MODIFIED VERSION OF THE MACFARLAND-KUBINYI MODEL AND ITS USE IN Q.S.A.R.

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The impact caused by the use of digital computers has provided a great advance in the drug design. In the last 35 years several mathematical models have been developed with the purpose of establishing a correlation between physicochemical parameters and biological activities. Nowadays the most used Q.S.A.R. model is probably the MacFarland nonlinear model modified by Kubinyi. A more realistic version of this model is mentioned in the literature and it is represented by the following equation:

$$log\,1/C = dd(n/2 + a)log\,P - nd\,log(b`P + 1) + cte,$$

where $log\,1/C$ is the biological activity and P is the partition coefficient.

The aim of this work is to analyze and apply the above version to adjust data from several series of compounds. This model is investigated demonstrating how to determine the lipophilic characteristic that achieves maximum activity. Besides that it is shown how to separate the contributions of the lipophilia to the transport and the interaction with the receptor. In both cases the results are expressed by using regression coefficients derived from the fitting experimental data. The asymptotic characteristics are analyzed by studying the behavior of the biological response for very hydrophilic and very lipophilic compounds. One of the fundamental results is the possibility to suppress the constraint $\beta<1$ without introducing any incompatibility to the conceptual hypothesis. The model is applied and discussed for several chemical series presenting different biological activities: guanylhydrazones -- inhibition of the vegetal cellular growth; picolinic acids -- inhibition of the dopamine oxidase; phenols -- bacterial inhibition. In every situation a slight improvement is obtained in relation to the classical MacFarland-Kubynyi model.