

Molecular Umbrellas Modulate the Selective Toxicity of Polyene Macrolide Antifungals

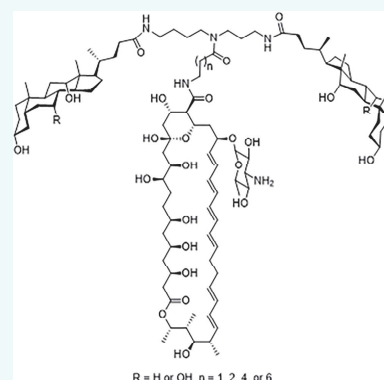
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S Supporting Information

ABSTRACT: Antifungal polyene macrolide antibiotics Amphotericin B (AmB) and Nystatin (NYS) were conjugated through the ω -amino acid linkers with diwalled “molecular umbrellas” composed of spermidine-linked deoxycholic or cholic acids. The presence of “umbrella” substituents modulated biological properties of the antibiotics, especially their selective toxicity. Some of the AmB-umbrella conjugates demonstrated antifungal in vitro activity comparable to that of the mother antibiotic but diminished mammalian toxicity, especially the hemolytic activity. In contrast, antifungal in vitro activity of NYS-umbrella conjugates was strongly reduced and all these conjugates demonstrated poorer than NYS selective toxicity. No correlation between the aggregation state and hemolytic activity of the novel conjugates was found.



INTRODUCTION

Disseminated (invasive) fungal infections remain one of the major problems in modern chemotherapy. The estimated number of cases is more than 2 million/year worldwide, with over 1.5 million deaths.¹ *Candida* species are the most common fungal etiological agents of life-threatening invasive infections in immunocompromised hosts, transplant recipients, and patients hospitalized in intensive care units. These species are also the fourth most common cause of nosocomial (hospital-acquired) bloodstream infections.² The high mortality rate of invasive mycoses is due to several factors, including shortcomings in diagnosing, a limited number of effective antifungal chemotherapeutics, and increasing fungal resistance to available drugs. Polyene macrolide antibiotics constitute an important group of antifungals, of which Amphotericin B, Nystatin, and Pimaricin are the approved drugs, but only the first is used for the treatment of invasive fungal infections. Nystatin (NYS) and Pimaricin are used exclusively for the topical applications. Amphotericin B (AmB) is known as a “gold standard” of antifungal chemotherapy, since it is fungicidal and demonstrates broad antifungal spectrum and lack of fungal resistance. The only (but important) drawback is its substantial mammalian toxicity, especially nephrotoxicity, which is a consequence of the mechanism of biological action.

Currently there are two major hypotheses about this mechanism. According to the “barrel-stave-pore” mechanism, AmB molecules form complexes with ergosterol in the membrane and a few such complexes (4–12) self-assemble to barrel-stave-like trans-membrane pores, giving rise to leakage of

low-molecular-weight cell components, including ions.³ In an alternative mechanism, called a “sterol sponge” model, AmB extracts ergosterol from the hydrophobic interior of a fungal membrane and deposits it on the membrane’s outer leaflet as single complexes or a “pile” of complexes.^{4,5} In both mechanisms, binding of AmB to ergosterol is the prerequisite for antifungal action but the antibiotic also binds to cholesterol in mammalian cell membranes. This is only a slightly higher affinity to ergosterol than to cholesterol that constitutes a molecular basis for selective toxicity of AmB. As a consequence, the minimal concentration at which AmB is toxic to mammalian cells is only 5–10 times higher than the minimal fungicidal concentration. Mechanism of antifungal action of NYS is much less known, although there is little doubt that binding to ergosterol is also crucial for the biological activity of this antibiotic. AmB, as other polyene macrolides, is poorly soluble in aqueous solutions. The monomeric form of AmB exists in water at concentrations below 10^{-6} M. At higher concentrations, AmB undergoes complex processes of self-association and formation of dimers and soluble oligomers. Finally, at concentrations higher than 10^{-5} M insoluble aggregates are observed. It was shown that water-soluble aggregates of AmB are toxic to erythrocytes and fungal cells, while the monomers are toxic only to fungal cells.⁶

It is believed that selective toxicity of polyene macrolides, especially AmB, can be improved by a proper chemical

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