Bioorganic & Medicinal Chemistry Letters 21 (2011) 1366–1370

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of β-aminoacyl containing thiazolidine derivatives as potent and selective dipeptidyl peptidase IV inhibitors

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ARTICLE INFO

Article history:
Received 8 November 2010
Revised 7 January 2011
Accepted 11 January 2011
Available online 14 January 2011

Keywords:
Diabetes
Thiazolidine
DPP-IV
Treatment

ABSTRACT

A series of β-aminoacyl containing thiazolidine derivatives was synthesized and evaluated for their ability to inhibit DPP-IV. Several thiazolidine derivatives with an acid moiety were found to be potent DPP-IV inhibitors. Among them, compound **2da** is the most active in this series with an IC_{50} value of 1 nM, and it showed excellent selectivity over DPP-IV related enzymes including DPP-2, DPP-8, and DPP-9. Compound **2da** is chemically and metabolically stable, and showed no CYP inhibition, hERG binding or cytotoxicity. Compound **2db**, an ester prodrug of **2da**, showed good in vivo DPP-IV inhibition after oral administration in rat and dog models.

Glucagon like peptide-1 (GLP-1)[1,2] is released from L cells of the small intestine in response to the digestion of food, and plays an important role in secretion of insulin. Increased activity of GLP-1 will lead to increase insulin secretion, which regulates an elevated glucose level. It also retards gastric emptying, induces of satiety and stimulates, regenerates, and differentiates islet β-cells.[3] Dipeptidyl peptidase IV (DPP-IV), a serine protease present in many tissues and body fluids, exist either with membrane bound or soluble enzyme. It degrades GLP-1 (GLP-1[7–36] amide) into inactive GLP [9–36] amide[4,5] at the N-terminus. Inhibition of DPP-IV increases the concentration of GLP-1, as a result increases insulin secretion,[6] which can ameliorate hyperglycemia in type 2 diabetes.

Many reports on the use of small molecules as DPP-IV inhibitor are available in the literature.[7] Among them, Merck described a series of structurally novel β-amino amide derivatives, of which MK-0431 (Sitagliptin) was approved for the treatment of type II diabetes in 2006.[8]

Merck researchers also identified a proline derived homophenylalanine derivative (**1**, Fig. 1), which is a potent and highly selective DPP-IV inhibitor, but exhibited poor bioavailability.[9]

Meanwhile, we have identified several series of β-aminoacyl derivatives.[10,11] as DPP-IV inhibitors (Fig. 2). However more active and less toxic compounds are still in great need.

Based on above mentioned compounds, we identified β-aminoacyl containing thiazolidine derivatives (**2**, Fig. 3), and now wish to report the synthesis and biological evaluation of β-aminoacyl-containing thiazolidine derivatives as DPP-IV inhibitors.

The general and key compound's syntheses are outlined in Schemes 1 and 2. As shown in Scheme 1, commercially available (*R*)-3-(*tert*-butoxycarbonyl amino)-4-(2,4,5-trifluorophenyl)butanoic acid **3** was coupled with racemic ethyl thiazolidine-2-carboxylate in presence of EDCI to provide the amide **4**, which was treated with LiOH to provide the corresponding acid **5**. The compound **5** was amidated with diverse amines to yield amide derivatives, which were deprotected by 4 M HCl to give compound **2**.

The chiral key compounds **2da** and **2db** were synthesized as shown in Scheme 2. Racemic ethyl thiazolidine-2-carboxylate was converted to optically active **6** (>99% ee) by crystallization induced dynamic resolution using L-tartaric acid.[12] (*S*)-Ethyl thiazolidine-2-carboxylate **6** treated with (*R*)-3-BocNH-4-(2,4,5-trifluorophenyl)butanoic acid in the presence of EDCI and DMAP to give the corresponding amide, which was hydrolyzed with LiOH to afford **7**. To complete the syntheses, 4-bromobenzonitrile reacted with D-valine **8** in the presence of copper iodide and K_3PO_4 in dimethylacetamide to afford compound **9**, which was reduced by nickel (II) chloride and sodium borohydride to give the corresponding amine which was protected with Boc_2O for purification and deprotected with 4 M HCl to give compound **10**. The compound **10** was then coupled with compound **7** to afford compound **11**, which was hydrolyzed by LiOH and deprotected with

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doi:10.1016/j.bmcl.2011.01.041

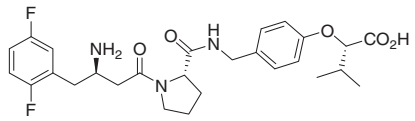


Figure 1. Merck's compound **1**.

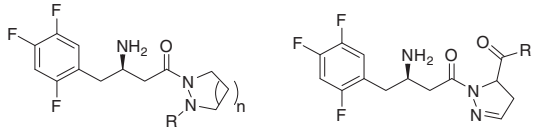
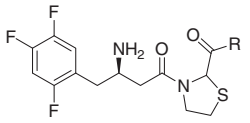
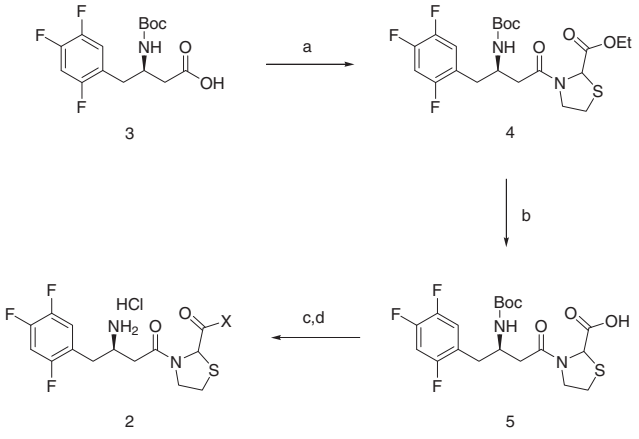


Figure 2. β-Aminoacyl derivatives discovered by the authors.



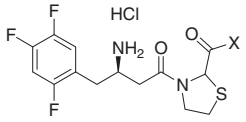
(2)

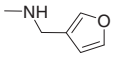
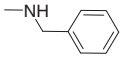
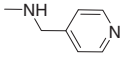
Figure 3. β-Aminoacyl-containing thiazolidine derivative.



Scheme 1. Reagents and conditions: (a) ethyl thiazolidine-2-carboxylate, EDCI, Et_3N, CH_2Cl_2, room temperature, 12 h; (b) LiOH, THF, H_2O, room temperature, 12 h; (c) amines, EDCI, Et_3N, CH_2Cl_2, room temperature, 12 h; (d) 4 M HCl, ethyl acetate, room temperature, 12 h.

Table 1
In vitro DPP-IV inhibition activity of β-aminoacyl thiazolidine derivatives



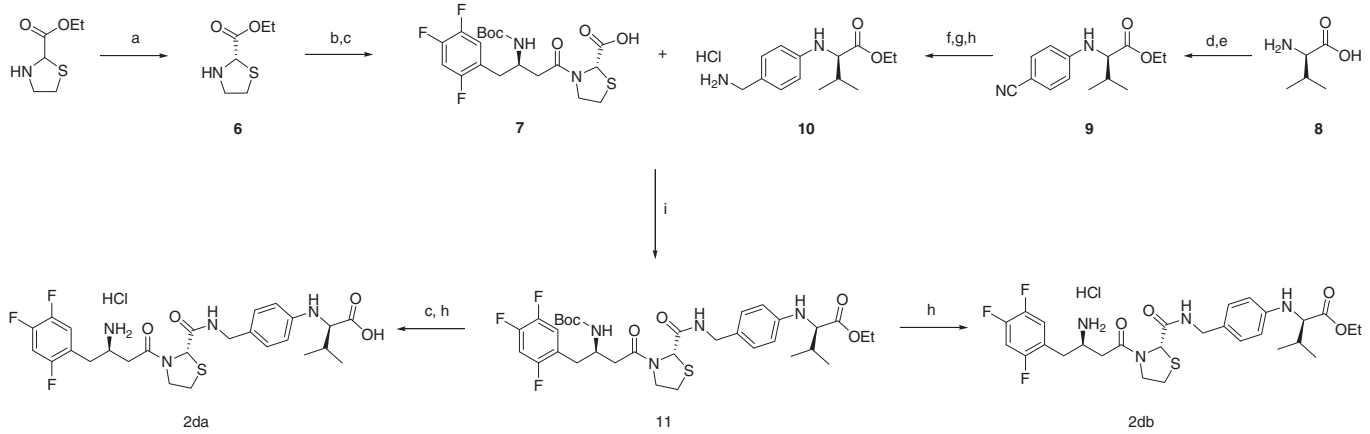
Compound	X	IC_{50}[a] (nM)
2a	OH	601
2b	OMe	204
2c	$NHCH_2CO_2H$	212
2d	$NHCH_2CO_2Et$	101
2e	$N(CH_3)_2$	1700
2f		807
2g		680
2h		88
2i		77
2j		357
MK-0431		20

[a] IC_{50} values were determined from direct regression curve analysis.

4 M HCl to give the final **2da**. Similarly, compound **11** was directly deprotected with 4 M HCl to afford final ester **2db**.

The β-aminoacyl containing thiazolidine derivatives were evaluated in vitro for DPP-IV inhibition, and the results are summarized in Table 1 through **5**. Sitagliptin (MK-0431) was used as a reference compound. β-Aminoacyl thiazolidine-2-carboxylic acid **2a** showed moderate inhibition activity with an IC_{50} value of 601 nM. Acid derivatives such as ester (**2b**) and amide (**2c** and **2d**) were 3–6-fold more potent than that of **2a**. However activities of N,N-disubstituted amides (**2e**, **2f**, and **2g**) were diminished. Arylalkyl amide derivatives (**2h** and **2i**) exhibited good in vitro activities with IC_{50} values in the range of 77–88 nM.

Based on the above data, we derivatized the benzyl group of **2i** with diverse substituents and their inhibitory activities are summarized in Table 2. Hydroxy (**2k**) or acid (**2l**) substituents showed moderate inhibitory activities with IC_{50} values in the range of 229–328 nM. *para*-Phenoxyacetic acid and ester derivatives (**2m** and **2n**) were active with IC_{50} values in the range of 41–51 nM.



Scheme 2. Reagents and conditions: (a) (i) L-tartaric acid, ethanol, diethyl ether, room temperature to 40 °C, 10 days; (ii) 10% sodium bicarbonate, diethyl ether, H_2O, 10 °C, 0.5 h; (b) (*R*)-3-BocNH-4-(2,4,5-trifluorophenyl)butanoic acid, room temperature, EDCI, DMAP, Et_3N, CH_2Cl_2, room temperature, 12 h; (c) LiOH, THF, MeOH, H_2O, room temperature, 3 h; (d) 4-bromobenzonitrile, K_3PO_4, CuI, dimethylacetamide, 90 °C, 48 h; (e) ethyl iodide, K_2CO_3, acetone, reflux, 2 h; (f) nickel (II) chloride, $NaBH_4$, ethanol, room temperature, 0.5 h; (g) Boc_2O, $NaHCO_3$, room temperature, 3 h; (h) 4 M HCl, dioxane, CH_2Cl_2, room temperature, 12 h; (i) EDCI, Et_3N, CH_2Cl_2, room temperature, 10 h.