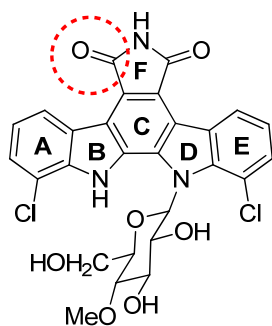


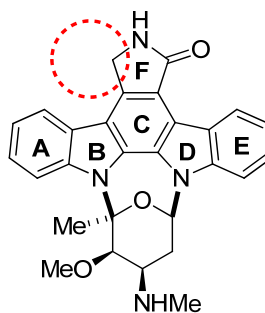
Investigating the Mechanism of Regioselective Oxidation in the Biosynthesis of Indolocarbazoles

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Rebeccamycin and staurosporine are representative members of a large family of natural products, the indolocarbazole alkaloids. Although the biosynthetic pathways responsible for rebeccamycin production in *L. aerocolonigenes* and staurosporine production in *S. longisporoflavus* are strikingly similar, the biological activities of the two compounds are completely different. Rebeccamycin is a potent inhibitor of DNA topoisomerase I ($IC_{50} = 1.75 \mu\text{M}$), whereas staurosporine is among the most effective inhibitors of protein kinase C ($IC_{50} = 2.7 \text{ nM}$). Notable structural differences include the number of glycosidic bonds connecting the sugar moiety to the indolocarbazole aglycon, halogenation, and the oxidation state of ring F. The oxidation state of ring F is determined by the flavin dependent monooxygenases RebC and StaC during the synthesis of rebeccamycin and staurosporine, respectively. Structural differences between the RebC and StaC active sites were hypothesized to account for the formation of the differentially oxidized products. The results of research designed to test this hypothesis will be presented.



Rebeccamycin



Staurosporine