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Bioorganic & Medicinal Chemistry Letters 17 (2007) 2879–2885
Bioorganic & Medicinal Chemistry Letters

# 4-Aminophenylalanine and 4-aminocyclohexylalanine derivatives as potent, selective, and orally bioavailable inhibitors of dipeptidyl peptidase IV

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Received 18 December 2006; revised 19 February 2007; accepted 21 February 2007
Available online 25 February 2007

**Abstract**—A novel series of 4-aminophenylalanine and 4-aminocyclohexylalanine derivatives were designed and evaluated as inhibitors of dipeptidyl peptidase IV (DPP-4). The phenylalanine series afforded compounds such as **10** that were potent and selective (DPP-4, $IC_{50}$ = 28 nM), but exhibited limited oral bioavailability. The corresponding cyclohexylalanine derivatives such as **25** afforded improved PK exposure and efficacy in a murine OGTT experiment. The X-ray crystal structure of **25** bound to the DPP-4 active site is presented.


Type 2 diabetes mellitus may be effectively treated by agents that induce the biosynthesis and secretion of insulin during periods of hyperglycemia. Two endogenous peptides that stimulate glucose-dependent insulin secretion are the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[1] Infusion of GLP-1 in patients with type 2 diabetes has resulted in significant decreases in plasma glucose and hemoglobin $A_{1c}$ levels.[2] Due to the rapid inactivation of GLP-1 by the serine protease dipeptidyl peptidase IV (DPP-4) this hormone must be administered by chronic intravenous administration to achieve sustained efficacy.[2] An alternative approach to increase the level of circulating GLP-1 involves the inhibition of DPP-4, and this method has emerged as an important potential therapy for the treatment of type 2 diabetes.[3]

Multiple small molecule DPP-4 inhibitors have been reported.[4] Research in these laboratories has focused on the development of a structurally diverse collection of potent DPP-4 inhibitors that lack significant inhibitory activity of the related proline-specific peptidases QPP, DPP8, and DPP9.[5] Inhibitory selectivity for DPP-4 over DPP8 and DPP9 was particularly emphasized. The inhibition of the latter two enzymes has been associated with profound toxicity in preclinical studies, although the relevance of this toxicity to humans has not been established.[6]

The *threo* isoleucyl thiazolidine **1** affords superior DPP-4 selectivity over the *allo* isomer **2** (Fig. 1),[6] and this discovery led to the development of selective β-substituted phenylalanine derived inhibitors **3** and **4**.[7] The latter two compounds represented significant advancements in DPP-4 potency, peptidase selectivity, and oral bioavailability, but each retained significant off-target activity against the human cardiac ion channel hERG ($IC_{50}$ = 1–5 μM). In a recent report from these laboratories, the selectivity of this class was improved with the incorporation of fused heterocycles such as **5** in the distal aromatic ring (hERG, $IC_{50}$ = 86 μM).[7c] Here we describe a complementary effort to decrease the lipophilic character of this lead class, and improve selectivity over

*Keywords*: Dipeptidyl peptidase IV; DPP-4; Kazmaier Claisen; Buchwald amidation; X-ray.
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doi:10.1016/j.bmcl.2007.02.066

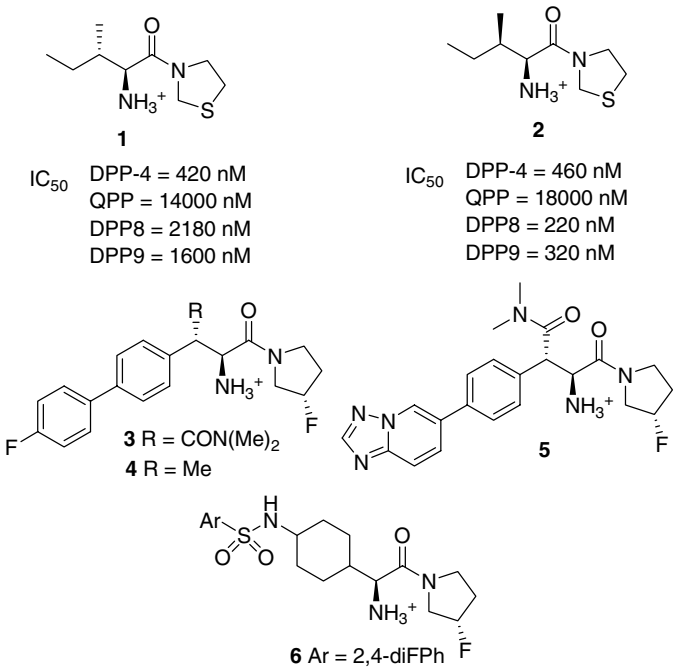



**Figure 1.** DPP-4 inhibitors.

hERG, by incorporating the structural features of the related cyclohexylglycine lead class of DPP-4 inhibitors such as **6** (hERG, $IC_{50}$ = 49 μM, Table 4).[8]

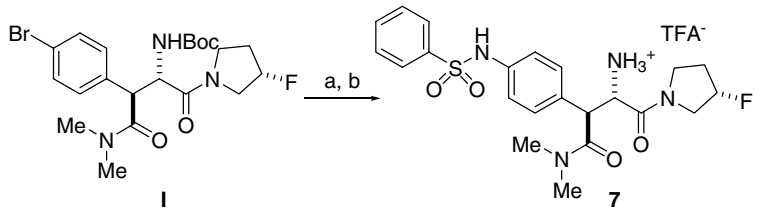
Our initial endeavor focused on the incorporation of 4-aminophenylalanine substituents as a replacement for the biphenyl moiety in **3** and **4**, and the synthesis of the sulfonamide **7** from this design is illustrated in Scheme 1. The β-dimethylamide aryl bromide **I** was prepared using Kazmaier's enolate–Claisen rearrangement as described previously.[7c] This intermediate was converted directly to the desired *N*-aryl amide or *N*-aryl sulfonamide by application of the copper-mediated amidation reaction developed by Buchwald and coworkers.[9] We found that the addition of a full equivalent of CuI and three equivalents of the diamine ligand afforded reproducibly high yielding coupling of the sulfonamide and amide substituents, although no further optimization of the reaction conditions was attempted.[10] The corresponding β-methyl derivatives were prepared in a similar fashion from the corresponding aryl bromide intermediate that has also been described previously.[7a]

The compounds synthesized were assayed for their inhibitory potency against the DPP-4 enzyme, as well as their selectivity over the related proline-specific enzymes QPP (DPP-II), DPP8, and DPP9, and the results are summarized in Table 1.[11]

Substitution of the biaryl species in **3** or **5** with the arylsulfonamide **7** resulted in a substantial loss of potency toward DPP-4 (Table 1). The *N*-methyl toluyl sulfonamide derivative **8** was somewhat more potent, but the DPP-4 inhibitory activity remained modest ($IC_{50}$ = 0.43 μM). Substitution of the aryl sulfonamide moiety in **7** with the benzamide moiety in **9** and **10** resulted in substantial gains in potency, and these compounds retained outstanding peptidase selectivity. The corresponding acetamide **12** and *N*-methyl acetamide **14** were less potent inhibitors of DPP-4. The β-dimethylamide substituent was previously found to enhance potency and selectivity over the β-methyl substituent, as with **3** and **4**,[7b] and this trend was retained in the amino phenylalanine derivative series. The β-dimethylamide derivatives **10**, **12**, and **14** were uniformly more potent than the corresponding β-methyl analogues.

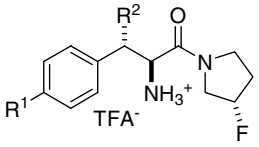
The pharmacodynamic characterization of **3**, reported previously,[7b] revealed a lower than expected efficacy in the murine OGTT experiment. This was attributed to a shift toward lower DPP-4 inhibitory potency in the presence of human or mouse serum. As illustrated in Table 2, the incorporation of the amide substituent in **10** afforded somewhat improved potency compared to compound **3** in the presence of 50% human serum ($IC_{50}$ = 0.16 μM). Compound **10** also afforded a substantial improvement over **3** in selectivity in the cardiac hERG binding assay. However, compound **10** exhibited comparatively poor oral bioavailability when dosed in rats, as illustrated by the lower dose-normalized oral AUC (nAUC) and higher clearance rate (Clp) (Table 2).

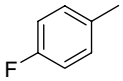
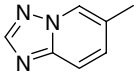
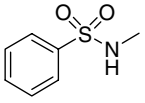
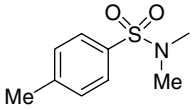
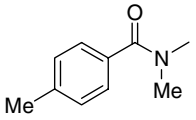
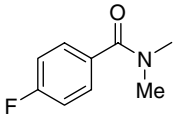
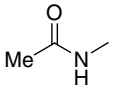
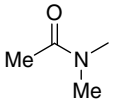
We sought to improve the pharmacokinetic properties of the lead class while preserving the selectivity and the decreased influence of serum on intrinsic potency. In previous reports from these laboratories, a series of 4-aminocyclohexylglycine amides and sulfonamides such as **6** (Fig. 1) were presented.[8] Many of these derivatives afforded acceptable PK profiles, but suffered from poor inhibitory selectivity over DPP8 and DPP9. We reasoned that we could combine the high peptidase




**Scheme 1.** Reagents and conditions: (a) $PhSO_2NH_2$ (2.5 equiv), $K_2CO_3$ (3 equiv), CuI (1 equiv), *N*,*N*′-dimethyl ethylene diamine (3 equiv), toluene, 110 °C (sealed tube), 48 h (80%); (b) TFA, $CH_2Cl_2$ (80%).

**Table 1.** Inhibitory properties of phenylalanine derivatives



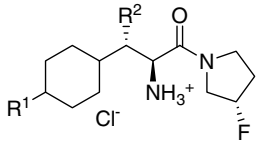

| Compound | $R^1$ | $R^2$ | $IC_{50}$ (μM) | | | |
|---|---|---|---|---|---|---|
| | | | DPP-4 | QPP | DPP8 | DPP9 |
| **3** |  | $CONMe_2$ | 0.012 | 45 | >100 | 69 |
| **4** | | Me | 0.064 | 2.7 | 87 | 86 |
| **5** |  | $CONMe_2$ | 0.004 | >100 | >100 | >100 |
| **7** |  | $CONMe_2$ | 0.87 | 80 | >100 | >100 |
| **8** |  | $CONMe_2$ | 0.43 | >100 | >100 | >100 |
| **9** |  | $CONMe_2$ | 0.025 | >100 | >100 | >100 |
| **10** |  | $CONMe_2$ | 0.028 | >100 | >100 | >100 |
| **11** | | Me | 0.30 | 4.7 | >100 | >100 |
| **12** |  | $CONMe_2$ | 0.16 | >100 | 60 | >100 |
| **13** | | Me | 0.60 | 70 | 82 | >100 |
| **14** |  | $CONMe_2$ | 0.15 | >100 | >100 | >100 |
| **15** | | Me | 0.21 | 22 | >100 | >100 |

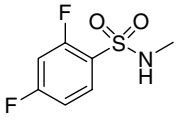
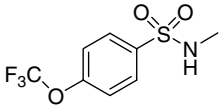
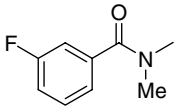
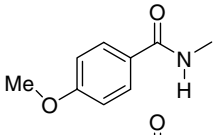
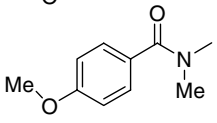
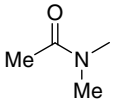
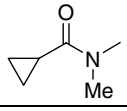
selectivity of the 4-aminophenylalanine class represented by compound **10**, and incorporate the desirable PK profile of the 4-aminocyclohexylglycine class represented by **6**. By merging the salient structural features of these classes, we designed the 4-amino cyclohexylalanine compounds represented by **16** (Table 3).

**Table 2.** Potency in the presence of 50% human serum, selectivity over hERG binding, and rat PK parameters

| Compound | $IC_{50}$ (μM) | | Rat PK(l/2mpk iv/po) | | |
|---|---|---|---|---|---|
| | DPP-4 (50% HS) | hERG | nAUC (μM h/mpk) | Clp (mL/min/kg) | *F* (%) |
| **3** | 0.39 | 4.6 | 6.23 | 4.8 | 67 |
| **10** | 0.16 | >90 | 0.03 | 73 | 6 |

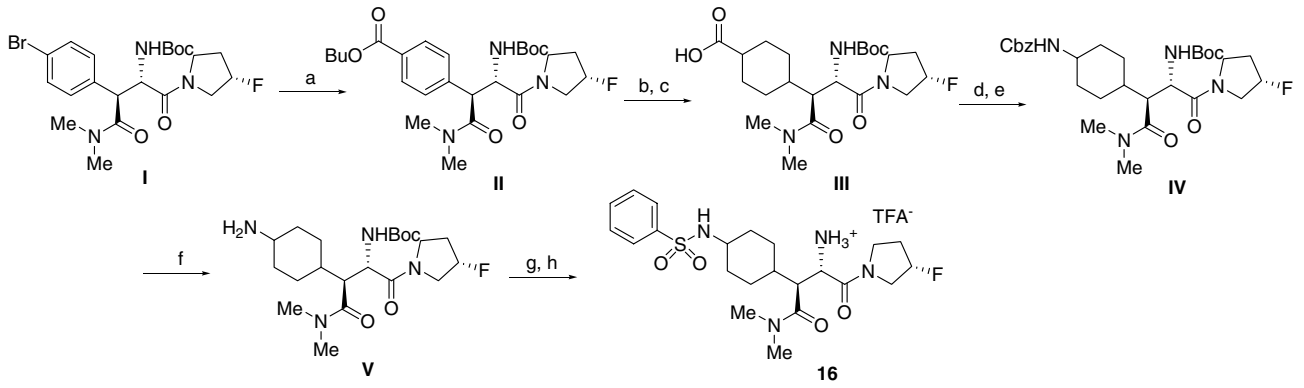
**Table 3.** Inhibitory properties of cyclohexylalanine derivatives




| Compound | $R^1$ | $R^2$ | $IC_{50}$ (μM) | | | |
|---|---|---|---|---|---|---|
| | | | DPP-4 (0% HS) | DPP-4 (50% HS) | DPP8 | DPP9 |
| **6** |  | | 0.048 | | 0.99 | 2.7 |
| **16** | | $CONMe_2$ | 0.33 | 0.51 | >100 | >100 |
| **17** | | Me | 0.46 | 1.49 | 21 | 42 |
| **18** |  | $CONMe_2$ | 0.36 | 1.28 | >100 | >100 |
| **19** | | Me | 0.44 | 3.47 | 11 | 26 |
| **20** |  | $CONMe_2$ | 0.024 | 0.20 | >100 | >100 |
| **21** | | Me | 0.022 | 0.092 | 6.3 | 46 |
| **22** |  | Me | 0.074 | 0.21 | 29 | 63 |
| **23** |  | Me | 0.027 | 0.097 | 30 | 46 |
| **24** |  | $CONMe_2$ | 0.029 | 0.19 | >100 | >100 |
| **25** | | Me | 0.016 | 0.040 | 25 | >100 |
| **26** |  | Me | 0.021 | 0.047 | 12 | 29 |

The synthesis of **16** is illustrated in Scheme 2. The ester **II** was prepared from intermediate **I** via palladium catalyzed carbonylation.[12] Hydrogenation of the aromatic group using platinum oxide afforded a 2:1 mixture of *cis* and *trans* isomers. The mixture was hydrolyzed to the acids, which were then treated with diphenylphosphoryl azide to effect the Curtius rearrangement. The intermediate isocyanates were trapped with benzyl alcohol, affording the isomeric mixture of benzyl carbamate-protected 4-aminocyclohexylalanine derivatives. The isomeric mixture was separated at this point by preparative normal-phase HPLC, affording each of the single diastereomers of **IV**. Removal of the benzyl carbamate by hydrogenation was followed by derivatization of the cyclohexylamine and removal of the Boc group, affording the final product. In each instance, both diastereomeric final products were prepared. The diastereomers typically differed by fivefold in their inhibitory potency of DPP-4, and only the data corresponding to the more potent diastereomer are presented.[13]

The potency and selectivity of the cyclohexylalanine derivatives are shown in Table 3, as well as the DPP-4 inhibitory potency of the compounds in the presence



**Scheme 2.** Reagents and conditions: (a) BuOH, $Et_3N$, $Pd(DPPF)_2$ (10%), CO (1 atm), 90 °C, 18 h (71%); (b) $H_2$ (3.8 atm), $Pt_2O$ (cat), AcOH, 48 h; (c) LiOH, THF, MeOH; (d) DPPA, $Et_3N$, toluene, 110 °C, 3.5 h, then BnOH, 110 °C (54%—4 steps, diastereomeric mixture); (e) HPLC (Chiracel OD, 10% EtOH / hexane); (f) $H_2$ (3.5 atm), 10% Pd/C (cat), MeOH, 3 h (99%); (g) $PhSO_2Cl$, DIEA, $CH_2Cl_2$; (h) HCl, dioxane (79%—2 steps).

of 50% human serum. Incorporation of the β-dimethylamide or β-methyl substituent into **6** afforded the homologues **16** and **17**. The latter two compounds exhibited diminished inhibitory potency of DPP-4, but retained a more favorable selectivity profile over DPP8 and DPP9. Additional sulfonamide derivatives such as **18** and **19** were prepared, and these were similarly less potent than the analogous compounds in the 4-aminocyclohexylalanine series.[8] A substantial improvement in potency was realized with amide derivatives such as **20** and **21**. While the β-dimethylamide derivative **20** retained greater selectivity over DPP8 and DPP9, the β-methyl derivative **21** retained greater intrinsic potency in the presence of human serum. This correlation was observed in **24** and **25**, as well as multiple other members of this lead class (data not shown). The *N*-methyl tertiary cyclohexylamide derivatives such as **23** afforded somewhat improved potency over the secondary amide derivatives such as **22**. Replacement of the aromatic benzamide substituent with the smaller aliphatic amides as in **24**–**27** afforded a further slight improvement in intrinsic potency, both in the absence and presence of human serum.

Several of the derivatives in Table 3 were profiled further for off-target activity, as indicated by binding to the hERG ion channel, and in PK experiments. The results are shown in Table 4. The β-methyl derivative **21** afforded greater oral exposure (nAUC) than the related β-dimethylamide derivative **20**, but **21** also exhibited higher clearance. This correlation was more pronounced in the acetamide derivatives **24** and **25**, with the β-methyl substituted **25** affording substantially improved oral bioavailability. The cyclopropyl acetamide derivative **26** afforded a similar PK profile to the acetamide **25**, albeit with diminished selectivity over the hERG channel and DPP8 (Table 3). The acetamide derivative **25** was further profiled in a canine PK experiment, and the compound maintained good oral bioavailability.

The X-ray crystal structure determination of the acetamide **25** co-crystallized with DPP-4 is shown in Figure 2.[14] Compound **25** (yellow) maintains similar enzyme interactions to those previously reported with inhibitor **5** (magenta) in the S1 hydrophobic pocket and amino group binding residues.[7c] The β-methyl substituent in **25** does not maintain the productive hydrogen bonding interaction with Tyr547 that is evident in the β-dimethylamide derivative **5**. However, the potential benefit of this interaction may be mitigated in these cyclohexylalanine derivatives, as suggested by the similar intrinsic potency of the β-methyl derivative **25** with the β-dimethylamide analogue **24** (Table 3). The cyclohexyl moiety in **25** precludes the edge to face $\pi$–$\pi$ interaction with Phe357 that has been implicated in related structures.[15] The cyclohexyl ring does provide an adequate tether for the terminal acetamide substituent to maintain a hydrophobic interaction with Phe357, and a hydrogen bonding interaction with Arg358.

The efficacy of the acetamide derivative **25** was investigated in an oral glucose tolerance test (OGTT) in lean

**Table 4.** hERG binding and PK parameters in rat and dog for selected DPP-4 inhibitors

| Compound | hERG (μM) | PK (1/2 mpk iv/po) | | | |
|---|---|---|---|---|---|
| | | Species | nAUC (μM h/mpk) | CLp (mL/min/kg) | *F* (%) |
| **6** | 49 | Rat | 0.90 | 24 | 53 |
| **20** | >90 | Rat | 0.31 | 27 | 25 |
| **21** | 78 | Rat | 0.74 | 40 | 72 |
| **24** | >90 | Rat | 0.09 | 18 | 3 |
| **25** | >90 | Rat | 0.68 | 42 | 56 |
| | | Dog | 9.82 | 4.4 | 83 |
| **26** | 39 | Rat | 0.44 | 49 | 46 |

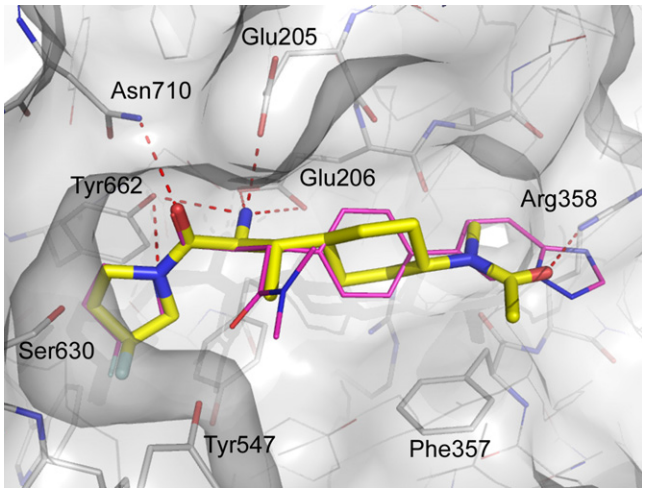



**Figure 2.** Compound **25** bound to the active site of DPP-4. The overlay of **25** (yellow) with **5** (magenta, 2FJP.pdb) shows the similar orientation of the two molecules. The interactions of **25** with DPP-4 are shown as red dotted lines.

mice. The compound reduced blood glucose excursion in a dose-dependent manner from 0.1 mpk (−26%) to 3.0 mpk (−56%). This level of efficacy was not improved over that observed previously with **3** in an identical experiment, despite the diminished influence of serum on the intrinsic potency of **25** (Tables 2 and 3).[7b] However, compound **25** afforded a substantially lower oral exposure (nAUC) than **3** in rat PK studies (Tables 2 and 4). The diminished oral exposure, if operative in mice as well, may have mitigated the improvements in serum-shifted intrinsic potency achieved with **25**.

The incorporation of structural features of the 4-aminocyclohexylalanine lead series into the β-substituted phenylalanine lead class of dipeptidyl peptidase IV inhibitors afforded compounds with similar intrinsic potency and diminished off-target activity. Furthermore, the derivatives incorporating the β-methyl substituent retained substantial potency in the presence of human serum. However, the lower oral exposure attained with these compounds may be the cause of the lack of improved efficacy observed with **25** as compared to analogous prior leads. Further optimization of the PK exposure of this class is underway, and will be reported in due course.

## Acknowledgments

We are very grateful to Donald Hora, Judy Fenyk-Melody, Irene Capodanno, Paul Cunningham, Marcie Donnelly, James Hausamann, Christian Nunes, Xiaolan Shen, John Strauss, and Kenneth Vakerich for in vivo pharmacokinetic studies.

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