Semisynthetic Amides of Polyene Antibiotic Natamycin

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Invasive fungal mycoses may affect over 300 million people each year and are responsible for the death of 1.5 million individuals globally. Skin and nail mycoses affect 20–25% of people in the world, which makes them one of the most frequent forms of infection. The most common fungal nosocomial infections are those of endogenous origin, difficult to avoid, because they are caused by opportunistically pathogenic fungi being a part of the human microflora. Natamycin, a macrolide polyene antibiotic, is known for its broad-spectrum antifungal activity and low toxicity. However, its poor bioavailability and limited water solubility restrict its use for systemic mycoses. To overcome these challenges, researchers synthesized seven semisynthetic natamycin amides by modifying the antibiotic's carboxyl group with diamines and a quaternary pyridinium salt (Fig. 1). These derivatives exhibited significantly improved water solubility, with some achieving up to a 1000-fold increase. Among the derivatives, amide 8 stood out for its enhanced potency against Candida auris clinical isolates and reduced toxicity toward mammalian cells, offering a more favorable therapeutic index (LD50/ED50 = 7.4) compared to amphotericin B. Unlike amphotericin B, which forms membrane pores, natamycin and its derivatives primarily act by binding to ergosterol, disrupting fungal cell division. In a mouse model of candidemia, amide **8** provided effective protection, though higher doses were required compared to amphotericin B. Amide **10**, while demonstrating strong antifungal properties, was limited by its high cytotoxicity.

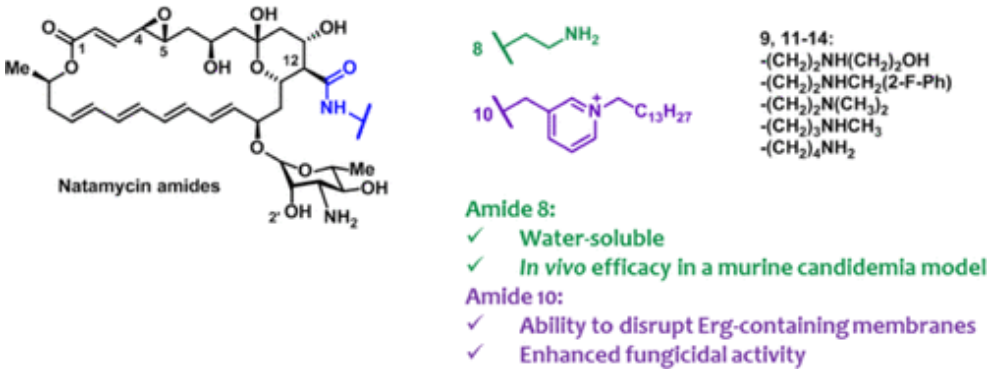

Fig. 1. Chemical structures of semisynthetic natamycin amides.

These findings suggest that amide **8** is a promising candidate for systemic antifungal therapy, though

1. Tevyashova A.N. et al., ACS Infect. Dis. 2023, 9, 1, 42–55, https://doi.org/10.1021/acsinfecdis.2c00237