9H-BENZOPHENOXAZIN-9-ONE (PX8) IS A POTENT MODULATOR OF MULTIDRUG TRANSPORTER Cdr1p MUTANT OF *Candida albicans*

K. ŚRODA, M. KOŁACZKOWSKI, A. B. HENDRICH, N. MOTOHASHI, M. KAWASE, K. MICHALAK

Wrocław Medical University, Poland

Candida drug resistance protein 1 (Cdr1p) belongs to the ATP binding cassette (ABC) superfamily of transporters. Increased expression of this protein plays an important role in azole antifungal resistance in *Candida albicans* infections. Molecular mechanisms that govern the function of Cdr1p as an efflux pump for azoles are not well understood.

For detailed structural and functional analysis a point mutation was introduced in Cdr1p. We have examined newly synthesized phenoxazine 9H-benzophenoxazin-9-one (PX8) for modulation of drug resistance using wild type Cdr1p and mutant overproduced in *Saccharomyces cerevisiae* strains. PX8 displayed strong antifungal activity in yeast mutant but not in wild type strain. Antagonistic action of ketoconazole in relation to this compound was also observed. It is important, that PX8 did not change the sensitivity of wild type strain to ketokonazol. The changes in the plasma membrane lipid composition were sometimes reported to be responsible for a reduced intracellular accumulation of drugs. Therefore, we decided to study in influence of PX8 on model lipid membranes. To characterize the influence of 9H-benzophenoxazin-9-one on the model lipid bilayer we carried out fluorescence spectroscopy and microcalorimetry studies. Experimental results allowed us to conclude that PX8 alters the properties of the gel state of lipids to a lesser extent than the liquid-crystaline state.