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3D QSAR and Pharmacophore Modelling on Chalcones as Antileishmanial Agents potential Trypanothione reductase Inhibitors

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ABSTRACT

Chalcones is an important auxiliary having various important clinical applications. A series of Chalcones as antileishmanial agents by were reported. Three dimensional quantitative structure-activity relationship (3D-QSAR), including, were performed to elucidate the 3D structural features which are important for the antileishmanial activity. The results of 3D QSAR model (q^2 = 0.8100, r^2 = 0.9355,) exhibited the highly degree of statistical significance and good predictive ability. The results generated 3D QSAR can provide important information about the structural characteristics which are contributors of the inhibitory potency of chalcones. In addition, docking analysis and pharmacophore mapping was applied to identify the binding modes between the ligands and the Trypanothione reductase and structural features of the ligands which are important for the biological activity of the molecules. The information obtained from this study could provide vital information for future development of potent instructions for the further development of potent antileishmanial agents as trypanothione reductase inhibitors.

INTRODUCTION

Chalcones are the integral component of many pharmacological active compounds like anti-protozoal, anti-inflammatory, immunomodulatory, nitric oxide inhibition, anticancer. (Nielsen et al,1998) The one of the objective of drug design is to explore more than one kind of activity which is associated with the molecules and it should include the QSAR and pharmacophore identification which can give idea about the structural features which are responsible for biological activity. Various antileishmanial chalcones have been reported in the literature. The molecular basis of the antilesishminal action still not well established (Hsieh et al, 1998). The Trypanothione reductase is a member of oxidoreductase family, which is becomed an attractive target foe development of novel antileishmanial agents. Trypanothione reductase is a flavoprotein which is unique in leishmania. Trypanothione system plays vital role in the growth of the lesishmania via generation of dithiol trypanothione which is required for the synthesis of DNA precursors (Li et al,1995). Trypanothione reductase is attractive target because it is essential for leishmania and does not been present in human. The current manuscript deals with 3D QSAR and Pharmacophore Modelling, docking analysis on the series of Chalcones as antileishmanial agents.

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MATERIAL AND METHODS

Experimental

Data Set

The data set for the present study was taken form literature reported by (Liu et al., 2001) table no1.

LIGAND PREPERATION

The structure of Chalcone was used as the template to build the molecules in the dataset in builder module of Vlife MDS 4.2. The ligand geometries were optimized by energy minimization using MMFF94 force field.

Molecular Alignment

The molecules of the dataset were aligned by the template based technique, using chalcones as a template for alignment of the molecules. The alignment of all the molecules on the template is shown in Figure 1.

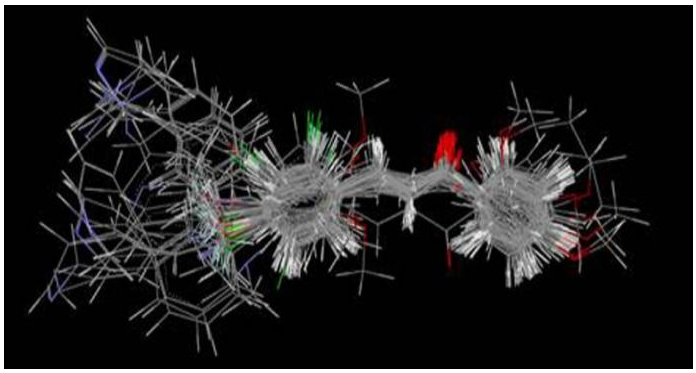


Fig. 1: Figure showing alignment of molecules.

Qsar Analysis

The dataset was divided into a training set and a test set using random selection method. The molar effective dose (PED50) values for anti-fibrotic activity were used for the present 3D-QSAR study**.**

Decriptor Calculation

The hydrophilic, steric and electrostatic interaction energies are computed using a methyl probe of charge +1.

3D-QSAR STUDY

Full Search Linear Regression Method

A relationship between independent and dependent variables (3D) fields and biological activities, respectively) were determined statistically using regression analysis.

Activity Prediction

To QSAR model is evaluated by the predictive results for the given dataset. Selected models having r2 above 0.7 were checked for their external predictivity. The predicted values for antileishmanial activity are shown in table no 2.

Docking Studies

To explore the inhibition modes molecules under study docking analysis were carried out using Biopredicta module of Vlife MDS 4.3. We utilized the crystal structure of Trypanothione reductase (PDB ID 2JK6). Prior to docking studies a systematic conformational search was performed to obtain the low energy conformations. These conformations were optimized till rms gradient energy of 0.001 kcal/molA° have been reached.

Pharmacophore Modeling

This Pharmacophore modeling was carried out in the mol sign module of Vlife MDS 4.3 software. Series of designed inhibitors were first aligned on the active molecule. A pharmacophore model is a set of three-dimensional features that are necessary for bioactive ligands.

RESULTS AND DISCUSSION

In present study the data set was randomly divided in to the training set (50 molecules) and test set (25 molecules). Different set of equations were generated one models were selected on the basis of r2, q2, pred r2, F and p values (table2).

Interpretation of QSAR Model A

Model A was found best to express antileishmanial activity as the selected 3D QSAR model A describes the structural features which are contributing towards the antileishmanial activity of the chalcones. A training set of 50 molecules, and a test set of 25 molecules is utilized to generate the 3D QSAR equation. The model was selected on basis of r2, q2, pred r2, and F and p values. The r2 value for model A was 0.90 compared to that of model B 0.89. The F test and p significance values were considered for the selection of model. The steric interaction fields are represented in green lattice points at S_1169, S_452, S_1637, S_665, S_1342,S_930, S_830, S_692, , S_1779 are positively contributing which signifies the importance of the lipophilic substitutions or bulkier group substitution on the chalcones backbone. The lipophilic substitutions can be responsible for entry of the molecules inside the lesmanial cell. The stric interaction at the lattice point S_816, S_695, S_456, S_1310 are negatively contributing with biological activity, which indicates steric interaction at these lattice points has to be minimized. The substitution of aliphatic groups at these lattice points will increase the biological activity of the molecules. The electrostatic interactions at lattice point E_1058 is also positively contributing towards the activity which indicates that the substitution of electron releasing groups or electron rich systems will be potentiate the antileishmanial activity of the chalcones.

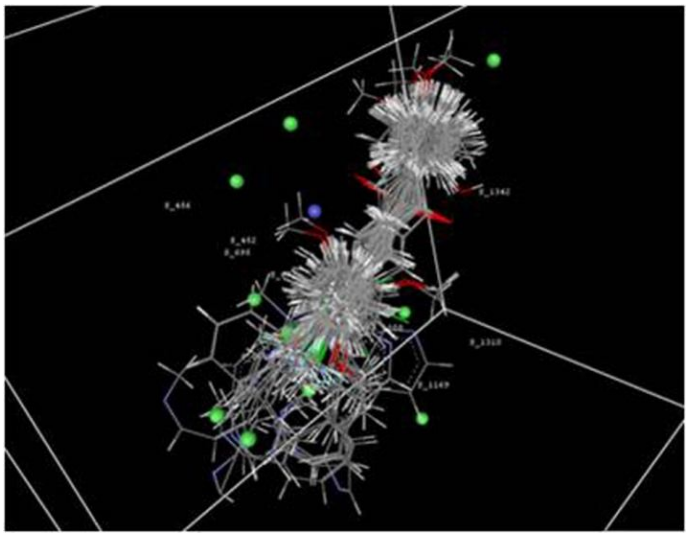
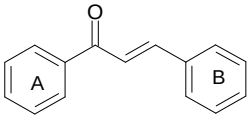


Fig. 2: Figure showing field point of selected QSAR model A .

Table. 1: Table showing the molecules understudy.



Compound	Ring B	Ring A	Compound	Ring B	Ring A
3	2',3',4' Trimethoxy	2,4-Dichloro	39	4-Ethoxy	4-Fluoro
4		4-Dimethylamino	121		2,4-Dichloro
6		4-Trifluromethyl	122		4-Trifluoromethyl
11		2,4-Dimethoxy	123		2,4-Dimethoxy
12		4-Methyl	124		4-Methyl
13		4-Ethyl	125		4-Nitro
27d		3-Quinolinyl	126		4-Dimethylamino
28d		4- Quinolinyl	127		4-Cyno
35		4-Methoxy	136		H
36		4-Fluoro	41[t]	4-Butoxy	2,4-Dimethoxy
40		4-Phenyl	201	2,4-Dihydroxy	2,4-Dichloro
128		2,4-Difluoro	202d		3-Quinolinyl
129		4-Nitro	203		2,4-Difluoro
130		3,4-Dichloro	204		2,4-Dimethoxy
131		4-Chloro	206		4-trifluoromethyl
132		2-Chloro	207d		2-Pyridinyl
133		3-Chloro	209d		4- Pyridinyl
134		H	210d		4-Quinolinyl
1	2'4'-Dimethoxy	2,4-Dichloro	211		4-Chloro
2		4-Trifluoromethyl	245		4-Methyl
5		2,4-Difluoro	213d		2-Quinoloinyl
7		2,4-Dimethoxy	214d		2-Pyridinyl
8		4-Ethyl	215d		4-Quinolinyl
29d		3-Quinolinyl	217		4-Chloro
30d		4- Quinolinyl	220		4-Methoxy
101		4-Methyl	221		4-Methyl
102		4-Methoxy	222		3-Methyl
104		4-Fluoro	224		4-Trifluoromethyl
105		4-Chloro	225		4-Nitro
106		4-Bromo	226		4-Fluoro
107		2-Chloro-4-Fluoro	227		3,4-Dichloro
108		3,4-Dichloro	228		4-Dimethylamino
109		4-Nitro	229		2,4-Dichloro
19	4'-Methoxy	4-Hydroxy	230		H
22		2,4-Difluoro	231	2-Hydroxy	2,4-Dichloro
23		4-Methoxy	232		4-Dimethylamino
31d		3-Quinolinyl	233d		3-Quinolinyl
32d		4- Quinolinyl	234		4-Chloro
38		4-Fluoro	235		4-Methyl
111		2,4-Dichloro	236		4-Methoxy
112		4-Trifluoromethyl	237		2,4-Dimethoxy
113		2,4-Dimethoxy	238		4-Trifluoromethyl
114		4-Methyl	239		4-Fluoro
115		4-Nitro	241d		2-Pyridinyl
116		4-Dimethylamino	244d		4-Quinolinyl
117		4-Cyno			
135		H			
25	4'-Ethoxy	2,4-Difluoro			
26		4-Methoxy			
33[d]		3-Quinolinyl			
34[d]		4- Quinolinyl			

Table. 2: Table showing selected QSAR model A.

Md No.	QSAR model	N	r^2	q^2	F	Pre r^2
A	PED_{50}= -0.0013+0.2096(±0.0272) S_1169+0.0697(±0.0079) S_452+27.0258(±54.5738) S_1637+0.0818(±0.0153) S_665+0.0181(±0.0040) S_1342+0.0084(±0.0023) S_930-0.0747(±0.0153) S_816+0.0632(±0.0153) S_830+0.0120(±0.0031) S_692-0.0092(±0.0026) S_695 -0.0931(±0.0245) S_456-1.6088(±0.5952) S_1310+0.0257(±0.0107) E_1058	75	0.90	0.82	23	0.71

Docking Results

Molecular docking is simulation process where a macro molecule and micro molecule interactions can be studied. The molecular docking were performed to establish the molecular basis of antileishmanial activity of the chalcones. All the 75 chalcone derivatives were docked with in the same site of trypanothione reductase. The hydrogen bond interaction was observed with carbonyl oxygen and amino nitrogen of SER14 and VDW interactions were observed with the amino acids GLY11, GLY13, ALA12, SER14A, ASP35, ALA46, GLY50, THR51, THR160, ALA159, ARG287A, ASP327, THR335 and hydrophobic interaction were observed with THR51 and TYR 198 (figure no3).

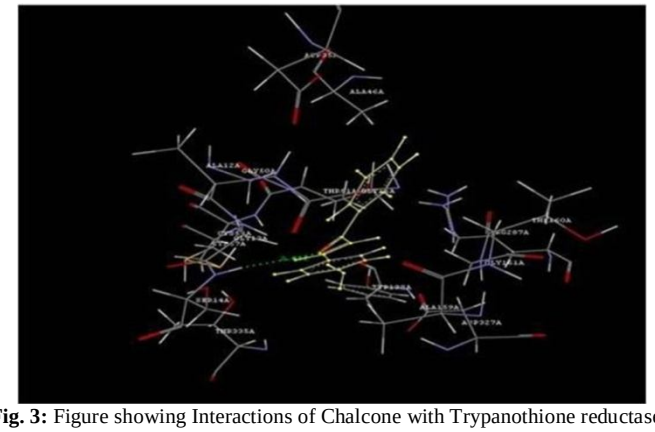


Fig. 3: Figure showing Interactions of Chalcone with Trypanothione reductase.

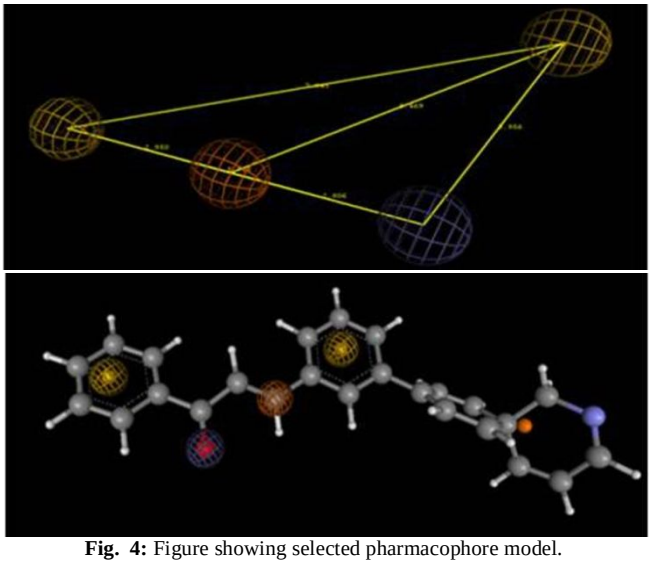


Fig. 4: Figure showing selected pharmacophore model.

Pharmacophore identification studies using Vlife MDS 4.3

A set of pharmacophore hypothesis was generated using the mol sign module of V life MDS 4.3 Each hypothesis was found to contain common features like aliphatic (brown color), aromatic (Golden color), hydrogen bond acceptor (blue color). The results of pharmacophore identification studies are given in figure no3. The results of the pharmacophore modelling indicated the two aromatic feature are 7.94 A^0, the aliphatic and hydrogen bond acceptor must be 2.8^0 apart from each other. The all the molecules where aligned with licochalcone A. which is naturally occurring antileishmanial agent. Structure and pharmacophoric features similarity of chalcone derivatives with the licochalcone A were searched which indicates the designed set of molecules are having hydrogen bond acceptor (blue color), aromatic features (golden color), aliphatic (brown color) features in common. Due to the features similarity the chalcones can show similar activity potential of licochalcone A (figure no4 and 5).

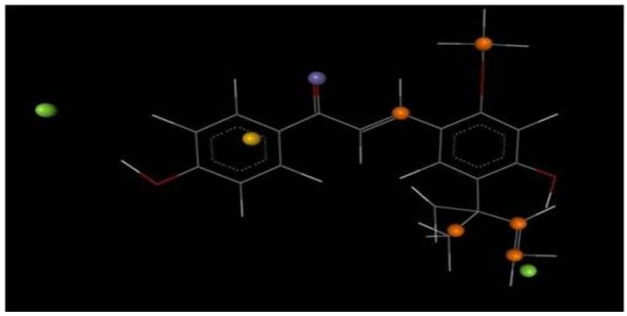


Fig. 5: Figure showing pharmacophoric features licochalcone A .

CONCLUSION

QSAR and docking analysi\s was employed to identify molecular structural features important for chalcones derivatives for acting as effective anti antileishmanial agents. Thus, the design and development of lead molecules on the basis of data obtained from this QSAR and docking analysis is likely to yield potent compounds with improved pharmacokinetics and pharmaco-dynamics.

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