl alcohol is used as an initiator to polymerize compounds 4 and 8 by anionic ring-opening polymerization. The NMR spectra of compounds 4, 8 and the copolymer are shown in figures 4, 5 and 6 respectively.

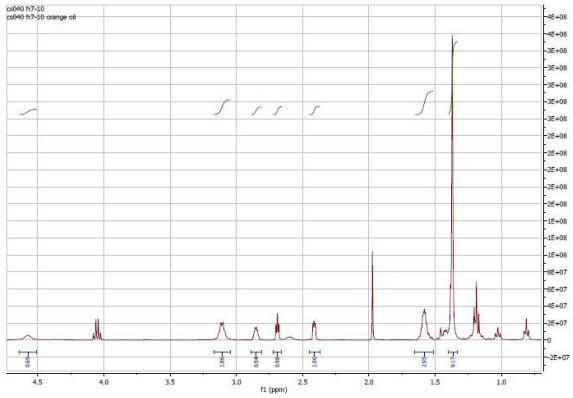

Fig. 4. NMR spectrum of compound 4.

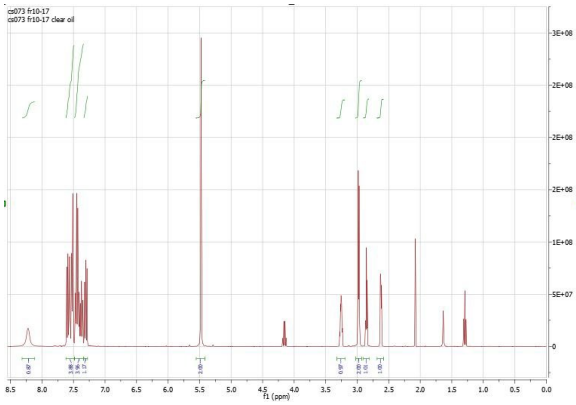

Fig. 5. NMR spectrum of compound 8.

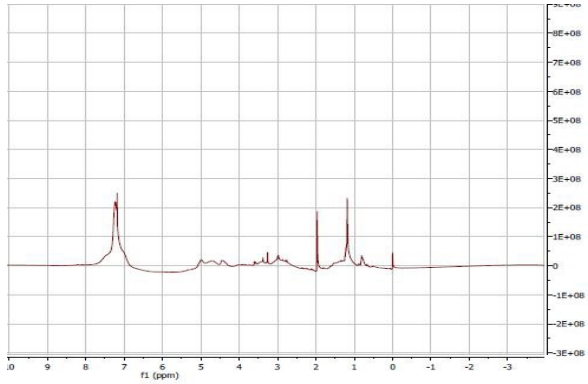

Fig. 6. NMR spectrum of deprotected and guanylated pegtide.

Acknowledgments

This publication has emanated from research conducted with the financial support of Science Foundation Ireland under Grant number 19/FFP/6889.

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