

**THE ANTIFUNGAL ACTIVITY OF DMAL AND PYG CLASS
LYSOSOMOTROPIC DRUGS RESULTED FROM THEIR EFFECT ON
CELL MEMBRANES**

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Lysosomotropic drugs accumulate by ion trapping inside fungal vacuoles, where they exert potent antifungal activity. Newly-synthesized DMAL and PYG class compounds (N,N-disubstituted glycine and alanine esters) with a potential lysosomotropic mode of action inhibit the growth of model yeast strains – *Saccharomyces cerevisiae*, *Shizosaccharomyces pombe*, *Rhodotorula glutinis* - and pathogenic clinical isolates – *Candida albicans*, *Candida tropicalis* and *Trichosporon cutaneum*. This effect is dependent on external pH (it is maximal at pH = 8.0) and the alkyl chain length (4-16 carbon atoms). The most active compounds were those with 12 and 14 carbon atoms in their alkyl chain (MIC of 10 µM after 72 h incubation). This probably reflects their strongest effect on plasma membrane lipids and possibly also on enzymes.

This activity dependence on external pH points to the following mode of action. The unprotonated forms of the compounds penetrate readily through the plasma membrane. The compounds accumulate in acidic vacuoles where they become protonated and acquire a net positive charge, preventing them from leaving the vacuoles. Once accumulated in the vacuoles, the compounds disrupt their structure and thereby cause cell damage.

S. cerevisiae was more sensitive to these compounds than pathogenic yeast-like strains (especially *C. albicans*). The different susceptibility of fungal strains to the compounds can reflect the different lipid composition of their plasma membrane. New compounds with higher potency against fungal pathogens are being synthesized. Since these compounds also exert a surfactant action, they can be used as an efficient means of treatment of mycoses.

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