The on-resin synthesis and pharmacokinetic evaluation of Wewakazole B: An anticancer peptide

Jillian Fougere[1], Zainab Bello[1], Wasundara Fernanda[2], Carlie Charron[1]
[1]Dalhousie university, Department of Chemistry
[2]Acadia University, Department of Biology

Abstract
Natural products serve as important lead compounds in drug discovery attributed to their intrinsic biological activity and potential to inspire novel therapeutic agents. Peptides are known to display low toxicity, high selectivity, and high specificity allowing them to be suitable anti-cancer therapeutics. Naturally occurring cyanobactins are a notable class of small cyclic peptides, containing heterocyclics, that produce antimalarial, antitumour, and antibacterial effects. In 2016, Wewakazole B, was isolated from cyanobacterium, *Moorea producens*, found in the Red Sea. This cyclic dodecapeptide contains 3 heterocyclic oxazole rings and is cytotoxic against MCF7 breast cancer and H460 lung cancer cell lines, however, the mode of action is still unknown. Previously established solution phase synthetic schemes for Wewakazole B are not feasible as they require tedious and time-consuming reaction and purification steps resulting in low yields. This study details how solid phase peptide synthesis can be used to synthesize Wewakazole B and first-generation analogues with minimal purification steps, increased yield while investigating their pharmacokinetic properties. Various methods to introduce oxazoles during solid phase synthesis will be showcased. The end goal is to have a complete SAR profile of Wewakazole B and create a library of analogues with optimized cytotoxicity against drug-resistant cancer cell lines.