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Aldose reductase inhibitors for diabetic complications: Receptor induced atom-based 3D-QSAR analysis, synthesis and biological evaluation

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ABSTRACT

Herein, atom-based 3D-QSAR analysis was performed using receptor-guided alignment of 46 flavonoid inhibitors of aldose reductase (ALR2) enzyme. 3D-QSAR models were generated in PHASE programme, and the best model corresponding to PLS factor four ($QSAR_4$), was selected based on different statistical parameters (*i.e.*, R^2_{train}, 0.96; Q^2_{test} 0.81; SD, 0.26). The contour plots of different structural properties generated from the selected model were utilized for the designing of five new congener molecules. These designed molecules were duly synthesized, and evaluated for their in vitro ALR2 inhibitory activity that resulted in the micromolar (IC_{50} < 22 μM) activity of all molecules. Thus, the newly designed molecules having ALR inhibitory potential could be employed for the management of diabetic complications.

1. Introduction

Worldwide, diabetes is achieving higher dimensions due to change in people life style, which lead to reduced physical activity and increased obesity, the main roots of diabetic conditions. As per world health organisation (WHO) diabetes webpage, 347 million people have diabetes, which is projected to be the 7th leading cause of deaths by 2030 [1]. Diabetes mellitus is one of the most common chronic metabolic diseases, characterized by chronic hyperglycaemia and the development of diabetes-specific microvascular and macrovascular pathology. Prolonged hyperglycemia is a primary causal factor of several diabetic complications. Large prospective clinical studies show a strong relationship between glycaemia and diabetic microvascular complications in both type 1 and type 2 diabetes [2,3].

Many studies have revealed a correlation between glucose metabolism via the polyol pathway (Fig. 1) and long-term diabetic complications. Aldose reductase, ALR2 (EC 1.1.1.21), is the first and rate-limiting enzyme in this pathway which normally reduces glucose to sorbitol using Nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor; at the same time another enzyme sorbitol dehydrogenase oxidizes sorbitol to fructose. However, in diabetic condition, the glucose level in this pathway is increased and sorbitol is produced faster than being oxidized to fructose [4]. The accumulated sorbitol cannot cross the cell membrane easily and therefore causes swelling and cell dysfunction in a number of tissues. In addition, fructose can become phosphorylated to fructose-3-phosphate, which is broken down to 3-deoxyglucosone, ultimately forming advanced glycation end products that are capable of cellular damage [5–7]. These abnormal metabolic results have been reported to be responsible for diabetic complications such as cataracts [8], retinopathy [9], neuropathy [10], and nephropathy [11]. The inhibition of ALR2 is a possible prevention or treatment of these effects [12].

The flavonoids are of low molecular weight plant products which are abundant, ubiquitously found in a wide variety of edible plants, fruits, nuts, seeds, and plant-derived beverages, such as juice and tea [13]. They are also called vitamin P[16] and have been described as health-promoting, disease-preventing dietary supplements [14]. They are relatively simple to synthesize and extremely safe and associated with low toxicity, making them excellent candidates for several interesting biological activity profiles in enzymatic systems, and as chemo-preventive agents [15]. They may exert an anti-hyperglycaemic effect by promoting peripheral utilization of glucose or enhancing the sensitivity of insulin in diabetic animals [16]. In addition, it was reported that the therapeutic benefits

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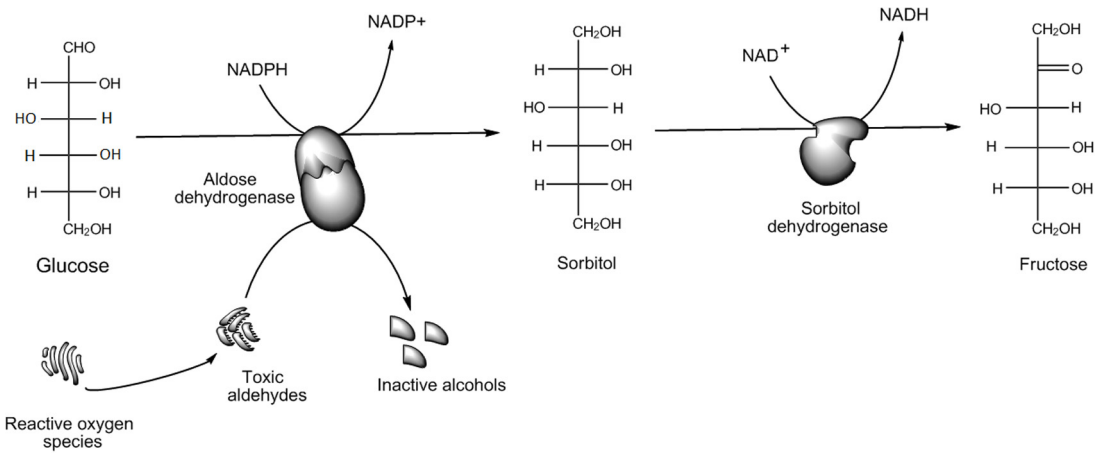

Fig. 1. The polyol pathway.

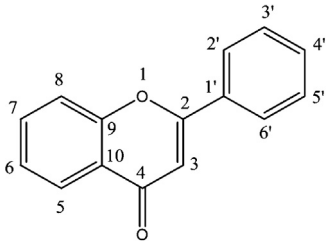

Fig. 2. Common template of phenyl-benzopyrane present in data set molecules.

of flavonoids are usually linked to two properties: (i) inhibition of certain enzymes such as xanthine oxidase, ALR2 [17], acetylcholinesterase [18], Janus kinase [19], Spleen Tyrosine Kinase [20] and (ii) antioxidant activity [21], consequently their study is greatly interested in many research fields.

Major pharmaceutical companies pay their attention to the speed up efficacious drug discovery with the primary aim of reducing cost per synthesized compound. Computer aided drug design (CADD) approaches which are able to predict the biological activities of compounds by their structural properties are powerful tools to design new active molecules. In this sense, quantitative structure–activity relationship (QSAR) studies have been successfully applied for modelling biological activities of natural and synthetic chemicals. QSAR studies have been carried out for modelling activities of several kinds of ALR2 inhibitor. Some recent reports have linked structural features of the ligands with their ALR2 inhibition by using topology indexes [17,22] three dimensional (3D)-QSAR methodologies [23,24], comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA) and artificial neural networks, etc. [25–27].

The current study involves the development of in silico models to predict the ALR2 inhibitory activity of a set of 46 flavonoids [17] mentioned in Table 1 and the common scaffold of these molecules is displayed in Fig. 2. Stefanic-Petek et al. reported a QSAR model for describing these compounds by using multi-linear regression analysis with classical and quantum chemical descriptors [28]. After that, Fernandez et al. reported linear and nonlinear QSAR models [29], and found that structural features related to the molecular topologies and charges are related to the inhibitory activity of these compounds. Caballero in 2010 reported 3D-QSAR by CoMFA and CoMSIA and Pharmacophore by GALAHAD (genetic algorithm with linear assignment of hyper-molecular alignment of the database) [30]. In the present paper, ALR2 structure guided atom based 3D-QSAR model was developed for throwing some light on the substituent requirements for lead optimization of flavones based

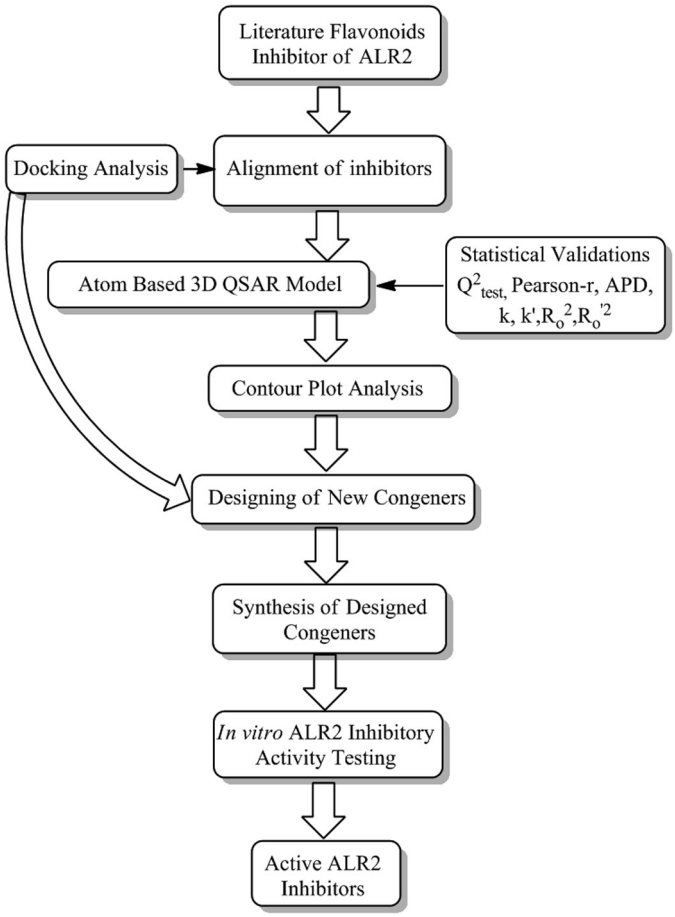

Fig. 3. Schematic view of the research protocol followed in the present study.

ALR2 inhibitor. A schematic workflow of proposed study is shown in Fig. 3.

2. Experimental

2.1. Selection and preparation of molecular dataset

A data set of 46 studied flavone inhibitors of ALR2 was selected from the published literature [17]. The ALR2 inhibitory activity of the selected molecules was reported as pIC_{50} value in the literature, which corresponds to the negative logarithm of dose