Int J Pharm Bio Sci 2012 Oct; 3(4): (P) 142 - 149

Research Article **Medicinal Chemistry**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

PREDICTING THE POSSIBILITY OF NOVEL 5-SUBSTITUTED BENZISOXAZOLE CONTAINING THIAZOLIDINE-2, 4-DIONE DERIVATIVES AS POTENT PPAR-γ AGONISTS.

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ABSTRACT

A new series of 5-substituted-3-phenyl-2, 1-benzisoxazole containing Thiazolidine-2, 4-dione derivatives were computationally designed and optimized using integrated web server called docking server to investigate the interactions between the target compounds and the amino acid residues of the PPAR-γ. In this study, the docking studies were done using auto dock between computationally designed substituted 2, 1-Benzisoxazole containing Thiazolidine-2, 4-dione derivatives and PPAR-γ receptor. The Calculated binding energy for compounds in the binding site of the docked ligands were from -5.21 to -7.06 kcal/mol for compounds S9-S12 and all the selected compounds were compared with standard drugs .It is calculated by the Lamarckian Genetic Algorithm (LGA).These values and the proposed interactions suggested that the designed 2, 1-Benzisoxazole containing Thiazolidine-2, 4-dione derivatives are excellent promoters of PPAR-γ.

Keywords: **5-substituted-2, 1-Benzisoxazole, Thiazolidine-2, 4-dione, PPAR-γ agonists, Molecular docking.**

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INTRODUCTION

Diabetes mellitus 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. Potency for activation of PPAR-γ, one of a subfamily of PPARs, particularly mirrors glucose lowering activity. Therefore, PPAR-γ act as a major target to treat type II diabetes. PPARs function as transcription factors regulating the expression of genes responsible for impairment in metabolism of essential biomolecules.[1]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 PPAR-γ and PPAR-α as being the primary targets for the thiazolidinediones (TZDs) and the lipid lowering fibrates, respectively, has provided new opportunities for the identification of novel compounds for the treatment of type 2 diabetes.[2,3] The successful identification of novel PPAR-γ selective agonists with good blood glucose lowering activity, using in vitro PPAR receptor binding is described. In addition, there are reports of peroxisome proliferative activated receptor delta (PPAR-δ) agonists with characteristic benzisoxazole ring[4].

Taking these points in to account, some novel 5-substituted-3-phenyl-2, 1-Benzisoxazole containing Thiazolidine-2, 4-dione ligands having different substitutions were designed computationally. In the present study, we designed new series of 5-substituted-3-phenyl-2,1-benzisoxazole containing Thiazolidine-2,4-dione derivatives as targeted for treatment of diabetes mellitus based on molecular docking between designed new ligands and PPAR-γ receptor (2PRG) using molecular docking server.

MATERIALS AND METHODS

Ligand Preparation

Docking calculations were carried out using Docking Server.[5] The MMFF94 force field[6] was used for energy minimization of ligand molecule using molecular docking server Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

2PRG Protein Preparation

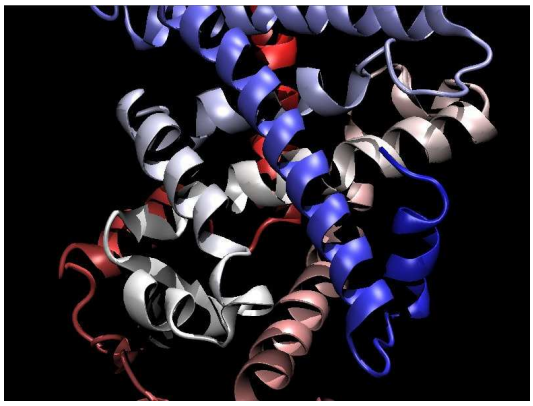
Docking calculations were carried out on 2PRG protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [7](Morris, Goodsell et al., 1998)8. Affinity (grid) maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program[7]. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Computational Methods

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis and Wets local search method[8]. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Figure 1

2PRG:X-Ray Crystal Structure Ligand binding domain of PPAR-γ from RCSB Protein data bank.



Compound code: S9

(5Z)-5-[(2-{2-[methyl(3-phenyl-2,1-benzoxazol-5-yl)amino]ethoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione:

Ligand in 2D ***Ligand in 3D***

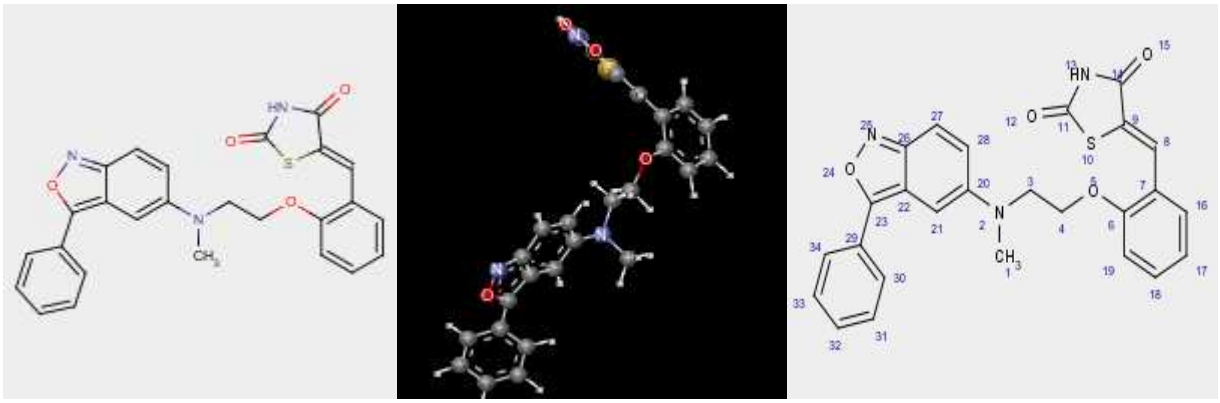


Table 1

Mol.formula	Mol.Wt.	logP	logD	Pka	logK
$C_{26}H_{21}N_3O_4S$	**472.53**	**4.76**	**4.67**	**7.60**	**-28.12**

Compound code: S10
(5Z)-5-[(2-{2-[ethyl(3-phenyl-2,1-benzoxazol-5-yl)amino]ethoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione:

Ligand in 2D **Ligand in 3D**

Table 2

Mol.formula	Mol.Wt.	logP	logD	Pka	logK
$C_{27}H_{23}N_3O_4S$	485.55	5.10	5.01	7.60	-32.47

Compound code: S11
(5Z)-5-[(2-{2-[propyl(3-phenyl-2,1-benzoxazol-5-yl)(propyl)amino]ethoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione

Ligand in 2D **Ligand in 3D**

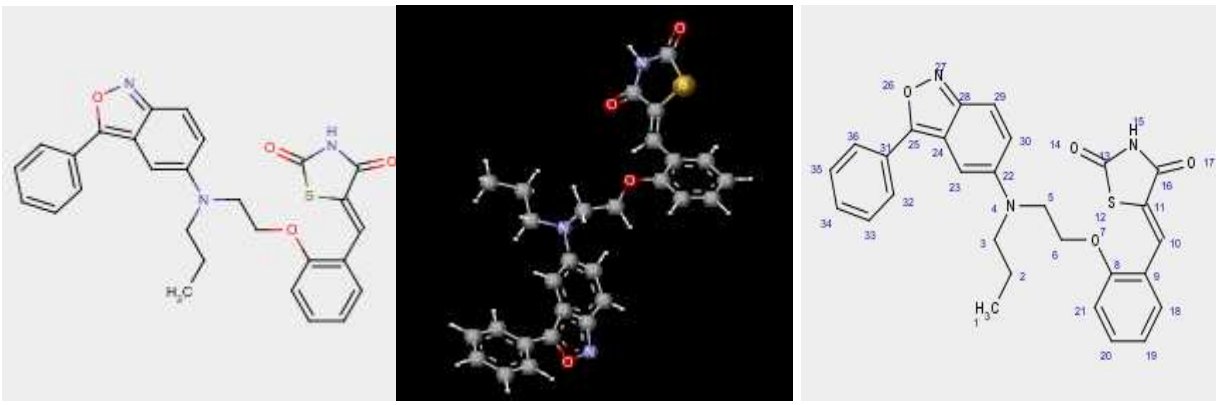


Table 3

Mol.formula	Mol.Wt.	logP	logD	Pka	logK
$C_{28}H_{25}N_3O_4S$	499.58	5.57	5.48	7.60	-37.06

Compound code: S12
(5Z)-5-[(2-{2-[butyl(3-phenyl-2,1-benzoxazol-5-yl)amino]ethoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione

Ligand in 2D **Ligand in 3D**

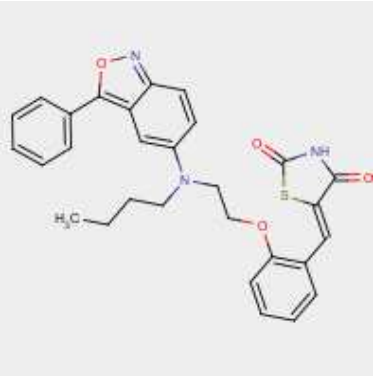
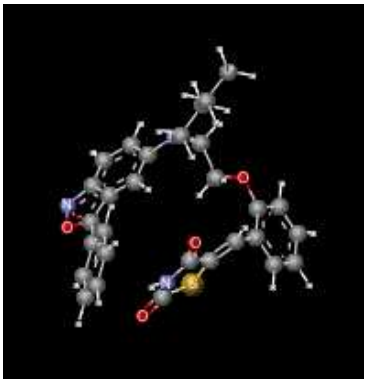
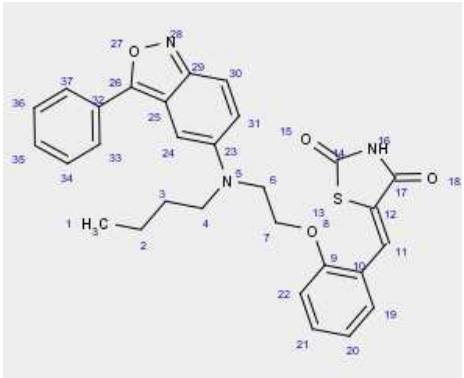




Table 4

Mol.formula	Mol.Wt.	logP	logD	Pka	logK
$C_{29}H_{27}N_3O_4S$	513.60	5.96	5.88	7.60	-41.97

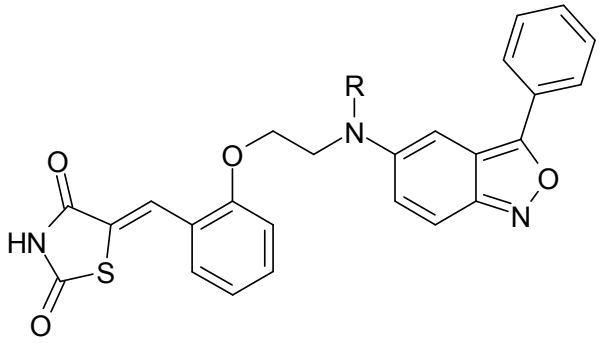
RESULTS AND DISCUSSION

Interestingly, docking results reveal that all the compounds inside PPAR-γ protein is outlined by different amino acids and the hydrophobic pocket is comprised of ILE 281, CYS 285, ILE 326, TYR 327,LEU 330 and MET 248. Small molecules are bound to human serum albumin by four binding modes such as hydrogen bonds, Van der vaals, electrostatic and hydrophobic interactions. The total energy of four binding modes is shown in the Table 5. Further, a comparison of different energies, interacting surfaces between designed compounds and rosiglitazone is given in Table 5. Calculated free energy of binding for compounds S9, S10, S11, S12 and rosiglitazone in the binding site were --6.56, -7.06, -5.21, -5.67 and -7.05 kcal/mol respectively in their best pose. The highest free energy of binding and lowest interactive surface is observed with Compound S10 than other docked molecules (S9, S11 and S12). Therefore, among all docked molecules, S10 is possess highest probability of interaction with binding site of PPAR-γ (2PRG) and it is comparable with that of Rosiglitazone, a standard PPAR-γ agonist. Furthermore, the present data showed that changing R from methyl substituent (compounds S9) to ethyl (compounds S10) resulted in improvement in PPAR-γ binding ability. Whereas, increase in carbon length at N-substitution (R) to n-propyl (compounds S11) and n-butyl (compounds S12) exhibited reduction in binding interaction with PPAR-γ.

Taken together, the structural activity relationship (SAR) studies reveals that the presence of N-ethyl substitution along with other pharmacophores such benzisoxazole and thiazolidine-2, 4-dione possess higher PPAR-γ binding activity than lower and higher N-alkyl substituents. The HB plot of all the four compounds is as shown in the figure & reveals the interaction of protein by forming hydrogen bond networks with the different amino acid residues.

Table 5
Energy Table and Interactions of 2, 1-benzisoxazole containing Thiazolidine-2, 4-dione derivatives with 2PRG (PDB Code)

Comp. Code	R	Est.Free energy of binding	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermol. Energy	Interact. Surface
S9	Me	-6.56	-8.43	-0.00	-8.43	780.87
S10	Et	-7.06	-11.16	-0.01	-11.18	763.07
S11	*n*-Pr	-5.21	-07.91	+0.05	-7.87	767.27
S12	*n*-Bu	-5.67	-10.53	-0.04	-10.57	786.87
Rosiglitazone		-7.05	-8.88	-0.05	-8.93	609.85



General Structure

VISUALIZATION OF THE LOWEST ENERGY CONFORMATION OF COMPOUNDS (S9-S12) to 2PRG COMPLEX IS SHOWN IN ASTEXVIEWER™ (AN IN BUILT APPLICATION OF MOLECULAR DOCKING SERVER).

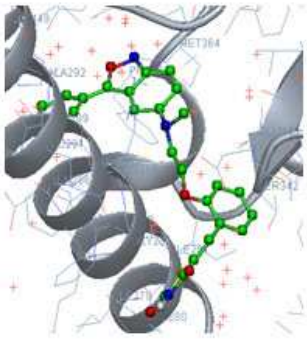


Figure 2: ***S9 to 2PRG - COMPLEX***

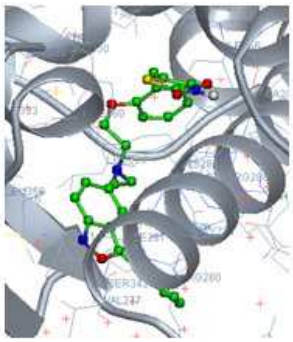


Figure 3: ***S10 to 2PRG – COMPLEX***

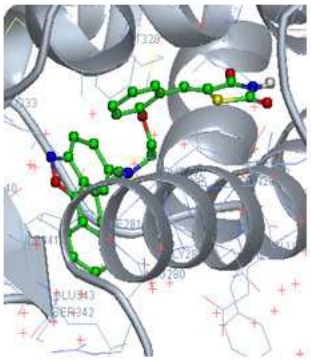


Figure 4: ***S11 to 2PRG – COMPLEX***

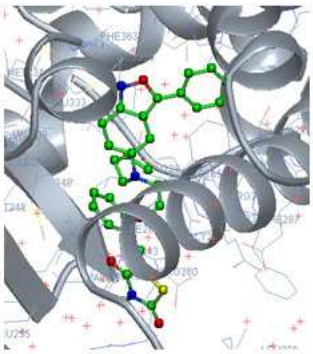


Figure 5: ***S12 to 2PRG – COMPLEX***

HB PLOT OF THE COMPOUNDS S9-S12 SHOWING INTERACTION WITH DIFFERENT AMINOACIDS OF THE PROTEIN.[9, 10]

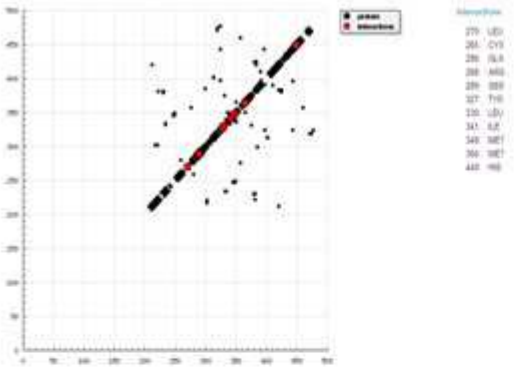


Figure 6: S9-2PRG Complex

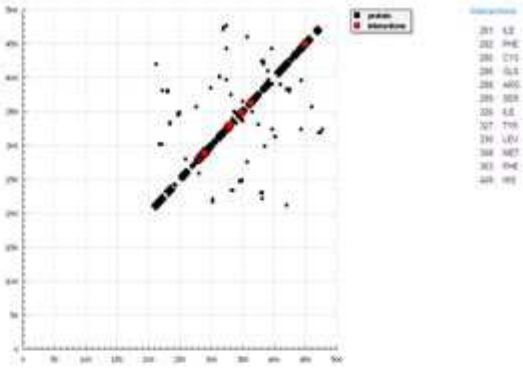


Figure 7: S10-2PRG Complex

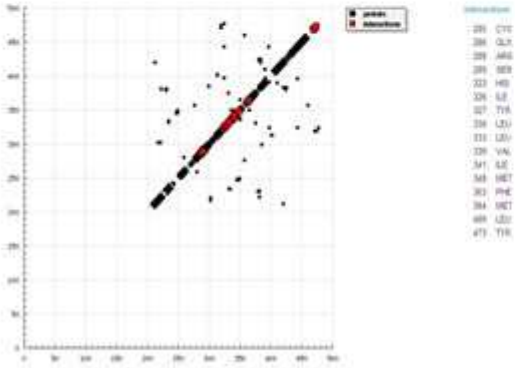


Figure 8: S11-2PRG Complex

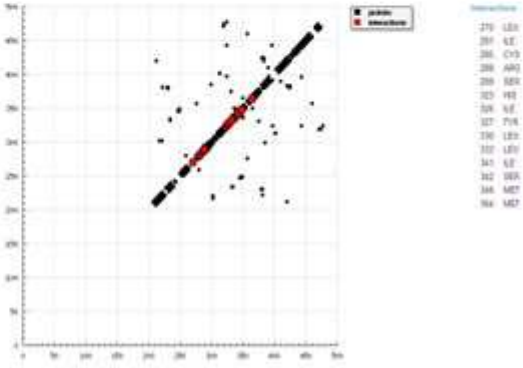


Figure 9: S12-2PRG Complex

CONCLUSION

All the computationally designed molecules have shown marked interaction to the PPAR-γ protein and it is observed that the compounds are highly hydrophobic and these interactions are important for the folding of proteins. This is important in keeping a protein alive and biologically active, because it allows the protein to decrease in surface area and reduce the undesirable interactions with water. Therefore, it is evident that these molecules can be good PPAR-γ agonists and will play vital role as anti-diabetic agents.

ACKNOWLEDGEMENTS

Our sincere thanks to Dr. V. H. Kulkarni, Principal, S.E.T.'s College of Pharmacy-Dharwad, India and President, Soniya Education Trust, Dharwad, India for providing necessary support during the research work.

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