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A diffusible analogue of N(3)-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid with antifungal activity.

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Abstract

N(3)-(4-Methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), a specific and potent inactivator of glucosamine-6-phosphate (GlcN-6-P) synthase from Candida albicans, exhibits relatively poor anticandidal activity, with an MIC value amounting to 50 microg ml(-1) (200 microM). Uptake of FMDP into C. albicans cells follows saturation kinetics and is sensitive to the action of metabolic inhibitors, thus indicating the active transport mechanism. However, the acetoxymethyl ester of FMDP penetrates the fungal cell membrane by free diffusion and is rapidly hydrolysed by C. albicans cytoplasmic enzymes to release the free FMDP. This mechanism gives rise to continuous accumulation of the enzyme inhibitor and results in higher antifungal activity of the FMDP ester (MIC=3.1 microg ml(-1), 10 microM). These results show that the 'pro-drug' approach can be successfully applied for the enhancement of antifungal activity of glutamine analogues that inhibit GlcN-6-P synthase.

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