

**THE MODULATION OF MULTIDRUG RESISTANCE BY NEWLY-SYNTHEZIZED PHENOTHIAZINE DERIVATIVES**

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The active efflux of antifungal, antibacterial and anticancer drugs by broad-specificity multidrug resistance (MDR) transporters is a major obstacle to successful chemotherapy of infectious diseases and cancer. The development of new antibiotics not affected by MDR transporters and efflux pump inhibitors to be used in combination with existing drugs are the major strategies to increase the efficiency of chemotherapy.

The azoles: fluconazole, itraconazole and ketoconazole are among the few antifungal agents suitable to treat often deadly systemic fungal infections. An increase in the incidence of such infections has occurred due to the global AIDS pandemic, the use of immunosuppressive drugs in transplant patients and anticancer chemotherapy.

*Candida albicans*, responsible for the majority of human fungal infections has become increasingly resistant to azoles, due to the overproduction of the MDR transporters Cdr1p and Cdr2p. Resistance in the baker's yeast *Saccharomyces cerevisiae* to a broad range of azoles is mediated by their structural and functional homologues Pdr5p and Snq2p, which are overproduced in several multidrug-resistant mutants.

Although numerous new compounds which potentiate the toxicity of anticancer drugs by the inhibition of the human MDR1 transporter have been identified, little is known about such fungal drug pump inhibitors.

We present the antifungal and ketoconazole resistance reversing activity of a series of newly-synthesized phenothiazine derivatives against *Saccharomyces cerevisiae*. The compounds with a free amino group were the most active, and potentiated a ketoconazole growth inhibitory effect at micromolar concentrations.