Characterization of physicochemical properties of model biological membranes modified by 5-*n*-alkylresorcinols

5-*n*-alkylresorcinols belong to a group of naturally occurring long-chain 1,3-dihydroxy-5-alk(en)ylbenzenes. They are present mainly in plants and bacteria. Alkylresorcinols are consumed in our daily diet. In particular, a rich source of saturated and unsaturated homologs of alk(en)ylresorcinols with variable length of the hydrocarbon chain are cereals. They contain saturated, mono- and diunsaturated homologs with an odd number of carbon atoms in aliphatic chains (eg, in the rye: C13 to C27). Numerous studies have confirmed a broad spectrum of biological activities of alk(en)ylresorcinols. They possess antibiotic, antifungal, and antitumor activities. Additionally, they may protect cellular lipids from oxidation processes and are non-toxic to animals. Alk(en)ylresorcinols, as amphiphilic compounds, have the ability to incorporate into lipid bilayer structures of both natural and model membranes and alter membrane properties and functions.

Alkylresorcinols showed the inhibitory effect on lipoxygenase and influence the metabolism of fatty acids and phospholipids. Other studies indicated a correlation between declined consumption of alky(en)ylresorcinols and the appearance of colon cancer. The *in vitro* studies have shown that resorcinolic lipids decrease a level of triglycerides.

A number of biological activities of alky(en)ylresorcinols may depend on their influence on the structure and physicochemical properties of lipid membranes. Because of still insufficient knowledge about the effect of alkylresorcinols on the structure and physicochemical properties of lipid membranes, further investigations are needed.

The main aim of this dissertation was characterization of the interactions between long-chain homologues of saturated alkylresorcinols (C15:0 - C25:0) and dipalmitoylphosphatidylcholine (DPPC) molecules and their effect on the thermotropic phase transition of alkylresorcinol-doped DPPC liposomes, as well as membrane hydration, formation of hydrogen bonds between alkylresorcinol and phospholipid molecules, the presence of phase separation and the size of alkylresorcinol-DPPC aggregates.

To evaluate the effect of alkylresorcinols on phospholipid bilayer microcalorimetric and spectroscopic (FTIR and fluorescence) techniques and chemometric analysis was used.
I started my research from a determination of the $\log P_{o/w}$ parameter and their melting point temperature. The melting temperature increased with an increase in the length of the aliphatic chain of alkylresorcinol molecules. An increase in hydrophobicity of examined compounds was observed as a function of the length of the hydrocarbon chain of alkylresorcinols. In addition, the obtained $\log P_{o/w}$ parameters may indicate detergent-like

properties of alkylresorcinols. Laurdan fluorescence study showed a shift of temperature of the main phase transition of DPPC liposomes doped with resorcinolic lipids with a different concentration. An increase in the membrane concentration of alkylresorcinols resulted in an increase in dehydration and stiffening of the bilayer. In addition, non-significant changes were observed due to the presence of alkylresorcinols in DPPC liposomes enriched with cholesterol. The results obtained for all tested liposomes excluded phase separation.

The independent analysis of the three vibrational regions (vCH2, vC=O, δCH2) of infrared spectra showed an increase in conformational relaxation (sharp increase in a content of gauche conformers) at a temperature of the main phase transition of the DPPC liposomes. At the same time, a disturbtion of in the hexagonal packing of the alkyl chains of the lipid bilayer and an increase in hydration of the lipid ester groups were shown. In the presence of homologs of alkylresorcinols those three processes were still occurring simultaneously, however, the temperature of the main phase transition was shifted toward higher temperatures in comparison to the DPPC liposomes. Additionally, we observed a decrease in cooperativity of the hydrocarbon chain melting as a function of an increase in the length of the side chain of incorporated alkylresorcinols.

Infrared studies of dry DPPC films doped with alkylresorcinol homologs showed a decrease in melting temperature compared to the value obtained for pure DPPC. In dry conditions, the hydrogen bond formation between the OH groups of alkylresorcinol molecules and the DPPC phosphate moiety was observed. Microcalorimetric studies have shown broadening and vanishing of the main phase transition of both tricosylresorcinol(C23:0)- and pentacosylresorcinol(C25:0)-mixed DPPC liposomes, which was also observed in ATR-IR studies. Alkyloreorcinol homologs influenced the size of resorcinol-mixed liposomes. The size of liposomes decreased as a function of an increase in the length of the aliphatic chain in the alkylresorcinol molecules.

The results presented in this thesis allowed me to characterize the physicochemical properties of model lipid membranes modified by the homologs of the alkylresorcinols. Determination of the above-mentioned structural and physicochemical parameters allowed to approximate the membrane-dependent mechanism of biological activity of resorcinolic lipids.