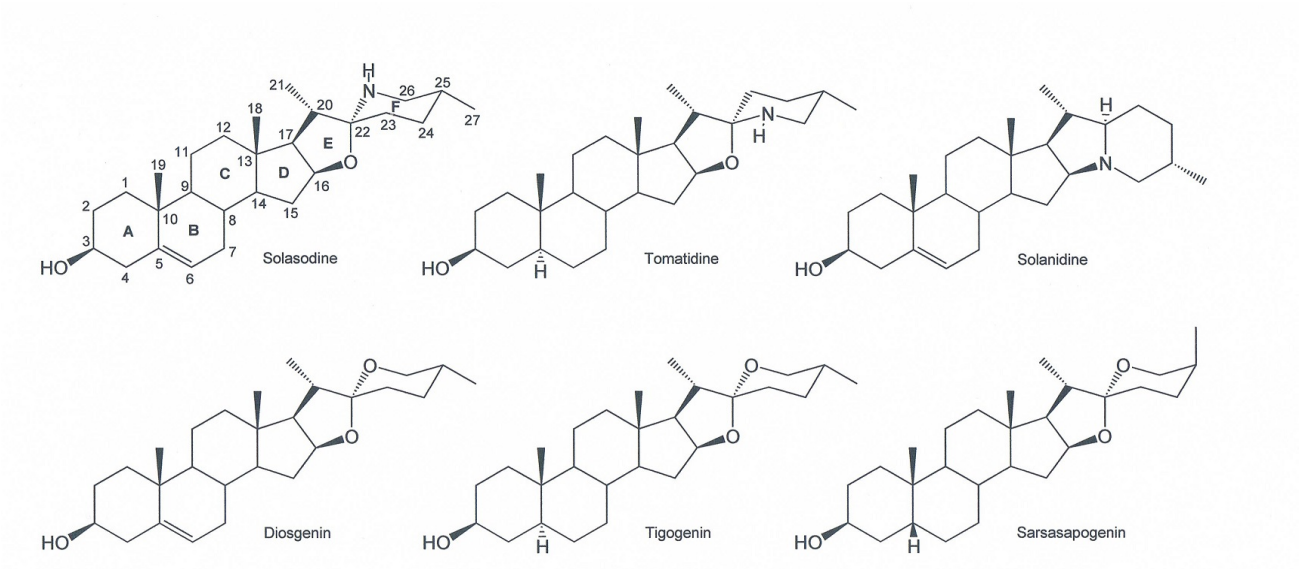
Synthesis of Solanum alkaloids and their analogs from steroidal sapogenins
(Description for the general public)

In general, steroidal alkaloids are an important class of nitrogen containing compounds that have a close structural relationship with steroids, i.e. they possess the same carbon skeleton. Interestingly, these alkaloids invariably occur in the plant kingdom (rarely in animals) as a combination with carbohydrate moieties (i.e. in form of glycosides).
Natural products can be divided into two broad classes: primary metabolites and secondary metabolites, the latter have been attracted the interest due to their biological effects on the living organisms. The main purpose of the research in the field of natural products is to search new pharmaceutically active drugs from natural sources that can be helpful for mankind. They also inspire synthetic chemists to make various modifications of natural products.
The family Solanaceae, also called as the „night shade", comprises mainly herbs, shrubs and small trees. Plants of the family have been of particular interest to man since olden times as important sources of food (potato, tomato, aubergine), as medicinal or poisonous plants, as spices (paprika, red-pepper) and for enjoyment (tobacco). The whole family is comprised of about 96 genera and 2300 species, widely distributed in tropical and temperate regions. In Poland 9 genera and about 20 species of Solanaceae have been so far identified.
The genus Solanum is the largest genus in Solanaceae and is one of the largest among all flowering plants. The genus Solanum consists of over 1700 species distributed worldwide, found in the tropical and temperate zones. A large number of Solanum species are used in the traditional medicine and they have a very wide range of pharmacological activities. The medicinal herbs contain unique alkaloids and constituents used for treatment of diverse ailments (diabetes, cholera, bronchitis, high blood pressure) and as laxatives. Many species of genus Solanum have been extensively used for treatment of several diseases including asthma, liver disorders and inflammation. The important components of genus Solanum are steroidal alkaloids of spirosolane or solanidine type, which generally occur as glycosides and show cytotoxic activities. These alkaloids and their glycosides show antiproliferative activities against human colon, liver, prostate, and breast cancer cells. Studies revealed that Solanum alkaloids also have antibacterial and antifungal activities. Glycoalkaloids of Solanum species also inactivate the herpes simplex virus.
The Solanum alkaloids are essentially the nitrogen-analogs of steroidal saponins. Some species of Solanum, namely: S. laciniatum and S. aviculare have been employed exclusively (i.e., the aglycone moieties) as the starting materials for the synthesis of several hormones and adreno-cortical steroids. These alkaloids are categorized into two groups according to the structure of the side chain. One group has an oxa-aza spiro structure as exemplified by tomatidine from S. lycopersicum (tomato) and solasodine from S. melongena (eggplant). Unlike, their oxygen counterparts, all these N-containing steroids (spirosolanes) may exhibit different configuration at C-22 (it is 22R in solasodine and 22S in tomatidine). In spirostanes (with a few exceptions) the configuration at C-22 is R as in diosgenin. The methyl group at C-25 in spirosolanes is usually equatorial, while in spirostanes it can be either equatorial (25R) (e.g. in diosgenin) or axial (25S) (e.g. in sarsasapogenin). The Solanum alkaloids of the secong group have an indolizidine moiety in their structure, as found in solanidine from S. tuberosum (potato).
Apart from the most common alkaloids mentioned above, many other alkaloids of a similar structure have been isolated from these plants. The anticancer activity of some Solanum alkaloids have been scientifically proved. Due to a potential clinical utility of these compounds, it is highly desirable to develop an efficient synthesis of these compounds, since they are poorly available from plant extraction. For example, solasodine usually occurs at ca. 0.0274-0.0426% of the extracts. Surprisingly, little attention has been paid to synthetic chemistry of Solanum alkaloids, and only a few synthesis of the spirosolane alkaloids have been achieved so far.



Keeping in mind pharmaceutical importance of genus Solanum we have undertaken chemical studies on Solanum alkaloids and their analogs. We hope to elaborate a simple method of synthesis of these alkaloids from steroidal sapogenins. Easily available steroidal sapogenins, such as diosgenin, tigogenin, and their derivatives, will be subjected to various chemical transformations including reactions with diisobutylaluminum amide, a new reagent recently introduced by us. We also plan to synthesize sapogenin analogs with sulphur or selenium atoms replacing the oxygen atom in the ring F. A series of alkaloid analogs will be prepared from steroidal precursors readily available by degradation of sapogenins. The reconstruction of the ring F in a few steps including the ring closing metathesis may lead to new analogs with one or two nitrogen atoms in the side chain. The obtained analogs will be subjected to further chemical transformation, e.g. oxidation. Also profound conformational analysis of the spirosolane system will be performed, including a careful analysis of NMR spectra with full signal assignment. Analysis of the

two-dimensional spectra will allow to distinguish between the C-22 isomers and to find diagnostic signals for each isomer. The structural conclusions concerning conformational preferences from NMR will be supported by DFT calculations. For crystalline products crystal structures will be determined by X-ray diffraction analyses.

Apart from the synthesis of spirosolane systems and other, less common, Solanum alkaloids and analogs, a series of imidazolium and imidazolinium salts based on a steroidal framework will be prepared. Among them are disteroidal salts that can be used for various purposes; such steroidal dimers with their intrinsic biological activity are particularly interesting synthetic targets. Also analogs of galeterone, recently developed as a new drug for treatment of prostate cancer, have been designed.

The biological investigations including cytotoxicity study of all final compounds, as well as their antibacterial, antifungal, anti-inflammatory activities, will be performed in cooperation with a research group of prof. M. Strnad from the Czech Academy of Sciences. In case of obtaining products of significant biological activity, the results will be patented.