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Diastereoselective synthesis and configuration-dependent activity of (3-substituted-cycloalkyl)glycine pyrrolidides and thiazolidides as dipeptidyl peptidase IV inhibitors

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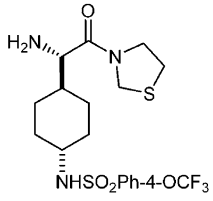
Abstract—A diastereoselective synthesis was used to prepare a series of (3-substituted-cyclopentyl and -cyclohexyl)glycine pyrrolidides and thiazolidides. The three chiral centers were generated in an unambiguous, stereochemically defined manner. Inhibitory activity was dependent on the configuration at each stereocenter and on the nature of the 3-substituent. In the cyclopentylglycine pyrrolidide series, high potency against dipeptidyl peptidase IV and good selectivity could be achieved.

The incretin hormone glucagon-like peptide 1 (GLP-1) stimulates insulin biosynthesis and secretion in response to meal ingestion, inhibits glucagon secretion, and promotes proliferation of pancreatic β cells.[1] Consequently, GLP-1 has become a prominent target candidate for treatment of type 2 diabetes.[1,2] However, therapeutic use of GLP-1 itself is severely compromised by lack of oral activity and rapid degradation by dipeptidyl peptidase IV (DP-IV).[1,2] DP-IV is a widely expressed serine peptidase, specific for cleavage of an Xaa-Pro (or Xaa-Ala) N-terminal dipeptide from its natural substrates.[3] Inhibition of DP-IV represents a promising indirect approach to achieve sustained elevation of endogenous GLP-1 levels, thereby improving glucose tolerance.[4] Because of the glucose-dependency of insulin stimulation by GLP-1, this approach entails minimal risk of hypoglycemia.[4] Another incretin, glucose-dependent insulinotropic peptide (GIP, formerly known as gastric inhibitory polypeptide) is also inactivated by DP-IV, although the therapeutic value of blocking GIP degradation in type 2 diabetes is less certain.[1e–g,5]

Previous work from these laboratories has described (4-substituted-cyclohexyl)glycine pyrrolidides and thiazolidides typified by **1** as potent, selective, orally bioavailable inhibitors of DP-IV.[6] We have now used a diastereoselective route to investigate corresponding cyclopentyl- and cyclohexylglycine derivatives **2** bearing ring substitution at the 3-position. Because these new derivatives contain three chiral centers, the effects of configuration at each center were of particular interest.



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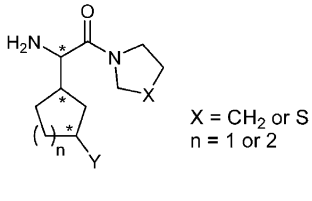

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The synthetic strategy was patterned after that employed by Eustache et al.[7] for a diastereomeric series of (3-amidinocyclopentyl)glycines. Two of the stereocenters were fixed in the first step. Using the approach of Schöllkopf,[8] the (*R*)-dimethoxydihydropyrazine chiral auxiliary **3** was converted via its lithio derivative to a cuprate, which underwent conjugate addition to 2-cyclopenten-1-one to afford the adduct **4** with very

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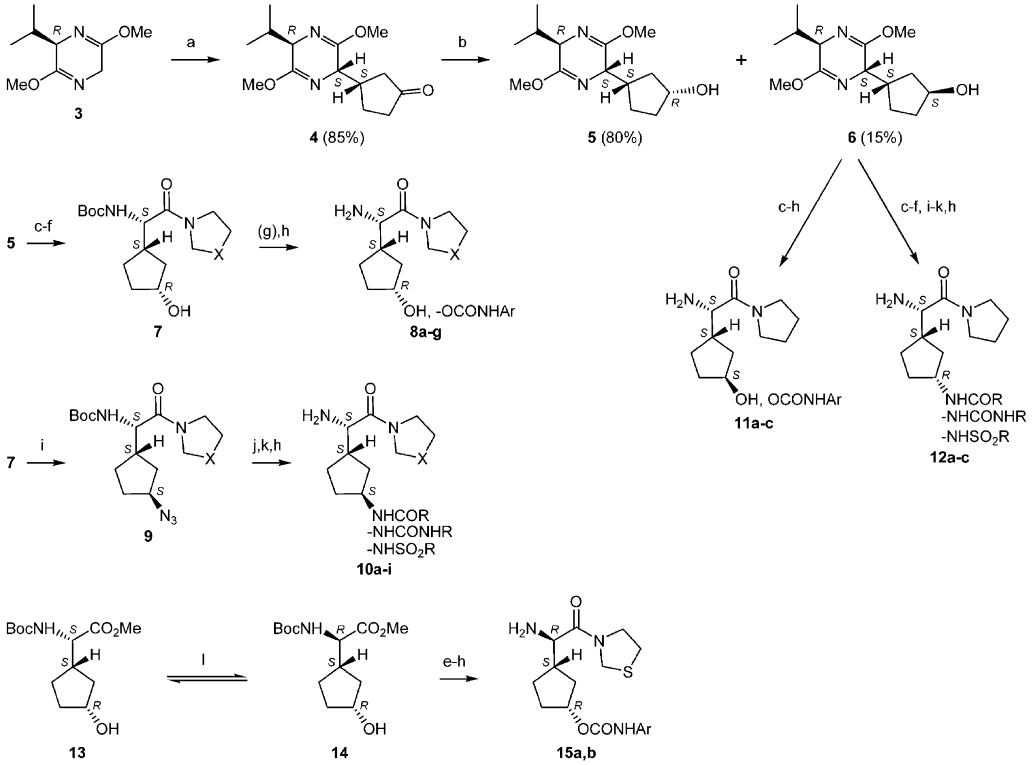
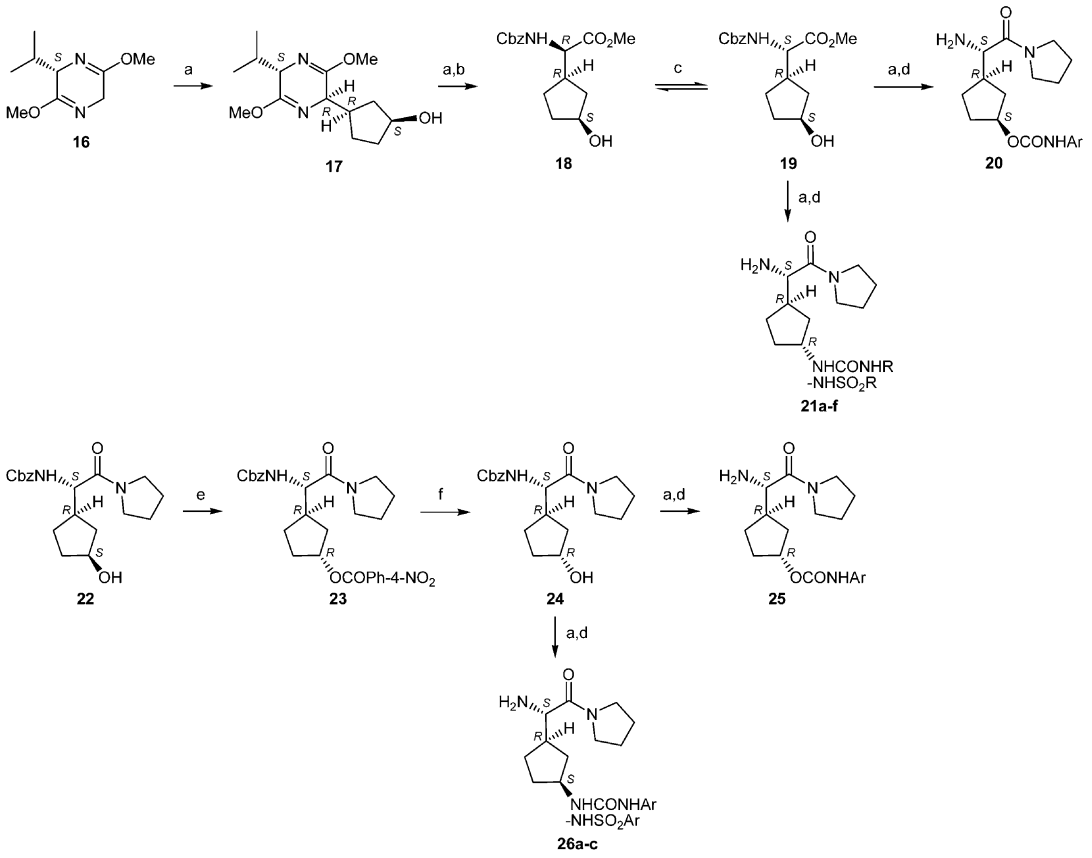


Scheme 1. Conditions: (a) (1) BuLi, THF, −78 °C; (2): 2-thienyl-Cu(CN)Li, −78 °C; (3) 2-cyclopenten-1-one, −78 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) aqueous HCl; (d) $(Boc)_2O$, Na_2CO_3, NaCl, $CHCl_3$; (e) LiOH, THF–MeOH–H_2O; (f) amine, HATU, HOAT, *i*-Pr_2NEt, DMF; (g) ArNCO, Et_3N, CH_2Cl_2; (h) HCl/dioxane; (i) DPPA, Ph_3P, DEAD, THF, 0 °C (dark); (j) Ph_3P, H_2O, THF, 45 °C; (k) RCOCl, RNCO, or RSO_2Cl, Et_3N, CH_2Cl_2; (l) 1N NaOMe, MeOH.

high diastereoselectivity (Scheme 1). Initially we used Schöllkopf's conditions[8] for generation of the cuprate ($CuBr{\cdot}SMe_2$ in the presence of dimethyl sulfide cosolvent). However, we found that the 'higher order cuprate' methodology of Lipshutz[9] with lithium 2-thienylcyanocuprate resulted in higher yield, easier workup, identical diastereoselectivity, and avoidance of the unpleasant odor of dimethyl sulfide. The absolute configuration of the enantiomer of **4** (derived from the antipode of **3**) was previously established by X-ray crystallography.[8] The final stereocenter was obtained by borohydride reduction of the ketone to give a readily separable mixture of *R*-alcohol **5**[7] and *S*-alcohol **6**[7] in about a 5:1 ratio. Transformation of **5** to the Boc-protected amides **7** proceeded by standard methods, although careful coupling conditions (HATU/HOAT in presence of excess amine) were required to avoid lactonization. Further elaboration yielded *S,S,R* targets **8**. *R*-alcohol **7** was converted to the *S*-azide **9** with diphenylphosphoryl azide under Mitsunobu conditions. By standard methods, this was reduced to the amine and elaborated to a series of substituted derivatives **10** in the *S,S,S* series. The minor *S*-alcohol **6** was converted as above to *S,S,S* targets **11** in the oxy series and *S,S,R* targets **12** in the amino series. The intermediate Boc-amino ester **13** (*S,S,R* configuration) was subjected to epimerization with sodium methoxide in methanol[7] to afford the α*R* product **14** (disfavored in the equilibrium), which was elaborated to the *R,S,R* targets **15**.

Similarly, the (*S*)-dimethoxydihydropyrazine chiral auxiliary **16** was transformed to the cyclopentanol **17** (Scheme 2). The configuration of the alcohol in this major diastereomer was unambiguously determined as *S* on the basis of NMR studies. The ^1H NMR signals of **17** and its minor diastereomer *iso***17** (not shown; mirror image of **6**) were assigned using COSY and HSQC. From 2D NOESY experiments, the *trans* relationship of cyclopentyl H-1 and H-3 in *iso***17** was clearly established, supporting the assignment of *iso***17** as the *R*-alcohol and therefore **17** as the *S*-alcohol. After conversion to the Cbz-protected amino ester **18**,[7] the α stereocenter was epimerized to *S*. Conversion of the resulting **19**[7] to the *S,R,S* targets **20** and the *S,R,R* targets **21** proceeded as above. Inversion of the alcohol in intermediate **22** was accomplished via displacement with 4-nitrobenzoic acid under Mitsunobu conditions and subsequent methanolysis[7] of **23** to give **24**, which led to the *S,R,R* target **25** and the *S,R,S* targets **26**.

The cyclohexylglycines were obtained by similar chemistry beginning with conjugate addition of chiral auxiliary **3** to 2-cyclohexen-1-one (Scheme 3). In this case, however, borohydride reduction led to an inseparable mixture of diastereomeric alcohols **27**. Later separation by preparative chiral HPLC gave *R*-alcohol **28** and *S*-alcohol **29** in about a 7:3 ratio. The structures of **28** and **29** were supported by ^1H NMR studies (after Boc removal), which confirmed that H-1 and H-3 were in a *cis*-diaxial arrangement in **28**, whereas **29** was consistent with H-1 axial and H-3 equatorial, in a *trans* disposition. Further elaboration of **28** and **29** yielded, respectively, the *S,S,R* targets **30** and the *S,S,S* targets **31**. No additional diastereomers were prepared in this series.



Scheme 2. Conditions: (a) as described in Scheme 1; (b) CbzCl, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; to 20 °C;; (c) 1N NaOMe, MeOH; (d) HBr/AcOH (< 15 min); (e) 4-nitrobenzoic acid, Ph_3P, DEAD, THF, 0–20 °C;; (f) 0.05N NaOMe, MeOH, CH_2Cl_2.

Compounds were determined as inhibitors of human recombinant DP-IV in a fluorometric assay[10] using the substrate Gly-Pro-AMC, which is cleaved by DP-IV to release the fluorescent leaving group, 7-amino-4-methylcoumarin. In addition, the compounds were counter-screened against other human proline-specific peptidases:[11] quiescent cell proline dipeptidase (QPP);[12] prolyl endopeptidase (PEP, also known as prolyl oligopeptidase); and aminopeptidase P (APP). All compounds reported here had IC_{50} values of > 100 μM against APP.

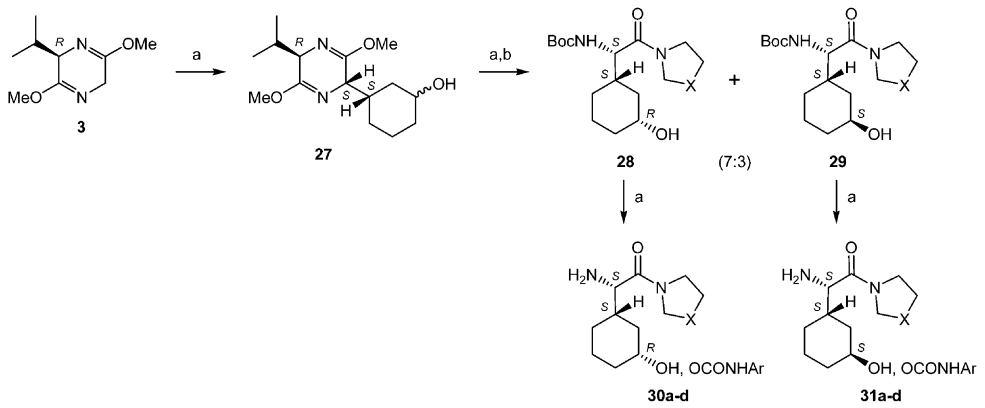
Cyclopentylglycine derivatives in the *S,S,R* series (Table 1, compounds **8a–g**, **12a–c**) tended to be poorly selective for DP-IV over QPP. Several were, in fact, QPP-selective (20-fold in the case of **8e**). Various 3-substituents with a hydrophobic aryl terminus enhanced DP-IV potency, but the presence of a bulky *ortho*-substituent was unfavorable (**8g**). Thiazolidide derivatives were more potent than the pyrrolidide analogues (**8c** vs **8b**).

R,S,R analogues **15a**,**b** still showed significant DP-IV inhibition (Table 1) but had lower affinity than the *S,S,R* analogues (by sixfold for **15b** vs **8f**) and were somewhat QPP-selective.

Compared with the *S,S,R* series, the *S,S,S* derivatives **10a–i**, **11a–c** (Table 1) were more potent (~4-fold for **11a** vs **8a**, **11b** vs **8b**, **11c** vs **8d**). The 1-naphthyl amide (**10a**) and urea (**10b**) thiazolidides were especially inhibitory (DP-IV IC_{50} < 50 nM) but poorly selective relative to QPP and PEP. An arylsulfonyl derivative bearing a carboxylic acid at the 4-position (**10c**, DP-IV IC_{50} = 72 nM) provided a breakthrough in selectivity (> 150-fold over QPP). DP-IV affinity was retained, but specificity was lost, upon replacing the carboxylic acid by a sulfonamide (**10d**). Among related analogues **10e–h**, a methanesulfonyl group at the 4-position (**10f**) uniquely imparted a desirable inhibition profile (DP-IV IC_{50} = 130 nM, 150-fold selective over QPP).

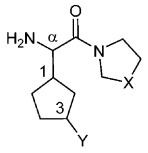
The *S,R,S* series (Table 1, compounds **20**, and **26a–c**) displayed only moderate DP-IV inhibition, three- to four-fold weaker than that of the *S,S,S* analogues (**20** vs **11c**, **26b** vs **10d**, **26c** vs **10f**). Unexpectedly, the *S,R,R* series (Table 1, compounds **21a–f**, **25**) proved to be markedly more active (~5–30-fold for **21a** vs **26a**, **21d** verus **26b**, **21e** vs **26c**, **25** vs **20**). Of the arylsulfonamide congeners **21b–e**, those with polar, electron-withdrawing substituents at the 4-position (**21c–e**) showed the best potency and selectivity. Particularly notable is the methyl sulfone **21e** (DP-IV IC_{50} = 13 nM, 120-fold selective over QPP). Although less potent (DP-IV IC_{50} = 71 nM), the 2-[(methanesulfonyl)amino]ethyl analogue **21f** displayed the highest selectivity among all the compounds (300-fold over QPP, > 1000-fold over PEP).

The cyclohexylglycine compounds (Table 2) in the *S,S,R* series (**30a–d**) were consistently more potent (three- to sixfold) than the corresponding *S,S,R* analogues in the cyclopentylglycine series (**30a** vs **8a**, **30b**



Scheme 3. Conditions: (a) as described in Scheme 1; (b) preparative HPLC on ChiralPak AD.

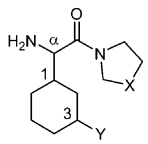
Table 1. Inhibition of DP-IV and other peptidases by diastereomeric cyclopentylglycine derivatives



Compd	Configuration			X	Y	IC_{50} (μM)		
	α	1	3			DP-IV	QPP	PEP
					(*S*,*S*,*R* Derivatives)			
8a	*S*	*S*	*R*	CH_2	OH	4.6	50	>100
8b	*S*	*S*	*R*	CH_2	OCONHPh-4-OMe	1.1	0.63	27
8c	*S*	*S*	*R*	S	OCONHPh-4-OMe	0.24	0.043	16
8d	*S*	*S*	*R*	CH_2	OCONHPh-4-I	0.66	0.16	35
8e	*S*	*S*	*R*	S	OCONHPh-3,4-Cl_2	0.28	0.014	19
8f	*S*	*S*	*R*	S	OCONHPh-3-F	0.21	0.075	>100
8g	*S*	*S*	*R*	CH_2	OCONHPh-2-Ph	3.9	0.87	22
12a	*S*	*S*	*R*	CH_2	NHCO-1-naphthyl	0.23	0.99	59
12b	*S*	*S*	*R*	CH_2	NHCONH-1-naphthyl	0.11	0.27	4.2
12c	*S*	*S*	*R*	CH_2	$NHSO_2$Ph-4-OCF_3	0.55	0.75	>100
					(*R*,*S*,*R* Derivatives)			
15a	*R*	*S*	*R*	S	OCONH-1-naphthyl	1.7	0.11	32
15b	*R*	*S*	*R*	S	OCONHPh-3-F	1.2	0.54	>100
					(*S*,*S*,*S* Derivatives)			
10a	*S*	*S*	*S*	S	NHCO-1-naphthyl	0.047	0.24	1.4
10b	*S*	*S*	*S*	S	NHCONH-1-naphthyl	0.043	0.026	2.1
10c	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-4-CO_2H	0.072	12	44
10d	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-4-SO_2NH_2	0.083	0.022	18
10e	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-4-SO_2NMe_2	0.11	0.053	40
10f	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-4-SO_2Me	0.13	19	>100
10g	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-4-SO_2CF_3	0.22	0.11	77
10h	*S*	*S*	*S*	CH_2	$NHSO_2$Ph-2-SO_2Me	0.15	1.0	>100
10i	*S*	*S*	*S*	CH_2	$NHSO_2(CH_2)_2NHSO_2$Me[a]	0.095	2.0	>100
11a	*S*	*S*	*S*	CH_2	OH	0.84	46	>100
11b	*S*	*S*	*S*	CH_2	OCONHPh-4-OMe	0.27	1.4	>100
11c	*S*	*S*	*S*	CH_2	OCONHPh-4-I	0.18	0.26	29
					(*S*,*R*,*S* Derivatives)			
20	*S*	*R*	*S*	CH_2	OCONHPh-4-I	0.67	0.25	>100
26a	*S*	*R*	*S*	CH_2	NHCONH-1-naphthyl	0.44	1.3	37
26b	*S*	*R*	*S*	CH_2	$NHSO_2$Ph-4-SO_2NH_2	0.25	3.1	>100
26c	*S*	*R*	*S*	CH_2	$NHSO_2$Ph-4-SO_2Me	0.42	4.0	>100
					(*S*,*R*,*R* Derivatives)			
21a	*S*	*R*	*R*	CH_2	NHCONH-1-naphthyl	0.094	0.43	20
21b	*S*	*R*	*R*	CH_2	$NHSO_2$Ph-4-OCF_3	0.17	1.7	>100
21c	*S*	*R*	*R*	CH_2	$NHSO_2$Ph-4-CO_2H	0.11	5.0	>100
21d	*S*	*R*	*R*	CH_2	$NHSO_2$Ph-4-SO_2NH_2	0.046	2.3	>100
21e	*S*	*R*	*R*	CH_2	$NHSO_2$Ph-4-SO_2Me	0.013	1.6	>100
21f	*S*	*R*	*R*	CH_2	$NHSO_2(CH_2)_2NHSO_2$Me[a]	0.071	21	>100
25	*S*	*R*	*R*	CH_2	OCONHPh-4-I	0.11	0.82	37

[a] Prepared from the (phthalimido)ethyl derivative after hydrazinolysis to give the free amine and reaction with methanesulfonyl chloride.

Table 2. Inhibition of DP-IV and other peptidases by diastereomeric cyclohexylglycine derivatives



Compd	Configuration			X	Y	IC_{50} (μM)		
	α	1	3			DP-IV	QPP	PEP
					(*S,S,R* Derivatives)			
30a	*S*	*S*	*R*	CH_2	OH	0.87	62	>100
30b	*S*	*S*	*R*	CH_2	OCONHPh-4-OMe	0.18	2.5	>100
30c	*S*	*S*	*R*	S	OCONHPh-4-OMe	0.083	0.22	76
30d	*S*	*S*	*R*	CH_2	OCONHPh-4-I	0.11	0.42	27
					(*S,S,S* Derivatives)			
31a	*S*	*S*	*S*	CH_2	OH	0.29	40	>100
31b	*S*	*S*	*S*	CH_2	OCONHPh-4-OMe	0.48	0.78	>100
31c	*S*	*S*	*S*	S	OCONHPh-4-OMe	0.42	0.44	>100
31d	*S*	*S*	*S*	CH_2	OCONHPh-4-I	0.33	0.11	>100

vs **8b**, **30c** vs **8c**, **30d** vs **8d**). In the cyclopentyl series, the *S,S,S* diastereomers were clearly preferred over the *S,S,R*. In the cyclohexyl series, however, the *S,S,S* arylcarbamate derivatives **31b–d** were distinctly less active than their *S,S,R* counterparts (**31b** vs **30b**, **31c** vs **30c**, **31d** vs **30d**). Only with an un-derivatized alcohol was the *S,S,S* diastereomer favored (**31a** vs **30a**). In fact, the 3*S*-hydroxy compound **31a** was at least as potent as any of the *S,S,S* carbamates and was far more selective (~140-fold over QPP).

In summary, a series of (3-substituted-cycloalkyl)glycine pyrrolidides and thiazolidides has been prepared by a diastereoselective route, allowing investigation of the biochemical effects of defined stereochemistry at each of the chiral centers. The general order of DP-IV inhibitory activity for the cyclopentylglycine diastereomers was $\alpha S,1R,3R > \alpha S,1S,3S > \alpha S,1S,3R \geq \alpha S,1R,3S > \alpha R,1S,3R$. In the cyclohexylglycine series, the activity order was $\alpha S,1S,3R > \alpha S,1S,3S$ for larger 3-substitutents but reversed for 3-hydroxy. Although the thiazolidides were more potent than the corresponding pyrrolidides, the thiazolidine derivatives were de-emphasized because of potential metabolic liabilities. The best combination of DP-IV potency ($IC_{50} = 13$ nM) and selectivity over QPP (120-fold) was observed for the *S,S,R* cyclopentylglycine pyrrolidide **21e** bearing a 4-(methanesulfonyl)benzenesulfonamido substituent at the 3-position. This compared favorably with the previously reported reference compound **1** (DP-IV $IC_{50} = 22$ nM, 50-fold over QPP).[6]

Appended groups at the 3-position of cycloalkylglycines can thus produce either favorable or unfavorable consequences for enzyme inhibition, depending on the configuration at the chiral centers and the nature of the substituent. Furthermore, these effects are sometimes quite divergent between DP-IV and other proline-specific peptidases. It can be concluded that enzyme surface interactions accessible to these ring substituents represent a potentially important determinant of potency and selectivity.

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12. QPP is also known as dipeptidyl peptidase VII and is very similar, if not identical, to dipeptidyl peptidase II. See ref 10.