**Short Communications**

**In silico** docking of ligand 3-hydroxy methyl xylitol with target protein ZnT-8 involved in type II diabetes

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ZnT-8 protein has been localized in insulin secretory granules. An automated molecule model for the target protein ZnT-8 was generated at Swiss 3D modeling. Ramachandran plot was used to determine the angles. ADMET properties were calculated for the ligand, 3-hydroxy methyl xylitol. Pre ADMET hyperchem tool was used to find the QSAR properties of the ligand. In *silico* docking of ligand 3-hydroxy methyl xylitol with target protein ZnT-8 involved in type II diabetes was carried out to assess the efficacy of the ligand in binding to the target. The study indicated high affinity between the ligand and the target protein, suggesting that 3-hydroxy methyl xylitol is a good drug to control blood glucose levels.

**Keywords:** *In silico* docking, ligand, target protein, type II diabetes

Type II diabetes is caused by a complicated interplay of genes, environment, insulin abnormalities, increased glucose production in the liver, increased fat breakdown and possibly defective hormonal secretion in the intestine. Genetic variations within four novel genetic loci (SLC30A8, HHEX, EXT2 and Loci 387761) have been reported to be more frequent in subjects with type II diabetes than in healthy controls. Individuals carrying type II diabetes risk alleles of SLC30A8 had lower fasting plasma insulin level or lower basal insulin secretion than non-carriers. Detrimental effects on glucose homeostasis were confirmed in human volunteers having SLC30A8 risk alleles. SLC30A8 located at chromosome 8q 24.11, codes for ZnT-8 protein which has 369 amino acids. ZnT-8 has been localized in insulin secretory granules. ZnT-8 is involved in the translocation of the cytoplasmic zinc into the intracellular vesicles. The target protein ZnT-8 was identified from the literature and its molecular crystallographic 3D-structure was generated using the Accelrys DS viewer.

Bioinformatics tools have become very important to pinpoint the targets for different ligands. In our previous study, we had identified a lead molecule, 3-hydroxy methyl xylitol, to be a good antidiabetic agent. We have tried to ascertain whether 3-hydroxy methyl xylitol is a good ligand to the ZnT-8 target protein using *in silico* docking with a view to understand whether it could be a good molecule to treat diabetes.

The ligand, 3-hydroxy methyl xylitol, isolated from *Casearia esculenta* roots, was selected based on our previous study. Ramachandran plot was used to determine the angles (Fig. 1; Table 1). PRE-ADMET was used to find out the pharmacological characteristics of the ligand.

The hyperchem tool was used to find the QSAR property. Q-SiteFinder is a new method of ligand binding site prediction (Fig 2). It works by binding hydrophobic (CH3) probes to the protein, and finding clusters of probes with the most favourable binding energy. http://www.bioinformatics.leeds.ac.uk/qsitefinder. Accelrys DS Visualizer is a ActiveX Control molecular viewer that provides interactive 3D visualization of docking (Fig. 3).

Pharmacological characteristics such as high intestinal absorption (26.37) cell permeability (mm/sec, 9.15), in *vitro* plasma protein binding (30.22%), negative toxicity (Ames TA 100, S9), negative carcinogenicity in rat and mouse were recorded. The following are the characteristics of the ligand: molecular formula, C6H14O5; molecular weight, 166:17; IUPAC name (2R,4R), 3 (hydroxy methyl pentene 1,2,4,5,tetrol. SMILES=OCCC(CO)C(O)CO.

The log P value of the molecular weight =166,H2 bod acceptor=0, donar=5,Log P=-4.751, molar refractivity =36.527.

QSAR study revealed the following results: Log P= 2.503; GPCR ligand=0.34; ion channel modulator=0.66; kinase inhibitor =-0.74; nuclear receptor ligand =-1.35.

This study indicated that ligand 3-hydroxy methyl xylitol had higher affinity to ZnT-8 target protein.

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Table 1—Phy/Psi angle of the Ramachandran plot

<table>
<thead>
<tr>
<th>Ram Page Server</th>
<th>H$_2$ bonding</th>
<th>Phy/Psi Angle</th>
<th>E.P.</th>
<th>Vander walls radii</th>
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<tbody>
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<td>-2086.18</td>
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<tr>
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<td>residue properties</td>
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<td>Max.</td>
<td>Maximum angular error donor –H-</td>
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<td>Bond length/angle: 5.7</td>
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<td>morris et al. class: 111.</td>
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<td>G Factors dihedrals=-0.08.</td>
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zinc content in the pancreatic beta cells is among the highest of the body\(^8\). Therefore, zinc appears to be an important metal for insulin secreting cells. Zinc is required for insulin secretion and storage\(^9\).

During insulin synthesis, the presence of ZnT-8 in insulin vesicles is necessary to allow zinc to be incorporated within these vesicles and to facilitate the formation of zinc-insulin solid hexamers.

References