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# Synthesis and antidiabetic activity of 2, 4- disubstituted furan derivatives

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**ABSTRACT**

*New 2,4 disubstitiuted furan derivatives **(5a-5u)** were prepared from commercially available furan-4-carboxylic acid ethyl ester and tested for anti diabetic activities. Most of the compounds were found to be active compared to acarbose.*

**Keywords:** 2,4-Disubstituted furans , Anti diabetic activity .

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## INTRODUCTION

It is well known that **α**-glucosidase (EC.3.2.1.20) catalyzes the final step of carbohydrate digestion in biological systems. This biological importance of **α**-glucosidase prompts various efforts to develop new agents capable of efficiently inhibiting **α**-glucosidase. These agents, namely **α**-glucosidase inhibitors, have wide applications, for example, in elucidating the action mechanism of **α**-glucosidase at molecular levels and in developing chemotherapeutic agents for clinic use in the treatment of carbohydrate mediated diseases such as diabetes, cancer, HIV, hepatitis, and certain forms of hyperlipoproteinemia and obesity [1–5]. Therefore in the past two decades, there has been increasing interest in the development of inhibitors that can probe the structure and function of **α**-glucosidase. Till date, many new and effective **α**-glucosidase inhibitors have been reported, such as acarbose and voglibose from microorganisms and 1-deoxynojirimycin isolated from plants [6,7].

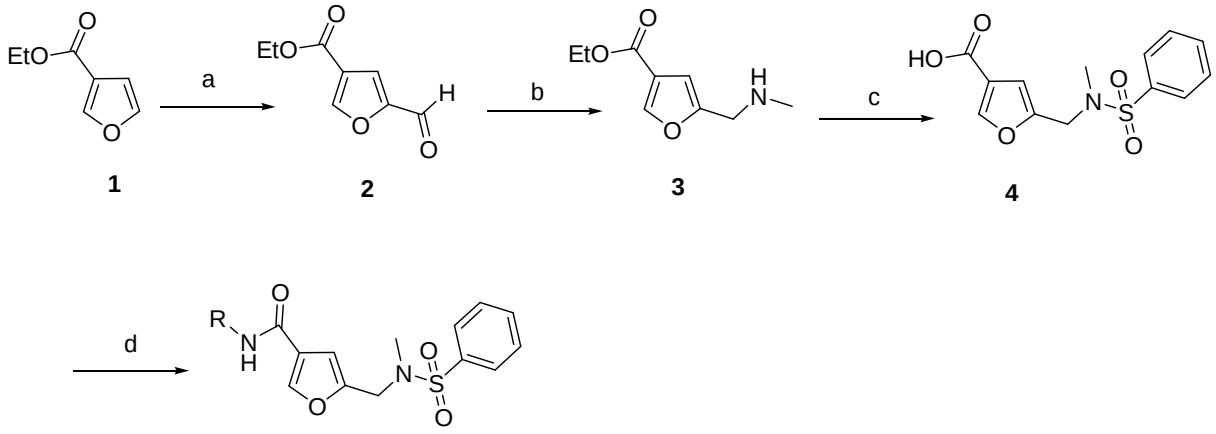
Furans, one of the most important five-membered ring heterocycles [8], can be found in many naturally occurring compounds originated from plants and marine organisms [9] it is a key component, in a number of biologically significant natural products, such as pinguisone [10], furodysinin [11], and methyl vouacapenate [12], a 2,3-disubstituted furan ring constitutes a distinctive structural feature. Various substituted furans are used as commercial pharmaceutical agents, flavor and fragrance compounds, insecticides, and antileukemic agents [13]. Polysubstituted furans can also be employed as building blocks for the total synthesis of complicated naturally occurring metabolites [14], and as versatile starting materials for the preparation of a variety of heterocyclic and acyclic compounds [15]. The significant biological activity and great utility have encouraged us to synthesize 2,4 disubstituted furan derivatives in a more efficient methods and evaluated their anti diabetic activity. This report describes the synthesis, spectroscopic identification and anti diabetic activity of some novel 2,4 disubstituted furan derivatives **(5a-5u)** .

## MATERIALS AND METHODS

Melting points were determined using open glass capillaries on a Mel-temp apparatus and are uncorrected.Thin-layer chromatography (TLC) was performed on E.Merk AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The $^1$H NMR spectra were recorded in $CdCl_3$ on a Varian EM-360 spectrometer (400 MHz). All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS.

**Experimental methods**

Synthetic route implied to prepare compounds (**5a-u**) is outlined in **Scheme 1**. Formylation of the ethyl furan-3-carboxylate **1** using α,α dichloromethyl methylether and $TiCl_4$ in dichloromethane at room temperature for 3 h afforded 2-formyl- furan-4-carboxylic acid ethyl ester **2** [16]. Reductive amination of compound **2** with methyl amine hydrochloride was achieved by using 5-ethyl-2-methylpyridine-borane complex **[PEMB]** in acetic acid at room temperature for 1 h gave compound **3** [17]. The N-methylamine derivative **3** was reacted with phenyl sulfonyl chloride in presence of aq;1M $Na_2CO_3$ at room temperature for 2 h produced compound **4** [18]. The acid derivative thus obtained was treated with various amines using 2-bromo phenyl boronic acid and activated molecular sieves in acetonitrile at 85 $^o$C resulted in corresponding amide derivatives (**5a-5u** ) [19] as depicted in **Scheme-1**.




**Scheme 1: Reagents and Conditions: a) α,α dichloromethyl methylether ,$TiCl_4$, DCM, RT, 3 h; b) 5-ethyl-2-methylpyridine-borane complex, methylamine hydrochloride, AcOH, RT, 1h; c) Benzenesulfonyl chloride, aq.1M $Na_2CO_3$, pH ~8.0 , RT, 2 h; d) various amines, o-bromophenyl boronic acid , 4A$^0$ molecular sieves , Acetonitrile , 85 °C, 3-18 h.**

**5-Formayl-furan-3-carboxylicacid ethyl ester (2):**

To a solution of compound **1** (40 g, 285 mmol) in DCM (400 mL) cooled to 0 $^o$C was added anhydrous $TiCl_4$ (54.14 g, 285 mmol) for 30 min and stirred for 1 h at 0$^o$ C. To the above reaction mixture was added α,α dichloromethyl methylether (32.8 g, 285 mmol) slowly for 30 min and allowed to stir at room temperature for 3 h. The reaction mixture was cooled and quenched with water and extracted with ethyl acetate (250 mL x 3). The organic layer was washed, followed by saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The obtained residue was purified by flash column chromatography (100-200 silica gel, 3:1 hexane/ethyl acetate) to obtain compound **2** as a pale yellow colored liquid (26.4 g, 55%). IR (Neat): $\upsilon_{max}$ 3030, 2825, 2720, 1724, 1692, 1400, 1212, 1085, 1037, 846 cm $^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1 H), 8.2 (s, 1 H), 7.58 (s, 1 H), 4.4 (q, *J* = 7.8 Hz, 2 H), 1.4 (t, *J* = 7.8 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$): 178.1, 159.4, 154.3, 148.8, 120.8, 116.5, 60.9, 14.1. MS: *m/z* = 168.1 ($M^+$)

**5-Methylaminomethyl-furan-3-carboxylicacid ethyl ester (3):**

To a solution of methylamine hydrochloride, (16.05 g, 377 mmol), compound **2** (20 g, 118.94 mmol ) in glacial acetic acid (5 mL), maintained at 20-30 $^o$C, was added PEMB (2.67 g, 198 mmol) over a period of 1 h, under $N_2$ atmosphere. After completion of reaction, judged by TLC, 50 mL of methanol and 1mL of concentrated HCl was added. The entire reaction mixture was heated to quench the excess borane followed by evaporation to remove most of the methanol and methylborate. The solid material was filtered and dried to yield compound **3** as a yellow solid

(16.4 g, 58%). IR (Neat): $\upsilon_{max}$ 3349, 2780, 1715, 1549, 1447, 1021.71, 763 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.1 (s, 1 H), 6.6 (s, 1 H), 4.5 (s, 2 H), 4.3 (q, *J* = 7.8 Hz , 2 H) , 1.4 (t, *J* = 7.8 Hz, 3 H ); $^{13}C$ NMR (100 MHz, $CDCl_3$): 160.5, 149.8, 146.0, 118.9, 106.7, 60.9, 52.4, 33.4,14.1; E-IMS: m/z (rel.abund.%) 183 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (4):**
The solid mixture of compound **3** (15 g, 81.8 mmol) and benzenesulfonyl chloride (14.45 g, 81.87 mmol.) was suspended in 30 mL water. The pH of the suspension was adjusted and maintained at 8.0 by adding 1M $Na_2CO_3$ aqueous solution at room temperature. It took 2 hours for the reaction to complete. Concentrated HCl was added to adjust the pH to 2.0. The precipitate was collected by filtration, washed with water and dried to afford compound **4** as a white solid (2.08 g, Yield: 98%). m.p. 199-201$^0$C; IR (KBr): $\upsilon_{max}$ 3442, 3158, 2927, 1692, 1677, 1551, 1448, 1225, 1161, 936 $cm^{-1}$; $^1H$ NMR (DMSO-*d6*): 8.2 (s, 1 H), 7.8 (d, *J = 7.2* Hz , 2 H,), 7.7 (t, *J = 7.6 Hz*, 1 H,), 7.65 (m, 2 H,), 6.6 (s, 1 H), 4.3 (d, *J = 8 Hz*, 2 H), 2.74 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 163.6, 150.6, 148.2, 136.8, 133.0, 129.3, 127.1, 120.2, 109.6, 45.9, 34.5, 29.3; EI-MS: m/z (rel.abund.%) 294 ($M^-$, 100).

**Representative procedure for the synthesis of amides (5):**
To a solution of dichloromethane containing **4** (500 mg, 1.17 mmol) was added *o*-bromophenyl boronic acid (3.52 mmol), activated 4A$^o$ molecular seives and the appropriate amine (1.17 mmol). The contents were heated at 85 °C for 3 h-18 h. After completion of the reaction, the reaction mixture was distilled and the crude compound obtained was dissolved in EtOAc, washed with $H_2O$, brine solution, dried over $Na_2SO_4$, filtered and evaporated under vacuum to obtain the crude amide derivatives which was purified by column chromatography.

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (3,5-dimethoxy-phenyl)-amide (5a):**
Yield: 76%; m.p. 163-165 $^o$C; IR (K,Br): $\upsilon_{max}$ 3391, 3122, 2934, 1668, 1601, 1545, 1218, 1149, 936 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 9.87 (br, 1 H), 8.29 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H,), 7.72 (t, *J* = 7.6 Hz, 1 H,), 7.65 (m, 2 H), 7.16 (s, 2 H), 6.90 (s, 1 H), 6.45 (s, 1 H), 4.32 (s, 2 H), 3.76 - 3.71 (s, 6 H), 2.60 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 160.3, 152.2, 150.7, 146.6, 136.5, 134.2, 130.2, 128.3, 108.2, 60.1, 56.4, 48.2, 34.2; EI-MS: m/z (rel.abund.%): 431 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2,4,6- trifluoro-phenyl)-amide (5b):**
Yield: 59%; m.p. 84-86$^0$C; IR (KBr): $\upsilon_{max}$ 3379, 3122, 2923, 1664, 1601, 1547, 1443, 1162, 936 $cm^{-1}$; $^1H$-NMR (DMSO-$d_6$): δ 9.22 (br.s, 1H), 8.25 (s, *J = 7.2* Hz, 1H,), 7.80 (d, *J* = 7.6 Hz, 2 H,), 7.65 (t, *J* = 8 Hz, 1 H,), 7.16 (s, 2 H), 6.90 (s, 2 H), 6.45 (s, 1H), 4.30 (s, 2 H,), 2.62 (s, 3 H, ); $^{13}C$ NMR (100 MHz, $CDCl_3$): 166.5, 164.3, 160.3, 150.7, 136.5, 134.2, 130.2, 128.3, 108.26, 100.2, 48.2, 34.2; EI-MS: m/z (rel.abund.%): 424.9 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-methoxy-phenyl)-amide (5c):**
Yield: 63%; m.p. 153-155 $^o$C; IR (KBr): $\upsilon_{max}$ 3323.9, 3130, 2935, 1652, 1546, 1487, 1460, 1340, 1156, 938 $cm^{-1}$; $^1H$-NMR (DMSO-$d_6$): δ 9.20 (br.s, 1 H), 8.32 (s, 1 H), 7.80 (d, *J* = 7.6 Hz 2 H,), 7.70 (t, *J* = 7.6 Hz, 1H,), 7.68-7.6 (m, *J* = 3Hz ,3 H,) , 7.20 (t, *J* = 8 Hz, 1 H), 7.10 (d, *J* = 5.2 Hz, 1 H,) 6.90 (t, *J* = 8.8 Hz, 1H), 6.85 (s, 1 H), 4.30 (s, 2 H), 3.80 (s, 3 H), 2.68 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 160.1, 151.4, 150.2, 145.8, 136.8, 133.0, 129.3, 127.2, 126.2,125.7, 124.7, 123.3, 120.1, 111.3, 106.9, 55.6, 46.0, 34.6; EI-MS: m/z (rel.abund.%): 401.1 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-methyl-4-nitro-phenyl)-amide (5d):**
Yield 62%; m.p. 132-135$^0$C; IR (KBr): $\upsilon_{max}$ 3323.9, 3130, 2935, 1652, 1546, 1487, 1460, 1365, 1156, 938 $cm^{-1}$; $^1H$-NMR (DMSO-$d_6$): δ 8.67 (br.s, 1 H,), 7.98 (m, 4 H), 7.8 (d, *J* = 7.6 Hz, 2 H ,), 7.6-7.5 (m, 2 H), 7.30 (t, 1 H), 6.43 (s, 1H), 4.30 (s, 2 H), 2.68 (s, 3 H), 2.50 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 164.3, 149.4, 143.9, 140.8, 139.8, 135.2, 132.0, 129.3, 124.7, 122.3, 181.3, 47.05, 32.4, 14.2; EI-MS: m/z (rel.abund.%): 430.4 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid 2-chloro-benzylamide (5e):**
Yield: 68%; m.p. 167-169$^0$C; IR (KBr): $\upsilon_{max}$ 3447.45, 3251, 2921, 1630, 1568, 1446, 1340, 1237, 1163.8, 933.6 $cm^{-1}$; $^1H$-NMR (DMSO-$d_6$): δ 8.70 (br.s, 1 H), 8.15 (s, 1 H), 7.8 (d, *J* = 7.2 Hz, 2 H), 7.70 (t, *J* = 7.6 Hz, 1H ,), 7.6 (m, 2 H), 7.46 (d, *J* = 7.2 Hz, 1 H,), 7.3 (m, 3 H), 6.85 (s, 1 H), 4.48 (d, *J* = 5.6 Hz, 2 H ,), 4.26 (s, 2 H), 2.68 (s, 3 H,); $^{13}C$ NMR (100 MHz, $CDCl_3$): 161.5, 150.1, 145.3, 136.8, 136, 137.0, 131.9, 129.3, 129.3, 128.7, 128.6, 127.1, 122.9, 108.6, 46.05, 34.6, 28.9; EI-MS: m/z (rel.abund.%): 419.1 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid cyclohexylmethyl -amide (5f):**
Yield: 61%; m.p. 123-125$^0$C; IR (KBr): $\upsilon_{max}$ 337.9, 2923, 2785, 1443, 1237, 1163, 938 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.20 (br.s, 1H), 7.93 (m, 2 H , *J* = 7.2 Hz), 7.76 (s, 1H), 7.60-7.50 (m, 2 H), 7.3 (t, *J* = 7.2 Hz, 1 H), 6.5 (s, 1 H), 4.3 (s, 2 H), 2.98 (d, *J* = 7.6 Hz, 2 H), 2.68 (s, 3 H), 2.06 (m, 1 H), 1.60-1.20 (m, 10 H); $^{13}$C NMR (100 MHz, $CDCl_3$): 167.6, 149.4, 139.7, 132, 129.5, 129.1, 104, 47.9,42.8, 37.9, 32.4, 30.7, 28.3, 25.5; EI-MS: m/z (rel.abund.%): 391.5 ($M^+$, 100).

**4-{5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carbonyl}-piperazine-1-carboxylic acid ter-butylester (5g):**
Yield 61%; m.p. 132-134$^o$C; IR (KBr): $\upsilon_{max}$ 3435, 3112, 2975, 2924, 1690, 1613, 1542, 1447, 1338, 1238 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 7.95 (s, 1 H), 7.80 (d, *J* = 7.2 Hz 2 H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.6 (t, *J* = 7.2 Hz, 2 H ,), 6.53 (s, 1H), 4.20 (s, 2 H), 3.5 (br.s, 4 H), 3.30 (m, 4 H), 2.6 (s, 3 H), 1.41 (s,9 H); $^{13}$C NMR (100 MHz, $CDCl_3$): 162.3, 153.7, 149.4, 144.08, 136.8, 132.9, 129.3, 127.1, 121,110.2, 79.15, 45.9, 34.8, 27.9; EI-MS: m/z (rel.abund.%): 408.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid cyclopropyl -amide (5h):**
Yield: 65%; m.p. 193-196 $^o$C; IR (KBr): $\upsilon_{max}$ 3443, 3248, 1632, 1250, 1163 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 8.0 (s, 1 H) , 7.80 (t, *J* = 7.2 Hz, 2 H ,), 7.70 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 H z, 2 H), 6.52 (s, 1 H), 6.2 (b.s,1 H), 4.20 (s, 2 H), 2.60 (s, 3 H), 2.4 (m, 1 H), 0.8 (m, 2 H), 0.6 (m, 2 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 164.1, 150.74, 149.6, 144.59, 143.68, 137.53, 132.9, 129.1, 127.37, 122.16, 110.2,107.9, 47.9, 32.4, 22.65, 6.6; EI-MS: m/z (rel.abund.%): ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-chloro-phenyl)-amide (5i):**
Yield 68%; m.p.167-169 $^o$C; IR (KBr): $\upsilon_{max}$ 3447.45, 3251, 2921, 1630, 1568, 1446, 1340, 1237, 1163.8, 933.6 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 8.70 (b.s, 1H), 8.15 (s, 1 H), 7.8 (d, *J* = 7.2 Hz, 2 H,), 7.70 (t, *J* = 7.6 Hz, 1H), 7.60 (t, 2 H, *J* = 7.6 Hz), 7.46 (d, 1H), 7.30 (m, 3 H), 6.85 (s, 1 H), 4.26 (s, 2 H), 2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 161.5, 150.1, 145.3, 136.8, 136, 137.03, 131.9, 129.3, 129, 128.7, 128.6, 127.1, 122.97, 108.6, 46.05, 28.9; EI-MS: m/z (rel.abund.%): 405.8 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-methoxy-5-chloro-phenyl)-amide (5j):**
Yield: 76%; m.p. 120-122 $^o$C; IR (KBr): $\upsilon_{max}$ 3419, 2969, 2937, 1658, 1592, 1485, 1329, 1158, 936 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.20 (br.s, 1 H), 8.3 (s, 1 H), 7.80 (d, *J* =7.2 Hz , 2 H), 7.60-7.50 (m, 4 H), 7.3 (d, *J* =9, 1H), 6.95 (d, *J*= 8, 1H), 6.85 (s, 1 H), 4.3 (s, 2 H), 3.8 (s, 3 H), 2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160.1, 151.4, 150.2, 145.8, 136.8, 133.03, 129.368, 127.2, 126.22,125.7, 124.7, 123.3, 120.1, 111.36, 106.9, 55.6, 46.05, 34.6; EI-MS: m/z (rel.abund.%): 401.1 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2,3,-dimethoxy-phenyl)-amide (5k):**
Yield: 76%; m.p. 131-133$^o$C; IR (KBr): $\upsilon_{max}$ 3322, 3123, 2960, 1651, 1600, 1547, 1485, 1328, 1224, 1161, 936 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.0 (br.s, 1 H), 8.30 (s, 1 H), 7.80 (d, *J* = 7.2 Hz , 2 H), 7.60 (t, *J* = 7.6 Hz, 2 H,), 7.40 (d, *J* = 8, 1 H), 6.90 (d, *J* = 7.2, 1H), 6.60 (d, *J* = 6.8, 1H), 6.70 (dd, *J* = 1.8, 6 Hz, 1H), 6.42 (s, 1 H), 4.30 (s, 2 H), 3.8 (s, 3 H), 3.74 (s, 3 H), 2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160.3, 159.1, 150.5, 145.8, 139.1, 136.8, 133.03, 129.3, 127.2, 126.2,125.7, 124.7, 123.3, 120.1, 111.36, 106.9, 55.6, 46.05, 34.6; EI-MS: m/z (rel.abund.%): 431.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (4-methoxy-phenyl)-amide (5l):**
Yield: 60%; m.p. 132-135$^o$C; IR (KBr): $\upsilon_{max}$ 3323.9, 3130, 2935, 1652, 1546, 1487, 1460, 1340, 1156, 938 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.79 (br.s, 1 H), 8.25 (s, 1 H), 7.8 (d, *J* = 6.8 Hz, 2 H), 7.65 (m, 2 H), 7.60-7.50 (m, 3 H), 6.90 (m, 3 H), 4.30 (s, 2 H), 3.74 (s, 3 H), 2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 159.1, 155.3, 151.4, 150.2, 145.8, 136.8, 133.03, 129.3, 127.2, 126.2, 125.7, 124.7, 123.3, 120.1, 111.3, 106.9, 55.6, 46.05, 34.6; EI-MS: m/z (rel.abund.%): 401.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (3-methoxy-phenyl)-amide (5m):**
Yield: 64%; m.p. 166-167$^o$C; IR (KBr): $\upsilon_{max}$ 3363.9, 3145, 2924, 1728, 1660, 1543, 1453, 1328, 1216, 1160, 936 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.87 (br.s, 1H), 8.29 (s, 1H), 7.80 (d, *J* = 7.2 Hz 2H), 7.70 (d, *J* = 7.2, 1H ), 7.60 (t, *J* = 7.6 Hz, 2 H), 7.4 (s, 1 H), 7.30-7.20 (m, 2 H), 6.90 (s, 1 H), 6.68 (dd, *J*=1.6, 8Hz, 1H), 4.3 (s, 2 H), 3.74 (s, 3 H),

2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160.3, 159.2, 150.6, 145.8, 139.2, 136.8, 133.03, 129.3, 127.2, 126.2, 125.7, 124.7, 123.3, 120.1, 111.3, 106.9, 55.6, 46.05, 34.6 EI-MS: m/z (rel.abund.%): 401.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2,5,-dimethoxy-phenyl)-amide (5n):**
Yield: 72%; m.p. 102-105 $^o$C; IR (KBr): $\upsilon_{max}$ 3322, 3123, 2960, 1651, 1600, 1547, 1485, 1328, 1224, 1161, 936 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.10 (br.s, 1 H), 8.30 (s, 1 H), 7.8 (d, J = 7.2 Hz , 2 H), 7.70 (t, *J* = 7.2 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz , 2 H,), 7.39 (dd, *J* = 2, 6.8 Hz, 1 H), 7.0 (d, *J* = 12 Hz, 1H), 6.80 (s, 1H), 6.70 (dd, *J*=1.8, 8 Hz, 1H), 4.3 (s, 2 H), 3.8 (s, 3 H), 3.74 (s, 3 H), 2.68 (s, 3H, N-$CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160, 159, 150, 145.8, 139, 136.8, 133.03, 129.368, 127.2, 126.22,125.7, 124.7, 123.3, 120.1, 111.36, 106.9, 55.6, 46.05, 34.6; EI-MS: m/z (rel.abund.%): 431.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (3,4,5,-trimethoxy-phenyl)-amide (5o):**
Yield 78%; m.p. 165-167 $^o$C; IR (KBr): $\upsilon_{max}$ 3351, 2937, 1655, 1603, 1335, 1224, 1151, 939 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.80 (br.s, 1 H), 8.30 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.70 (t, *J* = 7.2, 1H), 7.65 (t, *J* = 7.6 Hz, 2 H), 7.16 (s, 2 H), 6.90 (s, 1 H), 4.30 (s, 2 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.60 (s, 3 H), 2.6 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$,): 160.2, 152.5, 150.8, 146.3, 136.6, 135.2, 134.4, 130.7, 128.3, 108.6, 98.02, 60.3, 55.6, 48.05, 34.6; EI-MS: m/z (rel.abund.%): 461.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (4-hydroxy-phenyl)-amide (5p):**
Yield: 67%; m.p. 225-227 $^o$C; IR (KBr): $\upsilon_{max}$ 3454, 3378, 3124, 1647, 1548, 1205, 1149, 938 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.70 (br.s, 1 H), 9.2 (br.s, 1 H), 8.30 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.65 (m, 3 H), 7.40 (m, 2 H), 6.90 (m, 1 H), 6.70 (m, 2 H), 4.30 (s, 2 H), 2.68 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 159.5, 153.6, 150.4, 145.5, 136.8, 133.03, 130.3, 129.3, 127.2, 123.6, 122.6, 115.3, 108.8, 55.6, 46.05, 34.6; EI-MS: m/z (rel.abund.%): 387.1 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2,6-dimethoxy-phenyl)-amide (5q):**
Yield: 74%; m.p. 164-166 $^o$C; IR (KBr): $\upsilon_{max}$ 3454, 3307.8, 2929, 1729, 1654, 1474, 1332, 1257, 1115, 938 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 9.0 (br.s, 1 H), 8.18 (br.s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.70 (m, 3 H), 7.20 (m, 1H), 6.80 (m, 1H) 6.70 (d, *J* = 7.2 Hz, 2 H), 4.20 (s, 2 H), 3.70 (s, 6 H), 2.68 (s, 3 H); ); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160.1, 156.2, 150.2, 145.5, 136.8, 133.5, 129.3, 127.8, 127.2, 123.3, 114.1, 109.3, 104.3, 55.6, 46.12, 34.6; EI-MS: m/z (rel.abund.%): 431.2 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-chloro-5-methoxy-phenyl)-amide (5r):**
Yield: 81%; m.p. 136-140 $^o$C; IR (KBr): $\upsilon_{max}$ 3446, 3231, 2929, 1649.6, 1340, 1223, 1163, 933 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 8.16 (d, *J* = 7.2, 1H), 7.90 (m, 2 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.60 (m, 1 H), 7.56 (t, *J* = 7.6 Hz, 2 H), 7.28 (t, *J* = 8.2 Hz, 1 H), 6.67 (dd, *J* = 4, 12 Hz, 1H), 6.50 (s, 1 H), 4.30 (s, 2 H), 3.80 (s, 3 H), 2.80 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 159.9, 158.99, 151.5, 145.33, 137.55, 134.86, 132.85, 129.17, 127.37, 123.64, 113.8, 111.35, 107.42, 106.39, 55.6, 46.5, 34.6; EI-MS: m/z (rel.abund.%): 435.0 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-chloro-4-hydroxy-phenyl)-amide (5s):**
Yield: 63%; m.p. 124-125 $^o$C; IR (KBr): $\upsilon_{max}$ 3460, 3369, 1727, 1626, 1499, 1342, 1196, 575 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 8.50 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.72 (t, 1H), 7.66 (t, *J* = 7.2 Hz, 2 H), 7.13 (d, 1 H), 6.90 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.8 (d, *J* = 8.8 Hz, 1H), 6.75 (br.s, 1H), 5.30 (s, 2 H), 4.29 (s, 2 H), 2.65 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 161.0, 151.2, 149.6, 142.8, 139.8, 136.7, 133.0, 129.4, 127.1, 122.2, 121.2, 118.5, 116.3, 115.1, 109.4, 45.8, 34.6; EI-MS: m/z (rel.abund.%): 421.1 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid (2-hydroxy-4-fluoro-phenyl)-amide (5t):**
Yield: 71%; m.p. 200-203 $^o$C; IR (KBr): $\upsilon_{max}$ 3343, 3115, 2924, 1651, 1608, 1325, 1161, 933 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 10.21 (br.s, 1 H), 9.29 (br.s, 1 H), 8.30 (s, 1 H), 7.80 (d, *J* = 7.6 Hz, 2 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 8 Hz, 2 H), 7.49 (t, *J* = 6.8 Hz, 1 H), 6.80 (s, 1 H), 6.72-6.61 (m, 2 H), 4.30 (s, 2 H), 2.74 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 161.0, 160.4, 158.6, 151.5, 150.2, 145.9, 136.8, 133.0, 129.3, 127.2, 126.5, 121.6, 108.9, 105.2, 103.1, 46.0, 34.6; EI-MS: m/z (rel.abund.%): 405.3 ($M^+$, 100).

**5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylicacid phenylamide (5u):**
Yield: 63%; m.p. 191-193$^{o}$C; IR (KBr): $\upsilon_{max}$ 3379, 2923, 1646, 1547, 1443, 1334, 1162, 936 cm$^{-1}$; $^{1}$H-NMR (DMSO-$d_6$): δ 9.90 (br.s, 1 H), 8.30 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.80-7.60 (m, *J* = 8.6 Hz, 5 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.10 (t, *J* = 8 Hz, 1 H), 6.90 (s, 1 H), 4.30 (s, 2 H), 2.67 (s, 3 H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 160.0, 150.3, 145.9, 138.7, 136.8, 133.0, 129.3, 128.6, 127.1, 123.5, 123.5, 120.1, 108.9, 46.0, 34.6; EI-MS: m/z (rel.abund.%): 371.1 ($M^+$, 100).

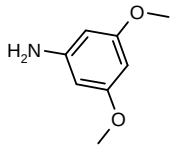
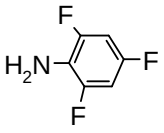
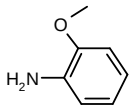
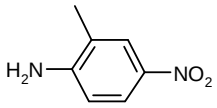
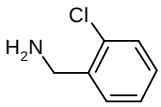
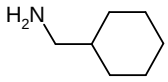
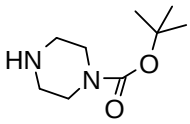
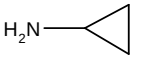
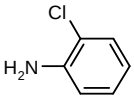
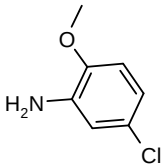
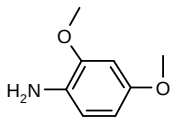
**Anti diabetic Bioassay**
The activity of α-glucosidase was tested**,** by measuring (absorbance at 410nm) the release of 4-nitrophenol from 4-NPGP (ρ-nitrophenyl-α-D-glucopyranoside) using spectrophotometric method [19]. The control reaction contains 0.1 mM PNPG and 0.1U enzyme (dissolved in 65 mM PBS buffer pH 6.5) and incubated at 35 ºC for 10 minutes. The inhibition activity of the AG has been conducted by adding plant extract or acarbose to the 0.1U enzyme and the reaction was carried out as control experiment. Additional blank incubations with only plant extracts, but without enzyme source were also run. Experiments were performed in triplicates and $IC_{50}$ values were calculated. The experiments were repeated three times and the mean values are reported.

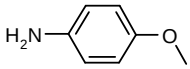
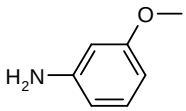
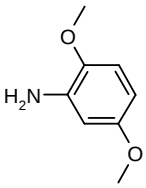
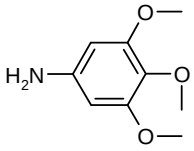
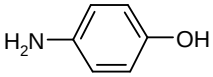
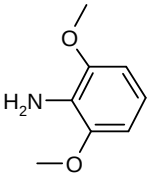
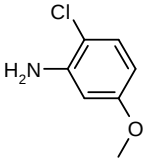
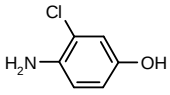
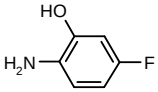
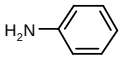
## RESULTS AND DISCUSSION

The antidiabetic activity of α-glucosidase was examined**,** by measuring (absorbance at 410 nm) the release of 4-nitrophenol from 4-NPGP (ρ-nitrophenyl-α-D-glucopyranoside) using spectrophotometric method according to the literature protocol [18]. The anti diabetic activity of the analogue was compared with standard drug Acarbose **(Table 1).**

The investigation of antidiabetic activity **(Table 1)** revealed that all the newly synthesized compounds have shown good to moderate minimum inhibitory concentration at 10-50µg / mL in 20% water in dimethyl sulfoxide. Compounds **5e, 5g, 5h, 5i and 5j** exhibited comparatively good MIC activity against the standard Acrbose. Compounds **5b, 5d, 5f, 5m, 5o & 5u** indicated moderate activity and the remaining compounds exerted low MIC activity when compared to the standard. Among the three positional isomeric analogues **5l**, **5c** & **5m** (*o*-OMe, *m*-OMe & *p*-OMe) the order of activity towards *α* -glucosidase is **5l** > **5c** > **5m** i.e., para and ortho isomers exhibited excellent activity than the control acarbose, where as meta isomer was a poor member. The mono substituent methoxy compound (compound **5l**), displayed high activity compared to di and trisubstituted methoxy compounds (compound **5o** and **5k**). The order of activity is **5l** > **5o** > **5k**. Among cyclic aliphatic amides, **5g** and **5h** exhibited excellent activity at lower concentrations, where as **5f** exhibited less activity at higher concentration. Among the di-methoxy substituents, 3,5 Disubstituted dimethoxy (compound **5a**) showed greater activity compared to **5k**, **5n** & **5q** (2,4 dimethoxy, 2,5 dimethoxy and 2,6 dimethoxy compounds respectively), the order of activity is **5a** > **5n** > **5k** > **5q**. Compound **5i**, which is ortho-chloro substituent exhibited excellent activity than the control and introduction of hydroxyl group at para position has reduced the activity of compound **5s**, finally interchanging the substitution on compound **5j**, reduced the activity in compound **5r** and compounds **5b**, **5o** and **5d** shows poor activity compared to the standard.

**Table 1 : Results of Anti diabetic activity of compounds 5a-5u**

| Entry | Compound | R | Inhibition at various concentrations (µg/ml) | | | |
|---|---|---|---|---|---|---|
| | | | 10 | 25 | 35 | 50 |
| 1. | **5a** |  | 15 | 35 | 65 | 85 |
| 2. | **5b** |  | 10 | 25 | 30 | 45 |
| 3. | **5c** |  | 25 | 33 | 61 | 83 |
| 4. | **5d** |  | 5 | 10 | 12 | 15 |
| 5. | **5e** |  | 25 | 75 | 95 | 98 |
| 6. | **5f** |  | 5 | 8 | 10 | 15 |
| 7. | **5g** |  | 35 | 65 | 85 | 95 |
| 8. | **5h** |  | 40 | 70 | 85 | 98 |
| 9. | **5i** |  | 25 | 45 | 60 | 78 |
| 10. | **5j** |  | 85 | 95 | 95 | 98 |
| 11. | **5k** |  | 7.5 | 15 | 35 | 45 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12. | **5l** |  | 35 | 50 | 85 | 98 |
| 13. | **5m** |  | 10 | 25 | 35 | 45 |
| 14. | **5n** |  | 12 | 18 | 25 | 35 |
| 15. | **5o** |  | 15 | 30 | 48 | 70 |
| 16. | **5p** |  | 2.5 | 5 | 10 | 12 |
| 17. | **5q** |  | 2.0 | 7.5 | 15 | 18 |
| 18. | **5r** |  | 2.5 | 5.0 | 10 | 15 |
| 19. | **5s** |  | 10 | 15 | 20 | 25 |
| 20. | **5t** |  | 5.0 | 7.5 | 15 | 20 |
| 21. | **5u** |  | 12 | 17 | 22 | 30 |
| 22. | **Acarbose** | | 15 | 25 | 45 | 65 |

## CONCLUSION

We have synthesized New 2,4 disubstitiuted furan derivatives **(5a-5u)** were prepared from commercially available furan-4-carboxylic acid ethyl ester and screened for the antidiabetic activity and was compared with the standard drug Acarbose. Most of the compounds were found to be active compared to acarbose. Among the three positional isomeric analogues **5l**, **5c** & **5m** (*o*-OMe, *m*-OMe & *p*-OMe), para and ortho isomers exhibited excellent activity.

The mono substituent methoxy compound (compound **5l**), displayed high activity compared to di and trisubstituted methoxy compounds (compound **5o** and **5k**). Thus further lead optimization is required to get wide spectrum of activity.

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