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METHODS FOR THE TOXICITY PREDICTION AND EVALUATION OF PHENOLS

Pushkarova Yaroslava
PhD, Associate Professor
Department of Analytical, Physical and Colloid Chemistry
Bogomolets National Medical University

Mustafa Al Saker
5th Year Student of the Faculty for Training of Foreign Citizens
Bogomolets National Medical University
Ukraine

Determining the toxicity of chemicals is one of the most important stages along the way creation of medicines. This the indicator is of great importance not only in pharmacology, but also in industry and many other areas of human activity where there is potential contact with harmful substances − agriculture, perfumes, detergents, etc. It is known that the experimental study of only one type of toxicity requires a large number of animals, considerable time and is time consuming. Computer prediction of the toxicity of chemical compounds began to develop in the 1980s. This was facilitated by the high cost of experimental studies in toxicology. In studies of various aspects of experimental determination of toxicity, it becomes very important to use calculation methods to predict these indicators, which allows you to assess in advance the possible risk of using chemicals without additional experiments [1].

Phenolic compounds are characterized by different medical and health uses (antioxidant effect, antibacterial effect, anti-cancer effect, cardioprotective effects). That is why they are interesting from a toxilogical point of view. The toxicity of phenols involves a number of different mechanisms of toxic action including polar narcosis, weak acid respiratory uncoupling, electrophilicity, and those compounds capable of being metabolised or oxidised to quinones. By far the largest number of toxicity data are available for the inhibition of growth to the protozoan ciliate Tetrahymena pyriformis [2-5].

Different approaches for classification and prediction of the toxicity of phenols was used. There have been many attempts to develop QSARs (quantitative structure activity relationship) for the prediction of the toxicity of phenolic compounds.

In 1996 Cronin and Schultz [6] were able to develop a two-parameter QSAR for the toxicity of phenols to Tetrahymena pyriformis based on descriptors for hydrophobicity and electrophilicity:

$$\log 1/IGC_{50} = 0.671(\pm 0.022)logP - 0.670(\pm 0.055)E_{LUMO} - 1.123, \quad (1)$$

$$n = 120,\ r^2 = 0.899,\ r^2_{CV}=0.893,\ s = 0.262,\ F = 523,$$

where IGC_{50} is the concentration in mmol/L of the toxicant causing 50% inhibition of growth to Tetrahymena pyriformis, P is the octanol–water partition coefficient, E_{LUMO} is the energy of the lowest unoccupied molecular orbital, n is the number of

observations, r^2 is the correlation coefficient, r_{CV}^2 is the cross-validated correlation coefficient using a leave one-one-out approach, *s* is the standard error of the estimate, *F* is the Fisher criterion and figures in parentheses are the standard errors on the coefficients.

Garg et al. [7] in 2001 demonstrated a similar relationship to equation 1, but replaced LUMO with Hammett constant σ:

$$\log 1/IGC_{50} = 0.64(\pm 0.04)logP + 0.61(\pm 0.12)\sigma + 1.84\ (\pm 0.13), \quad (2)$$

n = 119, r^2 = 0.896, r_{CV}^2=0.887, s = 0.265, F not given.

A variety of methods were utilised to develop QSARs for the prediction of the toxicity of 200 phenols to Tetrahymena pyriformis and are compared in [5]: the response-surface approach, stepwise regression, partial least squares. The response-surface, or two parameter, approach was found to be successful, but only following the removal of compounds known to form quinones. Stepwise regression produced a seven parameter QSAR with good statistical fit, but was less interpretable and transparent than the response-surface. Partial least squares produced a good model for phenolic toxicity following supervised selection of parameters, this, however, was the least transparent of all approaches attempted.

The stepwise linear discriminant analysis (LDA) was used for classification of the toxic mechanisms of action for 221 phenols, for which toxicity data to the ciliate Tetrahymena pyriformis were available [8]. The compounds were a priori grouped into the following four mechanisms according to structural rules: polar narcotics, weak acid respiratory uncouplers, pro-electrophiles and soft electrophiles. Hydrophobicity with and without correction for ionisation, acidity constant, frontier orbital energies and hydrogenbond donor and acceptor counts were used as molecular descriptors. LDA models employing 3 ± 6 variables achieved 86 ± 89% overall correct classification of the four mechanisms, with more varied performance for respiratory uncouplers and pro-electrophiles.

Dieguez-Santana et al. [9] were used the multiple linear regression technique to develop a linear quantitative-structure toxicity relationship (QSTR) model for prediction of phenols toxicity to Tetrahymena pyriformis. The obtained model was statistically significant and robust indicating the capability of predicting the aquatic toxicity of phenol derivatives in the impairment of the population growth of Tetrahymena pyriformis.

Abbasitabar and Zare-Shahabadi [10] were used genetic algorithm and decision tree-based modeling approach for in silico prediction of toxicity of phenols to Tetrahymena pyriformis. The advantage of proposed algorithm is that one can use the resultant tree to predict phenol toxicity with high accuracy with no a priori knowledge about chemical class or mechanism of action of phenols.

Chen et al. [11] were used popular classification algorithm random forest learner for in silico prediction of toxic action mechanisms of phenols to Tetrahymena pyriformis. One global and four local classification models were constructed by employing random forest in the cost-sensitive learning framework. The statistical results in the paper confirmed that random forest was a competitive tool for building classification models of toxicity mechanisms prediction.

Ren [12] was used the decision tree in classifying and predicting the aquatic toxicity mechanisms of phenols was investigated. Using molecular descriptors as splitting variables, a three level decision tree with six terminal nodes was obtained. Validation of the decision tree approach indicated that the overall mechanism prediction accuracy was approximately 85%.

Conclusion. The toxicity prediction and evaluation of phenols has become an area of active research, which is confirmed by a variety of approaches to solving this task.

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