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Research Article

α-GLUCOSIDASE INHIBITORY ACTIVITY OF 4-ARYL-N-(2,4-THIAZOLIDINEDIONE-5-ACETYL)-1,3-THIAZOL-2-AMINES

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ABSTRACT: A series of N-(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides **3a-k** and N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides **3l-n** are synthesized and evaluated for their α-glucosidase inhibitory activity. N-[4-(*m*-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**3g**) and N-[4-(*o*-fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**3j**) have shown very good inhibition. The remaining compounds have exhibited moderate to good activity ranging from 37- 63 % of α-glucosidase enzyme inhibition.

Keywords: Thiazole, thiazolidinedione, acetamides, HBTU, postprandial hyperglycemia (PPHG), α-glucosidase, diabetes

INTRODUCTION

Postprandial hyperglycemia (PPHG) is a prominent and early defect in ensuing T2DM (Carroll M.F, et.al, 2003). The deterioration of glucose homeostasis in T2DM patients progresses in several stages from postprandial to the fasting hyperglycemia (Monnier L, et.al, 2007). In diabetes, the postprandial phase is characterized by a rapid and abnormal increase in blood glucose levels, and these postprandial "hyperglycemic spikes" are believed to be responsible for the onset of cardiovascular complications (Ceriello A, 2005). The impact of the post meal hyperglycemia on the markers of cardiovascular disease such as oxidative stress, inflammation, endothelial dysfunction and carotid IMT has been understood (Gallwitz B, 2009). Ross S.A, et.al (2004) and Misra S, et.al, (2011) have reported that inhibitors of α-glucosidase exhibit useful anti-hyperglycemic effects by slowing down digestion and absorption of dietary carbohydrates and could help in reducing the risk of diabetes and consequential diseases. As suggested by Gerich J.E. (1989) and Gupta D, et.al (2005), the combination of proper diet, exercise and hypoglycemic agents is a better therapeutic strategy to treat patients with noninsulin-dependent diabetes mellitus (NIDDM).

It is known that 2,4-thiazolidinediones (2,4-TZDs) are a new class of antidiabetic agents, effective in normalizing glucose and lipid metabolism associated with insulin resistance. Hence, they are expected to be useful in the treatment of patients with both type 2 diabetes mellitus and obesity (Sohda T, et.al, 1990; Suter S, et.al, 1992; Iwamoto Y, et.al, 1991; Costantino L, et.al, 1997). The thiazolidinedione nucleus is present in pioglitazone and KRP-297 molecules used in the treatment of diabetic patients (Murakami K, et.al, 1998). In addition, thiazole derivatives have exhibited a variety of biological properties such as antibacterial activity (Tsuji K, et.al, 1994), anti-inflammatory activity (Sharma R N, et.al, 2009), antihypertensive activity (Patt W C, et.al, 1992), anti-HIV activity (Bell F W, et.al, 1995), hypnotics activity (Ergenc N, et.al, 1999), antischizophrenia activity (Jaen J C, et.al, 1990), antiallergic activity (Hargrave K D, et.al, 1983), antitumor and cytotoxic activity (Gulsory E, et.al, 2007). Some 2-aminothiazolamides have been reported as potential radical scavengers (Kim K M, et.al, 2003).

The N-(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides and N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide derivatives (Koppireddi S, et.al, 2013) have shown anti-inflammatory and antioxidant activity (DPPH radical scavenging, superoxide anion scavenging, lipid peroxide inhibition, erythrocyte hemolytic inhibition).

These molecules contain both thiazolidine and thiazole nuclei separated by amide linkage. In our quest to evaluate various 2-(2,4-dioxo-1,3-thiazolidin-5-yl) acetamide derivatives for possible α-glucosidase inhibition activity, we have prepared several of these compounds by a known procedure (Koppireddi S, et.al, 2013), and obtained their α-glucosidase inhibition potential.

EXPERIMENTAL SECTION

General: Melting points are determined on the Veego (VMP-MP) melting point apparatus and are uncorrected. IR Spectra are recorded on a Perkin-Elmer FT-IR 1600 spectrometer using KBr optics.^{1}H NMR spectra are recorded on Bruker-300 MHz, spectrometer in CDCl3 using TMS as internal standard. Mass spectral analysis using electrospray ionization (ESI) and high resolution mass spectrometry (HRMS) experiments are performed using a quadrupole time-of-flight mass spectrometer (QSTAR XL, Applied Biosystems/MDS Sciex, Foster City, CA, USA), equipped with an ESI source.

Preparation of of N-(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-l)acetamides (3a-k) and N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide derivatives (3l-n)

General procedure

The general protocol followed by us in obtaining 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide compounds **4a-n** is illustrated for the synthesis of N-(4-phenyl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**4a**) as an example [23]. A solution of compound **1** (0.4 g, 2.55 mmol) in DCM (10 mL) is cooled to 0 ^{o}C and then charged with HOBT (0.36 g, 2.4 mmol), followed by HBTU (0.90 g, 2.4 mmol). The reaction mixture is stirred at 0 ^{o}C for 45 minutes. After that, a solution of 4-phenylthiazol-2-amine, **3a** (0.29 g, 1.70 mmol) and DIEA (0.8 mL, 5.1 mmol) in a mixture of DCM (5 mL) and DMF (2.5 mL) is added drop wise over 5 minutes. The reaction temperature is initially maintained at 0 ^{o}C for 1 h and later at RT for 10 h. Completion of reaction is evidenced by TLC analysis. After evaporating the DCM solvent on rotavapor, the reaction mixture is diluted with 40 mL of distilled water and extracted with (3 x 15 mL) of ethyl acetate. The combined organic layer is washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL), followed by saturated aqueous sodium chloride solution (2 x 20 mL). After drying over anhydrous sodium sulfate, the organic layer is filtered and the filtrate is stripped off the solvent. The crude product thus obtained is purified by column chromatography over silica gel. The rest of the 2-(thiazolidinedion-5-yl)acetamide derivatives (**4b-n**) are prepared similarly by reacting 2,4-dioxo-1,3-thiazolidine-5-acetic acid (**1**) with the appropriate amine (**3b-n)**.

N-(4-Phenyl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3a).
IR (KBr): *v* 3340, 3170, 3040, 1750, 1692, 1556, 1407, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.06-3.14 (m, 1H, CH_2), 3.38 (dd, *J* = 17.1, 3.5 Hz, 1H), 4.56 (dd, *J* = 9.2, 3.5 Hz, 1H), 7.20 (s, 1H), 7.23-7.38 (m, 3H), 7.78 (d, *J* = 7.1 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.5, 45.8, 106.7, 125.1, 127.0, 127.8, 133.7, 149.0, 157.0, 167.0, 171.4, 174.0 ppm.

N-[4-(p-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3b). IR (KBr): *v* 3379, 3136, 3042, 1747, 1673, 1154, 1075, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) : δ 3.15 (dd, *J* = 17.1, 8.6 Hz, 1H), 3.38-3.40 (m, 1H), 4.77 (dd, *J* = 8.6, 3.7 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.1, 45.5, 107.0, 126.2, 127.6, 132.1, 147.0, 156.8, 166.8, 171.1, 174.4 ppm.

N-[4-(p-Fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3c).
IR (KBr): *v* 3240, 3162, 3041, 1760, 1680, 1560, 1410, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.15-3.23 (m, 1H), 3.37 (dd, *J* = 17.7, 3.7 Hz, 1H), 4.59-4.62 (m, 1H), 7.06-7.11 (m, 2H), 7.23 (s, 1H), 7.81-7.85 (m, 2H), 11.96 (br s, 1H, D_2O exchangeable), 12.37 (br s, 1H, D_2O exchangeable) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 35.5, 44.5, 105.8, 113.4, 113.7, 125.7, 129.0, 146.2, 155.7, 166.2, 170.4, 173.7 ppm.

N-[4-(p-Bromophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3d).
IR (KBr): *v* 3371, 3140, 3043, 1748, 1677, 1155, 1065, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.14-3.18 (m, 1H), 3.36 (dd, *J* = 17.1, 3.5 Hz, 1H), 4.58 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.34 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 11.95 (br s, 1H, D_2O exchangeable), 12.39 (br s, 1H, D_2O exchangeable) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 36.3, 45.0, 106.9, 119.8, 126.1, 130.1, 132.1, 146.8, 156.3, 166.4, 170.7, 174.0 ppm.

N-[4-(p-Iodophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3e).
IR (KBr): *v* 3200, 3112, 3040, 1747, 1680, 1159, 1065, 625 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.05 (dd, *J* = 17.1, 9.6 Hz, 1H), 3.37 (dd, *J* = 17.3, 3.3 Hz, 1H), 4.55-4.59 (m, 1H), 7.25 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 36.9, 45.4, 99.2, 107.2, 126.7, 132.9, 136.5, 156.8, 169.9, 174.4 ppm.

N-[4-(o-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3f). IR (KBr): *v* 3211, 3134, 3075, 1756, 1701, 1138, 1039, 748 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.09 (dd, *J* = 17.1, 9.2 Hz, 1H), 3.40 (dd, *J* = 17.1, 3.7 Hz, 1H), 4.61 (dd, *J* = 9.2, 3.7 Hz, 1H), 7.25-7.37 (m, 2H) 7.44-7.47 (m, 2H), 7.81-7.85 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.5, 45.8, 111.9, 126.0, 128.0, 129.6, 130.3, 131.0, 132.6, 145.5, 156.0, 167.1, 171.5, 174.7 ppm.

N-[4-(m-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3g)

IR (KBr): *v* 3288, 3174, 3052, 1753, 1676, 1156, 1074, 741 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.16 (dd, *J* = 17.1, 8.4 Hz, 1H), 3.99 (dd, *J* = 14.1, 6.9 Hz, 1H), 4.78 (dd, *J* = 8.6, 3.9 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.7, 7.9 Hz, 1H), 7.82 (s,1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.95 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.7, 45.9, 108.0, 123.3, 125.5, 127.0, 129.4, 133.7, 135.7, 143.0, 158.9, 167.3, 171.6, 174.8 ppm.

N-[4-(o-Tolyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3thiazolidin-5-yl)acetamide (3h).
IR (KBr): *v* 3291, 3155, 3054, 1739, 1687, 1167, 1064, 740 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 2.44 (s, 3H), 3.07(dd, *J* = 17.5, 9.3 Hz, 1H), 3.42 (dd, *J* = 16.5, 4.1 Hz, 1H), 4.59-4.61 (m, 1H), 6.92 (s, 1H), 7.19-7.21 (m, 3H), 7.53 (d, *J* = 7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 20.1, 37.1, 45.5, 109.5, 124.7, 126.8, 128.5, 129.8, 133.7, 134.7, 148.8, 155.9, 166.7, 171.2, 174.4 ppm.

N-[4-(m-Tolyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3i).
IR (KBr): *v* 3275, 3154, 3050, 1748, 1699, 1161, 1091 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 2.39 (s, 3H), 3.08 (dd, *J* = 17.1, 9.6 Hz, 1H), 3.44 (dd, *J* = 17.1, 3.7 Hz, 1H), 4.58 (dd, *J* = 9.8, 3.7 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.17 (s, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.63 (d, *J* = 6.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 21.0, 36.9, 46.3, 108.0, 122.7, 126.2, 128.4, 128.5, 134.0, 137.7, 148.9, 157.2, 168.1, 172.4, 175.7 ppm.

N-[4-(o-Fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3j). IR (KBr): *v* 3226, 3153, 3053, 1739, 1687, 1169, 1062, 739 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.09 (dd, *J* = 17.1, 9.6 Hz, 1H), 3.45 (dd, *J* = 17.1, 3.5 Hz, 1H), 4.59 (dd, *J* = 9.8, 3.5 Hz, 1H), 7.11-7.23 (m, 2H), 7.39 (d, *J* = 1.8 Hz, 1H),7.56 (s, 1H), 8.01 (t, *J* = 7.5, 7.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.2, 45.6, 108.3, 111.1 (d, *J* = 13.7 Hz), 114.9, 115.2, 123.3, 128.0, (d, *J* = 8.8 Hz), 128.4, 142.5, 156.0, 166.9, 171.3, 174.6 ppm.

N-[4-(o-Methoxyphenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3k). IR (KBr): *v* 3251, 3184, 3070, 1759, 1670, 1115, 1056, 750 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz): δ 3.09-3.14 (m, 1H), 3.45 (dd, *J* = 16.8, 3.3 Hz, 1H), 3.95 (s, 3H), 4.59 (dd, *J* = 10.1, 3.3 Hz, 1H), 6.99-7.02 (m, 2H) 7.26 (t, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 8.08 (d, *J* = 6.7 Hz, 1H) 11.8 (br s, 1H, D_2O exchangeable), 12.1 (br s, 1H, D_2O exchangeable) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 36.9, 46.3, 55.3, 111.6, 111.8, 120.4, 122.4, 128.8, 155.7, 144.7, 156.5, 168.0, 172.5, 175.7 ppm.

N-(6-Nitro-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3l).
IR (KBr): *v* 3275, 3193, 2917, 1747, 1704, 1165, 1044, 749 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 3.17 (dd, *J* = 17.9, 8.9 Hz, 1H), 3.50 (dd, *J* = 17.9, 2.9 Hz, 1H), 4.62 (dd, *J* = 8.9, 3.9 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 8.27 (d, *J* = 8.9 Hz, 1H), 8.77 (s, 1H), 11.96 (brs, 1H, D_2O exchangeable), 12.84 (brs, 1H, D_2O exchangeable) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 37.2, 46.0, 118.8, 120.6, 121.7, 132.1, 143.0, 153.2, 162.8, 169.7, 172.3, 175.5 ppm.

N-(6-Methoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3m).
IR (KBr): *v* 3207, 3094, 3008, 1738, 1675, 1172, 1060, 639 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz): δ 3.05 (dd, *J* = 17.1, 9.6 Hz, 1H), 3.40 (dd, *J* = 17.1, 3.5 Hz, 1H), 3.85 (s, 3H), 4.54 (dd, *J* = 9.4, 3.3 Hz, 1H), 6.92-6.96 (m, 1H), 7.26 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 38.8, 49.6, 53.4, 102.0, 112.0, 118.0, 130.6, 140.5, 153.9, 168.3, 188 ppm.

N-(6-Ethoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (3n).
IR (KBr): *v* 3205, 3100, 2928, 1743, 1681, 1175, 1060, 717 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): δ 1.39 (t, *J* = 6.9 Hz, 3H), 3.06-3.15 (m, 1H), 3.37 (dd, *J* = 17.1, 3.7 Hz, 1H), 4.02 (q, *J* = 6.7, 6.9 Hz, 2H), 4.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.91 (dd, *J* = 11.1, 2.2 Hz 1H), 7.28 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 13.21, 36.2, 44.7, 62.2, 103.0, 113.0, 119.0, 131.6, 141.5, 153.8, 154.1, 166.7, 170.5, 173.9 ppm.

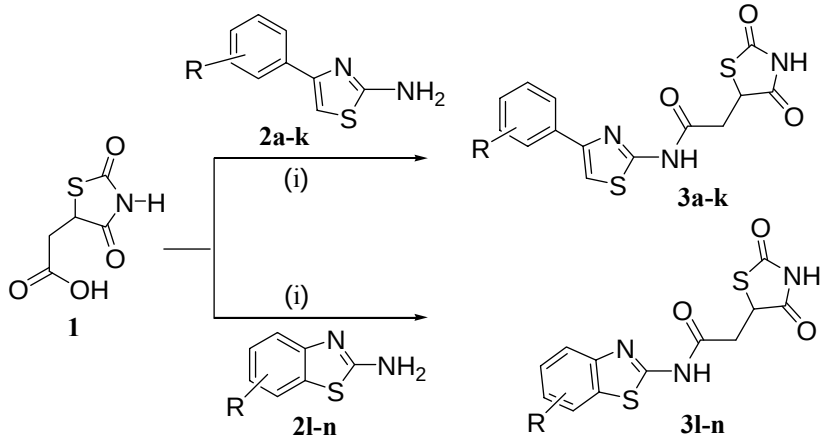
***In vitro* α-glucosidase inhibitory assay**

The general protocol followed for determining the α-glucosidase inhibitory activity of compounds **3a-n** is described here. Rat intestinal acetone powder in normal saline (100: 1; w/v) is sonicated thoroughly and the supernatant is used as a source of crude intestinal α-glucosidase after centrifugation. In brief, 10 µL of test samples dissolved in dimethyl sulfoxide (DMSO) are reconstituted in 100 µL of 100 mM-phosphate buffer (pH 6.8) in 96-well microplate and incubated with 50 µL of crude intestinal α-glucosidase or yeast α-glucosidase (0.76 units/mL) for 5 minutes before 50 µL substrate (5 mM, p-nitrophenyl-α-D-glucopyranoside prepared in same buffer) is added. Release of p-nitrophenol is measured at 405 nm spectrophotometrically ($Spectra_{max}$ $Plus^{384}$, Molecular Devices Corporation, Sunnyvale, CA, USA) 5 min after incubation with substrate. Individual blanks for test samples are prepared to correct background absorbance where substrate is replaced with 50 µL of buffer. Control sample contained 10 µL DMSO in place of test samples. Percentage of enzyme inhibition is calculated as (1-B/A) x 100 where [A] represents absorbance of control without test samples, and [B] represents absorbance in presence of test samples.

RESULTS AND DISCUSSION

Chemistry

2-(2,4-Dioxo-1,3-thiazolidin-5-yl)acetic acid (**1**) is obtained in good yield by refluxing maleic anhydride and thiourea in concentrated hydrochloric acid for 5 h as reported earlier (Zimenkovskii B S, et.al, 2006). The 4-aryl-1,3-thiazol-2-amines (**2a-k**) are synthesized as per previously reported protocol (Carroll King L, et.al, 1950). N-(4-Aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides **3a-k** are obtained in 65-71% yield by slowly adding a solution of 4-aryl-1,3-thiazol-2-amine (**2a-k**) and N,N-diisopropylethylamine (DIEA) in dry dimethylformamide (DMF) to a dry dichloromethane (DCM) solution containing 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetic acid (**1**) activated by N-hydroxybenzotriazole (HOBT) and O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), and reacting under vigorous stirring for 12 h. In a similar reaction, 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetic acid (**1**) is initially activated with HOBT and HBTU in dry DCM and then reacted *in situ* with commercially available 2-aminobenzothiazoles **2l-n** in dry DMF in presence of DIEA for 12 h to obtain N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3- thiazolidin-5-yl)acetamide derivatives **3l-n** in 54-61% yield. The detailed reaction sequence is shown in scheme 1. The spectral characteristics of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide derivatives **3a-n** are given in the experimental section.



R = H, Cl, F, Br, I, Me, OMe, OEt, NO2

Scheme 1. Synthesis of compounds **3a-n**; Reagents and conditions:
(i). HOBT, HBTU, DIEA, DCM, DMF, 0 ^{0}C - RT, 12 h.

Biology

α-Glucosidase inhibitory activity

The compounds (**3a-n**) have been screened in vitro for their α-glucosidase inhibitory activity by using α-glucosidase enzyme which is taken from rat intestine that serves as potential target for screening of antihyperglycemic agents active against carbohydrate-induced postprandial hyperglycemia (Kumar J A, et.al, 2010). The results are summarized in table 1.

All the compounds have exhibited moderate to very good α-glucosidase inhibitory potential ranging between 37.4-88.5 % inhibition. The N-[4-(*m*-chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**3g**) and N-[4-(*o*-fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**3j**) have exhibited highest activity with 88.4 and 88.3 % inhibition, and are considered as potent molecules in the series. The compounds **3c**, **3f**, **3l**, **3m** and **3n** have displayed very good activity with 53.1-63.1 % enzyme inhibition. These results have suggested that presence of *m*-Cl or *o*-F substituent on the phenyl ring at 4-position of 1,3-thiazole ring as in compounds **3g** and **3j** respectively, enhances the enzyme inhibiting activity. Similarly, replacing the 6-OEt group on the 1,3-bezothiazole ring of N-(6-ethoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**3n**) with 6-NO_2 has also contributed to the enhancement of α-glucosidase inhibitory action of N-(6-nitro-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide **(3l**).

Table 1: α-Glucosidase inhibitory potential and physical data of 2-(2,4-dioxo-1,3-thiazolidin-5- yl)acetamide derivatives

Product	R	HRMS-ESI $[M+H]^+$ m/z calcd. /found	mp ^oC	Yield (%)	Intestinal α-glucosidase inhibition (%)
3a	H	334.0320/ 334.0312	236-238	71	47.35 ± 2.01
3b	*p*-Cl	367.9930/ 367.9929	>260	67	49.13 ± 7.32
3c	*p*-F	352.0226/ 352.0220	212-216	69	60.63 ± 0.00
3d	*p*-Br	411.9425/ 411.9425	252-254	67	49.05 ± 0.50
3e	*p*-I	459.9287/ 459.9281	242-244	62	37.43 ± 1.62
3f	*o*-Cl	367.9930/ 367.9924	216-218	68	53.16 ± 0.17
3g	*m*-Cl	367.9930/ 367.9928	212-214	68	88.46 ± 1.00
3h	*o*-Me	348.0477/ 348.0466	192-194	69	48.93 ± 2.84
3i	*m*-Me	348.0477/ 348.0470	218-220	69	46.13 ± 0.84
3j	*o*-F	352.0226/ 352.0220	220-222	68	88.30 ± 0.00
3k	*o*-OMe	364.0426/ 364.0421	228-230	65	56.13 ± 3.35
3l	6-NO_2	353.0014/ 353.0015	272-274	56	63.11 ± 1.64
3m	6-OMe	338.0269/ 338.0261	262-264	54	59.68 ± 0.00
3n	6-OEt	352.0426/ 352.0423	246-248	58	53.32 ±1.95

CONCLUSIONS

A collection of 2,4-thiazolidinedione-5-acetamides of 4-aryl-1,3-thiazol-2-amines and 6-substituted-benzothiazol-2-amines are synthesized and screened *in vitro* for α-glucosidase inhibition efficacy. The presence of either *m*-Cl or *m*-F substituents on 4-phenyl ring as in compounds **3g** and **3j**, or 6-NO_2 group on 1,3-thiazole moiety of **3l** have exhibited very good α-glucosidase inhibitory activity. Thus, incorporating suitable substituent at appropriate position in N-(2,4-thiazolidinedione-5-acetyl)-4-aryl-1,3-thiazol-2-amines can lead to potential therapeutic agents in treating T2DM.

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