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Synthesis, spectral characterization and anti-diabetic activity of sulfonamide derivatives

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ABSTRACT

A series of substituted 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamide were designed & synthesized keeping in view the structural requirements of pharmacophore.For establishing the structure, spectral characterization like FT-IR, ^{1}H NMR, GC-MS and elemental analysis (CHNS) has been performed. They were evaluated for anti-diabetic activity against Alloxan induced diabetes mellitus animal model. On comparing the resulting pharmacological data with standard drug tolbutamide, possible mechanism of action could be as agonist upon binding to peroxisome proliferator-activated receptor (PPAR γ).

Keywords: *Benzenesulfonamide; synthesis; anti-diabetic; spectral characterization.*

1. INTRODUCTION

Diabetes mellitus (DM) has been considered as one of the major health problem all around the world today [1]. It is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. DM is one of the most daunting challenges posed by chronic diseases resulting from insulin deficiency or insulin resistance [2].

In this condition, pancreas do not produces enough insulin or cells stop responding to insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body [3]. India has today become the diabetic capital of the world with over 20 million diabetic's patients and this number is set to increase to 57 million by 2025.

It is ranked 7th among the leading causes of death and is considered 3rd when its fatal complications are taken into account. Several drugs such as sulfonylureas are presently available to reduce hyperglycaemia in diabetes mellitus. These drugs have demonstrated significant side effects and thus searching for a new class of compounds is essential to overcome these problems. There is continuous search for alternative drugs treatment of diabetes without any side effects is still a challenge to the medicinal chemist [4].Statistical data and epidemiological data clearly show increasing prevalence of diabetes with time. Hence, there is a crying need to synthesize more effective and oral antidiabetic agents [4]. The clinical and medicinal importance of sulfonamides is well documented. The sulfonamide moiety (–SO_2NH_2) is an active pharmacophore, plays very vital role in the development of various biologically active agents such as anti-microbial, anti-malarial, insulin-releasing antidiabetic, anti-HIV, high ceiling diuretic, antithyroid, and anti-tumor. Among the broad spectrum of activities exhibited by sulfonamides, their role as antidiabetic is more considerable[5].

The development of sulfonamides is a fascinating and informative area in medicinal chemistry. A large number of sulfonamides derivatives are widely used in clinical medicine as pharmacological agents with a wide variety of biological actions [5].

Experimental animal models are one of the best strategies for the understanding of pathophysiology of any disease in order to design and develop the drugs for its treatment. Numerous animal models have been developed for the past few decades for studying diabetes mellitus and testing anti-diabetic agents that include chemical, surgical and genetic manipulations. One of the most potent methods to induce experimental diabetes mellitus is chemical induction by Alloxan. It is a well- known diabetogenic agent that is used to induce Type I diabetes in experimental animals [1].

2. EXPERIMENTAL SECTION

2.1. Material and methods.

2.1.1. Synthesis and spectral characterization.

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), Himedia (India) and S. D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105^o C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds.

Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The ^{1}H-NMR spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using

TMSas an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m). The mass spectra were recorded on a Waters Micro-Mass ZQ 2000 mass spectrometer.

2.1.2 Synthesis of substituted acyl chlorides.

Substituted acid (0.1 mol) and thionyl chloride (0.4 mol) were placed in a 250 ml flask equipped with a magnetic stirrer bar and a condenser with a drying tube. The reaction mixture was stirred and heated in a 70^0 C oil bath. After 0.5 hours, the reaction mixture was allowed to cool at room temperature with opened flask; this facilitates the evaporation of remaining thionyl chloride and lefts acyl chloride in the flask [6, 7].

2.1.3.Synthesis of substituted 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamide.

For the synthesis of an appropriate amide, the substituted acyl chloride/substituted benzyl chloride (0.009 mol) of an individual acid dissolved in 20 ml. of dry acetone was added dropwise to a stirred solution of suitable aromatic aminosulfonamide (0.0092 mol) and pyridine (0.0091mol) in 50 ml. of dry acetone.

After addition, the reaction mixture was stirred for about 12 hours at room temperature and then the solvent was evaporated under reduced pressure. The residue was dissolved in 100 ml. ethyl acetate and the organic phase washed three times with 20 ml. of distilled water. Then 10% HCl solution was added until pH 1 was reached, and the organic phase was separated from the aqueous phase and washed three times with brine. The aqueous solutions were combined and extracted with ethyl acetate.

The ethyl acetate extracts were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Further, the dried products have been purified by subjecting it with ethanol: petroleum ether (1:3) mixture to give white to off white crystals. [6, 7].

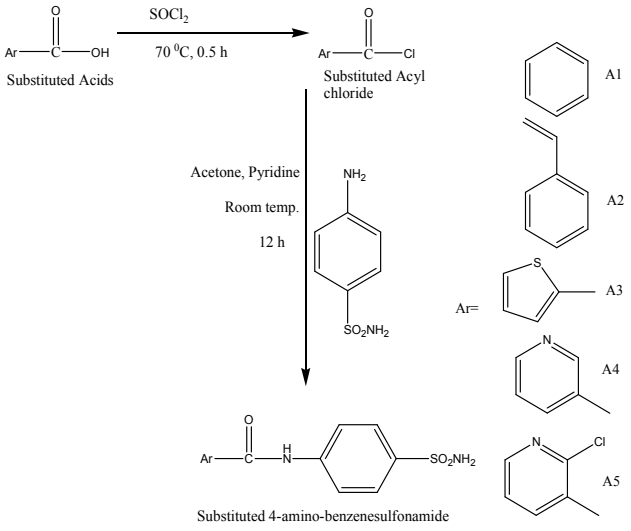


Figure 1. Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted acids (A1, A2, A3, A4, A5).

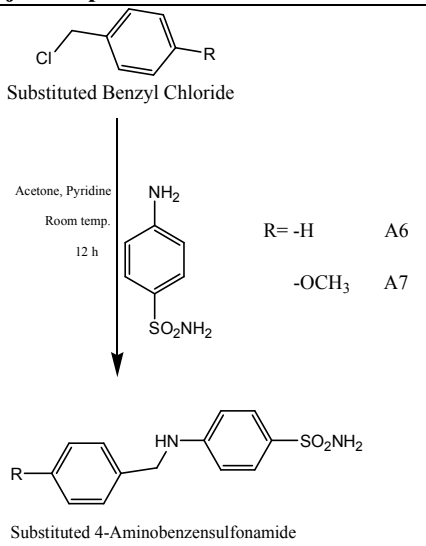


Figure 2. Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted benzyl chloride (A6, A7).

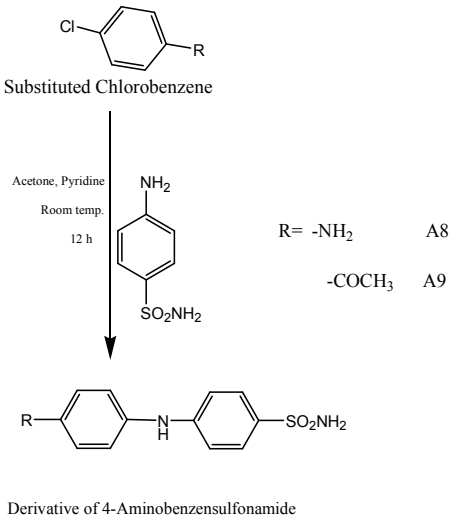


Figure 3. Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted chlorobenzene (A8, A9).

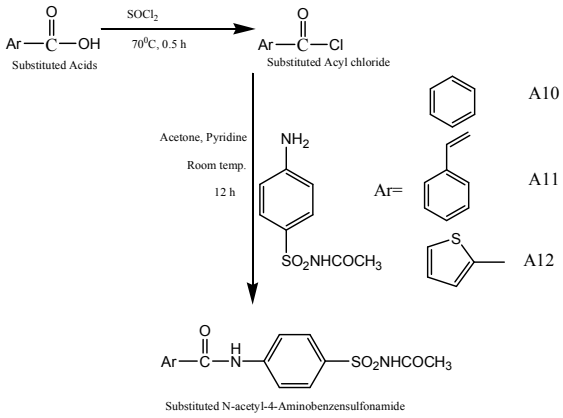


Figure 4. Synthetic scheme of substituted N-acetyl-4-amino-benzenesulfonamide from substituted acids (A10, A11, A12)

2.2.Pharmacological evaluation.

Albino mice were procured from the disease free animal house of S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar. The animals were housed in standard polypropylene cages (two rats/cage) and maintained under controlled room temperature (25 ± 2 ºC) and humidity (55 ± 5%) with12 hr light and 12 hr dark cycle. All the ratswere provided with commercially available rat normal pellet diet (NPD) and water ad libitum, prior to the dietary manipulation.

2.2.1.Acute toxicity studies.

Groups of six albinomice, weighing 25–35 g were fasted overnight andtreated orally with the test compounds[3]. Thedosage was varied from 200 mg/kg body weights. Theanimals were observed for 24 h for any signs of acutetoxicity such astremors, increased or decreased motor activity, convulsion,lacrimation, sedation etc. Nomortality of the animals was observed even after 24 to 36 hr.Hence the LD_{50} cut-off value of the test compounds wasfixed as 200 mg/kg,so that 20 mg/kg i.e., 1/10 ofcut-off value was taken as screening dose for evaluation of antidiabetic activity. Animal experimentswere conducted by the approval of Institutional Animal Ethics Committee (IAEC), S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar, India. During the study, guidelines of CPCSEA(Committee for the Purpose of Control and Supervision of Experiments on Animals) and IAEC were followed for the maintenance of animals.

2.2.2Antidiabetic activity.

A mice were fasted overnight for at least 8 hr. Hyperglycaemia was induced in each fasted mice by administeringalloxan monohydrate (150 mg/Kg body weight; intraperitoneal) in normal saline. The control was administered normal saline intraperitoneally.A blood glucose range of 300–350 mg/dL was used for the experiment. Hyperglycemia was confirmed in animals after 72 h of alloxan monohydrate injection [3].

Experimental design- Animals were dividedinto 06 sets of 6 animals (n = 6): Set01- diabeticanimals (Vehicle) received 0.5% CMC (1ml); Set02 (standard) diabetic animals receivedTolbutamide 100 mg/kg.Set (03 to 06) diabetic animals receivedcompoundsA1-A12 in a single dose of 20 mg/kg body weight per oral.

Blood glucose measurement: At the end of0, 8thand 16th hr, blood sample was withdrawn from atail vein by snipping the tip of the tail and the blood glucose level was measured by glucometer (Accu-Chek Active, Roche Diagnostics)

Statistical analysis: Values are represented asmean ± SEM given in table 2. Data were analysed using analysis ofvariance and group means were analyse by ANOVA test.

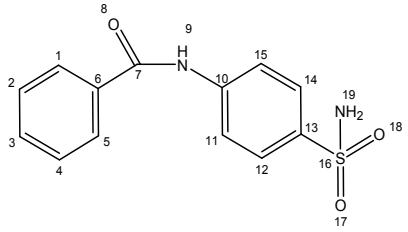
3. RESULTS SECTION

After synthesizing the designed compounds, they were treated for physical data like percentage yield, retention factor (R_f), melting point and elemental data (CHNS analysis).

The physical and elemental data of the synthesized compounds are reported in table 1.

3.1 Spectral characterization of synthesized substituted 4-amino-benzenesulfonamides / *N*-acetyl-4-amino-benzenesulfonamide derivatives.

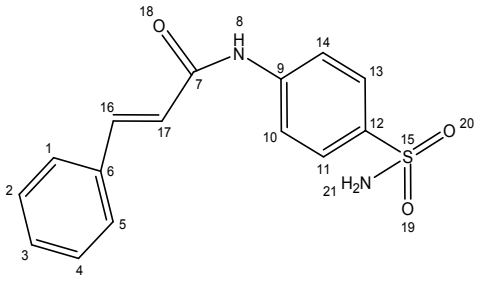
***N*-(4-Sulfamoyl-phenyl)-benzamide(A1)**



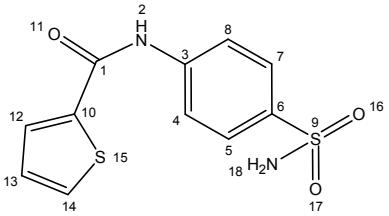
IR (KBr, cm^{-1}, υ): 3340.53 (-NH_2-); 3250.94 (-NH-); 1659.10 (>C=O); 1397.80(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 7.286(s, 2H, -NH_2); 7.548-7.580(d, 2H, Ar-H of C12 and C14); 7.616-7.648(t, 1H, Ar-H of C3); 7.809-7.826(t, 2H, Ar-H of C2 and C4); 7.958-7.994 (d, 4H, Ar-H of C1, C5, C11 and C15); 10.564(s, 1H, >NH). MS (m/z, %): 277.30 (M^++1, 95).

3-Phenyl-*N*-(4-sulfamoyl-phenyl)-acrylamide(A2)

IR (KBr, cm^{-1}, υ): 3359.69(-NH_2-); 3182.61(-NH-); 1674.59(>C=O); 1400.63(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 7.271(s, 2H, -NH_2); 2.5-3.3(d, 2H, C16 and C17); 7.489-7.492(d, 2H, Ar-H of C11 and C13); 7.631-7.663(t, 1H, Ar-H of C3); 7.791-7.809(t, 2H, Ar-H of C2 and C4); 7.857-7.875(d, 4H, Ar-H of C1, C5, C10 and C14); 10.551(s, 1H, >NH). MS (m/z, %): 303.70 (M^++1, 100).

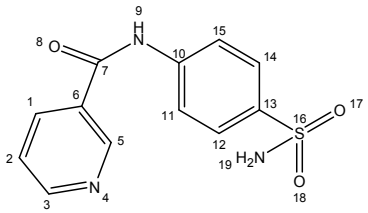


Thiophene-2-carboxylic acid (4-sulfamoyl-phenyl)-amide (A3)



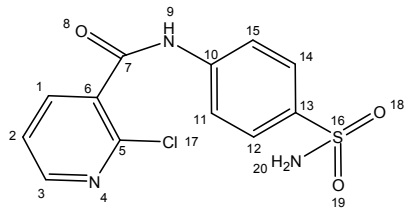
IR (KBr, cm^{-1}, υ): 3375.09(-NH_2-); 3275.82(-NH-); 1650.90(>C=O); 1408.75(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 7.289(s, 2H, -NH_2); 7.248-7.265(d, 1H, Thiophene-H of C14); 7.804-7.822(t, 1H, Ar-H of C13); 7.907-7.947(d, 4H, Ar-H of C4, C5, C7 and C8); 8.132-8.141(d, 2H, Thiophene-H of C12); 10.603(s, 1H, >NH). MS (m/z, %): 283.71 (M^++1, 100).

***N*-(4-Sulfamoyl-phenyl)-nicotinamide(A4)**



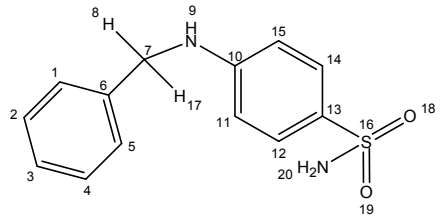
IR (KBr, cm^{-1}, υ): 3345.93 (-NH_2-); 3230.94 (-NH-); 1659.19 (>C=O); 1390.70(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 7.279(s, 2H, -NH_2); 7.568-7.590(d, 2H, Ar-H of C12 and C14); 7.656-7.688(d, 1H, Ar-H of C3); 7.819-7.836(t, 2H, Ar-H of C2); 7.918-7.924 (d, 3H, Ar-H of C1, C11 and C15); 7.89(s, 1H, Ar-H of C5); 10.584(s, 1H, >NH). MS (m/z, %): 278.10 (M^++1, 88).

2-Chloro-*N*-(4-sulfamoyl-phenyl)-nicotinamide(A5)



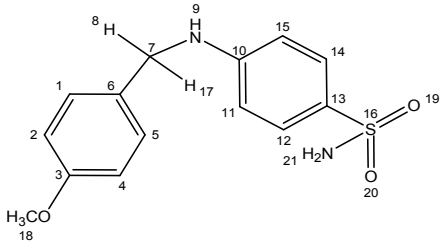
IR (KBr, cm^{-1}, υ): 700.10(>C-Cl), 3348.83 (-NH_2-); 3238.94 (-NH-); 1657.19 (>C=O); 1390.70(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 7.299(s, 2H, -NH_2); 7.588-7.593(d, 2H, Ar-H of C12 and C14); 7.686-7.689(d, 1H, Ar-H of C3); 7.820-7.836(t, 2H, Ar-H of C2); 7.928-7.929(d, 3H, Ar-H of C1, C11 and C15); 10.594(s, 1H, >NH). MS (m/z, %): 311.80 (M^++1, 90).

4-Benzylamino-benzenesulfonamide (A6)



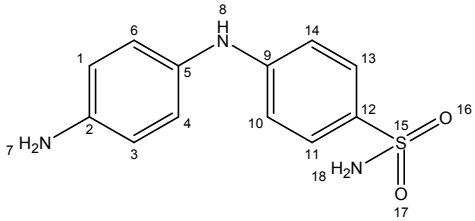
IR (KBr, cm^{-1}, υ): 3340.53 (-NH_2-); 3250.94 (-NH-); 1397.80(-SO_2-); 1465.76(>C-H). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 1.343(d, 2H of C7); 7.306(s, 2H, -NH_2); 7.558-7.590(d, 2H, Ar-H of C12 and C14); 7.626-7.638(t, 1H, Ar-H of C3); 7.819-7.827(t, 2H, Ar-H of C2 and C4); 7.918-7.904(d, 4H, Ar-H of C1, C5, C11 and C15); 10.563(s, 1H, >NH). MS (m/z, %): 263.30 (M^++1, 95).

4-(4-Methoxy-benzylamino)-benzenesulfonamide(A7)



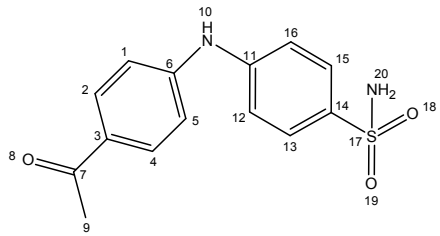
IR (KBr, cm^{-1}, υ): 3340.53 (-NH_2-); 3250.94 (-NH-); 1397.80(-SO_2-); 1315.87(>C-O-); 1465.76(>C-H). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 0.899(s, 3H, -CH_3); 1.383(d, 2H of C7); 7.316(s, 2H, -NH_2); 7.508-7.510(d, 2H, Ar-H of C12 and C14); 7.828-7.829(d, 2H, Ar-H of C2 and C4); 7.910-7.914(d, 4H, Ar-H of C1, C5, C11 and C15); 10.523(s, 1H, >NH). MS (m/z, %): 293.10 (M^++1, 90).

4-(4-Amino-phenylamino)-benzenesulfonamide(A8)



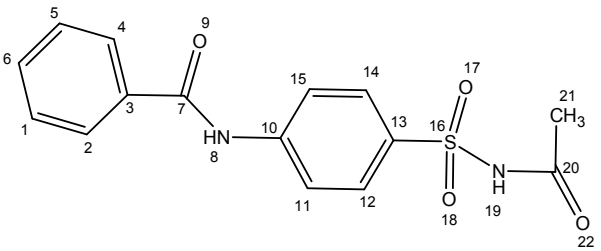
IR (KBr, cm^{-1}, υ): 3337.23(-NH_2- of C2); 3342.83 (-NH_2-); 3190.84 (-NH-); 1679.10 (>C=O); 1387.90(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 6.986(s, 2H, -NH_2); 7.236(s, 2H, -NH_2); 7.498-7.550(d, 2H, Ar-H of C11 and C13); 7.819-7.829(d, 2H, Ar-H of C1 and C3); 7.928-7.964 (d, 4H, Ar-H of C4, C6, C10 and C14); 10.524(s, 1H, >NH). MS (m/z, %): 264.80 (M^++1, 89).

4-(4-Acetyl-phenylamino)-benzenesulfonamide(A9)



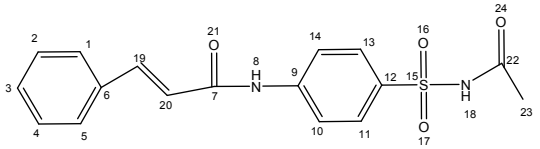
IR (KBr, cm^{-1}, υ): 3348.83 (-NH_2-); 3193.84 (-NH-); 1639.70 (>C=O); 1392.90(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 0.909(s, 3H of C9); 7.256(s, 2H, -NH_2); 7.428-7.510(d, 2H, Ar-H of C13 and C15); 7.839-7.859(d, 2H, Ar-H of C2 and C4); 7.978-7.994 (d, 4H, Ar-H of C1, C5, C12 and C16); 10.584(s, 1H, >NH). MS (m/z, %): 291.30 (M^++1, 98).

***N*-(4-Acetylsulfamoyl-phenyl)-benzamide(A10)**



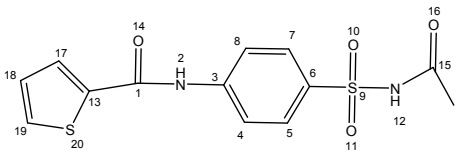
IR (KBr, cm^{-1}, υ): 3245.53, 3250.94 (-NH-); 1678.30, 1659.10 (>C=O); 1396.50(-SO_2-). ^{1}H NMR (DMSO, 400 MHz, δ in ppm): 0.919(s, 3H, -CH_3); 7.512-7.530(d, 2H, Ar-H of C12 and C14); 7.596-7.628(t, 1H, Ar-H of C6); 7.839-7.846(t, 2H, Ar-H of C1 and C5); 7.908-7.954 (d, 4H, Ar-H of C2, C4, C11 and C15); 10.497, 10.527(s, 1H, >NH). MS (m/z, %): 319.90 (M^++1, 70).

***N*-(4-Acetylsulfamoyl-phenyl)-3-phenyl-acrylamide(A11)**



IR (KBr, cm^{-1}, υ): 3188.98, 3181.61(-NH-); 1681.09, 1678.59(>C=O); 1420.63($-SO_2-$). ^1H NMR (DMSO, 400 MHz, δ in ppm): 0.917(s, 3H, $-CH_3$); 2.518-3.398(d, 2H, C19 and C20); 7.479-7.482(d, 2H, Ar-H of C11 and C13); 7.611-7.623(t, 1H, Ar-H of C3); 7.781-7.701(t, 2H, Ar-H of C2 and C4); 7.859-7.870(d, 4H, Ar-H of C1, C5, C10 and C14); 10.534, 10.550(s, 1H, >NH). MS (m/z, %): 345.70 (M^++1, 94).

Thiophene-2-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide(A12)



IR (KBr, cm^{-1}, υ): 3252.83, 3277.80(-NH-); 1659.07, 1654.90(>C=O); 1408.75($-SO_2-$). ^1H NMR (DMSO, 400 MHz, δ in ppm): 0.927(s, 3H, $-CH_3$); 7.247-7.255(d, 1H, Thiophene-H of C19); 7.807-7.820(t, 1H, Ar-H of C18); 7.937-7.949(d, 4H, Ar-H of C4, C5, C7 and C8); 8.134-8.142(d, 2H, Thiophene-H of C17); 10.567, 10.603(s, 1H, >NH). MS (m/z, %): 325.81 (M^++1, 100).

3.2 Pharmacological Activity.

Several experimental studies have demonstrated that alloxan shows a sudden rise in level of insulin secretion in the presence or absence of glucose which appeared just after alloxan treatment [8-9]. This particular alloxan-induced insulin release occurs for short duration followed by the complete suppression of the islet response to glucose even when high concentrations of glucose were used [10]. Further, the alloxan action in the pancreas is preceded by its rapid uptake by pancreatic beta cells that have been proposed to be one of the important features determining alloxan diabetogenicity.

The oral administration of a single dose of synthesized compounds caused a significantreduction in blood glucose in diabetic rats. These resultsrevealed thatsulfonamide derivatives may be effectiveintype-I diabetes mellitus. The significant hypoglycemic effects ofsulfonamidederivatives in diabetic mice indicate that it can be mediated bystimulation of glucose utilization by peripheral tissues.Since the sulfonamide derivatives are having activityresemblance with tolbutamide, it can be expected that the mode of action ofthe sulfonamide derivatives may be similar to tolbutamide derivatives [11]. Hence sulfonamide derivatives mayact as agonist upon binding to peroxisome proliferator-activated receptor (PPAR γ)

Table 1. Physical and elemental data of all the synthesized compounds

Comp.	Molecular formula (MW)	Yield (%) [R_f]	MP (^{0}C)	Elemental analysis (%) : Found (Calculated)			
				C	H	N	S
A1	$C_{13}H_{12}N_2O_3S$ (276.306)	68.75 [0.4]	205-208	56.42 (56.50)	3.260 (4.377)	10.13 (10.14)	11.16 (11.60)
A2	$C_{15}H_{14}N_2O_3S$ (302.342)	71.92 [0.84]	220-222	59.44 (59.58)	1.922 (4.667)	9.224 (9.267)	10.63 (10.60)
A3	$C_{11}H_{10}N_2O_3S_2$ (282.41)	56.73 [0.63]	210-212	39.89 (46.77)	0.969 (3.569)	8.540 (9.921)	19.16 (22.73)
A4	$C_{12}H_{11}N_3O_3S$ (277.052)	10.47 [0.34]	211-212	45.42 (51.98)	2.08 (4.00)	14.18 (15.16)	10.80 (11.54)
A5	$C_{12}H_{10}ClN_3O_3S$ (311.013)	86.18 [0.8]	230-231	46.15 (46.23)	2.90 (3.24)	13.25 (13.49)	10.03 (10.26)
A6	$C_{13}H_{14}N_2O_2S$ (262.077)	23.04 [0.24]	170-172	59.48 (59.52)	4.80 (5.38)	10.10 (10.69)	11.92 (12.20)
A7	$C_{14}H_{16}N_2O_3S$ (292.088)	41.98 [0.16]	180-182	57.21 (57.52)	3.90 (5.52)	9.20 (9.59)	10.02 (10.95)
A8	$C_{12}H_{13}N_3O_2S$ (263.072)	93.42 [0.46]	208-210	54.34 (54.74)	3.52 (4.98)	15.41 (15.97)	11.92 (12.15)
A9	$C_{14}H_{14}N_2O_3S$ (290.072)	84.88 [0.25]	216-218	57.36 (57.92)	2.98 (4.86)	9.42 (9.65)	10.87 (11.02)
A10	$C_{15}H_{14}N_2O_4S$ (318.067)	29.21 [0.18]	250-252	55.99 (56.59)	3.98 (4.44)	8.72 (8.81)	9.92 (10.05)
A11	$C_{17}H_{16}N_2O_4S$ (344.083)	62.18 [0.66]	265-266	59.12 (59.29)	3.23 (4.69)	8.11 (8.14)	9.10 (9.29)
A12	$C_{13}H_{12}N_2O_4S_2$ (324.023)	33.95 [0.2]	225-227	47.92 (48.14)	2.65 (3.73)	8.21 (8.64)	19.04 2(19.73)

Table 2. Antidiabetic activity of compounds (A1-A12) in Alloxan induced diabetic mice

Comp.	Blood glucose level (mg/dL) mean±SEM		
	0 hr	8th hr	16th hr
A1	348.3±4.5	288.7±3.4**	212.6±5.2**
A2	344.4±4.3	320.3±5.2*	249.7±5.3**
A3	332.5±5.6	278.3±6.3**	210.3±6.1*
A4	345.6±4.7	304.3±5.4*	234.6±5.8**
A5	342.2±5.8	290.2±4.7**	245.6±6.1**
A6	340.9±4.1	300.7±4.5**	230.6±4.8*
A7	340.0±4.9	308.3±5.7**	257.8±4.6*
A8	322.7±5.3	280.8±4.6*	222.6±4.7**
A9	333.6±5.6	290.3±5.4**	273.3±6.1**
A10	339.7±5.8	299.5±3.5**	270.7±5.4**
A11	343.4±5.7	310.2±5.6*	280.5±6.2*
A12	332.8±4.8	301.1±4.6*	260.4±7.1*
Vehicle	346.4±4.7	351.2±6.4*	360.7±4.3**
Tolbutamide	343.8±4.6	260.8±4.9**	190.3±3.4*

*p<0.005 and **p<0.01

4. CONCLUSIONS

In order to obtain substituted acyl chlorides, substituted acids were treated with thionyl chloride and then substituted acyl chloride/substituted benzyl chloride/substituted chlorobenzene were treated with aminosulfonamides in the presence of pyridine for obtaining the substituted 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamides. The structures of synthesized compounds were confirmed by physical, analytical and elemental analysis. Compounds A1 and A3 shows good antidiabetic activity whereas compounds A6 and A8 having moderate activity. Rest compounds, other than A1, A3, A6 and A8 were found with below satisfactori activity. On comparing the resulting pharmacological data with standard drug tolbutamide, possible mechanism of action could be as agonist upon binding to peroxisome proliferator-activated receptor (PPAR γ).Although a systemic biochemical study of synthesized compounds is necessary to confirm the findings.

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