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Design and synthesis of DPP-4 inhibitor for the treatment of type 2 diabetes

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Abstract

An efficient stereoselective synthesis of the rigid aza-bicyclo[3.2.0]heptane scaffold has been developed to provide 2-cyano pyrrolidine alpha-amino amide **1** as DPP-4 inhibitor.

Keywords: DPP-4 inhibitor; Aza-bicyclo[3.2.0]heptane scaffold; 2-Cyano pyrrolidine alpha-amino amide derivative; Synthesis; Type 2 diabetes

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]. Continuous infusion of GLP-1 in patients with type 2 diabetes has resulted in significant decreases in plasma glucose and hemoglobin A1c levels [2]. However, active GLP-1 is rapidly converted to inactive GLP-1 by the serine protease dipeptidyl peptidase IV (DPP-4), thus limiting its therapeutic practicality. Inhibition of DPP-4 increases the level of endogenous intact GLP-1. Consequently, inhibition of DPP-4 is rapidly emerging as a novel therapeutic approach for the treatment of type 2 diabetes [3,4]. Saxagliptin [5] (Onglyza®, BMS-477118) was recently approved by US FDA to be marketed for the treatment of type 2 diabetes (Fig. 1). The 1,6 spatial relationship of the NH_2 and CN group is required for inhibition for this class of compound, but also favors the intramolecular cyclization to form the rearranged compound **3** which is devoid of inhibitory activity [6]. The presence of the cyclopropyl group on the pyrrolidine ring, as a steric barrier, has been shown to discourage the cyclization and therefore increases the stability and half life of BMS-477118 [7]. We reasoned the cyclobutyl group would be sterically as effective as the cyclopropyl group and the introduction of the gem-difluoro group, which otherwise was much more difficult to be introduced in cyclopropyl group, would further provide electronic repulsion to the incoming nitrogen nucleophile which may result in longer acting. Herein, we described the synthesis and biological activities of the novel difluorocyclobutyl pyrrolidine derivative **1** (Fig. 1).

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1. Experimental

Compound **1** was prepared from difluorocyclobutyl pyrrolidine amide **4** and adamantylglycine **5** [7] (Fig. 1).

As shown in Scheme 1, *anti*-[2+2] cycloaddition of the enantiomerically pure enecarbamate **6**, which derived from ethyl Boc-D-pyroglutamate [8], with dichloroketene generated *in situ* occurred to provide the desired product **7** in 65% yield to set up the stereochemistry at the ring junction of the bicyclic core. Reductive dechlorination of **7** proceeded cleanly with Zn dust in the presence of ammonium chloride to provide the corresponding azabicyclic cyclobutanone **8** in 70% yield. Treatment of **8** with DAST gave the difluoromethylene derivative **9**. As anticipated, conformational inversion of the carboxylic acid ethyl ester in **9** employing LDA occurred cleanly in good yield (**10**:**9** = 9:1). After hydrolysis and amidation, compound **4** was obtained, which coupled with adamantylglycine **5** [7] under HATU conditions. Dehydration of amide **11** with TFAA, followed by deprotection of the N-terminus, gave the target compound **1** as its TFA salt [9].

2. Results and discussion

Inhibitory selectivity for DPP-4 over DPP-8 and DPP-9 was particularly emphasized. The inhibition of the latter two enzymes may be associated with profound toxicity [10,11]. The data for DPP-4, DPP-8 and DPP-9 inhibitions were summarized in Table 1. Compound **1** exhibited excellent potency against DPP-4 and high selectivity over DPP-8 and DPP-9. The IC_{50} of compound **1** was 27 nmol/L. The DPP-4 IC_{50}/DPP-8 IC_{50} ratio was 99-fold compared with BMS-477118 which ratio was 28-fold. At the same time, selectivity against DPP-9 was also observed.

In conclusion, an efficient stereoselective synthesis of the rigid aza-bicyclo[3.2.0]heptane scaffold was developed starting from compound **6** which led to the synthesis of new DPP-4 inhibitor **1**. Despite the potency and favorable selectivity, development of compound **1** has to await more in-depth evaluation of related analogs because of its moderate pharmacokinetic profile. With an efficient synthesis in hand, further medicinal chemistry efforts focusing on chemical diversification of intermediates such as **8**, **9** and **10** that possess multiple diversifiable functional groups to identify new DPP-4 inhibitors meeting the target profiles concerning the stability, selectivity, pharmacokinetics and efficacy are in progress (Table 2).

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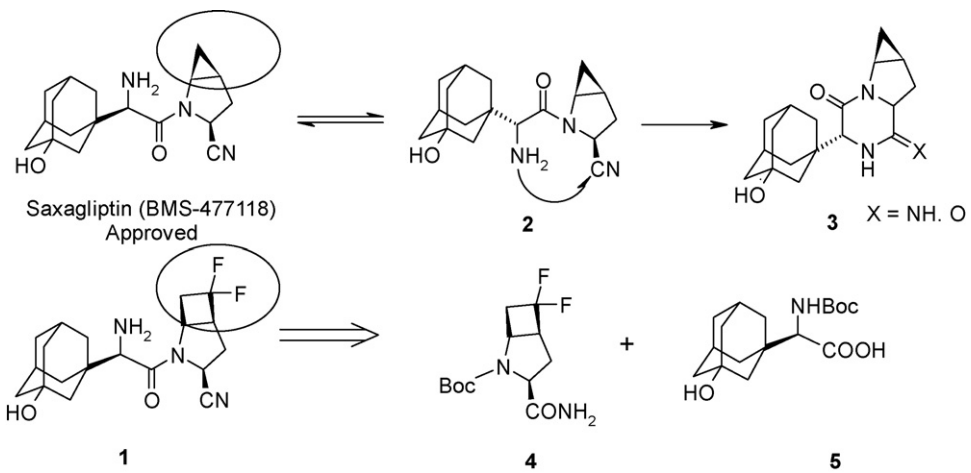
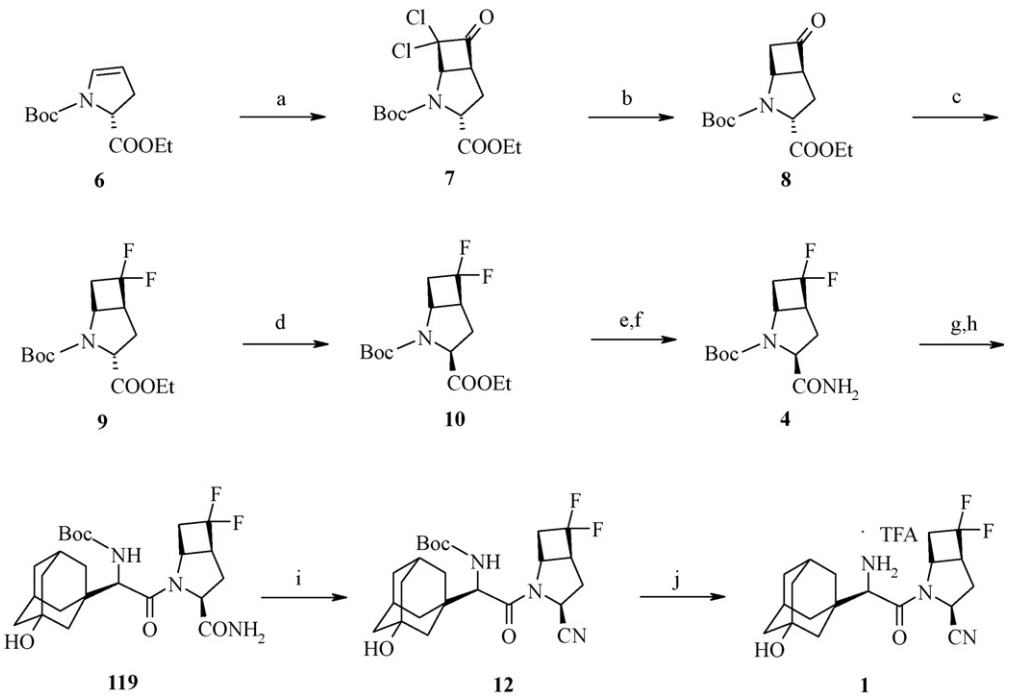


Fig. 1. Rational design of compound **1**.



Scheme 1. Reagents and conditions: (a) 1.5 equiv. $Cl_2CHCOCl$, 2.0 equiv. Et_3N, 40 °C, 65%; (b) 11.0 equiv. Zn dust, MeOH (sat. NH_4Cl aqueous), rt, 70%; (c) 2.5 equiv. DAST, CH_2Cl_2, 0 °C → 40 °C, 57%; (d) 1.5 equiv. LDA, 2.0 equiv. *i*-PrOH, THF, −78 °C, 70%; (e) 3.0 equiv. LiOH, EtOH/H_2O, rt, 100%; (f) 1.2 equiv. EDCI, 1.2 equiv. HOBt, 1.5 equiv. DIPEA, 3.0 equiv. $(NH_4)_2CO_3$, THF, rt, 85%; (g) HCl, ethyl acetate, rt; (h) 1.0 equiv. HATU, **5**, 2.0 equiv. DIPEA, DMF, rt, 72%; (i) 2.5 equiv. TFAA, 5.0 equiv. pyridine, THF, 0 °C → rt, 50%; (j) TFA, CH_2Cl_2, rt, 98%.

Table 1
Potency and selectivity of compound **1**.

Compound	IC_{50} (μmol/L)		
	DPP-4	DPP-8	DPP-9
1	0.027	2.66	1.66
BMS-477118	0.019	0.54	0.307

Table 2
Pharmacokinetic parameters of **1** (mean ± SD)[a].

Parameters	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC 0-t (ng/mL h)	Vz/F (l/kg)	CLz/F (l/h/kg)
1	0.32 ± 0.17	270 ± 144	0.92 ± 0.21	347 ± 200	14.4 ± 7.46	11.7 ± 6.74

[a] Oral administrations of 3.0 mg/kg to Sprague–Dawley rats.

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