Search for the new generation of the antifungal drugs based on the polyene antibiotics

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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. Current methods of preventing fungal infections remain unsatisfactory. Amphotericin B (AmB) is the drug of choice for treating the most serious systemic fungal or protozoan infections. Nevertheless, its application is limited by low solubility in aqueous media and serious side effects such as infusion-related reactions, hemolytic toxicity, and nephrotoxicity. Owing to these limitations, it is essential to search for the polyene derivatives with better chemotherapeutic properties. With the objective of searching of a promising drug candidates for the treatment of systemic fungal infections, we synthesized a series of semisynthetic derivatives of natural antibiotics of the AmB group - natamycin, nystatin and AmB.[1,2] The screening of antifungal activity in vitro revealed that N-(2-aminoethyl)amide of AmB (Amphamide) had superior antifungal activity compared to that of the paternal AmB.

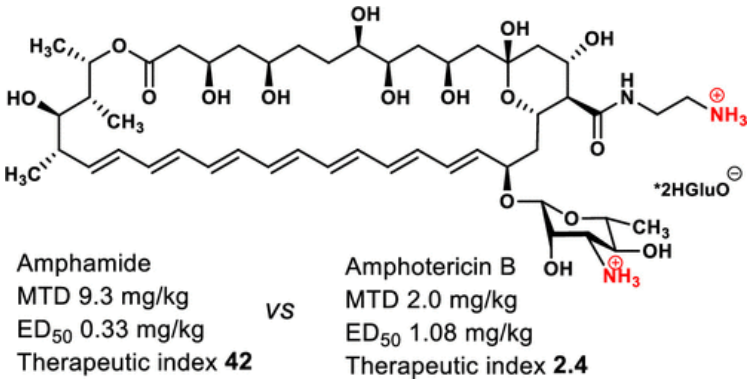

Fig. 1. Chemical structure and biological activity of Ampamide in comparison with AmB.

Preclinical studies in mice confirmed that this compound had a much lower acute toxicity and higher antifungal efficacy in the model of mice candidosis sepsis compared with that of AmB (Fig. 1). Thus, the discovered Amphamide is a promising drug candidate for the second generation of polyene antibiotics and is also prospective for in-depth preclinical and clinical evaluation.

1. Tevyashova A.N. et al., ACS Infect. Dis. 2020, 6, 8, 2029–2044. https://doi.org/10.1021/acsinfecdis.0c00068

2. Tevyashova A.N. et al., Antibiotics 2023, 12(1), 151. https://doi.org/10.3390/antibiotics12010151