

Synthesis, Structure Analysis and Antibacterial Activity of New Potent Sulfonamide Derivatives

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ABSTRACT

Modification of sulfonamide drug using different principles of chemical reactions was investigated. These reactions involve the condensation of an amino group with triethyl orthoformate and dimethylformamide dimethyl acetal. Ability of sulfa to condense with active keto compounds, like ethyl pyruvate and piperazine carboxyaldehyde was studied. Alkylation of sulfa with different chloro derivatives was also reported. The structure of the isolated compound was elucidated and confirmed using elemental analysis and spectral data. The bioactivity of the obtained compounds was investigated against different gram positive and gram negative bacteria. The study reveals that most of the modified drugs show high to moderate antibacterial activity.

Keywords: Sulfonamide, Sulfa Drug, Gram Positive, Gram Negative Bacteria

1. Introduction

The demand for novel chemotherapeutic antibacterial remains attractive in the field of medicinal chemistry. The discovery of sulfonamides as antibacterial in the early 30s was the beginning of the most fascinating era of chemotherapeutic agents [1-4]. Since the introduction of prontosil over 70 years ago, sulfa drugs have been widely used to treat a broad spectrum of microbial diseases [5]. However, due to the rapid emergence of sulfonamide resistance organisms and the development of more potent drugs have limited their clinical use. The sulfonamide group is considered as a pharmacophore which is present in a number of biologically active molecules, particularly in antimicrobial agents [6-10]. In addition, numerous sulfonamide derivatives have been reported as carbonic anhydrase inhibitors [11-15], anti-cancer [16], and anti-inflammatory agents [17]. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. Therefore, there is an overwhelming need to develop more effective antibacterial agents to treat infections caused by antibiotic resistant bacterial pathogens. Sulfonamides exert their effect by targeting on dihydropteroate synthase (DHPS) enzyme, which catalyzes folic acid pathway in bacteria and some eukaryotic cells [18] but is not present in human cells [19]. This is the

basis for the selective effect of sulfonamides on bacteria and for their broad spectrum of antibacterial activity. Since sulfanilamide first came into use, different derivatives have appeared on the market. Chemically modified sulfanilamide is prepared to achieve more effective antibacterial activity, wider spectrum of microorganisms affected, or more prolonged action. Because of their low cost they are still used in many parts of the world. The substances are still used to treat some urinary tract infections, leprosy, and in combination with other drugs, fungal diseases such as toxoplasmosis. The pharmaceutical industry has responded with new classes of drugs, thus a great insight to search for potential pharmacologically active sulfanilamide and its derivatives is still of interesting.

This study deals with the synthesis of *N*-substituted sulfonamide derivatives. The structure was established and confirmed using elemental analysis and spectral data e.g. IR, ¹H NMR, ¹³C NMR and MS spectra. Biological activity of the synthesized compounds against gram positive and gram negative bacteria has been investigated.

2. Materials and Methods

Sulfanilamide, triethyl orthoformate, ethyl pyruvate, 3-chloro-2,4-pentanedione, dimethylformamide dimethylacetal (DMFDMA), piperazinecarboxyaldehyde, chloro-

acetonitrile and chloroacetone (aldrich, milwaukee, wi) were used as received. All other chemicals were reagent grade and were used without further purification.

2.1. Elemental Analysis and Physical Measurements

All melting points are uncorrected. IR spectra were recorded in KBr with a IR spectrophotometer Shimadzu 408. ¹H NMR and ¹³C NMR spectra were recorded on Varian EM-390 MHz spectrometer using TMS as an internal reference with the chemical shifts expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. Microanalytical data were obtained from the ANALAB Unit at chemistry department, Kuwait University.

2.2. Synthesis of *N, N'*-(4-sulfonamido) formamidine (**2b**); of *N, N'*-Bis (4-sulfonamido) formamidine (**3**); Ethyl *N*-(4-benzenesulfonamido)-2-Iminopropanoate (**4**); 4-(Pipra- Zin-1-ylmethyleneamino) benzenesulfonamide (**7**); 4-(Cyanomethylamino) benzenesulfonamide (**8**); 4-(2-Oxopropylamino) benzene-Sulfonamide (**9**); 4-(2,4-Dioxopentan-3-ylamino)benzenesulfonamide (**10**)

To a solution of **1** (0.01 mol) in toluene (20 ml) and DMF (10 ml) mixture, dimethyl formamide dimethyl acetal or triethyl orthoformate or ethyl pyruvate or piperazine carboxyaldehyde or chloroacetonitrile or 1-chloro-2-propanone or 3-chloro-2,4-pentanedione (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under vacuum and the solid product formed after cooling was collected by filtration, washed by ether and crystallized from proper solvent (*cf.* Table 1).

2.3. 4-(3,5-Dimethyl-1*H*-pyrazol-4-ylamino) benzenesulfonamide (**11**)

To a solution of **10** (0.01 mol) in DMF (20 ml), hydrazine hydrate (0.01 mol) was added. The reaction mixture was heated under reflux for 3h. The solvent was evaporated under vacuum and the yellow solid product so formed after cooling was collected by filtration, washed by ether and crystallized from ethanol. Compound **11** was collected as pale brown crystal 66% yield (*cf.* Table 1).

2.4. Drug Susceptibility Test

The drugs were tested by disc-diffusion method. Diluted bacterial cultures (100 mL) were spread on sterile Mueller-Hinton agar plates, after which 8 mm diameter discs (sterile blank) impregnated with drug for testing (10-100 mg) were placed on the plates. The plates were incubated for 24 h at 37°C under aerobic conditions and the diame-

ter of the inhibition zone around each disc was then measured and recorded. If the drugs were found to be active in the disc diffusion test (inhibition zone > 10 mm), they were further evaluated for determining minimum inhibitory concentration (MIC) values.

2.5. Minimum Inhibitory Concentration (MIC)

The drugs were screened for their antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*. MIC was evaluated by turbidity method. A loop full of bacteria was inoculated in 100 mL of nutrient broth at 37°C for 20 h in a test-tube shaker at 150 rev min⁻¹. The test compounds were prepared by dissolving in a minimal volume of DMSO and were serially diluted in Mueller-Hinton broth at concentrations in the range of 1 - 100 mg/mL. The 24-h bacterial cultures were then transferred into 10 mL of Muller-Hinton broth (control and test compounds) and incubated at 37°C for 24 h. The growth of the bacteria was determined by measuring the turbidity after 24 h. Thus, the MIC was generally read as the smallest concentration of drug in the series that prevents the development of visible growth of test organism. All the experiments were done in triplicate.

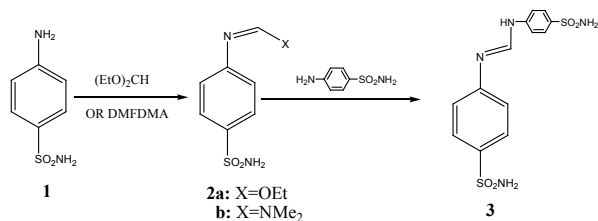
2.6. Statistical Analysis

The MIC value and modified drug susceptibility test were measured in triplicate. Statistical analysis of the MIC value was performed using the unpaired Student's *t*-test. Differences were considered significant when *P* < 0.01.

3. Results and Discussion

3.1. Chemistry

Sulfanilamide **1** reacted with triethyl orthoformate to give 4-(ethoxymethyleneamino) benzenesulfonamide **2a** or *N, N'*-bis (4-sulfonamido)formamidine **3** (*cf.* scheme 1). Compound **2a** was ruled out based on accurate mass *m/z* 354.04 which referred that the reaction took place with 1:2 molar ratios and was in agreement with the molecular formula C₁₃H₁₄N₄O₄S₂ (*cf.* Table 1). While in the case of dimethyl formamide dimethyl acetal (DMFDMA) *N, N'*-(4-sulfonamido)formamidine **2b** was isolated. Further reaction of **2b** with **1** gives **3**. The structure of com-



Scheme 1

compound **3** was established based on elemental analysis and spectral data. The IR reveals the presence of amino groups and NH at 3461, 3293 (assigned for $-\text{NH}_2$), and 3203 cm^{-1} (assigned for NH). The stretching vibrations assigned to the C-S linkage occur in 801 and 704 cm^{-1} . Two characteristic bands for sulfonamide absorb strongly at 1295 and 1145 cm^{-1} . In addition, ^1H NMR reveals the presence of imine proton at δ 6.74 ppm (cf. **Table 2, 3**). Activity of amino group in sulfanilamide **1** towards active ketone compound was investigated. Thus, compound **1** reacted with ethyl pyruvate to give the condensation product, ethyl *N*-(4-benzenesulfonamido)-2-iminopropanoate **4** or **5** (cf. **scheme 2**). The latter compound **5** was ruled out based on the spectral data. Thus, accurate mass assigned to compound **4** was found to be m/z 270.07 in agreement with the molecular formula $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$. ^1H NMR reveals the presence of the ethyl group as a triplet and a quartet at 1.71 and 4.21 ppm with *J* value 6.8 Hz, respectively (cf. **Table 3**). Moreover, a characteristic band for ester carbonyl in IR was observed at 1738 cm^{-1} . Sulfanilamide **1** reacted with piperazine carboxyaldehyde **6** to give the condensation product, 4-(piperazin-1-ylmethyleneamino) benzenesulfonamide, **7** (cf. **scheme 3**). The structure of the reaction product was

believed to be formed through the addition of nucleophilic amino group to the electrophilic carbonyl carbon followed by loss of water molecule to give the isolated product **7**. ^1H NMR reveals the presence of aromatic protons as dd at δ 7.46, 7.43 ppm with *J* value 8.0 Hz and imine protons at δ 6.62 ppm. In addition, the methylene protons of piperazine ring appeared at δ 2.62 and 2.57 ppm. ^{13}C NMR with ^1H NMR are confirmed the presence of $-\text{CH}=\text{N}-$ carbon and proton at δ 160.30 ppm and 6.62 ppm, respectively. Alkylation of sulfanilamide **1** with chloroacetonitrile, chloroacetone and 2-chloro-2,4-pentadione was created to yield *N*-alkylated derivatives **8-10**, respectively (cf. **scheme 4**). The accurate mass of the alkylated products **8-10** was m/z 211.04, 228.05 and 270.07, respectively. Compound **10** reacted with hydrazine hydrate to afford the *N*-pyrazolylsulfanilamide derivative **11**. ^1H NMR showed bands at δ 7.46, 7.40, 6.61 and 6.59 ppm for aromatic protons with *J* value 8.0 Hz. The pyrazole-H appeared at δ 7.30 ppm with *J* value 7.6 Hz other protons are shown in Table 2. Furthermore, ^{13}C NMR showed bands at δ 151.94, 149.08, 135.35, 129.86, 127.90, 127.36 and 126.66 assigned for aromatic carbons and pyrazole carbons. Two sp^3 carbons were appeared at δ 26.68 and 25.16 ppm.

Table 1. Data , accurate mass and elemental analysis of the prepared compounds.

Compound No.	Mp ($^{\circ}\text{C}$)	Solvent (yield %)	Accurate mass	Elemental analysis Calcd/found (%)			
				C	H	N	S
2b	159-160	DMF/EtOH 89%	$\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ 227.07	47.56	5.77	18.49	14.11
				47.76	5.88	18.29	14.27
3	273-274	DMF/EtOH 60%	$\text{C}_9\text{H}_{14}\text{N}_4\text{O}_4\text{S}_2$ 354.04	44.06	3.98	15.81	18.10
				44.07	4.20	15.88	17.96
4	142-144	EtOH 73%	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ 270.07	48.88	5.22	10.36	11.86
				48.80	5.22	10.54	11.81
7	153-155	EtOH 60%	$\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ 268.10	49.24	6.01	20.88	11.95
				49.22	5.99	21.01	12.11
8	134-135	EtOH 78%	$\text{C}_8\text{H}_9\text{N}_3\text{O}_2\text{S}$ 211.04	45.49	4.29	19.89	15.18
				45.51	4.31	19.88	15.21
9	182-185	EtOH 76%	$\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ 228.05	47.35	5.30	12.27	14.05
				47.34	5.30	12.31	13.97
10	>250	DMF/EtOH 71%	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ 270.07	48.88	5.22	10.36	11.86
				49.01	5.12	10.33	12.01
11	179-180	EtOH 75%	$\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$ 266.08	49.61	5.30	21.04	12.04
				49.60	5.22	21.22	11.89

Table 2. IR of the prepared compounds.

Cpd No.	IR (cm^{-1})
2b	3451, 3351(NH_2); 1275, 1135 ($-\text{SO}_2\text{NH}_2$); 844, 689 (S-O)
3	3461,3293 (NH_2); 3203 (NH); 1295, 1145 ($-\text{SO}_2\text{NH}_2$); 801, 704 (S-O)
4	3463, 3374 (NH_2); 1738 (ester CO); 1629 (C=N); 1311, 1151 ($-\text{SO}_2\text{NH}_2$); 829, 722 (S-O)
7	3471, 3372 (NH_2); 3252 (NH); 1632 (C=N);1312, 1145 ($-\text{SO}_2\text{NH}_2$); 827, 692 (S-O)
8	3477, 3382(NH_2); 2200 (CN); 1310, 1150 ($-\text{SO}_2\text{NH}_2$); 825, 694 (S-O)
9	3477, 3382 (NH_2); 3318 (NH); 1723 (CO); 1310, 1150 ($-\text{SO}_2\text{NH}_2$); 825, 741 (S-O)
10	3476, 3373, 3272 (NH_2 & NH); 1698 (CO); 1295, 1145 ($-\text{SO}_2\text{NH}_2$); 801, 704 (S-O)
11	3473, 3374, 3265 (NH_2 , NH); 1318, 1148 ($-\text{SO}_2\text{NH}_2$); 840, 686 (S-O)

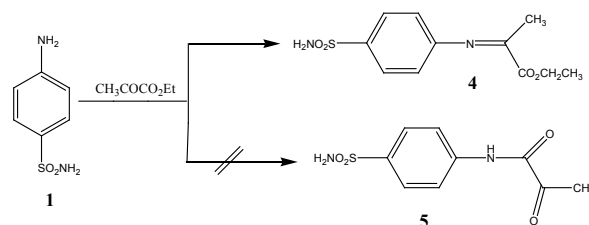
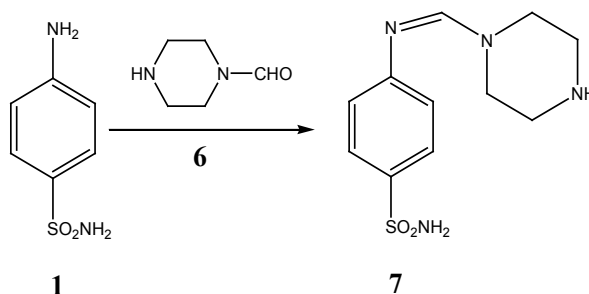
Table 3. ^1H NMR and ^{13}C NMR of the prepared compounds.

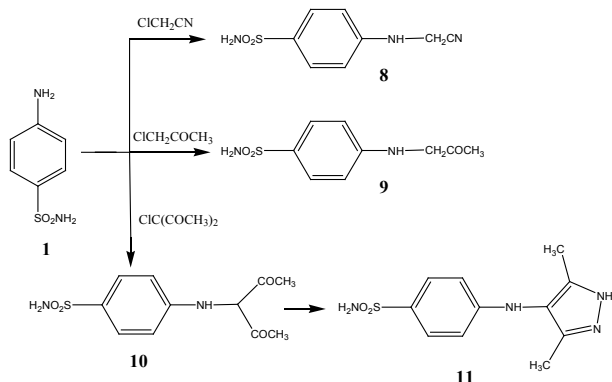
Cpd No.	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)
2b	11.40, 11.37 (br 2H, NH_2 , D_2O -exchange); 8.54-6.76 (dd, 4H, C_6H_4 , $J=8.8$); 6.74 (s, 1H, $\text{CH}=\text{N}$); 2.75, 2.74 (s, 6H, 2Me).	162.35 (imine carbon); 157.96, 141.71, 128.07, 127.27, 121.26, 121.13 (aromatic carbons)
3	11.38 (d, 1H, NH , D_2O -exchange); 7.88, 7.77 (br, 4H, 2 NH_2 , D_2O -exchange); 8.52-7.30 (m, 8H, 2 C_6H_4); 6.74 (d, 1H, $-\text{CH}=\text{N}$, $J=7.6$ Hz)	162.38 (imine carbon); 158.03, 155.75, 140.91, 140.85 (C and C4 in two benzene rings); 121.27, 121.34, 128.88, 128.78 (other aromatic-C).
4	9.00 (br, 2H, NH_2 , D_2O -exchange); 7.95-6.57 (dd, 4H, C_6H_4 , $J=8.8$); 4.21 (q, 2H, CH_2 , $J=6.8$ Hz); 1.71 (t, 3H, Me, $J=6.8$ Hz)	163.45 (CO); 161.12 (imine carbon); 152.36, 138.42, 128.01, 123.29 (aromatic carbons); 61.24 (CH_2); 15.62, 14.35 (2 Me).
7	8.00 (d, 2H, NH_2); 7.46, 7.43 (dd, 4H, C_6H_4 , $J=8.4$ Hz); 6.62 (s, 1H, $\text{CH}=\text{N}$); 5.72 (s, 1H, NH); 2.62, 2.57 (tt, 8H, 4 CH_2 , $J=5.6$ Hz)	160.3 (imine carbon); 152.11, 131.01, 128.21, 112.64 (aromatic carbons); 5.32, 47.01 (piperazine carbons).
8	7.51, 7.49 (d, 2H, C_6H_4 , $J=8.0$ Hz); 6.95 (br, 1H, NH , D_2O -exchange); 6.65, 6.63 (d, 2H, Ar-H, $J=8.0$ Hz); 5.80 (br, 2H, NH_2 , D_2O -exchange); 2.86 (s, 2H, CH_2)	151.88, 132.70, 127.44, 112.53 (aromatic carbons); 129.90 (CN); 30.80 (CH_2).
9	7.56 (d, 2H, C_6H_4 , $J=8.4$ Hz); 6.75 (d, 2H, C_6H_4 , $J=8.8$ Hz); 6.91 (br, 2H, NH_2 , D_2O -exchange); 8.02 (br, 1H, NH , D_2O -exchange); 4.45 (s, 2H, CH_2); 2.91 (s, 3H, Me)	162.45 (CO); 152.67, 130.84, 127.86, 112.90 (aromatic carbons); 35.49 (CH_2); 30.35 (Me).
10	7.46 (d, 2H, C_6H_4 , $J=8.4$ Hz); 6.93 (br, 2H, NH_2 , D_2O -exchange); 6.60 (d, 2H, C_6H_4 , $J=8.0$ Hz); 5.83 (s, 1H, NH , D_2O -exchange); 3.42 (s, 1H, CH); 2.50 (s, 6H, 2Me)	169.00 (CO); 151.99, 130.00, 127.47, 112.46 (aromatic carbons); 85.00 (CH); 25.50 (Me)
11	7.46, 7.40 (d, 2H, C_6H_4 , $J=8$ Hz); 7.30 (d, 1H, pyrazole-H, $J=7.6$ Hz); 6.97 (br, 1H, NH , D_2O -exchange); 6.61, 6.59 (d, 2H, C_6H_4 , $J=8$ Hz); 5.51 (br, 2H, NH_2 , D_2O -exchange); 1.67 (s, 6H, 2Me)	151.94, 149.08, 135.35, 129.86, 127.90, 127.36, 126.66 (aromatic & pyrazole carbons); 26.68, 25.16 (2Me)

3.2. Antimicrobial Activity

Substitution on the sulfanilamide nitrogen is referred to as *N*1-substitution and *N*4-substitution on the 4-amino group as *N*-substitution. The therapeutically active derivatives are usually *N*1-substituted. The MIC values (average of triplicates) of the sulfanilamide and sulfanilamide derivatives are shown in **Table 4** and **Figures 1-5**. It can be observed from **Figures 1** and **2** that the antimicrobial results of compound **2b** has high effect on *S. Aureus* and *E. coli*, while compound **9** and **4** have a low effect. In the case of *E. coli* compound **8** showed high effects as compared to compound **4** at low concentration (10-40 mg mL^{-1}). In contrast at high concentration (70-100 mg) compound **4** showed greater effects than compound **8**. Similar behavior was observed in the case of *E. coli* with compound (**3** and **8**) and (**7** and **9**). Severe effect was observed by compound **9** toward *P. Aeruginosa* and *B. subtilis* (cf. **Figure 3** and **4**). In general most compounds showed better effect with increase its concentration. In contrast to this, for compounds **2b** and **7** at high concentration (more than 80 mg mL^{-1}), the effect of compound **2b** was more than compound **7**, while at low concentration (less than 80 mg mL^{-1}) compound **7** showed greater effect than compound **2b**. **Figure 5** represents the average zone of inhibition against sample number.

It shows that the effect of compound **2a** on microorganism can be arranged as follows: *E. coli* > *S. Aureus* > *P. Aeruginosa* > *B. subtilis* (from highest to lowest); in the case of compound **3** the only observed effect is on *E. coli* followed by *S. Aureus*. Compound **4** showed severe

**Scheme 2****Scheme 3**



Scheme 4

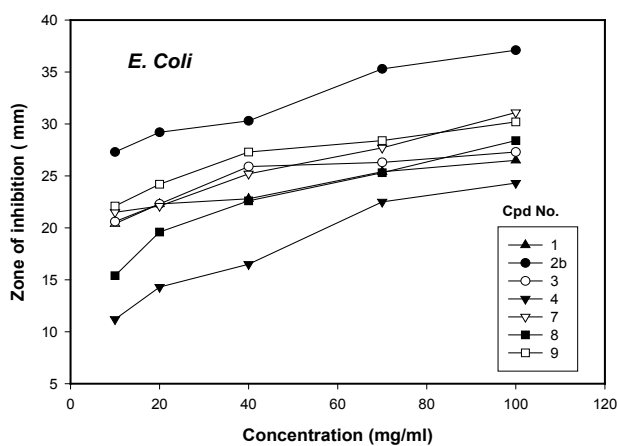


Figure 1. Effect of concentration of sulfa derivatives on *E. Coli*.

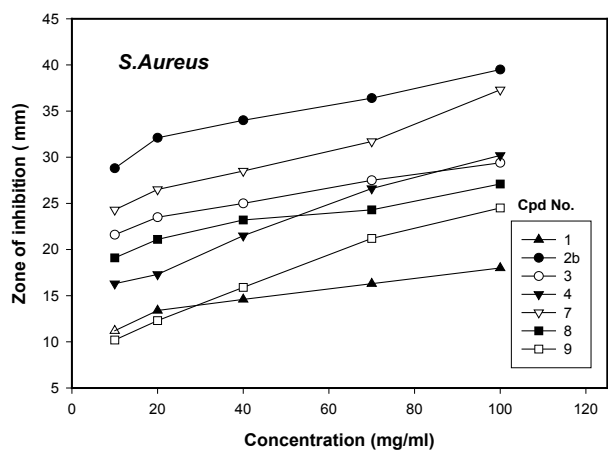


Figure 2. Effect of concentration of sulfa derivatives on *S. Aureus*.

effect with *S. Aureus* followed by *P. Aeruginosa*, *B.subtilis* and *E. coli*. Compound 7 showed a severe effect in the case of *S. Aureus* followed by *E. Coli*. Both *P. Aeruginosa* and *B. subtilis* showed approximately the same zone of inhibition. Compound 8 showed effect only

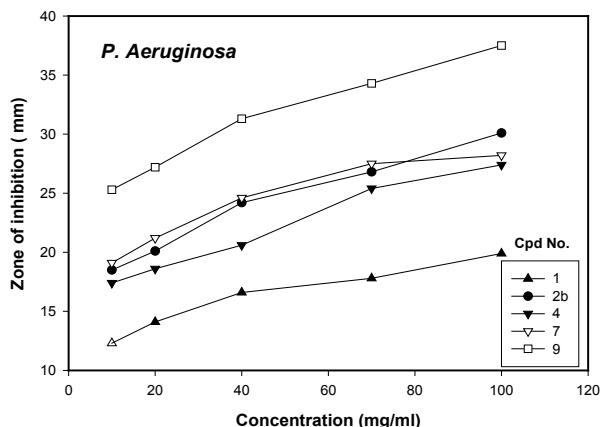


Figure 3. Effect of concentration of sulfa derivatives on *P. Aeruginosa*.

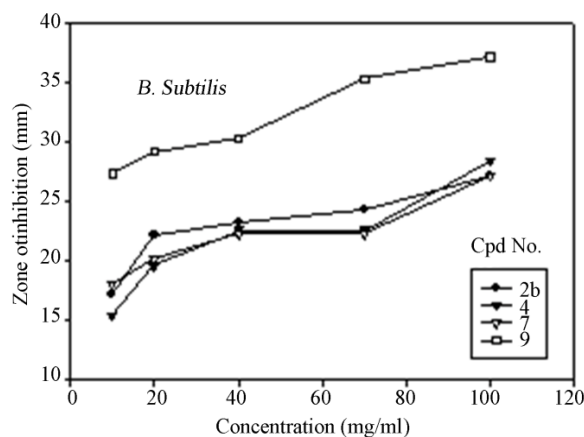


Figure 4. Effect of concentration of sulfa derivatives on *B. Subtilis*.

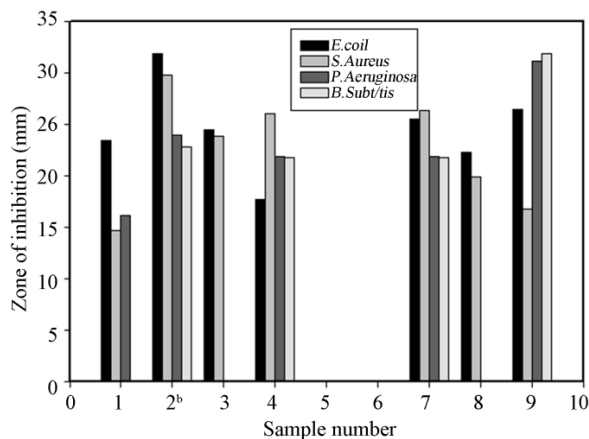


Figure 5. Zone of inhibition (mm) at different concentration against sample number.

on *E. coli* and *S. Aureus*. Compound **9** showed a severe effect on *P. Aeruginosa* and *B. subtilis*. A moderate effect on *E. coli* and low effect was observed on *S. Aureus*.

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