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2D QSAR Analysis of Pyrazinecarboxamides derivatives as an herbicidal agent

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ABSTRACT

A set of nineteen Pyrazinecarboxamides derivatives with herbicidal activity was subjected to the two dimensional quantitative structure activity relationships studies using Vlife molecular drug design 3.0. Drug Designing module contain various combinations of thermodynamic, electronic, topological and spatial descriptors. Pyrazinecarboxamides taken as the lead molecule and QSAR model developed using multiple regression approach. For each set of descriptors, the best multi-linear QSAR equations were obtained by the stepwise variable selection method using leave-one-out cross-validation as selection criterion. Logarithmic inverse value of IC_{50} was taken as dependent variable and H-Acceptor Count and T_T_O_7 topological parameter was taken as independent variable. The best QSAR model (r^2 = 0.85, Fisher test value F=29.26, r^2 se = 0.12) has acceptable statistical quality and predictive potential as indicated by the value of cross validated squared correlation coefficient (q^2=0.73). From the build model it seems to be clear that H-Acceptor Count and T_T_O_7 topological parameter contribute negative biological activity. Thus this validated model brings important structural insight to aid the design of novel herbicidal agents.

Keyword: Pyrazinecarboxamides, Herbicidal, QSAR, Descriptors.

INTRODUCTION

Herbicides are inhibitors of individual metabolic processes in plants, used in agriculture as a selective means of defense against weeds. Weeds compete with crops for sunshine, water, nutrients, and physical space and are thus capable of greatly influencing the growth of crops and undermining both crop quality and yield. Also, many weeds are the harbor or nest of pathogens, viruses, and pests, which may result in the occurrence and spread of plant diseases and insect pests in crops. Herbicides, as the main weed control tool, play a very important role in modern agriculture. Crop protection continually needs the discovery of novel herbicides.

Since the discovery of the herbicide 2, 4-dichlorophenoxyacetic acid (2, 4-D) and 2, 4, 5-trichlorophenoxyacetic acid (2, 4, 5-T) Fig. 1, the agrochemical industry has successfully developed a wide array of herbicides with various chemical structures and modes of action [1]. However, an inevitable problem associated with the use of herbicides is the occurrence of herbicide resistant weeds [2]. Therefore, it is necessary to develop efficient herbicides with novel structures or modes of action to overcome the resistance of weeds.

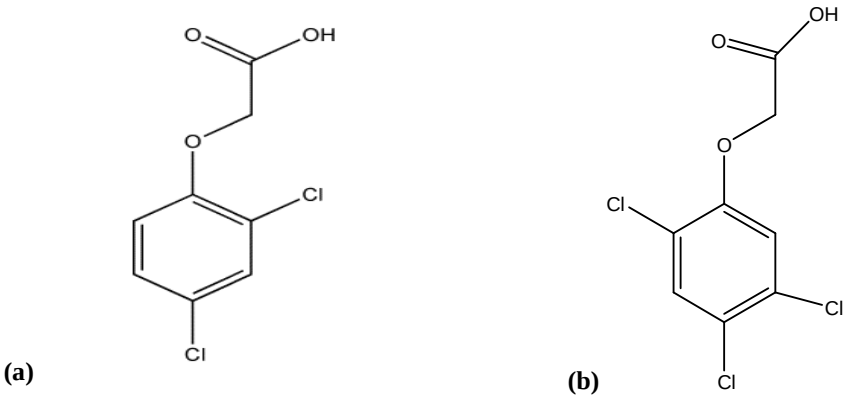


Figure 1- Structure of (a) 2, 4-D and (b) 2, 4, 5-T.

Analogues of pyrazinecarboxamides belong to the group of herbicides inhibiting the photosynthetic electron transport in spinch chloroplast. On the other hand, the pyrazinamide ring system has received much attention in biologically active molecules, such as potent inhibitors of mycobacterium and fungal. Herein, a series of novel pyrazinecarboxamides derivatives were performed the semi empirical quantum chemical method and molecular modeling.

MATERIALS AND METHODS

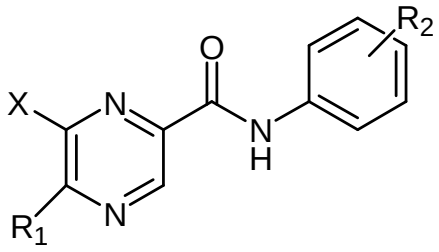
The biological data used in this study are the OER inhibition in spinach chloroplast (IC_{50}) of a series of pyrazine-2-corboxylic acid amides derivative. The synthesis and determination of the activity of these compounds have already been reported in literature [3]. Their study indicated that the pyrazinecarboxylic acid derivatives interested in binuclear analogue with the –CONH- bridge for herbicidal activity [4-6].

The general structure of these analogues and list of the structural features with herbicidal activity of the respective compounds under study is reported in Table 1. The biological data were converted to logarithmic scale (pIC_{50}) in mathematical operation mode of software to reduce skewness of data set and then used for subsequent QSAR analysis as dependent variables.

The molecular modeling studies were performed using MDS 3.0, supplied by V Life science [7]. The structure of each compound was drawn in 2DAppl mode of software and create the 3D model. Energy minimization was performed of each model using Merk Molecular Force Field (MMFF). Complete geometry optimization was performed taking the most extended conformations as starting geometries. The basis of energy minimization is that the drug binds to effectors/receptor in the most stable form i.e. minimum energy state form.

The relationship between biological activities and various descriptors (Physiochemical and alignment-independent) were established by sequential multiple regression analysis (MLR) using MDS 3.0, in order to obtain QSAR models. The MDS 3.0 program was employed for the calculation of different quantum chemical descriptors including heat of formation, dipole moment, local charges, and different topological [8, 9] and constitutional descriptors for each molecule. Chemical parameters including molar volume (V), molecular surface area (SA), hydrophobicity (log P), hydrogen acceptor count (HAC), hydration energy (HE) and molecular polarizability (MP) were also calculated by using software.

Table 1- BA of Data of Pyrazinecarboxamides Derivatives as an Herbicidal Agents.



Compounds	X	R_1	R_2	IC_{50} (µmol/L)
1.	H	H	2-Cl-5-OH	722
2.	H	H	4-F	480
3.	H	H	2-CF_3	376
4.	H	H	3-CF_3	130
5.	H	H	4-CH_3	1475
6.	Cl	H	2-Cl-5-OH	624
7.	Cl	H	4-F	384
8.	Cl	H	2-CF_3	557
9.	Cl	H	3-CF_3	229
10.	Cl	H	4-CH_3	1524
11.	H	$(CH_3)_3C$	4-F	524
12.	H	$(CH_3)_3C$	2-CF_3	55
13.	H	$(CH_3)_3C$	3-CF_3	283
14.	H	$(CH_3)_3C$	4-CH_3	164
15.	Cl	$(CH_3)_3C$	2-Cl-5-OH	625
16.	Cl	$(CH_3)_3C$	4-F	103
17.	Cl	$(CH_3)_3C$	2-CF_3	205
18.	Cl	$(CH_3)_3C$	3-CF_3	173
19.	Cl	$(CH_3)_3C$	4-CH_3	73

The calculated descriptors were gathered in a data matrix. First, the descriptors were checked for constant or near constant values and those detected were discarded from the original data matrix. Then, the descriptors were correlated with each other and with the activity data. Among the collinear descriptors detected, the one most highly correlated with activity was retained and the rest were omitted. Finally, MLR with stepwise selection and elimination of variables was applied to the development of QSAR models using software. The resulting models were validated by leave-one-out cross-validation procedures to check their predictivity and robustness. All calculations were run on a Pentium IV (2.6 MB CPU) with the Windows XP operating system. For the generation of the QSAR model we have selected the six test set and thirteen training set.

RESULTS AND DISCUSSION

When these compounds were subjected to QSAR analysis, in order to develop QSAR models, various statistically significant two parametric models were obtained. The parameters H-Acceptor Count (~70%) and T_T_O_7 (~30%) were negatively contributed in herbicidal activity (Fig. 2).

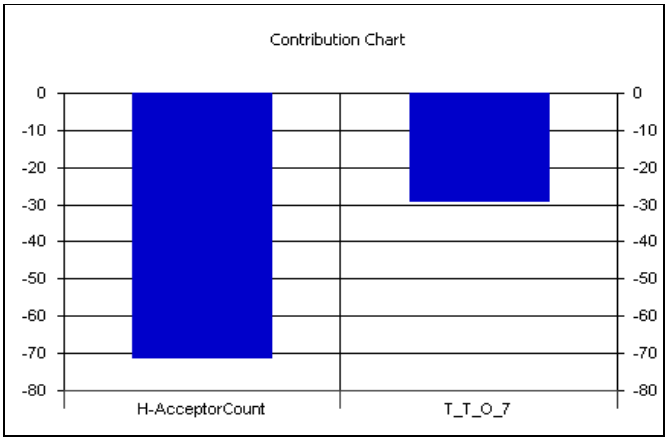


Figure 2- Contribution chart of descriptor for model 1

For each set of descriptors, the best multi-linear regression equations were obtained by the stepwise selection methods of MLR subroutine of the software. The squared correlation coefficient (r^2), standard error of estimate (r^2_se & q^2_se) and Fisher's value (F) which represents the F-ratio between the variance of actual and predicted activity, were employed to judge the validity of regression equation.. In order to validate the generated QSAR models leave one out (LOO) method was used. Squared cross correlation coefficient (q^2), predicted r^2 for external test set (pred_r^2), Z score calculated by q^2 in randomization test (Zscore_Q^2), highest q^2 value in the randomization test (best_ran_Q^2) and Statistical significance parameter obtained by randomization test (α) were also calculate for each model to estimate the predictive potential of model. The resulting regression equations that is model 1 and 2given as:

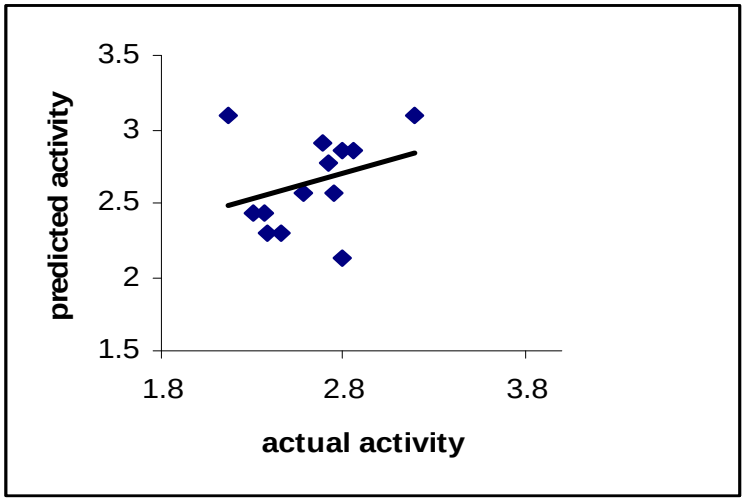
Model 1 (best model)
Log 10(IC_{50}) = 3.5153 - 0.1893 H Acceptor Count -0.0452 T_T_O_7
(r^2=0.85, q^2= 0.73, F=29.26, r^2se=0.12, Pred_r^2 =0.46)
Model 2
Log 10(IC_{50}) = 1.579 -0.1282 chi2
(r^2= 0.65, q^2= 0.58, F= 15.35, r^2 se= 0.54, Pred_r^2= 0.13)

In the above two QSAR models, models 1 is the best model, that indicate the effects of the two types of descriptors on the herbicidal activity of the studied pyrazinecarboxamides derivatives. A unified QSAR model 1 with high statistical quality (r^2 = 0.85, F=29.26, r^2 se = 0.12, Pred_r^2= 0.46 and q^2=0.73) was obtained from the pool of all type of descriptors. This equation contains T_T_O_7 this is count of any atoms (single, double or triple bonded) separated from any oxygen atom by 7 bond distance in a molecule and H acceptor count (signifies a number of hydrogen bond acceptor atoms).

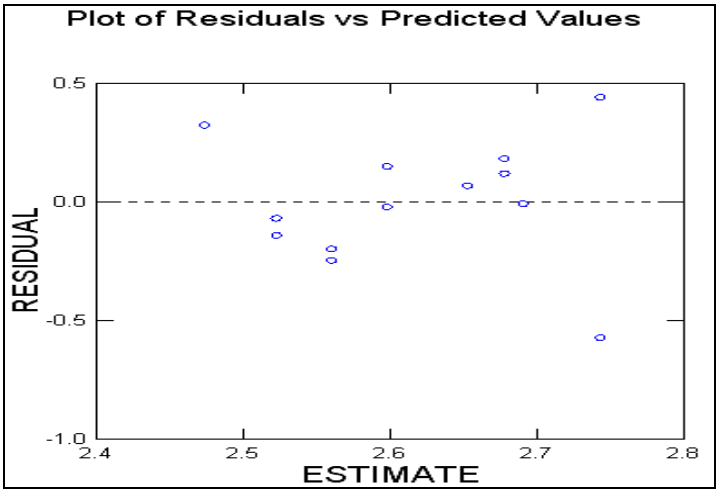
All compound from the data for MLR resulted in the generated model with improved statistical significance and predictive ability, this generated model can be developed for the series. All these models were screened on the basis of $q^2 > 0.7$ and the intercept to best fit line. Hence the best statistical results are reported in Table 2 and actual activity and predicted activity of best model shown in Table 3. The plots of cross-validated calculated activity and the corresponding residuals against the experimental values are represented in Fig. 3A and 3B, respectively. The residual plot shows the relatively uniform distribution of data around the zero line.

Table 2- Statistical Parameter of QSAR for model 1

n (Train/Test)	r^2	q^2	F	r^2se	q^2se	Pred_r^2	Pred_r^2se	Best Rand Q^2	DOF
13/6	0.85	0.73	29.26	0.12	0.16	0.46	0.27	0.148	10



(a)



(b)

Figure 3- Plot of (a) cross-validated calculated activity obtained and (b) residuals against the experimental activity for pyrazinecarboxamides derivatives.

Table 3- Actual and Predicted data of herbicidal Activity

Training set		Test set	
Actual Activity	**Predicted Activity**	**Actual Activity**	**Predicted Activity**
2.3800	2.2974	1.7404	2.4330
2.3118	2.4330	1.8133	2.9553
2.3598	2.4330	2.0128	2.7665
2.4518	2.2974	2.1139	2.4330
2.5752	2.5686	2.2148	2.4558
2.6812	2.9021	2.5843	2.9021
2.7193	2.7665		
2.7459	2.5686		
2.7952	2.8569		
2.7959	2.1212		
2.8585	2.8569		
2.1688	3.0914		
3.1830	3.0914		

The best model explains 85.41% variance in herbicidal activity. Low standard error of estimate of this model (<0.2) demonstrates the accuracy of the model. The model shows overall significance level better than 99% as the calculated F value exceed the tabulated $F_{(1, 10\ \alpha 0.05)}$ = 4.96 and higher q^2 value (> 0.7) and pred_r^2 (>0.4) reflects good predictive potential of the model.

In conclusion, above QSAR study reveals that the Hydrogen acceptor count and T_T_O_7 contributes the negatively, which indicate that Hydrogen acceptor count and T_T_O_7 contributes the negatively impact on herbicidal activity. This suggest that, by decreasing in H bond acceptor group and reduced the any atoms (single, double or triple bonded) separated from any oxygen atom by seven bond distance in a molecule will be helpful for designing of more potent herbicidal agents.

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