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Abstract

Motivation. Meningoencephalitis, caused by the virulent fungus *Cryptococcus neoformans*, is an important cause of mortality in case of immunocompromised individuals, and new antifungal agents are required to treat such infections. Coumarins have antimeningoencephalitic activity, and here we report our attempt to find out the structural features required for more active congeners.

Method. In vitro antifungal activity of coumarins, expressed as MIC_{50} values (μg/mL) was considered as the biological activity parameter. QSAR study of the data set of coumarins was performed using different parameters, namely physicochemical, topological, geometrical, constitutional, and semiemperical quantum chemical descriptors as well as whole molecular descriptors. Multiple regression analyses were performed to develop QSAR models.

Results. The QSAR study highlights the atomic features and molecular descriptors, information content descriptors, topological and constitutional descriptors that affect the antifungal activity of these coumarin analogs.

Keywords. Coumarins; *Cryptococcus neoformans*; antimeningoencephalitic activity; molecular descriptors; information content; structural information content; quantitative structure–activity relationships; QSAR.

Abbreviations and notations

QSAR, quantitative structure–activity relationships
IC, information content
SIC, structural information content

1 INTRODUCTION

Fungal infection or mycoses can be caused by fungi, budding yeast and hyphae. Although *Candida* species are the most frequent causes of human fungal infection, *Cryptococcus neoformans* can be considered as the major virulent fungi on the basis of severity of infection [1]. *Cryptococcus neoformans* is an encapsulated yeast that causes meningoencephalitis in normal individuals as well

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as immunocompromised persons. In Southeast Asia and Africa, cryptococcal meningoencephalitis is more common in immunocompromised individuals [2]. It is one of the major causes of morbidity and mortality in immunosuppressed patients [3].

Meningoencephalitis is the inflammation of subarachnoid space and brain parenchyma. It is manifested as headache, fever, malaise, papilloedema, cranial nerve palsies and decreased consciousness [2]. Increased cranial pressure in the absence of ventricular dilatation may cause visual and hearing loss along with cognitive impairment and gait ataxia [2]. *C. neoformans* are present in the soil and bird droppings. Infection starts when these are inhaled by the host. The virulence factors associated with this microbe include (*a*) a polysaccharide capsule that prevents phagocytosis of these microbes by alveolar macrophages, (*b*) formation of melanin that prevents entering of these microbes from nervous epinephrine oxidative system and (*c*) biosyntheses of enzymes like serine protease that cleaves fibronectin and other proteins of the host [1]. The infection may be prevented in normal individuals but it becomes complicated and unmanageable in case of immunocompromised patients. Amphotericin B or combinations of amphotericin B with flucytosine or fluconazole or liposomal amphotericin B (intolerant cases) with or without the administration of specific monoclonal antibody as a part of the immunotherapeutic strategy are preferred drug regimen to treat complicated cryptococcal meningoencepalitis of immunocompromised persons. Expensive treatment of cryptococcal meningoencephalitis is another factor for its increased mortality rate amongst immunocompromised patients. To reduce complications as well as expenses, new generation of antifungal compounds or new lead molecules are to be introduced to fight the dreaded disease particularly those are having the immunological problem.

As a part of our composite program of drug design, discovery and development [4–39], quantitative structure activity relationship (QSAR) study was done on a series of coumarin derivatives. Physicochemical, constitutional and semiempirical quantum chemical descriptors as well as whole molecular topological descriptors were used to identify the atom/ fragment required for the activity. For the QSAR study, the antifungal activity against *Cryptococcus neoformans* expressed as minimum inhibitory concentration (MIC_{50}) (μg/ml) was used. MIC_{50} values were collected from the published work of Sourish *et al*. [40]. These values were converted to the negative logarithms of MIC_{50} ($pMIC_{50}$) to get the linear relationship with the independent variables. The general structure of coumarins is shown in Figure 1. The arbitrary numbering of the common atoms and substituents were maintained as fixed numbers in coumarin molecules and are also shown in Figure 1.

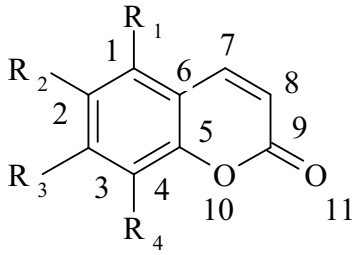

Figure 1. General structure of coumarins with arbitrary numbering.

2 MATERIALS AND METHODS

2.1 Dataset and Parameters

The biological activity data were collected from the work of Sourish *et al*. [40]. The negative logarithm of the minimum inhibitory concentration ($pMIC_{50}$) of these analogs against *Cryptococcus neoformans* was chosen as the biological activity parameter. The data set was taken in such a way to get a meaningful QSAR study. The biological activity data are shown in Table 1.

Table 1. Biological Activity Data of Coumarins [40]

Cpd [a]	R_1	R_2	R_3	R_4	MIC_{50} (μg/ml) [b]
1	H	H	–O–CH=CH–		250.0
2	H	H	–CH=CH–O–		62.5
3	H	H	H	H	500.0
4	H	OH	–OH	H	1000.0
5	H	H	OH	H	500.0
6	H	H	–O–CH(COOH)=CH–		2000.0
7	H	H	–O–CH($COOHCH_2CH_3$)=CH		250.0
8	H	H	–O–CH(O=C–NH–CH_2–CH_2–CH_3)=CH–		125.0
9	H	H	–O–CH(O=C–NH–$(CH_2)_9CH_3$		31.3
10	H	H	–O–CH(O=C–NH–CH–CH=CH–$(CH_2)_{12}CH_3$		31.3
11	H	OH	–O–CH_2–CH=CH_2–		250.0
12	H	–OCH_2–C_6H_5	–O–CH_2–CHO	H	500.0
13	H	–OCH_2–C_6H_5	H	–O–CH_2–$CHOHCH_2OH$	250.0
14	H	–OCH_2–C_6H_5	OH	CH_2CH=CH_2	500.0
15	H	OH	OH	$CH_2CH_2CH_3$	125.0
16	H	–OCH_2–C_6H_5	OH	$CH_2CHOHCH_2OH$	1000.0
17	H	–OCH2–C6H5	OH	CH2C(OCH3)2H	125.0
18	H	–OCH_2–C_6H_5	–OCH=CH_2–		250.0
19	H	–OH	–OCH=CH_2–		125.0
20	H	–OCH_3–	–OCH=CH_2–		250.0
21	–OCH_3	–OCH_3–	–OCH=CH_2–		500.0
22	H	–CH_2CH=CH_2	–OCH=CH_2–		500.0
23	H	–OC=O–CH_3	–OCH=CH_2–		62.5
24	H	$CH_2CH_2CH_3$	–OCH=CH_2–		250.0
25	CH_2–C_6H_5	–OC=O–CH_3	–OCH=CH_2–		500.0

[a] Compound number
[b] Minimum inhibitory concentration

QSAR studies of 25 coumarins were performed using different parameters like physicochemical, constitutional and semiempirical quantum chemical descriptors as well as whole molecular topological descriptors.

Information content descriptors [41–43]

Molecules can be considered as structures and may be partitioned into subsets of elements which are almost equivalent. This equivalency is related to a particular descriptor. When P is a partition of a set of N elements into k subsets each consisting of N_k elements, equivalence class can be considered as 1, 2, …, k. The number of element in each is N_1, N_2, …, N_k. The partition P is:

$$P = N(N_1, N_2, \ldots, N_k) \tag{1}$$

A probability distribution (p_i) based on the partition is:

$$p_i = N_i/N \tag{2}$$

where p_i is the probability for a randomly chosen element for the class i. The degree of uncertainty can be shown by entropy H_i:

$$Hi = -\text{ lb } p_i \tag{3}$$

where lb stands for the base–2 logarithm.

The mean entropy (H) of this probability distribution is:

$$H = -\sum_{i=1}^{k} p_i \text{lb} p_i \tag{4}$$

It can be considered as a measure of the mean quantity of information contained in each structure element (in bits per element). The partition P, the probabilities p_i and the mean quantity information H are responsible for the calculation of all information theoretic descriptors [41–43].

Multigraph information content indices (**IC**, **SIC**) [41–43]

To each vertex v, an *unordered* sequence of *ordered* pairs can be given: {(m_1, n_1), (m_2, n_2), ..., (m_k, n_k)}, termed as a *coordinate* and:

$$k = \text{the valence of the vertex} \tag{5}$$

where one ordered pair (m_j, n_j) per each neighboring vertex v_j is available.

For every j = 1, 2, …, k, the valence of v_j is n_j. The bond between v and v_j is of the order m_j.

Having given coordinates to vertices, the partition of vertices is done in the usual way where two vertices are taken as equivalent if their coordinates are the same (as unordered k–tuples, *i.e.*, the repetitions of ordered pairs are not nullified as these would be if the k–tuples were considered as sets). The index responsible directly to this partition is the index IC (Information Content) [41–43].

Bonding Information Content is defined as:

$$\text{BIC} = \text{IC} / \text{lb (number of bonds counting bond orders)} \tag{6}$$

Structural Information Content is defined as:

$$\text{SIC} = \text{IC} / \text{lb (number of vertices)} \tag{7}$$

Table 2. Descriptors Used

Cpd[a]	$pMIC_{50}$[b]	SAA	RBF	nO	nR06	TI2	PJI2	Lop	IC2	SIC1	SIC2	D/Dr05	T(N..O)	FEH3	FEH9	FEH11	FEL1	FEL9
1	3.60	256.04	0.00	3	2	1.36	1.00	0.54	3.81	0.67	1.00	19.17	0	0.00	0.01	0.08	0.29	0.08
2	4.20	256.31	0.00	3	2	1.36	1.00	0.54	3.38	0.67	0.89	19.17	0	0.10	0.01	0.10	0.13	0.04
3	3.30	243.76	0.00	2	2	1.21	1.00	0.63	3.28	0.59	0.95	0.00	0	0.18	0.01	0.17	0.25	0.07
4	3.30	267.03	0.00	4	2	1.38	0.75	0.77	3.39	0.69	0.92	0.00	0	0.25	0.01	0.11	0.27	0.07
5	3.30	259.56	0.05	3	2	1.34	1.00	0.73	3.53	0.66	0.85	0.00	0	0.26	0.00	0.12	0.28	0.08
6	2.70	309.29	0.05	5	2	1.92	1.00	0.92	3.85	0.65	0.94	25.06	0	0.02	0.01	0.11	0.44	0.07
7	3.60	390.84	0.14	5	2	2.54	1.00	1.32	4.14	0.66	0.98	29.74	0	0.01	0.01	0.11	0.42	0.08
8	3.90	427.19	0.18	4	2	2.96	0.83	1.49	4.32	0.74	1.00	32.32	17	0.00	0.01	0.10	0.37	0.09
9	4.50	640.93	0.36	4	2	6.11	0.89	2.35	4.25	0.66	0.91	50.25	17	0.00	0.01	0.10	0.36	0.09
10	4.50	889.11	0.49	3	2	9.92	1.00	3.07	3.74	0.56	0.74	74.64	17	0.07	0.00	0.01	0.33	0.08
11	3.60	357.63	0.12	3	2	2.53	0.80	1.43	3.86	0.55	0.83	0.00	0	0.26	0.00	0.11	0.29	0.08
12	3.30	322.36	0.15	5	3	3.43	1.00	1.09	3.88	0.48	0.74	0.00	0	0.22	0.01	0.09	0.28	0.07
13	3.60	323.07	0.26	6	3	3.51	1.00	1.30	4.21	0.60	0.91	0.00	0	0.02	0.00	0.00	0.29	0.06
14	3.30	422.85	0.20	4	3	3.48	1.00	0.97	4.23	0.62	0.94	0.00	0	0.28	0.01	0.11	0.27	0.08
15	3.90	312.11	0.12	4	2	1.60	0.75	1.25	3.88	0.74	0.97	0.00	0	0.24	0.01	0.00	0.28	0.07
16	3.00	450.24	0.22	6	3	3.49	1.00	1.17	4.37	0.64	0.94	0.00	0	0.27	0.01	0.11	0.29	0.07
17	3.90	494.30	0.25	4	3	3.54	1.00	1.24	4.44	0.65	0.95	0.00	0	0.15	0.01	0.12	0.27	0.07
18	3.60	367.76	0.08	4	3	3.47	1.00	0.41	4.15	0.56	0.93	33.97	0	0.02	0.01	0.07	0.29	0.08
19	3.90	266.08	0.00	4	2	1.32	0.75	0.65	3.91	0.71	1.00	20.55	0	0.03	0.01	0.07	0.29	0.07
20	3.60	300.09	0.06	4	2	1.37	1.00	0.88	4.00	0.70	1.00	22.21	0	0.03	0.01	0.07	0.29	0.07
21	3.30	337.20	0.10	5	2	1.24	1.00	1.02	3.73	0.67	0.89	26.44	0	0.01	0.01	0.05	0.34	0.07
22	3.30	332.90	0.11	3	2	1.66	0.80	1.09	3.97	0.71	0.97	24.12	0	0.00	0.01	0.08	0.28	0.08
23	4.20	327.53	0.10	0	0	1.96	0.80	1.13	3.95	0.69	0.95	26.02	0	0.01	0.01	0.08	0.32	0.07
24	3.60	181.42	0.11	3	2	1.66	0.80	1.09	3.97	0.73	0.97	24.12	0	0.00	0.01	0.08	0.28	0.08
25	3.30	390.94	0.12	5	3	2.42	1.00	0.92	4.13	0.61	0.89	41.37	0	0.00	0.01	0.06	0.35	0.07

[a]Compound number; [b]Negative logarithmic value of minimum inhibitory concentration

Constitutional descriptors and whole molecular topological descriptors were calculated by the software DRAGON [44]. Constitutional descriptors used to develop QSAR models are nO, nR06 and RBF. nO indicates the total number of oxygen atoms in the molecule. nR06 is the number of 6 membered rings. RBF defines the rotatory bond friction of the molecule. Whole molecular topological descriptors include IC2, T(N..O), TI2, SIC1, SCI2, Lop, PJI2 and D/Dr05. IC2 encodes the information content index (neighborhood symmetry of second order). T(N..O) indicates the sum of topological distances between nitrogen and oxygen atoms in the molecule. Lop is the Lopping centric index. TI2 is the second Mohar index. SIC1 is the structural information content (neighborhood symmetry of 1^{st} order). SIC2 describes the structural information content (neighborhood symmetry of 2^{nd} order). PJI2 gives information about the two dimensional (2D) Petitjean shape index. D/Dr05 encodes the information of distance/detour ring index of order 5. The quantum chemical descriptors like atomic charges and molecular surface area were calculated by using Hyperchem Pro Release 7.0 Pro package [45]. The Molecular Mechanics (MM+) force field was applied for the preliminary structures for geometry optimization and study of the conformational behavior of each compound. These energy minimized structure were used for the geometry optimization by the Austin model 1 (AM1) semiempirical method using Polak–Rebiere algorithm with RMS gradient of 0.01 kcal/ Å mole. Using the Hyperchem software, after energy minimization these compounds, frontier electron density related to the highest occupied molecular orbital (FEH) as well as frontier electron density related to lowest unoccupied molecular orbital

(FEL) were calculated.

To obtain linear relationship with independent variables, the minimum inhibitory concentration (MIC_{50}) of coumarin derivatives was converted to the negative logarithmic scale ($pMIC_{50}$) for the development of QSAR models. $pMIC_{50}$ values of these compounds and the selected parameters used to develop QSAR models are listed in Table 2.

2.2 Computational Procedures

Multiple linear regression (MLR) analysis [46–48] was carried out by the computer program 'Multi Regress' [49] developed in our laboratory. Parameters like correlation coefficient (R), adjusted R^2 (R^2_A), variance ratio (F), standard error of estimate (SEE) justified the statistical quality of all equations. Correlation analyses [46] were done and the intercorrelated parameters were eliminated stepwise. The validation of models was done by using Leave–one–out (LOO) cross validation method and parameters like PRESS, SSY, R^2_{CV}, SDEP and S_{PRESS} were considered for validation. PRESS stands for predicted residual sum of squares, SSY is the total sum of squares, R^2_{CV} denotes the cross–validated R^2, SDEP expresses the standard deviation of error of prediction and S_{PRESS} denotes the standard error of PRESS. The correlation matrix of the biological activity and various parameters are shown in Table 3.

Table 3. Correlation matrix of biological activity and parameters used

	$pMIC_{50}$	SAA	RBF	nO	nR06	TI2	PJI2	Lop	IC2	SIC1	SIC2	D/Dr05	T(N..O)	FEH3	FEH9	FEH11	FEL1	FEL9
$pMIC_{50}$	1.00	0.50	0.46	–0.41	–0.34	0.49	–0.20	0.54	0.12	0.11	–0.10	0.51	0.59	–0.30	–0.11	–0.34	–0.16	0.04
SAA		1.00	0.90	0.10	0.13	0.94	0.21	0.87	0.36	–0.30	–0.43	0.61	0.75	–0.05	–0.44	–0.27	0.30	0.34
RBF			1.00	0.21	0.23	0.92	0.17	0.90	0.52	–0.30	–0.43	0.44	0.68	–0.03	–0.57	–0.39	0.26	0.34
nO				1.00	0.75	0.11	0.35	0.02	0.42	–0.20	–0.05	–0.11	–0.05	0.04	–0.17	–0.23	0.29	–0.10
nR06					1.00	0.20	0.48	–0.10	0.38	–0.50	–0.19	–0.24	–0.12	0.27	–0.17	–0.03	–0.12	–0.10
TI2						1.00	0.23	0.86	0.32	–0.50	–0.54	0.57	0.72	–0.03	–0.55	–0.33	0.21	0.33
PJI2							1.00	–0.10	0.07	–0.50	–0.28	0.07	–0.07	–0.02	–0.30	0.12	0.04	–0.20
Lop								1.00	0.27	–0.20	–0.43	0.56	0.79	–0.09	–0.50	–0.38	0.36	0.42
IC2									1.00	0.02	0.26	0.13	0.21	–0.22	0.00	–0.17	0.38	0.34
SIC1										1.00	0.75	0.03	0.02	–0.29	0.43	–0.04	0.06	0.01
SIC2											1.00	–0.12	–0.21	–0.34	0.52	0.17	0.10	0.08
D/Dr05												1.00	0.66	–0.69	–0.15	–0.33	0.43	0.35
T(N..O)													1.00	–0.25	–0.26	–0.17	0.31	0.44
FEH3														1.00	–0.02	0.28	–0.40	–0.20
FEH9															1.00	0.45	–0.04	0.01
FEH11																1.00	–0.06	0.01
FEL1																	1.00	0.56
FEL9																		1.00

3 RESULTS AND DISCUSSION

Multiple regression analysis was done using these variables. Intercorrelated parameters were eliminated stepwise depending on their correlation with the biological activity. The QSAR models generated were as follows:

$$pMIC_{50} = 4.1783\ (\pm 0.694815) - 0.2399\ (\pm 0.045)\ nO + 0.558\ (\pm 0.193)\ IC2 + 0.0498\ (\pm 0.010)\ T(N..O) - 3.642(\pm 1.314)\ FEH11 - 22.303\ (\pm 6.320)\ FEL9$$
$$n = 25;\ R = 0.883;\ R^2 = 0.781;\ R_A^2 = 0.723;\ F\ (5, 19) = 13.524;\ p < 0.00001\ SEE = 0.238;\ SSY = 4.891;\ PRESS = 2.197;\ R^2_{CV} = 0.551;\ SDEP = 0.296;\ S_{PRESS} = 0.340 \quad (8)$$

where n is the number of data. R, $R^2_{A,}$ F, p, SEE, SSY, PRESS and R^2_{cv} are correlation coefficient, adjusted R^2, variance ratio, probability factor related to F– ratio, standard error of the estimate, total sum of squares, predicted residual sum of squares and cross–validated R^2 respectively. Here, T(N…O) is the sum of topological distances between nitrogen and oxygen atoms, nO is the number of oxygen atoms, IC2 is the information content index (neighborhood symmetry of 2nd order), FEH11 is frontier electron density related to the highest unoccupied molecular orbital of the atom number 11, FEL9 is frontier electron density related to the lowest unoccupied molecular orbital of the atom number 9. Information content index (neighborhood symmetry of 2nd order) (IC2) and the sum of topological distances between nitrogen and oxygen atoms [T(N..O)] have positive effects on the biological activity. It means that the increased value of IC2 may increase the biological activity. The higher value of topological distances between nitrogen and oxygen atoms [T(N..O)] may increase the biological activity as well. FEH11 and FEL9 have detrimental effects on the biological activity. Thus, nucleophilic substitution may be favorable to the atom number 9 and electrophilic attack may be favorable to the atom number 11.

Two compounds (compound **7** and **23**) with larger residuals were found and these might act through different mechanism(s) of action. These two compounds were deleted to get the model as shown in Eq. (9):

$$pMIC_{50} = 4.3500\ (\pm 0.581) - 0.3617(\pm 0.058)\ nO + 0.762(\pm 0.184)\ IC2 + 0.049(\pm 0.008)\ T(N\ldots O) - 4.6863(\pm 1.125)\ FEH11 - 27.878\ (\pm 5.488)\ FEL9$$
$$DC = \mathbf{7}, \mathbf{23},\ n = 23;\ R = 0.926;\ R^2 = 0.857;\ R_A^2 = 0.815;\ F(5,17) = 20.348;\ p < 0.00001;\ SEE = 0.195;\ SSY = 4.513;\ PRESS = 1.302;\ R^2_{CV} = 0.712;\ SDEP = 0.238;\ S_{PRESS} = 0.277 \quad (9)$$

where DC is deleted compound. The above mentioned equation is a statistically significant equation. Information content index IC2 and whole molecular topological descriptor T(N…O) have positive effects on the biological activity indicating that with the increase of these values the antifungal activity may increase. The negative coefficients of FEH11 and FEL9 imply that with the decrease of these values there may be higher chances of electrophilic attack at the atom number 11 as well as nucleophilic attack at the atom number 9 may lead to better active antifungal compounds.

Another model was developed as:

$$pMIC_{50} = 4.097\ (\pm 0.405) + 0.709\ (\pm 0.121)\ Lop - 1.974\ (\pm 0.539)\ FEH3 + 75.987\ (\pm 35.937)\ FEH9 - 5.092\ (\pm 1.095)\ FEL1$$
$$n = 25;\ R = 0.841;\ R^2 = 0.707;\ R_A^2 = 0.649;\ F\ (4, 20) = 12.094;\ p < .00004;\ SEE = 0.267;\ SSY = 4.891;\ PRESS = 2.006;\ R^2_{CV} = 0.590;\ SDEP = 0.283;\ S_{PRESS} = 0.317 \quad (10)$$

where FEH9 is the frontier electron density related to the highest unoccupied molecular orbital of

the atom number 9, FEH3 is the frontier electron density related to the highest unoccupied molecular orbital of the atom number 3, FEL1 is frontier electron density related to the lowest unoccupied molecular orbital of the atom number 1 and Lop stands for the Lopping centric index. Lop and FEH9 have positive effects on the biological activity. Thus, increased values of these two parameters may increase the biological activity. FEH3 and FEL1 have negative effects. These mean the nucleophilic attack may be favorable for the atom number 1 whereas the electrophilic attack may be conducive to the atom number 3.

Two compounds (compound **22** and **24**) with larger residuals were found. Deletion of these two compounds yielded the model shown in Eq. (11):

$$\begin{gathered} pMIC_{50} = 4.284(\pm0.331) + 0.750\ (\pm0.098)\ Lop - 2.495\ (\pm0.461)\ FEH3 + 92.746\ (\pm29.441)\ FEH9 - 5.862\ (\pm0.912)\ FEL1 \\ DC = \mathbf{22}, \mathbf{24},\ n = 23;\ R = 0.908;\ R^2 = 0.825;\ R_A^2 = 0.786;\ F(4,18) = 21.230;\ p < .00001; \\ SEE = 0.215;\ SSY = 4.513;\ PRESS = 1.292;\ R^2_{CV} = 0.731;\ SDEP = 0.237;\ S_{PRESS} = 0.268 \end{gathered} \quad (11)$$

We tried to develop another equation that is shown below:

$$\begin{gathered} pMIC_{50} = 2.977\ (\pm0.881) - 0.167\ (\pm0.049)\ nO + 0.196(\pm0.039)\ TI2 + 2.828(\pm1.080)\ SIC1 - 14.755(\pm7.085)\ FEL9 \\ n = 25;\ R = 0.797;\ R^2 = 0.636;\ R_A^2 = 0.563;\ F(4,20) = 8.739;\ p < .00030;\ SEE = 0.298; \\ SSY = 4.891;\ PRESS = 3.211;\ R^2_{CV} = 0.343;\ SDEP = 0.358;\ S_{PRESS} = 0.401 \end{gathered} \quad (12)$$

where nO is the total number of oxygen atoms in the molecule, TI2 is the second Mohar index, SIC2 is the structural information content (neighborhood symmetry of 2nd order). Eq. (12) showed that the second Mohar index (TI2) and the structural information content (neighborhood symmetry of 2nd order) (SIC2) have positive influences on the biological activity. Higher values of these indices may increase the biological activity. The equation also showed that if the total number of oxygen atom decreases the antifungal activity may increase. Decrease of the frontier electron density related to the lowest unoccupied molecular orbital at atom number 9 suggests that nucleophilic attack may be favorable at the atom number 9. This may be beneficial as far as the antifungal activity is concerned. Compounds **4** and **6** have larger residuals. These were deleted. After deletion, the equation developed is shown in Eq. (13):

$$\begin{gathered} pMIC_{50} = 2.932(\pm0.697) - 0.141\ (\pm0.039)\ nO + 0.185(\pm0.031)\ TI2 + 3.073(\pm0.860)\ SIC1 - 16.491(\pm5.649)\ FEL9 \\ DC = \mathbf{4}, \mathbf{6};\ n = 23;\ R = 0.850;\ R^2 = 0.723;\ R_A^2 = 0.661;\ F(4,18) = 11.743;\ p < 0.00007; \\ SEE = 0.236;\ SSY = 3.615;\ PRESS = 1.757;\ R^2_{CV} = 0.514;\ SDEP = 0.276;\ S_{PRESS} = 0.312 \end{gathered} \quad (13)$$

By further improving the structure–activity relationship, we obtained the following equation:

$$\begin{gathered} pMIC_{50} = 5.056\ (\pm0.384) + 2.007\ (\pm0.581)\ RBF - 0.305(\pm0.098)\ nR06 + 0.009(\pm0.004)\ D/Dr05 - 4.045(\pm1.076)\ FEL1 \\ n = 25;\ R = 0.826;\ R^2 = 0.683;\ R_A^2 = 0.620;\ F(4,20) = 10.782;\ p < 0.00008\ SEE = 0.278; \\ SSY = 4.891;\ PRESS = 2.718;\ R^2_{CV} = 0.444;\ SDEP = 0.330;\ S_{PRESS} = 0.369 \end{gathered} \quad (14)$$

where rotatory bond friction (RBF) and distance/detour ring index of order 5 (D/Dr05) have

positive effects on the biological activity whereas number of 6 membered rings (nR06) and frontier electron density related to the lowest unoccupied molecular orbital of the atom number 1 (FEL1) may have detrimental effects on antifungal activity. Thus, nucleophilic attack may be favorable at the atom number 1 and decrease in the six membered rings in these molecules may be beneficial for higher antifungal activity. Two compounds (compounds **10** and **22**) with larger residuals have been found. Thus, these compounds were deleted. After deleting compounds 10 and 22, the model obtained is shown in Eq. (15):

$$\begin{gathered} pMIC_{50} = 5.298\ (\pm 0.343) + 2.728\ (\pm 0.607)\ RBF - 0.340\ (\pm 0.086)\ nR06 + 0.014\ (\pm 0.004)\ D/Dr05 - 5.019(\pm 1.003)\ FEL1 \\ DC = \mathbf{10}, \mathbf{22},\ n = 23;\ R = 0.858;\ R^2 = 0.736;\ R_A^2 = 0.678;\ F(4,18) = 12.572;\ p < 0.00005; \\ SEE = 0.241;\ SSY = 3.970;\ PRESS = 1.637;\ R^2_{CV} = 0.588;\ SDEP = 0.267;\ S_{PRESS} = 0.302 \end{gathered} \quad (15)$$

Another model obtained was:

$$\begin{gathered} pMIC_{50} = 5.602\ (\pm 0.643) + 0.002\ (\pm 0.001)\ SAA - 1.413\ (\pm 0.592)\ PJI2 - 2.027\ (\pm 0.589)\ FEH3 - 4.291\ (\pm 1.160)\ FEL1 \\ n = 25;\ R = 0.807;\ R^2 = 0.651;\ R_A^2 = 0.5817;\ F(4,20) = 9.3455;\ p < 0.00020\ SEE = 0.292; \\ SSY = 4.890;\ PRESS = 2.812;\ R^2_{CV} = 0.425;\ SDEP = 0.335;\ S_{PRESS} = 0.375 \end{gathered} \quad (16)$$

where two dimensional (2D) petitjean shape index (PJI2), frontier electron density related to the highest occupied molecular orbital of the atom number 3 (FEH3) and frontier electron density related to the lowest unoccupied molecular orbital of atom number 1 (FEL1) have negative effects whereas surface active area (SAA) has positive effect on the biological activity. The increase of surface active area may improve the biological activity. Eq. (16) suggests that at the atom number 3, attachment of electrophilic group and at the atom number 1, attachment of nucleophilic group may increase antifungal activity. *t*–statistics and p–values of the final equations are presented in Table 4.

Table 4. *t*– and *p*–values of QSAR Models

Eq. (9)	*t*–values	*p*–values	Eq. (15)	*t*–values	*p*–values
Intercept	6.01	0.00000	Intercept	13.16	0.00000
nO	–5.33	0.00000	RBF	3.45	0.00000
IC2	2.89	0.01000	nR06	–3.10	0.01000
T(N.O)	5.08	0.00000	D/Dr05	2.49	0.02000
FEH11	–2.77	0.01000	FEL1	–3.76	0.00000
FEL9	–3.53	0.00000			
Eqn. 11	*t*–values	*p*–values	Eqn. 17	*t*–values	*p*–values
intercept	10.12	0.00000	Intercept	8.72	0.00000
Lop	5.87	0.00000	SAA	4.97	0.00000
FEH3	–3.66	0.00000	PJI2	–2.39	0.03000
FEH9	2.11	0.05000	FEH3	–3.44	0.00000
FEL1	–4.65	0.00000	FEL1	–3.70	0.00000
Eqn. 13	*t*–values	*p*–values			
intercept	3.38	0.00000			
nO	–3.40	0.00000			
TI2	5.05	0.00000			
SIC2	2.62	0.02000			
FEL9	–2.08	0.05000			

Compounds **4** and **22** have larger residual, and are deleted to give the QSAR model:

$$pMIC_{50} = 6.611(\pm0.518) + 0.002\ (\pm0.000)\ SAA - 2.307(\pm0.477)\ PJI2 - 2.060\ (\pm0.455)\ FEH3 - 4.657\ (\pm0.851)FEL1$$
$$DC = \mathbf{4}, \mathbf{22};\ n = 23;\ R = 0.904;\ R^2 = 0.817;\ R_A^2 = 0.776;\ F(4,18) = 20.070;\ p < 0.00001;$$
$$SEE = 0.212;\ SSY = 4.402;\ PRESS = 1.430;\ R^2_{CV} = 0.675;\ SDEP = 0.249;\ S_{PRESS} = 0.282 \quad (17)$$

Calculated activities of these compounds using all final equations are shown in Table 5.

Table 5. Observed (Obs.), calculated (Calc.) and residual (res.) activities

Cpd	Obs.	Eq. (9)		Eq. (11)		Eq. (13)		Eq. (15)		Eq. (17)	
		Calc.	Res.	Calc.	Res.	Calc.	Res.	Calc.	Res.	Calc.	Res.
1	3.60	3.52	0.08	3.57	0.04	3.60	0.00	3.45	0.16	3.52	0.08
2	4.20	4.26	–0.06	4.28	–0.08	4.08	0.13	4.23	–0.02	4.05	0.15
3	3.30	3.25	0.06	3.37	–0.07	3.72	–0.42	3.34	–0.04	3.28	0.02
4	3.00	3.13	–0.13	3.24	–0.24	–	–	3.24	–0.24	–	–
5	3.30	3.27	0.03	2.96	0.34	3.30	0.00	3.33	–0.03	3.01	0.30
6	2.70	2.96	–0.26	2.97	–0.27	–	–	2.92	–0.22	2.91	–0.21
7	3.60	–	–	3.36	0.25	3.48	0.12	3.29	0.31	3.16	0.44
8	3.90	4.19	–0.29	3.85	0.06	3.65	0.25	3.73	0.17	3.91	–0.01
9	4.50	4.15	0.36	4.52	–0.02	4.04	0.46	4.51	–0.01	4.28	0.23
10	4.50	4.57	–0.07	4.59	–0.08	4.57	–0.06	–	–	4.58	–0.08
11	3.60	3.51	0.09	3.41	0.19	3.46	0.15	3.47	0.13	3.64	–0.04
12	3.30	3.07	0.23	3.55	–0.25	3.22	0.09	3.30	0.00	3.27	0.03
13	3.60	3.66	–0.05	3.55	0.06	3.63	–0.03	3.56	0.04	3.65	–0.04
14	3.30	3.50	–0.20	3.23	0.07	3.76	–0.46	3.46	–0.16	3.38	–0.08
15	3.90	3.85	0.05	3.69	0.21	3.56	0.34	3.55	0.36	3.77	0.14
16	3.00	2.99	0.01	3.27	–0.27	3.52	–0.52	3.44	–0.44	3.39	–0.39
17	3.90	3.84	0.06	3.89	0.01	3.96	–0.06	3.60	0.30	3.80	0.10
18	3.60	3.58	0.02	3.54	0.06	3.75	–0.15	3.55	0.05	3.74	–0.14
19	3.90	3.55	0.35	3.71	0.19	3.60	0.30	3.48	0.43	4.08	–0.17
20	3.60	3.56	0.04	3.86	–0.26	3.56	0.05	3.65	–0.05	3.56	0.04
21	3.30	3.30	0.00	3.50	–0.20	3.24	0.06	3.54	–0.24	3.42	–0.12
22	3.30	3.62	–0.32	–	–	3.56	–0.26	–	–	–	–
23	4.20	–	–	3.84	0.36	4.22	–0.01	4.36	–0.16	4.00	0.20
24	3.60	3.60	0.00	–	–	3.55	0.05	3.84	–0.24	3.84	–0.23
25	3.30	3.32	–0.02	3.41	–0.11	3.33	–0.03	3.42	–0.12	3.51	–0.21

4 CONCLUSIONS

In a molecule, all atoms may not be responsible for the biological activity. A part of the structure or some specific atoms, called pharmacophore, are required for the desired activity. Surface activity area (SAA), rotatory bond friction (RBF), information content index (neighborhood symmetry of 2nd order) (IC2), lopping centric index (Lop) and the sum of topological distances between nitrogen and oxygen atoms [T(N..O)] have positive inhibitory effects on the fungal growth. Thus, the increased value of IC2, i.e., the increase of the value of the information content index (neighborhood symmetry of 2nd order), the structural information content (neighborhood symmetry of 2nd order) (SIC2) and the sum of the topological distances between nitrogen and oxygen atoms [T(N..O)] may increase inhibitory effects. Lopping centric index (Lop) and frontier electron density related to the highest occupied molecular orbital of the atom number 9 (FEH9) may play pivotal roles on this fungal inhibition. The atom numbers 1 and 9 may be favorable for the nucleophilic

attack whereas atom numbers 3 and 11 may be favorable for the electrophilic attack. The second Mohar index (TI2) has positive influence on the inhibitory effect. The increase in the molecular flexibility by incorporation of rotatable bonds (RBF) may be conducive for antifungal effect. The increase of surface area (SAA) may improve the interaction in respect to the inhibitory effect of these compounds. Atoms and substituents important for antimeningoencephalitic activity are shown in Figure 2.

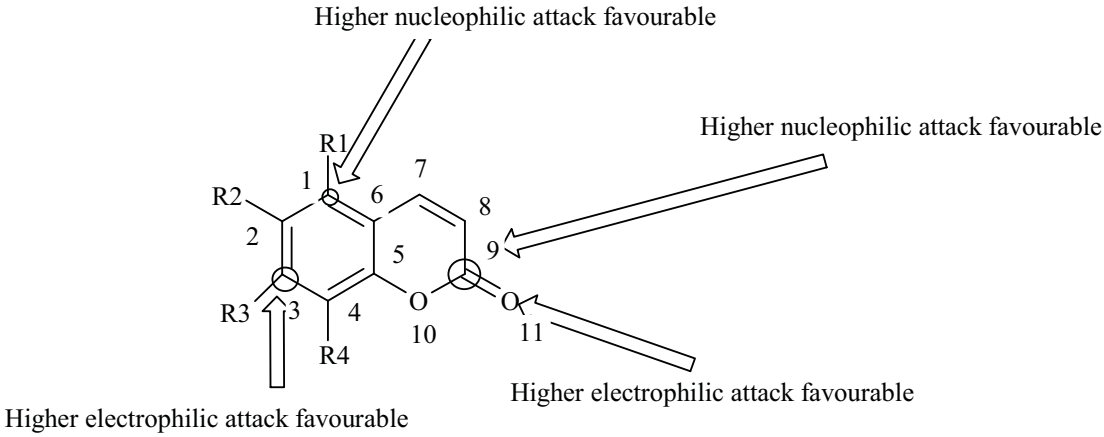

Figure 2. Requirements of coumarin analogs for antimeningoencephalitic activity.

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