APPLICATION OF MICELLAR LIQUID CHROMATOGRAPHY (MLC) TO DETERMINE LIPOPHILICITY OF NEW PURINDIONE DERIVATIVES OF POTENTIAL ANTICONVULSANT ACTIVITY

Piotr Kawczak[a], Ann Detroyer[b], Yvan Vander Heyden[b], Antoni Nasal[a], Anna Drabczyńska[c] and Katarzyna Kieć-Kononowicz[c]

[a]Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gen. J. Hallera 107, 80-416 Gdańsk, Poland
[b]Department of Pharmaceutical and Biomedical Analysis, Pharmaceutical Institute, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussel, Belgium
[c]Department of Chemical Technology of Drugs, Jagiellonian University, Medical College, Medyczna 9, 30-688 Kraków, Poland

Lipophilicity or lipid/water partition properties affect most of the processes at the basis of drug action. Therefore, determining lipophilicity parameters of drug candidates is necessary at the early stage of the drug development process. Modern, highly efficient synthesis procedures typically provide large numbers of target compounds. That requires procedures for determining lipophilicity parameters that are rapid and can be used with very small samples. For quantitative comparison of relative lipophilicities of drugs, the most suitable are the logarithms of retention factors corresponding to pure buffer as hypothetical mobile phase, $log\ k_w$, obtained by extrapolation of the reversed-phase high-performance liquid chromatography (RP HPLC) retention coefficients, *log k*, vs. volume fraction of organic modifier in the binary aqueous eluents. Micellar liquid chromatography (MLC) is a kind of RP HPLC which utilises a mobile phase that contains an amount of micelle-forming surfactant above its critical micellar concentration (CMC). The formed micelles have a structure that, contrary to the n-octanol-water or the classic RP HPLC system, contain both hydrophobic and electrostatic interaction sites, thus making them resemble biomembranes more than the classical RP HPLC stationary phase.

A series of 110 new aryl-, alkyl-, arylalkyl- and cykloalkyl-, substituted derivatives of pyrimido-, oxazolo- and diazepino-purindiones of potential anticonvulsant activity showing a large range of lipophilicity were subjected to micellar liquid chromatography (MLC). Three columns were used: a classic hydrocarbon silica *Symmetry* C_{18} (Waters, Milford, MA, USA) column and two monolithic columns: *Chromolith SpeedROD RP-18e* and *Chromolith Performance RP-18e* (both from Merck, Darmstadt, FRG). Sodium dodecyl sulfate (SDS) was employed in concentrations of 0.075, 0.1125 and 0.15 M as a micelle forming agent. The organic modifier was n-propanol used in proportions of 5, 10 and 15 (% v/v) to phosphate buffer in the eluent. The obtained MLC lipophilicity parameters of the analytes were logarithms of retention factors, *log k*, corresponding to a mobile phase containing a given molar concentration of SDS and volume fraction of n-propanol. For the columns studied relatively good correlations ($r > 0.8$) between *log k* and theoretically calculated n-octanol-water partition coefficients, *CLOGP*, of purindiones were found. The *log k* values of analytes were also related by the regression equations to their RP HPLC lipophilicity parameters, $log\ k_w$. The highest correlation coefficients ($r \sim 0.9$) were observed in the case of *Symmetry* C_{18} column. The results obtained confirm that MLC could be a convenient method of determination of lipophilicity of newly synthesized compounds of potential pharmacological activity.