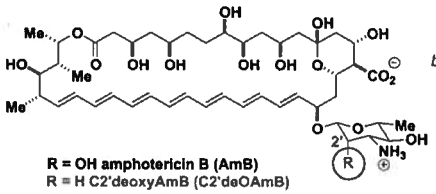
C2'-OH of Amphotericin B Plays an Important Role in Binding the Primary Sterol of Human Cells but Not Yeast Cells

Matthew M. Endo, Brandon C. Wilcock, Brice E. Uno, and Martin D. Burke

The polyene macrolide natural product, amphotericin B (AmB), is the archetype for both small molecules that form ion channels in living cells and antibiotics that are inherently refractory to microbial resistance. However, AmB is also highly toxic, which limits its usage as an antimycotic. Binding ergosterol has been shown to be the primary mechanism of how AmB kills yeast and binding cholesterol is likely the primary mechanism of toxicity in humans. In the leading model, the C2' hydroxyl group of the mycosamine sugar of AmB forms a critical hydrogen bond with both sterols. Surprisingly, the derivative lacking the C2' hydroxyl, C2'deOAmB, still maintained the capacity to bind ergosterol and maintained potent antifungal activity. Even more interestingly, C2'deOAmB showed no evidence of binding to cholesterol and demonstrated no toxicity to human cells. C2'deOAmB represents a powerful probe in the understanding of AmB's mechanism and is a promising candidate as a new antifungal drug.



	AmB	C2'deOAmB
binds ergosterol	✓	✓
binds cholesterol	✓	×
S. cerevisiae	0.5	1
C. albicans	0.25	1
human RBCs	8.5	>500
human renal cells	2.4	>80

toxic dose (μM)

Oxidative Amination of Olefins through Aerobic Palladium Catalysis

Daniel Kohler and Kami L. Hull

Olefins are a prominent functionality found throughout commodity, fine, and specialty chemical industries, as well as being common synthetic organic intermediates. Transition-metals are known to activate alkenes for functionalization reactions; the development of regio-, chemo-, and stereoselective transition metal-catalyzed reactions to achieve selective functionalization of alkenes is of great interests to chemists worldwide.

Herein we report our current findings on the oxidative amination of phthalimide-protected allylic amines through aerobic palladium catalysis. The tunable reaction allows for the formation of either the Markovnikov or anti-Markovnikov products, giving synthetically useful selectivity, with only a slight modification in the conditions. The reaction discovery, optimization, and scope will be discussed.