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Discovery of triazole-based uracil derivatives bearing amide moieties as novel dipeptidyl peptidase-IV inhibitors

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ABSTRACT

Dipeptidyl peptidase-IV (DPP-4) is a validated target for T2DM treatment. We previously reported a novel series of triazole-based uracil derivatives bearing aliphatic carboxylic acids with potent DPP-4 inhibitory activities *in vitro*, but these compounds showed poor hypoglycemic effects *in vivo*. Herein we further optimized the triazole moiety by amidation of the carboxylic acid to improve *in vivo* activities. Two series of compounds **3a-f** and **4a-g** were designed and synthesized. By screening in DPP-4, compound **4c** was identified as a potent DPP-4 inhibitor with the IC_{50} value of 28.62 nM. Docking study revealed compound **4c** has a favorable binding mode and interpreted the SAR of these analogs. DPP-8 and DPP-9 tests indicated compound **4c** had excellent selectivity over DPP-8 and DPP-9. Further *in vivo* evaluations revealed that compound **4c** showed more potent hypoglycemic activity than its corresponding carboxylic acid in ICR mice and dose-dependently reduced glucose levels in type 2 diabetic C57BL/6 mice. The overall results have shown that compound **4c** could be a promising lead for further development of novel DPP-4 agents treating T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a growing metabolic disease manifested by progressive beta cell dysfunction and insulin resistance in addition to progressive microvascular and macrovascular complications [1,2]. The global population with T2DM is around 422 million worldwide in 2014 [1], and this number is predicted to increase to 592 million by 2035 [3,4]. Currently, DPP-4 is a validated target for T2DM treatment [5]. It is a serine protease involved in the rapid inactivation of incretin hormone glucagon-like peptide-1 (GLP-1) [6,7]. GLP-1 lowers plasma glucose by stimulating glucose-dependent insulin secretion and inhibiting glucagon secretion and contributes to the maintenance of postprandial glycemic level [8]. Inhibition of DPP-4 prevents the degradation of GLP-1, thus blocks the inactivation of GLP-1, and in turn, enhance insulin secretion [9]. Several DPP-4 inhibitors, including sitagliptin [10], vildagliptin [11], saxagliptin [12], linagliptin [13], alogliptin [14] and anagliptin [15] (Fig. 1), have already been launched as therapeutic agents for T2DM. However, some of the DPP-4 inhibitors were associated with an increased risk of hospitalization for heart failure [16,17], and might cause severe joint pain side effect [18]. Thus there remain important unmet medical needs to develop novel DPP-4 inhibitors with increased safety and durability for the treatment of T2DM.

There are four subsites including S1, S2, S1′, and S2′ subsites in the active site of the DPP-4 enzyme [19]. A variety of DPP-4 inhibitors were reported to bind in the S1, S2, and S1′ subsites, and the binding modes of these inhibitors in S1, S2, and S1′ subsites have been fully understood [20]. However, only a few inhibitors bind into the S2′ subsite and thus leaving more to be explored [19]. We have previously reported some triazole-based uracil derivatives bearing aliphatic carboxylic acids interacted with S2′ subsite to increase their inhibitory activities [21]. Some of them showed potent DPP-4 inhibitory activity, in which compound **1** bearing 3-propanoic acid group exhibited low nanomolar activity with the IC_{50} of 12.45 nM, and compound **2** containing acetic acid moiety displayed the IC_{50} value of 84.72 nM [21] (Fig. 1). However, both compounds **1** and **2** showed poor *in vivo* hypoglycemic effect due to low membrane permeability caused by the formation of a zwitterion between the carboxyl group and the amino group [21]. Thus herein we further optimized the triazole moieties by covering the acid, which focused on the formation of amide to avoid generating the zwitterion to increase membrane permeability. Novel amide compounds **3a-g** and **4a-f** were designed and

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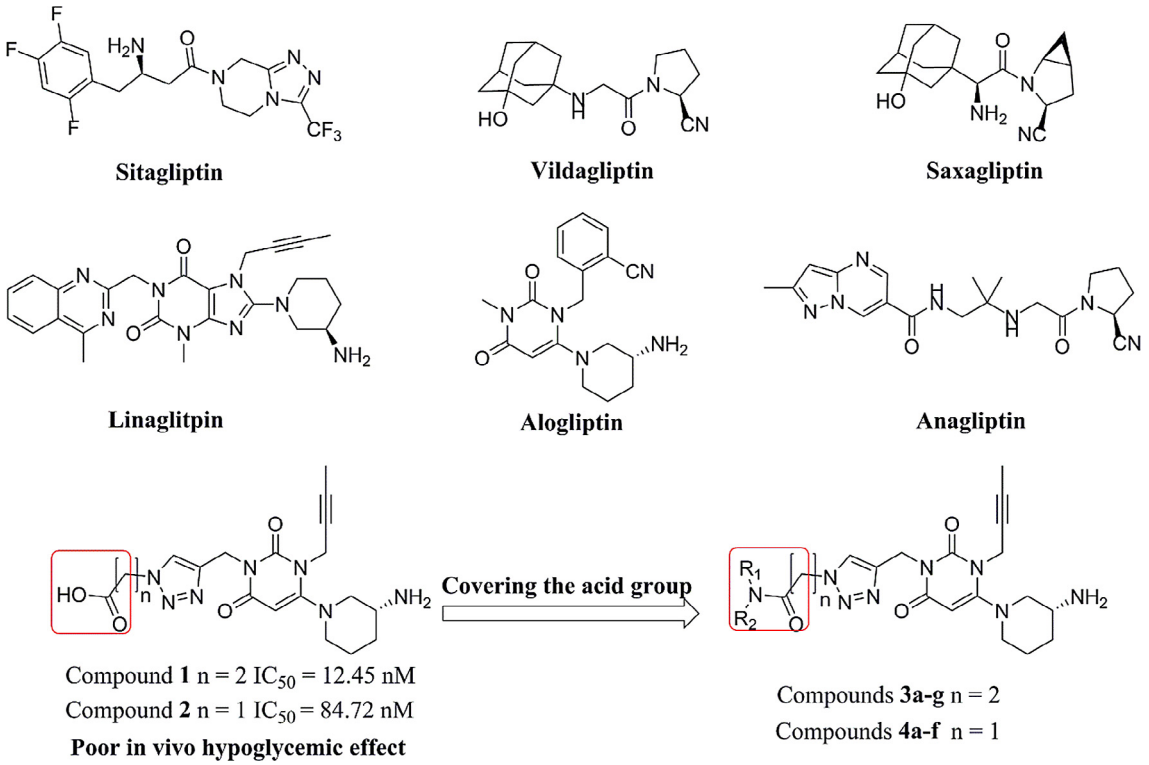

Fig. 1. The structure of marketed DPP-4 inhibitors and the design of target compounds.

synthesized. After systematic exploration of SAR and application of molecular modeling, the promising candidate **4c** and its interaction modes were identified. In subsequent *in vivo* pharmacological studies, compound **4c** showed a robustly hypoglycemic effect in both ICR mice and type 2 diabetic C57BL/6 mice.

2. Results and discussion

2.1. Design strategy

In order to identify novel DPP-4 inhibitors with potent hypoglycemic effects *in vivo*, we performed docking studies for all the triazole-based uracil derivatives with aliphatic carboxylic acids we reported previously [21]. Docking studies revealed that most of the compounds including compound **1** are found to bind to the active site of DPP-4 in a similar way to linagliptin (Fig.2A) [21], but the compound **2** has a binding mode that is different from linagliptin (Fig.2B). As shown in Fig.2A, 2-butynyl group of compound **1** have hydrophobic interaction with S1 subsite, 3-(*R*)-aminopiperidine group is remained to form salt bridges with Glu205 and Glu206 and Tyr662, the uracil ring interacts with Tyr547 through π-π stacking in S1′ subsite, the carboxyl group of compound **1** interacts with Arg125 by charge-reinforced hydrogen bonds [21]. Published X-ray co-crystal structures suggested that Arg125 in the S2 subsite is an ideal targeting residue for achieving a potent activity of DPP-4 [22], for instance, alogliptin take the cyano group to interact with Arg125 [22], the carbonyls of amide in carmegliptin [23] and nicotinic amide derivatives [24] interact with Arg125 through hydrogen bonds. Considering the carbonyl of amide can keep the hydrogen bonds interaction with Arg125, We envisioned introduction of amide to acid group may retain

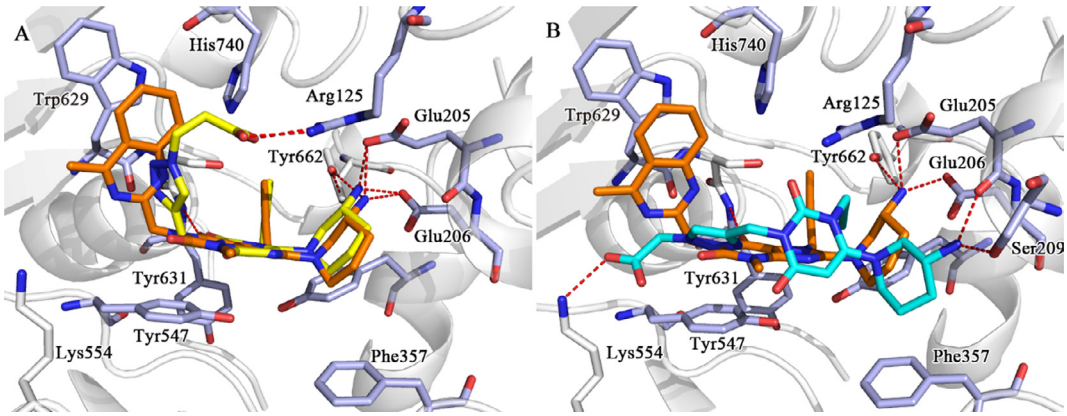

Fig. 2. The overlay of linagliptin against docking compounds 1 and 2 in DPP-4 active site. Hydrogen bonds are depicted as dashed red lines. DPP-4 in ribbon representation is coloured blue, linagliptin (orange), 1 (yellow, Figure A), 2 (cyan, Figure B) are represented in stick.