QSAR Study of 3-Phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones as Antifungal Agents: The Dominant Role of Electronic Parameter

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To explore physicochemical properties of 3-phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones derivatives responsible for their antifungal activity, a quantitative structure activity relationship, Hansch approach was applied on sixteen compounds of above mentioned derivatives. Various physicochemical descriptors and reported minimum inhibitory concentration values of different fungal organisms were used as independent variables and dependent variable respectively. The best models for twelve different fungal organisms were first validated by leave-one-out cross validation procedure. Further, bootstrapping method was adopted to assess the robustness of the models. It was revealed that electronic parameters were found to have overall significant correlationship with antifungal activity and these studies provide an insight to design new molecules.

Key words QSAR; 3-phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-one derivative; Hansch approach; lowest unoccupied molecular orbital energy and antimycotic agent

Intensive efforts in antifungal discovery is of immediate need to develop more promising and effective antifungal agents because only few newer agents are presently available and their clinical efficacy in some invasive fungal infections such as *Aspergillus* and *fusariosisis* is not appreciable. In addition, major increase in the incidence of systemic fungal infections caused by the yeast *Candida albicans* and other fungi such as *Aspergillus fumigatus*, *Microsporum canis etc.* has been observed in the past two decades, particularly in immuno compromised patients.[1,2] In last few decades, the antifungal agents designed with azole nucleus were found to have better antifungal pharmacophore as indicated from extensive structure activity studies.[3] Both activity and toxicity of antifungal agents with azole moiety is attributed to coordination binding of the nitrogen atom of azole ring with iron atom of the heme in cytochrome P450 enzyme, which play an important role in the bio-synthesis of ergosterol, a membrane component in fungus.[4]

Lanosterol 14α-demethylase (CYP 51) is a member of the cytochrome P450 super-family, which catalyses the oxidative removal of 14α methyl group (C-23) of lanosterol *via* three successive mono oxygenation reactions. Two of these reactions are conventional cytochrome P450 hydroxylations that produce the 14-hydroxy methyl and 14-carboxy aldehyde derivatives of lanosterol. In the final step, the 14-aldehyde group is eliminated as formic acid with concomitant introduction of a $\Delta^{14,15}$ double bond.[5—7] $P450_{14DM}$ occur in different kingdom such as fungi, higher plants and animals with the same metabolic role *i.e.* removal of the 14-methyl group of precursor such as lanosterol, obtusifoliol, dihydrolanosterol and 24 (28) methylene 24, 25 dihydrolanosterol.[8]

Selective inhibition of the enzyme would cause depletion of ergosterol and accumulation of lanosterol and some other 14-methyl sterol, which results in growth inhibition of fungi cell. Most of the currently available imidazole and triazole antifungal agents like Ketoconazole, Fluconazole, Itraconazole, and Voriconazole specifically inhibit the lanosterol 14α-demethylase. Other drugs from this class currently under clinical trials include D-0870, SM-9167, ER-30346, SDZ-89485, TAK-187 and SM-8668 as described in literature.[9—11]

Azole antifungal agents inhibit the CYP-51 by the mechanism in which heterocyclic nitrogen atom (N-3 of imidazole and N-4 of triazole) binds to the heme at the binding site of enzyme in fungus. It has also ability to bind with mammalian CYP3A4 enzyme[3,12] that causes fatal hepatotoxicity.[13] All these findings urged us to learn more about novel non-azole lead compounds with more structural specificity for the fungal enzyme to improve their activity while decreasing their toxicity.

The quantitative structure–activity relationship (QSAR) study is a useful tool for rational search of bioactive compounds. QSAR study describes a definite role in a quantitative term of a structural feature in molecule with a definite contribution to the activity of a particular physiochemical property of the structural feature. Thus, QSAR studies have predictive ability and simultaneously provide deeper insight into the mechanism of drug receptor interactions.[14] We, therefore, report here a QSAR study on 3-phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones[15] for their antifungal activity against human fungal pathogens such as *Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *C. parapsilosis* ATCC22019, *C. krucei* ATCC6258, *C. krucei* E28, *C. troicalis* 156, *C. globrata* 20/I, *C. lucitaniae* 2446/I, *Trichoporon beigelii* 1188, *Aspergillusis fumigates* 231, *Absidia*

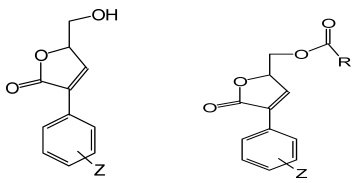

Fig. 1. Parent Structure of 3-Phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones Derivatives Used in Present Study

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corymbifera 272, and *Trichophyton mentogrophytes* 445, to explore the physicochemical properties requirements for inhibition and thus, may be helpful in designing new molecules. This is our one more step in the field of obtaining potent model of QSAR of compounds for various biological interest.[16—19)]

Experimental

A set of 16 compounds of 3-phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones derivatives has been selected from the reported work of Pour *et al.*[15)] and is given in Table 1. The biological activity data MIC was converted to free energy values using the $\Delta G = -RT\ln K$, for QSAR analysis.[20)] Molecular Modeling studies were performed using CS Chem-Office Software version 6.0 (Cambridge software) running on a P-III processor.[21)] All molecules were constructed using Chem Draw Ultra ver 5.0 and it was saved as the template structure. For every compound, the template structure was suitably changed considering its structural features, copied to Chem 3D ver 6.0 to create the 3-D model and finally the model was cleaned up and subjected to energy minimization using molecular mechanics (MM_2). The minimization is executed until the root mean square (RMS) gradient value reaches a value smaller than 0.1 kcal/mol·Å. The Austin Model-1 (AM-1)[22—25)] method was used for re-optimization until the root mean square (RMS) gradient attains a value smaller than 0.0001 kcal/mol·Å using MOPAC. The lowest energy structure was used for each molecule to calculate physicochemical properties using Chem3D ultra version 6.0. The regression analysis were carried out using a computer program *VALSTAT*[26)] developed in our laboratory. The auto-correlated parameters were eliminated depending on their individual correlation with the biological activity in order to avoid simple collinearity problem. All possible combinations of parameters were considered for the QSAR study.

The predictive powers of the equations were validated by Leave-One-Out (LOO) cross-validation method.[27,28)] Predicted residual sum of square (PRESS), total sum of squares (SSY), cross-validated R^2 (Q^2), and standard deviation error of prediction (SDEP) were considered for the validation of these models.

The results from cross-validated analysis were expressed as the cross-validated squared correlation coefficient (Q^2). The Q^2 is defined as,

$$Q^2 = 1 - \sum (Y_{pred} - Y_{act})^2 / \sum (Y_{act} - Y_{mean})^2$$

Where Y_{pred}, Y_{act}, and Y_{mean} are predicted, actual and mean values of the target property ($-\log IC_{50}$) respectively. $\sum (Y_{pred} - Y_{actual})^2$ is the Predictive Residual Error Sum of Squares (PRESS).

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. To further access the robustness and statistical confidence of the derived models, bootstrapping analysis was performed (25 runs). The r^2_{bs} is average squared correlation coefficient calculated during the validation procedure which is computed from a subset of variables used one at a time for the validation procedure. Following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), standard deviation (s), F-test, Cross-validated R^2 (Q^2). A data point is considered as an outlier if it has a large magnetite (when the residual value exceeds twice the standard error of estimate of the model).

The various physicochemical properties considered for QSAR studies have been given in Table 2. The descriptor values for all the molecules were calculated using "compute properties module" of the program.

Results and Discussion

In the present study, an attempt has been made to find structural requirement for inhibition of different fungal strains using QSAR Hansch approach on furan derivatives reported by Pour *et al.* with electronic, thermodynamic and physicochemical property descriptors. QSAR models against different 12 organisms have been obtained after removal of few compounds as outliers.

The statistical quality of the regression equations were justified by parameters like correlation coefficient (r), percentage of explained variance (%EV), probability factor related to F-ratio, standard error of estimate (s). All the final equa-

Table 1. 3-Phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones and Their Antifungal Activity against Different Strains Log(1/MIC)

No.	Substituents		CA1[a)]	CA1[b)]	CP[c)]	CK1[d)]	CK2[e)]	CT[f)]	CG[g)]	CL[h)]	TB[i)]	AF[j)]	AC[k)]	TM[l)]
1	*p*-OCH_3	H	−1.19	−1.49	−1.19	−1.80	−2.09	−2.09	−1.49	−2.69	−2.09	−1.49	−2.39	−1.79
2	*m*,*p*-Cl_2	H	−1.80	−2.40	−1.19	−2.40	−2.39	−1.79	−2.09	−2.69	−1.79	−2.09	−2.39	−2.09
3	*m*-Cl	H	−1.49	−2.40	−1.19	−3.00	−2.69	−1.79	−2.39	−2.39	−1.49	−2.09	−2.69	−3.00
4	*p*-Br	H	−1.49	−2.40	−1.19	−2.70	−2.39	−2.09	−2.39	−2.09	−1.79	−2.39	−2.39	−2.69
5	*p*-OCH_3	*p*-Cl-ph	−0.29	−1.50	−0.89	−1.50	−1.49	−1.79	−1.79	—	−1.49	−1.49	−1.79	−1.49
6	*p*-OCH_3	$-CH_3$	—	−1.50	−0.89	−1.80	−1.49	−1.49	−1.49	−1.79	−0.59	−1.79	−1.49	−1.79
7	*p*-OCH_3	$-C(CH_3)_3$	0.01	−1.50	−0.89	−1.80	−1.49	−1.49	−1.49	−1.79	−0.89	−1.79	−1.49	−1.79
8	*m*,*p*-Cl_2	*p*-Cl-ph	0.92	−0.29	0.01	−0.60	−0.29	0.01	−0.29	0.51	0.01	−1.19	−0.29	−0.59
9	*m*,*p*-Cl_2	$-CH_3$	0.31	−0.59	0.01	−0.30	−0.59	0.01	−0.29	0.51	0.01	−1.19	−0.59	−0.59
10	*m*,*p*-Cl_2	$-C(CH_3)_3$	0.31	−0.29	0.62	−0.89	−0.59	0.31	−0.29	0.51	−0.29	−0.89	−0.59	−0.59
11	*m*-Cl	*p*-Cl-ph	−0.29	−0.89	−0.29	−0.89	−1.19	−0.29	−0.89	−0.89	−0.29	−0.59	−0.89	−1.19
12	*m*-Cl	$-CH_3$	0.01	−0.59	−0.29	−0.59	−0.89	—	−0.59	−0.59	−0.29	−0.59	−0.89	−0.89
13	*m*-Cl	$-C(CH_3)_3$	—	−0.59	−0.29	−0.89	−0.89	—	−0.59	−0.59	—	−0.89	−0.89	−0.89
14	*p*-Br	*p*-Cl-ph	−0.29	−0.59	−0.29	−0.89	−0.89	−0.29	−0.59	−0.59	0.01	−0.89	−0.89	−0.89
15	*p*-Br	$-CH_3$	—	−0.29	−0.29	−0.59	−0.89	0.01	−0.29	−0.59	0.01	−0.89	−0.89	−0.59
16	*p*-Br	$-C(CH_3)_3$	0.31	−0.29	−0.29	−0.59	−0.89	−0.29	−0.59	−0.89	0.01	−0.89	−0.59	−0.89

a) Candida albicans ATCC44859, *b) Candida albicans* ATCC90028, *c) C. parapsilosis* ATCC22019, *d) C. krucei* ATCC6258, *e) C. krucei* E28, *f) C. troicalis* 156, *g) C. globrata* 20/l, *h) C. lucitaniae* 2446/l, *i) Trichoporon beigelii* 1188, *j) Aspergillus fumigates* 231, *k) Absidia corymbifera* 272, *l) Trichophyton mentogrophytes* 445.

Table 2. Descriptors Used in Present QSAR Study

S. No.	Descriptors	Type	Descriptions (units)
1	BP	Thermodynamic	Boiling point (Kelvin)
2	CP	Thermodynamic	Critical pressure (Kelvin)
3	CT	Thermodynamic	Critical temperature (bar)
4	HF	Thermodynamic	Heat of formation (kcal/mol)
5	HLC	Thermodynamic	Henrys Law constant
6	IGTC	Thermodynamic	Ideal gas thermal capacity
7	LogP	Thermodynamic	Logarithmic partition coefficient
8	MP	Thermodynamic	Melting point (Kelvin)
9	MR	Thermodynamic	Molar refractivity (cm^3/mol)
10	SGP	Thermodynamic	Standard Gibb's free energy (kJ/mol)
11	VDW	Thermodynamic	Van der Waals force (kcal/mol)
12	PARTCOEFF	Thermodynamic	Partition coefficient for water/octanol
13	NVDW	Thermodynamic	Non 1,4. van der Waals force (kcal/mol)
14	STERG	Thermodynamic	Stretch energy (kcal/mol)
15	STBERG	Thermodynamic	Stretch bend energy (kcal/mol)
16	TORERG	Thermodynamic	Torsion energy (kcal/mol)
17	CAA	Steric	Connolly accessible surface area (Å)
18	CMA	Steric	Connolly molecular surface area (Å)
19	CSEV	Steric	Connolly solvent-excluded volume (Å)
20	EM	Steric	Exact mass (g/mol)
21	MOLWT	Steric	Molecular weight (atomic mass units)
22	OVAL	Steric	Ovality (unitless)
23	PMI-X	Steric	Principal moments of inertia-x (g/mol Å)
24	PMI-Y	Steric	Principal moments of inertia-y (g/mol Å)
25	PMI-Z	Steric	Principal moments of inertia-z (g/mol Å)
26	DIPOLE-X	Electronic	Dipole moment-X axis (Debye)
27	DIPOLE-Y	Electronic	Dipole moment-Y axis (Debye)
28	DIPOLE-Z	Electronic	Dipole moment-Z axis (Debye)
29	EERG	Electronic	Electronic energy (eV)
30	HOMO	Electronic	Energy of highest occupied molecular orbital (eV)
31	UMO	Electronic	Energy of lowest unoccupied molecular orbital (eV)
32	REPLERG	Electronic	Repulsion energy (eV)
33	BENDERG	Electronic	Bending energy (kcal/mol)
34	DDERG	Electronic	Dipole–dipole energy (kcal/mol)
35	TOT	Electronic	Total energy (eV)

tions show significance (F) more than 95% level. Use of more than one variable in the multivariate equation was justified by autocorrelation study. Among the several models generated, 12 best models excluding outliers were selected for the discussion. The selection was based on the statistical parameters *viz.*, squared coefficient ($r^2>0.8$), cross validated coefficient ($Q^2>0.3$), standard deviation ($s<0.3$), Fischer values $>99.99\%$ and all the selected models explain more than 80% variance in the biological activity. The bootstrapping values (r^2_{bs}) for all models showed that they were quite robust.

The statistically significant results for fungal inhibitory activity of furan derivatives against 12 different fungal pathogenic strains have been summarized in Table 3. It should be noted that regression were allowed only for the descriptors, which are orthogonal in nature. The validation data (observed and predicted values) is given in Table 4. A close look at these equations suggests that fungal inhibition is predominantly governed by electronic and thermodynamic factors. All equations have electronic parameters as the most prominent descriptor.

In majority of cases, electronic parameter appears to produce their effect from the substituted phenyl ring. The electronic descriptor dipole moment along the z-axis (Dipole Z) is present in the all selected models except equation 3. The negative coefficient of the descriptor indicates that electron-releasing substituents may increase the biological activity. In addition, the most potent molecules have two chlorine atoms in parent compounds.

Dipole moment-X representing the dipole moment along x-axis was found to be in the equations 2, 4, 5, and 8. The parameter bears a negative coefficient in these equations, which indicates that polar substituents in the x-axis of the molecule decrease the inhibitory potency.

The electronic parameter LUMO which denotes energy of the lowest unoccupied molecular orbital bears a negative coefficient in equations 6, 7, 9, 10 and 12. The energy of LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule towards attack by nucleophiles.[29] The negative coefficient of LUMO indicates that lowering of LUMO energy will increase the magnitude of inhibitory activity of furan derivatives. Energy of LUMO can be decreased by electron donating substituents and saturation of the conjugated system. The descriptor here in highlights that inhibitory effect of furan in greatly hindered by the π electron system.

The role of thermodynamic descriptors in only evident in equations 3, 9, and 11 in which the thermodynamic parameter *viz.* HLC, LogP and NVDW are present respectively. HLC represents Henry's law constant, which deals with solubility of the molecules in biological system and determines the chemical stability (conformation) and reactivity of the molecules during interaction with receptor. The negative coefficient of the HLC in the equation 3 indicates that conforma-

Table 3. Summary of Multiple Linear Regression (MLR) Analysis with Validation Using Various Parameters

C. No.	Equations	n	r	Q^2	Std	F	r^2_{bs}	PRESS	SDEP
1	BA=[−1.890(±1.423)]+D-Z [−0.394568(±0.323)] +DDERG [0.133(±0.154)]	13	0.92	0.71	0.353	29.3	0.880	0.495	0.434
2[b]	BA=[−2.322(±0.2667)]+D-X [−0.193(±0.086)] +D-Z [−0.679(±0.079)]+TOT [−0.0001(±0.040e−005)]	14	0.99	0.95	0.134	164.2	0.970	0.190	0.160
3	BA=[−0.398(±1.268)]+HLC [−0.257(±0.1229)] +DDERG [0.142(±0.060]+EERG [−1.595e −005(±0.1617e−005)]	16	0.94	0.71	0.195	34.1	0.890	0.321	0.278
4[a]	BA=[−2.593(±0.572)]+D-Z [−0.698(±0.171)] +D-X [−0.227(±0.153]+TOT [−0.0001(±0.0001e−005)]	15	0.95	0.83	0.294	35.7	0.904	0.393	0.336
5[a]	BA=[−2.325(±0.523)]+D-Z [−0.588(±0.156)] +D-X [−0.171(±0.401]+TOT [−0.0001(±0.0001e−005)]	15	0.94	0.56	0.269	29.8	0.908	0.539	0.461
6[a]	BA=[−3.618(±1.291)]+D-Z [−0.364(±0.209)] +LUMO [−1.058(±1.229)]+DDERG [0.0953(±0.116)]	16	0.93	0.72	0.285	28.5	0.891	0.429	0.371
7	BA=[−4.689(±1.619)]+LUMO [−3.349(±1.55)] +D-Z [−0.414(±0.206)]	14	0.92	0.71	0.384	31.8	0.869	0.538	0.477
8[b]	BA=[−2.888(±0.863)]+D-Z [−0.524(±0.183)] +D-X [−0.309(±0.119)]+DDERG [0.103(±0.093)]	15	0.96	0.87	0.239	47.8	0.940	0.321	0.275
9	BA=[−3.237(±1.404)]+D-Z [−0.522(±0.190)] +LUMO [−2.343(±1.591)]+LogP [0.0922(±0.020)]	15	0.89	0.60	0.553	15.5	0.872	0.801	0.680
10[c]	BA=[−3.055(±0.801]+D-Z [−0.469(±0.094)] +TOT [−0.0002(±0.0001)]+LUMO [−1.051(±0.851)]	14	0.96	0.86	0.172	92.6	0.960	0.342	0.289
11[a]	BA=[−2.275(±0.450)]+D-Z [−0.581(±0.120)] +NVDW [0.092(±0.0127)]+TOT [−0.0001(±0.0001e−005)]	14	0.94	0.87	0.209	54.5	0.933	0.304	0.257
12[b]	BA=[−5.147(±1.081)]+D-Z [−0.477(±0.146)] +LUMO [−2.480(±0.995)]+DDERG [0.0783(±0.0780)]	14	0.95	0.91	0.189	76.8	0.951	0.270	0.228

Q^2 denotes cross-validated correlation coefficient. PRESS and SDEP denote predicted residual sum of squares and standard deviation error of predictions respectively. Standard error of estimate (s), variance ratio (F) at specified degrees of freedom (df) and bootstrap r^2 (r^2_{bs}). *a*) Compound No. 1 is outlier. *b*) Compound No. 1 and 5 are outliers. *c*) Compound No. 5 is outlier.

Table 4. Observed and LOO Predicted Values of 3-Phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones derivatives

C. No.	^{1}Pred[a]	Obs[b]	^{2}Pred[a]	Obs[b]	^{3}Pred[a]	Obs[b]	^{4}Pred[a]	Obs[b]	^{5}Pred[a]	Obs[b]	^{6}Pred[a]	Obs[b]
1[c]	−1.73	−1.19	—	—	−1.65	−1.19	—	—	—	—	—	—
2	−0.88	−1.79	−2.19	−2.39	−0.78	−1.19	−2.64	−2.39	−2.63	−2.09	−1.98	−2.39
3	−1.58	−1.49	−2.58	−2.39	−1.15	−1.19	−2.74	−3.00	−2.61	−3.00	−2.71	−2.69
4	−1.61	−1.49	−2.23	−2.39	−1.24	−1.19	−2.59	−2.69	−2.42	−2.69	−2.69	−2.39
5[c]	0.14	−0.29	—	—	−0.77	−0.89	−1.04	−1.49	−1.26	−1.49	−1.20	−1.49
6	—	—	−0.80	−1.49	−0.56	−0.89	−1.31	−1.79	−2.40	−1.79	−1.36	−1.49
7	−0.11	0.1	−1.69	−1.49	−0.73	−0.89	−1.70	−1.79	−1.79	−1.79	−1.75	−1.49
8	0.13	0.92	−0.71	−0.29	−0.20	0.01	−0.81	−0.59	−0.90	−0.59	−0.59	−0.29
9	0.19	0.30	−0.60	−0.59	0.09	0.01	−0.93	−0.29	−0.94	−0.59	−0.62	−0.59
10	0.31	0.30	−0.26	−0.29	−0.11	0.61	−0.38	−0.89	−0.52	−0.59	−0.47	−0.59
11	0.10	−0.29	−0.90	−0.89	−0.48	−0.29	−1.04	−0.89	−1.10	−1.19	−1.02	−1.19
12	−0.06	0.01	−0.88	−0.59	−0.22	−0.29	−1.11	−0.59	−1.17	−0.89	−1.23	−0.89
13	—	—	−0.52	−0.59	−0.21	−0.29	−0.75	−0.89	−0.83	−0.89	−1.08	−0.89
14	0.08	−0.29	−0.57	−0.59	−0.55	−0.29	−0.71	−0.89	−0.79	−0.89	−0.82	−0.89
15	—	—	−0.19	−0.29	−0.31	−0.29	−0.52	−0.59	−0.60	−0.59	−0.81	−0.89
16	−0.08	0.30	−0.11	−0.29	−0.31	−0.29	−0.37	−0.59	−0.37	−0.89	−0.82	−0.89

C. No.	^{7}Pred[a]	Obs[b]	^{8}Pred[a]	Obs[b]	^{9}Pred[a]	Obs[b]	^{10}Pred[a]	Obs[b]	^{11}Pred[a]	Obs[b]	^{12}Pred[a]	Obs[b]
1[c]	−3.08	−2.09	—	—	−3.60	−2.69	−1.95	−2.09	—	—	—	—
2	−1.18	−1.79	−1.89	−2.09	−1.38	−2.69	−1.51	−1.79	−2.19	−2.09	−2.21	−2.39
3	−1.98	−1.79	−2.68	−2.39	−2.44	−2.39	−1.89	−1.49	−2.24	−2.09	−2.53	−2.69
4	−1.51	−2.09	−2.21	−2.39	−2.17	−2.09	−1.69	−1.79	−2.11	−2.39	−2.46	−2.39
5[c]	−0.88	−1.79	—	—	—	—	—	—	−0.98	−1.49	—	—
6	−1.05	−1.49	−1.38	−1.49	−1.01	−1.79	−0.36	−0.59	−0.70	−1.79	−1.02	−1.49
7	−1.71	−1.49	−1.50	−1.49	−1.95	−1.79	−0.87	−0.89	−2.55	−1.79	−2.00	−1.49
8	−0.13	0.01	−0.49	−0.29	−0.31	0.51	−0.09	0.01	−0.68	−1.19	−0.74	−0.29
9	−0.16	0.01	−0.43	−0.29	−0.65	0.51	−0.20	0.01	−1.15	−1.19	−0.74	−0.59
10	−0.06	0.30	−0.02	−0.29	−0.12	0.51	0.06	−0.29	−0.88	−0.89	−0.54	−0.59
11	−0.69	−0.29	−1.02	−0.89	−0.59	−0.89	−0.21	−0.29	−0.87	−0.59	−0.97	−0.89
12	—	—	−1.11	−0.59	−0.97	−0.59	−0.28	−0.29	−0.96	−0.59	−1.03	−0.89
13	—	—	−0.71	−0.59	−0.55	−0.59	—	—	−0.95	−0.89	−0.84	−0.89
14	−0.23	−0.29	−0.60	−0.59	−0.17	−0.59	−0.12	0.01	−1.07	−0.89	−0.71	−0.89
15	−0.17	0.01	−0.39	−0.29	−0.05	−0.59	−0.02	0.01	−1.05	−0.89	−0.53	−0.892
16	−0.15	−0.29	−0.18	−0.59	−0.05	−0.89	0.00984	0.01	−0.88	−0.89	−0.58	−0.592

a) Predicted values: LOO predicted activity calculated using best equation. *b*) Observed activity: observed activity is defined as log(1/MIC) where MIC is minimum concentration required inhibiting fungal. *c*) Outlier compounds not included in the equation.

tional stability of the molecules is not favorable to the biological activity.

In the equation 9 logP contributes positively and, this hydrophobic parameter is mainly considered in QSAR equation for the lipophilic nature of drugs. This evidence was clearly described in lipid theory advanced by Meyer and Overton. According to this theory, penetration and distribution potency of the drug should be directly related to its hydrophobic nature (octanol/water).[30,31]

Later it was reported that logP not only considers the penetration and distribution and also deals with interaction of drugs with receptors. Non1, 4 van der Waal's energy (NVDW) is the energy for the through-space interaction between pair of the atoms that are separated by more than three atoms.[32] The positive contribution of NVDW in equation 11 suggests the ability of furan derivatives to interact with receptor by NVDW forces during drug–receptor interaction. It indicates presence of electronic π–π interaction between molecules and active site residues.

Overview of Hansch Analysis On the basis of the results discussed above, it can be concluded that the importance of electronic withdrawing constituents in enhancing the biological activity is evident from the contribution of parameters; D-X, D-Z, TOT, LUMO and DDERG. The charge-transfer was found to play major role in the antifungal action of furan analogs. Reduction of LUMO energy being favorable for the antifungal activity indicates charge-transfer phenomenon taking place in a drug receptor interaction upon binding, moreover inverse relationship between D-X and D-Z and the biological activity is shown by their negative influence on the antifungal activity.

The thermodynamic parameters LogP and NVDW show positive contribution to the biological activity respectively as indicated by equations 9 and 11. LogP is a measure of hydrophobicity which is important for the penetration and distribution of the drug but also for the interaction of drug with receptors. The positive contribution of LogP thus suggests its significant participation in the enzyme inhibition. The other thermodynamic parameter NVDW refers to the ability of molecules to interact with the receptor by non-van der Waals forces and hydrogen bonding during drug–receptor interaction. However, this parameter being unfavorable for the biological activity, it should be decreased.

From the above 12 models, it can be concluded that strong electronic influence of the substituent in the phenyl ring is important for the antifungal activity and some thermodynamic parameters also contribute significantly to the activity. In conclusion, it can be suggested that electronic and thermodynamic properties have to be checked while designing potent antifungal agents as they are the deciding factors for its activity.

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