Synthesis of Aza-Amanitins to Enhance Cytotoxicity for Targeted Cancer Therapeutics

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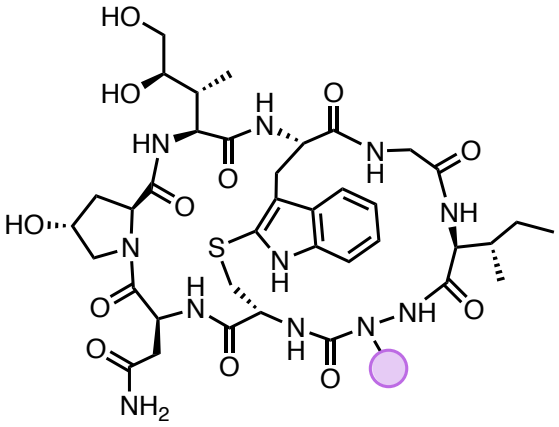
Natural products continue to be a source of potential drugs due to their specificity towards their targets after years of natural selection. α-Amanitin is an example of a unique octapeptide that has excellent specificity for RNA polymerase II. The design and synthesis of amanitin analogs can provide cytotoxic payloads to be used for targeted cancer therapeutics, such as antibody drug conjugates. The azaGly amanitin analog, wherein glycine-7 was replaced by an aza-glycine amino acid, resulted in increased cytotoxicity compared to the natural product. These promising results and the knowledge that aza-amino acids can enhance β-turns in peptides, led to the exploration of functionalized aza-amino acid derivatives. Herein I report a structure-activity relationship study demonstrating the effect of replacing glycine at position 7 with aza-amino acid moieties. Three toxins, AzaVal^7, AzaPentanyl^7, and AzaCycloPentanyl^7 have been synthesized, all of which display comparable cytotoxicity to the natural product, and encouragingly AzaVal^7 was 3x more toxic on HEK293 cells.



Aza-Amanitin Scaffold