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QSAR with Constitutional Descriptors for the Herbicidal Properties of Fluorovinyloxyacetamides

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QSAR with Constitutional Descriptors for the Herbicidal Properties of Fluorovinyloxyacetamides[#]

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Abstract

The family of Dragon descriptors was used to assess the herbicidal property of a fluorovinyloxyacetamide set of compounds. The best model was obtained with constitutional descriptors, which explained more than 83 % of data variance, stressing the importance of mean atomic Sanderson electronegativity, molecular polarizability as well as the number of O and F atoms and aromatic bonds, to describe herbicidal properties. On the other hand, this model was superior to those obtained with Galvez topological charge indexes, 2D autocorrelation and Randić molecular profiles descriptors, when we use the same numbers of variables. This approach provides a good method for assessing herbicidal properties of this type of compounds, which could be extended to other chemicals.

Keywords. QSAR; herbicide; Dragon software; constitutional descriptors; fluorovinyloxyacetamide.

1 INTRODUCTION

Oxyacetamide has been developed as an herbicide, showing good herbicidal activity for annual weeds through inhibition of cell division and amino acid biosynthesis [1]. Especially, the excellent selectivity between crop (rice) and weeds (barnyard grass), an important weed in paddy fields, is a merit of oxyacetamide herbicide [2]. In this research, we sought to describe the Quantitative Structure–Activity Relationship (QSAR) study of fluorovinyloxyacetamide. QSAR is a powerful method for the design of bioactive compounds and the prediction of corresponding activity with physical and chemical properties [3–10].

[#] Dedicated to Professor Nenad Trinajstić on the occasion of the 65th birthday.
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In the context of *in silico* methods for modeling physicochemical and biological properties of chemicals, the Dragon software [11] is a powerful tool for developing QSAR models. The constitutional, Galvez topological charges indexes, 2D autocorrelations, Randić molecular profiles and WHIM descriptors have been applied to the description of physicochemical and biological properties of organic compounds [11]. The successful applications of these theoretical approaches have inspired us to develop this study in order to evaluate the family of Dragon descriptors and their application on the discovery of herbicidal compounds.

2 MATERIALS AND METHODS

In order to obtain suitable theoretical models a set of 57 fluorovinyloxyacetamide derivatives were evaluated. Molecule structures and data of herbicidal activity expressed as –log EC_{50} of barnyard grass, were taken from reference [2].

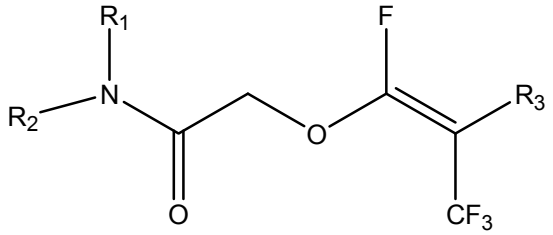
Constitutional, Galvez topological charges indexes, 2D autocorrelations and Randić molecular profiles descriptors were calculated using the Dragon software, and they are depicted in Table 1. The reason of this comparison is to demonstrate the ability of the Constitutionals descriptors to model this property in comparison with other 2D descriptors.

The input file, for descriptors calculations, containing information of atoms, bond types, and atomic spatial coordinates relative to the minimum energy conformation of the molecule, were obtained by the semi–empirical method of Dewar (AM1) [12], using the package Hyperchem 6.0 [13]. A model for predicting herbicidal properties was obtained with each family of descriptors. Linear regression analysis, mode to each descriptors set, was performed with the statistic package Statistic version 6.0 [14].

The statistical processing to obtain the QSAR models was carried out by using the forward stepwise regression methods, were the independent variables are individually added or deleted from the model at each step of the regression, depending on the Fisher ratio values selected to enter and to remove, until the “best” model was obtained.

Examining the regression coefficient, standard deviation, F of fisher, cross validation leave–one–out and the proportion between the cases and variables in the equation determined the quality of the model. Additionally, the validation of the model was carried out by calculating the regression coefficient in the external prediction set. Compounds in the external prediction set were never used to develop the prediction function.

Table 1. Observed and predictions activity; residuals and structures of the fluorovinyloxyacetamides herbicides used in the training set



No	R_1	R_2	R_3	Observed Activity	Predicted Activity	Residual
1	$-(CH_2)_5-$		$3-CH_3-C_6H_4$	2.114	2.104	0.009
2	$-(CH_2)_5-$		$4-C_2H_5-C_6H_4$	1.738	1.815	–0.077
3	$-(CH_2)_5-$		$3,5-Cl_2-C_6H_3$	1.674	1.716	–0.042
4	$-CH(CH_3)(CH_2)_4-$		$4-CH_3-C_6H_4$	1.574	1.815	–0.241
5	$-CH(C_2H_5)(CH_2)_4-$		$4-CH_3-C_6H_4$	1.807	1.654	0.152
6	$-CH(CH_3)(CH_2)3CH(CH_3)-$		$3-Cl-C_6H_4$	1.738	1.540	0.197
7	$-(CH_2)_6-$		$3-CH_3-C_6H_4$	2.102	2.101	0.001
8	$-(CH_2)_6-$		$4-C_2H_5-C_6H_4$	1.867	1.940	–0.073
9	$-(CH_2)_6-$		$3,4-(CH_3)2-C_6H_3$	1.992	1.940	0.051
10	$-(CH_2)_6-$		$3,5-(CH_3)_2-C_6H_3$	1.910	1.940	–0.030
11	$-(CH_2)_6-$		$3-CH_3O-C_6H_4$	2.036	2.063	–0.027
12	$-(CH_2)_6-$		$4-Cl-C_6H_4$	2.066	1.987	0.078
13	C_2H_5	$n-C_4H_9$	$4-CH_3-C_6H_4$	1.614	1.675	–0.061
14	C_6H_5	CH_3	C_6H_5	2.408	2.490	–0.082
15	C_6H_5	CH_3	$3-CH_3-C_6H_4$	2.366	2.203	0.162
16	C_6H_5	CH_3	$4-CH_3-C_6H_4$	2.398	2.203	0.194
17	C_6H_5	CH_3	$4-C_2H_5-C_6H_4$	1.860	1.914	–0.054
18	C_6H_5	CH_3	$4-C_2H_50-C_6H_4$	1.937	1.876	0.060
19	C_6H_5	CH_3	$3-CF_3-C_6H_4$	2.046	2.016	0.029
20	C_6H_5	CH_3	$3-F-C_6H_4$	2.387	2.387	0.000
21	C_6H_5	CH_3	$4-Cl-C_6H_4$	2.169	2.088	0.080
22	$4-CH_3-O-C_6H_4$	CH_3	$3-CH_3-C_6H_4$	2.030	1.876	0.153
23	$4-CH_3-O-C_6H_4$	CH_3	$3,4(CH_3)_2-C_6H_3$	1.737	1.715	0.021
24	$4-CH_3-O-C_6H_4$	CH_3	$3,4-OCH_2O-C_6H_3$	1.896	1.943	–0.047
25	$4-F-C_6H_4$	CH_3	C_6H_5	2.387	2.387	0.000
26	$4-F-C_6H_4$	CH_3	$4-CH_3-C_6H_4$	1.941	2.098	–0.157
27	$4-F-C_6H_4$	CH_3	$4-CH_3O-C_6H_4$	1.763	2.060	–0.297
28	$2,4-F_2-C_6H_3$	CH_3	$3-Cl-C_6H_4$	2.034	2.008	0.025
29	$2,4-Cl_2-C_6H_3$	CH_3	$4-F-C_6H_4$	1.896	1.710	0.185
30	C_6H_5	C_2H_5	$4-F-C_6H_4$	2.209	2.098	0.110
31	$4-CH_3O-C_6H_4$	C_2H_5	C_6H_5	1.937	1.876	0.060
32	$3-CF_3-C_6H_4$	C_2H_5	$4-CH_3-C_6H_4$	1.259	1.440	–0.181
33	$4-Cl-C_6H_4$	C_2H_5	$4-CH_3-C_6H_4$	1.517	1.639	–0.122
34	$4-CH_3O-C_6H_4$	$n-C_3H_7$	$4-CH_3-C_6H_4$	1.360	1.428	–0.068
35	C_6H_5	$i-C_3H_7$	$3,5-(CH_3)_2-C_6H_3$	1.309	1.591	–0.282
36	C_6H_5	$i-C_3H_7$	$4-CH_3O-C_6H_4$	1.860	1.715	0.144
37	C_6H_5	$i-C_3H_7$	$4-C_2H_5O-C_6H_4$	1.608	1.428	0.179
38	$3-CH_3-C_6H_4$	$i-C_3H_7$	C_6H_5	2.036	1.753	0.282
39	$3-CH_3-C_6H_4$	$i-C_3H_7$	$4-C_2H_5-C_6H_4$	1.070	1.302	–0.232
40	$3-CH_3-C_6H_4$	$i-C_3H_7$	$3-CH_3O-C_6H_4$	1.470	1.428	0.041
41	$3-CH_3-C_6H_4$	$i-C_3H_7$	$3-F-C_6H_4$	1.673	1.648	0.024
42	$4-CH_3O-C_6H_4$	$i-C_3H_7$	C_6H_5	1.806	1.715	0.090
43	$4-CH_3O-C_6H_4$	$n-C_3H_7$	$4-CH_3-C_6H_4$	1.581	1.478	0.102
44	$4-CH_3O-C_6H_4$	$i-C_3H_7$	$4-CH_3-C_6H_4$	1.574	1.428	0.145
45	$4-CH_3O-C_6H_4$	$i-C_3H_7$	$4-CH_3O-C_6H_4$	1.259	1.390	–0.131
46	$4-CH_3O-C_6H_4$	$i-C_3H_7$	$4-F-C_6H_4$	1.618	1.612	0.005

Table 1. (Continued)

No.	R_1	R_2	R_3	Observed Activity	Predicted Activity	Residual
47	4–F–C_6H_4	*i*–C_3H_7	3–CF_3–C_6H_4	1.360	1.335	0.024
48	4–F–C_6H_4	*i*–C_3H_7	4–F–C_6H_4	1.896	1.832	0.063
49	3–Cl–C_6H_4	*i*–C_3H_7	4–F–C_6H_4	1.672	1.534	0.137
50	4–CH_3–C_6H_4	CH_3	C_6H_5	2.143	2.203	–0.060
51	3,4$(CH_3)_2$–C_6H_3	CH_3	4–CH_3–C_6H_4	1.672	1.753	–0.081
52	3–Cl–C_6H_4	CH_3	3,4–$(CH_3)_2$–C_6H_3	1.579	1.639	–0.060
53	3–Cl–C_6H_4	CH_3	4–C_2H_5–C_6H_4	1.548	1.639	–0.091
54	3–Cl–C_6H_4	CH_3	4–CH_3O–C_6H_4	1.670	1.763	–0.093
55	4–Cl–C_6H_4	CH_3	C_6H_5	1.988	2.088	–0.100
56	4–Cl–C_6H_4	CH_3	3–CH_3O–C_6H_4	1.691	1.763	–0.072
57	4–Cl–C_6H_4	CH_3	4–CH_3O–C_6H_4	1.670	1.763	–0.093

Table2. Statistical parameters of the lineal regression models for herbicidal property obtained for the four types of descriptors

Descriptors	# Var	*N*	*S*	R^2	F	q^2	S_{cv}
Constitutional	6	57	0.134	0.831	40.933	0.784	0.190
Galvez topological charges indices	6	57	0.165	0.744	24.226	0.687	0.232
2D autocorrelations	6	57	0.166	0.741	23.813	0.662	0.241
Randić Molecular profiles	6	57	0.219	0.545	9.989	0.385	0.342

3 RESULTS AND DISCUSSION

Statistical parameters of linear regression models obtained for all studied descriptors are shown in Table 2. As it can be appreciated all four models are statistically significant ($p < 0.05$), meaning that all variables are significant. These models can predict the studied property, because they have the same number of significant variables using the same training set of 57 fluorovinyloxyacetamides. However, there are differences in experimental variance (R^2) among them. For example, the model based on constitutional descriptors explains 83.1% of the herbicidal property, having the higher Fischer's F (F = 40.93) and the best standard deviation of cross validation (S = 0.19), which are very important factors for selecting the best model to be used afterward. Standard deviation was computed with the following equation:

$$S = \sqrt{\frac{\sum_{i=1}^{n} (y_i - \hat{y})^2}{n-1}}$$

Predicted *vs*. observed values of –log (EC_{50}) for the training set can be appreciated in Figure 1. It was also found that the model obtained using constitutional descriptors had a greater correlation coefficient (q^2) and a smaller standard deviation (S_{cv}) when a leave–one–out cross–validation procedures was used to validate these models. The S_{cv} was obtained using the equation:

$$S_{CV} = \sqrt{\frac{\sum_{i=1}^{n} (y_i - y_i')^2}{n-1}}$$

The equation obtained with constitutional descriptors is:

$$-\log(EC_{50}) = -7.767(\pm 0.127) - 0.185(\pm 0.056)\cdot Sp + 0.1632(\pm 0.023)\cdot nO + 0.245(\pm 0.025)\cdot nAB + 0.285(\pm 0.058)\cdot nF - 12.78(\pm 0.941)\cdot Me - 0.081(\pm 0.004)\cdot nSK \quad (1)$$

The definition of these descriptors is show in Table 3. However, before making the interpretation of this equation we can orthogonalize the molecular descriptors included in such models due to the intercorrelation between some of them.

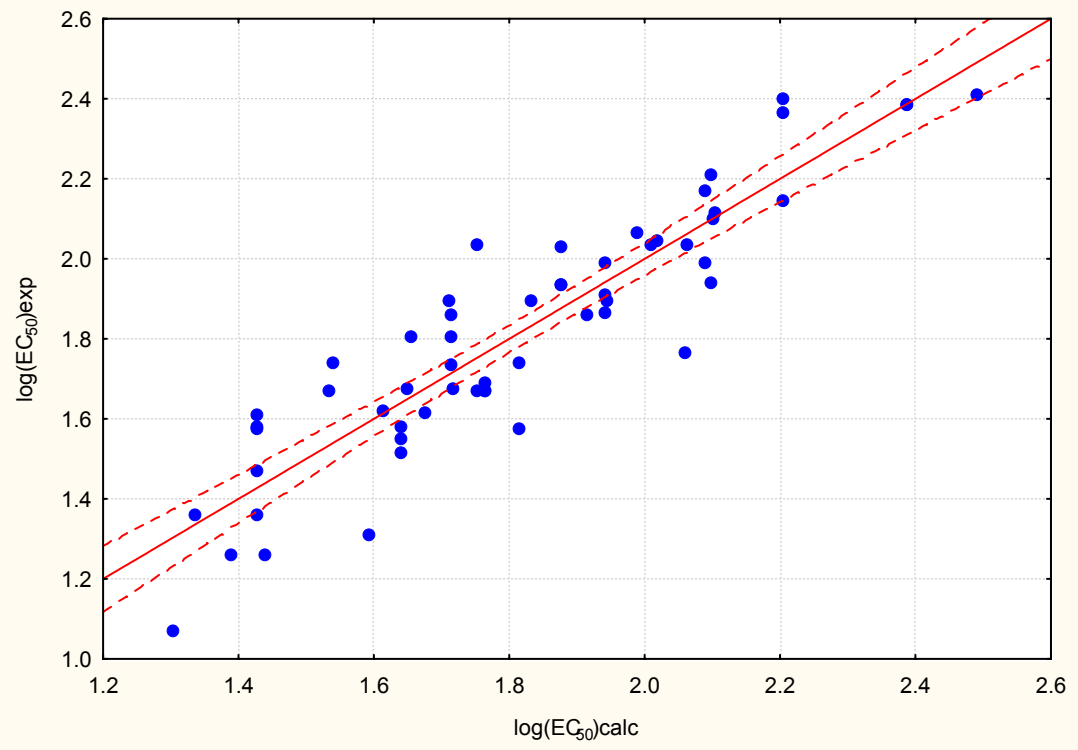


Figure 1. The linear relation between observed and predicted herbicidal property for the compounds of the training set.

Table 3. Symbols for constitutional descriptors used in the model and their definitions

Sp	Sum of atomic polarizabilities (scaled relative to C)
nO	Number of O atoms
nAB	Number of aromatic bonds
nF	Number of F atoms
Me	Mean atomic Sanderson electronegativity (scaled relative to C)
nSK	Number of non hydrogen atoms

3.1 The Orthogonalization of Molecular Descriptors

In order to avoid collinearity, Randić's orthogonalization procedure was carried out [15–18]. The main philosophy of this approach is to avoid the exclusion of descriptors on the basis of collinearity with other variables previously included in the model. It is known that the interrelatedness among the different descriptors can result in highly unstable regression coefficients, which makes impossible to know the relative importance of an index and underestimates the utility of the regression coefficients in a model.

The Randić method of orthogonalization has been described in details in several publications [14–19]. Thus, we will give a general overview here. The first step in orthogonalizing the molecular descriptors in model 2 is to select the appropriated order of orthogonalization, which in this case is the order in which the variables were selected in the forward stepwise search procedure of the linear regression analysis.

In this sense, in Eq. (2) we used $S_p = {}^1O(S_p)$ as the first orthogonal variable. Afterwards, the successive residuals of the step–by–step regressions between each variable selected in the model and the others in order of statistical significance were calculated [20]. All these residuals were used as the remnant orthogonal variables in the Eq. (2) [20]. In this analysis the least squares method selected all orthogonal analogs of collinear variables. It ensured us that, in spite of variables collinearity, each variable have an amount of information do not encoded in the others [17,20,21].

3.2 Interpretation of the QSAR Model

As a result of the orthogonalization of the Eq. (1) we obtain:

$$\begin{aligned} -\log(EC_{50}) = &-7.767(\pm 0.127) - 0.185(\pm 0.056)\cdot {}^1OSp - 0.0932(\pm 0.002)\cdot {}^2OnO \\ &+ 0.141(\pm 0.035)\cdot {}^3OnAB + 0.985(\pm 0.068)\cdot {}^4OnF + 4.78(\pm 0.523)\cdot {}^5OMe - 0.121(\pm 0.025)\cdot {}^6OnSK \end{aligned} \quad (2)$$

As can be appreciated, the variable ^{1}OSp, in the above equation, has a negative influence in the studied property. Due to the fact that this variable represents the sum of molecule's atomic polarizabilities, it suggests that relatively bigger atoms, which are potentially polarizable would have significantly elevate ^{1}OSp value and negatively contribute to the herbicidal property of this family of compounds. The same reasoning could be followed for the influence exerted by variable ^{5}OMe, which represents the atomic mean of Sanderson's electronegativities; that is, structures formed by atoms with high atomic radii would have a lower electronegativity and consequently, their positive contributions to the herbicidal property would be considerably decreased.

On the other hand, the number of aromatic bonds in fluorovinyloxyacetamides is a very important factor contributing to increase the herbicidal power of these compounds; so, it is possible that the target, where they do their action, has low electronic density receptors able of interacting with such aromatic systems [1].

Another deduction about their way of performing their herbicidal action could be done if we consider the influence of variable ^{6}OnSK, which represents the number of atoms different from hydrogen, having a negative contribution. It could mean that receptor interacts only with compounds having an adequate size, or the site was these herbicidal compounds are transported, have such restrictions.

It is also remarkable that our model has a variable represented by the number of oxygen atoms in a molecule (^{2}OnO), which has a negative contribution. If we take a close examination to the training set, with which our model was built, it could be appreciated that this set is composed mostly by oxygen containing aliphatic and aromatic ethers. Therefore, we are unable why the presence of those oxygen atoms in fluorovinyloxyacetamides decreases their herbicidal activity.

Finally, using Eq. (2), the efficacy of our model for evaluating on external prediction set of 14 compounds belonging to this family, with known herbicidal properties, was corroborated. The result of this analysis is shown in the following Table 4, where no significant differences between observed and predicted values can be appreciated. In addition, the standard error of estimation was of 0.232.

Table 4. Experimental and predicted values of herbicidal property of fluorovinyloxyacetamides compounds in the predicting set

No	R_1	R_2	R_3	Observed Activity	Predicted Activity	Residual
1	4–CH_3O–C_6H_4	CH_3	3,5–$(CH_3)_2$–C_6H_3	1.641	1.706	0.065
2	4–CH_3O–C_6H_4	CH_3	4–CH_3O–C_6H_4	1.924	1.631	–0.292
3	4–CH_3O–C_6H_4	CH_3	4–Cl–C_6H_4	1.807	1.920	0.113
4	4–F–C_6H_4	CH_3	3–CH_3–C_6H_4	1.971	1.920	–0.050
5	4–F–C_6H_4	CH_3	3,5–$(CH_3)_2$–C_6H_3	1.653	1.745	0.092
6	4–F–C_6H_4	CH_3	3–CH_3O–C_6H_4	1.908	1.810	–0.097
7	C_6H_5	C_2H_5	4–CF_3–C_6H_4	1.787	1.831	0.044
8	4–CH_3–C_6H_4	C_2H_5	4–F–C_6H_4	1.836	1.754	–0.081
9	4–CH_3O–C_6H_4	C_2H_5	4–F–C_6H_4	1.830	2.090	0.260
10	2–Cl–C_6H_4	C_2H_5	4–CH_3–C_6H_4	1.520	1.929	0.409
11	3–Cl–C_6H_4	C_2H_5	C_6H_5	1.973	2.052	0.079
12	4–Cl–C_6H_4	C_2H_5	C_6H_5	1.775	1.718	–0.056
13	C_6H_5	*i*–C_3H_7	4–CH_3–C_6H_4	1.790	1.929	0.139
14	C_6H_5	*i*–C_3H_7	3,4–OCH_2O–C_6H_4	1.896	1.763	–0.133

4 CONCLUDING REMARKS

Constitutional descriptors were used to predict the property herbicide of a set of 57 fluorovinyloxyacetamides. The QSAR models revealed that the charges, the dipole moment of the molecule and the distance among their connections are very important factors when predicting the herbicidal properties for this family of compounds. Taking into consideration the calculation speed and the easy interpretation of these descriptors, as well as the good results obtained in this study, we plat to extend this prediction methodology to other families of compounds and other properties.

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