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Review Article

AN INSIGHT INTO DPP-IV INHIBITORS: NOVEL ORAL ANTI-HYPERGLYCAEMIC AGENTS

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Abstract:

Emerging as an epidemic of the 21st century type II diabetes has become a major health problem throughout the globe. Known treatments for diabetes have limitations such as weight gain and hypoglycaemias. A new perspective is the use of incretin hormones and incretin enhancers which are novel approach for treatment of type 2 diabetes is based on the gut hormone glucagon-like peptide-1 (GLP-1), which is antidiabetic due to its combined action to stimulate insulin secretion, increase beta-cell mass, inhibit glucagon secretion, reduce the rate of gastric emptying. DPP IV rapidly inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). Inhibition of DPP IV prolongs and enhances the activity of endogenous GLP-1 and GIP, which serve as important prandial stimulators of insulin secretion and regulators of blood glucose control.

Keywords: type-II diabetes, GLP-1(glucagon like peptide), GIP (glucose dependent insulinotropic polypeptide), DPP (dipeptidyl peptidase).

Diabetes Milletus:

Diabetes mellitus is a chronic metabolic disorder characterised by a high blood glucose concentration-hyperglycaemia(fasting plasma glucose > 7.0mmol/l, or plasma glucose > 11.1mmol/2hours after a meal) caused by insulin deficiency, often combined with insulin resistance.[1] Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis.

Types of diabetes mellitus:

- Type-I DM
- Type-2 DM
- Gestational DM

TYPE-I DIABETES known as insulin-dependent diabetes mellitus IDDM (or) juvenile –onset diabetes. In type-IDM, there is an absolute deficiency of insulin resulting from autoimmune destruction of Beta cells. It was traditionally termed as juvenile diabetes because it represents a majority of the diabetes cases in children.

TYPE-2 DIABETES known as non-insulin dependent diabetes mellitus-NIDDM (or) maturity-onset diabetes.Type-2 diabetes is accompanied both by insulin resistance and by impaired insulin secretion. Over 90% cases are type-2DM.

GESTATIONAL DIABETES resembles type-2 diabetes in several aspects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-5% of all pregnancies and may improve (or) disappear after delivery. About 20-50% of affected women develop type-2 diabetes later in life.

SIGNS & SYMPTOMS:

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes, sustained sensible glucose control usually returns lens to its original shape.

A number of skin rashes can occur in diabetes that are collectively known as diabetic dermadromes.

FACTORS RESPONSIBLE FOR TYPE-2 DM:

- **Factors related to diet:** Diet is one of the most important factors triggering DM. Indeed, DM is a condition in which the blood sugar level increases and so, any diet that contains carbohydrates, are directly responsible for increasing the overall blood sugar level.
- **Factors related to lifestyle:** DM is a lifestyle disease. It has been observed that this disease is more rampant in the upper classes, since they tend to binge more on unhealthy foods.[2]

- **Stress** is another very important cause of DM. In some high-risk people, stress can cause malfunctioning of the pancreas and hence, secretion of insulin.
- **Environmental & external factors:** People who take steroids and other drugs that alter the hormonal balance are very susceptible to DM, as the amount of insulin can be reduced. Infections can also cause DM. Some micro-organisms can infect the pancreas and reduce its functioning.
- **HEREDITARY FACTORS:** DM type-2 is definitely hereditary, but it is compounded in future generations due to other problems such as obesity, hypertension and high blood pressure. People can also get a defective mechanism from their preceding generations due to which the B-cells of the islets of langerhans can be impaired in their functions.
- **FACTORS RELATED TO AGE:** DM type-2 mostly occurs in the adulthood.
- **SEX:** The prevalence of type-2 DM in the pediatric population is higher among girls than boys, just as it is higher among women than men.

CURRENT TARGETS FOR TREATMENT OF TYPE-2 DM:[3-11]

Table: 1

CLASS	MECHANISM	DRUGS	ADVERSE EFFECTS
Sulfonyl ureas	These drugs stimulate the insulin secretion by stimulating β cells of islets of Langerhans	Tolbutamide, Acetohexamide, Chlorpropamide, Glipizide, Glibenclamide.	Hypoglycaemia and weight gain.
Meglitinides	By closing the k+ channels of the pancreatic B-cells, they open the calcium channels, hence enhancing insulin	Repaglinide Nateglinide	Weight gain and hypoglycaemia.

	secretion.		
Biguanides	These drugs stimulate glucose utilization by muscles & they also suppress degradation of insulin.	Metformin, Phenformin.	Gastrointestinal disturbances, lactic acidosis.
Thiazolidinediones	These drugs produce improvement in insulin sensitivity.	Troglitazone, Pioglitazone, Rosiglitazone.	Weightgain, oedema, anaemia.
Alpha-glucosidase inhibitors	These drugs inhibit α-glucosidase: an enzyme that increases absorption of glucose at the gastrointestinal tract.	Acarbose, Miglitol.	Gastrointestinal disturbances.
PTP-1 inhibitors	PTP-1B can dephosphorylate the phosphotyrosine residues of the activated insulin receptor kinase.		
Glucagon like peptide analogs and agonists	GLP agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic β-cells is increased.	EXENATIDE TASOGLUTIDE	Nausea.
Amylin analogues	These drugs slows gastric emptying and suppress glucagon. They have all incretin actions except stimulation of insulin secretion.	PRAMLINITIDE	Nausea

DPP-IV: Introduction

Dipeptidyl peptidase IV (DPP IV or DPP-4) is a prolyl peptidase which preferentially cleaves proteins and peptides after a proline amino acid residue. DPP IV is commonly characterised by an ability to cleave Xaa-Pro or Xaa-Ala dipeptides preferentially from the N-terminus of polypeptides (where Xaa is any amino acid except Pro). DPP-IV is also the CD26 T-cell activating antigen found in almost all human organs and tissues.[12] Tissues which strongly express DPP IV include the exocrine pancreas, kidney, gastrointestinal tract, biliary tract, thymus, lymph nodes, uterus, placenta, prostate, adrenal, sweat glands, salivary and mammary glands. DPP IV is anchored to the plasma membrane of endothelia of almost all organs examined, and is also found solubilised in body fluids such as blood plasma and cerebrospinal fluid.[13] The broad distribution of DPP IV gives it ready access to endocrine peptides, neuropeptides and a wide range of paracrine and autocrine peptides and polypeptides. Although DPP IV is a pleiotropic enzyme that cleaves and generally inactivates a wide variety of peptide hormones, it has become renowned for its inactivation of two intestinal hormones known as the incretins. These include glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Initial interest in the incretin hormones as potential antidiabetic hormones was aroused by their potent insulin-secretory activity,[14] and consequent lowering of prandial plasma glucose. However, degradation of GLP-1and GIP by DPP IV is rapid (half-life less than two minutes) and leads to formation of metabolites that are devoid of insulin-releasing activity. Thus, preventing the degradation of the incretin hormones, by DPP IV inhibition, became an attractive therapeutic strategy.[15] The present review evaluates the concept, therapeutic potential and limitations of DPP IV inhibitors as potential antidiabetic agents.

OTHER MEMBERS OF THE DPP-IV ENZYME FAMILY: Improvements in our knowledge of DPP IV, and in particular the discovery of a family of enzymes with DPP IV-like activity, have reopened the issue of inhibitor selectivity. Examples of enzymes which possess DPP IV-like activity are: fibroblast activation protein (FAP), dipeptidyl peptidase II (DPP II, also known as DPP 7 or quiescent cell proline dipeptidase [QPP]), dipeptidyl peptidase 8 (DPP 8) and dipeptidyl peptidase 9 (DPP 9). Dipeptidyl-peptidase I **(DPP-I**), a cysteine proteinase, was

recently demonstrated to play a requisite role in removing the activation dipeptide from many of the leukocyte and mast cell granule-associated proteinases including human cathepsin G, leucocyte elastase, mast cell chymase and tryptase, and lymphocyte granzymes B and H. DPP-I, originally called cathepsin C, was discovered when extracts of kidney were found to catalyze the hydrolysis of Gly-Phe-β-naphthylamide. It is a lysosomal enzyme widely expressed in many tissues that is felt to be important in intracellular degradation of proteins. **Dipeptidyl peptidase 2** is an essential survival factor in the regulation of cell quiescence. DPPII (dipeptidyl peptidase II) has been demonstrated in various mammalian tissues. However, a profound molecular and catalytic characterization, including substrate selectivity, kinetics and pH-dependence, has not been conducted. The human enzyme appeared as a 120 kDa homodimer. Mass spectrometric analysis after tryptic digestion together with a kinetic comparison indicate strongly its identity with **QPP** (quiescent cell proline dipeptidase), also called dipeptidyl peptidase 7. Natural human DPPII showed high efficiency towards synthetic substrates containing proline at the P_1 position and lysine at P_2. The importance of the P_1' group for P_2 and P_1 selectivity was revealed, explaining many discrepancies in the literature. Furthermore, substrate preferences of human DPPII and dipeptidyl peptidase IV were compared based on their selectivity constants. **FAP** is a membrane-bound protease capable of dipeptidyl peptidase activity to cleave N-terminal dipeptides from polypeptides. FAP also possesses collagenolytic activity that can degrade gelatin and type I collagen.[16] Although FAP does not appear to be expressed ubiquitously like other members of the DPP IV enzyme family, it has been found in the alpha cells of the pancreas and in serum.[17]DPP II is expressed across a range of human tissues.[18] Similarity between the activities of DPP II and DPP IV is most neatly demonstrated by the fact that many of the established inhibitors of DPP II activity were originally described as DPP IV inhibitors. **DPP 8** and **DPP 9** are widely distributed post-proline cleaving dipeptidases. Their DPP IV-like activity is demonstrated by their ability to hydrolyse substrates derived from H-Ala-Pro and HGly- Pro. Although DPP 8 and DPP 9 have not yet been associated with any particular biological process, it remains a distinct possibility that many of the functions ascribed to DPP IV may actually be derived from the activity of DPP 8 and/or DPP 9. Selective inhibition of DPP 8/9-attenuated T-cell activation suggests that these enzymes are involved in the immune

system.[19] Earlier observations that the plasma of DPP IV-deficient mice is capable of cleaving the substrate Gly-PropNA indicates that, in hindsight, the existence of other DPP IV-like enzymes could have been foreseen.

DPP-IV STRUCTURE AND ITS FUNCTION:

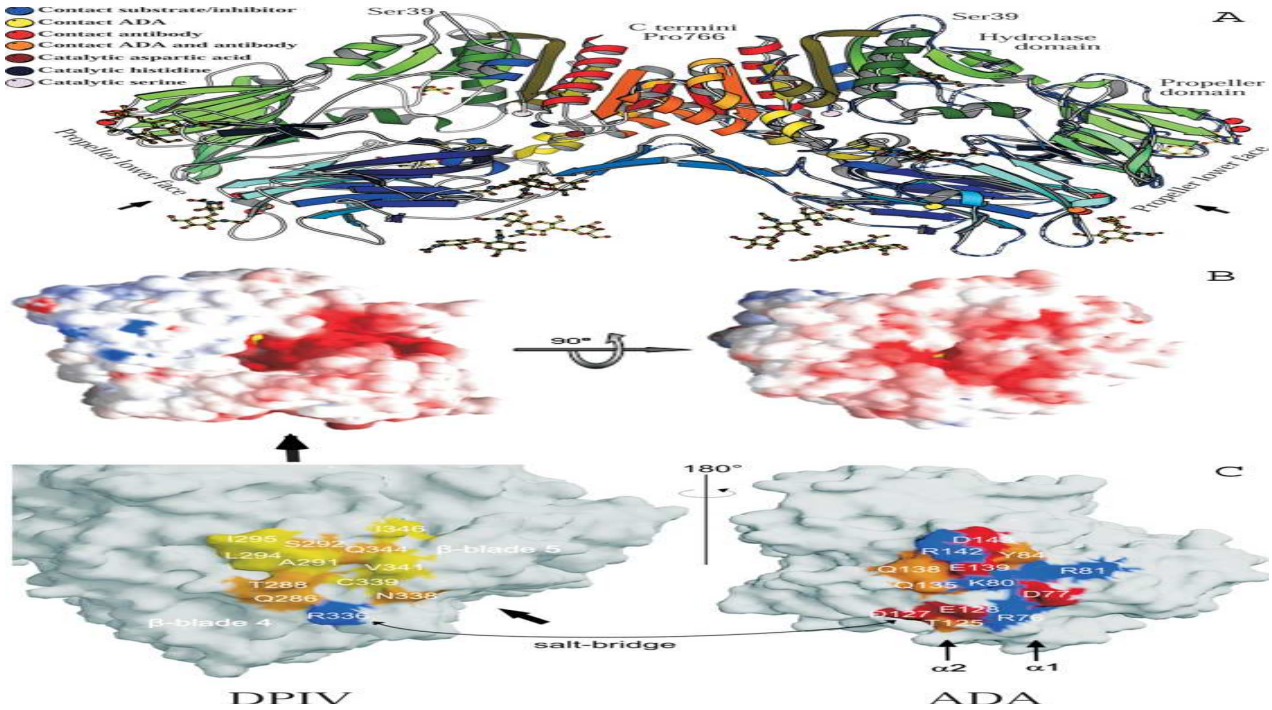


Figure 1 - Secondary, tertiary and quaternary structure of DPIV

(A) The DPIV homodimer as a ribbon diagram with each monomer coloured blue to red; carbohydrates are depicted in ball-and-stick representation and positions of important amino acids as spheres. The orange and yellow residues Leu294 and Val341 are essential for ADA binding, whereas the red positively charged residues Arg343 and Lys441 are important in epitopes of antibodies that inhibit ADA binding. Glu205 and Glu206, coloured blue, are essential for enzyme activity. Both domains contribute to the dimerization interface, the *β*-propeller contributing two *β*-strands that protrude from blade 4. Substrate access to the catalytic site occurs via the side openings that face each other and are between the eight-blade *β*-propeller (bottom) and *α*/*β* hydrolase (top) domains. The transmembrane domain (residues 7–28) is above the molecule in this view of the extracellular portion, residues 39–766, of human DPIV. (B) A surface representation of the DPIV monomer with the negatively charged surface coloured red and positively charged surface coloured blue. Viewed side-on (on left) and towards the propeller lower face (on right). An inhibitor is coloured yellow to indicate the position of the catalytic pocket. (C) In these surface

representations of DPIV and its ligand, ADA, amino acids in the binding interface are labelled. Positively and negatively charged residues are blue and red, and non-polar and polar uncharged residues are yellow and orange respectively. The helices 1 and 2 of ADA are labelled α1 and α2. The DPIV monomer is oriented similarly to the monomer on the right in (A). In each image, a large arrow points towards the central opening of the propeller lower face.

THE THREE-DIMENSIONAL STRUCTURE OF DPIV: The DPPIV crystal structures recently reported reflect a sudden global interest in the pharmaceutical design of DPPIV inhibitors .The DPPIV glycoprotein is a dimer. Each monomer subunit consists of two domains, an α/β-hydrolase domain (residues39–51 and 501–766) and an eight-blade β-propeller domain (residues 59–497), that enclose a large cavity of approx. 30–45A° (1A°=0.1nm)in diameter. Access to this cavity is provided by a large side opening of approx. 15A°.[20] However, only elongated peptides, or unfolded or partly unfolded fragments, can reach the small pocket with in this cavity that contains the active site. DPPIV contains nine N-linked glycosylation sites that lie predominantly on the propeller domain near the dimerisation[21] interface and perhaps shield this trypsin-resistant extracellular protein from proteolysis.

The active site and catalytic mechanism

The residues forming the catalytic triad are Ser630, Asp708 and His740. In addition, Tyr547 in the hydrolase domain is essential for catalytic activity and in the crystal structure appears to stabilize the tetrahedral oxyanion intermediate form of a substrate.[22] Two glutamate residues in the catalytic pocket, Glu205 and Glu206 (Figure), align the substrate peptide by forming salt bridges to its N-terminus, leaving room for only two amino acids before the peptide reaches the active serine residue, thus explaining its dipeptide-cleaving activity. Furthermore, in the substrate second position only amino acids with smaller side chains such as proline, alanine and glycine can fit into the narrow hydrophobic pocket. Thus the crystal structures have helped to explain the substrate specificity of DPPIV and the mutation data showing that Glu205 and Glu206 are essential for catalysis. An intriguing aspect of DPPIV biochemistry is the dependence of peptidase activity upon homodimerization. Dimerization requires the

hydrolase domain and a protrusion from the fourth blade of the β-propeller (Figure above). A single amino acid point mutation near the C-terminus, His750→Glu, is sufficient to prevent dimerization.[23]

The unusual propeller of DPPIV: *β*-Propellers have four to eight blades formed by a repeated subunit containing at least 30 and generally 50 amino acids in a *β*-sheet of four anti-parallel strands. Propellers commonly act as scaffolding for protein–protein interactions.[24-25] The points of contact with ligand and antibodies are formed by loops contributed by adjacent propeller blades such that binding epitopes depend upon tertiary structure. DPPIV has all of these characteristics. The structure of DPPIV is unique among leucocyte surface molecules. Other leucocyte surface antigens that include a *β*-propeller[26] domain areCD100 and integrin *α*-chain,[27] which have seven-blade propellers. As DPPIV is a type II protein, the propeller domain points its lower face towards the extracellular milieu (see above Figure). The eight-blade *β*-propeller domain of DPIV is more disordered than other propellers.

The ADA binding site on DPPIV:

ADA (adenine deaminase) is a soluble globular enzyme present in all mammalian tissues. ADA catalyses the irreversible deamination of adenosine to inosine and of 2_-deoxyadenosine to 2_-deoxyinosine. ADA derived from rabbits, cattle and humans binds to human, but not mouse, DPPIV. ADA binds human DPPIV with a *K*A of 4–20 nM. Both monomeric and dimeric DPPIV bind ADA .Localizing ADA to the cell surface by its binding to CD26 probably reduces inhibition of T-cell proliferation by extracellular adenosine. Three charged residues on ADA, Glu139, Arg142 and Asp143 have been identified by point mutation as important for ADA–DPPIV binding.[28-29] The crystal structure of DPPIV with ADA shows that the ADA binding is located, as predicted from the model, on the outer edges of the fourth and fifth blades on the lower side near the lower face of the *β*-propeller domain of DPPIV. Only one salt bridge binds ADA to DPPIV (Figure C). Most of the involved residues on DPPIV are hydrophobic and most of the 13 involved residues on ADA, which are all polar, are charged. Generally, protein–protein binding primarily involves hydrophobic surfaces with some salt bridges that are mostly peripheral in the binding interface. Thus the amino acid composition of the ADA– DPPIV binding site is unusual, perhaps due to the short evolutionary time that it has undergone selective pressure. ADA binding to human DPPIV is blocked by

certain anti-DPPIV MAb (monoclonal antibodies) that define a similar epitope. MAb that block ADA binding rely upon Val341 and Thr440-Lys441 of DPPIV for binding. The DPPIV structure shows that these amino acids are on one side of the propeller and distant from both of the openings, which explains the lack of interference from either ADA or MAb with the catalytic activity of DPPIV or ADA. This location of ADA binding also positions ADA away from the cell surface and perhaps increases accessibility to ligands such asA1-adenosine receptor and plasminogen-2.

FUNCTION: The protein encoded by the DPPIV gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction, and apoptosis. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. DPP-IV plays a major role in glucose metabolism. It is responsible for degradation of incretins such as GLP-1. It appears to work as a suppressor in the development of cancers and tumours. It plays an important role in tumour biology and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms. DPP-4 also binds the enzyme adenosine deaminase specifically and with high affinity

THE INCRETIN CONCEPT

Because orally ingested glucose leads to a far greater insulin response than intravenous glucose with similar postprandial plasma glucose excursions, the phenomenon has been termed the "incretin effect". Up to two thirds of insulin normally secreted in relation to meal intake is thought to be due to the insulinotropic actions of the so called incretin hormones. Studies have revealed that secretion of incretin hormones is diminished in type 2 diabetes.

TWO MAJOR INCRETIN HORMONES

Two gastrointestinal hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are the 2 major incretin hormones identified to date. GLP-1 is a product of the glucagon gene, which is mapped on the human chromosome 2q36-q37. It is expressed in pancreatic a-cells and the L-cells located predominantly in the ileum and colon, although GLP-1- producing L-cells have also been identified more proximally in the duodenum and jejunum. The protein product of the glucagon gene in pancreatic a-cells is

glucagon while the expression in the L-cells is the release of the C-terminal products GLP-1 and GLP-2, which show approximately a 50% sequence homology with glucagon. On the contrary, GIP (also known as gastric inhibitory polypeptide) is a 42-amino acid hormone produced from a different gene on chromosome.

Physiological Functions of GLP-1

- Stimulates insulin secretion, glucose-dependently
- Increases b-cell mass in animal models
- Decreases glucagon secretion, glucose-dependently
- Delays gastric emptying, decreases food intake and body weight
- Improves insulin sensitivity; enhances glucose disposal
- Has beneficial cardiovascular effects
- Has beneficial CNS effects in animal models

IMPORTANCE OF DEVELOPING SELECTIVE DPP-IV INHIBITORS:

Development of small molecules as selective inhibitors of DPP-IV is a major challenge. Although experimental results obtained using non-selective DPP-IV inhibitors implicated a role for DPP-IV in the control of immune regulation, transplantation biology, cancer cell growth and metastasis, there is limited date for similar studies using highly selective DPP-IV inhibitors that have been generated for the treatment of type-2 diabetes.[30] More recent experiments comparing the actions of DPP-IV selective versus non-selective inhibitors suggest that preferential inhibition of DPP-8/9 and quiescent cell proline dipeptidase (QPP) in vivo was associated with a species and tissue specific profile of different toxicities. Inhibition of DPP-8/9 produced alopecia, thrombocytopenia, splenomegaly and multi organ pathology, leading to death in rats and gastrointestinal toxicity in dogs. Moreover similar toxicities were observed in wild type, DPP-IV mice treated with DPP-8/9 inhibitors. In contrast, inhibition of the related enzymes QPP produced reticulocytopenia in rats, whereas selective inhibition of DPP-IV was not associated with detectable toxicity in rats or dogs similarly, inhibition of DPP-8/9 but not DPP-IV, was associated with reduction of mitogen-stimulated proliferation of human mononuclear cells in vitro.[31] Curiously,

some but not all DPP-IV inhibitors have been reported to produce skin lesions in monkey studies. The extent to which these finding reflect differential selectivity of specific agents for the monkey enzymes whether the lesions are completely attributable to non-DPP-IV dependent mechanisms remains poorly understood. Collectively, these findings illustrate that data obtained using non-selective DPP-IV inhibitors needs to be interpreted with caution in regard to the putative role of DPP-IV in the development of specific organ pathologies.

MECHANISM OF ACTION: DPP-IV inhibitors competitively inhibit the enzyme DPP-IV. This enzyme breakdown the incretins GLP-1 and GIP, gastrointestinal hormone that are released in response to a meal. By preventing GLP-1 and GIP inactivation,[32] GLP-1 and GIP are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose levels approaches normal, the amounts of insulin released and glucagon suppressed diminishes thus tending to prevent an "overshoot" and subsequent low blood sugar(hypoglycaemia) which is seen with some other oral hypoglycaemic agents.

ADVANTAGES OF DPP-IV INHIBITORS:[33]

- Oral administration
- Long acting
- Effect less strong compared with incretin mimetics(except decrease in HbA1c)
- Monothreapy or adjunctive therapy
- Increase in endogenous GLP-1 concentrations
- Inhibited glucagon secretion
- Stimulated insulin secretion
- No change in fasting glucose
- Slight reduction in prandial glucose
- Drug overdose is non-toxic(except liver toxicity and QT prolongation for vildagliptin)
- No weight gain

VARIOUS CLASSES OF DPP-IV INHIBITORS:

DPP-4 inhibitors, are a class of oral hypoglycemics that block DPP-4. They can be used to treat diabetes mellitus type 2.The first agent of the class - sitagliptin - was approved by the FDA in 2006.

As a therapeutic class, the DPP-IV inhibitors comprise a diverse group of compounds, which can be broadly divided into those compounds such as ;

Sitagliptin(β-aminoacid based)

Vildagliptin and saxagliptin (nitrile containing inhibitors)

Alogliptin(modified pyrimidinone)

Linagliptin(xanthine based)

Dutegliptin

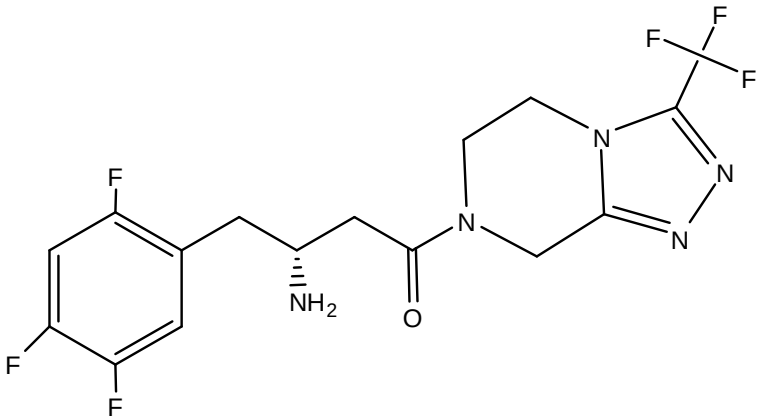
Siitagliptin, alogliptin,and linagliptin form non-covalent interactions with residues in the catalytic site. In contrast, inhibition of DPP-IV by vildagliptin and saxagliptin has been described as a two-step process that involves the formation of a reversible covalent enzyme-inhibitor complex in which there is a slow rate of inhibitor binding and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms. This means that the catalytic activity will be inhibited even after the free drug has been cleared from the circulation.

Sitagliptin entered the Australian drug market in late 2007 for the treatment of difficult-to-control diabetes mellitus type2.Dipeptidyl peptidase-4 (DPP-IV) inhibitors like sitagliptin and vildagliptin 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 hypoglycaemia (low blood sugar levels leading to unconsciousness and other symptoms). DPP-IV inhibitors have a favorable tolerability profile and represent the most recently approved class of agents for the treatment of Type 2 diabetes.[34] They prevent the DPP-IV enzyme from breaking down GLP-1, thereby increasing the levels of this hormone in the digestive tract and the blood. The increased levels of intact GLP-1 stimulate insulin production by the pancreatic beta cells and reduce glucagon

production by the pancreas, both of which result in reduced blood glucose levels. In clinical trials to date, DPP-IV inhibitors have been well tolerated and have provided clinically meaningful reductions in HbA1c when used as the sole medical treatment, as well as important incremental decreases in HbA1c when used in combinations with other anti-diabetic medications. DPP-IV inhibitors also offer several advantages over other types of diabetes therapies, including: absence of weight gain and edema, low risk of hypoglycemia, and potential for improved beta cell function.

Since the new DPP-IV inhibitors may influence immune function 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 but data so far are lacking. Until new information arrives, DPP-IV inhibitors should only be used under controlled conditions and in individual patients.

SITAGLIPTIN: `Sitagliptin is an oral antihyperglycemic of the dipeptidyl peptidase-4 (DPP-IV) inhibitor class. This enzyme-inhibiting drug is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for treatment of diabetes mellitus type 2. The benefit of this medicine is its lower side-effects (e.g., less hypoglycemia, less weight gain) in the control of blood glucose values. Exenatide (Byetta) also works by its effect on the incretin system.



Systematic (IUPAC) name: - (*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6 dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

Formula : $C_{16}H_{15}F_6N_5O$

Mechanism of action: Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-IV). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones that are released in response to a meal. By preventing GLP-1 and GIP inactivation, GLP-1 and GIP are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents.

Adverse effects: Side effects of sitagliptin are cold(running nose), stuffy nose, diarrhea, also sore throat, headache were observed. Recently, post-marketing reports of anaphylaxis, angioedema and rashes including steven-johnson syndrome, in sitagliptin treated patients have emerged. There have been several reports of pancreatitis (some fatal) in people treated with sitagliptin,[34] and the U.S. package insert carries a warning to this effect, although the causal link between sitagliptin and pancreatitis has not yet been fully substantiated.

The DPP-4 enzyme is known to be involved in the suppression of certain malignancies, particularly in limiting the tissue invasion of these tumours.[35] Inhibiting the DPP-4 enzymes may allow some cancers to progress. A study of DPP-4 inhibition in human non-small cell lung cancer (NSCLC) concluded that "DPPIV functions as a tumor suppressor, and its downregulation may contribute to the loss of growth control in NSCLC cells.

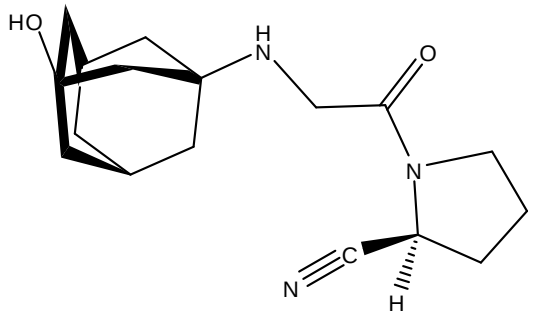
Drug interaction: The combination of sitagliptin with pioglitazone results in pheripheral oedema(4%). Glitazones probably posses a cardiotoxic effect(increased heart attack) and worsening of heart failure. It is not sure whether the increase of cardiotoxic effects is only a result of this combination therapy. Although sitagliptin is not as likely to cause hypoglycaemia as some other oral diabetes medications, be careful while prescribing any other drug that can potentially lower blood sugar, such as: probenicid, NSAIDS, aspirin or other salicylates, sulfa drugs; a monoaminooxidase inhibitors or β-blockers. An interaction with any antidiabetic drugs has not been observed.

Vildagliptin: a potent and specific inhibitor of DPP-4: Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits the inactivation of GLP-1 and GIP by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas. vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellitus.

Pharmacokinetic profile: Vildagliptin is an N-substituted glycyl-2-cyanopyrrolidine. It is a potent competitive and reversible inhibitor of human and rodent DPP-4 *in vitro*, with a median inhibitory concentration (IC50) ~2–3 nmol/L. Importantly, vildagliptin inhibits DPP-4 with high specificity relative to other similar peptidases where its IC50 exceeds 200 μmol/L. This specificity is of potential clinical importance as inhibition of DPP-8 and DPP-9 has been associated with immune, histopathological and gastrointestinal toxicity in various animal models. In healthy humans, vildagliptin is rapidly and almost completely absorbed (~85% of administered dose) after oral administration with a tmax of 1–2-hours. Plasma levels were linearly related to dose and the plasma half-life ranged from 1.5–4.5 hours with doses from 25 to 200 mg. The drug does not appear to accumulate with multiple dosing and the pharmacokinetics are not affected by food. Most of the drug is metabolised with hydrolysis of the cyano moiety dominating (55%), but a fraction (22%) is also excreted unchanged by the kidneys. The drug is minimally metabolised by the major cytochrome P450 enzymes that metabolise many other drugs and is neither an inhibitor nor an inducer of these enzymes. In the circulation, vildagliptin is not extensively protein bound (4–17%). No adjustment of dose is necessary in either hepatic or renal insufficiency.37 Single doses of vildagliptin (25–200 mg) rapidly inhibit plasma DPP-4, achieving > 90% inhibition within 30–60 minutes. The duration of inhibition is dose dependent; with the anticipated therapeutic doses of 50 mg and 100 mg, DPP-4 activity is inhibited by ~70 and 90% at 12 hours and remains inhibited by ~40% at 24 hours with the higher dose.

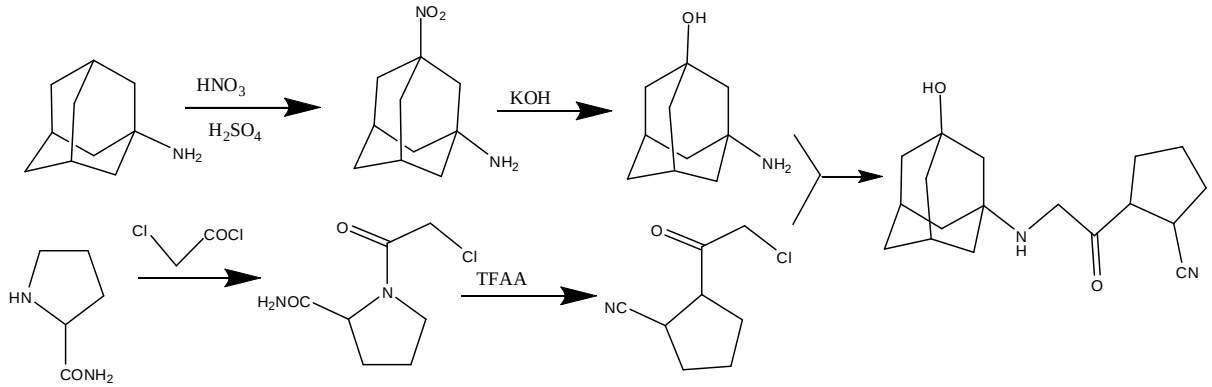
In drug naïve patients with type 2 diabetes, four weeks of treatment with vildagliptin at a dose of 100 mg per day reduced both fasting and postprandial plasma glucose levels, resulting in significant decreases in HbA1C. Vildagliptin treatment also improved insulin secretion, as assessed by the insulin responses relative to the glucose

responses to a standard mixed meal, increased both basal and postprandial GLP-1 levels, and decreased glucagon levels. The drug appeared well tolerated.



(*S*)-1-[*N*-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile

Molecular formula: $C_{17}H_{25}N_3O_2$



Synthesis:

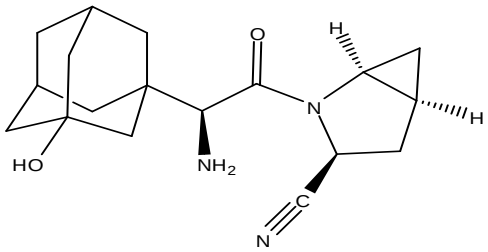
Source: 1-[[(3-Hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine

Dosage, administration, and formulations: Vildagliptin (Galvus) can be prescribed to patients with type 2 diabetes at a dosage of 50 mg once daily in combination with a sulfonylurea, or 50 mg twice daily with metformin or a thiazolidinedione such as pioglitazone. A 100 mg formulation of vildagliptin is available in Brazil and Mexico. A fixed dose combination of vildagliptin 50 mg plus metformin 850 mg or vildagliptin 50 mg plus metformin 1000 mg (Eucreas®) has also been approved for twice-daily use in patients inadequately controlled with metformin alone or who are already receiving each drug separately.

Adverse effects: The adverse effects of vildagliptin were headache, nasopharyngitis, dizziness, pheripheral edema, increased sweating and cough. Similar rates of these adverse effects were reported in the placebo groups. Hypoglycaemias are rare in response to vildagliptin combined with pioglitazone(0.3%) but were higher with

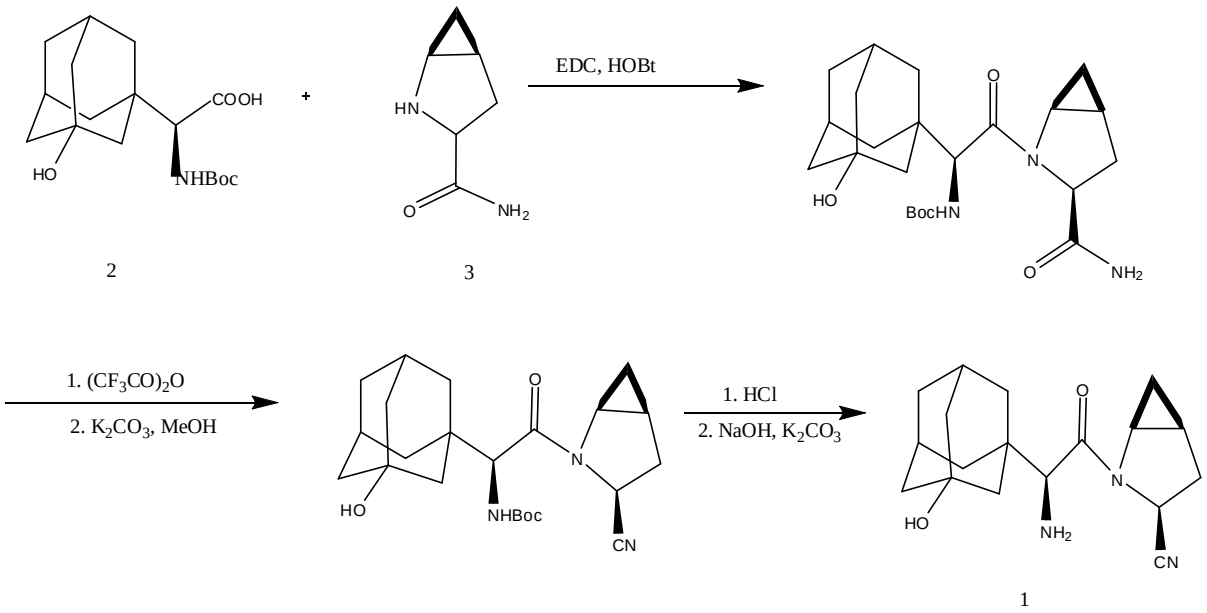
pioglitazone being used alone(1.9%). Pioglitazone increased body weight (1.4kg) Which is further increased using a combination with 100mg vildagliptin(2.7kg).

SAXAGLIPTIN: Saxagliptin previously identified as BMS-477118, is a new oral hypoglycemic (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. It was developed by Bristol-Myers Squibb. A New Drug Application for saxagliptin in treatment of type 2 diabetes was submitted to the FDA in June 2008.[36] It was based on a drug development program with 8 randomized trials: 1 phase 2 dose-ranging (2.5–100 mg/d) study; 6 phase 3, 24-week controlled trials with additional controlled follow-up from 12 to 42 months, double-blinded throughout; and one 12-week mechanism-of-action trial with a 2-year follow-up period. In June 2008, it was announced that Onglyza would be the trade name under which saxagliptin will be marketed Dipeptidyl peptidase-4's role in blood glucose regulation is thought to be through degradation of GIP and the degradation of GLP-1.



Systematic (IUPAC) name: (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

Synthesis: Saxagliptin is produced industrially by Bristol-Myers Squibb by the amide coupling of N-Boc-3-hydroxyadamantylglycine (2) and methanoprolineamide (3) with EDC. The former is commercially available, whereas the latter is available as the N-Boc analog. The prolineamide moiety is subsequently dehydrated with trifluoroacetic anhydride to give the cyanide as the trifluoracetate ester, which is hydrolyzed. Removal of the Boc protecting group, followed by neutralization gives the desired product.



2 3 1

Mechanism of Action:

saxagliptin is an orally-active inhibitor of the DPP4 enzyme. D-PP4 inhibitors work by affecting the action of natural hormones in the body called incretins .Increased concentrations of the incretin hormones such as glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. This saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner.

CombinationTherapy:

In trials evaluating Onglyza in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone), Onglyza 2.5 mg and 5 mg plus combination provided significant improvements in A1C, FPG, and PPG compared with placebo plus combination.

Side Effects:

Adverse events associated with the use of Onglyza may include, but are not limited to, the following:

- Upper respiratory tract infection
- Urinary tract infection
- Headache
- Nasopharyngitis

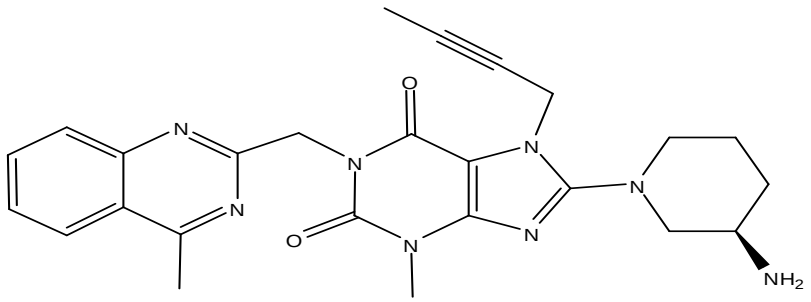
Tolerability

Both monotherapy and combination therapy with other agents was generally well tolerated in clinical trials.

Linagliptin:

Linagliptin is the most advanced investigational compound for the treatment of type2diabetes with in the Boehringer Ingelheim diabetes portfolio. It belongs to the class of dipeptidyl peptidase (DPP)-4 inhibitors and is being developed as an oral once daily tablet.[37] In clinical studies to date, linagliptin has been shown to:

- Provide significant, sustained and clinically meaningful improvements in blood glucose control
- Have an excellent safety and tolerability profile, and low risk of hypoglycaemia
- Not cause weight gain
- Not require dose adjustment, irrespective of concomitant disease or co-medication, even in patients with renal impairment.



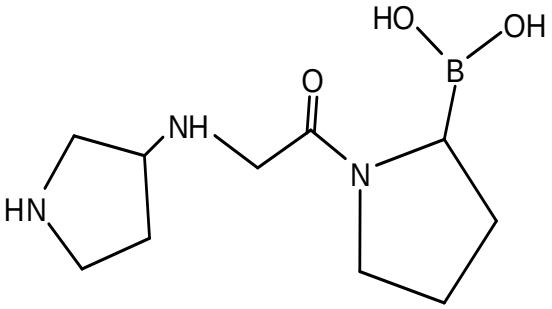
Systematic (IUPAC) name: 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3- methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione

Mechanism of action:

DPP-IV inhibitors represent an innovative approach to type2 diabetes treatment with a unique mechanism of action compared to other classes in this therapeutic area. By binding to the DPP-IV enzyme, they inhibit the breakdown of the two incretin hormones, glucagon like peptide (GLP) -1 and glucose dependent insulinotropic peptide (GLP). GLP-1 and GIP are naturally occurring hormones, which are released by the gut after meals and target the pancreas by increasing glucose dependent insulin secretion and suppressing glucagon secretion. DPP-IV inhibitors increase the GLP-1 plasma concentrations within the physiological range in contrast to injectable GLP-1 mimetics which have supra-physiological plasma levels and are assosciated with an increased GI side effect rate such as nausea and vomiting.

The inhibition of DPP-IV is beneficial for type 2 diabetes patients to control blood glucose levels , a primary goal of type 2 diabetes management. A dose-finding period at the begining of therapy is not needed when treating with a DPP-IV inhibitors . This is because of their rapid mode of action. And the fact that their favourable tolerability profile does not cause nausea, vomitting and has a low risk of drug –drug interactions. This makes them appropriate for monotherapy or as add-on to existing treatment regimens.

DUTOGLIPTIN: Dutogliptin tartrate is currently in Phase 3 clinical development. Dutogliptin is a dipeptidyl peptidase-4, or DPP-IV, inhibitor that we are advancing as a once daily, oral treatment for Type 2 diabetes. DPP-IV inhibitors have a favorable tolerability profile and represent the most recently approved class of agents for the treatment of Type 2 diabetes. They prevent the DPP-IV enzyme from breaking down GLP-1, thereby increasing the levels of this hormone in the digestive tract and the blood. The increased levels of intact GLP-1 stimulate insulin production by the pancreatic beta cells and reduce glucagon production by the pancreas, both of which result in reduced blood glucose levels. In clinical trials to date, DPP-IV inhibitors have been well tolerated and have provided clinically meaningful reductions in HbA1c when used as the sole medical treatment, as well as important incremental decreases in HbA1c when used in combinations with other anti-diabetic medications. DPP-IV inhibitors also offer several advantages over other types of diabetes therapies, including: absence of weight gain and edema, low risk of hypoglycemia, and potential for improved beta cell function.



ALOGLIPTIN: Alogliptin is a dipeptidyl peptidase-4 inhibitor that is approved in japan for treatment of adult patients with type-2DM that is inadequately controlled by diet and exercise alone or by diet plus treatment with an α-glucosidase inhibitor. In general, the incidence of hypoglycaemia was similar to that seen in placebo groups and alogliptin treatment had neutral effects on body weight and lipid parameters.[38] The long-term safety of alogliptin therapy remains to be established in clinical studies and with clinical experience. In the meantime, alogliptin is a promising new option for the treatment of patients with type-2 diabetes, including elderly patients.

Systematic (IUPAC) name: 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile.

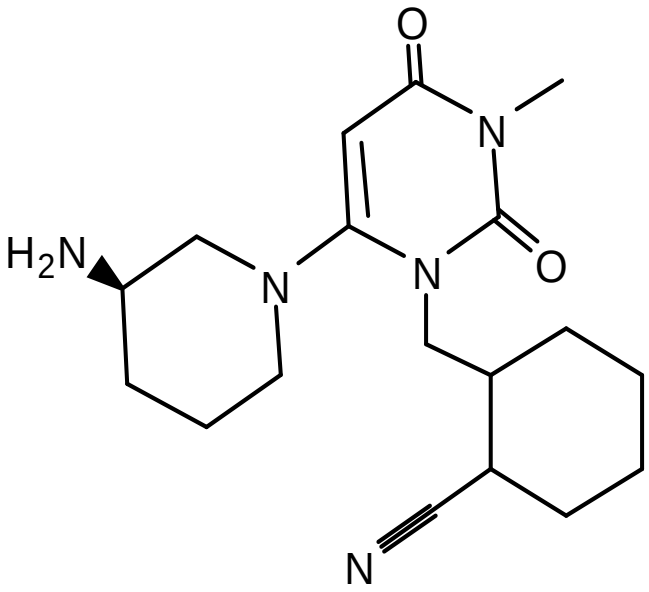


Table-2: DPP-IV inhibitors in various stages of clinical development:

NAME	COMPANY	STAGE IN DEVELOPMENT
SITAGLIPTIN	Merck	In market
VILDAGLIPTIN	Novartis	In market
ALOGLIPTIN	Takeda	Phase-III
SAXAGLIPTIN	Bristol-Myers Squibb	Phase-III
PSN-9301	OSI Pharmaceuticals	Phase-II
R1438	Roche	Phase-II
TA-6666	Tanabe	Phase-II
PHX1149	Phenomix	Phase-II
GRC8200	Glenmark Pharmaceuticals	Phase-II
SYR-619	Takeda	Phase-I
TS-021	Taisho Pharmaceuticals	Phase-I
SSRT62369	Sanofi-Aventis	Phase-I
ALS2-0426	Alantos Pharmaceuticals	Phase-I

FUTURE PROSPECTS:

- The therapeutic potential of inhibitors of post-proline cleaving enzymes like DPP-IV has been the focus of recent pharmaceutical research.

- DPP-IV inhibitors are evaluated being as monotherapies or in combination with other anti-diabetic drugs eg: metformin, thiozolidinediones, PPAR-□ agonists.
- Although human trails results in type-2 diabetes with DPP-IV inhibitors look promising, the lack of selectivity i.e; inhibition of the structurally related enzymes DPP-8 and DPP-9, has been a potential concern.
- Based on the crystal structure resolved, it is expected to develop certain therapeutic agents such as small peptide via binding to the catalytic binding site as a "substrate selective" DPP-IV inhibitors.
- Recently, one exiting finding is to show the activity of such DPP-IV inhibition is due to in part of their specific absorption by a small intestinal di- and tripeptides uptake transporter, PEPT1, thus establishing a system for optimising the orally active peptidomimetic drugs such as amino acid-based DPP-IV inhibitors.
- DPP-4 inhibitors mainly causes the progressive growth of the cancer in various tissues or in the body by decreasing the anti tumour activity and causes less lyososomal activity in the cells due to that the the choice of carcinogenicity is increased. This is the main problem araised in the clinical trials of the INDs of so many drugs.
- Most of the research is going on the DPP-4 inhibitors that mainly focussed to reduce the adverse effects that mainly causes tumour progression is to be considered.
- Metabolic control can be markedly improved by administration of exogenous GLP-1, but the native peptide is almost immediately degraded by the enzyme dipeptidyl peptidase IV (DPP IV) and, therefore, has little clinical value.
- Orally active inhibitors of DPP IV have now been developed and have been shown to enhance endogenous levels of GLP-1, resulting in improved glucose tolerance, lasting improvement of HbA1C and improved beta-cell function. In general the DPP IV inhibitors are weight neutral, and well tolerated.
- The beneficial effects of DPP-IV inhibitors on treatment for type-2 diabetes not only offer advantages over the current therapies but also provides more therapeutic applications beyond the treatment for diabetes due to the biological diversity of DPP-IV.

Conclusion: In general, the safety profiles of most DPP-IV inhibitors are very promising but additional studies are certainly needed to obtain a thorough insight in the *in vivo* effects of DPP-IV inhibition. The beneficial effects of DPP-IV inhibitors on treatment for type 2 diabetes not only offer advantages over the current therapies but also provide more therapeutic applications beyond the treatment for diabetes due to the biological diversity of DPP-IV. So far, there is no sufficient data available to make sweeping generalization about the long-term effects of various DPP-4 inhibitors on T-cell signalling and immune functions *in vivo*. The development of selective inhibitors of DPIV proteolytic activity and identification of ligand-binding activities in this gene family would lead to rapid advances in understanding DPIV biology.

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