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Facilitated diffusion of glucosamine-6-phosphate synthase inhibitors enhances their antifungal activity.

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Abstract

N3-(4-Methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP) and 2-amino-2-deoxy-D-glucitol-6-phosphate (ADGP) are strong inhibitors of the essential fungal enzyme, glucosamine-6-phosphate synthase, but their antifungal activity is poor, due to slow penetration of these agents through the cytoplasmic membrane. In the present studies we have exploited the possibility of enhancement of ADGP and FMDP antifungal activity by improving their transport properties. It has been found that membrane-permeabilising polyene macrolides amphotericin B (AMB) and its N-methyl-N-fructosyl methyl ester derivative (MF-AME), at subinhibitory concentrations, facilitate diffusion of ADGP through the fungal cell membrane, thus allowing a decrease of its minimal inhibitory concentration (MIC). Synergistic effects have been observed for combinations of ADGP with AMB or MF-AME. Fractional inhibitory concentration (FIC) indexes, determined against a number of Candida spp., have been in the 0.18-0.81 range. Weak antifungal synergistic effects have been found for combinations of FMDP with AMB or MF-AME. ADGP can be easily encapsulated into unilamellar lipid vesicles. Liposomal preparations of ADGP demonstrated stronger antifungal activity against some fungal strains than free ADGP.

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