Classical QSAR Study on Chromene Derivatives as Lanosterol 14α-Demethylase Inhibitor: A Non Azole Antifungal Target

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Abstract: A lanosterol 14α-demethylase inhibitors of chromene series were subjected to classical quantitative structural activity relationship studies. Apart from the indicator variables encoding for different group contribution, there are various physico-chemical descriptors like steric, thermodynamic and electronic parameters, which were applied to explore the structural requirements for inhibition of enzyme. Multiple linear regression analysis shows that substituents on the appended alkylated ether and the carbon chain length, which should not be more than six at R3 and R1 positions in the parent nucleus, are essential to modulate the activity. Electronic parameters such as highest occupied molecular orbital energy and dipole dipole energy have been found to play an important contribution for biological activity. From the orientation or distribution of the total molecular structures in 3D space, it was assessed that Principal Moments of Inertia at X-axis is detrimental for fungal inhibitory activity. Thus validated models bring important structural insights to aid the design of potent lanosterol 14α-demethylase inhibitors prior to their synthesis.

Key Words: QSAR, cytochrome P450, chromene derivative, highest occupied molecular orbital, austin model-1 calculation and anti mycotic agents.

INTRODUCTION

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 have been observed in the past two decades, particularly in immuno-compromised patients [1]. Although we have some newer and less toxic antifungal agents that are currently available for clinical use, their clinical efficacy in some invasive fungal infections such as Aspergillus and fusariosis is not appreciable. Intensive efforts in antifungal discovery are urgently needed to develop more promising and effective antifungal agents for use in the clinical arena. Subsequently 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 [2]. 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 (CYP450) enzyme, which plays an important role in the bio-synthesis of ergosterol, a membrane component in fungus [3-10].

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 [11] that causes fatal hepatotoxicity [12]. All these findings urged us to learn more about novel nonazole lead compounds with more structural specificity for the fungal enzyme to separate their activity from toxicity. In this context, we have tried to explore QSAR of a series of lanosterol 14α-demethylase inhibitor Chromene derivatives [13] for their antifungal activity against human fungal pathogens such as *Candida albicans, Candida parapsilosis, Cryptococcus neoformans, Sporothrix schenckii, Fonsecaea pedrosoi, Aspergillus fumigatus, Trichophyton rubrum and Microsporum canis*, using classical QSAR tools. This is our one more step in the field of obtaining potent QSAR model for compounds of various biological interests [14-17].

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METHODS OF CALCULATION

QSAR and Descriptor Values for All the Molecules Using Compute Properties Module

The Lanosterol 14α-demethylase inhibitory activity of chromene derivatives has been reported [13] in terms of minimum inhibitory concentration (MIC) (in μm/ml) against various fungal pathogens. These MIC values were used as log (1/MIC) with MIC in terms of μm/ml. (Table **1**). Molecular Modeling studies were carried out using CS Chem-Office Software version 6.0 (Cambridge soft) [18] running on a P-III processor. The structures of compounds were drawn in Chem. Draw ver. 6.0 cleaned and copied to Chem.3D ultra ver 6.0 to create the 3D model. Each 3D molecular structure was subjected to energy minimization technique using a semi-empirical quantum mechanics package namely MOPAC version, AM1 (Austin model-1). Hamiltonians approximations method, using closed shell restricted wave function was used [19-21]. The various

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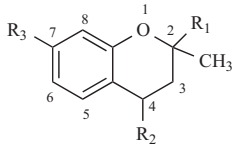
Table 1. ***In Vitro*** **Inhibitory Data of Chromene Derivatives for Lanosterol 14α -demethylase Inhibition**



C. No	Substituents			[a]Fungal Pathogen pMIC							
	R_1	R_2	R_3	1	2	3	4	5	6	7	8
1	$CH_2(CH_2)_3CH_3$	OH	7-OH	-2.20	-1.60	-1.90	-1.30	-1.60	-1.90	-1.30	-1.00
2	$CH_2(CH_2)_5CH_3$	OH	7-OH	-1.60	-1.30	-1.60	-1.60	-1.90	-1.90	-1.30	-0.43
3	$CH_2CH_2CH=C(CH_3)_2$	OH	7-OH	-1.90	-1.90	-2.20	-1.90	-2.20	-2.20	-1.90	-1.00
4	$CH_2(CH_2)_3CH_3$	=NOH	7-OH	-2.20	-1.60	-1.60	-1.60	-1.60	-1.90	-0.70	-0.76
5	$CH_2(CH_2)_5CH_3$	=NOH	7-OH	-1.60	-1.30	-1.30	-1.00	-1.60	-1.00	-1.43	0.20
6	$CH_2CH_2CH=C(CH_3)_2$	=NOH	7-OH	-1.90	-1.90	-1.60	-1.60	-1.30	-1.60	-0.76	-0.43
7	$CH_2(CH_2)_3CH_3$	=O	7-OH	-2.51	-2.20	-2.20	-1.90	-1.90	-2.20	-1.30	-1.60
8	$CH_2(CH_2)_5CH_3$	=O	7-OH	-2.20	-2.20	-1.90	-1.60	-1.90	-2.20	-1.60	-1.90
9	$CH_2CH_2CH=C(CH_3)_2$	=O	7-OH	-2.20	-1.90	-2.20	-2.20	-2.20	-1.90	-1.90	-1.60
10	$CH_2(CH_2)_7CH_3$	=O	7-OH	-	-	-	-	-	-1.90	-	-1.90
11	$CH_2CH(CH_3)_2$	=O	7-OH	-	-2.51	-2.51	-2.51	-2.20	-2.20	-2.20	-1.60
12	$CH_2(CH_2)_3CH_3$	=O	7-OCH_3	-	-	-	-	-	-2.20	-	-1.90
13	$CH_2(CH_2)_5CH_3$	=O	7-OCH_3	-	-2.51	-	-1.60	-	-	-2.50	-1.60
14	$CH_2CH_2CH=C(CH_3)_2$	=O	7-OCH_3	-	-	-	-2.51	-	-2.20	-	-1.90
15	$CH_2(CH_2)_3CH_3$	OH	7-OCH_3	-2.51	-2.20	-2.20	-	-	-1.90	-1.30	-1.30
16	$CH_2(CH_2)_5CH_3$	OH	7-OCH_3	-2.51	-2.20	-1.90	-1.60	-2.20	-1.90	-1.90	-1.90
17	$CH_2CH_2CH=C(CH_3)_2$	OH	7-OCH_3	-	-2.20	-2.20	-2.51	-2.51	-2.20	-2.20	-2.20
18	$CH_2(CH_2)_3CH_3$	_[3,4]	7-OCH_3	-	-	-2.51	-	-	-	-	-2.51
19	$CH_2(CH_2)_5CH_3$	_[3,4]	7-OCH_3	-	-	-	-	-	-	-	-2.51
20	$CH_2CH_2CH=C(CH_3)_2$	_[3,4]	7-OCH_3	-	-	-	-2.51	-	-	-1.60	-1.90

[1]Candida albicans, [2] Candida parapsilosis, [3] Cryptococcus neoformans, [4] Sporothrix schenckii, [5] Fonsecaea pedrosoi, [6]Aspergillus fumigatus, [7] Trichophyton rubrum, [8] Microsporum canis

indictor variables considered for QSAR studies are given in Table **2** and Quantum mechanical descriptors like highest occupied molecular orbital energy (HOMO), lowest un-occupied molecular orbital energy (LUMO) and Dipole dipole energy (DDE) were calculated using MOPAC. Thermodynamic descriptors like logarithm of partition coefficient (LogP), molecular refractivity (MR), heat of formation (HF), critical pressure (CT), were calculated using the chem. Pro pro server. Special descriptors viz., Principal Moments of Inertia- X component (PMI-X), Principal Moments of Inertia-Y(PMI-Y), Principal Moments of Inertia Z component (PMI-Z), Ovality, Connolly Accessible Surface Area (CAA), Connolly Molecular Surface Area (CMSA), Connolly Solvent- Excluded Volume (CSEV) and Non 1, 4 van der Waals Force (NVW1,4) were calculated using chem. Pro std server.

Multivariate Regression Analysis

The statistical quality of the equations was judged by the parameters like *explained variance* (R^2, *i.e.*, adjusted R^2), correlation coefficient (*r* or *R*), standard error of estimate (*s*), variance ratio (*F*) at specified degrees of freedom (*df*), 90% confidence intervals of the regression coefficients. Leave–one–out cross validation R^2 (Q^2) [22], predicted residual sum of squares (*PRESS*), standard deviation based on *PRESS* (*SPRESS*), standard deviation of error of prediction (*SDEP*). All the statistical work was calculated by

Table 2. Terms and Definition of Indicator Variables

I_{OH}	I_{OH} Presence (value 1) or absence (value 0) of hydroxyl group at the R_3 position (Carbon atom 7) of chromene nucleus
I_{un}	Presence (value 1) or absence (value 0) of un saturation in carbon chain R_1 position (Carbon atom 2) of chromene nucleus
I_{cl}	Carbon chain length higher than six (Presence) or below than six (absence) at R_1position (Carbon atom 2) of chromene nucleus
I_{oxime}	Presence of oxime group (value 1) absence (valve 0) R_2position (Carbon atom-2) of chromene nucleus

VALSTAT software [23], which was developed in our laboratory. A compound was considered as an outlier if the residual is more than twice the standard error of estimate for a particular equation.

RESULTS AND DISCUSSION

Among several models, one "best" model was chosen for further analysis for each microorganism based on statistical parameters viz. correlation coefficient, cross-validated r^2 (Q^2) and standard deviation (s). The statistically significant results for fungal inhibitory activity of chromene derivatives against 8 different fungal pathogenic organisms have been summarized in Table **3**. The selection was based on the statistical parameters viz, squared coefficient, cross validated coefficient (Q^2>0.3), standard deviation (s<0.3). It should be noted that regression were allowed only for the descriptors, which are orthogonal in nature. The validation data (Calculated and predicted values) is given in Table **4**.

All regression coefficient of equation-1 are significant at 90% level. The 90% confidence intervals of the regression coefficient are shown within parenthesis. This equation can explain 68.8% variance in the lanosterol 14_-demethylase inhibiting activity in *Candida albicans*. An attempt was made to obtain superior relation using physico-chemical (HOMO-LUMO, CT, logP, MR, Dipole-dipole energy, PMI-X, PMI-Y and PMI-Z) and suitable indicator variables. However in the final relation, HOMO and I_{OH} contribute positive and negative coefficient respectively.

Equation 1 shows the importance of Electronic parameter HOMO energy which is contributing positively. HOMO is highest occupied molecular orbital energy, obtained by molecular orbital calculation and relates to the presence of high electron density, so molecules with high HOMO energy are able to donate their electron in charge transfer phenomena. Positive contribution of HOMO energy in this equation demonstrates that the requirement for critical electron density may be favorable for antifungal activity. Negative contribution of I_{OH} in the equation 1 suggests that presence of alkyl group in the R3 position of chromene derivatives is favorable for the inhibition activity.

Equation-2 explains 74.8% variance; predict 58.8% in the biological activity (*Candida parapsilosis*). The standard error and predicted standard error of the equation are 0.215 and 0.244, respectively; the positive coefficient of HOMO

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

Eq.no	Equations	n	r	Q^2	F	s	SDEP	PRESS
1	$_p$MIC=[6.9052(±7.40825)]+I_{OH}[-0.76675 (±0.46564)] + HOMO [0.995123(±0.824439)]	11	0.817	0.455	8.061	0.215	0.235	0.276
2	$_p$MIC= [9.75648 (±5.64327)]+I_{OH}[-0.70465 (±0.312812)] + HOMO [1.2871(± 0.64607)]	14	0.864	0.588	8.061	0.215	0.244	0.275
3	$_p$MIC= [-1.8238 (±0.20582)]+I_{cl}[-0.40723 (±0.23188)] +I_{oxime} [0.59531(±0.25529)]	14	0.901	0.714	22.33	0.175	0.187	0.211
4	$_p$MIC= [-6.4506 (±1.907)]+I_{un} [0.2256 ±(0.2737)] +I_{OH} [-0.7540 (±0.322)]+ CSEV [0.01954(±0.0076)]	15	0.925	0.733	21.91	0.206	0.241	0.281
5	$_p$MIC= [-1.98571 (±0.187525)]+ I_{OH} [-0.369286 (±0.397801)] +I_{oxime} [0.485714 (±0.3423)]	12	0.832	0.448	10.12	0.215	0.249	0.288
6	$_p$MIC= [-2.17345 (±0.48029)] + I_{oxime} [0.43079 (±0.20473)] +CLogP [0.0829 (±0.09689)]+ DDE [-0.23305 (±0.110469)]	16	0.919	0.723	22.02	0.137	0.159	0.184
7	pMIC = [-0.17 (± 1.05)] +PMI-X [-0.001 (± 0.001)] +DDE [-0.47 (± 0.21)]	15	0.801	0.470	12.05	0.320	0.235	0.238
8	$_p$MIC= [-22.9392 (±10.7602)] +I_{oxime} [0.686671 (±0.641358) + CT [0.02696 (±0.0135)] + LUMO [1.22781 (±0.63086)] + PIM-Z [-0.000347 (±0.000280)]	20	0.887	0.572	13.916	0.372	0.429	0.483
9*	$_p$MIC= [-16.5375 (±9.4920)] + I_{oxime} [0.97264 (±0.605769) + CT [0.02696 (±0.0135)]+ LUMO [1.15626 (±0.63301)]	19	0.872	0.620	15.96	0.383	0.429	0.483

QSAR models abbreviation: correlation coefficient (r), Leave–one–out cross validation r2 ($Q2$) PRESS and SDEP denote predicted residual sum of squares and standard deviation error of predictions respectively. Standard error of estimate (s) and variance ratio (F) at specified degrees of freedom (df).* Model obtained by omitting data point 17 as outlier.

Table 4. Calculated and Predicted pMIC Values of QSAR Model Exhibiting Lanosterol 14_-demethylase Inhibitory Activity

No	*C.alb.*		*C.par.*		*C.neo.*		*S.sch.*		*F.ped.*		*A.fum.*		*T.rub.*		*M.can.*	
	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.	Cal.	Pred.
1	-1.73	-1.83	-1.53	-1.53	-2.23	-2.27	-1.46	-1.49	-1.98	-2.05	-2.02	-2.06	-1.30	-1.37	-1.26	-1.31
2	-1.89	-1.83	-1.60	-1.60	-1.82	-1.90	-1.24	-1.14	-1.98	-2.00	-1.93	-1.94	-1.30	-1.54	-0.96	-1.12
3	-1.82	-1.84	-1.48	-1.48	-2.23	-2.23	-1.98	-2.01	-1.98	-1.95	-2.07	-2.04	-1.90	-1.53	-1.00	-1.00
4	-2.0	-2.03	-1.83	-1.83	-1.63	-1.65	-1.82	-1.86	-1.50	-1.45	-1.75	-1.62	-0.70	-1.34	-0.60	-0.52
5	-1.85	-1.78	-1.54	-1.54	-1.22	-1.16	-1.17	-1.23	-1.50	-1.45	-1.00	-1.04	-1.39	-1.07	0.04	-0.05
6	-2.14	-2.11	-1.90	-1.90	-1.63	-1.65	-1.78	-1.87	-1.50	-1.6	-1.73	-1.84	-0.69	0.35	-0.42	-0.42
7	-2.19	-2.27	-2.10	-2.10	-2.23	-2.23	-2.01	-2.05	-1.98	-2.00	-2.14	-2.13	-1.30	-1.77	-1.81	-1.84
8	-2.30	-2.27	-2.10	-2.10	-1.82	-1.79	-1.34	-1.29	-1.98	-2.00	-2.05	-2.02	-1.60	-1.87	-1.60	-1.54
9	-2.35	-2.30	-2.22	-2.22	-2.23	-2.23	-2.04	-1.99	-1.98	-1.95	-2.19	-2.22	-1.90	-1.94	-1.57	-1.57
10	-	-	-	-	-	-	-	-	-	-	-1.96	-2.04	-	-	-1.34	-1.11
11	-	-	-2.06	-2.06	-2.23	-2.19	-2.32	-2.11	-1.98	-1.95	-2.19	-2.18	-2.20	-1.57	-2.03	-2.09
12	-	-	-	-	-	-	-	-	-	-	-2.12	-2.11	-	-	-2.06	-2.09
13	-	-	-2.83	-2.83	-	-	-1.70	-1.75	-	-	-	-	-2.50	-2.65	-1.83	-1.89
14	-	-	-	-	-	-	-2.42	-2.39	-	-	-2.17	-2.17	-	-	-1.80	-1.79
15	-2.50	-2.50	-2.10	-2.10	-2.23	-2.23	-	-	-	-	-1.98	-1.99	-1.30	-1.61	-1.47	-1.53
16	-2.51	-2.51	-2.10	-2.10	-1.82	-1.79	-1.61	-1.62	-2.35	-2.51	-1.89	-1.89	-1.90	-1.79	-1.16	-0.97
17	-	-	-2.12	-2.12	-2.23	-2.23	-2.36	-2.31	-2.35	-2.20	-2.03	-2.00	-2.20	-1.87	-*	-
18	-	-	-	-	-2.23	-2.19	-	-	-	-	-	-	-	-	-2.04	-1.94
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-1.98	-1.99
20	-	-	-	-	-	-	-2.61	-2.65	-	-	-	-	-1.60	-1.57	-1.26	-1.31

Abbreviations: C .alb., Candida albicans ;C.par. , Candida parapsilosis; C.neo., Cryptococcus neoformans; S.sch., Sporothrix schenckii; F.ped, Fonsecaea pedrosoi; A.fum., Aspergillus fumigatus;T.rub;Trichophyton rubrum; M.con; Microsporum canis, *Outlier compounds not included in the equation.

indicates the positive contribution of electron donating capacity of the compounds to the receptor. The negative coefficient of I_{OH} suggests that the decrease of activity in the presence of hydroxyl group attached in phenyl ring (7^{th} position), substituting alkyl group may favors the activity.

Eq. 3 is a two-variable relation predicting 71.4% and explaining 80.2% of the variance of the biological activity. The 99.99% confidence intervals of the regression coefficients are shown within parentheses. The standard error and predicted standard error of the equation are 0.175 and 0.187, respectively. Eq 3 suggests the importance of oxime substitution in the R2 position of the chromene derivatives. Unshared lone pair of electrons in the oxime group may participate in the nucleophilic attack on lanosterol 14_-demethylase enzyme. Negative coefficient of Icl denotes that on increasing carbon chain length above six, the biological activity will decrease.

According to equation 4, which accounts for the significant correlation with the biological activity, it has satisfactory correlation (r = 0.925) and shows statistically 99.99% significance. In addition, the equation has shown less standard deviation (0.206) and high Q^2 (0.733). The 99.99% confidence intervals of the regression coefficients are shown within parentheses. In eq. 4, the variables I_{un}, I_{OH} and CSEV could predict 73.31% and explain 85.66 % of the variance to the inhibitory activity. The standard error and predicted standard error of the equation are 0.206 and 0.241, respectively. CSEV is the volume contained within the contact molecular surface created when a spherical probe (representing the solvent) is rolled over the molecular model. Equation 4 suggests that the positive contribution of special descriptor CSEV gives an indication of the extent to which the ligands are exposed to intermolecular interaction with the solvent (water) and clearly enunciates the needs of bulky substituents for better drug receptor interaction.

From the equation 5, it is found that there exist good correlation (r=0.832) between the biological activity against *Fonsecaea pedrosoi* and the indicator variables for the presence of oxime group in R2 and the hydroxyl group in the R3 position. The indicator variable for oxime group has positive effects on biological activity while the indicator variable for -OH group contributes negatively for the biological activity. The standard deviation of this mode is low (s=0.215) with the significance of 95%. Predicted

standard error and standard deviation of predicted residual sum of squares standard deviation (PRESS) of the equation is 0.2495 and 0.2881, respectively.

The equation 6 shows that the correlation between the biological activity against *Aspergillus fumigatus* and the independent variables is high (r=0.919) with low standard deviation and this could predict and explain 72.3% and 84.6 % of the variance in the inhibitory activity. The regression coefficient of equation-6 is significant at 99.99% level. The indicator parameter for oxime group in R2 and the hydrophobic parameter (logP) contributes positively for the biological activity but the parameter DDE has negative effect on the inhibitory activity. Hydrophobic parameter (logP) plays an important role not only in the penetration and distribution phenomena but also with the interaction with receptor. Dipole- Dipole Energy (DDE) is sum of the electrostatic energy terms resulting from interaction of two dipole. Negative correlation with Dipole –Dipole Energy may be due to a binding process that involves dipole interaction removing drug molecule from active site.

Eqn. 7 obtained from the QSAR analysis for *Trichophyton rubrum* shows less correlation (r = 0.81) and regression coefficient of equation-7 are significant at 99% level against the biological activity. And Q^2 is 0.47, which is quite low. The variance in activity for eq.7 is 66 % and the standard deviation is 0.32. Electronic parameters such as PMI-X and Dipole-Dipole Energy contribute negatively to the activity. PMI-X represents the orientation or distribution of the total molecular structural in three-dimensional spaces. The negative contributions of PMI-X and DDE implicate that the orientation of side chain in X-axis and energy produced by interaction of two dipoles, respectively, is detrimental for fungal inhibitory activity.

Eq. 8 is a four variable relation predicting 57.2% and explaining 78.7% of the variance of the biological activity. The 99% confidence intervals of the regression coefficients are shown within parentheses. In eq. 8 a data point is considered as outlier and was eliminated whilst deriving equation 9. The outlying behavior of compound 17 is as outlier attributed to the steric hindrance of the lengthy carbon chain with hydrophilic hydroxyl group in the presence of methoxyl group in the parent nucleus with receptor.

The equation 9 shows a tremendous improvement in terms of its statistical parameter. And it indicates that the indicator variables for oxime in R2, CT and LUMO influence the inhibitory activity against *Microsporum canis* positively. The standard error and predicted standard error of the equation are 0.3835 and 0.4296 respectively.

In conclusion, it can be suggested that alkylated ether in the 7th carbon atom of Chromene derivatives (R3 position) and oxime substitution in the 4th carbon atom of Chromene derivatives (R2 position) are favorable for the inhibitory activity. Unshared lone pair of electrons in the oxime group may be involved in the electron charge transfer phenomenon with the active site of lanosterol 14α-demethylase enzyme. The negative coefficient of I_{cl} denotes that increasing the carbon chain length above six decreases the biological activity. Further, at 2nd carbon atom (R1position), the carbon chain length should be below six for optimum activity. Apart from this, the parameters such as LUMO, HOMO, CSEV, ClogP, DDE, PMI-X and CT also contribute significantly for the biological activity. As these parameters are the deciding factors for the biological activity, their contributions have to be considered while developing the potent lanosterol 14α-demethylase inhibitors, as they are the deciding factors for its activity.

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