Bioorganic Chemistry 79 (2018) 131–144

Contents lists available at ScienceDirect

Bioorganic Chemistry

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

Molecular modelling and synthesis of spiroimidazolidine-2,4-diones with dual activities as hypoglycemic agents and selective inhibitors of aldose reductase

Manar G. Salem, Yasmine M. Abdel Aziz, Marwa Elewa*, Hosam A. Elshihawy, Mohamed M. Said

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Suez Canal University, P.O. 41522, Ismailia, Egypt

ARTICLE INFO

Keywords:
Spiroimidazolidinedione
Hypoglycaemic agents
Aldose reductase
*In Silico*Prediction
Mixed pharmacophore

ABSTRACT

Novel derivatives of spiroimidazolidinedione were synthesized and evaluated as hypoglycemic agents through binding to sulfonylurea receptor 1 (SUR1) in pancreatic beta-cells. Their selectivity index was calculated against both aldehyde reductase (ALR1) and aldose reductase (ALR2). Aldehyde reductase is a key enzyme in the polyol pathway that is involved in the etiology of the secondary diabetic complications. All structures were confirmed by microanalysis and by IR, ^{1}H NMR, ^{13}C NMR and EI-MS spectroscopy. The investigated compounds were subjected to molecular docking and an *in silico* prediction study to determine their free energy of binding (ΔG) values and predict their physicochemical properties and drug-likeness scores. Compound 1′-(5-chlorothiophene-2-ylsulfonyl)spiro[cyclohexane-1,5′-imidazolidine]-2′,4′-dione showed IC_{50} 0.47 µM and 79% reduction in blood glucose level with a selectivity index 127 for ALR2.

1. Introduction

Diabetes mellitus is a metabolic disease characterized by a chronic increase in blood glucose level. This is mainly attributed to impaired insulin secretion by pancreatic β cells and insulin resistance in peripheral target tissues [1,2]. Sulfonylureas are common in the design of oral hypoglycemic agents such as tolazamide 1 and glibenclamide 2 [3,4]. These derivatives play a crucial role in the improvement of insulin secretion and the reduction of insulin resistance. They exert their action via several mechanisms including pancreatic ones through increasing insulin secretion from pancreatic beta-cells and the others are extra-pancreatic by improving insulin resistance in peripheral target tissues [5,6]. Despite numerous trials to control hyperglycemia, most diabetic patients still suffer from one or more of the long-term diabetic complications including retinopathy, nephropathy, neuropathy and cataract [7,8]. The enlarged glucose flux during the polyol pathway, which occurs in hyperglycemic conditions, is a potential factor in the onset and progression of such chronic complications (Fig. 1) [9,10]. Aldose reductase enzyme (ALR2, E.C.1.1.1.21) is the first and key enzyme involved in the polyol pathway. The main role of ALR2 is to catalyze the NADPH-dependent reduction of glucose to sorbitol. Aldose reductase inhibitors (ARIs), therefore, could be considered as a pharmacologically direct management for diabetic complications [11].

Various compounds have been designed to inhibit aldose reductase (AR) [12]. These compounds can be classified into two main categories, the first category comprises those containing a carboxylic acid moiety, for example, 3-thiazolidineacetic acid derivative, which has been reported to be a potent ARI with IC_{50} 9 nM [13]. The second category includes those based on a cyclic imide in the form of spirohydantoin such as sorbinil **3** [11]. The carboxylic acid inhibitors were found to be less potent than the spirohydantoin inhibitors *in vivo* [14]. This might be due to the higher ability of the carboxylic acid derivatives to ionize at physiological pH. Subsequently, these derivatives could not easily cross the biological membranes. Moreover, the selectivity of a specific aldose reductase (ALR) is crucial to avoid the undesirable side effects of non-selective inhibitors. Thus, the medication of choice should discriminate between aldehyde reductase (ALR1, EC 1.1.1.2) and aldose reductase (ALR2, EC 1.1.1.21), since, ALR1 is responsible for an important detoxification mechanism in the liver [15,16]. However, the structure of ALR1 has 65% homology with ALR2, however some differences in their respective active sites provide the basis for their selective inhibition [17,18]. The present work has aimed to design and synthesize a single medication that can control the plasma glucose level and also reduce adjunctive secondary diabetic complications via applying a mixed pharmacophore theory (Fig. 2) [19,20].

A literature survey showed that, in 2013, Iqbal et al. reported the design and synthesis of 3′-(4-chlorophenylsulfonyl)spiro[cycloheptane-1,5′-imidazolidine]-2′,4′-dione **4** with an IC_{50} value of 1.8 µM against

---

* Corresponding author.
E-mail address: marwa_elewa@pharm.suez.edu.eg (M. Elewa).

https://doi.org/10.1016/j.bioorg.2018.04.028
Received 22 March 2018; Received in revised form 30 April 2018; Accepted 30 April 2018

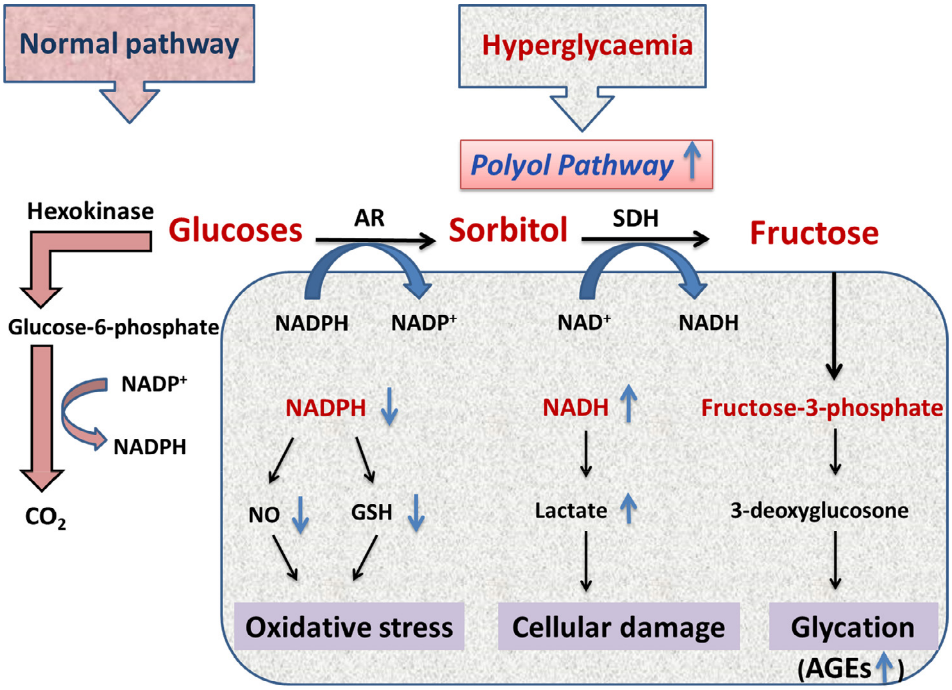

Fig. 1. A schematic interaction diagram elucidating the metabolism of glucose to sorbitol in polyol pathway by aldose reductase (AR) under hyperglycemic conditions [11]. **AGE**: Advanced glycated end product; **AR**: Aldose reductase; **GSH**: Glutathione; **SDH**: Sorbitol dehydrogenase.

ALR2 [21]. In 2015, they also found that 3′-(4-chlorophenylsulfonyl) spiro[fluorene-9,5′-imidazolidine]-2′,4′-dione **5** was 53-fold more selective towards ALR2 (with an IC_{50} value of 0.89 μM) compared with ALR1 [5]. In 2017, Andleeb et al. reported the design and synthesis of (*Z*)-4-((3-(2methoxyphenyl)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl-4-chlorobenzene-sulfonate **6** as an aldose reductase inhibitor with an IC_{50} value of 0.46 μM and 93-fold selectivity for ALR2 over ALR1 with no apparent potential for hypoglycemic activity [14]. Herein we assumed the optimization of the structure of these valuable candidates; compounds **4** and **5**. Therefore, this study has been focused on modifying spirohydantoin derivatives based on the enhancement of the binding affinity of the newly synthesized compound and improvement of its physicochemical properties according to Lipinski's “rule of five” “Ro5” [22–24]. This was applied through two main strategies. Strategy one was the design of various hydrophobic moieties attached to the spirohydantoin core particularly the flexible cyclohexanonyl ring and the rigid fluorenonyl one. Strategy two was studying different aryl and heteroaryl sulfonyl moieties and exploring their biological influence.

2. Results and discussion

2.1. Chemistry

Spiroimidazolidinedione derivatives **II** and **VI** were prepared as previously reported [5,25]. The synthetic procedures involved the reaction of 9-fluorenone **I** (Scheme 1, series A) and cyclohexanone **V** (Scheme 2, series B) with ammonium carbonate (NH_4CO_3) and potassium cyanide (KCN) in 50% aq. Ethanol [25]. 3-Arylsulfonyl derivatives **IIIa** and **IIIb** (series A) and **VIIa–d** (series B), respectively, were prepared via the coupling of compounds **II** and **VI** with various arylsulfonyl chlorides ($ArSO_2Cl$) in triethylamine (Et_3N) and dimethylaminopyridine (DMAP) in CH_2Cl_2 [26]. Compounds **IIIa**, **IIIb** and **VIIa–d** were further converted to their 1-arylsulfonyl analogues **IVa**, **IVb** and **VIIIa–d**, respectively using sodium hydride (NaH) under dry conditions (Schemes 1 and 2) [27].

The structures of the newly synthesized compounds were confirmed by microanalyses and spectral data (IR, ^1H NMR, ^{13}C NMR and EI-MS), which showed full agreement with their structures. The IR spectra showed bands for anti-symmetric and symmetric O=S=O absorptions in the range of 1350–1322 cm^{-1} and 1175–1140 cm^{-1}, respectively. The presence of a band for the N–H stretching in the range of 3400–3200 cm^{-1} also indicated the successful coupling between the aryl sulfonyl chloride derivatives and spirohydantoin compounds resulting in the synthesis of 3-arylsulfonylspiroimidazolidine-2,4-diones, **IIIa** and **IIIb** (series A) and **VIIa–d** (series B). The ^1H NMR spectra of compounds **IIIa**, **IIIb** and **VIIa–d** displayed singlets at 5.70–6.00 ppm. This peak referred to only one imidazolidinedione NH group and confirmed the successful coupling of the other NH moiety. The characteristic multiplets assigned to fluorenonyl protons appeared downfield at 7.15–8.08 ppm and hexanonyl protons upfield at 1.39–2.08 ppm. Compounds **IIIa** and **IVa** showed doublets assigned to thienyl protons at 6.41–7.04 ppm. Moreover, compounds **IIIb** and **IVb** displayed doublets assigned to the phenyl protons at 8.09–8.20 ppm. The ^{13}C NMR spectra showed signals for spiro[fluorene-9,5′-imidazolidine]-2′,4′-dione, phenyl, thienyl and spiro[cyclohexan-1,5′-imidazolidine]-2′,4′-dione rings at the expected regions. Additionally, the mass spectra of compounds **IIIa**, **IIIb**, **IVa** and **IVb** (series A) and for compounds **VIIa**, **VIIb**, **VIIIa** and **VIIIb** (series B) showed the presence of molecular ion peaks M^+ and their isotopes $M^+ + 2$, characteristic for sulfur and halogen-containing compounds. The ^1H NMR spectra of compounds **IVa** and **IVb** and compounds **VIIIa–d** confirmed the successful rearrangement by the appearance of the downfield singlets at 12.16–12.55 ppm assigned to the NH group at position 3. This was accompanied by the disappearance of the upfield singlets corresponding to the NH group at position 1 observed in the spectra of compounds **IIIa**, **IIIb** and compounds **VIIa–d**, respectively. Regarding series B, compounds **VIIb–d** and **VIIIb–d** displayed doublets assigned to the phenyl protons at 7.49–7.96 ppm. Furthermore, the ^1H NMR spectra of compounds **VIIc** and **VIIIc** are characterized by the appearance of singlets at 2.30 and 2.19 ppm, respectively, assigned to the protons of the methyl group. Concerning compounds **VIId** and **VIIId**, their ^1H NMR spectra are characterized by the appearance of singlets at 3.90 and 3.80 ppm, respectively, referred to the protons of the methoxy groups.