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Article

Antifungal Activity of Homoaconitate and Homoisocitrate Analogs

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Abstract: Thirteen structural analogs of two initial intermediates of the L-α-aminoadipate pathway of L-lysine biosynthesis in fungi have been designed and synthesized, including fluoro- and epoxy-derivatives of homoaconitate and homoisocitrate. Some of the obtained compounds exhibited at milimolar range moderate enzyme inhibitory properties against homoaconitase and/or homoisocitrate dehydrogenase of *Candida albicans*. The structural basis for homoisocitrate dehydrogenase inhibition was revealed by molecular modeling of the enzyme-inhibitor complex. On the other hand, the trimethyl ester forms of some of the novel compounds exhibited antifungal effects. The highest antifungal activity was found for trimethyl *trans*-homoaconitate, which inhibited growth of some human pathogenic yeasts with minimal inhibitory concentration (MIC) values of 16–32 μg/mL.

Keywords: homoisocitrate; homoaconitate; synthesis; inhibitors; molecular modeling; antifungal activity

1. Introduction

Microbial resistance to antibiotics and synthetic drugs is an emerging challenge for clinicians and the pharmaceutical industry. The multidrug-resistant fungi are the major cause of failure in chemotherapy of disseminated mycoses [1,2]. Thus, the need for novel antifungals is especially urgent.