Original Article

RECENT UPDATE ON PYRIMIDINE DERIVATIVES AS POTENTIAL DPP-IV INHIBITORS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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Abstract

There has been a lot of interest in the use of dipeptidyl peptidase-IV (DPP-IV) inhibitors for the treatment of type 2 diabetes because of their proven long-term efficacy and enhanced capacity to maintain appropriate blood sugar levels. DPP-IV inhibitors are essential for the regeneration and differentiation of pancreatic beta-cells and have been proved to be safe and effective. They also minimise the risk of hypoglycemia and cardiovascular side effects. Vildagliptin, saxagliptin, sitagliptin, alogliptin, linagliptin, gemigliptin, anagliptin, and teneligliptin are only a few examples of the fundamentally diverse DPP-4 inhibitors presently accessible. One of medicinal chemistry's most crucial and flexible scaffolds is pyrimidine. Antidiabetic, anti-inflammatory, anticancer, antibacterial, antihypertensive, antifungal, and antituberculous actions are only some of the many that may be attributed to pyrimidines. The *in vitro* DPP-IV inhibitory activity of some of the synthesised *N*-methylated and *N*-benzylated pyrimidinediones is also rather high. Good IC_{50} values were found for these compounds when novel pyrimidinedione derivatives were investigated for their DPP-IV inhibitory activity and *in vivo* anti-hyperglycemic efficacy. Due to their potential as DPP-IV inhibitors in the treatment of T2DM, we have reviewed a few newly reported pyrimidine derivatives in this study.

Keywords: DPP-IV inhibitors; pyrimidine derivatives; T2DM; GIP; GLP-1

1. Introduction

Patients with non-insulin dependent diabetes mellitus (NDDM), also known as type-2 diabetes, are characterized by having hyperglycemia (constantly elevated blood glucose levels) that are brought on by insulin resistance, inadequate insulin secretion, or both. This predicament is comparable to one of the infectious illnesses that has spread the quickest in the 21st century[1–3]. According to projections made by the International Diabetes Federation (IDF), the number of people living with diabetes will increase to 552 million by the year 2030[4]. This presents a significant obstacle for medical facilities and those doing research in the field of medicine[5]. The fact that the number of fatalities caused by diabetes is predicted to be 3.8 million per year despite the fact that the disease is on the increase indicates an unacceptable lack of glycemic control with the medicines that are now accessible. As a result, more effective strategies and therapeutic targets for the treatment of diabetes and the problems linked with diabetes are quite desired[6].

Antidiabetic medications currently available include sulfonylureas, meglitinides, thiazolidinediones, biguanides, and alpha-glucosidase inhibitors, all of which work to reduce glucose production in the liver, increase insulin secretion, decrease glucose absorption, and maximize glucose utilization in the periphery. These medicines,

however, are not without their share of unwanted side effects, such as weight gain and hypoglycaemia, both of which compromise long-term glycemic control. Therefore, several recently developed methods have arisen with unique mechanism of action for improved T2DM control[7].

Dipeptidyl peptidase-IV (DPP-IV) inhibitors, have garnered considerable attention in the treatment of type 2 diabetes due to their shown long-term effectiveness and improved ability to maintain healthy blood sugar levels. It has been shown that DPP-IV inhibitors are well tolerated, reduce the risk of hypoglycemia and cardiovascular adverse effects, and play a key role in the regeneration and differentiation of pancreatic beta-cells[8]. DPP-IV, also known as EC 3.4.14.5, is a member of the serine proteases family and is made up of 766 different amino acids. It is made up of a cytoplasmic tail that is comprised of 6 amino acids, a transmembrane domain that is made up of 22 amino acids, and a substantial extracellular region[9]. The extracellular domain is the part of the protein that is important for ligand binding and DPP-IV action. DPP-IV is a soluble plasma enzyme that is expressed at high quantities in the capillary bed of the gut mucosa, as well as in various immune cells such as T cells and epithelial cells[10]. In addition to being expressed in the kidney, the liver, the gut, and the lungs, DPP-IV may also be found in these organs. Inaccurate expression of soluble DPP-IV is a contributing factor in the development of a wide variety of biological conditions, such as solid tumours, diabetes mellitus type 2, obesity, autoimmune illnesses, and hepatitis[11].

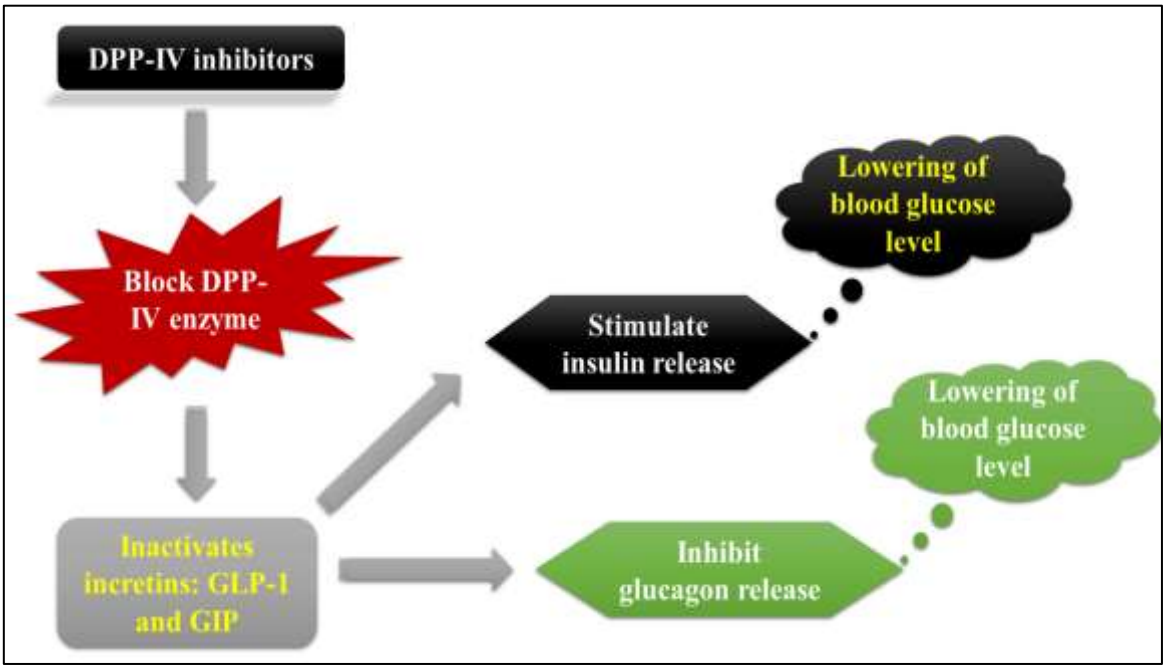
2. Catalytic Function of DPP-IV and Diabetes Mellitus

A series of metabolic hormones known as incretins are responsible for modulating the glucose metabolism and stimulating a reduction in the amount of glucose found in the blood. Both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are members of the incretin hormone family[12]. These hormones are very important in the process of controlling the amount of glucose in the blood. Incretins are secreted into the vasculature from the small intestine as a response to the consumption of a meal. This response stimulates a significant chain of events, some of which include the synthesis of insulin, the release of GLP-1 and GIP hormones, the suppression of glucagon release, and a delay in the emptying of the stomach[13,14].

Several studies have shown that GLP-1 and GIP responses are responsible for around 50–60% of the total insulin that is produced over the course of a meal[15]. However, the glucoregulatory impact of GLP-1 in particular is only temporary because of its short half-life (approximately half a minute), which is caused by the quick breakdown and inactivation of the molecule by the DPP-IV enzyme. The L-cells in the small intestine are responsible for the synthesis of the 30 amino acids that make up GLP-1[16,17]. In point of fact, the most active version is called glucagon like peptide-1 (7–36) amide. As illustrated in Figure 1, the DPP-IV enzyme is responsible for removing the insulinotropically inactive *N*-terminal dipeptides (His7–Ala8) from the GLP-1 (7–36) molecule so that it may be converted into the insulinotropically inactive GLP-1 (9–36) form. Due to the activity of the DPP-IV enzyme, GLP-1 itself cannot be utilized as a treatment for diabetes since its half-life is so short. This makes it impossible to employ GLP-1 to treat diabetes[18,19].

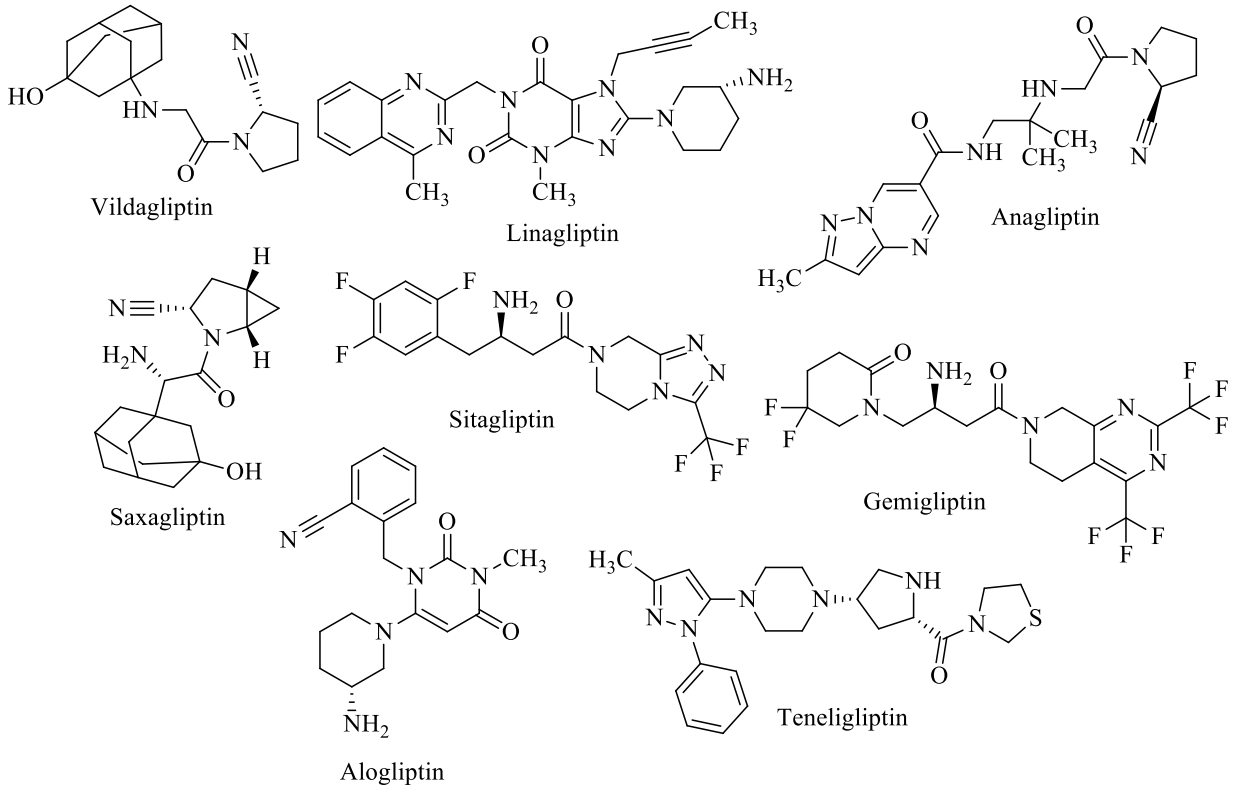
After eating, patients with type 2 diabetes showed considerably lower quantities of the hormone GLP-1. As a consequence, suppression of the DPP-IV enzyme is an effective method for extending the half-life of GLP-1 in order to enhance its concentration and to reduce the harmful effects that patients with hyperglycemic situations as a result of diabetes mellitus experience[20].

Figure 1. Mechanism of DPP-IV inhibitors in treatment of T2DM



There are now a number of structurally distinct DPP-4 inhibitors available, some of which are already on the market and include vildagliptin, saxagliptin, sitagliptin, alogliptin, linagliptin, gemigliptin, anagliptin, and teneligliptin (Figure 2)[21]. Pyrimidines represented one of the most important and versatile scaffolds in medicinal chemistry. Pyrimidines possess a wide variety of activities, including those that are antidiabetic, anti-inflammatory, anticancer, antibacterial, antihypertensive, antifungal, and antituberculous. In addition, several of the synthesized *N*-methylated and *N*-benzylated pyrimidinediones have shown considerable levels of *in vitro* DPP-IV inhibitory action. When new pyrimidinedione derivatives were tested for their DPP-IV inhibitory activity and *in vivo* anti-hyperglycemic effectiveness, good IC_{50} values were obtained for these compounds[22]. Therefore in present article, we have reviewed some recently reported pyrimidine derivatives as potential DPP-IV inhibitors for the treatment of T2DM.

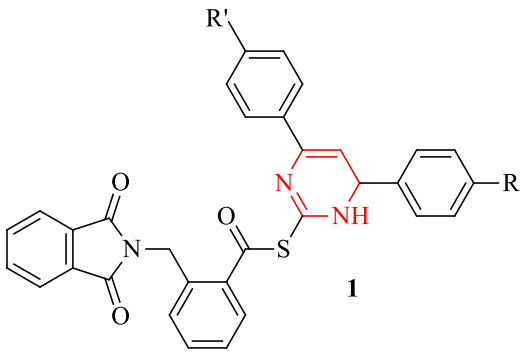
Figure 2. The structures of some approved DPP-IV inhibitors



3. Review of some Pyrimidine Derivatives as Potential DPP-IV inhibitors

Ahmed A. E. Mourad et al.[22] synthesized and evaluated a novel series of dihydropyrimidine phthalimide hybrids (Compound **1**, Structure 1) for their *in vitro* and *in vivo* DPP-IV inhibition activity and selectivity using alogliptin as reference. Oral glucose tolerance test was assessed in type 2 diabetic rats after chronic treatment with the synthesized hybrids ± metformin. Additionally, molecular docking study with DPP-IV and structure activity relationship of the novel hybrids were also studied. Among the synthesized hybrids, many compounds had stronger *in vitro* DPP-IV inhibitory activity than alogliptin. Moreover, an *in vivo* DPP-IV inhibition assay revealed that two compounds have the strongest and the most extended blood DPP-IV inhibitory activity compared to alogliptin. In type 2 diabetic rats, hybrids exhibited better glycemic control than alogliptin, an effect that further supported by metformin combination.

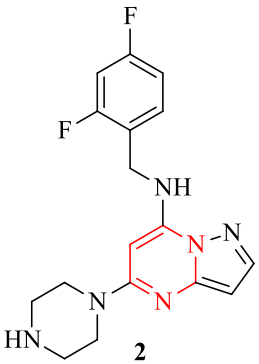
Structure 1. Dihydropyrimidine phthalimide hybrids reported by Ahmed A. E. Mourad et al. as DPP-IV inhibitors



Jian Shen et al.[23] reported highly potent and selective pyrazolo [1,5-a]pyrimidine (Compound **2**, Structure 2) as DPP-IV inhibitors using fragment-based drug design strategies. Compound **2** (IC_{50} = 2 nM) exhibits a 2-fold

increase of inhibitory activity than Alogliptin (IC_{50} = 4 nM), and remarkable selectivity over DPP-8 and DPP-9 (>2000 fold). Further docking studies confirmed that the pyrazolo [1,5-a]pyrimidine core interacts with the S1 pocket whereas its substituted aromatic ring interacts with the sub-S1 pocket. The interactive mode in this case resembles that of Alogliptin and Trelagliptin. Further *in vivo* IPGTT assays in diabetic mice demonstrated that compound **2** effectively reduces glucose excursion by 48% at the dose of 10 mg/kg, suggesting that compound **2** is worthy of further development as a potent anti-diabetes agent.

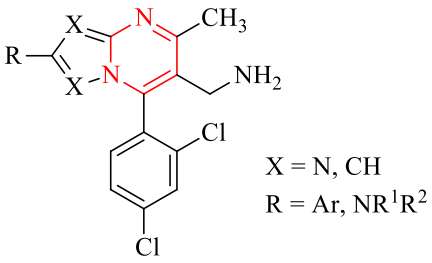
Structure 2. Pyrazolo [1,5-a]pyrimidine reported by Jian Shen et al. as potential DPP-IV inhibitors



2

Robert P. Brigance et al.[24] synthesized and evaluated several pyrazolo-, triazolo-, and imidazolopyrimidines as DPP-IV inhibitors. Of these three classes of compounds, the imidazolopyrimidines (Compound **3**, Structure 3) displayed the greatest potency and demonstrated excellent selectivity over the other dipeptidyl peptidases. SAR evaluation for these scaffolds was described as they may represent potential treatments for type 2 diabetes.

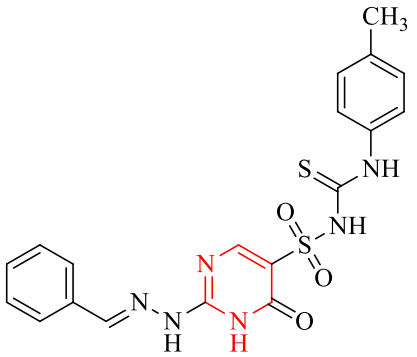
Structure 3. The imidazolopyrimidines reported by Robert P. Brigance et al. as DPP-IV inhibitors



3

Shahenda Mahgoub et al.[25] prepared some novel pyrimidinone and thio-pyrimidinone derivatives, which were then screened for their antidiabetic activity and DPP-IV inhibition. Most of the synthesized compound showed antihyperglycemic activity. Five derivatives showed antidiabetic efficacy with plasma DPP-IV reducing effect. The active derivatives were evaluated for their antioxidant and anti-inflammatory activities. Compound **4** (Structure 4) offered the highest activity as DPP-IV, with promising anti-inflammatory/antioxidant effects and may be able to mitigate COVID-19 in type 2 diabetic patients.

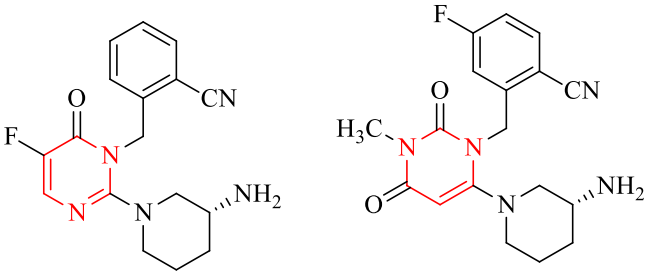
Structure 4. Novel pyrimidinone and thio-pyrimidinone derivatives reported by Shahenda Mahgoub et al.



4

Zhiyuan Zhang et al.[26] designed and synthesized some pyrimidinone and pyrimidinedione as inhibitors of DPP-IV. After a single oral dose, these potent, selective, and noncovalent inhibitors provide sustained reduction of plasma DPP-IV activity and lowering of blood glucose in animal models of diabetes. Compounds **5** and **6** (Structure 5) were selected for the development.

Structure 5. Some pyrimidinone and pyrimidinedione as inhibitors of DPP-IV reported by Zhiyuan Zhang et al.

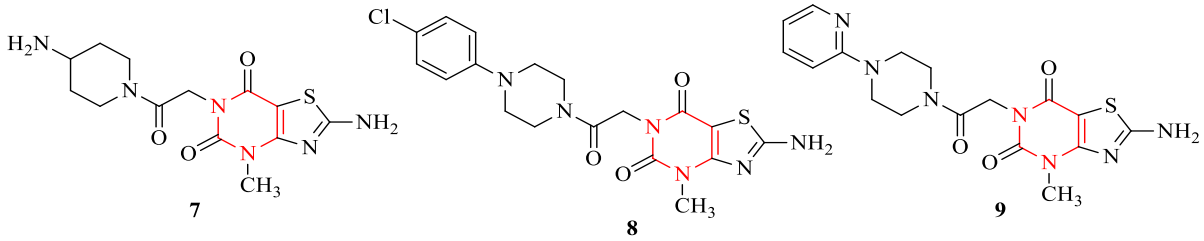


5 IC_{50} = 6 nM

6 IC_{50} = 4 nM

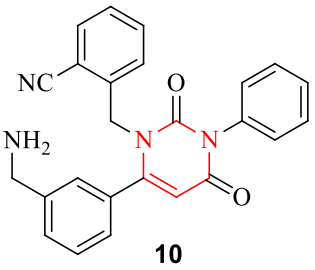
A series of thiazolopyrimidine derivatives was designed, synthesized and screened for *in-vitro* inhibition of DPP-IV by Mani Sharma et al.[27]. The SAR study indicated the influence of substituted chemical modifications on thiazolopyrimidine scaffold. Compound **7** (IC_{50} = 0.489 μM) and **8** (IC_{50} = 0.329 μM) having heterocyclic-substituted piperazine with acetamide linker resulted as most potent DPP-IV inhibitors among all the compounds screened. Single dose (10 mg/kg) of both the compounds 9 and 10 significantly reduced glucose excursion during oral glucose tolerance test in streptozotocin induced diabetic rat model. Molecular docking studies illustrated the probable binding mode and interactions of thiazolopyrimidine nucleus and its derivatives at binding site of receptor. The binding site for DPP-IV is composed of active site region (catalytic triad of Ser630, Asp708 and His740) including S1 and S2 subpocket. The aryl moiety of compounds **7**, **8**, and **9** (Structure 6) were observed to occupy S2 binding pocket and interacted with aromatic ring of Tyr662 and Tyr666 acquired through p-p interaction. Thus, it is indicated that occupancy of the highly hydrophobic S2 pocket is more important for DPP-IV inhibitory activity. The present study on substituted thiazolopyrimidine derivatives shows good to moderate inhibitory potential of DPP-IV enzyme.

Structure 6. A series of thiazolopyrimidine derivatives reported by Mani Sharma et al.



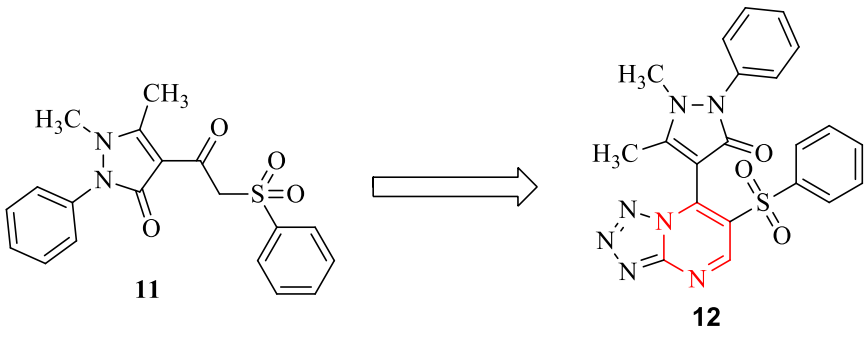
Ankita et al.[28] have designed different novel DPP-IV inhibitors based on alogliptin which act as an antidiabetic agent with the help of Autodock vina molecular docking software. Among designed molecules, compound **10** (Structure 7) showed good binding affinity (-10.7 kcal\mol) which is better than alogliptin (-9.6 kcal/mol).

Structure 7. DPP-IV inhibitor reported by Ankita et al.



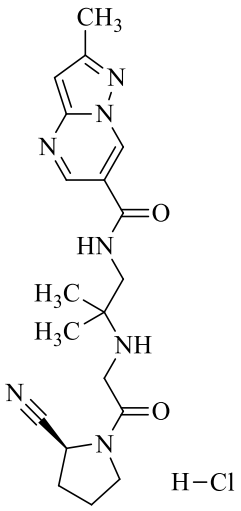
The binding mode of the lead compound **11** (Structure 8) produced by Sobhi M. Gomha et al.[29] was estimated. Using a multicomponent process and microwave heating in a tightly controlled environment, many derivatives including bridging nitrogenous heterocycles have been produced. Anti-diabetic activity was measured in relation to DPP-IV protein and compared to that of sitagliptin. Comparable DPP-IV inhibitory action was seen for compounds with small to medium nitrogenous bridges and sitagliptin, with the latter perhaps achieved by targeting Glu203 and Glu204. Remarkably, adding an extra nitrogen atom to the heterocyclic linker dramatically enhanced this interaction (compound **12**, Structure 8). Compounds exhibiting sub-micromolar IC_{50} values for hypoglycemic activity in the oral route were further tested in a diabetic mice model.

Structure 8. 1,5-Dimethyl-2-phenyl-4-(2-phenyl-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidin-7-yl)-1*H*-pyrazol-3(2*H*)-one reported by Sobhi M. Gomha et al. as DPP-IV inhibitor



Noriyasu Kato et al.[30] reported synthesis and evaluation of a series of pyrazolo[1,5-a]pyrimidine derivatives which led to the discovery of *N*-[2-({2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt: compound **13**, Structure 9) as a highly selective and potent inhibitor of DPP-IV.

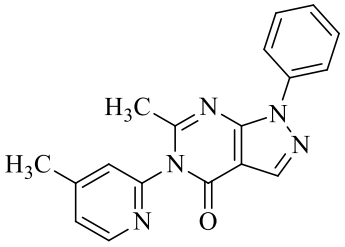
Structure 9. *N*-[2-({2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride reported by Noriyasu Kato et al.



13

Sneha R. Sagar et al.[31] designed, synthesized, performed biological activity, and docking studies of series of novel pyrazolo[3,4-*d*]pyrimidinones as DPP-IV inhibitors in diabetes. Molecules were synthesized and evaluated for their DPP-IV inhibition activity. Many compounds were found to be potent inhibitors of DPP-IV enzyme. Amongst all the synthesized compounds, 6-methyl-5-(4-methylpyridin-2-yl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (compound **14,** Structure 10) was found to be the most active based on *in vitro* DPP-IV studies and also exhibited promising *in vivo* blood glucose lowering activity in male Wistar rats.

Structure 10. 6-methyl-5-(4-methylpyridin-2-yl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one as DPP-IV inhibitor reported by Sneha R.Sagar et al.



14

Conclusion

Inhibitors of DPP-IV have recently gained attention as potentially useful diabetes treatments. In this review, the synthetic pyrimidine compounds that act as DPP-IV inhibitors are segmented. The majority of the compounds discussed in this study have very effective DPP-IV inhibitory properties, with IC_{50} values in the low nanomolar range. Several hybrid drugs with heterocyclic scaffolds were developed, all of which shown strong DPP-IV inhibition after being tested. The DPP-IV inhibiting actions of heterocyclic compounds may be significantly improved by modifying them with fluorine, methoxyethanesulfonyl, dimethylcarbamoyl, imidazole, amide, or cyanide groups, among other groups. In clinical studies, a number of different DPP-IV inhibitors have been investigated. Strategies based on computer-aided drug design (CADD) need to be used to a much higher level in medication development for DPP-IV.

Conflict of Interests

Authors declared that there is no conflict of interest exists.

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