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Synthesis of dipeptidyl peptidase-4 inhibitors: a brief overview

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Abbreviations: T2DM, Type 2 Diabetes Mellitus; SU, sulfonylurea; TZD, thiazolidinedione; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; HTS, high-throughput screening; DIAD, diisopropyl azodicarboxylate; EDC (or) EDAC*N*-ethylcarbodiimide, *N*-(3-dimethylamino propyl)-hydrochloride; NMM, *N*-methylmorpholine; HOBT, Hydroxybenzo- triazole; Dde, 1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; DIPEA, Diisopropyl ethylamine; IPA, Isopropyl alcohol; DMAP, Dimethyl aminopyridine; DMAc, Dimethylacetamide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DCM, Dichloromethane; TFA, Trifluoroacetic acid; LAH, Lithiumaluminiumchloride; PDH/FDH enzyme, pyruvate dehydrogenase enzyme; Fmoc, Fluorenylmethyloxycarbonyl chloride; TBTU, *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; PS Carbodidimide, polymer supported carbodiimide; DEAD, diethyl azodicarboxylate; PTSA, *p*-toluenesulphonic acid; WSCl, tungstensulphidechloride; MTBE, methyl-*tert*-butylether; HBTU, *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HATU, *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; LiHMDS, Lithium bis(trimethylsilyl) amide; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; TFAA, Trifluoroacetic anhydride; DIPA, Diisopropyl amine; DIC, *N*,*N*′-diisopropylcarbodiimide.

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1. Introduction: dipeptidyl peptidase-4 inhibitors for type 2 diabetes

Type 2 diabetes mellitus (T2DM), a metabolic disorder characterised by impaired control of blood glucose level, is prevalent worldwide affecting almost 6% of the population. It is one of the fastest growing health concerns worldwide and could affect 366 million people in the next 30 years if proper preventive measures are not implemented in the immediate future. The current oral treatment options for T2DM include metformin, sulfonylurea (SU), or thiazolidinedione (TZD) derivatives, glycosidase inhibitors and the recently introduced dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors inhibit the enzyme DPP-4, a serine protease that degrades the incretin hormone, glucagon-like peptide-1 (GLP-1), rapidly to its inactive form. GLP-1 is released in the gut in response to the ingestion of food and stimulates insulin biosynthesis and secretion, while inhibiting the release of glucagon. Apart from several other beneficial effects, GLP-1 regulates insulin in a strictly glucose-dependent manner. Thus, inhibition of DPP-4 has been shown to increase the half-life of GLP-1 and to prolong the beneficial effects of this incretin hormone. Moreover, DPP-4 inhibitors did not show the undesirable side effects, such as weight gain and hypoglycemia, that are observed with the use of other *anti*-diabetic agents. Intense research activities in this area have resulted in the launch of sitagliptin and vildagliptin (in Europe only) and the advancement of a few other potential drugs into preregistration/phase 3, e.g., saxagliptin, alogliptin and ABT-279. A number of review articles are now available that cover various aspects of DPP-4 inhibitors extensively.[1] This review will mainly focus on the various synthetic strategies and methods utilised, along with the challenges encountered, during the synthesis of lead DPP-4 inhibitors that are either in various stages of clinical development or that have been launched on the market (for patient use).

2. Structural diversity and classification of reported inhibitors

While a large number of DPP-4 inhibitors with structural diversity have been reported in the literature, a general classification based on their structural features is shown in Figure 1. These inhibitors can be divided into two major classes, i.e., peptidomimetic and non-peptidomimetic series. The first series can be further subdivided into (a) glycine-based inhibitors (α-series) and (b) β-alanine-based inhibitors (β-series). In the case of the α-series, pyrrolidine derivatives have been widely explored due to the specificity of DPP-4 for substrates having an amino-terminal proline at C-2. Depending on the presence of a substituent, e.g., R at C-2 of the pyrrolidine ring, the α-series can be further subdivided into two classes, e.g., (a) irreversible {when R=diphenylphosphonate ester [−P(O)(OPh)$_2$] or *O*-acylhydroxamic acid (CONHOCOR′)} and (b) reversible {when R=boronic acid [B(OH)$_2$], nitrile (CN) or hydrogen} inhibitors. Notably, the 2-cyanopyrrolidine-based inhibitors that belong to the reversible class of the α-series have been studied most extensively. The β-series was generally developed from a lead obtained via high-throughput screening (HTS) and a number of inhibitors based on a β-amino amide backbone have been reported. Non-peptidomimetic inhibitors are distinctly different from the traditional α- or β-series in terms of their structures and an impressive number of compounds that belong to this class have been reported. In most of the cases, X-ray crystallographic studies showed that, in spite of their distinct structural features, these inhibitors interacted well with the DPP-4 active site. It is worthy of note that, apart from the classification mentioned above, DPP-4 inhibitors can also be classified as covalent and non-covalent inhibitors, depending on the nature of their interactions with the enzyme active site, as determined by the X-ray studies. Although covering all of the inhibitors is beyond the scope of this article, the lead inhibitors presented in the following sections can be grouped based on either of the above classifications.

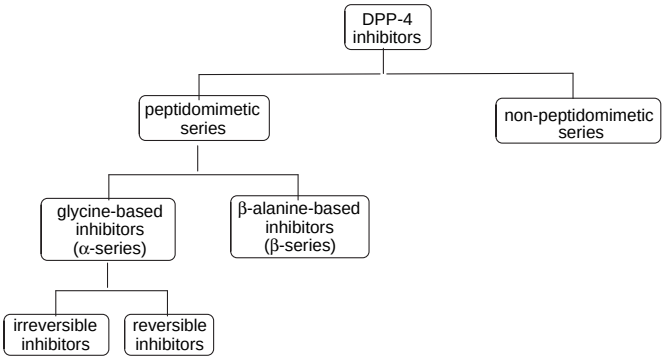


Figure 1. Classification of DPP-4 inhibitors.

3. Reported syntheses of lead inhibitors

A wide range of synthetic methodologies have been reported for the preparation of various lead inhibitors. These include sitagliptin, a β-amino acid-based drug presently on the market, and vildagliptin, a cyanopyrrolidine-based drug that was expected to reach the market before sitagliptin. The other inhibitors presented in the following section include a methanoprolinenitrile-based inhibitor, i.e., saxagliptin, presently waiting for FDA approval and alogliptin that belongs to the non-peptidomimetic series. The early and extensively studied inhibitor NVP DPP-728, the thiazolidide-based inhibitor P32/98 and one of the promising inhibitors, melogliptin, have also been covered. Many other inhibitors, such as dutogliptin, MP-513, PHX-1149, denagliptin, K-579, TS-021, ABT-279, E-3024, LC-150444, DP-893, carmegliptin, R-1579, linagliptin, ER-319711, etc., are included in this review.

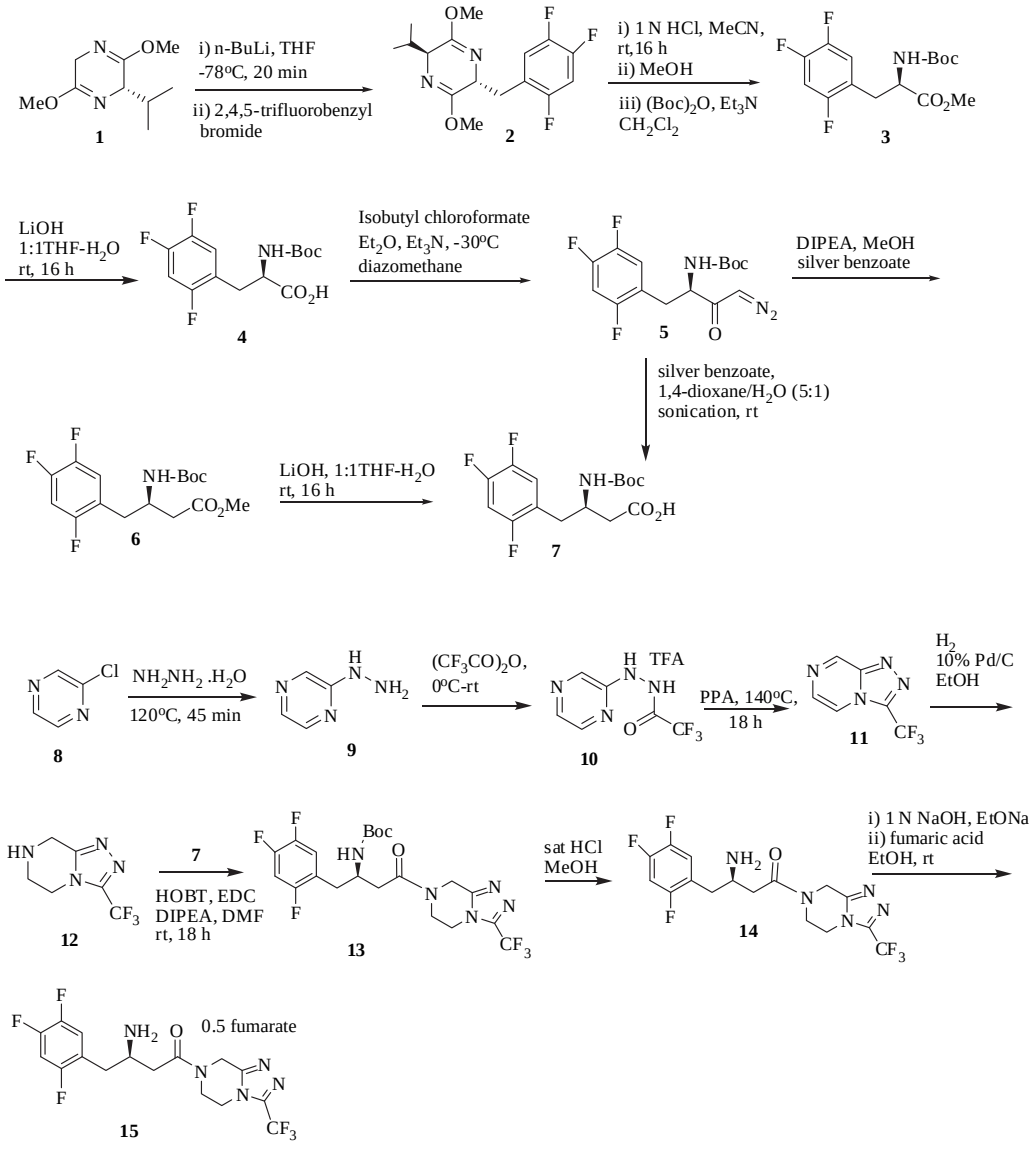
4. Sitagliptin (Januvia™): a β-amino acid-based blockbuster drug presently on the market

Sitagliptin, a highly selective triazolopiperazine-based DPP-4 inhibitor, was evaluated in clinical trials as a monotherapy, or as an add-on therapy with existing *anti*-diabetic agents, such as metformin.[2] It was generally well tolerated with an overall incidence of adverse experiences comparable to placebo, a low risk of

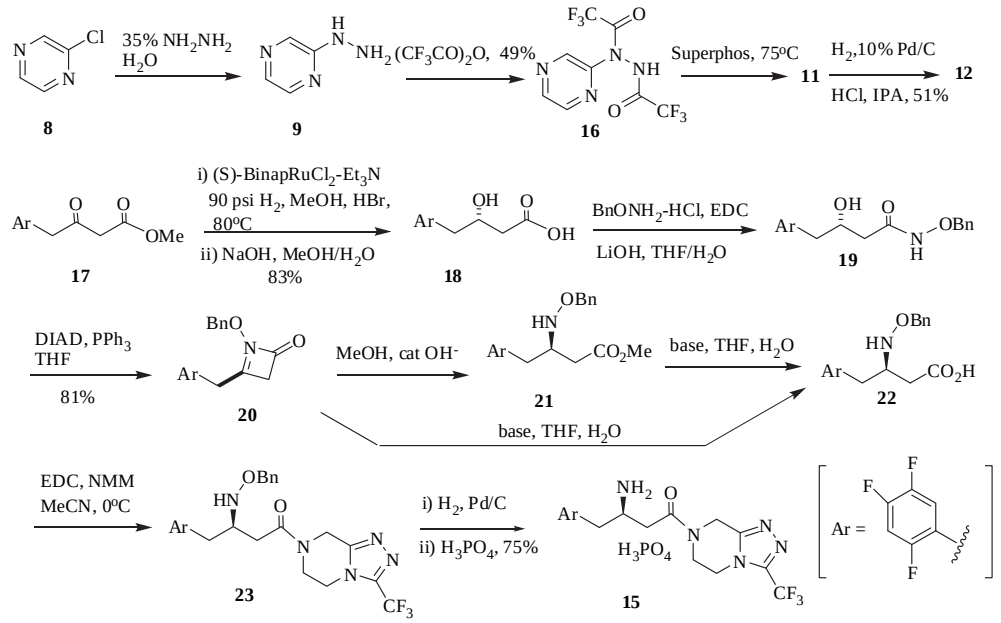
hypoglycemia or gastrointestinal (GI) disturbances, and a neutral effect on body weight.[2,3] The synthesis of sitagliptin (Scheme 1) involved the reaction of a Schollkopf reagent **1** with 2,4,5-trifluorobenzyl bromide to give the compound **2**, which after converting into the ester **3** was hydrolysed. The resulting α-amino acid **4** on treatment with isobutyl chloroformate followed by diazomethane provided the diazo ketone **5**, which was converted into the desired β-amino acid **7** via the ester **6**. The β-amino acid **7** could also be prepared in one step by sonication of the diazo ketone **5** in the presence of silver benzoate.[4] The other key intermediate, tetrahydrotriazolopyrazine **12**, was prepared[5] from chloropyrazine **8** via the hydrazinopyrazine **9**, which on acylation with trifluoroacetic anhydride gave the compound **10**. Polyphosphoric acid (PPA)-mediated intramolecular cyclisation of **10** and then catalytic hydrogenation of the resulting triazolopyrazine **11** provided the desired compound. Coupling of **12** with β-amino acid **7** provided compound **13**. Deprotection of the amine group of **13** provided sitagliptin **14**, which was then converted into the corresponding hemi fumarate salt **15**.[6]

A first-generation process for sitagliptin was reported[7] (Scheme 2) in 2005. Thus, treating **8** with hydrazine followed by acylation of the resulting compound **9** with trifluoroacetic anhydride provided the bis-trifluorohydrazide **16**, which on treatment with polyphosphoric acid and then hydrogenation provided **12**. The asymmetric hydrogenation of β-keto ester **17**[8] using the (*S*)-BinapRuCl$_2$/triethylamine complex in methanol[9] and a catalytic amount of HBr gave the β-hydroxy ester.[10] Following asymmetric reduction, the ester was hydrolyzed and the carboxylic acid **18** was isolated. Lactam **20** was then prepared in a two-step sequence from **18**. First, hydroxamate **19** was synthesised by coupling the carboxylic acid with BnONH$_2$/HCl using *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC). The cyclisation of compound **20** was then carried out directly using diisopropyl azodicarboxylate (DIAD) and PPh$_3$.[11] Addition of a catalytic amount of 0.1% NaOH to compound **20** afforded the compound **21**. Lactam **20** or ester **21** was hydrolysed to amino acid **22** that was coupled with the triazole **12** at 0 °C using EDC/HCl and *N*-methylmorpholine (NMM) to give the compound **23**. Hydrogenation of compound **23** using Pd/C followed by treatment of the resultant product with phosphoric acid gave the phosphate salt of sitagliptin **15**.

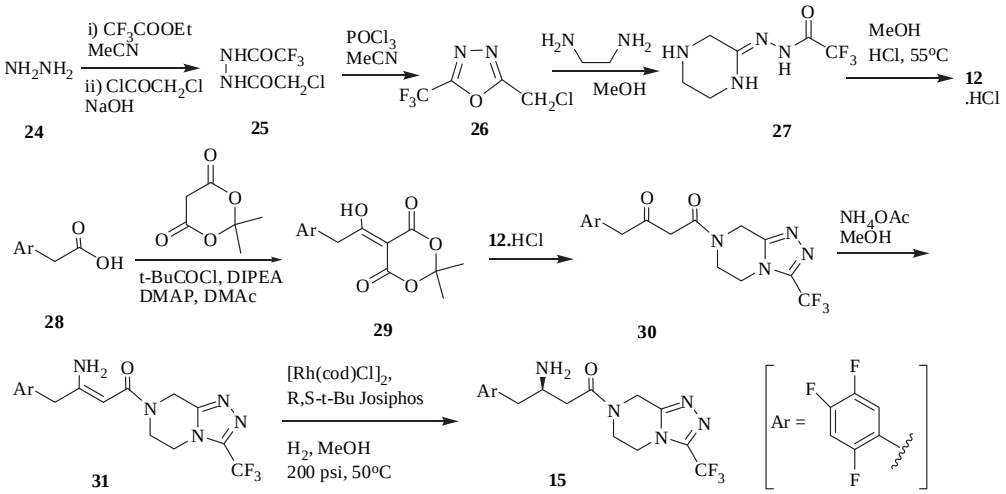
Another synthesis of sitagliptin is shown in Scheme 3, according to which the triazolopyrazine **12** was prepared by



Scheme 1. Synthesis of sitagliptin.



Scheme 2. Second approach to sitagliptin.



Scheme 3. Third approach to sitagliptin.

reacting hydrazine **24** with ethyl trifluoroacetate and chloroacetyl chloride to give bishydrazide **25**. Treating **25** with phosphorous oxychloride provided the oxadiazole **26**, which was converted into triazolopyrazine **12** via piperazinylidene trifluoroacetohydrazide **27**. Trifluorophenylacetic acid **28** on reaction with Meldrum's acid gave the compound **29**, which was then coupled with triazolopyrazine **12** to form diketone **30**. The ketoamide **31** obtained from **30** on treatment with $[Rh(cod)Cl]_2$[12,13] and (*R,S*)-*tert*-butyl Josiphos gave the required sitagliptin **15**.[14]

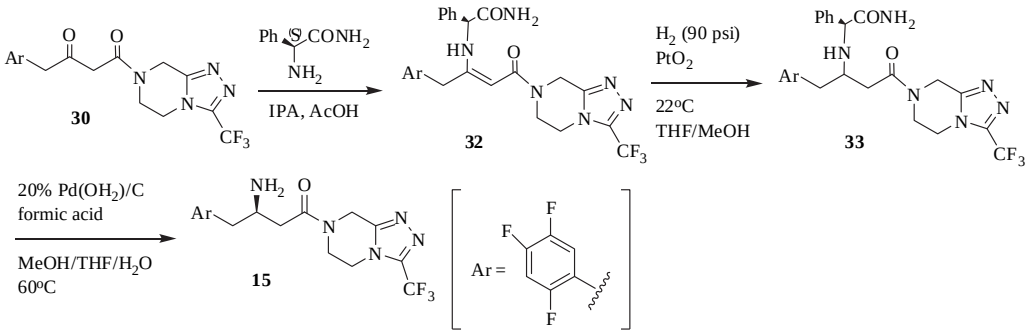
In another process (Scheme 4), sitagliptin was prepared via conversion of the diketone **30** into the compound **32** followed by reduction and subsequent deprotection of the amino group of the resulting compound **33**.[15]

Sitagliptin has also been prepared via the reaction of 2,4,5-trifluorobenzyl bromide **34** (Scheme 5) with 2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine to give the compound **35**, which was converted into an acid **37** via the ester **36**. The acid **37** after homologation provided the compound **38** that was coupled with **11** to give sitagliptin **15**,[16] as the hydrochloride salt.

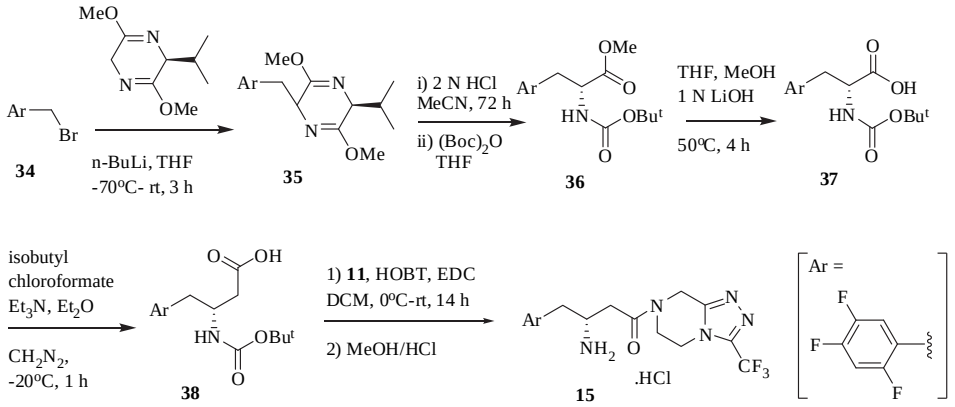
5. Vildagliptin (Galvus): the first cyanopyrrolidine-based drug to reach the market

Vildagliptin, developed by Novartis AG for T2DM,[17] showed 85% bioavailability[18] in healthy human volunteers and sustained DPP-4 inhibition for more than 10 h.[19–23] The synthesis of vildagliptin **44** (Scheme 6) involved N-acylation of L-proline **39** using chloroacetyl chloride to give the compound **40**,[24] which on treatment with DCC provided the amide **41**. Treating **41** with trifluoroacetic acid (TFA) gave the nitrile derivative **42**, which on treatment with 3-hydroxy-1-amino-adamantane **43** afforded the desired compound **44**.[25]

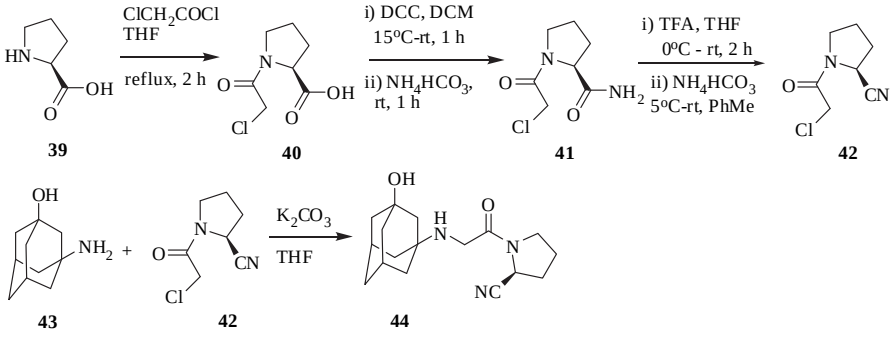
A shorter synthesis of **44** (Scheme 7) involved N-acylation of L-prolinamide **45** followed by the treatment with trifluoroacetic acid and, finally, reaction with 3-hydroxy-1-amino-adamantane **43**.[17]



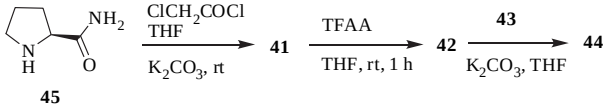
Scheme 4. Fourth approach to sitagliptin.



Scheme 5. Fifth approach to sitagliptin.

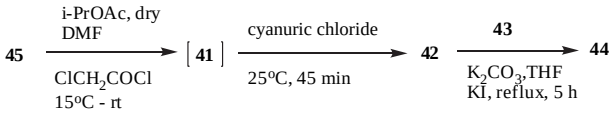


Scheme 6. Preparation of vildagliptin.



Scheme 7. Alternative preparation of vildagliptin.

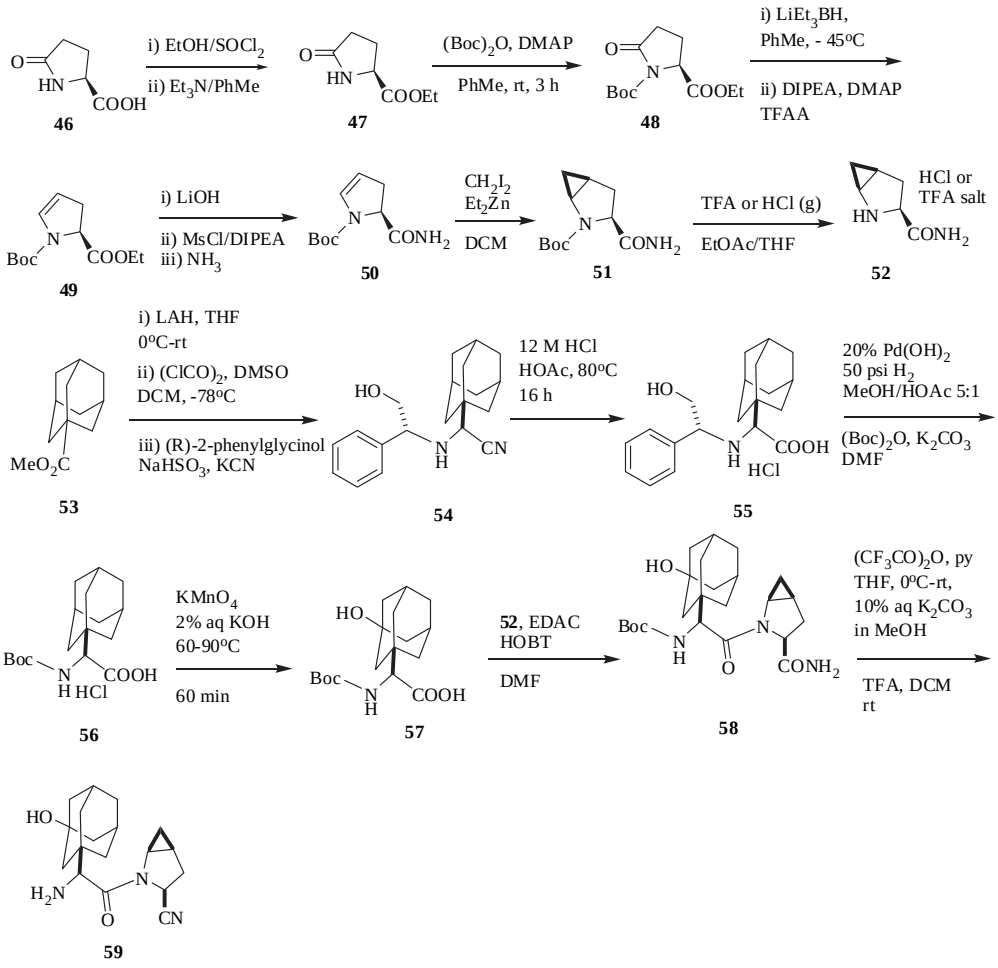
Alternatively, **45** was converted directly into the N-acylated nitrile **42** via **41** and then reacted with **43** to give the expected product **44** (Scheme 8).[26]



Scheme 8. Third approach to vildagliptin.

6. Saxagliptin (BMS-477118): a methanoprolinenitrile-based inhibitor waiting for FDA approval

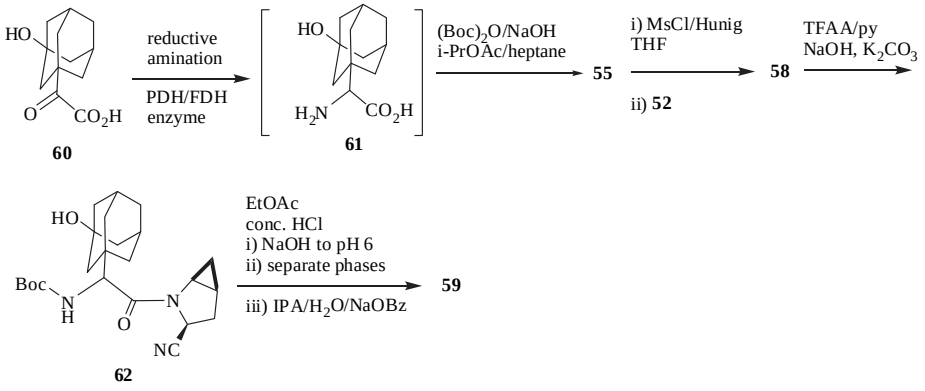
Saxagliptin, developed by Bristol/Myers Squibb (BMS), showed better stability[27] and several beneficial effects in clinical studies. It was well tolerated in a single dose (100 mg) or in combination with metformin (100 mg each).[28] It significantly improved glycaemic control (0.7–0.9% reduction in HbA1c) and was weight neutral.[29] It was also tested in combination with SU or TZD drugs in patients with inadequately controlled T2DM.[30] At present, it is waiting for the approval from the FDA.[30] The synthesis of Saxagliptin **59** (Scheme 9) involved the preparation of a key intermediate, i.e., the methanoprolinamide core **52**, from L-pyroglutamic acid **46**. Boc protection of the ester **47** obtained from **46** gave the compound **48**, which was converted into compound **49**. Amidation of **49** gave the compound **50**, which on cyclopropenation via a Simmons/Smith



Scheme 9. Preparation of saxagliptin.

reaction and, finally, deprotection of the resulting compound **51** gave **52**. The other key intermediate **57** was obtained from the commercially available adamantanecarboxylic acid methyl ester **53**. Reduction of **53** followed by oxidation afforded the requisite aldehyde, which on condensation with (*R*)-(−)-2-phenylglycinol and KCN afforded the desired homochiral *R*,*S* diastereomer **54**. Hydrolysis of **54** to the acid **55** followed by the removal of the chiral auxiliary and subsequent protection afforded **56**. Hydroxylation of **56** followed by coupling with **52** and, finally, conversion of the amide **58** into nitrile and subsequent deprotection of the Boc-protected amine afforded **59**.[27]

Saxagliptin was also prepared (Scheme 10) via reductive amination of the commercially available hydroxyadamantanecarboxylic acid **60** followed by subsequent reactions of the intermediate **61** generated in situ leading to the compound **62**.[31]

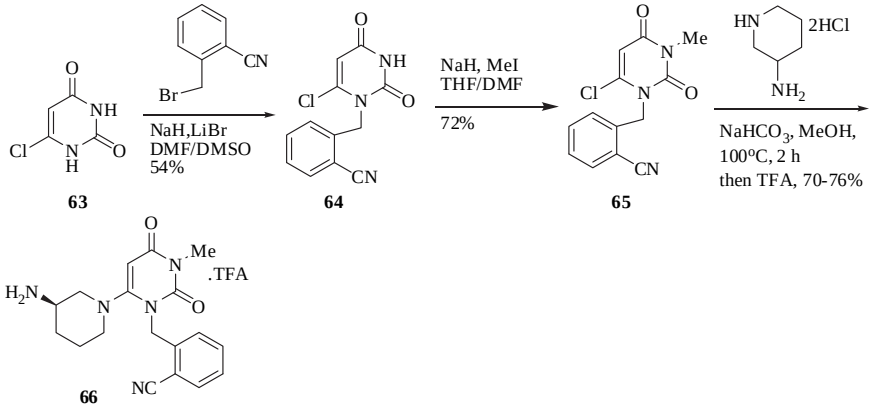


Scheme 10. Alternative synthesis of saxagliptin.

7. SYR-322 (alogliptin): an inhibitor from the non-peptidomimetic series

Alogliptin or (2-[[6-[(3*R*)-3-amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl]methyl]benzonitrile monobenzoate) is a potent ($IC_{50}<10$ nM) and selective inhibitor (selectivity >10,000 over DPP-8 and -9) currently being evaluated

in phase 3 clinical trials.[32–35] The synthesis of alogliptin **66** (also known as SYR-322) involved the reaction of 4-chlorouracil **63** (Scheme 11) with 2-(bromomethyl)benzonitrile to give the compound **64**,[36] which on methylation followed by reaction of the resulting compound **65** with 3-(*R*)-aminopiperidine provided the desired compound,[32,37] **66** as the TFA salt.

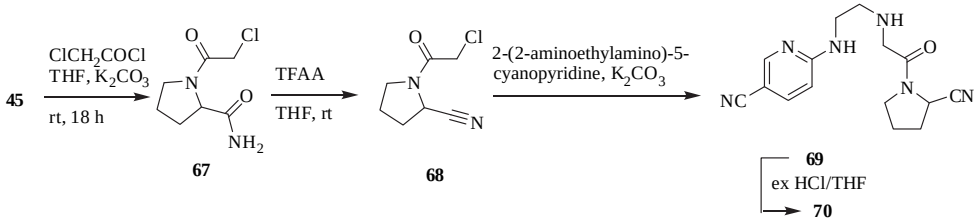


Scheme 11. Synthesis of alogliptin.

8. NVP DPP-728: an early and extensively studied inhibitor

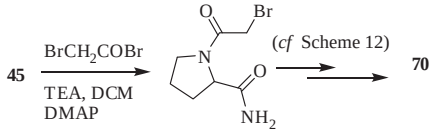
NVP DPP-728, discovered by Novartis AG, inhibited DPP-4 activity (IC_{50}=22 nM) in plasma and improved glucose tolerance in diabetic Zucker rats.[38–40] In a randomised, double-blind, placebo-controlled, multicentre 4-week study, NVP DPP-728 (100 mg t.i.d or 150 mg b.i.d) showed a marked improvement in glycaemic control (0.6% reduction in HbA1c) to a similar extent in both dosing regimens. This compound was synthesised (Scheme 12) by coupling L-prolinamide **45** with chloroacetyl chloride followed by converting the amide moiety of the resulting compound **67** into the cyano derivative **68**. Coupling of **68** with an excess of 2-(2-aminoethylamino)-5-cyanopyridine provided the desired compound **69**, which was converted to the dihydrochloride salt of **70**.[40,41]

The compound **70** was also synthesised (Scheme 15) in high yield by using a rink resin-bound key intermediate 80 that was prepared from compound **76** via **77**, **78** and then **79** following a similar method reported earlier.[44] The intermediate **80** allowed a rapid derivatisation of its primary amino group. Initial attempts to use formaldehyde, as in the solution-phase synthesis, proved to be unsuccessful as complex mixtures were obtained after cleavage from the resin. Thus, 2-acetyldimedone was added to the resin 80 to afford the Dde [1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl]-protected primary amine **81**.[45] Addition of Boc anhydride followed by deprotection of the Dde group with hydrazine afforded the Boc-protected compound **82**. 6-Chloronicotinonitrile **71** was then reacted with **82** to give the compound **83** under vigorous conditions (48 h at 80 °C). After cleavage from the resin and concomitant removal of the Boc group, the carboxamide was dehydrated under standard conditions to afford the trifluoroacetamide **84**, which afforded the product **70** after treatment with methanolic ammonia.[43] Notably, all steps in the solid-phase synthesis were found to be clean, as indicated by a ^{1}H NMR study.



Scheme 12. Synthesis of NVP DPP-728.

Notably, the chloroacetyl chloride could be replaced by bromoacetyl bromide in the synthesis of the target compound **70** (Scheme 13).[42]



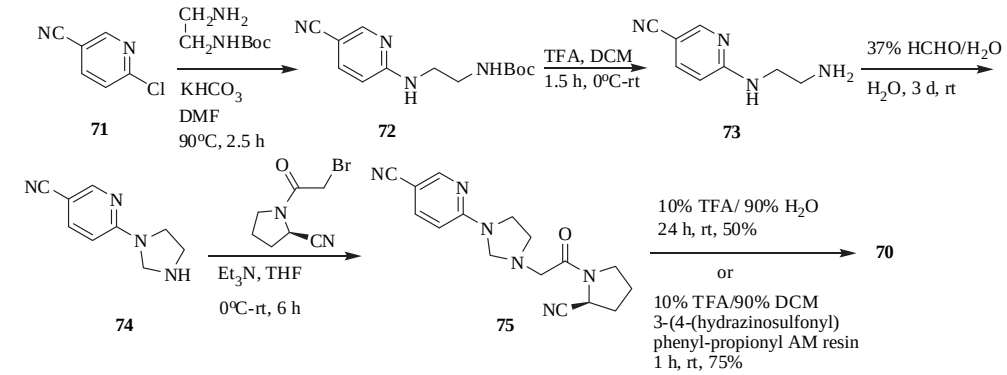
Scheme 13. Alternative approach to NVP DPP-728.

In an alternative approach (Scheme 14), 6-chloronicotinonitrile **71** was reacted with *tert*-butyl-(2-aminoethyl)carbamate to give the compound **72**, which was deprotected to **73**. On treatment with aqueous formaldehyde, compound **73** provided the imidazolidine derivative **74**, which was coupled with 1-(2-bromoacetyl)pyrrolidine-2-carbonitrile to afford the compound **75**. Finally, opening of the imidazolidine ring of **75** afforded the desired product **70**.[41,43]

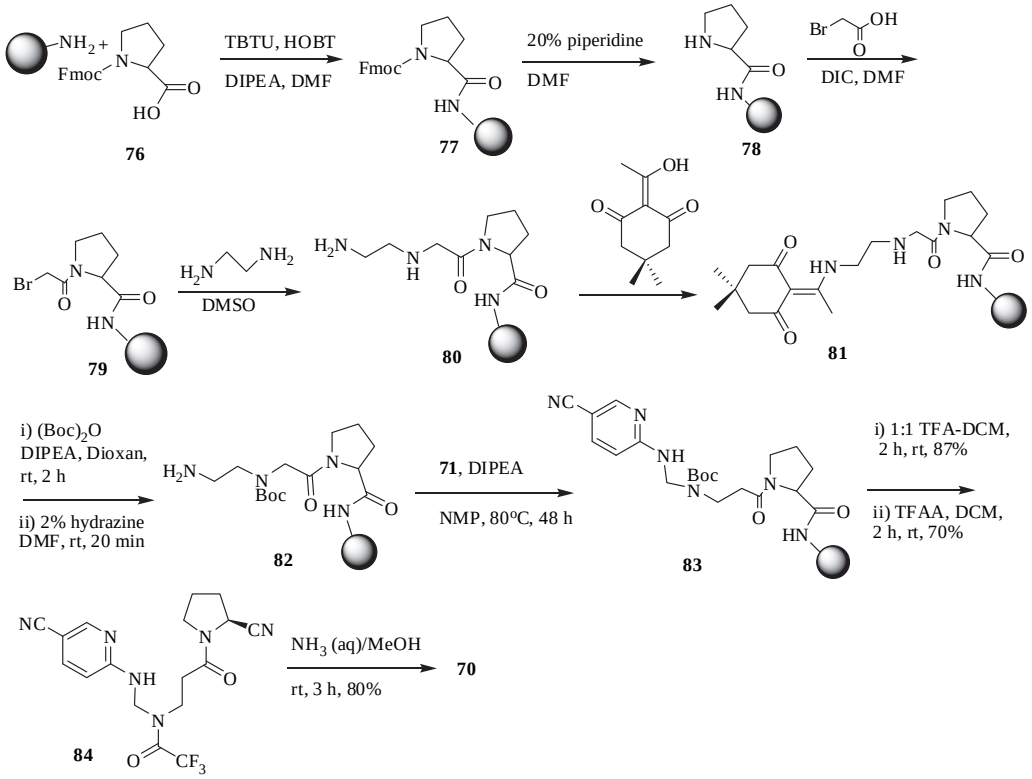
9. P32/98: a thiazolidide-based inhibitor

(*S*)-Isoleucine thiazolidide[46,47] or P32/98, developed by Probiodrug showed a significant postprandial improvement in glucose tolerance in diabetic patients.[48] Although P32/98 entered clinical trials, it was not considered for further development, due to the observed toxicities. P32/98 was synthesised (Scheme 16) by treating *N*-(*tert*-butoxycarbonyl)-L-isoleucine **85** with thiazolidine **86** to give 3-(*N*-[*tert*-butoxycarbonyl]-L-isoleucyl)thiazolidine **87**. N-deprotection of **87** afforded the desired product **88**.[49,50]

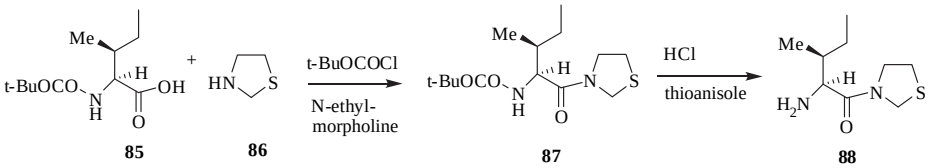
The coupling of **85** with **86** can also be carried out by several other methods, e.g., using (i) HOBT hydrate and EDAC chloride or



Scheme 14. Imidazolidine-based approach to NVP DPP-728.



Scheme 15. Preparation of NVP DPP-728 via a rink resin-bound intermediate.

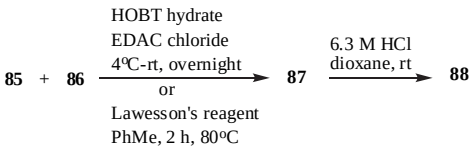


Scheme 16. Synthesis of P32/98.

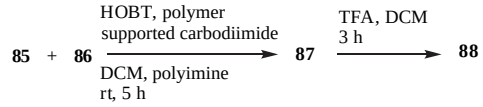
(ii) Lawesson's reagent (Scheme 17)[51] or (iii) HOBT, polymer supported carbodiimide and polyimine (Scheme 18).[52]

10. Melogliptin (GRC 8200): an emerging inhibitor

Melogliptin, from Glenmark, is a potent (IC_{50}=1.61 nM) and selective (selectivity ~ 10,000-fold over DPP-2, post-proline cleaving enzyme and other proteases tested)[53,54] inhibitor that showed a good pharmacokinetic profile with a reported oral bioavailability of

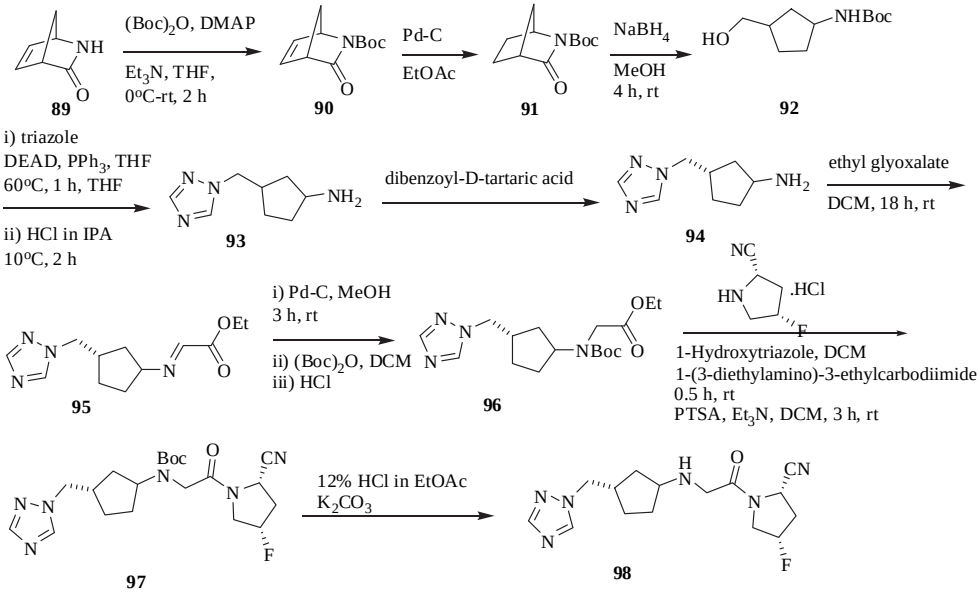


Scheme 17. Alternative synthesis of P32/98.



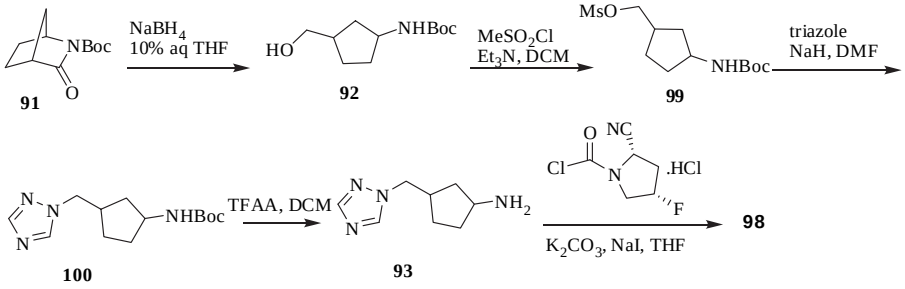
Scheme 18. Third approach to P32/98.

50–95%.[55,56] The results of a phase 1 trial suggested that both single ascending and multiple ascending doses of the drug were well tolerated with a linear pharmacokinetic profile, supporting a once-daily dosing.[57,58] The inhibition of plasma DPP-4 was more than 90% within an hour of dosing. Currently, melogliptin is in phase 2 trials. Its synthesis (Scheme 19) started from compound **89**, which on Boc protection followed by reduction of the resulting compound **90** provided the ketone **91**. The amino alcohol **92** obtained from **91** was coupled with triazole to give the amine **93**. The amine **94** obtained from **93** after resolution was converted into **96** via **95**, which on further coupling with a pyrrolidine derivative followed by N-deprotection of the resulting compound **97** afforded melogliptin **98**.[59]



Scheme 19. Synthesis of melogliptin.

In an alternative route, **98** was synthesised (Scheme 20) via the reduction of **91** followed by mesylation and subsequent coupling of **99** with triazole to give the protected amine **100**. Deprotection of **100** followed by coupling with a pyrrolidine derivative gave **98**.[60]



Scheme 20. Alternative synthesis of melogliptin.

11. MP-513: another cyanopyrrolidine-based inhibitor

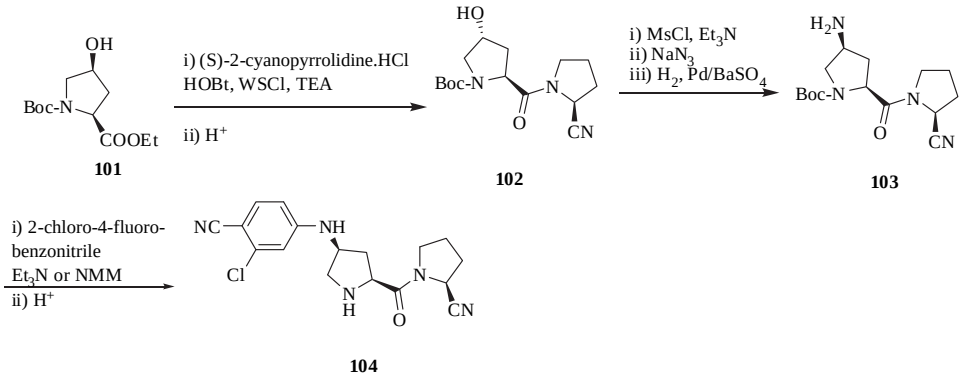
The DPP-4 inhibitor, MP-513 or 1-[(*S*)-γ-[(3-chloro-4-cyanophenyl)amino]prolyl]-(*S*)-2-cyanopyrrolidine, from Mitsubishi Tanabe,[61] is presently undergoing phase 2 clinical trials in Japan and phase 1 trials in Europe and the U.S. Its synthesis (Scheme 21) involved amidation of the *trans*-hydroxypyrrolidine ester **101** with (*S*)-2-cyanopyrrolidine,[62] followed by transformation of the *trans*-hydroxy group of **102** into a *cis*-amino group, affording the amine **103**. The reaction of **103** with 2-chloro-4-fluorobenzonitrile and subsequent removal of the Boc group afforded MP-513 (**104**).

In another method (Scheme 22), MP-513 was synthesised from *trans*-hydroxypyrrolidine **105** following a process similar to that shown in Scheme 21.[63]

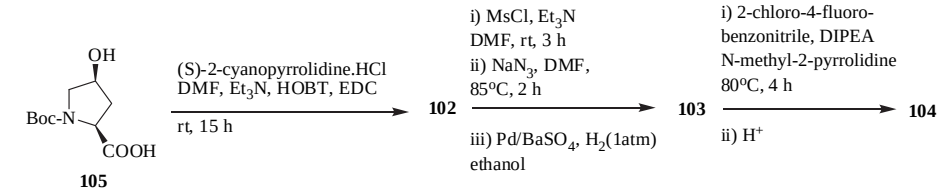
12. PHX-1149 (dutogliptin tartrate): a boronic acid based inhibitor

PHX-1149, developed by Phenomix Corporation, showed a good safety profile.[64] The synthesis of PHX-1149 (Scheme 23) started from pyrrolidine **106**, which on protection followed by treating the resulting compound **107** with trimethoxyborane provided **108**. The reaction of (+)-pipanediol with **108** gave the compound **109**, which on coupling of the pyrrolidine derivative **112** provided the compound **113**. Compound **112** was prepared from *N*-protected 3-aminopyrrolidine **110** via compound **111**. Nevertheless, reduction of compound **113** to **114** followed by deprotection provided the desired compound PHX-1149 (**115**).[65]

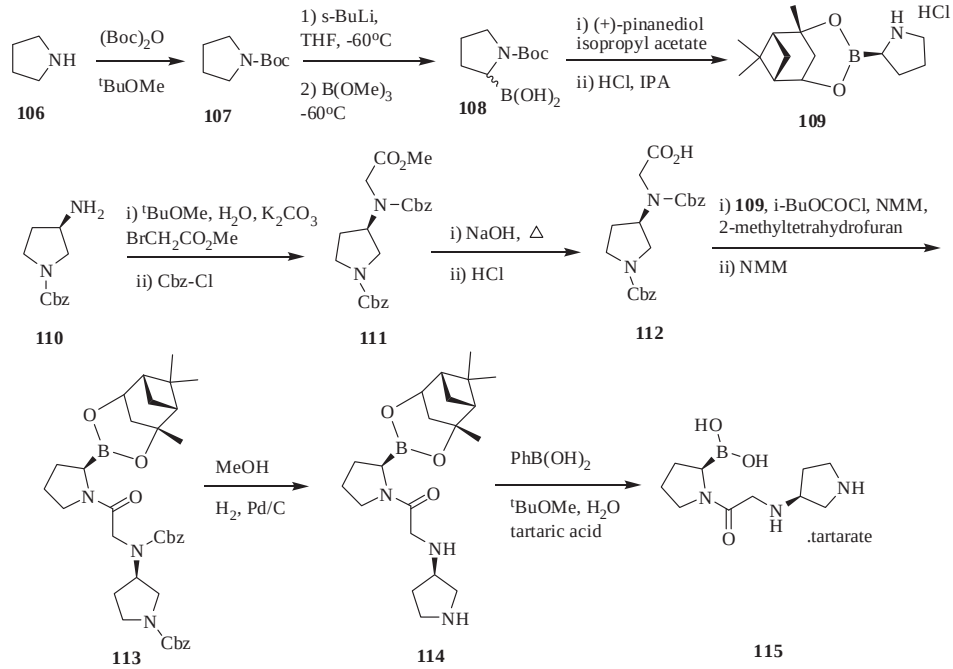
In another method, PHX-1149 was synthesised (Scheme 24) from the compound **109**, which on treatment with chloroacetyl chloride gave the compound **116**. Subsequent reaction of **116** with aminopyrrolidine and then deprotection provided the desired compound **115**.[66]



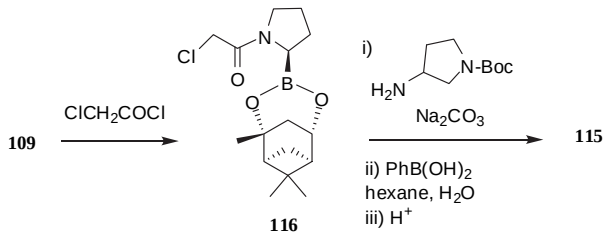
Scheme 21. Synthesis of MP-513.



Scheme 22. Alternative synthesis of MP-513.



Scheme 23. Synthesis of dutogliptin.

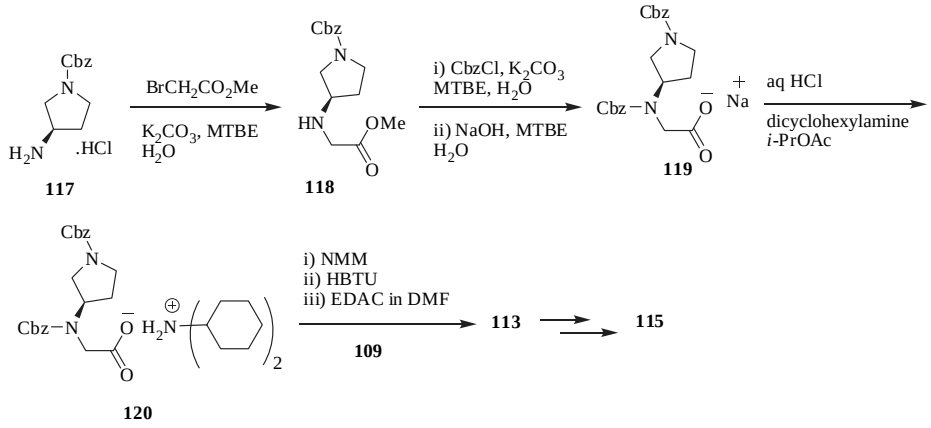


Scheme 24. Alternative synthesis of dutogliptin.

The third method (Scheme 25) involved the reaction of Cbz-protected pyrrolidine **117** with methyl bromomethyl acetate to give **118** followed by further Cbz protection to afford **119**. The dicyclohexylamine salt **120** obtained from **119** was coupled with **109** to give **113** and, finally, **115**.[67]

13. Denagliptin (GW823093): a cyanopyrrolidine-based bis-aryl derivative

Denagliptin or (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl) propanoyl]-4-fluoro pyrrolidine-2-carbonitrile was developed by

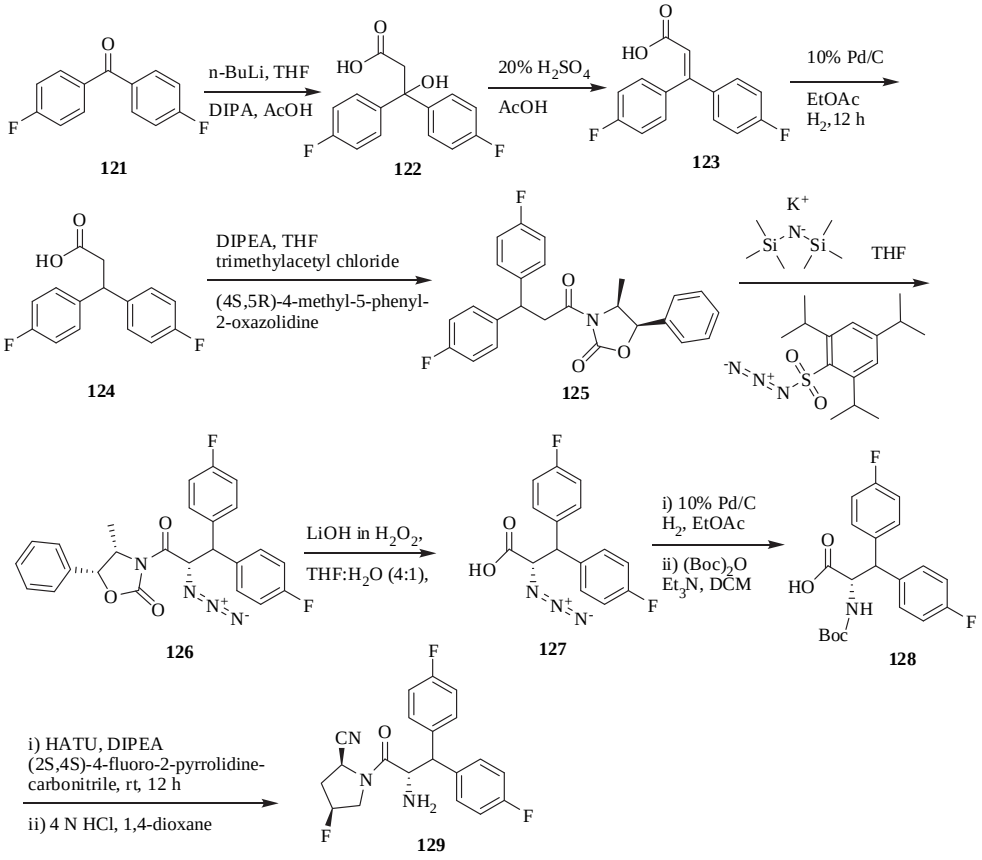


Scheme 25. Third approach to dutogliptin.

SmithKline Beecham Corporation[68] for the treatment of T2DM. The synthesis of denagliptin (Scheme 26) involved the use of 4,4′-bis-fluorobiphenyl **121** as a precursor of hydroxy acid **122**, which was converted into the acid **124** via **123** and subsequently to an oxazolidine amide **125**. The introduction of an azide moiety into **125** provided the compound **126**. Regeneration of the carboxylic acid group followed by reduction of the azide moiety of **127** to an amine compound **132** on reaction with 4-fluoro-2-pyrrolidinecarbonitrile afforded **129**.[70]

14. K-579: a long-acting inhibitor

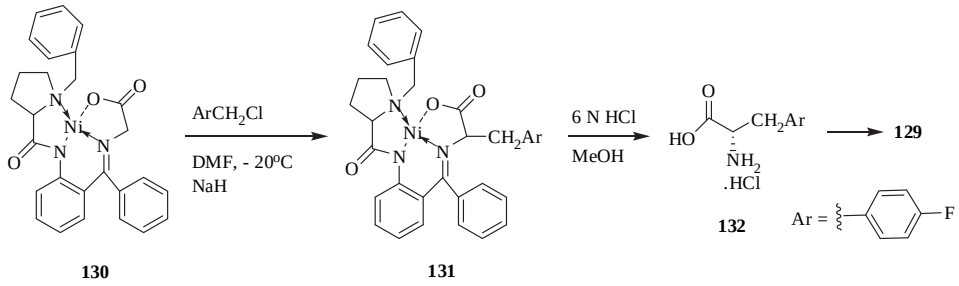
The DPP-4 inhibitor, K-579 or [(*S*)-1-[4-methyl-1-(2-pyrimidinyl)-4-piperidylamino]acetyl-2-pyrrolidine carbonitrile, from



Scheme 26. Synthesis of denagliptin.

and subsequent protection provided the compound **128**. Finally, the reaction of **128** with 4-fluoro-2-pyrrolidinecarbonitrile followed by deprotection of the amine gave denagliptin **129**.[68,69]

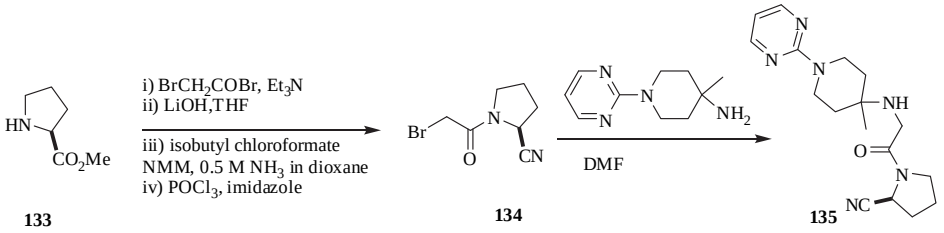
Another synthesis of denagliptin (Scheme 27) was carried out via alkylation of the complex **130** followed by treating the alkylated product **131** with 6 N HCl to give the amino acid **132**. The the Pharmaceutical Research Institute, Kyowa Hakko Kogyo Ltd, was found to be more effective than glibenclamide alone when combined with SU.[71,72] The inhibitory effects of K579 on plasma DPP-4 lasted longer than those of NVP-DPP728, which is reported to have a short duration of inhibitory activity[73] and an instability in solution due to intramolecular cyclisation.[73,74] K-579 was



Scheme 27. Alternative synthesis of denagliptin.

synthesised (Scheme 28) via reacting the pyrrolidine ester **133** with bromoacetyl bromide followed by conversion of the ester moiety into a nitrile group to give the compound **134**. The reaction of bromide **134** with 4-amino-4-methyl-1-(2-pyrimidinyl)piperidine provided K-579 (**135**).[75,76]

was carried out by the reaction of amino hydrochloride **136**[78] with bromoacetyl bromide followed by dehydration of the resulting compound **137** to yield the cyano derivative **138**. The reaction of 2-hydroxy-1,1-dimethylethylamine with **138** afforded TS-021 (**139**).



Scheme 28. Synthesis of K-579.

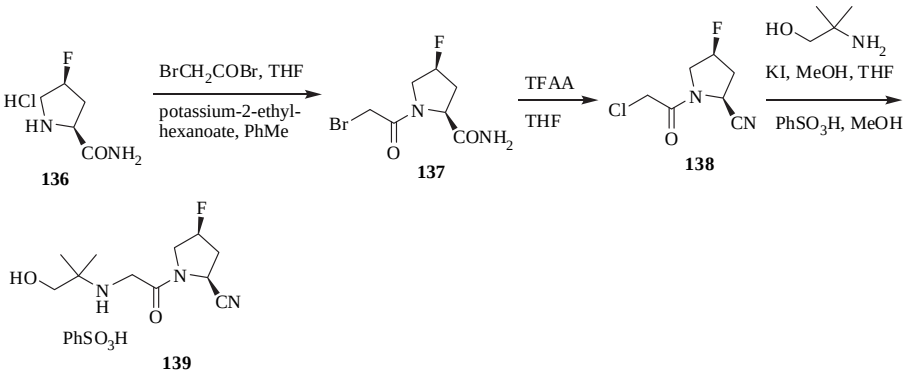
15. TS-021: an inhibitor devoid of aryl/heteroaryl groups

TS-021 or (2*S*,4*S*)-4-fluoro-1-[*N*-(2-hydroxy-1,1-dimethylethyl)glycyl]pyrrolidine-2-carbonitrile benzenesulfonate (Taisho pharmaceutical) is a potent (IC_{50}=4.6 nM) inhibitor that showed a promising antihyperglycemic activity.[77] X-ray studies on TS-021 bound with DPP-4 indicated that its 2-hydroxy-1,1-dimethylethyl side chain could interact with the pocket created by Phe357, Arg358, Ser201, His126 and Arg358, thereby accounting for its high affinity towards DPP-4. The synthesis of TS-021 (Scheme 29)

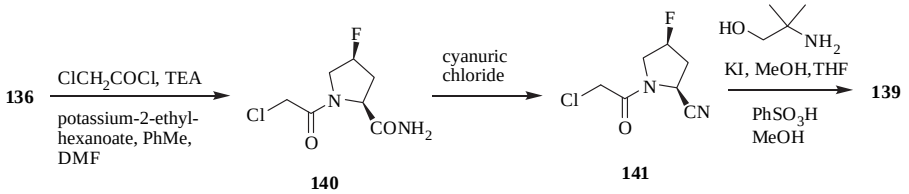
Alternatively,[78] **136** was converted into the chloroacetate **140** (Scheme 30), which was dehydrated in the presence of cyanuric chloride to yield the cyano derivative **141**. Finally, the compound **141** was converted into the salt **139**.

16. ABT-279: an alkynylcyanopyrrolidine-based inhibitor

ABT-279 or 2-[4-[[2-(2*S*,5*R*)-2-cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethylamino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic acid,[79] from Global pharmaceutical R&D, showed good potency

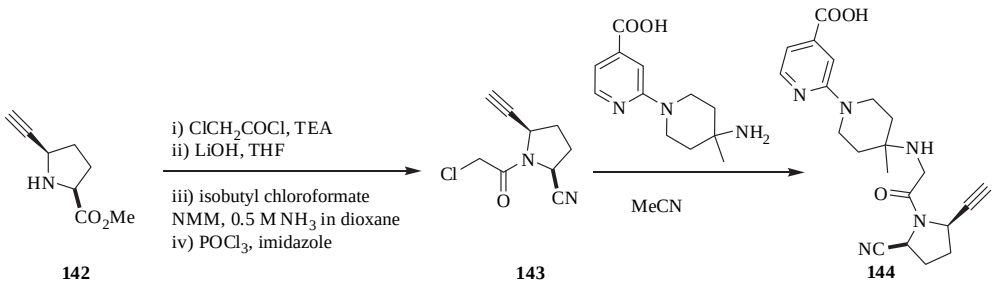


Scheme 29. Synthesis of TS-021.



Scheme 30. Alternative synthesis of TS-021.

(IC_{50} ~ 1.0 nM) along with selectivity against DPP-7, DPP-8, DPP-9, prolyl oligopeptidase (POP) and fibroblast-activating protein-R.[80–82] An X-ray crystal structure of ABT-279 bound in the active site of human DPP-4 revealed several critical interactions necessary for inhibition. Specifically, the pyridine moiety of ABT-279 stacks with Arg 125 of DPP-4, and His126 forms a salt bridge to the carboxylate of ABT-279. Moreover, the narrow tunnel formed by Tyr547 and Phe357 of DPP-4 accommodated the ethynyl group of ABT-279. This compound was efficacious in a Zucker diabetic fatty (ZDF) rat model of impaired glucose tolerance. The synthesis of ABT-279 (Scheme 31) involved the reaction of alkynylpyrrolidine **142** with chloroacetyl chloride followed by stepwise conversion of the ester group into nitrile to give the compound **143**. The reaction of **143** with 4-amino-4-methyl-3,4,5,6-tetrahydro-2*H*-(1,2′)bipyridinyl-4′-carboxylic acid *tert*-butyl ester gave ABT-279 (**144**).[79,83]



Scheme 31. Synthesis of ABT-279.

17. E-3024: an imidazopyridazinone-based non-peptidomimetic inhibitor

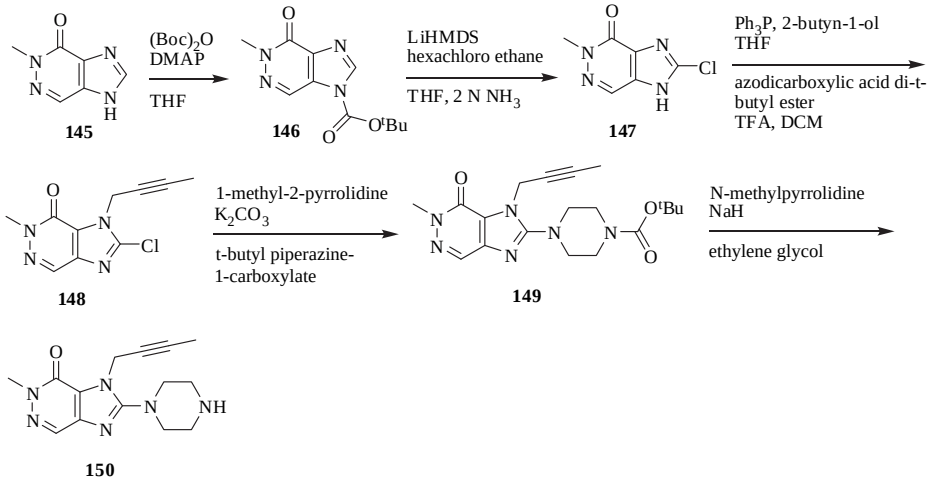
A novel inhibitor, E-3024 or 3-but-2-ynyl-5-methyl-2-piperazin-1-yl-3,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one tosylate, from Tsukuba Research Laboratories, inhibited DPP-4 in human, mouse, rat and canine plasma with IC_{50} values in the range of 140–400 nM. E-3024 did not inhibit DPP-8 or DPP-9 activity. Kinetic analysis indicated that E-3024 is a competitive DPP-4 inhibitor. In Zucker fa/fa rats, E-3024 (1.0 mg/kg) reduced glucose excursion after glucose load, with increases in plasma insulin and active glucagon-like peptide-1 (GLP-1) levels.[84] The synthesis of E-3024 (Scheme 32) was carried out using 5-methyl-3,5-dihydroimidazo[4,5-*d*]pyridazin-4-one **145** that was protected with $(Boc)_2O$ to give **146** and then converted into the chloro derivative **147**. The reaction of 2-butyn-1-ol with compound **147** provided the alkyne **148**, which on reaction with *tert*-butyl piperazine-1-carboxylate gave **149**. Removal of the carboxylate protecting group of **149** gave E-3024 (**150**).[85–88]

18. LC-150444: a derivative of 2-phenyl-1,3,4-oxadiazole

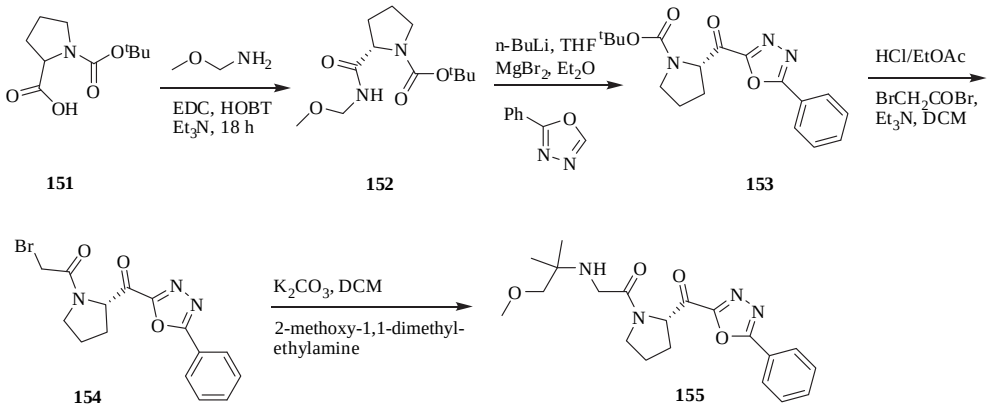
The inhibitor LC-150444, from L.G. Life Sciences, was synthesised (Scheme 33) by using a Boc-protected proline **151** that on reaction with methoxymethylamine gave **152**. The reaction of **152** with 2-phenyl-1,3,4-oxadiazole gave the compound **153**. Treating the compound **153** with bromoacetyl bromide provided the compound **154**, which on reaction with 2-methoxy-1,1-dimethylethylamine afforded the final product **155**.[88]

19. DP-893: a pyrrolidinedicarbonitrile-based inhibitor

DP-893 or 1-({[1-(hydroxymethyl)cyclopentyl]amino}-acetyl) pyrrolidine-2,5-*cis*-dicarbonitrile was identified as an achiral inhibitor of DPP-4 that showed selectivity over DPP-2, DPP-3, DPP-8, DPP-9, amino peptidase protein (APP) and fibroblast activation protein (FAP).[89] It exhibited oral bioavailability in the rat (77%), dog (93%) and monkey (42%) and displayed in vivo efficacy in a mouse oral glucose tolerance test (OGTT). The X-ray crystallography data suggested that the *cis*-2,5-dicyanopyrrolidine moiety was involved in a covalent interaction with S630 through one nitrile group, while the other nitrile forced the Y547 side chain to move and subsequently made a π-stacking interaction as well as an H-bond with Y666. The secondary amine was recognised by E205, E206, N710

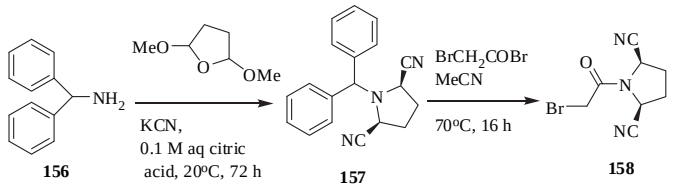


Scheme 32. Synthesis of E-3024.



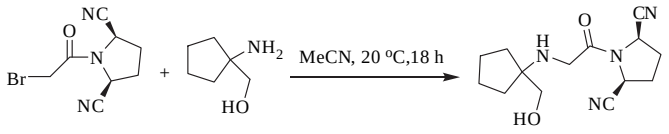
Scheme 33. Synthesis of LC-150444.

and Y662.[89] DP-893 was prepared via a key intermediate **158** that was obtained[90] (Scheme 34) by the Strecker reaction of 2,5-dimethoxytetrahydrofuran and aminodiphenylmethane **156** to give the *cis*-dinitrile **157**, which on reaction with bromoacetyl bromide provided the desired intermediate **158**.[89]



Scheme 34. Preparation of *cis*-dinitrile intermediate (**158**).

Alternatively, the compound **158** was prepared (Scheme 35) from diethyl *meso*-dibromoadipate,[91,92] which on reaction with excess benzylamine **159** followed by crystallisation afforded predominantly the *cis*-isomer of the diethyl ester **160**. The free base **161** obtained from **160** on treatment with excess ammonia afforded

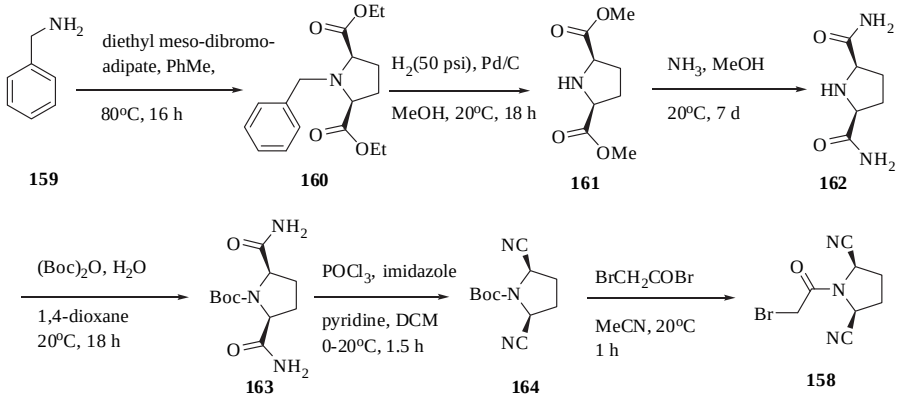


Scheme 36. Synthesis of DP-893.

169. On treatment with an excess of ammonia, the diester **169** afforded the diamide **162**, which was converted into **166** following the steps shown in Scheme 36.[93]

20. R-1579 (carmegliptin): a pyrrolidinone-based inhibitor

The inhibitor R-1579 was jointly developed by Roche and Chugai as a backup for another inhibitor R-1438 (discontinued by Roche earlier).[94] The results of a single-centre, double-blind phase 1 trial suggested that both single and multiple ascending doses of R-1579 were tolerated and more than 50% reduction in DPP-4 activity was observed, even after 10 h of dosing.[95] The synthesis of R-1579



Scheme 35. Alternative preparation of *cis*-dinitrile intermediate (**158**).

the crystalline diamide **162**. The *N*-Boc derivative **163** on dehydration with phosphoryl chloride gave the Boc-protected dinitrile **164**, which on reaction with bromoacetyl bromide gave the bromoacetamide **158**.

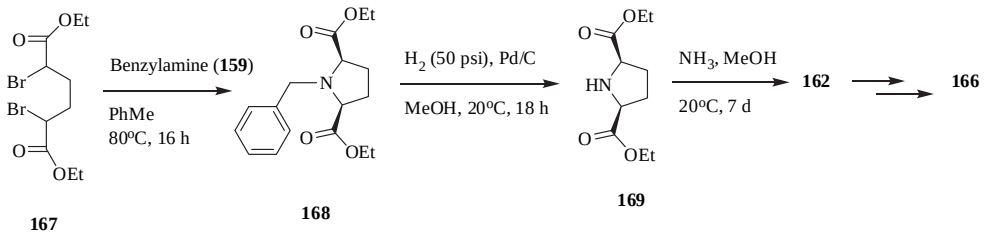
Finally, DP-893 was prepared (Scheme 36) by coupling the bromoacetamide **158** with an excess of 1-(hydroxymethyl)cyclopentylamine(**165**).[89]

In another process, DP-893 was prepared (Scheme 37) by treating diethyl 2,5-dibromoadipate **167** with benzylamine (**159**) to give the compound **168**, which was then converted into the diester

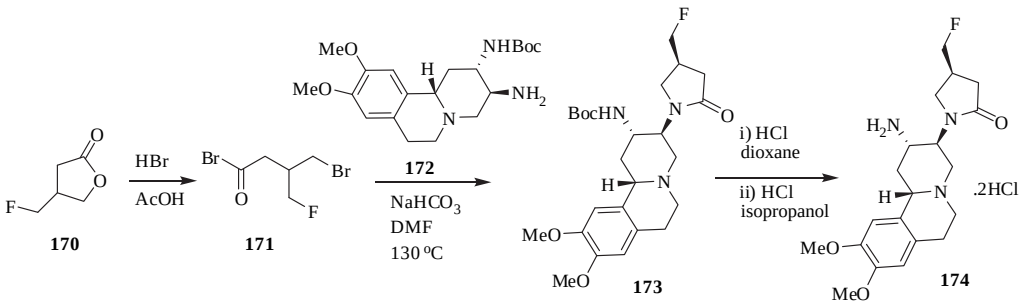
(Scheme 38) was carried out using fluoro furanone **170** that was converted into the acid bromide **171**. The reaction of pyridoisoquinoline amine **172** with **171** afforded the compound **173**, which after deprotection provided R-1579,[96] (**174**) as its dihydrochloride salt.

The intermediate **173** can also be prepared via the compound **175** following another route, as shown in Scheme 39.[96]

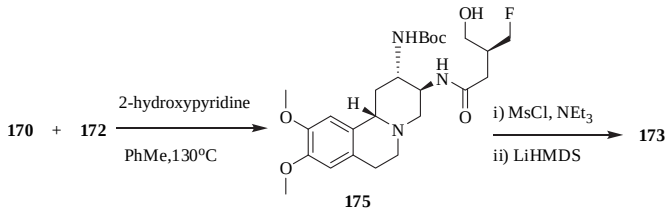
The compound **172** in turn was prepared (Scheme 40) from the anhydride **176** that was converted into the compound **178** via **177**. The amino ester **179**, obtained from **178**, afforded the desired compound **172** after converting to **181** via **180**.[97]



Scheme 37. Alternative synthesis of DP-893.



Scheme 38. Synthesis of carmegliptin.

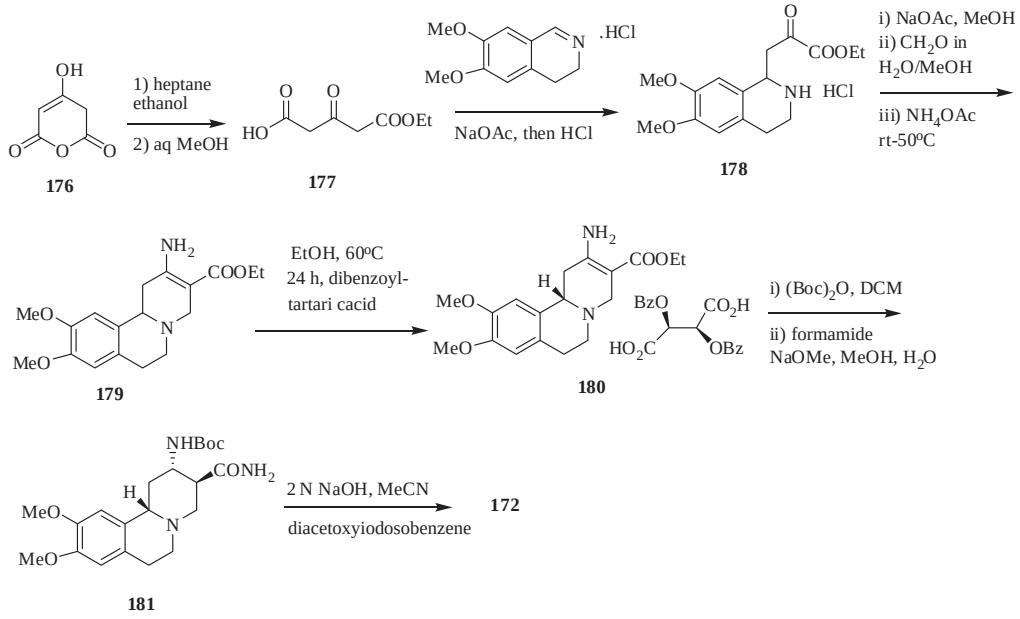


Scheme 39. Alternative preparation of pyridoisoquinoline intermediate (**173**).

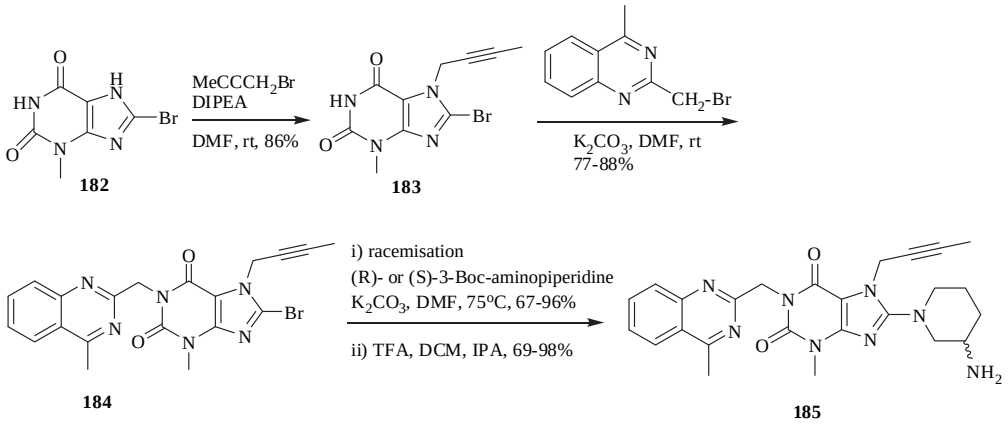
21. Linagliptin (BI-1356): a promising dihydropurinedione-based inhibitor

Linagliptin or 8-(3-(*R*)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione, also known as BI 1356 or Ondero (Boehringer Ingelheim), is a long-acting inhibitor that exhibited a persistent DPP-4 activity over a period of 24 h.[98] It also showed GLP-1 elevation in animals even 24 h after dosing. Since an increase in basal GLP-1 levels may provide the conditions for β-cell regeneration,[99] a drug of this class could therefore be more beneficial to treat T2DM.[100] The synthesis of linagliptin (Scheme 41) involved the treatment of xanthine **182** with 1-bromo-2-butyne to furnish the alkyne-substituted product **183**. N-alkylation of **183** followed by nucleophilic substitution at C-8 of the resulting **184** by 3-aminopiperidine and then N-deprotection provided linagliptin **185**.[101]

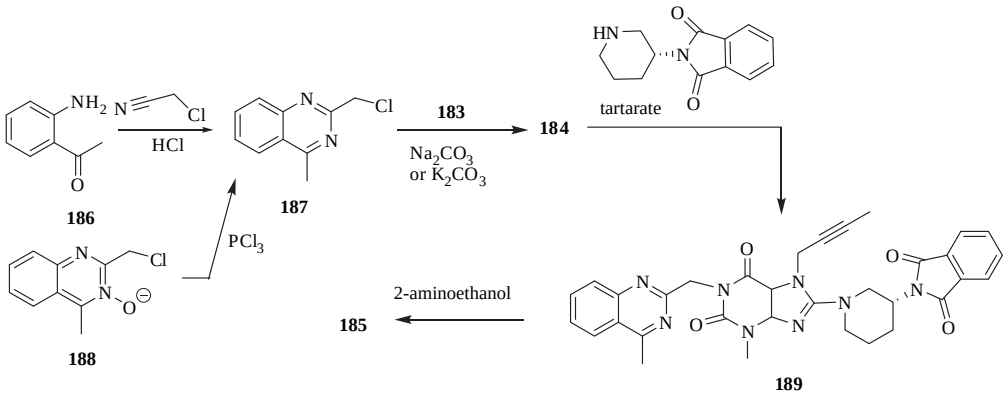
Linagliptin was also synthesised (Scheme 42) via the cyclisation of 2-aminoacetophenone **186** with chloroacetonitrile or the reaction of quinazoline oxide **188** with PCl_3 to give the quinazoline **187**. Coupling of **187** with the xanthine derivative **183** gave the compound **184**, which on condensation with a piperidine derivative afforded the adduct **189**. Treatment of the compound **189** with 2-aminoethanol gave **185**.[102–105]



Scheme 40. Preparation of pyridoisoquinoline amine (**172**).



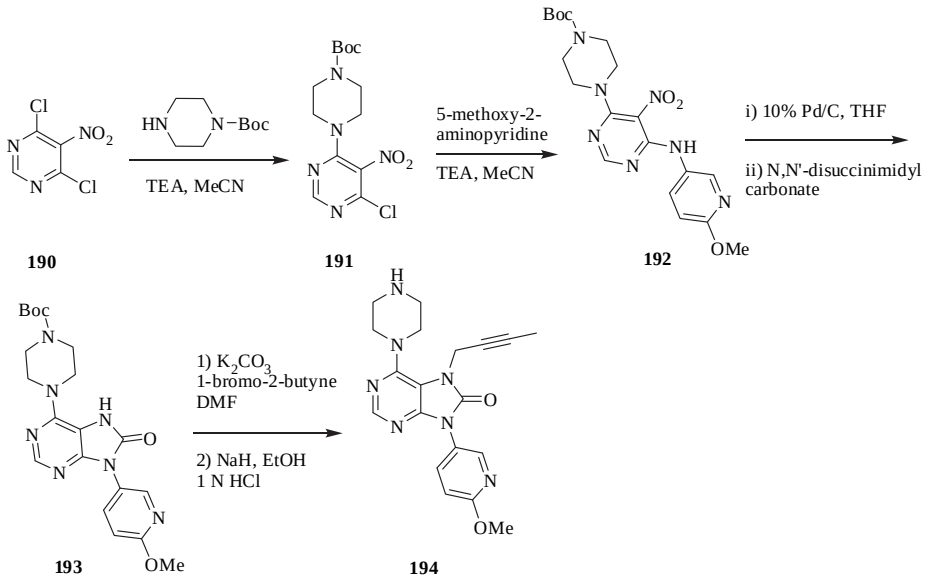
Scheme 41. Synthesis of linagliptin.



Scheme 42. Alternative synthesis of linagliptin.

22. ER-319711: a dihydropurinone-based inhibitor

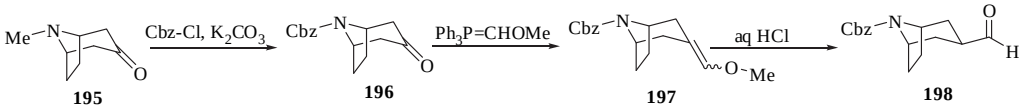
ER-319711 or 7-but-2-ynyl-9-(6-methoxy-pyridin-3-yl)-6-piperazin-1-yl-7,9-dihydro-purin-8-one, a potent (IC_{50}=0.089 μM) and selective inhibitor, was synthesised (Scheme 43) via the reaction of 4,6-dichloro-5-nitropyrimidine **190** with piperazine-1-carboxylic acid *tert*-butyl ester to give the compound **191**. The reaction of **191** with 5-methoxy-2-aminopyridine afforded the corresponding pyrimidine derivative **192**, which was then converted into the compound **193** by using *N*,*N*′-disuccinimidyl carbonate. Compound **193** on reaction with 1-bromo-2-butyne afforded ER-319711 (**194**).[105,48]



Scheme 43. Synthesis of ER-319711.

23. Azabicyclooctanyl derivative as a DPP-4 inhibitor

An azabicyclooctanyl derivative, 1-{3-[(*R*)-1-amino-2-(2,4,5-trifluorophenyl)ethyl]-8-azabicyclo[3.2.1]oct-8-yl}-2-(morpholine-4-sulfonyl)ethanone, a selective inhibitor, was prepared from the aldehyde **198**. Thus, demethylation and protection of tropinone **195** (Scheme 44) afforded the *N*-protected ketone **196**, which on Wittig olefination furnished the enol ether **197**. Hydrolysis of **197** gave the aldehyde **198**.



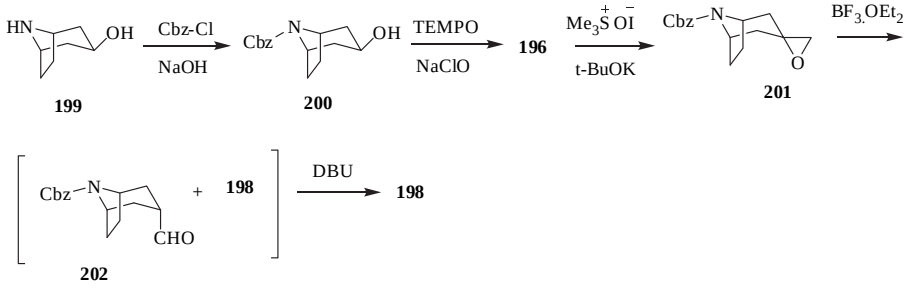
Scheme 44. Preparation of aldehyde intermediate.

The aldehyde **198** can also be synthesised using nortropine **199** (Scheme 45), which on N-protection gave **200**. Oxidation of **200** using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) gave **196**, which on epoxidation using a Corey/Chaywovsky reaction,[106] provided the epoxide **201**. Meinwald rearrangement[107] of **201** with BF_3/OEt_2 gave a mixture of isomers **198** and **202**, which on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the thermodynamically stable **198**.

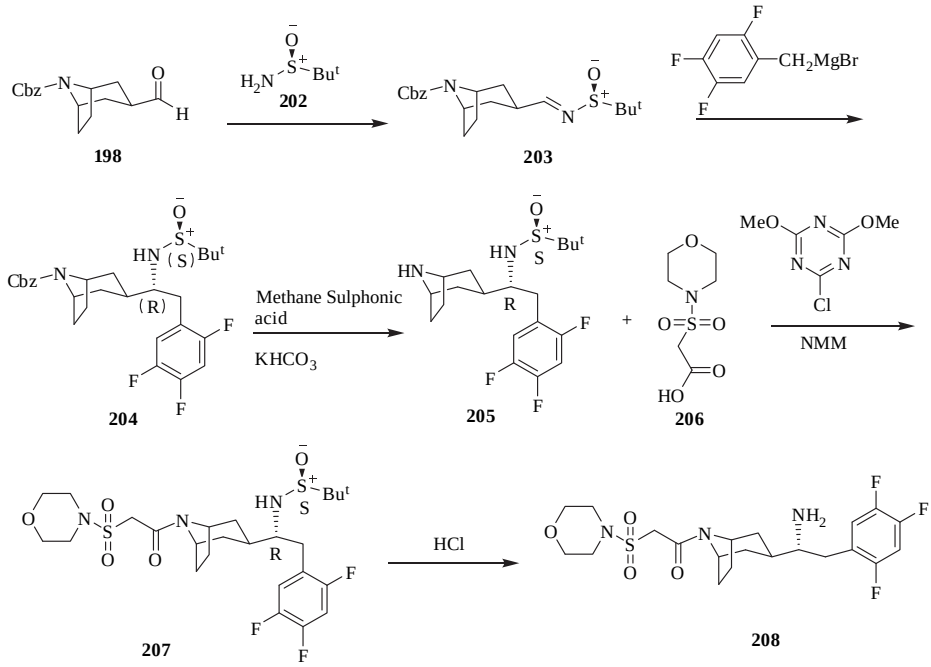
Finally the azabicyclooctanyl-based inhibitor was synthesised (Scheme 46) by condensation[108] of **198** with (*S*)-*tert*-butane-sulfinamide **202** to give **203**, which on treatment with a Grignard reagent[109] followed by deprotection afforded **205** via **204**. Condensation of **205** with the acid **206** afforded **207**, which on further deprotection gave the desired compound **208**.[110]

24. Conclusions: demonstration of the power of synthetic chemistry

Despite the challenges encountered in developing potent inhibitors possessing the required selectivity towards DPP-4 over DPP-8 and DPP-9, a number of promising inhibitors were



Scheme 45. Alternative synthesis of aldehyde intermediate.



Scheme 46. Synthesis of azabicyclooctanyl derivative.

discovered by medicinal chemists. This was achieved through the creativity and imagination demonstrated by the researchers in designing suitable and appropriate inhibitors followed by conducting extensive structure activity relationship (SAR) studies. As evident from the previous sections, the power of synthetic chemistry was unleashed while introducing appropriate substituents, groups or moieties to the target scaffold. The medicinal chemists undertook a long journey of drug discovery of DPP-4 inhibitors that has been full of twists and turns, excitements and setbacks, but remarkable progress has been made towards identifying diverse classes of inhibitors, some of which are in various stages of clinical development and others are already launched on the market. Research on DPP-4 inhibitors will continue and the power of synthetic chemistry will continue to assist researchers in inventing the next blockbuster drug to treat T2DM.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.088. These data include MOL files and InChiKeys of the most important compounds described in this article.

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