HETEROCYCLE FUSED CYCLOHEXYLGlyCINE DERivATIVES AS NOVEL DIPEPTIDYL PEPTIDASE-IV INHIBITORS


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Abstract – A new class of potent inhibitors of dipeptidyl peptidase IV (DP-IV) for the treatment of type II diabetes are described. Presented herein is the synthesis of indole-fused and thiazole-fused cyclohexylglycines. Pyrrolidine-derived amides of these novel heterocycles led to the discovery of thiazole derivatives (3f) and (11a), both low nanomolar inhibitors of DP-IV (IC\textsubscript{50} = 6 nM).

Inhibition of dipeptidyl peptidase IV (DP-IV) is emerging as a new approach for the treatment of type-II diabetes.\textsuperscript{1} Recent research from Merck laboratories led to the discovery of substituted 4-aminocyclohexylglycine derivatives (1) as potent DP-IV inhibitors.\textsuperscript{2} As part of this program, we hoped to improve the \textit{in vitro} profile of these derivatives by incorporating a fused heterocycle onto the cyclohexyl moiety of 1. In this communication, we present the synthesis and biological evaluation of indoles (2) and thiazoles (3).

The synthesis of indole derivatives (2) is described in Scheme 1. Readily available cyclohexylglycine derivative (4)\textsuperscript{2b} (cis/trans mixture) was saponified and the resulting acid coupled to pyrrolidine using standard peptide coupling conditions. The alcohol was then oxidized using Dess-Martin periodinane (DMP) to provide ketone (5) in good overall yield (46%, 3 steps). Attempts to use 5 in a Fisher indole synthesis\textsuperscript{3} resulted in partial thermolysis of the tert-butoxycarbonyl (Boc) group and so the protecting...
group was converted to the more thermally stable benzyloxycarbonyl (Cbz) group in 6. Exposure of 6 to commercially available arylhydrazines in the presence of p-toluene sulfonic acid (p-TsOH) in hot ethanol yielded the desired fused system as a mixture of diastereomers. Catalytic hydrogenolysis of the carboxybenzyl group afforded indoles (2) in moderate to good yields (Table 1). In examples where the aryl hydrazines bear a benzoic acid, a mixture of acid and the corresponding ethyl ester were isolated from the same reaction mixture (2d/e and 2f/g).

![Scheme 1](image1)

Conditions: a) LiOH (aq.), MeOH, THF; b) EDC, HOBr, DIEA, DCM, pyrrolidine; c) DMP, CH₂Cl₂; d) i) CH₂Cl₂, TFA; ii) NaHCO₃ (aq.), THF, CbzCl; e) ArNHNH₂, p-TsOH, EtOH, Δ; f) Pd(OH)₂, EtOH, H₂.

The preparation of thiazoles (3) relies on the Hantzsch synthesis (Scheme 2). Methyl ester (4) was first converted to the fluoropyrrolidide amide (8) using conditions outlined above, and then treated with phenyltrimethylammonium tribromide (PhNMe₃Br₃) to afford the intermediate α-bromo ketone, which was used without purification due to stability concerns. The α-bromo ketone was heated with thioamides to provide a mixture of the protected diastereomeric thiazoles, which were separable by chiral chromatography. The protecting group of each diastereomer was removed using iodotrimethylsilane to afford the desired ammonium salts (3) after purification.

![Scheme 2](image2)

Conditions: a) LiOH (aq.), MeOH, THF; b) EDC, HOBr, DIEA, (S)-3-fluoropyrrolidine, CH₂Cl₂; c) DMP, CH₂Cl₂; d) i) CH₂Cl₂, TFA; ii) NaHCO₃ (aq.), THF, CbzCl; e) PhNMe₃Br₃, THF, 0 °C; f) RCSNH₂, DMF, 120 °C; g) TMSI, MeCN.

We next sought to make derivatives of the aminothiazole group (Scheme 3). Since the Boc protected diastereomers of 10 were more readily resolved by chiral chromatography than the corresponding Cbz derivative, a different synthetic protocol using Boc as the protecting group was used to access the
diastereomerically pure aminothiazoles (10) (Scheme 3). After deprotection of each pure diastereomer of 10, the more active isomer was determined to be the isomer (3d). Acylation of the more active diastereomer of 10 followed by deprotection of the Boc group then afforded pure diastereomers of 11.

![Chemical structures](image)

**Scheme 3**

Table 1. Yields and biological activity of fused heterocyclic inhibitors of DP-IV

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yielda %</th>
<th>DP-IV IC50 (nM)</th>
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<th>R</th>
<th>Yielda %</th>
<th>DP-IV IC50 (nM)</th>
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<td>220</td>
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aYields represent the combined yields of Fisher indole cyclization and deprotection steps (conversion of 6 to 2).
bYields represent the overall conversion of 8 to 3, including the resolution of diastereomers before deprotection (max yield = 50%). cOnly active diastereomers are shown. dYields are for the conversion of 10 to 11. 1H NMR spectra of representative examples: 3b (500 MHz, CD3OD) δ 8.08 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2H), 5.39 (m, 1 H, CHF), 4.39 (dd, J = 41 Hz and 6.6 Hz, 1 H), 3.31-3.97 (m, 4 H), 2.52-2.73 (m, 4H), 2.09-2.40 (m, 4H) 1.69-1.75 (m, 1H); 3d (500 MHz, CD3OD) δ 5.34 (m, 1 H, CHF) 4.21 (dd, J = 35.1 Hz and 6.8 Hz, 1 H), 3.31-3.97 (m, 4 H), 2.53-2.73 (m, 4H), 2.09-2.40 (m, 4H) 1.69-1.75 (m, 1H); 3d (500 MHz, CD3OD) δ 5.36 (m, 1 H, CHF), 4.22 (dd, J = 43.3 Hz and 6.7 Hz, 1 H), 3.50-3.99 (m, 4 H), 2.52-2.66 (m, 4H) 1.95-2.42 (m, 4H), 1.65-1.78 (m, 1 H); 11a (500 MHz, CD3OD) δ 8.35-8.41 (m, 2 H), 7.53 (t, 1 H, J = 9.5 Hz), 5.28-5.47 (m, 1 H, CHF), 4.14 (dd, J = 245.5 Hz and 5.7 Hz, 1 H), 3.55-4.02 (m, 4 H), 2.82-2.92 (m, 2 H), 2.69-2.78 (m, 2H), 2.02-2.57 (m, 4H), 1.8 (m, 1 H).
Many of the above compounds are potent inhibitors against DP-IV, with IC$_{50}$'s in the low nanomolar range (Table 1). For example $\textbf{3b}$ and $\textbf{11a}$ were extremely potent, each with a 6 nM inhibition of the enzyme even though lacking a serine trap.

In conclusion, this work demonstrates that changing the nature of the cyclohexyl ring in cyclohexylglycine derived DP-IV inhibitors can afford compounds with equal or greater potency than other reported compounds (i.e. $\textbf{1}$). Furthermore, we have succeeded in developing simple synthetic methodologies for accessing indole-fused and thiazole-fused cyclohexylglycine derivatives.

**REFERENCES**


4. (S)-3-Fluoropyrrolidine was prepared by a modification of the method of G. Giardina, G. Dondio, and M. Grugni, *Synlett*, 1995, 55. The modification is described in Ref. 2 (c)

5. Diastereomeric mixtures were resolved using ChiralCel columns. Type OJ (isocratic method, 50% ethanol/hexane) was used for $\textbf{3a}$ and type AS (isocratic method, 50% ethanol/hexane) was used for $\textbf{3b}$.

6. All final products were purified by reverse phase HPLC to afford TFA salts.

7. The two diastereomers of $\textbf{10}$ were separated using a ChiralCel column type AD (isocratic method, 75% EtOH/hexane). The most potent deprotected compound ($\textbf{3d}$) is derived from the faster eluting isomer.


9. The less active diastereomers of $\textbf{3a}$ and $\textbf{3b}$ were IC$_{50} = 385$ nM and 171 nM respectively.