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Title: **Synthesis, Structural Elucidation, and Biological Potential of Novel Sulfonamide Drugs**

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Synthesis, Structural Elucidation, and Biological Potential of Novel Sulfonamide Drugs

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Abstract

Sulfonamides are anti-microbial and anti-inflammatory agents used widely for the treatment of infections. The current research dealt with the synthesis of four sulfonamides formed by the reaction of *p*-toluenesulfonyl chloride with 4-amino phenyl acetic acid, 5-amino isophthalic acid, 4-piperidine carboxylic acid, and toluidine. The respective structures of sulfonamide drugs were verified by elemental analysis (CHNS), FT-IR spectroscopy, and thermogravimetry. The elemental analysis (CHNS) data conformed to the proposed chemical composition of the products 1-4. The FT-IR spectra verified the formation of sulfonamide drugs. Thermogravimetric analysis (TGA) of data in the range of 25-800^{o}C showed that the evolved components and residues were in good agreement with the molecular skeletons of the products. The antibacterial potential of sulfonamide drugs was evaluated against bacterial strains using the disc diffusion method. The zones of inhibition were found to be larger against *Escherichia coli* as compared to *Bacillus Subtilis*. Cytotoxicity of products was in the acceptable range of 0.3-3.1%, as compared to triton X100. It indicates the safety of these products as future medicinal drugs for human beings.

1. Introduction

Sulfonamide functional group is the basis of numerous sulfa drugs which find very important applications in medicinal and synthetic organic chemistry [1]. Sulfonamides are one of the earliest developed antimicrobial agents [2] which are still considered important therapeutic agents for the empiric and definitive treatment of numerous infectious diseases [3]. Sulfonamides are well-known motifs in medicinal chemistry [4] and an important class of synthetic bacteriostatic antibiotics that are commonly used for the therapy of

bacterial and other microbial infections [5]. They were considered the major therapeutic antimicrobial agents before the discovery of penicillin in 1941 [5]. The first sulfonamide antibiotic Prontosil was credited after the pioneering work of Gerhard Domagk. Till then, sulfonamide drugs are widely employed as therapeutic agents due to their antitumor [6], antidepressant, anticancer, antifungal, antimalarial, antiviral, antibacterial [7], anti-carbonic anhydrase diuretic [8], hypoglycemic [9], protease inhibitor activity [10], and anti-thyroid activity [11, 12]. They found clinical uses for the treatment of dandruff, inflammation, glaucoma, cancer, and Alzheimer's disease which were effective as antiviral HIV protease inhibitor amprenavir [5]. Sulfonamide moiety is the backbone of numerous anti-microbial [13], antioxidant, antiparasitic [14], anticonvulsant, antiglaucoma, anticancer, uricosuric agents, and many other drugs [15]. However, it is also worth mentioning that despite the numerous therapeutic uses of sulfonamides, their utilization is also associated with some allergic responses [3, 16] including hypersensitivity reactions and rashes [17]. Also, human pathogens can acquire resistance against sulfonamides [18]. The presence of sulfonamide antibiotics in aquatic environments has been recognized as an issue warranting consideration [19, 20]. Their presence has also been detected in other environmental samples including agricultural soils [21]. They have been known to effect the structural diversity and function of the soil microbial community [22]. Biodegradation demonstrated a very significant role in sulfonamide dissipation in both engineered and natural ecosystems [23]. With the increase in the number of multidrug-resistance microbial pathogens, there is a dire need to develop new antimicrobial agents with lower resistance and improved performance. Medicinal chemistry largely focused the formation of less harmful and novel sulfonamides or sulfonamide-bearing analogs [24].

Sulfonamide is considered a 'scaffold' in medicinal chemistry for the drug development owing to its biological activities. Sulfonamides also find industrial applications in some products of food colorants, health, and others. Therefore, it is necessary to continue with new research projects of sulfonamide syntheses [9]. Owing to their wide uses/applications [25, 26], current studies were performed to synthesize four sulfonamide drugs and characterize their structures by elemental analysis (CHNS), FTIR spectroscopy, and thermogravimetry. The synthesized products were tested for their antimicrobial potential and hemolytic effects.

2. Materials and Methods

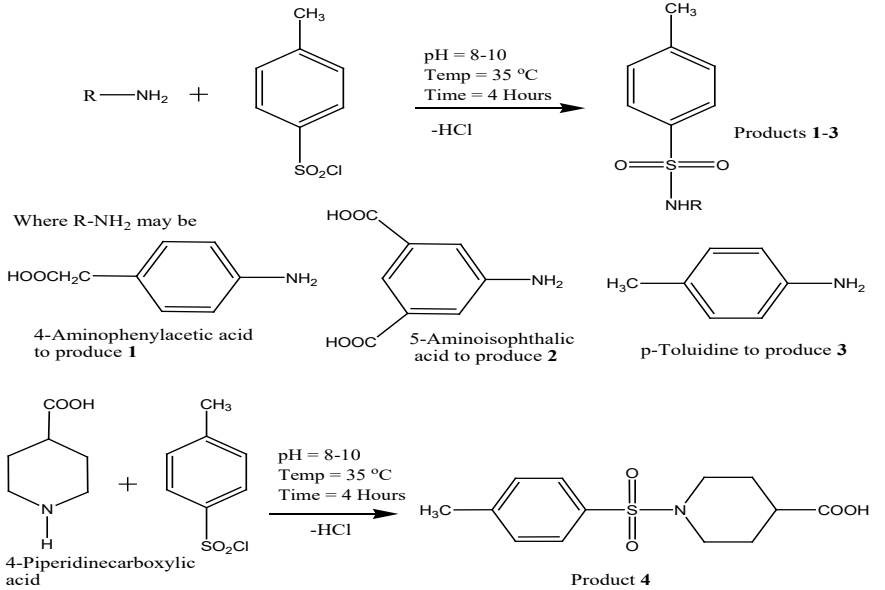
The sodium carbonate (Sigma), hydrochloric acid (Merck), methanol (Merck), ethanol (Merck), acetone (BDH), chloroform (Merck), *n*-hexane (Merck), and *p*-toluenesulfonyl chloride (Merck) were used. Other chemicals having (-NH) group in their structure were also used; they include 4-aminophenylacetic acid (Sigma Aldrich), 5-Aminoisophathalic acid (Merck), p-toluidine (Merck), and 4-pipridinecarboxylic acid (Sigma Aldrich). The purification of novel products was tested by TLC plates and spots were located by UV light.

Elemental analysis was performed by CHN-932 elemental analyzer Lesco Corporation USA. Thermo Nicolet 6700 FTIR was used to record the IR spectra of the products while the thermogravimetric characterization was done by the Metler Toledo instrument. Compounds were tested for their antibacterial potential against two

bacterial strains *Bacillus Subtilis* and *Escherichia coli* by disc diffusion method [27-29]. Ampicillin was used as the standard antibacterial drug. A concentration of 1 mg/ml of a test sample in DMSO solvent was used for all the antibacterial tests [30, 31]. The in *vitro* hemolytic activities of the sulfonamides were performed with human red blood cells while reporting the average lysis concerning the PBS as a negative control (0% lysis) and triton X-100 as a positive control (100% lysis) [32-34].

2.1. Syntheses of Sulfonamides 1-4

1 mmol (0.0151g) of 4-aminophenylacetic acid was added into 15 mL distilled water in a round bottom flask and the mixture was stirred for 10 minutes. Then 1 mmol of 0.019g of p-toluenesulfonyl chloride was carefully added and the reaction was allowed to proceed with constant stirring. *p*-toluene sulfonyl chloride initially floated on the surface of the solution. The progress of the reaction was examined by a significant decrease the in pH of the reaction mixture due to the formation of HCl as a product and it was monitored a by using pH meter. Initial pH was 4, after one the minute of beginning the reaction. The pH was strictly maintained at 8-10 by adding Na_2Co_3 (having pH13) after regular intervals. Completion of reaction was confirmed by no further change in pH of solution due to the consumption of all the sulfonyl chloride in sulfonamide formation. On the completion of reaction, 0.1M HCl was added to the solution in order to precipitate out the product 1. The formation of the product was confirmed by thin layer chromatography (TLC) in ethanol and dichloromethane (2:3) as mobile phase. Using 5-aminoisophathalic acid, p-toluidine, and 4-pipridinecarboxylic acid in place of 4-aminophenylacetic acid has produced the products 2-4, respectively. All the chemical reactions are displayed in Scheme 1.



Scheme 1: Synthesis of Products 1-4

3. Results

3.1. Physical Analysis

Products 1-4 were stable in the air and have shown sharp melting points. They were soluble in common organic solvents. The elemental analysis data (CHNS) agreed well with the molecular composition of the products. The physical data of products 1-4 are summarized in Table 1.

3.2. FTIR Spectroscopy

Products 1-4 were analyzed by FTIR spectroscopy in the range of 500-4000 cm^{-1} to evaluate the functional groups present in the compound. The FTIR data is presented in Table 2 and a representative spectrum of compound 1 is shown in Figure 1.

Table 1. Physical Data of the Products 1-4

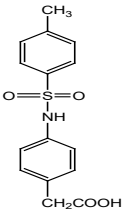
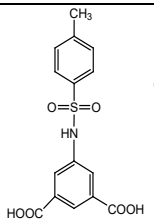
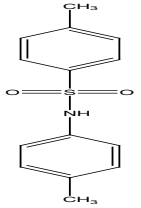
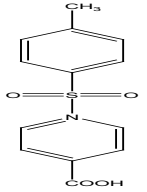
Comp. No.	Structural Formula	Molecular Formula	Mol. Mass	Melting Point (^{0}C)	Solubility	Yield %	Elemental Analysis (Calculated/found)			
							C	H	N	S
1		$C_{21}H_{27}NO_4S$	389.51	140	DMSO, Methanol Ethanol, Water, DCM, Acetone	77	64.75/64.49	6.99/6.89	3.60/3.59	8.23/8.29
2		$C_{15}H_{13}NO_6S$	335.33	170	DMSO, Methanol Ethanol, Water	80	53.73/53.72	3.91/3.90	4.18/4.09	9.56/9.59
3		$C_{14}H_{15}NO_2S$	261.34	120	DMSO, Ethanol, Methanol, DCM	70	64.34/63.99	5.79/5.98	5.36/5.298	9.47/9.39
4		$C_{13}H_{12}NO_4S$	278.3	250	DMSO, Ethanol, Methanol	75	56.10/56.09	4.35/4.34	5.03/506	8.34/8.33

Table 2. FTIR Data (cm^{-1}) of Compounds 1-4

Comp. No.	-N-S=O	C-N	C-H (Methyl)	N-H	C-H (Aromatic)
1	1148	1023	2956	3358	3050
2	1150	1030	2950	3356	3055
3	1145	1025	2959	3360	3060
4	1140	1020	2954	-	3045

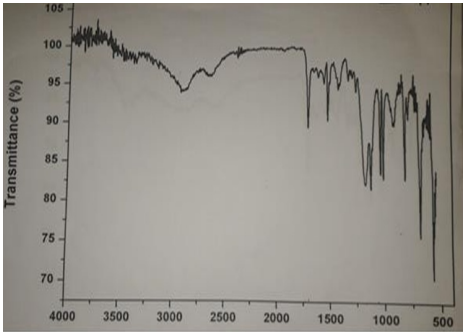


Figure 1. FTIR Spectrum of Compound 1

3.3. Thermogravimetric Analysis (TGA)

Compounds 1-4 were subjected to the thermo gravimetric analysis in order to identify their modes of decomposition and thermal stabilities [35, 36]. The compounds were analyzed under nitrogen atmosphere in the absence of oxygen. The obtained data is shown in Table 3 and the representative spectrum has been displayed in Figure 2.

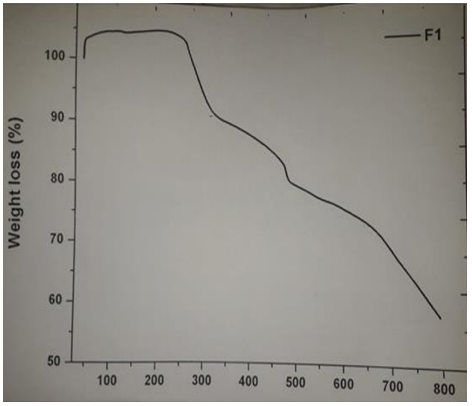


Figure 2. Thermogram of Product 1

Table 3. Thermogravimetric Data of Compounds 1-4

Comp. No.	Molecular Formula	Temperature Range (^{0}C)	Evolved Components	%Weight Loss (Calculated)	% Weight Loss Observed
1	$C_{21}H_{27}NO_4S$	250-320	NS	11.2	11
		320-490	CHO	11	11
		490-670	$2H_2O$	10	10
		670-800	C_2H_6, $8H_2$	14	14
		Residue left behind	18C	56.5	57
2	$C_{15}H_{13}NO_6S$	25-110	$2H_2O_2$,O	14.3	14.5
		110-340	H_2O,H_2	5.9	6
		340-490	H_3S^{+},H_2	11.04	11
		490-650	O	4.77	5
		650-800	NO	8.9	8.5
		Residue left behind	15C	53	55

		25-240	S	12	12
		240-310	H_2, H_2O	15	15
3	$C_{14}H_{15}NO_2S$	310-490	NH	5	5
		490-800	C_2H_6	11	12
		Residue left behind	12C	55	56
		25-300	H_2O_2,H_2	11	11
		300-490	NO	10	10
4	$C_{13}H_{12}NO_4S$	490-610	H_2S,H	12	12
		610-800	H_3O^+,H_2	7	7
		Residue left behind	12C	51	58

3.4. Antibacterial Studies

The synthesized sulfonamides 1-4 were tested for their antibacterial potential against two bacterial strains *Bacillus Subtilis* and *Escherichia coli* by disc diffusion method [28, 29]. Ampicillin was used as the standard antibacterial drug. A concentration of 1 mg/ml of a test sample in DMSO solvent was used for all the antibacterial tests [30, 31]. The zone of inhibition was measured in mm by a zone reader. The antibacterial activity data is displayed in Table 4.

3.5. Hemolytic Activities

The sulfonamides 1-4 were tested for their toxicological hemolytic effects because in the presence of these effects the compound cannot be used as a drug even if it possesses strong antimicrobial action. The cytotoxicity was evaluated by using a standard procedure. Triton X100 was used as a positive control while phosphate buffer solution was used as a negative control; the positive and negative controls have 100% and 0% lysis, respectively [33, 34]. The obtained data is shown in Table 5.

Table 4. Antibacterial Activity Data of Sulfonamides 1-4; zones of inhibition are given in millimeters (mm)

Comp. No.	*Bacillus subtilis*	*Escherichia coli*
1	22	29
2	20	26
3	25	30
4	26	25
Ampicillin	34	35

Table 5. Hemolytic Activity Data (%) of Sulfonamides 1-4

Comp. No.	1	2	3	4	Triton X100	PBS
Hemolytic Activity (%)	1.2	2.6	3.1	0.3	100	0

4. Discussions

Sulfonamides 1-4 can be produced by a nucleophilic substitution reaction of *P*-toluene sulfonyl chloride with any one from 4-amino phenyl acetic acid, 5-aminoisophathalic acid, p-toluidine, and 4-

pipridine carboxylic acid. The reactions are facilitated in alkaline environment which favoured the removal of hydrogen from amino group and resulted in the formation of an ionic bond between negatively charged nitrogen of amide and positively charged sulfur of sulfonyl group. The synthetic method in the current studies is economical in terms of its cost-effectiveness, time of reaction, reaction conditions, aqueous medium (environmentally friendly), significant % age yield, and products purity.

4.1. FTIR Spectroscopy

Infrared spectroscopy provides very important information about the functional groups of synthetic products [37]. The FTIR spectra (Table 2) of investigated products 1-4 displayed a large number of peaks but N-S=O, C-N, and N-H are the peaks of special interest. A strong peak appeared at 1140-1150 cm^{-1} which corresponds to asymmetric stretch of N-S=O [38]. The peak at 1020-1030 cm^{-1} was assigned to C-N [38] whereas the one at 3350- 3360 cm^{-1} represented the presence of N-H group. N-H peak was absent in product 4. Two separate peaks appeared at 2950-2960 cm^{-1} and 3045-3055 cm^{-1} which were assigned to C-H bonds of methyl groups and aromatic moieties, respectively.

4.2. Thermogravimetric Analysis (TGA)

The synthesized sulfonamides were subjected to thermogravimetric analysis under the N_2 atmosphere to investigate their thermal stability, degradation pattern, and % purity [23]. It was found that thermally decomposed data agreed well with the expected chemical composition of compounds 1-4. The products have shown an almost common pattern of degradation leaving behind only carbon residue (Table 3). The hydrogen, oxygen, and sulfur contents evolved either in elemental, gaseous, or combined form. The thermal decomposition data agreed well with the molecular skeletons of the synthesized products. The initial increase in the weight of product **1** demonstrated the absorption of nitrogen gas from its surrounding environment in the thermoanalyzer.

4.3. Antibacterial Studies

Many sulfonamides have been applied as potential biological molecules due to their broad range of biological applications, better efficacy, and less toxicity [39]. Their antibacterial activities are commonly investigated by many researchers [14, 40]. The newly synthesized sulfonamides 1-4 have shown significant antibacterial potential (Table 4). However, the activities of tested compounds were comparatively lower as compared to those (34 against *B. subtilis* and 35 mm against *E. coli*) of the standard drug (ampicillin). In tested sulfonamides, 1-4, the zones of inhibitions (25-30 mm) against *Escherichia coli* were larger in size as compared to those (20-26 mm) against *Bacillus subtilis*. Against *B. subtilis*, the highest activity (26 mm) was displayed by compound 4 while the lowest activity (20 mm) was shown by sulfonamide 2. However, the highest activity (30 mm) was displayed by compound 3 while the lowest activity (20 mm) was shown by sulfonamide 2 when activities were tested against *E. coli*. So, it can be culminated that all the sulfonamides are sufficiently active against the tested bacterial strains, however, sulfonamide 2 possessed the lowest antibacterial potential against both the tested bacterial strains namely *E. coli* and *B. subtilis*.

4.4. Hemolytic Activities

Hemolytic potential of the synthesized sulfonamides was investigated because, even if a compound demonstrates potent antimicrobial potential, its use in medicine

would be prohibited if it displays significant hemolytic potential [23].

The hemolytic data (Table 5) of products 1-4 clarifies that the toxicity of all the sulfonamides lies in acceptable range of 0.3-3.1%. The literature showed that a compound having toxicity lower than 10% can be safe for human medicinal uses [41]. The cytotoxicity of compound **4** was found lowest as compared to the other sulfonamides 1-3.

4.5. Conclusion

The sulfonamides 1-4 were produced by a nucleophilic substitution reaction of *P*-toluene sulfonyl chloride with any one from 4-amino phenyl acetic acid, 5-amino isophathalic acid, p-toluidine, and 4-pipridine carboxylic acid. The structures of newly synthesized sulfonamides were verified by elemental analysis, FTIR, and thermogravimetric analysis. The results of microanalysis (CHNS) were in agreement with the molecular formulas of the products. FTIR spectroscopy verified the presence of the characteristic N-S=O and C-N bands of sulfonamides. The results of thermogravimetric analysis agreed with the molecular skeletons of the products 1-4. Sulfonamide drugs show significant antibacterial activities against *B. subtilis* and *E. coli*. In the same vein, the evaluation of hemolytic activities demonstrates the safety of the complexes for human medicinal use.

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