# ABSTRACT

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Doctoral Thesis: Synthesis of photoactive derivatives of phthalocyanines and study of their biological activity

Phthalocyanines (Pc) are macrocyclic compounds with conjugated system of double bonds with absorption maximum around 650 – 750 nm. They are characterized by high singlet oxygen production which makes them suitable candidates for photosensitizers in photodynamic therapy. However, they form inactive aggregates in water environment because of their planar hydrophobic aromatic core. There are many strategies to solve this problem, and this thesis is focused on fighting aggregation of Pc by their supramolecular interactions with cucurbiturils (CB). Subphthalocyanines (SubPc) are similar macrocyclic compounds composed of only three (instead of four) isoindol units with boron as a central atom, which has also axial substituent. Because of their cone-shape and axial substituent they are less aggregated in water but usually not very soluble, which could also be solved by interaction with CB.

First part of this thesis was focused on synthesis of Pc with aminoadamantyl substituents on macrocyclic core in $\alpha$ or $\beta$ position, because 1-aminoadamantane forms strong supramolecular complexes with CB[7]. It was followed by study of interaction of phthalonitrile precursors and also Pc with CB[7]. Phthalonitrile precursors formed stable complex with CB[7] in ratio 1 : 1 with association constants around $10^{12}$ $M^{-1}$. This interaction was detected by NMR titrations where signals of adamantane hydrogens were significantly shifted upon complexation. Interaction between Pc and CB[7] was monitored by NMR and by changes in absorption and fluorescence spectra. All Pc were aggregated in water ($\beta$ substituted were more aggregated compared to $\alpha$ substituted Pc) and significant improvement in monomerization of Pc was observed after gradual addition of CB[7]. Pc-CB[7] complex had lower log P values compared to just Pc, which indicated higher hydrophilicity of the complex. Biological *in vitro* studies did not confirm higher photodynamic activity expected as a result of improved monomerization of Pc-CB[7] complex. It was due to highly hydrophilic Pc-CB[7] complex which was not able to go into cells.

Second part of this thesis was focused on synthesis of SubPc with aminoadamantyl substituents on macrocyclic core and bulky lipophilic substituent in axial position, which was expected to help in intercalation of SubPc-CB[7] complex into cell membrane. Results of fluorescence spectroscopic studies of SubPc-CB[7] complex were inconsistent and even though with one compound there were some changes in its fluorescence spectrum, it was not possible to determine under what conditions the complex is formed. *In vitro* biological testing was not successful, because only no SubPc had any activity against cells, either alone or after addition of CB[7].

Third part of this thesis was focused on synthesis of α-aminophthalocyanines with absorption maximum in near IR region and then study of their properties in acid environment. In the presence of acid there is a protonation of nitrogens of peripheral amines and then also protonation of azomethine nitrogens of the macrocycle.

The last part of this thesis was focused on light-triggered release of cargo from liposomes. Drug delivery systems, such as liposomes or nanoparticles, can improve drug properties and they are being used more and more frequently. Release of the drug from these systems is often non-specific, therefore new drug delivery systems are developed which could release drugs after initial impulse such as light, pH or temperature. In this work, two types of liposomes (EYPC, DOPC) were tested, with two different cargos (basic orange 14 and doxorubicin). Different amphiphilic Pc intercalated into liposomal membrane were tested. They produced singlet oxygen after irradiation, which was responsible for disruption of liposomes and subsequent cargo release. Apart from amount of singlet oxygen, also other factors contributed to rate of release, such as level of aggregation or absorbance in excitation wavelength of Pc. Both cargos were released faster from DOPC liposomes due to more double bonds in lipid structure which are more susceptible to oxidation by singlet oxygen.