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# Molecular Docking Interaction of Pinitol (Ligand) with Dipeptidyl Peptidase-4 Receptor (PDB 3C45)

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**Abstract:** D-chiroinositol (pinitol) is chemically related to the phosphatidylinositol phosphates which participate in the insulin signalling pathways for stimulating transport of glucose. Pinitol was reported to have insulin like properties. Molecular docking interaction of pinitol with dipeptidyl peptidase-4 receptor (PDB 3C45) was studied by using V-Life QSAR software. Various ligand (pinitol) poses were studied with dipeptidyl peptidase-4 receptor. Ligand (pinitol) poses 10, 33, 39, 48, 49 shown effective molecular docking interactions with dipeptidyl peptidase-4 receptor. These interactions indicates the antidiabetic activity of pinitol as reported in literature. These QSAR studies may be useful in designing pinitol derivatives having more potent antihyperglycemic properties and also important for molecular docking interactions studies of pinitol using other receptors protein data bases.

**Key words:** Pinitol · Ligand Pose · QSAR · Dipeptidyl Peptidase-4 Receptor · Molecular Docking Interactions

## INTRODUCTION

Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin release. They slow down the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. They also inhibit glucagon release from the alpha cells of the Islets of Langerhans. The incretins are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic polypeptide or GIP). Both incretins GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 is not very useful for treatment of type 2 diabetes, as to be administered by continuous subcutaneous infusion. Several long-lasting analogues like exenatide and liraglutide, have been developed. Another approach is to inhibit the enzyme DPP-4 which inactivates GLP-1 and GIP. DPP-4 inhibitors can be administered orally [1].

Type 2 diabetes (NIDDM-Noninsulin dependent diabetes mellitus) is most common (˜ 90% of diabetic cases) and affecting common man all over the globe [2-4]. Automatic instrumental devices are commonly used now a day to monitor blood glucose level [5]. Diabetes cases are increasing due to many factors like genetic factors, aging, environmental factors, stress, food habits etc [6, 7]. Identification of drug targets (receptors) for development of newer therapeutic agents for treatment of diabetes is in progress [8]. Pinitol is a cyclitol (cyclic polyol) known as D-chiroinositol participates in the insulin signalling pathways that stimulate glucose transport [9, 10]. Pinitol decreases urinary excretion in animal models and human subjects with impaired glucose tolerance and insulin resistance [11-13]. Pinitol also decreases plasma glucose concentrations in streptozotocin (STZ)-diabetic rats and increased glucose utilization in insulin-resistant monkeys. D-chiroinositol also improved glucose tolerance in normal rats and increased glycogenesis [14-16]. Plants are used traditionally for treatment of diabetes since ancient time [17]. D-chiroinositol was isolated from plant sources and reported to have insulin like properties [18]. These findings indicates the potency of pinitol for treatment of diabetes and hence selected for molecular docking studies which may be useful for molecular modification in pinitol in search of leads having potent antihyperglycemic properties.

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Oral dipeptidyl peptidase-IV inhibitors improve islet function by increasing α-cell and β-cell responsiveness to glucose. They are not associated with hypoglycemia or weight gain and appear to have a benign safety profile. Oral dipeptidyl peptidase-IV inhibitors may prove valuable in the treatment of diabetes, as their effectiveness in reducing glycated hemoglobin with neutral weight effects and without the adverse effects. Dipeptidyl peptidase-IV inhibitors appear to improve islet function and may modify the course of diabetes treatment. It is to be confirmed with long-term controlled studies to demonstrate sustained glycemic control.

Medical plants play a major role in the management of type 2 diabetes mellitus. Traditional plant-based remedies have been for diabetic cure around the world and many studies have confirmed the benefits of medicinal plants with hypoglycemic effects [19-25]. Various mechanisms of antidiabetic action have been proposed for extracts of the antidiabetic plants. One target of interest for the antidiabetic action of the extracts is the serine protease dipeptidyl peptidase-IV (DPP-IV; EC 3.4.14.5) [26].

The first DPP-IV inhibitor marketed was sitagliptin (by Merck and Co.), followed by vildagliptin (by Novartis) and saxagliptin (by Bristol-Myers Squibb and AstraZeneca) [27-29]. The efficacy and safety profile of DPP-IV inhibitors have been promising and advantageous to date. In contrast to sulfonylureas, DPP-IV inhibitors do not have an intrinsic risk of inducing hypoglycemia. The two key binding-site areas for molecular interaction of DPP-IV are the lipophilic S1 pocket (formed by Tyr631, Val656, Trp659, Tyr662, Tyr666 and Val711) and the negatively charged Glu205/206 pair [30]. Recently, researchers are using QSAR techniques for drug discovery process [31-35].

**Experimental:** VLifeDock software provides a choice of methods for molecular docking. Three methods, Grid based docking, GA docking and VLife's own GRIP docking offer unique 'Accuracy-Speed' options from rapid screening to exhaustive precision docking. VLifeDock also has batch docking facility to enable prioritizing the pinitol based on their binding scores. The choice of systematic and stochastic methods with an array of scoring functions makes VLifeDock a truly versatile method.

**Systemic Methods:** A Grid based algorithm is implemented for systematic docking. The algorithm exhaustively explores binding mode of pinitol over a grid on the protein cavity. The Grid based method is a type of rigid docking where both the pinitol and receptor are treated as rigid.

**Stochastic Methods:** A genetic algorithm based method provides a stochastic method for docking. GA based docking in VLifeDock takes flexibility of pinitol into consideration. It generates a wide population of initial poses, which ultimately evolve into the optimal binding mode.

**GRIP Docking:** GRIP is a rapid yet accurate docking methodology available exclusively through VLife software. The GRIP scoring function enables fast and precise capturing and prediction of pinitol-receptor interactions in the active site of proteins. GRIP docking is available as rigid as well as flexible docking, where unique conformers of a set of pinitol are taken as input.

**Scoring Functions:** It provides an array of scoring functions such as PLP score, XCscore and Steric + Electrostatic score for evaluation of docked poses.

Molecular docking interaction of pinitol (Fig. 1) with dipeptidyl peptidase-4 receptor (PDB 3C45) (Fig. 2) was studied by using V-Life QSAR software. Various ligand (pinitol) poses were studied with dipeptidyl peptidase-4 receptor. Ligand (pinitol) poses 10, 33, 39, 48, 49 shown effective molecular docking interactions with dipeptidyl peptidase-4 receptor (Figs. 3-7). These interactions indicate the antidiabetic activity of pinitol as reported in previous studies [18].

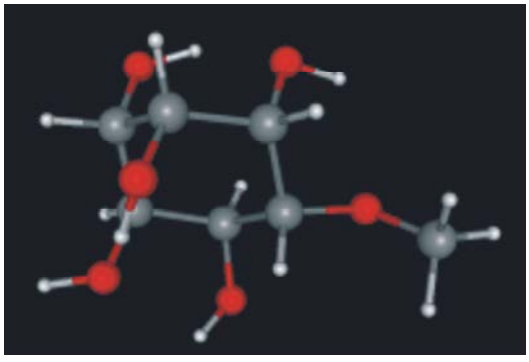

Fig. 1: Model of Ligand Pinitol Used for Docking with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45)

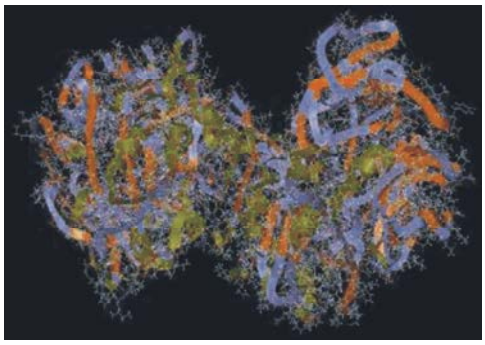

Fig. 2: Crystal Structure Model of Human Dipeptidyl Peptidase IV Receptor (PDB 3C45)

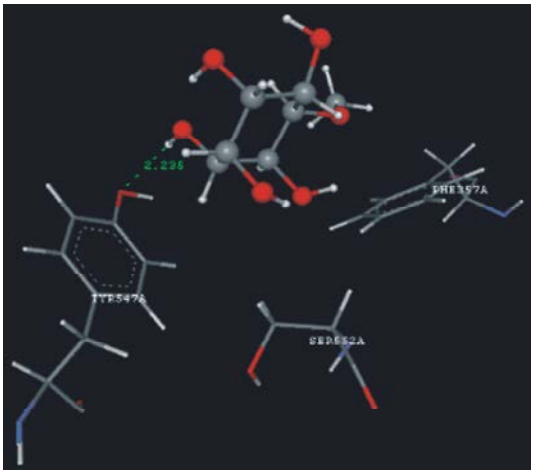


Fig. 3: Molecular Docking Interaction of Pinitol (LP 10) with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45), Green Line Indicates H-Bonding.

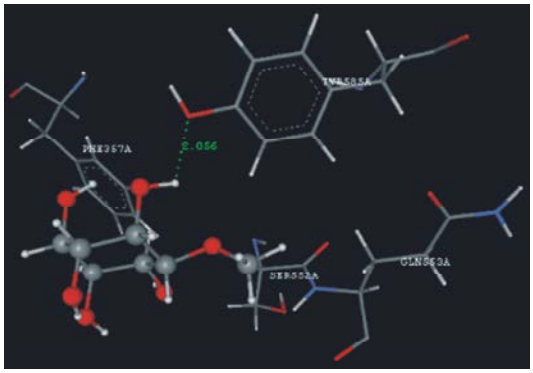


Fig. 4: Molecular Docking Interaction of Pinitol (LP 33) with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45), Green Line Indicates H-Bonding.

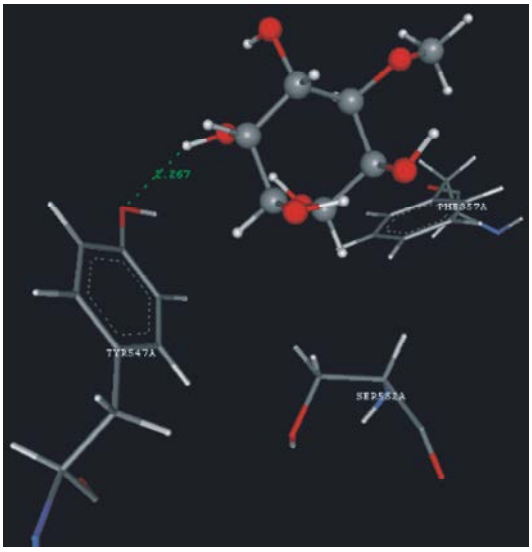


Fig. 5: Molecular Docking Interaction of Pinitol (LP 39) with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45), Green Line Indicates H-Bonding.

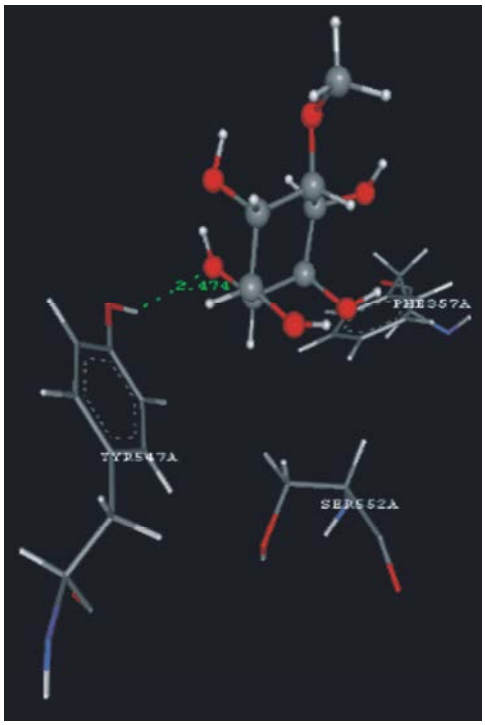


Fig. 6: Molecular Docking Interaction of Pinitol (LP 48) with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45), Green Line Indicates H-Bonding.

Ligand pose 10 shows effective molecular docking interaction with dipeptidyl peptidase-4 receptor (PDB 3C45). Ligand forms hydrogen bond with tyrosin residue of receptor. Hydrogen bond length is 2.235 A°, as indicated by green colour (Fig. 3). Ligand pose 33 shows effective molecular docking interaction with dipeptidyl peptidase-4 receptor (PDB 3C45). Ligand forms hydrogen bond with phenylalanine (PHE) residue of

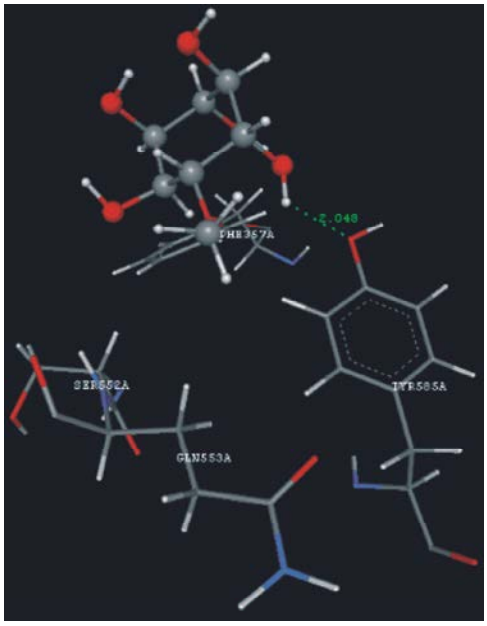

Fig 7: Molecular Docking Interaction of Pinitol (LP 49) with Human Dipeptidyl Peptidase IV Receptor (PDB 3C45), Green Line Indicates H-Bonding.

receptor. Hydrogen bond length is 2.056 A°, as indicated by green colour (Fig. 4). Ligand pose 39 shows effective molecular docking interaction with dipeptidyl peptidase-4 receptor (PDB 3C45). Ligand forms hydrogen bond with tyrosin residue of receptor. Hydrogen bond length is 2.235 A°, as indicated by green colour (Fig. 5). Ligand pose 48 shows effective molecular docking interaction with dipeptidyl peptidase-4 receptor (PDB 3C45). Ligand forms hydrogen bond with tyrosin residue of receptor. Hydrogen bond length is 2.474A°, as indicated by green colour (Fig. 6). Ligand pose 49 shows effective molecular docking interaction with dipeptidyl peptidase-4 receptor (PDB 3C45). Ligand forms hydrogen bond with tyrosin residue of receptor. Hydrogen bond length is 2.048A°, as indicated by green colour (Fig. 7).

## CONCLUSIONS

Molecular docking interaction of pinitol (D-chiroinositol) with dipeptidyl peptidase-4 receptor (PDB 3C45) was studied by using V-Life QSAR software. Various ligand (pinitol) poses were studied with dipeptidyl peptidase-4 receptor. Ligand (pinitol) poses 10, 33, 39, 48, 49 shown effective molecular docking interactions with dipeptidyl peptidase-4 receptor. The molecular interaction indicates the antidiabetic activity of pinitol as reported in literature. These studies may be useful in designing pinitol derivatives having more potent antihyperglycemic properties and also important for molecular docking interactions studies of pinitol using other receptors protein data bases.

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