Study on Aldose Reductase Inhibitors Based on Quinoxalin Structure

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Abstract. The purpose of this study is to design and synthesize a multifunctional aldose reductase inhibitor with both aldose reductase inhibitory activity and direct antioxidant activity. Based on the quinoxalin structure, we modify side chain of C3-N1. Specifically, the activity of N-1 is further enhanced by the introduction of carboxyl group. And the hydroxy phenol was introduced to the C-3 position. And then test external biological activity to confirm its reductase inhibition and inoxidizability. Finally, the synthetic compounds were analyzed and demonstrated by molecular simulation. The target compound had an aldose reductase IC50 of 26.5 nM. Also we use the software of Molecule docking to explain the rationality of the design.

1. Introduction

Diabetes is a metabolic disorder syndrome which is caused by a variety of genetic and environmental causes, and it is characterized by chronic hyperglycemia. In the persistent state of hyperglycemia, the body will inevitably induce a variety of complications and these complications often pose a great threat to human health, seriously affecting people's normal life [1]. The enzyme aldose reductase (ALR2) is thefi rst rate-determining enzyme in the polyol pathway and catalyzes the reduction of glucose to sorbitol in the presence of NADPH as a cofactor (Figure 1) [2-4]. Aldose reductase inhibitors can effectively inhibit the accumulation of sorbitol, thereby indirectly inhibiting the body's oxidative stress. Therefore, the purpose of this study is to design and synthesize an aldose reductase inhibitor with both aldose reductase inhibitory activity. The molecular docking simulation shows that only the side groups in the side chain can be well matched with the cavities on the aldose reductase protein only when the side chains are grafted at the N1-C3 positions.

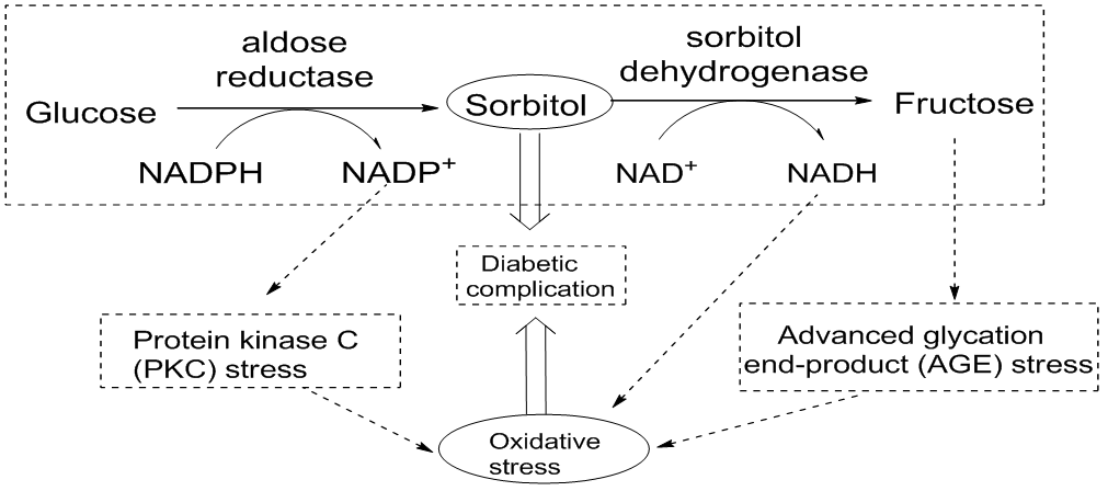

Figure 1. Polyol pathway of glucose metabolism and pathogenesis of diabetic complications.

2. Design and Synthesis of the Target Compound

Research ideas as shown in Figure 2. quinoxalin as the mother nucleus, the N1 position is configured to connect the hydrogen bond donor - acceptor group -CH2COOH, C3 position coupled to the p-hydroxyphenol.

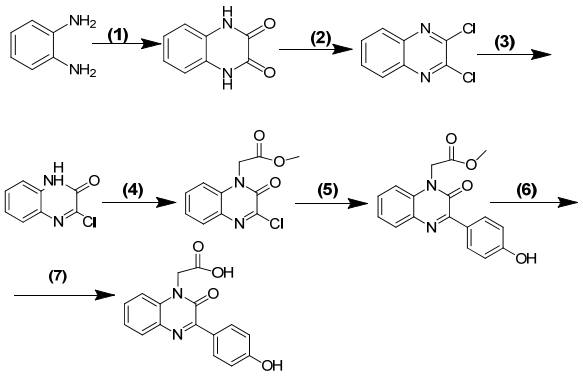

Figure 2. Synthesis of quinoxalinone derivatives

3. Aldose Reductase Inhibitory Activity of Compounds

The aldose reductase inhibitory property of the compounds are the primary method of evaluating the activity of a compound. In the reaction system, the substrates D, L-glyceraldehyde and D-glucuronide are respectively reduced to glycerol and glucose under the action of ALR2 and its coenzyme NADPH. Coenzyme NADPH due to participation in the reaction, the concentration will decrease with the progress of the reaction, and its absorbance will be smaller. We use UV to monitor the change. of NADPH absorbance to monitor the progress of the reaction. The measurement procedure is shown in Table 1.

Table 1. Test steps of aldose reductase activity

Solution	Reference tube	Sample tube
Buffer	0.50	0.25
Distilled water	0.15	0.15
ALR2	0.10	0.10
NADPH solution	0.25	0.25
Compound	0.005	0.005
D, L-glyceraldehyde	----	0.25
Total	1.00	1.00

When testing compound inhibition rates, four concentrations are typically tested. The percent inhibition of enzyme inhibition is calculated as follows. First, absorbance A is plotted on the vertical axis and time t is plotted on the horizontal axis. Based on the UV data for the first 5 minutes of the test, each absorbance corresponds to one absorbance. In the coordinate system shown as a point (two-dimensional coordinates), all the points obtained for linear regression, you can get a straight line , the absolute value of the slope of the line is the enzyme activity.

As shown in Fig. 3, the percent inhibition is expressed as I%. The slope of the linear equation for linear regression of the enzyme activity is I0. The slope of the linear equation of the linear regression after addition of the compound is Ix.

$$I\% = (I_0 - I_X/I_0) \times 100\% \quad (1)$$

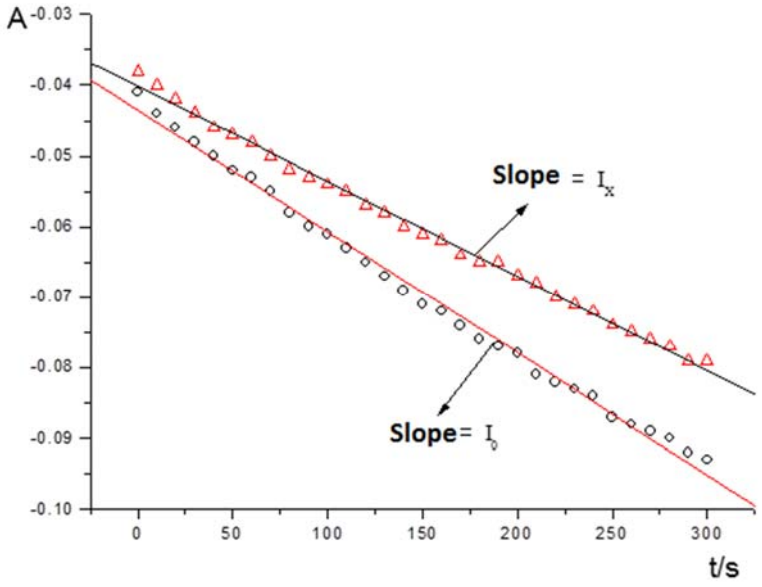

Figure 3. Linear regression of enzyme activity

As shown in Fig. 4, based on the percent inhibition of the four concentrations obtained from the test, different concentrations were selected on the horizontal axis and the percentages of inhibition were plotted on the vertical axis for linear regression to obtain a straight line, . When y = 50%, find the corresponding x value, the logarithm of the logarithm of the concentration value, is the IC50 value.

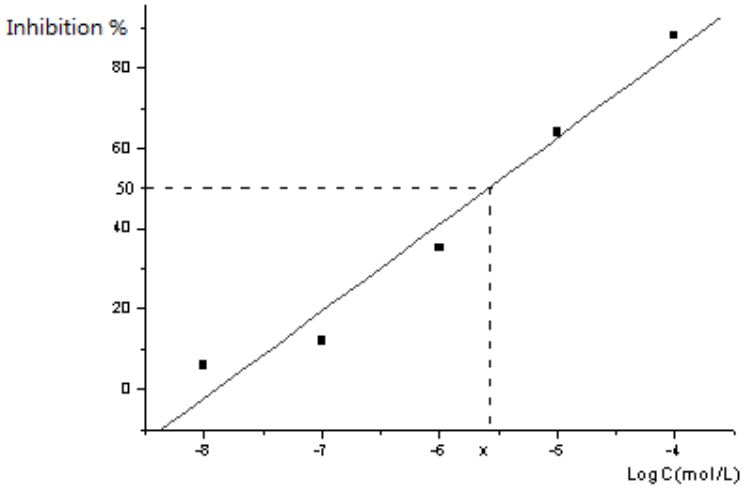

Figure 4. Inhibition rate linear regression line

4. Molecular Docking Simulation

Won Suck Sun et al.[5] used molecular docking to simulate a series of carboxylic acid compounds as the interaction of ARIs with ALR2. Drawing on the experience, this article simulated the docking of the target compound molecule with the aldose reductase molecule. The results are shown in Figure 5.

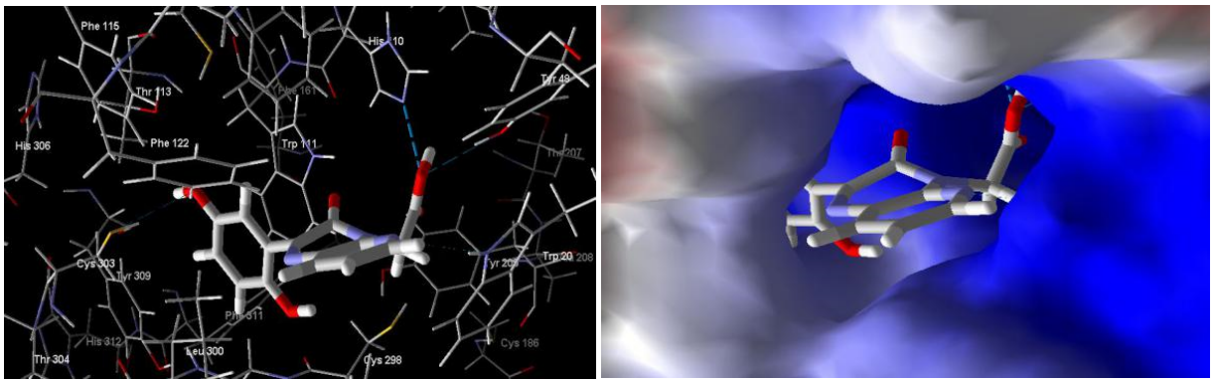

Figure 5. Docking simulation of target compound molecule and enzyme ALR2

From Figure 5. we can see that the oxygen atom of the carboxy group of compound can form hydrogen bonds with the amino acid residues His110, Tyr48 and Trp20 of the hydrophilic active region of ARL2, so that it can well insert these three amino acid residues. The formation of these interactions described above demonstrates that Compound has good binding ability to ALR2 and explains the reason why Compound has high enzyme inhibitory activity.

5. Conclusion

In this paper, a new aldose reductase inhibitor was synthesized and has good aldose reductase inhibitory activity. The molecular docking experiment further proves the design rationality of the target compound. The compound is expected to become a drug for the prevention and treatment of diabetic complications.

Acknowledgements

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