Medicinal chemistry of cyanobacterial natural products: Synthesis of Majusculamide D analogs

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Majusculamide D (MJS-D) is a lipopentapeptide originally isolated from Lyngbya majuscule, a species of filamentous cyanobacteria, and reisolated from a Moorea sp. MJS-D was found to be responsible for the in vitro activity of a Moorea sp. extract that presented promising selectivity and potency against pancreatic and glioblastoma cell lines. Given its promising biological profile, a scalable total synthesis of MJS-D was designed that produced significant quantities of MJS-D. Our goal is to synthesize analogs of the cytotoxic MJS-D molecule to evaluate their biological activity in cellular assays. Our approach is to disconnect the MJS-D molecule at two key points resulting in three fragments of similar molecular weight that can be synthesized separately and coupled together. Our efforts consist of synthesizing 5 variations of tripeptide backbones (first MJS-D fragment), each with different amino acid units, using peptide coupling reagents to promote amide bond formations and 5 variations of pyrrolylproline fragments (second MJS-D fragment) synthesized via imide coupling. These fragments will then be coupled together along with (2R,4 R)-2,4-Dimethyl Octanoic Acid (third MJS-D fragment) to produce 25 MJS-D analogs. The biological screening of these analogs will allow us to learn more about what specifically gives MJS-D its cytotoxic properties.