A first attempt to identify repurposable drugs for type 2 diabetes: 3D-similarity search and molecular docking

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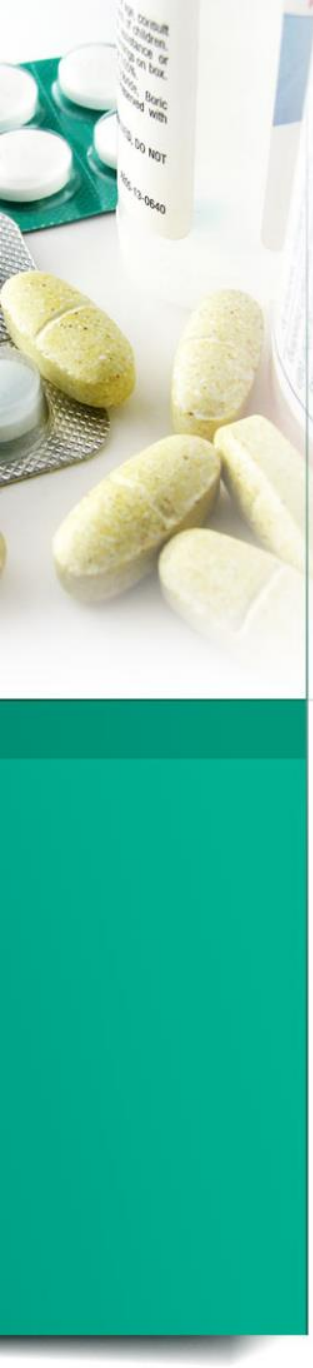
ABSTRACT

- Drug repositioning involves the investigation of existing drugs for new therapeutic purposes such as type 2 diabetes. This disease affects the health and quality of life for individuals around the world.

- Sitagliptin, a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor, is used to treat type 2 diabetes mellitus by effective fasting and improved glycemic control. Despite this advantage, serious hypersensitivity reactions have been acknowledged for patients receiving sitagliptin.

- In this context, new drugs with enhanced profile and targeting DPP-4 are necessary to be developed. Sitagliptin, ((2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihidro[1,2,4]triazolo[4,3-A] pirazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine), was used as a query in a 3D similarity search on the approved DrugBank.

- Based on the TanimotoCombo parameter, the first 10 approved DrugBank drugs were docked in the 4FFW active site to identify effective anti-diabetic effects for possible repurposable drugs marketed with other indications.



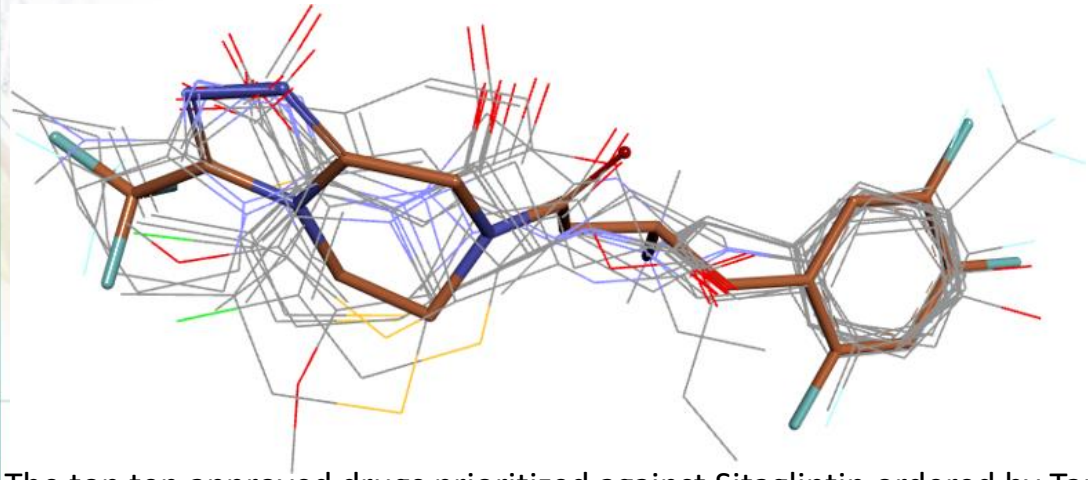
METHODS

- 2454 approved DrugBank
  https://go.drugbank.com/
- Ionization states and tautomers
  https://www.schrodinger.com/ligprep
- Conformational space
  https://www.eyesopen.com/omega
- 3D-similarity search
  https://www.eyesopen.com/rocs
- Molecular docking
  https://www.eyesopen.com/oedocking

RESULTS and DISCUSSIONS

3D –similarity search:

ROCS- Rapid Overlay of Chemical Structures



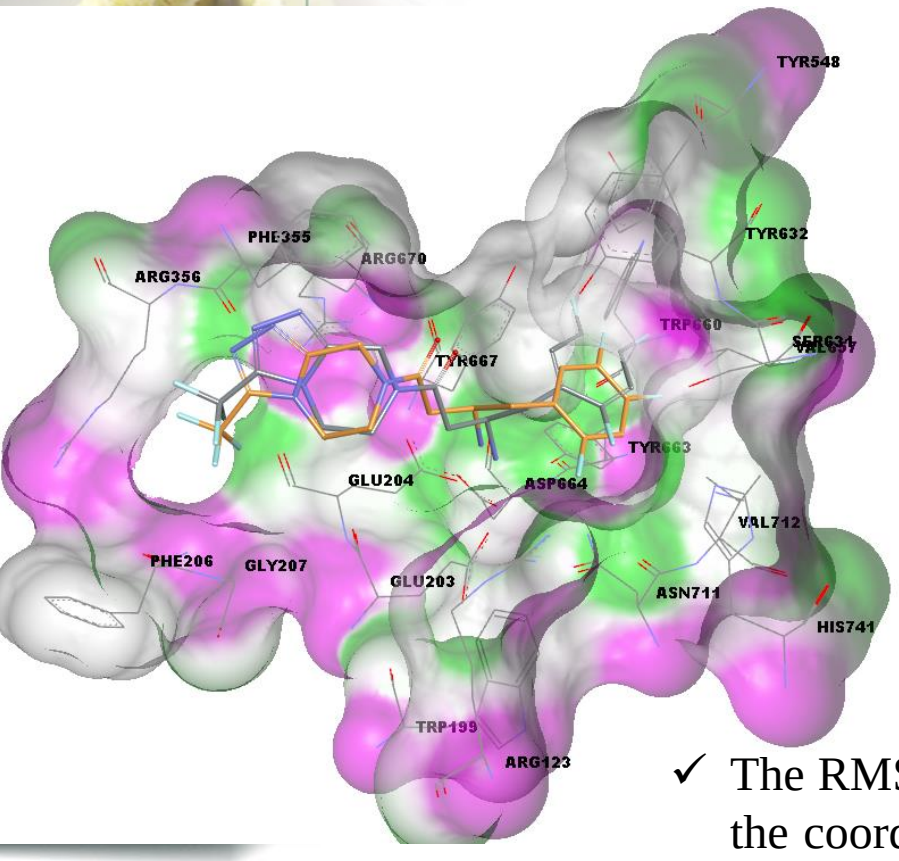
3D similarity coefficients based on shape, color and a combination between these two are listed in Table 1

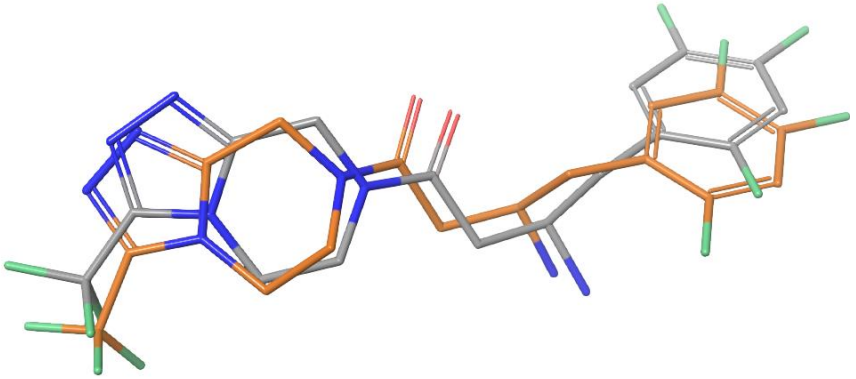
Table 1. The top ten approved drugs prioritized against Sitagliptin ordered by TanimotoCombo

Name	Tanimoto Combo	Shape Tanimoto	Color Tanimoto	FitTversky Combo	Fit Tversky	FitColor Tversky	RefTversky Combo	Ref Tversky	RefColor Tversky	Scaled Color	Combo Score	Color Score	Overlap
DB09089	1.203	0.69	0.513	0.8	0.716	1.516	0.834	0.644	1.479	0.721	1.411	-5.765	1,034.86
DB00298	1.098	0.77	0.328	0.806	0.466	1.272	0.945	0.526	1.47	0.463	1.233	-3.705	1,036.78
DB09195	1.068	0.765	0.303	0.88	0.466	1.346	0.854	0.466	1.319	0.466	1.231	-3.725	1,143.70
DB01333	1.02	0.707	0.312	0.759	0.555	1.314	0.912	0.417	1.329	0.565	1.273	-4.523	975.524
DB00447	1.017	0.704	0.313	0.763	0.556	1.318	0.902	0.417	1.319	0.566	1.27	-4.528	980.782
DB00567	1.008	0.67	0.339	0.738	0.59	1.327	0.879	0.443	1.321	0.601	1.27	-4.805	948.703
DB13858	1.004	0.45	0.554	0.524	0.632	1.156	0.762	0.819	1.58	0.624	1.074	-4.993	667.898
DB00833	1	0.677	0.322	0.741	0.568	1.31	0.887	0.427	1.314	0.579	1.257	-4.633	952.603
DB01150	1	0.748	0.252	0.828	0.533	1.361	0.886	0.323	1.209	0.553	1.301	-4.427	1,069.74
DB01060	0.995	0.718	0.277	0.782	0.597	1.379	0.899	0.34	1.239	0.623	1.342	-4.988	1,006.84

Molecular docking:
FRED - Fast Rigid Exhaustive Docking

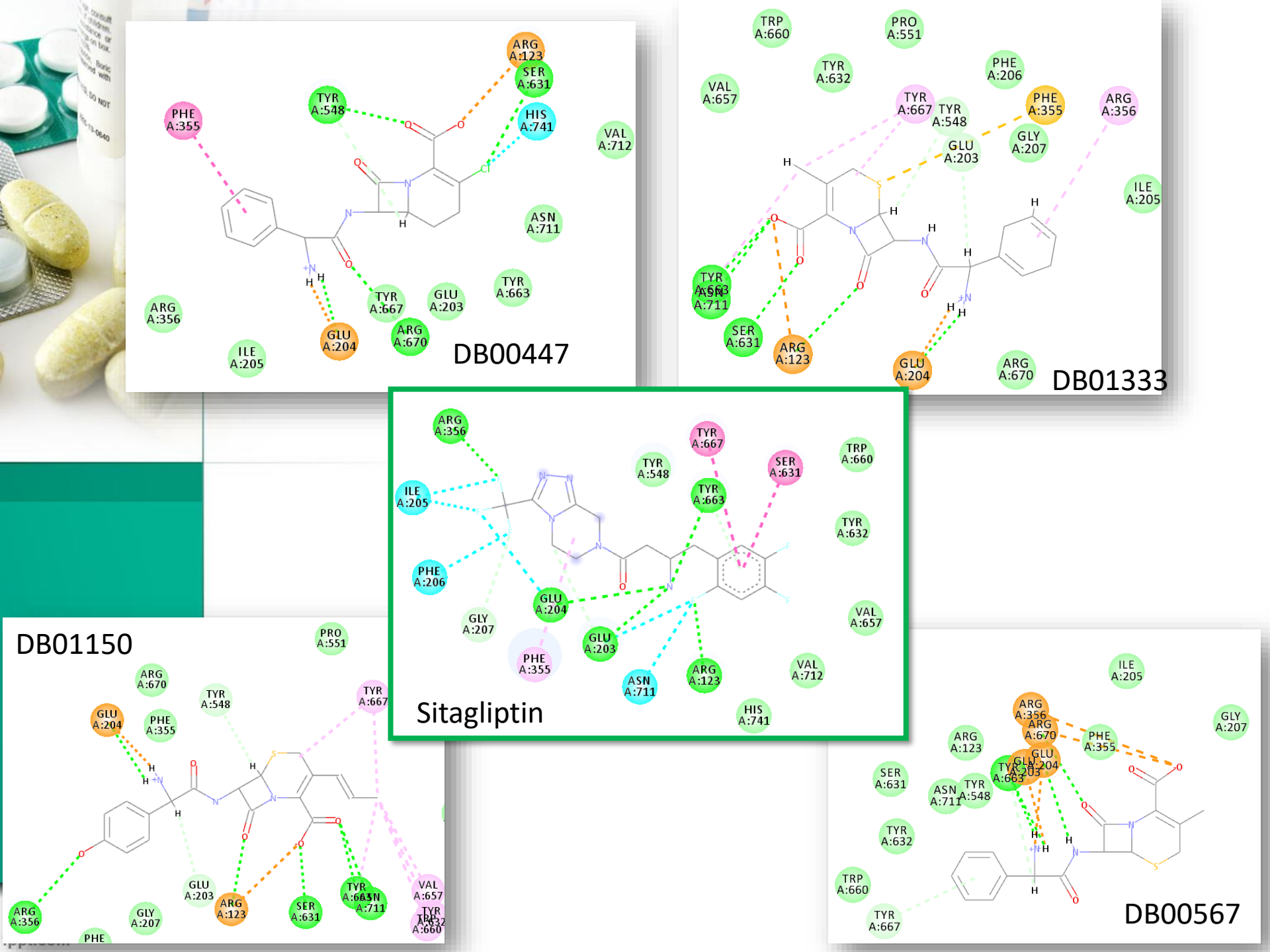
- ✓ The performance of the docking experiment was checked by redocking co-crystallized ligand, sitagliptin, into active sites of DPP4 (4FFW)





Sitagliptin RX-structure (4FFW) – orange
Sitagliptin – docked pose - grey

- ✓ The RMSD (Root Mean Square Deviation) value between the coordinates of the atoms of co-crystallized ligand and docked pose was **1.706**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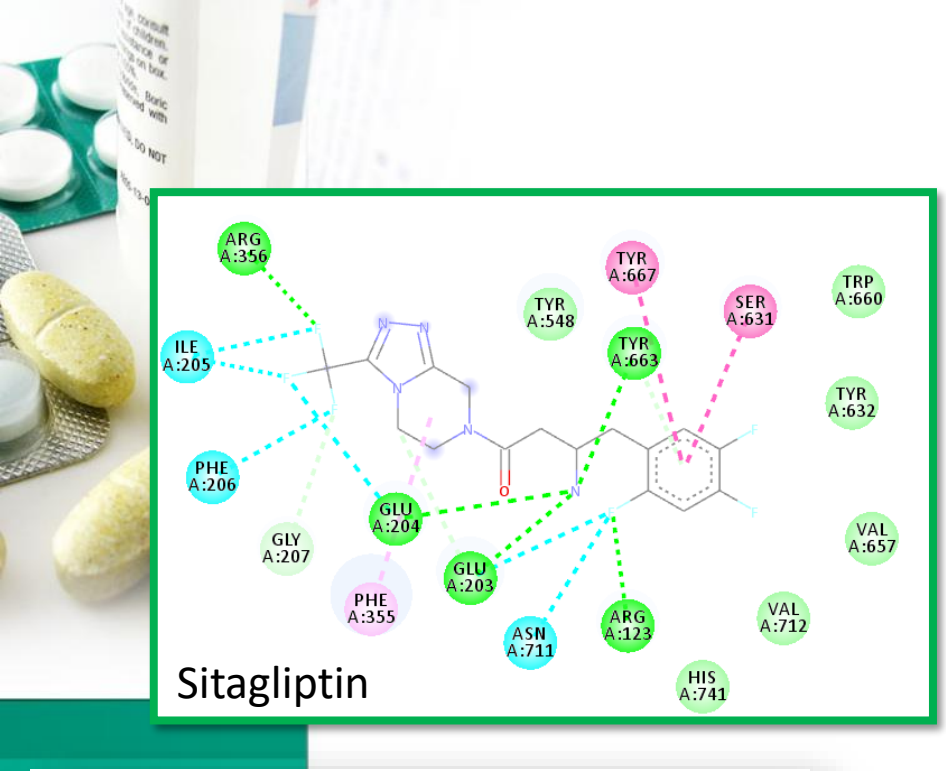
Sitagliptin
DB01150
DB00567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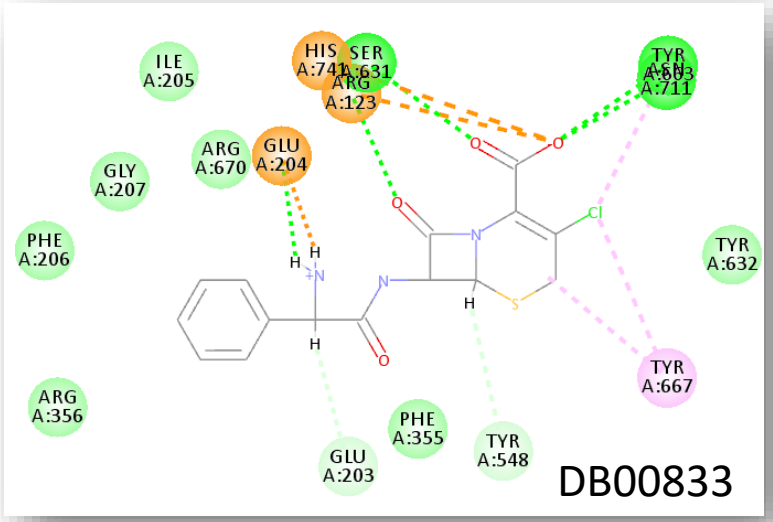
Sitagliptin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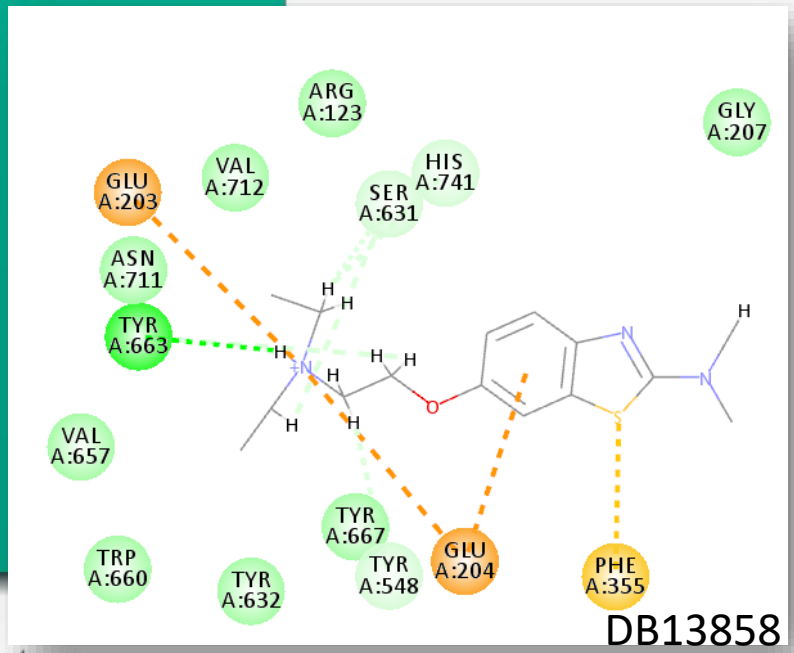
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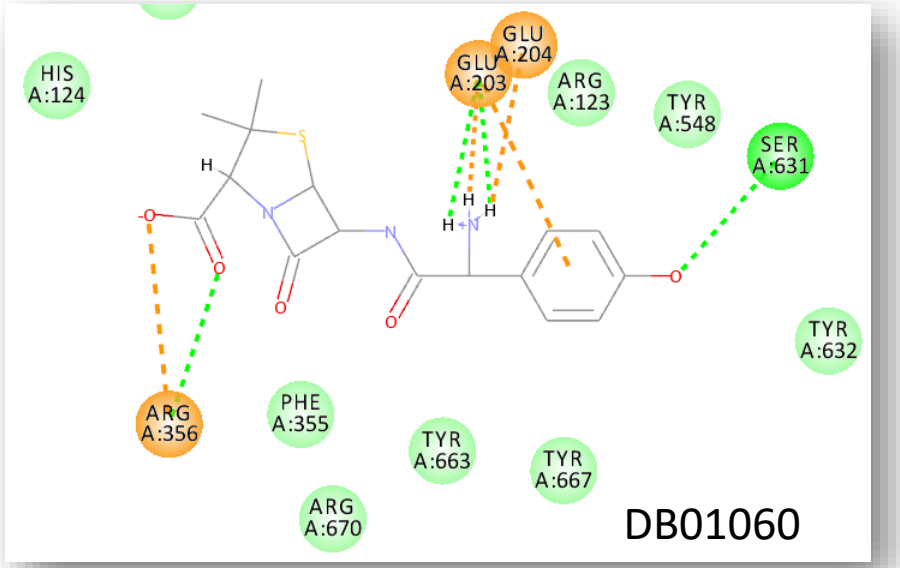
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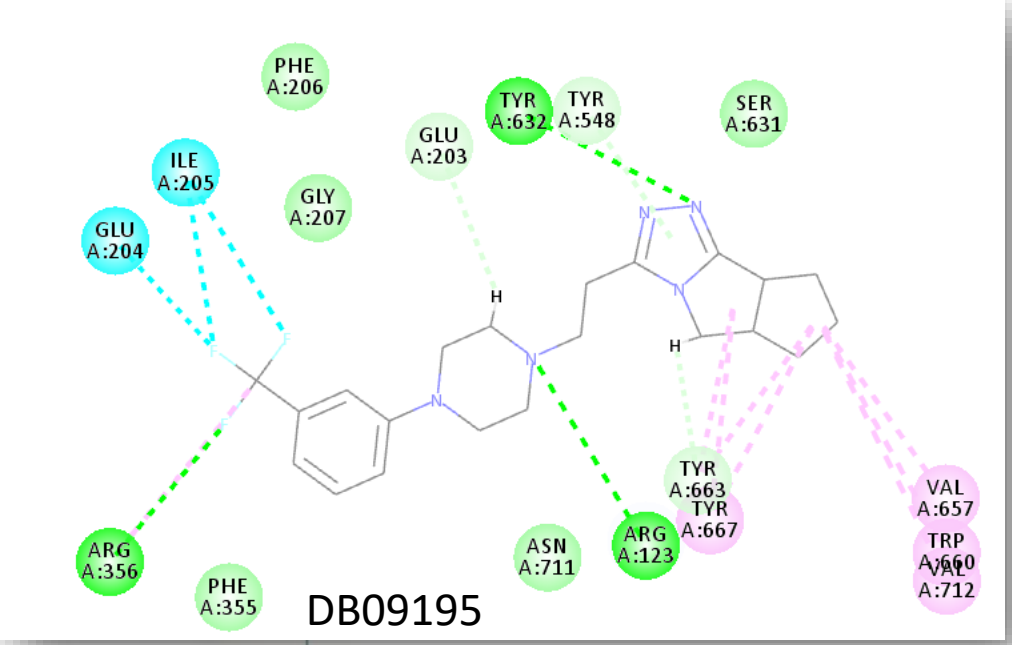
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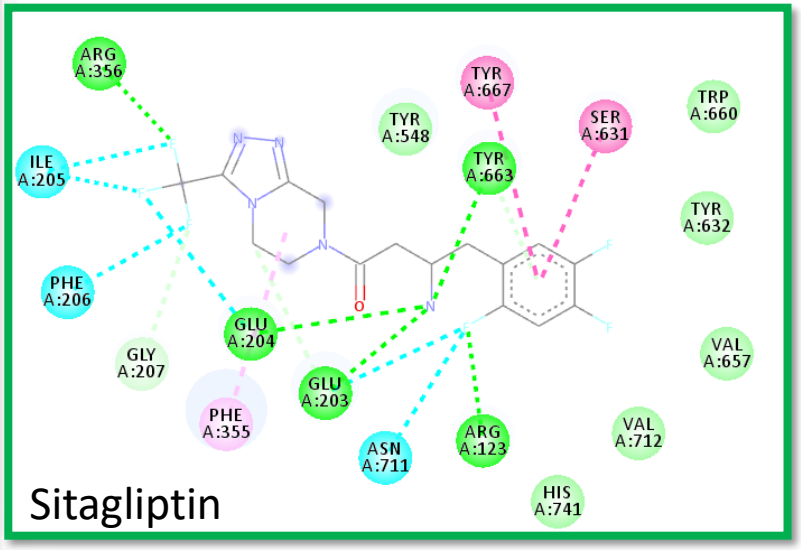
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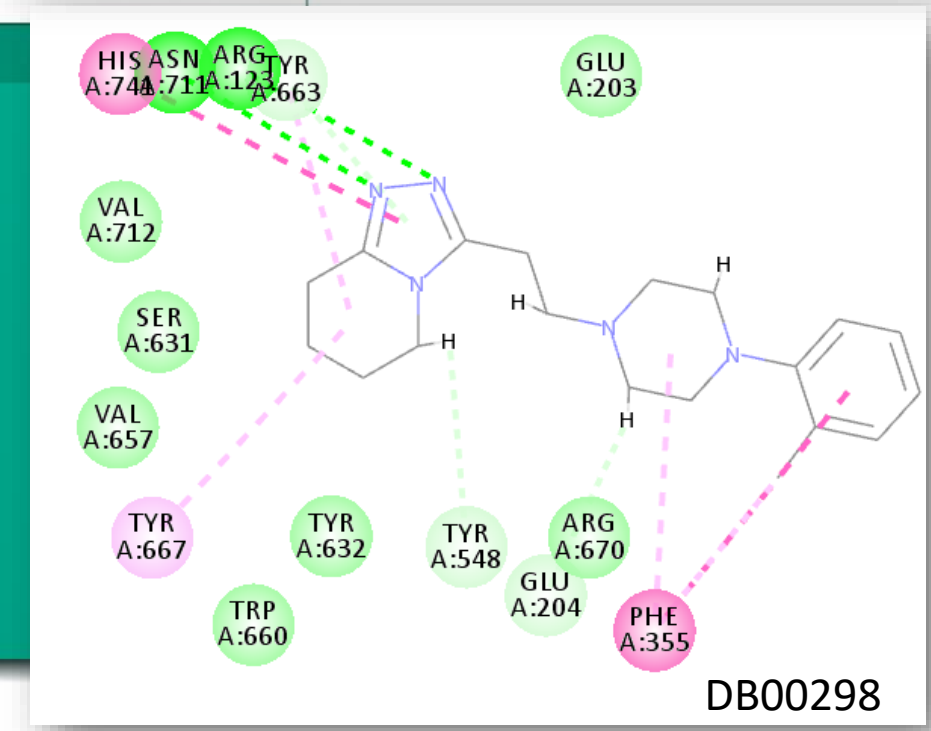
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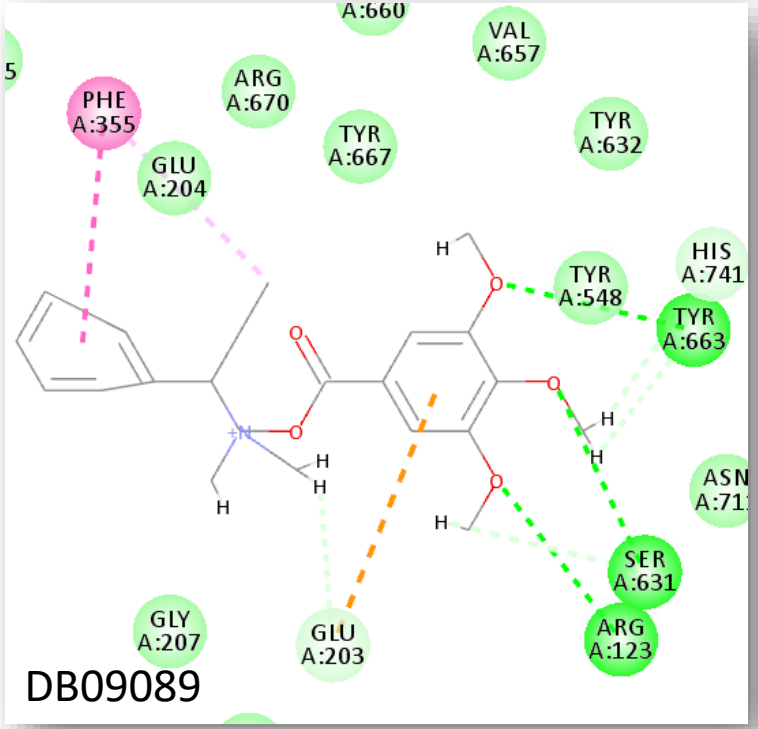
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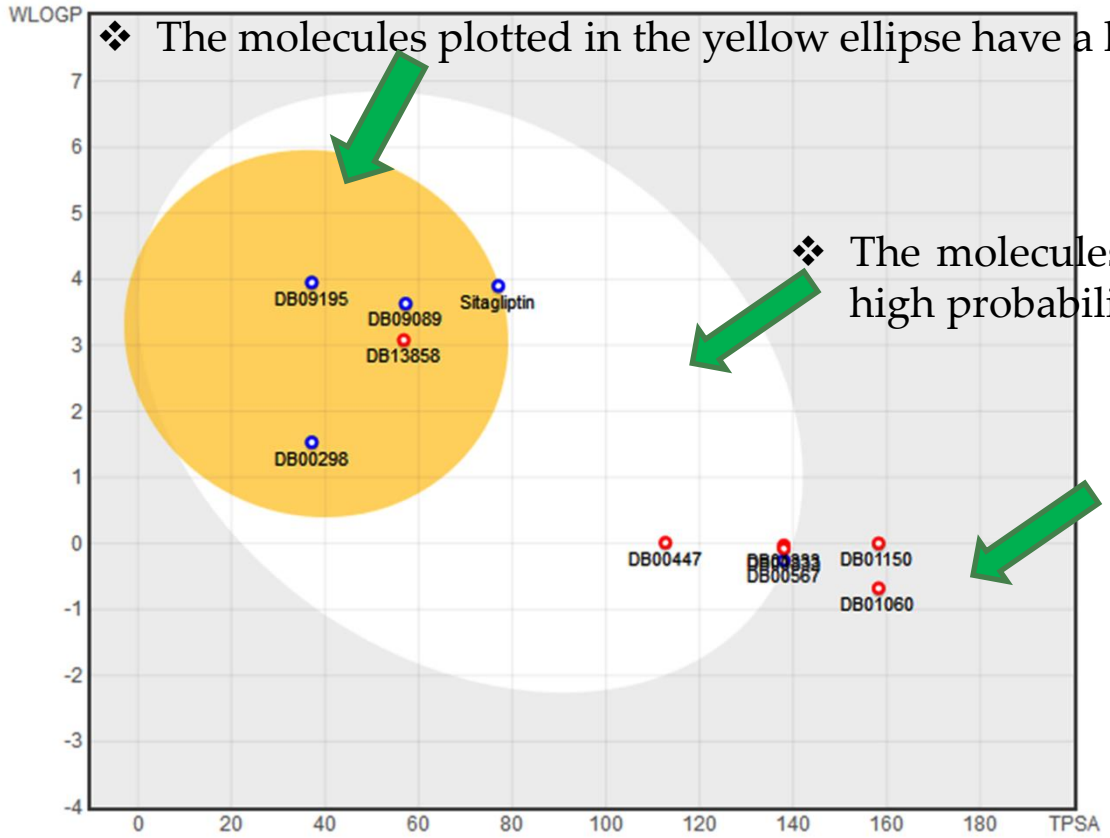
"Boiled egg"

BBB - blood-brain barrier permeation
HIA - passive gastrointestinal absorption



- The molecules plotted in the yellow ellipse have a high probability of a good BBB crossing.
- The molecules plotted in the white ellipse have a high probability of good HIA
- Molecules predicted to be unabsorbed by GI and BBB non-permeable are placed in the gray area.
- The blue dots (o) indicate molecules predicted as a substrate of P-glycoprotein (PGP +)
- The red dots (o) indicate molecules predicted as non-substrate of P-glycoprotein (PGP-)

CONCLUSIONS

- The ten approved drugs prioritized by TanimotoCombo coefficient (Table 1) were docked in the active site of DPP4 (4FFW).

- The SwissADME parameters, passive gastrointestinal absorption (HIA) and brain permeability (BBB), indicated approved drugs to passively permeate the BBB (yellow region – DB09195, DB09089, DB00298, DB13858) and not to be effluated from the CNS (red dot - DB13858).

- In the current work, drug reposition strategy was used to explore the efficacy of already approved drugs that could potentially be repurposed for treating type 2 diabetes.

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