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Erratum: Evaluation of benzaldehyde derivatives as being bovine kidney aldose reductase inhibitors

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Inhibition, molecular docking, polyol pathway, benzaldehydes

Abstract: Aldose reductase (AR) catalyzes the production of sorbitol from glucose in the polyol pathway, and it is a critical enzyme that causes an aberrant aggregation of sorbitol in insulin-independent tissues, create some problems including retinopathy, neuropathy, and nephropathy. AR inhibition has been shown to be a viable approach for reducing these side effects. The current study aimed to introduce new AR inhibitors to the literature. For this purpose, benzaldehydes were examined as being AR inhibitors. Firstly, the homogenate was prepared from the bovine kidney, then inhibition studies were carried out. It was found that all derivatives inhibited AR. The inhibitory potency of 4- Phenyl benzaldehyde (3) and 2- Bromobenzaldehyde (6), having IC_{50} values as 0.23 and 1.37 µM, respectively, was determined higher than standard inhibitor sorbinil. After *in vitro* inhibition studies, estimated binding energies and binding modes of derivatives with enzyme were predicted by molecular docking. Compound 3 exhibited a maximum docking score of -8,61 kcal/mol. In conclusion, these compounds especially compound 3 may be guiding agents that can be used to synthesize new drug candidate molecules to treat or prevent diabetic complications.

Düzeltilmiş: Benzaldehit türevlerinin sığır böbrek aldoz redüktaz inhibitörleri olarak değerlendirilmesi

Anahtar Kelimeler
İnhibisyon, moleküler doking, poliol yolu, benzaldehit

Öz: Aldoz redüktaz (AR), poliol yolunda glikozdan sorbitol üretimini katalize eder ve insülinden bağımsız dokularda anormal sorbitol agregasyonuna neden olan, retinopati, nöropati ve nefropati gibi bazı problemler yaratan kritik bir enzimdir. AR inhibisyonunun bu yan etkileri azaltmak için uygun bir yaklaşım olduğu gösterilmiştir. Mevcut çalışma, literatüre yeni AR inhibitörlerini tanıtmayı amaçlamıştır. Bu amaçla AR inhibitörleri olarak benzaldehitler incelenmiştir. İlk olarak sığır böbreğinden homojenat hazırlanmış, ardından inhibisyon çalışmaları yapılmıştır. Çalışılan bütün benzaldehit türevlerinin AR'yi inhibe ettiği bulundu. 0,23 ve 1,37 µM IC_{50} değerlerine sahip olan 4- Phenyl benzaldehyde (3) ve 2- Bromobenzaldehyde (6)'in inhibitör aktivitesi, standart inhibitör sorbinilden daha yüksek olduğu tespit edildi. *In vitro* inhibisyon çalışmalarından sonra, tahmini bağlanma enerjileri ve türevlerin enzime bağlanma modları moleküler docking ile tahmin edildi. Bileşik 3, -8,61 kcal/mol'lük bir maksimum yerleştirme puanı sergiledi. Sonuç olarak, bu bileşikler, özellikle bileşik 3, diyabetik komplikasyonların tedavisinde veya önlenmesinde yeni ilaç aday moleküllerinin sentezi için yol gösterici moleküller olabilir.

1. INTRODUCTION

Diabetes is a chronic metabolic disease marked by high blood sugar levels that cause long-term damage to blood vessels, nerves, kidneys, heart, and eyes [1, 2] Type 2 diabetes, the most prevalent type, develops in adults when the body becomes insulin resistant or produces insufficient insulin [3]. According to the 2019 data of the International Diabetes Federation (IDF), the incidence of diabetes in adults between the ages of 20-79 was 9.33%. The number of people with diabetes was reported as 463 million in 2019 and the IDF predicts that this number may increase to approximately 580 million in 2030 and 700 million in 2045 [4]. In Turkey, its prevalence increased to

21% in 2015 [5]. In the 2020 data on diabetes prevalence it has been reported that nearly 15% of the total adult population in Turkey has diabetes [6].

Many pathways are regulated during the development and evolution of diabetes to deal with excess glucose in the body. One of these mechanisms is the polyol pathway (PP) [5,6]. Aldose reductase (AR, EC 1.1.1.21) is the first enzyme of PP and reduces glucose to sorbitol in the presence of cofactor NADPH [8]. And then, in the presence of NAD^+, sorbitol dehydrogenase (SOD, EC 1.1.1.14) transforms sorbitol to fructose [9].

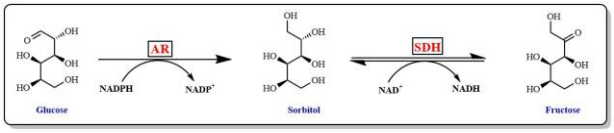

Figure 1. Poliol pathway

In a healthy body, only a small amount of glucose is converted to sorbitol so, blood glucose levels are within normal ranges [10,11]. Sorbitol is not able to penetrate through cell membranes and accumulate in the cell and produced an osmotic effect, causing tissue hydration [12]. Diabetic patients will have difficulties as a result of the problems that have occurred for their health quality. As sorbitol builds up in tissues, it sets in motion a cascade of events that leads to long-term diabetes consequences such as kidney damage, retinal disease, and cardiovascular disease [9-11]. Inhibition of AR activity of the AR for preventing glucose conversion to sorbitol could help avoid cell-level complications [16]. AR converts aldehydes derived from reactive oxygen species (ROS) into inert alcohols in the presence of the NADPH cofactor, in addition to converting glucose to sorbitol [17], [18]. The loss of NADPH induces an increase in GSH levels in cells with high AR activity, resulting in an increase in oxidative stress [15, 19, 20].

The function of aldose reductase in diabetes has been completely elucidated using AR inhibitors and knockout animals, and its inhibitors have been demonstrated to be able to ameliorate diabetes [21]. AR deletion or knockout investigations in mice have showed that AR deletion prevents the development of diabetes-induced retinal capillary degeneration, which is mediated by the creation of superoxide. AR knockout mice have also been shown to develop resistance to diabetic nephropathy [14,15]. Based on the above-mentioned explanations, the goal of this research was to study the *in vitro* inhibition effects of benzaldehyde derivatives (Figure 2) on AR to guide the synthesis of drugs that can be used in the treatment of diabetes. Besides, inhibitor-enzyme interactions were predicted by molecular docking study.

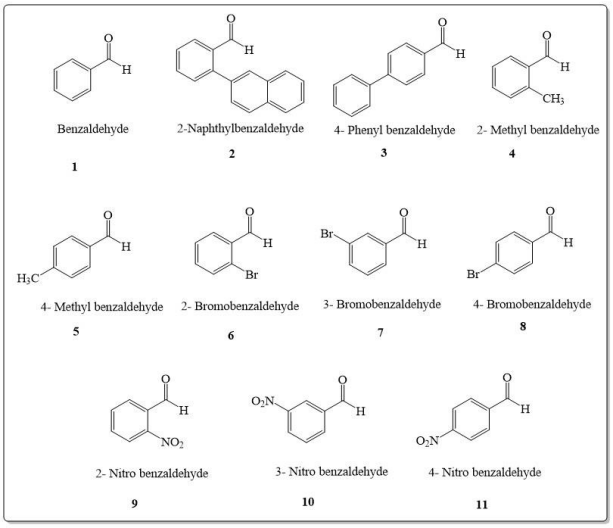

Figure 2. Benzaldehyde derivatives with investigated inhibition profile

2. MATERIAL AND METHOD

2.1. Materials

All chemicals that are used in activity determination and as inhibitors were procured from Sigma-Aldrich Co. and Merck (Darmstadt, Germany). The bovine kidney was obtained from a local butcher in Erzurum, Turkey.

2.2. Preparation of Kidney Homogenate

Kidney samples were washed with isotonic NaCl (0.9%) solution three times. About 10 g of the kidney tissue was chopped into small pieces, and then the cell membranes were ruptured by treatment with liquid nitrogen. The prepared sample was homogenized in 30 mL of 0.01 M phosphate buffer (pH 7.4) and was centrifuged at 13.500xg, at +4º for an hour by using refrigerated centrifuge. Then, the precipitated cell wastes were removed [24].

2.3. AR Activity Assay

The enzyme activity was measured using a modified method put by Cerelli et al.[25]. The depleted amount of NADPH at 340 nm was monitored spectrophotometrically for 3 minutes at 25ºC. About 1mL total volume of the enzymatic reaction mix contained 0.8 M Naphosphate buffer (pH=5.5), 4.7 mM DL-glyceraldehyde, 0.11mM NADPH and enzyme solution.

2.4. Determination *In vitro* Inhibition Effects

For the determination of compounds' *in vitro* effects, the enzyme activities were assayed in the presence of at least five various compound concentrations. The control measurement having no compound was assumed as 100% and measurements in the presence of compounds were calculated as % activity [26]. Data were drawn as Activity%-[compound] graphs, and IC_{50} values were calculated from the equations of these graphs [27].

2.5. Molecular Docking Studies

The three-dimensional (3D) structure of the aldose reductase (PDB ID: 2FZD, 1.08 Å) [28] was received from the PDB (Protein Data Bank). The structure of the receptor was arranged, minimized and optimized with the assistance of the Protein Preparation Wizard [29] module using the OPLS3e force field in the Maestro interface [30]. The LigPrep module was used to create two-dimensional drawings and three-dimensional conversions of the benzaldehyde derivative ligands. The OPLS3e force field was utilized to prepare and minimize protonation shows at pH 7.0 ± 2.0 and tautomers. The docking grid was created using the Receptor Grid Generation instrument and was placed on the center of the co-crystallized ligand, Tolrestat. The Glide extra precision (XP) method was used to molecularly attach all of the benzaldehyde derivatives to the target receptor AR [31]. In addition, Tolrestat was isolated from the crystal structure of the enzyme (AR) and docked again in order to validate the docking procedure. The best ligand pose was superpositioned with the co-crystallized ligand subsequent the re-docking method, and the RMSD (Root Mean Square Deviation) value was computed. Following the re-docking method, the top ligand posture was superpositioned with the co-crystal ligand, and the Root Mean Square Deviation (RMSD) value was calculated. The docking protocol's validation is shown by an RMSD value of less than 2 Å [32].

3. RESULTS

To examine the *in vitro* inhibition effects of benzaldehydes, bovine kidney homogenate was used as the source of AR enzyme. It was found that all benzaldehydes inhibited enzyme and 4- phenyl benzaldehyde (3) was the most effective inhibitor with IC_{50} value of 0.23 µM which was lower than the IC_{50} value of standard inhibitor determined by Rakowitz et al. [33] as 3.420 µM (Table 1).

Table 1. IC_{50} values of benzaldehyde derivatives on bovine kidney AR

Compound No	Compound Name	IC_{50} (µM)
1	Benzaldehyde	6300
2	2-Naphthylbenzaldehyde	34.65
3	4- Phenyl benzaldehyde	0.23
4	2- Methyl benzaldehyde	2650
5	4- Methyl benzaldehyde	2400
6	2- Bromobenzaldehyde	1.37
7	3- Bromobenzaldehyde	23.1
8	4- Bromobenzaldehyde	57.75
9	2- Nitro benzaldehyde	19.25
10	3- Nitro benzaldehyde	10.5
11	4- Nitro benzaldehyde	18.2
SOR (Rakowitz et al. 2006)	Sorbinyl	3.420

For the prediction of binding affinities and best poses, molecular docking studies were performed with AR receptor. Firstly, docking validation was performed with the co-crystalized ligand. The current study's docking results revealed that compound 3 had the highest effect, with a docking score of -8.31 kcal/mol, as shown in Table 2.

Table 2. XP docking scores and binding energies of benzaldehyde derivatives with AR receptor. Predicted docking scores and binding energy values were calculated as kcal/mol.

Compound Number	Docking Score	XP GScore	Glide emodel
1	-6,33	-6,33	-30,54
2	-8,01	-8,01	-39,57
3	-8,61	-8,61	-41,74
4	-6,84	-6,84	-30,15
5	-6,74	-6,74	-30,53
6	-6,57	-6,57	-27,34
7	-6,91	-6,91	-30,75
8	-6,81	-6,81	-31,7
9	-5,14	-5,14	-29,75
10	-6,05	-6,05	-34,18
11	-6,03	-6,03	-34,39
Sorbinyl*	-8,3	-8,35	-44,78

* Sorbinyl was used as standard inhibitor for AR.

4. DISCUSSION AND CONCLUSION

Diabetes Mellitus (DM), a common disease, can cause health issues including blindness, neuron diseases, heart, and kidney failure [34]. In diabetic management, the level of PP becomes the most strategic aims to achieve [33, 34]. AR is the first enzyme of the PP. Various AR inhibitors have been studied extensively, with encouraging results in terms of preventing and reducing diabetes progression [37], [38]. In this paper, some benzaldehyde derivatives were examined being bovine kidney AR. Besides, molecular interactions of compounds and enzyme were estimated by the molecular docking method. As a result of *in vitro* inhibition studies, all derivatives were found to inhibit the enzyme and activity%-[derivative] graphs were drawn. The graphs of the two best inhibitors are given in Figure 3. Compound concentrations that halved the activity were calculated from the equations of these graphs (Table 1). The two most effective inhibitors were found as derivatives 3, 4-phenylbenzaldehyde and 6, 2-Bromobenzaldehyde, with IC_{50} values of 0.23 and 1.37 µM correspondingly. These results determined that 3 and 6 are more effective than standard inhibitor, sorbinyl of which IC_{50} value was found as 3.420 µM by Rakowitz et al. [33]. It was seen from Table 1 that benzaldehyde had 6300 µM IC_{50} value and methyl derivatives of benzaldehyde had less inhibitory potency than other derivatives.

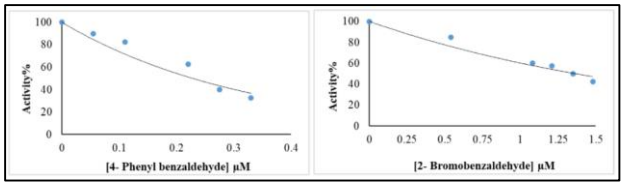

Figure 3. Activity%-[derivative] graphs of the two best inhibitors

The earlier study also found that a large number of synthesized derivatives such as thiazole-based compounds, 4H-1,2,4-triazole derivatives, N-benzyl(oxotriazinoindole), 2,4-thiazolidinediones, benzothiazolone-based carboxylic acid inhibited AR [25,26]. The study finds the inhibition potencies of 3 and 6 were higher than thiazole-based compounds, 4H-1,2,4-triazole derivatives and coumarin-thiosemicarbazone

hybrids [11,37,39]. The effectiveness of inhibitory effects of benzaldehyde derivatives was determined less than N-benzyl(oxotriazinoindole) and benzothiazolone-based carboxylic acid [35, 38, 40, 41, 42].

Molecular docking studies were also completed to theoretically support the experimental inhibition effects of benzaldehyde derivatives on the AR enzyme. Benzaldehyde derivatives and the positive control compound sorbinyl were docked to the ligand-binding site identified for the target protein using the extra precision (XP) docking methodology. The docking scores and estimated binding energies of benzaldehyde derivatives for the AR target enzyme are summarized in Table 2.

The re-docking approach was employed to verify the docking methodology in this research. Tolrestat was isolated from the crystal structure of the enzyme (AR) and docked again in order to validate the docking procedure. The best ligand pose was superpositioned with the co-crystallized ligand following on re-docking procedure, and the RMSD (Root Mean Square Deviation) value was computed. For the tolrestat ligand, the RMSD value was discovered to be 0,103 Å (Figure 4).

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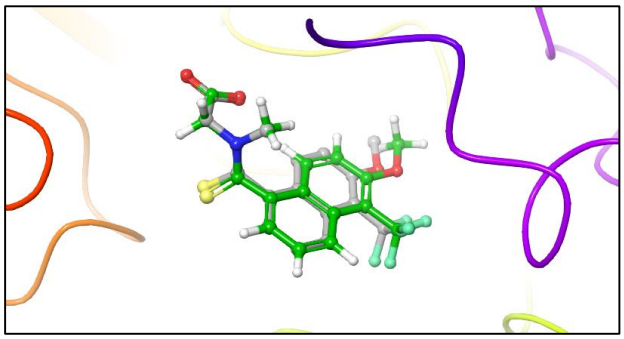

Figure 4. Docking validation of tolrestat adduct AR enzyme. AR receptor is depicted in the ribbon model. The co-crystallized ligand is represented in gray ball and stick modeling, while the re-docked ligand is shown in green ball and stick modeling.

As seen from Table 2, only the docking score of derivative 3 (-8,61 kcal/mol) was found to be higher than the standard inhibitor, sorbinyl, which had a docking score of -8,3 kcal/mol. Trp79, Trp20, Trp219, Trp111, Leu300, and Phe122 are among the residues in the highly hydrophobic active site pocket of AR [30,31]. When we examine the forms of interactions, we can see that; sorbinyl had an H bond with HIS110 residue and also showed pi-pi stacking interaction upon benzene moiety with indole moieties of Trp79 and Trp111 amino acids. And it displayed so many hydrophobic interactions with the active side pocket (Figure 5). Derivative 3, which is the most effective inhibitor based on the results of *in vitro* inhibition experiments and molecular docking estimations, affected AR in a similar manner with standard inhibitor. As seen from Figure 6, compound 3, had two hydrogen bonds with TYR48 and HIS110 residues. Benzene moiety of 3 also exhibited a pi-pi stacking interaction with the indole group of TRP111. Derivative 3 had so many polar and hydrophobic interactions through the same residues as sorbinyl. These interactions are consistent with a previous study, which was conducted by Salem et al. [47]. They reported in their study on the inhibition effects of novel meglitinides on AR that 15C and 12B had interaction with residues similar to those of our study.

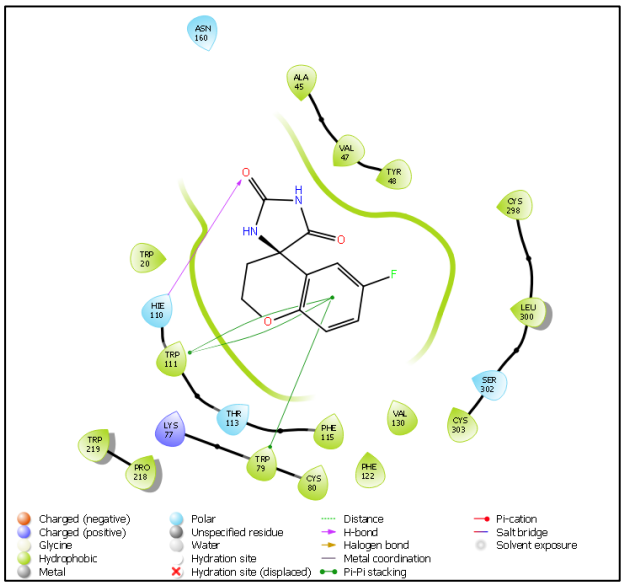

Figure 5. 2D ligand-receptor interaction diagram of standard AR inhibitor sorbinil

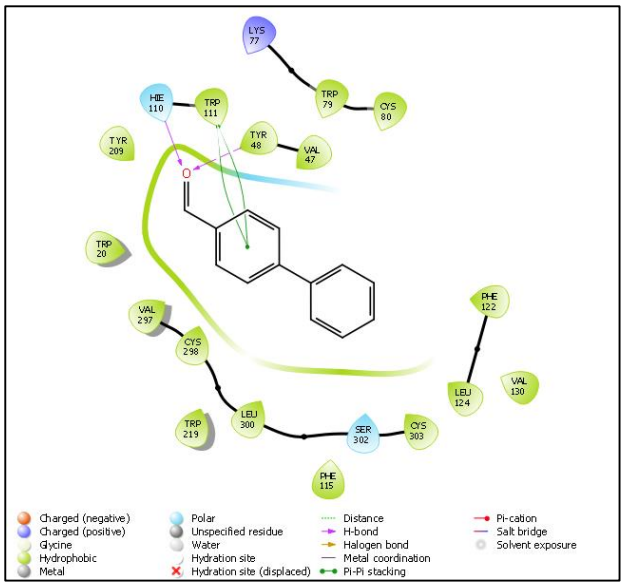

Figure 6. 2D ligand-receptor interaction diagram of best-scored compound derivative 3.

In conclusion, the PP is activated when blood glucose levels are high and it is critical for preventing diabetes and diabetes-related complications. As a result, the AR inhibition strategy holds promise for the treatment of diabetes and related illnesses. In conclusion, all benzaldehyde derivatives inhibited AR in the micromolar range and compounds 3 and 6 had higher inhibitory potency than standard inhibitor with IC_{50} values of 0.23 and 1.37 µM respectively. The docking score of 3 was also found to be higher than the standard inhibitor with the value of -8.61 kcal/mol. The results of the current study are hoped to be able to guide for further research on new drug candidates in the treatment of diabetes.

Conflict of Interest

The author declares that there is no potential conflict of interest.

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CRediT authorship contribution statement

Bülent Şengül: Conceptualization, Methodology, Data curation, Visualization, Investigation, Writing - review & editing**.**

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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