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Original Article

3D QSAR STUDIES OF IDENTIFIED COMPOUNDS AS POTENTIAL INHIBITORS FOR ANTI - HYPERGLYCEMIC TARGETS.

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ABSTRACT

Background: The identification of potential targets for an anti-hyperglycemic makes real challenges in the pharmaceutical industry. Library of compounds have introduced so far, but identifying the specific target which makes more significant. The objective of this study is to identify the Pharmacophoric features using QSAR analysis.

Materials and Methods: The optimized inhibitors are screened by executing molecular docking analysis. According to the docking outcome, the inhibitors were taken and extended for QSAR studies in order to optimize and to reveal their pharmacophoric features. These models were generated based on the test and training set.

Results: The significant model was taken according to their hydrophobic and electrostatic interactions. Docking studies validated that, identified target having interactions towards the active site and QSAR studies shows, this target is having better pharmacophoric activities. The predictive ability of both models was determined using a randomly chosen test set gave predictive correlation coefficients of $r^2 = 0.9$.

Conclusion: This inhibitor shows good interaction, energy and Pharmacophoric activity and will be suitable for further experiments of an anti-hyperglycemic target.

Keywords: QSAR, PHASE, DPP4, Anti – hyperglycemic targets, Docking studies, 3DQSAR

INTRODUCTION

Discovering three-dimensional pharmacophores which can explain the activity of a series of ligands is one of the most significant contributions of computational chemistry to drug discovery[1]. Quantitative drug design embraces two major activities, the quantitative description of the structural differences among series of chemical compounds of biological interest, and the formulation of "QSAR" useful in the design of new and better therapeutic agents[2]. A QSAR is a mathematical relationship between a biological activity of a molecular system and its geometrical chemistry relationships [2].

QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds 3D models are more easily interpretable than 2D descriptor or fingerprint-based QSAR models, making it easier to suggest new compounds for synthesis. It should also be possible to make connections from such activity models to structure-based design [3].

The binding mode of the inhibitor in the active site amino acid residues was performed by docking using GLIDE. The macromolecules were targeted towards this approach viz., IRTK, PTP1B and DPP4, where the Dipeptidyl peptidase 4 (DPP4) has have a better response towards the drug-like compound than others [4,5]. Here, this study deals with the outcome of molecular docking was exploited to perform this investigation. So, further investigation was carried out with this drug-like compound.

Materials and Methods

In the drug design approach, identification of the pharmacophore is one of the most important steps to achieve the stipulated goal. To execute this analysis, the PHASE (Pharmacophore Alignment and Scoring Engine) module of Schrodinger used to develop ligand-based pharmacophore model for Type II diabetes Mellitus (T2DM). This algorithm performs based on the conformational sampling and different scoring techniques to identify common pharmacophore hypothesis, each hypothesis is accompanied by a set of aligned conformations which are necessary for the ligand to bind to the receptor [3]. The developed model has the ability to find potential inhibitors from 3D-virtual databases of drug-like molecules. The conformations of active compounds obtained from the alignment of pharmacophoric points are used to derive 3D-QSAR models[4].

Dataset for Analysis

A dataset comprising of the test set and training set, the generated compounds of the ten compounds taken as test set and remaining as the training set filtered manually [9]. The dataset has been chosen by which covers the information about its binding affinity values *ie.,* glide score and energy values[4,5]. The datasets consists of some highly active and middle-level molecules, with very few molecules in between.

Generation of Hypothesis

QSAR is a mathematical approach to relate the set of compounds to find the biological property. QSAR study was applied using PHASE module of Schrodinger to establish correlation between 2D/3D descriptors and experimental activity for set of compounds using statistical methods.

PHASE provides a standard set of six pharmacophore features, hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionizable (N), positively ionizable (P), and aromatic ring (R). Common pharmacophoric sites where selected from a set of variants and with the option Create Sites, number of acceptors were modified to 2, negatively ionizable to 0, others were kept default and produces different variants [6].

A more descriptors can taken to count to generate 2D QSAR model viz., logP, molecular refractivity, topological index etc., To generate the 3D QSAR makes a different way by finding the penetration of the

molecules which includes hydrophillic, electrostatic field with default values of 30 Kcal/mol as generated as a significant value. These values are generated using k-nearest neighbour principle with stepwise, genetic algorithm and simulated annealing methods.

RESULTS AND DISCUSSIONS

Molecular docking study

Balajee *et al.,* 2012 has reported the outcome of molecular docking performed using GLIDE (Schrodinger, LLC, New York, USA). Where, the crystal structure was retrieved from Protein Data Bank (PDB ID: 3NOX) and the ligand were retrieved from the Interbioscreen Russia (www.ibscreen.com) According to the requirement Protein was prepared using Protein Preparation Wizard were the protein is preprocessed, optimized and minimized with force field of OPLS2005 and RMSD of 0.30 Å using the protein preparation wizard. Grid was generated using the centroid of workspace ligand. The docking was performed using Glide with enabling the option and keeping the rest default. Further, the ligand was prepared using LIGPREP with the default pH and generating the 1 molecule from the tautomerism[4].

The GLIDE docking method is applied to various compounds were screened to the taken macromolecules[5]. The sets of different inhibitors are generated by scoring functions; it was characterized by orientations and Hydrogen bond positions. According to the energy values and the parameters the identified compound shows a better activity with the DPP4 producing -43.50 Kcal/mol as Glide Energy [7] shown in **Fig. 1**.

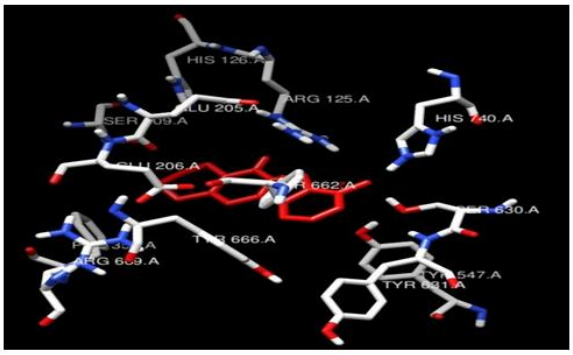

Fig. 1. Interaction between DPP4 and taken ligand molecule.

QSAR outcome

The dataset was randomly divided into training and test set with a bias given to the structural diversity in both the set ratio for a QSAR study using the Multiple Linear regression analysis (MLR). A common pharmacophore Hydrogen bond Acceptor (A), Hydrogen Bond Donor (D), Negative ionizable group (N) Aromatic ring (R) Aromatic Ring (R) (AADNHRR) with three variants was generated after identification of pharmacophoric sites in all the molecules in the dataset[8]. The variant with a site score 0.79, vector score 0.79 and volume score 0.69 has shown as a better target towards our study which shown in shown in Table – 1.

Table 1 QSAR hypothesis score

VARIANTS	SURVIVAL	SITE	VECTOR	VOLUME
AADNHRR.13**	**3.43661**	**0.788704**	**0.788704**	**0.682103**
AADRR.8	3.41336	0.766313	0.766313	0.687369
AADRR.7	3.41336	0.766313	0.766313	0.687369
AAHRR.11	3.40891	0.763329	0.763329	0.669836
ADHRR.9	3.40320	0.788645	0.788645	0.648730
AANRR.9	3.40239	0.763330	0.763330	0.663374
AADRR.2	3.38240	0.766209	0.766209	0.656513
AADNR.8	3.35778	0.724376	0.724376	0.666975
AADNR.10	3.35540	0.695013	0.695013	0.690633
ADNRR.6	3.34310	0.705488	0.705488	0.671782
AADNR.9	3.32600	0.694898	0.694898	0.661315
ADHRR.10	2.97440	0.585231	0.585231	0.456620
AAHRR.1	2.96362	0.539245	0.539245	0.472757
AADRR.1	2.94446	0.539495	0.539495	0.482739
AADNR.2	2.82848	0.449297	0.449297	0.446261
ADNRR.2	2.82557	0.496640	0.496640	0.448712
AADNR.3	2.80170	0.384549	0.384549	0.475324
ADNRR.5	2.78209	0.408738	0.408738	0.446238

****Selected Model for QSAR**

The identified inhibitor represented the 3D QSAR model of k Nearest Neighbor =2; n = 34, Degree of Freedom=28; Q2 = 0.75, R2 =0.95 and Selected Descriptors = 0.89 which shown in Table 2.

Table 2 QSAR model for the Taken identified compound

VARIANTS	#Factors	SD	R^2	F	P	RMSE	Q-squared	Pearson – R
AADNHRR.13	1	0.898	0.9503	58.78	$8.93e^{-009}$	0.05	0.7512	0.73

The volume occlusion maps for the Atom – based PHASE 3D – QSAR model (donor, Ionic Interaction) represented by color codes in **Fig. 1**. This purpose of analyzing the map is to represent the existence of compound in the regions of favorable and unfavorable interactions. The volume occlusion maps of hydrogen bonding interactions linked towards the acceptor groups and it is in favorable interactions.

This generated model demonstrates that the activity having donor groups with the binding site of the receptor. Also, this pharmacophoric model indicated above in **Fig. 1** comprises about the one ionizable, donor and three acceptors with one hydrophobic result the hypothesis of AADNHRR variant used for this QSAR model.

QSAR Hypothesis Score

The 3D QSAR studies for the set of identified compounds were carried out for finding the common pharmacophore hypothesis; the dataset was divided into active and inactive sets. Molecules were taken according to Energy values; due to it is a novel compound the best value of the biological properties were predicted and shown in Fig. 2.

Analysis of Atom based Phase 3D QSAR

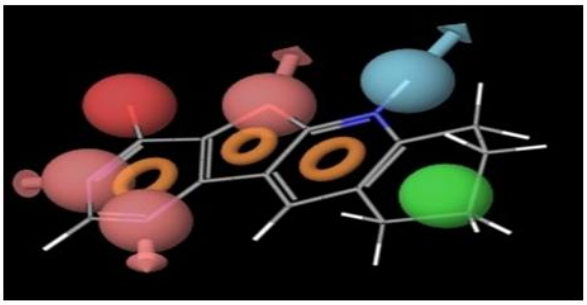

Fig. 1. Atom based Phase 3D QSAR

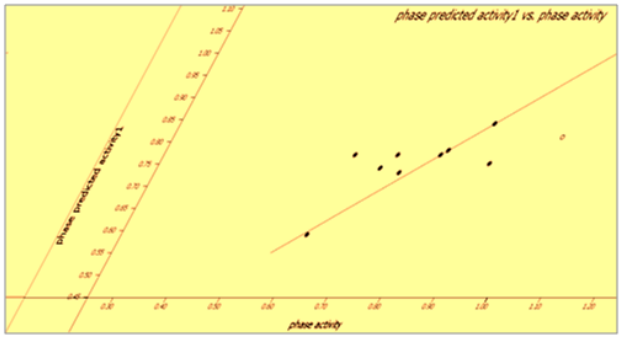

Fig. 2 QSAR Hypothesis Score

DISCUSSIONS

The pharmacophore hypothesis AADNHRR is active when compared to all the molecules aligned. The 3D-QSAR model generation, molecules in the dataset were the aligned based on the matching with at some Pharmacophoric features *viz.,* hydrophobicity, positive and negative electrostatic potential *etc.,*

The PHASE statistical analysis for each of the test set selection methods is summarized in Table – 2. The validity of each of the models was predicted from the calculated correlation coefficient for the randomly chosen set comprising of diverse structures. The Squared correlation for the test set (R^2_{pred} = 0.95) confirms the good predictability of the final QSAR model for the test set.

Depicted Model found to be statistically significant with respect to external and internal predictive ability of about r^2 = 0.9. This model shows an evidence of the contributions of electrostatic acidic groups and hydrophobicity towards the ring grouped descriptors in the activity selected ligand targets. The conformations of active compounds obtained from the alignment of pharmacophoric points are used to derive 3D-QSAR models.

CONCLUSIONS

The Dipeptidyl Peptidase 4 (DPP4) has shown better interactions towards the taken drug-like compounds from the outcome of molecular docking. Here, that outcome has examined through 3D QSAR study with descriptors like electrostatic, hydrophobicity to improvise the characteristics of that compound. Also, these descriptors having a better activity towards the binding site which came to light strongly after performing QSAR analysis. As a result, the identified compound would be new potential inhibitor for DPP4 as well as their families. Best hypothesis obtained was AADNHRR.1 with two hydrogen bond acceptor and the aromatic rings. This Compound has a best result generated by 3D QSAR and shows it is active. This QSAR analysis information may sufficient to experiment with further approaches.

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