

Aromatic Heterobicyclics-Based Design of Aldose Reductase Inhibitors as Drug Candidates for the Treatment of Diabetic Complications

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Abstract

Aldose reductase (ALR2) plays a pivotal role in the development of diabetic complications. ALR2 inhibitors (ARIs) have proven efficient to prevent and delay the chronic diseases, and thus attracted significant research interest. This article reviews a series of aromatic heterobicyclics-based ARIs developed over recent years, and discusses about their structure-activity relationships as well as their multifunctionalities such as antioxidant property.

Introduction

Diabetes mellitus (DM) is associated to the abnormal metabolism of the glucose and is always characterized by long-term complications, such as neuropathy, nephropathy, cataracts, retinopathy [1]. In recent decades, DM is the major threat to human health all over the world and the situation is getting worse rapidly, as over 171 million people worldwide were suffering with this disease in 2000 and this figure is considered to grow more than twice and reach to 366 million by 2030 [2]. In fact, diabetic patients in China have reached 92 million in 2007, and even rocketed to 114 million in 2010 [3,4]. Furthermore, people with any kind of diabetes of sufficient duration, including both type 1 and type 2 diabetes mellitus, are vulnerable to these complications, which are the major distress for the diabetic patients. Increasing evidence demonstrated that aldose reductase (ALR2, EC, 1.1.1.21) plays a pivotal role in development of chronic diabetic complications, as this enzyme accompanied with sorbitol dehydrogenase forms the polyol pathway of glucose metabolism, which supposed to be the main pathogenesis of diabetic complications. In the pathway (Figure 1), the glucose is firstly reduced to sorbitol by ALR2 catalysis with NADPH as coenzyme, and then sorbitol dehydrogenase converts sorbitol into fructose with reduction of NAD⁺ [5-7]. (Figure1)

Normally, ALR2 has a low activity and only a small amount of the glucose is metabolized through this pathway. In hyperglycemia, however, ALR2 is activated and one third of the total metabolic glucose turns to the alternative polyol pathway, which leads to the accumulation of sorbitol in tissues possessing insulin-independent uptake of glucose, such as kidney, lens, retina, peripheral nerves [1,5]. Sorbitol is hardly excreted across cell membranes due to strong polarity, and therefore its intracellular accumulation would lead to osmotic imbalance, cell swelling, and changes of membrane permeability, mainly in lens. Also, the abnormal level of NADPH and NAD⁺ caused by the polyol pathway would induce modification in cellular redox potentials, and unconventionally activated enzymes such as nitric oxide synthase (NOS) and glutathione reductase would give rise to the cellular oxidative stress. As a consequence, the imbalance between increased production of radical oxygen species (ROS) and reduced intracellular antioxidant

defense occurs [5]. Furthermore, the increased accumulation of advanced glycation-end products (AGEs) aroused by the enhanced level of glycating agents would cause other pathological alteration in the functions of intracellular proteins and result in further accumulation of ROS [8]. All these stress responses evoked by the activated ALR2 in down-stream of the polyol pathway have also been proposed to form pathogenic mechanisms of the multiple diabetic complications. Therefore, suppression of the ALR2 activity and further oxidative stress, particularly ALR2 inhibitors (ARIs) having antioxidant property, could be an efficient strategy to prevent or delay the progression of diabetic complications.

In the recent few years, the aromatic heterobicyclic structures including benzothiadiazine, pyridythiadiazine, benzothiazine, and quinoxalinone have been found to be excellent framework for the ARI drug design, which led to a number of novel and potent series 1-7 (Figure 2) [2,8-16] as promising drug candidates for the treatment of diabetic complications. (Figure 2)

Table 1 shows the specific structure and inhibitory activity data of representative samples of each heterocyclic scaffold. Obviously, potent ARIs have been obtained in each of the core structure indicating these

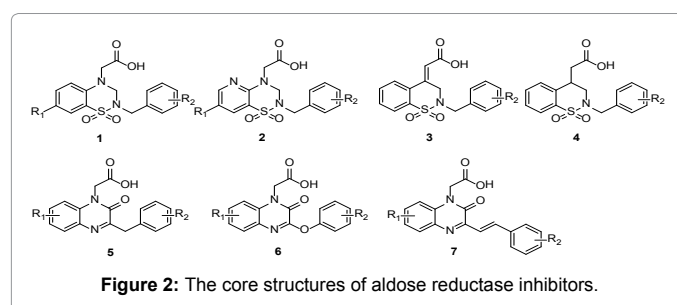


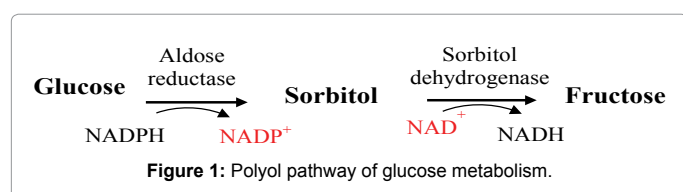
Figure 2: The core structures of aldose reductase inhibitors.

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Compd.	Substituent		IC ₅₀ (nM) ^a for ALR2
	R ₁	R ₂	
1a [2]	H	2-F,4-Br	125
1b [2]	F	2-F,4-Br	90
1c [2]	Cl	2-F,4-Br	41
1d [2]	Br	2-F,4-Br	71
1f [2]	H	2,4,5-F ₃	111
1g [2]	F	2,4,5-F ₃	66
1h [2]	Cl	2,4,5-F ₃	32
1i [2]	Br	2,4,5-F ₃	52
1j [2]	F	4-CF ₃	931
1k [2]	Cl	4-CF ₃	595
2a [16]	CH ₃	2-F,4-Br	127
2b [16]	Cl	2-F,4-Br	44
2c [16]	Br	2-F,4-Br	69
2d [16]	CH ₃	2,4,5-F ₃	84
2e [16]	Cl	2,4,5-F ₃	38
2f [16]	Br	2,4,5-F ₃	69
2g [16]	Cl	4-CF ₃	1010
2h [16]	Cl	4-OCH ₃	6540
3a [15]	H	2,4,5-F ₃	590
3b [15]	H	2-F,4-Br	110
4a [15]	H	2,4,5-F ₃	340
5a [13]	H	2-F,4-Br	35
5b [13]	7-Cl	2-F,4-Br	10
5c [13]	7-F	2-F,4-Br	6.4
5d [13]	6-Cl	2-F,4-Br	59
5e [13]	7-Cl	4-Br	23
6a [14]	H	2-F,4-Br	45
6b [14]	7-F	2-F,4-Br	23
6c [14]	H	4-Br	27
6d [14]	7-F	4-Br	11

^a IC₅₀ values represent the concentration required to produce 50% enzyme inhibition

Table 1: The biological activity of ARIs.

scaffolds are in favor of designing ARIs that could intensively interacted with ALR2. Particularly, the samples **1h**, **2b**, **3b**, and **5c** (IC₅₀=32, 44, 110, and 6.4 nM, respectively) are the most active compounds to the relevant core. Comparison of the scaffolds to each other indicates that the quinoxalinone may be the core promising for further ARI developments when **5b** (IC₅₀=10 nM) in the quinoxalinone series is found to have the ALR2 inhibition greater than its counterparts **1c** (IC₅₀=41 nM) and **2b** (IC₅₀=44 nM) in benzothiadiazine and pyridythiadiazine series, respectively (Table 1).

For ARIs based on the present scaffolds, the aromatic side chains including benzyl and phenoxy groups are the other crucial factor besides the typical carboxylate side chain, which has long been the most important group [17]. Benzyl groups as the side chains in the case of quinoxalinone series seem to have more impact on the inhibitory activity against ALR2 than phenoxy groups as comparing the compounds **5c** (IC₅₀=6.4 nM) and **6b** (IC₅₀=23 nM) as shown in Table 1, but this effect is depending on substituents both at aromatic rings of the side chain and scaffold. Moreover, longer length of carbon chain spacer of the side chain leads to increase in the potency of quinoxalinone ARIs [8,13].

At the aromatic ring of side chains in all series in this review,

groups of 2-F,4-Br, 2,4,5-F₃, or 4-Br proved to be preferred substituents whereas the bulky groups of trifluoromethyl and methoxyl had negative substitution effect as comparing **2b** (IC₅₀=44 nM) with **2g** (IC₅₀=1010 nM) and **2h** (IC₅₀=6540 nM). At the aromatic ring of the scaffold, halogens including chloro and bromo are always better substituents than methyl group. However, bulky hydrophobic substituents were found to be favorable for enhancing the ARI activity, and the flexible amide group as one of the substituents could significantly enhance the activity but also selectivity [18].

In the benzothiazine series including compounds **3-4**, the orientation of the carboxylic acid head is likely to have a strong influence on the interaction between the ALR2 and inhibitors. Z-isomers of **3** is more active than E-isomers, [11] while R(-)-enantiomers of **4** (IC₅₀=500 M) than S-(+)-enantiomers (IC₅₀=4150 nM) [10,19] (Table 2).

In order to obtain multifunctional ARIs having antioxidant property, phenolic hydroxyl groups have been introduced to the aromatic ring of the side chain in the quinoxalinone series as shown in Table 2. Hydroxyl substituted phenoxy side chains integrated good antioxidant activity to ARIs. However, more success resulted from the key strategy by the use of vinyl group as the spacer in combination with the phenolic hydroxyl in the side chain because the products may be more potent in the ALR2 inhibition and antioxidation. These efforts led to achievement of a number of ARIs showing significant antioxidant activity by testing their DPPH radical scavenging rate. Of them, **6g** and **7c** are excellent both in the ALR2 inhibition and antioxidant activity. Particularly, the antioxidant activity of **7c** was also confirmed by testing its inhibition of lipid peroxidation in vivo using animal models [8,9].

In summary, the aromatic heterobicyclics of benzothiadiazine, quinoxalinone, and their analogues have been proved effective scaffolds for the design of ARIs, and in particular quinoxalinone is excellent for the construction of multifunctional ARIs having antioxidant property. However, all these designed inhibitors are in the carboxylate ARI class, which has a shortcoming of poor tissue penetration resulting in poor distribution from blood to the tissues and then in pharmacokinetic drawbacks and even low in vivo efficacies [20]. Therefore, new design of non-carboxylate series of ARIs based on these frameworks may be expected.

Compd.	Substituent			IC ₅₀ (nM) _{ALR2} ^a	DPPH sca. %	
	R ₁	R ₂	X		100μM	50μM
6e [9]	6-F	4-OH	O	20	23.7	b
6f [9]	7-Cl	4-OH	O	179	84.8	47.3
6g [9]	7-Cl	3,5-(OH) ₂	O	566	91.3	83.7
7a [8]	H	4-OH	CH ₂ =CH ₂	182	71.8	55.8
7b [8]	7-F	4-OH	CH ₂ =CH ₂	153	67.2	45.7
7c [8]	H	3-OCH ₃ ,4-OH	CH ₂ =CH ₂	419	95.4	68.8
epalrestat				91	b	b
Trolox				b	98.2	90.2

^a IC₅₀ values represent the concentration required to produce 50% enzyme inhibition.

^b Not determined.

Table 2: Biological activity of multifunctional ARIs based on quinoxalinones.

References

1. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. *Nature* 414: 813-820.
2. Chen X, Zhu C, Guo F, Qiu X, Yang Y, et al. (2010) Acetic acid derivatives of 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide as a novel class of potent aldose reductase inhibitors. *J Med Chem* 53: 8330-8344.
3. Yang W, Lu J, Weng J, Jia W, Ji L, et al. (2010) Prevalence of diabetes among men and women in China. *N Engl J Med* 362: 1090-1101.
4. Xu Y, Wang L, He J, Bi Y, Li M, et al. (2013) Prevalence and control of diabetes in Chinese adults. *JAMA* 310: 948-959.
5. Maccari R, Vitale RM, Ottanà R, Rocchiccioli M, Marrazzo A et al. (2014) Structure-activity relationships and molecular modelling of new 5-arylidene-4-thiazolidinone derivatives as aldose reductase inhibitors and potential anti-inflammatory agents. *European Journal of Medicinal Chemistry* 81: 1-14.
6. Ramana KV, Srivastava SK (2010) Aldose reductase: a novel therapeutic target for inflammatory pathologies. *Int J Biochem Cell Biol* 42: 17-20.
7. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, et al. (2006) Long-Term Clinical Effects of Epalrestat, an Aldose Reductase Inhibitor, on Diabetic Peripheral Neuropathy: The 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care* 29: 1538-1544.
8. Qin X, Hao X, Han H, Zhu S, Yang Y, et al. (2015) Design and synthesis of potent and multifunctional aldose reductase inhibitors based on quinoxalinones. *J Med Chem* 58: 1254-1267.
9. Zou Y, Qin X, Hao X, Zhang W, Yang S, et al. (2015) Phenolic 4-hydroxy and 3,5-dihydroxy derivatives of 3-phenoxyquinoxalin-2(1H)-one as potent aldose reductase inhibitors with antioxidant activity. *Bioorg Med Chem Lett* 25: 3924-3927.
10. Parveen S, Hussain S, Qin X, Hao X, Zhu S, et al. (2014) Copper-catalyzed asymmetric synthesis and comparative aldose reductase inhibition activity of (+)/(-)-1,2-benzothiazine-1,1-dioxide acetic acid derivatives. *Journal of Organic Chemistry* 79: 4963-4972.
11. Shagufta P, Saghir H, Shaojuan Z, Xiangyu Q, Xin Hao, et al. (2014) Selective synthesis and comparative activity of olefinic isomers of 1,2-benzothiazine-1,1-dioxide carboxylates as aldose reductase inhibitors. *Rsc Advances* 4: 21134-21140.
12. Hussain S, Parveen S, Hao X, Zhang S, Wang W, et al. (2014) Structure-activity relationships studies of quinoxalinone derivatives as aldose reductase inhibitors. *European Journal of Medicinal Chemistry* 80: 383-392.
13. Wu B, Yang Y, Qin X, Zhang S, Jing C, et al. (2013) Synthesis and structure-activity relationship studies of quinoxaline derivatives as aldose reductase inhibitors. *ChemMedChem* 8: 1913-1917.
14. Yang Y, Zhang S, Wu B, Ma M, Chen X, et al. (2012) An efficient synthesis of quinoxalinone derivatives as potent inhibitors of aldose reductase. *ChemMedChem* 7: 823-835.
15. Chen X, Zhang S, Yang Y, Hussain S, He M, et al. (2011) 1,2-Benzothiazine 1,1-dioxide carboxylate derivatives as novel potent inhibitors of aldose reductase. *Bioorg Med Chem* 19: 7262-7269.
16. Chen X, Yang Y, Ma B, Zhang S, He M, et al. (2011) Design and synthesis of potent and selective aldose reductase inhibitors based on pyridylthiadiazine scaffold. *Eur J Med Chem* 46: 1536-1544.
17. Kador PF, Kinoshita JH, Sharpless NE (1985) Aldose reductase inhibitors: a potential new class of agents for the pharmacological control of certain diabetic complications. *J med chem* 28: 841-849.
18. Zhang S, Chen X, Parveen S, Hussain S, Yang Y, et al. (2013) Effect of C7 modifications on benzothiadiazine-1,1-dioxide derivatives on their inhibitory activity and selectivity toward aldose reductase. *ChemMedChem* 8: 603-613.
19. Hao, X, Qin X, Hussain S, Parveen S, Zhang W, et al. (2015) Chiral resolution, determination of absolute configuration, and biological evaluation of (1,2-benzothiazin-4-yl)acetic acid enantiomers as aldose reductase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry* 30: 846-851.
20. Mylari BL, Armento SJ, Beebe DA, Conn EL, Coutcher JB, et al. (2005) A novel series of non-carboxylic acid, non-hydantoin inhibitors of aldose reductase with potent oral activity in diabetic rat models: 6-(5-chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one and congeners. *J Med Chem* 48: 6326-6339.