ejpmr, 2015,2(4), 935-946

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

AN ELABORATIVE STUDY ON DIPEPTIDYL PEPTIDASE-IV INHIBITORS IN THE MANAGEMENT OF DIABETES

Gaurav Kayal*[1] and Snehlata Kayal[2]

[1]Modern Institute of Pharmaceutical Sciences, Indore, M.P., India.

[2]Smriti College of Pharmaceutical Education, Indore, M.P., India.

Article Received on 08/06/2015 **Article Revised on 29/06/2015** **Article Accepted on 20/07/2015**

***Correspondence for Author**

Gaurav Kayal

Modern Institute of Pharmaceutical Sciences, Indore, M.P., India.

ABSTRACT

Type-2 diabetes mellitus is a metabolic disorder due to insulin resistance, reduced insulin sensitivity or reduced insulin secretion. This form of diabetes is commonly treated with a range of drugs designed to increase insulin production, decrease insulin resistance, decrease glucose production by the liver or slow intestinal absorption of carbohydrates. One recent advance in the management of type 2 diabetes has been the development and clinical use of DPP-4 inhibitors. The development of this class of drug was based upon observations from the early twentieth century when it was noted that factors secreted from the gut participated in the regulation of pancreatic endocrine secretion. These factors were collectively termed 'incretins'. Several drugs are presently available to reduce hyperglycemia such as sulfonylureas and biguanids. These drugs have various side effects as reported in literatures and thus searching for a new class of compounds is essential to overcome these problems. The purpose of this study is to review the Anti-Diabetic potentials of various DPP-IV inhibitors and to generate a comparative SAR that may support to improve their anti-hyperglycaemic activity by newer and potent diverse structural modifications of synthesized derivatives.

KEYWORDS: DPP-IV inhibitors, structural diversity, anti-hyperglycaemic activity.

1. INTRODUCTION

DPP-4 (Dipeptidyl Peptidase-IV) inhibitors work to potentiate the effect of incretin hormones that are secreted from the gastrointestinal tract into the bloodstream in response to food intake. incretin hormones includes GLP-1 (Glucagon Like Peptide-1) and glucose-

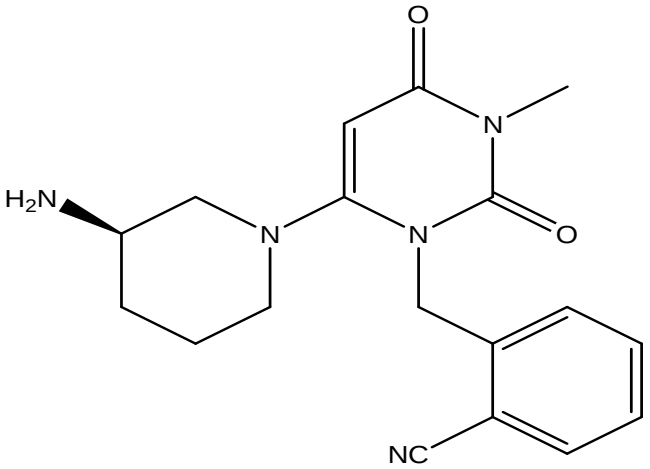
dependent insulin topic polypeptide, also known as gastric inhibitory peptide (GIP). GLP-1, in particular, appears to be responsible for the majority of the in cretin effects on the pancreatic β-cell function.[1],[2] Despite their common mechanism of action, the DPP- 4 inhibitors show marked differences in their chemical structure.[3] They do not show significant drug-drug interactions the fact can be explained by their favorable pharmacokinetic characteristics and their low plasma protein binding.[4,5] In short term studies these inhibitors have been found to be well tolerated. Common reported adverse effects include nasopharyngitis, urinary tract infections, pancreatitis and headaches, anaphylactic reactions, angioedema and exfoliative dermatological reactions.[6]

One of the first DPP-4 inhibitors employed as a biological tool to understand DPP-4 was a tripeptide (Ileum-Pro-Ileum) called disporting A.[7,8] Structural studies using human DPP-4 revealed that disporting A covalently bonded to Ser630 in the catalytic site and this irreversibly blocked the enzyme active site.[9] First DPP-4 inhibitors to be developed and tested in animal models of type 2 diabetes was P32/98 (isoleucine thiazolidide). Its Oral administration acutely improved glucose tolerance in Sucker fatty rats.[10] Chronic treatment (12 weeks) of Suckers rats with P32/98 improved glucose tolerance and increased plasma insulin levels, Another inhibitor, LAF-237 (later named vildagliptin), dose-dependently controlled glycaemia in insulin-resistant rats over a three-week period.[11] Another inhibitor called NVP-DPP728 improved glucose tolerance and increased the circulating levels of active GLP-1.[12]

Considering DPP-IV as a promising target for lowering glucose levels is supported by rodents analysis with inactivating DPP-IV mutations. The levels of glycemic excursion were reduced after glucose loading in DPP-IV knockout mice and the Fischer DPP-IV mutant rat conforming the increased levels of circulating GLP-1 and insulin.[13,14] DPP-IV inhibitors were found to lower the blood glucose via the mechanisms based on incretion action which also leads to improved glucose-stimulated insulin secretion.[15,16]

2. COMPARATIVE STUDY OF DPP-IV INHIBITORS

2.1 Modification on piperidine nucleus of Alogliptin: Kodimuthali, A.[17] reported the synthesis of Alogliptin analogue by condensation in which one of the derivatives bears a spirocyclic ring on the piperidine moiety. They carried out the preparation of this intermediate by preparing Cyclopropyl ring before the piperidine moiety.[17]



(*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile

Fig.1 Alogliptin

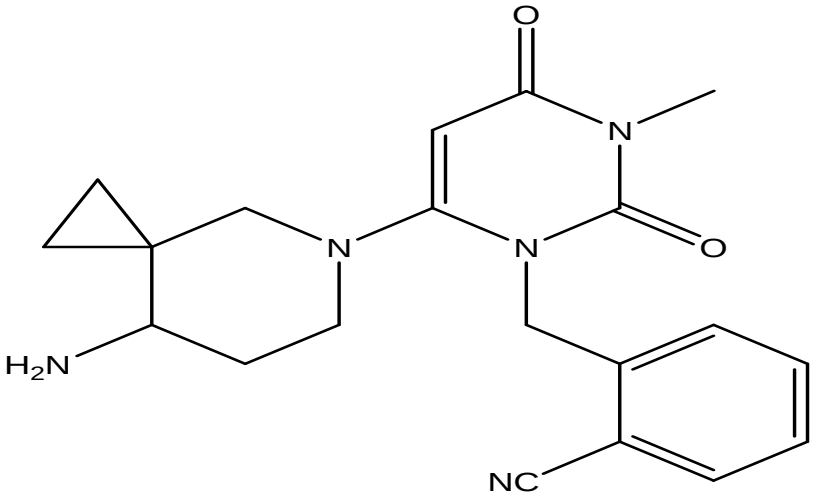


Fig.2 Compound C

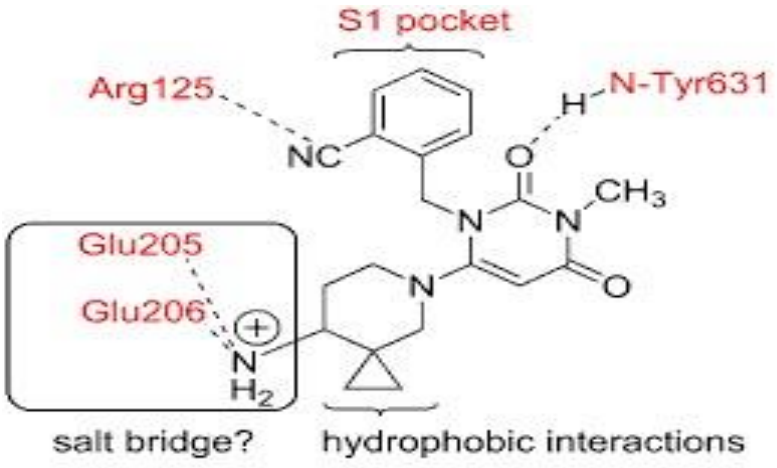


Fig.3 Interaction sites for other DPP-IV Inhibitors [17]

They tested compound C (fig.2) for its ability to inhibit DPP-4 enzyme in vitro.[17] They observed a significant inhibition of DPP-4 which was however less potent than Alogliptin (fig.1). Cyclopropyl ring might be residing in the empty space to develop the hydrophobic interactions with DPP-4 but the aminopiperidine motif of C (fig.3) could not form an effective salt bridge to Glu205/Glu206 leading to lower potency of C (fig.1) in comparison to Alogliptin (fig.1).

2.2 Combination of DPP-IV inhibitors and pioglitazone: Mikhail, N.[18] described about the Combination therapy with DPP-4 inhibitors and pioglitazone in type-2 diabetes. The combination was found to have no significant effect on the insulin sensitivity during the ongoing pioglitazone therapy. (Rosenstock et al 2006). The combination was also found to have negligible effect or slight exacerbation of weight gain by pioglitazone.[18]

Table1: Advantages and limitations of the DPP-4 inhibitor/ pioglitazone combination[18]

Advantages	Limitations
1. DPP-4 inhibitors generally maintain consistent efficacy for HbA1c reduction similar to trials of immunotherapy of DPP-4 inhibitors. 2. Easy administration with possible once daily dosing irrespective of meal intake. 3. Generally well tolerated. 4. No increase in risk of hypoglycemia. 5. Absence of or minimal extra weight gain (~1 kg) compared with pioglitazone immunotherapy 6. Can be particularly useful in patients who cannot take motorman or sulfonylurea 7. Can be used with renal insufficiency	1. Moderate efficacy 2. Associated with weight gain (~1.5 kg on the average) and edema (3%–9%) attributed to the pioglitazone component. 3. Lack of long-term efficacy and safety data on the DPP-4 inhibitors 4. Relatively high cost 5. Bias in presenting data cannot be ruled out.

2.3 Mechanisms for anti-hyperglycemic effect of sitagliptin

Muscelli *et al.*[19] reexamined the mechanism of glucose-lowering effect by sitagliptin. They performed two studies, one at baseline and the other after a period of six weeks. They also investigated the measurement of glucose fluxes before and after treatment via a dual-label mixed meal. They observed that Sitagliptin suppressed the endogenous glucose production and decreased meal appearance due to improved β-cell function and decreased glucagon concentrations. Their data enthrallingly described the favorable effect of DPP-4 inhibition on insulin action.

2.4 DPP-IV inhibition in NOD (Non-Obese Diabetic) Mice with Overt Diabetes

L. Vargová *et al.*[20] reported that fully developed diabetes with sustained hyperglycemia was diagnosed in all mice at the time of inclusion into the sitagliptin (Fig.4) or the diabetic control

groups. The glycaemia control was not improved in the sitagliptin group compared to the diabetic control group. Treatment with sitagliptin did not increase the number of remissions as it is seen in the curves of glycaemia (fig.5A & 5B). In both diabetic groups, one case of remission was observed out of 28 mice.

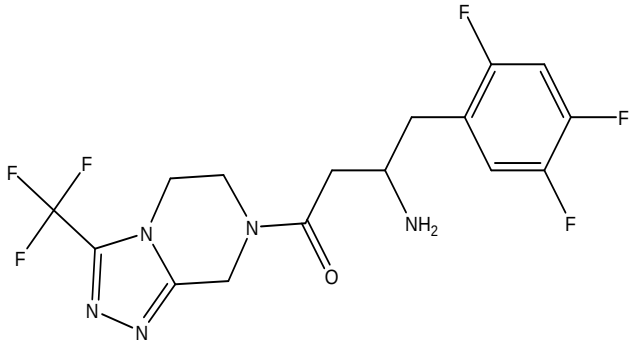


Fig.4 Sitagliptin

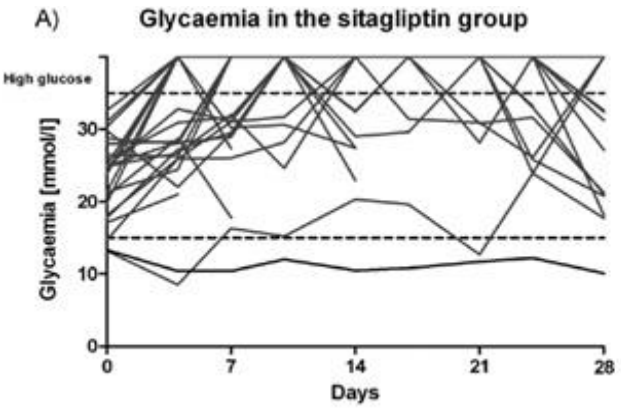


Fig. 5(A)Curves of Glycaemia after sitagliptin administration[20]

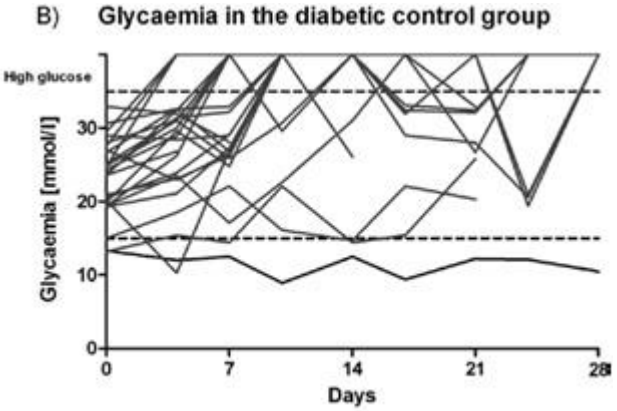


Fig. 5(B) Curves of Glycaemia in the diabetic control group[20]

2.5 Renoprotection in Diabetic Nephropathy by DPP-IV Inhibition: Panchapakesan *et al.*[21] hypothesized that DPP IV is involved in the processing of luminal peptides influencing the kidney tubulointerstitium in diabetes. HK2 cells (human kidney proximal tubular cell line) were used to expose PTC cells to high glucose conditions. Markers like DPP4, fibronectin, collagen IV, transforming growth factor beta (TGFβ), activator protein 1(AP-1) and nuclear factor-kappa B (NF-κB) were measured. They showed that linagliptin interferes with the activation of TGFβ and downstream reduction in fibronectin but not collagen IV expression. Linagliptin reduced High Mobility Group Box 1 protein (HMGB1) and high glucose induced AP-1 binding but not high glucose induced NF-κB binding.[22] They hypothesized that the DPP-IV alters the regulation of peptides in the lumen and affects the tubulointerstitium in diabetes patients.[21]

2.6 Saxagliptin as a selective DPP-IV inhibitor: Shubrook *et al.*[23] reviewed Saxagliptin as a selective DPP-4 Inhibitor for the treatment of Type 2 Diabetes Mellitus. They described that Saxagliptin is a once daily DPP-4 inhibitor that is safe and efficacious for the treatment of type 2 diabetes. They also described that being having limited side effects, single day dosing and limited drug interactions it is considered as a new agent to treat type 2 diabetes. They also included that Saxagliptin can be used as monotherapy or in combination with metformin, sulfonylureas, or pioglitazone. It is a much more potent DPP-4 inhibitor in comparison with other DPP-4 inhibitor available in the United States (sitagliptin), but is clinically insignificant when comparing duration of action or clinical efficacy. They have detailed about a study [24] which shows that the combination therapy of Saxagliptin with metformin had shown improved results when compared to metformin alone.

Rosenstock et al[25] examined the safety and efficacy of saxagliptin in both high and low dose of antidiabetic drug in type 2 diabetic patients with a baseline HbA1c ≥ 6.8 to 9.7%. Results showed that there was a 0.7%–0.9% reduction from the average baseline HbA1c of 7.9% vs. placebo. Saxagliptin also showed significant placebo-subtracted reductions in fasting serum glucose and 1 hour postprandial glucose levels.

Rosenstock et al[26] had also conducted a randomized placebo-controlled trial that examined the effect of saxagliptin on a variety of endpoints concerning glucose control. Statistically significant lowering of HbA1c and FPG was observed with saxagliptin treatment at all doses. Significant lowering of the area under the curve (AUC) for fasting plasma glucose (FPG) and postprandial glucose (PPG) was also observed.

2.7 Vildagliptin as a selective DPP-IV inhibitor: Kalra S[27] had described the emerging role of Vildagliptin in type II diabetes. Vildagliptin was found to have an IC_{50} value of 4.5 nmol/L of DPP-4 inhibition which was more potent than sitagliptin having IC_{50} of 26 nmol/L.[28-29] The drug was found to increase the effect of GLP-1 and GIP on islet cells and promoting glucose-dependent insulin secretion by prolonging their half-lives. Vildagliptin seems to reduce the glucose dependent β-cell function and improve insulin sensitivity along with the enhanced sensitivity of α-cells towards glucose.[30]

The therapeutic efficacy of oral vildagliptin was investigated as monotherapy and in combinations. Greater reduction in HbA1c levels from baseline was seen with Vildagliptin compared with placebo after 12 weeks treatment.[29,31]

Vildagliptin has also been evaluated in combination therapy to metformin, Sulphonylureas, Thiazolidinediones and insulin treatment and in initial combination with pioglitazone. Vildagliptin and metformin were administered as separate agents in all the trials.[33-42] Out of this Four trial were placebo controlled[33-35],[37] and one each had pioglitazone[37] and TZDs[39] and two had glimepiride[38,40] as comparative agent. In T2DM patients Vildagliptin achieved greater glycemic control as compared with placebo, as an add-on to metformin,[33] pioglitazone[34] and glimepiride[35] therapy and was as effective as pioglitazone, when added to metformin but without weight gain as associated with pioglitazone therapy.[36] Among the various novel analogs of orally administered DPP-4 inhibitors vildagliptin seems to be the most efficacious drug for improving glycemic control in diabetic patients.[27]

2.8 Isoindoline derivatives as DPP-IV inhibitors: Kato *et al.*[43] described synthesis and pharmacological characterization of isoindoline Dipeptidyl peptidase IV inhibitors. Various isoindolines were synthesized (Table2) and evaluated in vitro for the inhibitory effect on human recombinant DPP-IV and for their selectivity over DPP-8/9. Monosubstituted benzene ring of Compound A was well tolerated with retention of high level of selectivity. Disubstitution over the benzene ring led to decreased potency (Compound B, Compound C).

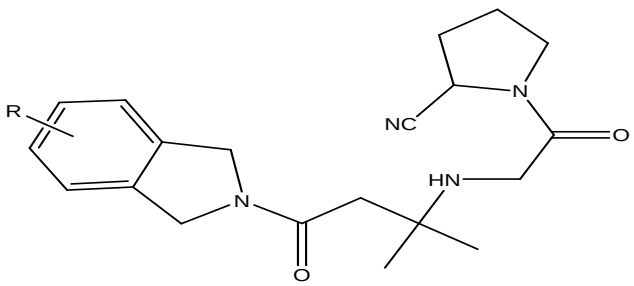


Fig.5 Isoindoline derivative[43]

Table2: Isoindoline derivatives with better DPP-IV inhibition[43]

Compound	R	IC_{50} (nM) (DPP-IV)[43]
A	-H	23
B	5,6-dichloro	22
C	4-Meo, 6-Me	16

3. CONCLUSION

The development of DPP-4 inhibitors has recently emerged as an approach that appears to be promising for the treatment of type 2 diabetes. They represent an important class of compounds that provide an alternative to other traditional therapies that are used in the management of type 2 diabetes. Although they do not appear to lower glucose to a greater extent than existing therapies although they offer the potential advantage of a low risk of hypoglycemia and weight gain when used alone. DPP-IV inhibitors have promising clinical results and may replace the current conventional therapy such as insulin injection, metformin, and sulfonylurea in type-2 diabetics whose represent more than 90% of diabetic patients. DPP-4 inhibitors such as sitagliptin and vildagliptin are also effective in controlling diabetes as monotherapy and combination therapy, including their use with insulin. On modifying the structure of Alogliptin the potency was found to be lowered due to steric properties, thus the position of amino group on the piperidine ring of Alogliptin must not be altered for the activity. Sitagliptin, Saxagliptin, Linagliptin and Vildagliptin have served as potent DPP-IV inhibitors and have significantly contributed to the blood glucose lowering in diabetic manifestations. Isoindoline derivatives have showed promising inhibition of DPP-IV and can be further modified structurally to develop more potent analogs. The presently available derivatives thus could be modified structurally for the development for better and potent DPP-IV inhibitors to combat diabetes in a much better way.

4. ACKNOWLEDGEMENT

We are highly obliged to the Principal of Modern Institute of Pharmceutical Sciences, Indore and Principal of Smriti College of Pharmaceutical Education for providing the facilities and their guidance in searching articles and journals which are of great help for the completion of this review article.

5. REFERENCES

1. Rucker DJ: Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. Expert Open Investing Drugs, 2003; 12: 87–100.

2. Amok A, Ascott-Evans BH, Berg GI, et al. The 2012 SEMDSA guideline for the management of type-2 diabetes (revised). JEMDSA. 2012; 17(2).
3. Neumiller JJ., Differential chemistry (structure), mechanism of action and pharmacology of GLP-receptor agonists and DPP-4 inhibitors. J Am Pham Assoc. 2009; 49 Suppler: S16-S29.
4. Scène AJ. Dipeptidyl peptitase-4 inhibitors (gelatins). Focus on drug-drug interactions. Clint Pharmacokinetics. 2010; 49(9): 573-588.
5. Pathway R, Bridgeman MB., Dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of diabetes. PT. 2010; 35(9): 509-513
6. Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. Diabetes Care. 2011; 34 Supplement 2: S276 -S278.
7. Abbott CA, Gorrell, MD, The family of CD26/DPIV and related ectopeptidases in ectopeptidases: CD13/ aminopeptidase N and CD26/Dipeptidyl peptidase IV. In: Langer J, Ansorge S (eds), Medicine and Biology, New York: Kluwer/Plenum, 2002: 171–91.
8. Green BD, Liu HK, McCluskey JT, et al., Function of a long-term, GLP-1-treated, insulin-secreting cell line is improved by preventing DPP IV-mediated degradation of GLP-1, Diabetes Obes Metab, 2005; 7: 563–9.
9. Rahfeld J, Schierhorn M, Hartrodt B, et al., Are diprotin A (Ile-Pro-Ile) and diprotin B (Val-Pro-Leu) inhibitors or substrates of dipeptidyl peptidase IV, Biochim Biophys Acta, 1991; 1076: 314–6.
10. Thoma R, Löffler B, Stihle M, et al., Structural basis of proline-specific exopeptidase activity as observed in human dipeptidyl peptidase-IV, Structure, 2003; 11: 947–59.
11. Pederson RA, White HA, Schlenzig D, et al., Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide, Diabetes, 1998; 47: 1253–8.
12. Burkey BF, Li X, Bolognese L, et al., Acute and chronic effects of the incretin enhancer vildagliptin in insulin resistant rats, J Pharmacol Exp Ther, 2005; 315: 688–95.
13. Holst JJ, Deacon CF: Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes, 1998; 47: 1663–1670.
14. Marguet D, Baggio L, Kobayashi T, Bernard AM, Pierres M, Nielsen PF, Ribel U, Watanabe T, Drucker DJ, Wagtmann N: Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. Proc Natl Acad Sci U S A, 2000; 97: 6874–6879.

15. Nagakura T, Yasuda N, Yamazaki K, Ikuta H, Yoshikawa S, Asano O, Tanaka I: Improved glucose tolerance via enhanced glucose-dependent insulin secretion in dipeptidyl peptidase-IV deficient Fischer rats. Biochem Biophys Res Commun, 2001; 284: 501–506.
16. Ahren B, Holst JJ, Martensson H, Balkan B: Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice. Eur J Pharmacol, 2000; 404: 239–245.
17. Kodimuthali A, Synthesis of a novel analogue of DPP-IV inhibitor Alogliptin: Introduction of a spirocyclic moiety on the piperidine ring, Beilstein J. Org. Chem. 2010; 6: 71.
18. Nasser Mikhail the theoretical consideration and therapeutic potential of Combination therapy with DPP-4 inhibitors and pioglitazone in type 2 diabetes Vascular Health and Risk Management 2008; 4(6): 1221–1227.
19. Muscelli E, Casolaro A, Gastaldelli A, Mari A, Seghieri G, Astiarraga BD, Chen Y, AlbaM, Holst Jj J, Ferrannini E, Mechanisms for the antihyperglycemic effect of sitagliptin in patients with type 2 diabetes. J Clin Endocrinol Metab, 2012; 97: 2818–2826.
20. Vargova L., Zacharovova K., The Effects of DPP-IV Inhibition in NOD Mice with Overt Diabetes, Folia Biologica (Praha), 2013; 59: 116-122.
21. Panchapakesan, DPP4 Inhibition in Human Kidney Proximal Tubular Cells Renoprotection in Diabetic Nephropathy, J Diabetes Metab 2013; S9.
22. Stiller D, Bahn H, August C Demonstration of glomerular DPP IV activity in kidney diseases. Acta Histochem, 1991; 91: 105-109.
23. Shubrook et al., Saxagliptin: A Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus, Clinical Medicine Insights: Endocrinology and Diabetes 2011: 4.
24. DeFronzo RA, Hissa M, Garber AJ, et al. The Efficacy and Safety of Saxagliptin when added to metformin therapy in patients inadequately controlled type 2 diabetes on metformin alone. Diabetes Care. 2009; 32(9): 1649–55.
25. Rosenstock J, Sankoh SL, L JF., Glucose-lowering activity of the Dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type-2 diabetes. Diabetes Obes Metab. 2008; 10: 376–86.
26. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment naïve patients with type 2 diabetes. Curr Med Res Opin. 2009. epub.

27. Kalra S, Emerging Role of Dipeptidyl Peptidase-IV (DPP-4) Inhibitor Vildagliptin in the Management of Type 2 Diabetes, JAPI april 2011; 59: 237-245.
28. Herman GA, Stevens C, Van Dyck K, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of Dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther 2005; 78: 675-88.
29. He YL, Wang Y, Bullock JM, et al. Pharmacodynamics of vildagliptin in patients with type 2 diabetes during OGTT analyses. J Clin Pharmacol, 2007; 47: 633-41.
30. Croxtall JD, Keam SJ. Vildagliptin: a review of its use in the management of type 2 diabetes mellitus. Drugs 2008; 68: 2387-409.
31. Ristic S, Byiers S, Foley J, et al. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. Diabetes Obes Metab 2005; 7: 692- 8.
32. Pratley RE, Jauffret-Kamel S, Galbreath E, et al. Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. Horm Metab Res 2006; 38: 423-8.
33. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ.; Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care 2007; 30: 890-5.
34. Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes Obes Metab 2007; 9: 166-74.
35. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S; Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. Diabetologia 2007; 50: 1148-55.
36. Bolli G, Dotta F, Rochotte E, et al. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab 2008; 10: 82-90.
37. Garber AJ, Foley JE, Banerji MA, Ebeling P, Gudbjörnsdottir S, Camisasca RP, Couturier A, Baron MA.; Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea. Diabetes Obes Metab 2008; 10: 1047-56.

38. Ahren B, Foley JE, Ferrannini E, Matthews DR, Zinman B, Dejager S, Fonseca VA.; Changes in prandial glucagon levels after a 2-year treatment with vildagliptin or glimepiride in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Diabetes Care 2010; 33: 730-2.
39. Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, et al.; Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab 2010; 12: 780-9.
40. Filozof C, Gautier JF.; A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med 2010; 27: 318-26.
41. Blonde L, Dagogo-Jack S, Banerji MA, Pratley RE, Marcellari A, Braceras R, Purkayastha D, Baron M.; Comparison of vildagliptin and thiazolidinedione as add-on therapy in patients inadequately controlled with metformin: results of the GALIANT trial-a primary care, type 2 diabetes study. Diabetes Obes Metab 2009; 11: 978-86.
42. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahrén B, Byiers S, Shao Q, Dejager S.; Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009; 11: 157-66.
43. Kato N, Oka M, Murase T, Yoshida M, Sakairi M, Yakufu M, Yamashita S, Yasuda Y, Yoshikawa A, Hayashi Y, Shirai M, Mizuno Y, Takeuchi M, Makino M, Takeda M and Kakigami T, Synthesis and pharmacological characterization of potent, selective, and orally bioavailable isoindoline class Dipeptidyl peptidase IV inhibitors Organic and Medicinal Chemistry Letters 2011; 1: 7.