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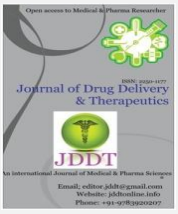

Open Access Research Article

De-novo Design of Some New Lead Compounds as Dipeptidyl Peptidase-IV Inhibitors

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ABSTRACT

The use of dipeptidyl peptidase-IV (DPP-IV) inhibitors has been an established practice in the management of type-2 diabetes mellitus in recent years. The present study undertakes *De-novo* design protocol for the exploration of some new lead compounds which can further be optimized for their development as DPP-IV inhibitors. The e-lea3d drug design pipeline was used to "grow" the molecules inside the active site of DPP-IV and molecular docking results were used for the filtration of compounds with important binding interactions.

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INTRODUCTION:

Diabetes mellitus (DM) has two major subtypes: Type-1 (T1DM) and Type 2 (T2DM). T1DM essentially results from inhibition of insulin secretion whereas a resistance to insulin is the characteristic of T2DM. Initially in T2DM, the enhanced synthesis and secretion of insulin by pancreas makes up for the resistance but, over time this ability decreases to keep up the blood glucose at normal levels. Amongst various reasons for insulin resistance, one is the very short half life of the incretin hormones glucagon like peptide (GLP) and gastric inhibitory peptide (GIP)[1]. These hormones improve the function and efficiency of pancreatic β cells leading to an indirect positive effect on insulin release. The truncation of GLP through hydrolysis by DPP-IV renders this enzyme a striking target for T2DM therapy. Furthermore in recent past there have been many DPP-IV inhibitors launched throughout the world, sitagliptin, vildagliptin, alogliptin and saxagliptin to name a few[1]. In continuation to the above efforts, new scaffolds can be explored for development of new DPP-IV inhibitors. Thus the present study employs de-novo design strategy for identification of new leads capable of DPP-IV inhibition. *De-novo* design is one of the essential tools in drug discovery process in modern age. As an iterative process using three-dimensional structure of the receptor to design newer molecules, it involves structure determination of the lead target complexes and designing of improved leads using molecular modeling tools. Design of new chemical classes of compounds that present similar substituents to the target using a template or scaffold, which is chemically distinct from previously characterized leads is one of the distinguishing features of this method[2].

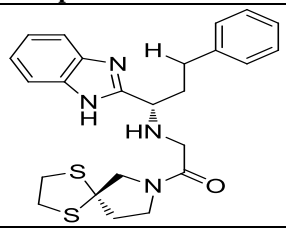
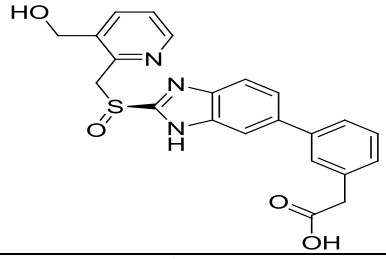
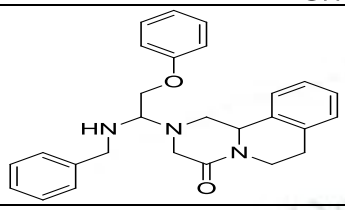
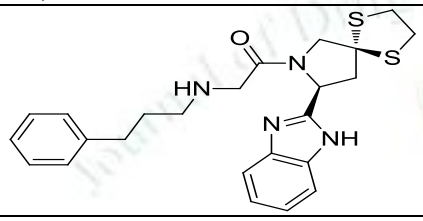
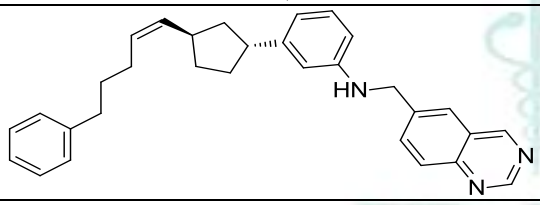
MATERIALS AND METHODS:

The e-lea3d drug design pipeline[2] was used for generating and rearrangement of fragments to generate new molecular structures. It uses PLANTS (Protein Ligand ANT System)[3] as the docking tool for docking and scoring of the newly generated structures. The crystal structure of DPP-IV bound to sitagliptin (PDB ID: 1X70) was retrieved from protein data bank[4]. The structure was prepared through addition of hydrogens and minimizing through YASARA web server[5]. The water molecules were removed from the minimized structure and the protein molecule was loaded to the pipeline. The active site coordinates were defined as X: 40.000, Y: 52.000, Z: 35.785 and the radius was defined as 10 Å.

RESULTS AND DISCUSSION

The present study encompasses exploration of new scaffolds as DPP-IV inhibitors through de-novo design approach. The program PLANTS was used for docking and scoring the structures generated through rearrangement of fragments of FDA approved drugs. Through iterative runs, different conformations of ~250 structures were docked and scored. Among these, some of the compounds with their binding scores and interactions are reported hereunder:

Table 1: Some of the Top scoring compounds retrieved from de-novo design strategy

S. No.	Compound structure	Binding score	Polar interactions
1		-106.313	GLU 205
2		-105.23	GLU 206, VAL 207, ARG 358, TYR 547, TYR 662, ASN 710
3		-104.865	GLU 205, TYR 547
4		-104.859	TYR 547, TYR 666
5		-103.891	-

Among the compound reported in Table 1, compound Nos. 1, 2 and 3 show polar interactions with either GLU205 or GLU206. The interaction with either or both the amino acids may render the enzyme inactive towards GLP inhibitory activity. Therefore these compounds are expected to show DPP-IV inhibitory activity. Further compound 2 shows additional interactions with VAL 207, ARG 358, TYR 547, TYR 662 and ASN 710 indicating that the interactions with the active site will be more stable as compared to compounds 1 and 3.

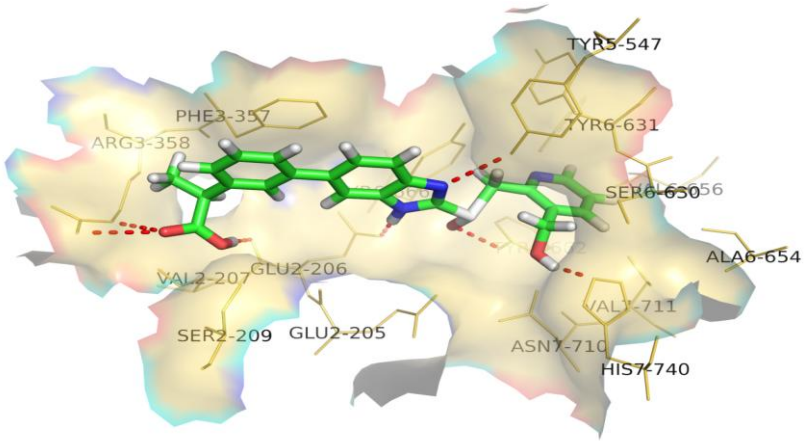


Figure 1: Binding mode of compound 2 (carbons: green, nitrogens: blue, oxygens: red, hydrogens: white) with the active site residues (yellow) of DPP-IV

CONCLUSION:

DPP-IV inhibition is among the validated strategies for management of diabetes. In the past decade, DPP-IV inhibitors have found their use both as second line (with metformin) and first line treatments of T2DM. The present study focused on finding new scaffolds for DPP-IV inhibition. Among these, a benzimidazole derivative, compound 2 ((S)-2-(3-(2-(((3-(hydroxymethyl)pyridin-2-yl)methyl)sulfinyl)-1H-benzo[d]imidazol-6-yl)phenyl)acetic acid) was found to have polar interaction with GLU206, which is responsible for DPP-IV enzymatic activity, signifying its DPP-IV inhibitory potential. Furthermore, interactions with other active site residues imply probable stability of the complex. Thus this compound can prove to be a promising lead for the development of novel DPP-IV inhibitors.

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