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Ultrasonicated Synthesis of Bio-potent Sulphonamides

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ABSTRACT

About more than 85% yields of some aryl sulphonamides were synthesised by sodium acetate catalysed ultrasonication promoted condensation of aryl amines and benzene sulfonyl chlorides in room temperature. The synthesised sulfonamides were analysed with their physical constants, micro analysis and spectral techniques. The antioxidant potential of these sulfonamides were assessed by DPPH radical scavenging activity measurement using L-ascorbic acid as a standard. Antimicrobial activities of these sulfonamides have been assessed by disc diffusion method against their antimicrobial stains. Most of the sulfonamides shows antimicrobial activity. Many of the hydroxy and methoxy substituted sulfonamides showed significant antioxidant activity.

***Keywords*:** Aryl sulfonamides, Ultrasonication, Sodium acetate, IR and NMR spectra, Antioxidant activity, Antimicrobial activity

1. INTRODUCTION

Sulfonamides are the sulphur-imino compounds and they have the functional group of -SO_2-NH- between the aryl or aliphatic segments with or without substituents [1]. They possess important biological activities such as antimicrobial [2], antifertile [3], antituberclosis [4], anti-cancer, antiviral and anti-HIV [5] etc. The sulfonyl, imine and the substituents in the aromatic or aliphatic moieties are responsible for their biological activities.

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They are also used for the organic compounds synthetic scaffoldings, and many industrial applications [6]. Numerous synthetic methods were reported for the synthesis of sulphonamides. The ultrasound also used for synthesis of many organic substrates such as ketones, unsaturated ketones, imines, acids, esters, heterocyclics and carbon nano crystalline etc. [7-9].

Within this synthetic method, many catalysts were employed in ultrasonication reactions. Such catalysts are Lewis acid and bases, β-Cyclodextrin [10] water [11, 2], pyridine [13], PPh_3 [14], DMAP [15], CsF-Celite [16], ZnO-nanoparticles [17], MgO [18]. Lakrout *et al.,* [19] have prepared some sulfonamide derivatives by sulfonylation of primary, secondary sulfonyl chlorides, amino acid esters and phenols under solvent-free microwave irradiation techniques.

Pan *et al.,* [11] synthesized a few sulfonamides via I_2-mediated reaction of sodium sulfinates with amines in an aqueous medium at room temperature. Recently Dineshkumar and Thirunarayanan prepared more than 80% yields of mesalazines type sulphonamides [20].

In the literature survey, there is no report available for the ultrasonic assisted sodium acetate catalyst catalyzed condensation of 4-hydroxybenzenesulfonyl chlorides and substituted anilines in ultrasonication conditions and its antioxidant activities.

Therefore, herein the author has interestingly investigated the ultrasound assisted synthesis of some sulphonamides and evaluation of antioxidant activities using the standard DPPH [21, 22] method. The antimicrobial activities of these sulfonamides were evaluated by Bauer-Kirby [23] disc diffusion method using various antimicrobes.

2. EXPERIMENTAL

2. 1. General

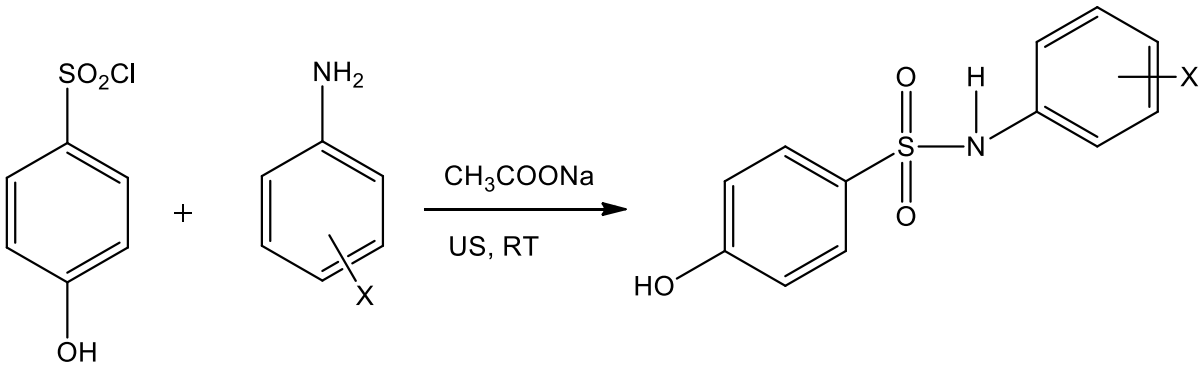
Sigma-Aldrich, Alfa Aesar and E-Merck chemical company chemicals used in this investigation. Mettler FP51 melting point apparatus was used for the determination melting points of all sulfonamides. The OMNIC Fourier-transform spectrophotometer was employed for recording Infrared spectra. The proton and carbon-13 spectra of all sulfonamides were recorded in Bruker AV400 & 500 NMR spectrometer in DMSO solvent using TMS as internal standard. Mass spectra were recorded on a SIMADZU GC-MS2010 spectrometer. The Thermo Finnigan CHN analyser was used for elemental analysis.

2. 2. Typical procedure for synthesis of sulfonamides

An equimolar concentration of 4-hydroxybenzenesulfonyl chloride (1 mmol), substituted anilines (1 mmol), 0.5 mL of 1M sodium acetate and 10 mL of ethanol were taken in 50 mL conical flask and mixed thoroughly. This mixture was subjected to ultrasound irradiation for 20-25 minutes in an ultrasonicator (Scheme 1) in room temperature [24].

During the reaction 0.1 mg of potassium carbonate was added to neutralize the formation of hydrochloride. The completion of the reaction was monitored by Thin layer chromatography. The resulting product was washed with *n*-hexane and separated the catalyst by filtration and dried to obtain the solids.

Further the crude was purified by column chromatogram using dichloromethane and ethyl acetate (3:1) as eluants.



X=H, 4-Cl, 3-OH, 4-OH, 3-OCH_3, 4-OCH_3, 3-CH_3, 4-CH_3, 3-NO_2, 4-NO_2

Scheme 1. Ultrasound assisted synthesis of
N-(substituted phenyl)-4-hydroxybenzene sulfonamides

2. 3. Measurement of antioxidant activity

The antioxidant activities of these synthesized sulfonamides were measured by DPPH radical scavenging ability. The 0.1M sodium acetate was prepared by dissolving1.64g of sodium acetate in15mL of water and 150 mL of acetic acid. The final volume was adjusted to 20 mL by adding water. About 0.2 mmole of DPPH solution was prepared by dissolving 3.9 g of DPPH in 50 mL of ethanol. L-ascorbic acid (1 µg in 10 mL of ethanol) solution was prepared. A series of test tubes are arranged with 1.0 mL of buffer solution was mixed with 0.5 mL of DPPH solution. A series of various concentrations of synthesized sulfonamides and L-ascorbic acid (1 µg in 1 mL of ethanol) are added to each tube and mixed well.

After 30 minutes at room temperature, absorbance of each solution was measured by UV-Vis spectrophotometer at 517 nm. A mixture of buffer solution and ethanol are used as the reference for the spectrophotometer. A graph was plotted with the weight of the compound vs absorptions and IC_{50} values.

The antioxidant activity was expressed in terms of IC_{50} (µg/mL, concentration required to inhibit DPPH radical formation by 50%). L-ascorbic acid was used as a positive control. From this experiment the sulfonamides **(3-6)** were found to have significant antioxidant activity.

2. 4. Measurement of antimicrobial activities

In this investigation, the author have assessed the antimicrobial activities of the synthesised sulfonamides by Bauer-Kirby [23] disc diffusion method by measurement of the mm of zone of inhibition against their respective antimicrobial stains.

For antibacterial measurement, each two gram positive stains such as *B. subtilis, S. pyogenes, E. coli* and *P. aeruginosa* were used. Ciprofloxacin as standard. For antifungal activity measurement *A. niger, A. flavus, F. oxysporum* and *P. chrysogenum* fungal stains used and Amphotericin-B was employed as standard DMSO as solvent.

3. RESULTS AND DISCUSSION

In our research laboratory the author has attempt to synthesis some sulfonamides by ultrasound assisted method. An equimolar concentration of 4-hydroxybenzene sulfonyl chloride (1 mmol), various electron with-drawing and electro donating substituted anilines (1 mmol), 0.5 mL of 1M sodium acetate and 10 mL of ethanol were taken in 50 mL conical flask and mixed thoroughly. This mixture was subjected to ultrasound irradiation for 20-25 minutes in a ultrasonicator (**Scheme 1**) in room temperature. This condensation gave more than 85% yields within short reaction time (12-20 minutes). The electron-donating substituted anilines gave more than 85% yields. The electron-withdrawing substituted anilines gave 85% yields. The synthesised sulfonamides were characterized by their physical constants, yields, time and micro analysis and are presented in Table 1. The spectral data of these sulfonamides were given in Table 2.

Table 1. Physical constants, analytical and mass spectral data of N-(substituted phenyl)-4-hydroxybenzenesulfonamides

Entry	X	MF	MW	Time (m)	Yield (%)	m.p. (ºC)	Micro analysis (%) Found (Calcd.)		
							C	H	N
1	H	$C_{12}H_{11}NO_3S$	249	12	86	112-113	57.84 (57.82)	4.41 (4.45)	5.59 (5.62)
2	4-Cl	$C_{12}H_{10}ClNO_3S$	284	14	85	121-123	50.84 (50.80)	3.51 (3.55)	4.92 (4.94)
3	3-OH	$C_{12}H_{11}NO_4S$	265	16	86	117-118	54.35 (54.33)	4.12 (4.18)	5.24 (5.28)
4	4-OH	$C_{12}H_{11}NO_4S$	265	15	87	134-135	54.32 (54.33)	4.14 (4.18)	5.25 (5.28)
5	3-OCH_3	$C_{13}H_{13}NO_4S$	279	10	89	116-117	55.94 (55.90)	4.62 (4.69)	4.97 (5.01)
6	4-OCH_3	$C_{13}H_{13}NO_4S$	279	11	88	126-127	55.92 (55.90)	4.64 (4.69)	4.99 (5.01)
7	3-CH_3	$C_{13}H_{13}NO_3S$	263	13	87	118-119	59.32 (59.30)	4.94 (4.98)	5.29 (5.32)
8	4-CH_3	$C_{13}H_{13}NO_3S$	263	15	86	123-125	59.34 (59.30)	4.96 (4.98)	5.28 (5.32)
9	3-NO_2	$C_{12}H_{10}N_2O_5S$	249	20	85	135-137	48.52 (48.49)	3.39 (3.43)	9.48 (9.52)
10	4-NO_2	$C_{12}H_{10}N_2O_5S$	249	20	86	117-118	48.51 (48.49)	3.40 (3.43)	9.49 (9.52)

Table 2. IR, NMR and Mass spectral data of N-(substituted phenyl)-4-hydroxy benzene sulphonamides.

Entry	X	IR (ν, cm^{-1})			
		OH	NH	SO_{2asym}	SO_{2sym}
1	H	3472.11	3267.11	1322.71	1164.73
2	4-Cl	3473.14	3268.78	1324.46	1164.82
3	3-OH	3452.61	3267.81	1324.62	1164.38
4	4-OH	3432.74	3259.16	1324.58	1164.68
5	3-OCH_3	3428.31	3260.19	1323.12	1164.18
6	4-OCH_3	3412.96	3261.72	1322.08	1164.21
7	3-CH_3	3416.78	3263.24	1322.17	1164.47
8	4-CH_3	3428.61	3266.74	1323.06	1164.49
9	3-NO_2	3479.78	3281.73	1323.81	1164.88
10	4-NO_2	3482.41	3283.48	1323.92	1164.97
Entry	**X**	**^{1}HNMR (δ, ppm)**			
		OH	**NH**	**Ar-H**	**X**
1	H	5.673	4.732	6.732-7.831	---
2	4-Cl	5.387	4.371	6.621-7.032	---
3	3-OH	5.291	4.289	6.691-7.632	5.371
4	4-OH	5.283	4.263	6.139-7.607	5.274
5	3-OCH_3	5.367	4.313	6.372-7.685	3.717
6	4-OCH_3	5.472	4.419	6.521-7.674	3.245
7	3-CH_3	5.532	4.520	6.782-7.690	3.022
8	4-CH_3	5.521	4.538	6.702-7.172	3.120
9	3-NO_2	5.674	4.738	6.183-7.572	--
10	4-NO_2	5.679	4.740	6.820-7.571	--

Entry	X	^{13}CNMR (δ, ppm)						Mass (m/z)
		C-OH	C- SO_2	C-NH	C_{ipso}	Ar-C	X	
1	H	163.25	134.75	129.63	123.42	120.56-152.48	--	249[M^+]
2	4-Cl	163.43	133.21	134.28	127.18	122.57-151.23	--	284[M^+]
3	3-OH	163.48	133.62	129.24	150.32	123.52-149.62	--	265[M^+]
4	4-OH	163.21	133.38	140.32	161.73	103.78-153.61	--	265[M^+]
5	3-OCH_3	163.32	133.14	139.72	162.78	106.73-153.29	66.78	279[M^+]
6	4-OCH_3	162.38	133.08	139.68	162.41	116.78-152.38	63.72	279[M^+]
7	3-CH_3	162.43	133.12	135.72	132.71	120.68-155.14	24.78	263[M^+]
8	4-CH_3	162.27	133.54	135.61	133.44	121.74-152.27	26.38	263[M^+]
9	3-NO_2	163.71	133.92	135.69	137.42	121.74-154.24	--	249[M^+]
10	4-NO_2	163.84	133.94	135.87	137.49	121.84-153.74	--	249[M^+]

In this reaction the author has studied the effect of catalyst by observed yields for the entry 1. The catalyst amount was increased from 0.1 to 0.7 mL, the yields of the sulfonamides were increased up to 0.5 mL then there is no increment in the yield beyond 0.5 mL. Within this observation the optimum catalyst was found to be 0.5 mL. The effect of catalyst was illustrated in the Figure 1 and the data was presented in Table 3.

Table 3. Effect of catalyst on the yield of sulfonamide (entry 1)

Qty. of Cat. (mL)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8
Yield (%)	33	45	50	60	85	85	85	85

Further the author was studied the effect of solvent on the condensation. In this condensation for the entry 1, various solvents such as methanol, acetonitrile, ethanol, ethyl acetate, dichloromethane, dioxane, tetrahydrofuron and n-propanol were used and found the yields in ethanol medium was presented in Table 4 and the statistical diagram was illustrated in Figure 2.

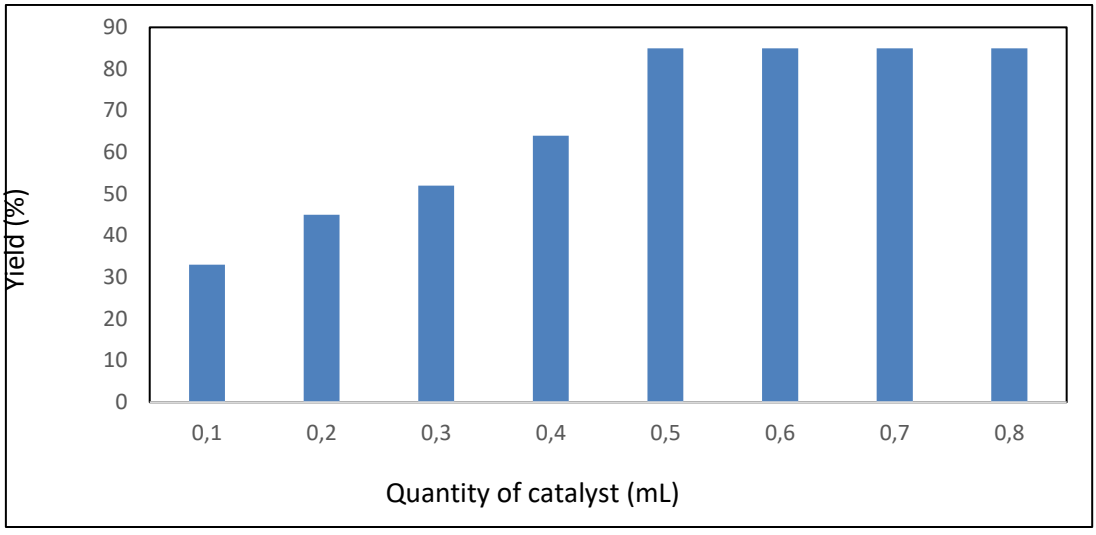


Figure 1. Effect of catalyst on the yields of sulfonamide (entry 1)

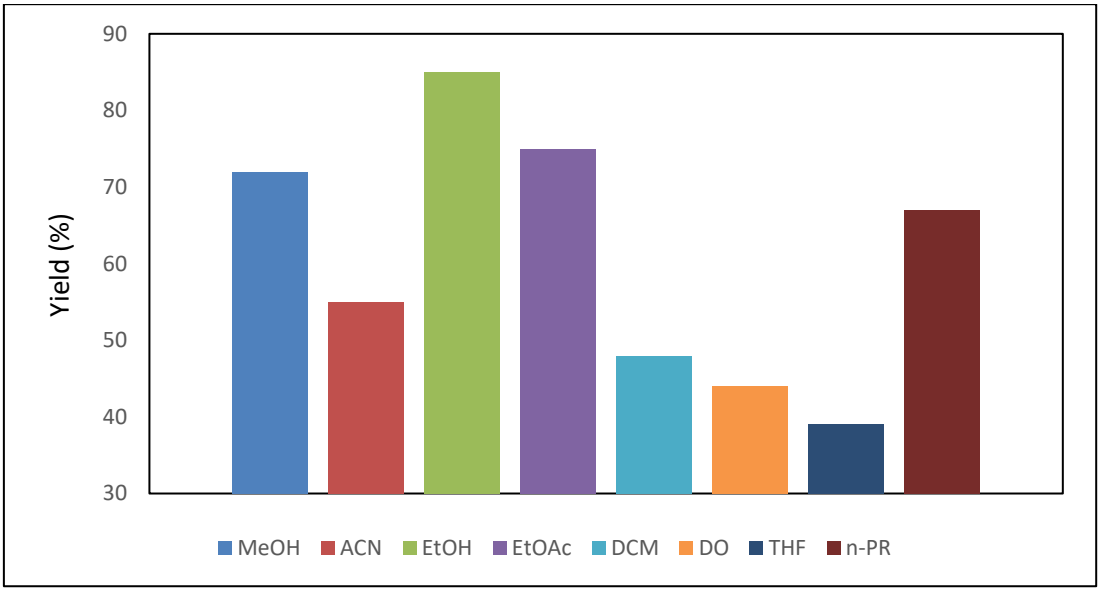


Figure 2. Effect of solvents on the yields of sulfonamide (entry 1)

Table 4. Effects of solvent on the yields of sulfonamide (entry 1)

Solvents	MeOH	ACN	EtOH	EtOAc	DCM	DO	THF	n-PR
Yield(%)	72	55	85	75	48	44	39	67

MeOH = Methanol; ACN = Acetonitrile; EtOH = Ethanol; EtOAc = Ethylacetate;
DCM = Dichloromethane; THF = Tetrahydrofuron; n-PR = n-Propanol

3. 1. Antioxidant activity

In this study the author measured the antioxidant activities of synthesised sulfonamides by DPPH radical scavenging activity. The observed antioxidant activities of all sulfonamides were presented in Table 5 and the statistical comparison column chart was illustrated in Figure 3. From the table all sulfonamides have satisfactory antioxidant activity due to presence of hydroxy group. While seeking the sulfonamides **3-6**, they possess significant antioxidant activity. Among these four sulfonamides the compound 6 shows most significant antioxidant activity. This activity was enhanced by the methoxy group in amine moiety.

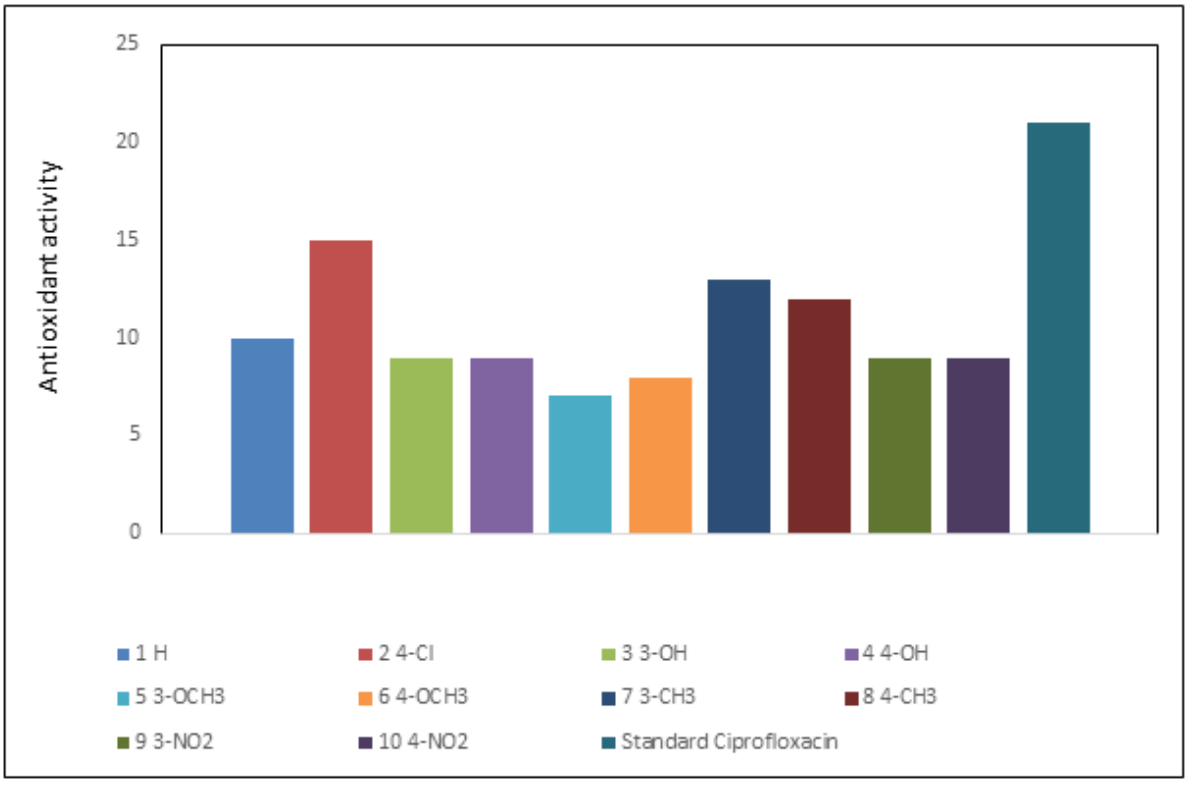


Figure 3. The statistical column chart of antioxidant activity of sulfonamides.

Table 5. Antioxidant activities of the synthesized N-(substituted phenyl)-4-hydroxy benzene sulphonamides

Entry	X	Antioxidant activity (DPPH radical scavenging ability)
1	H	32.27±0.05
2	4-Cl	32.00±0.17
3	3-OH	32.01±0.15

4	4-OH	32.24±0.08
5	3-OCH_3	32.68±0.01
6	4-OCH_3	32.74±0.05
7	3-CH_3	31.19±0.19
8	4-CH_3	31.27±0.45
9	3-NO_2	31.18±0.28
10	4-NO_2	31.66±0.72
Standard: L-Ascorbic acid		32.75±0.06

3. 2. Antimicrobial activity

3. 2. 1. Antibacterial activity

The measured antibacterial activities by means of mm of zones of inhibition of all synthesised sulfonamides were presented in Table 6. The statistical correlated clustered column chart was illustrated in Figure 4. From the Table 6, chloro- substituted sulfonamides shows good antibacterial activity against all bacterial stains. Parent and methyl substituted sulfonamides showed satisfactory antibacterial activity against *B. substilis* stains. Remaining sulfonamides shows moderate and least antibacterial activity. Methoxy substituted sulfonamides shows satisfactory antibacterial activity against *S. syogenes* stain. Remaining sulfonamides showed moderate and least activity. Parent and methyl substituted sulfonamides showed satisfactory antibacterial activity against *E. coli* stain. The parent and methoxy substituted sulfonamides shoed satisfactory antibacterial activity against *P. aeruginosa* stain.

Table 6. Antibacterial activities of sulfonamides

Entry	**X**	**MM of zone of inhibition**			
		Gram +ve bacterial stain		**Gram -ve bacterial stain**	
		B. subtillis	***S. pyogenes***	***E. coli***	***P. aerugenisoa***
1	H	10	9	10	11
2	4-Cl	15	14	13	17
3	3-OH	9	9	6	8
4	4-OH	9	8	7	6
5	3-OCH_3	7	11	4	7

6	4-OCH_3	8	10	9	10
7	3-CH_3	13	8	7	9
8	4-CH_3	12	8	11	8
9	3-NO_2	9	7	8	9
10	4-NO_2	9	5	8	7
Standard	Ciprofloxacin	21	18	16	19
Solvent	DMSO	---	---	---	---

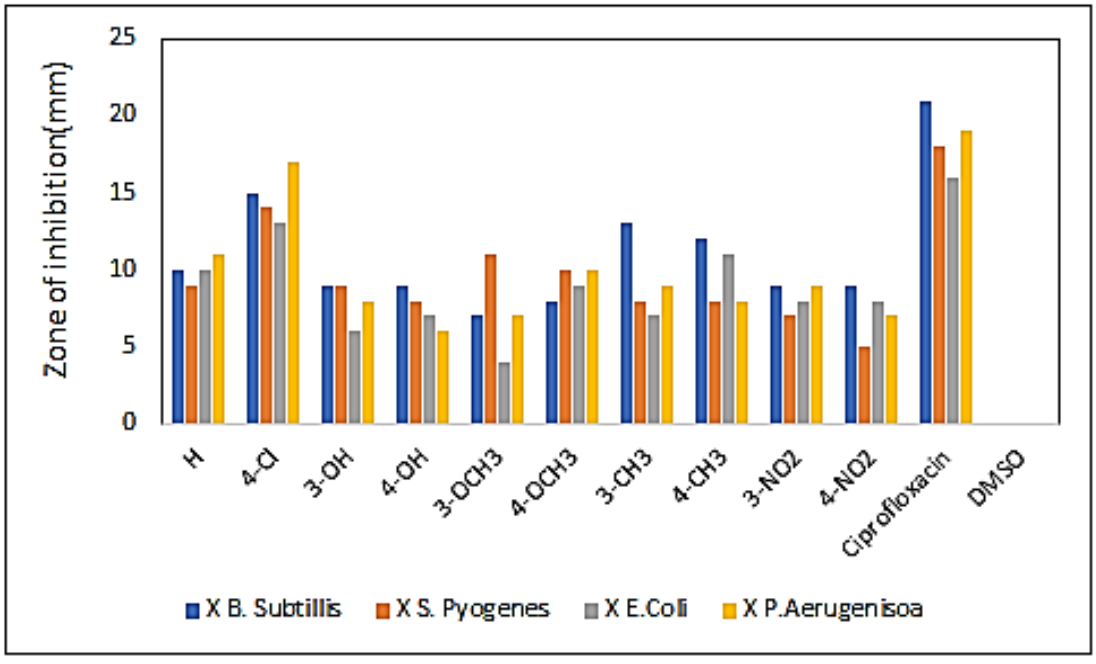


Figure 4. Antibacterial activity of sulfonamides-clustered column chart

3. 2. 2. Antifungal activity

The measured antibacterial activities by means of mm of zones of inhibition of all synthesised sulfonamides were presented in Table 7. The statistical correlated clustered column chart was illustrated in Figure 5. From the table 7, chloro- and nitro substituted sulfonamides shows good antifungal activity against *A. niger* and *A. flavus* fungal stains. Remaining sulfonamides showed moderate and least antifungal activity.

Parent, chloro, hydroxy, methoxy and methyl substituted sulfonamides showed good antifungal activity against *F. Oxysporum* stain. Parent, hydroxy, methoxy and nitro substituted sulfonamides shows good antifungal activity against *P. chrysogenum* fungal stain. Remaining sulphonamides exists with satisfactory and least antifungal activity.

Table 7. Antifungal activities of sulfonamides

Entry	X	MM of zone of inhibition			
		A. niger	***A. flavus***	***F. oxysporum***	***P. chrysogenum***
1	H	9	8	10	6
2	4-Cl	13	11	12	15
3	3-OH	7	9	11	9
4	4-OH	6	9	10	8
5	3-OCH_3	5	6	9	7
6	4-OCH_3	7	7	8	10
7	3-CH_3	6	9	3	8
8	4-CH_3	8	6	9	6
9	3-NO_2	11	12	7	9
10	4-NO_2	12	8	4	10
Standard	Amphotericin-B	17	18	16	19
Solvent	DMSO	---	---	---	---

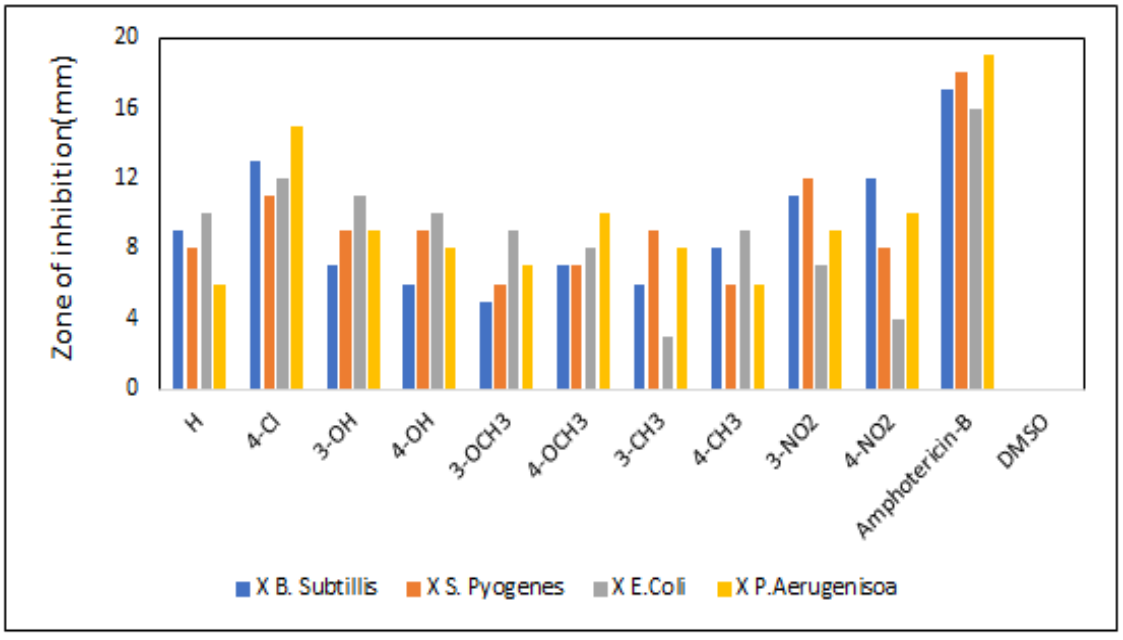


Figure 5. Antifungal activity of sulfonamides-clustered column chart

4. CONCLUSIONS

The author has synthesised more than 85% yields of some N-(substituted phenyl)-4-hydroxybenzene sulfonamides by ultrasonication method in room temperature. These are characterised by their physical constants and spectroscopic data. The effect catalyst and solvents on the yield was investigated. The antioxidant activity of these compounds was studied by DPPH radical scavenging activity measurement. From the experiment all sulfonamides shows antioxidant activity against the standard L-ascorbic acid.

The compound **6** N-(4-methoxyphenyl)-4-hydroxybenzene sulfonamide shows good antioxidant activity. All sulfonamides are active antibacterial activity against their stains. chloro- substituted sulfonamides shows good antibacterial activity against all bacterial stains. Parent and methyl substituted sulfonamides showed satisfactory antibacterial activity against *B. substilis* stains. Methoxy substituted sulfonamides shows satisfactory antibacterial activity against *S. pyogenes* stain. Parent and methyl substituted sulfonamides showed satisfactory antibacterial activity against *E. coli* stain.

The parent and methoxy substituted sulfonamides shoed satisfactory antibacterial activity against *P. aeruginosa* stain. Chloro- and nitro- substituted sulfonamides shows good antifungal activity against *A. niger* and *A. flavus* fungal stains. Parent, chloro, hydroxy, methoxy and methyl substituted sulfonamides showed good antifungal activity against *F. oxysporum* stain. Parent, hydroxy, methoxy and nitro substituted sulfonamides shows good antifungal activity against *P. chrysogenum* fungal stain. Remaining sulfonamides exists with satisfactory and least antifungal activity.

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