Research Article

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INFERENCES FROM THE ADME ANALYSIS OF PREDICTED INHIBITORS TO DPPIV

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Abstract: The incretin hormone glucagon-like peptide 1 (GLP-1) stimulates insulin biosynthesis and secretion, and inhibits glucagon release in a glucose-dependent manner. However, active GLP-1 is rapidly degraded in vivo through the action of dipeptidyl peptidase IV (DPP-4), a serine protease that cleaves a dipeptide from the N-terminus to give the inactive GLP-1 amide. Small-molecule inhibitors of DPP-4 have been shown to prolong the beneficial effects of this incretin hormone. The interactions between the DPPIV and their corresponding receptors are highly selective. Therefore, the structure of this protein was screened using molecular docking techniques. This exercise indentified compounds with better binding and ADME (Absorption, Digestion, Metabolism, and Excretion) properties compared to known standard compounds. These observations find application for the consideration of such compounds for further validation towards inhibiting DPPIV.

Keywords: DPP-IV, Protein- Ligand interactions, Glide, ADME Prediction

INTRODUCTION

Dipeptidyl peptidase (DPP) IV is a ubiquitous type II transmembrane glycoprotein and clinically validated target for type-2 diabetes [1]. It belongs to a family of peptidases such as serine protease of the S9 prolyl-oligopeptidase by 766 amino acids that are widely distributed in numerous tissues with 110-kDa molecular weight. Due to its unique post-proline cleavage specificity mechanism that is expressed on numerous cell types with multiple biological functions [2] has proved remarkable in the fields of immunology, haematology, endocrinology, endothelial cell, and cancer biology. Now, DPPIV has become a novel target for Type II diabetes therapy [3]. The dipeptidyl peptidase IV gene family contains the four peptidases dipeptidyl peptidase IV, fibroblast activation protein, dipeptidyl peptidase and dipeptidyl peptidase. Dipeptidyl peptidase IV and fibroblast activation protein are involved in cell–extracellular matrix interactions and tissue remodelling. It plays an important role in immune regulation, signal transduction, apoptosis and in glucose metabolism [4]. It is responsible for the degradation of incretins such as GLP-1[5].

It also known as the lymphocyte cell surface protein CD26 [6]. The signaling properties of membrane-associated CD26 have been most extensively characterized in T cells. It has its role in immunology, type-II diabetes and cancer biology [7]. A key facet of CD26/DPPIV biology is its enzymatic activity and its physical and functional interaction with other molecules. It is a rather indiscriminate enzyme for which at least 62 substrates are known. The substrates of CD26/DPPIV are proline-containing peptides and include growth factors, chemokines [8], neuropeptides, and vasoactive peptides. In this paper, an attempt has been made to observe the protein ligand interactions to identify its pharmacokinetic properties.

MATERIALS AND METHODS

The structure of the protein was downloaded from PDB database [18] with id 2IIT.pdb. The 3D structure of the protein with its ligand was taken from pdb and its appropriate inhibitory molecules were also taken from the research article a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes [9][10] for docking studies. The structures were drawn by using ISIS/Draw [11], a chemical structure drawing program for Windows**.** PYMOL is used to process the images [12].

Protein-ligand docking: Molecular Docking is the process in which two molecules fit together in 3D space both geometrically and energetically to the binding site of a protein. It is a key tool in structural biology and computer-aided drug design [13] [14]. The goal of ligand and protein docking is mainly to predict the predominant, promising and consistent scoring scheme to evaluate the protein-ligand complex in order

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to select the best binding conformations with a protein of known three-dimensional structure [15]. For the molecular docking analysis the Schrodinger 9.3 was used. In that QikProp tool was used for screening of pharmacological and pharmacokinetic parameters. Receptor docking was done by Glide in Schrodinger suite [16]. Glide [Grid-Based Ligand Docking with Energitics] is an integrated platform and a systematic approach for searching conformations, orientations and positions of ligand in the receptor site using a series of hierarchical filters which improves the binding affinities by lowering the penalties.

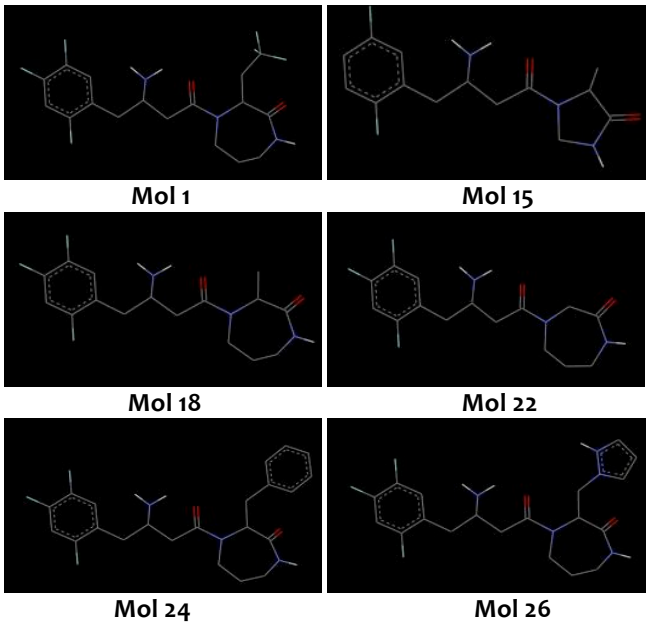

Figure 1: Showing the molecules designed from the article

ADME prediction

Using the QikProp module of the Schrödinger 9.3 software to predict pharmacokinetic properties. This is standard as being dissimilar to other 95% of the known drugs. Predicted significant ADME properties in accordance with Lipinski's rule of five, QikProp were used to evaluate the drug-likeness of the lead molecules by assessing their physicochemical properties to observe the range of the Lipinski rule for drug-like molecules [17]. These compounds were also evaluated for their drug-like behavior through analysis of pharmacokinetic parameters required for ADME.

Compounds obtained finally after ADME analysis is to be prepared for docking using glide xp mode. Ligprep tool is used for preparing Ligands by optimizing geometries through OPLS-2001 Force Field. Prepared Ligands were rigidly docked to receptors of 2IIT using Glide extra precision function. Initially, a set of ligand poses, which were generated by torsional minima, were clustered and docked as a single object. Ligands with more than 300 atoms or 50 rotatable groups were not docked.

RESULTS AND DISCUSSION

Molecular docking has become a vital part of contemporary drug research. In this study, all these ligands are docked with the original protein 2IIT. The process of docking using the Receptor Grid Generation protocol with centroid at the active site of the enzyme generated grid file represented the shape and properties of receptor on a grid for more accurate scoring of ligand pose. Docked ligands with the high throughput screening (HTVS) mode and obtained molecules which were subjected to the Glide extra precision (XP) mode of docking performed extensive sampling and provides reasonable binding poses those interacted with the residues that bind substrate analogs in the active site. Docked poses with original ligand 2IIT resulted with the hydrogen bond and ligand interactions with amino acid residues such as serine, glutamic acid, tyrosine respectively. Where as in other selected compounds, screened against original protein resulted that the interactions of H-Bonds formed by the Ligand with the active residues of 2IIT i.e. serine, glutamic acid, tyrosine, aspargine, arginine, Histidine with modest discrepancy with its amino acid positions (Table 1). This amino acid positions play a vital role in determined the activity of the screened ligands when compared with the original ligand. Binding affinity glide scores [G-scores] were better than the reference i.e. standard score (Table 2).

Table 1: Showing the molecules from the article with their respective IC 50 values and interactive residues along with Hydrogen bonds.

Molecule id	Activity (IC_{50}) in nM	No of H-bonds	Interacting residues
2IIT ligand	2.6	3	SER 630,TYR 662, GLU 206,
Mol 1	2.6	5	TYR 662, GLU 206, GLY549, SER552
Mol 15	160	4	TYR 662,SER209, GLU 206,TYR 547
Mol 18	6.6	4	TYR 662,GLU 206, GLU 205
Mol 22	140	6	SER 630, TYR 547, TRP 629, ASN 710, ARG 125,
Mol 24	0.91	3	SER 630, HIS 740, ARG 125, CYS551
Mol 26	0.29	2	ARG560, TYR 547, GLU 205

Table 2: Values described about ADME molecular properties.

Ligand	G-Score	CNS	mol_MW	QPlogBB	Human Oral Absorption	Percent Human Oral Absorption	Rule Of Five	#Ring atoms	Rule Of Three
CRYSTAL LIGAND	-6.78	1	411.346	0.138	3	75.944	0	13	0
mol-1	-3.09	2	436.763	1.709	1	100	1	14	2
mol-15	-5.13	2	324.548	1.292	1	100	1	11	2
mol-18	-2.82	2	380.656	1.514	1	100	1	14	2
mol-22	-3.03	2	366.629	1.465	1	100	1	14	2
mol.24	-2.86	2	456.753	1.371	1	100	1	20	2
mol-26	-2.6	2	464.816	1.554	1	100	1	19	1

Properties based on ADME analysis assessed for their drug-like properties of these ligands with their molecular weights were < 500 Daltons with < 5 hydrogen bond donors, < 10 hydrogen bond acceptors and QPlogPo/w < 5; these properties are well within the acceptable range of the Lipinski rule for drug-like molecules. Bioavailability of these compounds resulted in the partition coefficient (QPlogBB) and water solubility (QPlogS), critical for estimation of absorption and distribution of drugs within the body, overall, the percentage human oral absorption for the compounds tested ranged from 75% to 100%. All these pharmacokinetic parameters are within the acceptable range (Table 2).

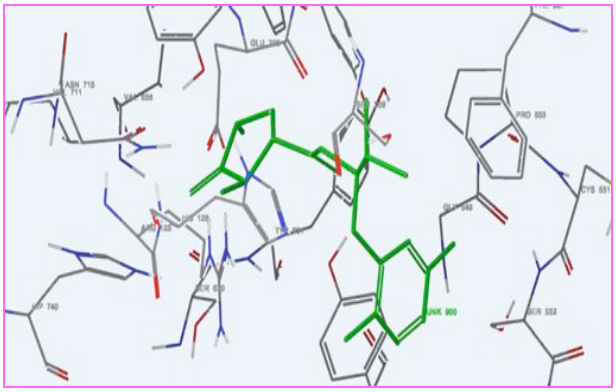

Figure 2: Showing the 2IIT_crystral ligand and its interactions with 2IIT.

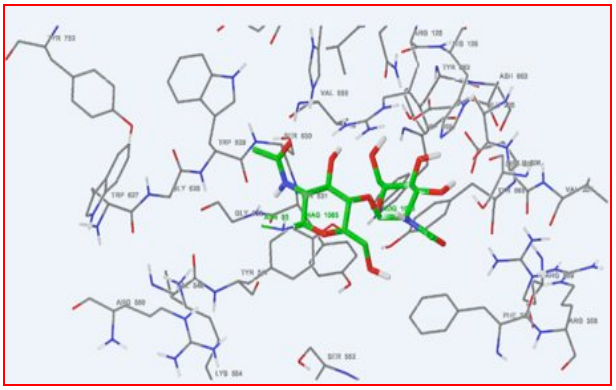

Figure 3: Showing the molecules mol_15 and its interactions with 2IIT.

Predictions of ADME molecular properties for selected ligands have been verified to be supportive, and they were hardened to illustrate a lot of molecular properties, such as lipophilicity, molecular flexibility, etc. In this study, we thoroughly examined the molecular properties that are extensively used in ADME predictions. Molecular properties include Molecular Weight, QPlogBB, CNS, Human absorption etc. All these properties are represented in (Table 2) for each ligand. It is a general phenomenon that increasing lipophilicity is usually favorable for the binding of the studied molecules to protein receptors.

In this study the mol-15 is inhibiting the DPP IV equally to the crystal ligand. When compare to crystal ligand the molecular weight is low and the Predicted brain/blood partition coefficient is high. Mol-15 is having the oral absorption is 100% while the crystal is having 76%. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion.

CONCLUSION

There is an increasing interest to inhibit DPPIV in the context of diabetes. Hence, the structure of DPPIV (PDB ID: 2IIT) was screened using molecular docking techniques for interactions with its hydrogen's and amino acid residues. Data presented in Table 1 with corresponding ADME data in Table 2 shows compounds with better binding and ADME properties compared to other compounds. MOL 15 exhibited with acceptable result. Therefore, these observations find application for the consideration of such compounds for further validation towards inhibiting DPPIV. This study demonstrates that structure-based virtual screening represents a viable approach to the development of new DPPIV inhibitors. Although this is a relatively small-scale study, 6 new micro molar inhibitors were discovered. These compounds appear to be suitable as leads for further studies.

REFERENCES

1. Barnett A, DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int. J. Clin. Pract, 2006, 60 (11): 1454–70.

2. Gupta R, Walunj SS, Tokala RK, Emerging drug candidates of dipeptidyl peptidase IV (DPP IV) inhibitor class for the treatment of Type 2 Diabetes, Curr Drug Targets, 2009,10: 71-87.

3. Orsakov, C. Diabetologia 1992, 35, 701.

4. Dardevet D, Moore MC, Neal D, DiCostanzo CA, Snead W, Cherrington AD, Insulin-independent effects of GLP-1 on canine liver glucose metabolism: duration of infusion and involvement of hepatoportal region. Am J Physiol Endocrinol Metab 2004, 287:E75–E81.

5. Behme, Margaret T, Dupré, John, McDonald, Thomas J, Glucagon-like peptide 1 improved glycemic control in type 1 diabetes, BMC Endocrine Disorders, 2003, 3:3.

6. Kameoka J, Tanaka T, Nojima Y, Schlossman SF, Morimoto C, Direct association of adenosine deaminase with a T cell activation antigen, CD26, Science 1993, 261 (5120): 466–9.

7. Pratley RE and Salsali A, Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. Curr Med Res Opin, 2007, 23: 919-931.

8. Van Damme, Paul Proost, The role cd26/dpp iv in chemokine processing, Chemokines By Alberto Mantovani

9. Tesfaye Biftu et al., (3R)-4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepan-2-one, a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes, Bioorganic & Medicinal Chemistry Letters, 2007,17 49–52

10. Kanchanamala P et al., Drug design studies on dipeptidyl peptidase IV using auto dock tools, Journal of Pharmacy Research 2011,4(11), 4113-4116.

11. Li Z, Wan H, Shi Y, Ouyang P, Personal Experience with Four Kinds of Chemical Structure Drawing Software: Review on ChemDraw, ChemWindow, ISIS/Draw, and ChemSketch. J. Chem. Inf. Comput. Sci. 2004, 44 (5): 1886–1890.

12. DeLano WL, The PyMOL User's Manual, Palo Alto, CA, USA, DeLano Scientific, 2002.

13. PW Walters, Virtual screening-an overview, Drug Discovery Today, 3:160 (1998).

14. SJ Daharwal Computer aided drug design and bioinformatics: A current tool for designingPharmainfo.net

15. Orgensen WL, Rusting of the lock and key model for protein-ligand binding, Science 1991, 254 (5034): 954–5.

16. Richard A. Friesner et al., Glide: A New Approach for Rapid, Accurate Docking and Scoring Method and Assessment of Docking Accuracy, J. Med. Chem., 2004, 47 (7), pp 1739–1749.

17. Lombardo F et al, In Silico ADME Prediction: Data, Models, Facts and Myths Mini Reviews in Medicinal Chemistry, 2003, Volume 3, Number 8, pp. 861-875(15).

18. www.rcsb.org/pdb:structure summary.

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