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RESEARCH ARTICLE

The Substantial Improvement of Amphotericin B Selective Toxicity Upon Modification of Mycosamine with Bulky Substituents

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Abstract: ***Background*:** It is assumed that the unfavorable selective toxicity of an antifungal drug Amphotericin B (AmB) can be improved upon chemical modification of the antibiotic molecule.

***Objective*:** The aim of this study was verification of the hypothesis that introduction of bulky substituents at the amino sugar moiety of the antibiotic may result in diminishment of mammalian *in vitro* toxicity of thus prepared AmB derivatives.

***Methods*:** Twenty-eight derivatives of AmB were obtained upon chemical modification of the amino group of mycosamine residue. This set comprised 10 *N*-succinimidyl-, 4 *N*-benzyl-, 5 *N*-thioureidyl- and 9 *N*-aminoacyl derivatives. Parameters characterizing biological *in vitro* activity of novel compounds were determined.

***Results*:** All the novel compounds demonstrated lower than AmB antifungal *in vitro* activity but most of them exhibited negligible cytotoxicity against human erythrocytes and three mammalian cell lines. In consequence, the selective toxicity of majority of novel antifungals, reflected by the selective toxicity index (STI = EH_{50}/IC_{50}) was improved in comparison with that of AmB, especially in the case of 5 compounds. The novel AmB derivatives with the highest STI, induced substantial potassium efflux from *Candida albicans* cells at concentrations slightly lower than IC_{50}s but did not trigger potassium release from human erythrocytes at concentrations lower than 100 μg/mL.

***Conclusion*:** Some of the novel AmB derivatives can be considered promising antifungal drug candidates.

Keywords: Antifungal agent, amphotericin B, chemical modification, selective toxicity, hemotoxicity, potassium efflux.

1. INTRODUCTION

Polyene macrolide antibiotics constitute the group of the most potent broad-spectrum antifungals. A member of this group, heptaenic macrolide Amphotericin B (AmB), is the drug of choice for the treatment of disseminated fungal infections, especially in immunocompromised patients [1]. This antibiotic, consisting of a large polyene macrolide ring and an amino sugar mycosamine, combines most of the features expected for an "ideal" antifungal chemotherapeutic, including the high antifungal efficacy at low drug concentration, broad antifungal spectrum covering the multidrug-resistant fungal species, a fungicidal mode of action and a very limited potential of inducing fungal specific resistance [2]. The important disadvantage of AmB is its substantial mammalian toxicity, being a consequence of mechanism of antibiotic action. According to the two hypotheses on this mechanism, the "barrel-stave-pore" [3] and a "sterol sponge" [4], binding of AmB to sterol present in the fungal or mammalian cell membrane is the necessary condition for its biological effect. In the "barrel-stave-pore" mechanism, AmB:sterol complexes assemble into transmembrane barrel-like pores facilitating efflux of monovalent ions, especially K^+. This efflux, causing impairment of membrane barrier function, is considered a primary effect leading to cell death. A slightly higher affinity of AmB to fungal ergosterol than to mammalian cholesterol constitutes a molecular basis for the selective toxicity of this antibiotic [5]. In consequence, the therapeutic window of AmB is very narrow. This disadvantage has been only in part overcome upon construction of AmB complexes with lipids or liposomal formulations, such as Abelcet®, Amphotec® or AmBisome®, at the price of a substantial rise in treatment cost [6].

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