PHD THESIS ABSTRACT

PHOTOSWITCHABLE SMALL-MOLECULE AND MACROMOLECULAR SYSTEMS FOR BIOMEDICAL APPLICATIONS

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Adverse effects are a result of the lack of selectivity in drug action. Minimizing these effects is one of the key challenges in modern medicine. This dissertation presents a photopharmaceutical approach to this issue through the use of so called photoswitches, which enable precise control of drug activity in both time and space using light. Photopharmacology, is a new field of pharmacology encompassing drugs which can be activated and/or deactivated with visible light. It offers unique solutions that enhance the efficacy of the therapy. By employing light of a specific wavelength, it becomes possible to achieve therapeutic effects selectively in the target area and in the optimal time, thereby reducing the risk of adverse effects.

This work presents the synthesis of an arylazopyrazole photoswitch PS1, featuring high stability of its *cis* photoisomer and reversible and almost quantitative photoisomerization when exposed to near UV or visible light. The PS1 photoswitch was applied to modify three biologically active compounds, i.e., cisplatin (an anticancer drug), heparin (a polymeric anticoagulant of natural origin), and a sulfonate synthetic block polymer with anticoagulant properties.

In cancer therapy, one of the most widely used drugs is cisplatin, a platinum(II) complex. Cisplatin-based therapy is often accompanied with severe adverse effects. They could potentially be avoided or at least minimized if the cytotoxicity of cisplatin to cancerous and normal cells could be selectively controlled in both time and location. To achieve this goal a new photoswitchable complex (*cis*-$PtCl_2(PS1)_2$) was synthesized and comprehensively characterized. It is an analogue of cisplatin in which the ammonia ligands were replaced with PS1 photoswitch ligands. This new compound shows a photocontrolled cytotoxicity, i.e., its toxicity can be precisely increased or decreased by irradiation with light of appropriate wavelengths. The studies have thus shown that the complexes of this type can be potentially

applicable in the treatment of cancers localized in areas which can be conveniently directly irradiated, e.g., skin cancers or in organs accessible to endoscopic irradiation.

Heparin, a natural polysaccharide with an anticoagulant activity, is crucial in preventing and treating thromboembolic disorders. This dissertation also presents research on photoswitchable heparins. Modifying the structure of unfractionated heparin (UFH) with the PS1 photoswitch allowed achieving some control over its biological properties. For instance, the *trans* photoisomer of the modified UFH stimulated the proliferation of murine fibroblasts 3T3-L1, while its *cis* photoisomer inhibited their growth. Unfortunately, the photocontrol over anticoagulant properties of UFH was not achieved. However, it was gained in the case of the third photopharmaceutical system developed, which were anticoagulant block polymers consisting of poly(sodium styrene sulfonate) (PSSS) block and poly(acrylic acid) (PAA) block functionalized with the PS1 photoswitch. The studies have shown that nonirradiated polymers prolonged the activated partial thromboplastin clotting time (aPTT) of a sample of Wistar rat blood. Irradiation of the sample with 365 nm, which induced the *trans*-*cis* polymerization of the polymeric photoswitch, significantly reduced anticoagulant activity of the polymer, observed as substantial decrease of aPTT which returned to near-normal level. On the other hand, subsequent irradiation of that sample with 530 nm light, stimulating *cis*-*trans* photoisomerization of the polymeric PS1 photoswitch restored the anticoagulant properties of the polymer. It was therefore shown that it is possible to change in both directions the anticoagulant properties of the polymers substituted with a photoswitch.

These findings identify new possibilities for targeted cancer therapy and blood clotting control using light. The application of photoswitches enables the development of drugs that can be activated only at specific time and location, thus minimizing adverse effects and improving therapeutic efficacy. Particularly promising are the results obtained for the photoswitchable platinum complex, which holds potential for cancer treatment, and the photoswitchable anticoagulant block polymers, which could be utilized for dynamic and precise blood clotting control during surgical interventions.