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Experimental and modelling studies on antifungal compounds

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Abstract: Antifungal activity of organic compounds (aromatic, salicylic derivatives, cinnamyl derivatives etc) on *Fusarium Rosium* (14 compounds) and *Aspergillus niger* (17 compounds) was studied and QSAR models were developed relating molecular descriptors with the observed activity. Back propagation Neural Network models and single and multiple regression models were tested for predicting the observed activity. The data fit as well as the predictive capability of the neural network models were satisfactory ($R^2 = 0.84$, $q^2 = 0.73$ for *Fusarium Rosium* and $R^2 = 0.75$, $q^2 = 0.62$ for *Aspergillus niger*). The descriptors used in the network for the former were X4 (connectivity) and Jhetv (topological); and TIC1 (information) and SPI (topological) for the latter fungus. Antifungal activities of these organic compounds were generally lower against the latter than with the former fungus.
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1 Introduction

Fungi constitute a large group of organisms, which are variable in form, behaviour and life cycle patterns. *Aspergillus* is a filamentous, cosmopolitan and ubiquitous fungus found in nature. It is commonly isolated from soil, plant debris, and indoor air environment. The genus *Aspergillus* includes over 185 species. Around 20 species have so far been reported as causative agents of opportunistic infections in man. Among these, *Aspergillus fumigatus*

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is the most commonly isolated species, followed by *Aspergillus flavus* and *Aspergillus niger*. *Aspergillus* niger causes storage rot of fruits and seeds. It is also used to extract a commercial enzyme pectinase that is used in coffee bean fermentation and wine and juice clarification [1]. *Fusarium* spp. are higher fungi whose sexual stage is unknown [2]. Due to the great variability within this genus, it is one of the most difficult of all fungal groups to distinguish taxonomically. Several mycotoxins are produced by F. roseum. Since the control of mycotoxin producing fungi is essential, constant screening is done to get new antifungal compounds. One of the potent antifungal agents with novel mode of action is UHDBT 1 (5-n-indecyl-6-hydroxy-4,7-dioxobenzothiazole). A series of UHDBT 1 analogues with 1,4-quinone moiety such as 4,7-benzimidazolediones and 4,7-dioxobenzothiazoles showed potent antifungal activity against pathogenic fungi [3]. Native Kenyan plants containing muzigadial, warburganal, polygodial, ugandensidial, muzigadiolide, and Azadirachtin have also been found to be effective against *Fusarium oxysporum, Alternaria passiflorae,* and *Aspergillus niger* [4].

Quantitative structure activity relationship (QSAR) of existing antifungals will aid in the design of new and better drugs. Two novel structural descriptors namely, lone-pair electrons index (LEI) and molecular volume index (MVI) were tested on 24 heterocyclic nitrogen containing compounds against miracidium, 19 benzyl alcohols against *Aspergillus niger* and 50 substituted phenols against tetrahymena pyriformis [5]. MIC values of 1,4-quinone derivatives on *Aspergillus niger* exhibited a strong correlation with steric and electrostatic factors of the 3D structure of the molecules [3]. The relative contributions of steric and electrostatic were 65.1% and 34.9%, respectively. Rungta et al have considered several structural descriptors to develop QSAR relationship to predict antifungal activity against *Fusarium* and *Aspergillus* species [4]. Biological activity of twenty four chlorinated aliphatic hydrocarbons has been studied in the mold *Aspergillus* nidulans and QSAR analysis indicated that toxic effects induced by these compounds are mainly dependent on steric factors, such as molar refractivity and ease with which they accept electrons, represented by LUMO (energy of the lowest unoccupied molecular orbital) [6]. Wiktorowicz et al have studied the quantitative structure activity relationships of a series of imidazole derivatives as potential new antifungal drugs [7]. Prabhakar et al have synthesised 2,3,4-substituted thiazolidines and studied their antifungal activity against *Candida albicans, Cryptococcus neoformans, Tricophyton mentagrophyte* and *Aspergillus fumigatus* [8]. The present paper discusses experimental and QSAR studies carried out on a set of organic compounds tested for their antifungal activity against *Aspergillus niger* and *Fusarium Rosium.*

2 Experimental

2.1 Experimental and biological activity determination

The fungi used for this study were isolated using dilution plating method in Czapek dox's medium [9]. In this method samples of residue were macerated, then diluted and spread

on the surface of selective agar plates. If suitable selective media are available which inhibit the growth of more rapidly growing saprophytes, plating can be a very sensitive method for detection. They were identified and documented in the Department of Biosciences, SSSIHL, PN, A. P. The fungi chosen for this study were all pathogenic to the plant species. The following compounds with their respective quantities shown below were dissolved in distilled water and the volume made up to one litre.

Sucrose	15 g
Glucose	15 g
Polypeptone	5 g
Dipotassium hydrogen phosphate	1 g
Magnesium sulphate	5 g
Potassium chloride	5 g
Ferrous sulphate	0.01 g

A pinch of amoxicillin was added to prevent bacterial growth.

5 ml fractions of the homogenized solution were taken in 25 ml test tubes and sterilized in an autoclave for a period of 45 min. 5 ml of the sterilized medium was inoculated with a pathogenic fungi and the fungus was incubated at 31^{o}C for a period of 24 h. To the 24 h culture 0.2 ml of the test solution (0.1 ppm concentration of the compounds in dimethyl formamide (DMF)) was added. The test tubes were shaken well and incubated for 48 h at 31^{o}C. DMF was used as the control solvent. The extent of inhibition (anti-fungal activity) was determined by measuring the increase in turbidity in terms of % transmission at 660 nm. Lower turbidity value indicated higher antifungal activity.

Fourteen organic compounds (listed in Table 1) were tested against *Fusarium Rosium* and seventeen compounds (listed in Table 2) were tested against *Aspergillus niger* for their antifungal activity. Eight of these compounds were common for both the fungi.

2.2 Modelling methodology

The chemical structure of the molecules (in Tables 1 and 2) was drawn and energy minimized by Hyperchem® software (Hypercube Inc. USA, version 7) using MM+ force field and PM3 semi-empirical quantum mechanical methods. 407 molecular descriptors from Dragon software® (Milano Chemometerics, Italy) that included constitutional, topological, charge, geometrical and empirical, aromaticity indices, and constitutive properties; 19 descriptors from Hyperchem software® that included quantum mechanics and thermodynamics; and 48 descriptors from Cerius^2 software® (Acceryls Inc, USA) were evaluated. Several literature reports give a very detailed description of these descriptors [10–14].

Table 1 Experimental activity data against *Fusarium Rosium*.

Compound	% Transmission ± error
Citral	59.1 ± 2.0
Geraniol	60.7 ± 2.0
Menthol	73.6 ± 2.5
Camphor	73.0 ± 2.4
Coumarin	83.1 ± 2.8
Chalcone	77.8 ± 2.6
Cinnamic acid	58.9 ± 2.0
Citronellol	61. 7 ± 2.1
Methyl benzoate	63.6 ± 2.1
Acetyl methyl salicylate	59.3 ± 2.0
Benzyl alcohol	65.2 ± 2.2
Benzoic acid	56.8 ± 1.9
Salicylic acid	64.3 ± 2.1
Methyl salicylate	79.3 ± 2.6

Table 2 Experimental activity data against *Aspergillus niger*.

Compound	% Transmission ± error
resorcinol aldehyde	36.8 ± 2.0
nitroresorcinol	65.0 ± 1.3
2,4dinitrophenol	64.2 ± 2.2
2-aminophenol	42.4 ± 1.5
4-aminophenol	53.8 ± 1.8
salicylic acid	34.9 ± 1.2
methyl salicylate	15.3 ± 0.6
salicylaldehyde	63.5 ± 2.1
benzoic acid	50.4 ± 1.7
benzaldehyde	64.5 ± 2.1
methyl benzoate	26.3 ± 1.0
benzylalcohol	58.5 ± 1.9
phenyl acetate	58.0 ± 1.9
coumarin	45.3 ± 1.5
chalcone	44.9 ± 1.5
cinnamic acid	34.6 ± 1.2
cinnamaldehyde	48.3 ± 1.6

Statistical techniques such as Cluster Analysis, Principal Component Analysis and Non linear regression analysis were performed on the data set using SYSTAT® (SPSS Inc., USA) and Ky Plot® (ver 2, Beta, free Application, USA) software. The same were used for estimating dissimilarity distance and correlation coefficients between various molecular descriptors. These analyses were carried out to select the best set of molecular descriptors, to be used in the regression and neural network models, from the large pool.

Neural Network simulations were performed using NEURALWARE® software (NeuralWare, Inc., PA USA). Back propagation neural network with TanH transfer function was used with Delta learning rule and 16 epochs for all the data sets. The learning was carried out with 50000 cycles. The data was divided into two sets, the learning data set and testing/validating data set. The learning data set was used to train the network. The testing/validation data set was used to test the predictive capability of the network. This is done to be sure that the data is not over fitted, which can happen in neural network. The number of processing element in the hidden layer is altered systematically so that it is minimum, but is able to fit the data well and as well as have good predictive capability. The goodness of the regression fits were estimated using parameters such as, R^2(= 1 - SSE / TSS), R^2_{adj}(= 1 – (n-1) (1- R^2) / (n-p-1)), q^2 (= 1- PRESS / TSS), F ratio (= (n-2) R^2 /(1- R^2)) and MSSE (= mean sum of square of error = SSE / n) where,
n = number of data points and p = number of parameters in the model

$$\mathrm{TSS} = \Sigma(\mathrm{y}_{data,i} - \mathrm{y}_{avg})^2 \tag{1}$$

$$\mathrm{SSE} = \Sigma g(\mathrm{y}_{model,i} - \mathrm{y}_{data,i})^2 \tag{2}$$

$$\mathrm{yavg} = \Sigma \frac{\mathrm{y}_{data,i}}{n} \tag{3}$$

$\mathrm{y}_{data,i}$ = data points and $\mathrm{y}_{model,i}$ = model predictions

PRESS = predictive sum of squares. A model is developed with only (n-1) data points and the n^{th} point, which is left out, is predicted using this model. This exercise is carried out for all the points. The sum of squares of the difference between these predicted data (using the 'leave-one-out' scheme) and the actual values are called PRESS.

Predictive capability of a model is gauged from q^2, which is defined above. A large F indicates that the model fit is not a chance occurrence. R^2, R^2_{adj}, and q^2 above a value of 0.6 indicate satisfactory model fit.

3 Results and discussions

Tables 1 and 2 list the antifungal activities of the organic compounds against *Aspergillus niger* and *Fusarium Rosium* respectively. Figures 1 and 2 show the cluster analysis of the activities. Activities of these organic compounds are generally lower against *Aspergillus niger* than with the other fungus. Coumarin exhibits the highest and benzoic acid the lowest antifungal activity against *Fusarium Rosium.* Benzaldehyde exhibits the highest and methyl salicylate the lowest antifungal activity against *Aspergillus niger.* The figures also show the grouping of the compounds into three clusters against both fungi.

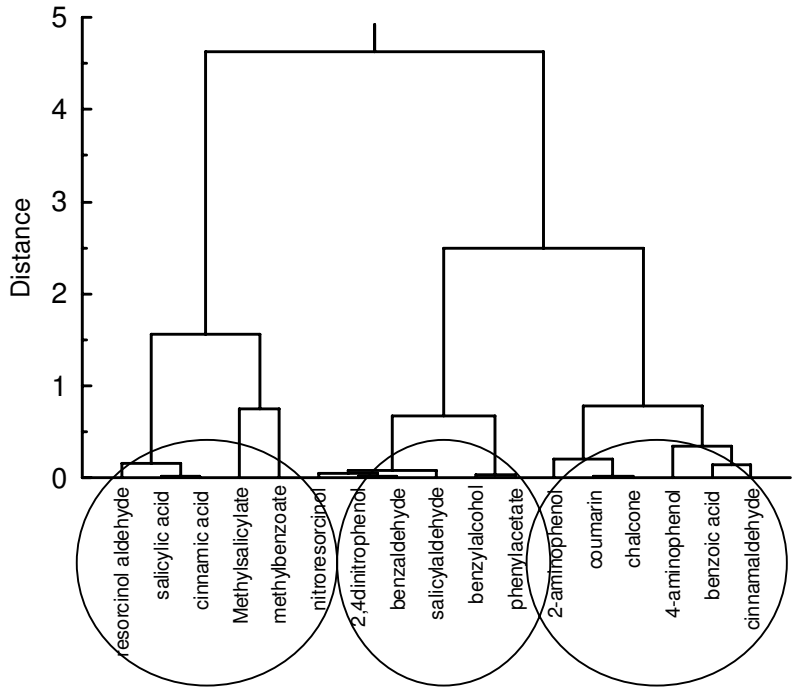


Fig. 1 Cluster analysis of compounds exhibiting antifungal activity against *Aspergillus niger*.

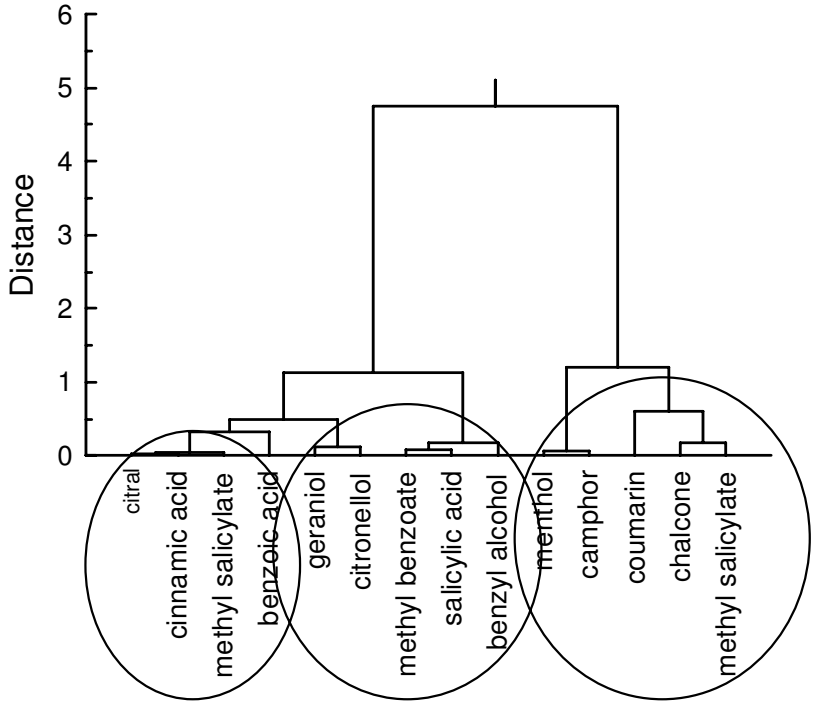


Fig. 2 Cluster analysis of compounds exhibiting antifungal activity against *Fusarium Rosium*.

Table 3 Descriptors that are highly correlated with antifungal activity against *Fusarium Rosium* .

Correlation coefficient	Descriptor	Detail	
0.71	PW4	path/walk 4 - Randic shape index	Topological descriptors
0.70	X4	connectivity index chi-4	Connectivity indices
0.70	X4sol	solubility connectivity index chi-4	Connectivity indices
-0.66	Jhetv	Balaban-type index from van der Waals weighted distance matrix	Topological descriptors

Table 4 Descriptors that are highly correlated with antifungal activity against *Aspergillus niger*.

Correlation coefficient	Descriptor	Detail	
0.62	SEigp	Eigenvalue sum from polarizability weighted distance matrix	Eigenvalue-based indices
-0.68	TIC1	total information content index (neighbourhood symmetry of 1-order)	Information indices
-0.74	SPI	superpendentic index	Topological descriptors
-0.74	Jurs-WPSA-3	Surface Weighted Charged Partial Surface Areas.	Jurs Charged Partial Surface Area parameters
-0.76	Jurs-DPSA-2	Total Charge Weighted Surface Areas.	Jurs Charged Partial Surface Area parameters

Tables 3 and 4 list the descriptors that are highly correlated with antifungal activity against *Fusarium Rosium* and *Aspergillus niger* respectively. Two topological descriptors (PW4, Jhetv) and two connectivity indices (X4, X4sol) have correlation coefficient greater than 0.66 in the case of *Fusarium Rosium*. Topological descriptors are indication of the shape and size of the molecule, while connectivity indices are an indication of the number of branching in the molecule (connectivity of atoms in a molecule) and are derived from graph theory. Higher connectivity index indicates higher branching [15].
Connectivity index has been successfully used to predict boiling points of aliphatic alcohols and toxicity of aliphatic ethers etc. Randic shape index is an indication of the molecular shape [16] while Balaban index is based on distances between various atoms [17]. A positive correlation coefficient indicates increasing the parameter increases activity, while negative correlation indicates that increasing the parameter decreases activity. QSAR studies relating antifungal activity of imidazole derivatives against *Candida albicans* and *Rhodotorula glutinis* lead to the conclusions that the overall antifungal activity

can be described by means of size and bulkiness related parameters as well as polar and lipophilic interactions (LogP) [7]. In the present study poor correlation is seen with LogP.

Topological descriptor such as superpendentic index (SPI), information content index (TIC1), and Eigenvalue based polarizability index (SEigp) are highly correlated with antifungal activity against *Aspergillus niger*. Superpendentic index is calculated from pendent oxygen atoms [18]. This descriptor relays branching information of the molecule with respect to terminal oxygen atoms. Presence of oxygen in the branches decreases activity. Atom information content (mean) is a measure of entropy of the element distribution in the molecule (including implicit hydrogen atoms but not lone pair pseudo-atoms). Let n_i be the number of occurrences of atomic number i in the molecule. Let $p_i = n_i$ / n where n is the sum of the n_i. The value of a_ICM is the negative of the sum over all i of p_i log p_i. Total atom information content is a_ICM times n. More details of this descriptor are discussed by Magnuson et al [19]. Eigenvalue describes the shape of the molecule and polarizability is an indication of ease to induce a dipole moment. QSAR studies carried out on antifungal activity of substituted thiazolidines lead to the conclusions that steric and electronic properties are the essential parameters [8]. QSAR models for the mutagenicity and carcinogenicity of simple aldehydes and unsaturated aldehydes pointed to the role of electrophilicity, bulkiness, and hydrophobicity as the important parameters [20]. Jurs-DPSA-2 (Total Charge Weighted Surface Areas) and Jurs-WPSA-3 (Surface Weighted Charged Partial Surface Areas) are descriptors that characterize molecules through the area of solvent accessible surface (SAS) and partial atomic charges. This set of descriptors [21] combines shape and electronic information to characterize the molecules. The descriptors are calculated by mapping atomic partial charges on solvent-accessible surface areas of individual atoms.

If only eight common organic compounds that were tested for antifungal activty towards both the fungi are considered (namely, coumarin, chalcone, methyl benzoate, cinnamic acid, benzyl alcohol, benzoic acid, salicylic acid, and methyl salicylate), then the correlation coeffcients increases by almost 0.1 (see Table 5). A linear regression equation is developed as shown below relating the SPI descriptor with antifungal activity for this small data set of compounds against *Aspergillus niger*. The $R^2$is good but the predictive capability of the model as depicted by q^2 is not good.

$$\% \text{ Transmission} = 64.7 - 2.39*\text{SPI} \quad (R^2 = 0.70,\ R^2_{adj} = 0.65,\ q^2 = 0.49,\ F = 13.9) \quad (4)$$

A linear regression equation is developed as shown below relating PW4 descriptor with antifungal activity for this small data set of compounds against *Fusarium Rosium*. The quality of the data fit as well as the predcitive capabiltiy of the model are good.

$$\% \text{ Transmission} = 16.3+555.1*\text{PW4} \quad (R^2 = 0.75,\ R^2_{adj} = 0.71,\ q^2 = 0.59,\ F = 18.3) \quad (5)$$

The activity for both the fungi depends mainly on topologial descriptors namely, SPI and PW4. SPI is an indication of oxygen atoms in the pendent while PW4 is an indication of the molecular shape.

Table 6 lists various regression equations (single and multiple) that have been tested relating the descriptors with antifungal activity of the entire set of compounds against

Table 5 Descriptors that are highly correlated with antifungal activity for a smaller set of compounds (coumarin, chalcone, methyl benzoate, cinnamic acid, benzyl alcohol, benzoic acid, salicylic acid, and methyl salicylate). Same compounds were tested for both the fungi

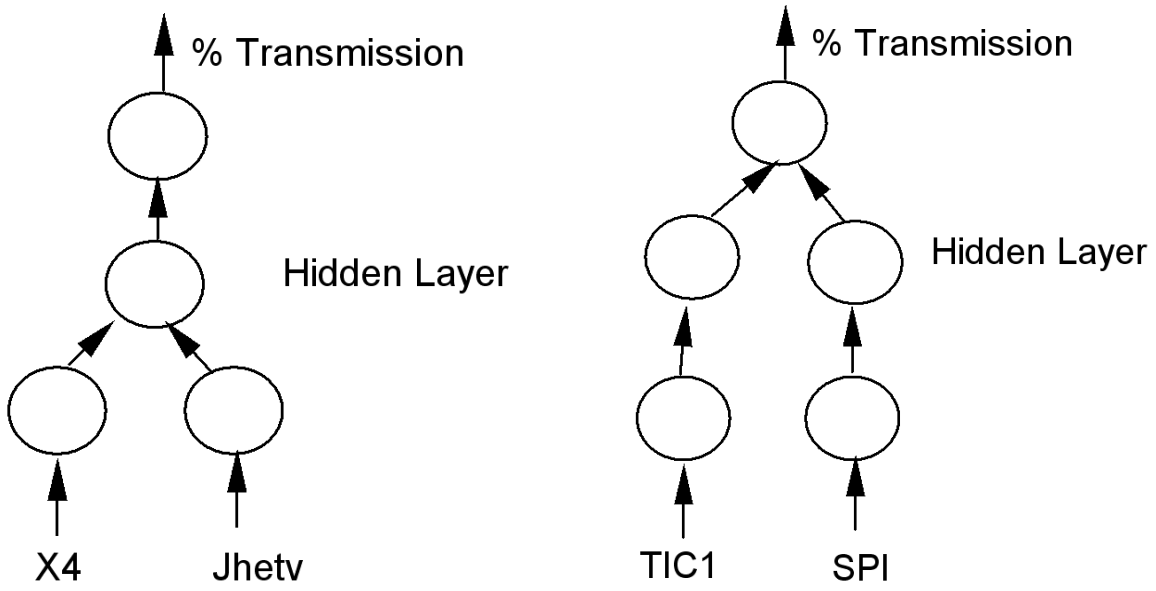
Against *Fusarium Rosium*		Against *Aspergillus niger*	
Correlation coeffcient	Descriptor	Correlation coeffcient	Descriptor
0.87	PW4	0.73	SEigp
0.76	X4	-0.78	TIC1
0.76	X4sol	-0.84	SPI
-0.76	Jhetv	-0.76	Jurs-DPSA-2

Table 6 Models (regression and NN) relating the descriptors with antifungal activity against *Fusarium Rosium*.

Regression equation	R^2	R^2_{adj}	q^2	MSSE	F
32.18+239.37 * PW4	0.51	0.47	0.40	33.1	6.6
48.59+7.73* X4	0.49	0.46	0.39	36.2	6.0
100.34 – 12.91* Jhetv	0.44	0.41	0.33	40.5	4.8
72.43+5.12*X4-6.82*Jhetv	0.55	0.45	0.34	31.2	6.9
BP Neural Network (2-1-1, Delta learning, TanH transfer function) (inputs = X4 and Jhetv)	0.82	0.75	0.70	8.1	55

Fusarium Rosium. The data fit in all cases are poor. The table also gives the results from the use of a 2-1-1 Back propagation Neural Network with Delta learning rule and TanH transfer function. This is a network with one processing element in the hidden layer. Figure 3a shows the topology of the Neural network. The inputs to the network are X4 (connectivity) and Jhetv (topological). The data fit as well as the predictive capability of the model are good ($R^2 = 0.84$, $q^2 = 0.73$).

Table 7 lists various regression equations (single and multiple) that have been tested relating the descriptors with antifungal activity against *Aspergillus niger* for the entire set of compounds. The data fit in all cases are poor. The table also gives the results from the use of a 2-2-1 Back propagation Neural Network with Delta learning rule and TanH transfer function. This is a network with two processing elements in the hidden layer. The inputs to the network are TIC1 (information) and SPI (topological). Figure 3b shows the topology of the Neural network The data fit as well as the predictive capability of the model are satisfactory ($R^2 = 0.75$, $q^2 = 0.62$). Figure 4 compares the Neural network model predictions with the experimentally observed data for *Aspergillus niger* (main graph). The inset is a comparison of the model with experimental data for the validation data set. The dotted lines in the inset are the 95% confidence limits on the predicted values. This figure once again confirms the predictive capability of the model.



(a) (b)

Fig. 3 Neural network architecture for (a) *Fusarium Rosium* and (b) *Aspergillus niger* systems.

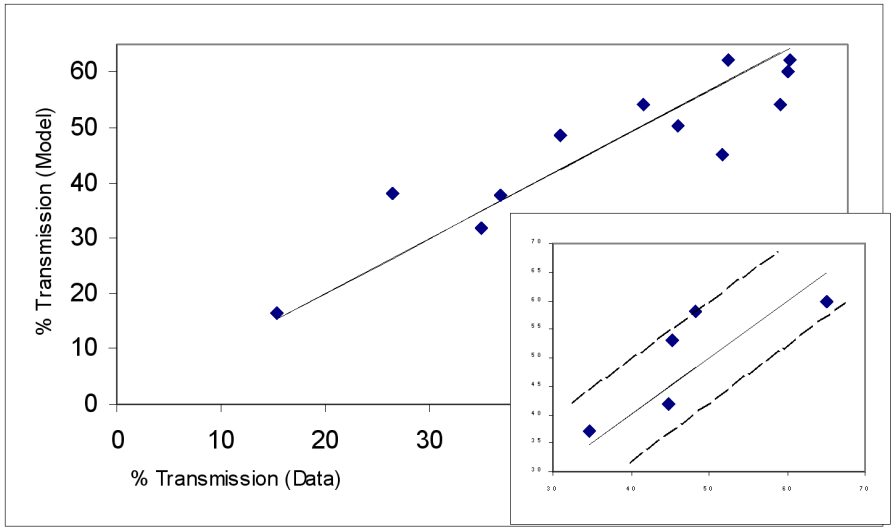


Fig. 4 Comparison of Neural network model predictions (inputs = TIC1 and SPI) and observed data against *Aspergillus niger* (main graph – comparison with learning data, inset – comparison with test data, dotted lines are ± 95% confidence limits).

4 Conclusions

This paper deals with the experimental and QSAR studies carried out on the antifungal activity of organic compounds on *Fusarium Rosium* and *Aspergillus niger*. Activities of these organic compounds are generally lower against the latter than against the former

Table 7 Models (regression and NN) relating the descriptors with antifungal activity against *Aspergillus niger*.

Regression equation	R^2	R^2_{adj}	q^2	MSSE	F
97.37-1.33*TIC1	0.45	0.38	0.33	91.3	5.5
68.64-2.43*SPI	0.55	0.49	0.41	81.2	6.7
79.96- (Jurs-DPSA-2)*0.0644	0.58	0.55	0.43	79	18
83.88-0.55*TIC1-1.76*SPI	0.58	0.52	0.45	74.3	8.55
73.59-0.06*(Jurs-DPSA-2)+0.419*SPI	0.60	0.53	0.36	72.1	8.91
BP Neural Network (2-2-1, Delta learning, TanH transfer function) (inputs = TIC1 and SPI)	0.74	0.68	0.61	43.0	27

fungus. In both the cases the activities were grouped into three sets (low, medium and high activity sets). For *Fusarium Rosium* topological descriptor and connectivity index correlate well with antifungal activity. For *Aspergillus niger* topological descriptor and information index correlate well with the antifungal activity, which matches with literature findings [22]. For both fungi a Back propagation Neural Network model with Delta learning rule and TanH transfer function predicts the data better than single and multiple regression models. Correlation values are higher when only eight compounds, which were tested on both the fungi, were used for model development.

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