Amphotericin Primarily Kills Human Cells by Binding Cholesterol

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Amphotericin B (AmB) is a clinically vital antimycotic, but is limited by its severe toxicity. Membrane permeabilization via channel formation has been thought to be responsible for AmB's toxicity. To further understand the mechanism of toxicity of AmB, a non-channel forming derivative of AmB, C35deOAmB was synthesized via an improved iterative cross-coupling based synthesis to enable the quantities needed for mechanistic studies. C35deOAmB was found to retain the ability to bind cholesterol like AmB, but no longer had the capacity to form ion channels in human red blood cells and renal proximal tubule cells. However, the channel-inactive derivative still maintained potent toxicity to both human cells. Collectively, these results demonstrate that AmB primarily kills human cells by binding cholesterol and that efforts to improve AmB's therapeutic index should focus on the problem of maximizing AmB's binding selectivity for ergosterol over cholesterol.

Catalytic Enantioselective *syn*-Dichlorination of Alkenes

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Electrophilic chlorination of olefins with chlorine or chlorine equivalent has been studied and utilized for more than a century, providing racemic mixtures of anti-dichloride products. As an extension of the methodology, transformation of alkenes into enantioenriched vicinal dichlorides has been practically unrealized in organic synthesis. Challenges lay in the need for selective installation of the intermediate chloriranium and subsequent selective ring opening. These issues have recently been overcome via catalytic employment of organoselenium compounds. Diaryl diselenides, in the presence of chloride ion and an oxidant, are effective catalysts for the selective conversion of alkenes to *syn*-dichlorides through ring-opening of a seleniranium ion intermediate and subsequent nucleophilic displacement of the selenium center. Appending a chiral Lewis-basic directing group to the aryl ligand on selenium has provided modest enantioenrichment of the dichloride product, providing access to a large variety of chlorinated molecules that are otherwise very difficult to prepare selectively.