Spycher S, Smejtek P, Netzeva TI, Escher BI.
Chem Res Toxicol. 2008 Apr;21(4):911-27. Epub 2008 Mar 22.

Abstract

A mechanistically based quantitative structure-activity relationship (QSAR) for the uncoupling activity of weak organic acids has been derived. The analysis of earlier experimental studies suggested that the limiting step in the uncoupling process is the rate with which anions can cross the membrane and that this rate is determined by the height of the energy barrier encountered in the hydrophobic membrane core. We use this mechanistic understanding to develop a predictive model for uncoupling. The translocation rate constants of anions correlate well with the free energy difference between the energy well and the energy barrier, Delta G well-barrier,A (-) , in the membrane calculated by a novel approach to describe internal partitioning in the membrane. An existing data set of 21 phenols measured in an in vitro test system specific for uncouplers was extended by 14 highly diverse compounds. A simple regression model based on the experimental membrane-water partition coefficient and Delta G well-barrier,A (-) showed good predictive power and had meaningful regression coefficients. To establish uncoupler QSARs independent of chemical class, it is necessary to calculate the descriptors for the charged species, as the analogous descriptors of the neutral species showed almost no correlation with the translocation rate constants of anions. The substitution of experimental with calculated partition coefficients resulted in a decrease of the model fit. A particular strength of the current model is the accurate calculation of excess toxicity, which makes it a suitable tool for database screening. The applicability domain, limitations of the model, and ideas for future research are critically discussed.