PROSPECTIVE ANTIOXIDANTS AND METABOLITOTROPIC ENDOTHELIOPROTECTORS AMONG 7,8-SUBSTITUED DERIVATIVES OF 3-R-XANTHINES – IN SILICO APPLIED STRATEGY AND ALGORITHM

Aleksandrova K. V., Shkoda O. S., Vasylyev D. A.
Zaporozhye State Medical University, Zaporizhzhya, Ukraine

The study of biologically active organic compounds is one of the most important directions in modern pharmaceutical and medicinal chemistry. The greatest practical importance such studies have in the development of new drug substances that are synthetic molecules. In the early stages of this process, special attention is paid to research and computer modeling of key properties of physiologically active substances. This simulation is usually performed using the calculated molecular descriptors (features), such as molecular weight, molar refraction, the number of potential donor and acceptor hydrogen bond, etc., which are equivalent numerical properties of the molecule (structure). The biological activity of compounds or biological response for this chemical compound is a cumulative effect of many processes, consider that virtually impossible (permeability material through the lipid layer, transport, absorption, ionization, the metabolism of compounds and interactions of metabolites of receptors) functional dependence bioavailability of molecular structure molecules are difficult to describe, but can be represented explicitly on the basis of compliance Lipinski-like filters.

A wide range of biological activity of natural xanthines has stimulated a search of bioactive compounds among their synthetic counterparts, which led to the creation of a number of drugs that have been successfully used to date. These are known drugs that are derivatives of 3-methylxanthine, and new xanthines containing varied substituents in the 3rd position.

So, the aim of our work was the selection of base structures of 8-substituted 3-R-xanthines for further chemical modifications of the positions of 1 and 7 of xanthine bicycle with an application of modern computer techniques.

Physico-chemical descriptors of bioavailability were determined by using programs Pallas 3.7.2.1 and Chemicalize.org, and the probable toxicity - using GUSAR. As descriptor of bioavailability was applied molecular weight (Mw), hydrophobicity (LogP or LogD for ionized compounds), the number of potential donors (DonorCount) and acceptor (AcceptorCount) of hydrogen bond, the amount of bonds that are rotated (RotatableBondCount), polar surface molecule (PSA), the number of atoms of the molecule (AtomCount), molar refraction molecules (Refractivity), the total number of cycles (RingCount) and the number of condensed aromatic rings (FusedAromaticRingCounts).

For affinity calculation with target proteins (receptors and enzymes) that are present in the endothelium synthesized compounds has been applied by automatic docking system AutoDock 4.2. The structures of target proteins (receptors and enzymes) were applied from a public ProteinDataBank (PDB).

The compounds with undesirable physical, chemical and biological properties were excluded on the initial stages of virtual screening wich significantly reduces the amount of financial contributions, labor hours, minimizing time-consuming experiments on animals to the humanization of the development process in general, and most importantly – significantly increases its efficiency.

According to the above, we have applied the search strategy algorithm of prospectime antioxidants and metabolitotropic endothelioprotectors of first and *de novo* synthesized 7,8-substitued derivatives of 3-R-xanthines.