

DIPEPTIDYL PEPTIDASE-4 INHIBITORS: A NEW APPROACH IN DIABETES TREATMENTGABA MONIKA^{1*}, SINGH SARBJOT², GABA PUNAM¹¹Department of Pharmaceutical Sciences, Asbasjism College of Pharmacy, Bela (Ropar)-140111, Punjab, India²Biology Research, Drug Discovery Research, Panacea Biotec Pvt. Ltd., Mohali, Punjab, India**ABSTRACT**

Type 2 diabetes is a progressive, metabolic disorder characterised by two fundamental defects: insulin resistance at peripheral target tissues and pancreatic beta-cell dysfunction. Insulin sensitivity declines as an individual moves from normal to impaired glucose tolerance state. Pancreatic beta cells compensate by hyper-secretion of insulin in order to maintain normoglycemia. When pancreatic beta cells exhaust and the function of pancreatic beta cells deteriorates progressively, an individual progresses from the state of impaired fasting glucose or impaired glucose tolerance to frank diabetes. Despite good compliance to treatment, the glycemic control of type 2 diabetes deteriorates progressively. Hence, new therapeutic agents are continuously being developed to help our diabetes population. Recent studies have shown that early intervention at prediabetes state and beta cell protection with insulin sensitizers may improve the prognosis of diabetes. Dipeptidyl peptidase-4 (DPP-4) is the enzyme responsible for inactivating the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), two hormones that play important roles in glucose homeostasis. Inhibition of dipeptidyl peptidase 4 is a promising new approach for the treatment of type 2 diabetes. DPP-4 inhibition results in increased blood concentration of the incretin hormones GLP-1 and GIP. This causes an increase in glucose-dependent stimulation of insulin secretion, resulting in a lowering of blood glucose levels. Research has demonstrated that DPP-4 inhibitors portray a very low risk of hypoglycemia development. DPP-4 inhibition is safe and well tolerated, the risk of hypoglycaemia is minimal, and DPP-4 inhibition is body-weight neutral. This is seen in association with good tolerability and weight neutrality. Hence, DPP-4 inhibition has the potential to be a novel, efficient and tolerable approach to treat type 2 diabetes.

to its solution form.

KEY WORDS: DPP-4 inhibitor, Incretin, Vildagliptin, Sitagliptin, Saxagliptin, Type 2 diabetes.

Introduction

In the natural history of type 2 diabetes, the development of insulin resistance, impaired glucose tolerance and finally type 2 diabetes occurs gradually over many years. It is one of the fastest growing health concerns in the world. Pancreatic islet cells are initially able to respond to increased insulin

resistance by increasing insulin secretion to maintain normoglycemia. As the disease develops, however, there is a progressive loss of β -cell function. The resultant hyperglycemia, if left untreated, can eventually lead to the debilitating vascular complications of type 2 diabetes, including retinopathy, end stage renal disease, neuropathy and

cardiovascular disease. As type 2 diabetes is a progressive disease, intensification of therapy is normally required over time. While current agents are all generally effective in the short- to medium term, traditional treatment algorithms often fail to address the progressive nature of the disease. Furthermore, current therapies may also be associated with an increased risk of hypoglycemia (sulphonylureas and insulin), weight gain (sulphonylureas, thiazolidinediones and insulin), and gastrointestinal intolerance (metformin), which represent major barriers to optimal glycemic control ^[1]. Research into the pathophysiology of diabetes has revealed that a complex interplay of hormonal and neural stimuli, not just insulin and glucagon, are involved in the regulation of plasma glucose levels. But the development of incretin hormone analogues and compounds that delay their degradation and therefore raise their concentration, and/or compounds that bind to their receptors, may facilitate achievement of optimal glycemic control. Furthermore, such therapies may target physiological defects not addressed by current medications, or may exhibit a mode of action that is additive or synergistic with current therapies. Current treatments are often inefficient at sustaining glycemic control and may cause undesirable side effects, such as weight gain and episodes of hypoglycemia. Dipeptidyl peptidase-4 enzyme plays major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1 ^[2]. Therefore, new and more effective drugs have been developed with DPP-4 inhibitors playing a significant role ^[3]. The development of the DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme responsible for their degradation, has recently emerged as one such approach that appears promising for the treatment of type 2 diabetes. New class of oral hypoglycemics dipeptidylpeptidase-4 inhibitors work by inhibiting the action of this enzyme, thereby prolonging incretin effect *in vivo* ^[4]. Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in insulin secretion and blood glucose control regulation ^[5]. This article provide information regarding history, development and discovery of novel oral antidiabetic agents.

History

Since its discovery in 1967, serine protease DPP-4 has been a popular subject of research ^[3]. Inhibitors of DPP-4 have long been sought as tools to elucidate the functional significance of the enzyme. The first inhibitors were characterized in the late 1980s and 1990s. Each inhibitor was important to establish an early structure activity relationship for subsequent investigation. It should be noted that the inhibitors fall into two main classes, those that interact covalent with DPP-4 and those that do not ^[6]. DPP-4 is a dipeptidase that selectively binds substrates that contain proline at the P1-position, thus many DPP-4 inhibitors have 5-membered heterocyclic rings that mimic proline, e.g. pyrrolidine, cyanopyrrolidine, thiazolidine and cyanothiazolidine ^[7]. These compounds commonly form covalent bonds to the catalytic residue Ser630 ^[8]. In 1994, researchers from Zeria Pharmaceuticals unveiled cyanopyrrolidines with a nitrile function group that was assumed to form an imidate with the catalytic serine. Concurrently other DPP-4 inhibitors without a nitrile group were published but they contained other serine-interacting motifs, e.g. boronic acids, phosphonates or diacyl hydroxylamines. These compounds were not as potent because of the similarity of DPP-4 and prolyl oligopeptidase and also suffered from chemical instability. Ferring Pharmaceuticals filed for patent on two cyanopyrrolidine DPP-4 inhibitors which they published in 1995. These compounds had excellent potency and improved chemical stability. In 1995, Edwin B. Villhauer at Novartis started to explore N-substituted glyciny-cyanopyrrolidines based on the fact that DPP-4 identifies N-methylglycine as an N-terminal amino acid. This group of new cyanopyrrolidines became extremely popular field of research

In the following years. Some trials with dual inhibitors of DPP-4 and vaso-peptidase have been represented, since vaso-peptidase inhibition is believed to enhance the antidiabetic effect of DPP-4 inhibition by stimulating insulin secretion. Vaso-peptidase-inhibiting motif is connected to the DPP-4 inhibitor at the N-substituent ^[6,9].

Structure of DPP-4

X-ray structures of DPP-4 give detailed information about the structural characteristics of the binding site. Many structurally

diverse DPP-4 inhibitors have been discovered and it is not that surprising while considering the properties of the binding site:^[10]

1. A deep lipophilic pocket combined with several exposed aromatic side chains for achieving high affinity small molecule binding.

2. A significant solvent access which makes it possible to tune the physico-chemical properties of the inhibitors that leads to better pharmacokinetic behavior.

DPP-4 is a 766 amino acid transmembrane glycoprotein which belongs to the prolyl oligopeptidase family. It consists of three parts; a cytoplasmic tail, a transmembrane region and an extracellular part. The extracellular part is divided into a catalytic domain and an eight-bladed β -propeller domain.

domain shows α/β -hydrolase fold and contains the catalytic triad Ser630 - Asp708 - His740. The S1-pocket is very hydrophobic and is composed of the side chains: Tyr631, Val656, Trp662, Tyr666 and Val711. Existing X-ray structures show that there is not much difference in size and shape of the pocket that indicates that the S1-pocket has high specificity for proline residues^[10,11].

Binding site

DPP-4 inhibitors usually have an electrophilic group that can interact with the hydroxyl of the catalytic serine in the active binding site (Fig. 1). Frequently that group is a nitrile group but can also be boronic acid or diphenyl phosphonate.

This

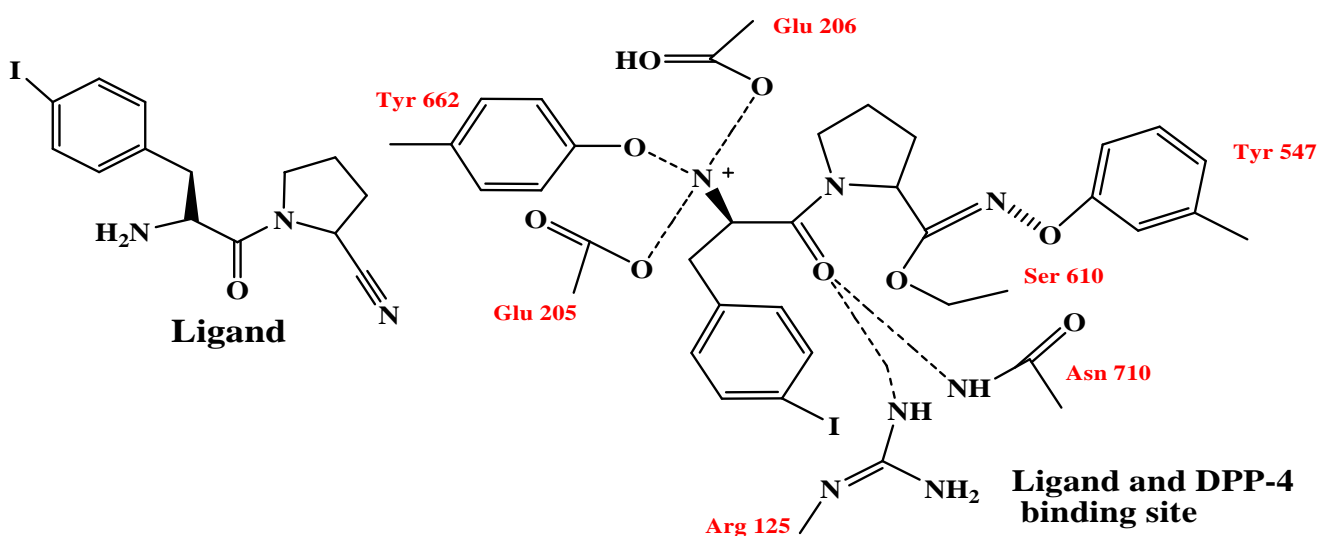


Figure 1: The key interactions between the ligand and DPP-4 complex. The ligand's basic amine forms a hydrogen bonding network.

The nitrile reacts with the catalytic active serine and forms an imidate adduct.

electrophilic group can bind to the imidate complex with covalent bonds and slow tight-binding kinetics but this group is also responsible for stability issues due to reactions with the free amino group of the P2-amino acid. Therefore, inhibitors without the electrophilic group have also been developed, but these molecules have shown toxicity due to affinity to other dipeptidyl peptidases, e.g. DPP-2, DPP-8 and DPP-9^[12]. DPP-4 inhibitors span diverse structural types. In 2007 few of the most potent compounds contain a proline mimetic cyanopyrrolidine P1 group. This group enhances the potency,

probably due to a transient covalent trapping of the nitrile group by the active site Ser630 hydroxyl, leading to delayed dissociation and slow tight-binding of certain inhibitors. When these potency enhancements were achieved, some chemical stability issues were noted and more advanced molecules had to be made. To avoid these stability issues, the possibility to exclude the nitrile group was investigated. Amino acids with aryl or polar side chains did not show appreciable DPP-4 inhibition and in fact, all compounds without the nitrile group in this research suffered a 20 to 50-fold loss of potency corresponding to the compounds containing the nitrile group^[13].

Discovery and Development of DPP-4 Inhibitors

It is important to find a fast and accurate system to discover new DPP-4 inhibitors with ideal therapeutic profiles. High throughput screening (HTS) usually gives low hit rates in identifying the inhibitors but virtual screening (VS) can give higher rates. VS has for example been used to screen for small primary aliphatic amines to identify fragments that could be placed in S1 and S2 sites of DPP-4. On the other hand, these fragments were not very potent and therefore identified as a starting point to design better ones. 3D models can provide a useful tool for designing novel DPP-4 inhibitors. Pharmacophore models have been made based on key chemical features of compounds with DPP-4 inhibitory activity. These models can provide a hypothetical picture of the primary chemical feature responsible for inhibitory activity [13]. The first DPP-4 inhibitors were reversible inhibitors and came with bad side effects because of low selectivity. Researchers suspected that inhibitors with short half-lives would be preferred in order to minimize possible side effects. However, since clinical trials showed the opposite, the latest DPP-4 inhibitors have a long-lasting effect. One of the first reported DPP-4 inhibitor is P32/98 from Merck. It used thiazolidide as the P1-substitute and is the first DPP-4 inhibitor that showed effects in both animals and humans. Another old inhibitor is DPP-728 from Novartis, where 2-cyanopyrrolidine is used as the P1-substitute. The addition of the cyano group generally increases the potency. Usually, DPP-4 inhibitors are either substrate-like or non-substrate-like [14].

a. Substrate-like inhibitors

Substrate-like inhibitors (Fig. 2) are more common than the non-substrate-likes. They bind either covalently or non-covalently and have basic structure where the P1-substituent occupies the S1-pocket and the P2-substituent occupies the S2-pocket. Usually they contain a proline mimetic that occupies the S1-pocket. Large substituents on the 2-cyanopyrrolidine ring are normally not tolerated since the S1-pocket is quite small [14]. Since DPP-4 is identical with the

T-cell activation marker CD26 and DPP-4 inhibitors are known to inhibit T-cell proliferation, these compounds were initially thought to be potential immunomodulators. When the function against type 2 diabetes was discovered, the cyanopyrrolidines became a highly popular research material. A little later vildagliptin and saxagliptin, which are the most developed cyanopyrrolidine DPP-4 inhibitors to date, are discovered [9].

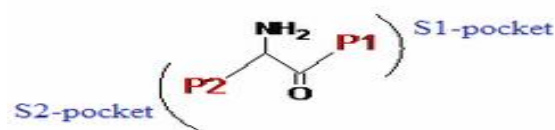


Figure 2: A generic structure of a substrate-like inhibitor.

Cyanopyrrolidines

Cyanopyrrolidines have two key interactions to the DPP-4 complex: [9]

1. Nitrile in the position of the scissile bond of the peptidic substrate is important for high potency. The nitrile group forms reversible covalent bonds with the catalytically active serine hydroxyl (Ser630), i.e. cyanopyrrolidines are competitive inhibitors with slow dissociation kinetics.
2. Hydrogen bonding network between the protonated amino group and a negatively charged region of the protein surface, Glu205, Glu206 and Tyr662. All cyanopyrrolidines have basic, primary or secondary amine which makes this network possible but these compounds usually drop in potency if these amines are changed. Nonetheless, two patent applications unveil that the amino group can be changed, i.e. replaced by a hydrazine, but it is claimed that these compounds do not only act *via* DPP-4 inhibition but also prevent diabetic vascular complications by acting as a radical scavenger.

Important structure-activity relationship studies shows that: [6]

1. Strict steric constraint exists around the pyrrolidine ring of cyanopyrrolidine-based inhibitors, with only hydrogen, fluoro, acetylene, nitrile or methano substitution.
2. Presence of a nitrile moiety on the pyrrolidine ring is critical to achieving potent activity.

Also, systematic structure activity relationship investigation

has shown that the ring size and stereochemistry for the P2 position is quite conditioned.

A 5-membered ring and L-configuration has shown better results than a 4-membered or 6-membered ring with D-configuration. Only minor changes on the pyrrolidine ring can be tolerated since the good fit of the ring with the hydrophobic S1 pocket is very important for high affinity. Some trials have been made, e.g. by replacing the pyrrolidine with a thiazoline. That led to improved potency but also loss of chemical stability. Efforts to improve chemical stability often led to loss of specificity because of interactions with DPP-8 and DPP-9. These interactions have been connected with increased toxicity and mortality in animals. There are strict limitations in the P1 position and hardly any changes are tolerated, on the other hand a variety of changes can be made in the P2 position. In fact, substitution with quite big branched side chains, e.g. *tert*-butylglycin, normally increased activity and chemical stability which could lead to longer-lasting inhibition of the DPP-4 enzyme. It has also been noted that biaryl-based side chains can also give highly active inhibitors. Originally it was believed that only lipophilic substitution would be tolerated; now it's stated that also the substitution of polar negatively charged side chains as well as hydrophilic substitution can lead to excellent inhibitory activity^[9].

Chemical stability

DPP-4 inhibitors generally are not very stable compounds. Therefore, many researchers focus on enhancing the stability for cyanopyrrolidines. The most widespread technique to improve chemical stability is to incorporate a steric bulk. The two cyanopyrrolidines that have been most pronounced, vildagliptin and saxagliptin, were created in this manner. K579 is a DPP-4 inhibitor discovered by researchers at Kyowa Hakko Kyogo. It does not only have improved chemical stability but also a longer-lasting action. That long-lasting action is due to slow dissociation of the enzyme-inhibitor complex and an active oxide metabolite that undergoes enterohepatic circulation. The discovery of the active oxide was in fact a big breakthrough as it led to the development of vildagliptin and saxagliptin

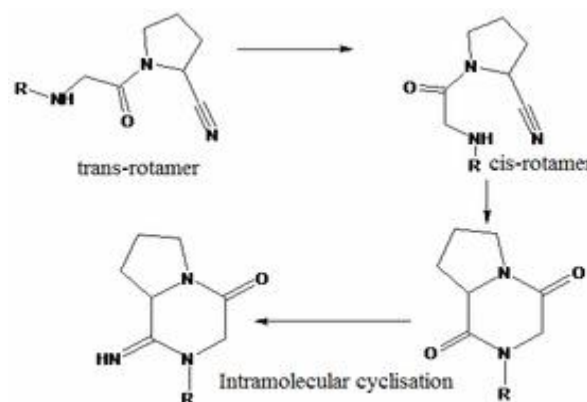


Figure 3: *Trans*-rotamers are more stable than *cis*-rotamers. *cis*-rotamers undergo intramolecular cyclisation.

. One major problem in DPP-4 inhibitor stability was intramolecular cyclisation. The precondition for the intramolecular cyclisation is the conversion of the *trans*-rotamer, which is the DPP-4 binding rotamer (Fig. 3). Thus, preventing this conversion will increase stability. This prevention was successful when incorporating an amide group into a ring, creating a compound that kept the DPP-4 inhibitory activity that didn't undergo the intramolecular cyclisation and was even more selective over different DPP enzymes. It has also been reported that a cyanoazetidone in the P1 position and a β -amino acid in the P2 position increased stability^[9].

Vildagliptin

Vildagliptin (Fig. 4) was first synthesized and discovered by Novartis in May 1998. Researchers examined adamantyl derivatives to be very potent. The adamantyl group worked as a steric bulk and slowed intramolecular cyclization with increasing chemical stability. Furthermore, the primary metabolites were highly active. To avoid additional chiral center a hydroxylation at the adamantyl ring was carried out (Fig. 3).

The product, vildagliptin, was even more stable, undergoing intramolecular cyclisation 30-times slower, and having high DPP-4 inhibitory activity and longer-lasting pharmacodynamic effect^[9].

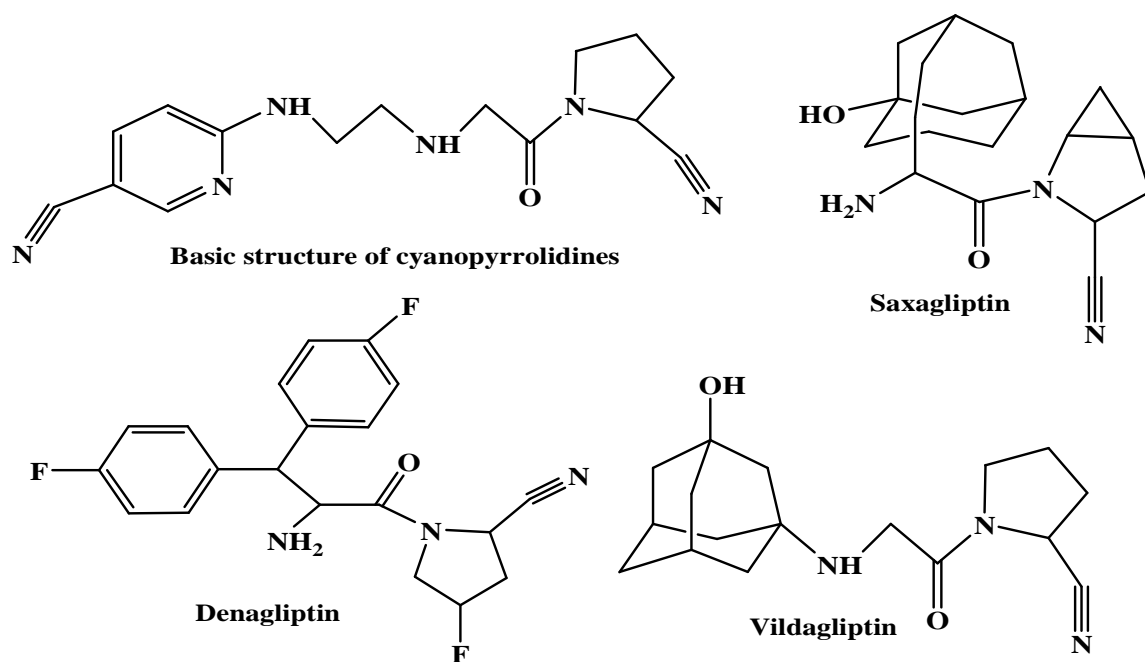


Figure 4: The basic structure of cyanopyrrolidines compared with vildagliptin, saxagliptin and denagliptin.

Saxagliptin

With increased steric bulk of the N-terminal amino acid side chain led to increased stability. To increase stability the *trans*-rotamer with a *cis*-4,5-methano substitution of the pyrrolidine ring, results in intramolecular van-der-Waals interaction, thus preventing intramolecular cyclisation. Because of this increased stability, the researchers continued their investigation on *cis*-4,5-methano cyanopyrrolidines and came across with a new adamantyl derivative which showed extraordinary *ex vivo* DPP-4 inhibition in rat plasma. After hydroxylation on the adamantyl group they had a product with better microsomal stability and improved chemical stability. That product was named saxagliptin (Fig 4)^[9].

Denagliptin

Denagliptin (Fig. 4) an advanced compound with a branched side chain at the P2 position, but also has (4*S*)-fluoro substitution on the cyanopyrrolidine ring^[9]. It is a well known DPP-4 inhibitor developed by GlaxoSmithKline. Biological evaluations have shown that the *S*-configuration of the amino acid portion is essential for the inhibitory activity since the *R*-

configuration showed reluctantly inhibition. These findings are useful in future for designing and synthesis of DPP-4 inhibitors^[15].

Azetidine based compounds

Azetidine-based DPP-4 inhibitors can roughly be grouped into three main subcategories; 2-cyanoazetidines, 3-fluoroazetidines and 2-ketoazetidines. The most potent ketoazetidines and cyanoazetidines have large hydrophobic amino acid groups bound to the azetidine nitrogen and are active below 100nM^[16].

b. Non-substrate-like inhibitors

Non-substrate-like inhibitors are non-covalent inhibitors and usually have an aromatic ring that occupies the S1-pocket, instead of the proline mimetic^[14]. In 1999, Merck started a drug development program on DPP-4 inhibitors. When they started internal screening and medicinal chemistry program, two DPP-4 inhibitors were already in clinical trials, isoleucyl thiazolidide (P32/38) and NVP-DPP728 from Novartis. Merck licensed *L-threo*-isoleucyl thiazolidide and its *allo* stereoisomer. In animal studies, they found that both isomers have similar affinity for DPP-4, similar *in vivo* efficacy, similar pharmacokinetic and metabolic profiles. Nevertheless,

the *allo* isomer was 10-fold more toxic. The researchers found out that this difference in toxicity was due to the *allo* isomer's greater inhibition of DPP-8 and DPP-9 but not because of selective DPP-4 inhibition. More research also supported that DPP-4 inhibition would not cause compromised immune function. Once this link between affinity for DPP-8/DPP-9 and toxicity was discovered, Merck decided on identifying an inhibitor with more than a thousandfold affinity for DPP-4 over the other dipeptidases. For this purpose they used positional scanning libraries. From scanning these libraries, both DPP-4 and DPP-8 showed a strong preference for breaking down peptides with a proline at the P1 position but they found a great difference at the P2 site, i.e. they found that acidic functionality at the P2 position could provide a greater affinity for DPP-4 over DPP-8. Merck kept up doing even more research and screening. They stopped working on compounds from the α -amino acid series related to isoleucyl thiazolidide due to lack of selectivity but instead they discovered a very selective β -amino acid piperazine series through SAR studies on two screening leads. When trying to stabilize the piperazine moiety, a group of bicyclic derivatives were made, which led to the identification of a potent and selective triazolopiperazine series. Most of these analogs showed excellent pharmacokinetic properties in preclinical species. Optimization of these compounds finally led to the discovery of sitagliptin^[17].

Sitagliptin

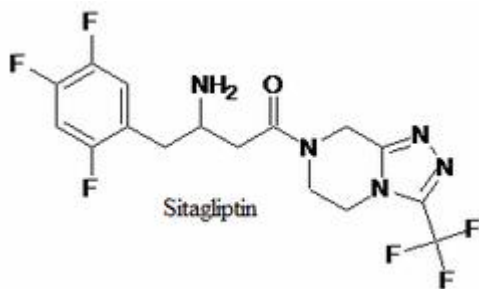


Figure 5: The structure of sitagliptin.

Sitagliptin has a novel structure with β -amino amide derivatives (Fig. 5). Since sitagliptin has shown excellent selectivity and *in vivo* efficacy it urged researches to inspect the new structure of DPP-4 inhibitors with appended β -amino acid moiety. Further studies are being developed to optimize these compounds for the treatment of diabetes.¹² Crystallographic structure of sitagliptin along with molecular modeling has been used to continue the search for structurally diverse inhibitors. A new potent, selective and orally bioavailable DPP-4 inhibitor was discovered by replacing the central cyclohexylamine in sitagliptin with 3-aminopiperidine. A 2-pyridyl substitution was the initial SAR breakthrough since that group plays a significant role in potency and selectivity for DPP-4^[3]. It has been shown with an X-ray crystallography how sitagliptin binds to the DPP-4 complex:^[14]

1. The trifluorophenyl group occupies the S1-pocket
2. The trifluoromethyl group interacts with the side chains of residues Arg358 and Ser209.
3. The amino group forms a salt bridge with Tyr662 and the carboxylated groups of the two glutamate residues, Glu205 and Glu206.
4. The triazolopiperazine group collides with the phenyl group of residue Phe357

Constrained phenylethylamine compounds

Researchers at Abbott Laboratories identified three novel series of DPP-4 inhibitors using HTS. After more research and optimization ABT-341 was discovered (Fig. 6). It is a potent and selective DPP-4 inhibitor with a 2D-structure very similar to sitagliptin. However, the 3D-structure is quite different. ABT-341 also has a trifluorophenyl group that occupies the S1-pocket and the free amino group, but the two carbonyl groups are orientated 180° away from each other. ABT-341 is also believed to interact with the Tyr547, probably because of steric hindrance between the cyclohexenyl ring and the tyrosine side chain^[14].

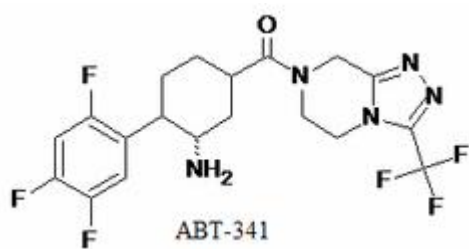
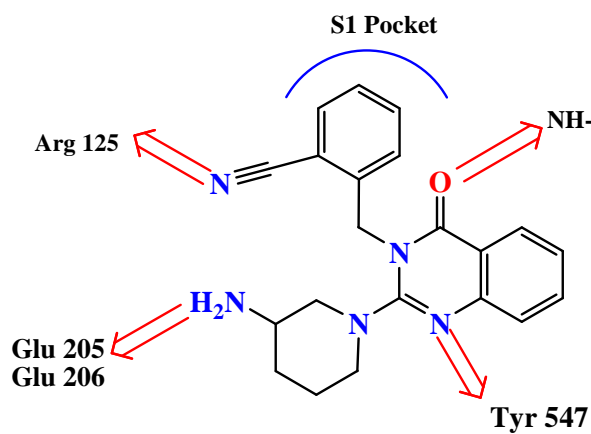
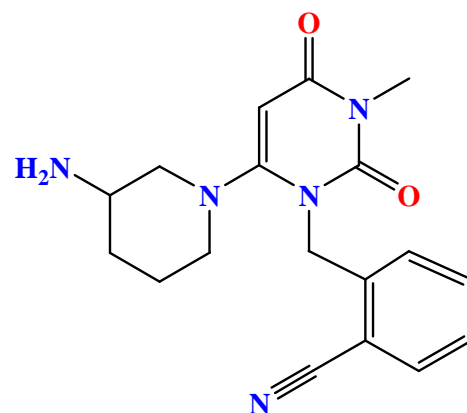


Figure 6: The structure of ABT-341.



Quinazolinone based structure



Alogliptin

Figure 7: Quinazolinone structure and alogliptin

. Pyrrolidine compounds

The pyrrolidine types of DPP-4 inhibitors are discovered after HTS [18]. Research showed that the pyrrolidine rings are the part of the compounds that fit into the binding site. Further development has led to fluoro substituted pyrrolidines that showed superior activity, as well as pyrrolidines with fused Cyclopropylrings are highly active [19].

Xanthine-based compounds

This is different class of inhibitors that are identified with HTS [15]. When xanthine based DPP-4 inhibitors are compared with sitagliptin and vildagliptin it has shown a superior profile [20]. Xanthines are believed to have higher potency, longer-lasting inhibition and longer-lasting improvement of glucose tolerance [21].

Alogliptin

Alogliptin (Fig. 7) is a novel DPP-4 inhibitor developed by the Takeda Pharmaceutical [22]. Quinazolinone based structure have the necessary groups to interact with the active site on the DPP-4 complex. Quinazolinone based compounds interact

effectively with the DPP-4 complex, but suffered from low metabolic half-life. It is found that when replacing the quinazolinone with a pyrimidinedione, the metabolic stability is increased and the results are potent, selective, bioavailable DPP-4 inhibitor named alogliptin. The quinazolinone based compounds shows potent inhibition and excellent selectivity over related protease, DPP-8. However, short metabolic half-life due to oxidation of the A-ring phenyl group is problematic. At first, the researchers tried to make a fluorinated derivative. The derivative shows improved metabolic stability and excellent inhibition of the DPP-4 enzyme. Alogliptin is discovered when quinazolinone is replaced with a pyrimidinedione. Alogliptin has shown excellent inhibition of DPP-4 and extraordinary selectivity, greater than 10,000 fold over the closely related serine proteases DPP-8 and DPP-9. Also, it does not inhibit the CYP 450 enzymes nor block the *hERG* (*human Ether Related Gene*) channel at concentration up to 30 μ M. [22].

Other xanthine based inhibitors

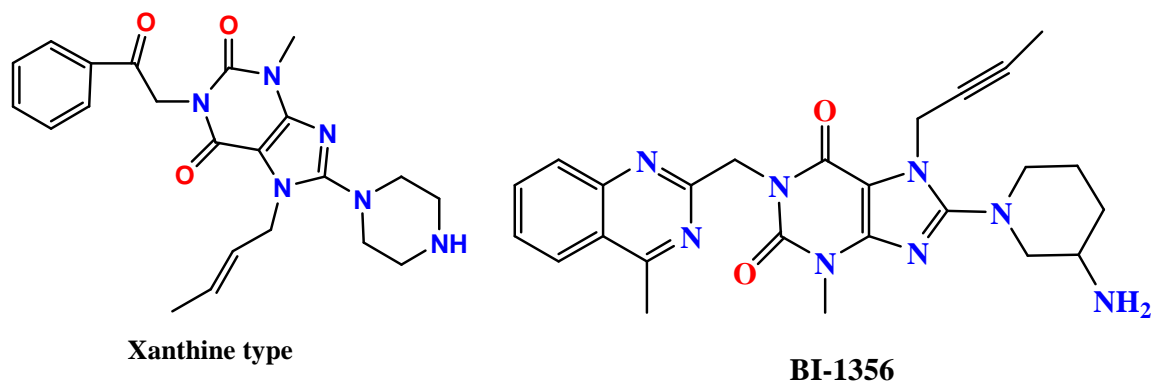


Figure 8: Xanthine type inhibitors and the potent candidate, BI-1356.

By using a buty-2-nyl group a potent candidate, called BI-1356 is discovered (Fig. 8). In 2008 BI-1356 underwent phase III clinical trials. X-ray crystallography has shown that xanthine type binds the DPP-4 complex in a different way than other inhibitors:^[14]

1. The amino group also interacts with the Glu205, Glu206 and Tyr662
2. The buty-2-nyl group occupies the S1-pocket
3. The uracil group undergoes a π -stacking interaction with the Tyr547 residue
4. The quinazoline group undergoes a π -stacking interaction with the Trp629 residue

Conclusion

DPP-4 inhibitors are promising new medicines for the treatment of type 2 diabetes mellitus. They are supposed to improve metabolic control (as measured by lowering blood glucose) without causing severe hypoglycemia. DPP-4 inhibitors as monotherapy may not be sufficiently active in patients with poor and longstanding disease so combination therapy with metformin, sulfonylureas, and thiazolidinediones is also suggested. Since the new DPP-4 inhibitors may influence immune function so additional long-term data on the safety of these drugs are necessary. Also, cardiovascular outcomes like heart attacks and strokes should not be

increased with any antidiabetic therapy. Based on the current evidence, these agents represent viable second-and third-line options in the management of type 2 diabetes. With the rising prevalence of diabetes, new therapies that provide glucose control are needed. Although many medications are available, tight glucose control is still a challenge.

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