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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Evaluation of rat kidney aldose reductase inhibitory activity of some *N*-acetyl dehydroalanine derivatives

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Abstract Aldose reductase (AR) is an enzyme that catalyzes the conversion of glucose to sorbitol, which is in turn converted to fructose by sorbitol dehydrogenase. Increased AR activity has been implicated in the pathogenesis of diabetic complications such as neuropathy, nephropathy, retinopathy, and cataract. Inhibitors of AR thus seem to have the potential to prevent or treat diabetic complications. At present, however, side effects and/or insufficient pharmacokinetic profiles have made most of the drug candidates undesirable. In this study, the synthesis (**l–o**) and ARI activity of 15 *N*-acetyl dehydroalanine derivatives (**a–o**) are described. The synthesized compounds mainly contained aliphatic and aromatic side chains. The insertion of ethyl and chloro propyl side chains were shown to be more effective than the rest of the compounds. Between the synthesized compounds *N*-ethyl (**b**) and *N*-propylchloride (**h**) derivatives showed the best ARI activities.

Keywords Aldose reductase · Polyol pathway · Inhibition · Dehydroalanine · Synthesis

Introduction

Diabetes mellitus is a chronic disease caused by deficiency in production of insulin by pancreas, and by resistance to insulin's effects. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damages many of the body's systems such as eyes, kidneys, nerves, heart, and blood vessels. Hyperglycemia has been shown to be the major risk factor responsible for the complications which are the cause of morbidity and mortality in patients with diabetes. Various biochemical pathways have been proposed to explain the adverse effects of hyperglycemia. Potential cellular mechanisms of hyperglycemia-induced diabetic complications are the activation of diacylglycerol-protein kinase C pathway (Koya and King, 1998), increased polyol pathway, enhanced reactive oxygen pathway (Brownlee, 2001), non-enzymatic glycation (Wendt *et al.*, 2006) and advanced glycation end products.

Aldose reductase (AR), the key enzyme of the polyol pathway, belongs to the aldo–keto reductase superfamily (Vander Jagt *et al.*, 1990). AR has been demonstrated to play an important role not only in cataract formation in lens but also in the pathogenesis of diabetic complications such as neuropathy, nephropathy, and retinopathy. As a result of increased polyol pathway during hyperglycemia sorbitol accumulates, as it is formed more rapidly than it is converted to fructose (Fig. 1) (Brownlee, 2001). Excess intracellular sorbitol accumulation through the polyol pathway correlates with the diabetic complications. The role of polyol pathway in diabetic complications may have different mechanisms, such as; accumulation of sorbitol or fructose (Vander Jagt *et al.*, 1990; Narayanan, 1993), myo-inositol depletion (Greene *et al.*, 1987), or alterations in NADPH/$NADP^+$ and NADH/NAD^+ ratios (Williamson *et al.*, 1993; Schrijvers *et al.*, 2004).

Sorbitol is also associated with myo-inositol metabolism (Greene *et al.*, 1987). AR, sorbitol, and myo-inositol may play a role in the osmoregulation of the kidney (Burg, 1995). In type 1 diabetes, increased sorbitol levels were determined (Chang *et al.*, 1991; Faiman *et al.*, 1993; Kicic and Palmer, 1994; Soulis-Liparota *et al.*, 1995; Raccah *et al.*, 1998; Kern

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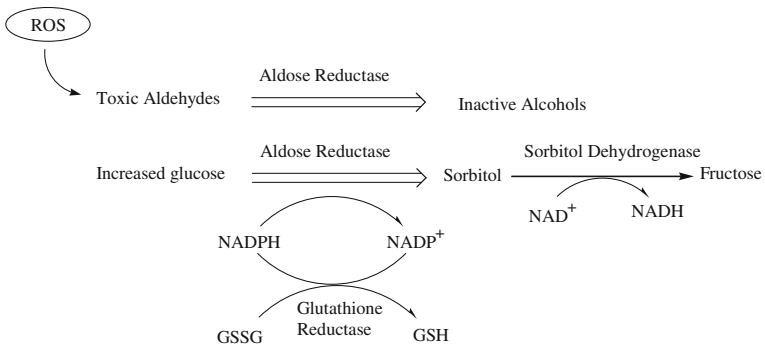
Fig. 1 Polyol pathway



and Engerman, 1999). Renal AR levels and activities were found to be increased in diabetic rats (Ghahary *et al.*, 1989; Ghahary *et al.*, 1991; Yoshii *et al.*, 2001). Several studies demonstrated that type 2 diabetic patients had higher serum and urine myo-inositol levels and sorbitol excretion compairing with healthy controls (Kouzuma *et al.*, 2001; Yoshii *et al.*, 2001). On the other hand, diabetic state is associated with oxidative stress. Polyol pathway is one of the reasons for the oxidative stress in diabetes. Enhanced polyol pathway decreases the ratio of NADPH/$NADP^+$ and increases the GSH ratio which results in reduced capacity for oxidation defence (Bravi *et al.*, 1997; Lee and Chung 1999). Henry *et al.* (1999) were showed that increased expression of glucose transporter-1 resulted with an enhanced AR expression and activity, increased sorbitol accumulation and protein kinase C levels.

Animal studies demonstrated that diabetic complications such as cataract, nephropathy, and slowing of nerve conduction can be ameliorated by the use of aldose reductase inhibitors (ARIs) (Narayanan, 1993; Alexiou *et al.*, 2009).

A range of structurally different compounds have been reported as ARIs but there are few studies about the influence of ARIs in the diabetic kidney. Mainly they can be classified in two general groups including rigid spirohydantoins or a related ring system, such as Sorbinil, and those like Epalrestat and Zenarestat, which contain a carboxylic acid moiety (Shao-Jie *et al.*, 2007). However, over the past decade N-substituted amino acids have an important place in research of amino acid type of ARIs (Süzen *et al.*, 2006).

Dehydroalanines (DHAs) are potential Michael acceptors and are present in a large number of natural products, thiopeptides and the lantibiotics (Lau and Rinehart, 1994; Dawson, 1998; Santos and Moriera, 2007). Most of the ARIs developed during the last two decades have failed in clinic trail, probably due to insufficient physiochemical or selectivity properties (Steuber *et al.*, 2006). In earlier studies, N-substituted glycine and alanine derivatives (Mayfield and DeRuiter, 1987) synthesised to be inhibitors of AR. This is followed by the synthesis of number of amino acid derivatives such as *N*-[4-(benzoylamino)phenylsulfonyl]glycine (BAPSG) (Sunkara *et al.*, 2000), *N*-benzoyl amino acids (Benvenuti *et al.*, 1998), *N*-(benzyloxy) glycine derivatives (Macchia *et al.*, 1998) as an effective ARIs. We also studied the AR inhibitory activities of benzodiazepine derivatives, 5-(3′-indolyl)-2-thiohydantoin derivatives, some pyridazine derivatives, 2-phenylindole derivatives, substituted-thiazolyl-thiazolidinedione derivatives (Buyukbingol *et al.*, 1994; Daş-Evcimen *et al.*, 1998; Şüküroğlu *et al.*, 2007; Süzen *et al.*, 2007; Bozdağ-Dündar *et al.*, 2007; Daş-Evcimen *et al.*, 2008; Bozdağ-Dündar *et al.*, 2008a, b).

Experimental studies indicated that ARIs has an effect on oxidative stress (Cunningham *et al.*, 1994; Obrosova and Fathallah, 2000; Obrosova *et al.*, 2002). Studies have shown that ARIs reduces the lipid hydroperoxides in diabetes (Ohmura *et al.*, 2009) and detoxify the reactive carbonyl compounds derived from oxidative stress (Endo *et al.*, 2009). However, none of the currently available treatments appear to achieve the necessary prevention of the development of diabetic complications in diabetic patients.

Olefins such as DHAs have been shown to inactivate free radicals by forming stabilized free radical adducts. Among these molecules *N*-acyl DHAs react with and scavenge oxygen and hydroxyl radicals. In our erlier study we showed that *N*-acetyl DHA derivatives have strong inhibitory effect on lipid peroxidation (Süzen *et al.*, 2006). These findings prompted us to screen and evaluate of *N*-acetyl DHA derivatives as ARIs because of the relevance of diabetic complications such as cataract and free radical production (Hashim and Zarina, 2006).

The aim of this study was to determine the AR inhibition capacity of some *N*-acetyl DHA derivatives which have significant hydroxyl radical scavenging activities and discuss the probable dual effect in diabetic complications.

Materials and methods

Materials

Male Albino rats weighing 200–250 g were used for experiments. They received standard diet. 30 rats were

killed and kidney tissues were discarded. AR enzyme was isolated from the kidney tissues and enzyme activity was determined following the isolation. All the enzyme experiments were performed in triplicate. Procedures involving the animals and their care conformed to institutional guidelines, in compliance with national and international laws and guidelines for the use of animals in biomedical research.

The method of Harada and Tagasaki (1984) was performed for the synthesis of *N*-acetyl-DHA derivatives (**a–o**). DCCI and HONSu were used for the coupling of acetamidoacrylic acid and appropriate amine. Synthesis and characterization of compounds **c–g** and **i–k** were published previously by our research group (Süzen *et al.*, 2006). Compounds **a** and **b** were characterized by Palmer *et al.* (1992) and Gulzar *et al.* (1995), respectively. The physical and spectral data of the newly synthesized compounds are given in Table 1.

Uncorrected melting points were determined with a Büchi SMP-20 apparatus. The ^{1}H NMR spectra were measured with a Varian mercury 400 MHz using TMS internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. ESI Mass spectra were determined on a Waters micromass ZQ. Chromatography was carried out using Merck silica gel 60 (230–400 mesh). The chemical reagents for the synthesis of compounds, AR isolation and activity tests were purchased from Sigma (Germany), Merck (Germany), and Aldrich (USA). The abbreviations used for chemicals are as follows: DCCI (1,3-dicyclohexyl carbodiimide), HONSu (*N*-hydroxysuccinimide), DMF dimethylformamide.

General procedure for the preparation of *N*-acetyl dehydroalanines

All the *N*-acetyl DHA derivatives were prepared in pure crystalline form using following procedure (Harada and Takasaki, 1984). Acetamidoacrylic acid (1 mol), DCCI (1.2 mol), HONSu (1.1 mol), and appropriate amine (1 mol) in ethylacetate were cooled at −10°C. The heterogeneous reaction mixture was then stirred at r.t. for 24 h. At the end of the reaction, the precipitated dicyclohexylurea was filtered and the filtrate was evaporated to dryness. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 60–80). The physical data for compounds **l**, **m**, **n**, and **o** that were not stated in the literature are given in Table 1.

Isolation of aldose reductase enzyme

The AR enzyme was isolated by a method (Cerelli *et al.*, 1986) described below. Pooled kidney were thawed on ice

Table 1 Physical and spectral data of synthesized compounds (**l–o**)

No.	Formula	Yield (%)	m.p. (°C)	^{1}H NMR data (δ ppm)	Mass data
l	$C_{12}H_{13}N_2O_2Cl$	42	140–143	d_6-DMSO: 2.0 (s, 3H, $COCH_3$), 3.38 (s, 2H, $C\underline{H_2}$-Ph), 5.42 (s, 1H, =CH), 6.00 (s, 1H, =CH), 8.92 (brs, NH), 9.14 (brs, NH)	291 (M + K, 5.12), 277 (M + 2 + Na, 15.70), 275 (M + Na, 39.91), 253 (M + 1, 7.01), 225 (19.11), 169 (100), 147 (89.27)
m	$C_{12}H_{13}N_2O_2Cl$	47	132–133	d_6-DMSO: 1.98 (s, 3H, $COCH_3$), 4.38 (d, 2H, $C\underline{H_2}$-Ph), 5.45 (s, 1H, =CH), 5.98 (s, 1H, =CH), 7.26–7.42 (m, 4H, Ar–H) 8.85 (brs, NH), 9.14(brs, NH)	291 (M + K, 5.09), 277 (M + 2 + Na, 31.15), 275 (M + Na, 85.71), 253 (M + 1, 8.04), 225 (96.65), 169 (69.32), 147 (100), 137 (32.21)
n	$C_{13}H_{16}N_2O_3$	51	103–104	d_6-DMSO: 2.0 (s, 3H, $COCH_3$), 3.77 (s, 2H, $OC\underline{H_3}$), 4.31 (d, 2H, $C\underline{H_2}$-Ph), 5.47 (s, 1H, =CH), 6.03 (s, 1H, =CH), 6.66–7.25 (m, 4H, Ar–H) 8.70 (brs, NH), 9.11 (brs, NH)	287 (M + K, 4.76), 272 (M + 1 + Na, 9.74), 271 (M + Na, 89.93), 249 (M + 1, 28.67), 225 (16.82), 169 (49.69), 147 (100) 137 (32.24)
o	$C_9H_{12}N_4O_2S$	40	118–120	d_6-DMSO: 1.22 (t, 3H, CH_2–$\underline{CH_3}$) 1.89 (s, 3H, $COCH_3$), 2.86 (q, 2H, $C\underline{H_2}$–CH_3), 4.48 (s, 1H, =CH), 4.68 (s, 1H, =CH), 8.20 (brs, NH), 10.55 (brs, NH)	279 (M + K, 4.12), 264 (M + 1 + Na, 5.34), 263 (M + Na, 38.44), 242 (M + 2, 39.67), 241 (M + 1, 100), 169 (39.65), 147 (65.73) 137 (28.24)

and homogenized with 3 volume of distilled water, followed by centrifugation at 10,000×*g* for 20 min. Saturated ammonium sulfate was added to the supernatant to 40% saturation. The thick suspension had been stirred for 15 min, followed by centrifugation at 10,000×*g* for 20 min. The inert protein left in the supernatant was removed by increasing the ammonium sulfate concentration to 50% saturation followed by centrifuging the mixture at 10,000×*g* for 20 min. The AR enzyme was precipitated from the 50% saturated solution by adding powdered ammonium sulfate to 75% saturation and was recovered by centrifugation at 10,000×*g* for 20 min. Protein concentration was measured by the method of Bradford (Bradford, 1976) using bovine serum as the standard.

Determination of aldose reductase activity

AR activity of the freshly prepared supernatant was assayed spectrophotometrically by determining the decrease in NADPH concentration at 340 nm by a UV-1700 Visible spectrophotometer (Cerelli *et al.*, 1986). DL-glyceraldehyde was used as a substrate. The enzyme was dissolved in 10 ml 0.05 M NaCl solution. 0.75 mg protein was added to a quartz cuvette containing 0.1 ml phosphate buffer (0.067 M, pH 6.2), 0.1 ml NADPH (2×10^{-5} M final concentration), 3.3×10^{-6} M of the test drug (solutions prepared in 50% DMF–50% methanol) and 2.4 ml distilled water to obtain 2.9 ml solution. The reaction is started by the addition of 0.1 ml DL-glyceraldehyde (5×10^{-5} M final concentration) to the cuvette and the decrease in NADPH concentration was recorded at 340 nm for 5 min at 37°C. Readings were taken at intervals in the periods when the changes in absorbance were linear. The results are shown in Table 2.

Results and discussion

Compounds that prevent or slow the action of AR may represent a means to prevent or delay complications of diabetes. With this study, 15 *N*-acetyl DHA derivatives (Table 1) were evaluated for their ability to inhibit rat kidney AR by an in vitro spectrophotometric assay.

It is known that oxidative stress is present in the diabetic state and causes tissue damage in patients with diabetes. It appears to be primarily due to the processes of nerve ischemia and hyperglycemia auto-oxidation (Süzen and Buyukbingol, 2003), also can develop due to increased free radical generation or by reduced free radical defenses (Traverso *et al.*, 1999; Pau *et al.*, 2004). In our earlier study (Süzen *et al.*, 2006), we found that *N*-acetyl DHA derivatives which are substituted with aliphatic (up to 3 carbons) and cyclic side chains (5 member) have significant hydroxyl radical scavenging activity.

The studies suggest that hydroxyl radical is indirectly inhibited by ARIs resulting from decreasing polyol levels and hydroxyl radical formation. ARIs possessing antioxidant activity would therefore seem to be desirable. Oxidative stress plays a fundamental role in the pathogenesis of diabetes mellitus, particularly through progressive damage to proteins (Nwose *et al.*, 2007; Maritim *et al.*, 2003). These results were prompted us synthesis and preliminary evaluation of *N*-acetyl DHA derivatives that have antioxidant activity as ARIs.

Compounds **a**–**o** were tested in vitro for their ability to inhibit AR from rat kidneys. The enzyme activity was assayed by spectrophotometrically monitoring NADPH oxidation, which accompanies the reduction of D,L-glyceraldehyde used as substrate. The inhibition study was performed merely by using 10^{-4} M concentration in which no additional study seemed to be necessary to obtain IC_{50} values. Fifteen *N*-acetyl DHA derivatives were performed and the inhibition % values are shown in Table 2.

Within *N*-acetyl DHA derivatives **b** and **h** have shown the highest inhibitory effect. The rest of the compounds have no significant inhibition potency at 10^{-4} M concentration. Compounds **b** and **h** which have the highest AR inhibition rates contains ethyl and chloropropyl side chains. This may explain why there was no sufficient inhibition values obtained with the aromatic and bulkier side chained compounds.

Non-proteinogenic amino acids constitute an important group of compounds in the field of peptide chemistry. These compounds have several applications, either as biologically active substrates or as individual structural components. Among these amino acids are α,β-dehydroa-

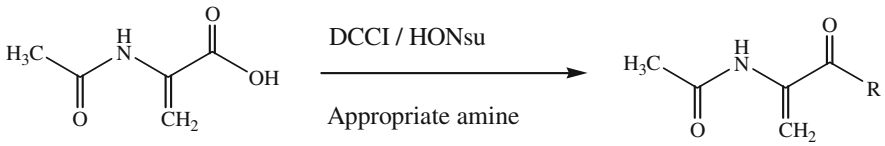


Table 2 AR inhibition % values of *N*-acetyl dehydroalanine derivatives

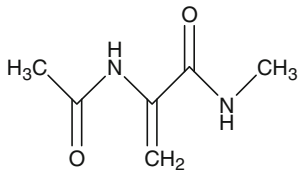
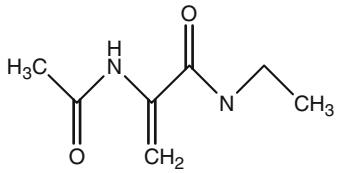
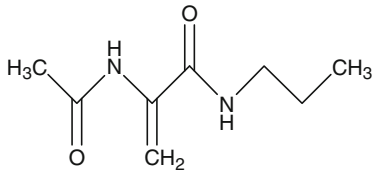
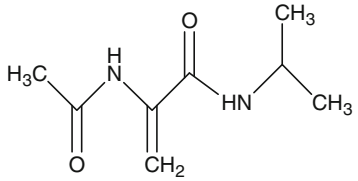
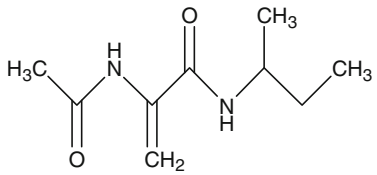
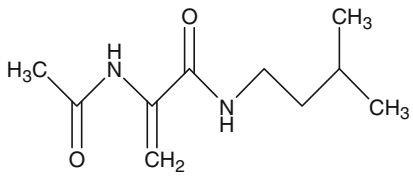
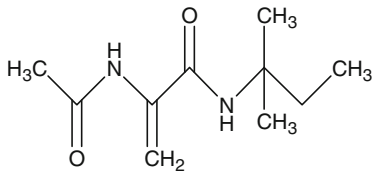
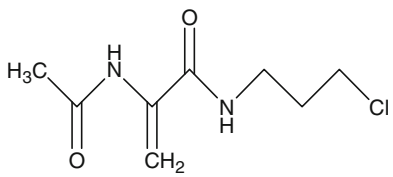
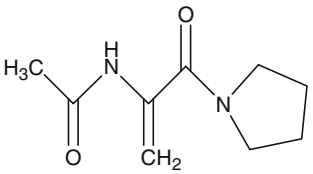
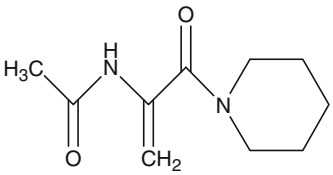
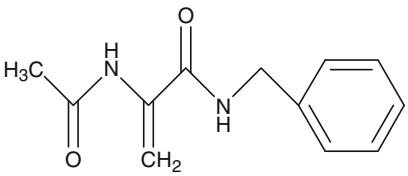
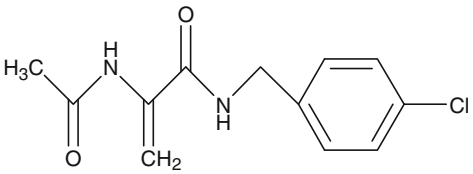
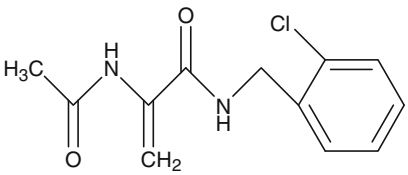
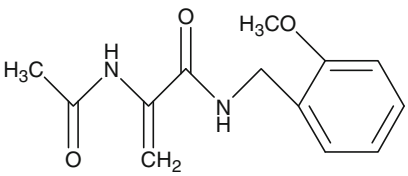
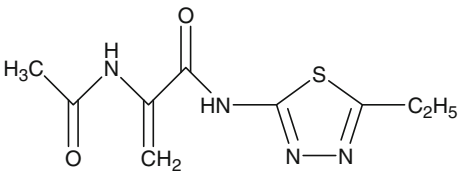
No.	Formula	Inhibition %
a		9.46 ± 0.73
b		13.13 ± 4.90
c		4.32 ± 2.77
d		3.77 ± 2.85
e		0.00 ± 0.00
f		4.13 ± 5.76
g		3.22 ± 4.04
h		19.56 ± 3.59

Table 2 continued

No.	Formula	Inhibition %
i		0.00 ± 0.00
j		3.40 ± 0.85
k		2.48 ± 3.75
l		2.30 ± 1.07
m		7.26 ± 2.22
n		0.00 ± 0.00
o		4.50 ± 0.58

mino acids and β-substituted alanines. There is still speculation as to the role of the dehydro units in biologically active compounds. Certainly, they have an influence as a conformational constraint due to their sp^2 hybridized carbon structure (Süzen *et al.*, 2006). Michael acceptors have been popular functionalities for the design of enzyme inhibitors and active site affinity labels (Santos and Moriera, 2007).

In summary, the synthesis (**l–o**) and ARI activity of 15 *N*-acetyl DHA derivatives (**a–o**) are described. The synthesized compounds mainly contained aliphatic and aromatic side chains. A considerable increase in potency was not observed when the aliphatic side chains were displaced with aromatic groups. The insertion of ethyl and chloro propyl side chains was shown to be more effective than the rest of the compounds. In conclusion, compounds **b** and

h has shown the best inhibitory activity among the other DHA derivatives.

The results of the biological evaluation allowed us to get insight into initial structural features critical for AR inhibition in this series. Thus, based on these findings further modifications are envisaged. Due to the shortage of drugs currently available for the treatment of diabetic complications, search for new ARIs endowed with more favorable biological properties is still a major pharmaceutical challenge.

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