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Discovery of 17 Gliptins in 17-Years of Research for the Treatment of Type 2 Diabetes: A Synthetic Overview

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Abstract: Gliptins, commonly known as clinical DPP-IV inhibitors have become a new class of potential drug candidate and are being hoped as a permanent eraser for type 2 diabetes. Therefore, gliptins have been a centre of research and development. As a result of the efforts made towards developing effective gliptins, the first clinical proof of concept for efficacy was confirmed in 1998 when NVP-DPP728 came into focus. Thus, from 1998 to 2014, these 17-years of the heightened research towards drug discovery has resulted in seventeen gliptins. Among these, eight gliptins are currently approved and in clinical usages for type 2 diabetes therapies, while others are in different stages of clinical trials. This review covers the various approaches and methodologies used in the syntheses of only those DPP-IV inhibitors in clinical uses having suffix gliptin. In addition, it also encompasses their biological activity and their binding interactions in the active site of DPP-IV that are responsible for their drug candidacy.

Keywords: Type 2 Diabetes; Glucagon like peptide (GLP-1); Dipeptidyl Peptidase-IV (DPP-IV) inhibitor; Gliptins; Binding interactions; Selectivity; Synthesis.

1. Introduction

Type 2 diabetes mellitus (T2DM) is prevalent and a rapidly growing metabolic disorder. It is a growing epidemic and considered as a major public health issue all over the world. T2DM accounts more than 95% of all diabetes cases affecting almost 6% of the overall population. Around 382 million people have diabetes mellitus in 2013 and it is projected to be over 592 million by 2035, if the preventive steps are not taken. India has the second highest number of diabetic patients after china, which is expected to rise from 65.1 million to 109 million by 2035 as predicted by the International Diabetes Federation (IDF).[1-3] A number of micro- and macrovascular complications such as coronary artery disease, hypertension, stroke, peripheral vascular disease, retinopathy, neuropathy and nephropathy are associated with T2DM.[4, 5]

To correct the glucose imbalance and to reduce the risks associated with T2DM, currently five main classes such as sulfonylureas (SU), non-SU secretagogues (Meglitinides), biguanides, thiazolidinediones (TZDs), α-glucosidase inhibitors and the recently introduced dipeptidyl peptidase-IV (DPP-IV) inhibitors are approved by the U. S. Food and Drug Administration (FDA). DPP-IV inhibitors inhibit the DPP-IV enzyme, a serine protease that cleaves the incretin hormones, glucgon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These incretins are released by the gut in response to food intake and stimulate the insulin secretion and biosynthesis in a glucose-dependent manner. Additionally, these incretins inhibit glucagon secretion, slow gastric emptying, induce satiety, inhibit hepatic glucose production and regenerate and differentiate islet β-cells.[6, 7] Thus, inhibition of DPP-IV prolongs the circulating half-life of GLP-1 and GIP. By increasing the circulating concentration of these incretins, DPP-IV inhibitors improve the glucose control in patient with type 2 diabetes.[8-10] Thus, the observed multiple biological effects and unlike other antidiabetic agents, absence of undesirable side effects such as weight gain and hypoglycemia exhibit the significance of DPP-IV inhibitors and it is hoped that the long term treatment with this class of antidiabetic agent may permanently erase the type 2 diabetes. Therefore, DPP-IV inhibitors (gliptins) have been a center of research and development. As a result of the efforts made towards developing effective gliptins, the first clinical proof of concept for efficacy was confirmed in 1998, when NVP-DPP728 came into focus. Thus, in search of a novel, potent and selective inhibitors of DPP-IV from 1998 to 2014, these 17-years of the heightened research towards drug discovery has afforded more than 80 clinically relevant DPP-IV inhibitors on the basis of potency, tolerability, efficacy and safety. Intense research activities towards these inhibitors have resulted in seventeen gliptins. Out of these, eight gliptins are currently approved and being used for type 2 diabetes therapies while others are advancing into pre-registration/phase 3 and looking forward for approval. Till date, a number of review articles have been published that extensively encompass the various aspects of DPP-4 inhibitors.[11-15] This review covers the various approaches and methodologies used in the synthesis of only those clinically relevant DPP-IV inhibitors having suffix gliptin in their name. In addition, it also encompasses their biological data and their binding interactions in the active site of DPP-IV that are responsible for their drug candidacy.

2. Reported Gliptins and their Syntheses

The seventeen gliptins as a result of 17-years of intense research have been achieved (Figure 1), which can be categorized into several groups based on the skeleton and binding mode similarities. Sitagliptin and its sister gliptins include retagliptin, gemigliptin, omarigliptin and evogliptin. Sitagliptin is the first gliptin of the DPP-IV inhibitor class approved for type 2 diabetes treatment. Cyanopyrrolidine-based gliptins include vildagliptin, saxagliptin, anagliptin, denagliptin, and melogliptin. Vildagliptin is the first marketed inhibitor of this class. Teneligliptin and gosogliptin are the diprolyl based gliptins. Linagliptin belongs to the xanthine based gliptin while alogliptin and trelagliptin are pyrimidinedione based gliptins. Dutagliptin and carmegliptin are included into boronic acid and tricyclic- based gliptins, respectively. In this review, a wide range of the recent and feasible approaches and methodologies, along with the challenges encountered have been described for the synthesis of these gliptins.

2.1. Sitagliptin

Sitagliptin is a triazolopiperazine based inhibitor of DPP-IV, which was discovered by Merck. It

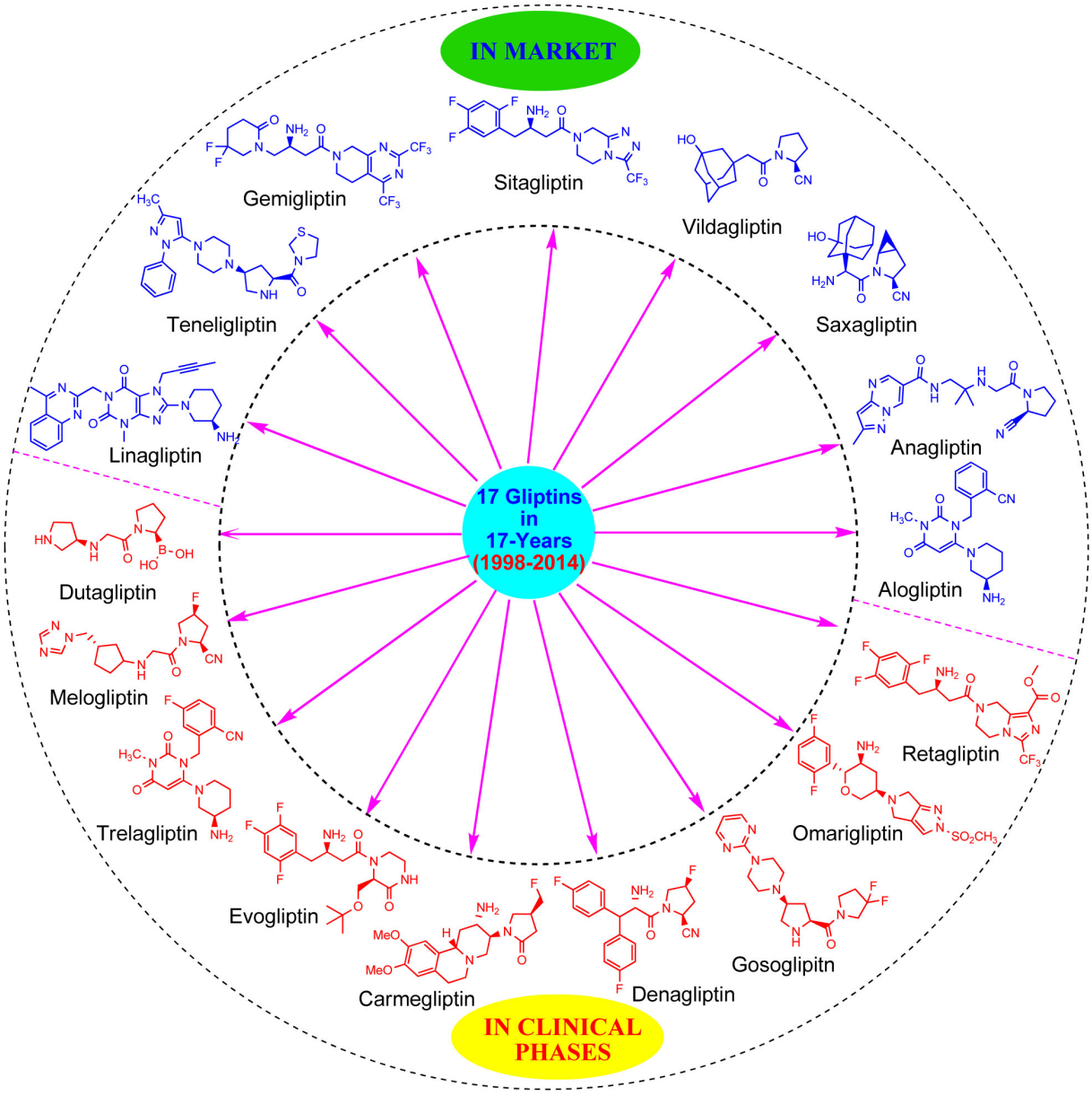


Figure 1. An Overview of 17 Gliptins in 17-Years of Research

is a potent (IC_{50}= 18 nM) and highly selective over DPP-8 (48000 nM), DPP-9 (>100000 nM) and other isozymes.[16] It enhances the pancreatic β-cell functions, fasting and post-prandial glycemic control in type 2 diabetic patients. In the crystal structure with DPP-IV, unlike other substrate-based DPP-IV inhibitors, the binding orientation of the amide carbonyl of sitagliptin is reversed, i.e. the aromatic trifluorophenyl moiety occupies S1 pocket and the β-amino amide moiety fits into S2 pockets. The amino group forms a salt bridge and hydrogen bonding interactions with Glu205 and Glu206, and Tyr662, respectively. The triazolopiperazine moiety occupies the S2 extended pocket and stacks against Phe357. The exhibited binding interactions of the trifluoromethyl group with the Arg358 and Ser209 are responsible

for its high selectivity profile. The presence of the trifluoromethyl group in the triazole ring also improves the oral bioavailability in animal models. Sitagliptin inhibited the plasma DPP-IV up to 80% and 47% at 2 and 24 h, respectively, after a single dose of 25.0 mg in a dose-dependent manner. In a 24-week study, sitagliptin significantly decreased fasting glucose levels and HbA_{1c} levels (0.8%) at doses of 100 mg q.d. Thus, sitagliptin is well tolerated and body weight neutral. It is the first DPP-IV inhibitor in the class approved by USFDA in 2006 and is used as either a monotherapy or in combination with metformin.[17-20]

Among the several approaches reported so far for the synthesis of sitagliptin, some are outlined in Schemes 1-3. The triazolopiperazine moiety **5** is a key intermediate and was prepared from the starting material, chloropyrazine **1** via hydrazinopyrazine **2**, which provided compound **3** via acylation reaction with trifluoroacetic anhydride. The intramolecular cyclization of compound **3** with polyphosphoric acid gave compound **4,** which on catalytic hydrogenation over Pd/C provided triazolopiperazine intermediate **5**.

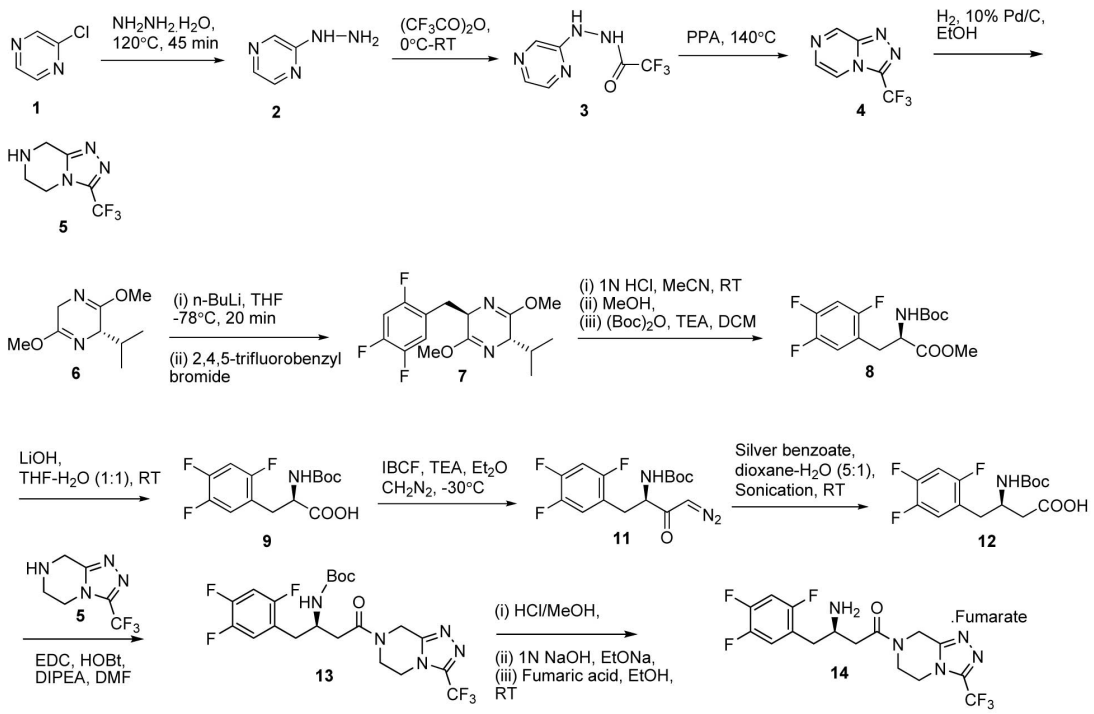
In the first synthetic approach, the synthesis of sitagliptin was started with the reaction of a Schollkopf reagent **6** with 2,4,5-trifluorobenzyl bromide to afford the compound **7**, which was converted to compound **9** via hydrolysis of ester **8**. The resulting Boc-protected amino acid **9** was converted to diazoketone **11** through mix anhydride protocol by using diazomethane. The intermediate **11** was converted to desired β-amino acid **12** by sonication in the presence of silver benzoate.[21] The sitagliptin (**14**) was synthesized by coupling of β-amino acid **12** with triazolopiperazine intermediate **5** followed by Boc deprotection of amino group of **13**, and its corresponding hemi fumarate salt was then prepared (Scheme 1).[16]

The second approach for synthesis of sitagliptin was started from asymmetric reduction of β-ketoester **15** using the (*S*)-$BinapRuCl_2$ complex with a catalytic amount of HBr in methanol followed by hydrolysis afforded the β-hydroxy acid **16**. Lactam **17** was synthesized by coupling of **16** with $BnONH_2$•HCl using N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC), followed by cyclization reaction with diisopropyl azodicarboxylate (DIAD) and PPh_3.[22] Treatment of a catalytic amount of 0.1% NaOH with lactam **17** hydrolyzed and directly afforded the β-amino acid **18.** This was coupled with triazolopiperazine **5** using EDC•HCl and N-methylmorpholine to provide the N-benzyloxy protected compound **19,** which after hydrogenation using Pd/C and by consequent treatment with phosphoric acid provided the phosphate salt of sitagliptin (**14**) (Scheme 2).

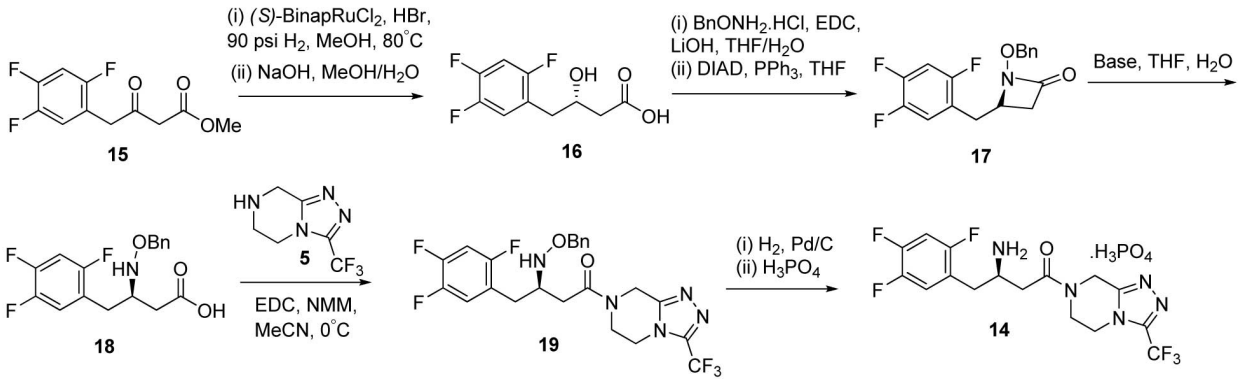
The third approach towards the synthesis of sitagliptin is outlined in scheme 3. Meldrum adduct **22** (Hunig's base salt) was synthesized from trifluorophenylacetic acid **20** by the formation of a mixed anhydride with pivaloyl chloride in the presence of Meldrum's acid **21**, DIPEA and catalytic amount of dimethylamino pyridine (DMAP) in acetonitrile. Treatment of **22** with TFA resulted compound **23**. β-keto amide **24** was formed on reaction of **23** with triazolopiperazine **5.** β-keto amide **24** on treatment with ammonium acetate in methanol formed a key intermediate, dehydrositagliptin **25** (enamine amide). This intermediate contains the entire structure of sitagliptin **14** except two hydrogen atoms. Thus, sitagliptin **14** was synthesized by enantioselective hydrogenation of dehydrositagliptin **25** in the presence of $[Rh(COD)_2OTf]$ 12,13 and ^{t}Bu JOSIPHOS in excellent yield with 95% ee.[23,24]

2.2. **Vildagliptin (LAF-237, Novartis)**

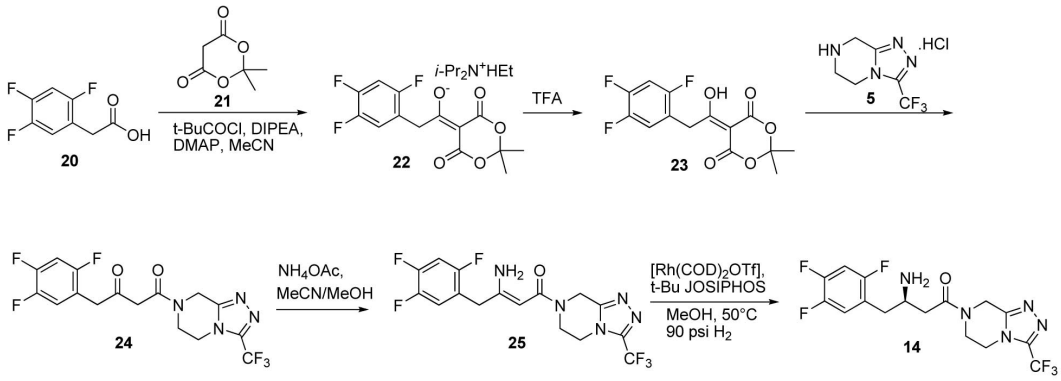
Vildagliptin (LAF-237) is the first generation inhibitor and the first gliptin of the



Scheme 1. First Generation Approach for Sitagliptin Synthesis



Scheme 2. Second Approach towards Sitagliptin Synthesis



Scheme 3. Third Approach towards Sitagliptin Synthesis

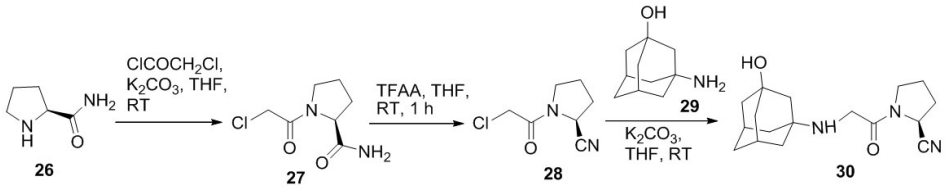
cyanopyrrolidine class approved for treatment of type 2 diabetes. It was discovered by Novartis. It is potent (IC_{50}= 3.5 nM) and modest selective for DPP-IV against DPP-8 (>250 fold) and DPP-9 (23 fold), but much more selective over DPP-2, FAP etc.[25] With the DPP-IV enzyme, the cyanopyrrolidine moiety occupies S1 pocket where the nitrile group forms a covalent imidate adduct with the hydroxyl of Ser630. The imidate's nitrogen establishes the hydrogen bonding interaction with the side chain of Tyr547. The adamantly moiety of vildagliptin is highly hydrophobic, which occupies the S2 pocket, and hydroxyl group forms hydrogen bondings with His126 and Ser209 through bridging of water molecules. The amine group exhibits salt bridge bonding with Glu205 and Glu206, and the carbonyl group also shows hydrogen bonding with side chains of Asn710. [26]

Vildagliptin showed a half-life of 1.5 h with 85% of bioavailability and improved the glycemic control (i.e. 0.7% reduction in HbA_{1c} levels).[27] It exhibited up to 80% DPP-IV inhibition for 7 h and still retained 40% after 24 h at a single dose of 100 mg. It also increased the insulin sensitivity and β-cell function. It is used either as monotherapy or in combination with other antidiabetic agents. Some common adverse effects are headache, constipation, dizziness, nasopharyngitis, increased sweating and cough[28] It was approved by European Medicines Agency (EMA) in 2008 for use within the EU. It is still waiting for FDA approval for use in the US.

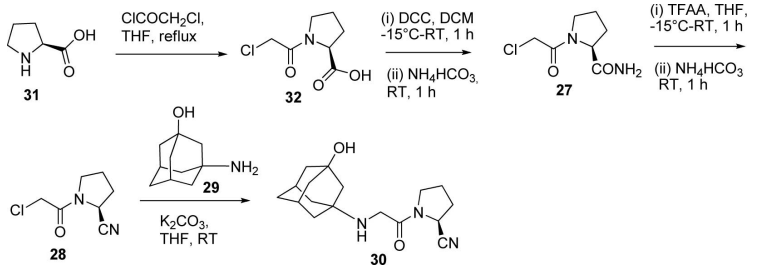
Initial synthesis of Vildagliptin is outlined in scheme 4. The amino group of L-prolinamide **26** was acylated by using chloroacetyl chloride to give compound **27,** which was converted to compound **28** by dehydration reaction with trifluoroacetic acid (TFAA). Finally, by reaction of 3-hydroxy-1-amino adamantine **29** with **28** gave afforded the Vildagliptin **30**. [25]

An alternative route for synthesis of Vildagliptin **30** involved the direct N-acylation of L-proline **31** with chloroacetyl chloride to afford the chloroacetamide **32**, which was converted to amide **27** by using DCC and ammonium bicarbonate. Further, amide group of compound **27** was converted to nitrile derivative **28** by treating dehydrating agent, trifluoroacetic acid (TFA) which on treatment with 3-hydroxy-1-amino adamantine **29** afforded Vildagliptin **30** (Scheme 5).[29]

2.3. **Dutagliptin (PHX1149, Phenomix**



Scheme 4. Synthesis of Vildagliptin



Scheme 5. Alternative approach for Vildagliptin synthesis

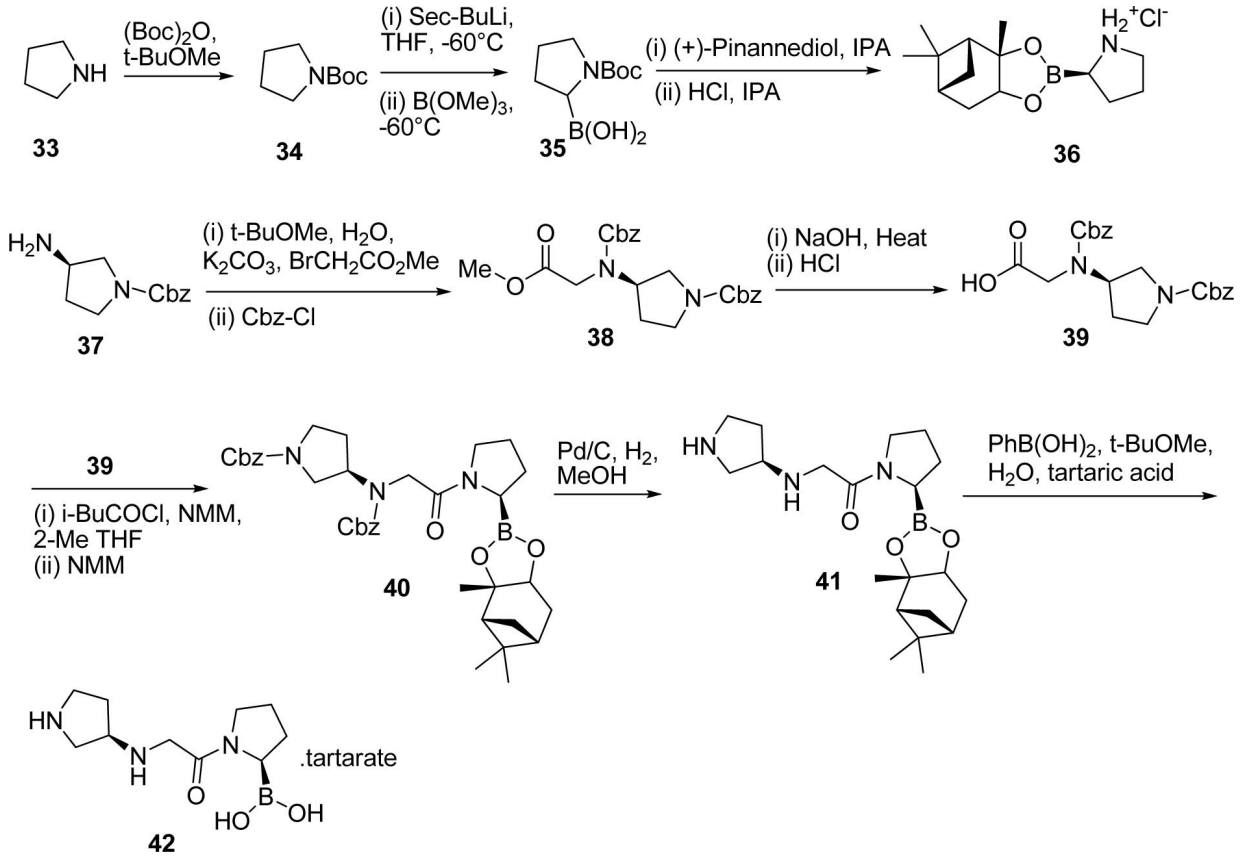
Corp)

Dutagliptin is a boronic acid-based inhibitor and second generation inhibitor of DPP-IV. It was developed by Phenomix Corp. Dutagliptin is potent (IC_{50} = 25 nM) and highly selective for DPP-IV against DPP-8 and DPP-9 (400-fold). It showed up to 50% and 80% inhibition of DPP IV in dogs and monkeys, respectively, even after 24 h at a single dose of 9 mg/kg. Dutagliptin exhibited a half-life ($t_{1/2}$) of 6.3 h and exhibited significant reduction in HbA_{1c} levels.[30] Thus, it shows the excellent safety profile and currently in Phase-III clinical trial.

Pyrrolidine **33** was the precursor for the synthesis of Dutagliptin, which after Boc protection gave Boc pyrrolidine **34**. Treatment of **34** with *Sec*-Butyllithium and trimethoxyborane resulted **35** which on reaction with (+)-pinannediol, followed by Boc deprotection provided key intermediate **36**. Another core intermediate **39** was prepared from N-protected 3-aminopyrrolidine **37** via compound **38** as presented in scheme 6. Now, the coupling of pyrrolidine intermediate **36** with **39** provided protected compound **40** which after cbz and (+)-pinannediol deprotection with hydrogenation and phenyl boronic acid, respectively, gave the desired compound Dutagliptin **42** via compound **41.**[31] Some alternative routes were also reported for the synthesis of Dutagliptin.[32,33]

2.4. **Saxagliptin (BMS-477118, Bristol-Myers Squibb)**

Saxagliptin is a methanopyrrolidine-based first generation inhibitor of DPP-IV for T2DM



Scheme 6. Synthesis of Dutagliptin

treatment. It is extremely potent (K_i = 0.6 nM) and moderately selective for DPP-IV against DPP-8 and DPP-9. The presence of the highest degree of β-branching and cyclopropane moiety in saxagliptin structure enhance the chemical stability towards the internal cyclization.[34, 35]

The cyanopyrrolidine moiety of saxagliptin occupies the S1 pocket of DPP-IV and forms a covalent bond interaction between the cyano group and side chain of Ser630 residue. The hydrophobic cyclopropane present at this moiety is stabilized with Tyr666 through hydrophobic interaction. The hydrophobic and bulkier adamantly group is well fitted into the S2 pocket. The hydroxyl group at adamantyl moiety shows hydrogen bond interaction with Tyr547 residue and is responsible for its improved potency. The amino group forms a salt bridge interaction with Glu205 and Glu206. This salt bridge interaction plays a significant role towards potency. Thus, these observed interactions with DPP-IV maintain the drug likeness of saxagliptin.

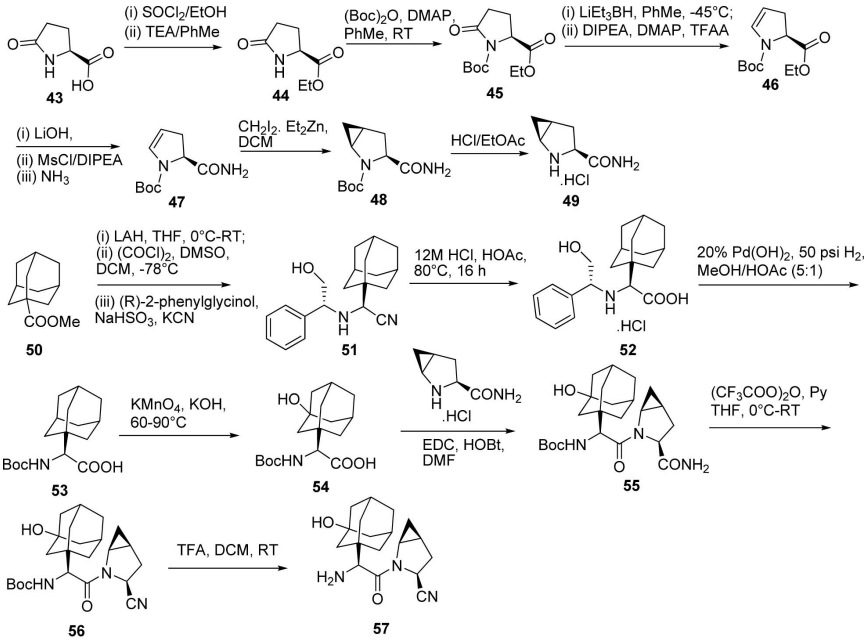
Saxagliptin inhibited 80% and 57% of DPP-IV activity up to 90 min and 24 h respectively, at a single dose of 10 mg. At a single dose of 100 mg, it inhibited more than 95% of DPP-IV activity. It exhibited a half life ($t_{1/2}$) of 2.5-3.0 h and significantly improved the reduction in HbA_{1C} levels. It has been approved by USFDA in 2009 and is being used as a monotherapy as well as in combination with metformin, thiazolidinedione, or sulfonylurea for treatment of type 2 diabetes.

The synthesis of Saxagliptin included the synthesis of its two main intermediates, the methanoprolinamide **49**, and hydroxy adamantyl glycine **54**. The methanoprolinamide intermediate **49** was prepared from L-pyroglutamic acid **43**. Compound **43** after esterification and Boc protection gave **45** via **44,** which was converted into **46**. Compound **46** was converted into **47** through amidation reaction. Using Simmons-Smith reaction, compound **47** was converted into Boc protected methanoprolinamide **48** via cyclopropanation process which after Boc deprotection provided desired intermediate methanoprolinamide **49.**

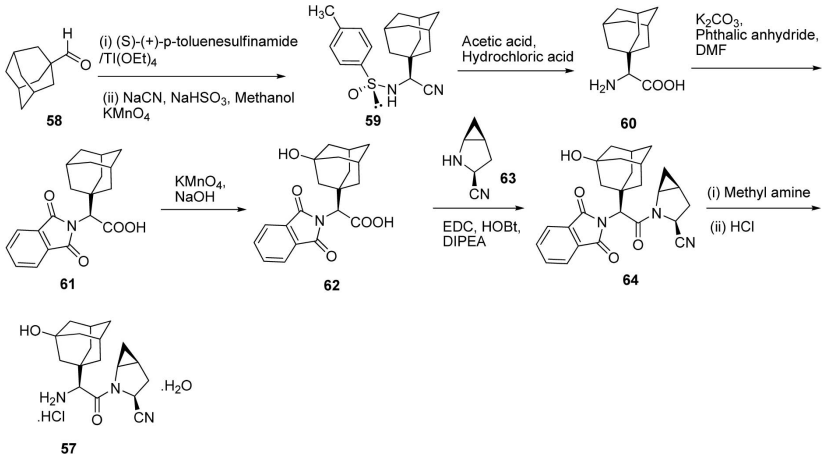
The synthesis of the other key intermediate **54** was started from adamantine carboxylic acid methyl ester **50** followed by reduction to aldehyde and its condensation with (R)-2-phenylglycinol and KCN provided the compound **51**. Compound **53** was obtained from **51** via **52** by following acid hydrolysis, hydrogenation mediated removal of the chiral auxiliary, and Boc protection, respectively. Hydroxylation of compound **53** gave the desired intermediate **54**. Thus, saxagliptin **57** was synthesized by coupling of key intermediates, **49** and **54** using EDC protocol followed by subsequent TFAA-mediated conversion of amide to nitrile and Boc deprotection (Scheme 7).[34]

Recently, Saxagliptin was also synthesized through asymmetric synthesis, which is outlined in scheme 8. Synthesis was started with adamantine-1-carboxaldehyde **58** followed by condensation with (S)-(+)-*p*-toluenesulfinamide and NaCN and gave compound **59**. After acid hydrolysis of **59**, compound **60** was obtained which was subjected to phthalic anhydride protection to give **61**. Hydroxylation of **61** afforded the key intermediate **62** which was coupled with methanopyrrolidine intermediate **63** to give **64** and methyl amine-mediated deprotection of phthalic deprotection gave Saxagliptin **57.**[36,37]

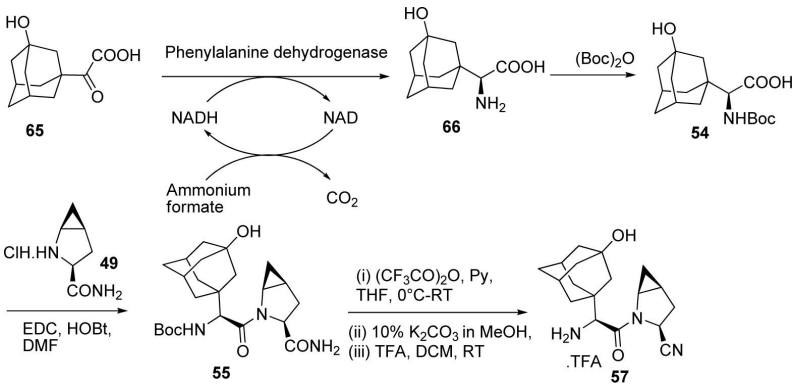
Saxagliptin was also synthesized via enzymatic approach (Scheme 9). (*S*)-*N*-Boc-3-hydroxyadamantylglycine **66** is the key intermediate of Saxagliptin, which was achieved from 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid **65** by reductive amination with phenylalanine dehydrogenase enzyme. After



Scheme 7 Earlier approach towards Saxagliptin synthesis



Scheme 8 Asymmetric approach towards synthesis of Saxagliptin

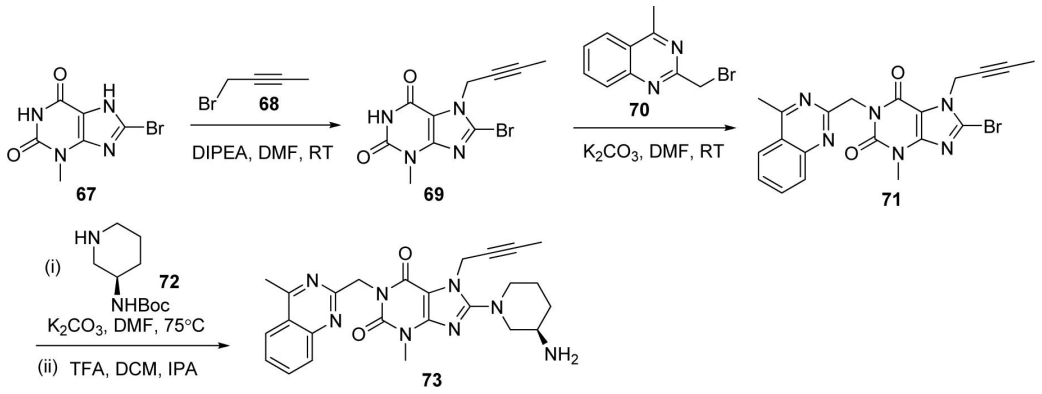


Scheme 9. Enzymatic approach towards synthesis of Saxagliptin

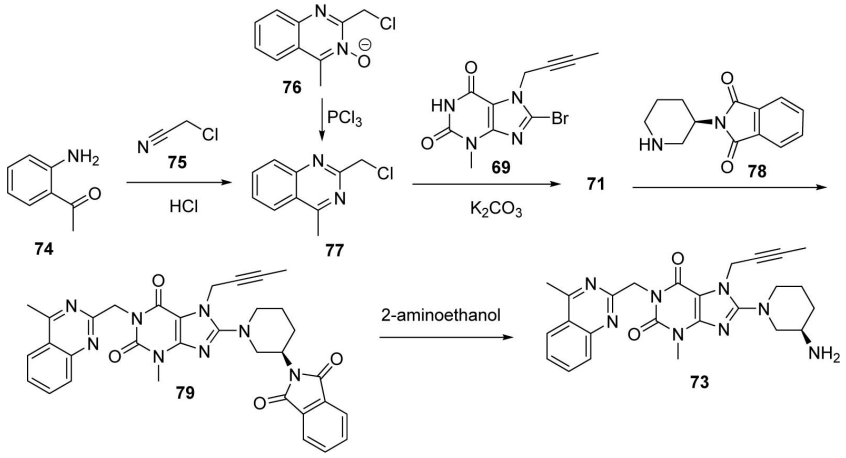
Boc protection followed by coupling with **49** and conversion of amide to nitrile afforded the compound **57.**[38,39]

2.5. **Linagliptin (BI-1356, Boehringer Ingelheim)**

Linagliptin is a xanthine-based second generation inhibitor of DPP-4. It is extremely potent (IC_{50} = 1.0 nM) and much more selective for DPP-IV against DPP-8 (10000), DPP-9 (>10000) and other homozygous peptidases.[40,41] The X-ray crystal structure study has revealed that the S1 pocket of DPP-IV is occupied by the butynyl group of Linagliptin and the S2 pocket is occupied by amino piperidine moiety in which the amino group establishes a salt bridge and hydrogen bonding interactions with diad Glu205 and Glu206, and Tyr662, respectively. The aromatic uracil moiety shows the π-π interaction with Tyr547. The carbonyl group at C-6 position also shows a hydrogen bonding with NH of Tyr631. These observed interactions enhance the potency and the π-π interaction between phenyl component at quinazoline substituent and Trp629 are responsible for the enhanced selectivity profile of Linagliptin. The oral bioavailability of Linagliptin was 51% and exhibited long half-life ($t_{1/2}$) of 113-131 h which was directly associated with its prolonged DPP-4 inhibitory activity.[42,43] It exhibited ≥80% of plasma DPP-4 inhibition over 24 hours at a single dose of 10.0 mg/kg [105]. It showed a significant lowering in HbA_{1c} levels (0.69%).[44] However, Linagliptin enhances the GLP-1 levels that are related to β-cell regeneration.



Scheme 10. Synthesis of Linagliptin



Scheme 11. Alternative approach towards Linagliptin synthesis

It has limited side effects with no risk of hypoglycemia observed even at higher doses and is approved by USFDA in May 2011 for treatment of type 2 diabetes.

The synthesis of linagliptin presented in scheme 10, was started with N-7 alkylation of xanthine moiety **67** with 1-bromo-2-butyne **68** to afford compound **69**. Further, N-1 alkylation of **69** with **70** resulted compound **71** which on nucleophilic substitution reaction at C-8 position by 3-aminopiperidine **72** and subsequent Boc deprotection afforded Linagliptin **73.**[40]

Some Alternative approaches were also reported for synthesis of Linagliptin.[45-48] The alternative route for synthesis of Linagliptin involved the preparation of a key intermediate **77** via either the cyclization of 2-aminoacetophenone **74** with chloroacetonitrile **75** or the reaction of quinazoline oxide 76 with PCl_3. Further, N-1 alkylation of **69** with **77** gave the compound **71**. Finally, linagliptin **73** was prepared from the nucleophilic substitution at C-8 position by piperidine derivative followed by removal of phthalic anhydride protection with 2-aminoethanol (Scheme 11).

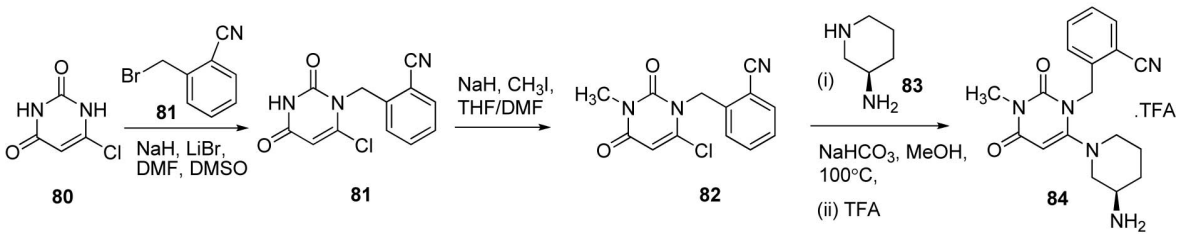
2.6. Alogliptin (SYR-322, Takeda)

Alogliptin (**5**) containing pyrimidinedione scaffold is the third generation inhibitor of DPP-IV. It is extremely potent having highly selective profile for DPP-IV over isozymes such as DPP-2, DPP-8, DPP-9, and FAP etc.[49] The X-ray study reveals that the cyanobenzyl group occupies the S1 pocket and makes interaction with Arg125. The aminopiperidine scaffold of alogliptin binds into the S2 pocket by making a salt bridge interaction with carboxylate groups of Glu205 and Glu206. The C=O group displays a hydrogen bonding with backbone NH of Tyr631 and the central uracil core shows a π-π interaction with side chain of Tyr547 residue. These interactions are the charcterstic features for alogliptin to become a clinical candidate for treatment of type 2 diabetes.

It exhibited a half-life of 5.7 h with bioavailabilites of 72-88% at different doses of 2.0, 10.0, and 30.0 mg/kg. Alogliptin displayed more than 90% of DPP-IV inhibition for a full 24 h at doses of 25.0 mg q.d.[50,51] It showed noteworthy improvement in the insulin levels and glucose tolerance, and a dose-dependent DPP-IV inhibition and elevated GLP-1 levels.[52,53] It also exhibited 0.2% reduction of HbA_{1c} at a dose of 3 mg/kg.[54] It has been approved by USFDA in January 2013 for treatment of type 2 diabetes.

In the synthesis of alogliptin (Scheme 12), 4-chlorouracil **80** was used a key starting material which on reaction with 2-(bromomethyl) benzonitrile afforded compound **81**.[55] The methylation reaction with methyl iodide of **81** followed by nucleophilic substitution with 3-(R)-aminopiperidine **83** presented alogliptin **84** as the TFA salt.[49,56]

2.7. Gemigliptin (LC15-0444, LG Life Sciences)



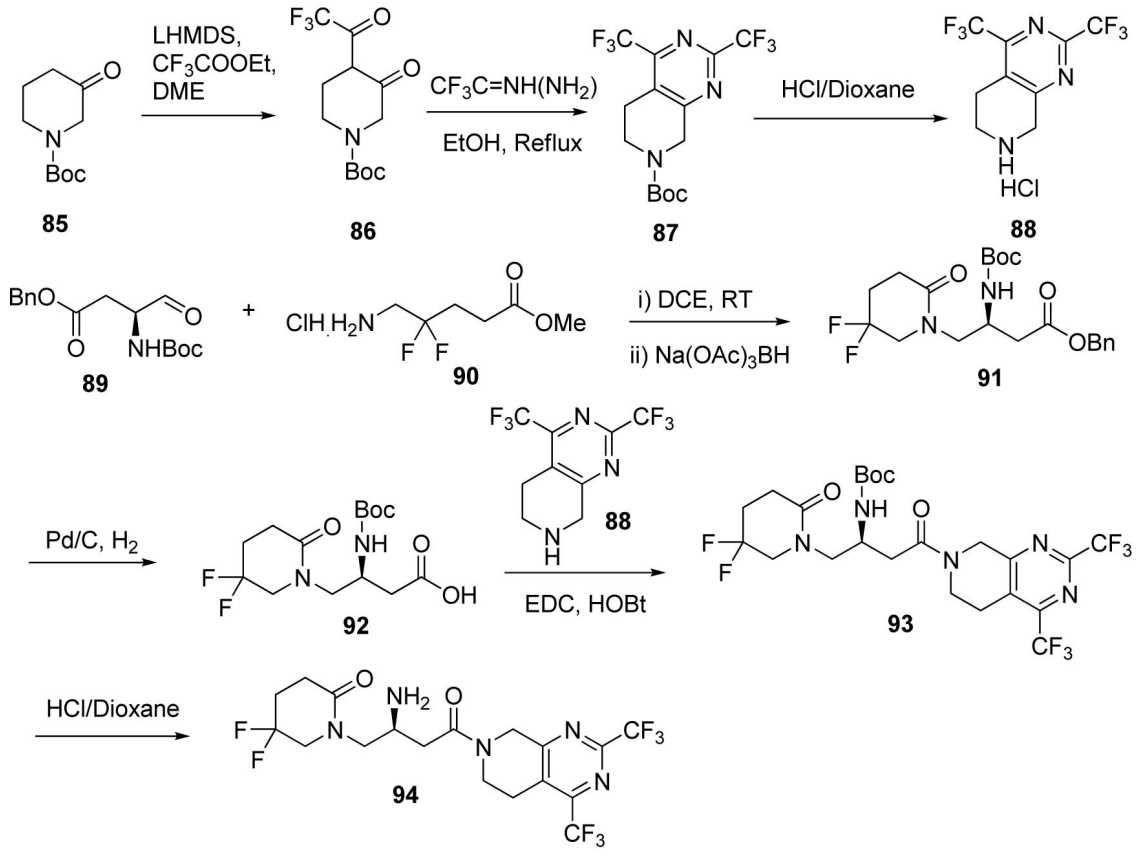
Scheme 12. Synthesis of Alogliptin

Gemigliptin is a sitagliptin analogue discovered by LG Life sciences Ltd, Korea via the derivatization of the compounds. It is potent and long acting DPP-IV inhibitor with high selectivity profile (3000-fold) against isoenzymes. The binding mode of gemigliptin is not reported, but expected as sitagliptin due to structural similarity. It inhibited more than 80% of DPP-IV activity and exhibited the bioavailability of 94% in rats. It also showed the lowering of blood glucose and elevating of GLP-1 levels in dose-dependent manner in the diet-induced obese mice. Gemigliptin displayed a noteworthy lowering in HbA_{1c} level (0.77%) at a dose of 3.0 mg/kg.[57] It is approved by Korean FDA in June 2012 for the treatment of T2DM.[58]

Synthesis of gemigliptin involved the preparation of two key intermediates dihydropyrido[3,4-d] pyrimidine moiety **88** and β-amino acid moiety **92**. Compound **86** was prepared by generating enolate from compound **85** using LHMDS and adding trifluoroacetate. Compound **86** gave the **87** in reflux condition which after Boc deprotection afforded key amine intermediate **88**. The β-amino derivative **91** was synthesized by cyclization reaction between **89** and **90**, which on benzyl deprotection using Pd/C gave desired β-amino intermediate **92**. Coupling of this intermediate with **88** using EDC/ HOBt followed by Boc deprotection offered gemigliptin **94** via **93** (Scheme 13).[59,60]

2.8. Teneligliptin (MP-0513, Mitsubishi Tanabe)

Teneligliptin is a bicyclic heteroarylpiperazine-derived constrained DPP-IV inhibitor discovered by Mitsubishi Tanabe in Japan. It



Scheme-13. Synthetic approach towards Gemigliptin

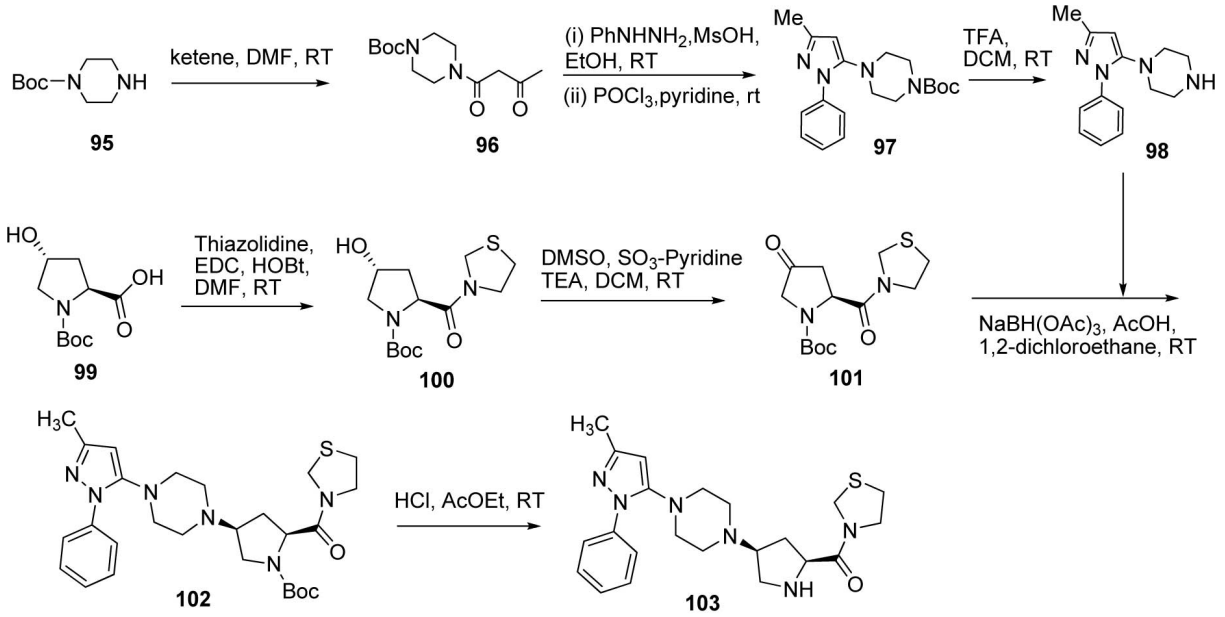
is extremely potent (0.37 nM) and selective for DPP-IV against DPP-8 (703 fold) and DPP-9 (1460 fold). The crystal structure reveals that like substrate based inhibitor, the thiazolidine moiety occupies the hydrophobic S1 pocket. The rest part of the inhibitor binds to the S2 and S2 extensive pocket. Like other inhibitors, the amino group of proline moiety forms a salt bridge with the diad of Glu205 and Glu206. The C=O group shows a hydrogen bonding with Asn710. The (1-phenylpyrazol-5-yl) piperazine part of this inhibitor is the ''anchor lock domain'' and occupies the S2 extensive pocket. The pyrazolyl ring is stacked with the phenyl ring of Phe357 residue and piperazinyl ring displays a CH-π interaction with side chain of Phe357 residue. The phenyl group of pyrazolyl ring shows hydrophobic interactions with Ser209 and Arg358.

Pharmacokinetic studies exhibited the half-lives of 8-16 h in rats with bioavailabilities of 63-86% after oral dosing from 0.1-1.0 mg/kg. It inhibited more than >50% of plasma DPP-IV activity upto 24 h at a single dose of 1.0 mg/kg and significantly lowered the increase blood glucose level in a dose dependent manner. Teneligliptin has been approved in Japan for the T2DM treatment.

Synthesis of teneligliptin (Scheme 14) involved the preparation of 4-Heterocycle-substituted piperazinyl intermediate **98** and diprolyl compound **101**. Intermediate **98** was prepared by treating the Boc piperazine **95** with ketene followed by dehydration and cyclodehydration of resulting β-ketoamide with phenyl hydrazine and phosphorus oxychloride in pyridine, respectively and subsequent Boc deprotection. Another key intermediate **101** was prepared by coupling of *N*-Boc-*trans*-4-hydroxy-L-proline **99** with thiazolidine followed by oxidation with dimethyl sulfoxide and sulfur trioxide. The reductive amination of ketone **101** with intermediate amine **98** afforded only the *cis* isomer of compound **102** which on subsequent Boc removal provided teneligliptin **103.**[61,62]

2.9. **Anagliptin (SK-0403, Sanwa Kagaku Kenkyusho)**

Anagliptin is a 2-methyl pyrazolopyrimidine-



Scheme 14. Synthesis of Teneligliptin

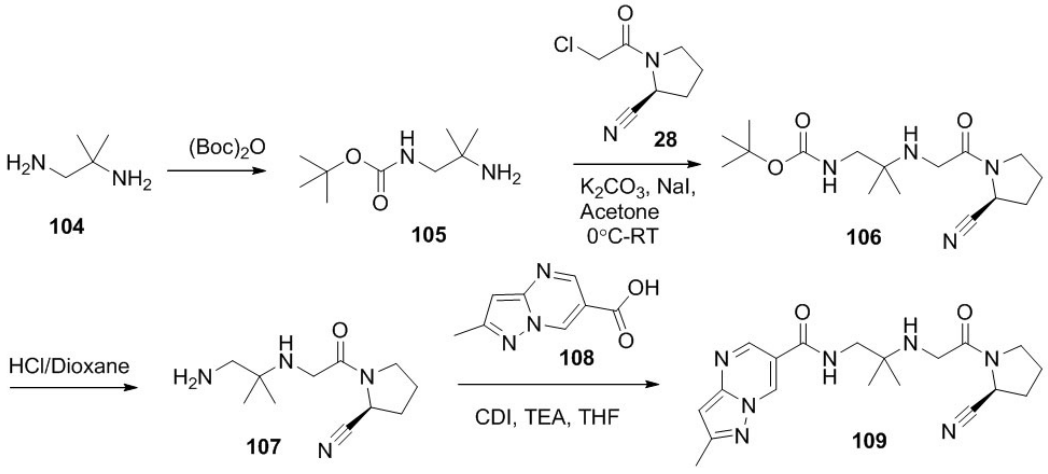
derived cyanopyrrolidine based DPP-IV inhibitor. It is potent (IC_{50}= 3.8 nM) and more than 10000-fold selective for DPP-IV against DPP-8 and DPP-9. It demonstrated a unique pharmacological profile. The pharmacokinetic study showed that anagliptin had a very high oral bioavailability (100%) in beagle dogs. It inhibited DPP-IV activity in a dose dependent manner. Anagliptin provided 95% inhibition of DPP-IV activity at a dose of 3.0 mg/kg and sustained more than 90% throughout the study. It also enhanced the GLP-1 levels, increased the insulin levels and improved the glycemic control. Thus, due to its unique profile, it has been approved for use in Japan for treatment of type 2 diabetes.[63]

Anagliptin was synthesized as described in scheme 1. The selective Boc protection of 2-Amino-2-methylpropylamine **104** with Boc anhydride followed by coupling with (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile **28** gave compound **106** via **105**. After deprotection of the Boc group, compound 106 was coupled with pyrazolo[1,5-a]pyrimidinecarboxylic acid **108** to afford anagliptin **109** in excellent yield. [64]

2.10. **Omarigliptin (MK-3102, Merck)**

Omarigliptin is a novel aminotetrahydropyran-based structurally distinct rigid analogue of sitagliptin in which the central linker of sitagliptin was modified to rigid cyclohexylamine. It is extremely potent (IC_{50}=1.6 nM) and long acting with excellent selectivity profile against isopeptidases. It is once-a-week oral agent rather than once a day like existing therapies in DPP-IV inhibitor. Omarigliptin binds in the DPP-IV active site very similar to sitagliptin and share the same interactions. The 2-F atom in the trifluorophenyl group occupied in S1 pocket shows a hydrogen bonding with the side chain of Arg125. On the other hand, the aminotetrahydropyran group binds to S2 pocket where the primary amine group makes salt bridges with the carboxylates of Glu205 and Glu206. The fused ring π-π stacks with the side chain of Phe347.[65]

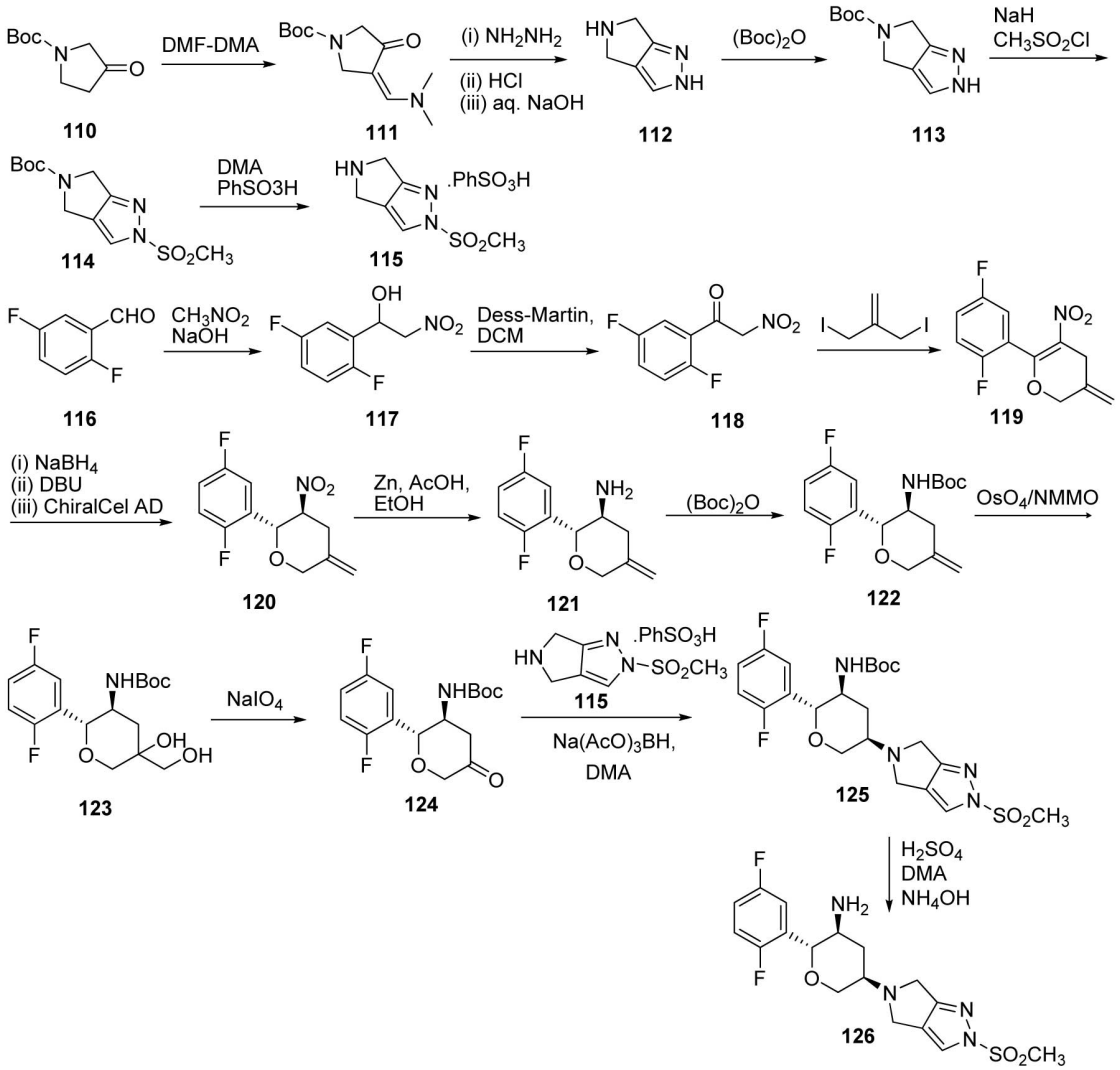
Omarigliptin exhibited a unique PK and pharmacological profile with the half-life of ~68 h. It markedly lowered the blood glucose levels and 0.57% of HbA_{1c} level at a dose of 25 mg in a 12 week study. It also exhibited 77-89% inhibition of plasma DPP-IV up to 168 h and enhanced two folds of GLP-1 levels. Omarigliptin is generally well tolerated with excellent safety profiles in healthy subjects. Currently, omarigliptin is in clinical trial Phase-III.[66-68]



Scheme 15. Synthesis of Anagliptin

Synthesis of Omarigliptin is illustrated in scheme 16 which involved the preparation of key intermediates methylsulfonylpyrrolopyrazole **115** and tetrahydropyranone **124**. The pyrrolopyrazole **115** was prepared by heating the Boc-protected ketone **110** with N, N-dimethylformamide-dimethylacetal (DMF-DMA) to form the enamine **111**, which on subsequent heating with hydrazine and hydrogen chloride in dry ethyl acetate, and neutralization with aqueous sodium hydroxide provided the pyrrolopyrazole compound **112**. The methylsulfonylpyrrolopyrazole **115** was prepared from the compound **112** followed by Boc protection and sequential reaction with sodium hydride, methanesulfonyl chloride, and Boc deprotection with benzene sulfonic acid.

Another key intermediate tetrahydropyranone **124** was made from nitroketone **118** which was prepared by reaction of aldehyde **116** with nitromethane in the presence of sodium hydroxide followed by oxidation of the resulted nitro alcohol **117** with Dess-Martin reagent. The reaction of the nitroketone **118** with 3-iodo-2-



Scheme 16. Synthetic approach of Omarigliptin

(iodomethyl)prop-1-ene afforded the pyran **119**, which after reduction with sodium borohydride provided a mixture of racemic *trans*- and racemic *cis*- isomers which were separated by chiral column chromatography. These *cis*-isomers were easily converted to the *trans* isomer in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The desired nitrosubstituted pyran **120** was reduced to compound **121** using zinc and hydrochloric acid. The amine compound **121** was protected with Boc anhydride to give compound **122** which on treatment with osmium tetraoxide and N-methylmorpholine N-oxide followed by reaction with sodium periodate afforded the desired ketone **124**. The reductive amination reaction of desired ketone intermediate **124** with methylsulfonylpyrrolopyrazole **115** in the presence of triacetoxyborohydride in dimethylacetal provided compound **125**, which after Boc deprotection and neutralization with ammonium hydroxide afforded omarigliptin **126** in crystalline form.[65,69]

2.11. **Gosogliptin (PF-00734200, Pfizer)**

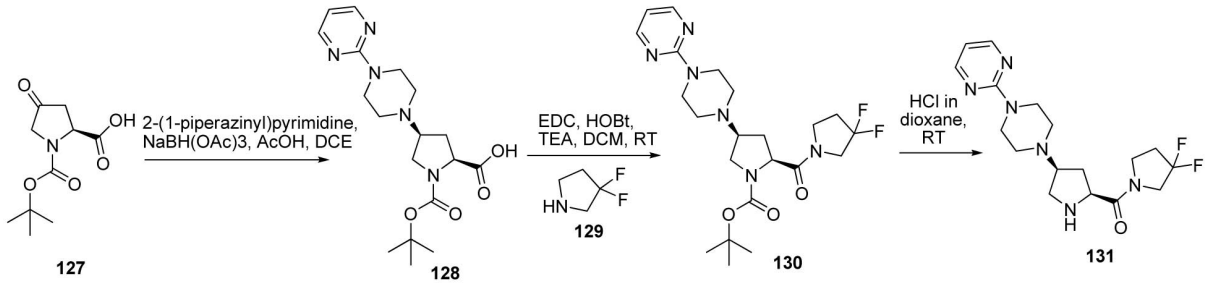
Gosogliptin is a diprolyl derived piperazine containing constrained inhibitor of DPP-IV. It is a potent (IC_{50} = 13 nM) and highly selective over DPP-2 and DPP-8 (100-fold). The interactions observed in the co-crystal structure of gosogliptin with recombinant human DPP-IV confirms the binding mode in the active site and inhibitory activity. The difluoropyrrolidide moiety is very hydrophobic and binds to the S1 pockets where it displays hydrophobic interactions with Trp659, Val 656, Tyr631, Ser630, Tyr666 and Tyr662. One of the fluorines forms hydrogen bonding with either Ser630 or the main chain amide of Tyr631. The remaining part of the inhibitor occupies the S2 pocket where the secondary amine of the pyrrolidine makes a salt bridge with carboxylates of Glu206 and Glu205. The pyrimidine moiety binds in the S2 extensive pocket and forms a pi-pi stacking interaction with the side chain of Phe357 which is responsible for the improvement in selectivity.

Gosogliptin exhibited excellent pharmacoloagical and ADME properties. It had a half-life of 2.7 h with a bioavailability of 109% in rats. In the clinical study, it enhanced the GLP-1 levels (two fold) at doses above 10 mg and displayed 75% DPP-IV inhibition at 24 h.[70,71]

N-Boc-L-ketoproline **127** was the starting material for gosogliptin synthesis. The stereoselective reductive amination reaction of ketone **127** with 2-pyrimidylpiperazine in the presence of triacetoxyborohydride afforded only the *cis* isomer **128**. The coupling of compound **128** with 3,3-difluropyrrolidine **129** using EDC/HOBt protocol followed by Boc deprotection of resulting compound **130** with HCl in dioxane offered gosogliptin **131** (Scheme 17).[71]

2.12. **Denagliptin (GSK-823093, GlaxoSmithKline)**

Denagliptin is a rationally designed



Scheme 17. Synthesis of Gosogliptin

cyanofluoropyrrolidine class of DPP-IV inhibitor. It inhibits human DPP-IV with IC_{50} value of 22 nM. The selectivity profile versus other peptidases is not available. The molecular docking study shows that denagliptin binds in the active site of DPP-IV as substrate based inhibitors and forms five strong hydrogen bonds with the side chain of Glu205, Glu206, Asn710, Tyr662 and Arg125.[72] Denagliptin exhibited maximal DPP-IV inhibition after 30 minutes and more than 85% after 24 h at a dose of 25 mg. During the treatment, GLP-1 and insulin levels were elevated and glucagon was suppressed.[73]

Denagliptin was synthesized by using bisfluorobiphenyl **132** as a precursor of hydroxy acid **133**, which was converted into acid **135** via **134** by successive treatment with H_2SO_4 and catalytic hydrogenation. Compound **135** was converted into oxazolidine amide **136.** Compound **136** on the introduction of an azide moiety provided compound **137,** which after hydrolysis followed by subsequent reduction to amine and Boc protection gave the desired intermediate **139** via **138**. Finally, the coupling of **139** with 4-fluoro-2-pyrrolidinecarbonitrile **139** followed by Boc deprotection of amine offered denagliptin **140** (Scheme 18)**.**[74,75]

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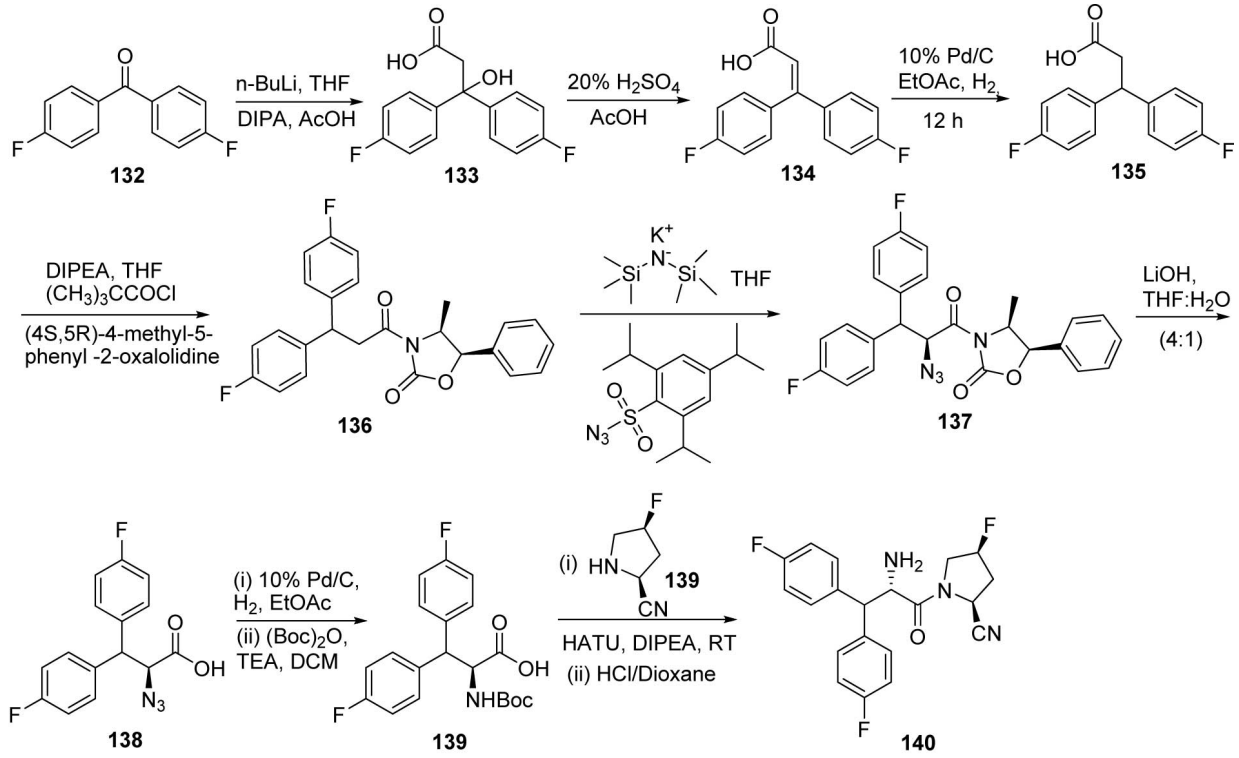
2.13. **Melogliptin (GRC 8200, Glenmark)**

Melogliptin was discovered through structure-based design strategy. It is a trazole containing, long acting inhibitor of DPP-IV. It is very potent (IC_{50} = 1.61 nM) and highly selective (10000 fold) for DPP-IV against related other isoenzymes. [76,77] The binding mode of melagliptin with DPP-IV is not reported but must be similar to other substrate based inhibitor. Melogliptin exhibited the half-lives of 1.28, 4.31 and 2.15 h with excellent oral bioavailabilities of 60, 90 and 94% in rat, dog and cynomolgus monkeys, respectively, at a dose of 5 mg/kg.[78] It displayed 30% of glucose lowering and enhanced the insulin levels two folds at a single oral dose of 3 mg/kg in *db/db* mice.[77] A single dose of 5 mg/

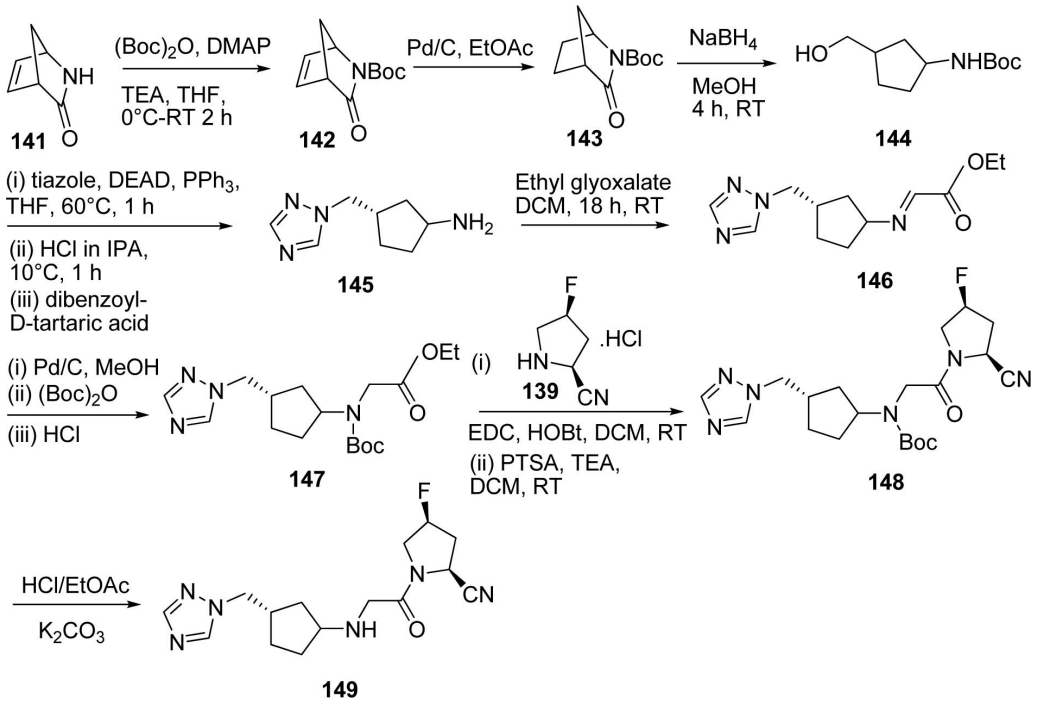


Scheme 18. Synthesis approach of Denagliptin

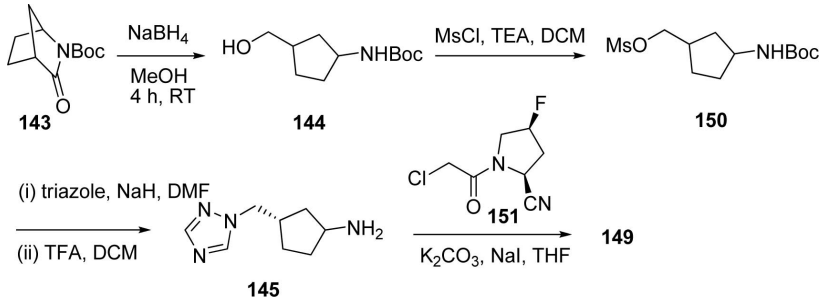
kg po of melogliptin inhibited maximal DPP-IV activity within one hour and more than 90% after 6 h in overnight fasted beagle dogs.[79] It also showed 0.75% and 0.60% of HbA_{1c} levels at a dose of 50 mg twice daily and 100 mg once daily doses. Currently, melogliptin is in phase 3 clinical trials.

Synthesis of melogliptin as illustrated in scheme 19 start with Boc protection of ketone **141** to give compound **142**. After palladium catalyzed reduction of **142**, the resulting compound **143** was reduced with sodium borohydride to give amino alcohol **144**. Compound **145** was prepared via Mitsunobu reaction followed by Boc deprotection and resolution with dibenzoyl D-tartaric acid. Compound **145** after reductive amination and successive Boc protection provided **147** via **146**. Compound **147** on further coupling with **139** followed by Boc deprotection afforded melogliptin **149** via **148.**[80]

The alternative route towards melogliptin synthesis (Scheme 20) involved the mesylation of compound **144** as prepared in scheme 19, gave **150**, which on reaction with triazole using sodium hydride followed by Boc deprotection offered compound **145**. Finally, the coupling



Scheme-19 Synthesis of melogliptin



Scheme 20. Alternative approach towards melogliptin synthesis

of chloroacetamide **151** with intermediate **145** gave melogliptin **149.**[76]

2.14. Trelagliptin (SYR-472, Takeda/ Furiex)

Trelagliptin is a pyrimidinedione-based long-acting inhibitor of DPP-4. It is potent with IC_{50} = 4 nM and highly selective (>100000 fold) over isopeptidases. Due to similarity in the skeleton with alogliptin, trelagliptin also exhibits similar binding profile at the active site of DPP-IV. The aminopiperidine moiety forms a salt bridge to Glu205 and Glu206, while the fluorocyanobenzyl group occupies the hydrophobic S1 pocket and interacts with Arg125. The carbonyl at 2-position forms an important hydrogen bond with the backbone NH of Tyr631, and the uracil core π-stacks with Tyr547.

Trelagliptin showed the favorable PK-PD profiles in dogs and monkeys with half-life 4.8 h and 6.2 h, respectively. It inhibited more than 80% of plasma DPP-IV activity after 24 h at a single oral dose of 7.0 mg/kg. It displayed the improvement in glucose tolerance and postprandial plasma insulin levels in Zucker *fa/fa* rats. Trelagliptin significantly reduced the HbAc1 levels in a dose dependent manner. Like omarigliptin, trelagliptin is also a once-weekly oral antidiabetic agent and has the safe profile. It is believed that trelagliptin will supersede all available gliptins reported so far because of its once-weekly oral treatment, superior efficacy, and qualification of cardiovascular safety tests. Currently, Trelagiptin is in Phase 3 clinical trials in Japan and has been submitted to New Drug Application (NDA) for treatment of type 2 diabetes.

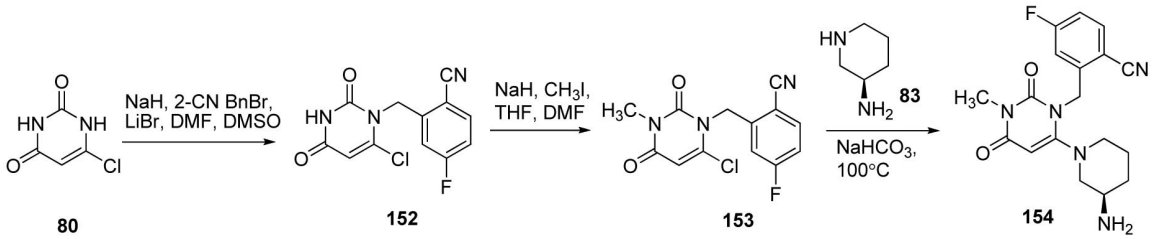
Synthesis of trelagliptin is outlined in scheme 21. Synthesis started with selective alkylation of chlorouracil **80**, followed by methylation provided compound **153** via **152**. The displacement of chloride with 3-(R)-aminopiperidine **83** afforded trelagliptin **154.**[81]

2.15. Retagliptin (SP-2086)

Retagliptin is a tetrahydro-imidazo[1,5-a] pyrazine derivative being developed by Jiangsu Hengrui Medicine. It is an improved version of sitagliptin. It is very potent (IC_{50}= 8 nM) and much more selective over DPP-8 (3263-fold) and DPP-9 (9438-fold). It lowered the blood glucose in OGTT. Its half life was 1.5 h. It is currently under clinical trial phase-III.[82 83]

Synthesis of retagliptin is illustrated in Scheme 22, which involved the preparation of two important intermediates **12** and **164**. The β-amino acid intermediate **12** was synthesized from compound **155** with treatment of 2,2-Dimethyl-[1,3]dioxane-4,6-dione **21** in the presence of DMAP and EDC followed by subsequent heating in ethanol, treatment with ammonium acetate in methanol, Boc protection and stereocontrolled hydrogenation, and hydrolysis afforded intermediate **12** via intermediates **156**, **157**, **158** and **159**.

The tetrahydro-imidazo[1,5-a]pyrazine



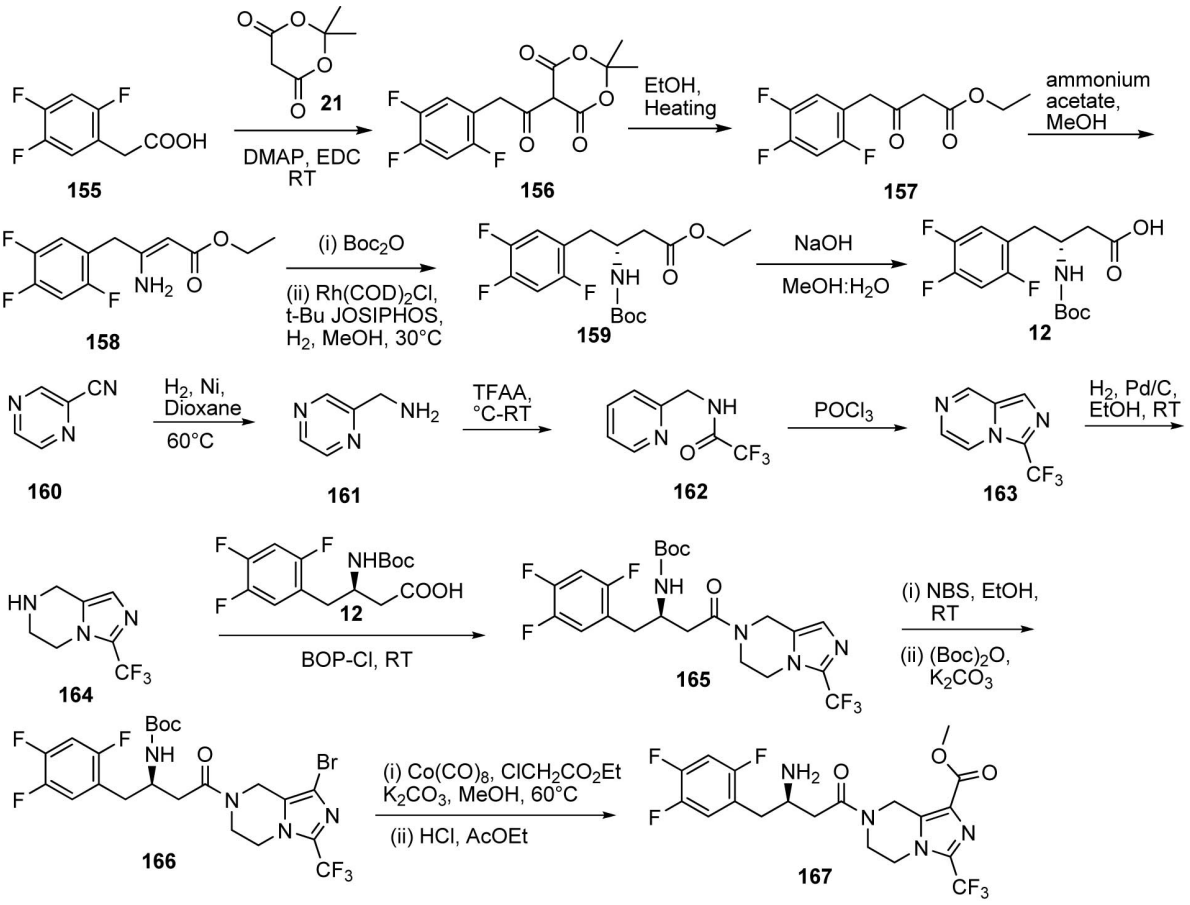
Scheme 21. Synthetic approach towards Trelagliptin

moiety **164** was prepared from pyrazine-2-carbonitrile **160** which on via Ni catalyzed hydrogenation followed by acylation reaction with trifluoroacetic anhydride gave compound **162** via **161**. The intramolecular cyclization of compound **162** with phosphorous oxytrichloride gave compound **163,** which on catalytic hydrogenation over Pd/C provided the tetrahydro-imidazo[1,5-a]pyrazine intermediate **164**. The coupling of the β-amino acid **12** with tetrahydro-imidazo[1,5-a]pyrazine intermediate **164** provided compound **165**, which on treatment with N-bromosuccinamide and Boc anhydride followed by the successive reaction with ethyl chloroacetate in the presence of octacarbonyldicobalt and potassium carbonate, and Boc deprotection afforded retagliptin **167.** [82,84,85]

2.16. **Evogliptin (DA-1229, Dong-A)**

Evogliptin is a β-amino amide derivative which was discovered by Dong-A Pharmaceutical in Korea. It is very potent (IC_{50} = 0.98 nM), long-acting and highly selective (6000-fold) over isoenzymes.[86] In the active site of the DPP-IV, the hydrophobic trifluorophenyl moiety binds into the hydrophobic S1 pocket and stabilized with Tyr547, Tyr662 and Tyr666. The β-amino amide moiety occupies in the S2 pocket. The amine group shows a salt bridge with Glu205 and a hydrogen bonding with a side chain of Tyr662. Piperazine-2-one moiety binds into the S2 extended pocket.

Evogliptin exhibited more than 80% of DPP-IV inhibition at a single dose of 5.0 mg in the



Scheme 22. Synthesis of Retagliptin

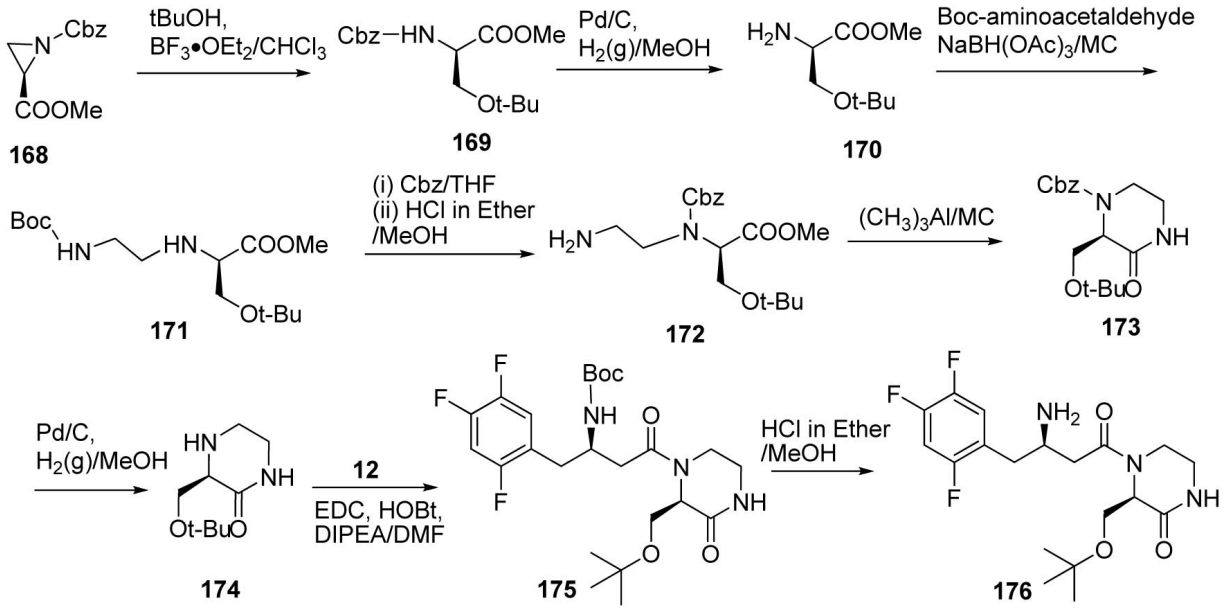
phase 1 clinical trial. In the long-term treatment it also showed the noteworthy improvement in the impaired glucose tolerance and insulin resistance. It showed a significant reduction in HbA_{1c} levels of 0.56% and 0.61% at doses of 2.5 and 5.0 mg, respectively. It was proven as efficacious, safe and well tolerated inhibitor at all doses [87] and currently, it has completed phase-II clinical trial.

Synthesis of evogliptin started with the preparation of piperazine-2-one moiety **174** from the boron trifluoride catalyzed ring opening of N-protected aziridine carboxyl ester **168** with tertiary butanol. The resulting compound **169**, after hydrogenation gave compound **170,** which after reductive amination with sodium triacetoxyborane followed by Boc deprotection and cbz-protection provided compound **172** via **171**. Compound **172** was conducted using trimethylaluminium followed by cbz deprotection gave the key intermediate **174**. The coupling of this key intermediate with β-amino acid **12** offered **175**, which after Boc deprotection using hydrochloride in ether provided evogliptin **176.**

2.17. Carmegliptin (R-1579, F. Hoffmann-La Roche)

Carmegliptin contains a tricyclic scaffold and was jointly developed by Roche and Chugai. It is very potent (IC_{50} = 6.8 nM) and selective inhibitor of DPP-IV against isopeptidases such as DPP-8 and DPP-9 (>100-fold) and DPP-II and FAP (>2000-fold). The X-ray crystal structure study reveals that the 4-fluoromethyl pyrrolidinone moiety binds into the hydrophobic S1 pocket in the active site of DPP-IV. The lactam C=O forms a hydrogen bonding with Tyr662 and the amido NH_2 of Asn710, and a cation-dipole interaction with the guanidine tail of Arg125. This amide carbonyl is the imitator of the carbonyl of substrate based inhibitors. The tricyclic moiety of the carmegliptin occupies perfectly in the S2 pocket. The amine group forms a salt bridge with the Glu205 and Glu206, and a hydrogen bonding with Arg125.

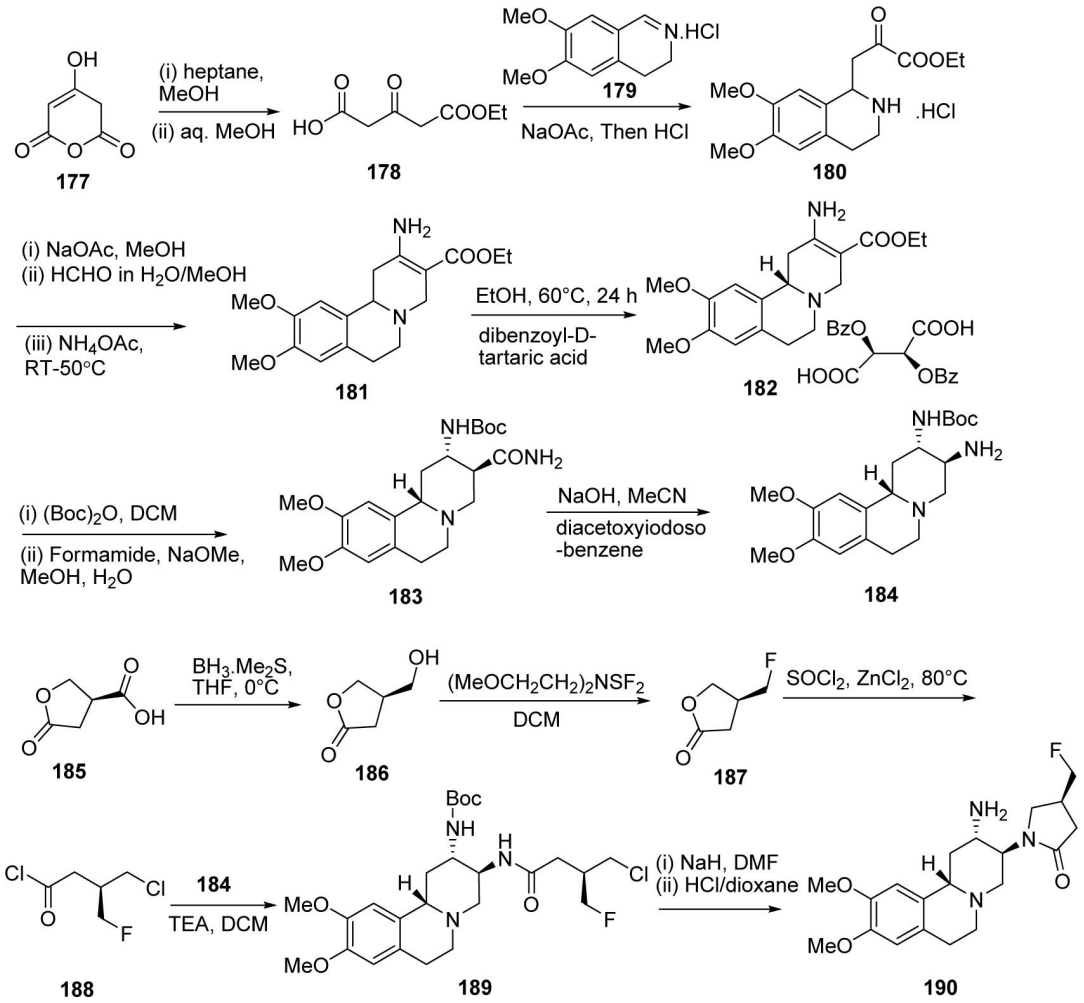
Carmegliptin showed a half-life of 6.8 h with a



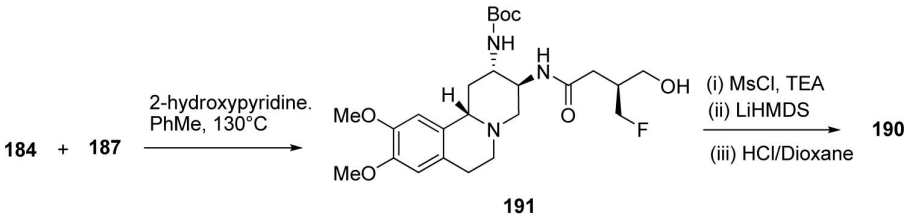
Scheme 23. Synthesis of evogliptin

bioavailability of 33% in cynomolgus monkey at an *i.v.* dose of 1.0 mg/kg. It exhibited the significant blood glucose lowering, and inhibited 40% and 60% of plasma DPP-IV activity after 24 h and 48 h, respectively, at a single oral dose of 3.0 mg/kg. The clinical trial results exhibited that it was efficacious and safe inhibitor for treatment of type 2 diabetes.[88]

The synthesis of carmegliptin is described in scheme 24. The pyridoisoquinoline amine **184** is the key intermediate for the carmegliptin synthesis. Compound **184** was prepared from the anhydride **177** that was transformed to **180** via the reaction of resulting compound **178** with **179**. Compound **180** was converted to **181** which after resolution provided **182.** Compound **182**



Scheme 24. Synthesis of Carmegliptin



Scheme 25. Alternative Approach towards Carmegliptin synthesis

was converted to **183** which on treatment with diacetoxyiodosobenzene afforded the desired intermediate **184**.

Another intermediate acid chloride **188** was prepared from (S)-paraconic acid **185** taken as starting material.[89] The reduction of **185** with borane-dimethyl sulfide complex gave the hydroxymethyl lactone **186**. Since compound **186** is known to racemise rather readily,[90] it was immediately treated with bis(2-methoxyethyl) aminosulfur trifluoride,[91] which gave fluoromethyl lactone **187.** On reaction of **187** with thionyl chloride in the presence of zinc chloride provided acid chloride **188** intermediate. Thus, the reaction of pyridoisoquinoline amine **184** with acid chloride **188** afforded the compound **189**, which after treatment of sodium hydride followed by Boc deprotection gave carmegliptin **190**. Carmegliptin could also be synthesized by an alternative route as outline in scheme 25.[92,93]

3. Conclusions

It is clear from the foregoing discussion that during the period of 17-years of research, 17 gliptins have been discovered from a large number of structurally diverse lead DPP-IV inhibitors. Gliptins are well tolerated, efficacious and safe. Till now, out of 17 gliptins, eight gliptins such as sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, teneligliptin, anagliptin and gemigliptin have been approved and are in clinical usage for the treatment of T2DM. Remaining gliptins are currently under clinical trials. Secretion of incretins (GLP-1 and GIP) is glucose dependent and induce insulin secretion and correct the insulin sensitivity. Thus, the long time treatment with gliptin may permanently erase the type 2 diabetes.

For the development of safe gliptin for treatment of type 2 diabetes, high selectivity profile for DPP-IV inhibitors against related isozymes such as DPP-2, DPP-8, DPP-9, and FAP., PK profile, CYP inhibition, and hERG channel inhibition are the major challenges due to which the lead candidate may fail or display adverse effects during the drug discovery. The selectivity issue can be resolved by designing the promising DPP-IV inhibitors, which target the selectivity triggering residues such as Ser209, Arg358 and Phe357, of the S2 extended pocket of DPP-IV. Secondly it is also evident from the foregoing discussion the power of synergy between process chemistry and biological activity in bringing about time attrition from laboratory discovery to clinical usage.

4. Acknowledgements

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5. References

1. International Diabetes Federation Diabetes Atlas, sixth ed., The Global Burden, **2013**, pp. 29-50. http://www.idf.org/diabetesatlas/download-book (accessed 18.05.2014).
2. American Diabetes Association, Diagnosis and classification of diabetes mellitus, *Diabetes Care,* **2010**, 33, S62-S69.
3. (a) T. Scully, Diabetes in numbers, *Nat. Outlook: Diabetes,* **2012**, 485, S2-S3; (b) P. Shetty, India's diabetes time bomb, *Nat. Outlook: Diabetes,* **2012**, 485, S14-S16.
4. W. B. Kannel and D. L. McGee, *Circulation*, **1979,** 59, 8–13.
5. A. S. Krolewski, E. J. Kosinski, J. H. Warram, O. S. Leland, E. J. Busick, A. C. Asmal, L. I. Rand, A. R. Christlieb, R. F. Bradley, and C. R. Kahn, *Am. J. Cardiol.*, **1987**, 59, 750–755.
6. J. J. Holst and C. F. Deacon, *Curr. Opin. Pharmacol.*, **2004**, 4, 589–596.
7. D. J. Drucker, *Gastroenterology*, **2002**, 122, 531–544.
8. B. Leiting, K. D. Pryor, J. K. Wu, F. Marsilio, R. A. Patel, C. S. Craik, J. A. Ellman, R. T. Cummings, and N. A. Thornberry, *Biochem. J.*, **2003,** 371, 525-532.
9. D. M. Evans, *Drugs*, **2002**, 5, 577-585.
10. A. E. Weber, *J. Med. Chem.* **2004**, 47, 4135-4141.
11. S. H. Havale and M. Pal, *Bioorg. Med. Chem.*, **2009**, 17, 1783-1802.

12. B. D. Patel and M. D. Ghate, *Eur. J. Med. Chem.,* **2014**, 74, 574-605.
13. S. L. Gwaltney II[nd], *Curr. Top. Med. Chem.,* **2008,** 8 (17), 1545-1552.
14. Y. Liu, Y. Hu, T. Liu, *Curr. Med. Chem.,* **2012,** 19 (23), 3982-3999.
15. N. Mulakayala, C. H. U. Reddy, J. Iqbal and M. Pal, *Tetrahedron*, **2010**, 66, 4919-4938.
16. D. Kim, L. Wang, M. Beconi, G. J. Eiermann, M. H. Fisher, H. He, G. J. Hickey, J. E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M. E. McCann, R. A. Patel, A. Petrov, G. Scapin, S. B. Patel, R. S. Roy, J. K. Wu, M. J. Wyvratt, B. B. Zhang, L. Zhu, N. A. Thornberry, A. E. Weber, *J. Med. Chem.,* **2005,** 48 (1), 141-151.
17. J. F. Todd, and S. R. Bloom, *Diabet. Med.,* **2007,** 24 (3), 223-232.
18. L. Xu, C. D. Man, B. Charbonnel, G. Meninger, M. J. Davies, D. Williams-Herman, C. Cobelli and P. P. Stein, *Diabetes Obes. Metab.,* **2008,** 10 (12), 1212-1220.
19. R. Scott, M. Wu, M. Sanchez, P. Stein, *Int. J. Clin. Pract.,* **2007,** 61 (1), 171-180.
20. G. A. Herman, A. Bergman, F. Liu, C. Stevens, A. Q. Wang, W. Zeng, L. Chen, K. Snyder, D. Hilliard, M. Tanen, W. Tanaka, A. G. Meehan, K. Lasseter, S. Dilzer, R. Blum and J. A. Wagner, *J. Clin. Pharmacol.,* **2006,** 46 (8), 876-886.
21. A. Muller, C. Vogt, N. Sewald, *Synthesis* **1988**, 11, 837-841.
22. M. J. Miller, P. G. Mattingly, M. A. Morrison, J. F. Kerwin, *J. Am. Chem. Soc*., **1980**, 102, 7026-7032.
23. K. B. Hansen, H. Yi, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski and J. D. Armstrong, *J. Am. Chem. Soc.*, **2009**, 131, 8798-8804.
24. Yi, Xiao, J. D. Armstrong, S. W. Krska, E. Njolito, N. R. Rivera, Y. Sun, T. Rosner, WO 2004/085378, 2004.
25. E. B. Villhauer, J. A. Brinkman, G. B. Naderi, B. F. Burkey, B. E. Dunning, K. Prasad, B. L. Mangold, M. E. Russell, T. E. Hughes, *J. Med. Chem.,* **2003,** 46 (13), 2774-2789.
26. M. Nabeno, F. Akahoshi, H. Kishida, I. Miyaguchi, Y. Tanaka, S. Ishii and T. Kadowaki, *Biochem. Biophys. Res. Commun*, **2013**, 434, 191-196.
27. S. Ristic, S. Byiers, J. Foley, D. Holmes, *Diabetes Obes. Metab.,* **2005,** 7 (6), 692-698.
28. Y. L. He, B. M. Sadler, R. Sabo, S. Balez, Y. Wang, J. Campestrini, A. Laurent, M. Ligueros-Saylan, D. Howard, *Clin. Pharmacokinet.,* **2007,** 46 (9), 787-802.
29. S. K. Singh, N. Manne and M. Pal, *Beilstein J Org Chem*, **2008**, 4.
30. (a) R. Gupta, S. S. Walunj, R. K. Tokala, K. V. Parsa, S. K. Pal, M. Singh, *Curr. Drug Targets,* **2009**, *10* (1), 71-87; (b) E. J. Verspohl, *Pharmacol. Rev.,* **2012**, 64 (2), 188–237.
31. Z. P. Wu, D. A. Campbell, J. M. Cherrington, WO 200827273, 2008.
32. D. A. Campbell, D. T. Winn, J. M. Betancort, U.S. 2006/0264400, 2006.
33. Z. P. Wu, D. A. Campbell, E. P. Leitao, P. Wang, WO 2008109681, 2008.
34. D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Y. Wang, L. M. Simpkins, P. Taunk, Q. Huang, S. P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker and L. G. Hamann, *J. Med. Chem.*, **2005**, 48, 5025-5037.
35. D. R. Magnin, J. A. Robl, R. B. Sulsky, D. J. Augeri, Y. T. Huang, L. M. Simpkins, P. C. Taunk, D. A. Betebenner, J. G. Robertson, B. E. Abboa-Offei, A. Y. Wang, M. Cap, L. Xin, L. Tao, D. F. Sitkoff, M. F. Malley, J. Z. Gougoutas, A. Khanna, Q. Huang, S. P. Han, R. A. Parker and L. G. Hamann, *J. Med. Chem.*, **2004**, 47, 2587-2598.
36. R. Kovi, K. R. Rapole, A. Naik, J. Kannapan, U. K. Madala, S. F. Thakor, US 2013/0023671 A1,
37. R. Kovi, K. R. Rapole, A. Naik, J. Kannapan, U. K. Madala, S. F. Thakor, WO 2012/162507.
38. T. C. Vu, D. B. Brzoz owski , R. Fox, WO 2004/ 052850 A2.
39. L. R. Hanson , L. S. Goldberg, B. D. Brzozowski, *Adv. Synth. Catal.,* **2007***,* 349, 1369-1378.
40. M. Eckhardt, E. Langkop, M. Mark, M. Tadayyon, L. Thomas, H. Nar, W. Pfrengle, B. Guth, R. Lotz, P. Sieger, H. Fuchs and F. Himmelsbach, *J. Med. Chem.*, **2007**, 50, 6450-6453.
41. L. Thomas, M. Eckhardt, E. Langkopf, M. Tadayyon, F. Himmelsbach, M. Mark, *J. Pharmacol. Exp. Ther.,* **2008,** 325 (1), 175-182.
42. T. Heise, E. U. Graefe-Mody, S. Huttner, A. Ring, D. Trommeshauser, K. A. Dugi, *Diabetes Obes. Metab.* **2009,** 11 (8), 786-794.
43. C. F. Deacon, and J. J. Holst, *Expert opin. Investing. Drugs,* **2010,** 19 (1), 133-140.
44. S. Del Prato, A. H. Barnett, H. Huisman, D. Neubacher, H. J. Woerle, K. A. Dugi, *Diabetes Obes. Metab.,* **2011,** 13 (3), 258-267.
45. N. Serradell, E. Rosa, R. Castaner, Y. Wang, R. Frederick, *Drugs future,* **2008**, 33, 473-477.
46. P. Waldemar, P. Thorsten, N. Thomas, R. Duran, U.S. 2006/0142310, 2006.
47. F. Himmelsbach, E. Langkopf, M. Eckhardt, M. Mark, R. Maier, R. H. Lotz, M. Tadayyon, U.S. 2004/0097510, 2004.
48. K. Kira, R. Clark, S. Yoshikawa, T. Uehara, U.S. 2006/0111362, 2006.
49. J. Feng, Z. Y. Zhang, M. B. Wallace, J. A. Stafford, S. W. Kaldor, D. B. Kassel, M. Navre, L. H. Shi, R. J. Skene, T. Asakawa, K. Takeuchi, R. D. Xu, D. R. Webb and S. L. Gwaltney, *J. Med. Chem.*, **2007**, 50, 2297-2300.
50. C. F. Deacon, *Diabetes Obes. Metab.,* **2011***,* 13 (1), 7-18.

51. P. Covington, R. Christopher, M. Davenport, P. Fleck, Q. A. Mekki, E. R. Wann, A. Karim, *Clin. Ther.,* **2008,** 30 (3), 499-512.
52. C. F. Deacon, *Curr. Opin. Investig. Drugs,* **2008,** 9 (4), 402-413.
53. A. Karim, P. Fleck, L. Hetman, T. Marbury, W. Ravis, C. Cannon et al., Presented at: 68th Scientific Sessions of the American Diabetes Association; June 6–10, 2008; San Francisco, CA. 2008, Abstract 538-P.
54. R. J. Christopher, J. M. Davenport, S. Gwaltney, S. Kaldor, D. Kassel, B. Lee, M. Navre, L. Shi, J. Stafford, R. Xu, and Z. Zhang, *Diabetes,* **2006**, 55, Abstract 452-P.
55. H. Liu, S. B. Ko, H. Josien, D. P. Curran, *Tetrahedron Lett.,* **1995**, 36, 8917-8920.
56. J. Feng, S. L. Gwaltney, J. A. Stafford, S. W. Kaldor, D. B. Kassel, Z. Zhang, E. J. Bruce, I. K; Paul, P. J. Grant, S. S. Jonathon, U. Luckner, WO 2007035629, 2007.
57. S. J. Yang, K. W. Min, S. K. Gupta, J. Y. Park, V. K. Shivane, S. U. Pitale, P. K. Agarwal, A. Sosale, P. Gandhi, M. Dharmalingam, V. Mohan, U. Mahesh, D. M. Kim, Y. S. Kim, J. A. Kim, P. K. Kim, and S. H. Baik, *Diabetes, Obes. Metab.*, **2013**, 15, 410–416.
58. S. H. Kim, S. H. Lee, and H. J. Yim, *Arch. Pharm. Res.*, **2013**, 36 (10), 1185-1188.
59. C. S. Lee, J. S. Koh, K. D. Koo, G. T. Kim, K. H. Kim, S. Y. Hong, S. Kim, M. J. Kim, H. J. Yim, D. Lim, H. J. Kim, H. O. Han, S. C. Bu, O. H. Kwon, S. H. Kim, G. C. Hur, J. Y. Kim, Z. H. Yeom, D. J. Yeo, WO 2006/104356 A1, 2006.
60. K. S. Park, J. M. Yun, B. C. Kim, Y. U. Kim, J. H. Lee, WO 2012/060590, 2012.
61. T. Yoshida, F. Akahoshi, H. Sakashita, H. Kitajima, M. Nakamura, S. Sonda, M. Takeuchi, Y. Tanaka, N. Ueda, S. Sekiguchi, T. Ishige, K. Shima, M. Nabeno, Y. Abe, J. Anabuki, A. Soejima, K. Yoshida, Y. Takashina, S. Ishii, S. Kiuchi, S. Fukuda, R. Tsutsumiuchi, K. Kosaka, T. Murozono, Y. Nakamaru, H. Utsumi, N. Masutomi, H. Kishida, I. Miyaguchi and Y. Hayashi, *Bioorg. Med. Chem.*, **2012**, 20, 5705-5719.
62. S. Fukuda-Tsuru, J. Anabuki, Y. Abe, K. Yoshida and S. Ishii, *Eur. J. Pharmacol.*, **2012**, 696, 194-202.
63. A. I. Graul, B. Lupone, E. Cruces and M. Stringer, *Drugs of Today,* **2013***,* 49 (1), 33–68.
64. N. Kato, M. Oka, T. Murase, M. Yoshida, M. Sakairi, S. Yamashita, Y. Yasuda, A. Yoshikawa, Y. Hayashi, M. Makino, M. Takeda, Y. Mirensha and T. Kakigami, *Bioorg. Med. Chem.*, **2011**, 19, 7221-7227.
65. T. Biftu, R. Sinha-Roy, P. Chen, X. X. Qian, D. Feng, J. T. Kuethe, G. Scapin, Y. D. Gao, Y. Yan, D. Krueger, A. Bak, G. Eiermann, J. He, J. Cox, J. Hicks, K. Lyons, H. He, G. Salituro, S. Tong, S. Patel, G. Doss, A. Petrov, J. Wu, S. S. Xu, C. Sewall, X. Zhang, B. Zhang, N. A. Thornberry, and A. E. Weber, *J. .Med. Chem.,* **2014** 57 (8), 3205-3212.
66. R. Krishna, C. Addy, D. Tatosian, X. S. Hou, I. N. Gendrano, A. N. Martucci, J. A. Wagner, S. A. Stoch, Presented at the 73rd Scientific Sessions of the American Diabetes Association (ADA) in Chicago, June 21-25, 2013.
67. R. Krishna, C. Addy, D. Tatosian, X. S. Hou, I. N. Gendrano, A. N. Martucci, J. A. Wagner, S. A., Presented at the 73rd Scientific Sessions of the American Diabetes Association (ADA) in Chicago, June 21-25, 2013; (b) Brunavs, M.; Cowley, P.; Ward, S. E.; Weber, P., Recent disclosures of clinical candidates (SMR award lecture). *Drugs of the Future,* **2013**, 38 (3), 127-133.
68. T. Biftu, P. Chen, X. X. Qian, D. Feng, J. Cox, J. Hicks, R. Sinha-Roy, G. Scapin, Y. D. Gao, G. Eiermann, J. F. He, H. B. He, J. Kuethe, K. Lyons, G. Salituro, S. Patel, A. Petrov, J. Wu, X. P. Zhang, B. Zhang and A. Weber, *Abstr. Pap. Am. Chem. S.*, **2013**, 246.
69. T. Biftu, P. Chen, J. M. Cox, A. E. Weber, aminotetrahydropyrans as dipeptidyl peptidase-IV inhibitors for the treatment of prevention of diabetes, US 2010/0120863 A1, 2010.
70. C. Muto, H. Q. Dai, J. G. Teeter, S. Johnson, A. B. Cropp, K. Chiba and T. Suwa, *Int. J. Clin. Pharmacol. Ther.,* **2012**, 50 (7), 505-509.
71. M. J. Ammirati, K. M. Andrews, D. D. Boyer, A. M. Brodeur, D. E. Danley, S. D. Doran, B. Hulin, S. P. Liu, R. K. McPherson, S. J. Orena, J. C. Parker, J. Polivkova, X. Y. Qiu, C. B. Soglia, J. L. Treadway, M. A. VanVolkenburg, D. C. Wilder and D. W. Piotrowski, *Bioorg. Med. Chem. Lett.,* **2009,** 19 (7), 1991-1995.
72. K. Anitha, G.; Gopi, Girish, S. P. Kumar, *Int. J. Res. Dev. Pharm. L. Sci.* **2013**, 2(5), 602-610.
73. T. W. V. Geldern, and J. M. Trevillyan, *Drug Dev. Res.,* **2006**, 67 (8), 627-642.
74. C. Haffner, D. L. Dougald, A. S. Randhawa, S. M. Reister, J. M. Lenhard, WO 03/002531, 2003.
75. D. H. Igo, P. R. Johnson, D. E. Patterson, A. S. Randhawa, WO 2005/009956, 2005.
76. A. Thomas, G. Balasubramanian, P. L. Rao, V. S. Shah, M. Daisy, WO06040625, 2006.
77. S. Narayanan, R. Anupindi, D. M. Shah and S. V. S. Vakkalanka, *Diabetes*, **2006**, 55, A324-A324.
78. Glenmark Pharmaceuticals Ltd Press Release, September 22 (2005).
79. Glenmark Pharmaceuticals Ltd Press Release, February 24 (2006).
80. A. Thomas, L.V.S. Prasada Rao, K.,B. Ashok, K. M. Suresh, P. K. Shantaram, U.V. Deepak, WO 2008/001195, 2008.
81. Z. Y. Zhang, M. B. Wallace, J. Feng, J. A. Stafford, R. J. Skene, L. H. Shi, B. Lee, K. Aertgeerts, A. Jennings, R. D. Xu, D. B. Kassel, S. W. Kaldor, M. Navre, D. R. Webb and S. L. Gwaltney, *J. Med .Chem.*, **2011**, 54, 510-524.
82. K. Yuan, S. Ma, L. Zhu, H. Liu, US 2012/0122875 A1, 2012.
83. P. Y. Sun, *From generic drug to new drugs: Hengrui's*

experience. 5th International conference and exhibition, China 2010 pharmaceutical R & D summit, Shanghai, April 5-6, 2010.

84. B. Deng, F. Yang, J. Fan, H. Feng, Y. Wang, T. Yang, CN 101468988 A, 2009.
85. P. C. Tang, F. Yang; J. Fan, H. Feng, Y. Wang, T. Yang, US 2010/0273786, 2010.
86. H. J. Kim, W. Y. Kwak, J. P. Min, J. Y. Lee, T. H. Yoon, H. D. Kim, C. Y. Shin, M. K. Kim, S. H. Choi, H. S. Kim, E. K. Yang, Y. H. Cheong, Y. N. Chae, K. J. Park, J. M. Jang, S. J. Choi, M. H. Son, S. H. Kim, M. Yoo and B. J. Lee, *Bioorg. Med. Chem. Lett.,* **2011,** 21 (12), 3809-3812.
87. K. S. Lim, J. Y. Cho, B. H. Kim, J. R. Kim, H. S. Kim, D. K. Kim, S. H. Kim, H. J. Yim, S. H. Lee, S. G. Shin, I. J. Jang and K. S. Yu, *Br. J. Clin. Pharmacol.,* **2009,** 68 (6), 883-890.
88. P. Mattei, M. Boehringer, P. Di Giorgio, H. Fischer, M. Hennig, J. Huwyler, B. Kocer, B. Kuhn, B. M. Loeffler, A. MacDonald, R. Narquizian, E. Rauber, E. Sebokova and U. Sprecher, *Bioorg. Med. Chem. Lett.,* **2010,** 20 (3), 1109-1113.
89. Y. L. He, B. M. Sadler, R. Sabo, S. Balez, Y. Wang, J. Campestrini, A. Laurent, M. Ligueros-Saylan and D. Howard, *Clin. Pharmacokinet.*, **2007**, 46, 787-802.
90. C. D. Lauster, T. P. McKaveney and S. V. Muench, *Am. J. Health-Syst. Pharm.* **2007,** 64, 1265-1273.
91. Barnett, A. *Int. J. Clin. Pract.* **2006**, 60, 1454-1470.
92. A. Stefan, J. M. Adam, A. Fettes, F. Joseph, B. Lohri, P. Mattei, G. Moine, R. Schimd, U. Zutter, WO 2006/125728, 2006.
93. A. Stefan, J. M. Adam, A. Fettes, S. Hilbrand, WO 2008/031749, 2008.