Derivatization of a Species-Selective Antibiotic for Probing its Mechanism of Action

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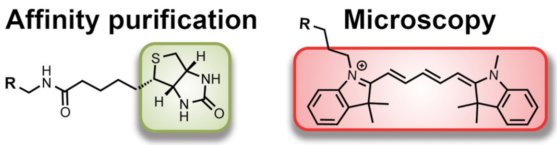
As drug-resistant pathogens pose an increasing threat to human health worldwide, there is a need for new antibacterial compounds with novel and selective targets. Plantazolicin (PZN) is a ribosomally produced peptide with extensive posttranslational modifications that exhibits exquisite selectivity for B. anthracis, the causative agent of anthrax, suggesting a species-specific and novel mechanism of action. In order to determine the molecular target, a structure-activity relationship study of PZN was initiated to identify moieties essential for bioactivity. Synthetically prepared truncations of the polyazole core of PZN displayed broader-spectrum antibacterial activity but were less potent than the full-length natural product, suggesting the cruciality of the polyheterocyclic core in bioactivity. Based on the ability to modify the C-terminus of PZN without significantly affecting bioactivity, biotinylated and Cy5-labeled derivatives of PZN were prepared. The PZN probes are being employed in affinity purification and fluorescence microscopy to demonstrate the unique mechanism of action of PZN.



Atypical Carotenoids as Potent Antilipoperoxidants

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Peroxidation of polyunsaturated fatty acids has been linked to an increasing number of human diseases including, asthma, neurodegenerative diseases and atherosclerosis. We identified three atypical carotenoids isolated from organisms that thrive in environments of extreme oxidative stress and hypothesized that they may be potent antilipoperoxidants. Synthesis and direct comparison of all three atypical carotenoids to astaxanthin, the current gold standard carotenoid antilipoperoxidant, in a human cell model of lipid peroxidation showed that peridinin is a highly potent antilipoperoxidant. Furthermore, we have begun to elucidate peridinin's mechanism of action in a series of liposome and solution phase studies which show that it is a rapid catalytic quencher of lipid peroxy radicals. Finally, solid-state NMR studies have revealed that despite extensive literature depicting astaxanthin in the bilayer, it is localized primarily (>66%) in a large extramembraneous aggregate.