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Search for non-acidic ALR2 inhibitors: Evaluation of flavones as targeted agents for the management of diabetic complications

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ABSTRACT

Diabetic complications (DC) follow multiple pathophysiological pathways and one of the key pathways is the polyol pathway which involves the metabolism of glucose via aldose reductase (ALR2) and sorbitol dehydrogenase (SDH). ALR2 inhibitors such as epalrestat has already been established as promising candidates for the management of DC. On the basis of pathophysiological understanding of polyol pathway, simultaneous inhibition of ALR2 and SDH may be expected to provide synergistic outcomes in the treatment strategies for DC. Thus, in this study, dual inhibitors of ALR2 and SDH were identified using pharmacophore-based virtual screening. For this purpose, the pharmacophore model for SDH (model ID: AAADH.343) was generated and validated. For screening against ALR2, the pharmacophore model (model ID: AADRR.1109) which was previously reported by our group was applied. Initially, flavones reported by our research group were screened by those two pharmacophore models to obtain hits with an optimum affinity for the catalytic domain of both ALR2 and SDH. Inhibitory potential of identified hits for ALR2 and SDH were then experimentally determined using enzymatic assays reported in the literature. Additional focus was laid on the selectivity of the designed molecules towards ALR2 over ALR1, thus evaluation against ALR1 was also performed. Overall, four molecules **FLV-2, FLV-11, FLV-12,** and **FLV-15** were found to possess significant dual inhibitory activity against ALR2 and SDH, with selectivity over ALR1. Among them, **FLV-2** displayed significant dual inhibitory potential with an IC_{50} value of 0.689 ± 0.018 μM and 0.174 ± 0.003 μM against ALR2 and SDH respectively with a selectivity index of 52.902 to ALR2 over ALR1.

1. Introduction

Diabetes mellitus (DM) is one of the major chronic metabolic diseases observed in the developed countries and the ninth major cause of death worldwide [1]. According to the national diabetes statistics report, about 23 million US adults (1.3 million with type 1 diabetes and 21.0 million with type II diabetes) have been diagnosed with diabetes [2]. Chronic hyperglycemia in DM is associated with microvascular and macrovascular pathological complications [3,4], which are recognized as a common clinical problem and contribute to diabetic distress [5]. Large prospective clinical studies have shown a strong relationship between hyperglycemia and diabetic microvascular complications in both type 1 and type 2 diabetes [6]. The correlation between glucose metabolism via the polyol pathway (downstream pathways) and long-term DC is also well established. Under hyperglycemic conditions, there is an increase in the flux of glucose through the polyol pathway that is mediated by two enzymes i.e. ALR2 and SDH. ALR2, the first and rate-limiting enzyme, reduces glucose to sorbitol using NADPH (Nicotinamide adenine dinucleotide phosphate) as a cofactor whereas sorbitol dehydrogenase (SDH) oxidizes resulting sorbitol to fructose using cofactor NAD^+ [7]. Overall, this increased flux of polyol pathway by over-activated ALR2 and SDH create an imbalance between NADPH/$NADP^+$ and NADH/NAD^+ ratio that subsequently increases the oxidative stress. The accumulated sorbitol also leads to swelling and cellular dysfunction in a number of tissues. Additionally, excessive fructose upon phosphorylation is broken down into 3-deoxyglucosone, resulting in the formation of advanced glycation end products (AGEs) which also cause cell damage [8]. These abnormal metabolic by-products have been

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