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Design of New Inhibitors of Dipeptidyl Peptidase-4 in Type 2 Diabetes by Computer Simulations

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ABSTRACT

The techniques of molecular modelling are widely used in chemistry, biology and the pharmaceutical industry. Most current drugs target enzymes. This theoretical approach allows us to predict the mode of interaction of a ligand with its receptor. Inhibition of Dipeptidyl Peptidase-4 "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 any of them being a pharmacological development. High-affinity inhibitors are used to inhibit DPP-4 as Linagliptin, Sitagliptin, Vildagliptin, Saxagliptin and Alogliptin but also as an adjuvant therapy for the treatment of Type 2 diabetes. It is for this purpose that molecular modelling techniques like docking and molecular dynamics have been developed. The results obtained in this work show the inhibition of DPP-4 by molecular modelling methods. The introduction of bulky groups causes a conformational rearrangement in the pocket of the active site that will probably be strengthened by the complementarity and therefore the activity increases. The results obtained in this study, by methods of molecular modelling which have been elucidated, allowed us to conclude that Linagliptin is a better inhibitor of DPP-4 than Sitagliptin, Vildagliptin, Saxagliptin and Alogliptin. Linagliptin has the potential to be the best inhibitor of DPP-4 in the treatment of Type 2 diabetes based on molecular modeling interaction.

Keywords: DPP-4, Type 2 diabetes, Inhibitor, Molecular docking, Molecular dynamics simulations

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INTRODUCTION

Diabetes is a metabolic disease that poses a major problem to public health, with it causing nearly four million deaths each year worldwide [1]. Type 2 diabetes is a condition of the general metabolism of carbohydrates, fats and proteins characterized by an abnormal increase in sugar levels in the blood (hyperglycemia). This condition is due to defective insulin secretion, itsinaction, or both combined [2]. Hyperglycemia is most often associated to more or less evocative external symptoms of disease severity. In addition to acute complications (hyperglycemia, ketoacidosis, hyperosmolar syndrome), hyperglycemia degenerates on more or less severe degenerative complications [3,4]. New approaches coming in full light are, for some years, on the market. They target Glucagon-like peptide-1 "GLP1". It is a digestive hormone helping the body to normalize blood glucose levels when it rises abnormally. However, the half-life of this hormone is very short due to its degradation by an enzyme: DPP-4 thus making its potential as a therapeutic agent considerably less. To work around this obstacle, two strategies have been adopted: firstly, the injectable exogenous development of analogues of GLP-1 resistant to the action of DPP-4, and secondly the use of oral medications that selectively block DPP-4 to extend the endogenous GLP-1 half-life [5,6]. We are interested in the latter, newer approach, aiming to treat Type 2 Diabetes by inhibiting DPP-4. DPP-4 is a relatively small molecule: therefore selectively inhibiting DPP-4 contributes significantly to normalize blood glucose levels with very few side effects [7].

MATERIALS AND METHODS

Dipeptidyl peptidase-4 (DPP-4) protein

DPP-4 consists of two broken intestinal hormones called incretins. The incretins are produced in the gut when food is consumed, and they stimulate insulin secretion, which lowers glucose levels in the blood. DPP-4 is an N-terminal dipeptidyl exopeptidase which comes as both a membrane-bound protein and as a soluble protein in plasma. Low-molecular weight inhibitors of DPP-4 have been investigated for many years. DPP-4 inhibitors lower blood glucose, improve glucose tolerance and ameliorate insulin response to glucose associated with patients in type 2 diabetes. Medicines to treat Type 2 diabetes have been developed that inhibit DPP-4, preventing the degradation of incretin and prolong insulin secretion, increasing its effect (Figure 1) [8].

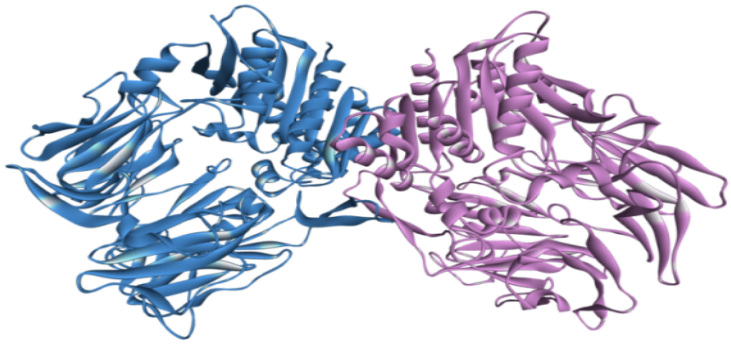


Figure 1: Structure of DPP-4 (3F8S)

DPP-4 was downloaded from the database Bookhaven 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].

Inhibitors of DPP-4

The following DPP-4 inhibitors Linagliptin, Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin that are used to treat type 2 diabetes were selected for the study which were previously compared in a similar study (Figure 2) [10].

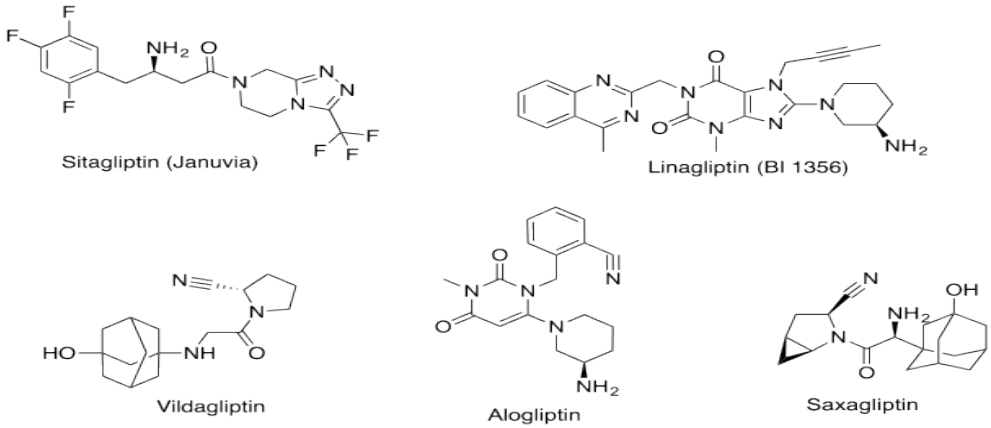


Figure 2 : DPP-4 inhibitors

METHODS

Treatment of protein

The protein to be used should be first processed using the following steps:

- Downloading proteins from the database Bookhaven Protein Data Bank (3F8S) [9].

- Removeng the water molecules to stabilise the protein.

- Eliminating Co-crystallisation of molecules to achieve a simplified model.

- Identifying the active site of the protein.

Construction of ligands

The ligands used in this work are drawn with Hyperchem8 software. A step of optimising the geometry becomes necessary. For this, we applied the semi-empirical method (AM1) [11]. The molecules thus obtained are recorded with pdb or mol.

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 GOLD [12] software, the ligand-receptor complex is formed, it will adapt to the most stable conformation, i.e., the one with the lowest energy level.

RESULTS AND DISCUSSION

Resultats energies

Molecular docking was performed to find the likely binding sites in the enzyme structure by exploring each ligand. Different configuration of inhibitors moored to the DPP-4 has been shown in yellow. The affinity range of configurations of different ligands was obtained for comparison purposes.

These results revealed that complex 2 has the lowest energy (-5.8 kcal/mol) compared to complex 4 (-5.7 kcal/mol), which is more active than complex 5 (-5.3 kcal/mol) and complex 1 (-5.2 kcal/mol) and finally complex 3 (-5.1 kcal/mol) [13].

The flexible molecular docking was performed for docking inhibitors Scoring and Minimisation with AutoDock Vina "SMINA" of the two subunits of the DPP-4 enzyme by using the "GOLD" programme [14].

Figures 3 and 4; Table 1 shows the interactions and key residues involved in the binding of the optimum configurations. Table 1 compares the interactions of the various ligands with subunits A and B. Due to the similarity of both subunits; we will be looking at the interactions with subunit A as a representative of DPP-4 inhibition.

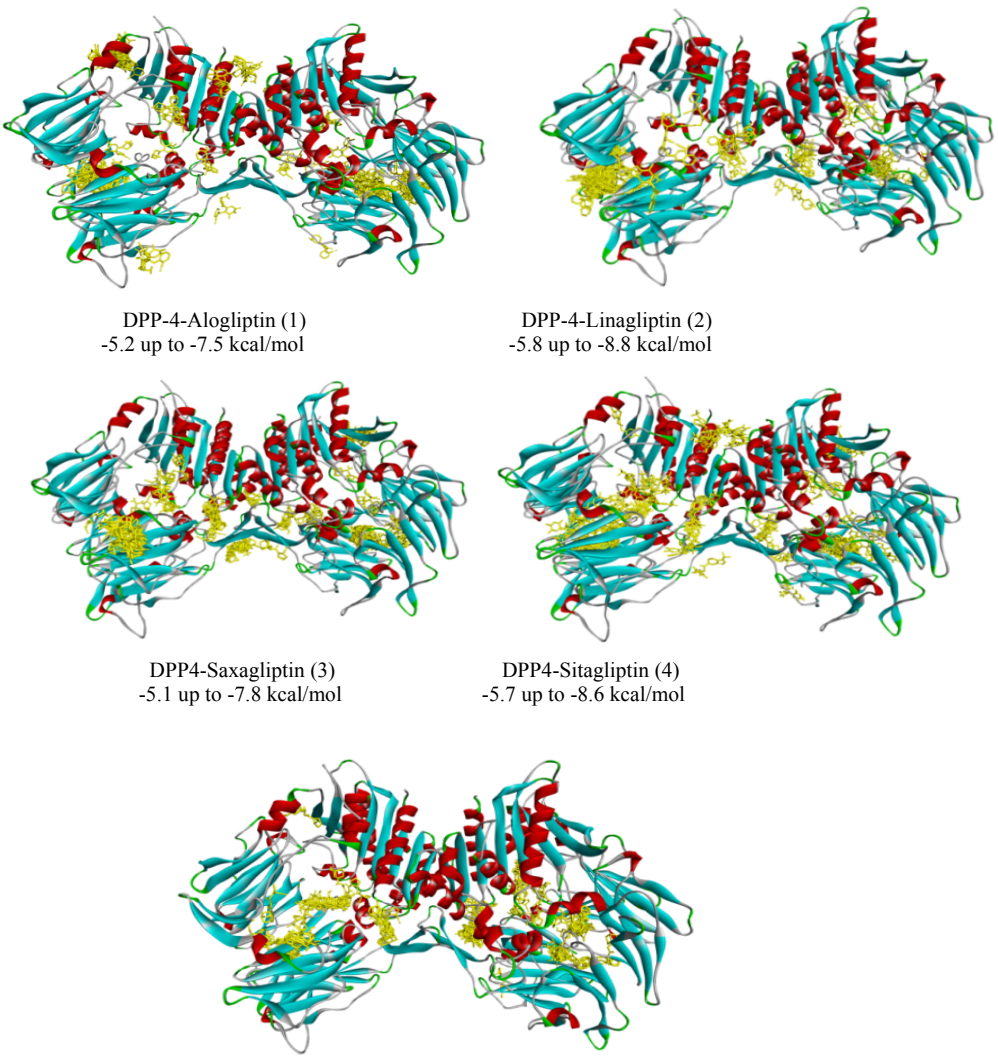


Figure 3: Training of five complexes. DPP4-Vildagliptin (5) -5.3 up to -7.5 kcal/mol

Table 1: Scores first and energies of the ten best configurations in each sub-unit of the ligands

GOLD Dock		Subunit A		Subunit B	
Inhibitor	**Pose**	**Score**	**ΔG (kcal/mol)**	**Score**	**ΔG (kcal/mol)**
Alogliptin	1	24.2833	-27.4694	28.7907	-32.3351
	2	24.1473	-26.4602	25.6575	-29.6252
	3	22.515	-24.641	25.0776	-29.6319
	4	22.4706	-24.6843	24.6586	-28.2412
	5	21.8998	-27.3105	24.593	-27.8472
	6	21.3756	-24.0187	24.5284	-27.1429
	7	21.2324	-24.2125	24.3619	-30.7246
	8	21.049	-23.2733	21.9342	-24.1572
	9	20.4129	-23.3047	21.0769	-23.7653
	10	19.7975	-22.1733	19.7646	-23.1044
Linagliptin	1	28.2722	-32.7574	28.7251	-31.6731
	2	26.8367	-30.6977	27.9524	-32.92
	3	26.4032	-29.8275	26.7342	-30.032
	4	26.2052	-31.6235	25.1695	-29.1058
	5	26.1985	-28.4223	24.8875	-27.4681
	6	26.0207	-28.1417	24.5765	-26.6135
	7	25.545	-26.862	23.8981	-26.651
	8	25.0193	-28.5349	23.2427	-29.3263
	9	24.1693	-27.2149	22.7775	-29.0569
	10	23.0544	-25.0351	19.869	-21.891
Saxagliptin	1	18.45	-23.635	20.8745	-35.039
	2	18.1415	-24.0851	18.6849	-30.4527
	3	17.2761	-25.2972	18.4761	-27.1952
	4	16.9608	-24.1166	18.0928	-24.4242
	5	16.6856	-23.3534	17.8877	-26.3579
	6	16.2364	-22.2317	17.5671	-23.6264
	7	16.2027	-23.9342	17.4301	-24.3478
	8	15.7268	-22.9351	17.2628	-25.4686
	9	15.1668	-27.0645	17.0553	-24.0509
	10	15.1369	-21.7267	16.0404	-23.5718
Sitagliptin	1	20.7784	-23.2586	18.6236	-21.7163
	2	20.5068	-23.8304	18.5445	-21.2497
	3	20.2044	-22.2315	17.4931	-19.4522
	4	18.6215	-20.1657	16.7882	-23.3579
	5	18.4644	-24.8575	16.679	-19.4241
	6	17.2034	-19.3484	16.0987	-18.2694
	7	16.636	-18.6934	16.0786	-17.6279
	8	16.2925	-22.4862	15.9459	-18.7672
	9	15.954	-19.0062	15.711	-22.0504
	10	14.7677	-16.3363	14.6111	-17.7776
Vildagliptin	1	20.8674	-24.5488	19.9771	-24.886
	2	20.7926	-24.271	18.8996	-23.4751
	3	19.8731	-23.7655	18.8895	-24.095
	4	19.7862	-23.8709	18.854	-23.1711
	5	19.5386	-29.3869	18.6019	-22.9466
	6	19.2019	-22.8798	18.3059	-21.6862
	7	19.1024	-23.0849	17.961	-24.862
	8	18.3083	-23.2181	17.7288	-23.4625
	9	18.2478	-22.4864	17.5509	-22.0521
	10	17.4971	23.9798	15.6392	-19.8865

Distance and visual analysis of interactions

Our results are supplemented by visual analysis of the interaction of each molecule with DPP-4. We measured the distances between the inhibitors and amino acids that constitute the active site. The measured distances varies, interactions between 2.5 Å and 3.1 Å are considered high and those between 3.1 Å and 3.55 Å are supposed to be average. Interactions greater than 3.55 Å are weak (Figure 5 and Table 2) [15].

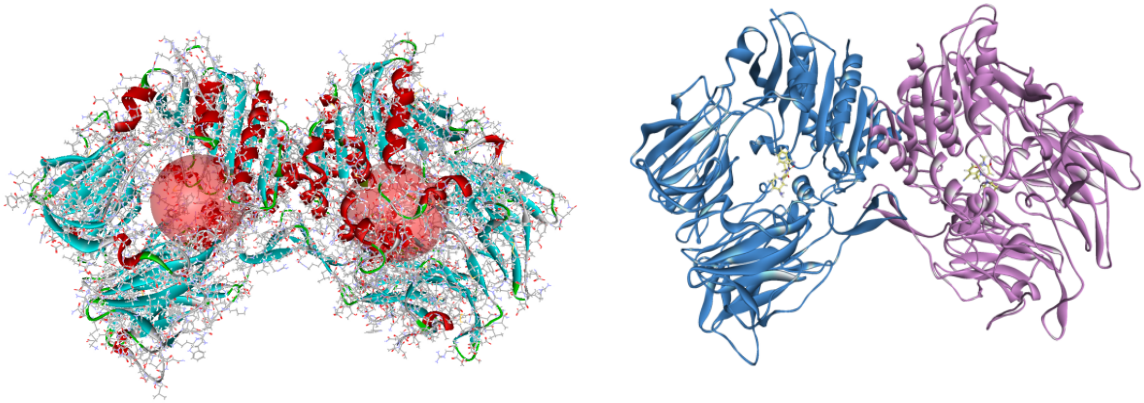


Figure 4: Complex formation in each subunit

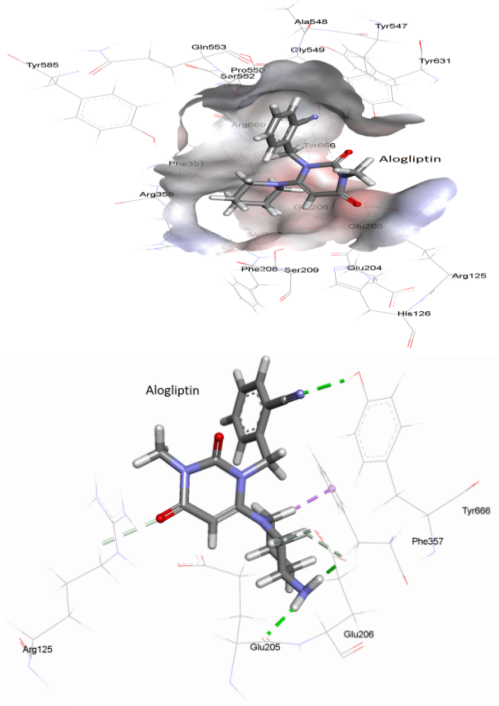


Figure 5: Points of interaction and orientation of alogliptin in the active site of DPP-4

Table 2: Distances and interactions of alogliptin with DPP-4 active site

DPP4-Alogliptin; atoms		Distance	Category	Type
Tyr666:HH	Alogliptin:N9	2.16486	Hydrogen Bond	Conventional Hydrogen Bond
Alogliptin:H37	Glu206:OE1	1.78679	Hydrogen Bond	Conventional Hydrogen Bond
Alogliptin:H38	Glu205: O	2.12623	Hydrogen Bond	Conventional Hydrogen Bond
Arg125:HD2	Alogliptin:O14	2.81983	Hydrogen Bond	Oxygen Hydrogen Bond
Alogliptin:H29	Glu206:OE1	2.61532	Hydrogen Bond	Oxygen Hydrogen Bond
Alogliptin:H30	Glu206:OE2	2.61598	Hydrogen Bond	Oxygen Hydrogen Bond
Alogliptin:H34	Phe357	2.31898	Hydrophobic	Pi-Sigma

We observe the presence of six non-covalent hydrogen bonds formed between alogliptin and the amino acids in the active site of DPP-4 in addition to one hydrophobic interaction. The first hydrogen bond is observed between tertiary amine N9 and hydrogen in Tyr666 hydroxyl residue (Alog-N9 ... H-Tyr666; d=2.16486 Å). H37 interacts withOxygen-E1 in Glu206 (Alog-H37 ... O-Glu206; d=1.78679 Å). A third hydrogen bond is formed between the H38 and Oxygen in Glu205 (Alog-H38 ... O-Glu205; d=2.12623 Å). One more hydrogen bond is observed between the O14 in the amide group and the hydrogen residue in Arg125 (Alog-O14 ... H-Arg125; d=2.81983 Å). The other hydrogen bond is seen between the H29 group and the oxygen-E1 residue in Glu206 (Alog-H29 ... O-Glu206; d=2.61532 Å). The last hydrogen bondis formed between H30 group and the oxygen OE2 in Glu206 (Alog-H30 ... O-Glu206; d=2.61598 Å). Finally Alogliptin is stabilised by a hydrophobic interaction formed by the Phe357 residue and the hydrogen's of the secondary carbon in aminopiperidine ring of alogliptin (Figure 6 and Table 3).

We observe four hydrogen bonds formed by hydrogen's 48, 44, 60 and 62 of linagliptin. The first hydrogen bond is observed between the H62 and O in Gln553 (Linag-H62 ... Gln553; d=1.97445 Å). H44 has a second hydrogen bond with O-Glu206 (Linag-H44 ... O-Glu206; d=3.0248 Å). A third hydrogen bond is formed between the H60 and an O Tyr585 (Linag-H60 ... O-Tyr585; d=2.38776

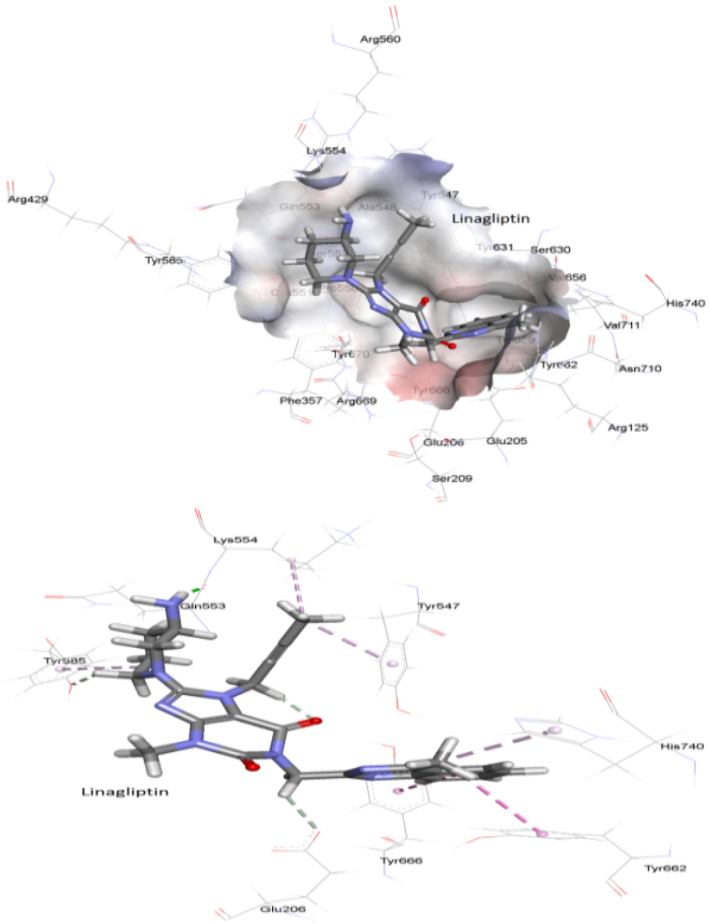


Figure 6: Link mode and Linagliptin orientation in the active site of the DPP-4

Table 3: Linagliptin distances and interactions with the active site of the DPP-4

DPP4-Linagliptin; atoms		Distance	Category	Type
Linagliptin:H62	Gln553: O	1.97445	Hydrogen Bond	Conventional Hydrogen Bond
Linagliptin:H44	Glu206:OE2	3.0248	Hydrogen Bond	Carbon Hydrogen Bond
Linagliptin:H48	Linagliptin:O21	2.44889	Hydrogen Bond	Carbon Hydrogen Bond
Linagliptin:H60	Tyr585:OH	2.38776	Hydrogen Bond	Carbon Hydrogen Bond
Tyr662	Linagliptin	4.38016	Hydrophobic	Pi-Pi Stacked
Tyr666	Linagliptin	4.3712	Hydrophobic	Pi-Pi T-shaped
Linagliptin:C28	Lys554	5.42691	Hydrophobic	Alkyl
Tyr547	Linagliptin:C28	3.84795	Hydrophobic	Pi-Alkyl
Tyr585	Linagliptin	4.86534	Hydrophobic	Pi-Alkyl
His740	Linagliptin:C11	4.10283	Hydrophobic	Pi-Alkyl

Å). There is also an internal H-bond formed between H48 and O21 of the xanthine. Finally Linagliptin is stabilised by hydrophobic interactions formed by residues Tyr662, Tyr666, Lys554, Tyr547, Tyr585 and His740 (Figure 7 and Table 4).

We observe the presence of three non-covalent hydrogen bonds formed between saxagliptin and amino acids in the active site of DPP-4 in addition to hydrophobic interactions. The first hydrogen bonding was observed between O4 oxygen and hydrogen in the Lys554 residues (Saxa-O4 ... H-Lys554; d=2.46342 Å). A second hydrogen bond is formed between oxygen and hydrogen in the O4 Lys554 residues (Saxa-O4 ... H-Lys554; d=2.42285 Å) .a third hydrogen bonding is observed between the oxygen in the residue Gln553 and hydrogen H48 (Saxa-H48 ... O-Gln553; d=1.78317 Å). Finally Saxagliptin is stabilised by hydrophobic interactions formed by the residues Lys554, Tyr547 and Trp629 (Figure 8 and Table 5).

We observe the presence of seven hydrogen bonds formed between sitagliptin and amino acids in the active site of DPP-4 in addition to hydrophobic interactions. The first hydrogen bonding was observed between F9 fluorine and hydrogen in the Arg125 residues (Sita-F9...H-Arg125; d=2.54763 Å). A second hydrogen bond is formed between hydrogen H36 and oxygen OE2 in Glu206 residues (Sita-H36... O-Glu206; d=1.99329 Å) .a third hydrogen bonding was observed between oxygen OE2 in Glu205 residues and hydrogen H37 (Sita-H37... O-Glu205; d=2.06458 Å) a fourth bond is formed between HB1 hydrogen in the residues Ser552 and the nitrogen N22 (Sita-N22 ... HB1-Ser552; d=2.6533 Å). The fifth hydrogen bond formed between HB2 in Ser552 residues and nitrogen N22 (Sita-N22 ... HB2-Ser552; d=2.91259 Å) .a sixth hydrogen bond formed in sitagliptin between H40 and F27

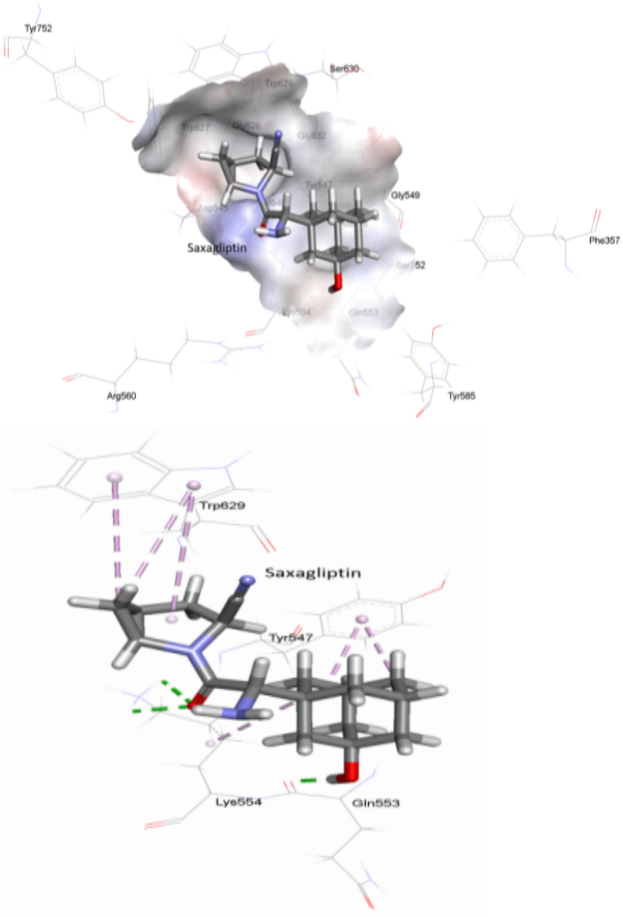


Figure 7: Connection mode and orientation of saxagliptin in the active site of the DPP-4

Table 4: Saxagliptin distances and interaction with the active site of the DPP-4

DPP4-Saxagliptin; atoms		Distance	Category	Type
Lys554:HZ2	Saxagliptin:O4	2.46342	Hydrogen Bond	Conventional Hydrogen Bond
Lys554:HZ3	Saxagliptin:O4	2.42285	Hydrogen Bond	Conventional Hydrogen Bond
Saxagliptin:H48	Gln553: O	1.78317	Hydrogen Bond	Conventional Hydrogen Bond
Saxagliptin	Lys554	5.49211	Hydrophobic	Alkyl
Tyr547	Saxagliptin	3.68343	Hydrophobic	Pi-Alkyl
Tyr547	Saxagliptin:C16	3.6753	Hydrophobic	Pi-Alkyl
Trp629	Saxagliptin	5.4418	Hydrophobic	Pi-Alkyl
Trp629	Saxagliptin:C10	5.12641	Hydrophobic	Pi-Alkyl

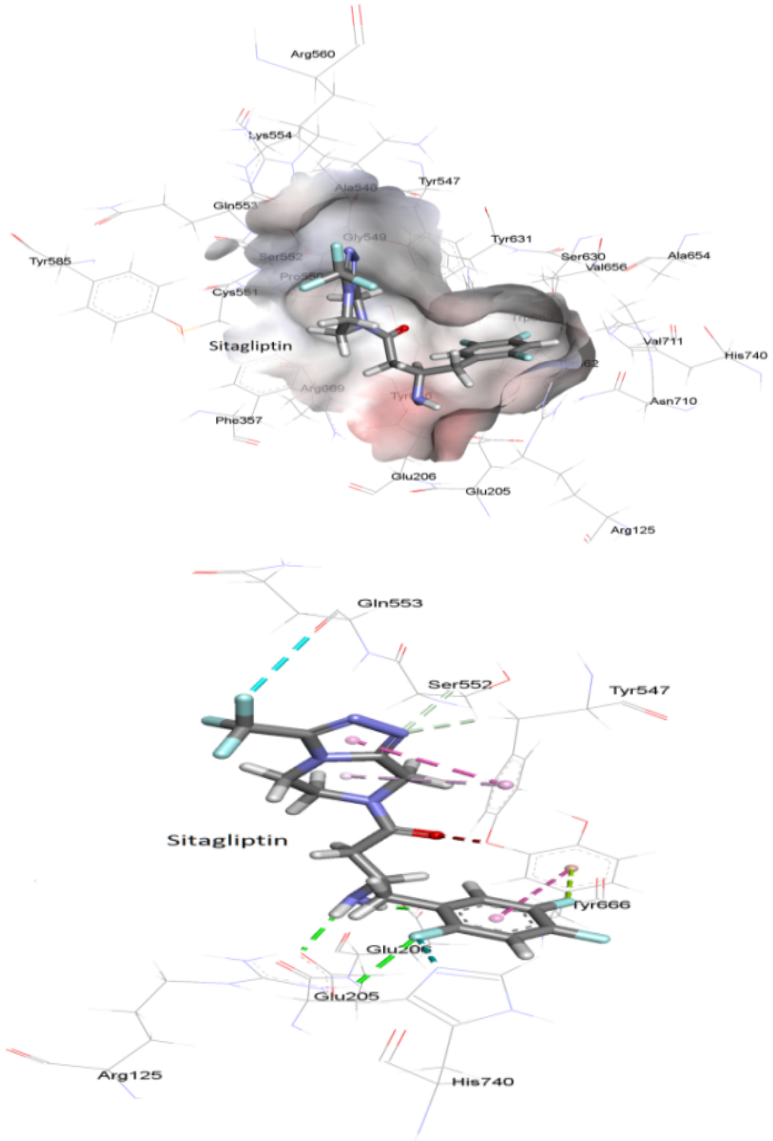


Figure 8: Connection mode Sitagliptin and orientation in the active site of the DPP-4

Table 5: Sitagliptin distances and interaction with the active site of the DPP-4

DPP4-Sitagliptin; atoms		Distance	Category	Type
Arg125:HH22	Sitagliptin:F9	2.54763	Hydrogen Bond;Halogen	Conventional Hydrogen Bond; Halogen (Fluorine)
Sitagliptin:H36	Glu206:OE2	1.99329	Hydrogen Bond	Conventional Hydrogen Bond
Sitagliptin:H37	Glu205:OE2	2.06458	Hydrogen Bond	Conventional Hydrogen Bond
Ser552:HB1	Sitagliptin:N22	2.6533	Hydrogen Bond	Carbon Hydrogen Bond
Ser552:HB2	Sitagliptin:N22	2.91259	Hydrogen Bond	Carbon Hydrogen Bond
Sitagliptin:H40	Sitagliptin:F27	2.97471	Hydrogen Bond	Carbon Hydrogen Bond
Sitagliptin:H41	Sitagliptin:F26	2.51025	Hydrogen Bond	Carbon Hydrogen Bond
Gln553: O	Sitagliptin:F28	3.34157	Halogen	Halogen (Fluorine)
His740:NE2	Sitagliptin:F9	3.44377	Halogen	Halogen (Fluorine)
Sitagliptin:F7	Tyr666	2.91379	Other	Pi-Lone Pair
Tyr666	Sitagliptin	5.29474	Hydrophobic	Pi-Pi T-shaped
Sitagliptin	Tyr547	4.19266	Hydrophobic	Pi-Pi T-shaped
Tyr547	Sitagliptin	4.70766	Hydrophobic	Pi-Alkyl

(Sita-H40 ... F27-sita; d=2.97471 Å) .a seventh bond hydrogen formed in sitagliptin between H41 and F26 (Sita-H41… sita-F26; d=2.51025 Å). We also note the presence of two halogen bonds: The first between the F28 fluorine and oxygen O in the Gln553 residue (Sita-F28 ... O-Gln553; d=3.34157 Å). The second between the F9 fluorine and NE2 nitrogen in His740 residues (Sita-F9...

NE2-His740; d=3.44377 Å) .on also noticed another link between the F7 fluorine and Tyr666 residues (Sita-F7...Tyr666; d=2.91379 Å). Finally Sitagliptin is stabilised by hydrophobic interactions formed by Tyr666 and Tyr547 residues (Figure 9 and Table 6).

We observe the presence of six non-covalent hydrogen bonds formed between vildagliptin and amino acids in the active site of DPP-4 in addition to a hydrophobic interaction. The first hydrogen bonding was observed between N7 amine and hydrogen in the Arg358 residues (Vilda-N7 ... H-Arg358; d=2.09505 Å). A second hydrogen bond is formed between the H47 and Tyr547 Oxygen (Vilda-H47 ... O-Tyr547; d=2.05703 Å). Finally vildagliptin is stabilised by hydrophobic interactions formed by Phe357 and Tyr547 residues.

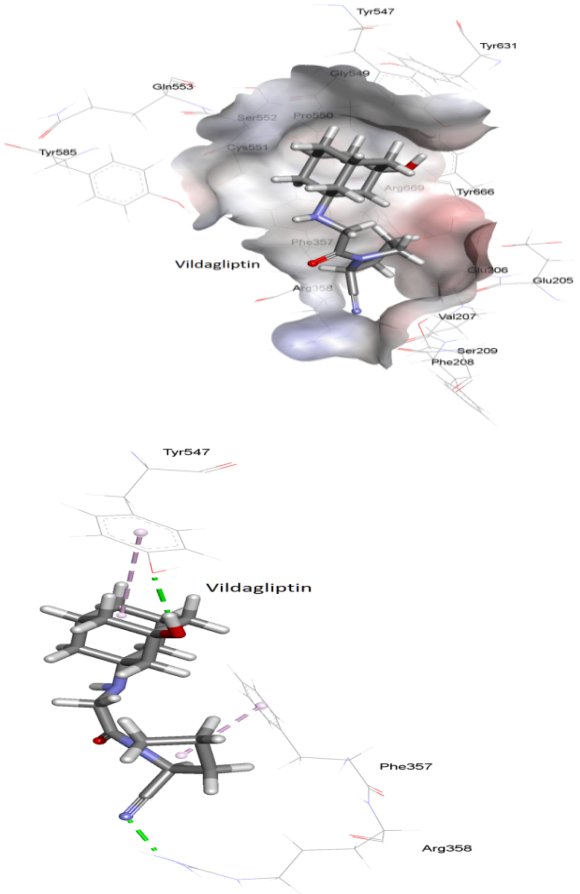


Figure 9: Link mode and vildagliptin orientation with the active site of the DPP-4

Table 6: Vildagliptin distances and interactions in the active site of the DPP-4

DPP4-Vildagliptin; atoms		Distance	Category	Type
Arg358:HH12	Vildagliptin:N7	2.09505	Hydrogen Bond	Conventional Hydrogen Bond
Vildagliptin:H47	Tyr547:OH	2.05703	Hydrogen Bond	Conventional Hydrogen Bond
Phe357	Vildagliptin	4.38135	Hydrophobic	Pi-Alkyl
Tyr547	Vildagliptin	4.60128	Hydrophobic	Pi-Alkyl

Simulation of molecular dynamics

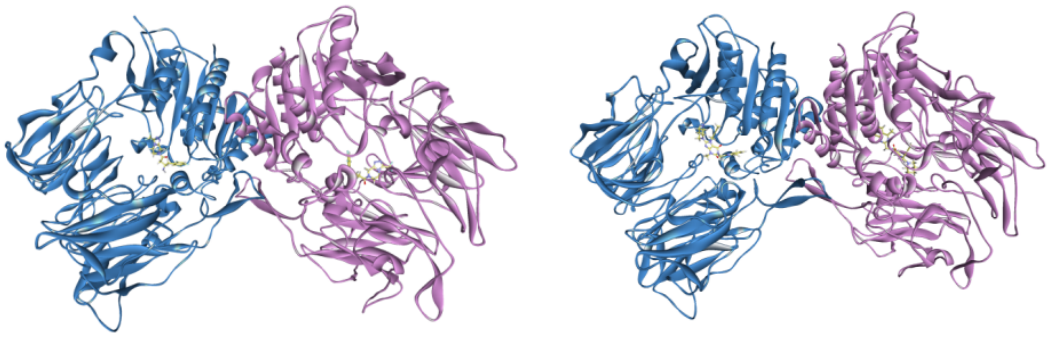
We studied the molecular dynamics simulation of Linagliptin and Sitagliptin ligands (both molecules have a good affinity to the DPP-4) and DPP-4 enzyme (Figure 10 and Table 7).

-Note that the DPP4-Lin this complex energy weakest interaction.

Energy of interaction between inhibitors and key residues DPP4

Energy interactions between Linagliptin and residues of reagents DPP-4 (blue) in the average structure extracted molecular dynamics simulation trajectories. Since the reactive residues are involved in hydrophobic interactions, therefore, the data show that they are key residues involved in binding and the effective interaction between the drug and the protein (Table 8).

Interaction energies between Sitagliptin and reactive residues (blue) in the average structure extracted molecular dynamics simulation trajectories. Since the reactive residues are involved in hydrophobic interactions, therefore, the data show that they are the key residues involved in binding and the effective interaction between the drug and the protein (Table 9).



DPP4-LIN DPP4-SIT

Figure 10: Training complexes results of simulations of molecular dynamics

Table 7: Mean energy intakes to form the DPP4-Lin complex and DPP4-Sit (kcal/mol) with their standard errors of the mean (in brackets)

Complex	DPP4-LIN	DPP4-SIT
ΔE_{ele}	-18.41(3.30)	-17.77(3.06)
ΔE_{vdw}	-49.41(2.26)	-25.28(1.96)
ΔE_{sur}	-6.83(0.16)	-3.76(0.44)
ΔE_{sol}	49.44(5.82)	28.81(4.40)
ΔG_{PB}	-18.38(4.73)	-14.24(2.94)
ΔG_{GB}	-28.15(2.02)	-14.70(1.87)

Table 8: Interaction energy between the DPP4-LIN complex and residues

Residue in average structure of DPP4-LIN complex	Residue Number	Interaction Energy
Leu	45	-9.5668
Leu	49	-20.562
Tyr	48	-17.383
Leu	567	-0.5185
Trp	563	-34.962
Tyr	566	-3.2955
Ala	654	-2.7636
Ile	651	-5.5098
Ser	630	-1.1091
Trp	627	-5.9096
Trp	629	-22.335
Val	653	-3.4054
Ile	703	-6.6113
Leu	701	-6.115
Asp	739	9.1322
Glu	738	-14.926
Met	733	-7.0030
Tyr	735	-32.372
Gln	761	-6.3704
Ile	759	-15.017
Lys	760	-11.472
Phe	758	11.4955
Arg	125	-2.3539

Table 9: Interaction energy between the DPP4-SIT and residues complex

Residue in average structure of DPP4-SIT complex	Residue Number	Interaction Energy
Leu	45	-10.137
Leu	49	-17.459
Tyr	48	-16.129
Leu	567	-0.5380
Trp	563	-34.842
Tyr	566	-3.3500
Ala	654	-2.7447
Ile	651	-5.7177
Ser	630	-0.3736
Trp	627	-5.7696
Trp	629	-25.355
Val	653	-3.7730
Ile	703	-7.0264
Leu	701	-6.0111
Asp	739	11.4118
Glu	738	-18.131
Met	733	-6.6414
Tyr	735	-34.594
Gln	761	-6.0914
Ile	759	-15.458
Lys	760	-12.216
Phe	758	12.0683

The Following figures and tables represent the interactions and directions of ligands in the DPP4 protein binding site in the average structure extracted from molecular dynamics trajectories in 2D and 3D.

Figure 11 shows the binding mode for Linaglptine using the curve of the 2D and 3D interaction with ligand specific amino acids [16], we see that the curve changed and although entry into the cavity so it has important interactions with the active site residues (Table 10).

Distance and visual analysis of interactions

We observe the presence of two hydrogen bonds formed between linagliptin and amino acids in the active site of DPP-4 and hydrophobic interactions. The first hydrogen bonding was observed between H13 hydrogen and oxygen OE1 in Glu205 residues (Lina-H13 ... OE1-Glu205; d=2.85342 Å). A second hydrogen bond is formed between H27 hydrogen and Tyr662 residues (lina-H27 ... Tyr662; d=2.34606 Å). Finally linagliptin is stabilised by hydrophobic interactions formed by the residues Tyr547, Pro550, Phe357, Trp629, Tyr666 and His740.

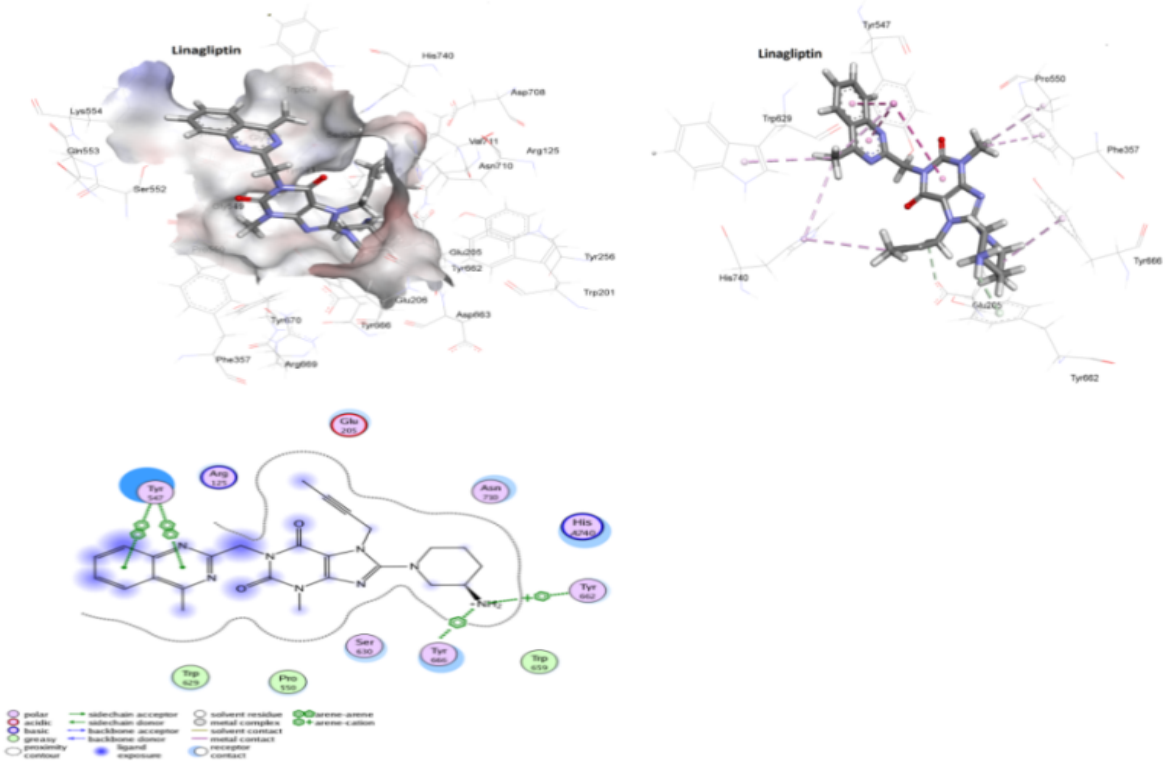


Figure 11: Connection mode linagliptin and orientation in the active site of the DPP4

Table 10: Distances and interactions of linagliptin in the active site of the DPP4

DPP-LIN		Distance	Category	Type
LIN767:H13	Glu205:OE1	2.85342	Hydrogen Bond	Carbon Hydrogen Bond
LIN767:H27	Tyr662	2.34606	Hydrogen Bond	Pi-Donor Hydrogen Bond
Tyr547	LIN767	3.78932	Hydrophobic	Pi-Pi Stacked
Tyr547	LIN767	3.94605	Hydrophobic	Pi-Pi Stacked
Tyr547	LIN767	5.68019	Hydrophobic	Pi-Pi T-shaped
LIN767:C13	Pro550	4.20283	Hydrophobic	Alkyl
Phe357	LIN767:C13	5.47279	Hydrophobic	Pi-Alkyl
Tyr547	LIN767:C12	4.47858	Hydrophobic	Pi-Alkyl
Trp629	LIN767:C12	4.79209	Hydrophobic	Pi-Alkyl
Tyr666	LIN767	4.29016	Hydrophobic	Pi-Alkyl
His740	LIN767:C12	4.94588	Hydrophobic	Pi-Alkyl
His740	LIN767:C20	5.0297	Hydrophobic	Pi-Alkyl

Figure 12 shows the binding mode for Sitagliptin using the curve of the 2D and 3D interactions with ligand specific amino acids [17], we see that the curve changed and allowed entry into the cavity so that it has important interactions with the active site residues (Table 11).

We observe the presence of a hydrogen bond formed between hydrogen and oxygen H6 sitagliptin of Gly741 residues (Sita-H6 ... Gly741; d=2.68959 Å). Sitagliptin is stabilised by hydrophobic interactions formed by the residues Tyr547, Trp629 and Ala743.

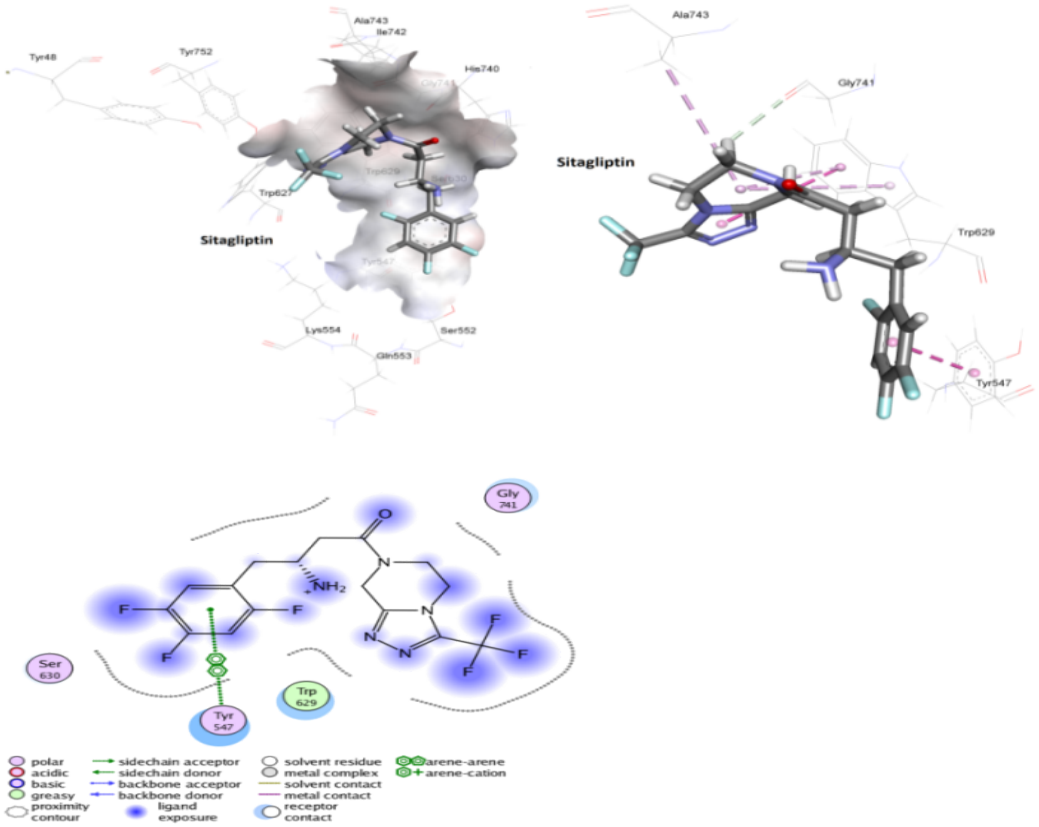


Figure 12: Connection mode and sitagliptin orientation in the active site of the DPP-4

Table 11: Distances and sitagliptin interactions in the active site of the DPP-4

DPP-SIT		Distance	Category	Type
SIT767:H6	Gly741: O	2.68959	Hydrogen Bond	Carbon Hydrogen Bond
Tyr547	SIT767	3.95149	Hydrophobic	Pi-Pi Stacked
SIT767	Trp629	4.96471	Hydrophobic	Pi-Pi T-shaped
Ala743	SIT767	5.42169	Hydrophobic	Alkyl
Trp629	SIT767	5.10137	Hydrophobic	Pi-Alkyl
Trp629	SIT767	4.65452	Hydrophobic	Pi-Alkyl

CONCLUSION

The results obtained in this study, by the methods of molecular modeling were elucidated, allowing us to conclude that Linagliptin is a better inhibitor of DPP-4. Linagliptin inhibits DPP-4 more effectively than Sitagliptin, Vildagliptin, Saxagliptin and Alogliptin.

Linagliptin has the potential to be the best inhibitor of DPP-4 in the treatment of type 2 diabetes.

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