Short Communication

COMPARATIVE DOCKING STUDIES ON THE EFFECT OF COMMERCIAL DRUGS ON DIPEPTIDYL PEPTIDASE-4 (DPP-4)

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ABSTRACT

Objective: The aim of our study was to validate the accuracy of computational tools in drug discovery and molecular interaction studies by studying the inhibitory activity of various commercial drugs on DPP-4.

Methods: In order to validate the accuracy of computational tools, 50 commercially available drugs were docked with DPP-4, a major target for type 2 diabetes treatment. Studies were performed using Discovery studio 3.5.

Results: The analysis showed that out of the fifty selected drugs, 33 drugs passed the Lipinski's rule and commercially prescribed drugs namely Sulfonylurea, Pregabalin and Metaformin were found to have maximum interaction with the target.

Conclusion: These major drugs which yielded the best results were found to be used in the treatment of diabetes which reconfirms the efficacy of these drugs, druggability of the target as well as the accuracy of the tool used.

Keywords: Type 2 diabetes, Dipeptidyl peptidase 4, Glucagon like peptide-1, Discovery Studio 3.5

Diabetes is a metabolic disorder characterized by hyperglycemia [Elevated blood glucose level] which results from insufficient insulin secretion, defects in insulin action or insulin resistance. Type 2 diabetes represents 90-95% of diabetic cases and is the most prevalent form. It is characterized by either the failure in secretion of insulin or in action [1]. The critical factors that play a role in the disease include gender, age, lack of sleep, life style, diet and obesity. The disease can cause a series of complications associated with dysfunction and long-term damage to eyes, heart, kidneys, blood vessels and nerves [2].

Dipeptidyl peptidase-4 (DPP-4) enzyme is a multifunctional type II transmembrane serine protease, which plays an important role in glucose metabolism [3, 4]. It is a complex enzyme that exists as an intrinsic membrane peptidase, responsible for the degradation of incretin such as glucagon-like peptide-1(GLP-1) which regulates the secretion of insulin from pancreas [5]. The action of GLP-1 is inactivated by the proteolytic activity of DPP-4. Thus by inhibiting DPP-4, the level of GLP-1 increases in blood and thereby releasing adequate insulin. Hence DPP-4 is a promising target for the treatment of type 2 diabetes [6]. Preclinical trials have also proved that DPP-4 inhibitors increase the level of GLP-1, which in turn increases insulin secretion and reduces glucagon secretion [7, 8].

The rapid development of computational tools remarkably helps in closing the gap between *in vitro* and *in silico* methods. Application of these tools varies from genome sequencing to drug discovery. New medicines are developed based upon biological targets and their specific interactions such as hydrogen bonding, hydrophobic interactions, Van der Waals interactions and so on. Molecular docking is one such method among the various computational techniques which is used to predict how a drug interacts with the binding site of a target protein and returns the best hit through a series of scoring functions and statistics. Many docking programs are currently available; the present work proves the efficacy of the software, Discovery Studio 3.5 for *in silico* interaction studies. The results also highlight the best hit against DPP-4, among the commercial fifty drugs evaluated.

The crystal structure of human apo dipeptidyl peptidase-4 (PDB ID: 1PFQ) was retrieved from Protein Data Bank. The protein was found to be complexed with the ligand 'N-acetyl-D-glucosamine' with chain A and B. Chain A alone was used for protein preparation while chain B, ligand and water molecules were removed. Protein preparation module of Discovery Studio 3.5 was used to manipulate and interrogate protein structure which included correcting geometries, inserting missing loops, grafting loops, managing conformers and modify protonation of termini and ionizable side chains. This was followed by energy minimization of the structure to find out stable conformation using CharmM Force field. The receptor-ligand protocol of Discovery Studio and molecular dynamic simulation was used to predict the binding sites of the energy minimized protein structure.

About fifty existing drugs for diabetes, cancer, HIV, cholesterol, Parkinson's, heart diseases, hypertension, Alzheimer's and diarrhea were randomly selected as ligands. The chemical structures of these compounds were retrieved from Pub Chem compound database [9]. These chemical compounds were filtered by Lipinski's rule of five [10]in order to predict their biological and pharmacological properties as active drugs. Selected drugs were successfully docked to the binding site of DPP-4 using CDOCKER protocol of Discovery Studio 3.5. The best hits were determined based on various scoring functions like CDOCKER energy, CDOCKER interaction energy, hydrogen bond interaction with the active site residues, binding energy, protein energy and complex energy.
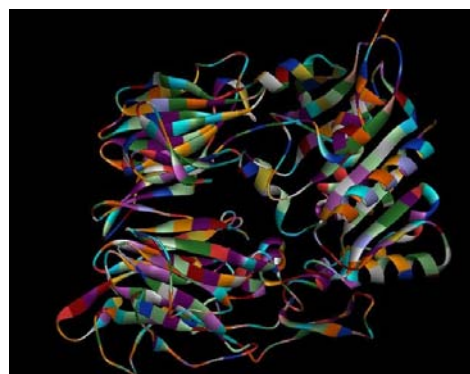

Fig. 1: Energy minimized structure of human apo dipeptidyl peptidase 4.

The retrieved structure of DPP-4 was prepared (fig. 1) and the active site was identified. Discovery studio was able to predict a binding site of the energy minimized structure with the amino acid residues GLN 314, SER 323, VAL 324, HIS 345, ILE 346, GLU 347, PHE 371, LYS 373, ILE 375 and PHE 387.

Out of fifty, only thirty three drugs satisfied Lipinski's rule. Drug likeness properties such as molecular weight, X log P, number of hydrogen bond donors and acceptors for the satisfied drugs are shown in table1.

Drugs which showed good interaction with the active site were found to be sulfonylurea, Pregabalin and Metaformin. These three drugs formed hydrogen bond interaction with the amino acid residue HIS 345 in the active site of the target protein. CDOCKER energy of Sulfonylurea, Pregabalin and Metaformin is 28, 23 and 17 respectively. Interaction of these drugs with the amino acids residues are shown in Fig. 2, 3 and 4 respectively. Binding energies of these drugs with the active site of DPP-4 were found to be -46.9507, -78.8461 and -10.9464 Kcal/mol respectively and are shown in table 2.

Table 1: Drug likeness of thirty three drugs

S. No.	Compound Name	Compound ID	Molecular weight (G/Mol)	XLOGP3-AA	H-Bond donor	H-Bond Acceptor
1	Aldara	57469	240.303	2.6	1	3
2	Anastrozole	2187	293.366	2.1	0	4
3	Calanolide-A	64972	370.439	3.8	1	5
4	Carboplatin	10339178	371.254	-	2	6
5	Cisplatin	83895	391.161	-	2	4
6	Crizotinib	11626560	450.336	3.7	2	6
7	Cycrimine	2911	287.439	3.9	1	2
8	Dacogen	16886	228.205	-1.2	3	4
9	Dasatinib	3062316	488.005	3.6	3	9
10	Exemestane	60198	296.403	3.1	0	2
11	Fluvastatin	446155	411.465	3.5	3	5
12	Mevacor	53232	404.539	4.3	1	5
13	Raltegravir	54671008	444.416	1.1	3	9
14	Simvastatin	54454	418.566	4.7	1	5
15	Zetia	150311	409.425	4	2	5
16	Abacavir	441300	286.332	0.9	3	6
17	Acenocoumarol	54676537	353.325	2.5	1	6
18	Amoxicillin	33613	365.404	-2	4	7
19	Ascorbic acid	54670067	176.124	-1.6	4	6
20	Aspirin	2244	180.157	1.2	1	4
21	Azacitidine	9444	244.204	-2.2	4	5
22	Donepezil	3152	379.491	4.3	0	4
23	Fluoxitine	3386	309.326	4	1	5
24	Gabapentin	3446	171.236	-1.1	2	3
25	Memantine	4054	179.301	3.3	1	1
26	Torasimide	41781	348.42	2.7	3	5
27	Metaformin	4091	129.163	-1.3	3	1
28	Sulfonylurea	104818	182.158	-2.5	4	4
29	Pregabalin	5486971	159.226	-1.6	3	2
30	Benazepril	5362124	424.489	1.3	2	6
31	Pravastatin	54687	424.527	1.6	4	7
32	Amoldipine	2162	408.875	3	2	7
33	Valsartan	60846	435.518	4.4	2	6

Table 2: Docking result of three drugs

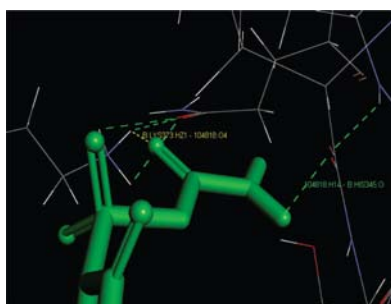| Compound	-CDOCKER Energy	-CDOCKER Interaction Energy	H Bond	H bond residues	Binding Energy	Protein Energy	Complex Energy
Sulfonylurea CID 104818	28	27	2	HIS345 LYS373	-46.9507	-27986.8	-28055.7
Pregabalin CID 5486971	23	24	3	HIS345 ILE346	-78.8461	-27986.8	-28155.2
Metaformin CID 4091	17	20	1	HIS345	-10.9464	-27986.8	-28021.2

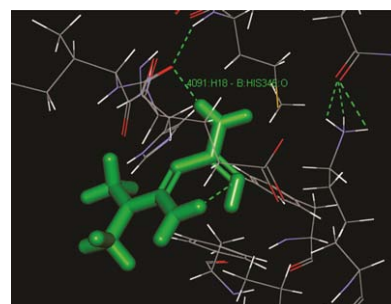**Fig. 2: Interaction of Sulfonylurea with DPP4**

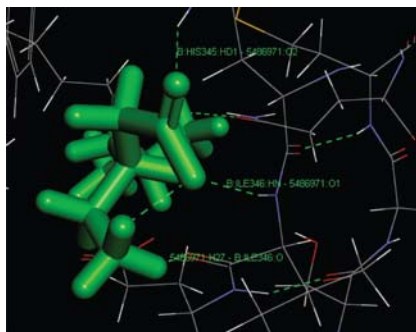**Fig. 3: Interaction of Pregabalin with DPP4**

Fig. 4: Interaction of Metaformin with DPP4.

Our study focused on the validation of docking software by testing the interaction of commercially available randomly selected drugs with DPP-4, a major target for diabetic treatment. Fifty drugs were randomly selected and the study confirmed that the widely used drugs for type 2 diabetes showed maximum interactions than the other selected drugs which are effective. For other diseases. Sulfonylurea, Pregabalin and Metaformin were the three drugs which showed good interaction with the target protein DPP-4 and also formed hydrogen bonds with the active site residue HIS 345, which confirms the residue as a major target for similar studies.

Thereby we validated docking protocols through our comparative study on commercially available drugs. This study could also reconfirm the druggability of DPP-4 as a major diabetic target. Such computational studies will reduce time, cost and risk factors in the drug discovery process than the traditional methods.

CONFLICT OF INTERESTS

Declared None

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