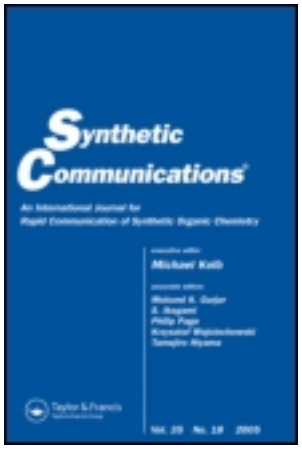

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 09 Dec 2009

To cite this article: Liutang Wang, Bin Zhang, Jianxin Ji, Bogang Li, Jufang Yan, Weiyu Zhang, Yong Wu, Xuechao Wang & Hui Hou (2009): Synthesis and Evaluation of Novel Compounds as Potent Dipeptidyl Peptidase IV Inhibitors, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:1, 52-57

To link to this article: http://dx.doi.org/10.1080/00397910902919522

Synthetic Communications®, 40: 52–57, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902919522

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SYNTHESIS AND EVALUATION OF NOVEL COMPOUNDS AS POTENT DIPEPTIDYL PEPTIDASE IV INHIBITORS

Liutang Wang,[1,2] Bin Zhang,[2] Jianxin Ji,[2] Bogang Li,[2] Jufang Yan,[2] Weiyu Zhang,[2] Yong Wu,[1] Xuechao Wang,[1,2] and Hui Hou[2]

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A series of new 2-cyanopyrrolidine derivatives with constrained imidazolidin ring were synthesized, Their structures were confirmed by ^{1}H NMR spectroscopy andlor mass spectrometry, and their activities were evaluated in vitro. They were proven to possess submicromolar inhibitory activities against dipeptidyl peptidase IV.

Keywords: Antidiabetic agent; 2-cyanopyrrolidine; dipeptidyl peptidase IV inhibitors; imidazolidin derivatives

INTRODUCTION

Inhibition of dipeptidyl peptidase IV (DPP-IV) has recently emerged as a promising new approach for the treatment of type 2 diabetes mellitus.[1] DPP-IV is the enzyme responsible for inactivation of the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These two hormones are secreted in response to nutrient ingestion, and each enhances the glucose-dependent secretion of insulin. Furthermore, in mammals GLP-1 has been shown to stimulate the secretion of insulin in a glucose-dependent manner, inhibit glucagon release, slow gastric emptying, induce satiety, and stimulate the regeneration and differentiation of islet β-cells, with all of these actions promoting the control of glucose homeostasis in patients with type 2 diabetes.[2] Thus, inhibition of DPP-IV could increase the half-life of active GLP-1 and GIP and prolong the beneficial effects of these incretin hormones, which would enhance insulin secretion and improve glucose tolerance. Therefore, much attention has been paid to DPP-IV as a

Received December 17, 2008.
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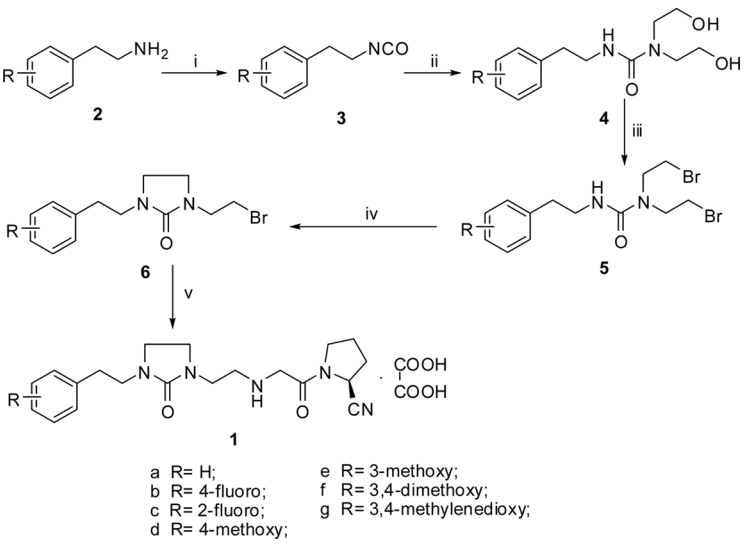


Scheme 1. Reagent and conditions: (i) triphosgene, toluene, heated, 4–8 h; (ii) diethanolamine, CH_2Cl_2, rt, overnight; (iii) PBr_3, CH_2Cl_2, 10°C, 5 h; (iv) $NaHCO_3$, pH ≈ 10, overnight; and (v) (1) (S)-1-(2-aminoacetyl)pyrrolidine-2-carbonitrile trifluoroacetate, K_2CO_3, CH_3CN, rt, 40–48 h; (2) oxalic acid, isopropanol.

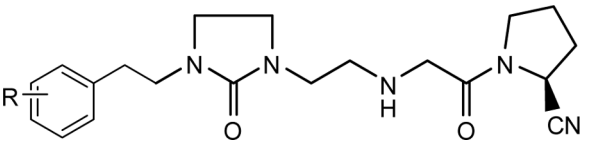
promising new target for drugs.[3] DPP-IV is a dipeptidase that selectively binds substrates with alanine or proline at the P1 position.[1a,4] Consequently, many DPP-IV inhibitors are shaped like dipeptides and contain a basic nitrogen and proline mimic. (S)-1-(2-Aminoacetyl)pyrrolidine-2-carbonitrile is one of the most potent moieties and contributes significantly to the binding affinity between DPP-IV and its inhibitors.[5,6] Thus, we have designed and synthesized a series of structurally constrained imidazolidin (S)-1-(2-aminoacetyl)pyrrolidine-2-carbonitrile derivatives **1**.

RESULTS AND DISCUSSION

The DPP-IV inhibitors were prepared as described in Scheme 1. Amine **2** was heated with triphosgene in toluene to afford isocyanate compounds (**3**), which were then reacted with diethanolamine in dichloromethane (DCM) at room temperature to provide substituted urea derivatives (**4**) in excellent yield. Compound **4** was brominated with tribromophosphine in DCM under ice-water conditions to yield the desired intermediates (**5**), followed by cyclization at base conditions to obtain the key imidazolidin-2-one derivatives (**6**). Compound **6** was coupled with (S)-1-(2-aminoacetyl)pyrrolidine-2-carbonitrile (prepared in three steps[7] from L-prolinamide) to provide the desired 2-cyanopyrrolidine derivatives (**1**).

Compounds **1a**–**g** were evaluated in vitro for their inhibition of DPP-IV (Table 1). KR-62436[8] was used as a reference compound. All of them were proven to possess submicromolar inhibitory activities against DPP-IV.

Table 1. DPP-IV inhibitory activity



Compound	R	IC_{50} (μM)
1a	H	0.08
1b	4-Fluoro	0.10
1c	2-Fluoro	0.10
1d	4-Methoxy	0.20
1e	3-Methoxy	0.12
1f	3,4-Dimethoxy	0.32
1g	3,4-Methylenedioxy	0.16
KR-62436		0.26

Note. Values are IC_{50} (μM) expressed as the mean of three independent determinations.

EXPERIMENTAL

General

Melting points were observed in an open capillary tube and are uncorrected. ^1H NMR spectra were obtained at 600 MHz on a Bruker Avance 600 instrument using $CDCl_3$ or dimethylsufoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were measured on an Agilent 1946B ESI-MS instrument. Specific rotations were measured on a Perkin-Elmer-341 instrument. All commercially available reagents were used without purification.

General Procedure for the Synthesis of 6

Triphosgene (85 mmol) was dissolved in toluene (200 mL), and the solution of **2** (100 mmol) in toluene was added dropwise with ice cooling. The temperature was gradually increased. The mixture was stirred for an hour at room temperature and then heated to 100°C for 3 h. The mixture was concentrated to about 80 mL, then added to the solution of diethanolamine (200 mmol) in CH_2Cl_2 (200 mL), and stirred overnight. The reacting solution was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **4**, which could be used for the next reaction without purification.

Tribromophosphine (120 mmol) was added to the solution of **4** in CH_2Cl_2 (200 mL) dropwise in an ice-water bath. The mixture was stirred for 3 h at room temperature, basified with saturated $NaHCO_3$ solution, and stirred overnight. The organic phase was isolated, and the aqueous layer was extracted with CH_2Cl_2 two times. The combined organic phase was washed with brine and dried over Na_2SO_4. Concentration was followed by purification by chromatography using silica gel (eluting sequentially with petroleum ether/ethyl acetate = 10/1 to 3/1) to afford **6**.

1-(2-Bromoethyl)-3-phenethylimidazolidin-2-one (6a). Yield: 35%. ^{1}H NMR δ ($CDCl_3$): 7.30–7.19 (m, 5H), 3.59 (t, 2H, $J = 6.7$ Hz), 3.47–3.44 (m, 4H), 3.40 (t, 2H, $J = 8.5$ Hz), 3.24 (t, 2H, $J = 8.3$ Hz), 2.83 (t, 2H, $J = 7.4$ Hz). ESI-MS (+): 297, 299 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(4-fluorophenethyl)imidazolidin-2-one (6b). Yield: 27%. ^{1}H NMR δ ($CDCl_3$): 7.19–7.17 (m, 2H), 6.98 (t, 2H, $J = 8.6$ Hz), 3.59 (t, 2H, $J = 6.3$ Hz), 3.46 (t, 2H, $J = 6.3$ Hz), 3.43–3.39 (m, 4H), 3.24 (t, 2H, $J = 7.3$ Hz), 2.80 (t, 2H, $J = 7.6$ Hz). ESI-MS (+): 315, 317 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(2-fluorophenethyl)imidazolidin-2-one (6c). Yield: 30%. ^{1}H NMR δ ($CDCl_3$): 7.23–7.17 (m, 2H), 7.09–7.00 (m, 2H); 3.58 (t, 2H, $J = 6.6$ Hz), 3.46–3.40 (m, 6H), 3.29 (t, 2H, $J = 7.4$ Hz), 2.88 (t, 2H, $J = 7.4$ Hz). ESI-MS (+): 315, 317 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(4-methoxyphenethyl)imidazolidin-2-one (6d). Yield: 23%. ^{1}H NMR δ ($CDCl_3$): 7.14 (d, 2H, $J = 8.5$ Hz), 6.84 (d, 2H, $J = 8.4$ Hz), 3.79 (s, 3H), 3.59 (t, 2H, $J = 6.5$ Hz), 3.46 (t, 2H, $J = 6.5$ Hz),3.42–3.38 (m, 4H), 3.24 (t, 2H, $J = 7.5$ Hz), 2.77 (t, 2H, $J = 7.6$ Hz). ESI-MS (+): 327,329 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(3-methoxyphenethyl)imidazolidin-2-one (6e). Yield: 26%. ^{1}H NMR δ ($CDCl_3$): 7.21 (t, 1H, $J = 7.8$ Hz), 6.83–6.75 (m, 3H), 3.79 (s, 3H), 3.59 (t, 2H, $J = 6.2$ Hz), 3.47–3.44 (m, 4H), 3.40 (t, 2H, $J = 8.4$ Hz), 3.25 (t, 2H, $J = 8.5$ Hz), 2.80 (t, 2H, $J = 7.9$ Hz). ESI-MS (+): 327, 329 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(3,4-dimethoxyphenethyl)imidazolidin-2-one (6f). Yield: 19%. ^{1}H NMR δ ($CDCl_3$): 6.81–6.76 (m, 3H); 3.87 (s, 3H), 3.86 (s, 3H), 3.59 (t, 2H, $J = 6.3$ Hz), 3.48–3.39 (m, 6H), 3.25 (t, 2H, $J = 8.5$ Hz), 2.78 (t, 2H, $J = 7.8$ Hz). ESI-MS (+): 357, 359 (1:1) $(M + H)^+$.

1-(2-Bromoethyl)-3-(3,4-methylenedioxyphenethyl)imidazolidin-2-one (6g). Yield: 15%. ^{1}H NMR δ ($CDCl_3$): 6.74–6.66 (m, 3H), 5.92 (s, 2H), 3.59 (t, 2H, $J = 6.3$ Hz), 3.46 (t, 2H, $J = 6.5$ Hz), 3.42–3.38 (m, 4H), 3.25 (t, 2H, $J = 7.3$ Hz), 2.74 (t, 2H, $J = 7.7$ Hz). ESI-MS (+): 341, 343 (1:1) $(M + H)^+$.

General Procedure for the Synthesis of 1

(S)-1-(2-Aminoacetyl)pyrrolidine-2-carbonitrile trifluoroacetate (24 mmol)was dissolved in acetonitrile, K_2CO_3 (64 mmol) was added, and the mixture was stirred for 30 min to liberate free amine. Then **6** (8 mmol) was added, and stirring continued for 48 h at room temperature. The mixture was filtered to remove the insoluble substance and concentrated in vacuo. Purification by flash-column chromatography (eluted with $CHCl_3$/MeOH = 10/1) yielded **1** as a viscous oil. The free base was dissolved in isopropanol, the solution of oxalic acid in isopropanol was added in drops, and precipitation occurred. Filtration was followed by drying in vacuo over P_2O_5.

(S)-1-(2-(2-(3-Phenethyl-2-oxoimidazolidin-1-yl)ethylamino)acetyl) pyrrolidine-2-carbonitrile Oxalate (1a). Yield: 28%. Mp 140–142°C. $[\alpha]_D^{20}$ −74° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 7.28 (t, 2H, $J = 7.7$ Hz), 7.23 (d, 2H,

$J = 7.3$ Hz), 7.19 (t, 1H, $J = 7.3$ Hz), 4.82 (dd, 1H, $J = 7.5$, 4.0 Hz), 4.00–3.88 (m, 2H), 3.59–3.56 (m, 1H), 3.42–3.38 (m, 1H), 3.34–3.30 (m, 4H), 3.27 (s, 4H), 3.00 (t, 2H, $J = 5.9$ Hz), 2.75 (t, 2H, $J = 7.6$ Hz), 2.18–2.15 (m, 2H), 2.07–2.00 (m, 2H). ESI-MS (+): 370 $(M + H)^+$.

(S)-1-(2-(2-(3-(4-Fluorophenethyl)-2-oxoimidazolidin-1-yl)ethylamino)-acetyl)pyrrolidine-2-carbonitrile Oxalate (1b). Yield: 23%. Mp 127–129°C. $[\alpha]_D^{20}$ −66° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 7.28–7.26 (m, 2H), 7.10 (t, 2H, $J = 8.8$ Hz), 4.83 (dd, 1H, $J = 7.2$, 4.2 Hz), 4.04–3.91 (m, 2H), 3.60–3.57 (m, 1H), 3.45–3.39 (m, 1H), 3.35 (t, 2H, $J = 5.8$ Hz), 3.32–3.28 (m, 6H), 3.03 (m, 2H, $J = 6.0$ Hz),2.75 (t, 2H, $J = 7.4$ Hz), 2.20–2.17 (m, 2H), 2.06–2.00 (m, 2H). ESI-MS (+): 388 $(M + H)^+$.

(S)-1-(2-(2-(3-(2-Fluorophenethyl)-2-oxoimidazolidin-1-yl)ethylamino)-acetyl)pyrrolidine-2-carbonitrile Oxalate (1c). Yield: 20%. Mp 139–141°C. $[\alpha]_D^{20}$ −71° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 7.34–7.12 (m, 4H), 4.82 (dd, 1H, $J = 7.1$, 3.8 Hz), 3.99–3.89 (m, 2H), 3.60–3.57 (m, 1H), 3.42–3.38 (m, 1H), 3.34–3.27 (m, 8H), 3.01 (t, 2H, $J = 7.4$ Hz), 2.79 (t, 2H, $J = 7.4$ Hz), 2.22–2.16 (m, 2H), 2.06–2.00 (m, 2H). ESI-MS (+): 388 $(M + H)^+$.

(S)-1-(2-(2-(3-(4-Methoxyphenethyl)-2-oxoimidazolidin-1-yl)ethylamino)-acetyl)pyrrolidine-2-carbonitrile Oxalate (1d). Yield: 25%. Mp 108–110°. $[\alpha]_D^{20}$ −64° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 7.15 (d, 2H, $J = 8.4$ Hz), 6.86 (d, 2H, $J = 8.6$ Hz), 4.83 (dd, 1H, $J = 6.8$, 3.5 Hz), 4.04–3.91 (m, 2H), 3.72 (s, 3H), 3.60–3.57 (m, 1H), 3.43–3.38 (m, 1H), 3.34 (t, 2H, $J = 6.1$ Hz), 3.29–3.26 (m, 6H), 3.03 (t, 2H, $J = 6.3$ Hz), 2.68 (t, 2H, $J = 7.9$ Hz), 2.20–2.16 (m, 2H), 2.07–2.00 (m, 2H). ESI-MS (+): 400 $(M + H)^+$.

(S)-1-(2-(2-(3-(3-Methoxyphenethyl)-2-oxoimidazolidin-1-yl)ethylamino)-acetyl)pyrrolidine-2-carbonitrile Oxalate (1e). Yield: 19%. Mp 114–117°. $[\alpha]_D^{20}$ −65° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 7.20 (t, 1H, $J = 8.04$ Hz), 6.08–6.76 (m, 3H), 4.82 (s, 1H), 4.00–3.90 (m, 2H), 3.74 (s, 3H), 3.58 (br, 1H), 3.43–3.39 (m, 1H), 3.34–3.28 (m, 8H), 3.02 (s, 2H), 2.72 (t, 2H, $J = 7.6$ Hz), 2.18 (br, 2H), 2.05–2.02 (m, 2H). ESI-MS (+): 400 $(M + H)^+$.

(S)-1-(2-(2-(3-(3,4-Dimethoxyphenethyl)-2-oxoimidazolidin-1-yl)ethylamino)-acetyl)pyrrolidine-2-carbonitrile Oxalate (1f). Yield: 16%. Mp 103–105°C. $[\alpha]_D^{20}$ −54° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 6.86 (d, 1H, $J = 8.2$ Hz), 6.82 (s, 1H), 6.73 (d, 1H, $J = 8.2$), 4.82 (dd, 1H, $J = 7.3$, 3.8 Hz), 4.00–3.90 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.60–3.57 (m, 1H), 3.43–3.39 (m, 1H), 3.34 (t, 2H, $J = 6.0$ Hz), 3.31–3.28 (m, 6H), 3.03 (t, 2H, $J = 6.0$ Hz), 2.68 (t, 2H, $J = 7.6$ Hz), 2.22–2.17 (m, 2H), 2.06–2.00 (m, 2H). ESI-MS (+): 430 $(M + H)^+$.

(S)-1-(2-(2-(3-(3,4-Methylenedioxyphenethyl)-2-oxoimidazolidin-1-yl)-ethylamino)acetyl)pyrrolidine-2-carbonitrile Oxalate (1g). Yield: 17%. Mp 120–122°C. $[\alpha]_D^{20}$ −61° (c = 1, H_2O). ^{1}H NMR δ (DMSO-d_6): 6.82–6.69 (m, 3H), 5.96 (s, 2H), 4.82 (dd, 1H, $J = 7.0$, 3.6 Hz), 3.99–3.89 (m, 2H), 3.60–3.57 (m, 1H), 3.43–3.39 (m, 1H), 3.33 (t, 2H, $J = 5.8$ Hz), 3.28–3.25 (m, 6H), 3.00 (s, 2H), 2.66 (t, 2H, $J = 7.6$ Hz), 2.20–2.17 (m, 2H), 2.06–2.00 (m, 2H). ESI-MS (+): 414 $(M + H)^+$.

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