Pharmacophore
(An International Research Journal)
Available online at http://www.pharmacophorejournal.com/
Original Research Paper

3D QSAR, PHARMACOPHORE INDENTIFICATION STUDIES ON SERIES OF IMIDAZOPYRIDINE ANALOGS AS NEMATICIDAL ACTIVITY

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ABSTRACT

Chalcone derivatives or 1,3-diphenyl-2-propen-1-ones and imidazopyridine are known for multiple anti-infective activities such as nematicidal activity. The advances in the computational chemistry can be use full for designing of new chemical entities. The pharmacophore identification and QSAR studies on imidazopyridine analogs have been carried out. 3D QSAR model developed considering training and test set approaches with step wise variable selection method. QSAR models which were further validated for statistical significance and predictive ability by internal and external validation. The hydrogen bond accepter, hydrogen bond donor, positively charged, aromatic carbon, steric and hydrophobic parameter is the important features which are contributing towards the activity. The selected best QSAR model A has a training set of 20 molecules and test set of 6 molecules with correction coefficient of 0.9641.

Keywords: 3-Diphenyl-2-propen-1-ones, Imidazopyridine, Nematicidal activity, 3D QSAR, PLS, Chalcone.

INTRODUCTION

Several studies have shown that chalcone derivative or 1, 3-diphenyl-2-propen-1- Ones compounds are active on infectious germs by inhibiting certain enzymes having thiol function, such as glutathione S-transferase. They may prevent degradation and excretion of anti-infective drugs. Moreover, their action could also delay or even prevent emergence of new drug-resistant strains of parasites. Such property could be exploited in the design, the synthesis and the development of novel anthelmintic agents. Such agents are used for fight against *Haemonchus contortus*. Moreover, resistance to anthelmintic agents observed in some parasites, in particular *Haemonchus contortus*. The main reason for this is related to the current misuse of usual anthelmintic drugs. Owing of their therapeutic efficacy, fight against *Haemonchus* was confined to the systematic use of various drugs especially those with benzimidazole structure (albendazole, mebendazole, fenbendazole, etc.). This led to the emergence of resistant parasite strains to these benzimidazole anthelmintics. The search for new molecules that can fight effectively against *Haemonchus* becomes crucial. In this context we are interested in chalcones and imidazopyridine. The imidazopyridine derivatives are known for their multiple anti-infective activities. Quantitative structure-activity (QSAR) studies are of great importance in modern chemistry. The goal of QSAR is to transform searches for compounds with desired properties using chemical knowledge and experience into a mathematically quantified form. Thus, the QSAR approach accelerates the process of development of

new molecules for use as drugs. In partial least squares regression is an extension of the multiple linear regression models. In it's simplest form, a linear model specifies the (linear) relationship between a dependent (response) variable Y, and a set of predictor variables X's. PLS regression, the X block of independent variables (descriptors) is correlated with the y vector (activities) in such a way that the projected coordinates. T, are good predictors of y. partial least squares regression is probably the least restrictive of the various multivariate extensions of the multiple linear regression model. We present here our Pharmacophore identification and 3D-QSAR studies using PLS method on training set of imidazopyridine derivatives as nematicidal activity by considering the steric and electrostatic influences.[1-6]

MATERIALS AND METHODS

Computational Details

Dataset

A dataset of 26 compounds was taken from the published nematicidal activity by Sissouma *et.al*.[7] The structures and their activities are listed in Table 1. The whole dataset was randomly divided into a training set of 20 compounds and a test set 6 of compounds (asterisked molecules in Table 1). The training set was used to construct 3D-QSAR models and the test set was used for the models validation.

Ligand preparation

The structure of imidazopyridine was used as template to build the molecules in the dataset in Vlife MDS 3.5. All the structure was minimized using the standard Merck Molecular Force Field (MMFF) with distance dependant dielectric function and energy gradient of 0.001 kcal/mol A^0.

Molecular alignment

The molecules of the dataset were aligned by the template based technique, using common structure of imidazopyridine. The alignment of all the molecules on the template is shown in figure.no.2.

Descriptor calculation

Like many 3D QSAR methods, a suitable alignment of given set of molecules was performed using the Vlife MDS 3.5 Engine. This was followed by generation of a common rectangular grid around the molecules. The hydrophilic, steric and electrostatic interaction energies which are computed at the lattice points of the grid using a methyl probe of charge +1.

3D QSAR studies using partial least squares regression

A relationship between independent and dependent variables (3D fields and biological activities, respectively) were determined statistically using regression analysis. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. The quality of fit for a regression equation was assessed relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. Quality of selected models was further ascertained to select the best model from cross-validated squared correlation coefficient (q2). For a regression model, r2 was used to describe the fitness of data and fitness is considered to improve as r2 approaches 1. Thus models having correlation coefficient above 0.7 were used to check the external predictivity while the significance of the model was decided on the basis of F value. Models showing q2 below 0.6 were discarded. The selected models are shown in Table 2.

Pharmacophore modeling

Pharmacophore modeling was carried out using the mol sign module of V Life MDS 3.5 software and ligand scout 3.02. Series of imidazopyridine derivatives were first aligned on the active molecule. The software was set to generate minimum 4 pharmacophoric features obtained keeping the tolerance limit at 10 A^0.

RESULTS

In the present study, 20 molecules were used in the training set (Table 1) to derive 3D QSAR models with the number of field grid points being not more than five per model. To evaluate the predictive ability of generated 3D-QSAR models, and test set of 6 molecules with regularly distributed biological activities was used (Table 1). On successful run of PLS two models were selected they are shown in table no 2.

DISCUSSION

Interpretation of 3QSAR Model

The optimum structural properties of imidazopyridine analogs for nematicidal activity were obtained in the form of the 3D descriptors of model A. The r^2 value for model A was 0.9641 while that of model B was 0.9185. Model A shows the first model which is selected on the basis of statistical coefficient like r2 (0.9641) and Pred r2 (0.5574). The contributing descriptor for model A are S_757, E_548, S_765, S_678 which are nothing but the electrostatic and steric interaction at that lattice point. The electrostatic interaction at lattice point E_548,steric interaction S_765, S_678 are negatively contributing means substitution of electron withdrawing groups can yield potent nematicidal. The steric interaction at the lattice point S_757 is positively contributing so the substitution favouring this interaction at that lattice point could yield active molecule. Model B r2 (0.9185) and Pred r2 (0.6337) is not as good as model A in terms of correlation (figure no. 2 & 3) of the selected field descriptors with biological activity as well as its predictive ability (table no2).

Pharmacophore Identification Studies Using V Life MDS 3.5

A set of pharmacophore hypothesis was generated using the mole sign module of V life MDS 3.5 on the reported nematicidal activity. Each hypothesis was found to contain common features like hydrogen bond doner, hydrogen bond acceptor, positive ionizable and aromatic.

The pharmacophore hypothesis generated in V life MDS 3.5 (figure no. 4) indicated the significance of presence of five aromatic features for the nematicidal activity; these features are contributed by the imidazopyridine nucleus, which are separated by 1.2 $A^{0.}$ The positive ionizable is also important feature for nematicidal activity, in present data set the phenolic group is contributing pi bonding. The carbonyl oxygen is contributing the hydrogen bond acceptance while the hydrogen bond donation is contributed by the substitution on the aromatic rings.

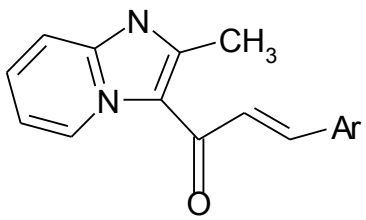
CONCLUSION

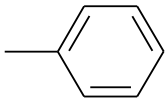
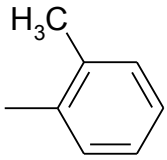
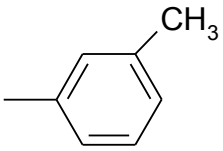
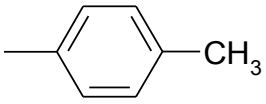
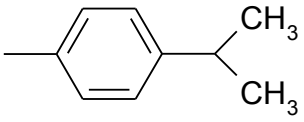
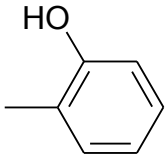
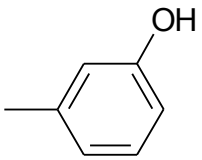
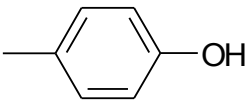
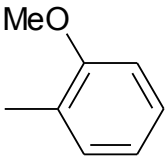
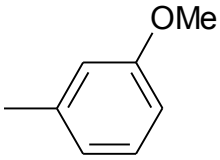
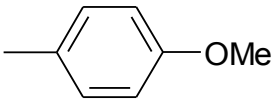
The present communication is an attempt to indentify the structural requirement of imidazopyridinyl analogs for nematicidal activity. The model derived from this investigation having good predictive ability, which could aid new nematicidal prior to their synthesis.

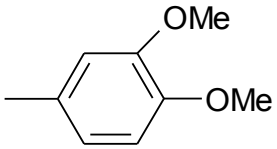
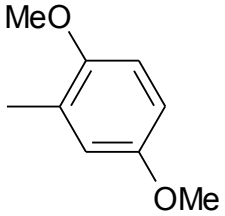
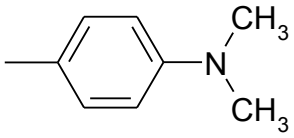
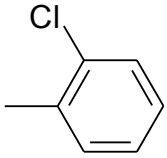
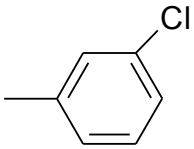
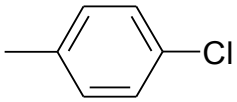
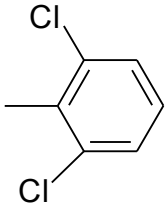
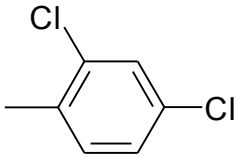
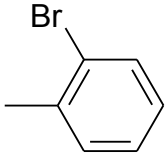
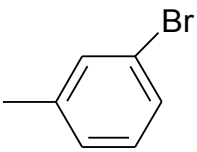
ACKNOWLEDGEMENTS

The authors are thanking full to Dr. H. N. More, Principal Bharati Vidyapeeth College of Pharmacy, Kolhapur for providing facilities to carry out the research work.

Table 1: Showing derivatives under study with observed and predicted activity



Sr. No.	Compound code	R	Observed activity	Predicted activity
1.	5a		0.380387	0.409166
2.	5b		0.380535	0.409166
3.	5c*		0.429747	0.409166
4.	5d		0.380387	0.409166
5.	5e		0.429747	0.409166
6.	5f		0.380535	0.409166
7.	5g*		0.380535	0.409166
8.	5h*		0.380535	0.409166
9.	5i		0.380535	0.409166
10.	5j		2.183969	0.409166
11.	5k		0.587099	0.409166

12.	5l		0.429747	0.409166
13.	5m		0.380535	0.409166
14.	5n		-0.30294	0.409166
15.	5o*		0.380535	0.409166
16.	5p		0.587099	0.409166
17.	5q		0.587099	0.409166
18.	5r*		0.380535	0.409166
19.	5s		-0.30294	0.409166
20.	5t*		-0.37051	0.409166
21.	5u		0.380535	0.409166

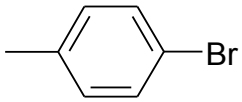
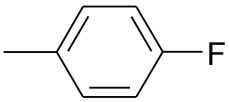
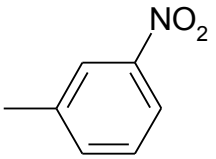
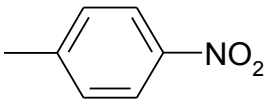
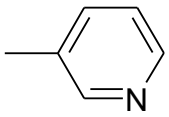
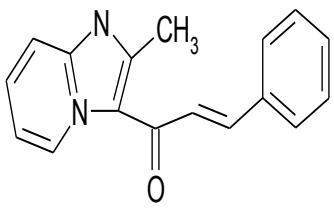
22.	5v		0.380535	0.409166
23.	5w		-0.37051	0.409166
24.	5x		0.380535	0.457882
25.	5y		0.380535	0.421148
26.	5z		0.380535	0.530215

Table 2: Showing the selected MLR QSAR equations along with statistical parameters employed for model selection.

Model No.	QSAR model	N	r2	q2	F value	Pred r2
A	Pic80= 0.0053+ 0.1250S_757-0.0403E_548-0.1491S_765-0.0135S_678	26	0.9641	0.94	100.8098	0.5574



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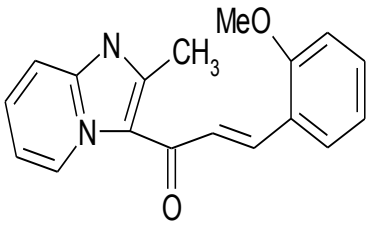

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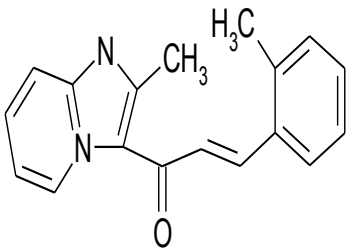

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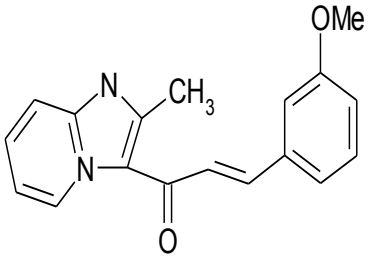

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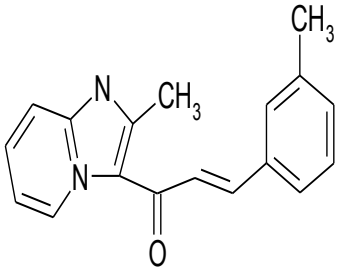

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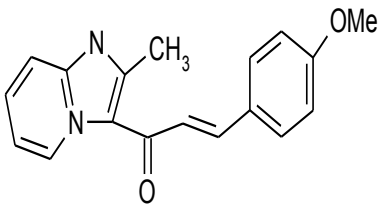

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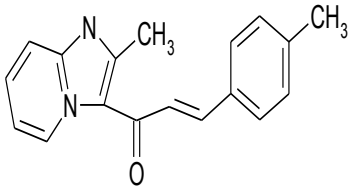

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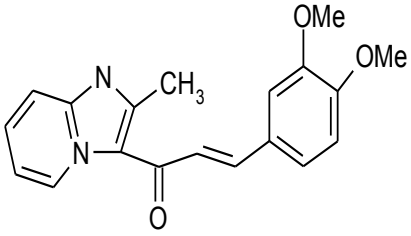

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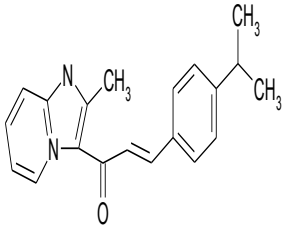

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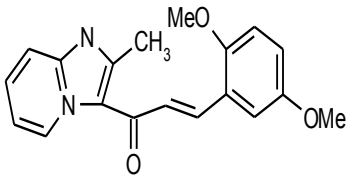

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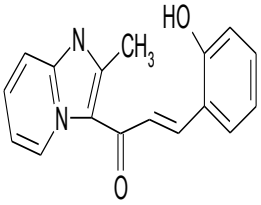

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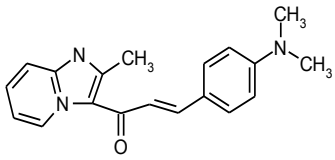

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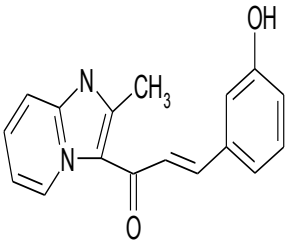

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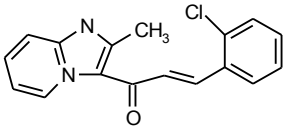

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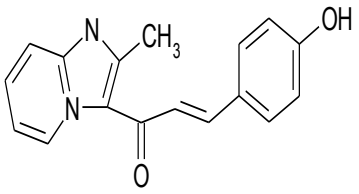

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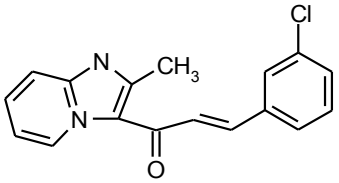

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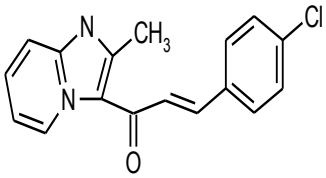

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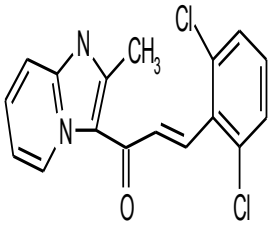

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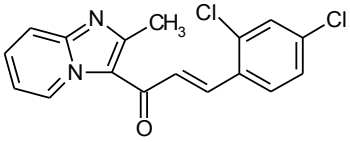

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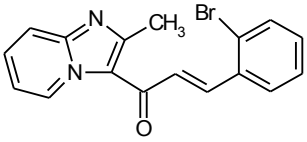

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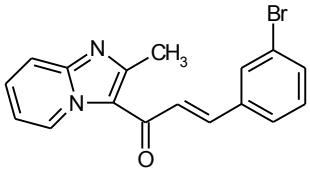

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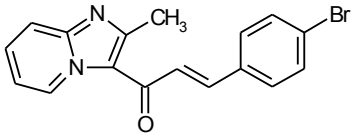

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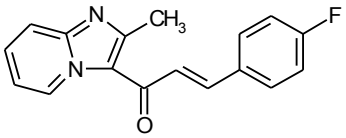

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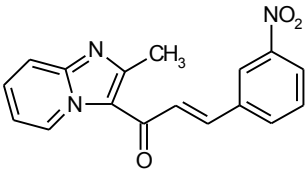

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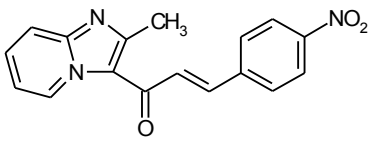

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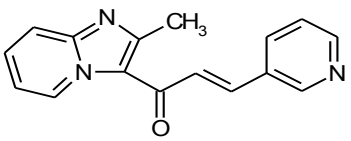

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Figure 1: Showing molecules under study

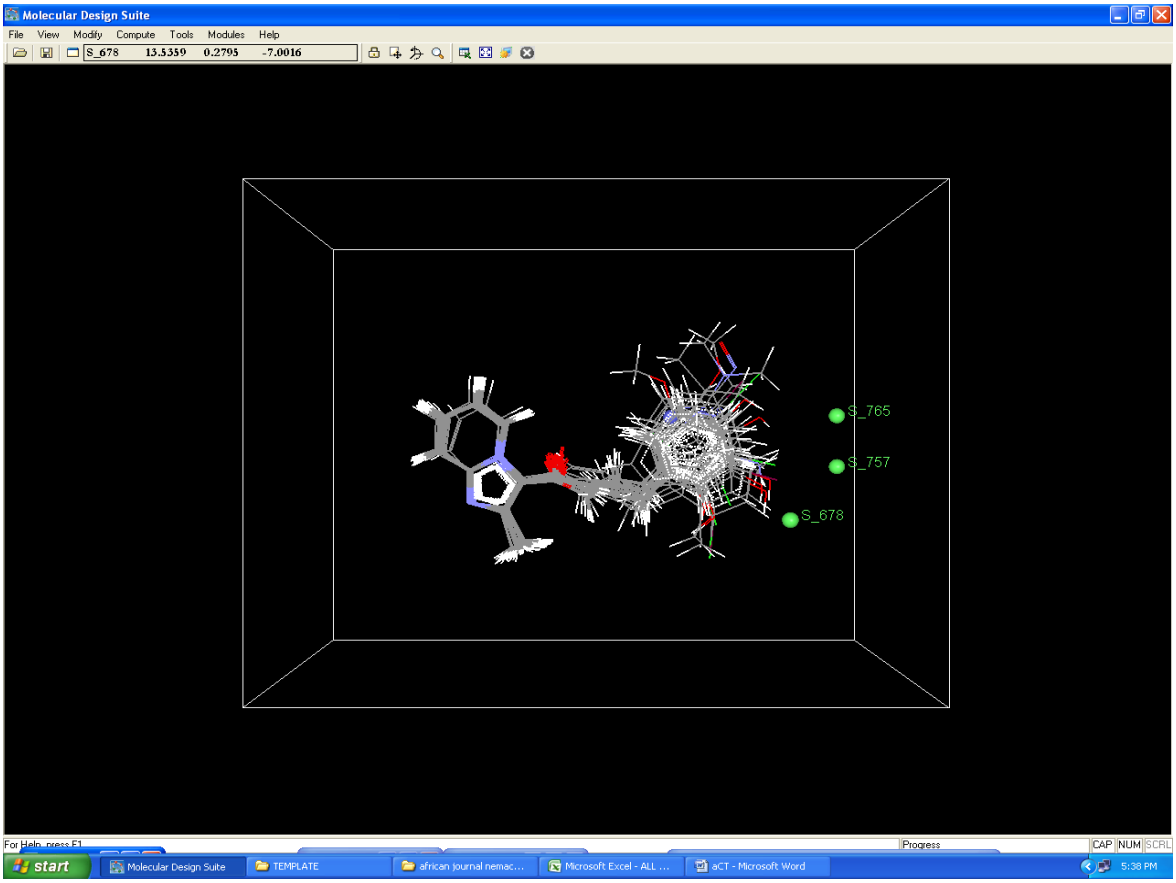

Figure 2: Showing the alignment of the molecules

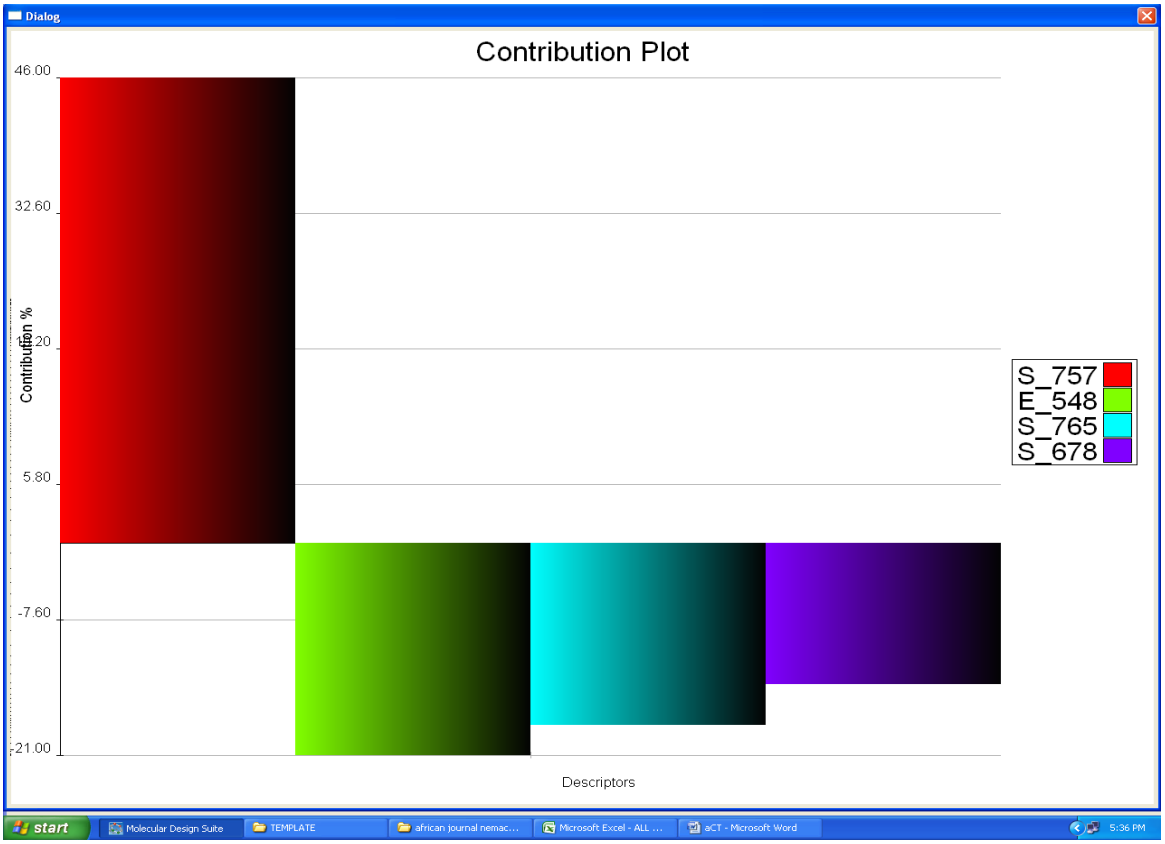

Figure 3: Showing contribution plot of selected QSAR model A

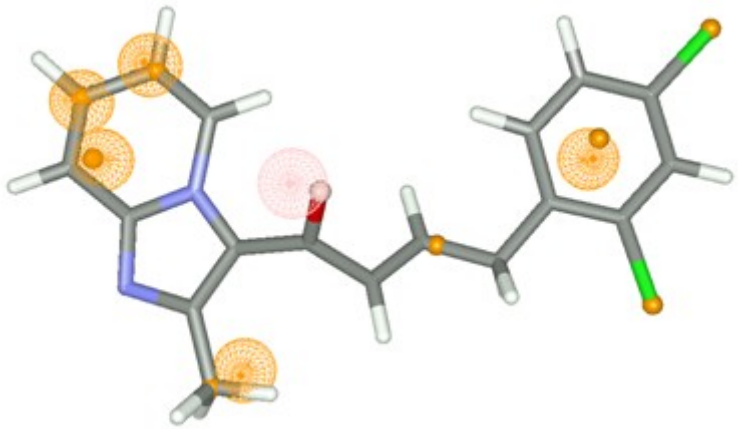

Figure 4: Showing selected pharmacophore model generated through V life MDS

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