IN SILICO LIGAND – RECEPTOR DOCKING OF FEW CYCLITOLS FOR TYPE II DIABETES USING HEX

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ABSTRACT
DPP-4 inhibitors are a newer class of drugs that lowers glucose by blocking an enzyme, thereby prolonging incretion effect in vivo. DPP-4 inhibitors like sitagliptin and vildagliptin are promising new medicines for the treatment of type 2 diabetes mellitus. The present study involves in silico docking of fifteen compounds and three drugs already available in the market, as ligands to DPP-4 using Hex 6.1 docking software. The molecular docking studies and Lipinski’s rules facilitate drug development avoiding expensive post clinical experiments. Calculation of Lipinski’s properties showed that most of the compounds followed all criteria. The cyclitols are computed to be good anti diabetic agents. Such studies reduce the time and costs involved in drug discovery process and have no adverse effect on the environment.

Keywords: Dipeptidyl peptidase-4, cyclitol, docking, Hex 6.1

INTRODUCTION
The interactions between a receptor and a ligand are fundamental to drug discovery. There are a number of methods for predicting and analyzing the interactions between protein receptors and ligands. A common technique central to receptor-ligand interactions is docking. Analysis of hypothetical poses is also possible via a series of scoring functions, hydrogen bonds and bumps, and high level physics-based scoring methods to predict binding energies. There are six classes of drugs to manage type 2 diabetes. They may work in different ways to help diabetes patients but they all help to maintain good blood glucose control. Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26, is a protein that, in humans, is encoded by the DPP4 gene [1]. DPP-4 inhibitors are a newer class of drugs that lowers glucose by blocking an enzyme. In 2009, the FDA expanded the warnings for this drug, adding information about reported cases of acute pancreatitis and the need for careful
monitoring. The protein encoded by the \textit{DPP4} gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. It is a rather indiscriminate enzyme for which a diverse range of substrates are known \[2\]. DPP-4 plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1 \[3\]. A new class of oral hypoglycemics called dipeptidyl peptidase-4 inhibitors work by inhibiting the action of this enzyme, thereby prolonging incretin effect \textit{in vivo} \[4\]. A once-daily oral agent that preserves the action of glucagon-like peptide 1 (GLP-1) by inhibiting the enzyme that degrades it, appears to improve glycemic control in patients with type 2 diabetes mellitus who are inadequately controlled with metformin \[5\]. DPP-4 inhibitors like sitagliptin and vildagliptin are promising new medicines for the treatment of type 2 diabetes mellitus. They are supposed to improve metabolic control (as measured by lowering blood glucose) without causing severe hypoglycaemia. Aminomethyl-pyridines have been synthesized, and investigated as potential inhibitors of DPP-4 \[6\]. Hence in the present study DPP4 has been chosen for docking ligands.

The aim of this study is to computer-dock selected cyclitols as ligands to DPP4. Miglitol is an oral anti-diabetic drug that acts by inhibiting the ability of the patient to breakdown complex carbohydrates into glucose. It is primarily used in Type 2 \textit{Diabetes mellitus} for establishing greater glycemic control by preventing the digestion of carbohydrates into monosaccharides which can be absorbed by the body. Similarly 3-hydroxymethyl xylitol has been reported to be a good drug to control blood glucose levels \[7\]. D-pinitol (1D-3-O-methyl-chiroinositol) isolated from the hypoglycemic plant: \textit{Bougainvillea spectabilis} exerts an acute and chronic insulin like antihyperglycemic effect in STZ-diabetic mice via interaction with part of a cellular signaling pathway that links insulin with glucose transport \[8\].

There are few other cyclitols found to show potent anti-diabetic activity and hence in the present study few cyclitols, their modified forms and isomers have been used to dock to DPP4 using Hex 6.1 docking software. \textit{In silico} fragment-based drug design (FBDD) is a relatively new approach inspired by the success of the biophysical fragment-
Recently docking ligands to receptors using rational drug design is on the increase owing to several problems in the conventional methods of drug designing. Many pharmaceutical companies utilize this rational drug designing in the development of new drugs as this computational method is less time consuming.

MATERIALS AND METHODS

**System Used:** Intel® Pentium® 4, 1.80 GHz, 512 MB RAM

**Operating platform:** Microsoft Windows XP Pro 2002 Service Pack 2

Bioinformatics and Cheminformatics tools, biological databases and software were used in the present study. Hex software [9,10] was used for docking studies. PubMed, (www.ncbi.nlm.nih.gov/pubmed), DrugBank, PDB (Protein Data bank) [11] were used.

**Marvin Sketch:** Marvin Sketch is an advanced Java based chemical editor for drawing and editing chemical structures, queries and reactions. The changes in the ligand structures to produce its analogues were made using Marvin Sketch. [12,13]

**PubMed:** Database developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), is designed to provide access to citations from biomedical journals. The literature on diabetes and oral antidiabetic drugs have been collected from this database.

**Protein Data Bank:** The structure of DPP4 which is an essential target for anti-diabetic drug design was retrieved from Protein Data Bank (1PFQ.pdb).

**PDB:** The PDB archive contains information about experimentally-determined structures of proteins, nucleic acids, and complex assemblies. It provides a variety of tools and resources to perform simple and advanced searches based on annotations relating to sequence, structure and function [11,14].

**Hex:** Docking of cyclitols and its analogues to DPP4 was done with HEX Docking software. Their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. Docking is the process of fitting together two molecules in 3-dimensional space. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. The molecules binding to a receptor, inhibit its function, and thus act
as drug. The structures of the cyclitols, their modified forms and isomers, drawn using Marvin sketch were used for docking analysis with Hex software.

Methodology

The parameters used in HEX for the docking process are:

- Correlation type – Shape only
- FFT Mode – 3D fast lite
- Grid Dimension – 0.6
- Receptor range – 180
- Ligand Range – 180
- Twist range – 360
- Distance Range – 40

The cyclitols and its modified forms or isomers were docked to the receptor DPP4 using the above parameters.

Lipinski’s rule of five

The ability to predict the pharmalogical properties of compounds based on their structure is important. There are specific rules that apply to predict activity. Lipinski’s Rule of Five is a refinement of drug-likeness and is used to predict whether a chemical compound will have pharmacological or biological activity as an orally active drug in humans. This rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small, lipophilic molecules \[15\]. The Lipinski "Rule of Five" states that compounds are likely to have good absorption and permeation in biological systems and are more likely to be successful drug candidates if they meet the following criteria:

- five or fewer hydrogen-bond donors
- ten or fewer hydrogen-bond acceptors
- molecular weight less than or equal to 500
- calculated logP less than or equal to 5

Compound classes that are substrates for biological transporters are exceptions to the rule.

The molecular docking studies and Lipinski’s rules facilitate drug development avoiding expensive post clinical experiments.
RESULTS AND DISCUSSION

The various cyclitols and their modified structures (Scheme 1) were docked to the receptor DPP4 (Fig 1) and the energy values computed using Hex (Table 1).

Docking allows one to virtually screen a number of compounds and predict the strongest binders based on scoring functions. It calculates how the receptor and the ligand fit together and dock to each other well. In the present work, drugs like miglitol, vidagliptin, saxagliptin and sitagliptin which are used in the control of type II diabetes were used to dock to DPP4 to produce energy values -161.54, 192.03, 196.05 and 244.0 respectively.

**TABLE 1: DOCKING RESULTS OF 1PFQ WITH PINITOL AND ITS MODIFIED FORMS AND LIPINSKI’S PROPERTIES OF DOCKED LIGANDS**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound docked</th>
<th>Molecular weight</th>
<th>-E value</th>
<th>Log P</th>
<th>H bond donor</th>
<th>H bond acceptor</th>
<th>Molar refractivity</th>
<th>No.of criteria met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule</td>
<td>Value to be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Valienol</td>
<td>104.07</td>
<td>122.15</td>
<td>1.75</td>
<td>0</td>
<td>4</td>
<td>40-130</td>
<td>At least 3</td>
</tr>
<tr>
<td>2</td>
<td>Conduritol</td>
<td>148.16</td>
<td>128.47</td>
<td>-1.94</td>
<td>4</td>
<td>4</td>
<td>33.46</td>
<td>4</td>
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<tr>
<td>3</td>
<td>Inositol</td>
<td>180.16</td>
<td>139.03</td>
<td>-3.78</td>
<td>6</td>
<td>6</td>
<td>35.77</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>L –Pinitol</td>
<td>194.18</td>
<td>140.09</td>
<td>-3.14</td>
<td>5</td>
<td>6</td>
<td>40.53</td>
<td>All</td>
</tr>
<tr>
<td>5</td>
<td>D-Pinitol</td>
<td>194.18</td>
<td>141.16</td>
<td>-3.14</td>
<td>5</td>
<td>6</td>
<td>40.53</td>
<td>All</td>
</tr>
<tr>
<td>6</td>
<td>Iso inositol</td>
<td>180.16</td>
<td>141.36</td>
<td>-3.78</td>
<td>6</td>
<td>6</td>
<td>35.77</td>
<td>4</td>
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<tr>
<td>7</td>
<td>Pinitol S</td>
<td>194.18</td>
<td>142.21</td>
<td>-3.14</td>
<td>5</td>
<td>6</td>
<td>40.53</td>
<td>All</td>
</tr>
<tr>
<td>8</td>
<td>Methyl myoinositol</td>
<td>194.18</td>
<td>143.18</td>
<td>-3.14</td>
<td>5</td>
<td>6</td>
<td>40.53</td>
<td>All</td>
</tr>
<tr>
<td>9</td>
<td>Dimethoxytetrol</td>
<td>208.21</td>
<td>144.66</td>
<td>-2.5</td>
<td>4</td>
<td>6</td>
<td>45.28</td>
<td>All</td>
</tr>
<tr>
<td>10</td>
<td>Ethoxypinitol</td>
<td>208.21</td>
<td>145.24</td>
<td>-2.78</td>
<td>5</td>
<td>6</td>
<td>45.27</td>
<td>All</td>
</tr>
<tr>
<td>11</td>
<td>Quebrachitot</td>
<td>194.18</td>
<td>146.16</td>
<td>-3.14</td>
<td>5</td>
<td>6</td>
<td>40.53</td>
<td>All</td>
</tr>
<tr>
<td>12</td>
<td>Modified pinitol</td>
<td>184.18</td>
<td>148.91</td>
<td>-3.79</td>
<td>6</td>
<td>6</td>
<td>40.66</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>Dulcitol</td>
<td>182.17</td>
<td>154.26</td>
<td>-3.73</td>
<td>6</td>
<td>6</td>
<td>38.40</td>
<td>3</td>
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<tr>
<td>14</td>
<td>Quebrachitot diacetonide</td>
<td>274.31</td>
<td>187.56</td>
<td>0.27</td>
<td>1</td>
<td>6</td>
<td>64.94</td>
<td>All</td>
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<tr>
<td>15</td>
<td>Pinitol diacetonide</td>
<td>274.31</td>
<td>200.62</td>
<td>0.27</td>
<td>1</td>
<td>6</td>
<td>64.94</td>
<td>All</td>
</tr>
<tr>
<td>16</td>
<td>Miglitol</td>
<td>207.22</td>
<td>161.54</td>
<td>-3.19</td>
<td>5</td>
<td>6</td>
<td>48.16</td>
<td>All</td>
</tr>
<tr>
<td>17</td>
<td>Vidaagliptin</td>
<td>303.40</td>
<td>192.03</td>
<td>-0.22</td>
<td>2</td>
<td>5</td>
<td>82.00</td>
<td>All</td>
</tr>
<tr>
<td>18</td>
<td>Saxagliptin</td>
<td>315.41</td>
<td>196.05</td>
<td>-0.88</td>
<td>3</td>
<td>5</td>
<td>83.99</td>
<td>All</td>
</tr>
<tr>
<td>19</td>
<td>Sitagliptin</td>
<td>407.31</td>
<td>244.00</td>
<td>1.26</td>
<td>2</td>
<td>5</td>
<td>87.49</td>
<td>All</td>
</tr>
</tbody>
</table>
Scheme 1

Valienol
Conduritol
Inositol
L Pinitol
D Pinitol
Iso inositol
Pinitol S
Methyl myoinositol
Dimethoxytetrol
Ethoxypinitol
Quebrachitol
Modified Pinitol
Dulcitol
Quebrachitol diacetonide
Pinitol diacetonide
The docking of miglitol and vidagliptin to the receptor is given in Figures 2 and 3. It is seen from the results that the cyclitols have decreased energy than that of the drugs which are available for lowering blood sugar levels. This is due to the better binding of the compounds with DPP4. The compound pinitol diacetonide was found to be more compatible with DPP4 compared to the other compounds studied as evident from its E value of -200.62. This may be due to the lesser number of H bond donors in the drug.

Drug-likeness (http://en.wikipedia.org) is a qualitative concept used in drug design for how drug-like a substance is. An effective drug should have optimal solubility in both water and fat. Orally administered drugs must pass through the intestinal lining and be transported in aqueous blood, then penetrate the lipid cellular membrane to reach the inside of a cell. The model compound for cellular membrane is octanol and the logarithm of the octanol/water partition coefficient, known as log \( P_{ow} \), is used to estimate solubility. Since the drug is transported in an aqueous media like blood and intracellular fluid, it has to be sufficiently water-soluble. Solubility in water can be estimated from the
number of hydrogen bond donors vs. the alkyl side chains in the molecule. Low water solubility translates to slow absorption and action. Too many hydrogen bond donors, on the other hand, leads to low fat solubility, so the drug cannot penetrate the cell wall. The lower the molecular weight, the better it is preferred. These have been the basis of Lipinski’s rule. The Lipinski’s properties calculated are summarized in Table 1. It is seen from the results that all the compounds adhere to at least 3 criteria for potent inhibitors. The compound 15 namely, pinitol diacetonide which showed decreased energy value was found to obey all the criteria, substantiating its usefulness in drug chemistry. The results also reveal that the lead molecule, the one with the maximum interaction having high negative E value for the receptor DPP-4 among the studied cyclitols is pinitol diacetonide.

![Figure 1] Structure of DPP4 receptor

![Figure 2] Binding of Miglitol to DPP4

![Figure 3] Binding of Vidagliptin to DPP4 receptor
CONCLUSION

Fifteen compounds and three drugs already available in the market have used in the present work to calculate the strongest binders based on scoring functions using Hex docking software. How well the receptor and ligand fit to each other has been calculated. Compared to the drugs the few cyclitols and its derivatives or modified forms or isomers were found to show good compatibility with the receptor owing to its strong binding with the receptor. Calculation of Lipinski’s properties showed that most of the compounds followed all criteria. The cyclitols are computed to be good anti diabetic agents. Such studies reduce the time and costs involved in drug discovery process and have no adverse effect on the environment.

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REFERENCES


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