Practical applications of predictive ADME in modern drug design

The products of CompuDrug are pioneers in the field of predictive pharmaceutical and ADME software: the first predictive software was released in 1983. During the last two decades CompuDrug has become a well known developer of predictive software, and the Pallas ADME prediction expert system is used at several hundreds of pharmaceutical and biotechnological companies. This paper demonstrates some recent examples of the application of Pallas prediction engines in the field of drug discovery. Since hydrophobicity has an important role in drug development, the logP and logD predictions were utilized most extensively.

In [1] lipophilicity is discussed with reference to the human drug-metabolizing P450 enzymes of families CYP1, CYP2 and CYP3. Compound lipophilicity is of key importance to P450 binding affinity and enzyme selectivity. From an extensive compilation of log P values for P450 substrates, and by analysis of relationships between partitioning energy and substrate-binding free energy, the relevance of lipophilicity and other factors pertaining to P450 binding affinity is explained, leading to the formulation of lipophilicity relationships within substrates of each human P450 enzyme involved in drug metabolism. The logP values have been collated from several sources, and the missing values have been calculated with the Pallas PrologP software. Analyzing the P450 binding affinity and logP values the authors assume that the compound lipophilicity will play a major role in substrate binding to cytochromes P450 in mammalian systems and this will have an effect on the overall clearance of such compounds.

The research of Jagellonian University (Krakow, Poland) [2] has searched for new ligands acting on benzodiazepine receptors among the fused 2-thiohydantoin derivatives, a series of 5-substituted imidazo[2,1-b]thiazepines was synthesized and investigated in radioligand binding studies at the benzodiazepine binding site of GABAA receptors in rat brain cortical membranes. Physicochemical properties calculated (log P and log D) by Pallas, as well as experimental thin layer chromatography data, were examined. Since the investigated compounds did not possess any acidic or basic functionality, the logP and logD values were equal. The lipophilicities expressed by R_{mo} values were determined by reverse phase thin layer chromatography, on the basis of the R_m values and the content of organic modifier in the mobile phase. The calculated logP values were corrected on the basis of experimental reverse phase thin layer chromatography [3,4].

The authors of [4] have investigated the lipophilic conjugates of methotrexate with short-chain alkylamino acids as DHFR inhibitors. The aim of these derivatives was to increase the uptake of the drug into transport-resistant tumor cell lines toward the uptake of methotrexate. The inhibitory activity of these compounds against the target enzyme, dihydrofolate reductase (DHFR), and a sensitive (CCRF-CEM), and a transport-resistant tumor cell subline (CEM-MTX) was assessed. The apparent partition coefficient at pH 7.4 was applied as a measure of the lipophilicity. The logD values calculated by Pallas

PrologD were coherent with the increase of cell membrane permeation. The calculated logD values reveal extremely high hydrophilicity and explain the lower inhibitory activity of ionizing compounds, while the logP value disregards this effect, thus the precipitate application of the logP might produce a false result. Applying the PrologD software the authors appointed that lipophilic chain could enhance the activity of methotrexate derivatives.

The articles cited demonstrate that the logP values calculated by PrologP can be an accurate measure of the lipophilicity of drug candidates, but the ionizing effects have to be considered using PrologD to describe the behavior of compounds at the pH value of blood. The majority of the researchers above applied older versions of Pallas and PrologP, so the results of the articles do not include the accuracy of the latest PrologP releases [5], that would provide a more elucidated source date for the models.

[1] Compound lipophilicity for substrate binding to human P450s in drug metabolism. David F. V. Lewis, Miriam N. Jacobs and Maurice Dickins, Drug Discovery Today Volume 9, Issue 12, June 2004, Pages 530-537

[2] Imidazo[2,1-b]thiazepines: synthesis, structure and evaluation of benzodiazepine receptor binding Katarzyna Kie-Kononowicz, Janina Karolak-Wojciechowska, Barbara Michalak, Elbieta Pkala, Britta Schumacher and Christa E. Müller European Journal of Medicinal Chemistry Volume 39, Issue 3 , March 2004, Pages 205-218

[3] B.Malawska, J. Palnar Chromatogr. 11 (1998) 137-140

[4] Lipophilic conjugates of methotrexate with short-chain alkylamino acids as DHFR inhibitors. Synthesis, biological evaluation, and molecular modeling Rosario Pignatello, Salvatore Guccione, Stefano Forte, Claudia Di Giacomo, Valeria Sorrenti, Luisa Vicari, Gloria Uccello Barretta, Federica Balzano and Giovanni Puglisi, Bioorganic & Medicinal Chemistry Volume 12, Issue 11, 1 June 2004, Pages 2951-2964

[5] *A Neural Network Based Prediction of Octanol-Water Partition Coefficients Using Atomic5 Fragmental Descriptors László Molnár, György M. Keseru, Ákos Papp, Zsolt Gulyás and Ferenc Darvas, Bioorg. Med. Chem. Lett. 14(4), 851-853, 2004*