Chemical and enzymatic modifications of betulin A ring in the synthesis of cytotoxic derivatives.

White birch bark, a waste product of paper industry, is an extremely rich source of **triterpenes** from the lupane family. Their contents are up to 30% of dry mass and lupanes may be easily isolated by a simple extraction with organic solvents. The main component of so called lupane fraction is betulin; lupeol and betulinic acid are isolated in smaller amounts. Lupane-type triterpenes as well as crude birch bark extract are proven to have a variety of biological applications, among them the most interesting are anti-tumor and anti-HIV uses, while their toxicity is usually relatively low. However, low solubility in bodily fluids limits their use as drugs. It is well known, that the attaching of sugar moieties to organic compounds significantly increases their solubility in water. Compounds in which hydrophilic mono- or oligosaccharides are attached to a hydrophobic triterpene by glycosidic bond are well known as **saponins**. Saponins are widely distributed in nature as common components of plants. They have interesting biological activity and are used in folk medicine as raw extracts, and also in pharmaceutical and cosmetic industries.

Proposed research program should increase our knowledge on the synthesis and biological activity of new lupane derivatives obtained from natural compounds. The main goal of the presented project is elaboration of effective synthetic methods which will allow us to prepare new terpenes and saponins based on their structure by degradation and modification of betulin and betulinic acid A ring. Detailed study on regioselectivity of chemical and enzymatic esterification of lupanes with cinnamic acid and its congeners will be conducted. All new compounds will be tested for anticancer activity. Also, the relationships between structure and activity will be studied.

During realization of this project we propose:

1. elaborate new synthetic methods for modification and degradation of betulin and betulinic acid A ring;
2. regioselective synthesis of lupane esters of cinnamic acid and its congeners by chemical and enzymatic methods;
3. preparation of mono- and disubstituted saponins;
4. application of microreactors (flow chemistry) in the preparation of the above compounds;
5. synthesis of derivatives bearing sulfur and selenium atoms;
6. test the anticancer activity of all new derivatives;
7. study the structure - activity relationships (SAR).

Preparation of compounds potentially useful in pharmaceutical and cosmetic industries is the most expected goal of the presented project.