# Insilico Design of a Ligand for DPP IV in Type II Diabetes

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**Abstract:** With the spread of western lifestyles, the occurrence of type II diabetes in the world's population is rising. A major goal for the treatment of type II diabetes is the enhancement of insulin secretion by pancreatic islet b-cells. The current therapeutic agents, although effective in increasing insulin secretion, are associated with undesirable side effects. Improved glucose tolerance in diabetic patients was achieved with several small molecules as DPP IV inhibitors, including sitagliptin.The current study was designed to identify a suitable inhibitor agent for DPP IV. Computer-assisted molecular modeling approach has contributed to the successful discovery of several novel antidiabetic DPP IV agents. In this work, we identified a DPP IV inhibitor by docking-based virtual screening method. Docking was performed with the Glide. *Maestro* v9.0 graphical user interface (GUI) workspace was used for all the steps involved in ligand preparation, protein preparation, HTVS and Docking. The newly designed molecule (TZD 6) has good score and energy when compared with standard. The compound TZD6 showed good orientation in the active pocket of DPP IV. We found a new compound TZD 6 have high predicted affinity for DPP IV; are synthetically accessible. This compound is expected to have good *in vivo* activity and would represent a potential scaffold as a DPP IV inhibitor.

**Key words:** Docking · DPP IV Inhibitor · Type II Diabetes · Molecular Modeling · Antidiabetic · Thiazolidine

## INTRODUCTION

Diabetes mellitus is a syndrome of multiple aetiologies [1] characterized by chronic hyperglycaemia with impaired metabolism of glucose [2], lipids and proteins [3]. Juvenile or type I diabetes, occurs at a relatively young age where the beta cells of the pancreas do not produce enough insulin to maintain euglycemia in the plasma [4]. The hallmark of another type of adult onset or type II diabetes is the resistance of peripheral tissues to insulin action [5].

Numerous reports stated the risk and incidence of coronary heart disease (CHD) and vascular disease, accounts for more than 60% of the morbidity and mortality in patients with diabetes mellitus [6-8]. The international diabetes federation report states that the possible causes and distribution of diabetes over the last 20 years has been extraordinary [9]. These studies continue to confirm that it is the low- and middle-income countries (LMICs), face the greatest burden of diabetes. However, many governments and public health planners still remain largely unaware of the current magnitude, or, more importantly, the future potential for increases in diabetes [10] and its serious complications in their own countries.

Dipeptidyl peptidase IV (DPP IV), a serine protease cleaves a dipeptide from the N-terminus of the incretin hormones to give the inactive amide [11, 12].The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) stimulates insulin biosynthesis, secretion and inhibits glucagon release in a glucose-dependent manner [13, 14]. Small-molecule inhibitors [15, 16] of DPP-4 have been shown to prolong the beneficial effects of this incretin hormone, as well as stabilize other incretin hormones such as glucose-dependent insulinotropic polypeptide (GIP) [17-19].

Time and cost required for designing a new drug are immeasurable and at an unacceptable level. Intervention of computers at some plausible steps is vital to bring down the cost and time required in the drug discovery process. The use of paired experimental and informatics techniques increases the chance of success in many stages of the discovery process, from the identification of

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novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties.

In Silico techniques save great amounts of time and money in R and D projects. It can help in identifying drug targets via bioinformatics tools. They can also be used to explore the target structures for possible active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics.

## MATERIAL AND METHODS

**Molecular Modeling:** Docking was performed with the Glide (*Grid-based Ligand Docking with Energetics*) [20] software v5.5 developed by Schrödinger running on Microsoft office workstation. *Maestro* v9.0 graphical user interface (GUI) workspace was used for all the steps involved in ligand preparation, protein preparation, HTVS and Docking.

**Selection of Protein File:** The protein data bank (PDB) is a repository contains information about experimentally-determined 3-D structural data of large biological molecules, such as proteins, nucleic acids and complex assemblies [21]. The crystal structure of DPP IV in complex with the sitagliptin inhibitor was retrieved from the protein data bank (PDB entry 2P8S) [22]. The PDB structure retrieved consists of heavy atoms, water molecules, cofactors, metal ions and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. Consequently the raw PDB structure should be prepared in a suitable manner for docking.

**Energy Minimization of Protein:** The protein preparation wizard module of maestro was used to prepare the protein in which water molecules and peptide substrates (NAG) were deleted. This follows the optimized potential for liquid simulations for all atoms (OPLS-AA) force fields for energy minimization.

**Designing Molecule:** The structures of all ligands were prepared using ChemBiodraw Ultra, chemical drawing tool developed by Cambridge Pvt. Ltd. It offers multiple advantages such as ease of use, high quality output, robust chemical intelligence and integration with the Chemoffice suite and with many third party products. This

accurately handles and predicts organic, organometallic and polymeric and biopolymer materials (including amino acids, peptides and DNA and RNA sequences) and to deal with advanced forms of stereochemistry.

**Ligand Preparation:** The ligands were prepared by the ligprep module of maestro, a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures and optimize the structures. Many of the steps are optional and are controlled by selecting options in the ligand preparation panel by specifying command-line options.

**Database Filteration:** Recently, inhibition of dipeptidyl peptidase IV has emerged as a new treatment option for type II diabetes. Development of small molecules as selective inhibitors of DPP IV includes peptidomimetic and non-peptidomimetic derivatives. The high throughput virtual screening (HTVS) of glide Schrödinger L.L.C was used as a tool to filter the datasets prepared. From the literature we designed 50 various cyclohexanamine derivatives. HTVS excluded those compounds which were not expected to bind with DPP IV and results 38 compounds. Among these the 16 thiazolidine derivatives which have the Glide score and Glide energy better than sitagliptin; have been chosen for induced fit docking (IFD) studies.

**Induced Fit Docking of Molecule:** In standard virtual docking studies, ligands are docked into the binding site of a receptor where the receptor is held rigid and the ligand is free to move. However, the assumption of a rigid receptor can give misleading results, since in reality many proteins undergo side-chain or backbone movements, or both, upon ligand binding. In IFD, both the ligand and the receptor are flexible which enables to dock the ligand at the receptor's binding site.

For IFD docking, a receptor grid where the ligand has to be docked in the inhibitor active site were prepared using the default bounding box sizes; with an inner box of 10 Å on each side and an outer box of 24 Å on each side. Flexible docking with default parameters was used. Glide XP (extra precision) were employed for all docking calculations [23]. By default, Schrödinger's proprietary Glide Score (G-score) multi-ligand scoring function is used to score the poses. The best docked poses were selected as the ones with the lowest G-score; the more negative the G-score, the more favorable the binding.

G-score takes into account a number of parameters like hydrogen bonds (H-bond), hydrophobic contacts (Lipo), van der-Waals (vdW), columbic (Coul), polar interactions in the binding site (Site), metal binding term (Metal), penalty for buried polar group (BuryP) and freezing rotatable bonds (RotB).G-score = H bond + Lipo + Metal + Site + 0.130 Coul + 0.065 vdW – BuryP – RotB. The thiazolidine derivatives were docked at the active site of 2P8S individually. The poses generated were ranked based on G-score. The pose that made the maximum hydrogen bond (H-bond) interactions from thiazolidine derivatives – 2P8S docked complexes were considered for further analysis and the results were compared with the standard sitagliptin.

**Visualization and Analysis:** The *PyMol* Molecular Graphics System [24] was used to analyze the hydrogen bond interactions and preparation of high resolution images.

## RESULTS

Two-dimensional representation of the optimized binding model of the compound TZD 6 with the crystallographic structure of standard sitagliptin is shown in Fig 1. The compound TZD 6 was considered as a lead based on the docking score and the energy. The docking score of TZD 6 is -9.24 and Glide energy is -51.72(for sitagliptin -8.12, 43.60, Table 1). The â-amino group in the intermediate chain of sitagliptin (yellow) formed one H bond with the oxygen atom in the side chain of Glu 206 in S1 pocket of DPP IV (red dotted lines). The oxygen in the intermediate chain of sitagliptin made H bond with N-H of Arg 125.The two cyclic nitrogen of the triazolo piperazine ring of sitagliptin made one H bond with His 126. A very similar binding model was observed for TZD 6. TZD 6 also made similar H bond interactions with Glu 205 and Tyr 662(green dotted lines). The oxygen in the side chain of the thiazolidine ring made a H bond with N-H of Arg 125. Another H bond between the O-H of TZD 6 and N of the His 126 was also predicted by glide.
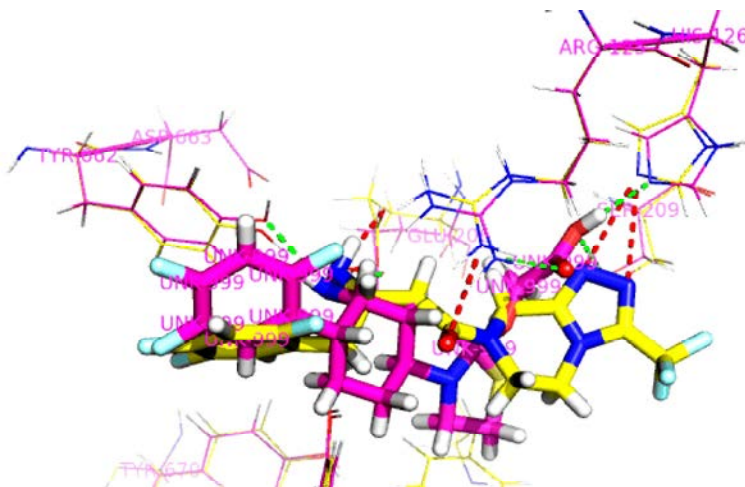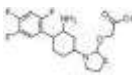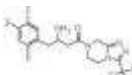


Fig. 1: Docked overlay images of the TZD6 (pink) with sitagliptin (yellow)

Table 1: Structure, physiochemical properties and results of extra precision docking studies of TZD6 and Sitagliptin

| Cpd Code | Structure | Mol.Wt (g/mol) | HD* | HA# | logP | Glide Score | Glide Energy (Kcal/mol) |
|---|---|---|---|---|---|---|---|
| TZD6 | | 390.42 | 1 | 4 | 2.4 | -9.24 | -51.72 |
| Sitagliptin (standard) | | 407.31 | 1 | 3 | 2.2 | -8.12 | -43.60 |

*= Number of hydrogen bond donor groups

#= Number of hydrogen bond acceptor groups

## DISCUSSION

The results of IFD showed TZD6 as the most suitable inhibitor from the 16 thiazolidine derivatives in terms of score and binding energy. The docking score and the energy were good for TZD 6 than the standard (Table 1). The overlay image shows that the TZD 6 molecule (pink) is well positioned in the active pocket of DPP IV. These observations are also consistent with the crystallographic structure of the DPP IV in complex with sitagliptin. As suggested previously[25], the interactions of the basic amine with the S1pocket of DPP IV formed by residues Glu205 and Tyr 662 and heterocyclic moiety occupies the S2 pocket also made interactions with His 126 explains the increase in activity. Similar H bonds are observed for TZD6 would have good *in vivo* activity, it was considered as a top hit for the further series of compound synthesis.

## CONCLUSION

In conclusion we have identified a best molecule of thiazolidine derivative as DPP IV inhibitor. From the docking studies of thiazolidine derivatives, we found the molecule TZD 6 bound to the active pocket of DPP IV and which is expected to give good *in vivo* activity. This compound TZD 6 is considered as a best molecule and we need to identify a series of compounds for synthesis and further studies.

**Conflict of Interest:** The authors confirm that this article content has no conflicts of interest.

## REFERENCES

1. Visweswara Rao, P. and M. Dhananjaya Naidu, 2010. Anti Diabetic Effect of Rhinacanthus nasutus Leaf Extract in Streptozotocin Induced Diabetic Rats. Libyan Agriculture Research Center Journal International, 1(5): 310-312.

2. Grijesh Kumar Mall, Pankaj Kishor Mishra and Veeru Prakash, 2009. Antidiabetic and Hypolipidemic Activity of Gymnema sylvestre in Alloxan Induced Diabetic Rats. Global Journal of Biotechnology and Biochemistry, 4(1): 37-42.

3. Baquer, N.Z., D. Gupta and J. Raju, 1998. Regulation of metabolic pathways in liver and kidney during experimental diabetes. Effects of antidiabetic compounds. Indian J. Clinical Biochem, 13: 63-80.

4. Eilyad Issabeagloo, Reza forughi, Mohammed Taghizadieh and Parviz Kermanizadeh, 2012. Effect of Alcohol on Blood Glucose Levels in Streptozotocin Induced Diabetic Rats. Middle-East Journal of Scientific Research, 12(3): 290-293.

5. Mohammad Yaheya Mohammad Ismail, 2009. Clinical Evaluation of Antidiabetic Activity of Trigonella Seeds and Aegle marmelos Leaves, World Applied Sciences Journal, 7(10): 1231-1234.

6. Satyanand Tyagi, Mohd. Hashim Mansoori, Narendra Kumar Singh, Manoj Kumar Shivhare, Poonam Bhardwaj and Rahul Kumar Singh, 2011. Antidiabetic Effect of Anacyclus pyrethrum DC in Alloxan Induced Diabetic Rats. European Journal of Biological Sciences, 3(4): 117-120.

7. Venkateshwarlu, E., B.S. Sharvana Bhava, P. Arvind, P. Rakeshkumar Reddy, P. Dileep and K. Mahathi, 2013. Evaluation of anti-diabetic and hypolipidemic activity of Pseudarthria viscida (Whole Plant) in Streptozotocin-Nicotinamide Induced TypeII Diabetic Rats. Global Journal of Pharmacology, 7(2): 192-197.

8. Garcia, M.J., P.M. McNamara, T. Gordon and W.B. Kannel, 1974. Morbidity and mortality in diabetes in Framingham population-sixteen year follow up study. Diabetes, 23: 105-111.

9. Kannel, W.B. and D.L. McGee, 1979. Diabetes and cardiovascular diseases-the Framingham study. JAMA, 241: 2035-2038.

10. Taylor, K.G., A.D. Wright, T.J. Carter, A.J. Valente, S.A. Betts and K.A. Mathews, 1981. High density lipoprotein cholesterol and apolipoprotein A-1 levels at diagnosis in patients with non-insulin dependent diabetes. Diabetologia, 20: 535-539.

11. Deacon, C.F., M.A. Nauck, M. Toft-Nielson, L. Pridal, B. Willms and J.J. Holst, 1995. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes, 44: 1126-1131.

12. Kieffer, T.J., C.H.S. McIntosh and T.A. Pederson, 1995. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 *in vitro* and *in vivo* by dipeptidyl peptidase IV. Endocrinology, 136: 3585-3596.

13. Orskov, C., 1992. Glucagon-like peptide-1 a new hormone of the entero-insular axis. Diabetologia, 35: 701-711.

14. Drucker, D.J., 1998. Glucagon-like peptides. Diabetes, 47: 159-169.

15. Weber, A., 2004. Dipeptidyl Peptidase IV Inhibitors for the Treatment of Diabetes. E.J. Med. Chem., 46: 4135-4141.

16. Deacon, C.F., 2007. Dipeptidyl peptidase 4 inhibition with sitagliptin: a new therapy for type II diabetes. Expert Opin. Investig. Drugs, 16: 533-545.

17. Ahren, B. and T.E. Hughes, 2005. Inhibition of Dipeptidyl Peptidase-4 Augments Insulin Secretion in Response to Exogenously Administered Glucagon-Like Peptide-1, Glucose-Dependent Insulinotropic Polypeptide, Pituitary Adenylate Cyclase-Activating Polypeptide and Gastrin-Releasing Peptide in Mice. Endocrinology, 146: 2055-2059.

18. Davies, J.W., M. Glick and J.L. Jenkins, 2006. Streamlining lead discovery by aligning in silico and high-throughput screening. Curr.Opin. Chem. Biol., 10: 343-351.

19. Gautier, J.F., S. Fetita, E. Sobngwi and C. Salaun-Martin, 2005. Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. Diabetes Metab, 31: 233-242.

20. Friesner, R.A., R.B. Murphy, M.P. Repasky, L.L. Frye, J.R. Greenwood, T.A. Halgren, P.C. Sanschagrin and D.T. Mainz, 2006. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes. J. Med. Chem, 49: 6177-6196.

21. Berman, H.M., 2008. The Protein Data Bank: a historical perspective, Acta Crystallographica Section A: Foundations of Crystallography, 64: 88-95.

22. Biftu, T., G. Scapin, S. Singh, D. Feng, J.B. Becker, G. Eiermann, H.He, K. Lyons, S. Patel, A. Petrov, R. Sinha-Roy, B. Zhang, J. Wu, X. Zhang, G.A. Doss, N.A. Thornberry and A.E. Weber, 2007. (3R)-4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepan-2-one, a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Bioorg. Med. Chem. Lett, 17: 49-52.

23. Sherman, W., T. Day, M.P. Jacobson, R.A. Friesner and R. Farid, 2006. Novel procedure for modeling ligand/receptor induced fit effects. J. Med. Chem., 49: 534-553.

24. Kini, R.M. and H.J. Evans, 1987. Structure-function relationships of phospholipases: The anticoagulant region of phospholipases A2. J. Biol. Chem., 262: 14402-14407.

25. Janardhan, S. and Y. Padmanabha Reddy, 2011. Homology modeling and molecular docking studies of human dpp8 and dpp9. Inter. J Pharm. Res. Development, 12(5): 131-146.