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Research Article

From sequence analysis of DPP-4 to molecular docking based searching of its inhibitors

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Abstract:
Literature data suggests that Dipeptidyl peptidase-4 (DPP-4) is a potential target for type 2 Diabetes Mellitus. Therefore, it is of interest to identify new DPP-4 inhibitors using molecular docking analysis. We document compounds such as STOCK1N-98884, STOCK1N-98881, and STOCK1N-98866 with optimal binding features with DPP-4 from the ligand database at https://www.ibscreen.com/ for further consideration.

Keyword: DPP-4, GLP-1, diabetes, docking analysis, inhibitor

Background:
Insulin resistance in type 2 diabetes and related issues are known **[1]**. Symptoms associated with the disease include retinopathy, edema, micro aneurysms, nephropathy outlines, symmetrical fringe neuropathy influencing engine and tactile nerves of the smaller attachments **[2-4]**. Several models of treatments using insulin, secretagogues (sulfonylureas and incretins) and hypoglycemias (biguanides, thiazolidinediones and a-glucosidase inhibitors) are currently available **[5-10]**. Inhibitors of the dipeptidyl peptidase-4 (DPP-4) are linked with the activities of GLP-1 and gastric inhibitory polypeptide (GIP) **[7, 8]**. Description of the structural models for DPP-4 is known [15-17]. Therefore, it is of interest to identify molecules to inhibit DPP-4 using molecular docking analysis.

Methodology:
Sequence to structure modeling and docking analysis of DPP-4:
The DPP-4 protein sequence downloaded from GenBank was analyzed in a comprehensive using tools such as Clustal Omega, Pfam, Prosite, SMART, PANTHER, PHYLIP, STRING and InterProScan, molecular docking and ligand-protein analysis tools to glean valuable insights **[11-22]**.

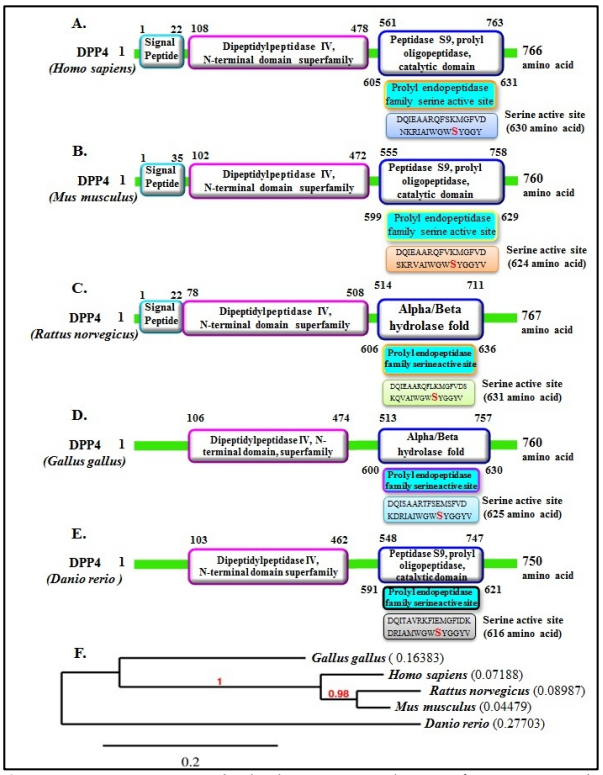

Figure 2: Domain and phylogeny analysis of DDP-4 in different organisms.

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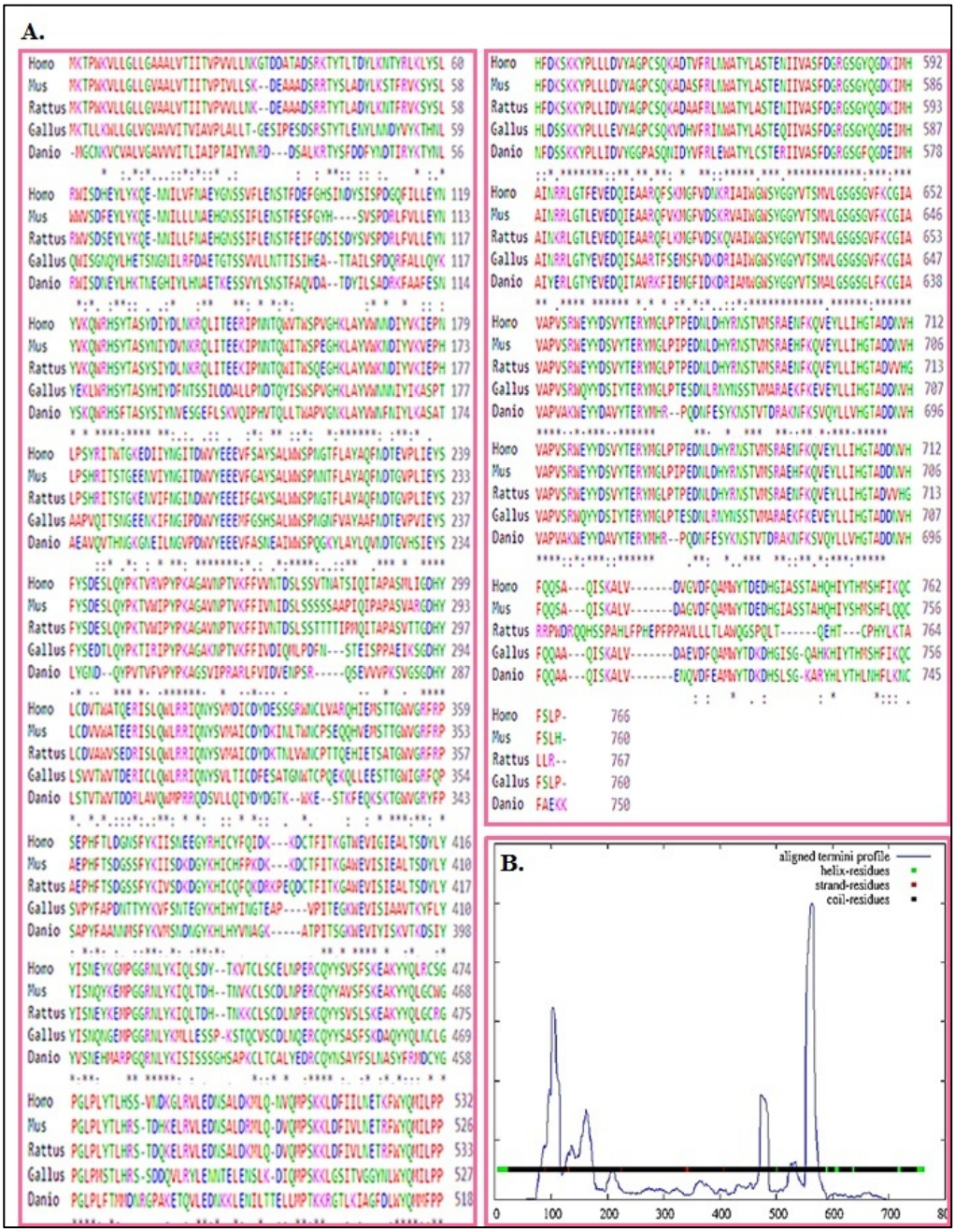

Figure 1: (A) MSA of DDP-4 from different organisms (*Homo sapiens, Rattus norvegicus, Mus musculus, Danio rerio* and *Gallus gallus*) (B) Secondary structure information on DDP-4

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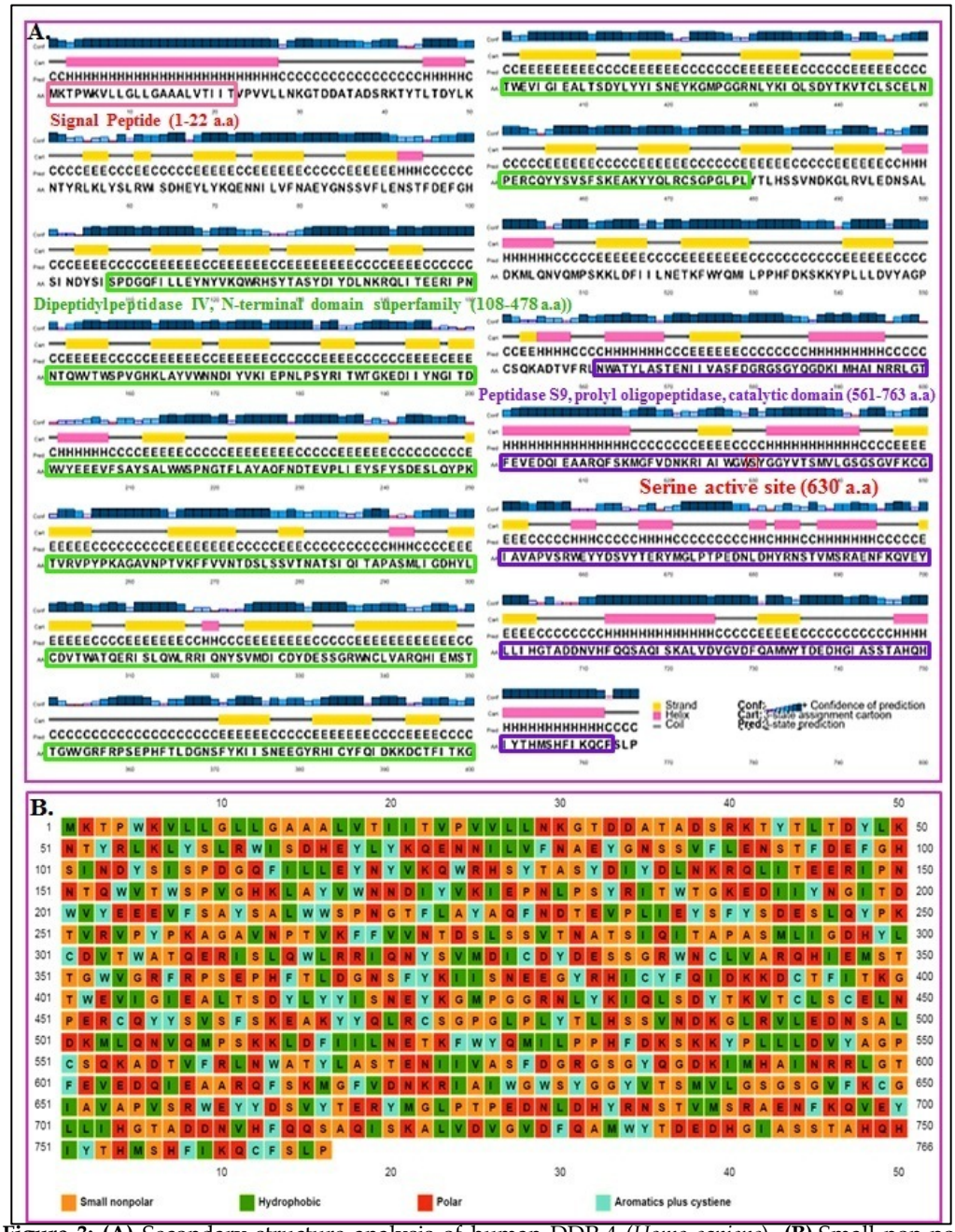

Figure 3: (A) Secondary structure analysis of human DDP-4 (*Homo sapiens*). **(B)** Small non-polar, hydrophobic, polar and aromatic plus cysteine residues in human DDP-4.

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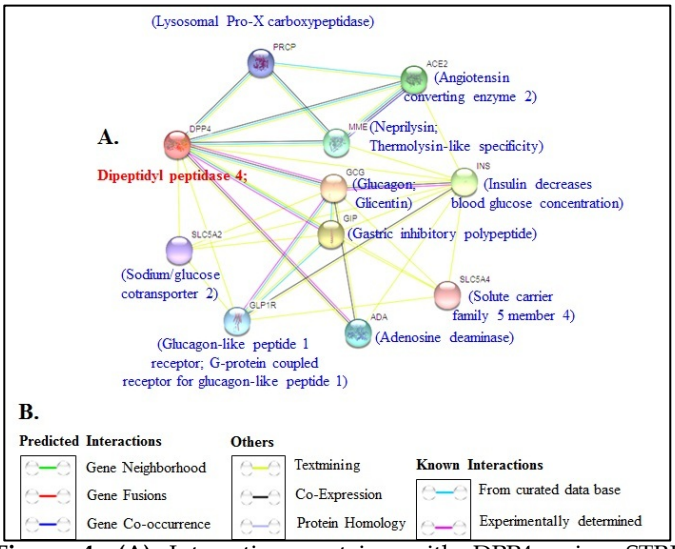

Figure 4: (A) Interacting proteins with DPP4 using STRING v10.database. **(B)** Explanation of interactions shown.

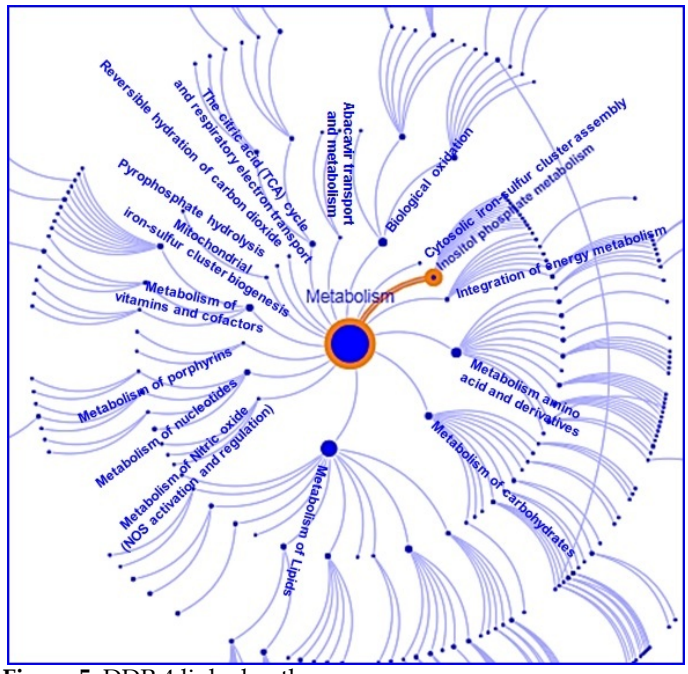

Figure 5: DDP-4 linked pathways.

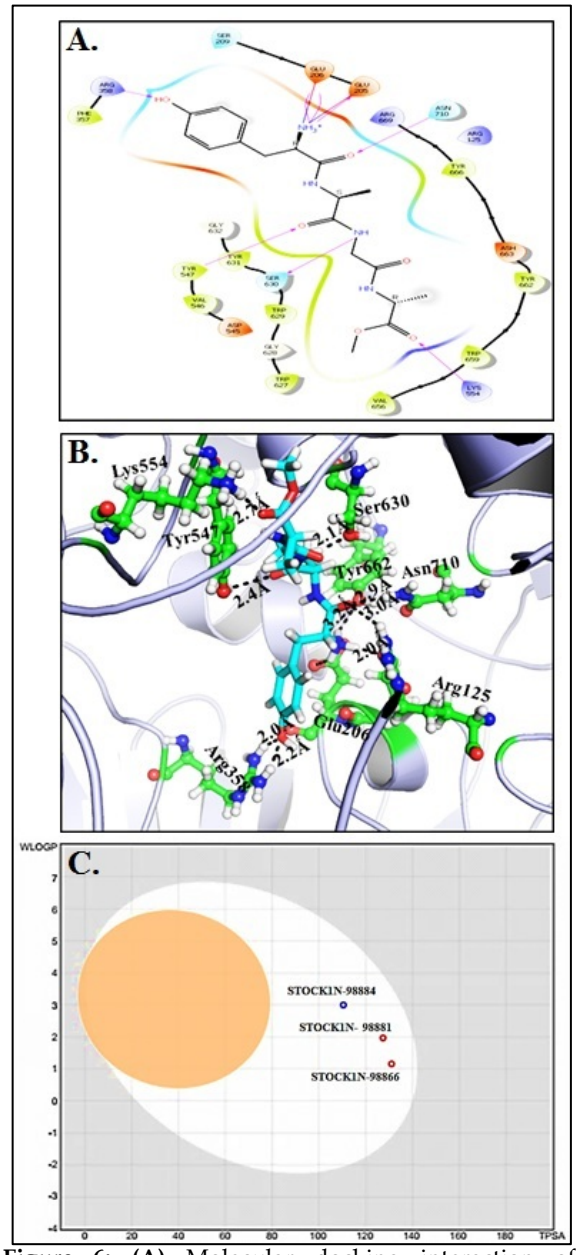

Figure 6: (A) Molecular docking interaction of DPP4 with STOCK1N-98884. **(B)** Cartoon interpretation of DPP4 with compound STOCK1N-98884. **(C)** Boiled-egg plot.

Table 1: Lowest binding energy for the Ligands-Protein interaction, along with scores for various interaction types, as detected by GLIDE

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GScore; Glide extra precision scores (kcal/mol) Lipophilic E Vdw; Chemscore lipophilic pair term and fraction of the total protein–ligand vdw energy HBond; Hydrogen-bonding term

Compounds ID	Binding Energy MM-GBSA (kcal/mol)	GScore	Lipophilic E vdw	H-bond	Electro	Protein ligands interaction
STOCK1N-98884	-72.7837	-11.56	-2.91	-6.87	-2.01	Glu:205, Glu:206, Try :547, Ser:630 and Asn710
STOCK1N-98881	-61.2792	-10.2	-3.37	-4.44	-2.41	Arg:125, Glu:205, Glu:206, Lys:554, Trp:629 and Ser:630
STOCK1N-98866	-59.2571	-9.58	-2.46	-3.65	-3.19	Arg:125, Try :547, Lys:554 and Trp:629
Known Inhibitor						
Linagliptin	-44.1282	-6.79	-2.22	-2.61	-0.34	Try :547, Ser:630 and Asn710

Electro; Electrostatic rewards Protein ligands interaction; p–p stacking, p–cat interaction and hydrogen bond between the ligands and protein

Table 2: Evaluation of drug-like properties of the lead molecules by Qikprop Maestro 10.5 molecular docking suite

Molecule	QPlog Po/w (-2.0 to 6.5)	Q P log HERG (acceptable ange: above -5.0)	QPP Caco (nm/s) <25—poor >500—great	Q P log, BB (-3 to 1.2)	QPP MDCK (nm/s)	Q Plog Kp (-8.0 to -0.1)
STOCK1N-98884	-0.30	-1.056	131.328	-0.94	70.119	-2.798
STOCK1N-98881	3.376	-0.015	283.926	-0.628	485.3	-2.406
STOCK1N-98866	2.219	-3.804	143.431	-1.641	60.643	-3.179

Predicted IC50 value for blockage of HERG K+ channels; (acceptable range above -5.0) Molecule STOCK, InterBioScreen's library (IBS), Q P log Poct; was predicted partition coefficient of octanol/gas, (8.0 to 35.0); QPP Caco, predicted apparent Caco-2 cell permeability in nm/s. Caco-2 cells is a model for the gut blood barrier (nm/s) <25—poor, >500—great. Q P log BB, predicted brain/blood partition coefficient; QPP MDCK, predicted apparent MDCK cell permeability in nm/s. MDCK cells are considered to be a good mimic for the blood–brain barrier; (nm/s) <25—poor, >500—great; Q P log KP, Predicted skin permeability; Q P log Khsa Prediction of binding to human serum albumin; (acceptable range -1.5 to 1.5)

Table 3: Boiled egg parameters

Molecule	MW	TPSA	XLOGP3	MLOGP	GI absorption	BBB permeant
STOCK1N-98884	430.88	159.85	-0.30	-0.66	High	No
STOCK1N-98881	624.04	158.30	2.99	0.23	Low	No
STOCK1N-98866	421.40	127.08	2.81	0.93	High	No

Table 4: Biological activity spectrum of compounds (Pa – Active; Pi – Inactive)

Molecule	Pa	Pi	Activity
STOCK1N-98884	1.219	0.449	Anti-diabetic
STOCK1N-98881	1.812	0.642	Anti-diabetic
STOCK1N-98866	1.121	0.318	Anti-diabetic

Results & Discussion:

A comprehensive analysis of DDP-4 using sequence and structure information is highly relevant in the fight against T2DM with reference to known data in the literature. The Multiple Sequence Analysis (MSA) of DDP-4 from different organisms such as *Homo sapiens* (DPP4, 766 amino acid), *Rattus norvegicus* (DPP4, 767 amino acid), *Mus musculus* (DPP4, 760 amino acid), *Danio rerio* (DPP4, 750 amino acid) and *Gallus gallus* (DPP4, 760 amino acid) is given in Figure 1. Secondary structure information of DDP-4 is also shown in **Figure 1**. Domain and phylogeny analysis of DDP-4 in different organisms is given in **Figure 2**. The Secondary structure analysis of human DDP-4 along with small nonpolar, hydrophobic, polar, and aromatic plus cysteine residues in human DDP-4 is shown in **Figure 3**. Protein-protein interaction network linked to DDP-4 is shown in **Figure 4**. We further show the DDP-4 associated pathways in **Figure 5**. The molecular docking interaction of DPP4 with STOCK1N-98884 is given in **Figure 6** and **Tables 1 to 4.** This information gleaned from the analysis of DDP-4 is relevant in the design and development of novel compounds in combating the disease.

Conclusion:

We document compounds STOCK1N-98884, STOCK1N-98881, and STOCK1N-98866 from the IBS ligand database with optimal binding features with DPP-4 towards combating T2DM.

Conflict of interest:

There are no conflicts of interest.

Acknowledgments:

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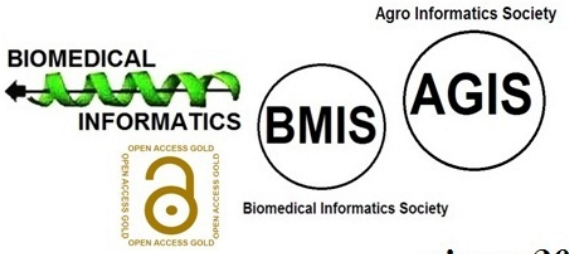

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