ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 05, pp.30809-30812, May, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

IN SILICO DESIGN OF PYRIMIDINEDIONE-BASED NOVEL DPP-IV INHIBITORS FOR ANTIDIABETIC ACTIVITY

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ARTICLE INFO

Article History:
Received 23rd February, 2016
Received in revised form
04th March, 2016
Accepted 26th April, 2016
Published online 10th May, 2016

Key words:
Dipeptidyl Peptidase IV,
Molecular Docking,
Pyrimidinedione,
Alogliptin,
Binding Scores etc.,

ABSTRACT

DPP-4 Inhibitors are the class of oral hypoglycemics that block DPP-4 (Dipeptidyl peptidase-4), used to treat T2DM. The first agent of the class Sitagliptin was approved by the FDA in 2006. Most of the antidiabetic have major side effects like weight gain, hypoglycemia, GI adverse reactions etc. DPP-IV Inhibitors are devoid of such major side effects. Designing pyrimidinedione-based compounds may probably give safe pharmacological profile with significant antidiabetic activity. Compounds are designed rationally and molecular docking studies are performed on DPP-IV subunits by PyRx 0.8 (Autodock vina based scoring function) and compared by Alogliptin (FDA Approved, 2013). These compounds possess significant binding scores on comparision with molecular docking study of Alogliptin. Futher, these compounds are designed on the basis of synthetic outcomes. Now, under synthetic procedures, may probably result in compounds with significant DPP-IV Inhibitory activity. Satisfactory *in vitro*, *in vivo* and toxicological activity can lead to the development of drug candidate since this category of compounds have negligible side effects.

Citation: Vibhu Jha, Anurag Agrawal, Swati Sahawal, Kumari Neha, Divya Agrawal, Neha Chopra and Sunanda Kr. Mandal 2016. "In silico design of pyrimidinedione-based novel dpp-iv inhibitors for antidiabetic activity", *International Journal of Current Research*, 8, (05), 30809-30812.

INTRODUCTION

The World Health Organization estimates the number of people with diabetes to be approximately 180 million. This number is projected to double by 2030. Type 2 diabetes (T2D) is a progressive disease characterized by high levels of glucose resulting from insulin resistance and impairment of insulin secretion. If left untreated, hyperglycemia may cause nephropathy, neuropathy, retinopathy, and atherosclerosis. T2D causes significant morbidity and mortality and results in considerable expense to patients, their families, and society (http://www.idf.org/diabetesatlas/5e/the-global-burden. (Acc essed 4.6.14.)). DPP-4 Inhibitors are the class of oral hypoglycemics that block DPP-4 (Dipeptidyl peptidase-4), used to treat T2DM. The first agent of the class Sitagliptin was approved by the FDA in 2006. Glucagon increases blood glucose levels and DPP-4 inhibitors reduce glucagon and blood glucose levels.

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The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels (Feng et al., 2007). DPP-4 Inhibitors have no major side effects but a marginally statistically significant increase in heart failure. The DPP-4 inhibitors are now considered as one of the well established therapies available for T2DM. At present six competitive reversible inhibitors are in market with USFDA approvals in different years while many more are in different phases of clinical trials. Saxagliptin, sitagliptin and linagliptin are licenced in most of the world; vildagliptin is licenced in Europe and Latin America and alogliptin is licensed in Japan and US (Takeda Submits New Drug Application for Alogliptin, 2008). Alogliptin (trade name Nesina in US and Vipidia in Europe) is an orally administered anti-diabetic drug in the DPP-4 inhibitor class, developed by Syrrx, a company which was acquired by Takeda Pharmaceutical Company in 2005. Like other members of the gliptin class, it causes little or no weight gain, exhibits relatively little risk of causing hypoglycemia, and exhibits relatively modest glucose-lowering activity.

Alogliptin and other gliptins are commonly used in combination with metformin in patients whose diabetes cannot adequately be controlled with metformin alone (Faber et al., 1990).

MATERIALS AND METHODS

Accession of Target Protein

The three-dimensional structures of DPP-IV (PDB ID: 3G0B) was downloaded from the RCSB protein Data Bank in pdb format (Zhang et al., 2011).

Selection of Ligands

Chemical structure of Alogliptin (Fig. 1) was extracted from. pdb file and prepared by using Chem BioDraw Ultra 12.0 and Chem 3D Ultra 8.0 and saved in pdb format. Similarly, ligands (Fig. 2-9) were designed and prepared (Li et al., 2004).

Optimization of Target Protein and ligands

PDB Coordinates of target protein, Alogliptin and ligands were optimized by using Discovery Studio 4.5, UCSF Chimera 1.10.2. and Chem 3DUltra 8.0. Mol2 file was converted to pdb file by using Open Babel GUI software (Pettersen et al., 2004).

Docking Analysis

A computational approach of ligand-protein docking was done to analyze the binding scores and interactions. Docking was done by PyRx 0.8 which uses autodock vina based scoring function (Trott et al., 2010). "Grid point" has been assigned for each with respect to DPP-IV protein. After getting binding scores, respective files were uploaded to Pymol 1.1 and Discovery Studio 4.5 for knowing the different interactions and amino acids involved.

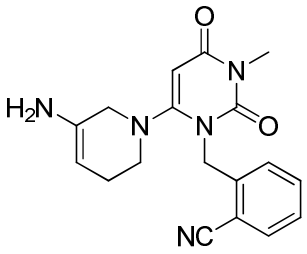

Fig. 1. Alogliptin

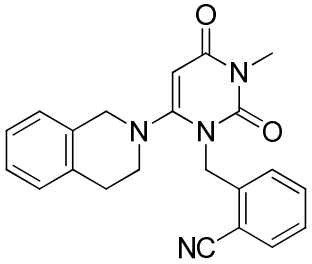

Fig. 2. Benzopiperidine(CN)

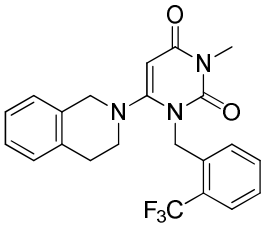

Fig. 3. Benzopiperidine (CF_3)

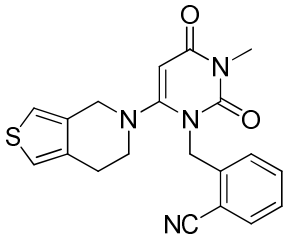

Fig. 4. Thienopiperidine (CN)

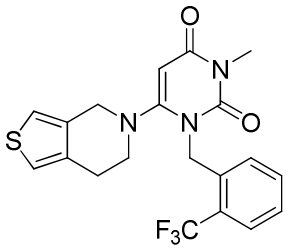

Fig. 5. Thienopiperidine (CF_3)

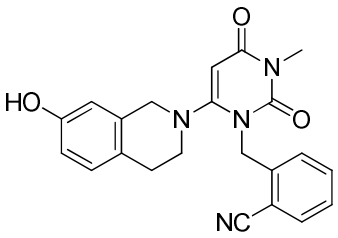

Fig. 6. Tetrahydroisoquinoline-7-OH (CN)

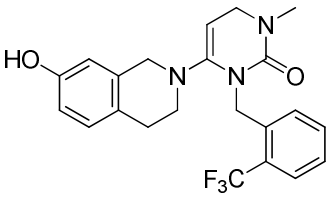

Fig. 7. Tetrahydroisoquinoline-7-OH (CF_3)

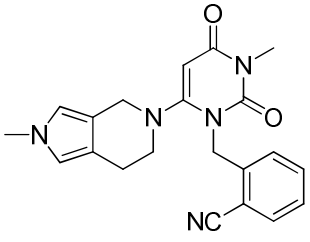

Fig. 8. Methyl pyrrolopiperidine (CN)

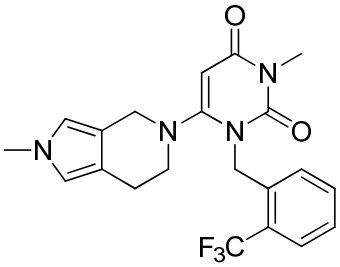

Fig. 9. Methyl pyrrolopiperidine (CF_3)

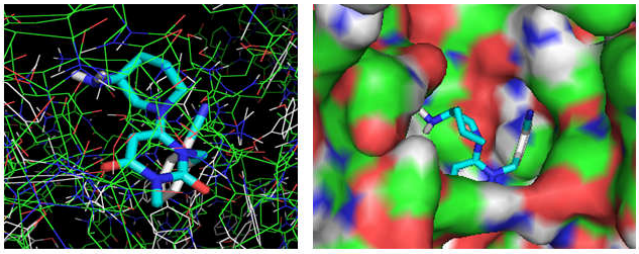

Fig. 10. Alogliptin in DPP-IV Subunits

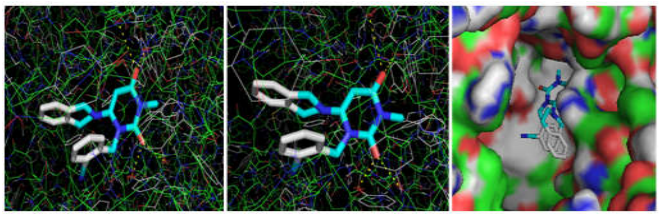

Fig. 11. Benzopiperidine (CN) in DPP-IV Subunits

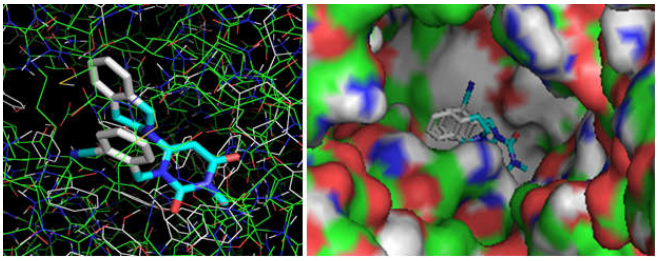

Fig 12. Benzopiperidine (CF_3) in DPP-IV Subunits

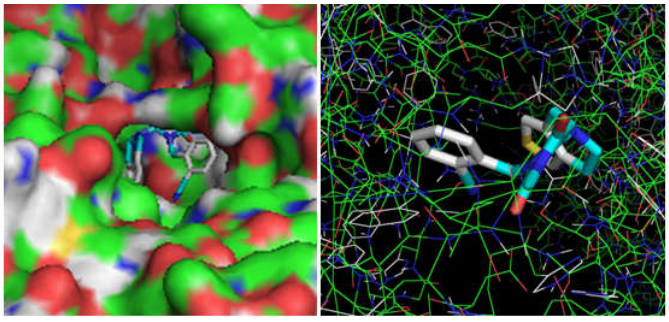

Fig 13. Thienopiperidine (CN) in DPP-IV Subunits

RESULTS AND DISCUSSION

Molecular modeling results of designed compounds are shown in Table 1.

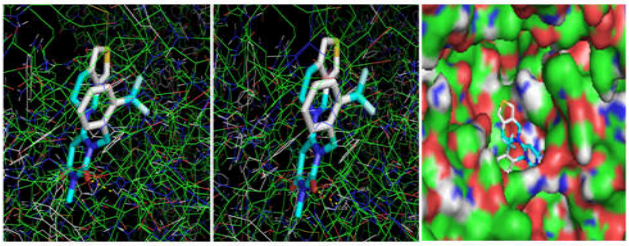

Fig 14. Thienopiperidine (CF_3) in DPP-IV Subunits

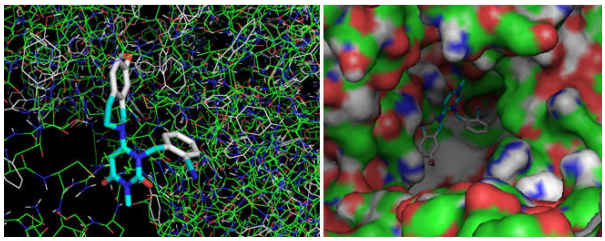

Fig 15. Tetrahydroisoquinoline-7-OH (CN) in DPP-IV Subunits

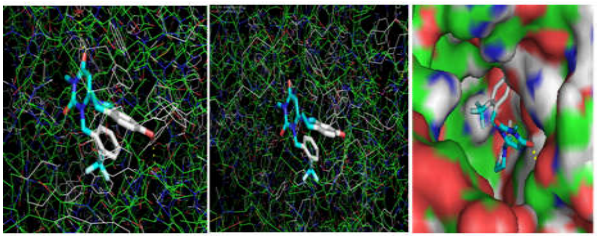

Fig 16. Tetrahydroisoquinoline-7-OH (CF_3) in DPP-IV Subunits

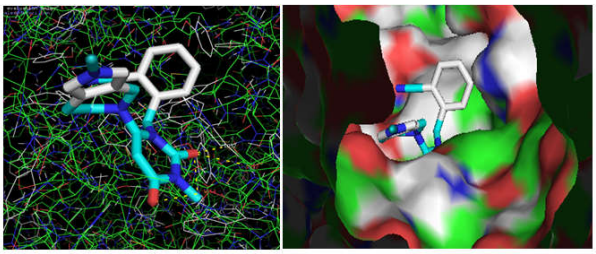

Fig 17. Methyl pyrrolopiperidine (CN) in DPP-IV Subunits

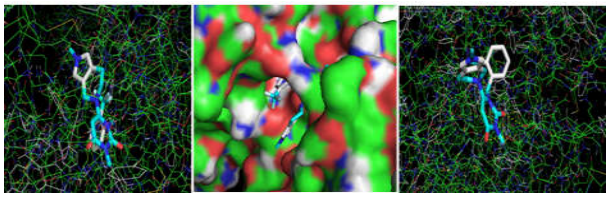

Fig 18. Methyl pyrrolopiperidine (CF_3) in DPP-IV Subunits

These compounds have shown highly significant binding energies as compared to standard drug Alogliptin which has been FDA approved in 2013. Some of the compounds lack Hydrogen bonding with DPP-IV subunits, that means they are highly involved in hydrophobic interactions with DPP-IV subunits.

Table 1. Docking results of Compounds on DPP-IV subunits

Sl. No.	Compound	Binding Affinity (kcal/mol)	RMSD Upper bound	RMSD Lower bound	Amino acids involved in H-bonding
1.	Alogliptin	-7.7	0.0	0.0	---
2.	Benzopiperidine(CN)	-8.2	0.0	0.0	Tyr 2809, Tyr 2694, Tyr 2813, Asn 2857
3.	Benzopiperidine(CF_3)	-9.4	0.0	0.0	---
4.	Thienopiperidine (CN)	-8.0	0.0	0.0	---
5.	Thienopiperidine (CF_3)	-7.9	0.0	0.0	Gln 2181
6.	Tetrahydroisoquinoline-7-OH (CN)	-8.3	0.0	0.0	---
7.	Tetrahydroisoquinoline-7-OH (CF_3)	-7.9	0.0	0.0	Gly 2888, Asp 2692
8.	Methyl pyrrolopiperidine (CN)	-8.3	0.0	0.0	Arg 1050, Arg 1052, Ser 1054
9.	Methyl pyrrolopiperidine (CF_3)	-8.3	0.0	0.0	---

The highest binding score was found to be -9.4 kcal/mol of Benzopiperidine (CF_3). Docking images of all compounds are given in Fig.10-18. These compounds were designed by the approach of ligand-based drug design. Alogliptin was taken as reference compound which has resulted in good antidiabetic activity with highly significant safety profile. Structurally similar compounds may show similar pattern of binding in DPP-IV pockets, therefore our next step is the synthesis of these pyrimidinedione-analogues. Most of the antidiabetic have major side effects like weight gain, hypoglycemia, GI adverse reactions etc. Designing these pyrimidinedione-based compounds may probably give safe pharmacological profile with significant antidiabetic activity after successful synthesis and characterization.

Conclusion

Designed compounds have shown significant binding energies, few of them are excellent in terms of binding in DPP-IV subunits. Structurally, these are pyrimidinedione-based compounds designed with the reference of Alogliptin. These compounds are now under synthetic procedures, after characterization, may probably give significant DPP-IV inhibitory *in vitro* activity. Further, satisfactory in vitro DPP-IV inhibitory activity may lead to in vivo and toxocoligal studies, ultimately to achieve a compound with good antidibaetic activity with less or negligible toxicity like Alogliptin.

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