

**THE ROLE OF PHENOTHIAZINE RING SUBSTITUTION
STRUCTURE IN THE INTERACTION OF PHENOTHIAZINE
DERIVATIVES WITH ZWITTERIONIC LIPIDS**

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Phenothiazines (e.g. chlorpromazine and trifluoperazine) are well known as potent antipsychotic drugs. Apart from this traditional medical usage in recent years they have also been found to possess certain anticancer properties. They modulate the activity of P-glycoprotein (P-gp), a protein responsible for the active outward transport of drugs from cancer cells. According to the vacuum cleaner hypothesis, drugs that passively move into the cell through a lipid bilayer do not reach the cytoplasm but are bound to the protein binding sites located in the inner leaflet of the cell membrane. In keeping with this model, it is very likely that the biophysical properties of the membrane should influence the effectiveness of P-gp modulation by phenothiazines. Although the relationship between the molecules' structure and its biological activity has been studied for phenothiazine derivatives, our present level of knowledge about their interactions with the lipid phase of the membranes is small. The aim of this study was to investigate – using microcalorimetry – the role of phenothiazine derivative structure in interactions with zwitterionic lipids: dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylethanolamine (DMPE).

Phenothiazine maleates (PM), which differ in the type of group substituting the phenothiazine ring in position 2 (-H, -Cl, -CF₃), when mixed with the studied lipids, changed the parameters of their thermotropic main phase transition. The character of the observed changes suggests that the studied PMs penetrate the bilayer and are presumably located at the polar/apolar interface of the lipid leaflet. In terms of their effect on phase transition change, the PMs could be ranked in the order: CF₃ > H > Cl substituted. Our opinion is that the difference in effect of the studied PMs relates to their location in lipid bilayer, which in turn depends on the type of phenothiazine ring substituent. Depending on its size, the substituting group perturbs the interactions between the lipid polar heads and thus influences the thermal phase behavior of the lipid. The fact that CF₃-substituted PM has the highest activity concurs with data obtained in structure-bioactivity studies.