

**PHENOTHIAZINE MALEATES – PUTATIVE MDR MODIFIERS –
DECREASE THE FLUIDITY OF MODEL PHOSPHATIDYLSERINE
MEMBRANES**

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Multidrug resistance (MDR) of cancer cells to chemotherapeutic agents is a major obstacle to successful cancer treatment. A large number of drugs (among them phenothiazines) have been shown to modify or reverse MDR. The proposed mechanism of their action is through the inhibition of multispecific transmembrane transporters (e.g. P-glycoprotein, MRP1), however drug interactions with lipid bilayers may also be of great importance. Our previous fluorescence spectroscopy and microcalorimetry studies showed that phenothiazines interact with lipids and change the properties of model membranes. The aim of this study is to check their membrane activity using fluorescence spectroscopy with the probe 1,6-diphenyl-1,3,5-hexatriene (DPH). Six newly-synthesized phenothiazine maleates with different substituents in their tricyclic ring were studied. All the compounds strongly influenced model membranes composed of bovine brain phosphatidylserine. The polarisation degree of DPH measured in the presence of phenothiazines was higher than for pure lipid. Such a change suggests the rigidifying influence of phenothiazine maleates on model phosphatidylserine membranes. Quenching of DPH fluorescence by phenothiazine maleates was also observed. The membrane activity of phenothiazine maleates was found to be strongly dependent on the chemical modification of the drug, particularly on substitutions in position 2 of the tricyclic ring. The derivatives with CF₃ in this position were the most efficient, whereas H- and Cl-substituted compounds were less active, both exerting a similar effect on model membrane fluidity. The length of the alkyl bridge connecting the phenothiazine nucleus with the amino group was also important, derivatives with a 4C bridge being more potent than 3C bridge derivatives. A correlation was found between these results and the phenothiazines' ability to quench the fluorescence of N-phenyl-1-naphthylamine (NPN) in the model lipid bilayers.