Research Journal of Chemical Sciences _____ ISSN 2231-606X
Vol. **4(3),** 76-80, March **(2014)** *Res. J. Chem. Sci.*

Inverse QSAR approach and Molecular docking studies to design novel methoxy substituted Chalcones and their Computational Anticancer activity evaluation

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Available online at: www.isca.in, www.isca.me
Received 2nd February 2014, revised 19th February 2014, accepted 16th March 2014

Abstract

Quantitative structure activity-relationship (QSAR) studies have emerged as promising tool to in silico prediction and optimization of potential bioactive compounds. The purpose of QSAR studies is to save time, cost, and animal toxicity and to support green chemistry. Present studies are efforts to design and identify novel chalcones having high potency and selectivity. Present investigations identify structural insights of methoxy substituted chalcones in Linear and non-linear QSAR models. QSAR studies identify the profound non-linear relationship among structures of methoxy substituted chalcones and their biological activity measures (IC_{50}). It concludes that any structural variation in present class of chalcones would bring a non-linear change in IC_{50}. MLR produced efficient QSAR models (R^2 = 0.809). We have designed new candidates employing structure-activity relationship obtained from QSAR models. Descriptor based inverse QSAR approach has been applied in computational modeling of new small molecules. Furthermore, they have been compared with synthesized dataset of methoxy substituted chalcones using molecular docking and ADMET studies. In course of molecular docking studies, newly designed molecules yielded promising results with better binding capacity (Docking rerank Score -103.089) than previously synthesized compounds. Computational pharmacokinetic and pharmacodynamic (ADMET) studies revealed their better intestinal absorption, skin permeability and blood brain barrier penetration. The aim of our work is computational designing of novel methoxy substituted chalcones using QSAR and flexible molecular docking based techniques.

Keywords: Inverse QSAR approach, flexible molecular docking, novel methoxy substituted chalcones, anticancer activity.

Introduction

Medicinal chemists today are facing a serious challenge because of the increased cost and enormous amount of time taken to discover a new drug, and also because of rigorous competition amongst different pharmaceutical companies. Thereby, importance of Computer Aided Drug Design (CADD) and molecular modeling is increasing nowadays. Target specific drug discovery is the need of the hour. Techniques evolved in the post genomic era have given us an opportunity to accelerate discovery process by looking at many cellular processes simultaneously. Advances in computational power, algorithms and modern database mining techniques are accelerating the discovery in science even more[1].

A major goal in current drug design is to develop new ligands with high affinity of binding toward a given protein receptor. Pharmacophore, which is the three dimensional arrangement of essential features that enable a molecule to exert a particular biological effect, is a very useful model for achieving this goal. If the three dimensional structure of the receptor is known, pharmacophore is a complementary tool to standard techniques such as docking, molecular modeling and offshoot of theoretical chemistry and an emerging new science, provides many technical advances in reducing the cost of drug discovery. A recent estimate puts about 8 months and $ 66 million savings for each drug due to use of this advance technology[2]. Molecular modeling and pharmaco-informatics, a new emerging field integrates bioinformatics and chemoinformatics applicable to drug discovery. This has been projected to save an additional 4-8 months time and about $70 million per drug.

Quantitative Structure Activity Relationships (QSAR) analyse the correlation between the structural features and the biological activity in order to predict the activity level of new compounds. Using statistical correlation methods, it builds models to predict quantities such as binding affinity, toxicity, or pharmacokinetic parameters of existing or hypothetical molecules[3]. 3D-QSAR analyse the three dimensional forces like hydrogen bonds, metal ligand contacts, polarization effect and the interaction between the electric dipoles.

Chalcones are the precursors of flavanoid and isoflavanoid family[4]. Chalcones are α,β -unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-[5]. Chalcones itself

and its derivatives are posses wide range of therapeutic activities as antioxidant,[4] cytotoxic,[6-8] antibacterial,[9] anti malarial, anti inflammatory[10,11], anti – HIV, antifungal, tyrosine kinase inhibitory activity[12,13]. Chalcones exhibit cancer cell proliferation by various mechanisms as inducing apoptosis; inhibiting tubulin polymerization[14,15], inhibiting angiogenesis[16,17], anti estrogenic activity, uncouple the mitochondrial respiration and collapse the mitochondrial membrane potential[18].

Methodology

Target Structure Selection and Preparation: In structure-based computational techniques, it is crucial that we retrieve and use appropriate 3D structure of drug target. It is even more recommendable to prepare 3D structure of target towards any missing chemical information in terms of hybridization, bond lengths, bond angles, torsions etc[19]. Present studies included 3D structure Tubulin-Cholchicin protein bound with stathmin-like domain complex (PDB code: 1SA0) available from protein data bank (PDB) at the Research Collaboratory for Structural Bioinformatics (RCSB). We decided to use this specific structure since we use only B-chain of the protein composed of cofactors, ligands, α-chain (a.c) length-451, β-chain (b.d) length-445 and E-chain of stathmin length-142. Molecules sketched, cleaned in 3D and saved in MDL SDF file format imported in the workspace. For protein preparation while import select the option always in assign all below in Molegro Virtual Docker (MVD). It assign bonds, assign bond orders and hybridization, create explicit hydrogen, assign charges, detect flexible torsions in ligands, assign tripos atom types. Preparation options (If Missing, Always, Never, Remove) applies to each individual molecule (not each individual bond or atom).

Docking Parameters: Molegro Virtual Docker (MVD) sets latest and efficient algorithms named PLANTS and PLP scores to calculate molecular fields and receptor-ligand interactions. PLANTS score was developed by Korb et al[20] while combined efforts of Yang et al[21] and Gehlhaar et al developed PLP score[22,23]. We have selected score as MolDock score [GRID] with GRID resolution of 20 A°. Ligand evaluation was applied with internal electrostatic ES, internal H-bond, sp2- sp2 torsions. Binding site coordinates: X- 116.763, Y-90.64, and Z-6.248 within a constraint of 10 A°. Though a receptor-ligand interaction is depicted by a lock and key model arbitrary, it is much more complex and case specific specially when there could be many keys (ligands) opening same lock (receptor) to various extents. Selection of accurate site and most favourable pose is bottle neck step in performing molecular docking[24]. Inhibitor binding site was identified from literature; in addition, all the available cavities were screened for possible binding.

Inverse QSAR- Design of novel Chalcones: The novel molecules were designed using inverse QSAR approach wherein we used QSAR models obtained. In this approach the significant descriptors responsible for regulation for IC_{50} (nM) values chalcones were studied and optimized. The MLR results of QSAR studies were employed to calculate or predict the potential (IC_{50}, nM) of new molecules designed computationally. The tetra-variable model used for designing of novel methoxy substitutes Chalcones,

Model-4 Tetra-variable: IC_{50} (nM) = 849.395 + 232.141($Mor21_u$) - 679.357(Mor29e) - 1023.803(Ele) + 91.605 (Depressant 50) N=26, R^2=0.809, R^2_A=0.773

Perusal reveals that increase in the value of coefficients for descriptors with negative coefficient and decrease in the coefficient value for descriptors with positive coefficient value could enhance the activity of the molecules and yield better molecules with best biological activity. 45 new molecules were designed using descriptor based approach.

Results and Discussion

QSAR Studies: In the present work novel methoxy substituted chalcones are designed. The molecular descriptors are numerical representation to evaluate and establish the structural activity relationship. The structures of chalcones drawn in ChemSketch, afterword they converted into SMILES data format (Simplified molecular line entry specification). The SMILES data format was used to calculate descriptors using E-Dragon (version 5.4). The 2500 descriptors belonging to various classes were calculated and imported into SARCHITECT evaluation version along with structures and their respective biological activity.

The MLR model of QSAR was prepared for methoxy substituted chalcones then significant and internally non-correlated sets of descriptors have been chosen with target size four (tetra-variable) limited to thumb rule. MLR results have been discussed using tri-variable and tetra-variable models with appreciable set of statistical parameters as shown in table 1. To produce the novel methoxy substituted chalcone compounds for anticancer activity, we used approximately 2000-2500 molecular descriptors in QSAR, out of that we divided descriptors in to training and test data sets.

Tetra-variable MLR model obtained (figure 1) shows linearity between predicted and observed IC_{50} (nM) activities.

Docking Studies: Docking studies have provided the comparative view for binding capacity of dataset molecules (synthesized) with new molecules designed using QSAR.

Docking is applied as evaluation criteria for newly designed molecules. Designed molecule TC-14 shows better binding capacity (Rerank Score -103.089) to that of dataset molecules reported in literature. While molecule No. 15 and 34 docked with rerank score -102.854 and -98.128 respectively. Table 2 presents predicted IC_{50} (nM) of newly designed chalcones and docking scores.

Table-1
Statistics of multivariate models used in MLR

Models	R^2	R^2_{CV}	R^2_A	S.E.	F-STAT
Uni-variable Ele	0.335	0.2327	0.308	67.884	12.130
Bi-variable Mor29e+Ele	0.562	0.4512	0.524	56.288	14.774
Tri-variable Mor21u+Mor29e+Ele	0.654	0.5241	0.607	51.098	13.922
Tetra-variable Mor21u+Mor29e+ Ele + Depressant-50	0.809	0.7209	0.773	38.87	22.288

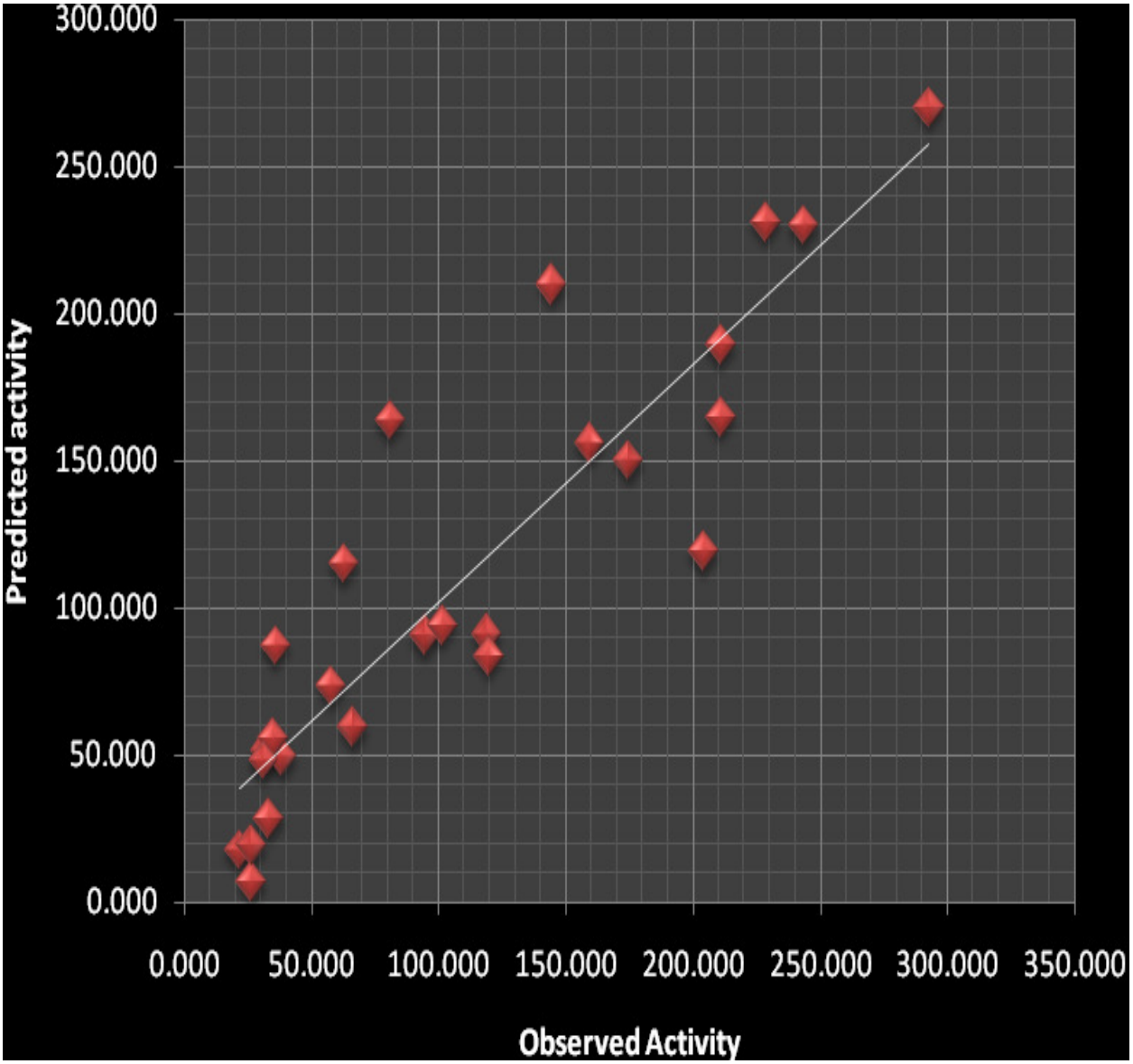

Figure-1
Training set correlation of observed and calculated IC_{50} nM using tetravariable model of MLR

Table-2
Docking results of newly designed molecules

Designed Molecule Code	MolDock Score(GRID) Score(GRID)	MolDock Score	Rerank Score	Torsions
TC-01	-101.33	-100.597	-86.5799	3
TC-02	-90.8473	-88.6096	-81.7398	3
TC-03	-99.3372	-100.126	-88.5429	3
TC-04	-99.3228	-99.1151	-85.4758	3
TC-05	-95.8902	-92.9692	-85.026	3
TC-06	-95.3092	-96.1909	-85.1984	4
TC-07	-101.141	-100.296	-86.7889	3
TC-08	-93.5568	-94.2729	-82.5531	2
TC-09	-93.5605	-94.2828	-82.5274	2
TC- 10	-91.408	-91.9753	-81.1378	2
TC-11	-93.1726	-93.7984	-82.3324	2
TC-12	-91.409	-92.0253	-81.2265	2
TC-13	-92.0234	-92.4188	-81.3354	2
TC-14*	-119.638	-119.321	-103.089	3
TC-15	-119.625	-119.289	-102.854	3
TC-16	-92.5672	-93.3589	-82.1232	2
TC-17	-91.4407	-92.1835	-81.1593	2
TC-18	-92.0636	-92.9503	-81.904	2
TC-19	-92.0636	-92.9464	-81.8328	2
TC-20	-98.4921	-99.8874	-81.7211	3
TC-21	-98.0289	-99.0462	-84.6618	3
TC-22	-98.137	-99.0713	-83.5998	3
TC-23	-98.1239	-99.0365	-84.5198	3
TC-24	-98.1495	-99.0723	-84.9271	3
TC-25	-95.5168	-96.1614	-83.5972	3
TC-26	-97.0112	-97.2025	-85.8632	3
TC-27	-97.6989	-98.5404	-87.5783	3
TC-28	-93.6295	-94.1854	-82.5108	3
TC-29	-95.9762	-96.5836	-84.9201	3
TC-30	-97.7272	-98.6252	-86.6424	3
TC-31	-132.964	-134.718	-97.0981	8
TC-32	-116.643	-116.631	-86.827	5
TC-33	-110.381	-107.472	-84.3514	2
TC-34	-109.997	-111.291	-98.1283	3
TC-35	-115.75	-115.295	-94.7381	3
TC-36	-105.414	-106.517	-92.0256	3
TC-37	-106.533	-107.605	-90.3713	2
TC-38	-106.457	-103.487	-91.1246	3
TC-39	-97.4048	-98.0125	-84.0592	2
TC-40	-95.4614	-96.1517	-83.9843	2
TC-41	-100.449	-101.212	-82.8946	2
TC-42	-101.094	-102.072	-84.3186	2
TC-43	-102.784	-103.706	-84.6786	2
TC-44	-101.973	-101.563	-81.7831	2
TC-45	-95.4339	-96.8008	-81.4733	3

Conclusion

Present investigation undertakes multiple linear regression (MLR) aided QSAR studies towards identification of structural insights of methoxy substituted chalcones. QSAR studies identified the profound linear relationship among structures of methoxy substituted chalcones and their biological activity measures IC_{50} (nM). It concludes that any structural variation in present class of chalcones would bring a linear change in IC_{50}. Tetra-variable QSAR model was found statistically fit (R^2=0.809) and significant in predictive powers. We designed new candidates furnishing the knowledge of present QSAR studies. Descriptor based inverse QSAR approach has been applied to computational modeling of new small molecules as chalcones derivatives. Furthermore, they have been compared with present dataset of methoxy substituted chalcones (synthesized) using molecular docking studies. In course of molecular docking studies newly designed molecules yielded promising results in terms of candidate TC-14 showing better binding capacity (Rerank Score -103.089) than dataset used in supervised training of QSAR studies.

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