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EVOLUTION AND FUTURE PROSPECTS OF HETEROCYCLIC SCAFFOLDS IN DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS: A MEDICINAL CHEMISTRY PERSPECTIVE

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Keywords:

Diabetes mellitus, DPP-4 inhibitors, Gliptins, Heterocyclic scaffolds, Structure-activity relationship (SAR), Medicinal chemistry, Drug design

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ABSTRACT: Dipeptidyl peptidase-4 (DPP-4) inhibitors, or gliptins, represent a cornerstone in the oral management of Type 2 Diabetes Mellitus (T2DM). Their mechanism, which potentiates endogenous incretin hormones, offers glucose-dependent efficacy with a minimized risk of hypoglycemia. The discovery and optimization of these agents are inextricably linked to the strategic deployment of heterocyclic chemistry. This review provides a critical analysis of the pivotal role heterocyclic scaffolds play in DPP-4 inhibitor design, from first-in-class drugs to next-generation candidates. We begin by elucidating the structural biology of DPP-4, detailing the catalytic triad (Ser630, Asp708, His740) and the key sub-pockets (S1, S2, S2 extensive) that serve as a blueprint for rational inhibitor design. A retrospective analysis of clinically approved gliptins including sitagliptin (pyrazolopyrimidine), saxagliptin (constrained cyanopyrrolidine), linagliptin (xanthine), and alogliptin (pyrimidinedione)-highlights how specific heterocyclic cores dictate potency, selectivity, and pharmacokinetic profiles. The core of this review surveys recent advances (2012–present) in novel heterocyclic chemotypes explored as DPP-4 inhibitors. We systematically categorize and discuss promising scaffolds such as pyrimidines, oxadiazoles, pyrrolidines, triazoles, triazines, piperazines, quinazolines, pyrazoles, and indolines, emphasizing structure-activity relationship (SAR) insights, computational modeling approaches, and *in-vitro/in-vivo* results. Finally, we examine the current clinical pipeline and future perspectives, addressing challenges like long-term safety and the pursuit of multi-target agents or once-weekly formulations. The integration of advanced computational tools, fragment-based design, and personalized medicine principles is poised to guide the development of next-generation heterocyclic DPP-4 inhibitors with enhanced therapeutic profiles.

INTRODUCTION: Type 2 Diabetes Mellitus (T2DM) is a global pandemic characterized by insulin resistance and progressive β-cell dysfunction, driving significant morbidity and mortality [1, 2]. The incretin system, involving hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), revolutionized T2DM therapy by offering a glucose-dependent pathway to enhance insulin secretion [3, 4]. However, the rapid inactivation of these hormones by the serine protease dipeptidyl peptidase-4 (DPP-4) presented a key therapeutic target [5, 6].

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Inhibiting DPP-4 prolongs the activity of endogenous incretins, forming the basis for the gliptin class of oral antihyperglycemic agents [7]. The clinical success of DPP-4 inhibitors, marked by robust efficacy, weight neutrality, and a favorable safety profile, is fundamentally a triumph

of medicinal chemistry [8, 9]. Each approved gliptin is built upon a unique heterocyclic scaffold, demonstrating how these privileged structures enable precise optimization of target binding, selectivity over related proteases (e.g., DPP-8/9), and drug-like properties [10].

This review aims to provide a comprehensive and critical analysis of heterocyclic scaffolds in DPP-4 inhibitors. We will dissect the structural foundations of first-generation agents, catalog and evaluate recent advances in novel heterocyclic chemotypes (post-2012), and forecast future directions driven by computational chemistry and evolving therapeutic needs.

Structural Biology of DPP-4: A Blueprint for Inhibitor Design: Rational design of DPP-4 inhibitors is predicated on a deep understanding of the enzyme's structure. DPP-4 enzyme structure is shown as in **Fig. 1**. DPP-4 is an α/β-hydrolase with a catalytic triad of Ser630, Asp708, and His740 [11, 12]. Its active site features distinct sub-pockets that have been masterfully exploited:

The S1 Pocket: A small, hydrophobic cavity that accommodates the cyanopyrrolidine pharmacophore present in most inhibitors, forming a reversible covalent bond with Ser630. The S2 Pocket & Glutamate Shelf: Features the anionic residues Glu205 and Glu206, which form critical salt bridges with a basic amine (e.g., aminopiperidine) in inhibitors, contributing massively to binding affinity. The S2 Extensive Pocket: A large, hydrophobic cavity unique to DPP-4. Occupation by lipophilic aromatic groups (e.g., the trifluorophenyl in sitagliptin) is key for high potency and selectivity against DPP-8/9 [13-15]. Non-enzymatic Function: As the cell surface protein CD26, DPP-4 has immunomodulatory roles, a consideration for future drug design [16, 17].

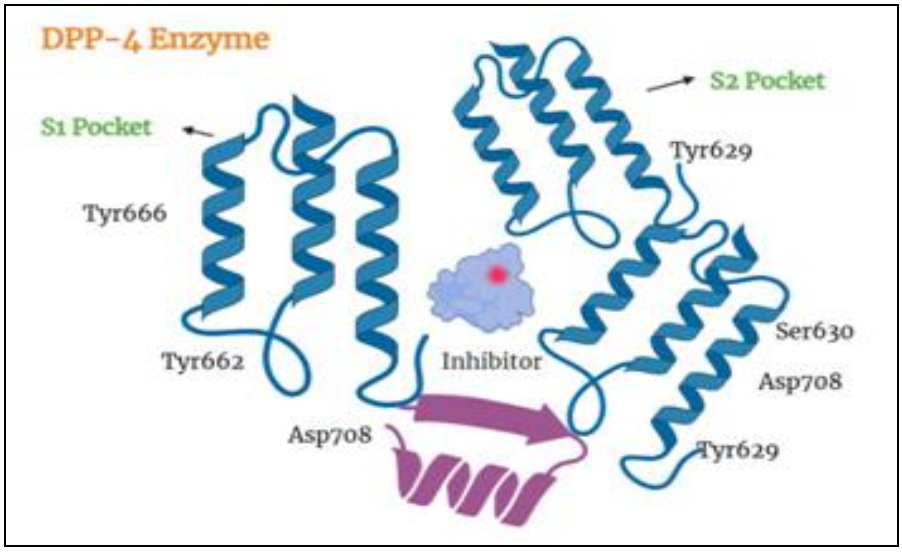


FIG. 1: DPP-4 ENZYME ACTIVE SITES

Mechanism of DPP-4 Inhibitor: DPP-4 inhibitors are a category of oral glucose-lowering medications designed to amplify the body's endogenous incretin response in individuals with type 2 diabetes.

Upon food intake, L-cells located in the distal gut secrete glucagon-like peptide-1 (GLP-1), while K-cells in the proximal gut release glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones act on pancreatic beta-cells, where GLP-1 and GIP potentiate glucose-stimulated insulin secretion. Furthermore, GLP-1 exerts additional effects by promoting beta-cell proliferation and inhibiting glucagon secretion from pancreatic alpha-cells. The resulting increase in insulin facilitates glucose uptake and utilization in peripheral tissues, specifically muscle and adipose tissue, while also acting on the liver. Concurrently, the suppression of glucagon further reduces hepatic glucose output as shown in **Fig. 2**.

The combined actions of enhanced peripheral glucose disposal and decreased hepatic glucose production culminate in the reduction of blood glucose levels [18].

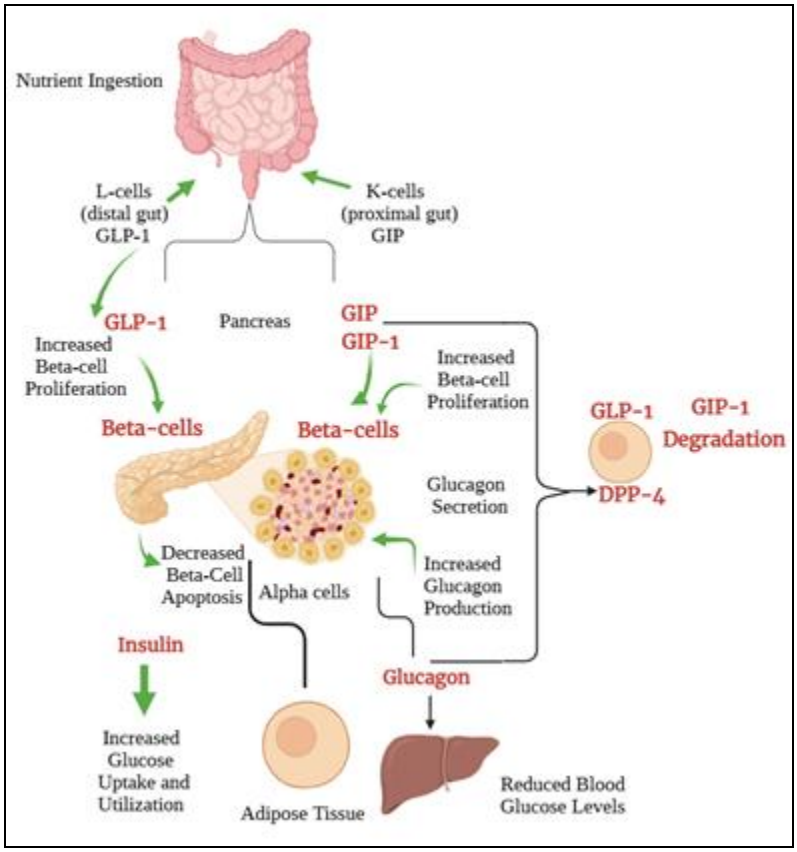


FIG. 2: MECHANISM OF DPP-4 INHIBITOR

Importance of DPP-4 Inhibitors over Other Oral Antidiabetic Agents: DPP-4 inhibitors represent a significant class of oral antihyperglycemic agents for managing Type 2 diabetes, characterized by a targeted mechanism and a well-regarded safety spectrum. Their primary action involves inhibiting the enzyme dipeptidyl peptidase-4, which degrades the endogenous incretin hormones GLP-1 and GIP. By preserving these hormones, DPP-4 inhibitors enhance glucose-dependent insulin secretion from pancreatic beta cells while simultaneously reducing glucagon secretion from alpha cells. This physiological mode of action provides effective glycemic lowering with a notably low risk of inducing hypoglycemia, a common adverse effect associated with insulin secretagogues like sulfonylureas. The clinical profile of these agents includes weight neutrality, a stark contrast to medications such as thiazolidinediones and sulfonylureas that can promote weight gain. They are typically associated with fewer gastrointestinal side effects than metformin and do not cause the nausea often seen with GLP-1 receptor agonists. The convenience of once-daily oral dosing supports patient compliance. Additionally, several DPP-4 inhibitors are considered safe and require only dosage adjustment, not avoidance, in patients with chronic kidney disease, offering an advantage over agents like metformin. Their efficacy is maintained in combination therapy with other glucose-lowering drugs, including metformin and SGLT2 inhibitors, without a significant increase in adverse events. Extensive cardiovascular outcome trials have confirmed their overall cardiovascular safety, though they do not provide the proven cardiorenal protection associated with some other newer classes. Collectively, the glucose-dependent efficacy, favorable tolerability, renal safety, and simple administration position DPP-4 inhibitors as a valuable and commonly selected option, particularly for patients where hypoglycemia risk, weight management, and complex medication regimens are key considerations [19].

Clinically Approved Gliptins: A Foundation of Heterocyclic Diversity: The evolution of marketed gliptins showcases the versatility of heterocycles in solving the DPP-4 inhibition puzzle **Table 1**. The genesis of the dipeptidyl peptidase-4 (DPP-4) inhibitor class is a landmark achievement in medicinal chemistry, seamlessly integrating

insights from incretin physiology with rational, structure-based drug design. Each clinically approved gliptin is built upon a distinct heterocyclic scaffold.

Sitagliptin: The pioneer, based on a pyrazolopyrimidine core. Its (R)-3-amino-piperidine anchors to the glutamate shelf, while the 2,4,5-trifluorophenyl group optimally fills the S2 extensive pocket [20].

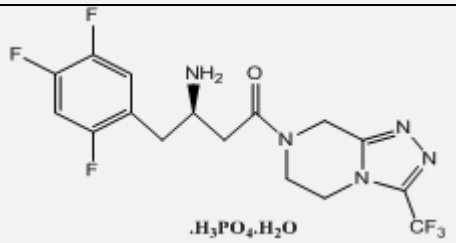
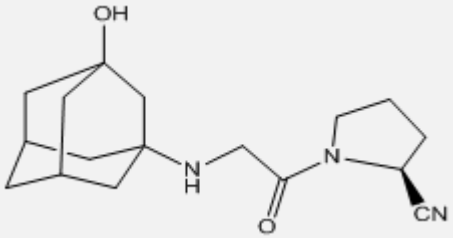
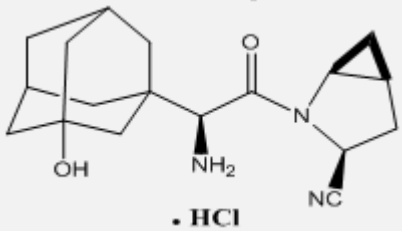
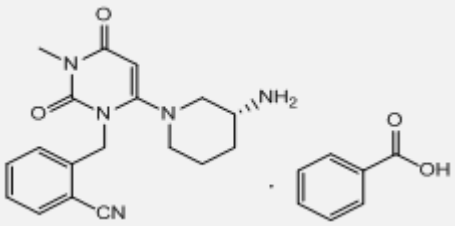
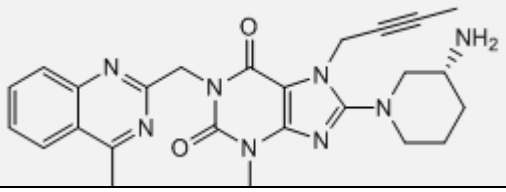
Saxagliptin: Features a conformationally constrained 2 azabicyclo [3.1.0] hexa-necyanopyrrolidine headpiece for metabolic stability and an (S)-hydroxyadamantylglycine tail that fills the S2 pocket *via* hydrophobic interactions and a key H-bond with Tyr547 [21, 22].

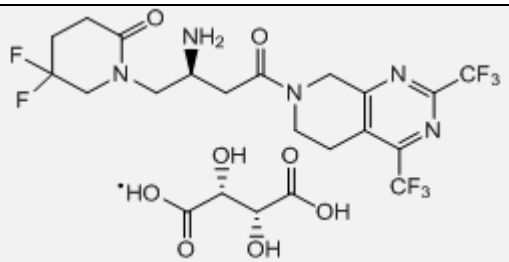
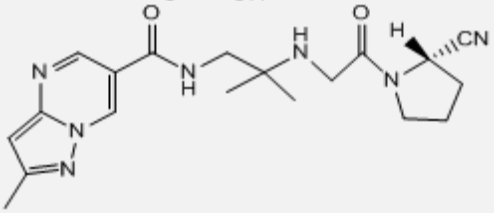
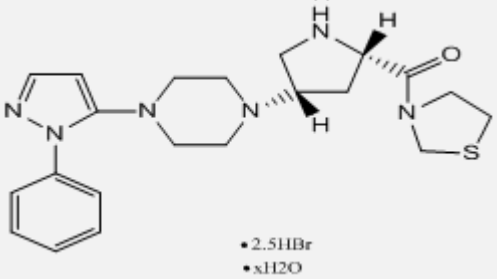
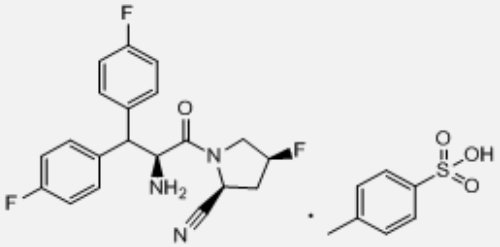
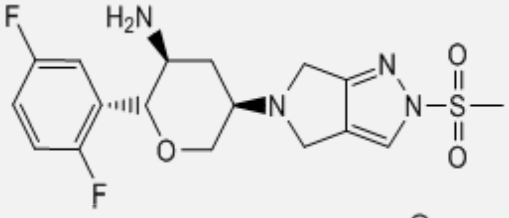
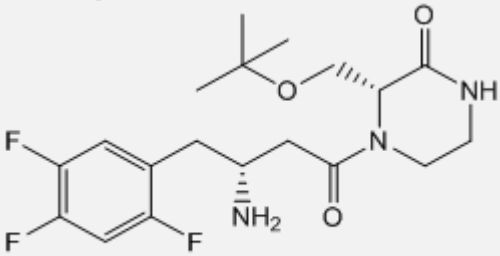
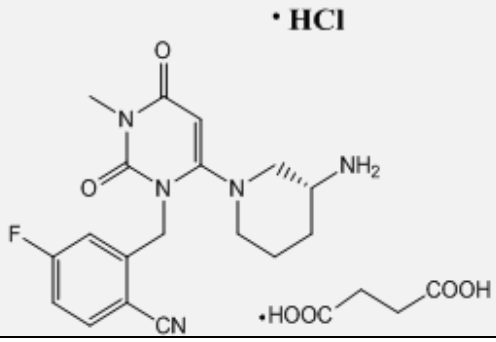
Linagliptin: Distinguished by a xanthine (dihydro-purinedione) core, granting high plasma protein binding and non-renal (hepatobiliary) excretion, eliminating the need for dose adjustment in renal impairment [23, 24].

Alogliptin: Utilizes a pyrimidinedione scaffold, with its aminopiperidine forming a unique salt bridge/H-bond network with Glu205 and Tyr662 [25].

Other Agents: This diversity extends to teneligliptin (thiazolidine scaffold) [26], omarigliptin (modified pyrazolopyrimidine for once-weekly dosing) [27, 28], and evogliptin (quinazolinone scaffold), among others.

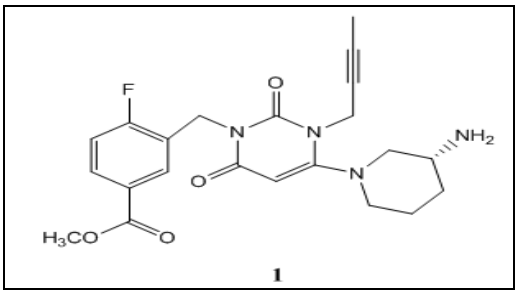
TABLE 1: APPROVED DPP-4 INHIBITORS [29–31, 32, 33, 34–39]

S. no.	Drug Name	Status	Company & Country	Structure
1	Sitagliptin phosphate monohydrate	2006 approved	Merck sharp &dohme; Ono pharmaceutical (U.S)	
2	Vildagliptin	2007 approved	Novartis (European Union)	
3	Saxagliptin hydrochloride	2009 approved	Bristol-Myers Squibb; Astrazeneca (U.S)	
4	Alogliptin benzoate	2010 approved	Takeda (Japan)	
5	Linagliptin	2011 approved	Boehringerlngelheim; Lilly (U.S)	

6	Gemigliptin L-tartrate sesquihydrate	2012 approved	LG life sciences (South Korea)	
7	Anagliptin	2012 approved	Sanwa kagaku Kenkyusho; Kowa (Japan)	
8	Tenegliptinhydrobromide hydrate	2012 approved	Mitsubishi Tanabe Pharma; Daiichio Sankyo (Japan)	
9	Denagliptintosilate	2014 approved	Glaxosmithkline (U.S)	
10	Omarigliptin	2015 approved	Merck Sharp & Dohme (U.S)	
11	Evogliptin hydrochloride	2015 approved	Dong-A- Pharmaceutical (South Korea)	
12	Trelagliptin succinate	2015 approved	Takeda (Japan)	

Recent Advances in Novel Heterocyclic Scaffolds (2012-Present): Post-2012 research has seen an explosion of innovative heterocyclic cores aimed at improving potency, selectivity, pharmacokinetics, and introducing polypharmacology. The clinical success of first-generation DPP-4 inhibitors established a formidable precedent, but the quest for improved agents has continued unabated. Post-2012 research has witnessed a flourishing of sophisticated heterocyclic chemistry, with medicinal chemists designing increasingly complex fused and polycyclic systems. These novel scaffolds aim not merely to replicate existing potency but to achieve superior profiles: enhanced selectivity, more favorable pharmacokinetics, prolonged duration of action, and the incorporation of ancillary benefits.

Pyrimidine Based Scaffolds: Qing Li *et al.* (2021): identified a novel family of oral accessible, potent DPP-4 inhibitors that are ester and carboxylic acid chemicals. Extensive SAR studies were carried out by comparing the 2-cyanobenzyl and 2-butynyl groups, conjugating various amino acids at the carboxyl handle, adding various halogen groups to the benzene ring, and investigating the optimal carboxyl position, all while starting with 3-substituted benzoic acid and its methyl ester. Based on molecular docking, acids and esters both had comparable binding patterns with significant hydrogen bond interactions with Trp629 and Lys554. The best compound 1, was shown to have exceptional oral pharmacokinetic characteristics, low cytotoxicity, adequate metabolic stability, and prolonged *in-vivo* DPP-4 inhibition [40].



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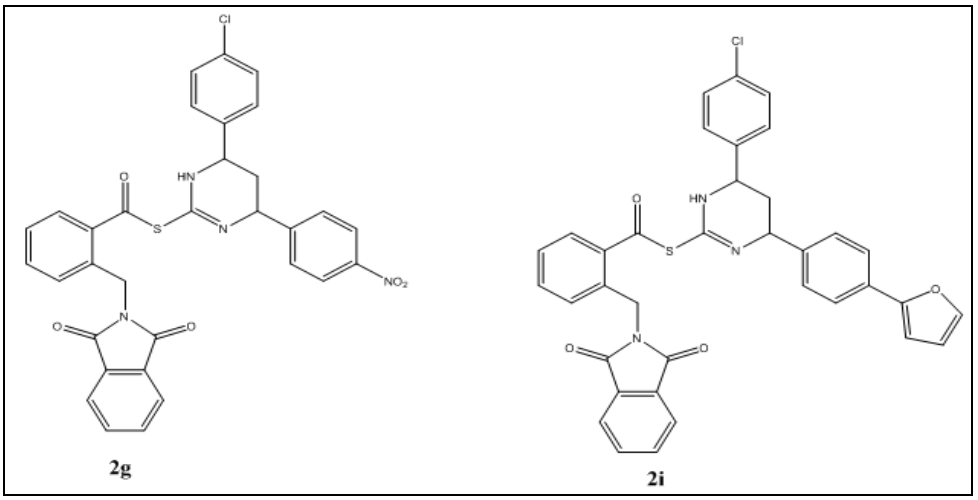
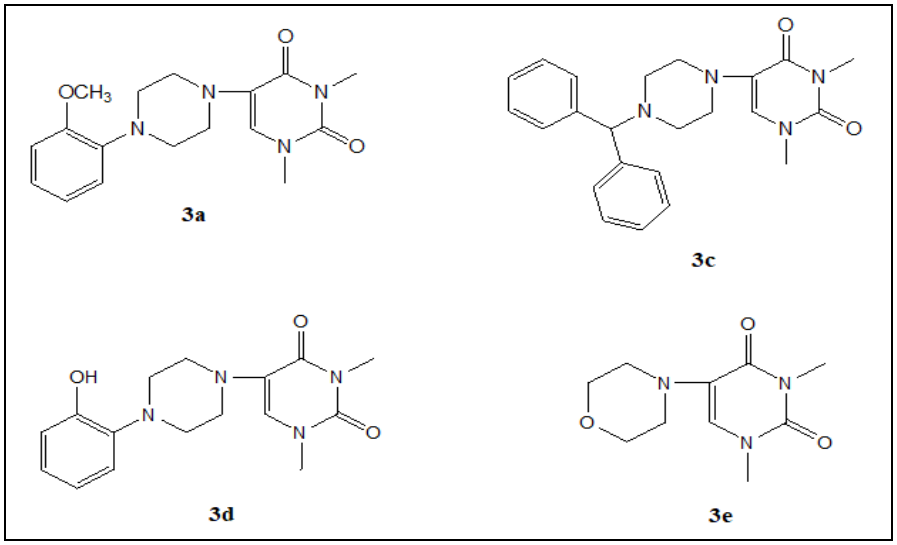
Ahmed A. E. Mourad *et al.* (2021): A new series of dihydropyrimidine-phthalimide hybrid compounds was designed, synthesized, and thoroughly characterized. These compounds were then assessed for their ability to inhibit DPP-4, along with their antioxidant properties. *In-vitro* DPP-4 inhibition assays revealed that several hybrids-specifically 2b,2d, 2e, 2g, and 2i-exhibited stronger inhibitory effects than the reference drug alogliptin. Notably, **2g** and **2i** demonstrated the most sustained and potent DPP-4 inhibition, surpassing both the other hybrids and alogliptin in activity [41].

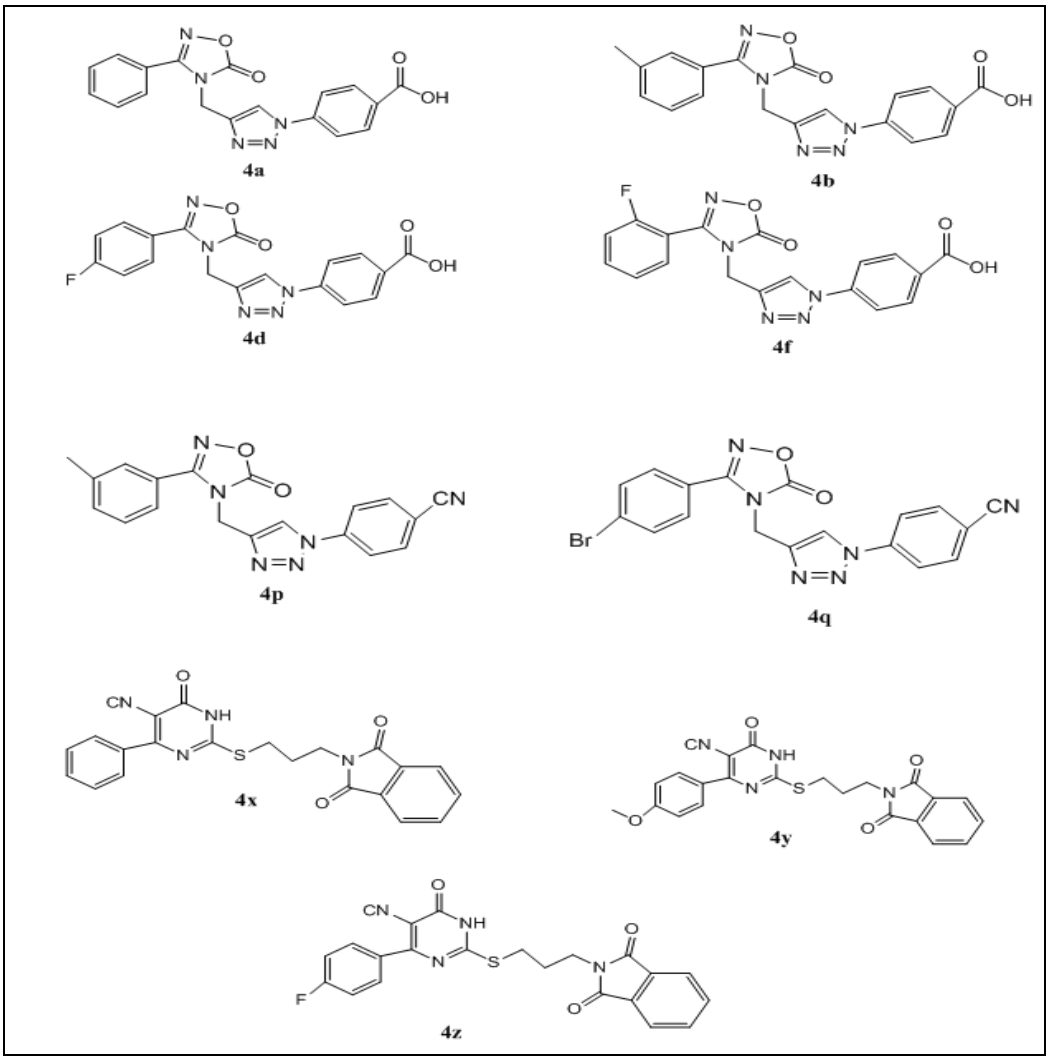


2g **2i**

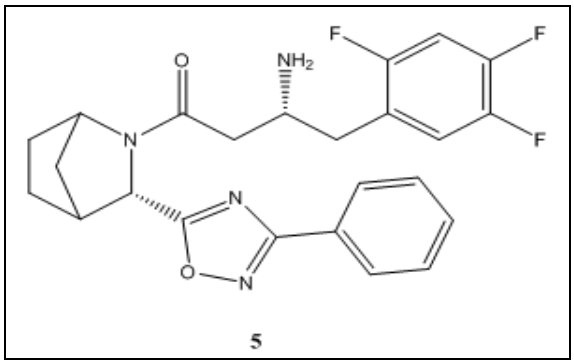
Vibhu Jha *et al.* (2018): The target compounds were synthesized as N-methylated and N-benzylated derivatives of pyrimidinedione. Their DPP-4 inhibition potential was assessed enzymatically, followed by molecular docking simulations to evaluate binding interactions. Notably, derivatives 3a and 3c-e, displayed significant *in-vitro* DPP-4 inhibition, with varying potency. Further docking analyses against the DPP-4 active site were performed, including a comparative assessment with established natural inhibitors (quercetin, resveratrol, and flavone) to contextualize their binding affinity [42].



S.G Diniz Feitosa *et al.* (2024): A series of 22 newly synthesized oxadiazolone and pyrimidinone derivatives were evaluated for their DPP-4 inhibitory effects using an *in-vitro* enzymatic assay. Molecular docking studies were performed to explore their binding interactions with the DPP-4 active site. Among these, nine derivatives (4a, 4b, 4d, 4f, 4p, 4q, 4x, 4y, and 4z) exhibited notable inhibition, with IC_{50} values between 0.3 and 1.86 mM, indicating significant potential as DPP-4 inhibitors [43].



Oxadiazole Based Scaffolds: Zinevich, T. V *et al.* (2025): Demonstrated that pseudopeptide structures containing (R)-3-amino-4-(2,4,5-trifluorophenyl) butanoic acid, a 2-azabicyclo [2.2.1] heptane unit, and 1,2,4-oxadiazole-based side chains function as highly potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitors. Through stereochemical optimization of oxadiazole-modified neogliptin analogs, the researchers identified compound 5 as a promising lead molecule warranting further investigation for the treatment of type 2 diabetes mellitus [44].



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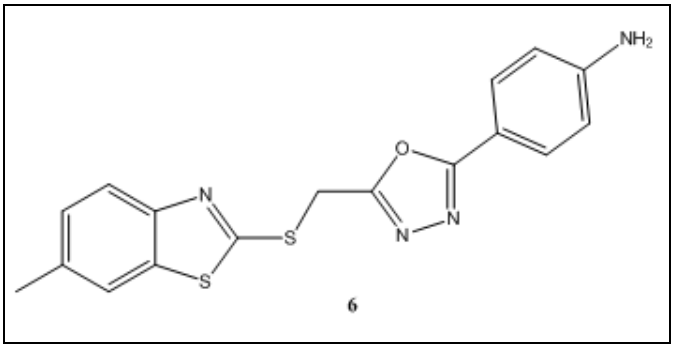
Kumar *et al.* (2016): Several novel 2-((benzothiazol-2-ylthio) methyl)-5-phenyl-1, 3, 4-oxadiazole derivatives were synthesized and evaluated for potential anti-diabetic activity in an *in-vivo* model, using glibenclamide as a positive control. While all tested compounds demonstrated significant oral hypoglycemic effects, derivative 6 exhibited the strongest activity at an oral dose of 350 mg/kg body weight [45].



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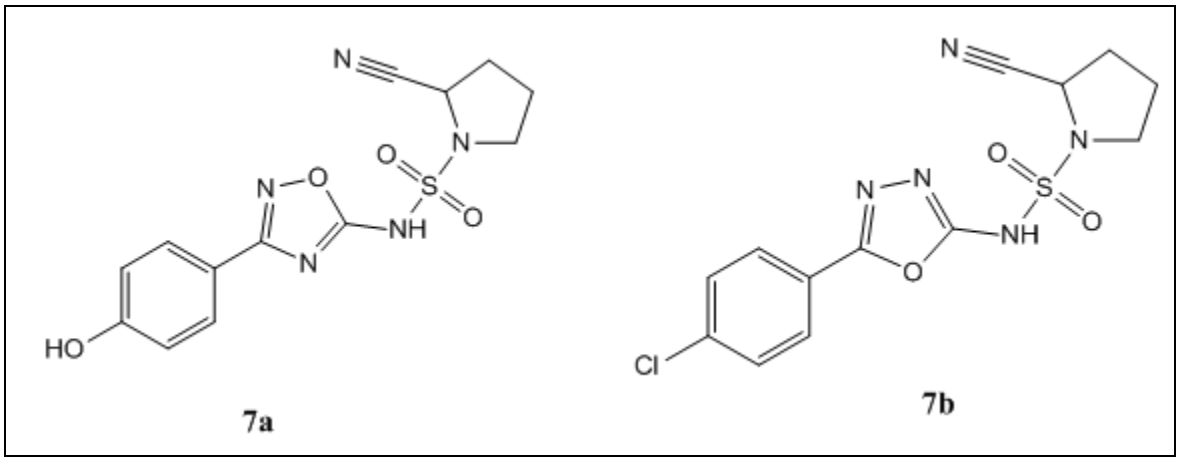
Salve, M. T *et al.* (2023): A series of sixteen cyclopyrrolidine-oxadiazole hybrid compounds were successfully synthesized. Molecular docking simulations were conducted to analyze the binding interactions and orientations of these synthesized molecules within the active site of the dipeptidyl peptidase-4 (DPP-4) enzyme (Protein Data Bank ID: 3W2T). Six selected compounds from the series were subsequently evaluated for *in-vivo* antidiabetic efficacy using a high-fat diet-streptozotocin-nicotinamide induced diabetic rat model, with vildagliptin employed as the reference standard.

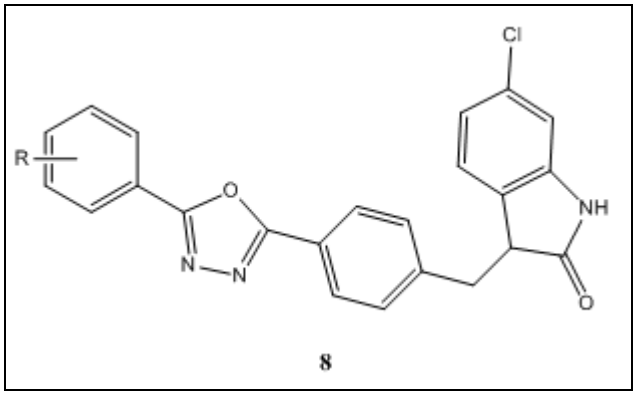
The experimental results demonstrated that compound 7a and 7b produced the most significant reduction in blood glucose levels among all tested analogues, achieving a value of 220 ± 4.56 mg/dL. This hypoglycemic effect surpassed that observed with the standard drug vildagliptin, which recorded a value of 215 ± 7.52 mg/dL in the same animal model [46].



7a 7b

Tukaram, S. M. *et al.* (2021): A novel series of 1,3,4-oxadiazole-based derivatives were synthesized and evaluated as potential antidiabetic agents. Molecular docking studies against the dipeptidyl peptidase-4 (DPP-4) enzyme (PDB ID: 3W2T) were performed to analyze the binding interactions of the newly synthesized compounds. Five derivatives exhibiting the most favorable

docking scores and notable DPP-4 inhibitory activity were selected for further *in-vitro* evaluation to determine their half-maximal inhibitory concentration (IC_{50}) values. Specifically, compound 8 exhibited the most potent inhibitory activity with an IC_{50} value of 12.05 ± 1.64 nM, positioning it as the most effective inhibitor among the fourteen synthesized derivatives and highlighting its promise as a DPP-4 inhibitor relative to the standard treatment [47].



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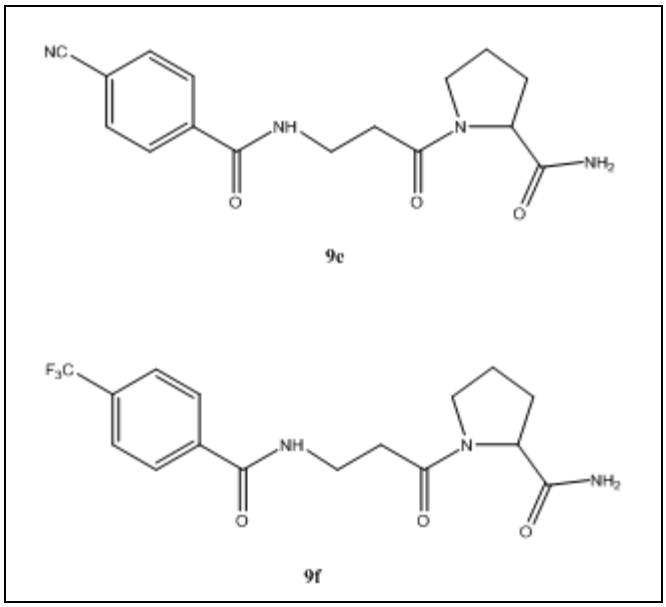
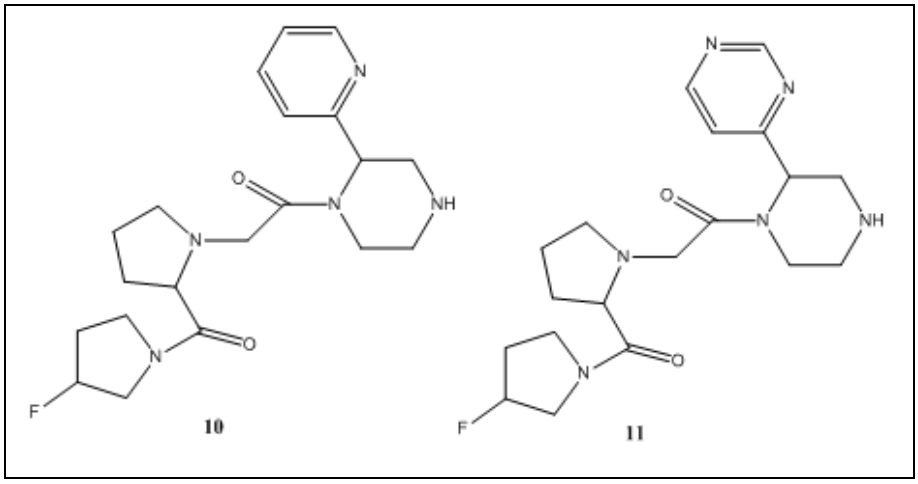
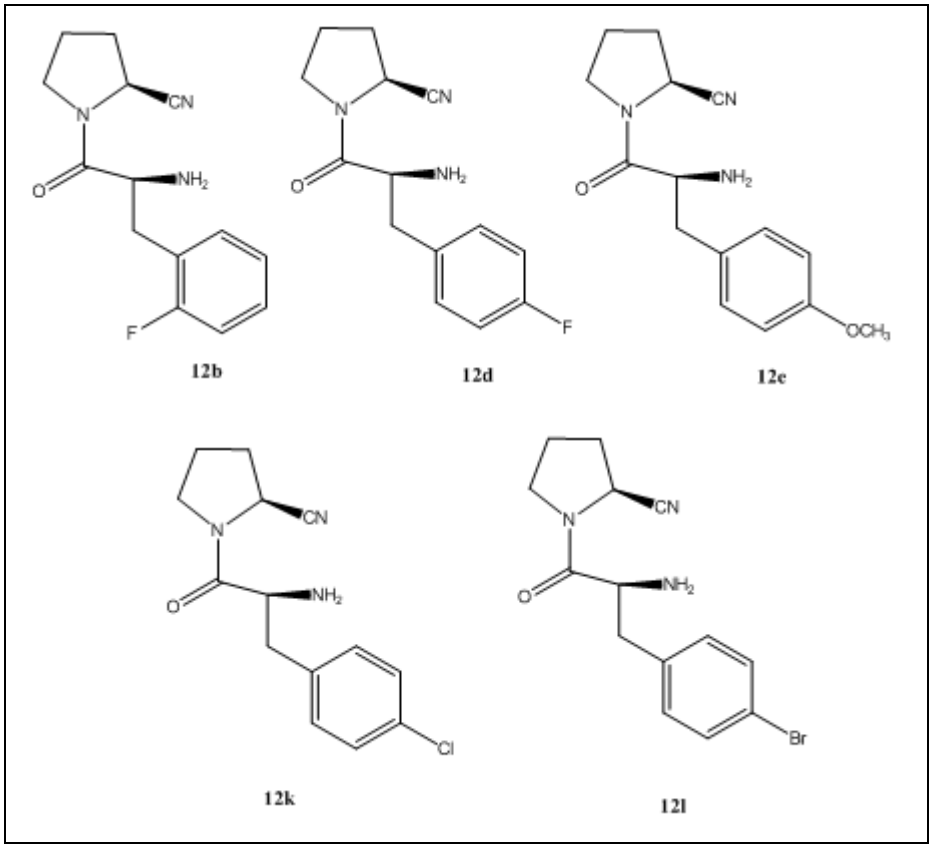
Pyrrolidine Based Scaffolds: Jadav *et al.* (2012): Using solid-phase peptide synthesis (SPPS), they developed a series of novel pyrrolidine-containing peptidomimetics structurally derived from cyanopyrrolidine DPP-4 inhibitors. The design incorporated a β-alanine linker between pyrrolidine and various para-substituted benzamide groups. Screening revealed two particularly potent analogs (9e and 9f) exhibiting sub-50 nM inhibitory activity (31 nM and 28 nM IC_{50} values, respectively) against DPP-4 [48].



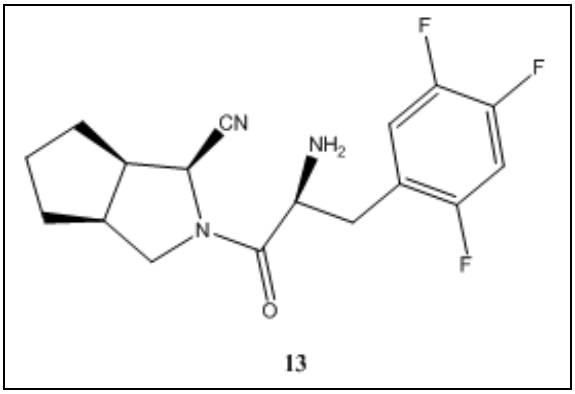
Mani Sharma *et al.* (2013): A series of prolyl-fluoropyrrolidine derivatives were designed and synthesized as DPP-IV inhibitors. Among these, compounds 10 and 11 demonstrated potent enzymatic inhibition, with IC_{50} values of 0.83 µM and 0.43 µM, respectively. Their antihyperglycemic efficacy was further confirmed in a streptozotocin-induced diabetic rat model, where both compounds significantly reduced blood glucose levels, indicating strong *in-vivo* activity [49].



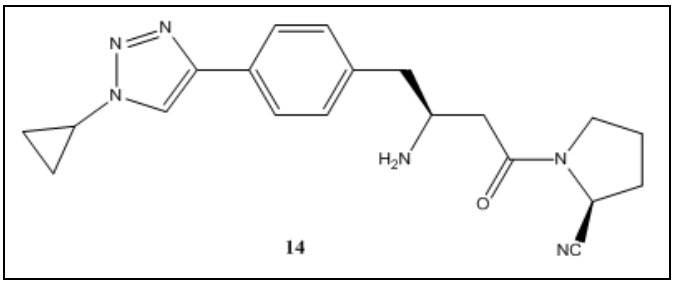
Wang *et al.* (2018): A novel series of pyrrolidine-2-carbonitrile derivatives were designed, inspired by vildagliptin and saxagliptin. To enhance drug-like properties, fluorinated analogs were also synthesized, as fluorination is known to improve bioavailability and binding affinity through conformational modulation. All compounds were screened for DPP-4 inhibition, with derivatives 12b, 12d, 12e, 12k, and 12l exhibiting particularly strong activity (IC_{50} = 4–18 nM) [50].



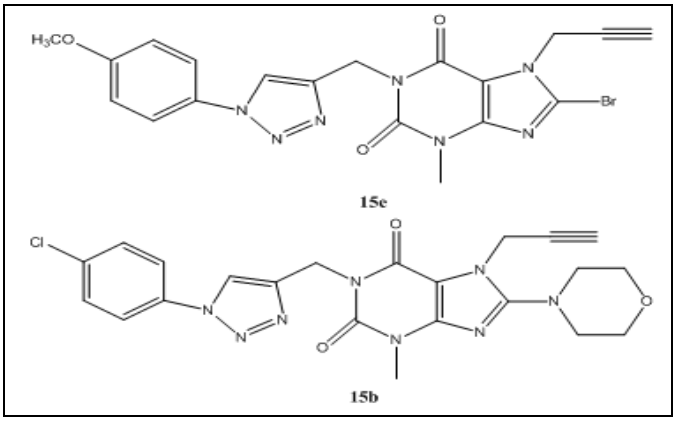
Ji *et al.* (2014): A novel series of octahydro-cyclopenta [b] pyrrole-2-carbonitrile derivatives were synthesized by incorporating a five-membered ring substitution on the pyrrolidine scaffold. Among these, derivative 13 emerged as the most potent inhibitor, displaying sub-micromolar activity (IC_{50} = 10 nM) and exceptional selectivity profiles (>500-fold against DPP-9 and >900-fold against DPP-8), suggesting high target specificity [51].

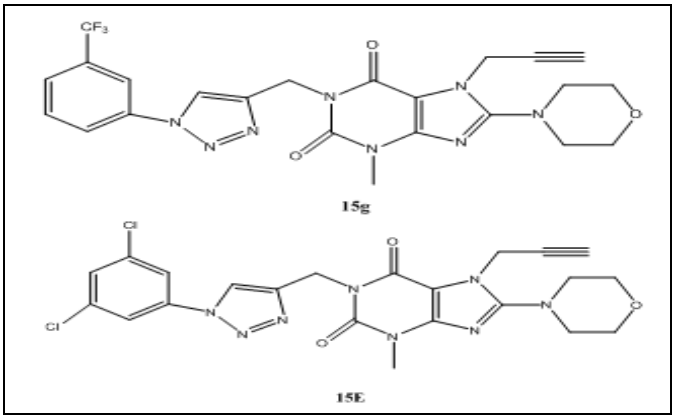


Triazole Based Scaffolds: Liu *et al.* (2013): A series of novel phenylalanine-based derivatives incorporating 1,2,3-triazole moieties were designed and synthesized as potential DPP-4 inhibitors. Through systematic *in-vitro* evaluation, derivative 14 demonstrated superior inhibitory potency (IC_{50} = 247 nM) compared to other analogs in the series [52].

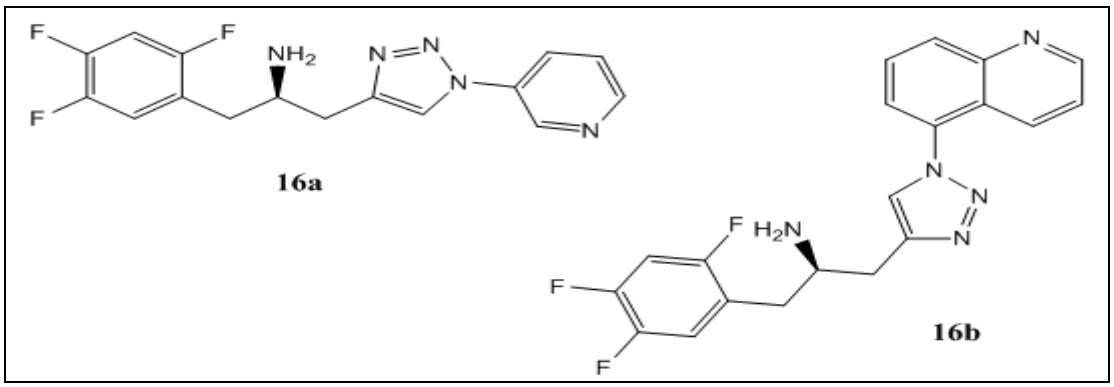


Narsimhaa S *et al.* (2020): A series of twenty novel 1,2,3-triazole-functionalized xanthine derivatives were synthesized in good yields via a copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. The inhibitory activity of the synthesized library against dipeptidyl peptidase-4 (DPP-4) was evaluated using an enzyme assay with Gly-Pro-p-nitroanilide as the substrate. Hydrolysis of this substrate by DPP-4 releases p-nitroaniline, allowing for kinetic measurement of inhibition. This screening identified several potent inhibitors, with compounds 15b, 15e, 15g, and 15E exhibiting significant DPP-4 inhibitory activity, demonstrating IC_{50} values of 87.41 nM, 16.34 nM, and two intermediate values, respectively [53].

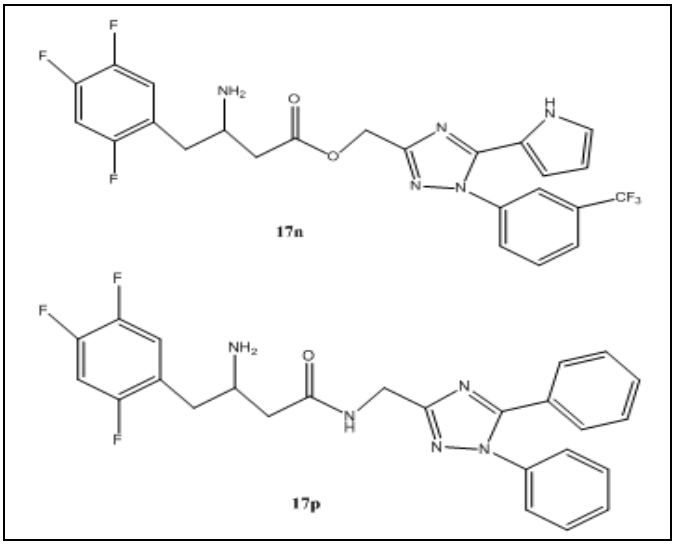




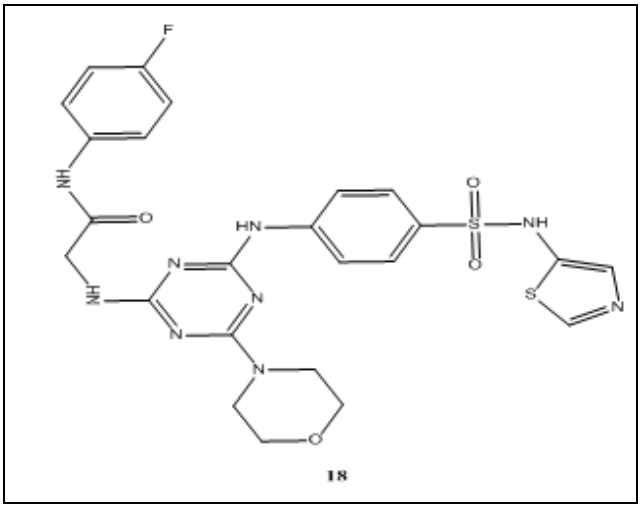
D-V. Vo *et al.* (2020): A series of novel 1,2,3-triazole analogues were synthesized and assessed for their human dipeptidyl peptidase-4 (hDPP-4) inhibitory activity. Among these, compounds 16a and 16b exhibited exceptional potency, demonstrating IC_{50} values of 28 nM and 14 nM, respectively. To further investigate their binding mechanisms, molecular dynamics (MD) simulations were conducted following initial docking studies, using the co-crystal structure of hDPP-4 in complex with sitagliptin (PDB ID: 1X70) as a reference. The *in-vitro* hDPP-4 inhibitory results of the synthesized 1,2,3-triazole derivatives showed strong correlation with the outcomes of the computational simulation analyses [54].



Fuh M T, *et al.* (2021): A series of novel 1,2,4-triazole-based inhibitors were designed featuring diverse linker architectures including glycolamide, glycinamide, and β-amino carbonyl motifs. The synthetic approach involved: (1) functionalization of a key chloroacetamide intermediate through hydroxylation or amination, followed by (2) conjugation with triazole carboxylic acid derivatives. For the β-amino carbonyl series, an efficient one-pot strategy was employed utilizing triazole-containing alcohols/amines and a protected amino acid precursor. Comprehensive screening identified potent analogs with sub-100 nM activity against DPP-4, including a particularly effective β-amino amide derivative ($IC_{50} \approx 34$ nM). These compounds 17n and 17p demonstrated exceptional selectivity against related proteases (QPP, DPP-8, DPP-9). Molecular modeling revealed enhanced stabilization through aromatic interactions with a key phenylalanine residue (Phe357), surpassing both reference compounds and other triazole analogs in binding affinity [55].

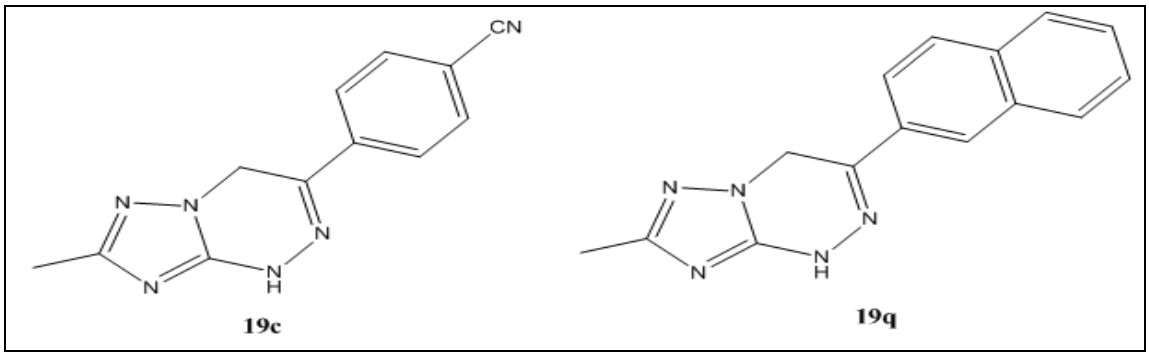


Triazine Based Scaffolds: Gao *et al.* (2016): A series of sulfonamide-linked 1,3,5-triazine-thiazole hybrids were designed and synthesized, incorporating morpholine substituents and a benzamide spacer to enhance DPP-4 inhibitory activity. Among the synthesized derivatives, compound 18 exhibited remarkable potency, displaying an IC_{50} value of 2.32 nM-slightly superior to the reference drug alogliptin (IC_{50} = 2.56 nM) [56].



18

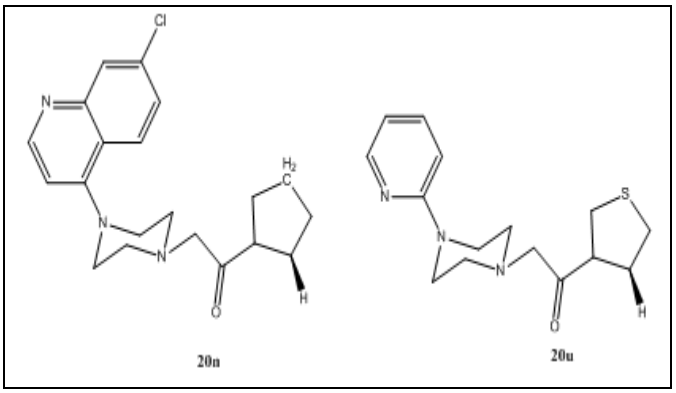
Bhumika D. Patel *et al.* (2017): A novel series of 3,7-disubstituted-1,4-dihydro[1,2,4] triazolo [5,1-c][1,2,4] triazine derivatives were designed through integrated computational approaches, including 3D-QSAR, pharmacophore modeling, virtual screening, and molecular docking. All 17 target compounds were synthesized efficiently, with yields ranging from 65–85%, and thoroughly characterized using FTIR, $^{1}H/^{13}C$ NMR, and ESI-MS spectroscopy. HPLC analysis confirmed high purity (>95%) for all analogs. *In-vitro* DPP-4 inhibition studies revealed two promising candidates 19q (benzofuran substituted derivative) and 19c (4-cyanophenyl-substituted derivative) showed 53.3% inhibition and 48.3% inhibition respectively [57].



19c 19q

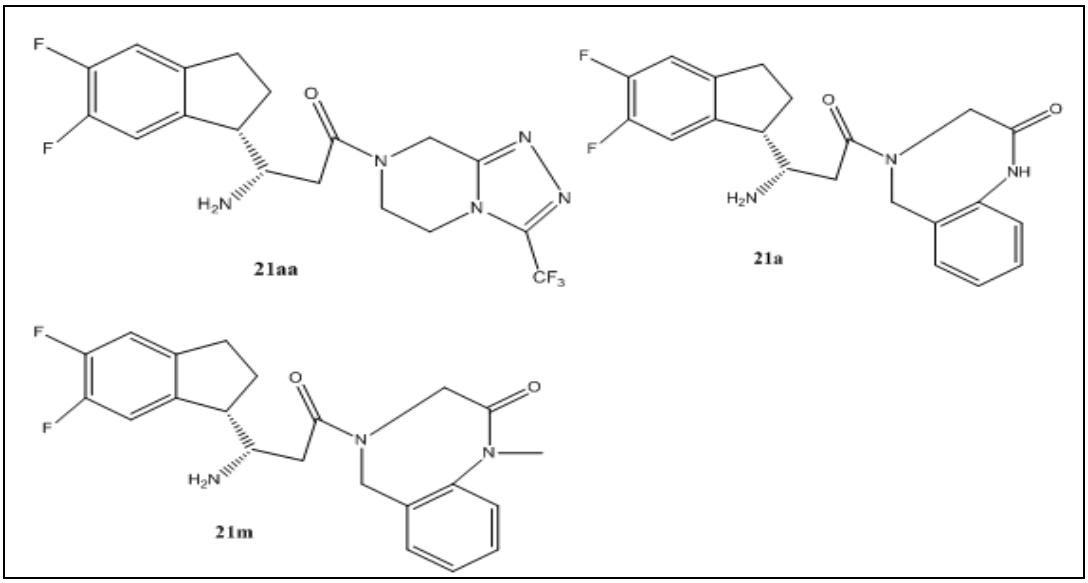
Piperazine Based Scaffolds: Kushwaha *et al.* (2015): A novel series of piperazine-containing derivatives were designed and synthesized to explore their dipeptidyl peptidase-4 (DPP-4) inhibitory potential.

Initial screening *via* an *in-vitro* enzymatic assay identified compounds with >50% inhibition, for which IC_{50} values were determined. In this study compounds 20n and 20u emerged as the most potent analogs, exhibiting 80.4% and 78.9% DPP-4 inhibition, respectively [58].

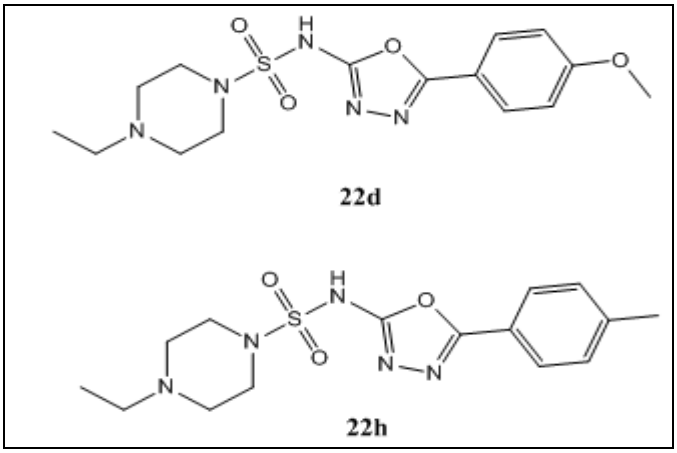


20n 20u

Jiang T *et. al* (2015): A series of novel fused β-homophenylalanine derivatives of Sitagliptin were designed, synthesized, and evaluated as new DPP-4 inhibitors. Most compounds exhibited potent DPP-4 inhibition and high selectivity. In particular, derivatives 21aa, 21a, and 21m demonstrated significant efficacy in an oral glucose tolerance test (OGTT) conducted in ICR mice, with IC_{50} values of 10.8 nM, 4.9 nM, and 3.0 nM, respectively. At a 10 mg/kg dose, the glucose-lowering effects of 18a (34%) and 18m (29%) were comparable to that of Sitagliptin (40%). Similarly, 9aa (57%) and 18n (48%) showed activity on par with Sitagliptin (55%) [59].

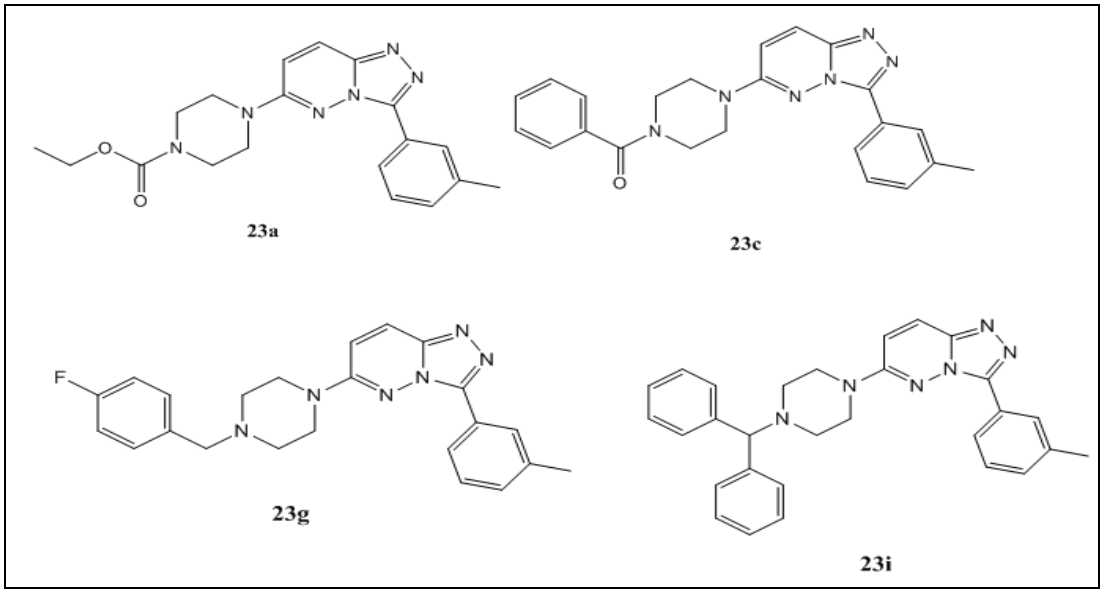


Kalli SB *et al.* (2022): A novel series of 4-ethyl-N-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl) piperazine-1-sulfonamide analogues (8a–8i), 1-ethyl-N-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl) piperazine derivatives incorporating pyridin-4-yl groups, and N-(5-(p-tolyl)-1, 3, 4-oxadiazol-2-yl) methanimine derivatives were synthesized. All novel analogues were subjected to *in-vitro* evaluation to determine their dipeptidyl peptidase-4 (DPP-4) inhibitory potency. The screening revealed that compounds 22d and 22h exhibited superior DPP-4 inhibition compared to other derivatives in the series, demonstrating percentage inhibition values of 28.73%, 27.32%, 26.39%, and 24.32%, respectively [60].

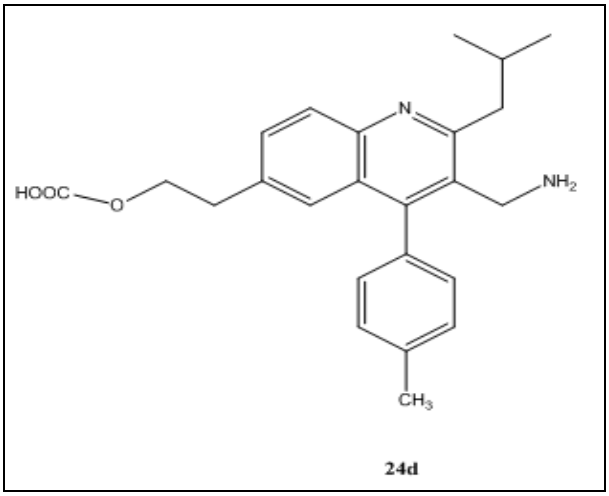


Bindu, B. *et al.* (2020): A series of twelve triazolo-pyridazine-6-yl-substituted piperazine derivatives were synthesized and assessed for their dipeptidyl peptidase-4 (DPP-4) inhibitory activity. The synthesis involved a two-step procedure: first, 6-chloro-3-(m-tolyl)-[1,2,4] triazolo[4,3-b]pyridazine was prepared *via* a one-pot reaction in toluene using pyridine, 3,6-dichloropyridazine, and 5-(3-methylphenyl) tetrazole. Subsequent conjugation of this intermediate with appropriate secondary

amines yielded the target compounds. The DPP-4 inhibitory potential of these derivatives was evaluated through both *in-silico* and *in-vitro* approaches, alongside assessment of their insulinotropic effects in 832/13 INS-1 cell lines. Among the synthesized compounds, derivatives 23a, 23c, 23g, and 23i exhibited notable antioxidant and insulinotropic activities, demonstrating efficacy levels up to 99% [61].

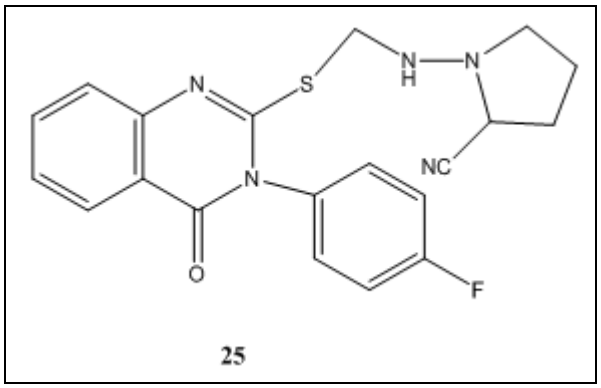


Quinoline-Quinazolinone Based Scaffolds: Maezaki *et al.* (2017): A new series of non-peptidomimeticquinoline-based DPP-4 inhibitors was developed. The molecular design leveraged a salt bridge interaction strategy, targeting the key Lys554 residue within the enzyme's active site. A set of analogues was synthesized by strategically incorporating a carboxylic acid functional group at the quinoline's 6-position, connected through a variable linker to fine-tune the molecular extension. This approach yielded several active compounds, with 24d proving to be the most potent, demonstrating significant inhibitory activity with an IC_{50} of 4.6 nM [62].



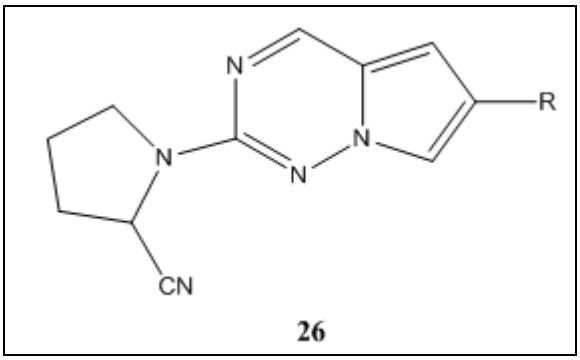
Wang *et al.* (2020): synthesized a series where the N-3 position held a 4-fluorophenyl group, and the C-2 position was linked *via* a 2-aminoethylthio tether to a (S)-cyanopyrrolidine. The lead compound 25 demonstrated an IC_{50} of 3.2 nM against human DPP-4. Crystallographic analysis (modeled on PDB: 5Y7R) revealed a canonical binding mode: the cyanopyrrolidine engaged Ser630, the quinazolinone core sat in the S1 pocket with its carbonyl oxygen accepting a hydrogen bond from the backbone NH of Tyr631, and the 4-fluorophenyl group penetrated the S2 extensive

pocket. Notably, the thioether linker, while effective, was identified as a potential metabolic soft spot. Subsequent optimization by the same group replaced it with a more robust aminomethylene (-CH_2NH-) linker, which maintained potency while improving microsomal stability by 40% [63].



25

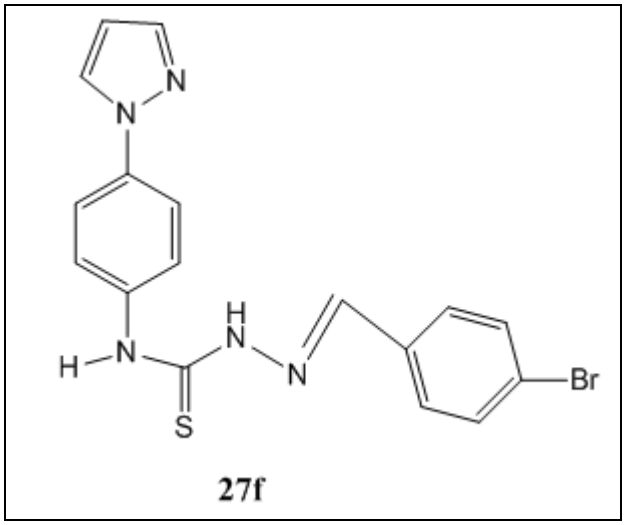
Zhang *et al.* (2021): reported a novel series based on a pyrrolo [2,1-b] quinazoline scaffold. This fused system incorporates an additional pyrrole ring, constraining the molecular conformation. Their most potent derivative 26, featuring a 9-chloro substituent on the quinazoline and a standard cyanopyrrolidine tail, achieved a remarkable IC_{50} of 0.7 nM. Molecular dynamics simulations suggested the fused pyrrole nitrogen formed an additional, water-mediated hydrogen bond network with Asp708, a residue in the catalytic triad, explaining the sub-nanomolar activity. This highlights a key advantage of polycyclic systems: they can pre-organize the molecule into a bio-active conformation and create novel interaction networks not accessible to simpler scaffolds [64].



26

Pyrazole Based Scaffolds: Belgin Sever *et al.* (2020): The synthesis of a new library of thiosemicarbazones was achieved through the reaction of aromatic aldehydes with 4-[4-(1H-pyrazol-1-yl) phenyl] thiosemicarbazide. The precursor, compound was first synthesized from 4-(1H-pyrazol-1-yl) phenylisothiocyanate and hydrazine hydrate.

The inhibitory activity of all synthesized compounds against dipeptidyl peptidase-4 (DPP-4) was assessed *via* a fluorescence-based assay. This screening revealed compound 27f as the standout candidate, demonstrating potent inhibition with an IC_{50} of 1.266±0.264 nM. Notably, this activity exceeds that of the standard inhibitor sitagliptin, which showed an IC_{50} of 4.380±0.319 nM under identical conditions [65].

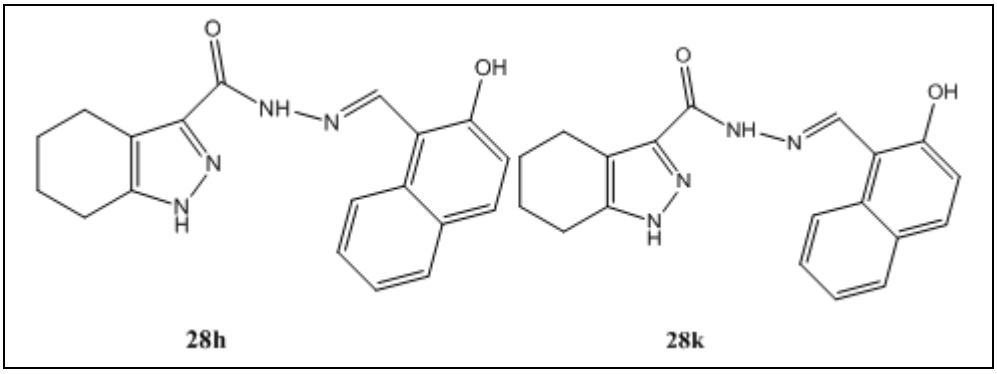


27f

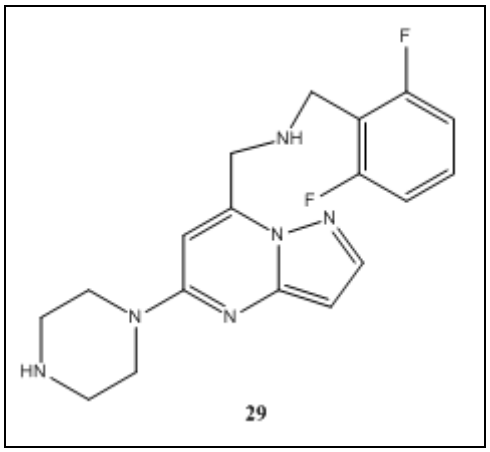
Wu Deyan *et al.* (2012): Novel dipeptidyl peptidase-4 (DPP-4) inhibitors featuring a pyrazole-3-carbohydrazone scaffold were discovered through a structure-based virtual screening approach.

A lead compound was identified and subsequently optimized through two cycles of chemical modification, resulting in the synthesis of seventeen novel analogues. Biological evaluation revealed that nine compounds exhibited inhibitory activity against DPP-4 at micromolar or low-to-mid-micromolar concentrations. Molecular docking studies provided a rational basis for the observed structure-activity relationships (SARs).

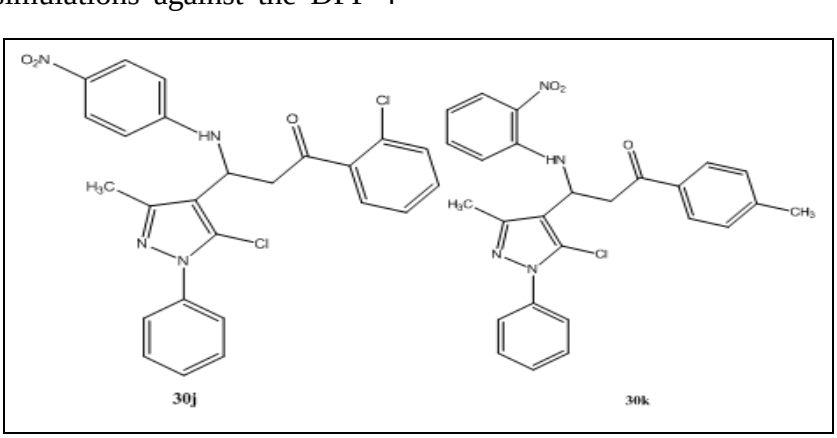
A pharmacophore model was generated based on eight key inhibitors, among which compounds 28h and 28k were the most potent, with IC_{50} values of 2.12 µM and 3.44 µM, respectively [66].



J. Shen *et al.* (2020): A series of novel pyrazolo [1,5-a] pyrimidine-based compounds were designed, synthesized, and evaluated as potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitors. These derivatives were engineered to mimic the binding mode of alogliptin within the DPP-4 active site. Among the synthesized compounds, 29 emerged as a leading candidate, demonstrating exceptional *in-vitro* potency with an IC_{50} value of 2 nM. This compound also exhibited a high degree of selectivity over the related proteases DPP-8 and DPP-9, and presented a favorable low cytotoxicity profile [67].

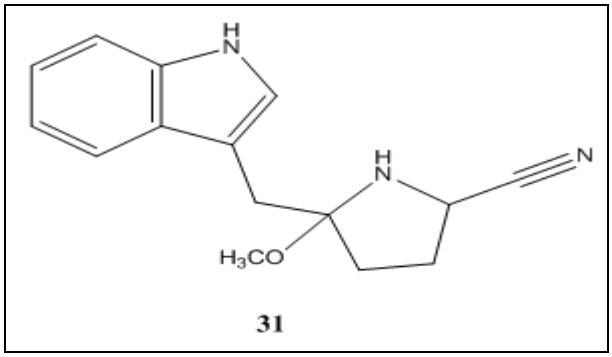


Nidhar *et al.* (2023): Designed and synthesized a novel series of pyrazole-based β-amino carbonyl derivatives as potential dipeptidyl peptidase-4 (DPP-4) inhibitors and antidiabetic agents. The compounds were efficiently synthesized in good yields *via* a Mannich reaction, optimized using bismuth nitrate ($Bi(NO_3)_3$) as a catalyst in ethanol. Molecular docking simulations against the DPP-4 enzyme (PDB: 2OLE) predicted that compounds 30j and 30k would exhibit strong binding interactions. Subsequent *in-vitro* enzymatic assays confirmed their potent DPP-4 inhibitory activity. The most active compounds demonstrated IC_{50} values in the low nanomolar range: 30j (4.16 nM) and 30k (7.50 nM) [68].



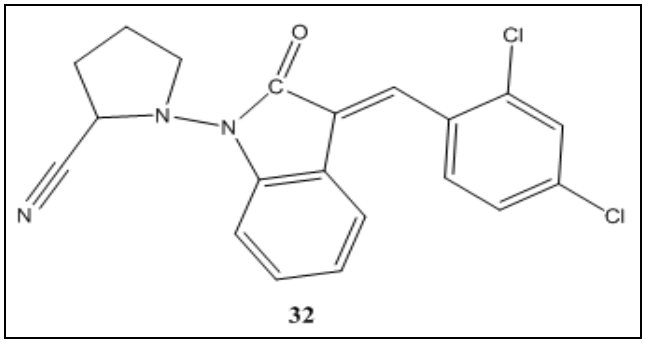
Indoline Based Scaffolds: Patel *et al.* (2022): pioneered a series of 2-((1H-indol-3-yl) methyl)-5-cyanopyrrolidines. The indole ring itself was intended to occupy the S2 pocket. Optimization revealed that a 5-methoxy substitution on the indole was optimal. The methoxy group engaged in a hydrogen bond with a structured water molecule near Glu206, stabilizing the complex.

The lead compound 31 (IC_{50} = 4.1 nM) was progressed to in vitro cell models, where it unexpectedly stimulated GLP-1 secretion from murine GLUTa genteroendocrine L-cells by 2.5-fold over baseline. While the precise off-target mechanism remains under investigation (preliminary data suggests potential modulation of the TGR5 bile acid receptor), this illustrates the potential for heterocyclic scaffolds to confer serendipitous, beneficial polypharmacology [69].



31

Singh *et al.* (2021): synthesized a series of (E)-3-(2, 4-dichlorobenzylidene)- 2 -(2- cyanopyrrolidin-1-yl) indolin-2-ones. The dichlorobenzylidene moiety provided excellent fill of the S2 extensive pocket, while the isatin N-2 cyanopyrrolidine engaged the catalytic site. Impressively, these compounds displayed a balanced dual inhibitory profile: DPP-4 $IC_{50} \approx 6.8$ nM and α-glucosidase $IC_{50} \approx 12.5$ μM. In a sucrose-loaded mouse model, the lead compound 32 reduced postprandial glucose spikes as effectively as the combination of sitagliptin and acarbose, validating the multi-target approach. The isatin core is also frequently coupled with rhodanine or thiazolidinedione moieties, aiming to combine DPP-4 inhibition with PPARγ modulation or aldose reductase inhibition for comprehensive anti-diabetic and anti-complication effects [70].



32

Clinical Pipeline and Future Perspectives: The clinical pipeline for DPP-4 inhibitors remains active, focusing on improved profiles **Table 2-5** for pipeline candidates). Fotagliptin, CPL2009-0031, and DBPR-108 are in Phase III, while besigliptin and imigliptin are in Phase II. Candidates like HSK-7653 (Phase I) aim for ultra-long-acting profiles. Gosogliptin and retagliptin are under regulatory review.

TABLE 2: DRUG CANDIDATES IN PHASE III DEVELOPMENT [71–72]

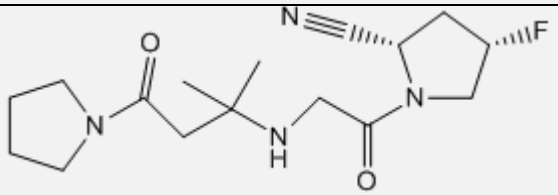
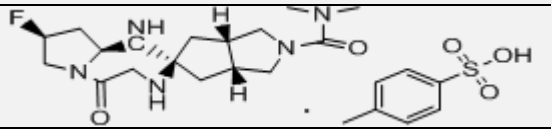
S. no.	Drug Name	Status	Company	Structure
1	Fotagliptin Benzoate	Active	FosunPharma; Fochon Pharmaceuticals; Salubris	
2	CPL2009-0031	Active	Cadila	Undisclosed
3	DBPR-108	Active	Zhongqi Pharmaceutical Technology	Undisclosed

TABLE 3: DRUG CANDIDATES IN PHASE II DEVELOPMENT [73–76]

S. no.	Drug Name	Status	Company	Structure
1	Besigliptin Tosilate	Active	Hansoh Pharma; Jiangsu Hengrui Medicine	

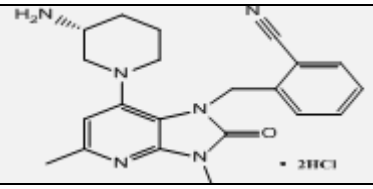
2	Imigliptin Hydrochloride	Active	Beijing Sihuan Pharmaceutical; XuanzhuPharma	

TABLE 4: DRUG CANDIDATES IN PHASE I DEVELOPMENT [77]

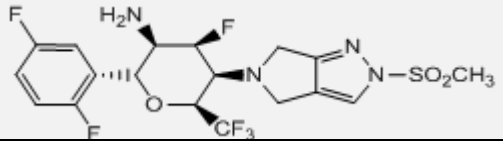
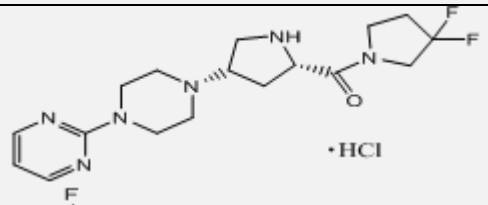
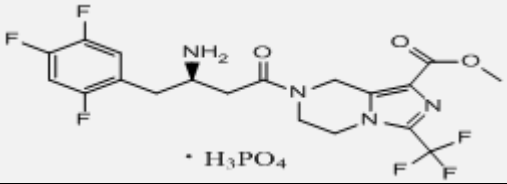
S. no.	Drug Name	Status	Company	Structure
1	DC291407	Active	Cisen Pharmaceutical	Undisclosed
2	Augliptin Hydrochloride	Active	Shanghai Sun-Sail Pharmaceutical science & Technology	Undisclosed
3	Yogliptin	Active	Easton Biopharmaceuticals	Undisclosed
4	HD118	Active	Hangzhou ZhongmeiHuadong Pharmaceutical	Undisclosed
5	ARI-2243	Active	Arisaph	Undisclosed
6	Cetagliptin phosphate	Active	CGene Tech (Suzhou, China)	Undisclosed
7	PBL-1427	Active	Panacea	Undisclosed
8	HSK-7653	Active	Liaoning haisike pharmaceutical; Sichuan Haisco Pharmaceutical	

TABLE 5: DRUG CANDIDATES FOR WHICH A NEW DRUG APPLICATION (NDA) HAS BEEN SUBMITTED TO A REGULATORY AGENCY [78, 79]

S. no.	Drug Name	Status	Company	Structure
1	Gosogliptin Hydrochloride	Active	Pfizer; SatRx	
2	Retagliptin Phosphate	Active	Jiangsu Hengrui Medicine	

Future Directions: The current landscape of DPP-4 inhibitor development reflects a strategic departure from glucose-centric therapeutic models, prioritizing instead the identification of compounds with established cardiorenal protective effects and broad anti-inflammatory properties. Parallel efforts in multitarget drug discovery seek to design hybrid molecules capable of concurrent inhibition of DPP-4 and complementary targets such as SGLT2 or α-glucosidase, offering the potential for enhanced efficacy through polypharmacological synergy. In parallel, the integration of pharmacogenomic principles into clinical decision-making enables the alignment of inhibitor characteristics-particularly excretion pathways like renal or hepatic clearance-with individual patient pathophysiology. Computational innovation underpins next-generation drug design, with techniques such as artificial intelligence, machine learning, and free-energy perturbation calculations enabling the rational construction of novel scaffolds and the fine-tuning of ADMET profiles. Beyond metabolic disease, the pharmacological versatility of DPP-4 inhibition is under active investigation in diverse non-diabetic conditions, including fibrotic disorders, non-alcoholic fatty liver disease (NAFLD), and systemic inflammatory syndromes, thereby expanding the translational relevance of this drug class.

CONCLUSION: Heterocyclic scaffolds play a central role in the design and development of DPP-4 inhibitors, a key class of oral antidiabetic agents. Their structural diversity enables precise

interaction with the DPP-4 active site, optimizing potency, selectivity, and pharmacokinetic properties. Recent advances have led to the discovery of novel inhibitors based on pyrimidine, oxadiazole, pyrrolidine, triazole, and other heterocyclic systems, with several candidates progressing through clinical trials. Despite their favorable safety and efficacy, ongoing challenges include managing rare adverse effects and enhancing therapeutic profiles.

Future progress will rely on computational approaches, multi-target designs, and personalized medicine to develop next-generation DPP-4 inhibitors with improved clinical outcomes. Heterocyclic chemistry is the driving force behind the DPP-4 inhibitor class. From establishing the fundamental pharmacophore in first-generation drugs to enabling sophisticated multi-property optimization in recent candidates, heterocyclic scaffolds provide the essential structural toolkit. The continued exploration of novel rings, fused systems, and hybrid architectures, guided by deep structural insights and cutting-edge computational methods, promises to yield next-generation DPP-4 inhibitors. These future agents will likely transcend mere glycemic control, offering tailored efficacy, improved safety, and multi-faceted therapeutic benefits for the comprehensive management of T2DM and its associated complications.

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REFERENCES:

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation 2021.
2. Zheng Y, Ley SH and Hu FB: Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018; 14(2): 88-98.
3. Drucker DJ: The biology of incretin hormones. Cell Metab 2006; 3(3): 153-65.
4. Holst JJ: The physiology of glucagon-like peptide 1. Physiol Rev 2007; 87(4): 1409-39.
5. Nauck MA and Meier JJ: The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2018; 6(6): 525-36.
6. Mentlein R: Dipeptidyl-peptidase IV (CD26)–role in the inactivation of regulatory peptides. Regul Pept 1999; 85(1): 9-24.
7. Deacon CF: Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. Front Endocrinol (Lausanne) 2019; 10: 80.
8. Bifano M, Capuano G and Renzetti AR: A Review of DPP-4 Inhibitors Based on Preclinical and Clinical Data. J Diabetes Res 2021; 2021: 5538752.
9. Green JB, Bethel MA and Armstrong PW: Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2015; 373(3): 232-42.
10. Campbell JE and Drucker DJ: Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013; 17(6): 819-37.
11. Rasmussen HB, Branner S, Wiberg FC and Wagtmann N: Crystal structure of human dipeptidyl peptidase IV/CD26 in complex with a substrate analog. Nat Struct Biol 2003; 10(1): 19-25.
12. Engel M, Hoffmann T and Wagner L: The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism. Proc Natl Acad Sci USA 2003; 100(9): 5063-8.
13. Kim D, Wang L and Beconi M: (2R)-4-Oxo-4-[3-(trifluoromethyl)-5, 6-dihydro[1, 2, 4] triazolo[4,3-a] pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine: A potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 2005; 48(1): 141-51.
14. Aertgeerts K, Ye S and Tennant MG: Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formation. Protein Sci 2004; 13(2): 412-21.

15. Lankas GR, Leiting B and Roy RS: Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidases 8 and 9. Diabetes 2005; 54(10): 2988-94.
16. Mulvihill EE and Drucker DJ: Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocr Rev 2014; 35(6): 992-1019.
17. Klemann C, Wagner L, Stephan M and vonHörsten S: Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clin Exp Immunol 2016; 185(1): 1-21.
18. Deacon CF: Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2019; 15(11): 642-53.
19. Davies MJ, Aroda VR and Collins BS: Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022; 45(11): 2753-86.
20. Thornberry NA & Weber AE: Discovery of JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes. Current Topics in Medicinal Chemistry 2007; 7(6): 557-568.
21. Augeri DJ, Robl JA and Betebenner DA: Discovery and preclinical profile of Saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 2005; 48(15): 5025-37.
22. He H, Tran P and Yin H: Absorption, metabolism and excretion of [14C]gemigliptin, a novel dipeptidyl peptidase 4 inhibitor, in humans. Xenobiotica 2014; 44(3): 242-51.
23. Eckhardt M, Langkopf E and Mark M: 8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes. J Med Chem 2007; 50(26): 6450-3.
24. Graefe-Mody U, Retlich S and Friedrich C: Clinical Pharmacokinetics and Pharmacodynamics of Linagliptin. Clin Pharmacokinet 2012; 51(7): 411-27.
25. Feng J, Zhang Z and Wallace MB: Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV. J Med Chem 2007; 50(10): 2297-300.
26. Kanki H, Sano H and Fukunaga N: Synthesis and structure-activity relationships of 2-[[(3S,5R)-5-[[(1S)-1-hydroxy-2-methylpropyl]amino]-3-piperidinyl]thio]quinazoline derivatives as novel dipeptidyl peptidase 4 (DPP-4) inhibitors. Bioorg Med Chem 2011; 19(23): 7221-7.
27. Biftu T, Sinha-Roy R and Chen P: Omarigliptin (MK-3102): A Novel Long-Acting DPP-4 Inhibitor for Once-Weekly Treatment of Type 2 Diabetes. J Med Chem 2014; 57(8): 3205-12.
28. Inagaki N, Onouchi H and Maezawa H: Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-inferiority study. Lancet Diabetes Endocrinol 2015; 3(3): 191-7.
29. Dhillon S: Sitagliptin: A review in type 2 diabetes. Drugs 2017; 77(2): 209-24.
30. Deacon CF: Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. Diabetes Obes Metab 2011; 13(1): 7-18.
31. Gallwitz B: Clinical use of DPP-4 inhibitors. Front Endocrinol (Lausanne) 2019; 10: 389.
32. Scheen AJ: Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. Diabetes Obes Metab 2010; 12(8): 648-58.
33. Baetta R and Corsini A: Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. Drugs 2011; 71(11): 1441-67.
34. Golightly LK, Drayna CC and McDermott MT: Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. Clin Pharmacokinet 2012; 51(8): 501-14.
35. Matsuda S, Seiryu M and Nagashima S: Pharmacological profile and clinical efficacy of teneligliptin (Tenelia®), a novel DPP-4 inhibitor. Folia Pharmacol JPN 2013; 142(3): 137-49.
36. Scott LJ: Omarigliptin: First global approval. Drugs 2015; 75(16): 1947-52.
37. Kim SH, Lee SH and Yim HJ: Gemigliptin: An update of its clinical use in the management of type 2 diabetes mellitus. Diabetes Metab J 2016; 40(5): 339-53.
38. Deeks ED: Evogliptin: First global approval. Drugs 2015; 75(17): 2045-9.
39. Scott LJ: Trelagliptin: First global approval. Drugs 2015; 75(10): 1161-4.
40. Li Q, Deng X, Jiang N, Meng L, Xing J and Jiang W: Identification and structure–activity relationship exploration of uracil-based benzoic acid and ester derivatives as novel dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus. Eur J Med Chem 2021; 225: 113765.
41. Mourad AAE, Khodir AE, Saber S and Mourad MAE: Novel potent and selective DPP-4 inhibitors: Design, synthesis and molecular docking study of dihydropyrimidinephthalimide hybrids. Pharmaceuticals (Basel) 2021; 14(2): 144.
42. Jha V and Bhadoriya KS: Synthesis, pharmacological evaluation and molecular docking studies of pyrimidinedione based DPP-4 inhibitors as antidiabetic agents. J Mol Struct 2018; 1159: 1-9.
43. Feitosa SGD, Lins IMS, Maciel LG and dos Anjos JV: Discovery of novel heterocyclic derivatives containing oxadiazolone or pyrimidinone cores as DPP-4 inhibitors. J Heterocyclic Chem 2024.
44. Zinevich TV, Maslov IO and Kirichenko OG: 3-(3-Azabicyclo[2.2.1]heptan-2-yl)-1,2,4-oxadiazoles as novel potent DPP-4 inhibitors to treat T2DM. Pharmaceuticals (Basel) 2025; 18(5): 642.
45. Kumar S, Rathore DS and Garg G: Synthesis and evaluation of some 2-((benzothiazol-2-ylthio) methyl)-5-phenyl-1,3,4-oxadiazole derivatives as antidiabetic agents. Asian Pac J Health Sci 2016; 3(4): 65-74.
46. Salve MT and Jadhav S: Synthesis of cyclopyrrolidine clubbed with oxadiazole bases and evaluation of their anti-diabetic activity through *in-vivo* model. Indian J Pharm Educ Res 2023; 57(3): 749-57.
47. Tukaram SM and Bhanuda JS: Molecular docking and in-vitro studies of some new oxadiazole derivatives as antidiabetic agent. Int J Pharm Res 2021; 13(1): 5269.
48. Jadav P, Bahekar R and Shah SR: Design, synthesis and biological evaluation of novel aminomethyl-piperidones based DPP-IV inhibitors. Bioorg Med Chem Lett 2014; 24(8): 1918-22.
49. Mani Sharma M, Gupta M, Singh D, Kumar M and Kaur P: Synthesis, evaluation and molecular docking of prolyl-fluoropyrrolidine derivatives as dipeptidyl peptidase IV inhibitors. ChemBiol Drug Des 2013; 82(2): 156-66.
50. Wang X, Zheng P, Huang G, Yang L and Zhou Z: Dipeptidyl peptidase–4 (DPP–4) inhibitors: promising new

agents for autoimmune diabetes. Clin Exp Med 2018; 18(4): 473-80.
51. Ji X, Xia C and Wang J: Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2-carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors. Eur J Med Chem 2014; 86: 242-56.
52. Liu Y, Wu Y and Wu H: Design, synthesis, biological evaluation, and docking studies of (S)-phenylalanine derivatives with a 2-cyanopyrrolidine moiety as potent dipeptidyl peptidase 4 inhibitors. Chem Biol Drug Des 2013; 82(2): 140-6.
53. Narsimha S, Swamy Battula K, Ravinder M, Reddy YN and Nagavelli VR: Design, synthesis and biological evaluation of novel 1,2,3-triazole based xanthine derivatives as DPP-4 inhibitors. J Chem Sci 2020; 132: 59.
54. Vo D-V, Hong KH, Lee J and Park H: Synthesis, *in-vitro* evaluation, and computational simulations studies of 1,2,3-triazole analogues as DPP-4 inhibitors. Bioorg Med Chem 2020.
55. Fuh MT, Tseng CC and Li SM: Design, synthesis and biological evaluation of glycolamide, glycinamide, and β-amino carbonyl 1,2,4-triazole derivatives as DPP-4 inhibitors. Bioorg Chem 2021; 114: 105049.
56. Gao HD, Liu P, Yang Y and Gao F: Sulfonamide-1,3,5-triazine–thiazoles: discovery of a novel class of antidiabetic agents *via* inhibition of DPP-4. RSC Adv 2016; 6(83): 83438-47.
57. Patel BD, Bhadada SV and Ghate MD: Design, synthesis and anti-diabetic activity of triazolotriazine derivatives as dipeptidyl peptidase-4 (DPP-4) inhibitors. Bioorg Chem 2017; 74: 345-58.
58. Kushwaha RN, Srivastava R, Mishra A, Rawat AK, Srivastava AK and Goel RK: Design, synthesis, biological screening, and molecular docking studies of piperazine-derived constrained inhibitors of DPP-IV for the treatment of type 2 diabetes. Chem Biol Drug Des 2015; 85(4): 439-46.
59. Jiang T, Zhou Y and Chen Z: Design, synthesis, and pharmacological evaluation of fused β homophenylalanine derivatives as potent DPP 4 inhibitors. ACS Med Chem Lett 2015; 6(5): 602-6.
60. Kalli SB and Velmurugan V: Design, synthesis and anti-diabetic activity of piperazine sulphonamide derivatives as dipeptidyl peptidase-4 inhibitors. Pharmacia 2022; 69(4): 987-93.
61. Bindu B, Vijayalakshmi S and Manikandan A: Synthesis and discovery of triazolo-pyridazine-6-yl-substituted piperazines as effective anti-diabetic drugs; evaluated over dipeptidyl peptidase-4 inhibition mechanism and insulinotropic activities. EJMC 2020; 187: 111912.
62. Maezaki H, Tawada M, Yamashita T, Tsubaki K and Tanaka T: Design of potent dipeptidyl peptidase IV (DPP-4) inhibitors by employing a strategy to form a salt bridge with Lys554. BMCL 2017; 27(15): 3565-71.
63. Wang Q, Wang Y and Li Y: Structure-based optimization of quinazolin-4(3H)-one derivatives as novel dipeptidyl peptidase 4 inhibitors. Bioorg Chem 2020; 94: 103378.
64. Zhang L, Chen X and Liu J: Discovery of novel pyrrolo[2,1-f][1,2,4]triazine derivatives as potent, selective, and orally bioavailable dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes. Eur J Med Chem 2021; 209: 112939.
65. Sever B, Soybir H, Görgülü S, Cantürk Z and Altıntop MD: Pyrazole incorporated new thiosemicarbazones: design, synthesis and investigation of DPP-4 inhibitory effects. Molecules 2020; 25(21): 5003.
66. Wu D, Jin F and Lu W: Synthesis, structure–activity relationship, and pharmacophoremodeling studies of pyrazole-3-carbohydrazone derivatives as dipeptidyl peptidase IV inhibitors. Chem Biol Drug Des 2012; 79(6): 897-906.
67. Shen J, Ma J and Wang T: Structural optimization of pyrazolo[1,5-a]pyrimidine derivatives as potent and highly selective DPP-4 inhibitors. Eur J Med Chem 2020; 187: 111967.
68. Nidhar M, Kumar V and Mahapatra A: Lead modification via computational studies: Synthesis of pyrazole-containing β-amino carbonyls for the treatment of type 2 diabetes. Chem Biol Interact 2023; 369: 110295.
69. Patel BD, Ghate MD and Jain MR: Indole-cyanopyrrolidine conjugates as novel dual activators of GLP-1 secretion and DPP-4 inhibition for type 2 diabetes. Eur J Med Chem 2022; 233: 114216.
70. Singh P, Sharma A and Kaur M: Isatin hybrids as dual inhibitors of α-glucosidase and DPP-4 for management of diabetes. Bioorg Chem 2021; 111: 104521.
71. Fochon Pharmaceuticals. A study to evaluate the efficacy and safety of fotagliptin in patients with type 2 diabetes mellitus (NCT05166687). ClinicalTrials.gov. 2023.
72. Singh AK: Dipeptidyl peptidase-4 inhibitors: Novel candidates for the treatment of type 2 diabetes. Indian J Endocrinol Metab 2014; 18(6): 833-44.
73. Haisco Pharmaceutical Group Co., Ltd. A phase II study to evaluate the efficacy and safety of HSK7653 in patients with type 2 diabetes (NCT03750035). ClinicalTrials.gov. 2021.
74. Beijing Sihuan Pharmaceutical Co., Ltd. A multiple-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of imigliptin in T2DM (NCT02104804). ClinicalTrials.gov. 2015.
75. Ahren B: DPP-4 inhibition and islet function. J Diabetes Res 2016; 2016: 1754137.
76. Drucker DJ: The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. Diabetes 2018; 67(9): 1710-9.
77. Zhang Z, Yang D and Li T: Discovery of novel dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: Based on a comprehensive search of the patent literature. Expert Opin Ther Pat 2020; 30(9): 707-27.
78. Pfizer. Pfizer and SatRx announce FDA acceptance of new drug application for Gosogliptin [press release]. Business Wire 2022.
79. Jiangsu Hengrui Medicine. Jiangsu Hengrui Medicine submits new drug application for Retagliptin in China 2023.

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