TOOLS FOR IN SILICO EVALUATION OF CYTOCHROME P450-MEDIATED COMPOUNDS METABOLISM

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Characterization of metabolic properties of chemical compounds is very important step in drug design pipelines. Metabolic stability is one of the parameters that often prevent new ligands from passing to the other stages of the drug development – despite high affinity to the desired panel of receptors, their half-lifetime is not sufficient to trigger the desired pharmacological response [1,2]. On the other hand, *in vitro* evaluation of metabolic stability is expensive and time-consuming, so construction of tools for its *in silico* estimation is highly desirable.

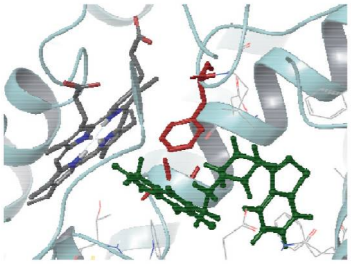

Fig. 1: Exemplary ligand-protein complex obtained for the selected cytochrome P450 isoform

In the study, a protocol for in silico evaluation of metabolic stability was developed. It constitutes a combination of *ligand-based* and *structure-based* approach. The former path is connected with the description of compounds with the use of a hybrid representation of various one-, two- and three-dimensional descriptors generated in the PaDEL-Descriptor [3] and QikProp [4] software. Then, a machine learning algorithm – Support Vector Machine adjusted for performing regression tasks [5] – was applied for metabolic stability assessment. The *structure-based* approach consists of docking into the binding site of selected cytochrome P450 subtypes (CYP3A4, CYP2D6, CYP2C9 and CYP1A2; **Fig. 1**) and the subsequent evaluation of the obtained ligand-protein complexes with the use of automatic tools. It involves description of the docking outcome by Structural Interaction Fingerprints [6] and evaluation of the obtained bit strings in the analogous manner as it was in the case of *ligand-based* path.
The methodology was evaluated on a series of long-chain arylpiperazines – representatives of 5-HT7R ligands.

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REFERENCES
[1] Masimirembwa C.M., Bredberg U., Andersson T. B., *Clin. Pharmacokinet.*, 42 (**2003**) 515-528
[2] Lin J.H., Lu A.Y.H. *Pharmacol. Rev.*, 49 (**1997**) 403-449
[3] Yap C.W. *J. Comput. Chem.*, 32 (**2011**) 1466-1474
[4] QikProp, version 4.3, Schrödinger, LLC, New York, NY, 2015
[5] Collobert R., Bengio S. *J. Mach. Learn. Res.* 1 (**2001**) 143-160
[6] Deng Z., Chuaqui C., Singh, J. *J. Med. Chem.* 47 (**2004**) 337-344