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Design, synthesis, and biological evaluation of triazolopiperazine-based β-amino amides as potent, orally active dipeptidyl peptidase IV (DPP-4) inhibitors

Jennifer E. Kowalchick,[a,*] Barbara Leiting,[b] KellyAnn D. Pryor,[b] Frank Marsilio,[b] Joseph K. Wu,[b] Huaibing He,[a] Kathryn A. Lyons,[a] George J. Eiermann,[c] Aleksandr Petrov,[c] Giovanna Scapin,[a] Reshma A. Patel,[c] Nancy A. Thornberry,[b] Ann E. Weber[a] and Dooseop Kim[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Metabolic Disorders, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

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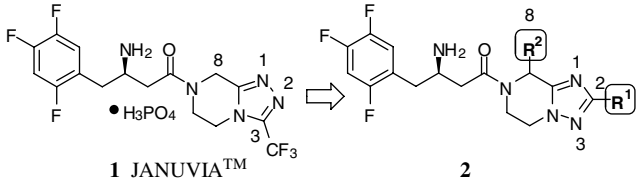
Abstract—Various β-amino amides containing triazolopiperazine heterocycles have been prepared and evaluated as potent, selective, orally active dipeptidyl peptidase IV (DPP-4) inhibitors. These compounds display excellent oral bioavailability and good overall pharmacokinetic profiles in preclinical species. Moreover, in vivo efficacy in an oral glucose tolerance test in lean mice is demonstrated.

In recent years, glucagon-like peptide 1 (GLP-1) therapy has emerged as an area of active investigation for the treatment of type 2 diabetes.[1] GLP-1 is an incretin hormone released in the gut upon food ingestion that regulates insulin in a glucose-dependent manner. Elevation of blood glucose levels causes GLP-1 to trigger insulin biosynthesis and secretion, inhibit glucagon release, slow gastric emptying, and induce pancreatic β-cell proliferation. The serine protease dipeptidyl peptidase IV (DPP-4) rapidly renders GLP-1 inactive through cleavage of its N-terminal two amino acids. Inhibition of DPP-4 prolongs the half life of GLP-1 and thus, leads to increased levels of active endogenous GLP-1. Accordingly, DPP-4 inhibition is a promising new treatment for type 2 diabetes.[2]

Compound **1**, JANUVIA™ (sitagliptin), was recently approved by the U.S. Food and Drug Administration for the treatment of patients with type 2 diabetes. Because the fused heterocycle moiety of sitagliptin is recognized as a key pharmacophore that contributes to its good pharmacokinetic profile, potency, and selectivity,[3] a new series of triazolopiperazines have been investigated. Moving the nitrogen from the 2- to the 3-position in the triazolopiperazine bicycle of sitagliptin brought about a new family of compounds. Herein, we focus on the evaluation of the following variations to this new triazolopiperazine structure: modification at the 2-position as well as the 8-position of the bicycle **2**.



1 JANUVIA™ (sitagliptin phosphate)
DPP-4 IC_{50} = 18 nM

2

The DPP-4 inhibitors in this report were prepared by standard peptide coupling of β-amino acids with fused

Keywords: Dipeptidyl peptidase IV; DPP-4; Dipeptidyl peptidase IV inhibitors; DPP-4 inhibitors; β-Amino amides; Triazolopiperazine; Triazolopiperazine-based β-amino amides; Type 2 diabetes.
* Corresponding author. Tel.: +1 570 594 2569; e-mail: jennifer_kowalchick@yahoo.com

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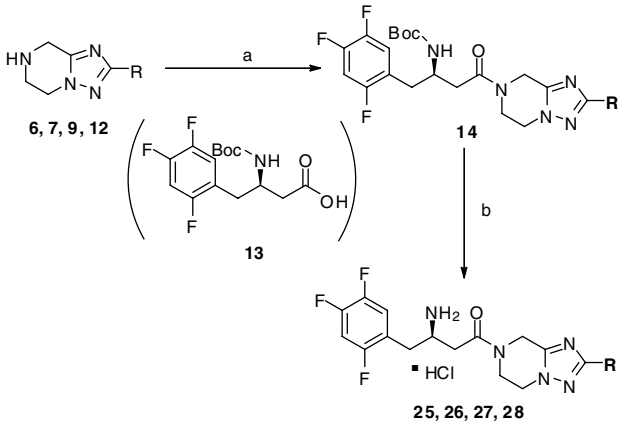
heterocycles as reported earlier.[3] The synthesis of non-commercially available β-amino acid (**13**) has already been reported.[3] Four different approaches to novel substituted triazolopiperazines are described in Scheme 1.

Following the procedures analogous to those reported in the literature, the target triazolopiperazine heterocycles were each prepared in four to five steps.[4–7] Aminopyrazine (**3**) was acylated with trifluoroacetic anhydride, cyclopropane carbonyl chloride, and benzoyl chloride to give acetamides **4**, **8**, and **10**, respectively.[4] The trifluoromethyl and benzyl acetamides were then treated with phosphorous pentachloride followed by hydroxylamine to afford their respective hydroxyimideamides, **5** and **11**.[5] Condensation in polyphosphoric acid (PPA) or superphosphoric acid at elevated temperatures followed by catalytic hydrogenation gave piperazine intermediates **6** and **12**.[6] The cyclopropyl acetamide **8** was subsequently treated with *O*-mesitylenesulfonyl hydroxyl amine, giving the aminopyrazinium salt,[7] which was then cyclized and reduced using the aforementioned method, to afford **9**. Heterocycle **7** was prepared from aminopyrazine using procedures outlined in the literature.[6]

As shown in Scheme 2, coupling of β-amino acid **13** with the respective piperazines, followed by deprotection of the amine, provided the desired compounds **25**–**28** in Table 1.

With piperazine analogs, α-substitution on the piperazine heterocycle has been shown to increase DPP-4 potency.[8] To boost the potency of compounds in the triazolopiperazine series of current focus, various substituents were added to the α-position of the fused bicycle. Several approaches to obtain α-substitution on the triazolopiperazine heterocycle are described in Scheme 3.

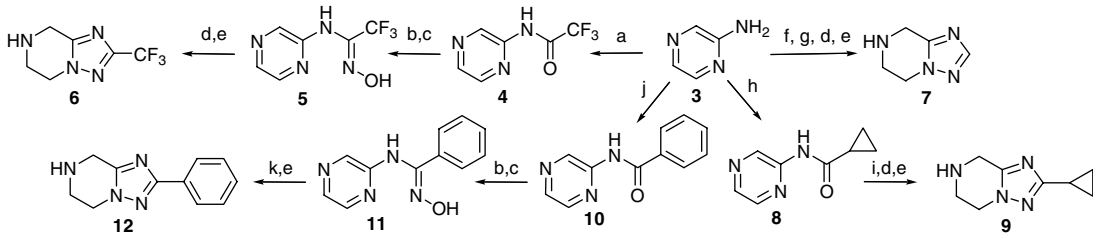
Boc-protection of amine **6** followed by alkylation at the α-position with the appropriate alkyl halides and subsequent deprotection gave **16**.[9] Alkylation of **15** with benzyl chloromethyl ether, followed by debenzylation, conversion to the mesylate (**17**),[10] and displacement with the desired heterocycle gave heteroaryl-substituted piperazines **18**. Reaction of **15** with cyclopropane carboxaldehyde gave hydroxyl intermediate **19**. Deprotection of **19** gave **20**, whereas fluorination with diethylaminosulfur trifluoride (DAST)[11] followed by deprotection gave



Scheme 2. Reagents and conditions: (a) **13**, HOBT, EDC, DMF, rt, 16 h; (b) satd HCl in CH_3OH, rt, 1 h.

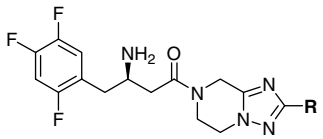
22. Treatment of **19** with 1,1-thiocarbonyldiimidazole resulted in elimination, which, followed by reduction and deprotection, gave **21**. Coupling of the triazolopiperazines **16**, **18**, **20**–**22** with β-amino acid **13**, followed by separation of the diastereomers on OD chiralcel or AS and AD chiral pak columns, and deprotection provided desired compounds **29a**–**b**, **30a**–**b**, **31a**–**b**, **32a**–**b**, **33a**–**d**, **34a**–**d**, **35**, **36**, **37**, and **37a**–**b**. In general, the slower eluting diastereomers on the OD and AS chiral columns and the faster eluting diastereomers on the AD chiral column were the more potent diastereomers, and are listed in Table 2.

The compounds listed in Tables 1 and 2 underwent in vitro evaluation for inhibition of DPP-4.[12] To screen for off-target activity, the analogs were also tested against homologs of DPP-4 in the same gene family as well as other proline-specific enzymes. Homologs tested include DPP-8,[13] DPP-9,[14] and fibroblast activation protein (FAP).[15] Other proline-specific enzymes that were tested include quiescent cell proline dipeptidase (QPP, also known as DPP-2),[12,16] prolidase, and amino peptidase P (APP). None of the compounds in this report showed any significant inhibition against FAP, prolidase, and APP (IC_{50}s > 50,000 nM), thus those data are not reported. Previous DPP-8/9 selective inhibitor studies suggest that DPP-8 and/or DPP-9 inhibition is associated with profound toxicity in preclinical species.[17] Furthermore, monkeys treated with a non-selective DPP-4, DPP-8, and DPP-9 inhibitor displayed

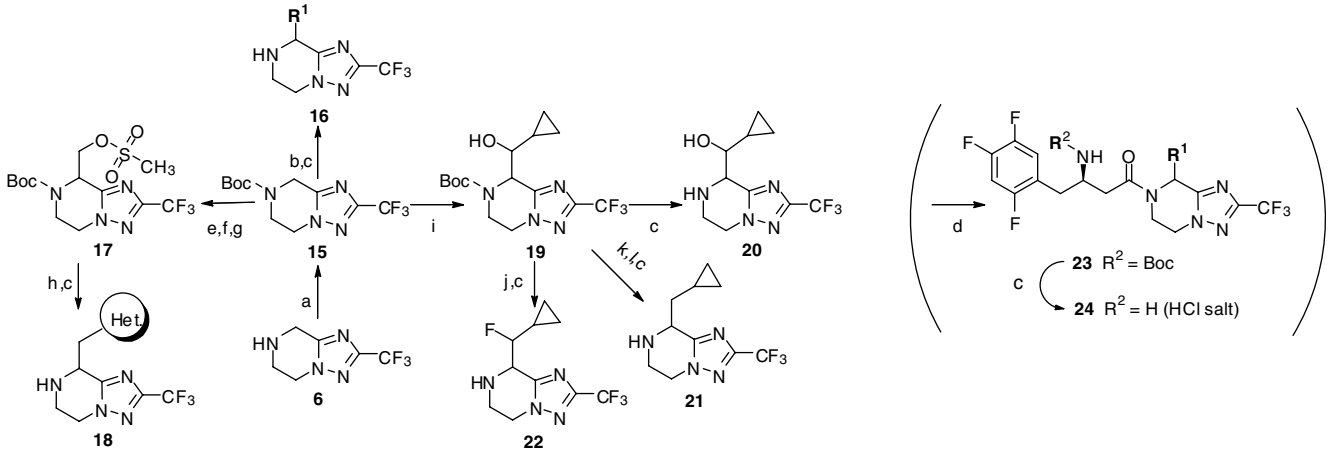


Scheme 1. Reagents and conditions: (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C–rt, 2h; (b) PCl_5, dichloroethane, reflux, 5 h; (c) 50% aq NH_2OH, THF, rt, 2 h; (d) polyphosphoric acid, 150 °C, 18 h; (e) H_2, 10% Pd/C, EtOH, rt, 18 h; (f) *N*,*N*-dimethylformamide dimethyl acetal, reflux, 2 h; (g) 50% aq NH_2OH, THF, reflux, 1.5 h; (h) cyclopropane carbonyl chloride, pyridine, chloroform, rt, 2 h; (i) *O*-mesitylenesulfonyl hydroxyl amine,[6] CH_2 Cl_2, 0 °C–rt, 1.5 h; (j) benzoyl chloride, pyridine, 0 °C–rt, 18 h; (k) superphosphoric acid, 110 °C, 3 h.

Table 1. Inhibitory properties of fused heterocycle-derived DPP-4 inhibitors with varied 2-position substituents



Compound	R	DPP-4 IC_{50}, nM	QPP IC_{50}, nM	DPP-8 IC_{50}, nM	DPP-9 IC_{50}, nM
25	CF_3	59	54,000	62,000	>100,000
26	H	100	>100,000	>100,000	>100,000
27		71	>100,000	>100,000	>100,000
28		68	4000	44,000	>100,000



Scheme 3. Reagents and conditions: (a) $(Boc)_2O$, DIPEA, CH_2Cl_2, rt, 18 h; (b) TMEDA, *n*-BuLi, R–X, −78 °C–rt, 1.5 h; (c) satd HCl in CH_3OH, 1 h; (d) **13**, HOAT, HATU, DIPEA, DMF, rt, 18 h, followed by chiral separation on Chiral OD, AD, or AS columns; (e) TMEDA, *n*-BuLi, benzyl chloromethyl ether, −78 °C–rt, 1.5 h; (f) H_2 (1 atm) 10% Pd/C, EtOH, rt, 29 h, followed by H_2 (42 psi) 12 h; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 4 h[10]; (h) heterocycle (imidazole, pyrazole, or 1,2,4-triazole) K_2CO_3, DMF, 50 °C or NaH (60%), DMF, rt, 0.6 h; (i) *sec*-BuLi, cyclopropane carboxaldehyde, −78 °C–rt, 1 h; (j) DAST, CH_2Cl_2, −78 °C–rt, 17 h; (k) 1,1-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux, 17 h; (l) H_2 (1 atm) 10% Pd/C, EtOH, rt, 18 h.

treatment-related dermatological toxicity.[18] Also, earlier β-amino acid-derived DPP-4 inhibitors were associated with significant QPP off-target activity.[19] Thus, activities against these three enzymes are reported in Tables 1 and 2.

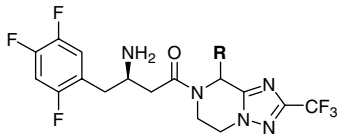
In vitro inhibitory activity for the selected triazolopiperazine-based DPP-4 inhibitors is listed in Tables 1 and 2, while Table 3 exhibits the pharmacokinetic properties of selected compounds with high DPP-4 potency.

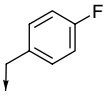
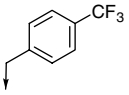
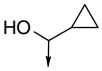
Variation of the substituent at the triazolopiperazine 2-position is reported in Table 1. Exchanging the 2-position nitrogen of compound **1** with its 3-position substituent produces a threefold decrease in DPP-4 potency, as seen in compound **25** (DPP-4 IC_{50} = 59 nM vs 18 nM for compound **1**). However, isomer **25** exhibits 100% oral bioavailability and a half life of 3.6 h in the rat (Table 3).

In an attempt to increase DPP-4 potency, the 2-position substituent was both varied and deleted; however, no substituent produced potency greater than that observed by the 2-trifluoromethyl group. Deletion of the trifluoromethyl substituent in compound **25** resulted in a twofold decrease in the DPP-4 potency (**26**). Cyclopropyl and phenyl-substituted compounds **27** and **28** both displayed decreased DPP-4 potency and selectivity and, thus, offered no advantage over compound **25**. Of those explored, the trifluoromethyl group was accepted as the optimal 2-position substituent, and this substituent was thus used in further SAR studies examining other modifications in the piperazine heterocycle.

Aiming to boost DPP-4 potency in the series, various substituents were added to the α-position of the fused bicycle. In Table 2, simple addition of an *R*-methyl group to the α-position of the triazolopiperazine (confirmed by X-ray analysis) increased DPP-4 potency twofold (DPP-4 IC_{50} = 25 nM) in comparison to **25**. This compound (**29b**) displayed outstanding oral bioavailability and a lengthened half life in rat, dog, and rhesus monkey models (Table 3). Notably, the half life of **29b** in the dog model was an exceptional 26 h.

Table 2. Inhibitory properties of fused heterocycle-derived DPP-4 inhibitors with varied 8-position substituents



Compound	R	DPP-4 IC_{50} (nM)	QPP IC_{50} (nM)	DPP-8 IC_{50} (nM)	DPP-9 IC_{50} (nM)
25	H	59	54,000	62,000	>100,000
29a	CH_3(*S*)	274	72,000	>100,000	>100,000
29b	CH_3(*R*)	25	25,000	>100,000	>100,000
30b[a]		4	60,000	25,000	27,000
31b[a]		4	15,000	16,000	27,000
32b[a]		7	7400	71,000	54,000
33b[a,c]		12	33,000	86,000	>100,000
33d[a,c]		14	18,000	>100,000	>100,000
34c[a,d]		18	5767	>100,000	77,000
34d[a,d]		11	4100	>100,000	63,000
35[b]		2	26,000	>100,000	27,000
36[b]		4	9600	>100,000	>100,000
37[b]		5	49,000	>100,000	>100,000
37a[a]		2	22,000	>100,000	>100,000

[a] Tentatively assigned *R*-stereochemistry.
[b] Mixture of diastereomers.
[c] Single diastereomer, configuration at OH unknown.
[d] Single diastereomer, configuration at F unknown.

Compound **29b** also displayed selectivity over QPP, DPP-8, and DPP-9. Compound **29a**, the *S*-diastereomer of **29b**, was significantly less active (DPP-4 IC_{50} = 274 nM) than the *R*-diastereomer. This 10-fold decrease in potency was observed in all other less potent diastereomers, which were assumed to be the *S*-diastereomers (not included in Table 2). The biological results of **29b** suggested that α-substitution could be used for enhancement of both DPP-4 potency as well as pharmacokinetic properties.

Following the lead of α-methyl-substituted triazolopiperazine compound **29b**, a number of other analogs containing α-substitution were evaluated. Among these compounds were the benzyl, cyclopropyl, and heteroaryl-substituted triazolopiperazines shown in Table 2. Benzyl substitution, as seen in compounds **30b** and **31b**, greatly enhanced DPP-4 potency (DPP-4 IC_{50} = 4 nM) when compared to compound **29b**; conversely, oral bioavailability (**30b**) suffered (%*F* = 32). Cyclopropyl substitution at the triazolopiperazine α-position was evaluated next. As compared to lead compound **29b**, potent diastereomers of the series cause a definite boost in DPP-4 potency and retain selectivity against DPP-8 and DPP-9. Upon further evaluation in pharmacokinetic studies, **33b** and **33d** did not show improvement relative to **29b**. Further efforts to improve pharmacokinetics then focused on heteroaryl incorporation

Table 3. Pharmacokinetic properties of fused heterocycle-derived DPP-4 inhibitors

Compound	Species	Clp (mL/min/kg)	$t_{1/2}$ (h)	AUC_{norm} (μM h kg mg^{-1})	*F* (%)
1	Rat	60	1.7	0.523	76
	Dog	6.0	4.9	8.3	100
	Monkey	28	3.7	1.0	68
25	Rat	60	3.6	1.143	100
29b	Rat	68	4.0	0.432	74
	Dog	1.0	26	30.240	67
	Monkey	16	7.7	1.640	65
30b	Rat	76	2.7	0.146	32
33b	Rat	91	5.1	0.199	51
33d	Rat	97	3.9	0.271	63
35	Rat	97	9.0	0.027	7.1
36	Rat	142	2.3	0.151	62
37	Rat	129	2.8	0.035	13

at the α-position of the bicycle. Diastereomeric separation could only be achieved for the 1-methyl-1H-1,2,4-triazole analog (**37**), so biological data is reported for the (*R*) and (*S*) diastereomeric mixtures of the heterocyclic analogs. These compounds displayed increased DPP-4 potencies of 5- to 10-fold over lead compound **29b** and good selectivity over other proline-specific enzymes. Further in vivo testing of **35** and **37** revealed an overall decrease in oral bioavailability (%*F* = 7.1 and 13, respectively), as well as diminished oral exposure in **35**, **36**, and **37** (po AUC_{norm} = 0.027, 0.151, and 0.035, respectively).

Of the compounds examined, compound **29b** displayed the best overall profile with regard to in vitro potency, selectivity, and pharmacokinetics, and thus, was selected for further biological evaluation in vivo. The ability of compound **29b** to reduce glucose levels in lean mice was assessed in an oral glucose tolerance test (OGTT).[3a] Single oral doses of **29b** administered 60 min prior to dextrose challenge reduced the blood glucose excursion in a dose-dependent manner from 0.1 mg/kg (14% inhibition) to 3.0 mg/kg (44% inhibition). Dose-dependent inhibition of glucose excursion appeared maximal at 1.0 mpk (39% inhibition) (Fig. 1).

X-ray crystal structure determination of compound **29b** (the more potent diastereomer) in complex with the DPP-4 enzyme demonstrates that the absolute stereochemistry at the triazolopiperazine α-position is (*R*) (Fig. 2).[20] In a similar manner to that shown in the crystal structure of sitagliptin, the S1 hydrophobic pocket in the DPP-4 enzyme is fully occupied by compound **29b**'s 2,4,5-trifluorophenyl moiety. Also, the (*R*)-β-amino group interacts with glutamate residues Glu205 and Glu206 through four hydrogen bonding interactions.[3a] The carboxylic oxygen and the hydroxyl of Tyr547 are bridged by a water molecule, and several other water-mediated interactions are also present between the nitrogen atoms of the triazolopiperazine and protein atoms. The triazolopiperazine is stacked against the side chain of Phe357.

The enhanced potency of **29b** (DPP-4 IC_{50} = 25 nM) in comparison to **25** (DPP-4 IC_{50} = 59 nM) corresponds to the (*R*)-α-methyl group of the triazolopiperazine occupying a relatively open area of the DPP-4 binding site, and thus, providing further surface complementarity to the Phe375 side chain. Since having an (*S*)-methyl group at the α-position would cause a clash with Phe357, a 10-fold decrease in potency is observed with its diastereomer, **29a** (DPP-4 IC_{50} = 274 nM).

Through variation of the heterocyclic moiety found in sitagliptin by exchanging the 2-position nitrogen with the 3-position substituent, a novel series of potent triazolopiperazine-based DPP-4 inhibitors have been discovered. These triazolopiperazine analogs are potent, selective DPP-4 inhibitors, and exhibit an excellent oral bioavailability and good overall pharmacokinetic profile, as demonstrated by isomer **25**. Introduction of alkyl, heteroaryl, and benzyl substitution at the α-position resulted in a pronounced boost in DPP-4 potency. Compound **29b**, the (*R*)-diastereomer, exhibited greater DPP-4 potency than its (*S*) counterpart. Due to its increased DPP-4 potency over compound **25**, good selectivity over other proline-specific enzymes, and both a long half life and excellent oral bioavailability in all preclinical species tested, compound **29b** was selected for further in vivo development. An OGTT revealed that when administered to lean mice, compound **29b** showed a dose-dependent inhibition of glucose excursion maximal at 1 mg/kg. As in sitagliptin, the fused heterocycle moiety of this series played a positive key role in

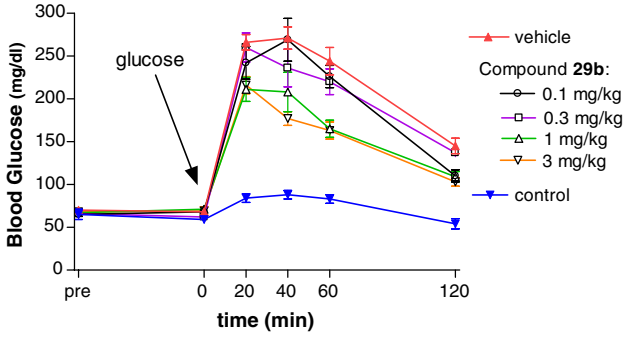


Figure 1. The effect of compound **29b** on glucose levels following an oral glucose tolerance test in lean mice. Single oral doses of **29b** administered 60 min prior to dextrose challenge, reduced the blood glucose excursion in a dose-dependent manner from 0.1 mg/kg (14% inhibition) to 3.0 mg/kg (44% inhibition).

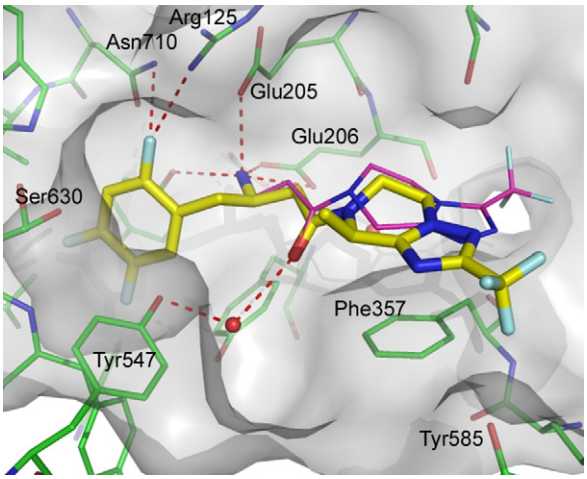


Figure 2. The binding of compound **29b** to the DPP-4 enzyme. Red dotted lines portray the interactions with **29b** with DPP-4. For clarity purposes, the extensive hydrogen bonding network between water molecules, compound **29b**, and protein atoms has been omitted.

DPP-4 potency, selectivity, and pharmacokinetics; however, due to unacceptable muscarinic receptor binding activities (M_2 K_i = 0.470 μM: and M_4 K_i = 0.800 μM), further development of compound **29b** was discontinued.

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