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Bullous pemphigoid induced by dipeptidyl peptidase-4 (DPP-4) inhibitors: A Pharmacovigilance-Pharmacodynamic/Pharmacokinetic assessment through an analysis of the VigiBase®

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Abstract

Objectives: To examine the signals of bullous pemphigoid (BP) with dipeptidyl peptidase-4 **(**DPP-4) inhibitors in VigiBase® and the potential role of pharmacodynamic/pharmacokinetic parameters of gliptins in the occurrence of BP.

Methods: Case/non-case analyses was performed in VigiBase® to examine the signal of BP [expressed as the reporting odds ratio (ROR)] for gliptins. Secondly, the authors performed linear regression analyses to explore the association between DPP-4 inhibitor signals for BP and their affinities towards different target enzymes (DPP-2, DPP-4, DPP-8 and DPP-9) and their volume of distribution (Vd).

Results: A significant BP signal was found for DPP-4 inhibitors. The ROR for pooled DPP-IV inhibitors was 179.48 (95% CI: 166.41– 193.58). The highest ROR was found for teneligliptin 975.04 (801.70–1185.87) and lowest for saxagliptin 18.9 (11.5–30.9). Linear regression analyses showed a considerable trend to significance for the linear correlation between the BP signal and gliptin affinity at DPP-4 (slope=1.316 [-0.4385–3.21], p=0.067, R^2=0.40) but not the other enzyme targets, nor for Vd.

Conclusion: The findings suggest a clinical relevance of gliptins selectivity for DDP-4 in the development of BP as a result of exposure to these drugs. Future preclinical and clinical studies are needed for a better understanding of this correlation.

Key words: dipeptidyl peptidase-4 inhibitors, bullous pemphigoid, VigiBase, drug safety, diabetes

1. Introduction

Bullous pemphigoid (BP) is an uncommon autoimmune subepithelial blistering disease that most frequently arises in elderly and is characterised by the presence of cutaneous bullae and erosive mucosal lesions. The mechanism that leads to BP is not fully understood, but most likely involves autoantibody-mediated damage to the epithelial basement membrane zone, a complex structure that mediates adhesion, permeability, and cellular organisation and differentiation [1]. Autoantibodies against two principal hemidesmosomal proteins, bullous pemphigoid antigen 180 (BP180) and bullous pemphigoid antigen 230 (BP230), are strongly linked to the clinical disease. Genetic factors and the phaenomenon of epitope spreading are also considered potential contributory factors [2-5].

Autoimmune reactions triggered by exposure to certain drugs may thus be a cause of BP, as a result of drugs acting as antigens in the basement membrane zone. Even though the strength of this association is uncertain [6], a variety of drugs has been associated with the development of BP (Supplementary Table 1) [7, 8]. In particular, dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of anti-hyperglycaemic drugs widely used in the treatment of diabetes mellitus, previously associated with hypersensitivity reactions (including anaphylaxis, angioedema) and blistering skin conditions (including Stevens-Johnson syndrome) in post-marketing reports, have emerged recently as a putative triggering factor of BP [9-13]. The association between DPP-4 inhibitors and the development of BP comes mainly from clinical reports, a few disproportionality analyses of pharmacovigilance databases and a limited number of case-controlled studies [9-13].

The only available metanalysis addressing this topic shows that DPP-4 inhibitors exposure is associated with a 3.2-fold increased risk for BP, with a variety of risks associated with each drug; however, the limited number of studies included in this analysis may have interfered with the findings, highlighting current gaps and the need to elucidate this issue better [14].

Despite the fact that an increasing number of cases of BP induced by DPP-4 inhibitor use is reported in the literature, the exact mechanism underlying this association

remains unclear and needs to be elucidated. Several different theories including selectivity of drug towards different DPP-4 family enzymes [15-18], higher volume of distribution and gliptin induced inhibition of the DDP-4/ cluster of differentiation 26 (CD26) mediated helper T cell type-1component of immunity have been postulated as potential mechanisms of the association between BP and DPP-4 exposure [19, 20].

Data mining of large pharmacovigilance databases is of great importance in the detection of the earliest possible signals; in addition, coupling information from disproportionality analyses with pharmacodynamic characteristics of drugs (such as receptor occupancy or enzyme inhibition) allows the investigation of a potential pharmacological mechanism of a given adverse drug reaction (ADR) [21].

The primary objective of the present study was to examine the potential signals of BP with DPP-4 inhibitors by performing a data-mining of cases of BP submitted to the largest and most comprehensive pharmacovigilance database, *i.e.* VigiBase®. Our secondary objective was to examine the potential role of pharmacological (pharmacodynamic/pharmacokinetic parameters) characteristics of different gliptins in the occurrence of BP risk as a result of exposure to DPP-4 inhibitors.

2. Material and methods

2.1 Data source

We analysed the reports of suspected ADRs in VigiBase®, the World Health Organization (WHO) global Individual Case Safety Reports (ICSRs) database [22], which aimed to identify the earliest possible pharmacovigilance signals. VigiBase® contains over 18 million Individual case safety reports (ICSRs) until February 2019 (started in 1968). Drugs recorded in the reports are coded according to the latest version of the WHO Drug™ dictionary. Adverse drug reactions are coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®). Analyses exploiting this database may be performed via queries in VigiLyze™ [23], which is an online resource delivering useful searches and subsequent data extractions of VigiBase®.

2.2 Case/non-case analysis

A case/non-case analysis was performed to quantify the association between DPP-4 inhibitors exposure and BP occurrence in the VigiBase®. In this analysis, disproportionality methods are used to identify statistical associations between drug and events in pharmacovigilance databases. Such methods compare the observed count for a drug-event combination with an "expected" count.

Cases were defined as all ICSRs corresponding to the BP (MedDRA Preferred Term "Pemphigoid") between January, 2006 to 3rd February, 2019. This time period was determined by the fact that the first ever DPP-4 inhibitor was approved in the USA in 2006. Non-cases were all reports of ADRs other than the ADR of interest (BP) during the same period. Exposure was defined as 'DPP-4 inhibitor(s)' [Anatomical Therapeutic Chemical classification fourth-level code A10BH] at the time of the ADR occurrence, where it is suspected in the occurrence of ADR. Our exposure definition also includes DPP-4 inhibitors with more limited geographical availability that do not have ATC codes (anagliptin, teneligliptin, trelagliptin, omarigliptin and gosogliptin).

2.3 Pharmacological data and data sources

We investigated the potential role of pharmacodynamic/pharmacokinetic characteristics of DPP-4 inhibitors in the appearance of BP. For this purpose, we coupled pharmacodynamic/pharmacokinetic data of DPP-4 inhibitors with their corresponding reporting risks for BP in VigiBase® as a result of the DPP-4 inhibitor exposure.

Enzymatic inhibition of the DPP-4 family by DPP-4 inhibitors is based on affinity measures such as IC_{50} (concentration at which there is 50% inhibition of measured activity in vitro, dependent on substrate concentration) and Ki (enzyme–inhibitor dissociation constant, independent of substrate concentration) values for their biological targets or interactions (DPP-2, DPP-4, DPP-8 and DPP-9). For each DPP-4 inhibitor studied, values of affinity measures for DPP-2, DPP-4, DPP-8, and DPP-9 potentially involved in gliptins-induced BP were searched in the BRENDA [24], BindingDB [25], PubChem, European Bioinformatics Institute-ChEMBL [26], KEGG LIGAND [27] and DrugBank databases [28]. For the purpose of this study, we treated all affinity measure available in the databases (IC_{50} or Ki) as equivalent.

The profiles of affinity measures (negative log of the IC_{50} or Ki value in molar) for different DPP-4 inhibitors at DPP-2, DPP-4, DPP-8, and DPP-9 are summarised in the supplementary table 2. Values of affinity measures are expressed as an arithmetic mean of values as determined in enzyme assays. Affinity measures obtained from assays performed on human samples were selected. Where data from the human sample were not available, we considered data from non-human sample assay as replacements. In the case of a lack of information (e.g. alogliptin for DPP-2), we used the Ki value of 4 in general. Alternatively, we also profiled fold selectivity data of each studied DPP-4 inhibitors for inhibition of DPP-4 enzyme over DPP-8/DPP-9. To make fold selectivity data levelled, we used base 2 logarithm for expressing the fold selectivity of DPP-4 enzyme vs. DPP-8/DPP-9 (supplementary table 3).

For pharmacokinetic data (volume of distribution), Integrated Database of ADMET and Adverse effects of Predictive Modelling (IDAAPM) [29], KEGG LIGAND [27] databases and individual monographs or regulatory documents were searched.

2.4 Data analyses

For the case/non-case analysis, the strength of an association between DPP-4 inhibitors and BP occurrence was estimated by computing measures of disproportionality, expressing as the reporting odds ratio (ROR) and its two-sided 95% confidence interval (CI). These measurements of disproportionality were based on a 2 × 2 contingency table. An ROR is considered significant when the lower limit of the 95% two-sided CI exceeds 1, and it is considered to reach a threshold value for the disproportionate reporting risk of BP. A minimum of three AE reports was the pre-requisite to consider a drug-event as clinically relevant and the same was selected for case/non-case analysis.

First, we performed a case/non-case analysis to investigate a potential BP signal for all DPP-4 inhibitors altogether. All the DPP-4 inhibitors were compared with all the other drugs stated in each report in the whole of VigiBase® during the study period. A similar analysis was carried out for each individual DPP-4 inhibitor drug (alogliptin, anagliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin, teneligliptin, trelagliptin, and vildagliptin) [analysis a]. Each DPP-4 inhibitor drug was compared with all the other drugs (including the other DPP-4 inhibitor drug) found in VigiBase®. To account for the possible role of

co-medication (co-suspect) as an effect modifier, stratified estimates were also computed after removing all cases where another medication (other than DPP-4 inhibitors) that are known to cause BP was also suspected in the occurrence of BP [analysis b]. Sensitivity analysis was also carried out by comparing DPP-4 inhibitors with all other drugs that are known to cause BP [analysis c].

In the same way, each anti-hyperglycaemic drug classes [biguanides, α-glucosidase inhibitors (α-GIs), glinides, glucagon-like peptide 1 receptor agonists (GLP-1), sulfonylureas, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and thiazolidines] excluding all kind of insulins was compared with all the other classes of drugs (including the other classes of anti-hyperglycaemics) and finally another one for each of the anti-hyperglycaemic drug belongs to above-mentioned classes. Because most patients with diabetes mellitus receive a combination of medications from different anti-hyperglycaemic drug classes, thus, to avoid co-prescription bias we also analysed each anti-hyperglycaemic drug after excluding cases that received DPP-4 inhibitors. Finally, we also examined drugs that are known to induce the BP stratified by pharmacological class or chemical group (Supplementary Table-1). Each drug was compared with all the other drugs (including DPP-IV inhibitors) found in VigiBase®.

For the pharmacodynamic analysis, we performed linear regression models including two quantitative variables: RORs estimated for each individual DPP-4 inhibitors [analysis a] and affinity measures for DPP-4 inhibitors at DPP-4 and off- targets (DPP-2, DPP-8, and DPP-9) or fold-selectivity for inhibition of DPP-4 to detect potential linear association(s) between them. RORs for BP was treated as the dependent variable and affinity measures as the independent one. For simplicity's sake of pharmacodynamic analysis, base 2 logarithms of the RORs were taken. A significant correlation suggests, while not proving with absolute certainty, that the affinity of a DPP-4 inhibitor drug for the off-target enzymes explain to some extent different level of BP reporting (quantified as ROR). Likewise, a pharmacokinetic parameter, the volume of distribution, was taken as an independent variable and RORs estimated for each individual DPP-4 inhibitors as a dependent. Statistical analyses were conducted using the software package STATA® (StataCorp, College Station, TX, USA). This investigation complied with the REporting

of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.

3. Results

3.1 Case selection

During the study period (between 2006 and 2019), 15,020,678 ICSRs were entered in the VigiBase®. Among these, 2,947 ICSRs were related to BP (cases). Of the 2,947 cases, 1,070 (36.3%) were involved at least one DPP-4 inhibitor suspect. Among 1,070 cases with DPP-4 inhibitor suspect, in 368 cases other drugs in addition to a DPP-4 inhibitor was also suspected in the bullous pemphigoid occurrence. In 35 cases, more than one DPP-4 inhibitor was involved as the suspect drug.

3.2 Characteristics of the cases

The number of gliptins suspected BP cases increased exponentially over time between 2006 and 2019, with a spike recorded in the year 2018 for which the highest number of cases (n=446) were recorded (figure 1). The proportion of gliptin suspected BP cases to the total number of BP reported to VigiBase in the studied period had also been steadily increasing over time.

The male-to-female ratio was 0.59 and the median age was 78 years [interquartile range (IQR) 70–83, range 41–100]. More than four-fifths (931/1070=87%) of the cases were designated adjudicated as serious by the reporter. Of serious 931cases, 55 (6%) were with fatal outcome. The improvement of the BP upon the withdrawal of DPP-IV inhibitor (positive DE-challenge) was reported in 57% (593/1028) of the cases whereas re-occurring of BP on re-administration of DPP-IV inhibitor (positive challenge) was mentioned in only seven cases. Metformin was a co-suspect with a DPP-IV inhibitor in 36 of 1070 cases (3.36%).

3.3 Case–noncase analysis

Comparison of DPP-4 inhibitors all together [including cases with co-suspect] showed an increase ROR for BP (179.48; 95% CI:166.41– 193.58) (Table 1). When each individual DPP-4 inhibitor [including co-suspect] compared with all other drugs in VigiBase®, the highest RORs were found for teneligliptin (975.04; 95% CI:801.70–1185.87), followed by omarigliptin (672.31; 95% CI: 376.68–1199.97), vildagliptin

(399.70 ; 95% CI: 362.26– 441.02) and trelagliptin (240.53 ; 95% CI: 118.25– 489.23). Of note, RORs for omarigliptin (n=13) and trelagliptin (n=8) were calculated from a small number of cases compared to other DPP-4 inhibitors. After removing all cases where drugs other than DPP-IV inhibitors were suspected in the occurrence of BP, the magnitude of signals of disproportionate reporting were markedly decreased. Sensitivity analysis of the comparison of the individual DPP-4 inhibitors with all other drugs known to induce BP (positive controls) or reported to be associated with the development of BP in the literature confirmed that the pooled RORs of DPP-4 inhibitors for BP (62.98; 95%: 57.66–68.79) were greater over the studied period than for any other drug suspected in BP occurrence.

Among other anti-hyperglycaemic drug classes after exclusion of cases who were receiving DPP-4 inhibitors, significant RORs were observed only for repaglinide (ROR: 10.23; 95%: 4.25–24.63) and for the sulphonamides: glimepiride, gliclazide, torsemide and glibenclamide (Table-1). When comparing each anti-hyperglycaemic class with all other drugs in VigiBase® (including drugs from other classes of anti-hyperglycaemic drugs), RORs for pooled DPP-4 inhibitors (ROR: 179.48; 95%: 166.41– 193.58) were far greater than for any other anti-hyperglycaemic drug class (Figure 2).

RORs for drugs that are known to induce the BP are presented in supplementary figure 1. ROR for furosemide (for which re-challenge evidence supports an association with BP) was (ROR: 15.8; 95% CI: 13.1–19.1).

3.4 Pharmacovigilance–pharmacodynamic/pharmacokinetic assessment

Details of the regression analyses for the putative association between RORs for individual DPP-4 inhibitors obtained from case/noncase analysis and various pharmacodynamic/pharmacokinetic predictable variables are presented in table 2. In general, there were no noticeable significant positive or negative correlations among all the tested predictor variables. Although affinity of DPP-4 inhibitors at DPP-4 was approaching significant association [slope=1.316±0.6088; (-0.4385–3.21), p =0.067] and this variable accounts for 40% of the variance in the outcome (R^2=0.40) (figure 3), except DPP-4 inhibitors affinity at DPP-2, and volume of distribution of drug showed non-significant linear relationship at conventional significance level. In contrast, there were non-significant inverse relationship between DPP-4 inhibitors affinity at DPP-2

[slope= - 4.822±3.535; (-0.123–2.756), p=0.214, R^2=0.21], volume of distribution of drug [slope= - 0.0005302 ± 0.001059 (-0.003034–0.001974), p= 0.632, R^2 = 0.034] and RORs.

4. Discussion

This is the first study aimed at evaluating the potential role of pharmacological parameters of different gliptins in the occurrence of BP as a result of exposure to DPP-4 inhibitors, by using the largest spontaneous reporting system database, *i.e.* VigiBase®.

Previous disproportionality analyses of European [30,31] and Japanese [13] pharmacovigilance databases investigating DPP-4 inhibitors-induced BP have found a significant association of it with DPP-4 inhibitors. In the present study using a worldwide pharmacovigilance database, the association was systematically examined for all currently clinically approved DPP-4 inhibitors between 2006 and 2019 with an enormously higher number of reports (15,024,872), strengthening the statistical power of the analyses.

Results obtained from case/non-case analyses of VigiBase® suggest there is a persistent increase in BP reporting risk as a result of DPP4 inhibitor exposure. The increased reporting risk of BP signals with DPP-4 inhibitors observed with a very large sample size in VigiBase® is in accordance with case-control studies [9, 10, 32]. Moreover, recently, Kridin et al. in a meta-analysis on 4 population-based observational studies, have found that DPP-4 inhibitor exposure is associated with a 3.2-fold increased risk for BP (pooled OR: 3.16; 95% CI: 2.57-3.89) [14].

Our analysis showed that the magnitude of signals of disproportionate reporting for BP with teneglíptin and omarigliptin were greater than for any other DPP4 inhibitors. It is pertinent to note that omarigliptin and teneglíptin were discovered and marketed firstly in Japan, and later approved in Argentina, Korea and India. As of June 2017, omarigliptin and teneglíptin have been suspected in 45 BP cases of the 695 non-cases and 1 BP case of 19 non-cases, respectively in the Japanese Adverse Drug Event Report (JADER) database [13]. Analysis of VigiBase® data showed a persistent increase in reporting of BP for these two drugs over a two-year period. However, the high

magnitude of signal of disproportionate reporting points to an increased possibility for confounding as an alternative explanation.

In VigiBase®, BP cases were reported relatively more frequently for sitagliptin and vildagliptin than for other gliptins. In case-control studies addressing this issue (pooled vildagliptin-specific OR: 10.16; 95% CI: 6.74-15.33), vildagliptin has been particularly implicated as the greatest risk factor in developing BP [31-33]; similarly, BP was reported with vildagliptin at disproportionately higher rates compared to any other individual DPP4i in previous disproportionality analyses of pharmacovigilance databases [30, 31]. In our analysis, in contrast, sitagliptin demonstrated a weaker association with BP in comparison to most DPP-4 inhibitors. This finding is also consistent with that obtained in a meta-analysis (pooled sitagliptin-specific OR: 1.29; 95% CI, 0.46-3.57) [14].

Of importance, in our dataset, is the fact that the ROR for saxagliptin was lower than that of all other DPP-4 inhibitors. To date, there is little evidence, even in case reports, for the association between saxagliptin use and BP. Previously, saxagliptin was suspected in 4 cases of BP reported to JADER [13], whereas in only one in the French pharmacovigilance database [31]. This could be explained by the fact that sitagliptin and vildagliptin (not saxagliptin) are the most prescribed gliptins worldwide. Like any pharmacoepidemiology studies, valid results from disproportionality analyses rely on accurate classification of event and drug exposure. Under-reporting of ADRs due to “no exposure misclassification” bias (patients exposed to the drug of interest may be more (or less) at risk for the adverse reaction than those exposed to other drugs) may explain a decrease in the number of reports of the comparator drug in case/non-case analyses, and henceforth in ROR [34]. Future studies adjusting disproportionality analyses on national dispensing data might unveil the true association of saxagliptin with BP.

It is worth mentioning that results obtained from the sensitivity analyses with other anti-hyperglyacemic drugs restricted to reports without DPP-4 inhibitors exposure confirmed stable signals of disproportionate reporting for all DPP-4 inhibitors, thus suggesting a class effect. Overall, suspected cases of BP for diabetes medications other than DPP4 inhibitors were substantially lower than the rate of suspected BP cases associated with D-PP4 inhibitor exposure. Furthermore, BP is reported relatively more frequently in

association with gliptins than with other medicinal products reported in the literature as plausible cause in the occurrence of BP.

Previously, Arai *et al* in the analysis of JADER described that after exclusion of cases received DPP-4 inhibitors, significant RORs disappeared for case subjects receiving all the other anti-hyperglycaemic drugs [13]. In our analysis of diabetes medications other than DPP4 inhibitors, repaglinide and sulphonamide oral anti-hyperglycaemic drugs significant associations with BP. Sulfonamide derivatives are common inducers of pemphigoid [35, 36]. Previous evidence regarding differences between anti-hyperglycaemic drugs in their potential for eliciting BP is inconclusive. Due to sample size issues, or as a result of "group analysis" of all the antidiabetic drugs apart from DPP-4 inhibitor group, most studies were unable to demonstrate risks associated with distinct anti-hyperglycaemic drug classes [6, 37-39]. However, no association with risk of development of BP was found for sulfonylureas, or any other classes of anti-diabetes drugs in a recent Finnish registry-based retrospective controlled study [38]. With the emergence of new antidiabetic therapies and their increasing use, there is a need for ongoing investigation and surveillance to further clarify the potential association between the newer diabetes medications and BP.

To date, the mechanism by which DPP-4 inhibitors induce BP is not well understood. By coupling RORs with the affinity values of DPP-4 inhibitors for each possible biological substrate, we investigated the potential mechanisms related to BP. Gliptins have pluripotent biological actions and they mainly interact with serine proteases of the DPP-4 family. The DPP-4 family includes four key enzymes, DPP-4, FAP (fibroblast activation protein), DPP-8 and DPP-9 [40]. Gliptin molecules have varying affinities towards the DPP-4 substrate. In general, the peptidomimetics (such as vildagliptin and saxagliptin) have lesser selectivity towards DPP-4 compared to DPP8/9. The lesser the relative selectivity towards DPP-4 and the greater the relative inhibition of DPP8/9, the greater the possibility of side effects (allergic skin manifestations etc) [18, 41, 42]. However, it is important to note that the potential for adverse effects associated with off-target inhibition of DPP-8 and DPP-9 by non-selective DPP inhibitors has been reported based on a single preclinical study [18]. Specific functions of DPP-8 and DPP-9 are

unclear; however, unlike DPP4, DPP8/9 are intracellular proteases responsible for T-cell activation [43].

We found that the correlation between DPP-4 affinity and the BP reporting signal with DPP-4 inhibitors showed a considerable trend towards significance (p =0.067). Of note, this trend toward significant association, albeit low coefficient of determination (R^2) of the linear regression model between DPP-4 affinity and RORs, underscores the potential role of DPP-4 and downplays the role of DPP8/9 in gliptin-induced BP.

Both teneligliptin and omarigliptin exhibit >10,000-fold selectivity for DPP-4 enzyme over other targets (*i.e.*, DPP-8 and DPP-9) [44, 45]; in VigiBase® the magnitude of the disproportionate reporting for suspected BP cases for both drugs was considerably greater than for any other gliptins (Table 1). Conversely, it is worth mentioning that the magnitude of the disproportionate reporting for moderately selective gliptins, namely vildagliptin (270-fold vs. DPP-8; 32-fold vs. DPP-9) and saxagliptin (31-fold vs. DPP-8; 77-fold vs. DPP-9) was considerably lower than for teneligliptin and omarigliptin; this suggests that DDP-4 selectivity plays a potential role in the development of BP.

Initially, it was thought that the inactivation of DPP-4 by a gliptin could provoke immune dysfunctions associated with DPP-4/CD26 inactivation (a marker of activated T-cell) [50]. Several lines of evidence from animal studies with DPP-4- *knockout* and wild-type mice indicate now that DPP-4 enzyme activity is not a prerequisite for the T-cell activation and proliferation [51-54]. Nevertheless, metabolic benefit aside, the interconnected immunological effects of long-term DPP-4 inhibition are not understood fully at this stage.

We found no significant correlation with the remaining biological targets. The apparent volumes of distribution among the gliptins range from 70 to 1200 L. It is also possible that the intracellular accumulation of drug may cause intracellular inhibition of DPP-8 or DPP-9. Nonetheless, the distribution of drug is strongly influenced by protein binding, a variable that depends on a variety of factors. There is also emerging evidence that the immuno-pathophysiology of DPP-4 inhibitor-induced BP differs from typical BP [10, 55] and interaction between genetic predisposition and drug intake may contribute to the manifestation of the disease [56].

Alternatively, one might hypothesize that different structural forms of DPP-4 inhibitors may play a role in developing BP. DPP-4 inhibitors are structurally diverse and they can be categorized into several groups based on the skeleton [57]. Despite structural heterogeneity, they share common binding interactions with the DPP-4, with exception of vidalaglitin and saxagliptin that possess an electrophilic trap such as nitrile group to form a covalent bond with Ser630 of the catalytic triad in the active site [58]. It has also been postulated that these DPP-4 inhibitors possessing the electrophilic trap are unstable and have a low selectivity against DPP-8 and DPP-9 that may result in multi-organ toxicities [18]. However, it remained unknown as to whether structural differences in gliptins and their binding characteristics might result in different susceptibility towards BP. Since most of the DPP-4 inhibitors have been reported to be associated with BP, it appears unlikely that chemical structure of DPP-4 inhibitor has clinical relevance in the development of BP.

4.1. Limitations

The use of a spontaneous reporting system (SRS) database has some important implicit limitations, reporting being influenced by such factors as the notoriety bias, selection bias and under-reporting, which precludes making causal inferences except in unusual circumstances [59]. As shown in figure 1, the observed increasing trend in reporting of gliptin suspected BP cases may attributed to a notoriety effect following publication of a clinical case report and case-control studies. This effect may leads to a bias that is responsible for an increase in the ROR for the drug in question. The actual risk and incidence rates cannot be determined from the analysis of SRS since the primary goal of such system are to signal the existence of a possible relationship between a drug or drug class and an ADR, and it does not prove causality. It is important to recognise that pharmacodynamic comparisons among the different gliptins based on the reported affinity data are difficult because DPP-4 enzyme assays are not standardised across the studies. From a combined data and methods limitation perspective, we took both Ki and IC_{50} affinity measures as equivalent. IC_{50} values are influenced by the concentration of substrate used and the ratio of substrate concentration to its Ki for that enzyme [60]. In most literature reporting affinity/selectivity data, methodology is incomplete and generally includes non-physiological conditions;

thus, we were unable to determine Ki values for biological targets. Nonetheless, in the absence of assay information, these two affinity measures can be mixed without any loss of quality if corrected by a factor of 2, which is the conversion factor most frequently used by databases) through comparing the IC50/Ki values in databases for the same protein-ligand systems [61]. The pharmacovigilance-pharmacodynamic (PV–PD) approach is based on pharmacological receptors theory that has its own limitations, for instance, target affinity does not directly reflect the intrinsic activity of a drug. The PV–PD approach allowed us to determine, to some extent, a positive linear relationship between the ROR of BP and the affinities for DPP-4, whilst not for other targets. These results, which appear at a first glance counterintuitive, are due to the fact that we could analyse only one biological target at a time. A more proper PD evaluation should comprise all possible targets at the same time; the applicability of such an approach, however, is increasingly limited as the pharmacological complexity of the mechanisms of action increases.

5. Conclusion

Our case/non-case analyses and sensitivity analysis of VigiBase® suggest that BP reported at a disproportionate rate. There is a gradually increasing trend of gliptin suspected BP cases in VigiBase®. With regard to the presented results, the risk of BP with DPP-4 inhibitor appears to be greater than any other drugs known to cause this disorder. This risk is higher than for other different anti-hyperglycaemic drug classes and other medicinal products reported in the literature as a plausible cause in the occurrence of BP. This disproportionality should only be considered exploratory in the context of signal detection, as it does not allow quantification of the true risk. The correlation between DPP-4 affinity and the BP reporting signal with DPP-4 inhibitors showed a considerable trend toward significance, suggesting clinical relevance of DDP-4 selectivity in the development of BP. Future pre-clinical and clinical studies aimed at evaluating better this correlation, including the potential mechanism of gliptin-induced BP, are needed.

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Author contributions

C Carnovale conceptualized and designed the study, interpreted the data drafted the manuscript, revised and approved the final manuscript as submitted. F Mazhar participated in the conceptualization and design of the study, carried out the initial analyses, revised the manuscript and approved the final manuscript as submitted. E Arzenton, U Moretti and M Pozzi participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, revised the article, and approved the final article as submitted. G Mosini, O Leoni and M Scatigna participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, revised the article, and approved the final article as submitted. E Clementi participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. S Radice conceptualized and designed the study, interpreted the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

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Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies,

honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Papers of special note have been highlighted as:

** of interest*

*** of considerable interest*

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Figure legends

Figure 1. Number of DPP-4 inhibitor(s) suspected Bullous Pemphigoid cases reported to the VigiBase® between 2006 and 2019. Proportions of DPP-4 inhibitor(s) suspected Bullous Pemphigoid cases to the total number of Bullous Pemphigoid cases reported to the VigiBase® are shown by a line.

Legend: BP: Bullous Pemphigoid

Figure 2. Results of the case/non-case analysis for different classes of antidiabetic agents. (each class of antidiabetic was compared with the all the other drugs in the VigiBase®)

Legend: α-GIs: glucosidase inhibitors; GLP-1: glucagon-like peptide 1 receptor agonists; SGLT2: sodium-glucose cotransporter 2 inhibitors

Figure 3. Linear regression plot between Dipeptidyl Peptidase-4 inhibitors affinities at DPP-4 and reporting odds ratio (log2) for bullous pemphigoid

Legend: ROR: reporting odds ratio; DPP-4: Dipeptidyl Peptidase-4

Table 1: Reporting odds ratios (RORs) for the association between different dipeptidyl peptidase-4 inhibitor, all other antihyperglycaemic drugs and Bullous Pemphigoid

Drug	With BP (n)	Without BP (n)	ROR (95% CI)
Dipeptidyl peptidase-4 inhibitor *[Including cases where drugs other than DPP-4 inhibitors were suspected in the BP occurrence]*	1,070[#]	47,561	179.50 (166.41– 193.58)
Alogliptin	35	1,246	144.89 (103.35– 203.14)
Anagliptin	9	320	143.80 (74.07– 279.18)
Linagliptin	173	6,538	143.23 (122.60– 167.33)
Omarigliptin	13	99	672.31 (376.68– 1199.97)
Saxagliptin	16	4,328	18.94 (11.58– 30.99)
Sitagliptin	223	26,386	46.52 (40.57– 53.36)
Teneligliptin	123	671	975.04 (801.70– 1185.87)
Trelagliptin	8	170	240.53 (118.25– 489.23)
Vildagliptin	505	7,768	399.70 (362.26– 441.02)
Dipeptidyl peptidase-4 inhibitor *[excluding cases where drugs other than DPP-4 inhibitors were suspected in the BP occurrence]*	702	47,929	97.69 (89.71–106.38)
Alogliptin	26	1,255	106.53 (72.13–157.35)
Anagliptin	7	322	111.07 (52.48–235.07)
Linagliptin	139	6,572	113.10 (95.22–134.33)
Omarigliptin	11	101	557.23 (298.75–1039.35)
Saxagliptin	11	4,333	12.99 (7.18–23.49)
Sitagliptin	164	26,445	33.42 (28.53–39.13)
Teneligliptin	85	709	629.23 (500.97–790.32)
Trelagliptin	6	172	178.18 (78.88–402.45)
Vildagliptin	394	7,879	294.08 (263.88–327.74)
Dipeptidyl peptidase-4 inhibitor *[Including cases where drugs other than DPP-IV inhibitors were suspected in the BP occurrence]* ***vs all other drugs known to cause BP***			
DPP-4 inhibitors	1,070	47,929	
All other drugs known to cause BP*	934	2,635,050	62.98 (57.66–68.79)
Biguanides *[excluding DPP-4 inhibitors]*			
Metformin	14	57,275	1.25 (0.74 – 2.11)
Glinides *[excluding DPP-4 inhibitors]*			
Repaglinide	5	2,494	10.23 (4.25– 24.63)
Glucagon-like peptide 1 *[excluding DPP-4 inhibitors]*			
Exenatide	11	65,119	0.86 (0.48–1.56)
Liraglutide	5	28,598	0.89 (0.37– 2.14)
Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors *[excluding DPP-4 inhibitors]*			
Canagliflozin	2	18,589	NA

Sulfonamide *[excluding DPP-4 inhibitors]*			
Glimepiride	6	9,038	3.39 (1.52–7.55)
Gliclazide	8	5,895	6.93 (3.46–13.88)
Torasemide	5	3,761	6.79 (2.82–16.33)
Glibenclamide	5	9,038	5.34 (2.22 –12.85)
Thiazolidinediones *[excluding DPP-4 inhibitors]*			
Pioglitazone	3	16,645	0.92 (0.30–2.85)

BP: Bullous Pemphigoid; NA: Not included in the statistical analysis because the analysis was based on unique drug–event combinations with at least three occurrences.
Non-significant RORs are presented in light text.
A report may contain more than one suspected DPP-4 inhibitor drug. For this reason, the total number of reports in which an individual DPP-4 inhibitor drug (n = 1070) was mentioned as the suspected drug was higher than the total number of reports in which DPP-4 inhibitor drug was mentioned as the suspected drug (n = 1105).
*See supplementary table 1 for the list of drugs known to cause BP.

Table 2: Summary of Linear regression analyses

Dependent Variable	Predictor variable	Slope (95 CI%)	p-value	R^2
Reporting odds ratio (RORs)	DPP-2 affinity[#]	-4.822 ± 3.535; (-0.1233–2.756)	0.214	0.21
	DPP-4 affinity[#]	1.316 ± 0.6088; (-0.4385–3.21)	0.067	0.40
	DPP-8 affinity[#]	0.02895 ± 0.4208; (-0.9661–1.024)	0.947	0.006
	DPP-9 affinity[#]	0.06907 ± 0.3853 (-0.842–0.9801)	0.862	0.0045
	Fold selectivity for DPP-4 vs. DPP-8	0.08034 ± 0.1332 (-0.2346–0.3953)	0.565	0.049
	Fold selectivity for DPP-4 vs. DPP-9	0.04271 ± 0.1111 (-0.2199–0.3053)	0.712	0.020
	Vol. of distribution	-0.0005302 ± 0.001059 (-0.003034–0.001974)	0.632	0.034

Each linear regression model included RORs (expressed in base 2 logarithms) for the different DPP-4 inhibitors as dependent variable and either affinity measures for DPP-2, DPP-4, DPP-8, and DPP-9 targets; fold selectivity for DPP-4 (expressed in base 2 logarithms) over DPP-8, DPP-9; and volume of distribution (in litres) as predictor variable.

[#]all affinity measures (pIC_{50} or pKi) available in the databases were treated as equivalent.

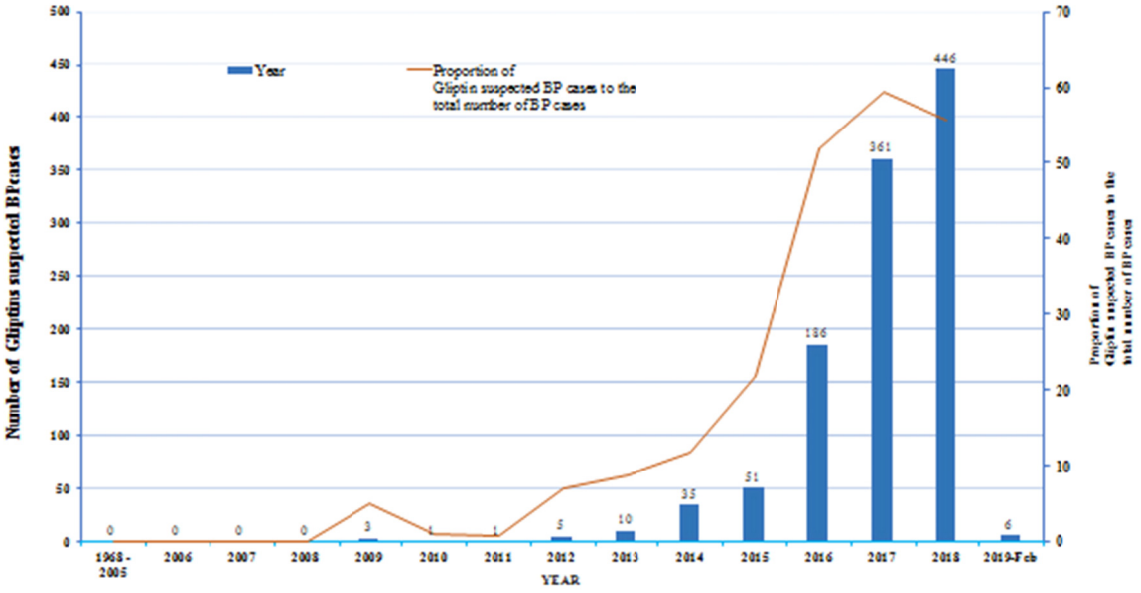

Number of Gliptins suspected BP cases
Proportion of Gliptin suspected BP cases to the total number of BP cases
Year
YEAR
1968 - 2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019-Feb
0
0
0
0
3
1
1
5
10
33
51
186
361
446
6

Fig 1

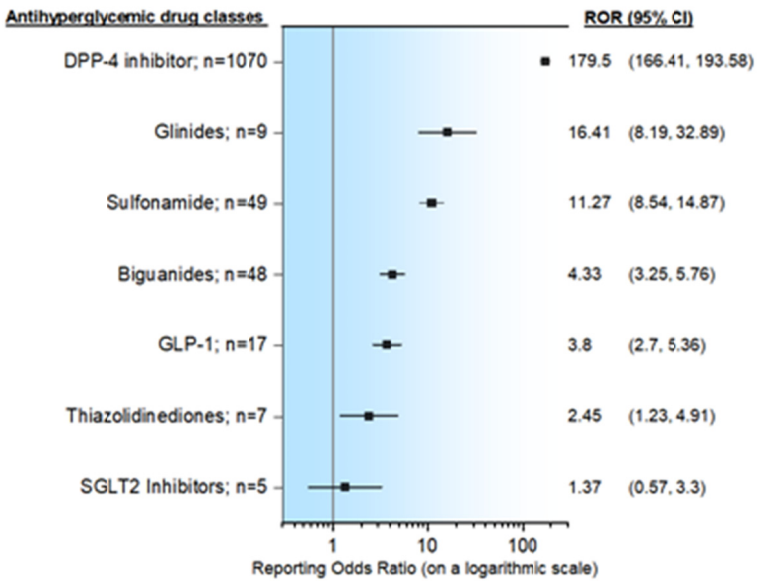

Antihyperglycemic drug classes
ROR (95% CI)
DPP-4 inhibitor; n=1070
179.5 (166.41, 193.58)
Glinides; n=9
16.41 (8.19, 32.89)
Sulfonamide; n=49
11.27 (8.54, 14.87)
Biguanides; n=48
4.33 (3.25, 5.76)
GLP-1; n=17
3.8 (2.7, 5.36)
Thiazolidinediones; n=7
2.45 (1.23, 4.91)
SGLT2 Inhibitors; n=5
1.37 (0.57, 3.3)
1
10
100
Reporting Odds Ratio (on a logarithmic scale)

Fig 2

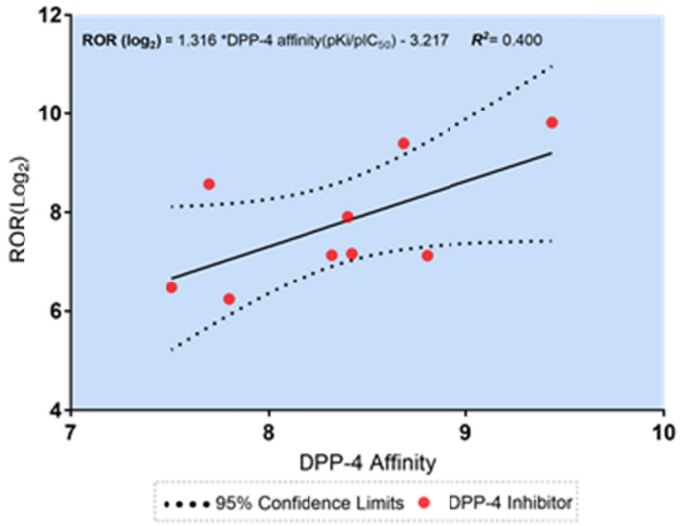
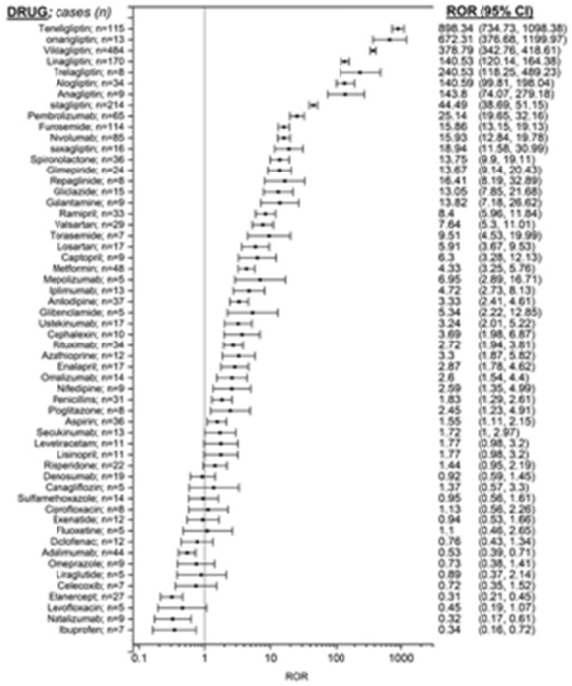


Fig 3



Sup fig 1

Supplementary table-1: List of drugs reported to induce bullous pemphigoid

Antibiotics		Salicylazosulfapyridine		Pilocarpine
Actinomycin	Antirheumatics			Timolol
Penicillins		D-penicillamine		
Cephalexin		Tiobutarit		
Ciprofloxacin	Other			
Chloroquine		Arsenic		
Dactinomycin		Azathioprine		
Levofloxacin		Clonidine		
Rifampin		Denosumab		
Sulfamethoxazole;Trimethoprim		Erlotinib		
NSAID		Fluoxetine		
Azapropazone		Flupenthixol		
Celecoxib		Gabapentin		
Diclofenac (topical)		Galantamine hydrobromide		
Ibuprofen		Ipilimumab		
Mefenamic acid		Gold thiosulfate		
Phenacetin		Interleukin-2		
Diuretics		Levetiracetam		
Furosemide		Mepolizumab		
Spironolactone		Methyldopa		
Anti TNF-α		Natalizumab		
Adalimumab		Terbinafine		
Efalizumab		Omeprazole		
Etanercept		Potassium iodide		
Antiarrythmics-antihypertensives		Risperidone		
Amlodipine		Nivolumab		
Nifedipine		Pembrolizumab		
Captopril		Omalizumab		
Enalapril		Rituximab		
Lisinopril		Secukinumab		
Ramipril		Ustekinumab		
Nadolol	Topical			
Practolol		Anthralin		
Losartan		Benzyl benzoate		
Valsartan		Coal tar		
Salicylates		5-fluorouracil		
Aspirin		Iodophor in adhesive bandage		
Sulphasalazine		Epinephrine		
		Idoxuridine		

Information from:

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Enzyme	Enzyme	Affinity measure		Reference (n)	Geometric mean
		value	parameter		
Alogliptin	Dipeptidyl peptidase VIII	4.0	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	4.17
		4.0	pIC_{50}	Zhang, Z., et al. (2011). "Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl peptidase IV." J Med Chem **54**(2): 510-524.	
		4.0	pIC_{50}	Ji, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		4.0	pIC_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
		4.0	pIC_{50}	Shu, C., et al. (2014). "Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **5**(8): 921-926.	
		4.6	pIC_{50}	Xie, H., et al. (2012). "Novel pyrrolopyrimidine analogues as potent dipeptidyl peptidase IV inhibitors based on pharmacokinetic property-driven optimization." Eur J Med Chem **52**: 205-212.	
		4.6	pIC_{50}	Deng, J., et al. (2011). "The highly potent and selective dipeptidyl peptidase IV inhibitors bearing a thienopyrimidine scaffold effectively treat type 2 diabetes." Eur J Med Chem **46**(1): 71-76.	
	Dipeptidyl peptidase IX	4.0	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	4.2
		4.0	pIC_{50}	Shu, C., et al. (2014). "Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **5**(8): 921-926.	
		4.0	pIC_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		4.0	pIC_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
		4.6	pIC_{50}	Deng, J., et al. (2011). "The highly potent and selective dipeptidyl peptidase IV inhibitors bearing a thienopyrimidine scaffold effectively treat type 2 diabetes." Eur J Med Chem **46**(1): 71-76.	
		4.6	pIC_{50}	Xie, H., et al. (2012). "Novel pyrrolopyrimidine analogues as potent dipeptidyl peptidase IV inhibitors based on pharmacokinetic property-driven optimization." Eur J Med Chem **52**: 205-212.	
	Dipeptidyl peptidase IV	7.62	pIC_{50}	Ding, H. X., et al. (2013). "Synthetic approaches to the 2011 new drugs." Bioorg Med Chem **21**(11): 2795-2825.	8.32
		8.0	pIC_{50}	Wang, L., et al. (2009). "Synthesis and evaluation of structurally constrained imidazolidin derivatives as potent dipeptidyl peptidase IV inhibitors." Eur J Med Chem **44**(8): 3318-3322.	
		8.12	pIC_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
		8	pI	Zhang, Z., et al. (2011). "Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl	

		.15	C_{50}	peptidase IV." J Med Chem **54**(2): 510-524.	
		8.15	pI C_{50}	Shu, C., et al. (2014). "Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **5**(8): 921-926.	
		8.16	pI C_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		8.4	pI C_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		8.47	pI C_{50}	Xie, H., et al. (2012). "Novel pyrrolopyrimidine analogues as potent dipeptidyl peptidase IV inhibitors based on pharmacokinetic property-driven optimization." Eur J Med Chem **52**: 205-212.	
		8.47	pI C_{50}	Deng, J., et al. (2011). "The highly potent and selective dipeptidyl peptidase IV inhibitors bearing a thienopyrimidine scaffold effectively treat type 2 diabetes." Eur J Med Chem **46**(1): 71-76.	
		8.5	pI C_{50}	Xie, H., et al. (2012). "Novel pyrrolopyrimidine analogues as potent dipeptidyl peptidase IV inhibitors based on pharmacokinetic property-driven optimization." Eur J Med Chem **52**: 205-212.	
		8.82	pI C_{50}	Xie, H., et al. (2013). "Highly potent dipeptidyl peptidase IV inhibitors derived from Alogliptin through pharmacophore hybridization and lead optimization." Eur J Med Chem **68**: 312-320.	
		9.0	pI C_{50}	Nishio, Y., et al. (2011). "2-({6-[(3R)-3-amino-3-methylpiperidine-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetra hydro-5H-pyrrolo[3,2-d]pyrimidine-5-yl}methyl)-4-fluorobenzonitrile (DSR-12727): a potent, orally active dipeptidyl peptidase IV inhibitor without mechanism-based inactivation of CYP3A." Bioorg Med Chem **19**(18): 5490-5499.	
	Dipeptidyl peptidase II	4.0	pI C_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	4.0
		4.0	pI C_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		4.0	pI C_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
Anagliptin	Dipeptidyl peptidase VIII	7.17	pI C_{50}	Kato, N., et al. (2011). "Discovery and pharmacological characterization of N-[2-({2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methyl pyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt) as a potent and selective DPP-IV inhibitor." Bioorg Med Chem **19**(23): 7221-7227.	7.17
	Dipeptidyl peptidase IX	7.22	pI C_{50}	Kato, N., et al. (2011). "Discovery and pharmacological characterization of N-[2-({2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methyl pyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt) as a potent and selective DPP-IV inhibitor." Bioorg Med Chem **19**(23): 7221-7227.	7.22
	Dipeptidyl peptidase IV	8.42	pI C_{50}	Kato, N., et al. (2011). "Discovery and pharmacological characterization of N-[2-({2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methyl pyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt) as a potent and selective DPP-IV inhibitor." Bioorg Med Chem **19**(23): 7221-7227.	8.42
	Dipeptidyl peptidase II	NA	-	-	4.0*
Linagliptin	Dipeptidyl peptidase VIII	4.0	pI C_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	4.26
		4.40	pI C_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		4.4	pI C_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	

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	Dipeptidyl peptidase IX	4.0	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	4,25
		4.0	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		4.0	pIC50	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
		5.0	c	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
	Dipeptidyl peptidase IV	9.0	pKi	Eckhardt, M., et al. (2007). "8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylme thyl)-3,7-dihydropurine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes." J Med Chem **50**(26): 6450-6453.	9.07
		8.70	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		8.70	pIC50	Jansen, K., et al. (2013). "Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold." ACS Med Chem Lett **4**(5): 491-496.	
		8.70	pIC50	Jansen, K., et al. (2014). "Extended structure-activity relationship and pharmacokinetic investigation of (4-quinolinoyl)glycyl-2-cyanopyrrolidine inhibitors of fibroblast activation protein (FAP)." J Med Chem **57**(7): 3053-3074.	
		9.0	pIC50	Patel, Bhumika, and Manjunath Ghate. "Computational studies on structurally diverse dipeptidyl peptidase IV inhibitors: an approach for new antidiabetic drug development." Med Chem Res 22.9 (2013): 4505-4521.	
		9.0	pIC50	Ding, H. X., et al. (2013). "Synthetic approaches to the 2011 new drugs." Bioorg Med Chem **21**(11): 2795-2825.	
		9.0	pIC50	Eckhardt, Matthias, et al. "8-(3-amino-piperidin-1-yl)-7-(but-2-ynyl)-xanthines, the preparation thereof and their use as pharmaceutical compositions." U.S. Patent No. 7,495,003. 24 Feb. 2009.	
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		9.0	pIC50	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		9.0	pIC50	Himmelsbach, Frank, et al. "8-[3-amino-piperidin-1-yl]-xanthines, their preparation and their use as pharmaceutical composition." U.S. Patent No. 7,645,763. 12 Jan. 2010.	
		9.0	pIC50	Eckhardt, M., et al. (2007). "8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylme thyl)-3,7-dihydropurine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes." J Med Chem **50**(26): 6450-6453.	
		9.0	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		10.0	pIC50	Sutton, J. M., et al. (2012). "Novel heterocyclic DPP-4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem Lett **22**(3): 1464-1468.	
		10.	pIC50	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	

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	Dipeptidyl peptidase II	4.0	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	4.0
		4.0	pIC_{50}	Jansen, K., et al. (2013). "Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold." ACS Med Chem Lett **4**(5): 491-496.	
		4.0	pIC_{50}	Jansen, K., et al. (2014). "Extended structure-activity relationship and pharmacokinetic investigation of (4-quinolinoyl)glycyl-2-cyanopyrrolidine inhibitors of fibroblast activation protein (FAP)." J Med Chem **57**(7): 3053-3074.	
		4.0	pIC_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		4.0	pIC_{50}	Wu, W. L., et al. (2016). "Discovery of Novel Tricyclic Heterocycles as Potent and Selective DPP-4 Inhibitors for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **7**(5): 498-501.	
omarigliptin	Dipeptidyl peptidase VIII	4.0	pIC_{50}	Chen, P., et al. (2015). "Structure-activity-relationship of amide and sulfonamide analogs of omarigliptin." Bioorg Med Chem Lett **25**(24): 5767-5771.	4.08
		4.17	pIC_{50}	Biftu, T., et al. (2014). "Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes." J Med Chem **57**(8): 3205-3212.	
	Dipeptidyl peptidase IX	4.17	pIC_{50}	Biftu, T., et al. (2014). "Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes." J Med Chem **57**(8): 3205-3212.	4.17
	Dipeptidyl peptidase IV	8.59	pIC_{50}	Chen, P., et al. (2015). "Structure-activity-relationship of amide and sulfonamide analogs of omarigliptin." Bioorg Med Chem Lett **25**(24): 5767-5771.	8.68
		8.65	pIC_{50}	Li, S., et al. (2016). "Discovery and Rational Design of Natural-Product-Derived 2-Phenyl-3,4-dihydro-2H-benzo[f]chromen-3-amine Analogs as Novel and Potent Dipeptidyl Peptidase 4 (DPP-4) Inhibitors for the Treatment of Type 2 Diabetes." J Med Chem **59**(14): 6772-6790.	
		8.8	pK_i	Biftu, T., et al. (2014). "Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes." J Med Chem **57**(8): 3205-3212.	
	Dipeptidyl peptidase II	4.0	pIC_{50}	Chen, P., et al. (2015). "Structure-activity-relationship of amide and sulfonamide analogs of omarigliptin." Bioorg Med Chem Lett **25**(24): 5767-5771.	4.08
		4.17	pIC_{50}	Biftu, T., et al. (2014). "Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes." J Med Chem **57**(8): 3205-3212.	
saxagliptin	Dipeptidyl peptidase VIII	6.89	pK_i	Madar, D. J. Et. Al. (2006). Discovery of 2-[4-{{2-(2 S, 5 R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl] amino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid (ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes. J Med Chem. 49(21), 6416-6420.	6.7
		6.61	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		6.62	pIC_{50}	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	
	Dipeptidyl peptidase IX	7.0	pIC_{50}	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	7.04
		7.15	pK_i	Madar, D. J. Et. Al. (2006). Discovery of 2-[4-{{2-(2 S, 5 R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl] amino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid (ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes. J Med Chem. 49(21), 6416-6420.	

		6.98	pIC50	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
	Dipeptidyl peptidase IV	7.3	pIC_{50}	Ding, H. X., et al. (2013). "Synthetic approaches to the 2011 new drugs." Bioorg Med Chem **21**(11): 2795-2825.	8.2
		9.22	pKi	Augeri DJ et. al. (2005). "Discovery and preclinical profile of Saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes." J Med Chem. 48(15):5025-37. Simpkins LM et. al. (2007). "Potent non-nitrile dipeptidic dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett. 1;17(23):6476-80	
		7.3	pIC_{50}	Juillerat-Jeanneret, L. (2014). "Dipeptidyl peptidase IV and its inhibitors: therapeutics for type 2 diabetes and what else?" J Med Chem **57**(6): 2197-2212.	
		7.52	pIC_{50}	Dong, J., et al. (2014). "Synthesis and biological evaluation of all eight stereoisomers of DPP-IV inhibitor saxagliptin." Bioorg Med Chem **22**(4): 1383-1393.	
		8.47	pIC_{50}	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	
		8.47	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		8.52	pIC_{50}	Betancort, J. M., et al. (2009). "Bicyclic cyanothiazolidines as novel dipeptidyl peptidase 4 inhibitors." Bioorg Med Chem Lett **19**(15): 4437-4440.	
		9.22	pIC_{50}	Van Goethem, S., et al. (2011). "Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?" J Med Chem **54**(16): 5737-5746.	
	Dipeptidyl peptidase II	4.52	pIC_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	4.52
sitagliptin	Dipeptidyl peptidase VIII	4	pIC_{50}	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem **53**(18): 6572-6583.	4.48
		4.16	pIC_{50}	Chen, P., et al. (2011). "Synthesis and evaluation of [(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes and 4-[(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]piperidines as DPP-4 inhibitors." Bioorg Med Chem Lett **21**(6): 1880-1886.	
		4.17	pIC_{50}	Ji, X., et al. (2014). "Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2-carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors." Eur J Med Chem **86**: 242-256.	
		4.3	pIC_{50}	Van Goethem, S., et al. (2011). "Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?" J Med Chem **54**(16): 5737-5746.	
		4.3	pIC_{50}	Van der Veken, P., et al. (2008). "Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads." Bioorg Med Chem Lett **18**(14): 4154-4158.	
		4.32	pIC_{50}	Kim, D., et al. (2007). "Triazolopiperazine-amides as dipeptidyl peptidase IV inhibitors: close analogs of JANUVIA (sitagliptin phosphate)." Bioorg Med Chem Lett **17**(12): 3373-3377.	
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		4.32	pIC_{50}	Gao, Y. D., et al. (2007). "Modeling assisted rational design of novel, potent, and selective pyrrolopyrimidine DPP-4 inhibitors." Bioorg Med Chem Lett **17**(14): 3877-3879.	

		4.32	pIC50	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		4.47	pIC50	Ji, X., et al. (2014). "Design, synthesis and biological evaluation of hetero-aromatic moieties substituted pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors." Eur J Med Chem **75**: 111-122.	
		4.48	pIC50	Namoto, K., et al. (2014). "Discovery of C-(1-aryl-cyclohexyl)-methylamines as selective, orally available inhibitors of dipeptidyl peptidase IV." Bioorg Med Chem Lett **24**(3): 731-736.	
		4.49	pIC50	Shu, C., et al. (2014). "Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **5**(8): 921-926.	
		4.49	pIC50	Jiang, T., et al. (2015). "Design, Synthesis, and Pharmacological Evaluation of Fused beta-Homophenylalanine Derivatives as Potent DPP-4 Inhibitors." ACS Med Chem Lett **6**(5): 602-606.	
		4.7	pIC50	Tsai, T. Y., et al. (2009). "Novel trans-2-aryl-cyclopropylamine analogues as potent and selective dipeptidyl peptidase IV inhibitors." Bioorg Med Chem **17**(6): 2388-2399.	
		4.7	pIC50	Tsai, T. Y., et al. (2009). "Rational design and synthesis of potent and long-lasting glutamic acid-based dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett **19**(7): 1908-1912.	
		4.7	pIC50	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	
		4.72	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	
		5.74	pIC50	Wang, S., et al. (2014). "(R)-3-amino-1-((3aS,7aS)-octahydro-1H-indol-1-yl)-4-(2,4,5-trifluorophenyl)butan- 1-one derivatives as potent inhibitors of dipeptidyl peptidase-4: design, synthesis, biological evaluation, and molecular modeling." Bioorg Med Chem **22**(23): 6684-6693.	
	Dipeptidyl peptidase IX	4.0	pIC50	Kim, D., et al. (2007). "Triazolopiperazine-amides as dipeptidyl peptidase IV inhibitors: close analogs of JANUVIA (sitagliptin phosphate)." Bioorg Med Chem Lett **17**(12): 3373-3377.	4.21
		4.0	pIC50	Biftu, T., et al. (2007). "Rational design of a novel, potent, and orally bioavailable cyclohexylamine DPP-4 inhibitor by application of molecular modeling and X-ray crystallography of sitagliptin." Bioorg Med Chem Lett **17**(12): 3384-3387.	
		4.0	pIC50	Gao, Y. D., et al. (2007). "Modeling assisted rational design of novel, potent, and selective pyrrolopyrimidine DPP-4 inhibitors." Bioorg Med Chem Lett **17**(14): 3877-3879.	
		4.0	pIC50	Van der Veken, P., et al. (2008). "Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads." Bioorg Med Chem Lett **18**(14): 4154-4158.	
		4.0	pIC50	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	
		4.0	pIC50	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem **53**(18): 6572-6583.	
		4.0	pIC50	Chen, P., et al. (2011). "Synthesis and evaluation of [(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes and 4-[(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]piperidines as DPP-4 inhibitors." Bioorg Med Chem Lett **21**(6): 1880-1886.	
		4.0	pIC50	Van Goethem, S., et al. (2011). "Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?" J Med Chem **54**(16): 5737-5746.	
		4.	pI	Shu, C., et al. (2014). "Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes." ACS Med Chem Lett **5**(8): 921-926.	

		06	C_{50}		
		4.06	pI C_{50}	Jiang, T., et al. (2015). "Design, Synthesis, and Pharmacological Evaluation of Fused beta-Homophenylalanine Derivatives as Potent DPP-4 Inhibitors." ACS Med Chem Lett **6**(5): 602-606.	
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		5.0	pI C_{50}	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
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		7.9	pK d	Li S. Et. al. (2016) "Discovery and Rational Design of Natural-Product-Derived 2-Phenyl-3,4-dihydro-2H-benzo[f]chromen-3-amine Analogs as Novel and Potent Dipeptidyl Peptidase 4 (DPP-4) Inhibitors for the Treatment of Type 2 Diabetes." J Med Chem. 59(14):6772-90.	
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		7.4	pI C_{50}	Van der Veken, P., et al. (2008). "Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads." Bioorg Med Chem Lett 18(14): 4154-4158.	
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		7.52	pI C_{50}	Tsai, T. Y., et al. (2009). "Rational design and synthesis of potent and long-lasting glutamic acid-based dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett 19(7): 1908-1912	
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		7.7	pIC$_{50}$	Ji, X., et al. (2014). "Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2-carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors." Eur J Med Chem **86**: 242-256.
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		4.0	pIC$_{50}$	Gao, Y. D., et al. (2007). "Modeling assisted rational design of novel, potent, and selective pyrrolopyrimidine DPP-4 inhibitors." Bioorg Med Chem Lett **17**(14): 3877-3879.	
		4.0	pIC$_{50}$	Ryabtsova, O., et al. (2012). "Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity." Bioorg Med Chem Lett 22(10): 3412-3417.	
		4	pI	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl	

		.0	C_{50}	peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		4.0	pI C_{50}	Biftu, T., et al. (2007). "Rational design of a novel, potent, and orally bioavailable cyclohexylamine DPP-4 inhibitor by application of molecular modeling and X-ray crystallography of sitagliptin." Bioorg Med Chem Lett **17**(12): 3384-3387.	
		4.0	pI C_{50}	Van der Veken, P., et al. (2008). "Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads." Bioorg Med Chem Lett 18(14): 4154-4158.	
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		4.0	pI C_{50}	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem 53(18): 6572-6583.	
		4.0	pI C_{50}	Chen, P., et al. (2011). "Synthesis and evaluation of [(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes and 4-[(1R)-1-amino-2-(2,5-difluorophenyl)ethyl]piperidines as DPP-4 inhibitors." Bioorg Med Chem Lett **21**(6): 1880-1886.	
		4.0	pI C_{50}	Van Goethem, S., et al. (2011). "Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?" J Med Chem 54(16): 5737-5746.	
		4.22	pI C_{50}	Wang, S., et al. (2014). "(R)-3-amino-1-((3aS,7aS)-octahydro-1H-indol-1-yl)-4-(2,4,5-trifluorophenyl)butan- 1-one derivatives as potent inhibitors of dipeptidyl peptidase-4: design, synthesis, biological evaluation, and molecular modeling." Bioorg Med Chem **22**(23): 6684-6693.	
		4.7	pI C_{50}	Tsai, T. Y., et al. (2009). "Rational design and synthesis of potent and long-lasting glutamic acid-based dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett 19(7): 1908-1912.(rational..)	
		4.7	pI C_{50}	Tsai, T. Y., et al. (2009). "Novel trans-2-aryl-cyclopropylamine analogues as potent and selective dipeptidyl peptidase IV inhibitors." Bioorg Med Chem 17(6): 2388-2399	
Teneligliptin	Dipeptidyl peptidase VIII	6.59	pI C_{50}	Yoshida, T., et al. (2012). "Discovery and preclinical profile of teneligliptin (3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-y lcarbonyl]thiazolidine): a highly potent, selective, long-lasting and orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes." Bioorg Med Chem **20**(19): 5705-5719.	6.59
	Dipeptidyl peptidase IX	6.27	pI C_{50}		6.27
	Dipeptidyl peptidase IV	9.43	pI C_{50}		9.43
	Dipeptidyl peptidase II	NA		NA	4.0*
Trelagliptin	Dipeptidyl peptidase VIII	4.0	pI C_{50}	Zhang, Z., et al. (2011). "Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl peptidase IV." J Med Chem **54**(2): 510-524.	4.0
	Dipeptidyl peptidase IX	4.0	pI C_{50}	Grimshaw, C. E., et al. (2016). "Trelagliptin (SYR-472, Zafatek), Novel Once-Weekly Treatment for Type 2 Diabetes, Inhibits Dipeptidyl Peptidase-4 (DPP-4) via a Non-Covalent Mechanism." PLoS One **11**(6): e0157509.	4.0
	Dipeptidyl peptidase IV	8.4	pI C_{50}	Zhang, Z., et al. (2011). "Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl peptidase IV." J Med Chem **54**(2): 510-524.	8.4
	Dipeptidyl peptida	4.0	pI C_{50}	Grimshaw, C. E., et al. (2016). "Trelagliptin (SYR-472, Zafatek), Novel Once-Weekly Treatment for Type 2 Diabetes, Inhibits Dipeptidyl Peptidase-4 (DPP-4) via a Non-Covalent Mechanism." PLoS One **11**(6): e0157509.	4.0

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Vildagliptin	Dipeptidyl peptidase VIII	4.85	pIC_{50}	Jiaang, W. T., et al. (2005). "Novel isoindoline compounds for potent and selective inhibition of prolyl dipeptidase DPP8." Bioorg Med Chem Lett **15**(3): 687-691.	5.29
		5.87	pKi	Madar, D. J. Et. Al. (2006). Discovery of 2-[4-{{2-(2 S, 5 R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl] amino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid (ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes. J Med Chem. 49(21), 6416-6420.	
		6.09	pKi	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem 20(19): 5864-5883.	
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		4.85	pIC_{50}	Tsu, H., et al. (2006). "2-[3-[2-[(2S)-2-Cyano-1-pyrrolidinyl]-2-oxoethylamino]-3-methyl-1-oxobutyl]- 1,2,3,4-tetrahydroisoquinoline: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." J Med Chem **49**(1): 373-380.	
		4.85	pIC_{50}	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem	
		4.85	pIC_{50}	Tsai, T. Y., et al. (2009). "Rational design and synthesis of potent and long-lasting glutamic acid-based dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett 19(7): 1908-1912.(rational..)	
		4.85	pIC_{50}	Tsai, T. Y., et al. (2009). "Novel trans-2-aryl-cyclopropylamine analogues as potent and selective dipeptidyl peptidase IV inhibitors." Bioorg Med Chem 17(6): 2388-2399.(novel..)	
		4.85	pIC_{50}	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem 53(18): 6572-6583.	
		5.05	pIC_{50}	Van der Veken, P., et al. (2008). "Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads." Bioorg Med Chem Lett 18(14): 4154-4158.	
		5.05	pIC_{50}	Van Goethem, S., et al. (2011). "Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?" J Med Chem 54(16): 5737-5746.	
		5.42	pIC_{50}	Cho, T. P., et al. (2010). "Synthesis and biological evaluation of azobicyclo[3.3.0] octane derivatives as dipeptidyl peptidase 4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem Lett **20**(12): 3565-3568.	
		5.71	pIC_{50}	Wang, J., et al. (2013). "Synthesis and biological evaluation of pyrrolidine-2-carbonitrile and 4-fluoropyrrolidine-2-carbonitrile derivatives as dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem **21**(23): 7418-7429.	
		5.71	pIC_{50}	Ji, X., et al. (2014). "Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2-carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors." Eur J Med Chem **86**: 242-256.	
		5.85	pIC_{50}	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	

		5.96	pIC_{50}	Liu, Y., et al. (2013). “Synthesis and biological evaluation of novel benzyl-substituted (S)-phenylalanine derivatives as potent dipeptidyl peptidase 4 inhibitors.” Bioorg Med Chem 21(18): 5679-5687.	
	Dipeptidyl peptidase IX	5.92	pIC_{50}	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.	6.6
		7.02	pK_i	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		7.17	pK_i	Madar, D. J. Et. Al. (2006). Discovery of 2-[4-{{2-(2 S, 5 R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl] amino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid (ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes. J Med Chem. 49(21), 6416-6420.	
		5.92	pIC_{50}	Tsai, T. Y., et al. (2010). “Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein.” J Med Chem 53(18): 6572-6583.	
		6.17	pIC_{50}	Van der Veken, P., et al. (2008). “Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads.” Bioorg Med Chem Lett 18(14): 4154-4158.	
		6.17	pIC_{50}	Van Goethem, S., et al. (2011). “Structure-activity relationship studies on isoindoline inhibitors of dipeptidyl peptidases 8 and 9 (DPP8, DPP9): is DPP8-selectivity an attainable goal?” J Med Chem 54(16): 5737-5746.	
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		6.7	pIC_{50}	Wang, J., et al. (2013). "Synthesis and biological evaluation of pyrrolidine-2-carbonitrile and 4-fluoropyrrolidine-2-carbonitrile derivatives as dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem **21**(23): 7418-7429.	
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		7.18	pIC_{50}	Liu, Y., et al. (2013). “Synthesis and biological evaluation of novel benzyl-substituted (S)-phenylalanine derivatives as potent dipeptidyl peptidase 4 inhibitors.” Bioorg Med Chem 21(18): 5679-5687.	
	Dipeptidyl peptidase IV	6.92	pIC_{50}	Ryabtsova, O., et al. (2012). “Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity.” Bioorg Med Chem Lett 22(10): 3412-3417.	7.66
		4.77	pK_i	Van der Veken P et. al. (2008). “Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads.” Bioorg Med Chem Lett. 18(14):4154-8.	
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		8.52	pK_i	Ikuma, Y., et al. (2012). "Discovery of 3H-imidazo[4,5-c]quinolin-4(5H)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors." Bioorg Med Chem **20**(19): 5864-5883.	
		6.92	pIC_{50}	Van der Veken, P., et al. (2008). “Inhibitors of dipeptidyl peptidase 8 and dipeptidyl peptidase 9. Part 1: identification of dipeptide derived leads.” Bioorg Med Chem Lett 18(14): 4154-4158.	

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		7.25	pIC50	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem 53(18): 6572-6583.
		7.29	pIC50	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-p yrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem Lett **20**(12): 3596-3600.
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		7.29	pIC50	Lu, I. L., et al. (2005). "Glutamic acid analogues as potent dipeptidyl peptidase IV and 8 inhibitors." Bioorg Med Chem Lett **15**(13): 3271-3275.
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		7.64	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.
		7.7	pIC50	Wang, J., et al. (2013). "Synthesis and biological evaluation of pyrrolidine-2-carbonitrile and 4-fluoropyrrolidine-2-carbonitrile derivatives as dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem **21**(23): 7418-7429.
		7.77	pIC50	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-p yrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem

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		8.05	pIC50	Cho, T. P., et al. (2010). "Synthesis and biological evaluation of azobicyclo[3.3.0] octane derivatives as dipeptidyl peptidase 4 inhibitors for the treatment of type 2 diabetes." Bioorg Med Chem Lett **20**(12): 3565-3568.	
		8.46	pIC50	Weber, A. E. (2004). "Dipeptidyl peptidase IV inhibitors for the treatment of diabetes." J Med Chem **47**(17): 4135-4141.	
		8.46	pIC50	Juillerat-Jeanneret, L. (2014). "Dipeptidyl peptidase IV and its inhibitors: therapeutics for type 2 diabetes and what else?" J Med Chem **57**(6): 2197-2212.	
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		8.52	pIC50	Liu, Y., et al. (2013). "Synthesis and biological evaluation of novel benzyl-substituted (S)-phenylalanine derivatives as potent dipeptidyl peptidase 4 inhibitors." Bioorg Med Chem 21(18): 5679-5687.	
		9.24	pIC50	Nishio, Y., et al. (2011). "2-({6-[(3R)-3-amino-3-methylpiperidine-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetra hydro-5H-pyrrolo[3,2-d]pyrimidine-5-yl}methyl)-4-fluorobenzonitrile (DSR-12727): a potent, orally active dipeptidyl peptidase IV inhibitor without mechanism-based inactivation of CYP3A." Bioorg Med Chem **19**(18): 5490-5499.	
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		4.0	pIC50	Bioorg. Med. Chem. Lett. (2005) 15: 687-691[PMID:15664838] Jiaang 2005	
		4.0	pIC50	Lu, I. L., et al. (2005). "Glutamic acid analogues as potent dipeptidyl peptidase IV and 8 inhibitors." Bioorg Med Chem Lett **15**(13): 3271-3275.	
		4.0	pIC50	Tsu, H., et al. (2006). "2-[3-[2-[(2S)-2-Cyano-1-pyrrolidinyl]-2-oxoethylamino]-3-methyl-1-oxobutyl]- 1,2,3,4-tetrahydroisoquinoline: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." J Med Chem **49**(1): 373-380.	
		4.0	pIC50	Ji, X., et al. (2014). "Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2-carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors." Eur J Med Chem **86**: 242-256.	
		4.0	pIC50	Jansen, K., et al. (2014). "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold." MedChemComm **5**(11): 1700-1707.	

		4.3	pIC$_{50}$	Yeh, T. K., et al. (2010). "(2S,4S)-1-[2-(1,1-dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV." Bioorg Med Chem
		4.3	pIC$_{50}$	Tsai, T. Y., et al. (2010). "Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein." J Med Chem 53(18): 6572-6583.
		4.7	pIC$_{50}$	Tsai, T. Y., et al. (2009). "Rational design and synthesis of potent and long-lasting glutamic acid-based dipeptidyl peptidase IV inhibitors." Bioorg Med Chem Lett 19(7): 1908-1912.(rational..)
		4.7	pIC$_{50}$	Tsai, T. Y., et al. (2009). "Novel trans-2-aryl-cyclopropylamine analogues as potent and selective dipeptidyl peptidase IV inhibitors." Bioorg Med Chem 17(6): 2388-2399.(novel..)

Supplementary Table 2: Summary of affinitiy profiles of DPP-4 inhibitors at DPP-4, DPP-2, DPP-8 and DPP-9.

pKi= logarithm with the base 10 of Ki; pIC$_{50}$= negative log of the IC$_{50}$ value; DPP= dipeptidyl peptidase. Valuaes extracted from from competition binding assays found in the IUPHAR (International Union of Basic and Clinical Pharmacology), BRENDA, BindingDB, PubChem, European Bioinformatics Institute-ChEMBL, LIGAND and DrugBank databases.

* no or lack of information, substituted by a value of 4

Supplementary table 3: Selectivity profile of different DPP-4 inhibitors for inhibition of DPP-4 enzyme over DPP-8/DPP-9 along with pharmacokinetic data

DPP-4 inhibitor	DPP-4 selectivity vs DPP-8		DPP-4 selectivity vs DPP-9		Haf life (hrs)	Volume of Distribution (L)	Ref.
	fold	log2 fold	fold	log2 fold			
Alogliptin	14,285	13.80	14,285	13.80	21	417	[1, 2]
Anagliptin	84,700	16.37	56,100	15.78	4.37	112	[3, 4]
Linagliptin	10,000	13.29	10,000	13.29	160	1,110	[5, 6]
Omarigliptin	10,000	13.29	10,000	13.29	22	77	[7-9]
Saxagliptin	72	6.17	31	4.95	3.8	151	[10, 11]
Sitagliptin	2,667	11.38	5,550	12.44	12.4	198	[12]
Teneligliptin	11,248	13.46	11,248	13.46	24.2	107	[13, 14]
Trelagliptin	100,000	16.61	100,000	16.61	55.56	1,194	[15, 16]
Vildagliptin	270	8.08	32	5.00	12.4	198	[17-19]

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