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ORIGINAL ARTICLE

Synthesis and Aldose Reductase Inhibitory Effect of Some New Hydrazinecarbothioamides and 4-Thiazolidinones Bearing an Imidazo[2,1-*b*] Thiazole Moiety

İmidazo[2,1-*b*]Tiyazol Çekirdeği Taşıyan Bazı Yeni Hidrazinkarbotiyoamitler ve 4-Tiyazolidinonların Sentezi ve Aldoz Redüktaz İnhibitör Etkileri

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ABSTRACT

Objectives: 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 their aldose reductase (AR) 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 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 inhibitory activity.

Conclusion: The findings of this study indicate that the different derivatives of the compounds in this study may be considered 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 türevlerini sentezlemek, yapılarını aydınlatmak ve aldoz redüktaz (AR) inhibitör etkilerini araştırmaktır.

Gereç ve Yöntemler: 2-[6-(4-bromofenil)imidazo[2,1-*b*]tiyazol-3-il]asetohidrazitten (**2**) 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 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

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by deficient production of insulin by the 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 to almost double by 2030.[1] Furthermore, hyperglycemia is the major risk factor responsible for the broad range of complications that are the main cause of mortality and morbidity in people with DM. There are two forms of complications: acute and chronic, 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 protein kinase C pathway, oxidative stress, and accelerated advanced glycation end-product formation.[2,3]

Aldose reductase (AR) (AR; ALR2; EC 1.1.1.21) is the first enzyme in the polyol pathway and reduces glucose to sorbitol in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). Sorbitol dehydrogenase, the second enzyme in the polyol pathway, oxidizes the intermediate sorbitol to fructose with NAD^+ as cofactor (Figure 1).[4,5] 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 the rate is more than 30% under hyperglycemia (20 mM).[6] Increased AR activity has been implicated in the pathogenesis of 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 AR inhibitors (ARIs) have been obtained over the last 30 years, the clinical efficacy of these compounds is not completely satisfactory and several of them have shown undesirable side effects.[14] Sorbinil, tolrestat, zopolrestat and ponalrestat were withdrawn from clinical trials because of their side effects.[15] Various thiazolidinedione derivatives are a newer class of antidiabetic drugs[16-20] that improve glycemic control in type 2 diabetes by increasing insulin action in skeletal muscles, the liver, and adipose tissue.[21,22]

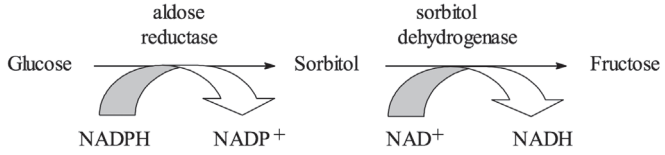


Figure 1. Polyol pathway

NADPH: Nicotinamide adenine dinucleotide phosphate

There has been considerable interest in the chemistry of 4-thiazolidinone ring systems, which are 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. Moreover, 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 ARIs[37-43] or different biological activities,[44-48] we report the synthesis of some novel imidazo[2,1-*b*]thiazole derivatives incorporating two known bioactive nuclei such as hydrazinecarbothioamide or 4-thiazolidinone.

EXPERIMENTAL

Chemical methods

Melting points were determined 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 dimethyl sulfoxide (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) was 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°C; 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°C; 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°C; 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°C; IR (KBr, cm^{-1}): 3178 (N-H), 1666; 1645 (C=O), 1172 (C=S); ^{1}H-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°C; IR (KBr, cm^{-1}): 3134 (N-H), 1674 (C=O), 1213 (C=S); ^{1}H-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°C; IR (KBr, cm^{-1}): 3296; 3134 (N-H), 1672 (C=O), 1236 (C=S); ^{1}H-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°C; 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 and 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°C; 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 and 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°C; 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 and 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°C; 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 and imidazothiazole C_2-H), 6.91-6.88 (m, 2H, phenyl), 4.36-3.83 (m, 4H, CH_2CO and 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°C; 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 and 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°C; 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°C; 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°C; 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°C; 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°C; 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 and 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 obtained from Wistar albino rats were thawed on ice and homogenized with 3 volumes of distilled water. The homogenate were centrifuged at 10,000 × g for 20 min. Saturated ammonium sulfate was added to the supernatant for 40% saturation. The thick suspension was stirred for 15 min and then centrifuged 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.[49] Protein concentration was measured as described by Bradford[50] using bovine serum albumin as a standard. The protein concentration was 5.13±0.09 mg/mL.

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. DL-glyceraldehyde was used as a substrate. The enzyme was dissolved in 10 mL of 0.05 M NaCl solution. Then 25 µL of enzyme was added to the incubation medium, which contained 175 µL of phosphate buffer (0.067 M, pH: 6.2), 25 µL of NADPH (2×10^{-5} M final concentration), and 25 µL of inhibitor compound (10^{-4} M stock solution). The reaction was started by adding 25 µL of DL-glyceraldehyde (5×10^{-5} M final concentration) to the incubation medium and the decrease in NADPH concentration was recorded at 340 nm for 10 min at

37°C. Readings were taken at intervals in the periods when the changes in absorbance were linear.[49]

The AR activity was calculated as,

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

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

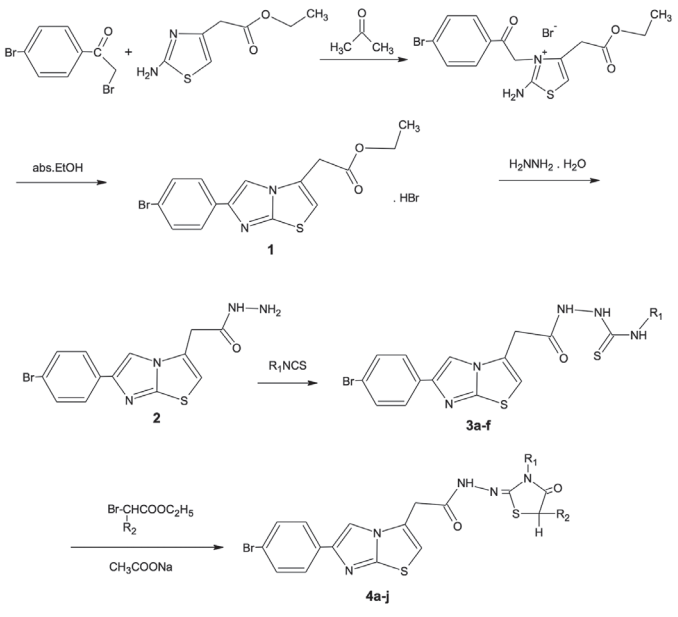
$$\text{Specific activity (U/mg protein)} = \frac{\text{Activity (U/mL)}}{\text{Protein Cont. (mg/mL)}}$$

The ARI activity of each sample was calculated using the formula.

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

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 was 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



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

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**).

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. Absorption bands at 1236-1163 cm^{-1}, which were attributed to the C=S stretching vibrations, were 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 a 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 double 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 the 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, confirming the carbon skeleton of the 4-thiazolidinone ring. Furthermore, ^{13}C-NMR resonances of the S-CH, C=N, and C=O carbons of the 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 in the expected regions.[55]

The *in vitro* ARI 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 ARI effect was found at the rate of 25.41% in compound **3d**. Among these inhibitors, in compound **3c**, which is the phenethyl substituted compound, 14.03% inhibition was observed, while in compounds **3e** and **3f**, which are 4-fluorophenyl and 4-methoxyphenyl substituted compounds, 21.31% and 13.73% inhibition were observed, respectively (Table 1). Compound **4g**, derived from compound **4b** as a result of methylation of the nitrogen atom on the thiazolidinone ring, showed 8.22% inhibition, while compound **4h**, obtained from compound **4c** by methylation of the nitrogen atom on the thiazolidinone ring, showed 5.93% inhibition (Table 1). Compounds **4i** and **4j**, 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 inhibition but 5-methyl

substituted thiazolidinone derivatives (**4g-j**) showed significant inhibition in the range 1.42-9.31%. A positive influence was exerted by 5-methyl substitution at the thiazolidinone ring on activity. The most efficient compounds were hydrazinecarbothioamide derivatives (**3c-f**) with 25.41-13.73% (Table 1).

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

SD: Standard deviation, n.t.: Not tested, *Values represent the mean ± SD of three individual experiments

CONCLUSION

ARIs 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 ARI activity effects of hydrazinecarbothioamides (**3a-f**) and 4-thiazolidinones (**4a-j**) bearing an imidazo[2,1-*b*] thiazole moiety. On the basis of our preliminary ARI 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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