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Synthesis and Biological Activity Evaluation of New Sulfonamid Derivatives

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Abstract
New sulfonamide derivatives comprising azide, 1, 2, 3- triazole, azo , chalcone and Schiff base moieties had synthesized. The structures of the new compunds have been confirmed byFT-IR and ^{1}H-NMR spectra. The synthesized derivatives have been screened for antimicrobial and *in vitro* antioxidant properties. The results of this investigation revealed that the newly synthesized compounds have good antimicrobialand antioxidant activities.

Keywords: Sulfonamide, Chalcone , Antimicrobial activity, Antioxidant activity, Azo compound.

تحضير وتقييم الفعالية البايولوجية لمشتقات السلفون أمايد الجديدة

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الخلاصة
حضرت مشتقات السلفونأمايد التي تضم مكونة الازايد، 3,2,1- ترايزول، آزو، جالكون و قاعدة شيف. وتم تشخيص تراكيب المركبات الجديدة باطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي البروتوني. وتم فحص الفعالية البايولوجية والفعالية المضادة للأكسدة خارج الجسم للمركبات المحضرة. أظهرت نتائج الفحص ان المركبات المحضرة لها فعالية بايولوجية وفعالية مضادة للأكسدة جيدة.

1. Introduction

Sulfonamides (sulfa drugs) have been the first drugs largely employed and systematically used as preventive and chemotherapeutic agents against many diseases [1-4]. In addition triazoles are an essential category of heterocycles due to a wide range of pharmaceutical applications [5, 6]. Azo dye, aromatic rings associated together through azo(-N=N) chromophores ,represent the largest category of dyes used in textile processing and other industries such as food colorant, printing, cosmetic, and pharmaceutical industries [7,8]. Chalcone derivatives contain α,β-unsaturated carbonyl moiety possess broad spectrum of biological activity in both medicinal and pharmaceutical, such as antimicrobial [9], anti-inflammatory [10], antitubercular [11], antioxidant [12] and anticancer [13].

2. Experimental

2.1. Materials and Measurements

All the reagents are commercially available from (Aldrich Co.) andused without further purification. Melting points were recordered by electric thermal melting point apparatus and are uncorrected. The purity of derivatives were checked on silica coated plates Merck TLC using water, benzene, chloroform and acetone as the mobile phase. FT-IR measurements have been recorded by

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Shimadzu FT-IR-8400S. ^{1}H NMR spectra were recorded by using Ultra Shield Bruker model in 300 MHz uisg DMSO-d_6 as a solvent and TMS as internal standard.

2.1.1Synthesis of N-(4-aminophenyl)-4-methylbenzenesulfonamide(1).

Amixture of toluene -4- sulfonyl chloride (tosyl chloride) (0.01 mole, 2.62 g) and 1,4- phenylene diamine (0.01mole,1.08g) with (0.01 mole,2mL) Triethyl amine in dry benzene (20 mL) was refluxed for 6hrs. After that, the excess of solvent was vaporated and the product wasfiltered off and recrystallized from chloroform to give compound with . Yield: 88% , M.P: 182-184 °C, FT-IR spectrum (υ, cm^{-1}): 3414, 3329υ (NH_2), 3246 υ (NH), 1317, 1155 υ (SO_2).^{1}H NMR spectrum (δ, ppm): 7.55-6.28 (m, 8H, Ar-H),6.15 (s, 1H, NH),4.7 (2H, NH_2), 2.24 (s, 3H, CH_3) .

2.1.2. Synthesis of N-(4-(chlorodiazophenyl)-4-tolylsulfonamide (2).

A solution of compound (1) (0.01 mole, 3.095g) in concentrated HCL (3mL) has been cooled to (0-5)˚C. A chilled solution of sodium nitrite (0.01 mole, 1.5 g) in 10 mL of water has been added drop by drop through 15 minute with stirring then the mixture was stirred for 10 minutes.

2.1.3. Synthesis of N-(4-azidophenyl)-4-methylbenzenesulfonamide (3).

An aqueous solution of sodium azide (0.012 mole ,3.45 g)wasadded dropwise to diazonium salt solution **(2)** . The mixture has been stirred for 25 minute to give dark brown solid compound **(3)** Yield: 84% , M.p.: 290-292°C, FT-IR(ν, cm^{-1}): 3228 υ (NH), 2117 υ (N_3), 1311,1151 υ (SO_2).^{1} H-NMRspectrum(δ, ppm): 7.79-6.55 (m, 8H, Ar-H), 6.15(s, 1H, NH), 2.24 (s, 3H, CH_3).

2.1.4. SynthesisN-(4-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl)phenyl)-4-methylbenzene-sulfonamide(4).

Azide compound **(3)** (0.01 mole,2.28g) has been cautiously added to a cold solution ofacetylacetone (0.01 mole,1.3mL) and sodium ethoxide (7 mL), the mixture has been heated under reflux on a water bath for 3h . The resulting solid was separated and recrystallized from chloroform.

Yield: 73%.M.p. 198-199 °C, FT-IRspectrum (ν, cm^{-1}): 3210 υ(N-H), 1690υ(C=O),1352, 1161υ (SO_2). ^{1} H-NMR spectrum(δ, ppm): 7.87-6 .35 (m, 8H, Ar-H), 7.67(s, 1H, NH), 2.24 (s, 3H, CH_3triazole), 2.38 (s , 3H, CH_3CO), 2.15 (s ,3H , CH_3) .

2.1.5. Synthesis of 5-methyl-1-(4-(4-methylphenylsulfonamido)phenyl)-1H-1,2,3-triazole-4-carboxylic acid (5).

A mixture of ethyl acetoacetate (0.01 mole, 1.03 mL) and azide compound **(3)** (0.01 mole, 2.28g) in absolute ethanol (25 mL) has been chilled to 0˚C. Sodium ethoxide (0.01 mol) in (25 mL) was added progressively to reaction mixture then was heated under reflux for 6hrs.The product has been recrystallized from acetone.Yield: 80% ; M.p: 250-251°C ; FT-IR spectrum (ν, cm^{-1}): 3300-3000υ (O-H), 3230 υ(N-H), 1699 υ (C=O), 1355,1160υ (SO_2); ^{1} H-NMR spectrum (δ, ppm): 11.32 (s,1H, O-H) , 7.67-6.54 (m, 8H, Ar-H), 4.7 (s, 1H, NH), 2.23 (s, 3H, CH_3), 2.33 (s, 3H, triazole).

2.1.6. Synthesis of N-(4-((3-formyl-4-hydroxyphenyl)diazenyl)phenyl)-4-ethylbenzene sulfonamide (6).

To a cold solution of salisaldelyde (0.01 mole ,1.26 g) in %10 NaOH (12mL) a solution of diazonium salt **(2)** was added gradually and very slowly . The solution was left for 30 min in ice bath .The precipitate was filtered and washed with water. Yield: 65% ;M.p.: 282-283 °C ; FT-IR spectrum (KBr, ν, cm^{-1}): 3228υ (N-H),1550 υ (N=N) ,1355-1160 υ(SO_2) ; ^{1} H-NMR spectrum (δ, ppm): 8.33-7.40 (m, 8H, Ar-H), 4.65 (s, 1H, NH), 2.3 (s, 3H, CH_3).

2.1.7 .Synthsis of-(4-((4-hydroxy-3-((pyrimidin-2-ylimino)methyl) phenyl)diazenyl)phenyl)-4-methylbenzenesulfonamide (7).

A mixture of 2-amino pyrimidine (0.01 mole, 0.94 g) and compound (**6**) (0.01 mole, 3.95g) in absolute ethanol(30mL) was refluxed for 6hrs. The mixture was cooland the product was recrystallized from acetone . Yield: 75% ; M.p.: 185-187 °C; FT-IR spectrum (υ , cm^{-1}): 3430-3112 υ (O-H), 1635υ (C=N), 1539, 1158 υ (SO_2) ; ^{1} H-NMR spectrum (δ, ppm): 8.90-8.79(m,3H,proton of pyrimidine) 8.5 (s, 1H, N=CH), 7.97-6.78 (m, 11H, Ar-H), 5.60 (s,1H,O-H), 4.75 (s, 1H, NH), 2.32 (s, 3H, CH_3).

2.1.8. SynthesisofN-(4-((4-hydroxy-3-(3-oxo-3-phenylprop-1-en-1-yl)phenyl)diazenyl)phenyl)-4-methylbenzenesulfonamide (8).

Compound **(6)** (0.01 mole, 3.95 g) in 30 mL absolute ethanol was added to solution of (0.01 mole, 1.20 g) of (acetonphenone) in (5 mL), %40 NaOH ,after 6hrs.of stirring, the mixture was left in the refrigerator for 24h, then the precipitate was filtered and washed with acetone. Yield: 70%.M.p.: 194-195°C; FT-IR spectrum (ν, cm^{-1}): 3250 υ (N-H), 1672 υ (C=O), 1640, υ (C=C),1354,1162 υ (SO_2); ^{1}

H-NMR spectrum (δ, ppm, 8.1 (s, 1H, CH-CO) ,8.27-7.63 (m, 16H, Ar-H and CH=CH), 5.6 (s ,1H, O-H) ,4.7 (s, 1H, NH), 2.3 (s, 3H, CH_3).

2.2. Study of Biological Activities

2.2.1. Antimicrobial Activity

Antimicrobial activity of sulfonamide derivatives **(4-8)** were tested against *Escherichia coli*, *K. pneumonia*, *Staphylococcus aureus*, *Streptococcus pyogenes* and two fungals *Aspergillus niger*, and *Candida albicans*by using diffusion method [14,15].

. The bacteria and fungi have been sub -commission cultured in agar and potato dextrose agar medium and these plates were incubated for 24 hours for bacteria and 48 hours for fungi at 37^{O}C. Inhibition zones observed around the cups after respective incubation has been measured in mm Table-1.

Table 1- Antimicrobial evaluation compound 4-8.

	Antibacterial Activity				Antifungal	
	Zone of inhibition (mm)					
	Gram negative		Gram positive		Fungi	
Compound	*E.coli*	*K.pneumonia*	*S.aureus*	*S.pyogenes*	*A.niger*	*C.albicans*
4	4	8	2	4	8	9
5	6	10	2	6	7	10
6	12	12	2	15	12	12
7	18	15	8	18	15	14
8	18	15	15	20	14	16
Ampicillin	24	25	22	26	-	-
Fluconazole	-	-	-	-	24	25

2.2.2.Antioxidant activity

The free radical scavenging activity of the derivatives to the radical 1,1-diphenyl-2-picryl hydrazyl has been measured as shown by reference [16]. The use of methanol as the solvent and ascorbic acid as the standard.The Sulfonamide stock solution (1mg/mL) was diluted to final concentration 20-100 µg/mL.Methanolic DPPH solution (1 mL, 0.3 mmol) has been added to sample solution in DMSO (3 mL) at different concentrations. The samples were strongly mixed and allowed to stand at room temperature for 30 min.to measure in 517 nm(As), using the "Shimadzu175spectrophoto-meter" Table-2 and methanol solution of DPPH as a sample control of the Ac.

% Radical scavenging activity= 100 × (Ac-As)/Ac …… (1)

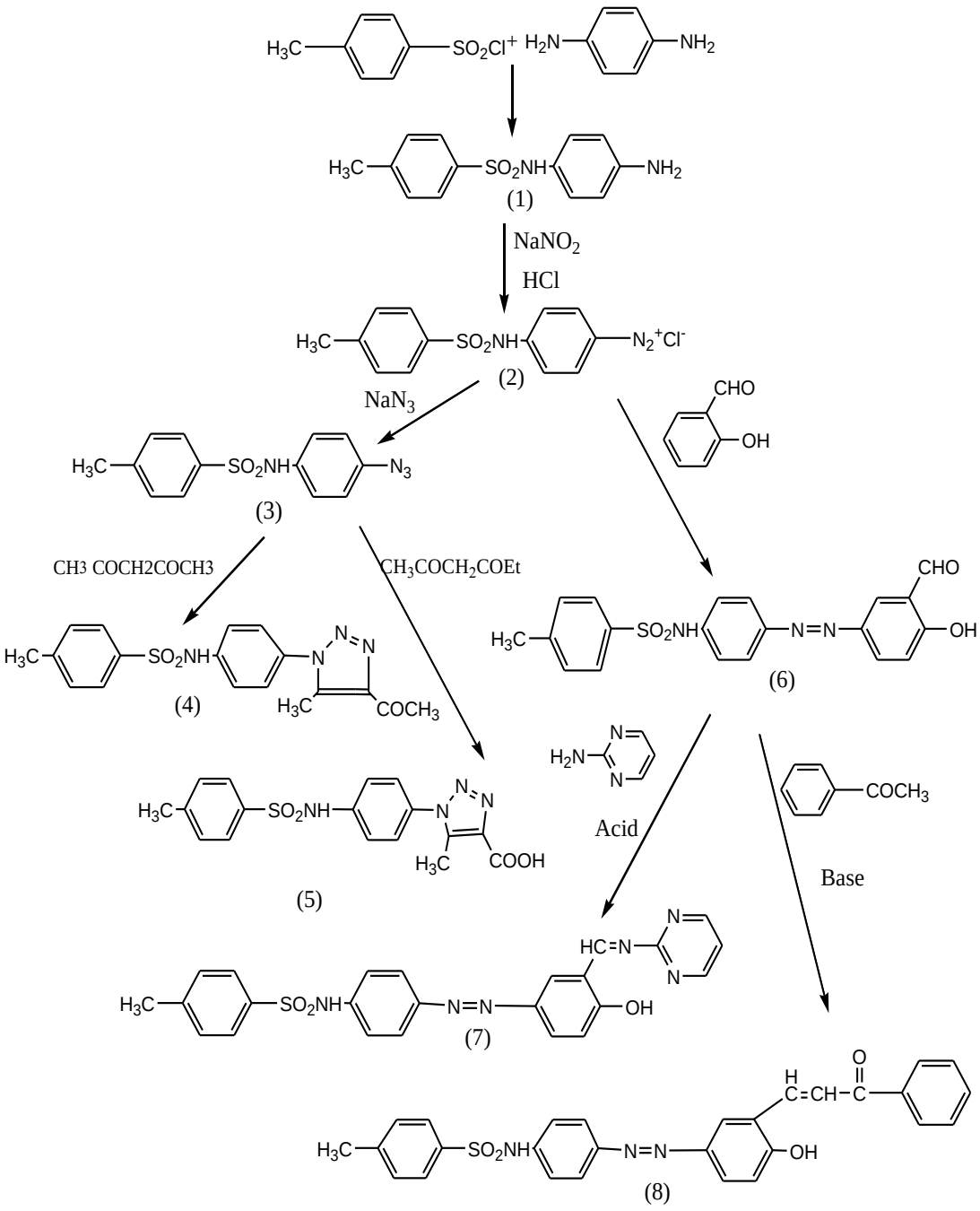
Table 2- Anti-oxidant activity of compounds (4-8) (expressed as % inhibition).

	10	20	30	40	50	60	70	80	90
4	10	22	30	40	51	60	71	81	90
5	12	23	32	43	52	63	72	82	91
6	13	24	33	44	54	64	73	84	92
7	13	26	34	45	55	66	75	85	93
8	14	27	36	47	57	67	76	86	94
Ascorbic acid	9	15	25	35	43	55	62	75	82

3. Results and Discussion

3.1. Synthesis

The new sulfonamidecompounds have been synthesizedin sequences reactions as describedin scheme 1.



Scheme 1

Reaction of toluene -4- Sulfonyl chloride with 1,4-phenylene diamine and triethylamine in dry benzene afforded of N-(4-aminophenyl)-4-methylbenzenesulfonamide (1). The structure of all compounds were confirmed by spectral data. FT-IR spectrum of compound (1) showed the characteristic bands at 3414 ,3329, 3246 and 1317, 1155 cm^{-1} which are due to υ NH_2, υ NH, and υ (SO_2), The ^{1}H- NMR spectrum indicated singlet signal at 2.24 ppm belonged to (CH_3) group protons and singlet signal at 6.15 ppm belong to NH group, multiplet signal at 7.55-6.28 ppm due to eight phenyl protons. Treatment of sulfonamide (1) with sodium nitrite in hydrochloric acid at 0-5°C afforded the diazonium salt (2). Reaction of diazonium salt (2) with sodium azide gave N-(4-azidophenyl)-4-methylbenzenesulfonamide (3). The IR spectrum of derivative (3) showed new absorption band at 2117 cm^{-1} due to stretching vibration of N3 and band at 3228 cm^{-1} belonged to stretching vibration of N-H Figure -1.

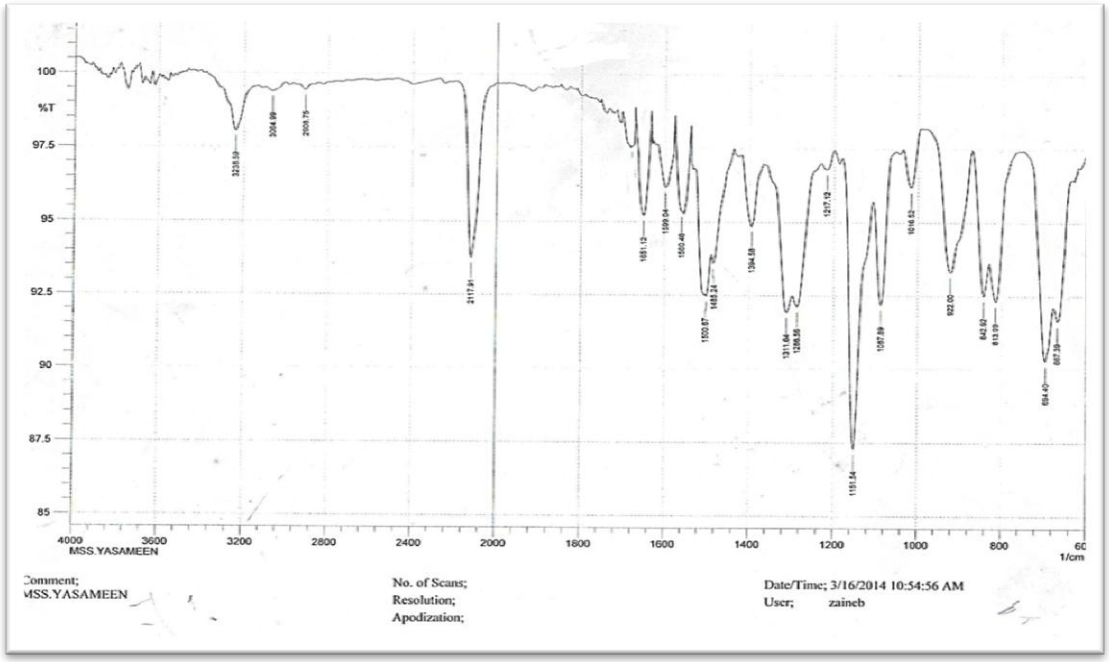


Figure 1-The FT-IR spectrum of compound 3.

The ¹H-NMR spectrum of compound (3) showed singlet signal at 2.24ppm assigned to three protons of methyl group and signal at 7.79 ppm was attributed to N-H proton, signals for aromatic protons appeared at 7.65-6.55 ppm.

Cyclization of azide derivative (3) with acetylacetone in the presence of sodium ethoxide afforded compound (4). FTIR absorption bands of triazole compound exhibited the disappearancs of absorption band due to N_3 stretching of compound (3) together with the presence of stretching band at 1690 cm^{-1} due to υ (C=O) group Figure-2.

¹H-NMR spectrum exhibited four singlet signals, 2.15ppm belong to protons of p-substituted methyl, 2.24 ppm was attributed to protons of methyl triazole, 2.38 ppm was assigned to three protons of acetyl group and 7.87ppm due to N-H.Signal for aromatic protons appeared at 7.50-6.35 ppm Figure-3 .

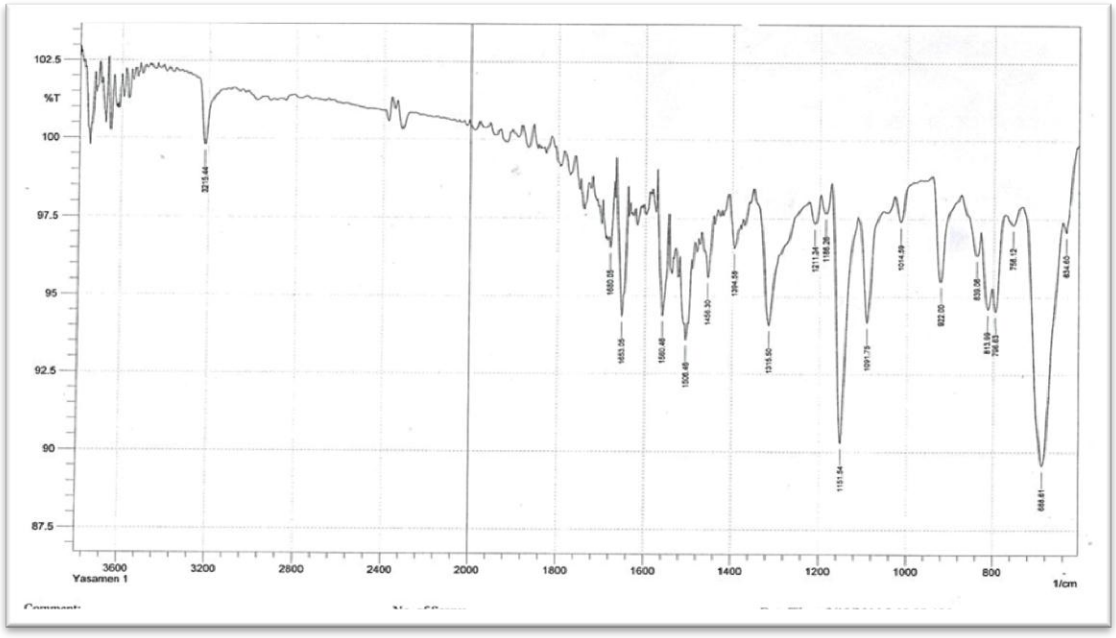


Figure 2- The FT-IR spectrum of compound 4.

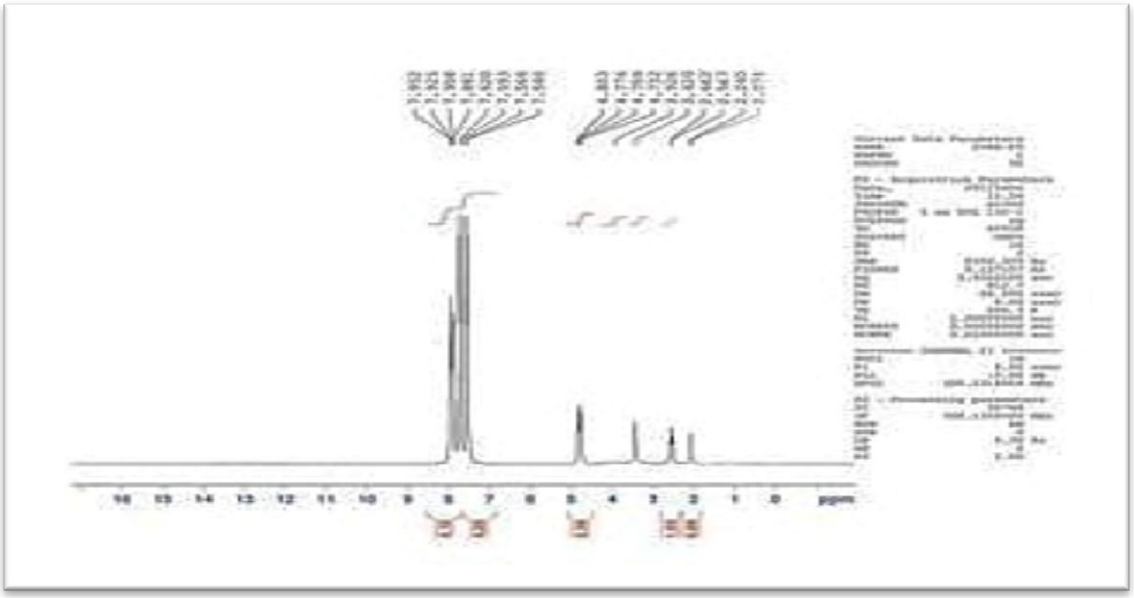


Figure 3- The ^{1}H- NMR spectrum of compound 4.

Moreover, cyclization of azide compound with ethylacetoacetate afforded triazole derivative (5). The FTIR spectrum of derivative (5) shows sharp absorption band at 1699 cm^{-1}which was attributed to υ (CO) group of the carboxylic acid and the abroad band at 3300 cm^{-1}due to υ (O-H) group Figure-4. ^{1}H-NMR spectrum of compound (5) showed singlet signals at 2.23 ppm was assigned to CH_3 protons ,2.33 ppm belong to CH_3 of triazole , 7.67 ppm was attributed to N-H proton and 11.32 ppm due to proton of (OH) carboxyl group. Signal for aromatic protons appeared at 7.52-6.54 ppm.

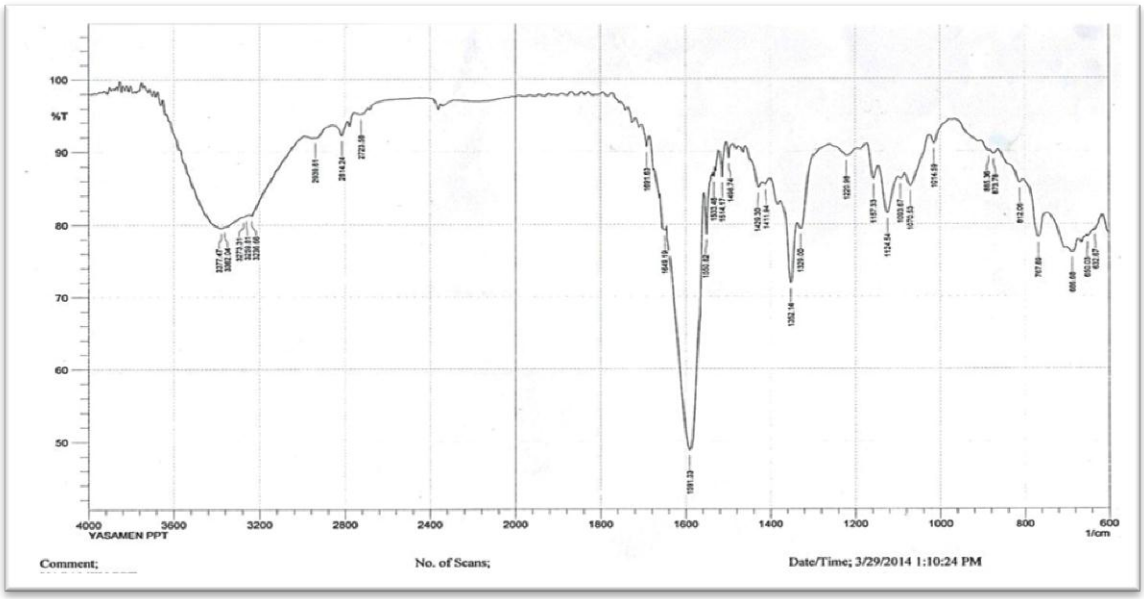


Figure 4- The FT-IR spectrum of compound 5.

The azo compound was synthesiszed by coupling between diazonium salt of amino sulfonamide derivative (2) with salicylaldehyde [14]. FT-IR spectrum of compound (6) exhibited the disappearancs of two absorption bands due to NH_2 stretching of compound (1) together with theappearance of stretching band at 1550 cm^{-1} due to υ (N=N) group . Band of hydroxyl does not appear due to the presence of intramolecular hydrogen bonding between O-H and CHO agroups Figure-5.

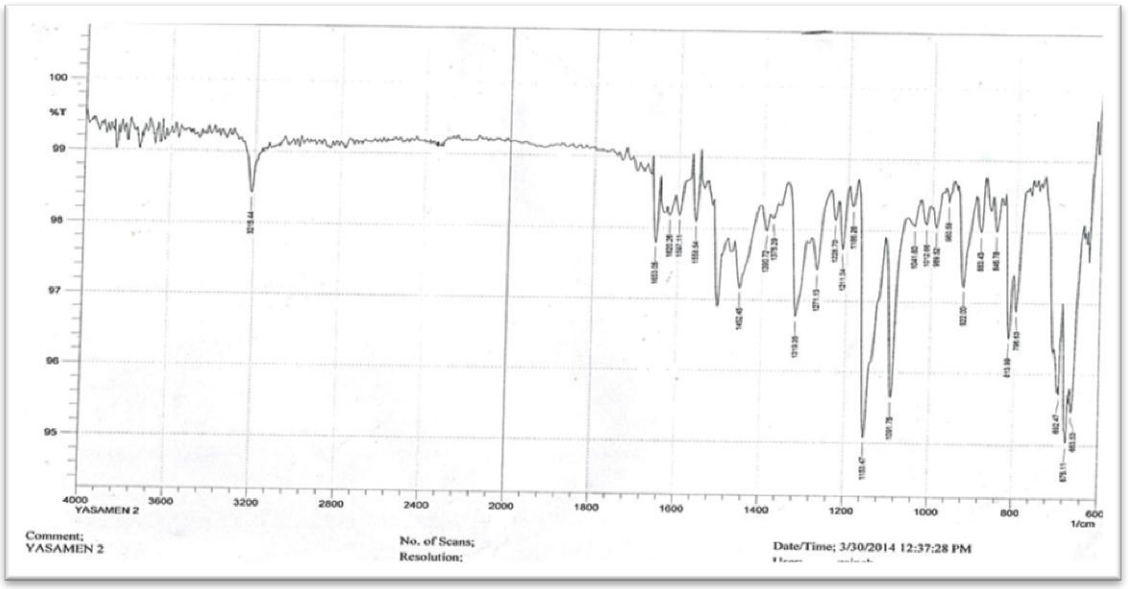


Figure 5- The FT-IR spectrum of compound 6.

¹H-NMR spectrum of azo compound exhibited singlet signal at 2.3 ppm was assigned to three protons of methyl group, signal at 5.65 ppm was attributed to O-H proton ,singlet at 4.65 ppm related to NH, double doublet signals at (7.40- 7.45) and (7.61-7.69) ppm belong to (8H, 2ph) protons which is interfered with the proton of salicylaldehyde ring and singlet at 9.96 ppm belong to proton of aldehyde.

Condensation of compound (6) with 2-amino pyrimidine in ethanol afforded Schiff base (7). The formulation of Schiff base was showed by the disappearance of NH_2 stretching band of 2-aminopyrimidine and carbonyl group of compound (6)combined with the presence of azomethine (CH=N) stretching band at 1635 cm^{-}.¹ Figure-6

The ¹H-NMR spectrum of compound (7) exhibited singlet signals at 2.32 ppm was assigned to CH_3 protons, 5.60 ppm due to proton of O-H, 7.97 ppm was attributed to N-H proton. Signal for aromatic protons appeared at 7.56 -6.78 ppm and a multiplet signals at 8.90- 8.79 ppm due to protons of pyrimidine ring . On the other hand, the reaction of compound (6) with acetophenone afforded chalcone deravtive (8). FT-IR spectrum of (8) shows bands at 1672 and 1640 cm^{-1} due to υ (C=O) and υ (C=C) respectively Figure-7.

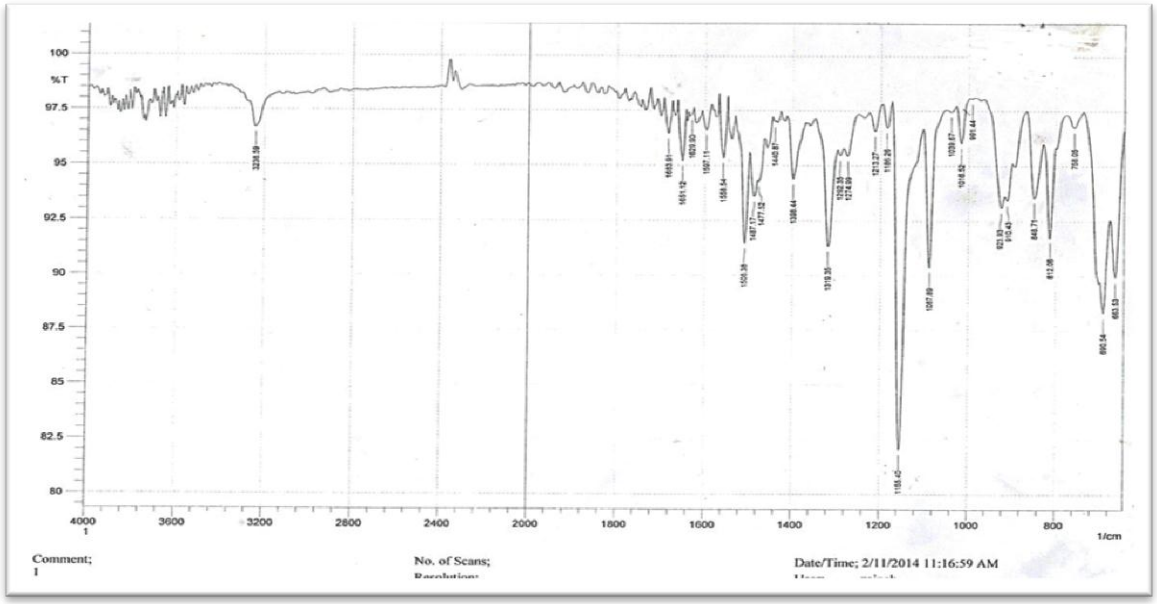


Figure 6- The FT-IR spectrum of compound 7.

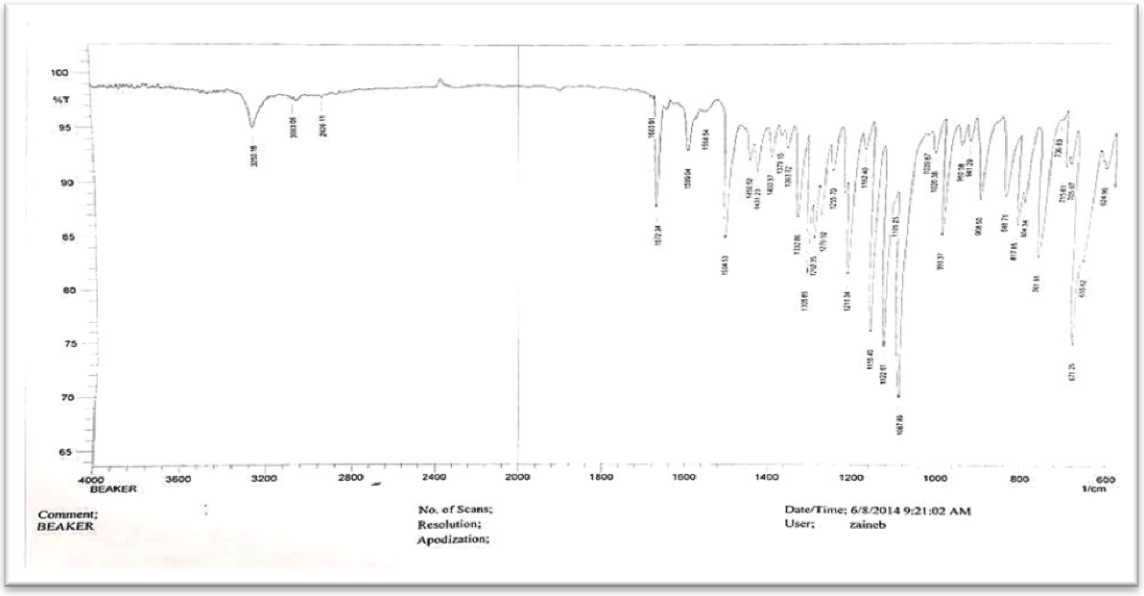


Figure 7-The FT-IR spectrum of compound 8.

^{1}H-NMR spectrum of chalcone (8) exhibited singlet signal: at 2.3 ppm which was assigned to CH_3 Protons 7.25 ppm was attributed to N-H proton , 5.6 ppm due to O-H proton. Amultiplet signals at 8.27 -7.63 ppm due to 16H aromatic protons and (C=CH), singlet signal at 8.1 ppm belong to (CH-CO).

3.2. Antimicrobial Activity

The synthesized sulfonamide carrying azo, 1, 2, 3-triazole, Schiff base, chalcone moieties which are accountable for antimicrobial activity. It seems that compounds 7, 8 are very significant for activity against both bacteria and fungi. All the compounds were found to exhibit moderate to good antifungal activity.

Standard antibacterial medication (Ampicillin) and antifungal medication (Fluconazole) were utilized for comparision. The examinations have been performed in triplicate keeping in mind minimize blunders Figure-8.

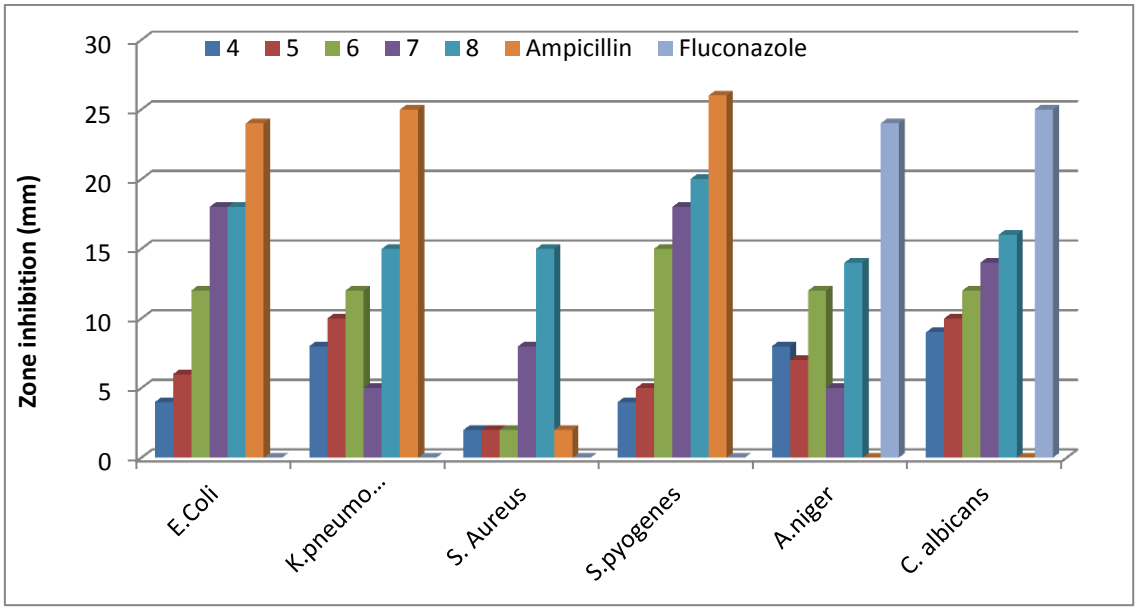


Figure 8- Antimicrobial evaluation of compounds (4-8).

3.3. In vitro antioxidant screening

The antioxidant screening of sulfonamide derivatives were identified on the basis of their scavenging of the stable (DPPH) free radical.

The results of antioxidant screening were depicted in (Table-2. Antioxidants can react with DPPH and generated 1, 1-diphenyl-2-picryl-hydrazine. The reducing abilities of the derivatives were strong minded by their interaction with the stable free radical 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) at five different concentrations for 30 minute. The highest scavenging activity observed in compounds 7, 8 due to the presence of azomethine and chalcone group Figure-9.

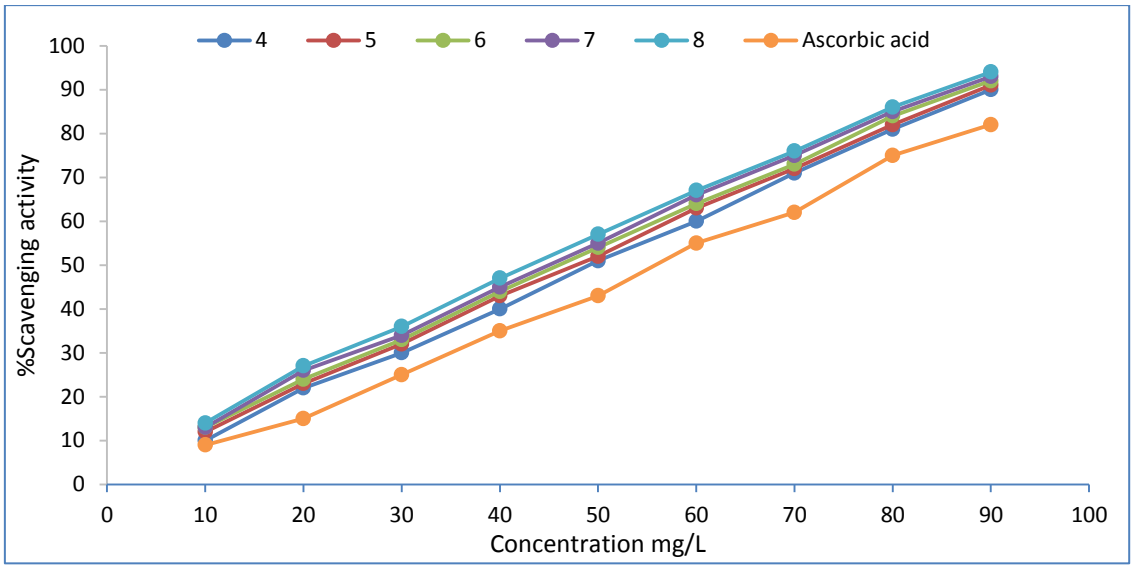


Figure 9- % Scavenging activity of the compounds (4-8) using DPPH.

4. Conclusion

New sulfonamide derivatives were prepared and characterized on the basis of analytical and spectral data .Screening of these compounds against pathogenic microorganism beside evaluation of scavenging activity reveals that sulfonamide derivatives showed moderate to noticeable antimicrobial and antioxidant activities.

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