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Original Research Article

Synthesis of 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-N-(un/substituted-phenyl)acetamides as anti-diabetic agents

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Abstract

Purpose: *To synthesize a series of new 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-N-(un/substituted-phenyl) acetamides, and evaluate their anti-diabetic potentials.*
Methods: *Synthesis of the parent compound N-(2,3-dihydro-1,4-benzodioxin-6-yl) benzenesulfonamide (3) was carried out by reacting 2,3-dihydro-1,4-benzodioxin-6-amine (1) with benzenesulfonylchloride (2) in aqueous basic medium under definite pH controls. After that 3 was further treated with various 2-bromo-N-(un/substituted-phenyl)acetamides (6a-l) to yield new compounds (7a-l) in polar aprotic solvent, DMF (dimethylformamide), using LiH as activator. The proposed structures of the synthesized compounds were confirmed using proton-nuclear magnetic resonance (^{1}H-NMR) and infra-red spectroscopy (IR), and CHN analysis. Their anti-diabetic potential was evaluated by α-glucosidase enzyme inhibitory studies.*
Results: *All the new compounds demonstrated weak (7a-h, 7j and 7l) to moderate (7i and 7k) inhibitory activities against α-glucosidase enzyme. IC_{50} (50 % inhibition concentration) values for 7i and 7k were 86.31±0.11 µM and 81.12±0.13 µM, respectively relative to acarbose (reference standard) with IC_{50} of 37.38±0.12 µM.*
Conclusion: *All the synthesized compounds have weak to moderate activity against α-glucosidase enzyme. These compounds can thus be considered as possible therapeutic entrants for type-2 diabetes.*

Keywords: *2,3-Dihydro-1,4-benzodioxin-6-amine, Benzenesulfonyl chloride, Anti-diabetic, α-Glucosidase, Type-2 diabetes*

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INTRODUCTION

Sulfonamides bearing –SO_2NH group have been extensively used as chemotherapeutic agents for the treatment of numerous microbial diseases [1]. First discovery of antibacterial activity of azo dye prontosil led to the first chemotherapeutic agent, sulfanilamide [2]. Afterwards, derivatives

of sulfonamides were widely used as antibacterial and antifungal [3-5], antitumor [6], antihypertensive [7] agents. They were also effective for the treatment of urinary and ophthalmic infections, scalds and intestinal diseases [8,9]. Some of the sulfonamides possessed good anti-proliferative activities, and showed promising broad spectrum of antitumor activity compared to the activities of the commonly used anticancer drugs. They also inhibit lactate dehydrogenase A and reverse aerobic glycolysis in cancer cells [10,11].

Sulfonamide derivatives also act as competitive antagonists of *p*-aminobenzoic acid, which is vital for the synthesis of folic acid both in protozoan and bacterial cells. Folic acid is a coenzyme used to produce nucleic acid in these cells. Thus, sulfonamides possess a bacteriostatic effect [12]. Furthermore, a number of derivatives of sulfonamides act as effective inhibitors of butyryl cholinesterase (BChE) and acetyl cholinesterase (AChE) [13], and also shows good inhibitory action potential against α-glucosidase and lipoxygenase enzymes [14].

Compounds having 1,4-benzodioxane moiety are known to have a wide range of biological activities, causing them to receive much attention in synthesis over the years. These compounds have a range of biological activities, such as antihepatotoxic [15], anti-inflammatory [16] and α-adrenergic blocking action [17]. Silymarin, isolated from the seeds of *Silybum marianum* (commonly known as 'milk thistle') has been found to be a potent antihepatotoxizc agent against a variety of toxicants. Its main component is silybin, which usually makes up 20-30% of the total flavonolignans containing benzodioxine ring system.

α-Glucosidase (EC 3.2.1.20), belongs to a family of hydrolase enzymes situated in the brush border surface membrane of small intestinal cells [18]. This enzyme hydrolyzes the 1,4-glycosidic linage from the non-reducing end of the α-linked oligosaccharide and α-glucosides substrates to yield α-D-glucose along with other monosaccharides which are the sources of carbon and energy [19]. α-Glucosidase inhibitors are generally utilized for the treatment of type-2 diabetic mellitus. These inhibitors can retard the excretion of D-glucose and consequently delay glucose absorption and reduce postprandial hyperglycemia. Postprandial hyperglycemia has an important role in the development of type-2 diabetes mellitus [20]. Hence, the inhibition of α-glucosidase enzyme is an important step in managing the disease.

Literature survey revealed that a small modification in the structure can result in qualitative as well as quantitative changes in activity.

Therefore, the purpose of this study was to synthesize a new series of substituted acetamides and explore their anti-diabetic potentials.

EXPERIMENTAL

General

The chemicals utilized were procured from Sigma Aldrich (St. Louis, Germany) and Alfa Aesar (Ward Hill, Massachusetts, United States). The solvents used in the reactions were of analytical grade, and were purchased from local suppliers and used as such. Pre-coated TLC silica gel G-25-UV_{254} Al-plates were used to monitor the reactions using various percentages of *n*-hexane and ethyl acetate as solvent system. The melting points of the compounds were recorded using a Gallenkamp melting point apparatus (UK) by an open capillary tube.

A MIDAC M2000 photon spectrometer (Westfield, USA) was used to record the FTIR spectra in KBr (υ, cm^{-1}). The Burker spectrometers (Billerica, Massachusetts, USA) operating at 25 ℃ at 400/600 MHz, was used to record the ^1H NMR spectra in $CDCl_3$. The coupling constant (J) is given in Hz and chemical shift (δ) in ppm. The abbreviations used in the interpretation of ^1H NMR spectra are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; br.t, broad triplet; q, quartet; quin, quintet; sex, sextet; sep, septet; m, multiplet.

Synthesis of *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzenesulfonamide (3)

N-(2,3-Dihydrobenzo[1,4]-dioxin-6-amine (**1**, 1mL, 0,002 mol) was suspended in 25 mL distilled water and stirred for half 30 min in 10% aqueous Na_2CO_3 to maintain the pH at 9-10 and the reaction mixture. Then, benzenesulfonyl chloride (**2**, 0.47 g, 0.002 mol) was added slowly to the mixture and further stirred for 3 hr till completion of the reaction, which was monitored by TLC till single spot. The product was precipitated at pH 2.0 using conc. HCl, filtered, washed with distilled water, and air-dried to afford *N*-(2, 3-dihydro-1,4-benzodioxin-6-yl)benzenesulfonamide (**3**) as light brown amorphous powder.

Synthesis of 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(un/substituted-phenyl)acetamides (7a-l)

Molecule **3** (0.2 g; 0.57 mmol) in 10 mL *N,N*-dimethyl formamide (DMF) was place`d into 50mL round bottomed flask along with lithium hydride (0.004 g) and the reaction mixture was stirred for 30 min at 25 ℃. Then, 2-bromo-*N*-(un/substituted-phenyl) acetamides (**6a-l** ; 0.60 mmol) was added to each reaction mixture, which was further stirred for 2-3 hr. The reaction was monitored by TLC till single spot. After completion, the reaction mixture was poured onto crushed ice and the precipitate was filtered, washed and air-dried to obtain a pure compound (**7a-l**). The structures of the compounds used in this synthesis are provided in Figure 1, while the substituents are shown in Table 1.

α-Glucosidase assay (anti-diabetic activity)

The enzyme inhibition activity against *α*-glucosidase was performed as previously described [20]. Phosphate buffer saline (50mM, pH 6.8, 70 µL), test compound (0.5mM, 10 µL) and enzyme (0.057 units, 10 µL) were made up to 100 µL, mixed well and pre-incubated for 10 min at 37 ºC and absorbance was taken at 400 nm. The substrate (*p*-nitrophenylglucopyranoside (0.5mM, 10 µL) was added to start the reaction and after incubation for 30 min at 37ºC, absorbance was noted again at 400 nm using microplate reader (Synergy HT). Change in absorbance was used as index for the measurement of % age inhibition using acarbose as positive control. Inhibition (%) was calculated using the equation:

$$\%\ age\ Inhibition\ = \frac{Control\ -\ Test}{Control} \times\ 100$$

EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA) was used to calculate IC_{50} values of the compounds. Serial dilutions of the compounds from 0.5 to 0.015625 mM were employed for determination of IC_{50} values.

Table 1: Different substituents (-R_1 & -R_2) used in the synthesis

Compd.	-R_1	-R_2
7a	-H	-H
7b	2-OCH_3	-H
7c	4-OC_2H_5	-H
7d	2-CH_3	-H
7e	3-CH_3	-H
7f	4-CH_3	-H

Compd.	-R_1	-R_2
7g	2-CH_3	3-CH_3
7h	2-CH_3	4-CH_3
7i	2-CH_3	5-CH_3
7j	2-CH_3	6-CH_3
7k	3-CH_3	4-CH_3
7l	3-CH_3	5-CH_3

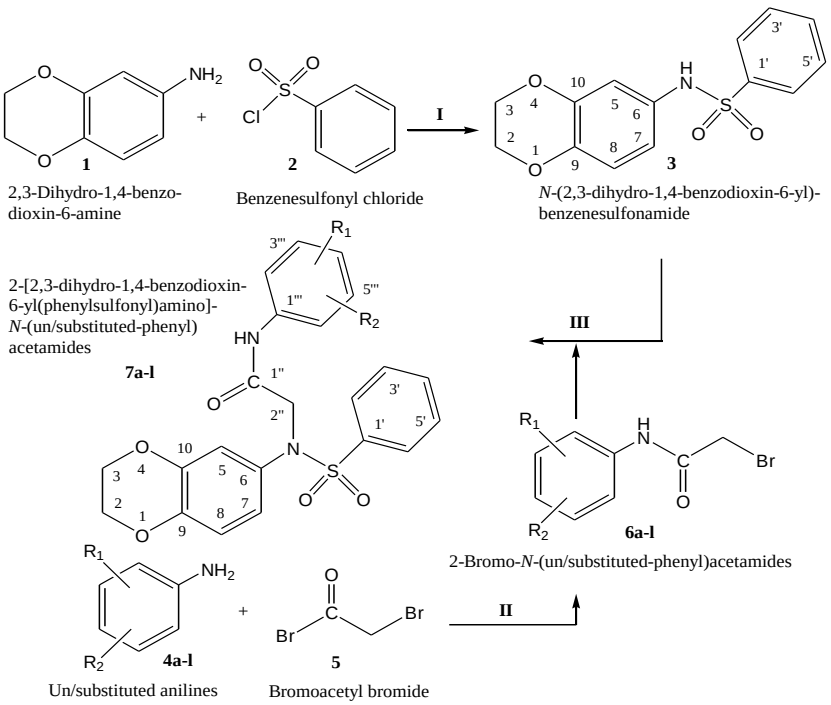

Figure 1: Outline for the synthesis of 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(un/substituted-phenyl) acetamides (**7a-l**). Reagents and conditions: (I) Aq. Na_2CO_3 soln./pH 9-10/stirring at RT for 3 hr. (II) Aq. Na_2CO_3 soln./pH 9-10/stirring at RT for 2-3 hr. (III) DMF/LiH/stirring at RT for 4-5 hr.

Statistical analysis

All the measurements were performed in triplicate, and statistical analysis was performed using Microsoft Excel 2010, and the results presented as mean ± SEM. IC_{50} values (50 % inhibitory concentration) were calculated using EZ-Fit Enzyme Kinetic Software (Perrella Scientific Inc. Amherst, USA).

RESULTS

The new 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(un/substituted-phenyl) acetamides (**7a-l**) were synthesized according to the protocol sketched in Scheme-1 and various substituents are listed in Table 1. The procedures and conditions of the reactions are explicated in the experimental section. The first step for the synthesis of targeted derivatives was the reaction of *N*-2,3-dihydrobenzo[1,4]-dioxin-6-amine (**1**) and benzenesulfonyl chloride (**2**) in aqueous alkaline media under 4-5 hr stirring at room temperature, yielding the parent *N*-(2,3-dihydrobenzo[1,4]-dioxin-6-yl) benzenesulfonamide (**3**) which was obtained as light brown amorphous powder in good yield by the acidification of the reaction mixture to pH 2-3 with concentrated HCl.

In a parallel reaction, different amines (**4a-l**, Table 1) were reacted one by one with bromoacetyl bromide (**5**) to obtain respective electrophiles, 2-bromo-*N*-(un/substituted-phenyl) acetamides (**6a-l**). In the final step, parent **3** was coupled with different electrophiles, **6a-l**, in polar aprotic solvent, i.e. DMF using LiH as a base to afford the targeted *N*-2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(un/substituted-phenyl)acetamides (**7a-l**). The spectral characterization of **7a-l** is given below. The *in vitro* inhibition study against *α*-glucosidase enzyme has been tabulated in Table 2.

Spectral characterization of 7a-l

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-phenylacetamide (7a)

Brown amorphous powder; Yield 88%; m.p. 107-108 °C; Molecular Formula: $C_{22}H_{20}N_2O_5S$; Molecular Mass: 424 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3249 (N-H), 3047 (Ar C-H), 2928 (Ar -CH_2), 1715 (C=O), 1630 (Ar C=C), 1385 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz,): d (ppm) 8.28 (s, 1H, NHCO), 7.64 (m, 5H, H-2', H-4', H-6', H-2''' & H-6'''), 7.52 (distorted br.t, *J* = 7.2 Hz, 4H, H-3', H-5', H-3''' & H-5'''), 7.32 (br.t, *J* = 7.6 Hz, 1H, H-4'''), 6.76 (d, *J* = 8.8 Hz, 1H, H-8), 6.65 (d, *J* = 2.4 Hz, 1H, H-5), 6.54 (dd, *J* = 2.4, 8.8 Hz, 1H, H-7), 4.22-4.21 (m, 6H, CH_2-2, CH_2-3, CH_2-2''); Anal. Calc. for $C_{22}H_{20}N_2O_5S$ (424.109): C, 62.25; H, 4.75; N, 6.60. Found: C, 62.37; H, 4.87; N, 6.73.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2-methoxyphenyl) acetamide (7b)

Dark brown semi-solid; Yield 83%; Molecular Formula: $C_{23}H_{22}N_2O_6S$; Molecular Mass: 454 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3251 (N-H), 3043 (Ar C-H), 2931 (Ar -CH_2), 1717 (C=O), 1635 (Ar C=C), 1380 (S=O); ^{1}H-NMR ($CDCl_3$, 600MHz): d (ppm) 8.04 (s, 1H, NHCO), 7.69 (m, 3H, H-2', H-4' & H-6'), 7.55 (br.t, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.09 (br.d, *J* = 7.2 Hz, 1H, H-6'''), 7.03 (br.d, *J* = 7.8 Hz, 1H, H-3'''), 6.95 (br.d, *J* = 7.8 Hz, 1H, H-5'''), 6.88 (br.t, *J* = 7.8 Hz, 1H, H-4'''), 6.63 (d, *J* = 8.4 Hz, 1H, H-8), 6.56 (d, *J* = 2.4 Hz, 1H, H-5), 6.48 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7), 4.15 (br.s, 4H, CH_2-2 & CH_2-3), 4.01 (s, 2H, CH_2-2''), 3.69 (s, 3H, 2'''-OCH_3); Anal. Calc. for $C_{23}H_{22}N_2O_6S$ (454.120): C, 60.78; H, 4.88; N, 6.16. Found: C, 60.89; H, 4.95; N, 6.23.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(4-ethoxyphenyl)acetamide (7c)

Pink amorphous powder; Yield 87%; m.p. 168-169 °C; Molecular Formula: $C_{24}H_{24}N_2O_6S$; Molecular Mass: 468 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3256 (N-H), 3047 (Ar C-H), 2937 (Ar -CH_2), 1713 (C=O), 1630 (Ar C=C), 1377 (S=O); ^{1}H-NMR ($CDCl_3$, 600MHz,): d (ppm) 7.98 (s, 1H, NHCO), 7.68-7.64 (m, 3H, H-2', H-4' & H-6'), 7.54 (br.t, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.33 (br.d, *J* = 9.0 Hz, 2H, H-2''' & H-6'''), 6.83 (br.d, *J* = 9.0 Hz, 2H, H-3''' & H-5'''), 6.72-6.70 (m, 2H, H-5 & H-8), 6.58 (dd, *J* = 2.4, 9.0 Hz, 1H, H-7), 4.34 (br.s, 2H, CH_2-2''), 4.20-4.18 (m, 4H, CH_2-2 & CH_2-3), 3.98 (q, *J* = 7.2 Hz, 2H, 4'''-OCH_2CH_3), 1.34 (t, *J* = 7.2 Hz, 3H, 4'''- OCH_2CH_3); Anal. Calc. for $C_{24}H_{24}N_2O_6S$ (468.136): C, 61.52; H, 5.16; N, 5.98. Found: C, 61.66; H, 5.28; N, 6.13.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2-methylphenyl)acetamide (7d)

Dark brown semi-solid; Yield 80%; Molecular Formula: $C_{23}H_{22}N_2O_5S$; Molecular Mass: 438 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3253 (N-H), 3049 (Ar C-H), 2935 (Ar -CH_2), 1719 (C=O), 1633 (Ar C=C), 1381 (S=O); ^{1}H-NMR ($CDCl_3$, 600MHz): d (ppm) 8.23 (s, 1H, NHCO), 7.70-7.66 (m, 3H, H-2', H-4' & H-6'), 7.56 (br.t, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.26 (br.d, *J* = 7.8 Hz, 1H, H-6'''), 7.18 (br.d, *J* =

7.8 Hz, 1H, H-3'''), 7.13 (m, 1H, H-5'''), 7.06 (br.t, *J* = 7.8 Hz, 1H, H-4'''), 6.74 (d, *J* = 8.4 Hz, 1H, H-8), 6.59 (d, *J* = 2.4 Hz, 1H, H-5), 6.48 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7), 4.39 (br.s, 2H, CH_2-2''), 4.22-4.19 (m, 4H, CH_2-2 & CH_2-3), 2.08 (s, 3H, CH_3-2'''); Anal. Calc. for $C_{23}H_{22}N_2O_5S$ (438.125): C, 63.00; H, 5.06; N, 6.39. Found: C, 63.16; H, 5.19; N, 6.48.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(3-methylphenyl)acetamide (7e)

Light pink amorphous powder; Yield 77%; m.p. 161-162 °C; Molecular Formula: $C_{23}H_{22}N_2O_5S$; Molecular Mass: 438 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3243 (N-H), 3047 (Ar C-H), 2941 (Ar -CH_2), 1711 (C=O), 1635 (Ar C=C), 1383 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz): d (ppm) 8.23 (s, 1H, NHCO), 7.66-7.62 (m, 3H, H- 2', H-4' & H-6'), 7.52 (br.t, *J* = 7.6 Hz, 2H, H-3' & H-5'), 7.27 (m, 1H, H-6'''), 6.78 (d, *J* = 1.4 Hz, 1H, H-2'''), 6.75 (d, *J* = 8.4 Hz, 1H, H-8), 6.70 (br.d, *J* = 7.8 Hz, 1H, H-4'''), 6.68 (m, 1H, H-5'''), 6.60 (d, *J* = 2.4 Hz, 1H, H-5), 6.48 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7), 4.22-4.19 (m, 6H, CH_2-2, CH_2-3 & CH_2-2''), 2.32 (s, 3H, CH_3-3'''); Anal. Calc. for $C_{23}H_{22}N_2O_5S$ (438.125): C, 63.00; H, 5.06; N, 6.39. Found: C, 63.13; H, 5.21; N, 6.43.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(4-methylphenyl)acetamide (7f)

Light pink amorphous powder; Yield 91%; m.p. 167-168 °C; Molecular Formula: $C_{23}H_{22}N_2O_5S$; Molecular Mass: 438 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3245 (N-H), 3051 (Ar C-H), 2930 (Ar -CH_2), 1711 (C=O), 1631 (Ar C=C), 1377 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz): d (ppm) 8.25 (s, 1H, NHCO), 7.64-7.61 (m, 3H, H-2', H-4' & H-6'), 7.50 (dist.t, *J* = 7.2 Hz, 2H, H-3' & H-5'), 7.37 (br.d, *J* = 8.4 Hz, 2H, H-2''' & H-6'''), 7.11 (br.d, *J* = 8.0 Hz, 2H, H-3''' & H-5'''), 6.75 (d, *J* = 8.8 Hz, 1H, H-8), 6.64 (d, *J* = 2.4 Hz, 1H, H-5), 6.52 (dd, *J* = 2.4, 8.8 Hz, 1H, H-7), 4.21 (br.s, 6H, CH_2-2, CH_2-3 & CH_2-2''), 2.29 (s, 3H, CH_3-4'''); Anal. Calc. for $C_{23}H_{22}N_2O_5S$ (438.125): C, 63.00; H, 5.06; N, 6.39. Found: C, 63.21; H, 5.11; N, 6.51.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2,3-dimethylphenyl) acetamide (7g)

Creamy amorphous powder; Yield 83%; m.p. 163-164 °C; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3243 (N-H), 3051 (Ar C-H), 2937 (Ar -CH_2), 1719 (C=O), 1635 (Ar C=C), 1379 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz,): d (ppm) 8.28 (s, 1H, NHCO), 7.64-7.61 (m, 3H, H-2', H-4' & H-6'), 7.53-7.48 (m, 3H, H-3', H-5' & H-6'''), 7.07 (br.t, *J* = 7.6 Hz, 1H, H-5'''), 7.00 (br.d, *J* = 7.2 Hz, 1H, H-4'''), 6.76 (d, *J* = 8.4 Hz, 1H, H-8), 6.67 (d, *J* = 2.4 Hz, 1H, H-5), 6.55 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7), 4.25-4.22 (m, 6H, CH_2-2, CH_2-3 & CH_2-2''), 2.28 (s, 3H, CH_3-3'''), 2.16 (s, 3H, CH_3-2'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.84; H, 5.39; N, 6.28.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2,4-dimethylphenyl) acetamide (7h)

Light pink amorphous powder; Yield 79%; m.p. 159-160 °C; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3247 (N-H), 3043 (Ar C-H), 2937 (Ar -CH_2), 1717 (C=O), 1631 (Ar C=C), 1385 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz): d (ppm) 8.23 (s, 1H, NHCO), 7.66-7.61 (m, 4H, H-2', H-4', H-6' & H-6'''), 7.49 (br.t, *J* = 7.6 Hz, 2H, H-3' & H-5'), 6.99-6.97 (m, 2H, H-3''' & H-5'''), 6.76 (d, *J* = 8.8 Hz, 1H, H-8), 6.66 (d, *J* = 2.4 Hz, 1H, H-5), 6.53 (dd, *J* = 2.4, 8.8 Hz, 1H, H-7), 4.23 (br.s, 2H, CH_2-2''), 4.22-4.21 (m, 4H, CH_2-2 & CH_2-3), 2.26 (s, 3H, CH_3-4'''), 2.24 (s, 3H, CH_3-2'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.62; H, 5.31; N, 6.26.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2,5-dimethylphenyl) acetamide (7i)

Light brown amorphous powder; Yield 87%; m.p. 128-129 °C; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3250 (N-H), 3053 (Ar C-H), 2933 (Ar -CH_2), 1713 (C=O), 1637 (Ar C=C), 1379 (S=O); ^{1}H-NMR ($CDCl_3$, 600MHz,): d (ppm) 8.22 (s, 1H, NHCO), 7.67 (m, 3H, H-2', H-4' & H-6'), 7.56 (br.t, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.08 (br.s, 1H, H-6'''), 7.05 (br.d, *J* = 7.8 Hz, 1H, H-3'''), 6.92 (br.d, *J* = 7.2 Hz, 1H, H-4'''), 6.74-6.73 (m, 2H, H-5 & H-8), 6.61 (dd, *J* = 2.4, 9.0 Hz, 1H, H-7), 4.38 (br.s, 2H, CH_2-2''), 4.22-4.19 (m, 4H, CH_2-2 & CH_2-3), 2.25 (s, 3H, CH_3-5'''), 2.03 (s, 3H, CH_3-2'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.78; H, 5.43; N, 6.24.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2,6-dimethylphenyl) acetamide (7j)

Light pink amorphous powder; Yield 80%; m.p. 143-144 °C; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3249 (N-H), 3043 (Ar C-H), 2933 (Ar -CH_2), 1715 (C=O), 1639 (Ar C=C), 1383 (S=O); ^{1}H-NMR ($CDCl_3$, 600MHz,): d (ppm) 8.21 (s, 1H, NHCO),

7.07-7.04 (m, 2H, H-3' & H-5'), 7.03 (m, 3H, H-2', H-4' & H-6'), 7.02 (br.d, *J* = 7.8 Hz, 2H, H-3''' & H-5'''), 6.78 (br.d, *J* = 7.8 Hz, 1H, H-4'''), 6.73 (d, *J* = 9.0 Hz, 1H, H-8), 6.56 (d, *J* = 3.0 Hz, 1H, H-5), 6.47 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7), 4.39 (br.s, 2H, CH_2-2''), 4.22-4.19 (m, 4H, CH_2-2 & CH_2-3), 2.09 (s, 6H, CH_3-2''' & CH_3-6'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.88; H, 5.44; N, 6.21.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(3,4-dimethylphenyl) acetamide (7k)

Light pink amorphous powder; Yield 87%; m.p. 153-154 °C; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3247 (N-H), 3041 (Ar C-H), 2937 (Ar -CH_2), 1711 (C=O), 1639 (Ar C=C), 1383 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz,): d (ppm) 10.12 (s, 1H, NHSO_2), 7.57 (br.d, *J* = 7.8 Hz, 2H, H-2' & H-6'), 7.27 (br.d, *J* =7.8 Hz, 2H, H-3' & H-5'), 7.24 (merged in the signal of $CDCl_3$, 2H, H-2''' & H-6'''), 7.05 (br.d, *J* = 8.0 Hz, 1H, H-5'''), 6.62 (d, *J* = 8.4 Hz, 1H, H-8), 6.56 (d, *J* =2.4 Hz, 1H, H-5), 6.47 (dd, *J* = 2.4,8.4 Hz, 1H, H-7), 4.40 (br.s, 2H, CH_2-2''), 4.15 (br.s, 4H, CH_2-2, CH_2-3), 2.23 (s, 3H, CH_3-3'''), 2.20 (s, 3H, CH_3-4'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.65; H, 5.27; N, 5.97.

2-[2,3-Dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(3,5-dimethylphenyl) acetamide (7l)

Dark brown semi-solid; Yield 90%; Molecular Formula: $C_{24}H_{24}N_2O_5S$; Molecular Mass: 452 $gmol^{-1}$; IR (KBr, cm^{-1}) υ: 3249 (N-H), 3051 (Ar C-H), 2931 (Ar -CH_2), 1717 (C=O), 1637 (Ar C=C), 1383 (S=O); ^{1}H-NMR ($CDCl_3$, 400MHz,): d (ppm) 10.12 (s, 1H, NHSO_2), 7.57 (br.d, *J* = 7.8 Hz, 2H, H-2' & H-6'), 7.27 (br.d, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.12 (br.s, 2H, H-2''' & H-6'''), 6.74 (br.s, 1H, H-4'''), 6.62 (d, *J* = 8.4 Hz, 1H, H-8), 6.56 (d, *J* =2.4 Hz, 1H, H-5), 6.47 (dd, *J* = 2.4,8.4 Hz, 1H, H-7), 4.38 (br.s, 2H, CH_2-2''), 4.15 (br.s, 4H, CH_2-2, CH_2-3), 2.28 (s, 6H, CH_3-3''' & CH_3-5'''); Anal. Calc. for $C_{24}H_{24}N_2O_5S$ (452.141): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.81; H, 5.46; N, 6.12.

Anti-diabetic activity

The synthesized compounds (**7a-l**), demonstrated weak to moderate inhibitory potential based on IC_{50} values (Table 2). Among these derivatives, **7k, 7i** and **7g** were found to be most promising relative to other derivatives in the series. These three molecules exhibited IC_{50} values of 81.12±0.13 µM, 86.31±0.11 µM, and 95.64±0.12 µM, respectively, relative to acarbose (reference standard) having IC_{50} value of 37.38±0.12 µM.

Table 2: α- Glucosidase inhibition studies of the synthesized compounds

Compound	α- Glucosidase	
	Inhibition (%) at 0.5 mM	***IC_{50} (µM)***
7a	79.42 ± 0.18	221.43 ± 0.13
7b	91.78 ± 0.14	121.35 ± 0.11
7c	78.61 ± 0.18	212.48 ± 0.13
7d	92.31 ± 0.18	143.52 ± 0.14
7g	91.76 ± 0.17	95.64 ± 0.12
7h	81.12 ± 0.14	114.36 ± 0.12
7i	91.23 ± 0.15	86.31 ± 0.11
7j	89.56 ± 0.16	136.29 ± 0.12
7k	95.68 ± 0.15	81.12 ± 0.13
7l	91.72 ± 0.21	305.26 ± 0.16
Acarbose	**92.23 ± 0.16**	**37.38 ± 0.12**

Note: IC_{50} values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA). Data is mean of three values (mean ± s.e.m., n = 3)

DISCUSSION

The multi-step synthesis of the designed molecules, **7a-l**, was accomplished by a facile strategy, and all these new compounds were obtained in very good yields. The structures of these molecules were established by the interpretation of their spectral and CHN analysis data. The structural assignment of one of the compounds is discussed here in detail for the convenience of the readers. The molecule, **7g**, was obtained as creamy amorphous powder in 83% yield, having a melting point of 163-164 °C. The molecular formula, $C_{24}H_{24}N_2O_5S$, of this compound was predicted by counting the number of protons in its ^{1}H-NMR spectrum, and it was also supported by its CHN analysis data. Various functional groups in this molecule were affirmed by its IR data. Therein, different absorption bands at υ 3243 (N-H), 3051 (Ar C-H), 2937 (Ar -CH_2), 1719 (C=O), 1635 (Ar C=C), and 1379 (S=O) were observed for the speculated functionalities. In its ^{1}H-NMR spectrum (Figure 1), the most de-shielded singlet at δ 8.28 was typical for an acetamidic proton (-NHCO). Similarly, the signals appearing at *d* 6.76 (d, *J* = 8.4 Hz, 1H, H-8), 6.67 (d, *J* = 2.4 Hz, 1H, H-5), and 6.55 (dd, *J* = 2.4, 8.4 Hz, 1H, H-7) were characteristic of 1,4-benzodioxine-6-yl moiety.

However, the signals of two methylenes of 1,4-benzodioxane and one methylene of the acetamido group, attached at nitrogen atom, were merged as a multiplet at d 4.25-4.22. The signals resonating at d 7.64-7.61 (m, 3H, H-2', H-4' & H-6'), and 7.53-7.48 (m, 3H, H-3', H-5' & H-

6''') were collectively assigned to the five protons of benzenesulfonyl group and one proton (H-6''') from the 2,3-dimethylphenyl ring. The latter ring was also fully characterized by the remaining signals at d 7.07 (br.t, *J* = 7.6 Hz, 1H, H-5'''), 7.00 (br.d, *J* = 7.2 Hz, 1H, H-4'''), 2.28 (s, 3H, CH_3-3'''), and 2.16 (s, 3H, CH_3-2'''). So, on the basis of above accumulative manifests, the structure of **7g** was named as 2-[2,3-dihydro-1,4-benzodioxin-6-yl(phenylsulfonyl)amino]-*N*-(2,3-dimethylphenyl) acetamide. Similarly, the structures of other molecules of the series were confirmed with a similar approach.

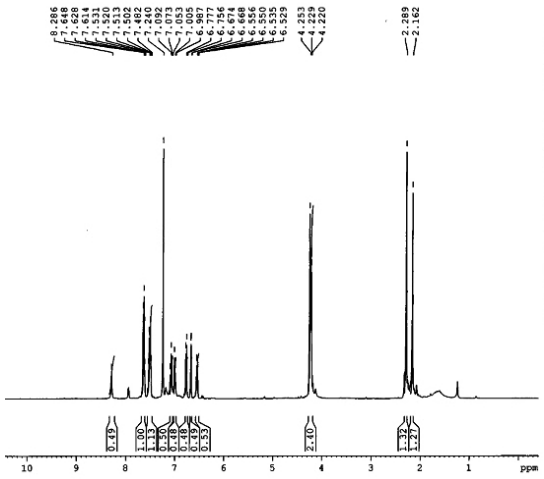

Figure 1: ^{1}H-NMR spectrum of **7g**.

As α-glucosidase inhibitors are generally employed as anti-diabetic agents. Therefore, the screening of these derivatives was ascertained against the *α*-glucosidase enzyme, whereby these molecules demonstrated moderate to weak inhibitory potential, as inferred from their IC_{50} values (Table 2). Among these derivatives **7k, 7i** and **7g** were found to be promising relative to other analogues in the series. The molecule **7k** with IC_{50} value of 81.12 ± 0.13 µM was identified as the most active compound among the series, and its promising inhibitory potential might be an attribute of the substitution of 3,4-dimethylphenyl group in this molecule. Similarly, the molecules **7i** and **7g** also rendered analogous inhibitory potentials with IC_{50} values of 86.31 ± 0.11 µM, and 95.64 ± 0.12 µM, respectively, and therefore, their activities might be relayed to the substitution of 2,5-dimethylphenyl and 2,3-dimethylphenyl groups respectively in these molecules. Acarbose was used as a reference standard in the assay having IC_{50} value of 37.38±0.12 µM.

CONCLUSION

The targeted multi-functional molecules have been synthesized in decent yields and some of them exhibit notable anti-diabetic potentials. Therefore, these acetamides might serve as possible therapeutic entrants for type-2 diabetes.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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