Research Article

Molecular Modeling Study of the Interaction and Affinity of DPP-4 (DipeptidylPeptidase-4) by Inhibitors whichare involvedin Type 2 Diabetes

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ABSTRACT

Molecular modeling techniques are widely used in chemistry, biology and the pharmaceutical industry. Most existing drugs to target enzymes. This theoretical approach predicts the mode of interaction of a ligand with its receptor. Inhibition of DPP-4 is an important approach in the treatment of disease in type 2 diabetes. Several inhibitors have already been identified, but their affinity is insufficient to consider a drug development. High-affinity inhibitors are used to inhibitDPP-4a slinagliptin (BI1356), sitagliptin (Januvia), vildagliptin, saxagliptin and alogliptin the but as adjuvant therapy for the treatment of diabetes Type 2. It is for this purpose that molecular modeling techniques grouped under the "docking" or "docking" molecular were developed. The results obtained in this work, have the inhibitionofDPP-4bymolecular modeling methods. The introduction of bulky groups causes a conformational rearrangement in the pocket of the active site that will probably best lengthened by complementary and therefore the activity. The results obtained in this study, by the methods of molecular modeling have been elucidated, allowing us to conclude that linagliptin (BI1356) has better inhibition of DPP-4. In conclusion, linagliptin (BI1356) inhibits DPP-4effectively than vildagliptin, sitagliptin, saxagliptin and alogliptin. Linagliptin (BI1356) has the potential to be the best inhibitor ofDPP-4in the treatment of type 2 diabetes.

Keywords: DPP-4, type 2 diabetes, molecular modeling (molecular docking).

INTRODUCTION

Diabetes is a metabolic disease that poses a major public health problem causing every year nearly four million deaths worldwide[1].

Type 2diabetes isa disease of the general metabolism of carbohydrates, fats and proteins characterized by an abnormal increase in the level of sugar in the blood (hyperglycemia). This condition is due to a defect in insulin secretion, its action, or both conjugates[2].

Hyperglycemia is most often associated with more or less external symptoms suggestive of disease severity. In addition to acute complications (hyperglycemia, keto acidosis, hyperosmolarsyndrome), hyperglycemia degenerates on more or less severe degenerative complications.[3, 4]

New approaches that are coming in full light, in recent years on the market. They use as target GLP1 (glucagon-like peptide-1). It is a digestive hormone helping the body to normalize blood glucose only when the latter rises. However, the half-life of this hormone is very short due to its degradation by an enzyme: dipeptidylpeptidase-4 (DPP-4) thus making its potential as a therapeutic agent extremely reduced.

To overcome this obstacle, two therapeutic strategies have been adopted: firstly, the development of injectable exogenous analogues of GLP-1 resistant to the action of DPP-4 and secondly, the use of oral medications selectively is blocking the DPP-4 to extend the endogenous GLP-1 half-life.[5, 6]

It is in this new approach to treatment of type 2 diabetes by inhibiting DPP-4, we are interested in this work. The DPP-4 is small molecules that selectively inhibit DPP-4 contributing significantly to normalize blood sugar with very few side effects[7].

MATERIALS AND METHODS

Dipeptidyl peptidase protein-4 (DPP-4)

DPP-4 is the short name for an enzyme called dipeptidylpeptidase-4, two broken intestinal hormones called incretins. The incretins are produced in the intestine when food is consumed, and they stimulate insulin secretion, which lowers glucose levels in the blood. In the disease known under the name of type 2 diabetes, there is not enough insulin, or it is less effective, and blood glucose levels rise. Drugs to treat type2 diabetes have been developed that inhibit DPP-4, preventing the degradation of incretin and extend the insulin secretion, thus increasing its effect[8].

The download Dipeptidyl peptidase-4 was performed from the database Book haven Protein Data Bank (access code 3F8S). The three dimensional structure of Dipeptidyl Peptidase-4 was obtained by X-ray diffraction with a resolution (2.43 Å)[9].

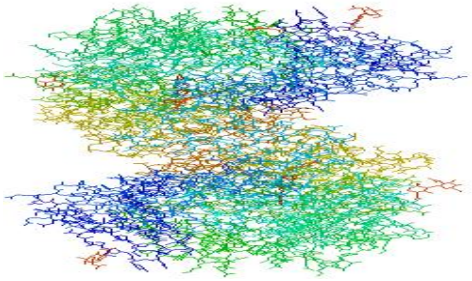

Figure 1: Structure ofDipeptidylpeptidase-4 (3F8S)

Inhibitors

We have chosen to inhibition of DPP-4 inhibitors of linagliptin (BI1356) Sitagliptin (januvia) Vildagliptin, Saxagliptin and alogliptin) that are involved in the disease of type 2 diabetes [10].

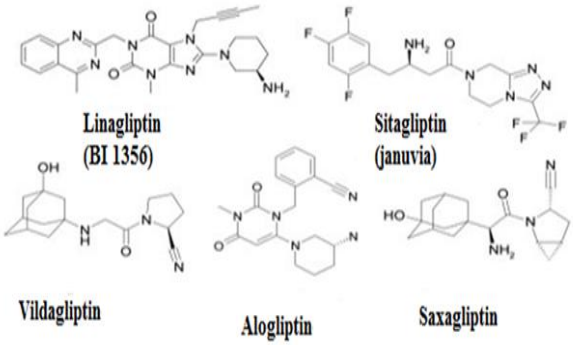

Figure 2: The five inhibitors studied

Methods

Protein processing

The protein to be used should first be processed. Thus, treating a protein, it performs the following steps: - Download of proteins from the data base Book haven Protein Data Bank (3F8S)[9].

- Remove the water molecules to the protein stability. - Eliminating certain residues, those not involved in the catalytic reaction of the enzyme.

- Eliminate co-crystallization of molecules to achieve a simplified model.

- Identify the active site of each protein.

Construction of ligands

The ligands used in this work are drawn with the Hyperchem 8 software, taking into account the hybridization state of each atom and the type of bond, double or triple. A step of optimization of the geometry becomes necessary. For this, we applied the semi-empirical method (AM1)[11]. The molecules thus obtained are recorded with bpsormol.

Molecular Docking and complex construction

The next step after the construction of ligands, and the positioning of these molecules in the active site of the enzyme (3F8S). For this, we used the module Auto dock V in a using the UCSF Chimera 1.10 software[12], the receptor-ligand complex is formed, it will adapt to the most stable conformation, i.e. with the lowest energy level.

RESULTS AND DISCUSSION

We conducted a series for each docking inhibitors, a number of poses called conformations are generated (9 poses for each complex).

The visualization of the results of molecular docking performed with five inhibitors shows that the ligands are properly positioned in the active site of DPP-4; they have perfects partial conformations (Figure 3).

Figures 3: Molecular Docking and training of five complexes

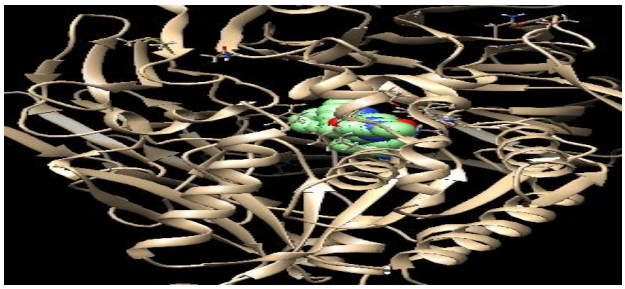

Figure a: Complex1 (3F8S+BI1356)

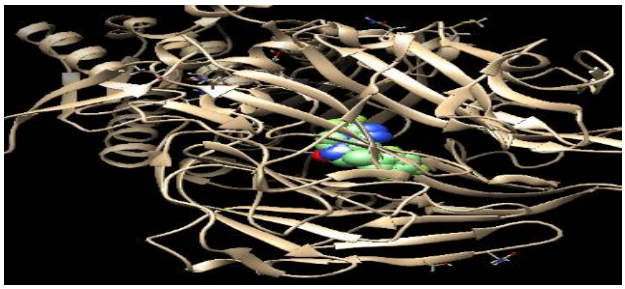

Figure b: Complex 2 (3F8S+Januvia)

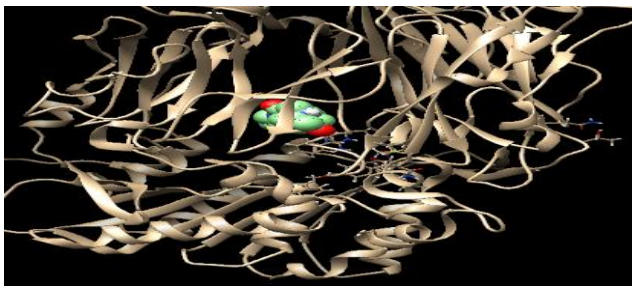

Figure c: Complex 3(3F8S+vildagliptin)

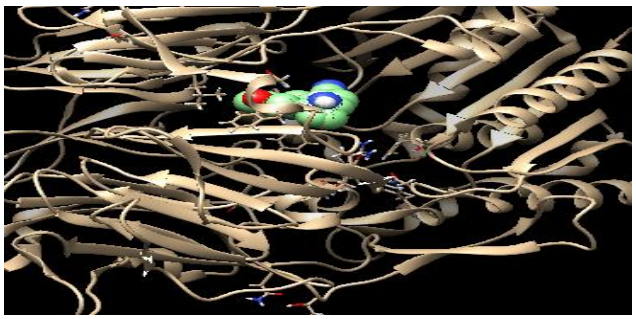

Figure d: Complex 4 (3F8S+alogliptin)

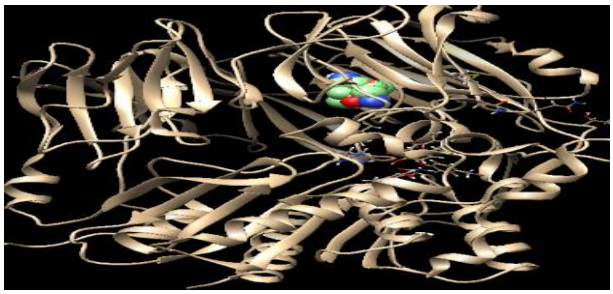

Figure e: Complex 5 (3F8S+Saxagliptin)

The results of the interaction energies obtained by the Chimera program are in the form of list energy (free energy change ΔG), the latter is correlated with the dissociation constant K_d of the same complex according to the following formula:

$$\Delta G = RT.LnK_d$$

With :ΔG, the change in free energy expressed in en K.cal.mol^{-1} ; R the gas constant (1.937 cal.mol^{-1}K^{-1}); T the temperature in Kelvin (298K) and K_d the dissociation constant of the receptor-ligand complex[13].

The IC_{50} values are determined experimentally in the literature by in vitro assays[10].

The following table summarizes the values of ΔG, IC_{50}, LogIC_{50} and K_d

Complexes	IC_{50} (nM)	LogIC_{50}	K_d	ΔG (Kcal/mol)
Complex 1	1	0	2.11 10^{-8}	- 10.2
Complex 2	19	1.278	47.86 10^{-8}	- 8.4
Complex 3	62	1.792	80.48 10^{-8}	- 8.1
Complex 4	24	1.380	8.46 10^{-8}	- 9.4
Complex 5	50	1.698	56.91 10^{-8}	- 8.3

When the value of the variation of free energy ΔG decreases, the dissociation constant K_d of the complex decreases proportionately, which informs about the increase in the affinity of the ligand to the receptor[13].

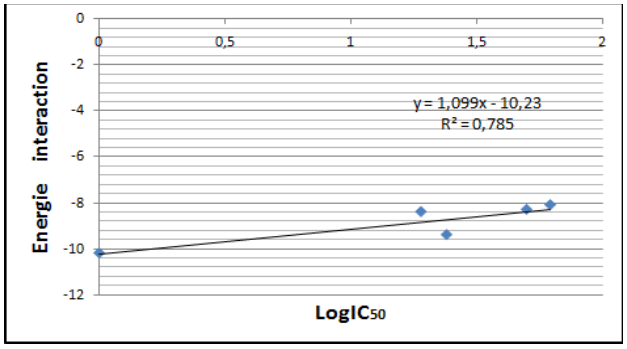

Figure 4: Correlation between the biological activity (LogIC_{50}) of the five ligands and their interaction energywithDPP-4

Linear regression analysis performed between the interaction energies and the IC_{50} (LogIC_{50}) provides a scatter plot (Figure 4) with a correlation coefficient equal to **0.785**. This value indicates that the two variables are highly correlated and thus demonstrates the high performance program Chimera[14, 15].

-The simulation performed by Chimera has allowed us to evaluate the interaction energy between linagliptin (BI1356), and DPP-4, this energy has estimated-10.2Kcal/Mol is significantly correlated to the inhibitory activity linagliptin (IB1356) with 1 nM IC_{50} is the strongest inhibitory activity.

-Modeling the interaction energy between Sitagliptin (januvia) and DPP-4gives an order of score-8.4Kcal/Mol. The theoretical determination of IC_{50} 19nM indicates that the inhibitory activity of this compound is average.

-The energy of interaction between vildagliptin and DPP-4 gives a score of -8.1Kcal/Mol. The theoretical determination of IC_{50} 62nM indicates that the inhibitory activity of this compound is relatively very low[16].

-L'énergie Interaction between alogliptin and DPP-4 gives as core around-9.4 Kcal/Mol. The theoretical value of IC_{50} 24nM indicates that the inhibitory activity of this compound is high.

-The energy of interaction between saxagliptin and DPP-4 gives a score of-8.3Kcal/Mol. The theoretical determination of IC_{50} 50 nM indicates that the inhibitory activity of this compound is relatively low [16].

- These results showed that the 1hasthelowest energy (-10.2 Kcal/mol) is more active than complex 4(-9.4 Kcal/mol), more active than complex 2(-8.4 Kcal/mol) more active than complex 5(-8.3 Kcal/mol), more active than complex 3(-8.1Kcal/mol) [17].

-The calculation of the dissociation constant has allowed us to confirm the affinity of the ligand for the receptor1, followed by the ligand4for the receiver.

CONCLUSION

The study of molecular docking with Chimera allowed us to check and complete the experimental data DPP4 inhibitors of the five molecules studied the 1 linagliptine compound (IB 1356), is considered the most potent inhibitor of DPP-4 characterized by the lower value of1 nM IC_{50} and lower energy interaction-10.2Kcal/Mol,

followed by the compound 4 alogliptin with an IC_{50} 24nM and interaction energy of-9.4Kcal/Mol.

The results of the dissociation constant obtained confirm the high affinity of these two compounds (linagliotine and alogliptin) fortheDPP-4.

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