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HETEROCYCLE FUSED CYCLOHEXYLGLYCINE DERIVATIVES AS NOVEL DIPEPTIDYL PEPTIDASE-IV INHIBITORS

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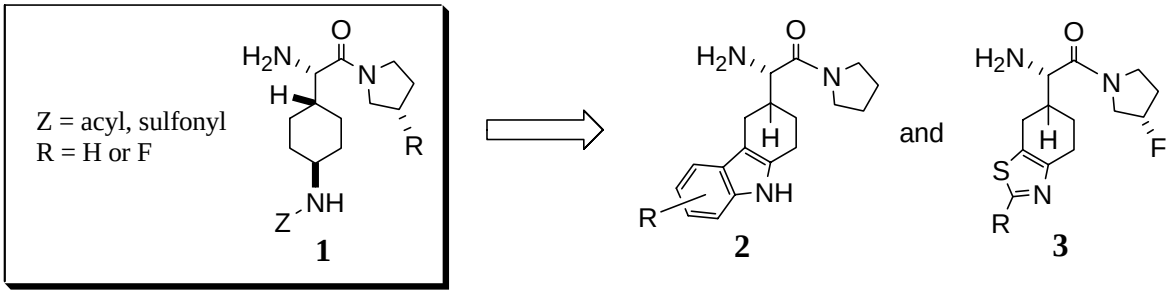
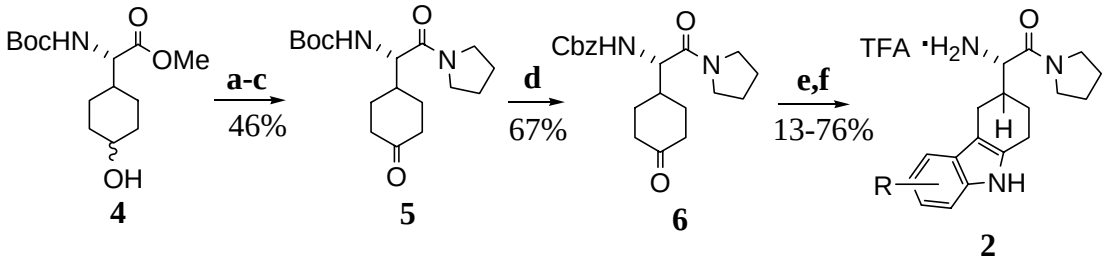
Abstract – A new class of potent inhibitors of dipeptidyl peptidase IV (DP-IV) for the treatment of type II diabetes are described. Presented herein is the synthesis of indole-fused and thiazole-fused cyclohexylglycines. Pyrrolidine-derived amides of these novel heterocycles led to the discovery of thiazole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

Inhibition of dipeptidyl peptidase IV (DP-IV) is emerging as a new approach for the treatment of type-II diabetes.[1] Recent research from Merck laboratories led to the discovery of substituted 4-aminocyclohexylglycine derivatives (**1**) as potent DP-IV inhibitors.[2] As part of this program, we hoped to improve the *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**)[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[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*-toluenesulfonic 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**).

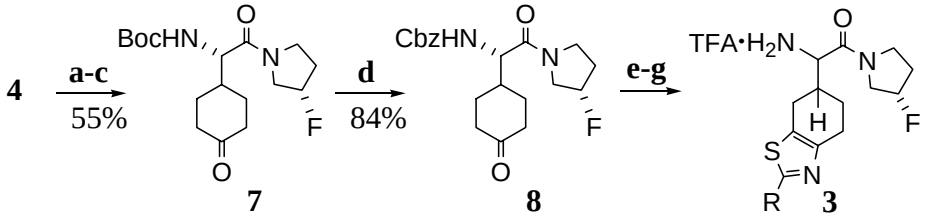


4 **5** **6** **2**

Conditions: a) LiOH (aq.), MeOH, THF; b) EDC, HOBt, DIEA, DCM, pyrrolidine; c) DMP, CH_2Cl_2; d) i) CH_2Cl_2, TFA; ii) $NaHCO_3$ (aq.), THF, CbzCl; e) $ArNHNH_2$, *p*-TsOH, EtOH, Δ; f) $Pd(OH)_2$, EtOH, H_2.

Scheme 1

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,[4] and then treated with phenyltrimethylammonium tribromide ($PhNMe_3Br_3$) 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.[5] The protecting group of each diastereomer was removed using iodotrimethylsilane to afford the desired ammonium salts (**3**) after purification.[6]



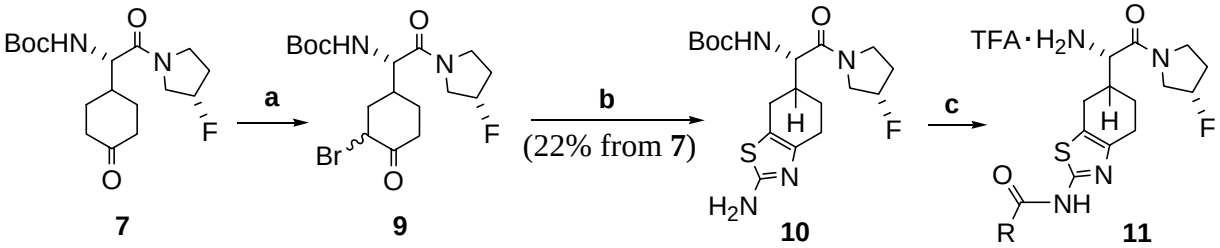
7 **8** **3**

Conditions: a) LiOH (aq.), MeOH, THF; b) EDC, HOBt, DIEA, (*s*)-3-fluoropyrrolidine, CH_2Cl_2; c) DMP, CH_2Cl_2; d) i) CH_2Cl_2, TFA; ii) $NaHCO_3$ (aq.), THF, CbzCl; e) $PhNMe_3Br_3$, THF, 0 ^oC; f) $RCSNH_2$, DMF, 120 ^oC; g) TMSI, MeCN.

Scheme 2

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

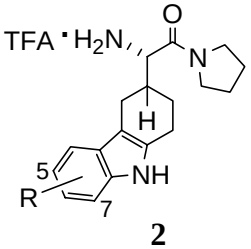
diastereomerically pure aminothiazoles (**10**) (Scheme 3). After deprotection of each pure diastereomer of **10**, the more active isomer was determined to be the isomer (**3d**).[7] Acylation of the more active diastereomer of **10** followed by deprotection of the Boc group then afforded pure diastereomers of **11**.



Conditions: a) $PhNMe_3Br_3$, THF, 0 ^oC; b) i) $SC(NH_2)_2$, EtOH, Δ; ii) Boc_2O, CH_2Cl_2, DIEA; c) RCOCl, CH_2Cl_2, DIEA; iii) TFA, CH_2Cl_2.

Scheme 3

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



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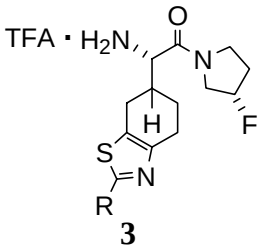
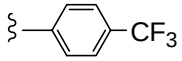
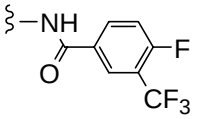


3

Entry	R	Yield[a] %	DP-IV IC_{50} (nM)	Entry	R	Yield[b] %	DP-IV IC_{50} (nM)
2a	5-Cl	76	67	**3a**[c]	-Me	6	43
2b	5-OCF_3	30	209	**3b**[c]		9	6
2c	5-CF_3	60	73	**3c**	-NH_2	32	185
2d	7-CO_2H	13	29	**3d**	-NH_2	32	61
2e	7-CO_2Et	14	13	**11a**[d]		11	6
2f	5-CO_2H	10	609	**11b**[d]	-NHAc	63	13
2g	5-CO_2Et	36	220				

[a]Yields represent the combined yields of Fisher indole cyclization and deprotection steps (conversion of **6** to **2**). [b]Yields represent the overall conversion of **8** to **3**, including the resolution of diastereomers before deprotection (max yield = 50%). [c]Only active diastereomers are shown.[9 d] Yields are for the conversion of **10** to **11**. ^1H NMR spectra of representative examples: **3b** (500 MHz, CD_3OD) 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), 3.58-4.02 (m, 4 H) 3.02-3.09 (m, 2H), 2.84-2.91 (m, 2 H) 2.08-2.59 (m, 4 H) 1.8-1.9 (m, 1 H); **3c** (500 MHz, CD_3OD) 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, CD_3OD) 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, 4 H) 1.95-2.42 (m, 4 H), 1.65-1.78 (m, 1 H); **11a** (500 MHz, CD_3OD) 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).[8] For example **3b** and **11a** were extremely potent, each with a 6 nM inhibition of the enzyme even though lacking a serine trap.[1]

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.* **1**). Furthermore, we have succeeded in developing simple synthetic methodologies for accessing indole-fused and thiazole-fused cyclohexylglycine derivatives.

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2. (a) E. R. Parmee, J. He, A. Mastracchio, S. D. Edmondson, L. Colwell, G. Eiermann, W. P. Feeney, B. Habulihaz, H. He, R. Kilburn, B. Leiting, K. Lyons, F. Marsilio, R. Patel, A. Petrov, J. Di Salvo, J. K. Wu, N. A. Thornberry, and A. E. Weber, submitted to: *Bioorganic & Medicinal Chemistry Letters*. (b) C. Caldwell, *et. al, manuscript in preparation*.
3. (a) J. A. Joule, 'Heterocyclic Chemistry,' ed. by J. A. Joule and K. Mills, Blackwell Sciences Ltd., Oxford, 2000, pp. 418-422. (b) L. A. Paquette, 'Principles of Modern Heterocyclic Chemistry,' W. A. Benjamin, Inc., Reading, MA, 1980, pp. 191-194.
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 **3a** and type AS (isocratic method, 50% ethanol/hexane) was used for **3b**.
6. All final products were purified by reverse phase HPLC to afford TFA salts.
7. The two diastereomers of **10** were separated using a ChiralCel column type AD (isocratic method, 75% EtOH/hexane). The most potent deprotected compound (**3d**) is derived from the faster eluting isomer.
8. For DP-IV assay conditions, see : B. Leiting, K. D. Pryor, J. K. Wu, F. Marsilio, R. A. Patel, C. S. Craik, J. A. Ellman, R. T. Cummings, and N. A. Thornberry, *Biochem. J.*, 2003, **371**, 525.
9. The less active diastereomers of **3a** and **3b** were IC_{50} = 385 nM and 171 nM respectively.