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Abstract

MARSplines Approach for Quantitative Relationships between Structure and Pharmacological Activity of Potential Drug Candidates †

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Abstract: A multivariate adaptive regression splines (MARSplines) approach was applied to the quantitative structure–activity relationship studies of antitumor activity against murine leukemia L1210 of anthrapyrazoles, as well as activated coagulation factor X (FXa) inhibitory activity of isosteviol analogues. These two different sets of molecules in the first stage underwent molecular modelling studies, i.e., geometrical optimization via the MM+ and the AM1 method using the Polak–Ribiere algorithm, and finally, about 5000 molecular descriptors encoding structural features were calculated. Afterwards, statistical analysis using the MARSplines algorithm was performed, which led to the establishment of a portfolio of submodels. As a result, the statistically significant MARS model that best describes quantitative structure–activity relationships for each set of the studied compounds was chosen. Elaborated models reveal which molecular properties have the greatest impact on the pharmacological activity of anthrapyrazole and isosteviol compounds. Among the independent variables appearing in the statistically significant MARS models, descriptors belonging to 2D Atom Pairs, 2D autocorrelations, 3D-MoRSE, GETAWAY, burden eigenvalues, RDF, and WHIM descriptors may be distinguished. The studies confirmed the benefit of using the MARSplines algorithm, the since high predictive power of the obtained models makes them useful for the prediction of antitumor and FXa inhibitory activity, and this approach can possibly be considered as a tool for searching for new drug candidates.

Keywords: anthrapyrazole derivatives; cancer; diabetes; FXa inhibitors; isosteviol derivatives; multivariate adaptive regressions splines; obesity; quantitative structure–activity relationships (QSAR)

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