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Docking studies on PPARγ of novel α-phenoxy phenyl propionic acid derivatives as antidiabetic agents

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ABSTRACT

PPAR (Peroxisome proliferated activated receptor) have been identified as potential targets of type II diabetes. Peroxisome proliferators-activated receptors (PPAR γ) are group of nuclear receptor proteins. They play essential role in the cellular metabolism of carbohydrates, lipids and proteins, cell differentiation and development. PPARs function as transcription factors regulating the expression of genes. A series of α-Phenoxy phenylpropionic acid derivatives were computationally designed and optimized with the AutoDock 4.0.1 to investigate the interactions between the target compounds and the amino acid residues of the PPARγ. In this study, the docking studies were done using auto dock between computationally designed α-Phenoxy phenylpropionic acid derivatives and PPAR γ receptor. The free energies of binding (Δ G) and inhibition constants (Ki) of the docked ligands were calculated by the Lamarckian Genetic Algorithm (LGA). These values suggested that the designed α-Phenoxy phenylpropionic acid derivatives are excellent promoters of PPAR γ. Computationally designed ligands were pre-filtered for their drug like properties by lipinski's rule. Lipinski's rule of five was calculated for all the eight ligand molecules that satisfy the 'rule-of-5' and it was found that all the ligand molecules satisfied the rule for potent inhibitors.

INTRODUCTION

Diabetus mellitus (Type II) is a metabolic disorder which is characterized by dysfunctioning of pancreatic beta cells along with insulin resistance, if not controlled leads to macro and micro vascular disorders. PPAR (Peroxisome proliferated activated receptor) have been identified as potential targets of type II diabetes. PPARs are group of nuclear receptor proteins and play essential role in the cellular metabolism of carbohydrates, lipids and proteins, cell differentiation and development. The molecular target of glitazones was reported to be PPAR-gamma which is

expressed in three forms; they are gamma-1(γ1), gamma-2(γ2), gamma-3(γ3). The role of PPAR in combating diabetes has provided us the rationale to carryout structure based drug design studies. The recent identification of the nuclear receptor peroxisome proliferator activated receptor PPARγ and PPARα as being the primary targets for the normoglycaemic thiazolidine-diones (TZDs) and the lipid lowering fibrates, respectively, has provided new opportunities for the identification of novel compounds for the treatment of type 2 diabetes[1,2]. The successful identification of novel PPARγ selective agonists with good blood glucose lowering activity, using in vitro PPAR receptor binding and *in-vitro* activation screening, has already been described[3-5].

The non-TZD alkoxy-propionic acid class of insulin sensitizers was choosen as the chemical lead, as this functional group would be less prone to racemization compared to TZD, which undergoes complete racemization under physiological conditions. This was important since only the (S)-enantiomers of the TZDs bind to the receptor with high affinity. Further, recent reports have suggested very potent in vitro and in vivo activities of the alkoxy-propionic class of compounds[8-11]. Lipinski rule of 5 helps in distinguishing between drug like and non drug like molecules.

Taking these points in to account several α-Phenoxy phenylpropionic acid ligands having different substitutions were designed computationally. In this study, we designed some α-Phenoxy phenylpropionic acid derivatives as targeted for Diabetes mellitus based on molecular docking between designed new inhibitors and PPAR γ receptor (2Q6S) using Auto dock. Also we have planned to calculate drug-likeness properties by applying Lipinski rule of 5 same α-Phenoxy phenylpropionic acid derivatives.

MATERIALS AND METHODS

Experimental Methods:

AUTO DOCK

Auto Dock is an automatic docking tool. It is designed to predict how small molecules, such as substrates, bind to a receptor of known 3D structures. A graphical user interface called Auto Dock Tools or ADT was utilized to generate grids, calculate the dock score and evaluate the conformers[12].

A total of 15 entries of PPARγ were selected from RCSB protein data bank, based on the presence of ligand, X-ray diffraction and 2.0-2.5 Aº resolution. Out of the 15 entries, 2Q6S was taken for docking analysis (based on the Ramachandran plot statistics) as it showed 418 most favoured regions, 35 in additionally allowed region and none of the residue is disallowed regions.

A comparative protein-ligand dock analysis was performed using 2Q6S extracted from Protein Data Bank (PDB)[13] to evaluate the algorithm and scoring function efficiency between Auto Dock 4.0.1 and experimental activities. All these computationally designed molecules as well as the bound ligand of the protein 2Q6S were docked by using the software Auto Dock and the score values are predicted. The protein ligand interactions were also studied in web server. Based on the score values against the activity in µM the molecules were represented as active, moderately

active and inactive. All molecules were drawn using integrated Chem Draw tool energy minimized using Tsar Software. Automated docking was used to locate the appropriate binding orientations and conformations of various inhibitors into the 2Q6S binding pocket. To perform the task, the powerful genetic algorithm method implemented in the program Auto Dock 4.0.1 was employed.

All water molecules were removed from the original Protein Data Bank file. Polar hydrogen atoms and Kollman charges 18 were added. Grid maps were generated by Auto Grid program. Each grid was centered at the crystal structure of the corresponding 2Q6S bound ligand PLB5001 (B).The grid dimensions were 60 Aº X 60 Aº X 60 Aº with points separated by 0.375 Aº.

Lipinski Rule of Five

Lipinski rule of 5 helps in distinguishing between drug like and non drug like molecules[14]. It predicts high probability of success or failure due to drug likeness for molecules complying with 3 or more of the following rules

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

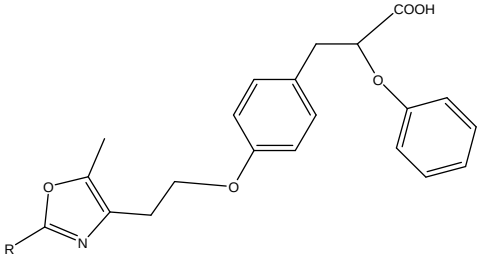
These filters help in early preclinical development and could help avoid costly late-stage preclinical and clinical failures. In this study, we also calculated all five parameters for all the designed compounds.

RESULTS AND DISCUSSION

Computational strategies for structure based drug discovery offer a valuble alternative to the costly and time consuming process of random screening. Auto Dock is employed to study the docking molecules within active site region of 2Q6S and Accelrys, DS visualizer 2.0 is used to study the H-bond interaction. At the end of each run, docked orientations are saved and the resultant molecules are checked for geometry and number of hydrogen bonds. The newly designed molecules were docked against the protein 2Q6S and the dock scores along with inhibition constant (Ki) were reported in Table-1 and it became evident that the newly designed molecules have docked scores more than -6.24 kcal/mol which is the docked score of 2Q6S. Figure 1 shows the interaction mode of compound 3 with 2Q6S receptor site.

Computationally designed ligands were pre-filtered for their drug like properties by lipinski’s rule. Lipinski's rule of five was calculated for all the eight ligand molecules that satisfy the 'rule-of-5' and it was found that all the ligand molecules satisfied the rule for potent promotors (Table 2).

Table 1: Docked scores of newly designed compounds



Compound	R	Auto Dock score (K Cal/mol)	Ki (µM)	No of H-bonds	Interacting residues
1	C_6H_5	-4.90	258.09	1	ARG 397
2	$C_6H_4(p)CF_3$	-4.42	574.19	1	ARG 397
3	**$C_6H_4(p)Cl$**	**-6.24**	**26.63**	**3**	ARG 443, ARG 397, LYS438
4	C_6H_3-2,6 Di-Cl	-5.53	87.8	2	ARG 443, ARG 443
5	$C_6H_4(p)NO_2$	-4.41	588.05	2	ARG443, LYS438
6	$C_6H_4(o)NO_2$	-4.7	356.4	1	ARG 397
7	C_6H_4 (p)OCH_3	-4.05	1.07mM	1	ARG 443
8		-5.7	65.8	1	ARG 397
Pioglitazone	-	-6.25	26.16	1	ARG 397
Rosiglitazone	-	-5.6	78.53	2	ARG 397

Figure.1 Binding mode of Compound 3 in the active site of with PPARγ (2Q6S) along with interacting amino acids

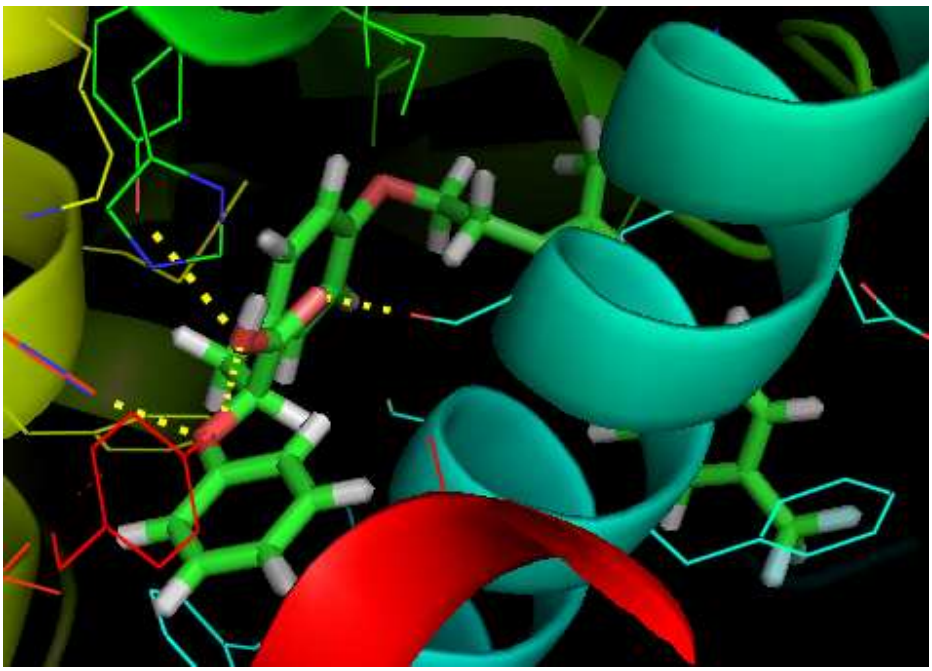


Table 2: Lipinski properties of the docked ligands

Compound	Molecular weight	Log P	H bond donor	H bond acceptor	Molar refractivity	Number of criteria met[15]
rule	< 500	<5	<5	<10	40-130	At least 3
1	443	4.85	1	5	125	All
2	511	4.92	1	5	131	3
3	**477**	**4.36**	**1**	**5**	**129**	**All**
4	512	4.83	1	5	132	3
5	488	4.61	1	5	127	All
6	488	4.61	1	5	127	All
7	473	4.82	1	6	124	All
8	433	3.85	1	6	117	All

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