Quantitive-Strucutre Activity Relationship(QSAR) study of a New Heterocyclic Insecticides Using CoMFA and CoMSIA

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Abstract Three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were carried out on a series of 33 anthranilic diamides related to their insecticide activity as ryanodine receptor activation using CoMFA and CoMSIA. All models were carried out over a training set including 29 anthranilic diamides. For CoMFA model, cross-validated correlation coefficient q^2 is 0.720, non-cross-validated correlation coefficient r^2 is 0.894, F values is 81.449 and standard error of estimate (SE) values is 0.465. For CoMSIA model, they are 0.732, 0.850, 0.554 and 54.706 respectively. The predictive ability of the models was validated by four compounds that were not included in the training set. The deviation between prediction and experiment is small. These research results can provide valuable information for designing new potential insecticides interacting with ryanodine receptor.
Keywords anthranilic diamides; 3D-QSAR; insecticidal activity

Introduction

The safe and effective use of insecticides to fight serious crop damage from harmful pests is an essential element in both guarantee of food supply and prevention of disease transmission. Due to the ability of insects to rapidly develop resistance, the discovery of agents that act on new biochemical targets is an important tool for effective pest management. A new class of insecticides has been discovered, the anthranilic diamides, that provides exceptional control through action on a novel target, the ryanodine receptor. Rynaxypyr™ (Dupont's) is the first new insecticide from the anthranilic diamides, characterized by its high levels of insecticidal activity and low toxicity to mammals attributed to a high selectivity for insect over mammalian ryanodine receptors [1]. Owing to their prominent insecticidal activity, unique modes of action and good environmental profiles, anthranilic diamides and their chemical synthesis have recently attracted considerable attention in the field of novel agricultural insecticides [2-4].

In addition, the mechanism of insecticidal action of anthranilic diamides has not yet been clearly established, and there is so far no report about the binding model of anthranilic diamides with the receptor, which is crucial for the design of novel molecules.[5,6] Due to the limited reports on structure-activity approach, 3D-QSAR study were performed applying comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Both 3D-QSAR techniques compare molecular interaction fields In CoMFA, interaction fields are represented as steric and electrostatic interaction energies calculated using Lennard-Jones potential and Coulombic potential for a molecule in the data set at the intersections of a grid embedding that molecule.[7] Another molecular interaction field in CoMSIA,[8] which uses Gaussian functions to describe the similarities of steric, electrostatic, hydrophobic, and hydrogen bond donor and acceptor properties.[9] The outcome of the present work can provide valuable information for designing potential ryanodine receptor activator with high insecticidal activities.

Materials and methods

Selection of compounds and activities

The title compounds (**1-33** in **Tables 1**) and activities studied in this work were taken from the literature[1, 10]. The insecticidal activity reported are against fall armyworm (*Spodoptera frugiperda, Sf*), insecticidal potency as LC_{50} in ppm, which were collected and transformed into log ($10^6/LC_{50}$) values. For a stronger evaluation of model applicability for prediction on new chemicals, the data set was divided into two subdata sets. Four compounds were chosen randomly as a test set and were used for external validation of the 3D-QSAR models; the training sets included all the remaining 29 compounds. The structures and insecticidal activities of anthranilic diamides are summarized in **Tables 1.**

Superposition of molecules

All molecular modeling studies, CoMFA and CoMSIA, were performed using the Sybyl 6.91 software of Tripos running on a SGI (Silicon Graphics, Inc.) workstation. Compound **16** (Rynaxypyr™) was used in the systematic conformational search. First, all of the rotatable bonds in compound **16** were varied by using a step of 10°. Then, the lowest energy conformation identified in this conformational search was used as a template to build the other molecular structures. Each structure was fully geometry-optimized using a conjugate gradient minimization algorithm based on the Tripos force field and Gasteiger-Hückel charges and then aligned by an atom-by-atom least-square fit. We used the backbone of the **16** in its optimized conformation as a template, the atoms marked with an asterisk were used for rms-fitting onto the corresponding atoms of the template structure as shown in **Tables 1** (Series **I**), the superposition of all 29 compounds as shown in **Figure 1.**

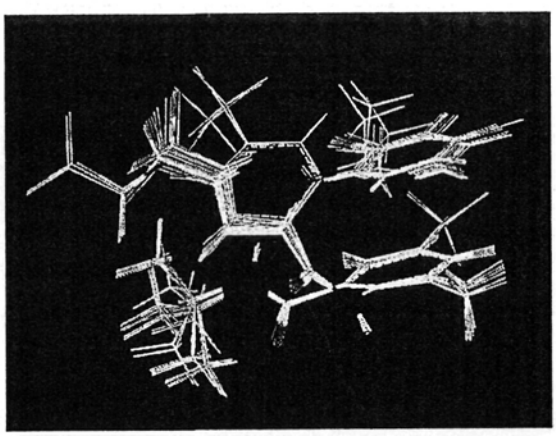


Figure 1 Superposition of 29 anthranilic diamides in the training and test sets

CoMFA and CoMSIA modeling

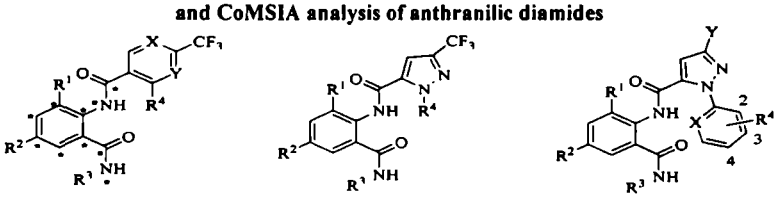
The steric and electrostatic potential fields for CoMFA were calculated at each lattice intersection of a regularly spaced grid of 2.0 Å. The lattice was defined automatically and was extended 4 Å units past Van der Waals volume of all molecules in X, Y, and Z directions. An sp^3 carbon atom with Van der Waals radius of 1.52 Å and +1.0 charge served as the probe atom to calculate steric (Lennard-Jones 6-12 potential) field energies and electrostatic (Columbic potential) fields with a distance-dependent dielectric at each lattice point. The steric and electrostatic contributions were truncated to 30.0 kcal/mol, and electrostatic contributions were ignored at lattice intersections with maximum steric interactions. The CoMFA steric and electrostatic

fields generated were scaled by CoMFA standard option given in SYBYL. In the CoMSIA analyses, similarity is expressed in terms of steric occupancy, electrostatic interactions, local hydrophobicity, and H-bond donor and acceptor properties, as the same method of CoMFA. The experimental and predicted activity values for the training and test set molecules by the 3D-QSAR model from CoMFA and CoMSIA analysis are given in **Table 1**. Both the CoMFA and CoMSIA models obtained exhibited a good predictability on these compounds.

Partial Least-Square (PLS) calculations and validations

PLS methodology was used for all 3D-QSAR analyses[11,12] , in which the CoMFA and CoMSIA descriptors were used as independent variables and LC_{50} values were used as dependent variables. The cross validation with leave-one-out (LOO) option and the SAMPLS program[13], rather than column filtering, were carried out to obtain the optimum number of components to be used in the final analysis. After the optimum number of components (n) was determined, a non-cross-validated analysis was performed without column filtering. The cross-validated correlation coefficient q^2, non-cross-validated correlation coefficient r^2, and F values and standard error of estimate (SE) values were computed according to the definitions in SYBYL.

Table 1 Structures, experimental activities and predicted activities by the 3D-QSAR model from CoMFA and CoMSIA analysis of anthranilic diamides



I II III

NO.	Series	R^1	R^2	R^3	R^4	X	Y	pLC_{50}	Predicted	
									CoMFA	CoMSIA
1	I	Me	H	*i*-Pr	Me	C	C	4.70	4.54	4.65
2	I	Me	H	*i*-Pr	Me	N	N	4.15	4.25	4.51
3	II	Me	H	*i*-Pr	Me	-	-	4.31	4.26	4.42
4	II	Me	H	*i*-Pr	Et	-	-	4.05	4.18	4.41
5	II	Me	H	*i*-Pr	*i*-Pr	-	-	4.64	4.87	4.53
6	III	Me	H	*i*-Pr	H	C	CF_3	4.32	4.15	4.31
7	III	Me	H	*i*-Pr	2-Cl	C	CF_3	6.70	5.32	5.10
8	III	Cl	H	*i*-Pr	2-Cl	C	CF_3	6.40	6.25	5.58
9	III	Me	H	*i*-Pr	H	C	CF_3	5.54	5.45	5.16
10	III	Me	H	*i*-Pr	2-F	C	CF_3	6.28	5.13	4.80
11	III	Me	H	*i*-Pr	3-Cl	C	CF_3	3.30	4.13	4.55
12	III	Me	H	*i*-Pr	4-Cl	C	CF_3	3.30	4.28	4.41
13	III	Me	H	*i*-Pr	2-Cl	N	CF_3	7.0	7.25	7.04
14	III	Me	Cl	Me	2-Cl	N	CF_3	7.70	7.46	7.14
15	III	Me	Cl	*i*-Pr	2-Cl	N	CF_3	7.52	7.73	7.32
16	III	Me	Cl	Me	2-Cl	N	Br	7.70	7.72	7.14
17	III	Me	Cl	*i*-Pr	2-Cl	N	Br	7.40	7.84	7.34
18	III	Me	Cl	Me	2-Cl	N	Cl	7.52	7.26	7.13
19	III	Me	Cl	*i*-Pr	2-Cl	N	Cl	7.30	7.07	7.09
20	III	Me	Br	*i*-Pr	2-Cl	N	CF_3	7.52	6.74	7.03
21	III	Me	Br	Me	2-Cl	N	Br	6.74	7.18	7.23
22	III	Me	I	Me	2-Cl	N	CF_3	6.59	6.67	7.27
23	III	Me	I	Me	2-Cl	N	Br	6.89	6.88	7.32
24	III	Me	CF_3	Me	2-Cl	N	CF_3	6.28	6.46	7.15
25	III	Me	CF_3	*i*-Pr	2-Cl	N	CF_3	6.41	6.87	7.20
26	III	Me	Cl	Me	2-Cl	N	OCH_3	6.17	6.46	6.62
27	III	Me	Cl	Me	2-Cl	N	OCF_2H	6.68	6.53	6.73

28	III	Me	Cl	*i*-Pr	2-Cl	N	OCF_2H	6.85	6.85	6.86
29	III	Me	Cl	*i*-Pr	2-Cl	N	OCH_2CF_3	7.52	7.26	7.00
30[a]	I	Me	H	*i*-Pr	Me	C	N	4.34	4.34	4.61
31[a]	III	Cl	H	*i*-Pr	2-Cl	N	CF_3	7.0	7.30	7.11
32[a]	III	Me	Cl	*i*-Pr	2-Cl	N	OCH_3	6.52	6.53	6.64
33[a]	III	Me	Cl	Me	2-Cl	N	OCH_2CF_3	6.96	7.08	6.90

[a] These compounds were used as a test set

Table 2 CoMFA and CoMSIA analysis results

Model	Cross-validated		Conventional			Relative contributions/%				
	q2	*n*	r^2	SE	F	Steric	Electrostatic	Hydrophobic	Hydrogen bond	Hydrogen receptor
CoMFA	0.720	3	0.894	0.465	81.449	67.4	32.6			
CoMSIA	0.732	3	0.850	0.554	54.706	7.1	23.2	42.7	26.4	0.5

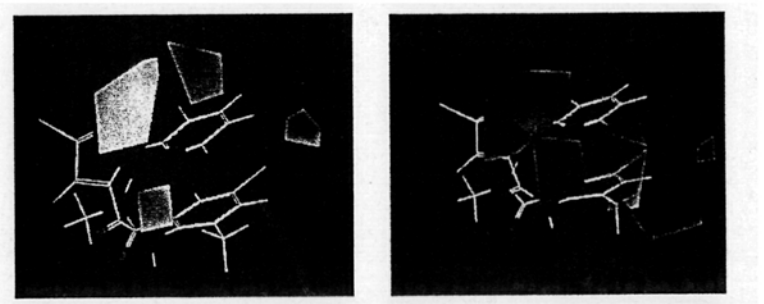
Result and discussion

CoMFA and CoMSIA analysis results

The results of CoMFA and CoMSIA studies are summarized in **Table 2**. The number of components in the PLS models was three. The two models had a high cross-validated correlation coefficient ($q^2 > 0.7$) and non-cross-validated correlation coefficient ($r^2 > 0.85$), a low standard error of estimate (SE) and a high Fischer ratio (F). The CoMFA analyses revealed that contributions of steric field and electrostatic field was 67.4% and 32.6%, respectively, the steric field had the major contribution in the model. In CoMSIA model, contributions of steric field, electrostatic field, hydrophobic field and hydrogen bond donor and acceptor field was 7.1%, 23.2%, 42.7%, 26.4% and 0.5%, respectively, the hydrophobic field had the major contribution in the model.

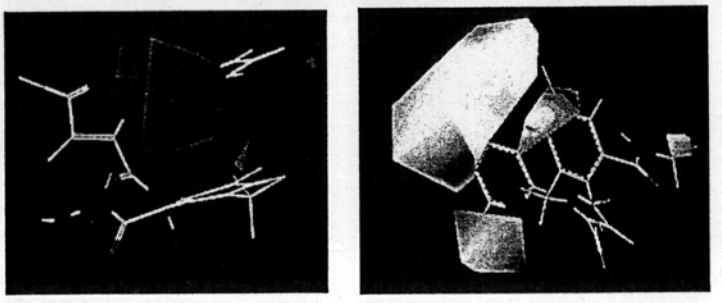
CoMFA and CoMSIA coefficient contour plots

The coefficient contour plots are helpful to identify important regions where any change in the steric, electrostatic, hydrophobic fields and hydrogen bond donor and acceptor field may affect the biological activity. The CoMFA and CoMSIA coefficient contour plots are shown in Figures **2** and Figures **3.** According to the CoMFA steric maps (Figures **2a**), which had the major contribution in the CoMFA model, the green contour defines a region where bulkier substituents at pyridyl position may give compounds with improved activity. For the electrostatic maps, CoMFA and CoMSIA analyses reveal essentially similar results here. The blue contour defines a region where increasing positive charge will result in increasing the activity, whereas the red contour defines a region of space where increasing electron density is favorable. A predominant feature of the electrostatic plot is the presence of a red contour surrounding the pyridylpyrazole ring. It could be reasonably presumed that there is a significant electrostatic interaction between the pyridylpyrazole ring and the possible receptor, and it may be assumed that the faction of receptor around the red region is electropositive. Gray and yellow contours of the currently reported CoMSIA model in Figure **3b** indicated the areas where hydrophilic and hydrophobic properties were preferred, respectively, and will be useful in selecting specific areas of the molecules to be utilized for adjusting the lipophilicity and hydrophilicity to improve insecticidal activity. According to the CoMSIA hydrophobic map, hydrophobic residues at 2-substitution position of phenylpyrazole or pyridylpyrazole (**Series III**) are preferred for increasing their insecticidal activity. This can be seen from the activities of compounds **7**, **8**, and **13** that possess hydrophobic groups at the 2-substituent (R^4) of phenylpyrazole or pyridylpyrazole.



(a) (b)

Figure 2 CoMFA model
(a) steric field; (b) electrostatic field



(a) (b)

Figure 3 CoMSIA model
(**a**) electrostatic field; (**b**) Hydrophobic filed

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