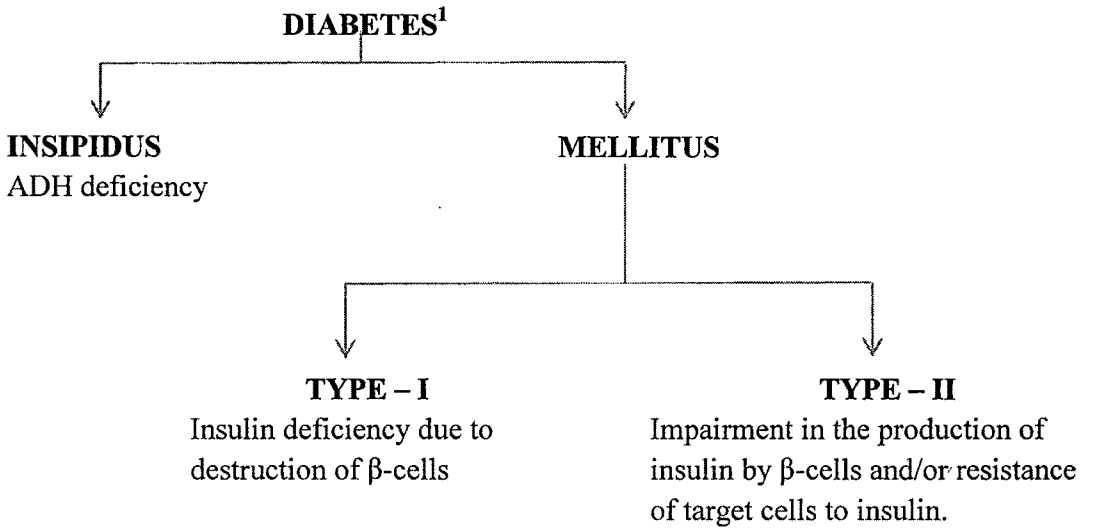
# SUMMARY

# CHAPTER 1: Introduction

Two of the most dreaded health problems are **Cancer** and **Diabetes.**
Present work relates primarily to the treatment of Type 2 diabetes and a part of it to the treatment of cancer.




Type 2 diabetes mellitus (T2D), one of the leading lifestyle diseases, is primarily characterized by insulin resistance or reduced insulin sensitivity combined with impaired insulin secretion and hyperglycaemia. One of the emerging, mechanistic approach for the treatment of T2D includes dipeptidyl peptidase IV (DPP-IV) inhibition which is a serine exopeptidase specifically cleaving dipeptides from glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Inhibition of DPP-IV increases the half-life of GLP-1 and GIP which in turn leads to sustained insulin secretion thus normalizing an elevated blood glucose level without increasing the risk of hypoglycemia.

- It is the leading cause of death in most developed countries.
- Many people living with diabetes are not even aware of their condition, often due to the absence of symptoms and may go undiagnosed until complications start to show.
- It is growing not just because of the world's population is expanding and getting older but also because of the rise of obesity across the globe.

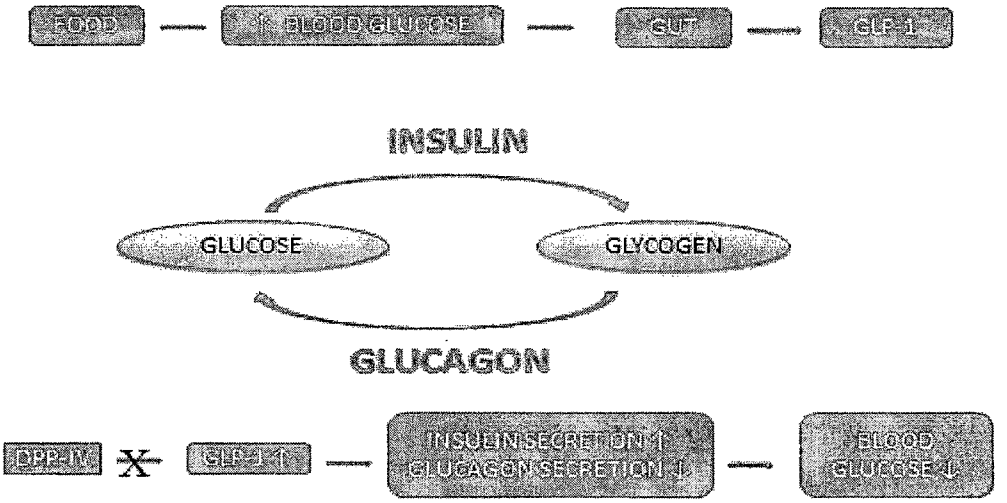



**Figure** : Flow chart of regulation of Blood Glucose

**Dipeptidyl peptidase IV** (DPP-IV), is an enzyme that degrades the incretins like the **GLP-1.**

Less than two minutes after the GLP-1 formation, DPP-4 quickly degrades the GLP-1 by cleaving off two terminal amino acids.

A possible solution to the rapid degradation of the incretins by DPP-4 is through the administration of **DPP-IV inhibitor.**

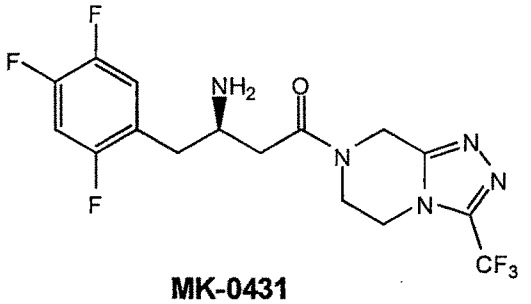
**DPP-IV inhibitors** attach to the DPP-4 enzyme and prevent it from breaking down the GLP-1 hormone. As a result GLP-1 remains active for a longer time so it can continue to act on pancreas. There it increases insulin production and holds back glucagon production both of which helps to reduce the amount of glucose circulating in the blood.

**DPP-IV inhibitors** can lower the blood glucose levels. Over the long term controlled blood glucose levels can help reduce the risk of potentially life threatening complications like

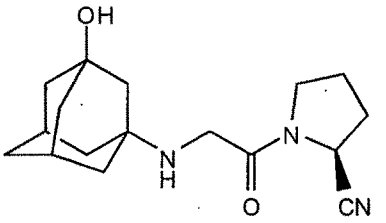
- Heart disease,
- Kidney problem,
- Nerve damage and
- Visual impairment.

**Some of the DPP-4 inhibitors**

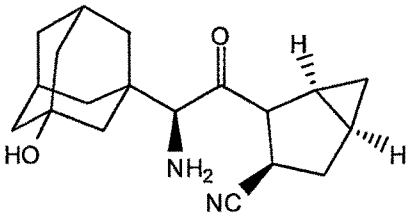
- Sitagliptin(FDA approved 2006, marketed by Merck & Co. as Januvia),
- Vildagliptin (EU approved 2007, marketed in the EU by Novartis as Galvus),
- Saxagliptin (FDA approved in 2009, marketed as Onglyza).




**MK-0431**




**NVP-LAF237**



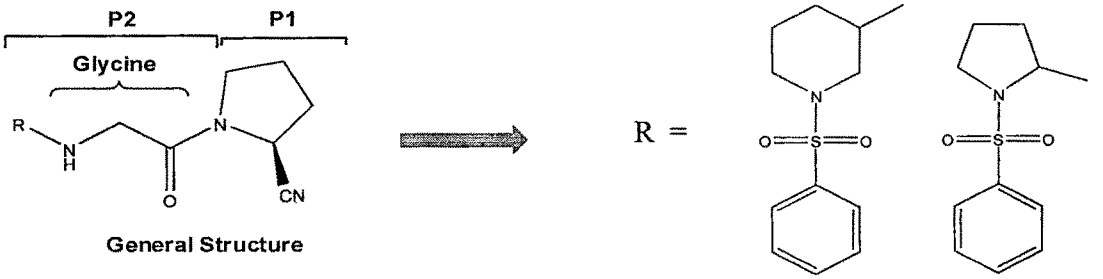

**BMS-477118**

Unlike many other type 2 diabetes treatment, DPP-4 inhibitors does not lead to obesity in type 2 diabetic patients. This is an advantage as body weight can be a challenge to manage.

When used in mono-therapy, DPP-4 inhibitors are not associated with an increased risk of hypoglycemia.

In addition to the diet and exercise, DPP-4 inhibitors are therefore an effective and simple option to help people control their blood glucose levels and type 2 diabetes.
Synthesis of various DPP-4 inhibitors which have been discussed from chapter 2 to chapter 4.

# CHAPTER 2: Synthesis of sulfonamide derivatives as DPP-4 inhibitors.




DPP-IV inactivates the incretin hormones (GLP-1 and GIP) cleaving the N-terminal two amino acids with proline or alanine in the second position. So, to inhibit the action of DPP-IV, synthesis of molecules similar to the proline or alanine is required.

Nipecotic acid and proline on reaction with benzene sulfonylchloride gave corresponding N-sulfonamide derivatives. The acid functional group of these sulfonamide was converted into corresponding amide (1a, 1b). These amides on reaction with trifluoro acetic anhydride gave corresponding nitrile derivatives (2a, 2b) which on reduction with LAH gave corresponding methyl amine derivatives.

L-proline amide on reaction with chloroacetyl chloride gave (S)-1-(2-chloroacetyl)pyrrolidine-2-carboxamide (3) which on dehydration with TFAA gave (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile (4).

Reaction of reduced forms of 2a, 2b with 4 gave the desired compounds 5a-B.

All the molecules thus synthesized have been charactersied by IR, $^{1}H$ NMR, $^{13}C$ NMR and ESI-MS analysis. 1a-b, 2a-b, 5a-b have been evaluated for *in-vitro* DPP-IV inhibition.

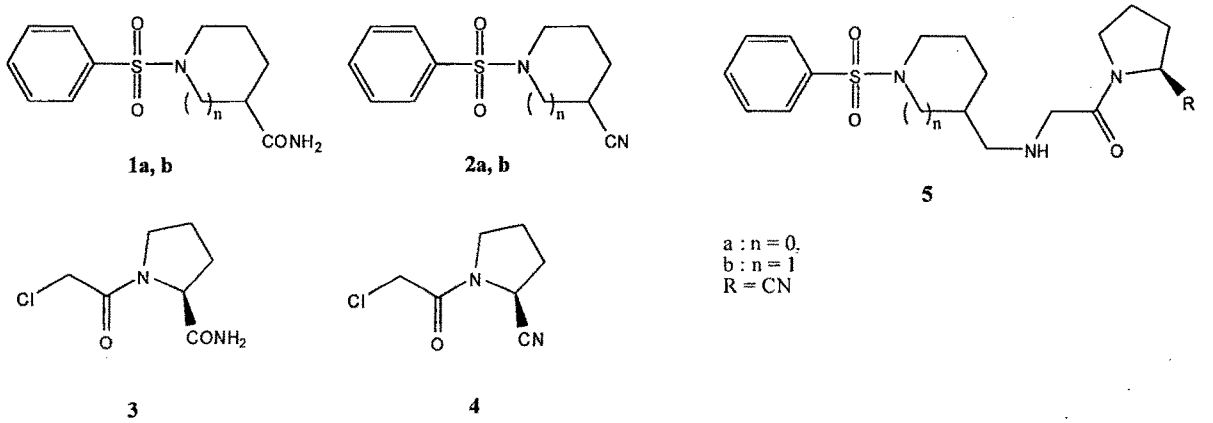
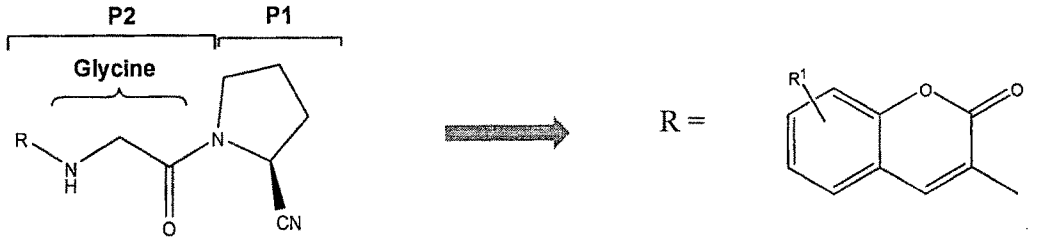



**Figure** : Sulfonamide derivatives as anti-diabetic agents.

# CHAPTER 3: Synthesis of 3-aminocoumarin derivatives as anti- diabetic agents




**General Structure**

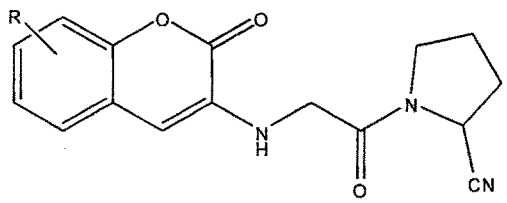
Various studies revealed that the cyano group and the P2 basic amine moiety underwent an intramolecular cyclization to form an inactive cyclic imidate and/or their diketopiperazine hydrolysed product.

However, this process could be slowed down by creating an appropriate steric crowding on the P2 fragment as shown in the figure.

So, instead of hydroxyl adamantyl group as it is in vildagliptin, we have synthesised various coumarin derivatives while keeping the active pharmacophore same.

Perkin reaction of various salisaldehyde derivatives with N-acetyl glycine in the presence of sodium acetate gave corresponding 3-acetamido coumarin derivatives which on hydrolysis with methanolic HCl gave corresponding 3-amino coumarin derivatives which on reaction with (S)-1-(2-chloroacetyl)pyrrolidine-2-carboxamide (3) and (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile (4) gave corresponding coumarin based DPP-4 inhibitors as shown in the figure.

All the final molecules have been charactersied by IR $^{1}$H NMR, $^{13}$C NMR, and ESI-MS analysis and evaluated for *in-vitro* DPP-IV inhibition.

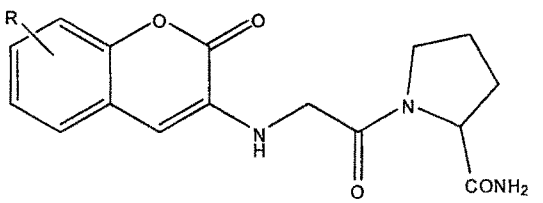



**R = H**

**7- OH**

**8 - $OCH_3$**

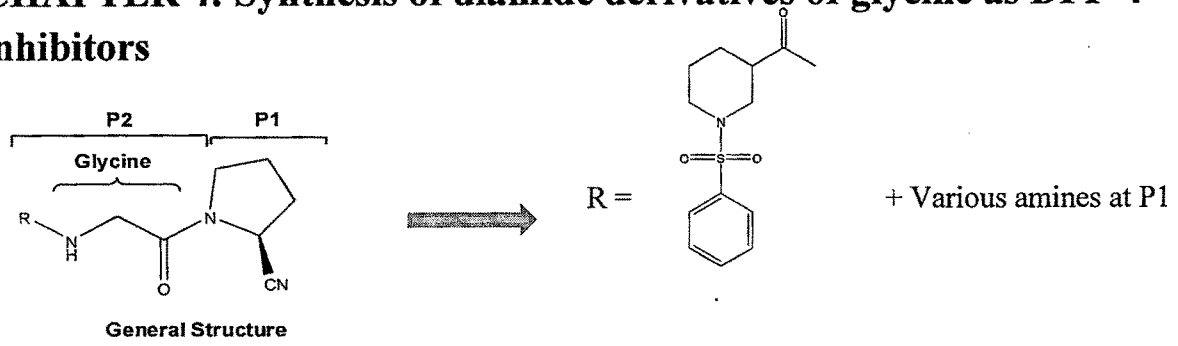
**7,8-Ph**




**R = H**

**Figure** : Coumarin based NCE's as anti-diabetic agents.

# CHAPTER 4: Synthesis of diamide derivatives of glycine as DPP-4 inhibitors




Herein, the sulphonamide of nipecotic acid was used and condensed at the N-terminus of with various amides (at the C-terminus) of glycine, to give diamides of glycine.
Herein, only the glycine moiety remains the same while the amide at the P1 site is formed by the substitution of various amines other than the 2-cyano pyrrolidine and the amide at the P2 site is formed by peptide coupling of the amine at the N-terminus of the glycine with 1-(phenylsulfonyl)-piperidine-3-carboxylic acid, formed by the reaction of nipecotic acid with benzene sulfonyl chloride in the presence of base.
Boc-protected glycine on reaction with various amines gave corresponding Boc-protected glycine amides. These on deprotection with trifluoroacetic acid gave various amide derivatives of glycine. These were then coupled with 1-(phenylsulfonyl)-piperidine-3-carboxylic acid in presence of peptide coupling agents gave various diamides derivatives of glycine, as shown in the figure.
Thus, eleven NCE's have been synthesized and characterized by $^{1}H$ NMR, $^{13}C$ NMR, IR, ESI-MS and CHN analysis and have been evaluated for *in-vitro* DPP-IV inhibition.

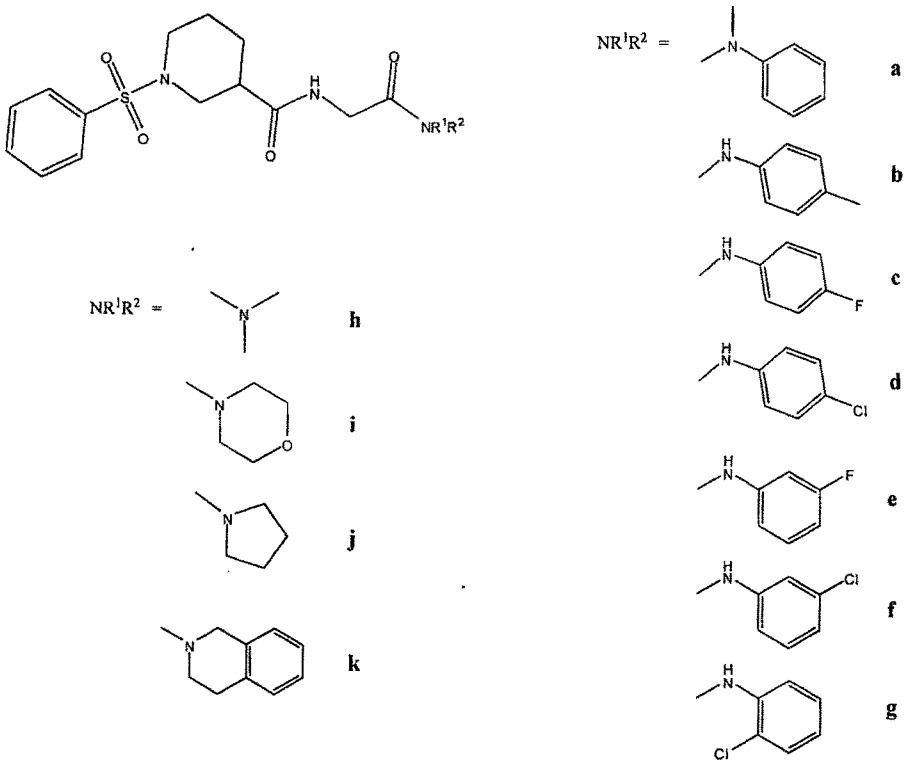
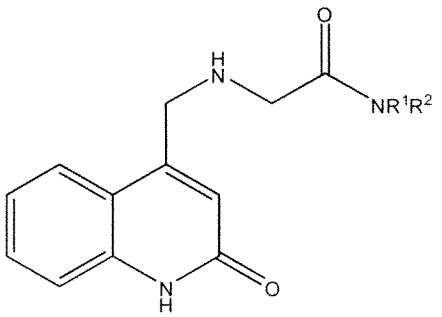



**Figure** : Various diamides derviatives of glycine as DPP-IV inhibitors.

# CHAPTER 5: Synthesis of 4-(aminomethyl)quinolin-2(1H)-one derivatives as anti-cancer agents

2-quinolone derivatives with 3-aryl and N-alkyl substitutions are reported to show good anti-cancer activity on breast cancer cell line.

Acetoacetanilide on bromination with bromine with bromine in acetic acid gave bromo-acetoacetanilide, which on cyclization using concentrated sulfuric acid gave 4-bromomethyl-quinolin-2(1H)-one. This bromoquinolone on reaction with various glycine amides in the presence of lithium hydroxide monohydrate as a base gave corresponding 4-(aminomethyl)quinolin-2(1*H*)-one derivatives. The anti-cancer activity (MTT assay) of these compounds against A549 lung cancer cell line has been carried out.



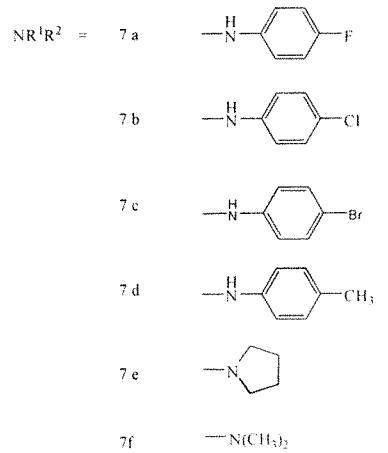




**Figure** : 2-quinolone derivatives as potential anti-cancer agents.