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BRIEF REVIEW ON MOLECULAR DOCKING OF DPP-4 INHIBITORS IN DIABETES

Gadge Shrutika Pralhad*[1], Lokhande Rahul Prakash[2], Gaikwad Sakshi Rajesh[3], Dere Aditya Sampat[4], Dongare Tanvi Sopan[5], Datkhil Parth Dnyaneshwar[5], Dhaygude Saurabh Hanumant[6], Gadekar Sainath Vijaysingh[7]

[1,3,4,5,6,7]Student, Samarth Institute of Pharmacy, Belhe, Maharashtra, India.
[2]Associate Professor, Department of Pharmaceutical Chemistry, Samarth Institute of Pharmacy, Belhe, Maharashtra, India.

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***Corresponding Author: Gadge Shrutika Pralhad**
Student, Samarth Institute of Pharmacy, Belhe, Maharashtra, India.
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ABSTRACT

Dipeptidyl Peptidase-4 (DPP-4) enzyme inhibitors have become an important group of drugs used to treat Type 2 Diabetes Mellitus (T2DM), mainly because they help increase incretin hormone levels and improve blood glucose control. In recent years, Molecular Docking has emerged as a valuable computational method for discovering and designing new DPP-4 inhibitors. It allows researchers to understand how different molecules interact with the enzyme at the molecular level. This review focuses on how docking techniques are used to study ligand–protein interactions, binding strength, and how well compounds fit into the active site of the DPP-4 enzyme. Important interactions such as hydrogen bonding, hydrophobic interactions, and π–π stacking with key amino acid residues like Glu205, Glu206, and Ser630 play a major role in inhibitor effectiveness. Additionally, combining docking with ADMET analysis and molecular dynamics simulations helps predict drug behavior and stability more accurately. Overall, molecular docking remains a cost-effective and efficient approach in developing safer and more effective antidiabetic drugs.

KEYWORDS: DPP-4 inhibitors, molecular docking, Type 2 diabetes mellitus, ADMET, virtual screening.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic and progressive metabolic disorder characterized by persistent hyperglycemia resulting from a combination of insulin resistance and impaired insulin secretion. It accounts for the majority of diabetes cases worldwide and is associated with serious long-term complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy. The rising global prevalence of T2DM has created an urgent need for effective, safe, and affordable therapeutic strategies.

One of the key physiological pathways involved in glucose regulation is the incretin system. Incretin hormones, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from the gut in response to food intake and stimulate insulin secretion in a glucose-dependent manner. However, these hormones are rapidly degraded by the enzyme Dipeptidyl Peptidase-4 (DPP-4) enzyme, which limits their therapeutic potential. Inhibition of DPP-4 prolongs the activity of incretin hormones, thereby enhancing insulin release, reducing glucagon levels, and improving overall glycemic control without causing significant hypoglycemia.

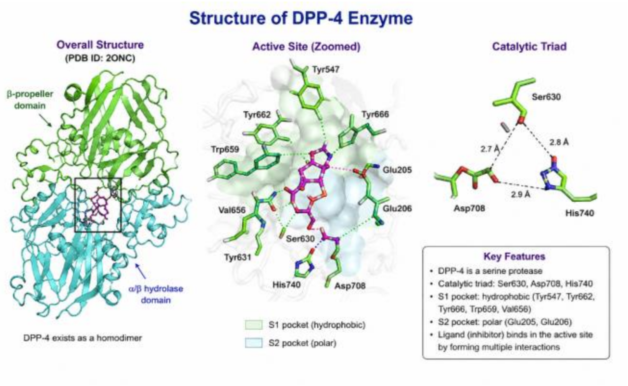
Based on this mechanism, DPP-4 inhibitors have emerged as an important class of oral antidiabetic drugs. Clinically approved agents such as Sitagliptin, Vildagliptin, Saxagliptin, and Linagliptin are widely used due to their favorable safety profile, weight neutrality, and low risk of hypoglycemia. Despite these advantages, limitations such as moderate efficacy, cost, and potential side effects have driven ongoing research to identify more potent and selective inhibitors.

In recent years, Molecular Docking has become a crucial tool in the field of drug discovery and development. It is a computational technique that predicts the preferred orientation of a ligand when bound to a target protein, helping researchers understand binding interactions at the molecular level. Docking not only provides insights into binding affinity and stability but also helps in identifying key amino acid residues involved in ligand interaction. This information is essential for rational drug design and optimization.

In the context of DPP-4 inhibitors, molecular docking has been extensively used to screen large libraries of synthetic compounds. These studies focus on identifying compounds that can effectively bind to the active site of the DPP-4 enzyme, particularly interacting with critical residues such as Glu205, Glu206, and Ser630. The results of docking studies are typically expressed in terms of binding energy, where more negative values indicate stronger interactions and higher inhibitory potential.

Furthermore, molecular docking is often integrated with ADMET analysis (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and molecular dynamics simulations to provide a comprehensive understanding of a compound's pharmacokinetic behavior and stability in a biological environment. This combined approach significantly enhances the efficiency of drug discovery by reducing the need for extensive experimental screening.

Structure of DPP-4



The Dipeptidyl Peptidase-4 (DPP-4) enzym**e** is a serine protease belonging to the prolyl oligopeptides family. It exists as a homodimer and contains two major domains:

- β-propeller domain – regulates substrate access
- α/β hydrolase domain – contains the catalytic site

Catalytic Mechanism

The catalytic triad consists of:

- Ser630 (nucleophile)
- Asp708 (stabilizer)
- His740 (proton donor/acceptor)

Binding Pockets

- S1 pocket: hydrophobic (Tyr662, Tyr666, Trp659)
- S2 pocket: charged (Glu205, Glu206)

Role of DPP-4 enzyme

1. Role in Glucose Metabolism (Main Function)

The most important function of DPP-4 is to break down incretin hormones such as GLP-1 (glucagon-like peptide-1) and GIP. These hormones are released after eating and help:

- Stimulate insulin secretion
- Reduce glucagon release
- Slow gastric emptying

However, DPP-4 rapidly inactivates these hormones (within minutes). Because of this, the beneficial effects of incretins are short-lived. In simple terms, DPP-4 acts like a “switch-off” mechanism for insulin-stimulating hormones. That is why inhibiting DPP-4 helps in managing Type 2 Diabetes Mellitus, as it allows incretin hormones to work longer and control blood glucose more effectively.

2. Role in Immune System Regulation

DPP-4 is also known as CD26 and is involved in immune responses. It helps in:

- Activation of T-cells
- Regulation of cytokine production
- Interaction with other immune signaling molecules

This means DPP-4 is not just a metabolic enzyme but also plays a role in immune function and inflammation.

3. Role in Protein and Peptide Regulation

DPP-4 removes dipeptides from the N-terminal end of proteins, especially those containing proline or alanine. Through this action, it regulates:

- Hormones
- Neuropeptides
- Chemokines

This affects various biological processes like appetite, mood, and cell signaling.

4. Role in Cardiovascular Function

DPP-4 indirectly influences cardiovascular health by regulating peptides involved in:

- Blood pressure control
- Vascular function
- Endothelial activity

Fundamentals of Molecular Docking

Molecular Docking is a computational approach used to predict the preferred orientation of a ligand when bound to a protein receptor.

Steps in Docking

1. Protein preparation (removal of water, addition of hydrogens)
2. Ligand preparation (energy minimization)
3. Grid generation (active site selection)
4. Docking simulation (pose generation)
5. Scoring and ranking

Scoring Functions

Binding affinity is expressed in kcal/mol:

- More negative value → stronger binding
- Includes van der Waals, electrostatic, and hydrogen bonding contributions

Key Binding Interactions in DPP-4 Inhibitors

The effectiveness of Dipeptidyl Peptidase-4 (DPP-4) enzyme inhibitors mainly depends on how well the drug molecule fits and interacts within the enzyme’s active site. You can think of it like a “lock and key” system—if the ligand (drug) fits perfectly into the enzyme (lock), it can block its activity effectively.

1. Hydrogen Bonding (Most Important Interaction)

Hydrogen bonds are one of the strongest and most critical interactions in DPP-4 inhibition.

- These bonds usually form between the ligand and key amino acids like **Glu205, Glu206, and Ser630**.
- They help anchor the drug firmly in the active site.
- More hydrogen bonds generally mean better binding stability and higher inhibitory activity.

2. Hydrophobic Interactions

The DPP-4 active site contains hydrophobic (water-repelling) regions, especially in the S1 pocket.

- Key residues involved: Tyr662, Tyr666, Trp659, Val656
- Non-polar parts of the drug interact with these residues

3. *π–π* Stacking Interactions

Many DPP-4 inhibitors contain aromatic rings (benzene-like structures).

- These rings interact with aromatic amino acids like Tyr547 and Trp629
- This stacking stabilizes the ligand inside the binding pocket

4. Electrostatic (Ionic) Interactions

- Occur between charged groups of the ligand and amino acids like Glu205 and Glu206
- These interactions strengthen binding and improve selectivity

5. Covalent/Strong Interaction with Catalytic Site

Some inhibitors interact closely with the catalytic residue Ser630.

- This can block the enzyme’s activity directly
- Seen in certain drugs like Vildagliptin

6. Role of Binding Pockets (S1 and S2)

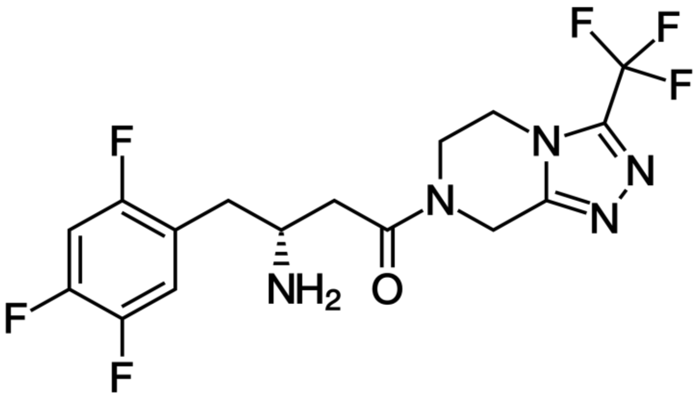
- S1 pocket (hydrophobic): Stabilizes non-polar parts of the drug
- S2 pocket (charged): Forms hydrogen bonds and ionic interactions

Molecular Docking of Synthetic DPP-4 Inhibitors

Molecular docking studies of synthetic inhibitors help us understand how different drug molecules interact with the Dipeptidyl Peptidase-4 (DPP-4) enzyme at the molecular level. These studies compare binding affinity, interaction patterns, and stability of inhibitors within the active site. Below is a comparative overview of 10 commonly studied synthetic DPP-4 inhibitors.

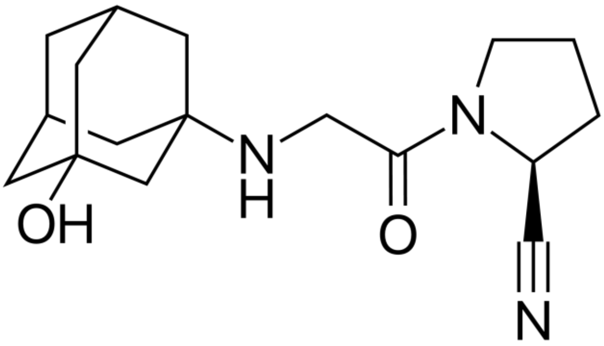
Sitagliptin

Sitagliptin is one of the most commonly used DPP-4 inhibitors and is often taken as a reference drug in studies. It binds strongly to the enzyme through hydrogen bonding, helping to control blood sugar effectively.



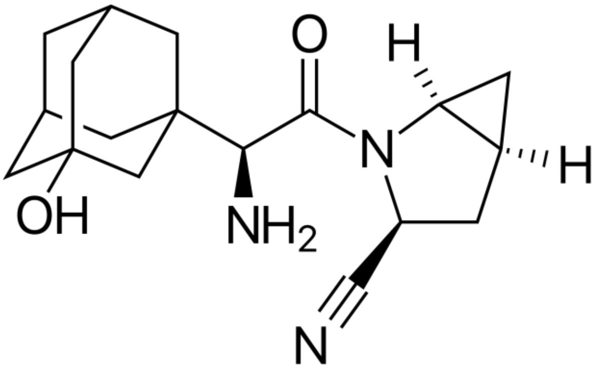
Vildagliptin

Vildagliptin works by interacting closely with the active site of the enzyme, especially the catalytic residue. This strong interaction helps block DPP-4 activity and improves insulin release.



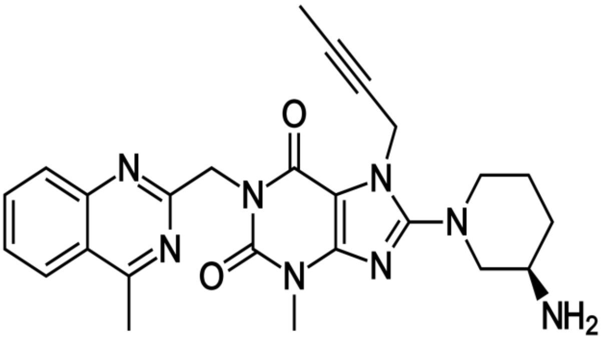
Saxagliptin

Saxagliptin shows good binding with both hydrophobic and hydrogen bond interactions. It fits well into the enzyme's active site, making it effective in lowering glucose levels.



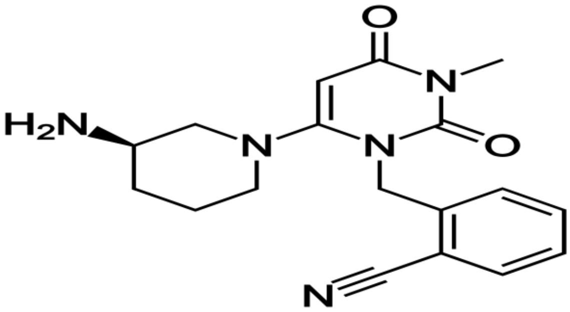
Linagliptin

Linagliptin has a strong and stable binding due to its aromatic structure. It forms multiple interactions, which makes it one of the more potent DPP-4 inhibitors.



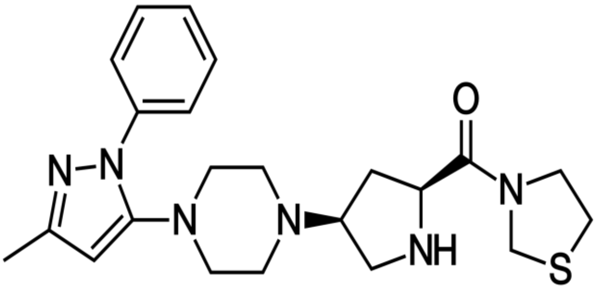
Alogliptin

Alogliptin binds selectively to the enzyme and forms stable interactions with key amino acids. It is known for its good safety profile and effective glucose control.



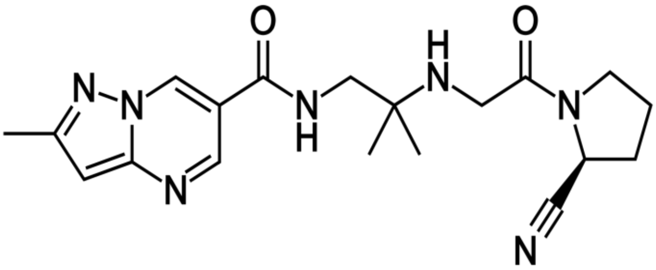
Teneligliptin

Teneligliptin has a unique structure that allows it to form multiple strong interactions inside the enzyme. This leads to high binding affinity and long-lasting action.



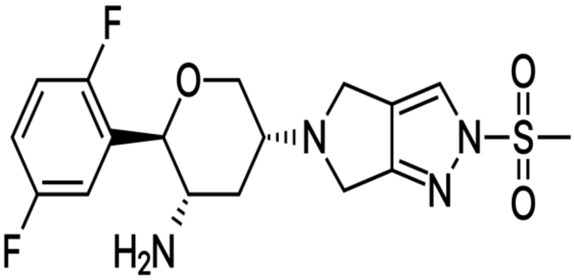
Anagliptin

Anagliptin shows moderate binding with the DPP-4 enzyme through hydrogen bonds. It provides a balanced effect in controlling blood glucose levels.



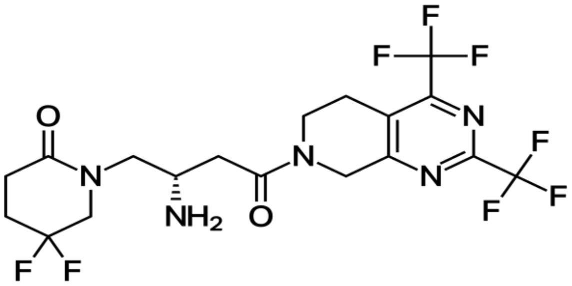
Omarigliptin

Omarigliptin is known for its long duration of action and is usually taken once weekly. It forms stable hydrophobic interactions with the enzyme.



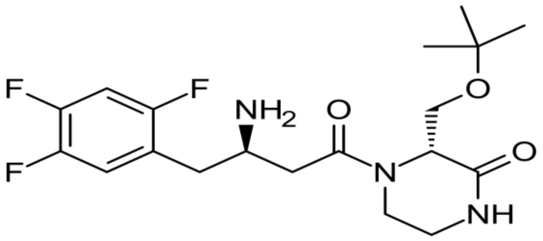
Gemigliptin

Gemigliptin exhibits strong binding due to multiple interactions like hydrogen bonding and π–π stacking. It is considered highly potent among DPP-4 inhibitors.



Evogliptin

Evogliptin binds effectively within the enzyme’s active site through hydrophobic interactions. It offers good stability and consistent glucose-lowering effects.



Drug	Docking Score (kcal/mol)	Key Interactions	Interpretation
Sitagliptin	−9.2 to −9.4	H-bonds (Tyr662, His740, Trp629)	Standard drug, very strong binding
Vildagliptin	~ −8.1	Interaction with Ser630	Strong catalytic inhibition
Saxagliptin	−6.4 to −7.7	H-bonds + hydrophobic	Moderate binding
Linagliptin	~ −9.3	π–π stacking + hydrophobic	Very strong and stable
Alogliptin	−7.5 to −8	H-bonds (Glu205, Glu206)	Good selectivity
Teneligliptin	~ −7.7	H-bonds + hydrophobic	Balanced interaction
Anagliptin	−7 to −8	Hydrogen bonding	Moderate affinity
Omarigliptin	−8 to −9	Hydrophobic + electrostatic	Long-acting drug
Gemigliptin	−8.5 to −9	π–π + H-bonds	Highly potent
Evogliptin	−8 to −9	Hydrophobic interactions	Stable binding

Virtual Screening and Drug Design

Virtual screening and drug design are modern computational approaches that have made drug discovery faster, more efficient, and less expensive. In simple terms, virtual screening allows researchers to examine thousands of chemical compounds on a computer and identify those most likely to interact with a target protein, such as the Dipeptidyl Peptidase-4 (DPP-4) enzyme. Instead of testing each compound in the laboratory, scientists use techniques like Molecular Docking to predict how well a molecule can fit into the active site of the enzyme and how strong the interaction will be. Once promising candidates are identified, drug design comes into play, where these molecules are carefully modified to improve their effectiveness, stability, and safety. Researchers aim to enhance important interactions such as hydrogen bonding and hydrophobic contacts while minimizing side effects. Additionally, selected compounds are evaluated using ADMET analysis to predict their absorption, distribution, metabolism, excretion, and toxicity.

Integration with ADMET Analysis

In modern drug discovery, **Molecular Docking** alone is not enough to identify a successful drug. A compound may bind very well to a target like the **Dipeptidyl Peptidase-4 (DPP-4) enzyme**, but it might fail inside the human body due to poor absorption, toxicity, or rapid metabolism. This is where **ADMET analysis** becomes essential.

ADMET stands for **Absorption, Distribution, Metabolism, Excretion, and Toxicity**, and it helps predict how a drug behaves in the body before actual laboratory or clinical testing.

Drug	**Absorption (Oral Bioavailability)**	**Distribution (PPB/BBB)**	**Metabolism (CYP450)**	**Excretion (t½ / Clearance)**	**Toxicity**
Sitagliptin	High (~85%), good solubility	Low PPB, no BBB	Minimal CYP metabolism	t½ ~12 h, renal excretion	Low toxicity
Vildagliptin	Moderate–high (~85%)	Low PPB, no BBB	Non-CYP metabolism	t½ ~2–3 h, renal	Very low toxicity
Saxagliptin	Good (~75%)	Moderate PPB	CYP3A4 metabolism	t½ ~2.5 h (active metabolite longer)	Low toxicity
Linagliptin	Moderate (~30%)	High PPB, minimal BBB	Minimal CYP metabolism	Long t½ (>100 h), biliary excretion	Low toxicity
Alogliptin	High (~100%)	Low PPB, no BBB	Minimal CYP metabolism	t½ ~21 h, renal	Very low toxicity
Teneligliptin	Good (~75%)	Moderate PPB	CYP3A4 + FMO metabolism	t½ ~24 h	Low toxicity
Anagliptin	Moderate	Moderate PPB	Limited CYP metabolism	t½ ~6 h	Low toxicity
Omarigliptin	High	Moderate PPB	Minimal metabolism	Very long t½ (~100 h, weekly dose)	Low toxicity
Gemigliptin	Good	Moderate PPB	CYP3A4 metabolism	t½ ~17 h	Low toxicity
Evogliptin	Good	Moderate PPB	CYP3A4 metabolism	t½ ~33 h	Low toxicity

Future Perspectives

1. Integration of AI and Machine Learning

Advanced tools like AI and ML will make Molecular Docking more accurate and faster. These technologies can analyze large datasets, predict better drug candidates, and reduce trial-and-error in designing new inhibitors.

2. Multi-Target Drug Development

Future drugs may not focus only on the Dipeptidyl Peptidase-4 (DPP-4) enzyme but also target other pathways like SGLT2 or PPAR-γ. This combined approach can improve overall treatment of Type 2 Diabetes Mellitus.

3. Improved Docking Accuracy

New algorithms will overcome current limitations such as rigid protein structures. More realistic simulations will better mimic the biological environment and improve prediction reliability.

4. Use of Molecular Dynamics (MD) Simulations

MD simulations will be increasingly used alongside docking to study the stability of ligand–protein complexes over time, giving more confidence in drug candidates.

5. Focus on Natural Compounds and Hybrid Molecules

Natural compounds (like flavonoids) will be used as starting points, and then modified chemically to create more potent and safer drugs.

6. Better ADMET Prediction Models

Integration with improved ADMET analysis tools will help identify drugs with good absorption, low toxicity, and better pharmacokinetic profiles early in development.

7. Personalized Medicine Approach

Future treatments may be tailored based on patient genetics and metabolism, ensuring that each person receives the most effective DPP-4 inhibitor.

8. Development of Long-Acting Drugs

More research will focus on drugs with longer half-lives (e.g., weekly dosing), improving patient compliance and convenience.

9. Green and Sustainable Drug Design

Eco-friendly synthesis methods and computational approaches will reduce chemical waste and make drug development more sustainable.

10. Integration with Experimental Validation

Computational results will be combined with laboratory (in vitro and in vivo) studies to ensure real-world effectiveness and safety.

11. Discovery of Novel Chemical Scaffolds

Researchers will explore new chemical structures beyond existing drug classes to develop more selective and potent inhibitors.

12. Reduced Side Effects and Improved Safety

Future drugs will aim to minimize adverse effects while maintaining strong therapeutic activity.

CONCLUSION

The Dipeptidyl Peptidase-4 (DPP-4) enzyme is an important target for managing Type 2 Diabetes Mellitus, as it controls incretin hormones and blood glucose levels. Studies using Molecular Docking show that synthetic inhibitors bind strongly to the enzyme through key interactions, explaining their effectiveness.

When combined with ADMET analysis, these methods help identify drugs that are not only potent but also safe and stable in the body. Overall, computational approaches play a major role in designing better DPP-4 inhibitors and improving diabetes treatment.

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