Synthesis and aldose reductase inhibitory effect of some new hydrazinecarbothioamides and 4-thiazolidinones bearing imidazo[2,1-*b*]thiazole moiety

İmidazo[2,1-*b*]tiyazol çekirdeği taşıyan bazı yeni hidrazinkarbotiyoamitler ve 4-tiyazolidinonların sentezi ve aldoz redüktaz inhibitör etkileri

ABSTRACT

Objectives: The aim of this study was to synthesize and characterize 2-[[6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl]-*N*-alkyl/arylhydrazinecarbothioamide and 3-alkyl/aryl-2-[((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-5-nonsubstituted/methyl-4-thiazolidinone derivatives and evaluate them for aldose reductase inhibitory effect.

Materials and Methods: 2-[[6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl]-*N*-alkyl/arylhydrazinecarbothioamides (**3a-f**) and 3-alkyl/aryl-2-[((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones (**4a-j**) were synthesized from 2-[6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide (**2**). Their structures were elucidated by elemental analyses and spectroscopic data. The synthesized compounds were tested for their ability to inhibit rat kidney aldose reductase (AR).

Results: Among the synthesized compounds 2-[[6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl]-*N*-benzoylhydrazinecarbothioamide (**3d**) showed the best AR inhibitor activity.

Conclusion: The findings of this study indicate that the different derivatives of the compounds in this study may be considered as interesting candidates for future research.

Key words: Hydrazinecarbothioamide, 4-thiazolidinone, imidazo[2,1-*b*]thiazole, Aldose reductase inhibition

ÖZ

Amaç: Bu çalışmanın amacı, 2-[[6-(4-bromofenil)imidazo[2,1-*b*]tiyazol-3-il]asetil]-*N*-alkil/arilhidrazinkarbotiyoamit ve 3-alkil/aril-2-[((6-(4-bromofenil)imidazo[2,1-*b*]tiyazol-3-il)asetil)hidrazono]-5-nonsübstitüe/metil-4-tiyazolidinon türevleri'ni sentezlemek, yapılarını aydınlatmak ve aldoz redüktaz inhibitör etkilerini araştırmaktır.

Gereç ve Yöntemler: 2-[6-(4-Bromofenil)imidazo[2,1-*b*]tiyazol-3-il]asetohidrazit (**2**)'ten hareketle 2-[[6-(4-Bromofenil)imidazo[2,1-*b*]tiyazol-3-il]asetil]-*N*-alkil/arilhidrazinkarbotiyoamit (**3a-f**) ve 3-alkil/aril-2-[((6-(4-bromofenil)imidazo[2,1-*b*]tiyazol-3-il)asetil)hidrazono]-5-nonsübstitüe/metil-4-tiyazolidinon türevleri (**4a-j**) sentezlenmiştir. Bileşiklerin yapıları elementel analiz ve spektroskopik bulgularla kanıtlanmıştır. Sentezlenen bileşikler sıçan böbrek aldoz redüktaz (AR) enzimini inhibe etme özellikleri açısından test edilmiştir.

Bulgular: Sentezlenen bileşikler arasından, 2-[[6-(4-bromofenil)imidazo[2,1-*b*]tiyazol-3-il]asetil]-*N*-benzoilhidrazinkarbotiyoamit (**3d**) en iyi AR inhibitör etkiyi göstermiştir.

Sonuç: Bu çalışmanın bulguları, bu çalışmadaki bileşiklerin farklı türevlerinin gelecek araştırmalar için ilginç adaylar olarak görülebileceğini göstermektedir.

Anahtar kelimeler: Hidrazinkarbotiyoamit, 4-tiyazolidinon, imidazo[2,1-*b*]tiyazol, Aldoz redüktaz inhibisyon

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by deficiency in production of insulin by pancreas, and by resistance to insulin's effects or in some cases both. According to the World Health Organization, more than 422 million people worldwide have diabetes and the number is expected to rise almost double by 2030[1]. Furthermore, hyperglycemia is the major risk factor responsible for the broad range of complications which are the main cause of mortality and morbidity in people with DM. There are two forms of complications; acute complications and chronic complications including nephropathy, neuropathy and retinopathy[2]. Various biochemical pathways have been proposed to explain the pathological mechanisms of diabetic complications. These include increased polyol pathway flux, activation of the PKC pathway, oxidative stress and accelerated advanced glycation end product (AGE) formation[2,3].

Aldose reductase (AR; ALR2; EC 1.1.1.21) is the first enzyme in the polyol pathway and reduces glucose to sorbitol in the presence of NADPH. Sorbitol dehydrogenase (SDH), second enzyme of polyol pathway, oxidizes the intermediate sorbitol to fructose with NAD^+ as cofactor[4,5] (Figure 1). It has been reported that AR enzyme activity increases in diabetes[6]. Total glucose utilization by AR-catalyzed reduction is less than 3 % under normoglycemia (5,5 mM) whereas this rate is more than 30 % under hyperglycemia (20 mM)[6]. Increased AR activity has been implicated in the pathogenesis of the diabetic complications[6,7]. Activated AR leads to cell damage through several mechanisms, including accumulation of sorbitol[8,9], NADPH depletion[10,11], increased NADH/NAD^+ ratio[12] and increased fructose levels[13]. Inhibitors of AR thus seem to have the potential to prevent or treat diabetic complications. Even though a wide number of aldose reductase inhibitors (ARIs) obtained over the last thirty years, the clinical efficacy of these compounds is not completely satisfactory and several of them have also shown undesirable side effects[14]. Sorbinil, tolrestat, zopolrestat and ponalrestat were withdrawn from clinical trials because of their side effects[15]. Various thiazolidindione derivatives are a newer class of antidiabetic drugs[16-20], which improve glycemic control in type 2 diabetes by increasing insulin action in skeletal muscles, liver, and adipose tissue[21,22].

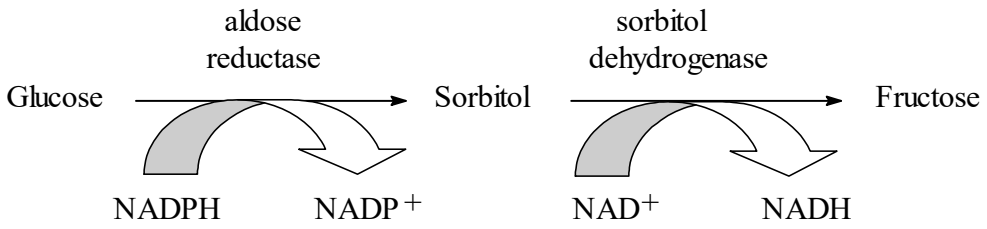

Figure 1. Polyol pathway

There has been considerable interest in the chemistry of 4-thiazolidinone ring systems, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities such as antidiabetic[7,23-26], anticancer[27-29], antiviral/anti-HIV[30], antibacterial and antifungal[31,32], antitubercular[33], antiinflammatory and analgesic[34] activities. On the other hand, imidazo[2,1-*b*]thiazole[35] and thiosemicarbazide[36] moieties are also associated with various biological properties including antidiabetic activity.

As a continuation of our previous studies on 4-thiazolidinone derivatives with aldose reductase inhibitors[37-43] or different biological activities[44-48] we report the synthesis of some novel imidazo[2,1-*b*]thiazole derivatives incorporating with two known bioactive nuclei such as hydrazinecarbothioamide or 4-thiazolidinone.

EXPERIMENTAL

Chemical Methods

Melting points were determined by using a Büchi B-540 melting point apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. IR spectra were recorded on KBr discs, using a Shimadzu IR Affinity-1 FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR (APT) spectra were measured on a Varian UNITY INOVA (500 MHz) spectrometer using *DMSO*-d_6. The starting materials were either commercially available or synthesized according to the references cited.

*General procedure for the synthesis of 2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-cycloalkyl/aralkyl/arylhydrazinecarbothioamides (**3a-f**)*

To a solution of 2-[6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide (**2**) (0.005 mol) in ethanol (30 mL) were added the appropriate isothiocyanate (0.005 mol). The resulting mixture was heated under reflux for 3 h. After cooling, the precipitate was separated and purified by washing with hot ethanol.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-cyclohexylhydrazinecarbothioamide (**3a**)*

Yield: 71 %; m.p. 246 ºC; IR (KBr, cm^{-1}): 3207 (N-H), 1672 (C=O), 1195 (C=S); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.09 (s, 1H, NH), 9.44; 9.18 (2s, 1H, NH), 8.27; 8.15 (2s, 1H, imidazothiazole C_5-H), 7.77-7.73 (m, 2H, 4-Brphenyl $C_{2,6}$-H), 7.66 (s, 1H, NH), 7.60-7.56 (m, 2H, 4-Brphenyl $C_{3,5}$-H), 7.10; 7.06 (2s, 1H, imidazothiazole C_2-H), 4.06 (s, 1H, cyclohexyl), 3.82 (s, 2H, CH_2CO), 1.77-1.03 (m, 10H, cyclohexyl). Anal. Calcd. for $C_{20}H_{22}BrN_5OS_2$: C, 48.78; H, 4.50; N, 14.22. Found: C, 48.25; H, 3.90; N, 13.97.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-benzylhydrazinecarbothioamide (**3b**)*

Yield: 88 %; m.p. 251-252 ºC; IR (KBr, cm^{-1}): 3217 (N-H), 1674 (C=O), 1195 (C=S); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.24 (s, 1H, NH), 9.63; 9.45 (2s, 1H, NH), 8.68 (s, 1H, NH), 8.21 (s, 1H, imidazothiazole C_5-H), 7.72 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{2,6}$-H), 7.57 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{3,5}$-H), 7.30-7.20 (m, 5H, phenyl), 7.10 (s, 1H, imidazothiazole C_2-H), 4.78 (s, 2H, CH_2), 3.83 (s, 2H, CH_2CO). Anal. Calcd. for $C_{21}H_{18}BrN_5OS_2$: C, 50.40; H, 3.63; N, 13.99. Found: C, 50.20; H, 3.65; N, 13.46.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-phenethylhydrazinecarbothioamide (**3c**)*

Yield: 89 %; m.p. 251 ºC; IR (KBr, cm^{-1}): 3197 (N-H), 1672 (C=O), 1163 (C=S); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.19 (s, 1H, NH), 9.55; 9.35 (2s, 1H, NH), 8.26 (s, 1H, NH), 8.21 (s, 1H, imidazothiazole C_5-H), 7.77 (d, 2H, *J*=9.27 Hz, 4-Brphenyl $C_{2,6}$-H), 7.58 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{3,5}$-H), 7.31-7.28 (m, 2H, phenyl), 7.25-7.20 (m, 3H, phenyl), 7.11; 7.06 (2s, 1H, imidazothiazole C_2-H), 3.83 (s, 2H, CH_2CO), 3.66 (q, 2H, *J*=7.81 Hz, N-CH_2), 2.82 (t, 2H, *J*=7.07 Hz, CH_2-Ph). Anal. Calcd. for $C_{22}H_{20}BrN_5OS_2$: C, 51.36; H, 3.92; N, 13.61. Found: C, 51.33; H, 3.82; N, 13.60.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-benzoylhydrazinecarbothioamide (**3d**)*

Yield: 73 %; m.p. 215 ºC; IR (KBr, cm^{-1}): 3178 (N-H), 1666; 1645 (C=O), 1172 (C=S); ^1H NMR (500 MHz, *DMSO*-d_6): δ 12.55 (s, 1H, NH), 11.77 (s, 1H, NH), 11.32 (s, 1H, NH), 8.35 (s, 1H, imidazothiazole C_5-H), 7.95 (d, 2H, *J*=8.78 Hz, phenyl), 7.78 (d, 2H, *J*=8.29 Hz, 4-Brphenyl $C_{2,6}$-H), 7.66-7.63 (m, 1H, phenyl), 7.60-7.57 (m, 2H, 4-Brphenyl $C_{3,5}$-H), 7.54-7.50 (m, 2H, phenyl), 7.15 (s, 1H, imidazothiazole C_2-H), 3.99 (s, 2H, CH_2CO). Anal. Calcd. for $C_{21}H_{16}BrN_5O_2S_2$: C, 49.03; H, 3.14; N, 13.61. Found: C, 48.97; H, 3.66; N, 12.89.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-(4-fluorophenyl)hydrazinecarbothioamide (**3e**)*

Yield: 90 %; m.p. 209-210 ºC; IR (KBr, cm^{-1}): 3134 (N-H), 1674 (C=O), 1213 (C=S); ^1H NMR (500 MHz, *DMSO*-d_6): δ 10.40 (s, 1H, NH), 9.81 (s, 1H, NH), 9.73 (s, 1H, NH), 8.24 (s, 1H, imidazothiazole C_5-H), 7.72 (d, 2H, *J*=8.29 Hz, 4-Brphenyl $C_{2,6}$-H), 7.58 (d, 2H, *J*=8.79 Hz, 4-Brphenyl $C_{3,5}$-H), 7.44-7.41 (m, 2H, phenyl), 7.20-7.17 (m, 2H, phenyl), 7.12 (s, 1H, imidazothiazole C_2-H), 3.88 (s, 2H, CH_2CO). Anal. Calcd. for $C_{20}H_{15}BrFN_5OS_2$: C, 47.63; H, 3.00; N, 13.88. Found: C, 47.66; H, 3.19; N, 13.29.

*2-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]-N-(4-methoxyphenyl)hydrazinecarbothioamide (**3f**)*

Yield: 86 %; m.p. 230 ºC; IR (KBr, cm^{-1}): 3296; 3134 (N-H), 1672 (C=O), 1236 (C=S); ^1H NMR (500 MHz, *DMSO*-d_6): δ 10.36 (s, 1H, NH), 9.70 (s, 1H, NH), 9.59 (s, 1H, NH), 8.25 (s, 1H, imidazothiazole C_5-H), 7.71 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{2,6}$-H), 7.57 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{3,5}$-H), 7.28 (d, 2H, *J*=8.79 Hz, phenyl), 7.12 (s, 1H, imidazothiazole C_2-H), 6.91 (d, 2H, *J*=8.79 Hz, phenyl), 3.87 (s, 2H, CH_2CO), 3.76 (s, 3H, OCH_3). ^{13}C NMR (APT) (500 MHz, *DMSO*-d_6): δ 181.50 (C=S), 162.20 (C=O), 157.59 (phenyl C_4), 149.53 (imidazothiazole C_{7a}), 145.47 (imidazothiazole C_6), 134.23 (4-Brphenyl C_1), 132.51 (phenyl C_1), 132.27 (4-Brphenyl $C_{3,5}$), 127.33 (phenyl $C_{2,6}$), 127.25 (4-Brphenyl $C_{2,6}$), 126.85 (imidazothiazole C_3), 120.50 (4-Brphenyl C_4), 114.10 (phenyl $C_{3,5}$), 111.46 (imidazothiazole C_2), 109.75 (imidazothiazole C_5), 55.92 (CH_3), 33.41 (CH_2). Anal. Calcd. for $C_{21}H_{18}BrN_5O_2S_2$: C, 48.84; H, 3.51; N, 13.56. Found: C, 49.05; H, 3.54; N, 13.71.

*General procedure for the synthesis of 3-cycloalkyl/aralkyl/aryl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones (**4a-j**)*

To a suspension of 2-[[6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl]-*N*-alkyl/arylhydrazinecarbothioamides (0.005 mol) in absolute ethanol (30 mL) were added anhydrous sodium acetate (0.02 mol) and ethyl bromoacetate/ethyl 2-bromopropionate (0.005 mol). The reaction mixture was refluxed for 20 h, then cooled, diluted with water and allowed to stand overnight. The crystals were filtered, dried and purified by crystallization from ethanol or ethanol/water.

*3-Benzyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4a**)*

Yield: 96 %; m.p. 232-233 ºC; IR (KBr, cm^{-1}): 3215 (N-H), 1720 (ring C=O), 1670 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ (NH proton not observed), 8.32; 8.10 (2s, 1H, imidazothiazole C_5-H), 7.76 (d, 2H, *J*=8.30 Hz, 4-Brphenyl $C_{2,6}$-H), 7.58 (d, 2H, *J*=7.32 Hz, 4-Brphenyl $C_{3,5}$-H), 7.38-7.19 (m, 5H, phenyl), 7.03; 6.84 (2s, 1H, imidazothiazole C_2-H), 4.82 (s, 2H, NCH_2), 4.15-3.83 (m, 4H, CH_2CO ve SCH_2). Anal. Calcd. for $C_{23}H_{18}BrN_5O_2S_2$: C, 51.11; H, 3.36; N, 12.96. Found: C, 50.74; H, 3.38; N, 13.10.

*3-Phenethyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4b**)*

Yield: 88 %; m.p. 134-135 ºC; IR (KBr, cm^{-1}): 3142 (N-H), 1716 (ring C=O), 1658 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.72; 10.55 (2s, 1H, NH), 8.28; 8.20 (2s, 1H, imidazothiazole C_5-H), 7.78 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{2,6}$-H), 7.59 (d, 2H, *J*=8.30 Hz, 4-Brphenyl $C_{3,5}$-H), 7.28-7.23 (m, 2H, phenyl), 7.21-7.16 (m, 3H, phenyl), 7.08; 7.05 (2s, 1H, imidazothiazole C_2-H), 4.08-3.82 (m, 6H, CH_2CO, SCH_2 ve NCH_2), 2.89 (t, 2H, *J*=7.32 Hz CH_2-Ph). Anal. Calcd. for $C_{24}H_{20}BrN_5O_2S_2.2H_2O$: C, 48.82; H, 4.10; N, 11.86. Found: C, 48.90; H, 3.51; N, 11.87.

*3-Benzoyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4c**)*

Yield: 53 %; m.p. 260 ºC; IR (KBr, cm^{-1}): 3197 (N-H), 1757 (ring C=O), 1681 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 11.48 (s, 1H, NH), 8.16 (s, 1H, imidazothiazole C_5-H), 8.06 (d, 2H, *J*=8.30 Hz, phenyl), 7.65-7.56 (m, 3H, 4-Brphenyl $C_{2,6}$-H and phenyl), 7.51-7.48 (m, 4H, 4-Brphenyl $C_{3,5}$-H and phenyl), 7.20 (s, 1H, imidazothiazole C_2-H), 4.28-4.12 (m, 4H, CH_2CO ve SCH_2). Anal. Calcd. for $C_{23}H_{16}BrN_5O_3S_2$: C, 49.83; H, 2.91; N, 12.63. Found: C, 50.46; H, 2.97; N, 13.02.

*3-(4-Fluorophenyl)-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4d**)*

Yield: 84 %; m.p. 279-281 ºC; IR (KBr, cm^{-1}): 3122 (N-H), 1751 (ring C=O), 1705 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 11.33 (s, 1H, NH), 8.14 (s,1H, imidazothiazole C_5-H), 7.56 (d, 2H, *J*=8.30 Hz, 4-Brphenyl $C_{2,6}$-H), 7.42 (d, 2H, *J*=8.30 Hz, 4-Brphenyl $C_{3,5}$-H), 7.19-7.14 (m, 3H, phenyl ve imidazothiazole C_2-H), 6.91-6.88 (m, 2H, phenyl), 4.36-3.83 (m, 4H, CH_2CO ve SCH_2). Anal. Calcd. for $C_{22}H_{15}BrFN_5O_2S_2$: C, 48.54; H, 2.78; N, 12.86. Found: C, 49.04; H, 2.99; N, 12.82.

*3-(4-Methoxyphenyl)-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4e**)*

Yield: 98 %; m.p. 277-279 ºC; IR (KBr, cm^{-1}): 3209 (N-H), 1732 (ring C=O), 1672 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ (NH proton not observed), 8.14 (s, 1H, imidazothiazole C_5-H), 7.53 (d, 2H, *J*=6.35 Hz, 4-Brphenyl $C_{2,6}$-H), 7.40 (d, 2H, *J*=8.79 Hz, 4-Brphenyl $C_{3,5}$-H), 7.15 (s, 1H, imidazothiazole C_2-H), 6.90 (d, 2H, *J*=6.83 Hz, phenyl), 6.82 (d, 2H, *J*=8.79 Hz, phenyl), 4.22-3.93 (m, 4H, CH_2CO ve SCH_2), 3.80 (s, 3H, OCH_3). ^{13}C NMR (APT) (500 MHz, *DMSO*-d_6): δ 169.23 (thiazolidinone C=O), 166.69 (C=O), 156.99 (phenyl C_4), 152.44 (C=N), 149.60 (imidazothiazole C_{7a}), 145.54 (imidazothiazole C_6), 141.16 (phenyl C_1), 134.02 (4-Brphenyl C_1), 132.31 (4-Brphenyl $C_{3,5}$), 127.14 (4-Brphenyl $C_{2,6}$), 126.69 (imidazothiazole C_3), 122.55 (phenyl $C_{2,6}$), 120.34 (4-Brphenyl C_4), 115.32 (phenyl $C_{3,5}$), 111.61 (imidazothiazole C_2), 109.39 (imidazothiazole C_5), 55.90 (OCH_3), 33.24 (CH_2), 30.75 (thiazolidinone C_5). Anal. Calcd. for $C_{23}H_{18}BrN_5O_3S_2$: C, 49.65; H, 3.26; N, 12.59. Found: C, 49.84; H, 3.11; N, 12.40.

*3-Benzyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (**4f**)*

Yield: 72 %; m.p. 171-172 ºC; IR (KBr, cm^{-1}): 3186 (N-H), 1720 (ring, C=O), 1668 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.68 (s, 1H, NH), 8.26; 8.11 (2s, 1H, imidazothiazole C_5-H), 7.77 (d, 2H, *J*=8.29 Hz, 4-Brphenyl $C_{2,6}$-H), 7.58 (d, 2H, *J*=8.29 Hz, 4-Brphenyl $C_{3,5}$-H), 7.34-7.23 (m, 5H, phenyl), 7.05; 6.87 (2s, 1H, imidazothiazole C_2-H), 4.87; 4.83 (2s, 2H, NCH_2), 4.52; 4.47 (2q, 1H, *J*=7.33; 7.32 Hz SCH), 3.92; 3.85 (2s, 2H, CH_2CO), 1.58; 1.54 (2d, 3H, *J*=7.32 Hz, CH_3). Anal. Calcd. for $C_{24}H_{20}BrN_5O_2S_2$: C, 51.99; H, 3.64; N, 12.63. Found: C, 51.47; H, 3.11; N, 12.17.

*3-Phenethyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (**4g**)*

Yield: 89 %; m.p. 224-225 ºC; IR (KBr, cm^{-1}): 3169 (N-H), 1712 (ring C=O), 1666 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 10.71; 10.54 (2s, 1H, NH), 8.28; 8.20 (2s, 1H, imidazothiazole C_5-H), 7.78 (d, 2H, *J*=8.78 Hz, 4-Brphenyl $C_{2,6}$-H), 7.58 (d, 2H, *J*=8.29 Hz, 4-Brphenyl $C_{3,5}$-H), 7.27-7.23 (m, 2H, phenyl), 7.19-7.16 (m, 3H, phenyl), 7.08; 7.06 (2s, 1H, imidazothiazole C_2-H), 4.33; 4.27 (2q, 1H, *J*=6.83; 7.32 Hz SCH), 4.10; 3.89 (2s, 2H, CH_2CO), 3.87-3.80 (m, 2H, NCH_2), 2.99-2.86 (m, 2H, CH_2-Ph), 1.44; 1.36 (2d, 3H, *J*=7.32 Hz, CH_3). Anal. Calcd. for $C_{25}H_{22}BrN_5O_2S_2$: C, 52.82; H, 3.90; N, 12.32. Found: C, 52.67; H, 3.75; N, 12.07.

*3-Benzoyl-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (**4h**)*

Yield: 88 %; m.p. 192-194 ºC; IR (KBr, cm^{-1}): 3219 (N-H), 1749 (ring C=O), 1697 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 11.52 (s, 1H, NH), 8.17; 8.15 (2s, 1H, imidazothiazole C_5-H), 8.07-8.03 (m, 2H, phenyl), 7.66-7.57 (m, 3H, 4-Brphenyl $C_{2,6}$-H and phenyl), 7.53-7.47 (m, 4H, 4-Brphenyl $C_{3,5}$-H and phenyl), 7.21; 7.20 (2s, 1H, imidazothiazole C_2-H), 4.52; 4.44 (2q, 1H, *J*=7.32 Hz SCH), 4.23-4.11 (m, 2H, CH_2CO), 1.63; 1.56 (2d, 3H, *J*=7.32 Hz, CH_3). Anal. Calcd. for $C_{24}H_{18}BrN_5O_3S_2$: C, 50.71; H, 3.19; N, 12.32. Found: C, 50.72; H, 3.29; N, 12.39.

*3-(4-Fluorophenyl)-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (**4i**)*

Yield: 90 %; m.p. 194-196 ºC; IR (KBr, cm^{-1}): 3118 (N-H), 1747 (ring C=O), 1701 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 11.36 (s, 1H, NH), 8.22; 8.14 (2s,1H, imidazothiazole C_5-H), 7.59-7.53 (m, 2H, 4-Brphenyl $C_{2,6}$-H), 7.45-7.42 (m, 2H, 4-Brphenyl $C_{3,5}$-H), 7.31-7.14 (m, 2H, phenyl), 7.03 (s, 1H, imidazothiazole C_2-H), 6.92-6.87 (m, 2H, phenyl), 4.54; 4.50 (2q, 1H, *J*=7.32 Hz SCH), 4.16-4.01 (m, 2H, CH_2CO), 1.58; 1.53 (2d, 3H, *J*=7.32 Hz, CH_3). Anal. Calcd. for $C_{23}H_{17}BrFN_5O_2S_2$: C, 49.47; H, 3.07; N, 12.54. Found: C, 49.68; H, 3.07; N, 12.51.

*3-(4-Methoxyphenyl)-2-[((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (**4j**)*

Yield: 64 %; m.p. 159-161 ºC; IR (KBr, cm^{-1}): 3163 (N-H), 1732 (ring C=O), 1672 (C=O); ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 11.34; 10.58 (2s, 1H, NH), 8.22; 8.12 (2s, 1H, imidazothiazole C_5-H), 7.77-7.71 (m, 2H, 4-Brphenyl $C_{2,6}$-H), 7.59-7.53 (m, 2H, 4-Brphenyl $C_{3,5}$-H), 7.42-6.80 (m, 5H, phenyl ve imidazothiazole C_2-H), 4.51; 4.48 (2q, 1H, *J*=7.32 Hz SCH), 3.83, 3.78 (2s, 2H, CH_2CO), 3.76 (s, 3H, OCH_3), 1.62; 1.53 (2d, 3H, *J*=6.84; 7.32 Hz, CH_3). ^{13}C NMR (APT) (500 MHz, *DMSO*-d_6): δ 175.00; 172.58 (thiazolidinone C=O), 166.44 (C=O), 159.84 (phenyl C_4), 151.40; 151.09 (C=N), 149.55 (imidazothiazole C_{7a}), 145.44 (imidazothiazole C_6), 140.98 (phenyl C_1), 134.20 (4-Brphenyl C_1), 132.30 (4-Brphenyl $C_{3,5}$), 127.29 (4-Brphenyl $C_{2,6}$), 126.28 (imidazothiazole C_3), 122.60 (phenyl $C_{2,6}$), 120.40 (4-Brphenyl C_4), 115.32 (phenyl $C_{3,5}$), 111.86 (imidazothiazole C_2), 109.60 (imidazothiazole C_5), 56.09 (OCH_3), 43.10; 40.49 (thiazolidinone C_5), 33.77 (CH_2), 19.90; 19.76 (thiazolidinone 5-CH_3). Anal. Calcd. for $C_{24}H_{20}BrN_5O_3S_2$: C, 49.60; H, 3.66; N, 12.23. Found: C, 49.17; H, 3.40; N, 12.54.

Biological Methods

Isolation of Aldose Reductase Enzyme

Kidneys which were obtained from wistar albino rats, were thawed on ice and homogenized with 3 volume of distilled water, homogenate were centrifuged at 10.000x g for 20 minutes. Saturated ammonium sulfate was added to the supernatant for 40% saturation. The thick

suspension was stirred for 15 minutes, was centrifuged at 10.000x g for 20 minutes. The inert protein left in the supernatant was removed by increasing the ammonium sulfate concentration to 50% saturation followed by centrifuging the mixture at 10.000x g for 20 minutes. The aldose reductase enzyme was precipitated from the 50% saturated solution by adding powdered ammonuim sulfate to 75% saturation and was recovered by centrifugation at 10.000x g for 20 minutes[49]. Protein concentration was measured by the method of Bradford[50] using bovine serum albumin as a standart. Protein concentration was 5,13 ± 0,09 mg/mL.

Determination of Aldose Reductase Activity

Aldose Reductase 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. DL-glyceraldehyde was used as a substrate. The enzyme was dissolved in 10 ml 0,05 M NaCI solution. 25 µl enzyme was added to incubation medium which contains 175 µl phosphate buffer (0,067 M, pH: 6,2), 25 µl NADPH (2 x 10^{-5} M final concentration) and 25 µl inhibitor compound (10^{-4} M stock solution). The reaction was started by the adding 25 µl DL-glyceraldehyde (5 x 10^{-5} M final concentration) to the incubation medium and the decrease in NADPH concentration was recorded at 340 nm for 10 minutes at 37 ^{0}C. Readings were taken at intervals in the periods when the changes in absorbance were linear[49].

The AR activity was calculated as;

$$Activity\ \left(\frac{U}{mL}\right) = \frac{(\Delta A\ Enzyme\ /min - \Delta A\ Control/min)}{(6.22 \times Volume\ of\ enzyme) \cdot (Total\ Volume)}$$

where, 6.22 is micromolar extinction coefficient of NADPH at 340 nm

$$Specific\ activity\ (U/mg\ protein) = \frac{Activity\ (U/mL)}{Protein\ Cont.\ (mg/mL)}$$

The AR inhibitory activity of each sample was calculated using the formula;

$$\% \ Inhibition = \left[1 - \frac{\Delta A \ Sample/min - \Delta A \ Blank/min}{\Delta A \ Control/min - \Delta A \ Blank/min}\right] \times 100$$

RESULTS AND DISCUSSION

The target compounds were prepared from 2-[6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide (**2**)[51], by a two step synthesis as shown in Scheme 1. By heating ethyl (6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetate hydrobromide[52] and hydrazine-hydrate in ethanol, 2-[6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide were obtained. Hydrazide and cycloalkyl/aralkyl/aryl isothiocyanates were heated in ethanol to yield 2-[[6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl]-*N*-cycloalkyl/aralkyl/aryl hydrazinecarbothioamides **(3a-f)**. **3a-f** were then reacted with ethyl α-bromoacetate/ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in absolute ethanol to yield 3-cycloalkyl/aralkyl/aryl-2-[((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones (**4a-j**).

Scheme 1

The IR spectra of **3a-f** displayed bands at about 3296-3118 and 1674-1645 cm^{-1} associated with the N-H and C=O functions. Absorbtion bands at 1236-1163 cm^{-1}, which were attributed to the C=S streching vibrations observed in the IR spectra of compounds **3a-f**. The three ^{1}H NMR resonances located in the region of 12.55-7.66 ppm were assigned to the NH protons of the hydrazinecarbothioamides and supported the structures of **3a-f**[53].

New C=O bands (1757-1712 cm^{-1}) in the IR spectra of 4-thiazolidinones (**4a-j**) provided confirmatory evidence for ring closure[54]. ^{1}H NMR and ^{13}C NMR data were also in agreement with the formation of 4-thiazolidinone ring. NH signals of **4b-d** and **4f-j** appeared at δ 11.52-10.54 ppm. In the ^{1}H-NMR spectra of compounds **4f-j**, C**H**-CH_3 protons appeared as a duble quartet (1H) at δ 4.54-4.33 and δ 4.50-4.27 ppm and CH-C**H$_3$** protons appeared as a double doublet (3H) at δ 1.63-1.44 and δ 1.56-1.36 ppm indicating the presence of two isomers in unequal proportions in *DMSO*-d_6. This may be explained on the basis of the difference in the relative stability of the *E* and *Z* isomers formed due to the rotational restriction about the exocyclic N=C bond at position 2 of the 4-thiazolidinone ring[54]. In the

^{13}C NMR (APT) spectra of **3f**, **4e** and **4j** chosen as prototypes, all the carbons resonated in the expected regions[55]. For example, the protons resonated at δ 30.75, δ 152.44 and δ 169.23 ppm in the ^{13}C NMR (APT) spectrum of compound 3-(4-methoxyphenyl)-2-[((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (**4e**) assigned for S-CH_2, C=N and C=O moieties, confirms the carbon skeleton of 4-thiazolidinone ring. Furthermore, ^{13}C NMR resonances of the S-CH, C=N and C=O carbons of compound bearing 5-methyl substituted 4-thiazolidinone (**4j)** were observed at δ 43.10; 40.49, δ 151.40; 151.09 and δ 175.00; 172.58 ppm, respectively. The protons of the imidazo[2,1-*b*]thiazole nucleus and the other protons resonated at the expected regions[55].

The *in vitro* AR inhibitory activity of the synthesized compounds is listed in Table 1. The enzyme activity was assayed by spectrophotometrically monitoring the NADPH oxidation that accompanies the reduction of DL-glyceraldehyde which is used as substrate. The inhibition study was performed merely by using a 10^{-4} M concentration of each drug. Depending upon the results the best aldose reductase inhibitory effect was found at the ratio of 25.41 % in compound **3d**. Among these inhibitors, in compound **3c** which the phenethyl substituted compound, was observed 14.03 % inhibition while, compound **3e** and **3f** which the are 4-fluorophenyl and 4-methoxyphenyl substituted compounds, were observed 21.31 % and 13.73 % inhibition, respectively (Table 1). Compound **4g** which is derived from compound **4b** as a result of methylation of the nitrogen atom on the thiazolidinone ring, showed 8.22 % inhibition while compound **4h** which is obtained from compound **4c** by methylation of the nitrogen atom on the thiazolidinone ring, showed 5.93 % inhibition. (Table 1). Compounds **4i** and **4j** which are obtained by methylation of compounds **4d** and **4e** showed 9.31 % and 1.42 % inhibition, respectively. According to these results, 5-nonsubstituted thiazolidinone derivatives (**4a-e**) did not show an inhibition but 5-methyl substituted thiazolidinone derivatives (**4g-j**) showed significant inhibition between the range 1.42-9.31 %. The positive influence was exerted by 5-methyl substitution at thiazolidinone ring on activity. The most efficient compounds were hydrazinecarbothioamide derivatives (**3c-f**) with the 25.41-13.73 % (Table 1).

Table 1

CONCLUSION

Aldose reductase inhibitors are one of quite a few types of drugs that have shown prevention of diabetic complications. It is still a challenge to develop a drug candidate molecule. We report the synthesis and aldose reductase inhibitory activity effects of the hydrazinecarbothioamides (**3a**-**f**) and 4-thiazolidinones (**4a**-**j**) bearing an imidazo[2,1-*b*]thiazole moiety. On the basis of our preliminary AR inhibitory screening results on imidazo[2,1-*b*]thiazole derivatives, we embarked on the synthesis of more derivatives to discover more active molecules.

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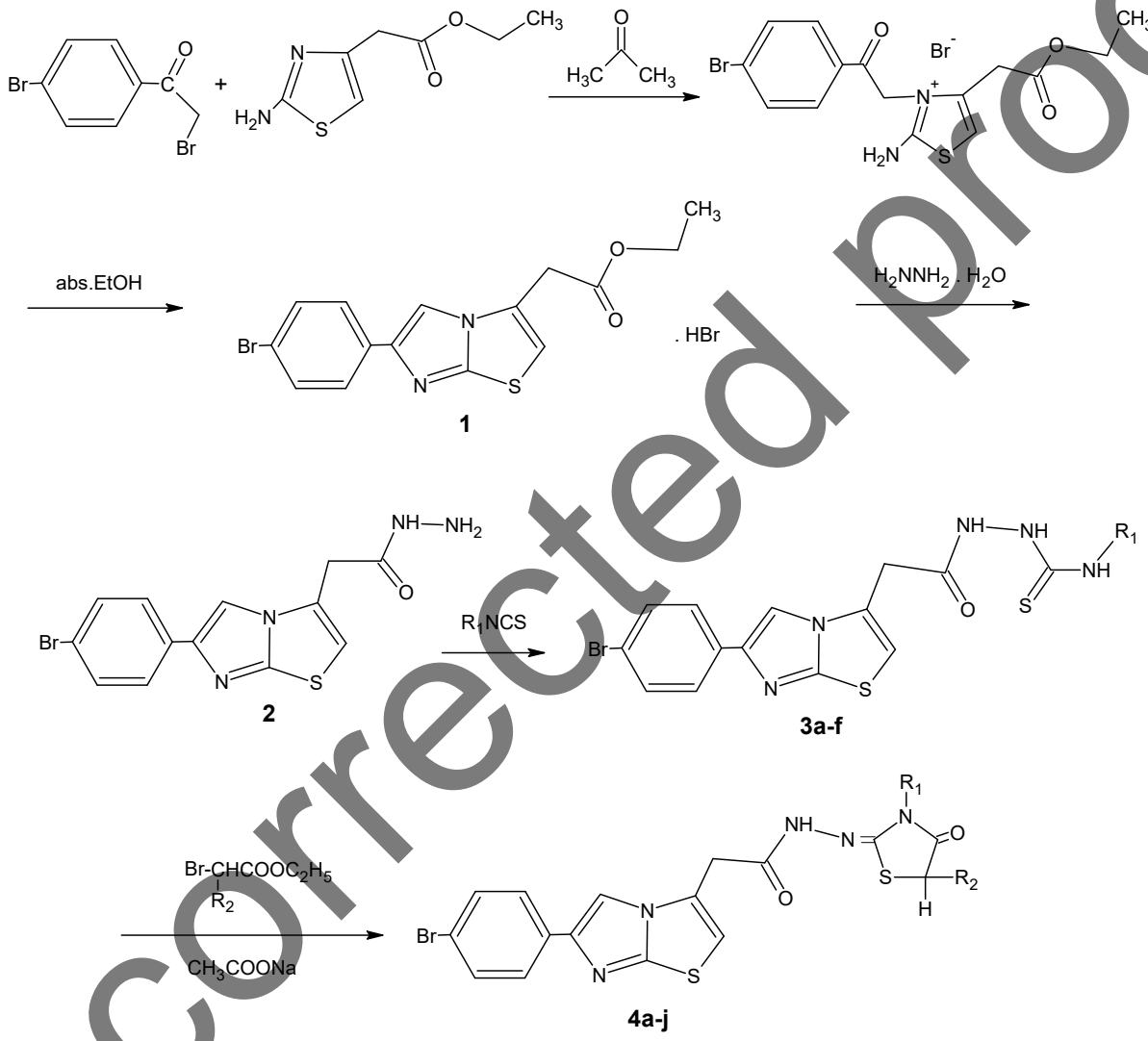

Scheme 1. Synthesis of title compounds **3a-f** and **4a-j**.

Table 1. Aldose reductase inhibition by compounds **3a**-**f** and **4a**-**j***.

Compounds	**R_1**	**R_2**	**Inhibition ± SD (%)**
3a	C_6H_{11}	-	0.00±0.00
3b	CH_2-C_6H_5	-	0.00±0.00
3c	CH_2-CH_2-C_6H_5	-	14.03±1.07
3d	CO-C_6H_5	-	25.41±0.12
3e	4-FC_6H_4	-	21.31±1.07
3f	4-$CH_3OC_6H_4$	-	13.73±0.49
4a	CH_2-C_6H_5	H	0.00±0.00
4b	CH_2-CH_2-C_6H_5	H	0.00±0.00
4c	CO-C_6H_5	H	n.t.
4d	4-FC_6H_4	H	0.00±0.00
4e	4-$CH_3OC_6H_4$	H	0.00±0.00
4f	CH_2-C_6H_5	CH_3	0.00±0.00
4g	CH_2-CH_2-C_6H_5	CH_3	8.22±1.55
4h	CO-C_6H_5	CH_3	5.93±2.05
4i	4-FC_6H_4	CH_3	9.31±1.90
4j	4-$CH_3OC_6H_4$	CH_3	1.42±1.79

* Values represent the mean ±S.D. of three individual experiments.

n.t.: not tested