УНИВЕРЗИТЕТ У НОВОМ САДУ
ТЕХНОЛОШКИ ФАКУЛТЕТ НОВИ САД

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Title of the project:
Chemometric approach to the issue of prion infectious agents potentially present in food by defining the guidelines for the continuous development of new anti-prion compounds

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Prions, Chemometrics, QSAR modeling, Biologically active compounds

Project summary:
The speculations about the nature of an infectious agent that causes serious damage of the brain tissue started in the second half of XX century. The end of those speculations was the established “prion hypothesis”. Generally speaking, the prions are considered to be the protein-structured infectious agents, with ability to cause different neurodegenerative

lethal diseases. However, prions are small membrane-associated protein molecules, present in the cells of mammals, including humans, with the biological function that still remains controversial. In humans, these so-called cellular prions (PrP^C) are composed of 253 amino acids. They are copper-binding proteins that primarily have certain roles in copper (Cu^{2+}) metabolism (related to the prevention of oxidative stress). The PrP^C prion contains three α-helixes and two short antiparallel β-sheets, where two longest α-helixes are connected with a single S-S bond. A prion becomes the infectious agent when its conformation is irreversibly changed into the conformation with higher β-sheet content, causing the formation of extracellular and intracellular agglomerates. This type of prions is labeled as a scrapie form – PrP^{Sc}. The PrP^{Sc} catalyzes misfolding of PrP^C into new PrP^{Sc} forms. Hence, the infective prion agent is actually protease-resistant PrPSc form. The agglomeration of the prion proteins causes the damage in the brain tissue inducing the cells death and finally the death of an individual. The conversion of PrP^C into PrP^{Sc} form induces the transmissible spongiform encephalopathies (TSEs) that are fatal neurodegenerative diseases, such as bovine spongiform encephalopathy (BSE), Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia and kuru. The causes of the PrPC prion misfolding can be various. Spontaneous change in conformation leads to sporadic prion diseases. However, in the familial form the mutation in the prion protein gene occurs. The induced (acquired) misfolding occurs when the abnormal prions from the environment reach the central nervous system (CNS). About 85% cases of CJD is sporadic, and 10-15% is familial or induced. The large amounts of misfolded isoforms of prions (PrP^{Sc}) can be observed in the brains of affected individuals. Because of their infectious nature and the resistance to physical and chemical inactivation, the prions can be considered to be the environmental pollutants, and ultimately the borderline between chemistry and biology.

Unfortunately, there are still no effective therapeutics for TSEs treatment, however many in vivo, in vitro and in silico trials in the World are aimed to find the lead compounds. Chemometrics and computational modeling of molecules has become a significant factor in drug design workflow. In many cases chemometric tools have facilitated the search for lead compounds in many drug discovery spheres. Quantitative structure–activity relationships (QSARs) are based on validated mathematical models and have certain advantage over classical structure–activity relationship (SAR) approach. The QSAR method is able to reveal some factors important for biological response, hidden in the form of molecular descriptors, which sometimes cannot be noticed by simple observation and comparison of the molecular structure and biological activity values. QSAR is based on many different mathematical and statistical methods, including linear (LR) and multiple linear relationships (MLR), principal component regression (PCR), partial least squares regression (PLSR), artificial neural networks regression (ANNR), hierarchical cluster analysis (HCA), principal component analysis (PCA), sum of ranking differences (SRD). This project is focused on the establishing the QSARs for three aforementioned groups of the compound with anti-prion activity and/or binding affinity toward human PrP^C ($huPrP^C$) protein: quinacrine analogs, pyridine dicarbonitrile analogs, diphenylthiazole and diphenyloxazole analogs. This project offers the possibility of the application of chemometric regression tools in prediction of binding affinity of the analyzed compound by using molecular descriptors. Also, the results present the guidelines in the search for novel antiprion compounds. Eventually, the compounds with the highest binding affinity have been subjected to the molecular docking analysis in order to predict the basic molecular interactions between them and $huPrP^C$.

Graphical abstract or graphical presentation of project results: