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Synthesis and biological evaluation of new derivatives of tertiary thiazolamines

Satish Koppireddi[a,*], Jayaram Reddy Komsani[a], Ashok K. Tiwari[b], Amtul Z. Ali[b] and Rambabu Yadla[a*]

[a]*Fluoroorganics Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, India*
[b]*Centre for Chemical Biology Division, CSIR- Indian Institute of Chemical Technology, Hyderabad*

ABSTRACT

*A series of new 4-(substitutedphenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amines (**6a-j**) and 4-(4-chlorophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amines (**7a-j**) have been synthesized. All the newly synthesized compounds are characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. Compound **6h** has shown promising α-glucosidase inhibitory activity, while compound **6j** and **7f** have displayed significant anticancer potential against neuroblastoma cells. Some of the targets have shown promising α-glucosidase inhibitory and anticancer activity.*

Keywords: Thiazole, 4-(trifluoromethyl)benzylchloride, tertiaryamines, α-glucosidase, postprandial hyperglycemia, human neuroblastoma cells, anticancer activity.

INTRODUCTION

Improvements in public facilities, ease of ample nutrition, modern lifestyle conditions and lack of physical exercise among the human beings are responsible in the prevalence of risk factors for diseases like T2DM, CVD, obesity, hypertension and strokes [1,2]. The homeostatic relationship is disturbed when glucose remains at supraphysiological level for a protracted period of time, a consequence referred to as glucose toxicity [3,4]. If any vitiation occurs, glucose metabolic pathway may lead to the impaired glucose metabolism and the increased blood glucose levels of fasting and postprandial caused postprandial hyperglycemia. The onset of postprandial hyperglycemia subsequently, turns to diabetes mellitus [5]. It is a painful fact that incidents of diabetic patients are continuously increasing worldwide and postprandial phase is confirmed by the simultaneous increase of both plasma triglycerides and glucose [6] in diabetic patients. Epidemiological studies and preliminary intervention studies have shown that postprandial hyperglycemia is a direct and independent risk factor for cardiovascular disease (CVD) [7]. α-Glucosidases are enzymes functioning in the digestion process through hydrolysis of α-glucosidic bond in carbohydrates and oligosaccharides to release α-D-glucose. Thus α-glucosidase inhibitors have greater role to play in the therapeutic strategy [8] for reducing risk of diabetes by lowering the blood glucose levels in PPHG through decrease in the α-glucosidase activity.

Although extensive research has been going on for treating cancer, still it is a major cause of increase in mortality rate in both developed and under developed countries [9]. Many of the chemotherapeutic agents are becoming ineffective in treating cancer due to the resistance developed by different types of tumor cells [10]. Hence, development of new potential anticancer agents is a continuous activity to combat cancer. In view of terrible complications of diabetes and cancer, it is desirable to develop newer antidiabetic and anticancer agents.

In addition, it is well known that thiazoles play an important role in medicinal chemistry. A number of thiazole analogues are claimed to possess interesting biological properties such as antibacterial-antifungal [11], anticancer [12], antiprion [13], antidiabetic [14], anticonvulsant [15], anti-inflammatory [16], antimalarial [17] and

antituberculosis activities [18]. In this communication, we report the synthesis, α-glucosidase inhibitory activity and anticancer activity of several tertiary amines of thiazoles.

MATERIALS AND METHODS

Melting points are determined on a Casiae-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra are recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR, ^{13}C NMR spectra are recorded on Bruker AV 300 MHz and AV 75 MHz in $CDCl_3$ (or DMSO-d_6) using TMS as an internal standard. Chemical shifts are given in δ ppm and coupling constants (*J*) are given in Hz. Electron Spray Ionization (ESI) and high-resolution mass spectra are recorded on a QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under electrospray ionization. Thin layer chromatography (TLC) has been performed on pre-coated silica gel 60 F254 (mesh); spots are visualized with UV light.

Preparation of 2-amino-4-(substituted-phenyl)-1,3-thiazoles (3a-k)

Title compounds **3a-k** are prepared following our earlier reported procedure [19]. A mixture of thiourea (50 mmol), the corresponding acetophenone (25 mmol) and iodine (25 mmol) is stirred at 100 ^{0}C for 8 h. Then the reaction mixture is cooled, extracted with diethyl ether to remove excess of acetophenone, and then washed with aqueous sodium thiosulfate to remove excess iodine and later with cold water. The crude product is dissolved in hot water, filtered to remove sulphone, and the filtrate is basified with aqueous Na_2CO_3 to yield the corresponding 2-amino-4-(substituted-phenyl)-1,3-thiazole. The crude product is purified by recrystallization from alcohol.

Preparation of 4-(substitutedphenyl)-N,N-bis(4-(trifluoromethyl)benzyl) thiazol-2-amine (6a-j) and 4-(4-chlorophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7a-j)

To a solution of 4-phenyl-thiazole-2-amine (**3a)** (0.2 g, 0.0012 mol) in dimethylformamide (DMF, 5 mL), 4-*(*trifluoromethyl)benzyl chloride (**4)** (0.27 g, 0.0013 mol), and cesium carbonate (0.741 g, 0.0022 mol) are added, stirred at 120 °C for 1h, and then cooled to room temperature. The reaction mixture is diluted with water (20 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layer is dried over anhydrous sodium sulfate, filtered and concentrated to get crude solid, which is purified by column chromatography (60-120 silica gel) using petroleum ether and ethyl acetate (88:12) (v/v) as an eluent to get pure compound **6a.** Similarly, compounds **7a-j** are obtained from 4-substitutedphenyl-thiazole-2-amine (**3a-j)** and 4-methoxybenzyl chloride (**5**).

4-Phenyl-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6a). Yield: 75.8%; mp 118-120 °C; IR (KBr) cm^{-1}: 2926 (Ar-CH str.), 1513 (C=N), 1158 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.78 (s, 4H, NCH_2), 6.78 (s, 1H, thiazole-H), 7.30 (t, *J* = 7.3, 1H, Ar-H), 7.37-7.42 (m, 6H, Ar-H), 7.59 (d, *J* = 8.0, 4H, Ar-H), 7.86 (dd, *J* = 8.3 Hz, 1.3 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.9, 151.6, 140.4, 134.5, 129.7 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 128.2, 127.7, 127.5, 125.7, 125.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 123.7(q, $^1J_{C\text{-}F}$ = 272.4 Hz), 101.0, 53.2 MS (ESI): m/z 493[M+H$^+$]; HRMS-ESI m/z [M+H$^+$] calcd. for $C_{25}H_{19}N_2F_6S$: 493.1167; found: 493.1158.

4-(4-Fluorophenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6b). Yield: 72.9%; mp 114-116 °C; IR (KBr) cm^{-1}: 2928 (Ar-CH str.), 1510 (C=N), 1158 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.77 (s, 4H, NCH_2), 6.70 (s, 1H, thiazole-H), 7.06 (t, *J* = 8.6 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.59 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.80-7.84 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.2, 162.4 (d, $^1J_{(C\text{-}F)}$= 247.4 Hz), 150.8, 140.5, 131.0 (d, $^4J_{(C\text{-}F)}$= 3.6) Hz, 130.0 (q, $^2J_{(C\text{-}F)}$= 32.6 Hz), 127.9, 127.7 (d, $^3J_{(C\text{-}F)}$ = 8.1 Hz), 125.6 (q, $^3J_{(C\text{-}F)}$= 3.6 Hz), 124.0 (q, $^1J_{(C\text{-}F)}$ = 271.5 Hz), 115.4 (d, $^2J_{(C\text{-}F)}$= 21.7 Hz), 100.8, 53.5. MS (ESI): m/z 511[M+H$^+$]; HRMS-ESI m/z [M+H$^+$] calcd. for $C_{25}H_{18}N_2F_7S$: 511.1073; found: 511.1061.

4-(4-Chlorophenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6c). Yield: 71.6%; mp 116-118 °C; IR (KBr) cm^{-1}: 2924 (Ar-CH str.), 1509 (C=N), 1161 (C-F), 725 (C-Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.78 (s, 4H, NCH_2), 6.75 (s, 1H, thiazole-H), 7.34 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.59 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.0, 150.4, 140.2, 133.1, 133.0, 129.8,(q, $^2J_{(C\text{-}F)}$ = 32.6 Hz), 128.4, 127.7, 127.0, 125.4 (q, $^3J_{(C\text{-}F)}$ = 3.6 Hz), 124.7 (q, $^1J_{(C\text{-}F)}$ = 271.5 Hz), 101.4, 53.3 MS (ESI): m/z 527[M+H$^+$]; HRMS-ESI m/z [M+H$^+$] calcd. for $C_{25}H_{18}N_2ClF_6S$: 527.0777; found: 527.0764.

4-(4-Bromophenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6d). Yield: 74.8%; mp 104-106 °C; IR (KBr) cm^{-1}: 2923 (Ar-CH str.), 1509 (C=N), 1161 (C-F), 652 (C-Br), ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.77 (s, 4H, NCH_2), 6.77 (s, 1H, thiazole-H), 7.40 (d, *J* = 8.1 Hz, 4H, Ar-H), 7.50 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.1, 4H, Ar-H), 7.72 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.8, 150.3, 140.1, 133.3, 131.1, 129.6 (q, $^2J_{(C\text{-}F)}$ = 32.5 Hz), 127.5, 127.1, 125.2 (q, $^3J_{(C\text{-}F)}$= 3.6 Hz), 123.7 (q, $^1J_{(C\text{-}F)}$ = 272.1 Hz), 101.3, 53.2. MS (ESI): m/z 571[M+H$^+$]; HRMS-ESI m/z [M+H$^+$] calcd. for $C_{25}H_{18}N_2BrF_6S$: 571.0272; found: 571.0265.

4-(4-Iodophenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6e). Yield: 70.7%; mp 84-86 °C; IR (KBr) cm^{-1}: 2924 (Ar-CH str.), 1529 (C=N), 1161 (C-F), 576 (C-I); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.77 (s, 4H, NCH_2), 6.78 (s, 1H, thiazole-H), 7.39 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.59 (m, 6H, Ar-H), 7.70 (d, *J* = 8.1 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.9, 150.5, 140.2, 137.3, 134.0, 129.8 (q, $^{2}J_{(C-F)}$ = 32.6 Hz), 127.7, 127.5, 125.4 (q, $^{3}J_{(C-F)}$ = 3.6 Hz), 124.1 (q, $^{1}J_{(C-F)}$ = 272.1 Hz), 101.6, 53.3. MS (ESI): m/z 619[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{18}N_2F_6IS$: 619.0134; found: 619.0134.

4-(4-Methoxyphenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6f). Yield: 72.6%; mp 100-102 °C; IR (KBr) cm^{-1}: 2906 (Ar-CH str.), 1540 (C=N), 1246 (C-O), 1158 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.83 (s, 3H, OCH_3), 4.77 (s, 4H, NCH_2), 6.64 (s, 1H, thiazole-H), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.40 (d, *J* = 7.9 Hz, 4H, Ar-H), 7.59 (d, *J* = 7.9 Hz, 4H, Ar-H), 7.79 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.1, 159.3, 151.6, 140.7, 135.2, 130.0 (q, $^{2}J_{(C-F)}$ = 32.5 Hz), 128.0, 127.3 125.6 (q, $^{3}J_{(C-F)}$= 3.3 Hz), 123.5 (q, $^{1}J_{(C-F)}$= 272.2 Hz), 114.9, 113.9, 99.5, 55.3, 53.6. MS (ESI): m/z 523[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{21}ON_2F_6S$: 523.1273; found: 523.1261.

N,N-Bis(4-(trifluoromethyl)benzyl)-4-(4-(trifluoromethyl)phenyl)thiazol-2-amine (6g).
Yield: 73.4%; mp 78-80 °C; IR (KBr) cm^{-1}: 2924 (Ar-CH str.), 1516 (C=N), 1163 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.80 (s, 4H, NCH_2), 6.88 (s, 1H, thiazole-H), 7.41 (d, *J* = 7.9 Hz, 4H, Ar-H), 7.58-7.64 (m, 6H, Ar-H), 7.95 (d, *J* = 8.1 Hz, 2H, Ar-H); MS (ESI): m/z 561[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{18}N_2F_9S$: 561.1041; found: 561.1031.

4-(2-Fluorophenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6h). Yield: 74.5%; mp 106-108 °C; IR (KBr) cm^{-1}: 2925 (Ar-CH str.), 1509 (C=N), 1161 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.77 (s, 4H, NCH_2), 7.08-7.13 (m, 2H, thiazole-H overlapped with Ar-H), 7.22-7.26 (m, 1H, Ar-H), 7.40 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.59 (d, *J* = 8.0 Hz, 4H, Ar-H), 8.14 (td, *J* = 7.7 Hz, 1.8 Hz, 1H, Ar-H); MS (ESI): m/z 511[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{18}N_2F_7S$: 511.1073; found: 511.1060.

4-(2-Methoxyphenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6i). Yield: 75.6%; mp 88-90 °C; IR (KBr) cm^{-1}: 2922 (Ar-CH str.), 1509 (C=N), 1163 (C-F), 1246 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.95 (s, 3H, OCH_3), 4.76 (s, 4H, NCH_2), 6.97-7.03 (m, 2H, thiazole-H overlapped with Ar-H), 7.20-7.23 (m, 2H, Ar-H), 7.41 (d, *J* = 7.9 Hz, 4H, Ar-H), 7.58 (d, *J* = 7.9 Hz, 4H, Ar-H), 8.20 (d, *J* = 7.6 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.1, 156.6, 147.2, 140.6, 134.9, 129.6, 128.1, 127.7, 125.3, 124.8, 124.7, 123.0, 122.9 (q, $^{1}J_{(C-F}$ = 271.5 Hz), 120.4, 118.5, 110.6, 106.1, 55.1, 53.2. MS (ESI): m/z 523[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{21}ON_2F_6S$: 523.1273; found: 523.1259.

N,N-Bis(4-(trifluoromethyl)benzyl)thiazol-2-amine (6j). Yield: 76.3%; mp 80-82 °C; IR (KBr) cm^{-1}: 2927 (Ar-CH str.), 1507 (C=N), 1162 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.74 (s, 4H, NCH_2), 6.56 (d, *J* = 3.6 Hz, 1H, thiazole-H), 7.2 (d, *J* = 3.6 Hz, 1H, thiazole-H), 7.36 (d, *J* = 8.1 Hz, 4H, Ar-H), 7.58 (d, *J* = 8.1 Hz, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.0, 140.2, 139.4, 120.7(q, $^{2}J_{(C-F)}$ = 32.7 Hz), 127.5, 125.4 (q, $^{3}J_{(C-F)}$ = 3.6 Hz), 123.2 (q, $^{1}J_{(C-F)}$ = 271.5 Hz), 107.0, 53.5. MS (ESI): m/z 417[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{19}H_{15}N_2F_6S$: 417.0854; found: 417.0852.

N,N-Bis(4-methoxybenzyl)-4-phenylthiazol-2-amine (7a). Yield: 78.3%; mp 117-119 °C; IR (KBr) cm^{-1}: 2928 (Ar-CH str.), 1543 (C=N), 1247 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.79 (s, 6H, OCH_3), 4.62 (s, 4H, NCH_2), 6.70 (s, 1H, thiazole-H), 6.85 (d, *J* = 8.3 Hz, 4H, Ar-H), 7.21-7.39 (m, 8H, Ar-H), 7.89 (d, *J* = 7.5 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): MS (ESI): m/z 417[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{25}O_2N_2S$: 417.1631; found: 417.1620.

4-(4-Fluorophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7b). Yield: 76.4%; mp 112-114 °C; IR (KBr) cm^{-1}: 2930 (Ar-CH str.), 1545 (C=N), 1247 (C-O), 1175 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.80 (s, 6H, OCH_3), 4.61 (s, 4H, NCH_2), 6.63 (s, 1H, thiazole-H), 6.83-6.88 (m, 6H, Ar-H), 7.05 (t, *J* = 8.7 Hz, 2H, Ar-H), 7.18-7.25 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): MS (ESI): m/z 435[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{24}O_2N_2FS$: 435.1537; found: 435.1524.

4-(4-Chlorophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7c). Yield: 74.6%; mp 118-120 °C; IR (KBr) cm^{-1}: 2920 (Ar-CH str.), 1549 (C=N), 1246 (C-O), 751 (C-Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.81 (s, 6H, OCH_3), 4.58 (s, 4H, NCH_2), 6.72 (s, 1H, thiazole-H), 6.81-6.90 (m, 4H, Ar-H), 7.15-7.31 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):. MS (ESI): m/z 451[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{24}O_2N_2ClS$: 451.1241; found: 451.1241.

4-(4-Bromophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7d). Yield: 71.8%; mp 114-116 °C; IR (KBr) cm^{-1}: 2929 (Ar-CH str.), 1547 (C=N), 1252 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.80 (s, 6H, OCH_3), 4.61 (s, 4H, NCH_2), 6.72 (s, 1H, thiazole-H), 6.86 (d, *J* = 8.6 Hz, 4H, Ar-H), 7.22(d, *J* = 8.6 Hz, 4H, Ar-H), 7.49 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.75(d, *J* = 8.5 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):170.4, 158.8, 150.1, 133.8, 131.2, 129.0, 127.3, 121.0, 113.7, 100.0, 54.9, 52.5. MS (ESI): m/z 495[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{24}O_2N_2BrS$: 495.0736; found: 495.0734.

4-(4-Iodophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7e). Yield: 77.6%; mp 118-120 °C; IR (KBr) cm^{-1}: 2927 (Ar-CH str.), 1545 (C=N), 1251 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.79 (s, 6H, OCH_3), 4.61 (s, 4H, NCH_2), 6.71 (s, 1H, thiazole-H), 6.85 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.21 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.62 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.69 (d, *J* = 8.5 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.6, 159.0, 150.4, 137.4, 134.6, 129.2, 128.6, 127.8, 113.9, 101.0, 92.8, 55.2, 52.8. MS (ESI): m/z 543[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{24}O_2N_2IS$: 543.0597; found: 543.0595.

N,N-Bis(4-methoxybenzyl)-4-(4-methoxyphenyl)thiazol-2-amine (7f). Yield: 75.4%; IR (KBr) cm^{-1}: 2925 (Ar-CH str.), 1511 (C=N), 1248 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.81 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 4.61 (s, 4H, NCH_2), 6.57 (s, 1H, thiazole-H), 6.85 (d, *J* = 8.6 Hz, 4H, Ar-H), 6.91 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.82 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.6, 159.0, 151.2, 129.2, 128.8, 128.2, 127.2, 113.7, 98.0, 55.2, 52.6. MS (ESI): m/z 447[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{27}O_3N_2S$: 447.1736; found: 447.1723.

N,N-Bis(4-methoxybenzyl)-4-(4-(trifluoromethyl)phenyl)thiazol-2-amine (7g). Yield: 73.6%; mp 80-82 °C; IR (KBr) cm^{-1}: 2925 (Ar-CH str.), 1550 (C=N), 1250 (C-O), 1171 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.79 (s, 6H, OCH_3), 4.63 (s, 4H, NCH_2), 6.82 (s, 1H, thiazole-H), 6.86 (d, *J* = 8.6 Hz, 4H, Ar-H), 7.22 (d, *J* = 8.6 Hz, 4H, Ar-H), 7.61 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.98 (d, *J* = 8.2 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.3, 158.6, 149.6, 137.9, 128.8, 128.1, 125.6,124.9, 113.5, 102.0, 54.8, 52.4. MS (ESI): m/z 485[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{24}O_2N_2F_3S$: 485.1505; found: 485.1491.

4-(2-Fluorophenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amine (7h). Yield: 76.3%; mp 86-88 °C; IR (KBr) cm^{-1}: 2926 (Ar-CH str.), 1546 (C=N), 1247 (C-O), 1175 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.80 (s, 6H, OCH_3), 4.62 (s, 4H, NCH_2), 6.85 (d, *J* = 8.6 Hz, 4H, Ar-H), 7.02 (d, *J* = 2.2, 1H, spatial coupling of thiazole-H with F), 7.07-7.12 (m, 1H, Ar-H), 7.16-7.19 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):169.1, 158.5, 144.6, 129.6, 128.8, 128.3, 127.8 (d, *J* = 8.7 Hz), 123.7, 115.2 (d, *J* = 21.9 Hz), 113.4, 105.4 (d, *J* = 15.3 Hz), 54.7, 52.3. MS (ESI): m/z 435[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{25}H_{24}O_2N_2FS$: 435.1537; found: 435.1522.

N,N-Bis(4-methoxybenzyl)-4-(2-methoxyphenyl)thiazol-2-amine (7i). Yield: 78.1%; mp 114 °C; IR (KBr) cm^{-1}: 2988 (Ar-CH str.), 1542 (C=N), 1246 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.81 (s, 6H, OCH_3), 3.83(s, 3H, OCH_3), 4.61 (s, 4H, NCH_2), 6.85 (d, *J* = 8.5 Hz, 4H, Ar-H), 6.96 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.02 (d, *J* = 7.3, 1H, Ar-H), 7.22-7.27 (m, 6H, Ar-H), 8.28 (d, *J* =8.3 Hz,1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):168.5, 158.7, 156.6,146.8, 129.9, 129.0,127.8,123.4, 120.4, 113.6, 110.6, 105.3, 55.0, 52.4. MS (ESI): m/z 447[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{26}H_{27}O_3N_2S$: 447.1736; found: 447.1722.

N,N-Bis(4-methoxybenzyl)thiazol-2-amine (7j). Yield: 79.1%; mp 91-93 °C; IR (KBr) cm^{-1}: 2925 (Ar-CH str.), 1512 (C=N), 1247 (C-O), ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.79 (s, 6H, OCH_3), 4.58 (s, 4H, NCH_2), 6.48 (d, *J* = 3.6 Hz, 1H, thiazole-H), 6.85 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.16 (d, *J* = 8.5, 4H, Ar-H), 7.20 (d, *J* = 3.6 Hz, 1H, thiazole-H), 8.28 (d, *J* =8.3 Hz,1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):. MS (ESI): m/z 341[M+H^+]; HRMS-ESI m/z [M+H^+] calcd. for $C_{19}H_{21}O_2N_2S$: 341.1318; found: 341.1321.

***In vitro* α-Glucosidase inhibitory assay**

α-Glucosidase inhibitory activities are determined according to earlier reported methods [24].

Rat intestinal acetone powder in normal saline (100: 1; w/v) is sonicated properly 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.

Cell cultures, maintenance and antiproliferative evaluation

The cell lines, A549, HeLa, IMR32, MCF-7, HCT116, DU145 which are used in this study are procured from American Type Culture Collection (ATCC), United States. The synthesized test compounds are evaluated for their *in vitro* antiproliferative activity in these four different human cancer cell lines. A protocol of 48 h continuous drug exposure is used, and a SRB cell proliferation assay is used to estimate cell viability or growth. All the cell lines are grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 °C). Cells are trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 µL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates are incubated at 37 °C, 5% CO2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs and are incubated for 48 hrs with different doses (0.01, 0.1, 1, 10, 100 µM) of prepared derivatives. After 48 h incubation at 37 °C, cell monolayers are fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 °C for 1 h and are then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB is washed with 1% acetic acid. The protein–bound dye is dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

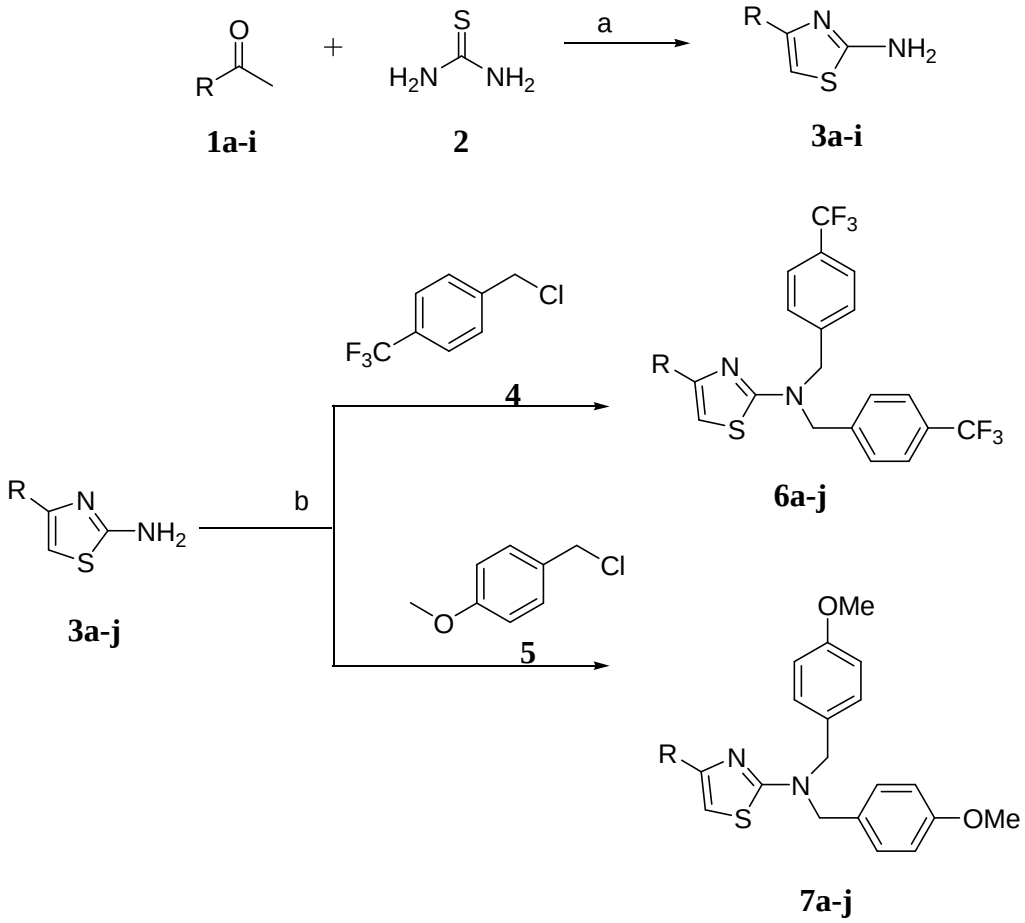
[(Ti-Tz)/(C-Tz)] x 100 for concentrations where Ti >/= Tz

[(Ti-Tz)/Tz] x 100 for concentrations where Ti < Tz.

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI_{50}) is calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The IC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

RESULTS AND DISCUSSION

The 4-aryl-1,3-thiazol-2-amines (**3a-i**) are prepared by iodine catalyzed condensation-cyclisation of thiourea with the respective acetophenone (**2a-i**) at 100 ^{o}C for 8 h [19]. 2-Aminothiazole (**3j**) is procured from commercial suppliers. The synthetic pathways of target compounds (**6a-j**) and (**7a-j**) are outlined in scheme 2. The 4-(substitutedphenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amines (**6a-j**) are obtained by the reaction of corresponding 4-aryl-1,3-thiazol-2-amine (**3a-j**) with 4-(trifluoromethyl)benzyl chloride (**4**) in the presence of cesium carbonate at 90 °C for 1 h under stirring in DMF solvent. Similarly, 4-aryl-1,3-thiazol-2-amines (**3a-j**) are treated with 4-methoxybenzyl chloride (**5**) to yield the respective 4-(4-substitutedphenyl)-N,N-bis(4-methoxybenzyl)thiazol-2-amines (**7a-j**). The structures of all the newly synthesized compounds (**6a-j**) and (**7a-j**) are confirmed by analytical and spectral data (^{1}H NMR, ^{13}C NMR, IR and mass). The physical characteristics and complete spectral data for each compound is provided in the experimental section. The salient spectral features observed in respect of one representative compound each from the two series, **6a-j** and **7a-j** are described here.



R = C_6H_5 (**6a**), 4-F-C_6H_4 (**6b**), 4-Cl-C_6H_4 (**6c**), 4-Br-C_6H_4 (**6d**), 4-I-C_6H_4 (**6e**), 4-MeO-C_6H_4 (**6f**), 4-CF_3-C6H4 (**6g**), 2-F-C_6H_4 (**6h**), 2-MeO-C_6H_4 (**6i**), H (**6j**), C_6H_5 (**7a**), 4-F-C_6H_4 (**7b**), 4-Cl-C_6H_4 (**7c**), 4-Br-C_6H_4 (**7d**), 4-I-C_6H_4 (**7e**), 4-MeO-C_6H_4 (**7f**), 4-CF_3-C_6H_4 (**7g**), 2-F-C_6H_4 (**7h**), 2-MeO-C_6H_4 (**7i**), H (**7j**).

Reagents and conditions: (a) I_2, 90 ^oC, 12 h; (b) Cs_2CO_3, dimethylformamide, 120 ^{o} C, 1h.

Scheme 1

The FT-IR spectrum of compound **6c** illustrates a band at 2924 cm^{-1} for aromatic C-H stretching frequency along with the bands at 725 and 1161 cm^{-1} assignable to C-Cl and C-F functions, respectively. ^{1}H NMR spectrum of compound **6c** showed two singlets at δ 4.78 and 6.75 ppm for NCH_2 hydrogens and thiazole ring proton, four doublets at δ 7.34, 7.40, 7.59 and 7.78 ppm belonging to aromatic protons. The ^{13}C NMR spectrum of **6c** has shown the signal for benzylic methelene carbon at δ 53.3 ppm and three signals at δ 170.0, 150.4, and 101.4 ppm for C_2, C_4, and C_5 carbons of thiazole ring. The quaternary aromatic carbon attached to methylene group has appeared at δ 140.2 ppm and the remaining aromatic carbons are seen in the range of δ 124.7-133.1 ppm. The -$\underline{C}F_3$ carbon has appeared at δ 124.7 as a quartet with coupling constant J = 271.5 Hz. It is also confirmed by HRMS data, which shows a peak for $C_{25}H_{18}N_2ClF_6S$ $[M+H]^+$ at m/z 527. The IR spectrum of compound **7f** contains absorption bands at ν 1248, 1511 and 2925 cm^{-1} due to C-O, C=N and aromatic C-H stretching frequency. The ^{1}H NMR spectrum of compound **7f** shows three singlet signals at δ 3.81, 3.83 and 4.61 ppm corresponding to -OCH_3, and NCH_2 protons respectively, along with a singlet signal at δ 6.57 ppm for thiazole ring proton. Also seen are four doublet signals at δ 6.85, 6.91, 7.22 and 7.82 ppm corresponding to the aromatic protons. The ^{13}C NMR spectrum of compound **7f** has shown signals at δ 52.6 and 55.2 ppm for benzylic -$\underline{C}H_2$- and O$\underline{C}H_3$ carbons. Three peaks appearing at δ 170.6, 151.2 and 98.0 ppm are assignable to C_2, C_4 and C_5 carbons of thiazole ring. A signal has appeared at δ159.0 ppm for the aromatic quaternary carbon attached to OCH_3. The remaining signals appearing from δ 113.7 to 129.2 ppm have been assigned to the aromatic carbons. The ESI mass spectrum of compound **7f** shows a stable molecular ion $[M+H]^+$ peak at m/z 447.

α-Glucosidase inhibitory activity

The compounds **6a-j** and **7a-j** synthesized in this study are screened 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 [20]. The activity results are summarized in Table 1. The difference in α-glucosidase inhibitory activity may be explained on the basis of molecular anatomy of the enzymes and source of its origin [21]. Glucosidase inhibition may also retard cancer growth [22]. All compounds have exhibited α-glucosidase inhibitory activity with 8.95-45.6 % inhibition. Compounds **7a-b**, **7d-e**, **7g**, and **7i** are not active, while compounds **4b**, **4g**, and **4j** have shown poor activity. Compounds **4f**, **4i** and **5h** have exhibited moderate activity. Among the series, compound **4h** has displayed promising intestinal α-glucosidase inhibitory activity with 45.6 % inhibition. It may be possible to develop a lead compound based on compound **4h** by incorporating proper substituents to carry out further antidiabetic studies.

Table 1 α-Glucosidase inhibitory activity of target compounds (6a-j) and (7a-j) at 5mg/mL concentration

Compound	R	Intestinal α-glucosidase inhibition (%)
6a	C_6H_5	25.25±0.14
6b	4-F-C_6H_4	22.93±0.11
6c	4-Cl-C_6H_4	29.36±0.08
6d	4-Br-C_6H_4	26.98±0.06
6e	4-I-C_6H_4	23.96±0.01
6f	4-OMe-C_6H_4	32.32±0.05
6g	4-CF_3-C_6H_4	17.08±2.91
6h	2-F-C_6H_4	45.61±0.95
6i	2-OMe-C_6H_4	35.47±0.01
6j	H	22.61±0.01
7a	C_6H_5	NA
7b	4-F-C_6H_4	NA
7c	4-Cl-C_6H_4	12.45±0.03
7d	4-Br-C_6H_4	NA
7e	4-I-C_6H_4	NA
7f	4-OMe-C_6H_4	13.41±0.01
7g	4-CF_3-C_6H_4	NA
7h	2-F-C_6H_4	30.97±0.82
7i	2-OMe-C_6H_4	NA
7j	H	8.95±0.28

Table 2 Anticancer activity of synthesized compounds (6a-j) and (7a-j)

Compound	GI_{50} (μM)			
	HeLa	MDA-MB-231	MIAPACA	IMR32
6a	35.1±0.09	1.8±0.06	3.0±0.2	2.5±0.04
6b	4.1±0.04	12.6±0.3	3.1±0.07	0.57±0.02
6c	11.9±0.08	1.4±0.2	2.9±0.05	10.0±0.2
6d	4.2±0.1	3.1±0.02	11.3±0.02	4.8±0.03
6e	4.7±0.04	0.48±0.04	50.9±0.7	8.7±0.6
6f	1.1±0.02	5.1±0.01	73.1±0.07	4.4±0.3
6g	6.4±0.08	4.6±0.04	5.3±0.1	3.9±0.08
6h	1.9±0.05	2.6±0.05	0.84±0.03	3.0±0.04
6i	32.3±0.2	37.4±0.2	2.6±0.08	12.9±0.7
6j	46.4±0.5	1.2±0.03	5.1±0.09	0.18±0.05
7a	47.9±0.06	3.2±0.1	7.0±0.6	9.2±0.07
7b	1.3±0.01	10.0±0.09	0.59±0.04	3.4±0.04
7c	0.81±0.07	13.3±0.2	26.7±0.08	0.89±0.02
7d	1.8±0.04	0.33±0.09	2.8±0.1	12.3±0.6
7e	42.9±0.3	0.25±0.05	0.4±0.01	0.31±0.02
7f	0.45±0.06	59.9±0.04	70.4±0.8	0.15±0.04
7g	2.3±0.04	0.97±0.5	>100	0.56±0.2
7h	2.8±0.3	1.2±0.06	10.0±0.5	1.9±0.3
7i	2.2±0.09	1.3±0.03	4.3±0.2	0.84±0.03
7j	2.0±0.04	1.6±0.05	7.8±0.3	0.79±0.03
Doxorubicin	<0.01±0.001	0.016±0.001	<0.01±0.002	<0.01±0.002
Paclitaxel	<0.01±0.001	0.025±0.001	0.016±0.002	0.035±0.002

Note: GI_{50} values are determined from SRB assay after 48 h incubation with test compounds. Doxorubicin and Paclitaxel are standards; GI_{50} values (required concentration of drug for 50% of maximal inhibition of cell proliferation) ranged from 0.01 > 50 μM (Table 2)

Anticancer activity

The anticancer activity of synthesized tertiary amines substituted with thiazole derivatives **6a-j** and **7a-j** was assessed in vitro on a panel of four cell lines consisting of HeLa human cervical carcinoma, MDA-MB-231 human breast carcinoma, MIA PaCa human pancreatic carcinoma and IMR32 human neuroblastoma cells by using the SRB

assay [23] and the results are summarized in Table 2. The data suggests that compounds **7c** and **7f** prove lethal to HeLa cells with GI_{50} values of 0.45 and 0.81 µM. Compounds **6e**, **7d**, **7e** and **7g** show remarkable affinity to MDA-MB-231 cells with GI_{50} values ranging from 0.2-0.9 µM. MIA PaCa cells are the most sensitive to compounds **6h**, **7b** and **7e**. In the case of neuroblastoma cells, compounds **6b**, **6j**, **7c**, **7e-f**, **7g** and **7j** have shown good potency than other compounds in the series. In the entire series, compounds **6j** and **7f** are considered as highly potent against neuroblastoma cells with least GI_{50} value of 0.1 µM.

CONCLUSION

In the present paper, we have reported the synthesis and α-glucosidase inhibitory, and anticancer activity of 4-(substitutedphenyl)-N,N-bis(4-(trifluoromethyl)benzyl)thiazol-2-amines (**6a-j**) and (**7a-j**). The results indicate that some of these compounds show moderate α-glucosidase inhibition, while most of the compounds in the series exhibit moderate to poor anticancer activity. Compound **6h** is found to be a potent molecule with 45% α-glucosidase inhibition, while compounds **6j** and **7f** have shown promising activity against IMR 32 cells.

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