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2D, 3D and Hybrid QSAR Studies for a Set of 3-Benzyl-(arylmethylene)furan-2(5H)-ones and Their Herbicide Activity

Authors: Pedro Oliveira Mariz de Carvalho, Márcia Miguel Castro Ferreira.

Address: Institute of Chemistry, State University of Campinas, Brazil.

Abstract: Agriculture is one of the main sources of food for the population. Pest control is important for high crop efficiency and, nowadays, it is done mainly by the application of synthetic pesticides. However, continuous use of pesticides with the same mechanism of action induces the adaptation of pests, which acquire resistance. Moreover, environmental concern increased over the years, leading to stringent regulation of pesticide use.[1,2] Therefore, the research for novel synthetic pesticides is essential for food production. QSAR study is an important tool on the research of biochemical processes, such as pesticides' action, because it is able to extract valuable information from experimental data. The objective of this work is: to use herbicide activity of a set of 34 nostoclide analogues (Image 1), which act into the photosystem II, to build QSAR models; then, to interpret the obtained models aiming for a better understanding of the ligand-receptor interactions between the photosystem II and these analogues. The substitutions are located on the arylidene group and the herbicide activity used were percentage of inhibition of the photosynthesis process ranging from 5.0 to 57.8% with mean value of 23.9%.[2] The structures were optimized, starting from crystallographic data, using Gaussian 09 at B3LYP/Def2-TZVPP level. For the 2D-QSAR study, several molecular descriptors (energies, gap, dipole moment, polarizability, charges and molecular coefficients) were calculated using Gaussian 09. The descriptors were selected firstly by excluding those presenting low correlation with the biological activity, then by building PLS models and looking for good statistical results (RMSECV, R^2, Q^2, regression vector etc.) in Pirouette software. For the 3D-QSAR study, the structures were converted to topology files using Topolbuild-1.3 (GAFF force field), and were aligned in a grid. The molecular descriptors were Coulomb and Lennard-Jones potential energies calculated by the NH_3^+ probe in each grid point (1 Å increment). Variable selection was carried out in three steps: (1) using Comparative Distribution Detection Algorithm (CDDA) in MATLAB; (2) by using OPS algorithm in QSAR Modeling; (3) by building PLS models and looking for good statistical results. For the hybrid QSAR study, the final molecular descriptors from the 2D and 3D QSAR models were merged and a new variable selection was carried out. The number of latent variables in PLS models were determined by leave-one-out cross-validation. One inactive compounds (inhibition lower than 5%) and four

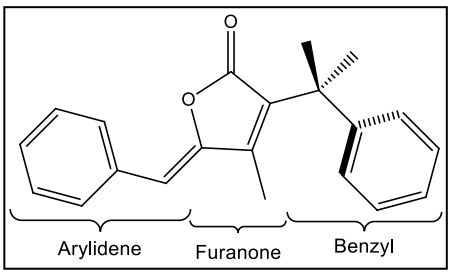

Image 1 – Nostoclide analogue.

others presented atypical behavior in all models. The statistics produced by all generated models are presented below. They were also validated according to their robustness and chance correlation by using the leave-N-out and y-randomization tests.[1,3]

2D-QSAR: n = 29; descriptors = 6; latent variables: 1 (LV1: 53.8%); RMSEC = 8.8105%; R^2 = 0.7353; RMSECV = 9.4110%; Q^2 = 0.6756.

3D-QSAR: n = 29; descriptors = 7; latent variables: 2 (LV1: 40.5%; LV2: 27.5%); RMSEC = 8.2149%; R^2 = 0.7784; RMSECV = 9.3189%; Q^2 = 0.6820.

Hybrid-QSAR: n=29; descriptors = 7; latent variables: 2 (LV1: 43.3%; LV2: 25.9%); RMSEC = 7.2378%; R^2 = 0.8280; RMSECV = 8.0807%; Q^2 = 0.7609.

A preliminary comparison among the models shows that the 2D and 3D QSAR models were statistically similar (3D slightly better than 2D) and the hybrid-QSAR model presented better correlations and lower errors than the other two.[3] The 2D atomic partial charge descriptors showed the importance of the benzyl ring, even though no substituents are located on it. This observation alongside with the photosystem II active site and the results from literature support the possibility of a ligand-receptor interaction by π-stacking between the benzyl group and a residue's aromatic ring.[4,5] The other 2D descriptors indicated important interactions involving the carbonyl group in the furanone ring, which is a good hydrogen bond acceptor, and the arylidene ring, where the substituents are located. The 3D descriptors showed similar interactions, emphasizing the results indicated by the 2D descriptors. However, the descriptors selected to build the hybrid-QSAR model showed that the 2D descriptors were better to describe the benzyl ring interactions, whilst the 3D descriptors were better to describe the other groups of the nostoclide analogues. Therefore, the 2D and 3D descriptors indicated similar results for the herbicide activity of these analogues, but it was possible to achieve better statistics when using them together, in the hybrid-QSAR model. Furthermore, the analysis of the descriptors used in the QSAR models indicated importance of the interactions involving, mainly, the benzyl aromatic ring and, secondarily, the carbonyl of the furanone ring and the substituents of the arylidene ring.[1]

Key-words: 2D-QSAR, 3D-QSAR, Quantum Chemistry, PLS regression, Herbicides.
Support: CNPq, FAPESP.
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