Bioorganic & Medicinal Chemistry Letters 27 (2017) 4760–4764

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Quinazolinone-based rhodanine-3-acetic acids as potent aldose reductase inhibitors: Synthesis, functional evaluation and molecular modeling study

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ARTICLE INFO

Article history:
Received 19 July 2017
Revised 20 August 2017
Accepted 22 August 2017
Available online 24 August 2017

Keywords:
Rhodanine-3-acetic acids
Aldose reductase inhibitors
Molecular modeling

ABSTRACT

A series of quinazolinone-based rhodanine-3-acetic acids was synthesized and tested for in vitro aldose reductase inhibitory activity. All the target compounds displayed nanomolar activity against the target enzyme. Compounds **3a**, **3b**, and **3e** exhibited almost 3-fold higher activity as compared to the only marketed reference drug epalrestat. Structure-activity relationship studies indicated that bulky substituents at the 3-phenyl ring of the quinazolinone moiety are generally not tolerated in the active site of the enzyme. Insertion of a methoxy group on the central benzylidene ring was found to have a variable effect on ALR-2 activity depending on the nature of peripheral quinazolinone ring substituents. Removal of the acetic acid moiety led to inactive or weakly active target compounds. Docking and molecular dynamic simulations of the most active rhodanine-3-acetic acid derivatives were also carried out, to provide the basis for further structure-guided design of novel inhibitors.

The incidence of diabetes mellitus has markedly increased over the last century due to changes in human life style and behavior.[1] Estimates indicate that about 400 million patient worldwide are affected by diabetes and by the year 2030, about 10% of world population will suffer from this chronic disease.[2] More importantly, the management of the debilitating complications associated with diabetes costs at least 10% of overall healthcare cost in many countries.[3] For these reasons, the discovery and development of drugs for prevention and treatment of diabetic complications will remain a major challenge to medicinal chemists. In this context, there has been a growing interest over the last few decades in aldose reductase inhibitors as therapeutic candidates for diabetic complications.[4–26] Aldose reductase (ALR-2) is the key enzyme of the polyol pathway through which glucose is metabolized under conditions of hyperglycemia associated with diabetes. In the polyol pathway, glucose is reduced by aldose reductase to sorbitol with the associated oxidation of NADPH to NADP. The accumulation of sorbitol in cells leads to osmotic stress. The second step in the polyol pathway involves the oxidation of sorbitol to fructose by the enzyme sorbitol dehydrogenase using NAD^+ as a cofactor. Alteration of the proportion of cytosolic NADH to NAD^+ results in oxidative stress which is associated with reduced intracellular concentrations of glutathione, activation of protein kinase C, and non-enzymatic glycation.[27,28] Aldose reductase inhibitors are categorized into two major classes: acetic acid derivatives and the cyclic imides. The acetic acid derivatives currently available include epalrestat, tolrestat, zenarestat, and ponalrestat. The cyclic imides include the hydantoins and their bioisosteres such as the rhodanines, 2,4-thiazolidinediones, and the succinimides. Sorbinil, fidarestat, and imirestat are hydantoins whereas, ranirestat and minalrestat belong to the succinimides. (Chart 1). Unfortunately, many of these agents were unsuccessful in clinical trials due to poor pharmacokinetics, adverse effects, or low efficacy. Only epalrestat, which is a rhodanineacetic acid derivative, was approved for clinical use in Japan, China and India.[29] Long-term studies have revealed that epalrestat is generally well tolerated with only mild side effects such as nausea, vomiting, and elevation of liver enzyme levels.[16,30–34] These findings urged us to address novel rhodanineacetic acid derivatives as potential useful therapeutic candidates for the management of diabetic complications. In the present investigation, a series of quinazolinone-based

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http://dx.doi.org/10.1016/j.bmcl.2017.08.050
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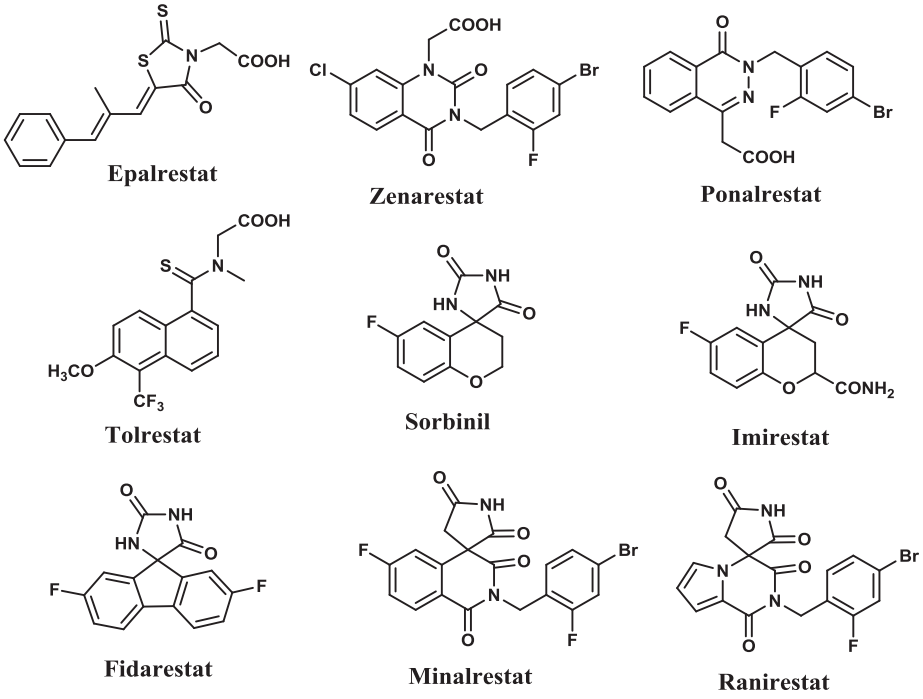
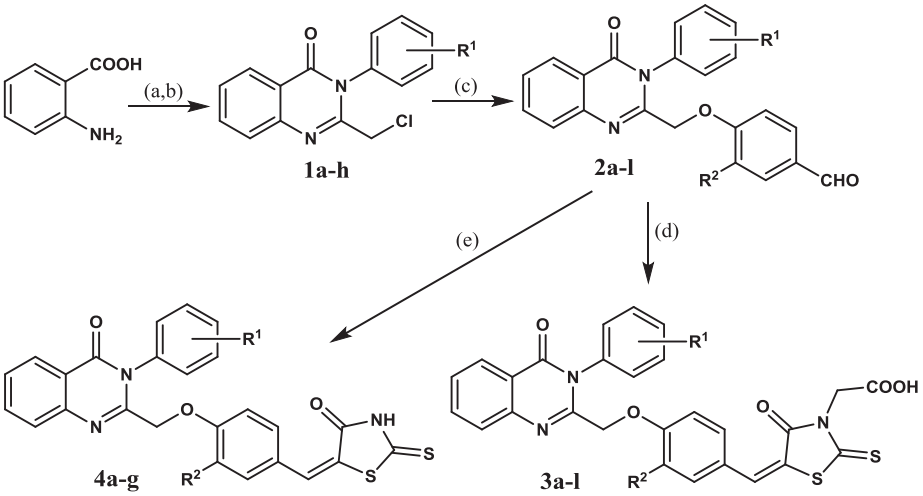


Chart 1. Chemical structure of available aldose reductase inhibitors.

rhodanineacetic acid derivatives was designed, synthesized, and tested for *in vitro* aldose reductase inhibitory activity. Another series of representative rhodanines lacking the acetic acid moiety was also tested for comparison purposes.

A straightforward synthetic pathway was adopted to synthesize the target compounds as outlined in Scheme 1. The starting chloromethylquinazolinones (**1a**–**h**) were synthesized from anthranilic acid in two steps following reported procedures.[35–38] The first step involves chloroacetylation of anthranilic acid using chloroacetyl chloride in dry benzene under reflux conditions. In the second step, cyclization to the desired chloromethylquinazolinones was achieved by direct reaction of the *N*-chloroacetyl anthranilic acid derivatives with the appropriate anilines in presence of phosphorous oxychloride as a condensing agent in dry toluene. Subsequently, 4-hydroxybenzaldehyde or vanillin was alkylated with the chloromethylquinazolinones (**1a**–**h**) in refluxing acetonitrile under the basic conditions of potassium carbonate and in the presence of potassium iodide to afford the aldehydes (**2a**–**l**) in good yields as previously reported by us.[39] The title rhodanineacetic acids (**3a**–**l**) were obtained in fair yields via Knoevenagel-type condensation of the aldehydes with rhodanine-3-acetic acid in refluxing acetic acid using β-alanine as a condensing agent. On the other hand, compounds **4a**–**g** were obtained by condensation of the appropriate aldehyde with rhodanine in the presence of sodium acetate. Structures of all the target compounds were fully characterized by means of ^{1}H and ^{13}C NMR spectroscopy and their purity were satisfactorily confirmed by elemental analysis.

All the novel synthesized compounds were tested *in vitro* for their aldose reductase inhibitory activity following standard



Scheme 1. Reagents and conditions: (a) Chloroacetyl chloride, benzene, reflux, 3 h. (b) Substituted aniline, $POCl_3$, toluene, 115 °C, 3 h. (c) 4-Hydroxybenzaldehyde or vanillin, K_2CO_3, KI, acetonitrile, reflux, 3 h. (d) Rhodanine-3-acetic acid, β-alanine, glacial acetic acid, 100 °C, 3 h. (e) Rhodanine, sodium acetate, glacial acetic acid, reflux, 24–48 h.