European Journal of Medicinal Chemistry 90 (2015) 342–350

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design and synthesis of sulfonamide derivatives of pyrrolidine and piperidine as anti-diabetic agents

Radhika Sharma, Shubhangi S. Soman*

Department of Chemistry, Faculty of Science, The M. S. University of Baroda, Vadodara, Gujarat 390 002, India

ARTICLE INFO

Article history:
Received 23 June 2014
Received in revised form
20 October 2014
Accepted 21 November 2014
Available online 22 November 2014

Keywords:
Sulfonamide derivatives of pyrrolidine and piperidine
Type 2 diabetes
Anti-diabetic agents

ABSTRACT

Type 2 diabetes (T2D) is a lifestyle disease affecting millions of people worldwide. Various therapies are available for the management of T2D and dipeptidyl peptidase-IV (DPP-IV) inhibition has emerged as a promising therapy for the treatment of type 2 diabetes (T2D). Here we report design, synthesis and *in vitro* efficacy of sulfonamide derivatives of pyrrolidine and piperidine as anti-diabetic agents. Amongst all the compounds synthesized in this series, **9a**, is the most potent (IC_{50} = 41.17 nM).

1. Introduction

Dipeptidyl peptidase IV (DPP-IV, E.C.3.4.14.5, CD26) is a widely expressed serine protease found in many tissues and body fluids of mammals and exists either as a soluble enzyme or in a membrane bound form. It is primarily found on the vascular endothelium, epithelial cells of kidney, liver, intestine, pancreas, lymphoid and myeloid cells and contributes to the extracellular matrix binding [1,2]. It functions as a protease, cleaving dipeptides comprising of either proline or alanine at the penultimate position from the N-terminal of the peptide or protein [3,4].

Glucagon like peptide 1 (GLP-1) [5] and glucose dependent insulinotropic polypeptide (GIP) are incretin hormones, released from the gut in response to the food intake, responsible for the glucose dependent stimulation of insulin secretion through pancreatic β-cells [6–10]. Furthermore, GLP-1 slows gastric emptying, stimulates regeneration and differentiation of pancreatic β-cells while inhibiting glucagon secretion [11–14]. But the therapeutic effects of both these hormones are lost due to their rapid degradation ($t_{½}$ ~ 1 min) by DPP-IV [5,14,15] enzyme. Thus inhibition of DPP-IV has emerged as a novel approach for the treatment of type 2 diabetes (T2D) [16,17]. Owing to DPP-IV's substrate specificity, various proline mimetics have been explored as DPP-IV inhibitors as shown in Fig. 1.

Most of the DPP-IV inhibitors reported till date have been designed taking into account the N-terminal dipeptide residue of enzymatic substrate which comprises of a proline mimic, usually a cyanopyrrolidine at the P1 site, coupled with an additional amino acid or a similar substituted amino acid at the P2 site by formation of an amide bond as shown in Fig. 2.

Thus a common structural motif in the design of majority of DPP-IV inhibitors comprises of an L-amino acid surrogate, at the P1 site and an N-substituted glycine with a protonable amine, responsible for the enhanced potency of the inhibitor, at the P2 site [18]. From the previously reported structure activity relationship studies of various DPP-IV inhibitors with N-substituted glycylamide P2 site and a proline mimic usually 2*S*-cyanopyrrolidine at the P1 site results in the enhanced potency of the enzyme inhibitor. Some laboratories have even reported entities with sulfonamide at the P2 site, **1** (IC_{50} = 6.7 nM) [19] and **2** (K_i = 39 nM) [20], as potent DPP-IV inhibitors as shown in Fig. 3.

Here we report the design, synthesis and characterization of some novel sulfonamide derivatives of pyrrolidine and piperidine with application as anti-diabetic agents. All these molecules thus synthesized have been screened for *in vitro* DPP-IV inhibition.

* Corresponding author.
E-mail address: shubhangiss@rediffmail.com (S.S. Soman).

http://dx.doi.org/10.1016/j.ejmech.2014.11.041
0223-5234/

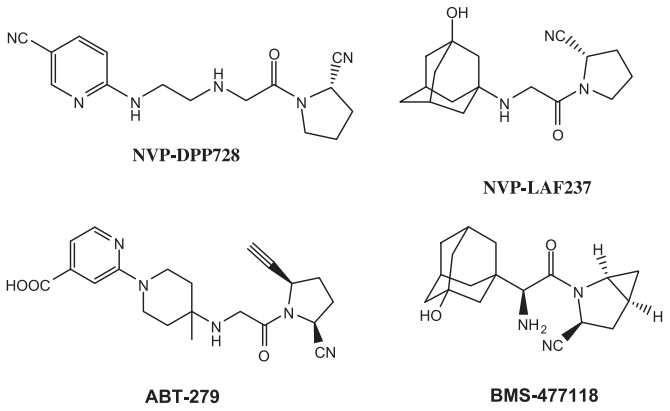

Fig. 1. Some proline mimetic DPP-IV inhibitors.

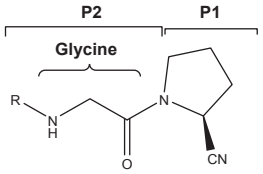

Fig. 2. General structure of DPP-IV inhibitors.

(EDCI), 1-hydroxybenzotriazole (HOBt) in DCM to give corresponding amide **8a**-**b**. The IR spectrum of **8a** showed two bands at 3346 and 3173 cm^{-1} for the −NH of two amide groups. The disappearance of peak at δ 8.89 in the ^1H NMR spectrum of **8a**, and appearance of two new peaks at δ 6.96 and 7.46 for $-NH_2$ protons, disappearing on D_2O exchange, thus confirmed the formation of **8a**. Addition of trifluoroacetic anhydride (TFAA) to a solution of **8a**-**b** in tetrahydrofuran (THF) leads to dehydration of the amide, thereby yielding nitrile **9a**-**b**. The IR spectrum of **9a** showed strong band at 2239 cm^{-1} for nitrile group. In the ^1H NMR spectrum of **9a**, the two peaks at δ 6.08 and 6.94 of **8a** for the $-NH_2$amide protons disappeared thus supported the formation of **9a**. Thereafter **9a**-**b** was reduced to its corresponding amine **10a**-**b** by lithium aluminium hydride (LAH). The formation of **10a** was confirmed from its ESI-MS spectrum. Reaction of amine **10a**-**b** with **5** gave **11a**-**b**, as shown in Scheme 1.

All the compounds were characterized by IR, ^1H NMR, ^{13}C NMR, ESI-MS and CHN analysis.

Attempts were made to synthesize molecules with substitution of amines other than those derived from proline at the P1 site while substituting sulfonamide at the P2 site.

For this purpose compound **7** was at first reacted with oxalyl chloride to give a reactive intermediate, acid chloride which on further reaction with methanol gave corresponding methyl ester **12** as shown in Scheme 2. The structure of **12** was confirmed from its

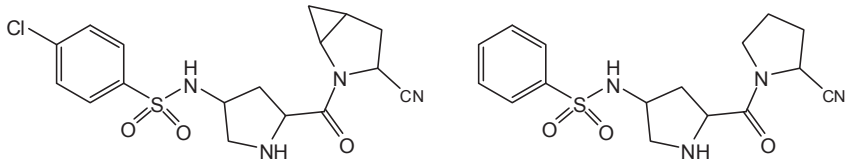

Fig. 3. Some sulfonamide containing DPP-IV inhibitors.

2. Results and discussion

2.1. Chemistry

Small molecule DPP-IV inhibitors have been synthesized using commercially available amino acids: L-proline amide, L-proline and piperidine-3-carboxylic acid. L-proline amide **3**, on reaction with chloroacetyl chloride gave (*S*)-1-(2-chloroacetyl)pyrrolidine-2-carboxamide **4**, which on dehydration with trifluoroacetic anhydride (TFAA) gave (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile **5**. The IR spectrum of **5** shows two strong bands at 2241 and 1656 cm^{-1} for the nitrile and amide groups respectively while its ^1H NMR spectrum showed a peak at δ 4.076 for the methylene protons of glycine and a multiplet at δ 4.69–4.71 for −CH proton of the cyanopyrrolidine thus confirming its structure.

Piperidine-3-carboxylic acid **6a** or L-proline **6b** on reaction with benzene sulfonyl chloride in (1:1) dichloromethane:water (DCM: H_2O), in the presence of sodium carbonate as base gave corresponding sulfonamide **7a** or **7b**. The structures of **7a** and **7b** were confirmed by its ^1H NMR which clearly showed presence of five aromatic protons at δ 7.54–7.79 along with aliphatic $-CH_2$ protons of piperidyl or pyrrolidyl ring from δ 1.65–3.83. A broad singlet at δ 8.89 indicated the presence of carboxylic acid proton which disappeared on formation of **8a**. The carboxylic acid group of **7a**, **7b** was then coupled with ammonium bicarbonate in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

IR spectrum which showed a band at 1726 cm^{-1} characteristic of carbonyl of the ester with the disappearance of a broad band at 3100–2500 cm^{-1} for the −OH of carboxyl group and the ^1H NMR spectrum wherein a peak at δ 8.98 for the −COOH proton of **7** disappears and a singlet at δ 3.59 for the $-OCH_3$ protons of the ester appears; ^{13}C NMR spectrum and also its ESI-MS spectrum with a peak at *m*/*z* 283.9 for $[M+H]^+$ confirmed the formation of methyl ester **12**. The methyl ester **12** on reduction with lithium aluminium hydride (LAH) yielded (1-(phenylsulfonyl)piperidin-3-yl)methanol **13**.

The IR spectrum of **13** showed absence of a band at 1726 cm^{-1} for the carbonyl of ester functionality while a strong band at 3531 cm^{-1} for the −OH group supported the structure of **13**. Also in the ^1H NMR spectrum of **13**wherein a multiplet at δ 3.50–3.60 for the two $-CH_2$ protons of methanol group was observed and ESI-MS spectrum showed a $[M+H]^+$ peak at *m*/*z* 256.0 thus confirmed formation of **13**. Reaction of **13** with methane sulfonyl chloride in the presence of base, triethylamine (TEA) gave **14**. The formation of **14** could be confirmed from its ^1H NMR spectrum wherein a singlet at δ 3.07 for the $-CH_3$ protons of the mesylate group was observed. The reaction of **14** with boc-de-protected glycylamide**17a**-**b** was unsuccessful. Hence the desired products **18a**-**b** could not be isolated.