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3D-QSAR STUDIES OF ANTI-BACTERIAL CHALCONES

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ABSTRACT: A Three -dimensional quantitative structure activity relationship (3D-QSAR) studies were conducted on a series 31 1,3-diarylpropane chalcones acting as potent antibacterial agents. The comsia analysis has been carried out to enhance the efficacy of chalcones by predicting important properties. The best predictions were obtained using regression analysis. The results are critically discussed on the basis of significant regression Coefficients (R^2=0.724). The obtained correlations also suggest that the presence of -OH group at proper position increase inhibitory activity of these molecules.
Keywords : 3 D-QSAR, 1,3-diarylpropane chalcones , comsia analysis , Antibacterial Agents, chalcones

1. INTRODUCTION

Chalcones either natural or synthetic are known to exhibit various biological activities. 1,3-diarylpropane are a class of compounds exhibit diverse pharmacological activities, such as antimalarial[1] , anti-inflammatory[2] , antileishmanial[3] , antioxidant[4-7] , antitumor[8] , and antibacterial activity[9]. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. Chalcones are prepared by condensing Aryl ketones with aromatic aldehydes in presence of suitable condensing agents. Depending on the substitution of the the two aromatic rings ,the chalcones can exhibit diff biological activity. The compounds effectiveness is estimated using Gram-negative and Gram positive bacteria , such as B.cereus, E.coli, P.aeruginosa and S.aureus . The present study is considered only on B.cereus bacteria.

3D- QSAR studies have been performed on a series of 31 1,3-diarylpropane chaclones to evaluate the influence molecular fields with the biological activity. biologically highest activity molecule taken as a template and compared all the molecules using Comparative Molecular Similarity Indices Analysis(COMSIA) .The studies suggesting that , alignment score is correlated with biological activity. i.e with increase in structure similarity(alignment score), biological activity also increased.

2. EXPERIMENTAL

2.1. Softwares

2.1.1 Molecular Modeling

The structures of molecules were drawn using Hyperchem 7.0 software[10]. The final geometries were obtained with the semi-empirical AM1 method in Hyperchem program. The molecular structures were optimized using the Polak-Ribiere algorithm until the root mean square gradient was 0.01 kcal mol-1.

2.1.2 Alignment software

FieldTemplater 2.1.1[11] is a tool for comparing molecules using their electrostatic, van der Waals effects and hydrophobic fields in order to find common patterns. When applied to several structurally-distinct molecules with a common activity, FieldTemplater can determine the bioactive conformations and relative alignments of these molecules**.** Similarity score is an average score of Field similarity and Volume similarity.

$$\text{Similarity} = \frac{\text{Field similarity} + \text{Volume similarity}}{2}$$

Field similarity : The total template similarity as measured using Cresset's field similarity metric Volume similarity : The total template volume (shape) similarity .

2.1.3 SPSS

SPSS[12] Inc . is a leading worldwide provider of predictive analytics software and solutions.

2.2 **Data Screening & Model Building:**

The selected descriptor (Similarity score) was calculated from the data of 31 1,3-diarylpropane chalcones[13] Inhibitors and tabulated in table 1 . The regression analysis were carried out using SPSS (version 17.0) software to derive the QSAR equations. Molecule structures, calculated similarity scores and molecules IC50 values were given in Table 2. Biologically highest activity molecule 18 taken as a template molecule to find alignment similarities with database molecules. A common substructure-based alignment similarity scores was adopted in the present study, The total Similarity Score of molecules is in terms of their surface and electrostatic properties: positive and negative electrostatic fields, van der Waals effects and hydrophobic effects on and near the surface of a molecule.

2.3 **Model building**:

The correlation matrix studies performed between biological activity (-log IC50) and alignment similarity score are presented in Table 2. The correlation matrix showing strong correlation between activity and Similarity as indicated by values near to 1(r=0.849) . The simple linear regression[14-16] method performs a standard linear regression calculation to generate QSAR equation. This method is good for exploring simple relationships between structure and activity. The present Similarity Score descriptor served as independent variable and activity
(-logIc50) values as a dependent variable in regression analysis in deducing the 3D-QSAR[17-18] models. The significant equation with high correlation are listed below.

Activity(-log IC50) =
=11.283 (± 1.303) * similarity + - 8.042
N= 31 R= 0.849 R^2 = 0.721
Adj R^2 = 0.711 SEE= 0.3903

2.4 **Model validation**:

The performance of model was evaluted using the leave one out (LOO) cross-validation method. The corresponding squared cross-validated correlation coefficient[19] R^2_{cv} is calculated for the model, which is calculated automatically by the validation module implemented in CODESSA[20] PRO package. The cross-validated correlation coefficient R^2_{cv} 0.682 is pretty close to the correlation coefficient R^2(0.721) , that suggests a good predictive ability of the best linear model as shown in in figure 3. It can be easily observed that our linear regression equation is better in terms of stability and predictive ability with a lower difference R^2 _ R^2_{cv}.

3. RESULTS AND DISCUSSIONS :

3d qsar studies were performed using Comparative Molecular Similarity Indices Analysis(COMSIA) . The comsia analysis carried out using four descriptor fields: surface and electrostatic properties: positive and negative electrostatic fields, van der waals effects and hydrophobic effects on and near the surface of a molecule. The similarity score of molecules taken in terms of these four properties summarization. The comsia analysis explained using similarity score. experimental biologically highest activity molecule 18 taken as a template and compared molecular fields[21] and hydrophobic areas of all molecules taken in table 1 . The hypothesis of work relies is that two molecules which both bind to a common active site tend to make similar interactions with the protein, hence high score similarity molecules may show good binding with protein .

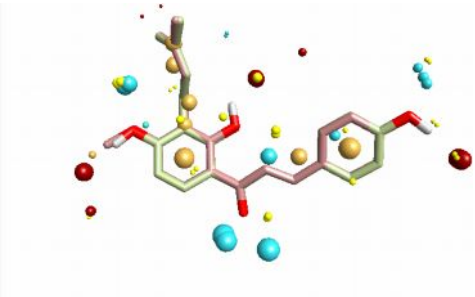
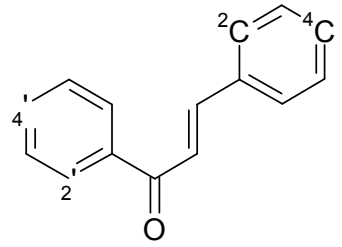


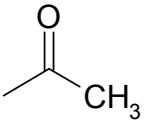
Fig1: Molecular algiments between template molecule and molecule 14
(Blue: Negative field points, Red: Positive field points ,Yellow: vander Waals surface field points, Gold/Orange: Hydrophobic field points)

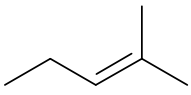
The statistics obtained from above Equation demonstrates the role of the alignment Score(Similarity Score) in the modeling of antibacterial chalcone Inhibitors to explain binding affinity. The equation also shows the direct relationship between similarity score and it's activity i.e., an increase in similarity score enhances the binding of chalcone inhibitors. The best linear model as shown in in figure 2 also explains relationship between activity and similarity . Molecules 1,3, 7,8,10,11, 29,30 are showing low activities wirh low similarity values. This is due to preence of blue color field points which not observed in template molecule, that is presence of electro negative groups at 2' position causing to less active. Molcules 13,15,16,19,showing high similarity with low activcity,this is causing common skelton and missing of some important groups,that is the absence of -OH group at 4 positon is importat to predicting the activity of molecules . Molecules 2,5,6,12,17,23,26, are showing moderate similarity with moderate activity. Molecules 9, 28,31 are showing above moderate activity with respectable similarity values due to absence of alkyl group at 5' position , So, this is indicate that presence of alkyl group at 5' position may increase the activity of the compounds. Where as Molecules 14,20,21,22, are high similarity scores with high activity , these molecules posses structurally-equivalent and the presence of -OH group at 4 positon given a common activity with template molecule .

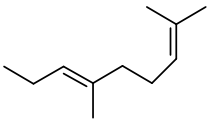
Table 1: Substitutions on the basic skelton



Chalcone No	c-2'	c-3'	c-4'	c-5'	c-6'	c-2	c-3	c-4	c-5	c-6
1	OMe		OMe	OMe		OMe		OMe	OMe	
2	OH		OMe	OMe				OMe		
3	OMe	OMe		OMe			OCH_2O			
4			OMe					OMe		
5		OMe	OMe			OH				
6		OMe	OMe							
7	OAC	OMe	OMe					OMe		OMe
8		OMe	OMe			OMe		OMe	OMe	
9	OMe		OMe	OMe		OMe				
10		OMe	OMe			OMe	OMe	OMe		OMe
11	OH									
12	OH							OH		
13	OH	Pr	OH							
14	OH	Pr	OH					OH		
15	OH	Pr	OMe							
16	OH	Pr	OMe			OH				
17	OH	Pr	OMe				OH			
18	OH	Pr	OMe					OH		
19	OH	Pr	OMe					OMe		
20	OH		OH					OH		
21	OH	Ge	OH					OH		
22	OH	Ge	OH					OH		
23	OH		O					OH		
24	OH	Py	O							
25	OH	Py	O					OH		
26	OH		O							
27			OMe					OH		
28						OH				
29	OMe		OMe	OMe			OCH_2O			
30	OMe		OMe	OMe						
31	OH		OH		OH			OH		

Ac = 

Py = 

Ge = 

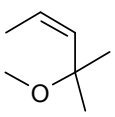
Py = 

Table 2: Biological activities and alignment scores of 1,3-diarylpropane Chalcones

Compound No	Similarity	IC50	-Log IC50	Predicted	Residual values
1	0.767	2000	0.7	0.6123	-0.0877
2	0.834	1000	1	1.3683	0.3683
3	0.756	2000	0.7	0.4882	-0.2118
4	0.765	2000	0.7	0.5897	-0.1103
5	0.825	1000	1	1.2667	0.2667
6	0.831	1000	1	1.3344	0.3344
7	0.753	2000	0.7	0.4543	-0.2457
8	0.768	2000	0.7	0.6236	-0.0764
9	0.844	250	1.6	1.4811	-0.1189
10	0.754	2000	0.7	0.4656	-0.2344
11	0.758	2000	0.7	0.5108	-0.1892
12	0.752	1000	0.7	0.4431	-0.2569
13	0.814	2000	0.7	1.1426	0.4426
14	0.848	31.2	1.51	1.5262	0.0162
15	0.805	2000	0.7	1.0411	0.3411
16	0.812	2000	0.7	1.1200	0.4200
17	0.859	1000	1	1.6504	0.6504
18	1	3.9	3.409	3.2413	-0.1677
19	0.827	2000	0.7	1.2893	0.5893
20	0.864	62.5	2.2	1.7068	-0.4932
21	0.865	15.6	2.81	1.7181	-1.0919
22	0.893	15.6	2.81	2.0340	-0.7760
23	0.832	1000	1	1.3457	.3457
24	0.762	2000	0.7	0.5559	-0.1441
25	0.764	2000	0.7	0.5785	-0.1215
26	0.836	1000	1	1.3908	0.3908
27	0.804	2000	0.7	1.0298	0.3298
28	0.829	500	1.3	1.3119	0.0119
29	0.758	2000	0.7	0.5108	-0.1892
30	0.766	2000	0.7	0.6010	-0.0990
31	0.864	250	1.6	1.7068	0.1068

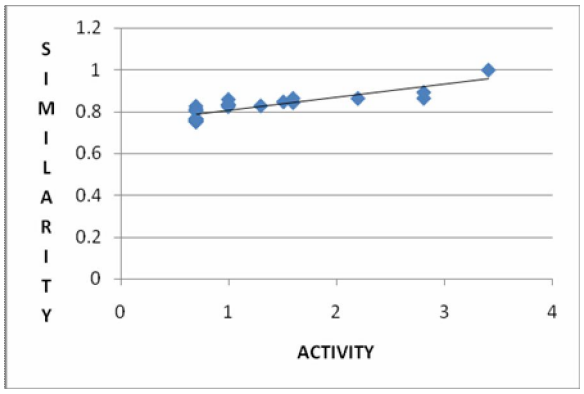


Fig 2: Plot of activity versus similarity

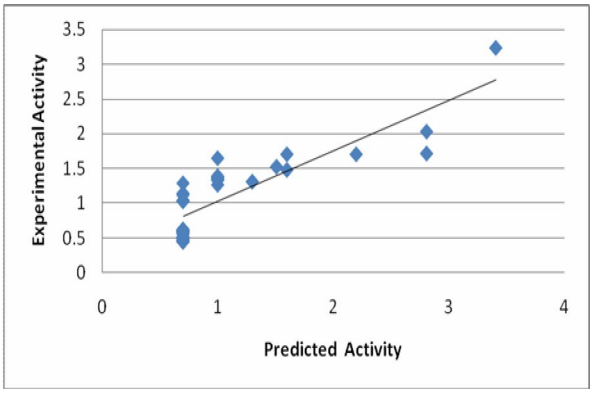


Fig 3: Plot of observed versus predicted activity

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