Public Abstract

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Title: STUDIES OF NATURAL PRODUCTS THAT REVEAL NOVEL STRATEGIES FOR EFFICIENT MODIFICATION OF DNA

DNA is the central molecule in cells. The correct function of cells depends on the structure of DNA. DNA damaging natural products often show cytotoxic or mutagenic properties, which many times land them medicinal value as antibacterial or anticancer therapeutics. Efficient DNA modifications by these agents usually endow them with outstanding biological efficiency. In the present dissertation, we investigated novel DNA damaging natural products with novel DNA modification strategies.

We showed that weak noncovalent binding of the natural product leinamycin to DNA accelerates its DNA-alkylation reaction (Chapter 1). We demonstrated that leinamycin intercalates DNA with an unprecedented DNA-intercalating functional group. Likewise, we uncovered novel molecular recognition features of the natural product azinomycin using similar tools (Chapter 4). We characterized novel, reversible chemical reactions of leinamycin (Chapter 3). Amongst these were reversible DNA-alkylation and reversible adduct formation with biologically relevant nucleophiles. We showed that thiols and chloride ion can add to the leinamycin episulfonium ion reveribly to protect it from unproductive hydrolysis and to help its transport to DNA. We synthesized precursors for the biosynthesis of leinamycin (Chapter 5) to prove the principle that synthetic molecules can be incorporated into the biosynthetic machinery of natural products.

We worked with the labile and mutagenic fatty acid metabolite: fecapentaene-12, and clarified its mechanism of oxidative DNA damage. We also showed that this poly-unsaturated hydrocarbon compound binds the DNA duplex noncovalently (Chapter 6).