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Synthesis of substituted pyridine based sulphonamides as an antidiabetic agent

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ABSTRACT

This research work describes the synthesis of a new series of heterocyclic compounds, namely sulfonamide derivatives. Sulfonamides are a diverse class of organic compounds having significant and potent biological activities. Diverse synthetic methods have been engaged to build up its various derivatives for different biological functions. In this study, the production of novel pyridine-based heterocyclic compounds having sulfonamide moieties has been elaborated. The obtained sulfonamide-based pyridine scaffold was used to investigate their alpha-amylase inhibition activity. The structures of freshly prepared compounds were described using ^{1}H NMR, ^{13}C NMR, and IR spectroscopic techniques. The molecular docking of sulfonamides performed against porcine pancreatic alpha-amylase using PDB file 1LP was used for generation of grid. All the new synthesized compounds were shown notable anti-diabetic activity.

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1. Introduction

Sulfonamides are an important pharmaceutical product which are employed as pharmaceutical agents against various diseases due to their fundamental role in biological activity [1]. More than 30 drugs containing this functionality are in clinical use, including antihypertensive agent [2], antibacterial [3], anti-protozoal [4], antifungal [5], anti-inflammatory [6], nonpeptidic vasopressin receptor antagonists [7], and translation initiation inhibitors [8]. Some important sulfonamide derivatives used as carbonic anhydrase inhibitors are of commercial importance [9]. They are also effective for the treatment of urinary intestine, and ophthalmic infections, scalds, ulcerative colitis [10], rheumatoid arthritis [11], male erectile dysfunction as the phosphodiesterase-5 inhibitor sildenafil-better known under its commercial name, Viagra [12], and obesity [13]. More recently, sulfonamides are used as an anticancer agent [14], as the antiviral HIV protease inhibitor amprenavir [15], and in Alzheimer's disease [16]. Earliest research demonstrated that pyridine derivative shows good antidiabetic activity in which Hoehn *et al.* [17] reported that pyridine based pyrazole derivatives possesses excellent hyperglycemic activity. Frike *et al.* [18] reported that pyridine based thioazolidine derivatives exhibit excellent anti-diabetic activity using GOD-POD method. Similarly, Fei Ma and co-workers [19] reported that thio-pyridine derivatives have promising antidiabetic activity using gluconeogenesis inhibition assay. Recently, many more researches reported on hybrid pyridine nucleus in Type-I and Type-II diabetic research, on the basis this vast literature, we have selected *N*,*N*-disubstituted pyridine nucleus for present investigation.

Sulfa drugs are the sulfonamide antibiotics and they are synthetic antimicrobial agents with broadly applied for the action of various communicable diseases [20,21]. These drugs were the first efficient treatment to be employed scientifically for the prevention and cure of bacterial infections.

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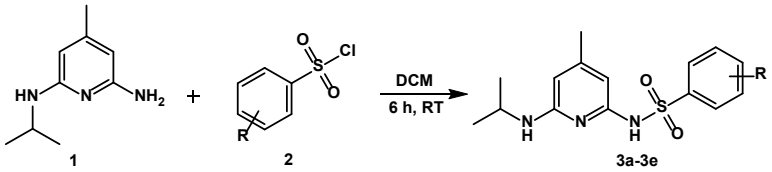

R = 3a (*o*-H), 3b (*o*-F), 3c (*m*-F), 3d (*p*-F), 3e (*2,6*-di-F)

Scheme 1

One of the initial sulfonamides recognized by Domagk *et al.* [22] was the red azo dye known as prontosil. There have been many analogues of sulfanilamide developed as pharmacological agents that exhibit a wide range of biological activities [23].

In addition, dorzolamide and brinzolamide have been launched as typically acting antiglaucoma pharmacological agents [24]. Till date, thousands of sulfonamide derivatives, analogues, and related compounds have been synthesized, which are effective as diuretics, anti-malarial, leprosy, and antithyroid agents and applied for other diseases [25]. Moreover, the aryl sulfonamides celecoxib and vadecoxib are used as COX-II inhibitors and anticancer agents [26]. Sildenafil was launched in 1998 as an anti-impotence drug and accountable for inhibiting the degradation of cyclic guanosine monophosphate [27]. It has been observed that sulfa drugs show increased biological activity when administered in the form of metal complexes [28]. Preparation of sulphonamide using sulphonyl chloride and substituted amine in presence of dichloromethane and catalytic amount of triethyl amine is well recognized method with the good scientific manner. Such a method was reported in different ways by many researchers like Sharma *et al.* [29] and Parai *et. al.* [30].

Furthermore, sulfonamide moiety has clinical and medicinal importance in the pharmaceutical industry. The sulfonamide moiety (-SO_2NH_2) is an active pharmacophore, exhibiting a wide variety of pharmacological activities such as antimicrobial, antimalarial, insulin-releasing antidiabetic, anti-HIV, high ceiling diuretic, antithyroid, and antitumor [31]. Moreover, next to their imperative role in human medicine they are also showing their promising significance in field of veterinary and agricultural sciences. Due to the presence of SO_2NH- group, the most important role of sulfonamide in the medicinal field is as an antibacterial agent. Due to the wide employability of sulfonamides, to find the potent and effective sulfonamide drug with high biological activity is highly desirable. Thus, synthesis of newly synthetic hybrid heterocyclic compounds is of great interest. Some of the most common and recent methods are used for the synthesis of sulfonamide via sulfonyl chloride treated with pyridine-based amines [32].

To the development of nitrogen and sulfur containing heterocyclic compounds in medicinal chemistry and pharmaceutical communities as these molecules has potent biological activities. In continuation, our research for the synthesis of the biologically active heterocyclic compounds [33]. We represent the study to synthesize a series of five new synthetic hybrid derivatives incorporating sulfonamide moieties via the reaction of p-toluene sulfonyl chloride with pyridine-based amine. These newly synthetic sulfonamide derivatives have remarkable interest in anti-diabetic activity.

2. Experimental

2.1. Apparatus and chemicals

Melting points were determined using Tanco PLT-276 Delux Model melting temperature apparatus. The IR spectra were measured as KBr pellets using a Shimadzu double beam infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethyl silane (TMS) as an internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS and the coupling constants are in Hertz (Hz). LC-MS spectra were run on a Shimadzu LCMS-QP1000 EX spectrometer at 70 eV. All derivatives employed in this study were prepared via direct reduction of nitro group of pyridines with iron in HCl solution following standard procedures [34].

2.2. General procedure for synthesis of compounds 3a-e

To a stirred solution of the appropriate amino pyridine (5 mmol) in dichloromethane (70 mL) was added a solution of the particular sulfonyl chloride (6 mmol) in dichloromethane (30 mL). To the resulting reaction mixture, stirring at room temperature (27 °C) for 2-6 hours at same temperature. The solvent was removed under reduced pressure, and the residue was washed with water. The resulting solid product was collected and recrystallized from ethanol:water (80:20, *v*:*v*) solution to give the desired **3a**-**e** (Scheme 1).

N-(6-(Isopropylamino)-4-methylpyridin-2-yl) benzenesulfonamide (**3a**): Color: Yellow. Yield: 80 %. M.p.: 120-122 °C. FT-IR (KBr, ν, cm^{-1}): 3493 (O-H), 3290 (N-H), 2962, 1643 (C=O), 1521, 1282. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.18 (d, 6H, *J* = 6.8 Hz, 2×CH_3), 2.15 (s, 3H, CH_3), 3.23 (m, 1H, CH) 6.68 (s, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 7.48 (m, 3H, Ar-H), 7.98 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.80 (s, 1H, H-N-CH(Me)$_2$), 9.40 (s, 1H, H-N-SO_2). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.2, 22.4, 26.6, 116.7, 124.5, 127.4, 128.8, 130.9, 131.2, 132.7, 134.7, 152.6, 166.5.

2-Fluoro-N-(6-(isopropylamino)-4-methylpyridin-2-yl)benzenesulfonamide (**3b**): Color: White. M.p.: 112-114 °C. Yield: 90 %. FT-IR (KBr, ν, cm^{-1}): 3400 (O-H), 3307 (N-H), 2945, 1614 (C=O), 1546, 1413, 1209. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.21 (d, 6H, *J* = 8 Hz, 2×CH_3), 2.17 (s, 3H, CH_3), 3.16 (m, 1H, CH), 6.39 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 7.19 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H),7.33 (s, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 8.78 (s, 1H, H-N-CH(Me)$_2$), 9.48 (s, 1H, H-N-SO_2). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.5, 22.5, 26.7, 116.4, 117.6, 121.2, 123.2, 125.7, 127.4, 130.2, 132.3, 133.5, 151.4, 159.6, 161.6, 162.7.

3-Fluoro-N-(6-(isopropylamino)-4-methylpyridin-2-yl)benzenesulfonamide (**3c**): Color: Orange. M.p.: 102-104 °C. Yield: 60 %. FT-IR (KBr, ν, cm^{-1}): 3294 (O-H), 3196 (N-H), 3076, 1643 (C=O), 1585, 1282, 1228, 1188. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.18 (d, 6H, *J* = 8 Hz, 2×CH_3), 2.14 (s, 3H, CH_3), 3.22 (m, 1H, CH), 6.68 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 7.24 (m, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.75 (dd, 1H, *J* = 11, 4 Hz, Ar-H), 7.83 (t, 1H, *J* = 8Hz, Ar-H), 8.81 (s, 1H, H-N-CH(Me)$_2$), 9.56 (s, 1H, 1×H-N-SO_2). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.3, 22.4, 26.8, 114.6, 117.5, 123.6, 124.3, 126.4, 129.6, 131.8, 136.7, 152.5, 160.4, 163.7, 164.6.

4-Fluoro-N-(6-(isopropylamino)-4-methylpyridin-2-yl)benzenesulfonamide (**3d**): Color: Orange. M.p.: 160-162 °C. Yield: 99 %. FT-IR (KBr, ν, cm^{-1}): 3400 (O-H), 3236 (N-H), 2964, 1643 (C=O), 1600, 1477, 1290, 1240, 1097. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.19 (d, 6H, *J* = 8 Hz, 2×CH_3), 2.15 (s, 3H, CH_3), 3.23 (m, 1H, CH), 6.69 (s, 1H, Ar-H), 6.98-7.24 (m, 3H, Ar-H), 8.03 (dt, 2H, *J* = 11, 4 Hz, Ar-H), 8.63 (s, 1H, 1×H-N-CH(Me)$_2$), 9.21 (s, 1H, 1×H-N-SO_2).

Table 1. Results of α-amylase inhibitory activity of compounds **3a**-**3e**.

Compound	Concentrations (µg/mL)				IC_{50}
	25	50	100	250	
3a	36.01	48.20	42.08	50.22	44.12±0.150
3b	38.66	40.33	41.69	48.24	42.23±0.150
3c	36.12	42.12	44.08	48.22	42.63±0.150
3d	38.52	46.20	50.50	52.22	46.86±0.150
3e	40.44	46.25	50.66	52.20	47.38±0.150
Acarbose	36.08	40.87	42.15	48.42	41.88±0.150

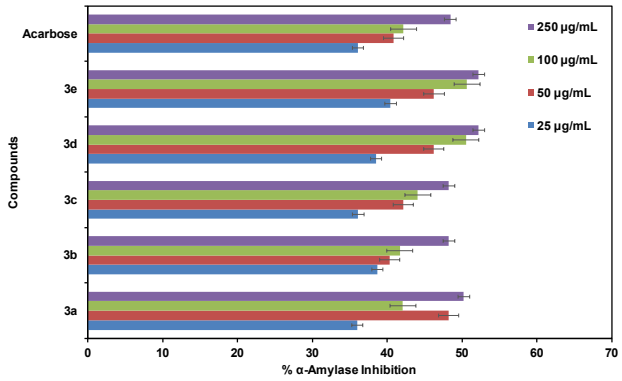

Figure 1. α-Amylase inhibitory activity of compounds **3a**-**e**.

^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.3, 22.5, 26.4, 114.6, 116.8, 124.6, 126.3, 129.0, 130.8, 131.5, 132.2, 152.3, 162.8, 163.9, 164.4, 165.5.

2, 6-Difluoro-N-(6-(isopropylamino)-4-methylpyridin-2-yl) benzenesulfonamide (**3e**): Color: Pale yellow. M.p. 168-170 °C. Yield: 92 %. FT-IR (KBr, ν, cm^{-1}): 3263 (O-H), 3194 (N-H), 3034, 2962, 1639 (C=O), 1529, 1346, 1220, 1197. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.18 (d, 6H, *J* = 8Hz, 2×CH_3), 2.17 (s, 3H, CH_3), 3.20 (m, 1H, CH), 6.68 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 7.04 (t, 2H, *J* = 7.6 Hz, Ar-H), 7.44 (m, 1H, Ar-H), 8.92 (s, 1H, H-N-$CH(Me)_2$), 9.74 (s, 1H, H-N-SO_2). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 17.4, 22.5, 25.30, 111.3, 115.2, 116.5, 123.7, 126.8, 130.9, 131.8, 132.7, 152.7, 157.8, 158.6, 160.8, 162.8.

2.3. Antidiabetic assay

2.3.1. α-Amylase inhibitory activity

Present assay was performed using previously published α-amylase inhibition assay [35], whole 250 µL of solutions of compounds having various concentrations were placed in different hard glass tubes and 250 µL of 0.02 M sodium phosphate buffer (pH = 6.9) containing α-amylase solution was added to it. All solutions were pre-incubated at 25 °C for 10 min, after which 250 µL of 1% starch solution in 0.02 M sodium phosphate buffer (pH = 6.9) was added at time intervals and then further incubated at 25 °C for 10 min. The reaction was terminated by adding 500 µL of dinitrosalicylic acid (DNS) reagent. The tubes were then incubated in boiling water for 5 min and cooled to room temperature. The reaction mixture was diluted with 5 mL distilled water and the absorbance was measured at 540 nm using spectrophotometer. A control was prepared using the same procedure replacing the compounds with water. Concentrations of samples resulting in 50% inhibition of enzyme activity (IC_{50}) were determined graphically.

2.4. Molecular modeling

The molecular docking of synthetic compounds performed against porcine pancreatic alpha-amylase complexed with acarbose using PDB file 1LP was used for generation of grid [36]. Pyridine based benzamides were optimized by TIP33.2 and conformers were generated using a 'rapid torsion angle' search approach followed by minimization of each generated structure using the AMBER ff99SB force field. The crystal structure of the carbohydrate inhibitor, acarbose (PDB ID: 1OSE) was obtained from the Protein Data Bank (PDB). The protein structure of porcine pancreatic alpha-amylase complexed with acarbose consists of four chains. The protein preparation was carried out using 'protein preparation wizard' in Maestro 8.0 in two steps, preparation and refinement [37]. After ensuring chemical correctness, water molecules in the crystal structures were deleted, and hydrogens were added, wherever necessary. Using the AMBER ff99SB force field, the energy of the crystal structure was minimized. In order to study the interaction of compounds at porcine pancreatic alpha-amylase complexed with acarbose; the molecules were selectively docked on a chain representing where porcine pancreatic alpha-amylase and cocrystal with acarbose is bound using extra precision (XP) docking mode. The final evaluation is done with glide score (docking score) and single best pose is generated as the output for particular ligand.

3. Results and discussion

3.1. Antidiabetic activity

Solutions with four concentrations are used for the present experiment. In which solutions with concentrations of 25, 50, 100, and 250 µg/mL are used. The experiments of each group are repeated three times. All synthesized derivatives show excellent α-amylase inhibitory activity at lower to higher concentrations (Table 1). The IC_{50} of compound **3a** is 44.12±0.123 µg/mL, also compounds **3b**, **3c**, and **3e** are 42.23±0.150, 47.38±0.150, 41.88±0.150 µg/mL, respectively, compound **3d** has the IC_{50} value 41.88±0.150 µg/mL comparable with acarbose is 41.88±0.150 µg/mL. Overall view of this activity suggested that compound **3e** having 54.18±0.150 µg/mL is most potent to inhibit the *α*-amylase (Figure 1). The interaction of the synthesized compounds with the active site of pancreatic α-amylase was investigated. It was found that the compounds with fluoro group substitution (**3c** and **3d**) at 2 and 3 position on the phenyl ring had a significant *α*-amylase inhibition activity. Compound **3b** has the highest binding scores in this experiment as shown Table 2.

Table 2. Binding energy and entropies of protein, ligand, and complexes.

No	Name	Binding energy	Complex energy	Protein energy	Ligand energy	Entropic energy	Complex entropy	Protein entropy	Ligand entropy
1	3a	-97.37	-9214.63	-9212.35	28.00	20.35	-36.412	-34.40	-22.36
2	3b	-44.40	-9252.98	-9212.35	18.80	20.37	-36.12	-34.40	-22.38
3	3c	-45.20	-9186.64	-9212.35	42.70	20.40	-36.12	-34.40	-22.44
4	3d	-46.15	-9253.31	-9212.35	22.15	20.34	-36.21	-34.40	-22.35
5	3e	-49.22	-9120.36	-9212.35	42.73	20.25	-36.12	-34.40	-22.25
6	Acarbose	-41.34	-9250.99	-9212.35	26.72	20.19	-36.12	-34.40	-22.18

Table 3. Docking score, steric score and structural parameter of synthesized derivatives.

No	Name	Docking score	Steric score	Desolvation	Hydrogen bond acceptor	Hydrogen bond donor
1	3a	-64.18	-76.85	13.21	-1.54	0.00
2	3b	-38.41	-82.73	12.95	-9.29	-0.32
3	3c	-40.90	-75.08	14.82	-6.22	-1.48
4	3d	-68.70	-87.63	13.06	-2.30	-1.85
5	3e	-46.90	-87.09	12.01	-4.59	-0.25
6	Acarbose	-28.40	-82.69	14.90	-9.45	-2.19

The compounds **3a**, **3b**, and **3c** show three-dimensional binding pose of two active compounds with human pancreatic α-amylase. A hydrophobic interaction was observed between the ligand and protein.

3.2. Molecular modeling

Molecular modeling is a computational operation that aims to predict the favored orientation of a ligand to its receptor target when these are sure to each other to form a stable complex. All the five synthesized molecules were docked (Tables 2 and 3). Table 2 shows the binding energy of all compounds. In silico studies revealed all synthesized molecules showed good binding energy.

4. Conclusion

A series of new functionalized pyridines containing benzene sulfonamide derivatives **3a**-**e** were synthesized using various substituted benzene sulfonyl chlorides treated with *N*-isopropyl-4-methylpyridine-2,6-diamine at room temperature for 6 h in dichloromethane solvent and checked for their anti-diabetic activity using α-amylase inhibition assay. From the screening results, it was found to possess antidiabetic activity comparable with standard (Acarbose). The results confirm that, the anti-diabetic activity is mainly dependent on the nature of hybrid pyridine nucleus. The pyridine derivatives generally led to dramatic enhancements in activity against both bacteria and fungi. In short, the present study can lead medicinal chemists to design and synthesize similar compounds with enhanced diabetic potency in future.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
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Sample availability: Samples of the compounds are available from the author.

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