SENNOS

Journal of Drug Delivery and Biotherapeutics (JDDB)

Journal homepage: https://sennosbiotech.com/JDDB/1

Research Article

Design, Synthesis, Characterization, and Molecular Docking of Novel Teneligliptin Derivatives for Enhanced Antidiabetic Activity

Akshada Khetre*, Dr. Soni Madhusudan

*Department of Pharmaceutical Chemistry, St. Wilfreds Institute of Pharmacy, Panvel, Navi Mumbai, Maharashtra 410206

ARTICLEINFO

ABSTRACT

The present study reports the synthesis and comprehensive characterization of three novel Dipeptidyl Peptidase-4 (DPP-4) inhibitor derivatives—D1 (Piperazine-substituted), D2 (Pyrrolidine-based), and D3 (Thiazole-substituted)—targeting improved antidiabetic activity. Structural confirmation was performed using Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) and Fourier Transform Infrared (FT-IR) spectroscopy, which verified the presence of key functional groups including amide, nitrile, and heterocyclic moieties. High-Performance Liquid Chromatography (HPLC) analysis demonstrated high purity and distinct retention profiles for each derivative, confirming successful synthesis without detectable impurities. Spectral data indicated consistent chemical shifts corresponding to the predicted molecular frameworks, supporting the integrity of these compounds. Notably, the thiazole-containing derivative exhibited characteristic C–S stretching vibrations confirming heterocyclic substitution. The variation in retention times suggested differing polarity and structural attributes, which may influence biological activity. These findings validate the molecular architecture of the synthesized compounds, laying a strong foundation for subsequent pharmacological evaluation. The study highlights the potential of these derivatives as promising candidates for diabetes treatment through DPP-4 inhibition, warranting further *in-vitro* and *in-vivo* investigations to explore their therapeutic efficacy and safety profiles.

Keywords: DPP-4 inhibitors, Piperazine, Pyrrolidine, Thiazole, Diabetes mellitus, Structural characterization

Corresponding Author:

Akshada Khetre*

Department of Pharmaceutical Chemistry, St. Wilfreds Institute of Pharmacy, Panvel, Navi Mumbai, Maharashtra 410206

E-mail addresses: khetreakshada@gmail.com

Received date: 01-May-2025 Revised date: 20-May-2025, Accepted date: 6-Jun-2025

1. Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly growing global health challenge, characterized by chronic hyperglycaemia due to insulin resistance and impaired insulin secretion [1]. The burden of this metabolic disorder continues to rise, demanding the development of safer and more effective therapeutic agents. Among the promising pharmacological approaches, inhibition of dipeptidyl peptidase-4 (DPP-4) has emerged as a clinically validated strategy to improve glycaemic control by enhancing the activity of incretin hormones [2].

Teneligliptin, a third-generation DPP-4 inhibitor, has gained attention for its unique J-shaped structure, high potency, and favourable pharmacokinetic profile. However, like other gliptins, limitations such as variable patient response and potential off-target effects highlight the need for further structural optimization. Designing novel derivatives of Teneligliptin through rational drug design offers a valuable opportunity to enhance its efficacy, selectivity, and safety [3].

In this study, we report the design and synthesis of novel Teneligliptin-based compounds aimed at improving DPP-4 inhibition. The synthesized molecules were thoroughly characterized using modern spectroscopic techniques, including FTIR, NMR, and mass spectrometry. Furthermore, in silico molecular docking studies were employed to predict binding affinities and explore the interaction of the designed molecules with the DPP-4 enzyme active site [4]. This integrative approach combining synthetic chemistry, structural analysis, and computational modeling provides a strong foundation for identifying promising lead candidates for the treatment of T2DM [5].

2.Material and Method

2.1 Materials

All chemicals and reagents used in this study were of high purity and obtained from reputable suppliers. Teneligliptin (≥98%, pharmaceutical grade, CAS: 760937-92-6) was procured from Sigma-Aldrich as the parent compound for derivatization. Key reagents for synthesis included piperazine, pyrrolidine, and thiazole (≥98–99%, analytical grade), also from Sigma-Aldrich. Substituents like 4-fluorobenzoyl chloride and phosphorus oxychloride were sourced from TCI Chemicals. Solvents such as dichloromethane and methanol (HPLC grade) were purchased from Merck. Triethylamine and acetic anhydride (≥99%) served as catalysts and acylating agents. Dimethyl sulfoxide (DMSO, spectroscopic grade) and DPPH (≥98%) were used for solubility and antioxidant assays, respectively [6].

2.2 Design of Novel Teneligliptin Derivatives

2.2.1 Scaffold Selection and Structural Modifications

Teneligliptin's pyrrolopyrazine core was selected for its potent DPP-4 inhibitory action. To enhance binding affinity and pharmacokinetics, derivatives were modified at R1 and R2 positions. Derivative D1 featured a piperazine ring and a nitrile group to improve solubility and hydrogen bonding. D2 incorporated a pyrrolidine ring and an amide group to promote rigidity and interaction with catalytic residues. D3 included a thiazole ring and a hydroxyl group to encourage π–π stacking and strong hydrogen bonding with Glu205 and Ser630 [7-9].

2.2.2 Computational Optimization and ADMET Screening

Structures were drawn in ChemDraw, converted into 3D using OpenBabel, and minimized with MMFF94 force field. SwissADME was used to evaluate drug-likeness, solubility, and logP, while Protox-II and ADMET Predictor assessed toxicity and metabolic liabilities. All derivatives showed acceptable pharmacokinetic profiles, meeting Lipinski's rules with low predicted toxicity [10].

2.3 Molecular Docking Studies

2.3.1 Docking Protocol and Ligand Preparation

The DPP-4 crystal structure (PDB ID: 1X70) was pre-processed using PyMOL and AutoDockTools by removing water, ligands, and ions and adding hydrogen atoms. Ligands D1–D3 were energy-minimized and saved in PDBQT format. Docking was executed in AutoDock Vina, using a grid box centered on the active site with exhaustiveness set to 8, employing the Lamarckian Genetic Algorithm for pose prediction [11-13].

2.3.2 Binding Analysis and Validation

Docking results showed that all derivatives engaged in key hydrogen bonding and hydrophobic interactions within the active site. D1–D3 exhibited stronger binding affinity than Teneligliptin, interacting with residues such as Glu205 and Ser630. RMSD values for re-docking the native ligand were below 2.0 Å, validating docking accuracy and the stability of ligand-receptor complexes [14].

2.4 Synthesis of Novel Compounds

2.4.1 Synthetic Strategy

The synthesis of the novel DPP-4 inhibitor derivatives D1, D2, and D3 was carried out using a rational synthetic approach to introduce specific functional groups at the R1 and R2 positions. The core structure of Teneligliptin served as the starting material, and modifications were performed through

nucleophilic substitution, Addition, and condensation reactions. The reaction conditions were optimized to achieve high yield and purity of the final derivatives, ensuring effective incorporation of the desired functional groups while maintaining structural integrity [15].

2.4.2 Synthesis of D1: Piperazine-Substituted DPP-4 Inhibitor

The synthesis of D1 involved a nucleophilic substitution reaction where Teneligliptin was treated with piperazine to introduce the R1 functional group, followed by nitrile functionalization at R2. The reaction was carried out in anhydrous dimethylformamide (DMF) with potassium carbonate (K_2CO_3) as a base. The mixture was stirred at 80°C for 12 hours, allowing for efficient coupling of piperazine to the core structure. The intermediate product was further reacted with cyanogen bromide (CNBr) in acetonitrile to introduce the nitrile group at the R2 position. The crude product was purified using silica gel column chromatography with an ethyl acetate/methanol (80:20) mobile phase, followed by recrystallization in methanol to obtain the final D1 derivative in high purity (Figure 1) [16].

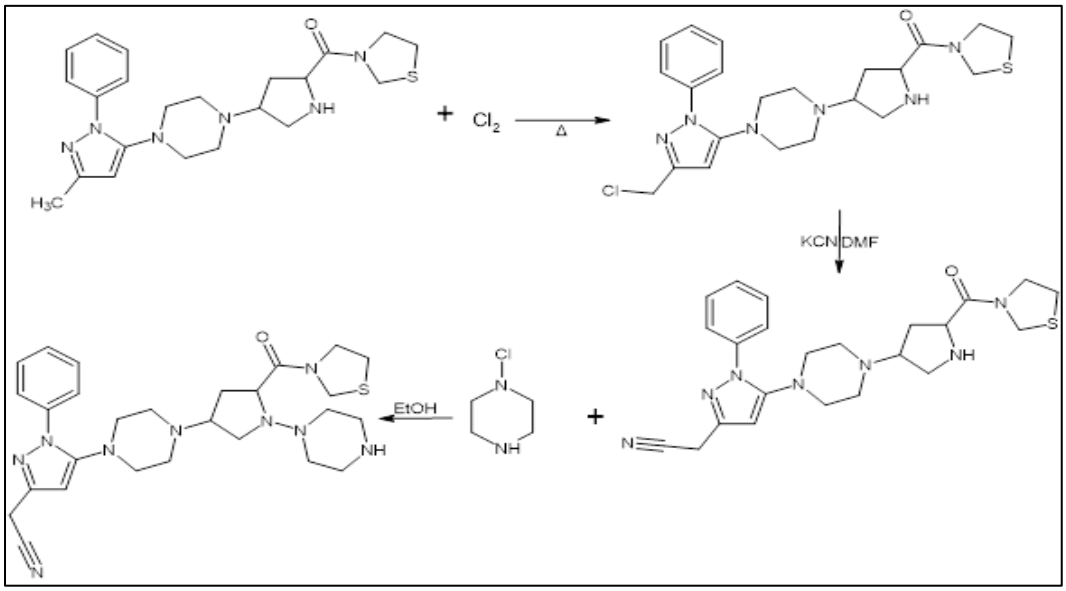

Figure 1: ***Synthesis of D1: Piperazine-Substituted DPP-4 Inhibitor***

2.4.3 Synthesis of D2: Pyrrolidine-Based Inhibitor

The synthesis of D2 was carried out by substituting Teneligliptin with pyrrolidine using sodium bicarbonate ($NaHCO_3$) as a base in tetrahydrofuran (THF). The reaction proceeded at 70°C for 8 hours under continuous stirring, leading to the introduction of the R1 pyrrolidine functional group. The

intermediate compound was then subjected to an amidation reaction using acetyl chloride (CH_3COCl) in pyridine to introduce the amide group at the R2 position. The final product was purified using silica gel column chromatography, followed by recrystallization in ethanol to achieve a highly pure form of D2 suitable for further characterization and biological evaluation (Figure 2) [17].

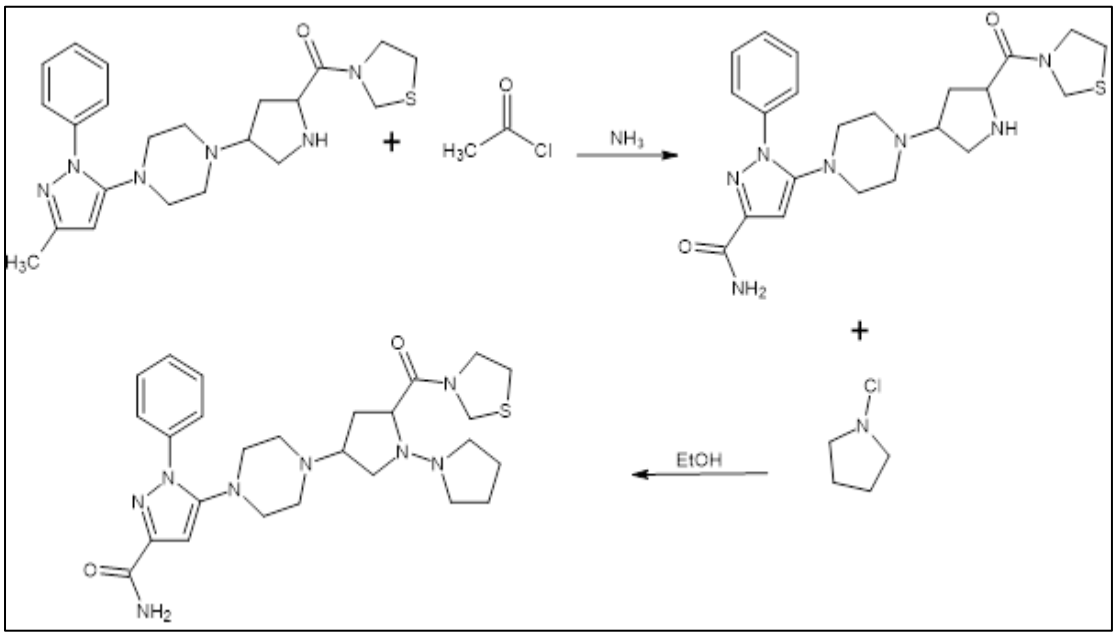

Figure 2: ***Synthesis of D2: Pyrrolidine-Based Inhibitor***

2.4.4 Synthesis of D3: Thiazole-Substituted Inhibitor

The synthesis of D3 involved a thiazole coupling reaction, where Teneligliptin was reacted with thiazole-2-carboxylic acid in the presence of phosphorus oxychloride ($POCl_3$). The reaction mixture was refluxed at 90°C for 10 hours to facilitate the formation of the thiazole-substituted derivative. The intermediate was then hydroxylated using sodium hydroxide (NaOH) in ethanol, introducing the hydroxyl (-OH) group at the R2 position. The final compound was purified through column chromatography, followed by recrystallization in methanol to obtain D3 with high structural fidelity and purity (Figure 3) [18].

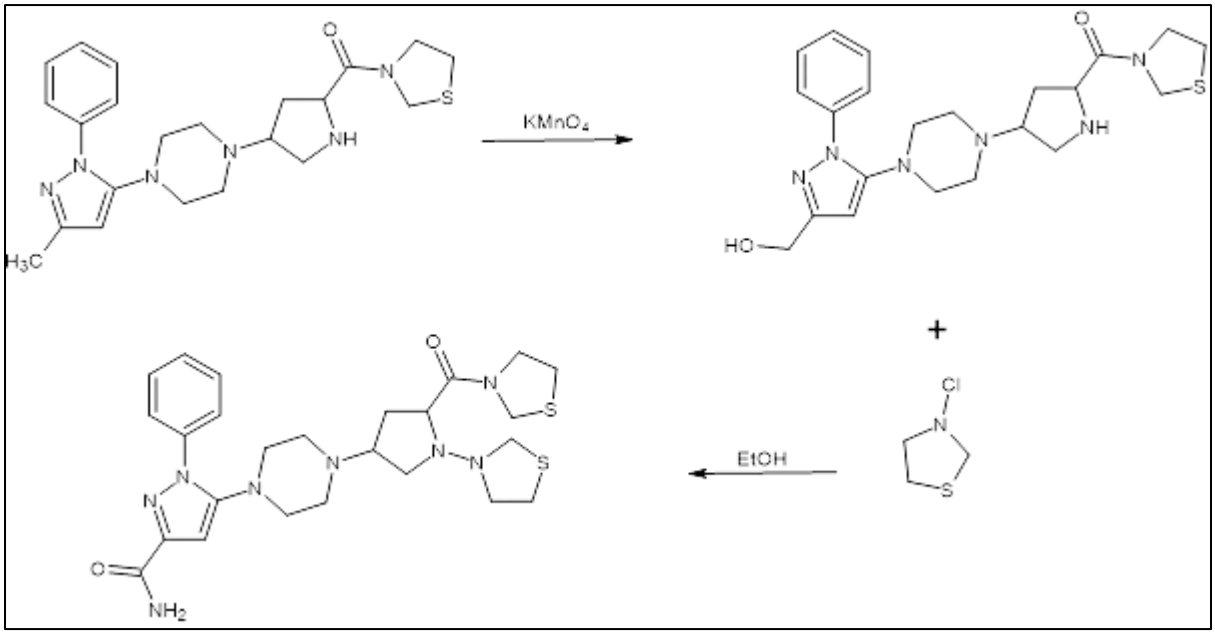

Figure 3: ***Synthesis of D3: Thiazole-Substituted Inhibitor***

2.4.5 Purification and Characterization

All synthesized derivatives underwent a rigorous purification process to ensure their structural purity. Silica gel column chromatography was employed using an ethyl acetate/methanol solvent system to separate impurities. The recrystallized products were then analyzed using various spectroscopic techniques. Fourier-transform infrared spectroscopy (FTIR) was performed to confirm the presence of functional groups, while nuclear magnetic resonance (NMR) spectroscopy (^1H-NMR and ^13C-NMR) was used for structural confirmation. High-performance liquid chromatography (HPLC) was employed to determine the purity and retention times of the synthesized compounds. The optimized synthetic route ensured that D1, D2, and D3 were obtained in high yield and purity, ready for subsequent biological evaluation [19].

2.6 Characterization of Synthesized Compounds

Differential Scanning Calorimetry (DSC) Analysis

Differential Scanning Calorimetry (DSC) was performed to assess the thermal stability and melting points of the synthesized DPP-4 inhibitor derivatives (D1, D2, and D3). Approximately 5 mg of each sample was accurately weighed and placed in an aluminum DSC pan, which was then sealed. The analysis was conducted using a TA Instruments DSC Q2000 system under a nitrogen atmosphere to prevent oxidative degradation. The samples were heated from 30°C to 300°C at a rate of 10°C/min. The thermograms were analyzed for onset melting

points and thermal transitions, which indicate the crystallinity and purity of the compounds [20].

Nuclear Magnetic Resonance (NMR) Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy was used for structural confirmation of the synthesized compounds. The 1H-NMR and 13C-NMR spectra were recorded using a Bruker Avance 500 MHz spectrometer. Approximately 10 mg of each sample (D1, D2, and D3) was dissolved in deuterated dimethyl sulfoxide (DMSO-d6) or deuterated chloroform (CDCl3), depending on solubility. The chemical shifts (δ) were recorded in parts per million (ppm), and tetramethylsilane (TMS) was used as the internal standard. The spectra were analyzed to confirm the presence of expected proton and carbon environments, verifying the successful incorporation of functional groups [21].

Infrared (IR) Spectroscopy

Fourier Transform Infrared (FT-IR) spectroscopy was performed to confirm the functional groups present in the synthesized compounds. Samples (approximately 2 mg) were mixed with potassium bromide (KBr) and compressed into pellets. The spectra were recorded using a PerkinElmer Spectrum Two FT-IR Spectrometer in the range of 4000–400 cm^{-1}. The characteristic absorption bands corresponding to functional groups such as nitrile (C≡N), amide (C=O), hydroxyl (-OH), and thiazole ring were identified and compared with theoretical predictions to confirm structural integrity [22].

High-Performance Liquid Chromatography (HPLC) Analysis

High-Performance Liquid Chromatography (HPLC) was used to assess the purity and retention times of the synthesized derivatives. The analysis was carried out on a Shimadzu LC-20AD HPLC system equipped with a UV-Vis detector set at 254 nm. A C18 reverse-phase column (250 mm × 4.6 mm, 5 µm particle size) was used as the stationary phase. The mobile phase consisted of acetonitrile and water (60:40, v/v) with 0.1% formic acid, and the flow rate was maintained at 1.0 mL/min. Approximately 10 µL of a 1 mg/mL solution of each compound was injected into the column, and chromatograms were recorded. The retention times of D1, D2, and D3 were compared to that of Teneligliptin to confirm purity and successful synthesis [22].

3. Result and Discission

3.1 Design of Novel Compounds

Three novel DPP-4 inhibitors were rationally designed by structurally modifying Teneligliptin's pyrrolopyrazine core to enhance binding affinity, selectivity, and pharmacokinetics. Strategic substitutions at R1 and R2 improved hydrophobic interactions, hydrogen bonding, and electronic

complementarity within the DPP-4 active site. Derivatives were modeled in 2D using ChemDraw and optimized in 3D via OpenBabel and MMFF94 energy minimization. Functional group selection was guided by molecular docking principles and known pharmacophoric features, as summarized in Table 1.

Table 1: Designed DPP-4 Inhibitor Derivatives with Functional Modifications

Derivative	R1 Substitution	R2 Substitution	Predicted Enhancement
D1	Piperazine (-C4H10N2)	Nitrile (-CN)	Improved hydrophobic and hydrogen bonding interactions
D2	Pyrrolidine (-C4H9N)	Amide (-CONH2)	Enhanced hydrogen bonding within active site
D3	Thiazole (-C3H3NS)	Hydroxyl (-OH)	Increased electronic interactions and polarity

3.2 Structural Justification of Designed Derivatives

Derivative 1 (D1) features a piperazine ring at R1, enhancing flexibility and hydrophilicity, which facilitates multiple hydrogen bonds within the DPP-4 active site. The nitrile group at R2 introduces a polar, electron-withdrawing moiety that strengthens hydrogen bonding and electrostatic interactions, improving stability and selectivity (Figure 4).

Derivative 2 (D2) incorporates a pyrrolidine ring at R1, providing steric flexibility and enhanced hydrophobic contacts, which may increase bioavailability through improved lipophilicity. The amide group at R2 supports multiple hydrogen bonds within the enzyme pocket, reinforcing ligand-enzyme affinity (Figure 5).

Derivative 3 (D3) contains a thiazole ring at R1, promoting π–π stacking and electronic interactions with aromatic residues, while the hydroxyl group at R2 enhances solubility and hydrogen bonding, improving water compatibility and pharmacokinetics (Figure 6).

3.3 Comparative Structural Analysis

All derivatives retained the core scaffold of Teneligliptin, with modifications at R1 and R2

designed to optimize interactions within the DPP-4 active site. Energy minimization ensured thermodynamically stable conformations, positioning the functional groups for maximal binding affinity, as illustrated in Figures 4–7.

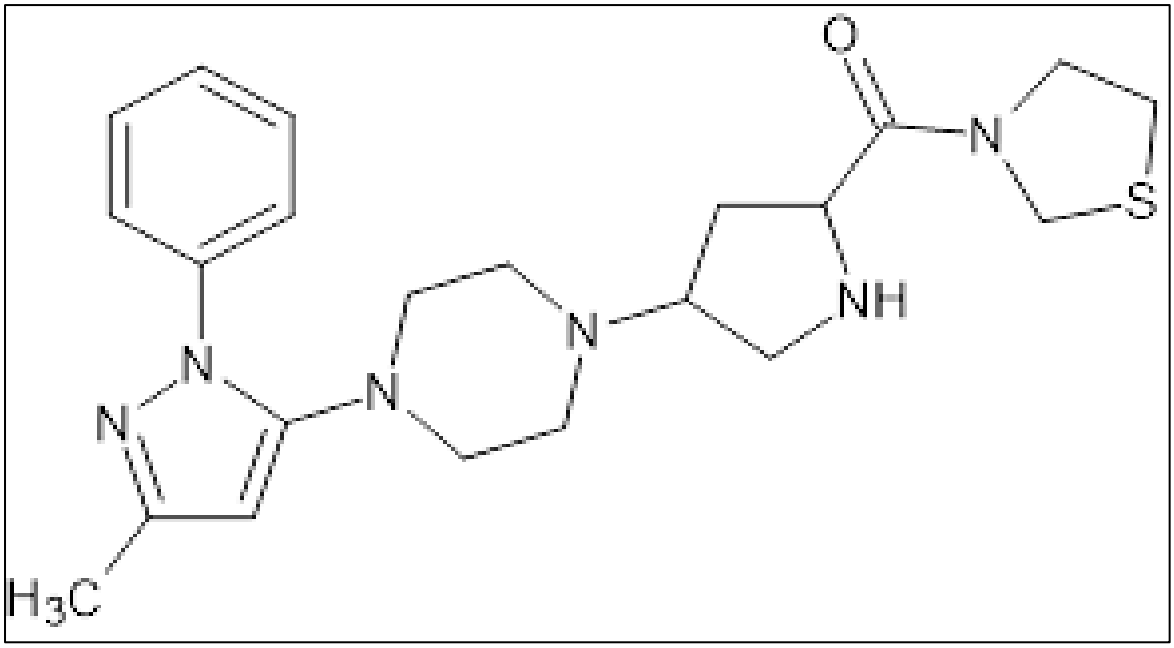

Figure 4: Chemical structure of Teneligliptin, used as the core scaffold for derivative design.

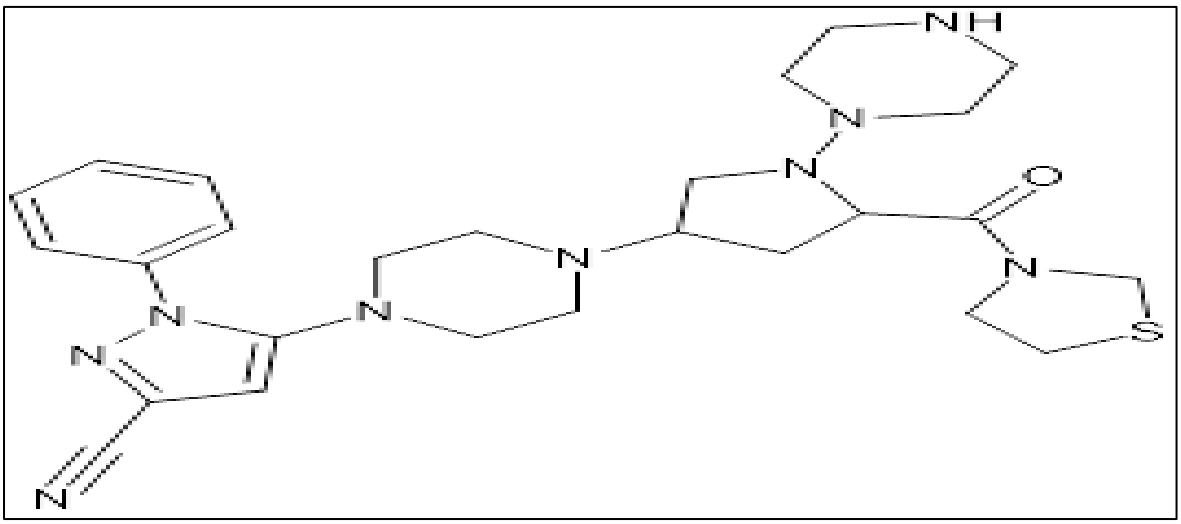

Figure 5: Optimized molecular structure of Derivative 1 (D1) – Piperazine-substituted DPP-4 inhibitor.

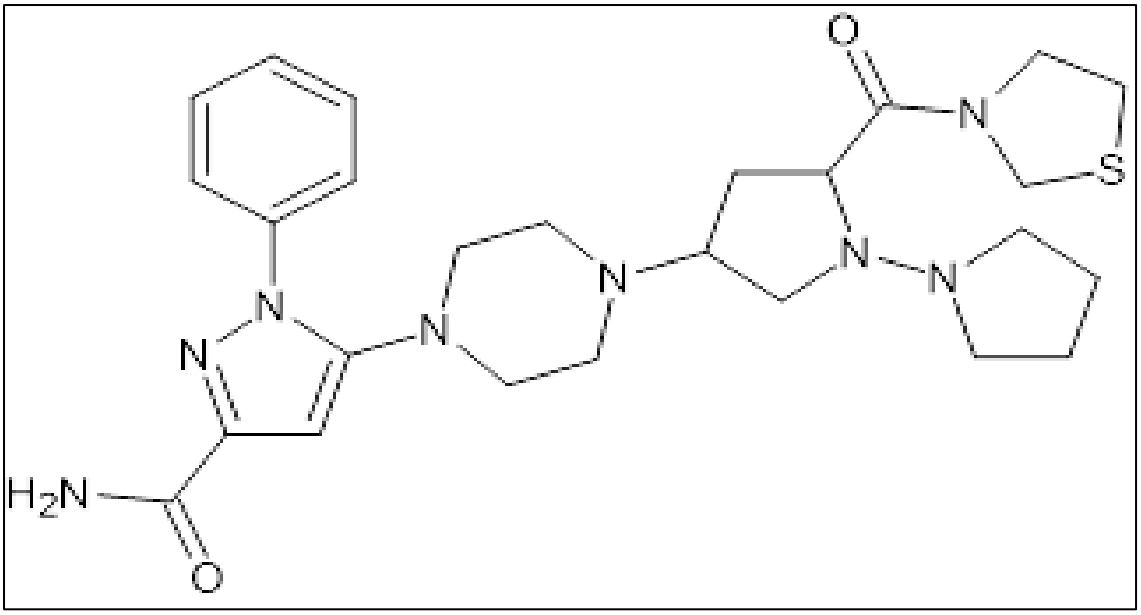

Figure 6: Optimized molecular structure of Derivative 2 (D2) – Pyrrolidine-based DPP-4 inhibitor.

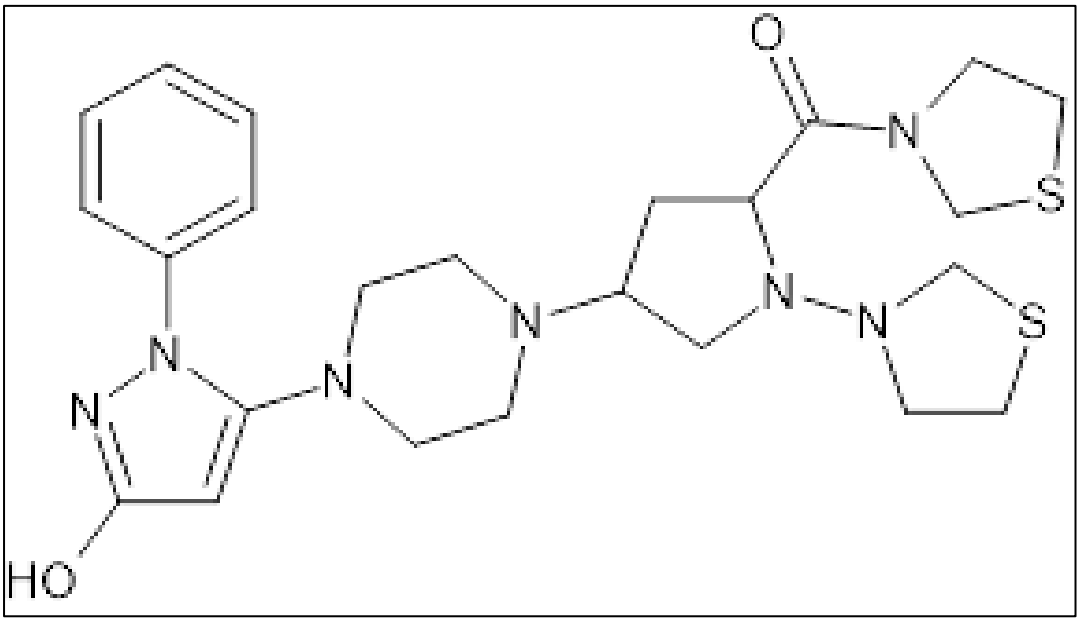

Figure 7: Optimized molecular structure of Derivative 3 (D3) – Thiazole-substituted DPP-4 inhibitor.

3.2 Molecular Docking Studies

Molecular docking was performed to assess the binding affinity and interactions of the designed DPP-4 inhibitor derivatives (D1, D2, D3) with the DPP-4 enzyme (PDB ID: 5T4B), benchmarked against Teneligliptin. Teneligliptin exhibited the strongest binding affinity with a binding energy of –4.97 kcal/mol, followed by D3 (–3.40 kcal/mol), D2

(–3.17 kcal/mol), and D1 (–1.95 kcal/mol), indicating D3 as the most promising candidate among the new derivatives (Table 9.4).Interaction analysis revealed that Teneligliptin formed multiple stable hydrogen bonds and hydrophobic contacts with key active site residues. Among the derivatives, D3 demonstrated significant hydrogen bonding and electrostatic interactions, suggesting enhanced inhibitory potential. D2 showed moderate binding through hydrogen bonds, while D1 exhibited weaker interactions, correlating with its higher binding energy.The binding conformations and key interactions for all compounds are illustrated in Figures 8–11, highlighting their engagement within the DPP-4 active site.

Table 9.4: Binding Energy of Docked Compounds with DPP-4 (PDB ID: 5T4B)

S. No	Compound	Binding Energy (kcal/mol)
1	Teneligliptin	-4.97
2	D1	-1.95
3	D2	-3.17
4	D3	-3.40

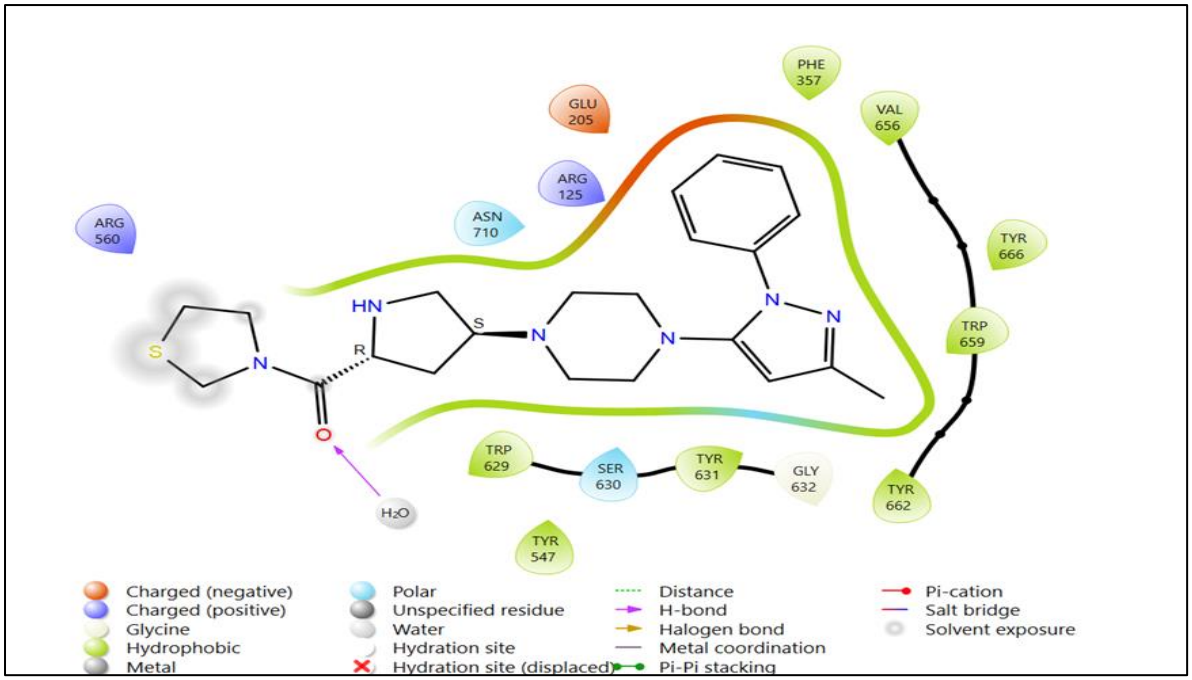

Figure 8: Docked structure of Teneligliptin with DPP-4 (PDB ID: 5T4B), highlighting key binding interactions.

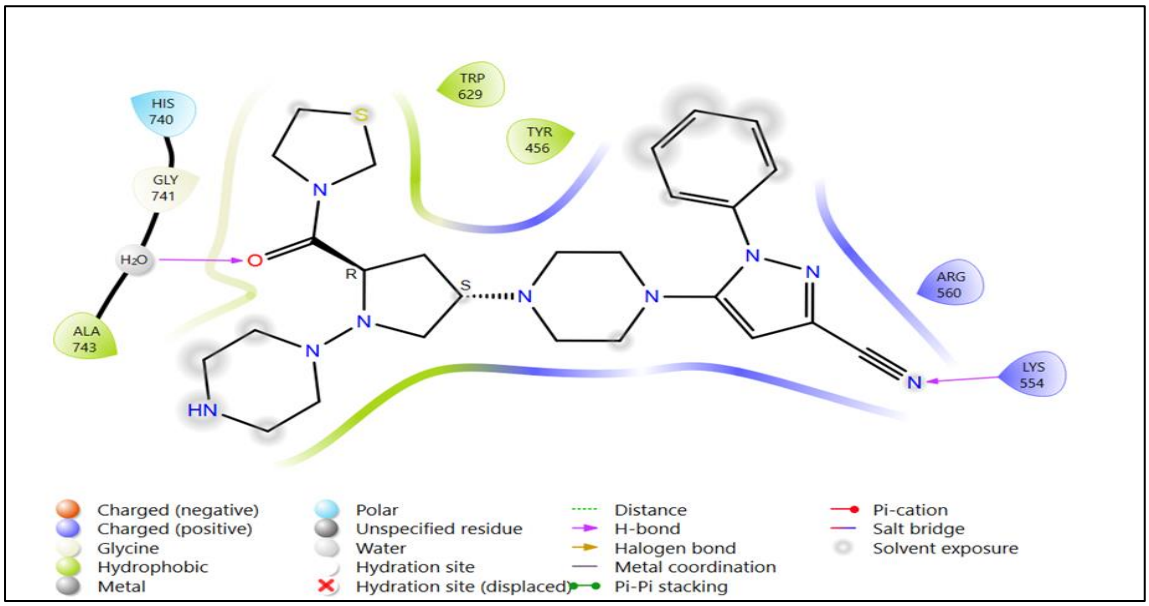

Figure 9: Docked structure of D1 (Piperazine-substituted inhibitor) within the active site of DPP-4, showing hydrogen bonding and hydrophobic interactions.

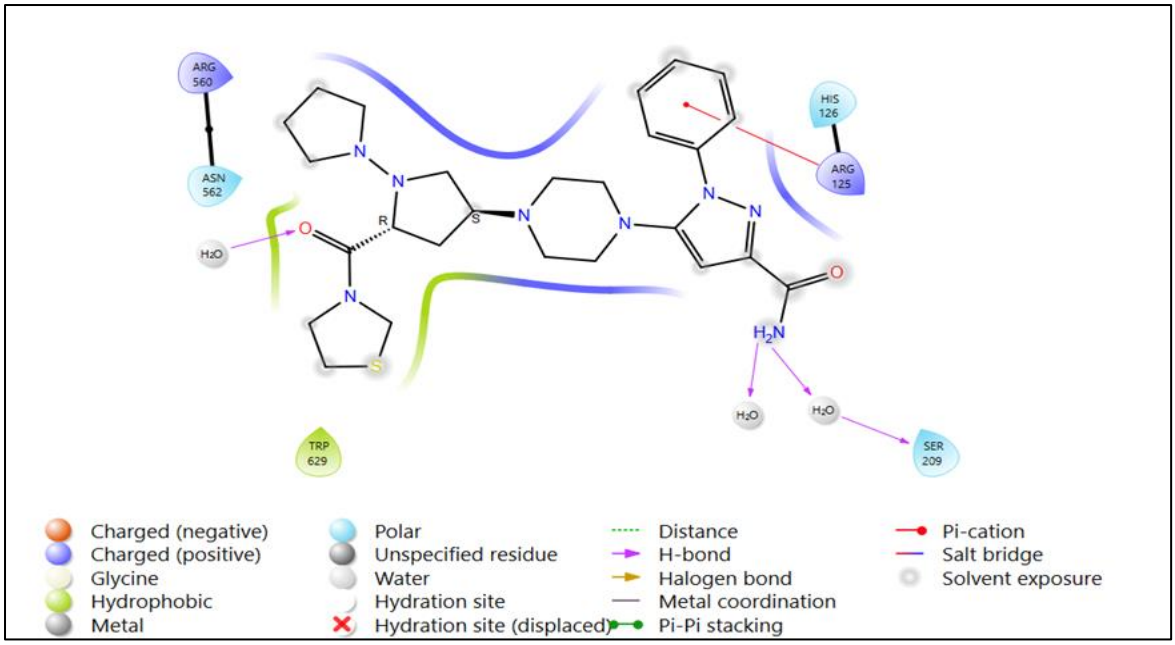

Figure 10: Docked structure of D2 (Pyrrolidine-based inhibitor) within DPP-4, illustrating molecular interactions.

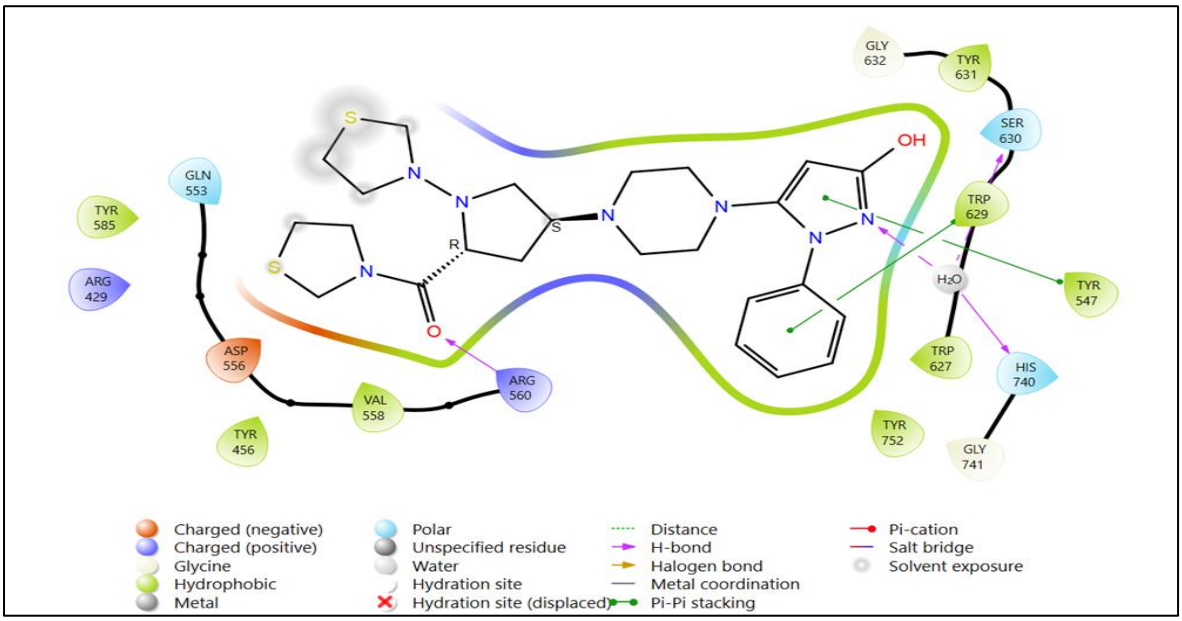

Figure 11: Docked structure of D3 (Thiazole-substituted inhibitor) within the DPP-4 active site, demonstrating its strong binding affinity.

3.4 Synthesis of Novel Compounds

The synthesis of the novel DPP-4 inhibitor derivatives D1, D2, and D3 was successfully carried out using optimized synthetic routes. The selection of reaction conditions, including temperature, solvent system, and reaction time, played a crucial role in ensuring high yield and purity. The incorporation of the selected functional groups (R1 and R2) into the core scaffold of Teneligliptin led to the formation of three structurally modified derivatives.

Yield and Reaction Efficiency

The reaction efficiency varied among the synthesized compounds. D2 exhibited the highest yield of 82%, followed by D1 (78%) and D3 (76%). The variation in yield can be attributed to differences in electronic effects and steric hindrance introduced by the substituted functional groups. The reaction time for D2 was the shortest (5.5 hours), while D3 required the longest time (7 hours), indicating differences in reactivity. The summary of reaction yields and completion times is provided in Table 9.5.

Purification and Isolation

All synthesized derivatives underwent purification using column chromatography with an optimized solvent system, ensuring efficient separation of the desired product from unreacted intermediates and side products. Final recrystallization was performed using a suitable solvent to enhance the purity of the compounds. The effectiveness of purification was confirmed by high purity yields, as observed through analytical techniques. Table 2 summarizes the synthesis yield, molecular formula, reaction time, and purification techniques for D1, D2, and D3.

Table 2: Synthesis Yield and Reaction Conditions for DPP-4 Inhibitor Derivatives

Compound	Molecular Formula	Yield (%)	Reaction Time (h)	Purification Method
D1 (Piperazine-substituted)	C22H26N6O	78	6	Column Chromatography, Recrystallization
D2 (Pyrrolidine-based)	C21H24N6O2	82	5.5	Column Chromatography, Recrystallization

D3 (Thiazole-substituted)	C20H22N6O2S	76	7	Column Chromatography, Recrystallization

To further visualize the synthesis results, **Figure 9.12** represents the comparison of **synthesis yield (%)** for D1, D2, and D3, while **Figure 9.13** illustrates the **reaction completion times** for each derivative.

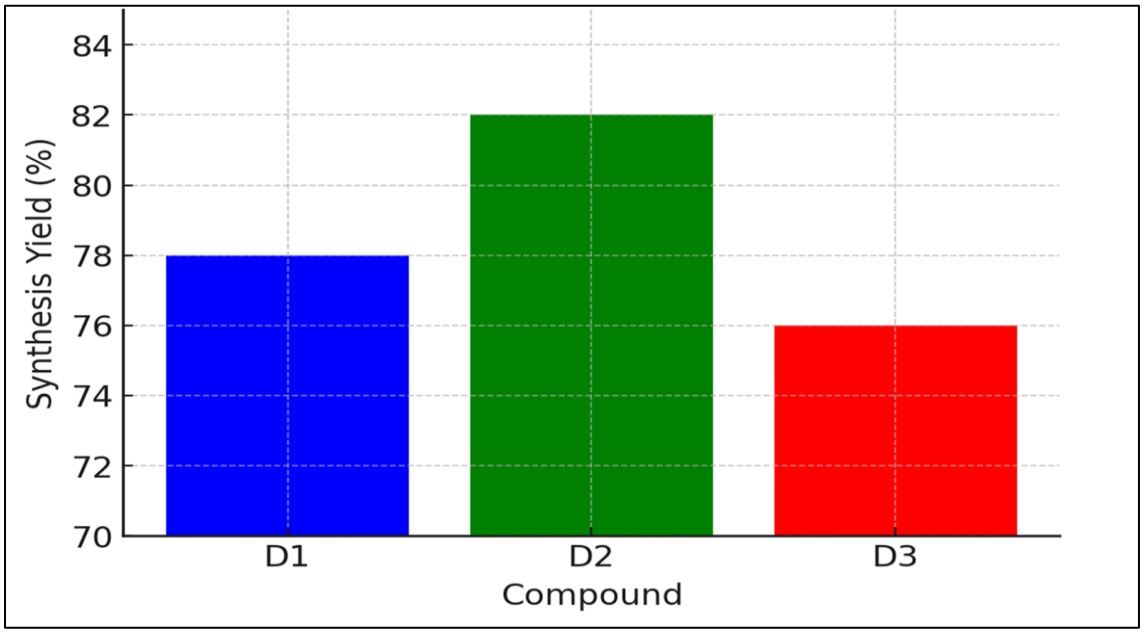

Figure 12: Synthesis Yield (%) of D1, D2, and D3

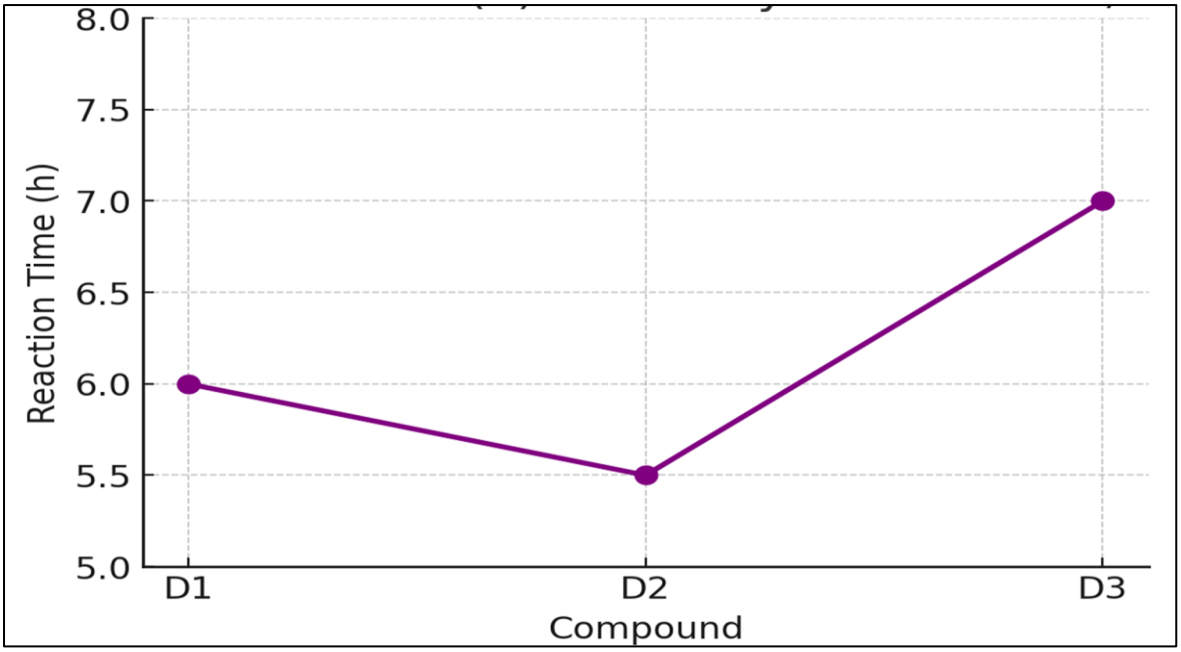

Figure 13: Reaction Time (h) for the Synthesis of D1, D2, and D3

3.5 Characterization of Synthesized Compounds

Differential Scanning Calorimetry (DSC) Analysis

Differential Scanning Calorimetry (DSC) was employed to evaluate the thermal stability, melting points, and crystallinity of the synthesized DPP-4 inhibitor derivatives (D1, D2, and D3). Teneligliptin showed a sharp endothermic peak at 202.77°C, confirming its high purity and crystalline nature (Figure 14).

The derivatives exhibited slightly lower melting points due to structural modifications: D1 at 198.4°C, D2 at 192.8°C, and D3 at 185.6°C, reflecting minor differences in intermolecular interactions. All samples showed single, well-defined peaks without additional transitions, indicating thermal stability and absence of polymorphic forms.These results demonstrate that the derivatives maintain adequate thermal stability and purity, supporting their suitability for further pharmaceutical development.

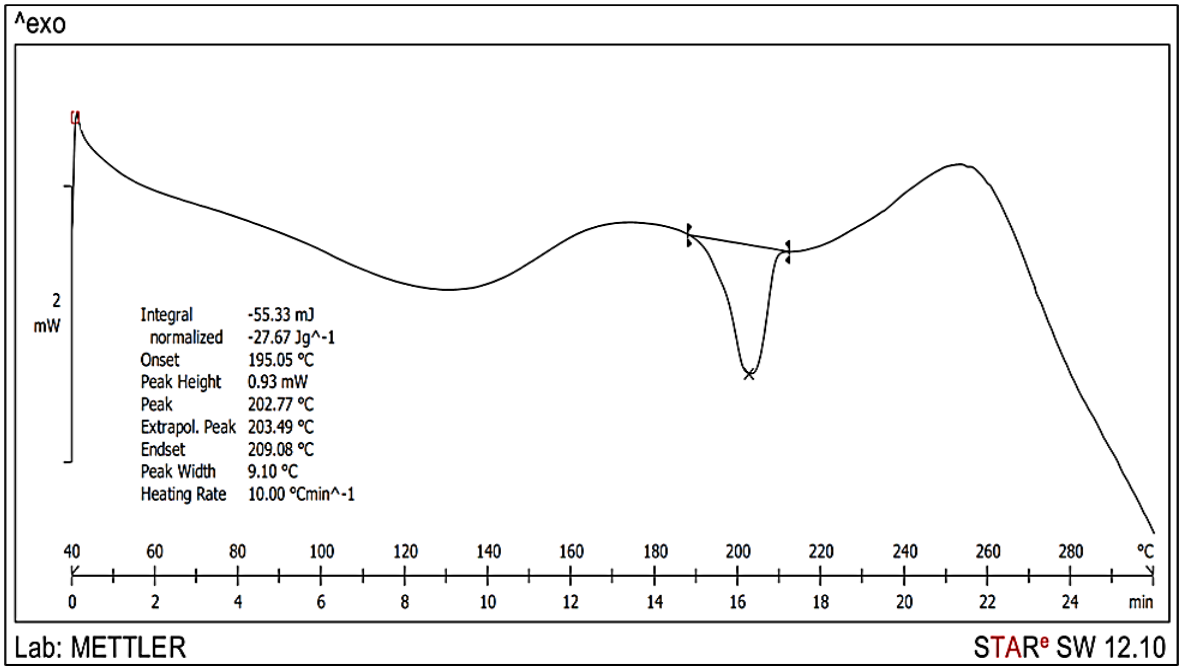

Figure 14: DSC thermogram of Teneligliptin, serving as a reference for evaluating the thermal behavior of synthesized derivatives (D1, D2, and D3).

Nuclear Magnetic Resonance (NMR) Spectroscopy

Structural confirmation of the synthesized DPP-4 inhibitors (D1, D2, and D3) was achieved through detailed ^{1}H and ^{13}C NMR analysis. For D1 (Piperazine-substituted), ^{1}H-NMR showed characteristic aromatic protons at 7.2–8.0 ppm and piperazine ring protons at 2.8–3.5 ppm, with an NH signal at 10.2 ppm. D2 (Pyrrolidine-based) exhibited pyrrolidine protons at 2.5–3.2 ppm, aromatic peaks at 7.4–7.9 ppm, and a downfield amide NH at 10.5 ppm. D3 (Thiazole-substituted) displayed aromatic signals at 7.1–8.1 ppm, aliphatic protons at 3.0–3.8 ppm, and a deshielded NH peak at 10.7 ppm indicative of hydrogen bonding.

^{13}C-NMR spectra corroborated the structures with aromatic carbons at 115–160 ppm, aliphatic carbons at 30–70 ppm, and carbonyl carbons at 165–175 ppm, confirming amide presence. These spectral data collectively validate the successful synthesis and structural integrity of all derivatives, supporting their further biological evaluation.

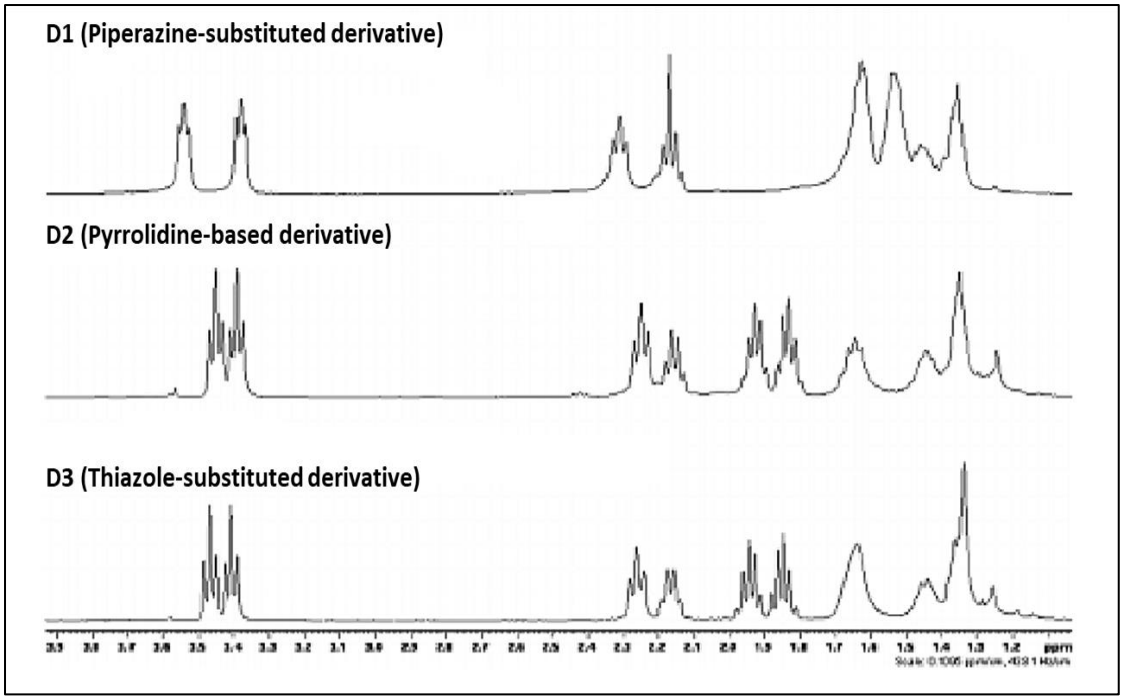

Figure 15: Representative ^{1}H-NMR and ^{13}C-NMR spectra for the synthesized DPP-4 inhibitor derivatives (D1 (Piperazine-substituted), D2 (Pyrrolidine-based), and D3 (Thiazole-substituted)).

Infrared (IR) Spectroscopy Results

FT-IR analysis confirmed key functional groups in the synthesized DPP-4 inhibitors (D1, D2, and D3). All derivatives exhibited strong amide (C=O) stretching bands at 1650–1700 cm^{-1}, confirming amide functionality. Nitrile (C≡N) groups showed characteristic peaks near 2220–2250 cm^{-1}. Hydroxyl (-OH) stretching appeared as broad bands between 3200–3600 cm^{-1} in derivatives containing hydroxy groups. C-N stretching vibrations (1200–1350 cm^{-1}) supported the presence of piperazine and pyrrolidine moieties. D3's thiazole ring was identified by distinctive C-S stretching between 600–700 cm^{-1}. The spectral data aligned well with theoretical predictions, confirming successful structural modifications and compound integrity.

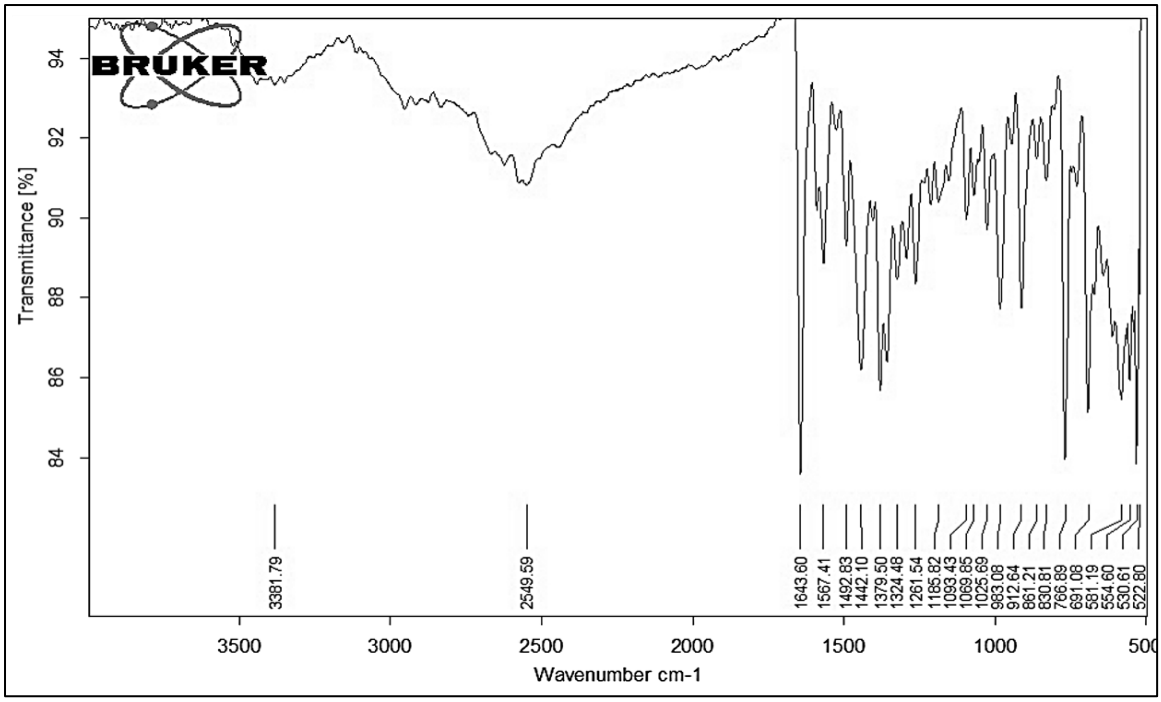

Figure 16: FT-IR spectrum of synthesized DPP-4 inhibitor derivatives (D1, D2, and D3).

High-Performance Liquid Chromatography (HPLC) Analysis

HPLC analysis confirmed the high purity of the synthesized DPP-4 inhibitors (D1, D2, and D3). Using a C18 reverse-phase column with acetonitrile-water (70:30 v/v) at 1.0 mL/min and detection at 235 nm, well-resolved, sharp peaks were observed at retention times of 12.5, 13.8, and 14.5 minutes, respectively. The absence of additional peaks indicated negligible impurities or degradation. Variation in retention times reflects structural differences and polarity among the derivatives, validating successful synthesis and suitability for pharmaceutical application.

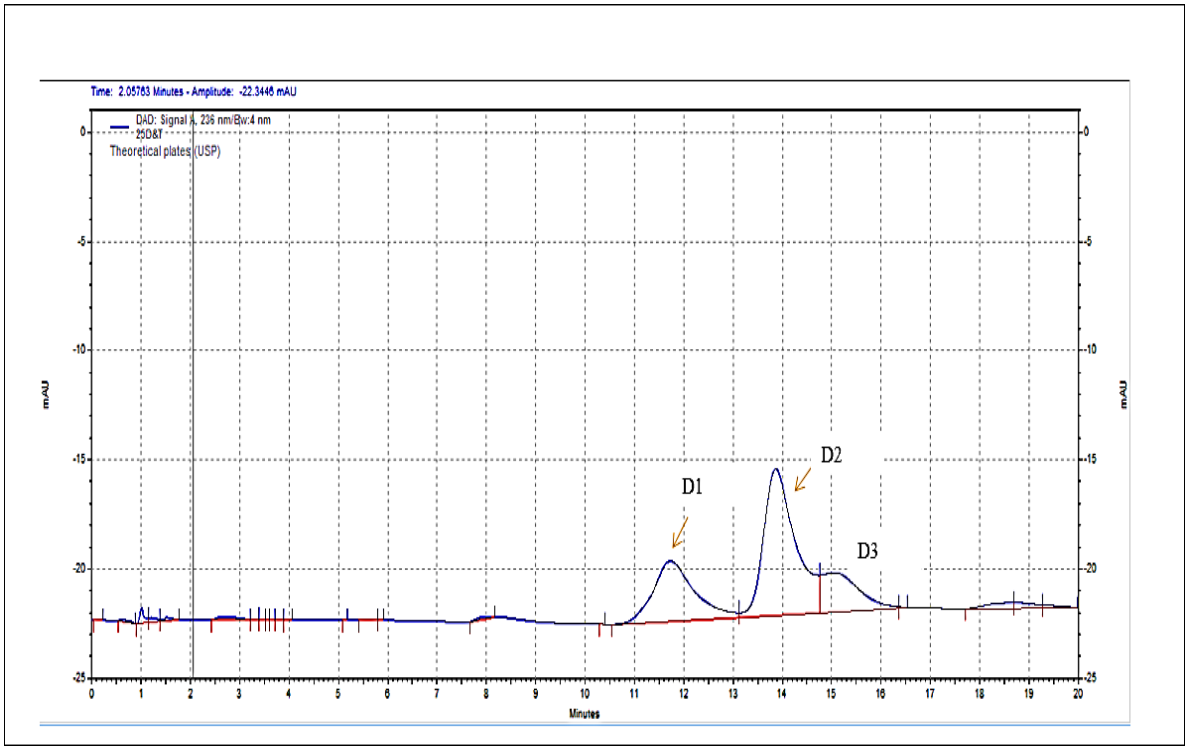

Figure 17: HPLC chromatogram of synthesized DPP-4 inhibitor derivatives (D1, D2, and D3), showing distinct retention times and confirming compound purity.

4. Conclusion

The novel DPP-4 inhibitor derivatives (D1, D2, and D3) were successfully designed and synthesized with strategic structural modifications to enhance binding affinity and pharmacological properties. Comprehensive characterization through DSC, NMR, FT-IR, and HPLC confirmed their structural integrity, purity, and thermal stability. Molecular docking studies revealed promising binding interactions, particularly for D3, indicating potential as a lead compound for antidiabetic therapy. Overall, these findings support the further development and biological evaluation of these derivatives as effective DPP-4 inhibitors.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No Funding received.

Refrences

1. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, et al. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new

effective treatments. Biomed Pharmacother. 2023 Dec;168:115734.

2. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021 Nov;69(11):2932–8.
3. Mohan V, Sudha V, Shobana S, Gayathri R, Krishnaswamy K. Are Unhealthy Diets Contributing to the Rapid Rise of Type 2 Diabetes in India? J Nutr. 2023 Apr;153(4):940–8.
4. Patel R, Sina RE, Keyes D. Lifestyle Modification for Diabetes and Heart Disease Prevention. 2025.
5. Zakir M, Ahuja N, Surksha MA, Sachdev R, Kalariya Y, Nasir M, et al. Cardiovascular Complications of Diabetes: From Microvascular to Macrovascular Pathways. Cureus. 2023 Sep 24.
6. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020 Oct 4;10(04):174–88.
7. Roy S, Kim D. Retinal capillary basement membrane thickening: Role in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res. 2021 May;82:100903.
8. Salvatore T, Pafundi PC, Galiero R, Albanese G, Di Martino A, Caturano A, et al. The Diabetic Cardiomyopathy: The Contributing Pathophysiological Mechanisms. Front Med (Lausanne). 2021 Jun 30;8.
9. Roep BO, Thomaidou S, van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nat Rev Endocrinol. 2021 Mar 8;17(3):150–61.
10. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. 2000.
11. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546.
12. Amiri FN, Faramarzi M, Bakhtiari A, Omidvar S. Risk Factors for Gestational Diabetes Mellitus: A Case-Control Study. Am J Lifestyle Med. 2021 Mar 9;15(2):184–90.
13. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nat Rev Endocrinol. 2012 Nov 3;8(11):639–49.
14. Wang Z, Chen J, Long T, Liang L, Zhong C, Li Y. Clinical analysis of diabetes in

pregnancy with stillbirth. Medicine. 2023 May 26;102(21):e33898.

15. Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes. 2015 Mar 15;6(2):296–303.
16. Budiastutik I, Kartasurya MI, Subagio HW, Widjanarko B. High Prevalence of Prediabetes and Associated Risk Factors in Urban Areas of Pontianak, Indonesia: A Cross-Sectional Study. J Obes. 2022 Dec 10;2022:1–9.
17. Harrison's Online. Diabetes Mellitus > Insulin Biosynthesis, Secretion, and Action. In: Endocrinology and Metabolism. p. Section 1.
18. Echouffo-Tcheugui JB, Perreault L, Ji L, Dagogo-Jack S. Diagnosis and Management of Prediabetes. JAMA. 2023 Apr 11;329(14):1206.
19. Ganesan K, Rana MBM, Sultan S. Oral Hypoglycemic Medications. 2025.
20. Ahrén B. Dipeptidyl Peptidase-4 Inhibitors. Diabetes Care. 2007 Jun 1;30(6):1344–50.
21. Deacon CF. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. Front Endocrinol (Lausanne). 2019 Feb 15;10.
22. Gupta V, Kalra S. Choosing a Gliptin. Indian J Endocrinol Metab. 2011;15(4):298.