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DPP IV INHIBITORS AS ANTIDIABETICS

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ABSTRACT

A new therapy used for treating type 2 diabetes which reduces glucagon and postprandial glucose levels is Incretin based therapy. This therapy provides long term therapeutic benefits by restoring beta cells. The most important incretin hormones called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which stimulates insulin secretion in response to meals gets inactivated by proteolytic enzyme dipeptidyl peptidase – IV. This leads to the development of DPP – IV inhibitors for the treatment of type 2 diabetes. The present review focuses on the various reported DPP IV inhibitor derivatives as well as DPP-IV-resistant GLP-1 or GIP analogs.

KEY WORDS

DPP IV Inhibitors, Type 2 diabetes, GIP analogs, GLP-1.

INTRODUCTION:

Number of oral hypoglycemic drugs were discovered to treat type 2 diabetes. To counteract side effects of these drugs, a novel therapy is used called Dipeptidyl pepitidase-4 inhibitors. This therapy provides long term therapeutic benefits by restoring beta cells. The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) stimulate insulin secretion in response to meals get inactivated by proteolytic enzyme Dipeptidyl peptidase IV (DPP–IV). DPP–IV enzyme is present in exocrine pancreas, lymph nodes, intestines, sweat glands, salivary glands, thymus, and biliary tract, kidney, liver, placenta, uterus, prostate, brain, and skin. It is attached to the plasma membrane of the endothelia of all organs in the body. It is also present in body fluids such as blood plasma and cerebrospinal fluid. DPP–IV inhibitors increase incretin levels which inhibit glucagon release, increases insulin secretion, decreases blood glucose levels and gastric emptying. This leads to the development of DPP – IV inhibitors for the treatment of diabetes mellitus type 2[1,2].

Sitagliptin was the first DPP-4 inhibitor launched in 2006. Subsequently anagliptin, gemigliptin, teneligliptin, evogliptin, omarigliptin and trelagliptin were launched. The global market is acquired by alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin DPP–IV inhibitors and others such as anagliptin, evogliptin, gemigliptin, omarigliptin, teneligliptin, trelagliptin available in Japan and Korea [3].

ROLE OF THE DPP-4 INHIBITORS:

Incretin hormones glucagon like peptide 1 (GLP-1) and glucose dependent gastric inhibitory polypeptide (GIP) are released at meal times [4,5]. It affects pancreatic beta cells and stimulates insulin secretion when glucose is in the blood stream. GLP-1 is the main incretin hormone involved in metabolism of glucose. GLP-1 inhibits glucagon secretion and stimulates insulin synthesis and secretion by the beta cells, delays stomach emptying, reduces appetite, and promotes regeneration of islet β-cells. GIP and GLP-1 rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 and GIP have proline or alanine in the second position which are important for biological activity are cleaved by DPP-4[6,7]. Half-lives of endogenous GIP and GLP-1 are prolonged by inhibition of the DPP-4 enzyme. This is the mechanism of DPP–IV inhibitors in type 2 diabetes mellitus.

CHEMISTRY:

There are two classes of DPP–IV inhibitors peptidomimetic and non-peptidomimetic inhibitors. β-amino acid based Sitagliptin [8], nitrile containing inhibitors such as Vildagliptin [9], Saxagliptin [10] which belongs to class of peptidomimetics, whereas Alogliptin (modified pyrimidinedione) [11] and linagliptin (xanthine-based) [12] are under non-peptidomimetic inhibitors (Table 1). Most of these compounds are competitive reversible inhibitors of DPP–IV, showing inhibition constants (Ki) in the low nanomolar range [10,13]. sitagliptin, Alogliptin and linagliptin interact non-covalently with residues in the catalytic site of DPP–IV. Whereas Vildagliptin and Saxagliptin inhibits DPP–IV by two-step process involving the formation of a reversible covalent enzyme–inhibitor complex in which there is a slow rate of inhibitor binding and inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms. Thus, when the free drug has been cleared from the circulation, catalytic activity will be inhibited. This is used to explain why vildagliptin and Saxagliptin inhibit DPP–IV activity for longer time.

DPP 4 Inhibitor	Class of Drug	Metabolism	Route of elimination
Sitagliptin	β-amino acid-based	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin	Cyanopyrrolidine	Hydrolyzed to inactive metabolite (P450 enzyme independent)	Renal (22% as parent, 55% as primary metabolite)
Saxagliptin	Cyanopyrrolidine	metabolized Hepatically to active metabolite	Renal (12–29% as parent, 21–52% as metabolite)
Alogliptin	Modified pyrimidinedione	Not appreciably metabolized	Renal (>70% unchanged as parent)
Linagliptin	Xanthine-based	Not appreciably metabolized	Biliary (>70% unchanged as parent); <6% via kidney

Table 1. DPP-4 inhibitors *class of drug*, metabolism *and* route *of* elimination.

ORGANIC SYNTHESIS OF DPP IV INHIBITORS:

KJL Augustyns et al synthesized homologues, unsaturated, open and 3-substituted analogues to determine the structure activity relationship of the P-1 site. *A*s P-2 amino acid L-Isoleucine was taken. 1-(L-Isoleucyl)-3(S)-fluoropyrrolidine *is a* competitive inhibitor *of DPP–IV* as active as the non-fluorinated compound. Other changes *made* abolish the activity [14].

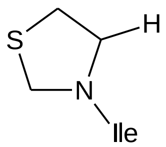

Fig. 1

A potent selective and orally bioavailable DPP IV inhibitor with *hypo*glycemic *activity has been* synthesized *by* Edwin B. Villhauer et al. 1-[(3-Hydroxy-1-adamantyl) amino acetyl]-2-cyano-(S)-pyrrolidine *was found to be most active compound* [15].

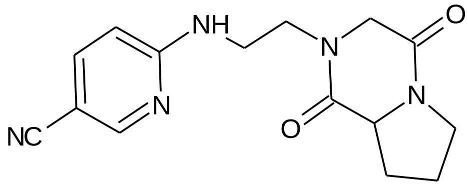

Fig. 2

Curt D. Haffner *synthesized* 2-cyano-4-fluoro-1-thiovalylpyrrolidine inhibitors of DPP IV *and evaluated for it's* DPP-IV inhibitor*y activity in rat and dog. Among the synthesized compound following compound was found to be* potent, selective, and orally active *with long* duration of action[16].

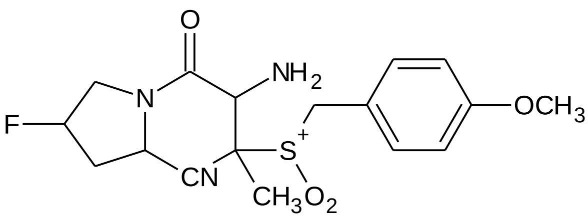

Fig. 3

Stephen W. Wright et al reported novel series of cis-2, 5-dicyanopyrrolidine R-amino amides and evaluated as inhibitors of dipeptidyl peptidase IV for the treatment of type 2 diabetes. 1-({[1 (Hydroxymethyl) cyclopentyl] amino}- acetyl) pyrrolidine-2,5-cis-dicarbonitrile is an achiral, slow-binding (time-dependent) inhibitor of ***DPP–IV*** that is selective for DPP-IV over other DPP isozymes and proline specific serine proteases, and which has oral bioavailability in preclinical species and in vivo efficacy in animal models. The mode of binding of the cis-2, 5-dicyanopyrrolidine moiety was determined by X-ray crystallography [17].

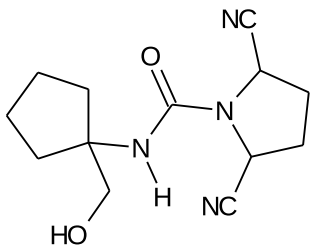

Fig. 4

Dooseop Kim et al prepared a series of b-amino amides bearing triazolopiperazines and evaluated as potent, selective, orally active dipeptidyl peptidase IV inhibitors. Efforts at optimization of the B - amino amides series, which ultimately led to the discovery of JANUVIA TM are described [18].

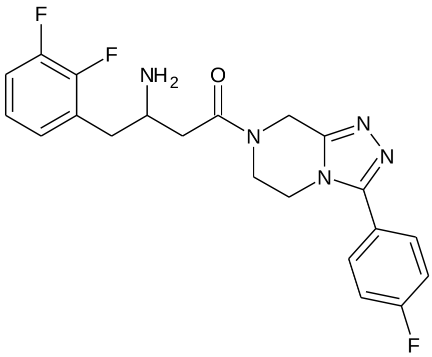

Fig. 5

Jennifer E. Kowalchick et al reported design, synthesis and biological evaluation of triazolopiperazine-based beta amino amides as potent, orally active ***DPP–IV*** inhibitors. Efforts at optimization of the beta- amino amides series, which ultimately led to the discovery of Sitagliptinphosphate[19].

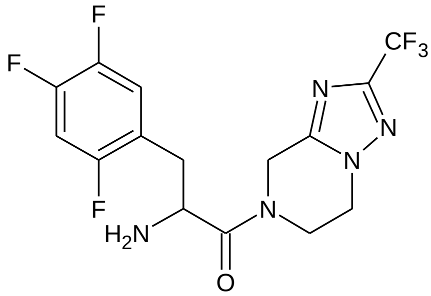

Fig. 6

Hiroshi Fukushima et al have developed a series of 2-cyanopyrrolidines that are among the most potent of DPP-IV inhibitors. They have focused on substitutions at the 3- or 4-position of 2-cyanopyrrolidines, and synthesized and evaluated various derivatives. Among them, the 4-fluoro derivative was found to exhibit better DPP-IV inhibitory activity and higher plasma drug concentrations after oral administration to rats than the 4-unsubstituted derivative [20].

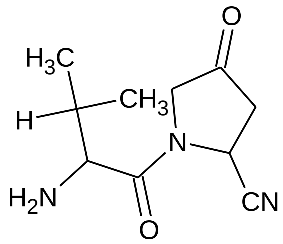

Fig. 7

Dooseop Kim, Jennifer E. Kowalchick et al synthesized series of beta-amino amides bearing triazolopiperazines as potent, selective, and orally active dipeptidyl peptidase IV inhibitors by extensive structure–activity relationship (SAR) studies around the triazolopiperazine moiety. Among these, following compound was found to have excellent in vitro potency (IC50=4.3 nM) against ***DPP–IV***, high selectivity over other enzymes, and good pharmacokinetic profiles and exhibited pronounced in vivo efficacy in an oral glucose tolerance test (OGTT) in lean mice [21].

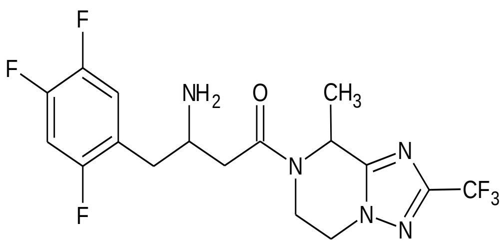

Fig. 8

Arnaud-Pierre Schaffner et al synthesized Aminomethyl-pyridines as ***DPP–IV*** Inhibitors. Optimization of the screening hit afforded a number of 5-aminomethyl-pyridines with inhibitory activity in the nanomolar range. Selected ***DPP–IV*** inhibitors were further evaluated for their selectivity over the closely related peptidase DPP-8. 5-Aminomethyl-4-(2,4-dichloro-phenyl)-6-methyl-pyridine-2-carboxylic acid cyanomethyl-amide showed high potency and excellent DPP-4 selectivity [IC_{50}: 10 (***DPP–IV***) and 6600 nM (DPP-8)] and no toxicity in mammalian cell culture [22].

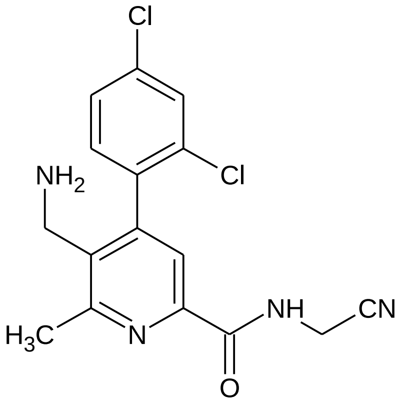

Fig. 9

Peng Cho Tang et al reported an efficient stereo selective synthesis of the rigid aza bicyclo[3.2.0]heptane scaffold to provide 2-cyano pyrrolidine alpha-amino amide 1 as ***DPP–IV*** inhibitor[23].

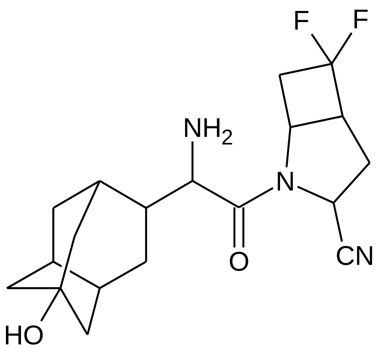

Fig. 10

Noriyasu Kato et al has discovered and pharmacological characterized N-[2-({2-[(2S)-2 cyanopyrrolidin-1-yl]-2-oxoethylamino)-2-methylpropyl]-2-methylpyrazolo [1,5-a] pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt) as a potent and selective DPP-IV inhibitor [24].

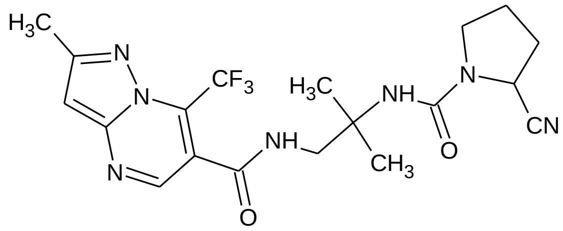

Fig. 11

Liu Y et al designed and synthesized a series of novel imidazolone derivatives via a rational drug design strategy. These compounds were obtained from 3-substituted imidazolidine-2,4-dione through alkylation, formylation, dehydration, and amination. All target compounds were screened for their ***DPP–IV*** inhibitory activity in vitro [25].

Reema Abu Khalaf et al reported design and synthesis of a series of N4-sulfonamido-succinamic, phthalamic, acrylic and benzoyl acetic acid derivatives. The synthesized compounds were evaluated for their in vitro anti-DPP IV activity. Some of them have shown reasonable bioactivity, where the most active one was found to have an IC50 of 33.5 µM [26].

Sanjay D. Sawant et al reported design, synthesis, QSAR studies and in vitro evaluation of novel triazolo piperazine based beta amino amides as DPP IV inhibitors. QSAR studies of reported triazolopiperazine class of DPP-IV inhibitors have led to the discovery of following compounds as selective and potent inhibitors of DPP-IV. The design, synthesis, QSAR studies and biological evaluation of novel triazolopiperazine based β-amino amides as DPP-IV inhibitors confirms the utility of QSAR techniques in optimizing the lead molecules in process of drug discovery. The results of the study indicate that DPP-IV inhibitory activities of triazolopiperazine based inhibitors can be successfully explained in terms of physicochemical parameters of the molecule [27].

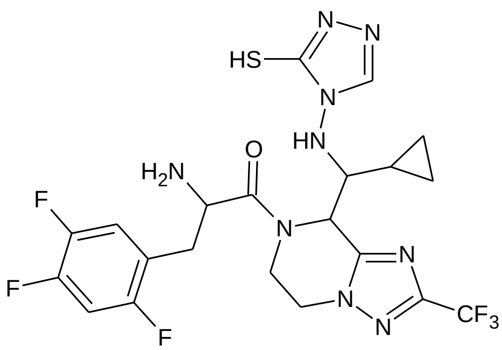

Fig. 12

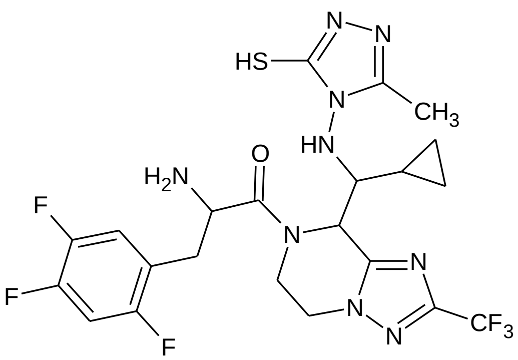

Fig. 13

Heyao Wang et al reported synthesis of a series of fused β-homophenylalanine derivatives as novel DPP-4 inhibitors. Most of them displayed excellent ***DPP–IV*** inhibitory activities and good selectivity. Following compound showed significantly greater potency than sitagliptin. It thus provides potential candidates for the further development into potent drugs targeting DPP-4[28].

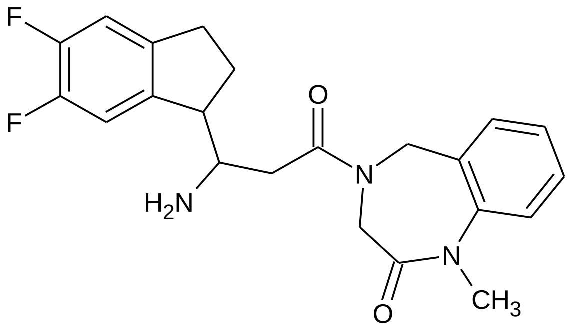

Fig. 14

Ram Najar Kushwaha et al designed, synthesized, and evaluated Novel piperazine-derived conformationally constrained compounds for in vitro Dipeptidyl peptidase-IV (DPP-IV) inhibitory activities. From a library of compounds synthesized, 1-(2-(4-(7-Chloro-4-quinolyl) piperazin-1-yl) acetyl) pyrrolidine was identified as a potential DPP-IV inhibitor exhibiting better inhibitory activity than P32/98, reference inhibitor. The in vivo studies carried out in STZ and db/db mice models indicated that the following compound showed comparable antihyperglycemic activity to the marketed drug Sitagliptin [29].

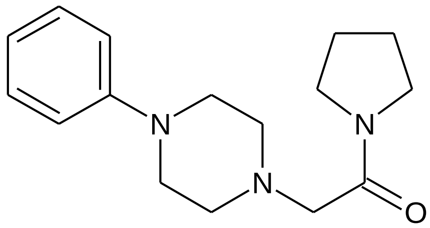

Fig. 15

A new therapy used for treating type 2 diabetes which reduces glucagon and postprandial glucose levels is Incretin based therapy. This leads to the development of DPP – IV inhibitors for the treatment of type 2 diabetes. The present review focuses on the various reported DPP IV inhibitor derivatives ***as well as*** DPP-IV resistant GLP-1 or GIP analogs.

CONCLUSION:

The ***DPP–IV*** inhibitors are the first new therapeutic class of oral antihyperglycaemic drug for T2DM for many years. Add-on therapy to metformin will likely be needed as the disease progresses. It is important to avoid therapies that increase the risk of weight gain and hypoglycemia and do not preserve β-cell function. Newer therapies such as ***DPP–IV*** inhibitors and GLP-1 receptor agonists effectively lower A1C and improve β-cell function without increasing the risk of hypoglycemia and weight gain. The present review focuses on the various reported ***DPP–IV*** inhibitor derivatives.

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