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DPP-4 INHIBITORS IN THE TREATMENT OF TYPE-2 DIABETES

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Abstract:

Type 2 diabetes mellitus is a major and growing health problem throughout the world. Current treatment approaches include diet, exercise, and a variety of pharmacological agents including insulin, biguanides, sulfonylureas and thiazolidinediones. New therapies are still needed to control metabolic abnormalities, and also to preserve _-cell mass and to prevent loss of _-cell function. Glucagon-like peptide 1 (GLP-1) is a drug candidate which potentially fulfils these conditions. GLP-1 is an incretin hormone secreted by intestinal L-cells in response to meal ingestion is a novel pharmacological target with multiple antihyperglycemic actions. GLP-1 glucoregulatory actions include glucose-dependent enhancement of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying and reduction of food intake. GLP-1 is rapidly inactivated by amino peptidase, dipeptidyl peptidase IV (DPP-IV) and the utility of DPP-IV inhibitors are also under investigation. There is a recent upsurge in the development of GLP-1 mimetics and DPP-IV inhibitors as potential therapy for type 2 diabetes. However, both the strategies are having their own advantages and limitations. The present review summarizes the concepts of GLP-1 based therapy for type 2diabetes and the current preclinical and clinical development in GLP-1 mimetics and DPPIV inhibitors. Further, the potential advantages and the limitations of both the strategies are discussed

Key Words: DPP4, Diabetes, GLP-1

INTRODUCTION:-

Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Therapies for type 2 diabetes (T2DM) based on the actions of the incretin

hormone, glucagon like peptide-1 (GLP-1), were first introduced in 2005. GLP-1 is an intestinal hormone, which has been shown to play an important role in the normal regulation of glucose homeostasis. It has a number of effects that contribute to the maintenance of glucose tolerance, such as improvements in α- and β -cell function, including the glucose- dependent stimulation of insulin and suppression of glucagon secretion, as well as non-pancreatic effects such as delaying gastric emptying and suppression of appetite. These actions are preserved in patients with T2DM, and the first clinical- proof-of-concept study, published in 2002, showed that GLP-1 could reduce HbA1c levels in T2DM patients when given by continuous subcutaneous infusion.

GLP-1 is, however, a labile peptide and is rapidly removed from the circulation by a combination of degradation and renal clearance. The enzyme that is responsible for the initial cleavage of GLP-1 (whereby it loses its insulinotropic action) in vivo is the serine protease dipeptidyl peptidase (DPP)-4. The identification of its key role in the metabolic clearance of GLP-1 in humans provided the rationale for inhibiting the enzyme (in order to increase the levels of endogenous intact GLP-1) as a therapy of T2DM. Preclinical studies showing that DPP-4 inhibition could prevent the degradation of GLP-1 in vivo, leading to increased insulinotropic activity, were followed by the first demonstration in humans, that a DPP-4 inhibitor could improve glycaemic control in subjects with T2DM. The principle of using DPP-4 inhibitors as therapy of T2DM [1,6] is now firmly established, and numerous inhibitors are in varying stages of clinical development, with four already approved: sitagliptin in 2006, vildagliptin in 2007 and more recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan). The purpose of this article is to review briefly the five leading compounds in the DPP-4 inhibitor class (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin, currently in phase 3 clinical development), with special emphasis on any features which may help to distinguish between them.

The prevalence of type 2 diabetes mellitus (T2DM) is increasing and numerous reports have documented the sharply increasing incidence of T2DM in the industrialized Western world. World Health Organization predicts the number of patients diagnosed with T2DM will be more than >300 million by 2030. The high prevalence of diabetes is combined with the associated increased mortality and morbidity, primarily as a result of macrovascular disease and microvascular longterm complications (Zimmet et al., 2001; Mokdad et al., 2003).

T2DM results from both peripheral insulin resistance and impaired insulin secretion. Insulin resistance arises as a consequence of obesity, a sedentary lifestyle and aging, with resulting hyperglycemia and diabetes, blood pressure elevation and dyslipidemia collectively called ‘metabolic syndrome X’. Current treatment approaches for T2DM include diet, exercise, and a variety of pharmacological agents including insulin, biguanides, sulfonylureas and thiazolidinediones.

Adverse effects of these agents include hypoglycemia, weight gain and edema. In many cases monotherapy gradually fails to improve blood glucose control and combination therapy is employed. The long-term success of these treatments varies substantially. Thus, there is an imperative need for novel therapeutic approaches for glycemic control that can complement

existing therapies and possibly attempt to preserve normal physiological response to meal intake. One such approach is based on the action of the incretin hormone glucagon-like peptide 1(GLP-1). Incretins, the best understood of which are GLP-1 and glucose-dependent insulinotropic peptide (GIP), the gut peptides released in response to nutrient ingestion that increase insulin and metabolized by dipeptidyl peptidase IV (DPP-IV). GLP-1 is a peptide hormone from the intestinal mucosa. It is secreted in response to meal ingest and normally functions in the so-called ideal brake, i.e. inhibition of upper gastrointestinal motility and secretion when nutrients are present in the distal small intestine. It also induces satiety and promotes tissue deposition of ingested glucose by stimulating insulin secretion. In addition, GLP- 1 has been demonstrated to promote insulin biosynthesis and insulin gene expression and to have trophic effects on the _-cells. The trophic effects include proliferation of existing cells, maturation of new cells from duct progenitor cells and inhibition of apoptosis (Holst, 2003). This review summarizes recent research results for the pharmacological approaches based on GLP-1 towards antidiabetic therapy. It briefly touches upon the advantages that treatment of type 2 diabetes with GLP-1 mimetics and or DPP-IV inhibitor may offer over current medications. In the main section, several important structural classes of GLP-1 mimetics and DPP-IV inhibitors are described and compared based on literature data. Finally, as clinical data are steadily emerging for some of the most advanced development candidates, the last section of this review is providing a brief overview of some efficacy data from recent clinical studies with DPP-IV inhibitors.

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are enzyme inhibitors that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4) and are a potent treatment for type 2 diabetes. 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. Type 2 diabetes is a chronic metabolic disease that can be caused by pancreas β-cell dysfunction, deficiency in insulin secretion, insulin resistance and/or increased hepatic glucose production. It is one of the fastest growing health concerns in the world. Current treatments are often inefficient at sustaining glycemic control and may cause undesirable side effects, such as weight gain and episodes of hypoglycemia. Therefore, new and more effective drugs have been developed with DPP-4 inhibitors playing a significant role.

History:

Since its discovery in 1967, serine protease DPP-4 has been a popular subject of research. 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 (SAR) 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.[3] DPP-4 is adipeptidase that selectively binds substrates that contain proline at the P1-position, thus many DPP-4 inhibitors have 5-membered heterocyclic ring that mimic proline, pyrrolidine, cyanopyrrolidine thiazolidine and

cyanothiazolidine. These compounds commonly form covalent bonds to the catalytic residue Ser630.

In 1994, researchers from Zeria Pharmaceuticals unveiled cyanopyrrolidines with a nitrile function group that was assumed to form animidate 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 (PEP) 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, Ed win B. Villhauer at Novartis started to explore N-substituted glycinyl-cyanopyrrolidines based on the fact that DPP-4 identifies N-methylglycine as a 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 vasopeptidase have been represented, since vasopeptidase inhibition is believed to enhance the antidiabetic effect of DPP-4 inhibition by stimulating insulin secretion. Vasopeptidase-inhibiting motif is connected to the DPP-4 inhibitor at the N-substituent.

Chemistry

As a therapeutic class, the DPP-4 inhibitors comprise a diverse group of compounds, which can be broadly divided into those that mimic the dipeptide structure of DPP-4 substrates and those which are non-peptidomimetic. Compounds such as sitagliptin (β-amino acid based), and vildagliptin and saxagliptin which are nitrilecontaining inhibitors, belong to the former class, whereas alogliptin (modified pyrimidinedione) and linagliptin (xanthine-based) are members of the latter.. The compounds which have been developed for therapeutic use are all competitive reversible inhibitors, which display high affinity for DPP-4, resulting in inhibition constants (Ki) in the low nanomolar range. There are, however, differences in the way in which they interact with the enzyme.

Thus, sitagliptin, alogliptin and linagliptin form non-covalent interactions with residues in the catalytic site. In contrast, inhibition of DPP-4 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 and may help to explain why vildagliptin and saxagliptin inhibit DPP-4 activity for longer than their relatively short half-lives would suggest. This may have repercussions in terms of their durations of action and dosing frequencies (see below).

DPP-4 mechanism

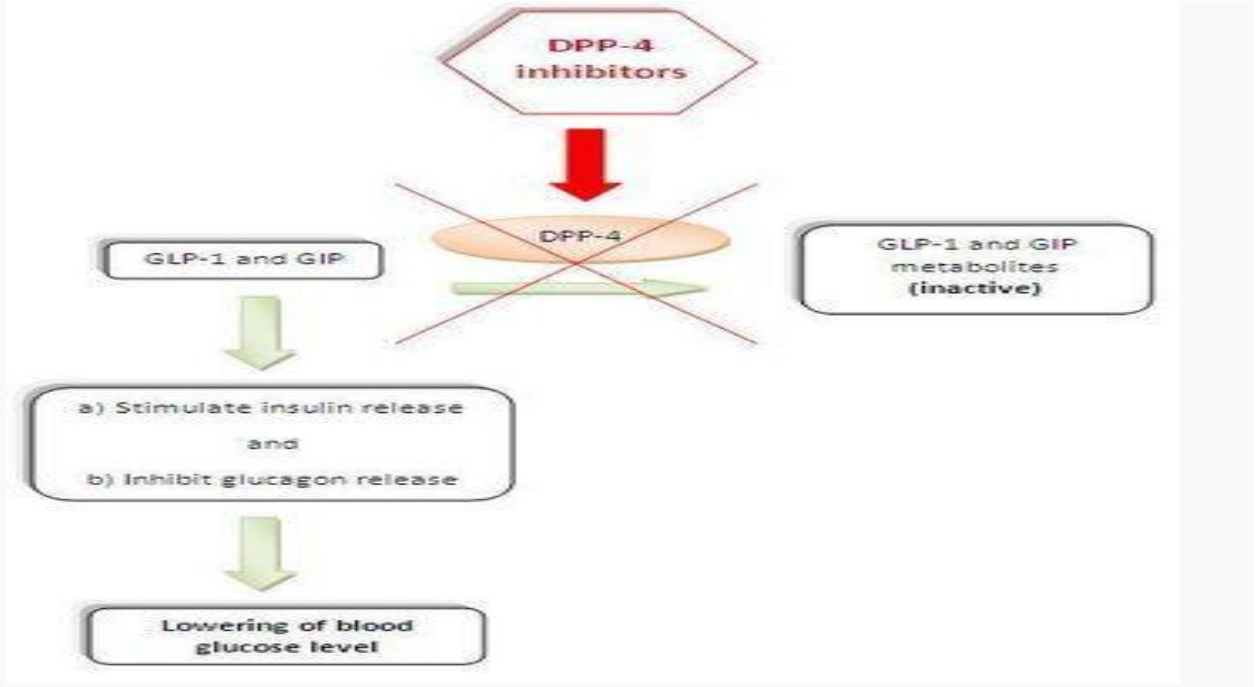

Fig.1: DPP-4 inhibitors inhibit DPP-4 and thus prolong the duration of GLP-1 and GIP activity, resulting in lower blood glucose level.

During a meal the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent gastric inhibitory polypeptide (GIP) are released from the small intestine into the vasculature. The hormones regulate insulin secretion in a glucose-dependent manner. GLP-1 has many roles in the human body; it stimulates insulin biosynthesis, inhibits glucagon secretion, slows gastric emptying, reduces appetite and stimulates regeneration of islet β-cells. GIP and GLP-1 have extremely short plasma half-lives due to a very rapid inactivation. Theenzyme responsible for the metabolism is DPP-4. Inhibition of DPP-4 leads to potentiation of endogenous GIP and GLP-1 and hence improves treatment of type 2diabetes.

DIABETES MELLITUS TREATMENT:-

The goal of diabetes management is to keep blood glucose levels as close to normal as safely possible. Since diabetes may greatly increase risk for heart disease and peripheral artery disease, measures to control blood pressure and cholesterol levels are an essential part of diabetes treatment as well.

People with diabetes must take responsibility for their day-to-day care. This includes monitoring blood glucose levels, dietary management, maintaining physical activity, keeping weight and stress under control, monitoring oral medications and, if required, insulin use via injections or pump. To help patients achieve this, UCSF's Diabetes Teaching Center offers self-management

educational programs that emphasize individualized diabetes care. The program enables patients to make more consistent and appropriate adjustments in their therapy and lifestyle.

DIETARY MANAGEMENT AND PHYSICAL ACTIVITY:-

Modifying eating habits and increasing physical activity are typically the first steps toward reducing blood sugar levels. At UCSF Medical Center, all patients work with their doctor and certified dietician to develop a dietary plan. Our Teaching Center conducts workshops that provide patients with information on food nutrient content, healthy cooking and exercise.

Insulin Therapy

People with type 1 diabetes require multiple insulin injections each day to maintain safe insulin levels. Insulin is often required to treat type 2diabetes too. Using an insulin pump is an alternative to injections. The pump is about the size of a pager and is usually worn on your belt.

Insulin is delivered through a small tube (catheter) that is placed under the skin (usually in the abdomen).

There are four major types of insulin:

- Rapid-acting
- Short-acting
- Intermediate-acting
- Long-acting

Your doctor will determine your dose and how often you need to take insulin. There is no standard insulin dose as it depends on factors such as your body weight, when you eat, how often you exercise and how much insulin your body produces.

Oral Medications

Sometimes blood sugar levels remain high in people with type 2 diabetes even though they eat in a healthy manner and exercise. When this happens, medications taken in pill form may be prescribed. The medications work in several different ways. These include improve the effectiveness of the body's natural insulin, reduce blood sugar production, increase insulin production and inhibit blood sugar absorption.Oral diabetes medications are sometimes taken in combination with insulin.

After many years, diabetes can lead to other serious problems:

- You could have eye problems, including trouble seeing (especially at night) and light sensitivity. You could become blind.
- Your feet and skin can get painful sores and infections. Sometimes, your foot or leg may need to be removed.
- Nerves in the body can become damaged, causing pain, tingling, and a loss of feeling.

Drugs belonging to this class are:

- sitagliptin (FDA approved 2006, marketed by Merck & Co. as Januvia),
- vildagliptin (EU approved 2007, marketed in the EU by Novartis as Galvus),
- saxagliptin (FDA approved in 2009, marketed as Onglyza),
- linagliptin (FDA approved in 2011, marketed as Trajenta by Eli Lilly Co and Boehringer Ingelheim)
- dutogliptin (being developed by Phenomix Corporation), Phase III
- gemigliptin (being developed by LG Life Sciences,Korea)[9]
- alogliptin (FDA approved 2013, marketed by Takeda Pharmaceutical Company)
- Berberine, the common herbal dietary supplement, too inhibits dipeptidyl peptidase-4, which at least partly explains its antihyperglycemic activity.

COMPARISON:-

- The following table compares some common anti-diabetic agents, generalizing classes, although there may be substantial variation in individual drugs of each class. When the table makes a comparison such as "lower risk" or "more convenient" the comparison is with the other drugs on the table

Comparison of anti-diabetic medication			
Agent	**mechanism**	**advantages**	**disadvantages**
• Sulfonylurea (glyburide,glimepiride, glipizide)	• Stimulating insulin release by pancreatic beta cells by inhibiting theKATP channel	• Fast onset of action • No effect on blood pressure • No effect on low-density lipoproteinn inexpensive lower risk of gastrointestinalprobles than with metformin more convenient dosing	• causes an average of 5–10 pounds weight gain • Increased risk of hypoglycemia • Glyburide has increases risk of hypoglycemia slightly more as compared with glimepiride and glipizide • Higher risk of death compared with metformin.
• Metformin	• Acts on liver to cause decrease in insulin resistance	• not associated with weight gain low risk of hypoglycemia as compared to	• increased risk of gastrointestinal problems • Contraindicated for people with moderate or severe

		alternatives • Good effect on LDL cholesterol • Decreases triglycerids • no effect on blood pressure inexpensive	kidney disease or heart failure because of risk of lactic acidosis increased risk of Vitamin B12 deficiency less convenient dosing Metallic taste
• Alpha-glucosidase inhibitor (acarbose,miglitol)	• Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates	• slightly decreased risk of hypoglycemia as compared to sulfonylurea • not associated with weight gain • decreases triglycerides • no effect on cholesterol	• less effective than most other diabetes pills in decreasing glycated hemoglobin • increased risk of GI problems than other diabetes pills • except metformin • inconvenient dosing • expensive

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

STRUCTURE-ACTIVITY RELATIONSHIP (SAR):-

Important structure-activity relationship:

1. Strict steric constraint exists around the pyrrolidine ring of cyanopyrrolidine-based inhibitors, with only hydrogen, fluoro, acetylene,nitrile, or methano substitution permitted.

2. Presence of a nitrile moiety on the pyrrolidine ring is critical to achieving potent activityAlso, systematic SAR 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. It was originally believed that only lipophilic substitution would be tolerated. Now it is stated that also the substitution of polar negatively charged side-chains as well as hydrophilic substitution can lead to excellent inhibitory activity.

Chemical stability

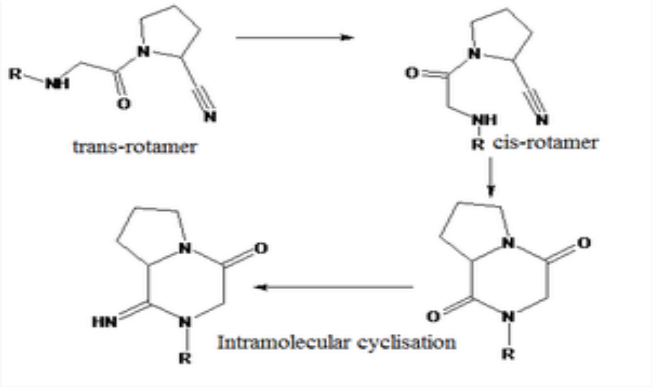

Fig.5: Trans-rotamers are more stable then cis-rotamers. Cis-rotamers undergo intramolecular cyclisation.

In general, DPP-4 inhibitors 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, vildagliptinand saxagliptin, were created in this manner. K579 is a DPP-4 inhibitordiscovered by researchers at Kyowa Hakko Kyogo. It had improved not only chemical stability but also a longer-lasting action. That long-lasting action was most likely 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. One major problem in DPP-4 inhibitor stability intramolecular cyclisation. The precondition for the intramolecular cyclisation is the conversion of the trans-rotamer, which is the DPP-4 binding rotamer (Figure 5). 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, did not undergo the intramolecular cyclisation and was even more selective over different DPP enzymes. It has also been reported that a cyanoazetidine in the P1 position and a β-amino acid in the P2 position increased stability.

Risks

Long-term effects of DPP-4 inhibitors on mortality and morbidity are so far inconclusive, although adverse effects, including nasopharyngitis (the common cold), headache, nausea,

hypersensitivity and skin reactions, have been observed in clinical studies. Other possible adverse effects, including hypersensitivity reactions and pancreatitis, have been reported.

CONCLUSION:-

The DPP-4 inhibitors are the first new therapeutic class of oral antihyperglycaemic drug for T2DM for many years. They were designed for the treatment of the disease based on prior knowledge of the physiology of the incretin hormone GLP-1 and an understanding of the target (DPP-4), contrasting with the development of other antidiabetic agents whose blood glucose-lowering effects were initially discovered more by chance than by design without fully knowing the underlying mechanisms (e.g. metformin, sulphonylureas and glitazones). Identification of the 3-dimensional/tertiary structure of the DPP-4 protein allowed the rational design of small molecule inhibitors which interact only with the catalytic site without interfering in any of the other functions of the DPP-4/CD26 molecule. This, together with the understanding of the role of GLP-1 in glucose homeostasis and its unique susceptibility to cleavage by DPP-4, probably accounts for the remarkable lack of adverse effects so far associated with the therapeutic use of the DPP-4 inhibitors.

As a class, the DPP-4 inhibitors comprise of a group of chemically diverse compounds, which differ in terms of their potency to inhibit the DPP-4 enzyme, their duration of action and their metabolism and elimination, as well as isolated compound-specific characteristics (Table 5). They are all apparently well tolerated (side-effect profile resembles placebo) and result in clinically meaningful reductions in blood glucose (fasting and postprandial) and HbA1c levels, with minimal risk of hypoglycaemia and without weight gain — in this latter respect, they are better than all other agents except metformin and the incretin mimetics. They are used without the need for dose titration and give broadly similar HbA1c lowering efficacy to other oral antidiabetic agents; they are compatible with first-line therapy and they give predictable additivity to other agents, where they can be used without dose adjustment of either agent.

At present, although there are some practical differences between the different DPP-4 inhibitors with respect to dosing frequency and their ability to be used in different patient subpopulations, there seems to be little to distinguish between them in terms of their efficacy as antidiabetic agents and their safety. Only long-term accumulated clinical experience will reveal whether compound-related characteristics lead to any clinically relevant differences.

REFERENCE:-

1. Deacon CF. Therapeutic strategies based on glucagon-like peptide 1.Diabetes 2004; 53: 2181–2189.
2. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and betacell function in type 2 diabetes: a parallel-group study. Lancet 2002; 359: 824–830.

3. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes 1995; 44: 1126–1131.
4. Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. Diabetes 1998; 47: 764–769.
5. Liu, L. T.; Lin, Y.; Wang, C. J.; Lin, M.; Yen, S.; Chen, H. Bioorg. Med. Chem. Lett. 1996, 1335.
6. (a) Ferna´ndez, R.; Matheu, M. I.; Echarri, R.; Castillo´ n, S. Tetrahedron 1998, 54, 3523; (b) Demange, L.; Me´ndez, A.; Dugave, C. Tetrahedron Lett. 1998, 39, 1169.
7. For assay conditions, see: Leiting, B.; Pryor, K. D.; Wu, J. K.; Marsilio, F.; Patel, R. A.; Craik, C. S.; Ellman, J. A.; Cummings, R. T.; Thornberry, N. A. Biochem. J. 2003, 371, 525.
8. Abbot, C. A.; Yu, D. M.; Woollatt, E.; Sutherland, G. R.; McCaughan, G. W.; Gorrell, M. D. Eur. J. Biochem. 2000, 267, 6140.
9. Olsen, C.; Wagtmann, N. Gene 2002, 299, 185.
10. Scallan, M. J.; Raj, B. K. M.; Calvo, B.; Garin-Chesa, P.; Sanz-Moncasi, M. P.; Healey, J. H.; Old, L. J.; Rettig, W. J. Proc. Natl. Acad. Sci. U.S.A. 1994, 91, 5657.
11. McDonald, J. K.; Leibach, F. H.; Grindeland, R. E.; Ellis, S. J. Biol. Chem. 1968, 243.
12. Lankas, G. R.; Leiting, B.; Sinha Roy, R.; Eiermann, G. J.; Beconi, M. G.; Biftu, T.; Chan, C.-C.; Edmondson, S.; Feeney, W. P.; He, H.; Ippolito, D. E.; Kim, D.; Lyons, Diabetes 2005, 54, 2988.