2D-QSAR study of antimutagenic flavonoids using Ordered Predictors Selection (OPS).

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Keywords: QSAR; PLS; variable selection; antimutagenic effect; flavonoids; 3-NFA.

Introduction

Nitroarenes, like the nitrofluoranthene (3-NFA), are generated by reaction of nitrogen oxides (NOx) with polycyclic aromatic hydrocarbons during incomplete combustion of organic materials. These compounds present mutagenic activities in bacterial and mammalian test systems and are associated with some types of cancer. However, carcinogenicity and mutagenicity of chemicals may be modulated by other chemicals. For example, it is known that the flavonoids found in food possess protective properties [1].

In this study was conducted a 2D-QSAR study with twenty selected flavonoids among that studied by Endeharder and Tang [1] that presented inhibition of mutagenic activity promoted by 3-NFA in *Salmonella typhimurium* TA98.

A total of 1221 descriptors were calculated with the programs Gaussian 03 (AM1), PClient (www.vcclab.org) and DRAGONWEB. A cut off was performed and 649 descriptors with correlation coefficient lower than 0.4 with the biological activity were eliminated. In a further step, a variable selection was carried out using the Ordered Predictors Selection (OPS) algorithm [2]. The OPS algorithm searches for the best models until 5 latent variables (LV), obey the criterion $N_{samples}/N_{LV} \geq 4$. The best model was submitted to a series of internal (cross-validation, y-randomization and leave-N-out) and external validation in order to confirm its reliability, robustness and check for chance correlation.

Results and Discussion

The OPS algorithm has suggested 330 different models and the best model was chosen based on the minimum S_{press} [3], resulting in a PLS model with 2 latent variables, 6 descriptors, and 70.78% of total information. One outlier was removed based on its Leverage and Studentized residual and the final model had 19 samples. The model (Table 1) presented good statistical results (R^2= 0.7708, SEC= 0.3162, $PRESS_{cal}$= 1.5997, Q^2_{LOO}= 0.5858, SEV= 0.3900, $PRESS_{val}$= 2.8905 and $F_{95\%}$= 28.692 for $F_{critical}$= 3.633). All of selected descriptors were topological. However G1e, SeaC2C3aa and GATSp indicate effects related to electronegativity and polarizability that should be taken into account.

Table 1. Descriptors of QSAR Model.

Descriptor	StandardizedCoefficient	Coefficient
Mor27m[1]	+0.149370	+1.1093
G1e[2]	+0.144911	+7.9206
R4u+[3]	+0.309093	+13.1737
SeaC2C3aa[4]	+0.227496	+0.1002
PJI2[5]	+0.281439	+1.9972
GATSp[6]	-0.135075	-2.3397
Independent term	-	3.9041

[1] 3D-Morse signal 27 weighted by atomic masses; [2] 1st component symmetry directional WHIM index weighted by atomic Sanderson eletronegativities; [3] R maximal autocorrelation of lag 4 unweighted.; [4] : molecular bond E-state índices type bond; [5] 2D Petitjean shape index; [6] 2D Geary autocorrelation lag 2 weighted by polarizability.

In the leave-N-out validation analysis (N= 1 to 5) the average Q^2 was 0.5649±0.024 (max: 0.5983; min: 0.5305), showing small oscillation in the results and confirming the robustness of the model. A y-randomization test was also performed (R^2's < 0.3 and Q^2's < 0.0), showing no chance correlation.

After all processes of internal validation, a test set with 5 samples were selected among the 19 samples of the full set and new models were built (similar statistics from Table 1). The external validation presented the following results: Q^2_{pred}= 0.9389, SEP= 0.2684, $PRESS_{pred}$= 0.3601 and average error of prediction 3.8012%. These results show that the model is also good to perform predictions.

Conclusions

The model obtained by OPS algorithm presented good statistical results, robustness and a great ability of prediction. Thus, it can be used as a guide to the synthesis of new flavonoids with better ability of chemoprevention regarding the antimutagenic effects caused by nitroarenes.

Acknowledgements

FAPESP, CNPQ and Universidade Estadual do Oeste do Paraná/Campus Cascavel

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