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3D QSAR AND PHARMACOPHORE MODELING ON SUBSTITUTED CYANOPYRROLIDINES AS TYPE II ANTI-DIABETIC AGENTS POTENTIAL DIPEPTIDYL PEPTIDASE-IV INHIBITORS

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ABSTRACT

3D QSAR and Pharmacophore modeling on substituted cyanopyrrolidines as Type II anti-diabetic agents potential Dipeptidyl Peptidase-IV Inhibitors. Cyanopyrrolidines are an important chemical compounds having diverse significant medical functions. A series of cyanopyrrolidines as Type II anti-diabetic agents by numerous researchers were reported. 3DQSAR was performed to elucidate the three dimensional structural features which are vital for the Type II anti-diabetic activity. The results of 3D QSAR model (r^2 a squared correlation coefficient 0.9945 and q^2 a cross validated squared correlation coefficient 0.9866) demonstrate the highly degree of statistical importance and excellent predictive capability. The results breed from 3D QSAR can give significant information regarding the structural characteristics which are providers of the inhibitory potency of cyanopyrrolidines. In addition, pharmacophore modeling was used to recognize the structural features of the cyanopyrrolidines which are essential for the biological activity of the compounds. The information acquired from this study can offer vital information for upcoming development of potent Type II anti-diabetic agents potential Dipeptidyl Peptidase-IV Inhibitors.

Keywords: Anti-diabetic, Cyannopyrrolidine, Drug design, Dipeptidyl Peptidase-IV Inhibitor, Pharmacophore, QSAR.

INTRODUCTION

Type II diabetes is a is a metabolic disorder, which is major public health issue all over the world, and world flattering a “diabetes epidemic” as confirmed by Zimmet.[1] Type II diabetes arises when reduction of insulin effects on liver and skeletal muscles and reduction of insulin secretion.[2] Glucagon-like peptide-1 (GLP-1) is an insulinotropic hormone with anti-diabetic potential due to its spectrum of effects, which include glucose-dependent stimulation of insulin and inhibition of glucagon secretion, tropic effects on the pancreatic β-cells, inhibition of gastric emptying and the decrease of appetite. Glucagon-like peptide-1 is, nevertheless, very quickly inactivated by the serine peptidase, dipeptidyl peptidase-IV (DPP-IV), so that the local peptide is not helpful clinically. A new approach to utilize the beneficial effects of glucagon-like peptide-1 in the treatment of type II diabetes has been the development of orally active dipeptidyl peptidase IV inhibitors which inhibit DPP-IV and prolong the duration of GLP-1 activity, resulting in lower blood glucose level.[3] Early preclinical experiments and smaller human studies of GLP1 analogs (exenatide, liraglutide) and DPP-IV inhibitors (saxagliptin, sitagliptin, vildagliptin) suggested that targeting the incretin axis might address the elusive goal of an anti-

diabetic agent that improves cardiovascular disease.[4] Clinical data reveals that the recent DPP-IV inhibitor offers many prospective advantages, counting no or less weight gain and no risk of hypoglycemia. Still, some side effects are with them, including throat infection, gastrointestinal problems like diarrhea and upper respiratory track infection. Apart from these side effects, reported compounds are of less potent.[5,6] Hence, great opportunities still present for computer-aided drug design in search of potent DPP-IV and accordingly to obtain insights into the active site of enzyme. Quantative Structure Activity Relationship (QSAR) studies and pharmacophore modelling are capable of providing information about the structural features accountable for biological activity.

To discover out the novel, selective and potent DPP-IV inhibitor for the treatment of diabetes, we executed QSAR studies and pharmacophore modelling on recently designed cyanopyrrolidine derivatives by using VLife-MDS 4.3 software.

MATERIALS AND METHODS

All computational studies were carried out using V-life MDS 4.3 suit installed in Dell inspiron 15 Laptop running on a 1.50 GHz Intel core i3 processor with 2GB RAM and 500 GB hard disk with Windows 8 operating system.

Experimental[8-14]

Date Set

The data set for the present study was taken from literature reported by I-Lin Lu *et al.*, 2005.[7] Structures of all the compounds used in study are given in table no 1. The biological activities of these 19 compounds were expressed in terms of IC_{50} values for inhibition of DPP-IV. All the IC_{50} values of the compounds were reported in terms of nano molar (nM) concentration. For correlation purposes, reported IC_{50} values were converted to their molar units and subsequently to free energy related negative logarithmic state, i.e. – log $(1/IC_{50})$.

Ligand Preparation

Molecules were sketched using the Chem Draw Ultra 8.0. Optimizations of the sketched compounds were done by batch minimization process using force field computations of the VLife^{TM} MDS.

Molecular Alignment

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

3D-QSAR Study

The hydrophilic, steric and electrostatic interaction energies are computed using a methyl probe of charge +1. A large number of descriptors were generated by the VLife$^{TM.}$ The number of descriptor was reduced by eliminating out the descriptors with constant and near constant values. Further reduction in the descriptor was done on basis of highly degenerate and the descriptors that were showing very low correlation with inhibitory activity. The remaining descriptors were taken into account for the analysis. The dataset was divided into a training set and a test set using random selection method. Generated data set was subjected to statistical analyses. Stepwise multiple regression analysis was used as statistical tool. The QSAR models were generated using biological activity as dependent variable and descriptors as independent variables. Correlations between different inhibitory activities and calculated predictor variables were established through simulated annealing method.

Activity Prediction

To QSAR model is assessed by the predictive results for the given dataset. Selected models having r2 above 0.9 were checked for their external predictivity. The predicted values for Type II anti-diabetic activity are shown in table no 2.

Pharmacophore Modelling

This Pharmacophore modelling study 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 gives details about ligands interaction with receptor site and used to identify required similar

properties and features in newly designed ligands which will interact to the given proteins receptor.

RESULT AND DISCUSSION

In current study the training set (13 molecules) and test set (6 molecules) was generated by divided 19 molecules randomly. Numbers of equations were produced and one model was selected on the basis of squared correlation coefficient (r^2), cross validated squared correlation coefficient (q^2), predicted squared correlation coefficient (pred_r^2), F and p values.

Interpretation of QSAR Model

The model was found to be most excellent towards expressing type II anti-diabetic activity; hence it was selected to describe the structural features which are contributing to the type II anti-diabetic of the cyanopyrrolidines. To create the 3D QSAR model a training set of 13 molecules and a test set of 6 molecules was utilized. The model was selected on basis of r^2, q^2, pred r^2, and F and p values. The r^2 value for model was 0.9945 and q^2 a cross validated squared correlation coefficient 0.9866. The F test and p significance values were considered for the selection of model. Best model generated giving descriptors which may contribute positively or negatively to activity includes E-550, S-1165 and E-1204. The steric interaction at the lattice point S-1165 is negatively contributing with type II anti-diabetic activity, which signifies steric interaction at these lattice points has to be minimized. The changeover of aliphatic groups at these lattice points will amplify the type II anti-diabetic activity of the molecules. The lattice point E-550 and E-1204 are showing electrostatic interactions which are positively contributing towards the type II anti-diabetic activity which indicates that the substitution of groups which are electron releasing or systems which are electron rich will contribute to increase the type II anti-diabetic activity of the cyanopyrrolidines.

Pharmacophore Identification Studies Using VLife MDS 4.3

Pharmacophore model was found to contain common features namely aliphatic (brown color), aromatic (Golden color), Hydrogen bond donor (Magenta color), positive charge (green color) and three hydrogen bond acceptor (blue color). In model the larger tessellated spheres are indicative of the common pharmacophore features identified in the molecules and smaller solid features are of the individual molecules. All these features are separated by more than 2.6 A^o from each other. The results of pharmacophore identification studies are given in figure no3. The cyanopyrrolidine template was found to be aligned with all the molecules.

CONCLUSION

3D QSAR and pharmacophore modelling studies was used to recognize molecular structural features important for cyanopyrrolidine derivatives for to have effective type II anti-diabetic agents. Therefore, the design and development of molecules on the foundation of information acquired from this QSAR and pharmacophore modelling studies is expected to give compounds with high potency and improved ADMET and pharmacological action. In conclusion, we generated 3D QSAR and pharmacophore model that accurately reveals the features of DPP-IV inhibitors. The 3D QSAR and pharmacophore model can be utilized as a quick and accurate tool to help out discovery of new DPP-IV inhibitors by database screening and/ or lead optimization method.

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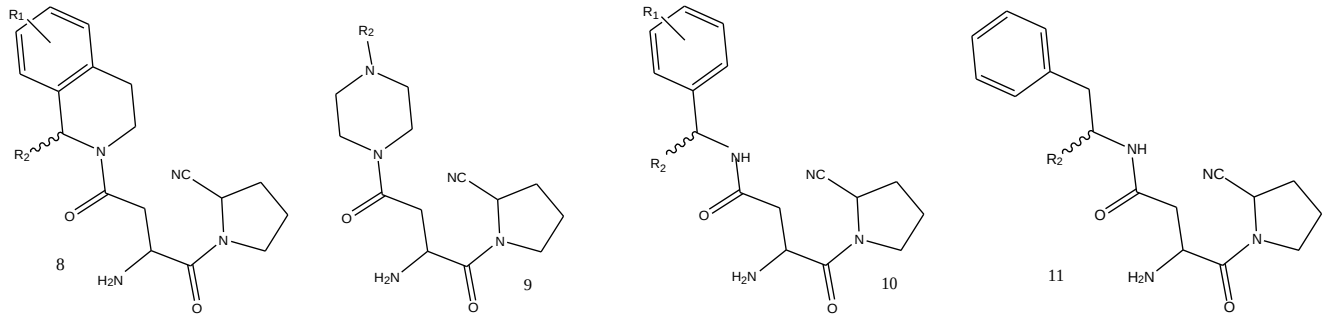

Figure 1: Showing general structure of molecules used for QSAR studies

Table 1: Presenting the molecules used in QSAR study

Compound	R_1	R_2	DPP-IV IC_{50} (nM)
8a	H	H	99
8b	6,7-$(OMe)_2$	H	63
8c	6,7-$(OMe)_2$	-$(CH_2)_2OH$	45
8d	6,7-$(OMe)_2$	Isopropyl	47
8e	6,7-$(OMe)_2$	Benzyl	97
8f	6,7-$(OMe)_2$	*tert*-Butyl	73
8g	6-OMe	*tert*-Butyl	72
8h	7-OMe	*tert*-Butyl	195
9a	H	-$CH(4\text{-}FC_6H_5)_2$	227
9b	H	Nicotinonitrile	87
9c	H	Benzoyl	123
10a	H	H	238
10b	H	Benzyl	252
10c	H	Ethyl	140
10d	H	Isopropyl	212
10e	H	*tert*-Butyl	251
11a	3,4-OMe	H	116
11b	H	CH2OMe	182
11c	H	Isopropyl	305

Table 2: Derivatives under study with observed and predicted activity

Sr. No.	Compound code	Observed activity	Predicted activity
1	8a	2.00	0.89
2	8b	1.80	1.20
3	8c	1.65	1.86
4	8d	1.67	0.69
5	8e	1.99	1.02
6	8f	1.86	1.66
7	8g	1.86	1..61

8	8h	2.29	0.59
9	9a	2.36	0.25
10	9b	1.94	1.59
11	9c	2.09	2.00
12	10a	2.38	1.87
13	10b	2.40	1.90
14	10c	2.15	1.57
15	10d	2.33	0.23
16	10e	2.40	1.25
17	11a	2.06	2.09
18	11b	2.26	1.52
19	11c	2.48	1.76

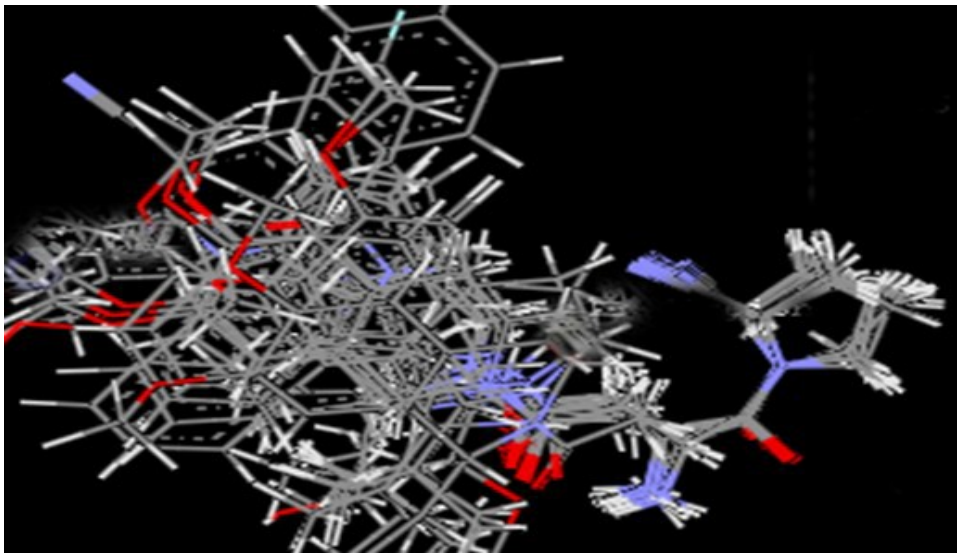

Figure 2: Showing alignment of molecules

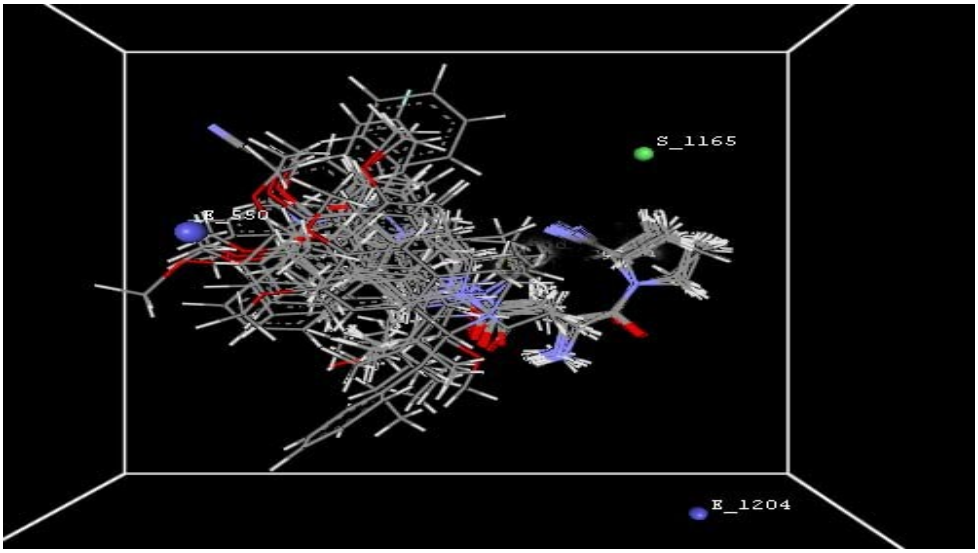

Figure 3: Field point of selected QSAR model

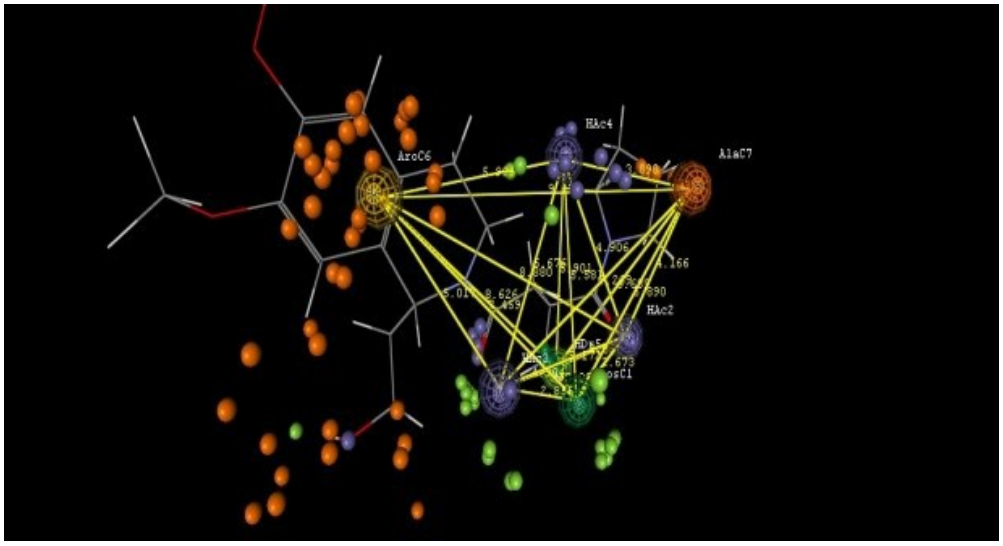

Figure 4: Showing selected pharmacophore model

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