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ORIGINAL ARTICLE

Synthesis, characterization and biological activities of some azo derivatives of aminothiadiazolederived from nicotinic and isonicotinic acids



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1,3,4-Thiadiazolederived;
Azo compounds;
Cyclization;
Microbial activity

Abstract In this study we synthesized the new compounds containing bis-1,3,4-thiadiazolederived **3(A–D)_n** from many reaction steps (cyclization, diazotization and etherification respectively). The compounds have been characterized by melting point, FT-IR and ¹H NMR data. All the synthesized compounds have been evaluated *in vitro* for their antimicrobial activities against several microbes like: *Escherichia coli*, *Klebsiellia pneumonia*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Staphylococcus aureus* and show that some of these compounds have very good antibacterial activity.

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1. Introduction

The aminothiadiazolederived have occupied an important place in drug industry. 1,3,4-Thiadiazolederived has wide applications in many fields. The earliest uses were in the pharmaceutical area as antibacterial drugs (Vasoya et al., 2005).

The 1,3,4-thiadiazolederived ring system has incorporated many substances with antibacterial, ameobicide, parasiticide and antifungal activities (Farzin and Rahil, 2008; Mohd et al., 2009). In addition, it was reported that 1,3,4-thiadiazolederived exhibit various biological activities possibly due to the presence of the N=C–S moiety (Holla et al., 2002).

It was also know that 3- and 4-substituted pyridines recorded pronounced antimicrobial activity such as isonicotinic acid hydrazide, which remains one of the most effective antibiotics against tuberculosis. Also, sulphanilamides effectiveness extends to acute chronic Gram negative and Gram positive infections. For example, sulfa pyridine is a chemotherapeutic agent for the treatment of pneumococcal and other bacterial infections (Osama and Salwa, 2005). There

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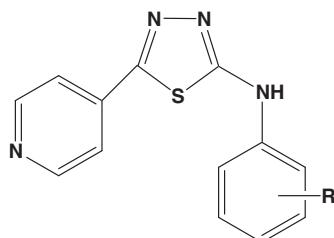
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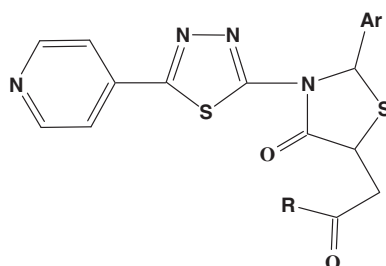
are many interesting studies on the biological activity of 2-amino-1,3,4-thiadiazole. Mohammad et al. (2009) found some derivatives of aminothiadiazole (**I**) having good anticonvulsant activity in the range of 33–100% in comparison to phenytoin, which completely inhibited the convulsions produced by an electroconvulsometer in albino mice.



R= H, *O*-CH₃, *P*-CH₃, *O*-OCH₃, *P*-Cl

(I)

Ranjina et al. (2006) synthesized a number of derivatives of aminothiadiazole containing 4-pyridyl and oxothiazolidin moieties in the same molecules (**II**).



Ar = 4-*O*CH₃C₆H₄, 4-ClC₆H₄, 3,4,5-*O*CH₃C₆H₂, 3-NO₂C₆H₄, 4-NO₂C₆H₄, C₆H₅, 2-Furyl, 4-(CH₃)₂NHC₆H₄, R= phthalimidoxy.

(II)

He found that all the compounds have good antimicrobial activity but the compounds in which a nitro group is present at the Meta and Para position of the aryl ring, respectively, possess stronger antibacterial activity than others.

In this study, we designed new azo compounds containing bis-1,3,4-thiadiazole ring derived from nicotinic and isonicotinic acids in the same molecules. This type of combination and rebuilding of these heterocyclic compounds are expected to have high biological activity largely as antimicrobial agents and we compared the biological activity results of these compounds with the analogous containing the same structural units except replacing the nicotinic and isonicotinic moieties with phenyl and cyclohexyl rings.

2. Experimental

2.1. Materials and physical measurements

All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on Electro-thermal capillary apparatus and are uncorrected. The FT-IR spectra were obtained using SHIMADZU model FT-IR-8400S. ¹H NMR spectra were obtained on BRUKER model Ultra shield 300 MHz spectrophotometer in DMSO-*d*₆ solution with the TMS as

the internal standard. *Note:* in some ¹H NMR spectra, the peaks at δ 2.5 and 3.35 are for the solvent (DMSO-*d*₆) and dissolved water in (DMSO-*d*₆), respectively.

2.2. Preparation methods and physical data of synthesized compounds **1(A–D)**–**3(A–D)**

2.2.1. General procedure for preparation of 2-amino-5-(substituted)-1,3,4-thiadiazole **1(A–D)**

A mixture of the corresponding carboxylic acid (10 mmol), thiousemicarbazide (0.91 g, 10 mmol) and phosphorous oxychloride (5 mL) was gently refluxed for 3 h. After cooling, water (25 mL) was added slowly and the reaction mixture was refluxed for 3 h and filtered. The solution was neutralized with concentrated potassium hydroxide solution and the precipitate was filtered and recrystallized from ethanol.

2.2.1.1. 2-Amino-5-(3-pyridyl)-1,3,4-thiadiazole (1A). This compound was obtained as a pale yellow powder, yield (69%), mp > 300 °C; FT-IR (KBr disk, cm⁻¹) 3308 and 3168 (NH₂), 1645 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz, δ) 9.19 (s, 1H, a-H, pyridine), 8.95 (d, 1H, d-H, pyridine), 8.62 (t, 1H, c-H, pyridine), 8.12 (d, 1H, b-H, pyridine), 7.55 (s, 2H, NH₂).

2.2.1.2. 2-Amino-5-(4-pyridyl)-1,3,4-thiadiazole (1B). This compound was obtained as a yellow powder, yield (74%), mp 239–240 °C; FT-IR (KBr disk, cm⁻¹) 3297 and 3123 (NH₂), 1641 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz, δ) 8.70 (d, 2H, HC=N, pyridine), 7.85 (d, 2H, HC=C, pyridine), 7.75 (s, 2H, NH₂).

2.2.1.3. 2-Amino-5-(4-phenyl)-1,3,4-thiadiazole (1C). This compound was obtained as an off white powder, yield (82%), mp 220–222 °C; FT-IR (KBr disk, cm⁻¹) 3320 and 3156 (NH₂), 1631 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz, δ) 7.78–7.47 (m, 5H, Ar-H), 7.43 (s, 2H, NH₂).

2.2.1.4. 2-Amino-5-(4-cyclohexyl)-1,3,4-thiadiazole (1D). This compound was obtained as a white powder, yield (91%), mp 238–240 °C; FT-IR (KBr disk, cm⁻¹) 3302 and 3117 (NH₂), 1633 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz, δ) 6.99 (s, 2H, NH₂), 1.99–1.15 (m, 11H, cyclohexyl).

2.2.2. General procedure for preparation of 2-(*p*-hydroxyphenyl-azo)-5-(substituted)-1,3,4-thiadiazole **2(A–D)**

Compounds **1(A–D)** (1.78 mmol) were dissolved by heating and stirring in (8 mL) of 85% phosphoric acid. The solution was cooled to 0 °C in an ice bath, and then concentrated nitric acid (4 mL) and a solution of sodium nitrite (0.13 g, 1.87 mmol) in (2 mL) of water was added. The mixture was stirred vigorously and maintained at below 5 °C during 10 min. Afterwards a solution of phenol (0.17 g, 1.78 mmol) in (0.5 mL) water was added dropwise with stirring. The mixture was poured into cold water (100 mL). The precipitate solid was filtered, washed several times with water and recrystallized from ethanol.

2.2.2.1. 2-(*p*-Hydroxyphenyl-azo)-5-(3-pyridyl)-1,3,4-thiadiazole 2(A). This compound was obtained as a dark red powder, yield (71%), mp 246–248 °C; FT-IR (KBr disk, cm⁻¹) 3450–3095 (broad O–H group), 1432 (N=N) cm⁻¹; ¹H NMR

(DMSO- d_6 , 300 MHz, δ) 9.29 (s, 1H, a-H, pyridine), 8.83 (d, 1H, d-H, pyridine), 8.57 (t, 1H, c-H, pyridine), 8.51 (s, 1H, OH), 8.20 (d, 1H, b-H, pyridine), 7.71 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H).

2.2.2.2. 2-(p-Hydroxyphenyl-azo)-5-(4-pyridyl)-1,3,4-thiadiazole 2(B). This compound was obtained as a dark brown powder, yield (77%), mp > 300 °C; FT-IR (KBr disk, cm^{-1}) 3431–3083 (broad O–H group), 1425 (N=N) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz, δ) 8.55 (s, 1H, OH), 8.35 (d, 2H, HC=N, pyridine), 7.93 (d, 2H, HC=C, pyridine), 7.46 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H).

2.2.2.3. 2-(p-Hydroxyphenyl-azo)-5-(phenyl)-1,3,4-thiadiazole 2(C). This compound was obtained as a brown powder, yield (86%), mp 196–198 °C; FT-IR (KBr disk, cm^{-1}) 3553–3112 (broad O–H group), 1417 (N=N) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz, δ) 8.59 (s, 1H, OH), 7.98–8.12 (m, 5H, Ar-H), 7.39 (d, 2H, Ar-H), 7.05 (d, 2H, Ar-H).

2.2.2.4. 2-(p-Hydroxyphenyl-azo)-5-(cyclohexyl)-1,3,4-thiadiazole 2(D). This compound was obtained as a deep orange powder, yield (71%), mp 118–121 °C; FT-IR (KBr disk, cm^{-1}) 3439–3097 (broad O–H group), 1397 (N=N) cm^{-1} ; ^1H NMR (DMSO- d_6 , 300 MHz, δ) 8.49 (s, 1H, OH), 8.27 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 2.08–1.13 (m, 11H, cyclohexyl).

2.2.3. General procedure for preparation of alkane-bis- α - ω -[2-(p-alkoxyphenyl-azo)-5-(substituted)]-1,3,4-thiadiazole 3(A–D)_n

These compounds were synthesized by alkylation's of dyes 2(A–D) using the described method by Vyas and Shah (1963). 2-(p-Hydroxyphenyl-azo)-5-(substituted)-1,3,4-thiadiazole 2(A–D) (10 mmol), appropriate 1,*n*-dibromo or iodo alkane (6 mmol) and anhydrous potassium carbonate (15 mmol) were added to dry acetone (10 mL). The reaction mixture was refluxed on a water bath for 24 h. Then it was added to ice-cold water. The crude solid product thus

obtained was triturated with cold 5% aqueous sodium hydroxide solution for 30 min so as to remove unreacted azo dyes and was washed with water several times. The products obtained after filtration were finally crystallized using ethanol. The physical properties and FT-IR spectral data of all compounds 3(A–D)_n are listed in Table 1.

2.2.3.1. Methane-bis- α - ω -[2-(p-alkoxyphenyl-azo)-5-(3-pyridyl)]-1,3,4-thiadiazole 3(A)₁. ^1H NMR (DMSO- d_6 , 300 MHz, δ) 9.18 (s, 2H, a-H, pyridine), 8.72 (d, 2H, d-H, pyridine), 8.37 (t, 2H, c-H, pyridine), 8.25 (d, 2H, b-H, pyridine), 7.76 (d, 4H, Ar-H), 7.58 (d, 4H, Ar-H), 6.46 (s, 2H, CH₂).

2.2.3.2. Ethane-bis- α - ω -[2-(p-alkoxyphenyl-azo)-5-(4-pyridyl)]-1,3,4-thiadiazole 3(B)₂. ^1H NMR (DMSO- d_6 , 300 MHz, δ) 8.58 (d, 4H, HC=N, pyridine), 7.97 (d, 4H, HC=C, pyridine), 7.39 (d, 4H, Ar-H), 7.01 (d, 4H, Ar-H), 4.19 (t, 4H, CH₂).

2.2.3.3. Butane-bis- α - ω -[2-(p-alkoxyphenyl-azo)-5-(phenyl)]-1,3,4-thiadiazole 3(C)₄. ^1H NMR (DMSO- d_6 , 300 MHz, δ) 7.81–8.23 (m, 10H, Ar-H), 7.22 (d, 4H, Ar-H), 7.02 (d, 4H, Ar-H), 4.07 (t, 4H, OCH₂CH₂), 2.12 (m, 4H, OCH₂CH₂).

2.2.3.4. Propane-bis- α - ω -[2-(p-alkoxyphenyl-azo)-5-(cyclohexyl)]-1,3,4-thiadiazole 3(D)₃. ^1H NMR (DMSO- d_6 , 300 MHz, δ) 8.21 (d, 4H, Ar-H), 7.34 (d, 4H, Ar-H), 4.21 (t, 4H, OCH₂) 2.32–1.09 (m, 24H, cyclohexyl and OCH₂CH₂CH₂O).

3. Results and discussion

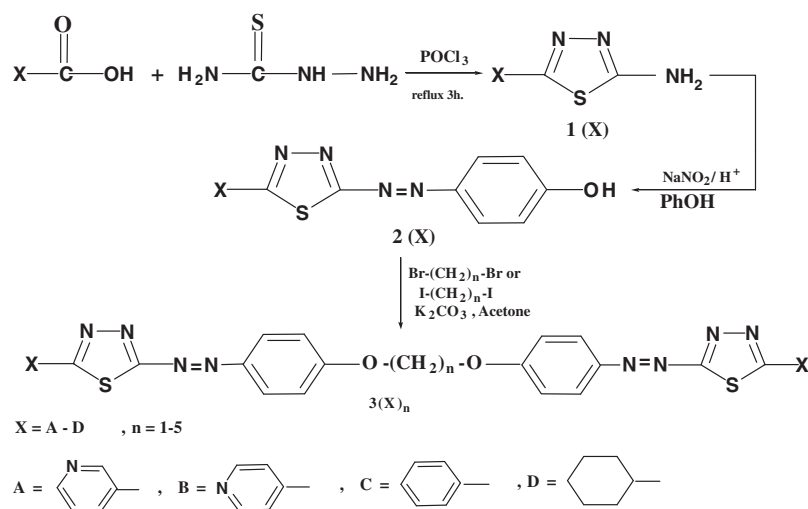
3.1. Synthesis

Scheme 1 outlines the synthetic sequences employed in our laboratories for the preparation of series 3(A–D)_n.

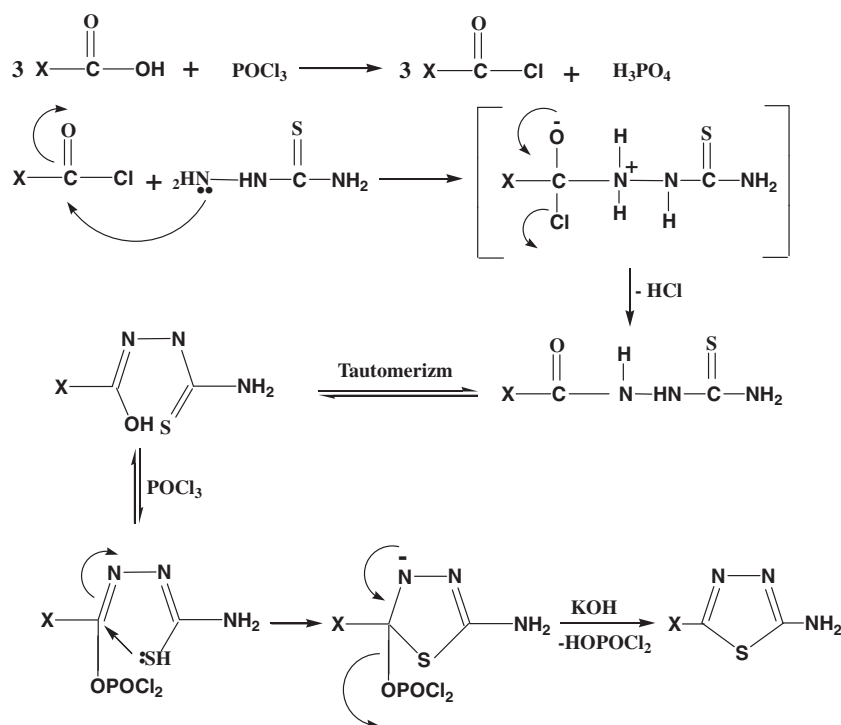
2-Amino-5-(substituted)-1,3,4-thiadiazole 1(A–D) were prepared in good yields by the reaction of the corresponding carboxylic acids with thiosemicarbazide in the presence of

Table 1 Physical properties and FT-IR data of compounds 3(A–D)_n.

Comp. No.	Color	Mp °C	Yield %	$\nu\text{C–H}$ Aliph.	$\nu\text{C–O–C}$ asym. and sym.
3(A) ₁	Red	> 300	43	2920, 2877	1255, 1051
3(A) ₂	Dark red	> 300	56	2929, 2871	1261, 1044
3(A) ₃	Dark red	289–291	41	2919, 2866	1266, 1053
3(A) ₄	Red	275–277	39	2932, 2880	1257, 1047
3(A) ₅	Dark red	281–285	57	2927, 2858	1247, 1049
3(B) ₁	Brown	> 300	33	2937, 2870	1247, 1046
3(B) ₂	Brown	> 300	42	2941, 2866	1251, 1061
3(B) ₃	Dark brown	> 300	52	2936, 2858	1259, 1043
3(B) ₄	Brown	> 300	56	2932, 2867	1244, 1045
3(B) ₅	Dark brown	285–288	57	2928, 2856	1263, 1074
3(C) ₁	Brown	> 300	37	2921, 2868	1266, 1081
3(C) ₂	Brown	> 300	48	2935, 2855	1259, 1077
3(C) ₃	Light brown	290–292	33	2924, 2854	1248, 1070
3(C) ₄	Dark brown	277–280	32	2937, 2862	1242, 1060
3(C) ₅	Brown	269–271	48	2943, 2871	1249, 1071
3(D) ₁	Deep orange	> 300	42	2929, 2854	1253, 1049
3(D) ₂	Deep orange	288–289	46	2934, 2859	1261, 1039
3(D) ₃	Orange	238–242	59	2941, 2844	1267, 1050
3(D) ₄	Orange	200–202	33	2929, 2852	1257, 1024
3(D) ₅	Brown	194–197	57	2931, 2857	1263, 1033



Scheme 1 Synthetic route for preparation of compounds **3(A-D)_n**.



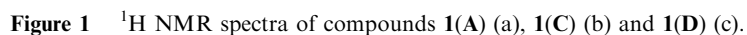
Scheme 2 The mechanism steps of formation of aminothiadiazole **1(A-D)**.

phosphorous oxychloride. The proposed mechanism of this reaction was described by Emad et al. (2009) and was shown in Scheme 2.

The FT-IR spectra of compounds **1(A-D)** indicated the presence of a C=N function ($1631\text{--}1645\text{ cm}^{-1}$) and two bands at ($3320\text{--}3297\text{ cm}^{-1}$) and ($3168\text{--}3117\text{ cm}^{-1}$), which could be attributed to asymmetric and symmetric stretching vibrations of NH_2 group. The ^1H NMR spectra of these compounds showed a singlet at δ (6.9–7.7) ppm due to the NH_2 protons. Fig. 1 showed the ^1H NMR spectra of compounds **1(A)**, **1(C)** and **1(D)**.

The azo compounds **2(A-D)** were synthesized by diazotization of compounds **1(A-D)** and coupling with phenol by following the method reported by Erlenmeyer and Ueberwasser (1942). This reaction may be outlined as follows in Scheme 3 (John, 2004).

The characteristic FT-IR absorption bands of azo compounds **2(A-D)** showed the disappearance of two absorption bands due to NH_2 group together with the appearance of a broad peak between 3550 and 3085 cm^{-1} due to the intermolecular hydrogen bonding of phenolic O–H bond for compounds **2(A-D)** (Prajapati and Bonde, 2006). It also shows a



compounds **2(A–D)** showed a singlet peak at δ (8.49–8.59) that could be assigned to the protons of the phenolic

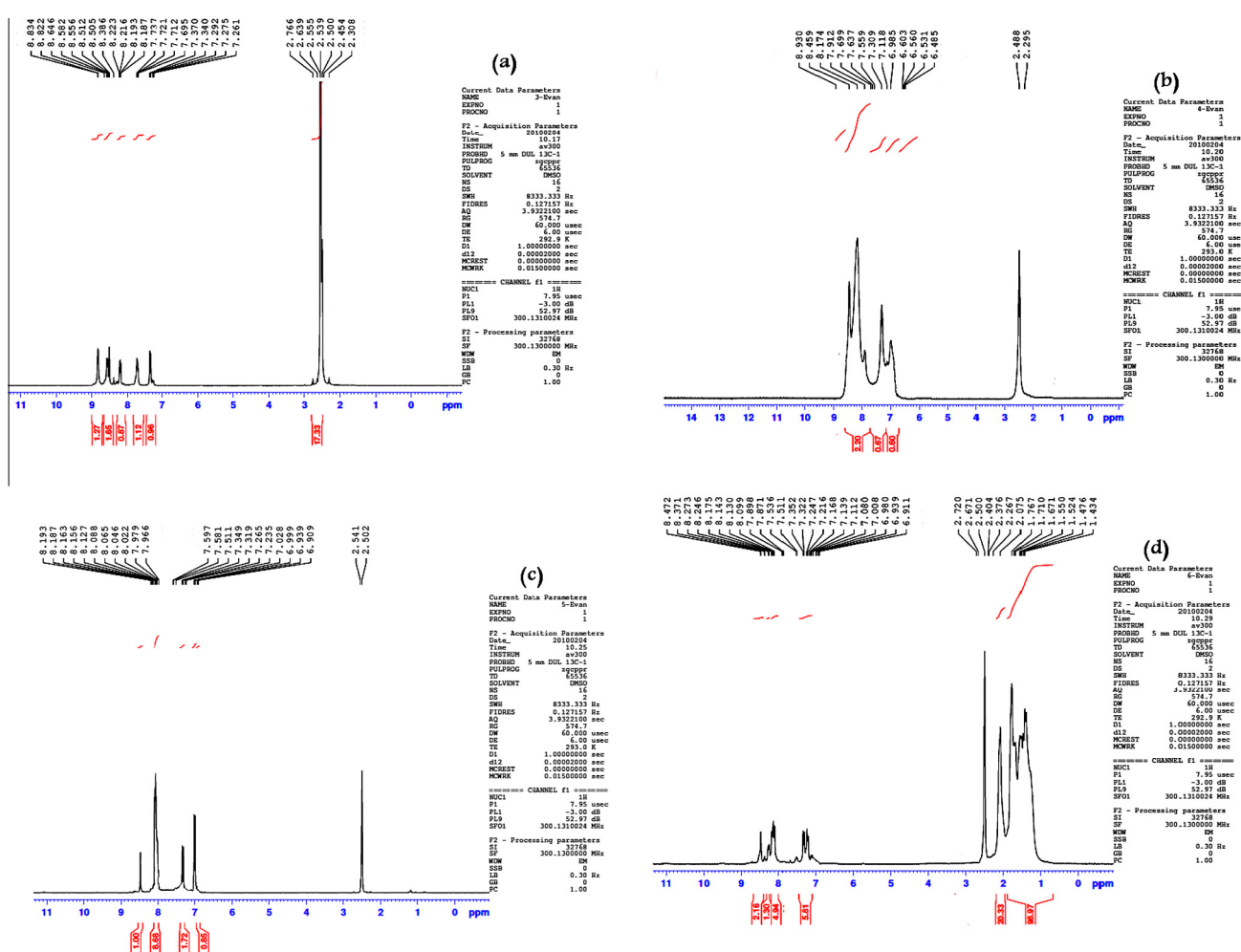


Figure 2 ^1H NMR spectra of compounds **2(A)** (a), **2(B)** (b), **2(C)** (c) and **2(D)** (d).

hydroxyl group. Fig. 2 showed the ^1H NMR spectra of compounds **2(A–D)**.

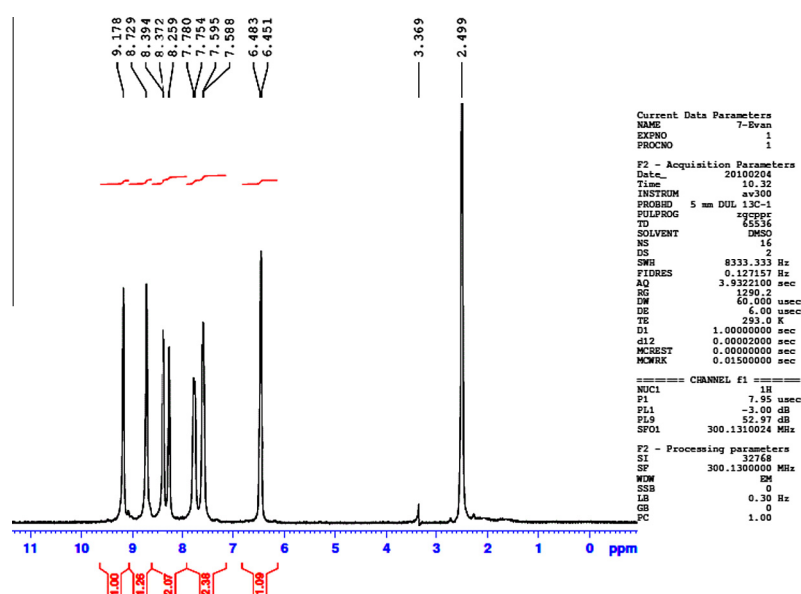
Condensation of azo compounds **2(A–D)** with α - ω dibromo or iodo alkane in dry acetone in the presence of anhydrous K_2CO_3 gave di ethers, series **3(A–D)_n**. The FT-IR spectra of compounds **3(A–D)_n** showed the C–H stretching absorption band near (2919 and 2880 cm^{-1}) and C–O–C stretching band, asymmetrical and symmetrical near 1267 cm^{-1} and 1024 cm^{-1} , respectively. Fig. 3 shows the ^1H NMR spectrum of compound **3(A)₁**, for example, of all compounds **3(A–D)_n**. The physical properties and FT-IR spectral data of all compounds **3(A–D)_n** are listed in Table 1.

3.2. Biological evaluation

All the synthesized compounds **3(A–D)_n** have been screened for antibacterial activities using cup-plate agar diffusion method (Barry, 1976) by measuring the inhibition zone in mm. Azithromycin (300 $\mu\text{g}/\mu\text{L}$) was used as a standard drug for antibacterial activity. The compounds were screened for antibacterial activity against *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Staphylococcus aureus* in Muller Hinton agar. These

sterilized agar media were poured into Petri-dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of a sterilized triangular loop. A stainless steel cylinder of 12 mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (300 $\mu\text{g}/\mu\text{L}$) were placed serially in cavities with the help of a micropipette and allowed to diffuse for one hr. DMF was used as a solvent for all compounds (as a stock) then the concentration (300 $\mu\text{g}/\mu\text{L}$) was prepared using sterile distilled water. These plates were incubated at 37 $^\circ\text{C}$ for 48 hr. The zone of inhibition observed around the cups after respective incubation was measured and percent inhibition of the compounds was calculated. The results are presented in Table 2.

When we show the data of (inhibition zone %) of all compounds **3(A–D)_n** in Table 2 we observe some important results: the first that the compounds **3(B)_n**, **3(C)_n** and **3(D)_n** showed good activity against *E. coli*, while only the compounds **3(A)_n** showed good activity against *K. pneumonia*. Also we showed that some of the compounds **3(A–D)_n** have good activity against *S. aureus*, while all compounds **3(A–D)_n** did not show any antibacterial activity against *P. aeruginosa* and *S. marcescens*. When we show the percentage of inhibition zone

Figure 3 ^1H NMR spectrum of compound 3(A)₁.Table 2 Antibacterial activities of compounds 3(A–D)_n.

Comp. No.	<i>Escherichia coli</i>		<i>Klebsiella pneumonia</i>		<i>Pseudomonas aeruginosa</i>		<i>Serratia marscens</i>		<i>Staphylococcus aureus</i>	
	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition
3(A) ₁	0	0	35	159.09	0	0	0	0	34	113.33
3(A) ₂	0	0	35	159.09	0	0	0	0	35	116.67
3(A) ₃	0	0	35	159.09	0	0	0	0	0	0
3(A) ₄	0	0	35	159.09	0	0	0	0	0	0
3(A) ₅	0	0	35	159.09	0	0	0	0	0	0
3(B) ₁	27	135.00	0	0	0	0	0	0	35	116.67
3(B) ₂	30	150.00	0	0	0	0	0	0	0	0
3(B) ₃	35	175.00	0	0	0	0	0	0	0	0
3(B) ₄	34	170.00	0	0	0	0	0	0	14	46.67
3(B) ₅	50	250.00	0	0	0	0	0	0	0	0
3(C) ₁	10	50.00	0	0	0	0	0	0	0	0
3(C) ₂	15	75.00	0	0	0	0	0	0	35	116.67
3(C) ₃	20	100.00	0	0	0	0	0	0	0	0
3(C) ₄	30	150.00	0	0	0	0	0	0	0	0
3(C) ₅	35	175.00	0	0	0	0	0	0	36	120.00
3(D) ₁	30	150.00	0	0	0	0	0	0	0	0
3(D) ₂	25	125.00	0	0	0	0	0	0	0	0
3(D) ₃	25	125.00	0	0	0	0	0	0	0	0
3(D) ₄	25	125.00	0	0	0	0	0	0	30	100.00
3(D) ₅	25	125.00	0	0	0	0	0	0	35	116.67
St.	20	100	22	100	28	100	35	100	30	100

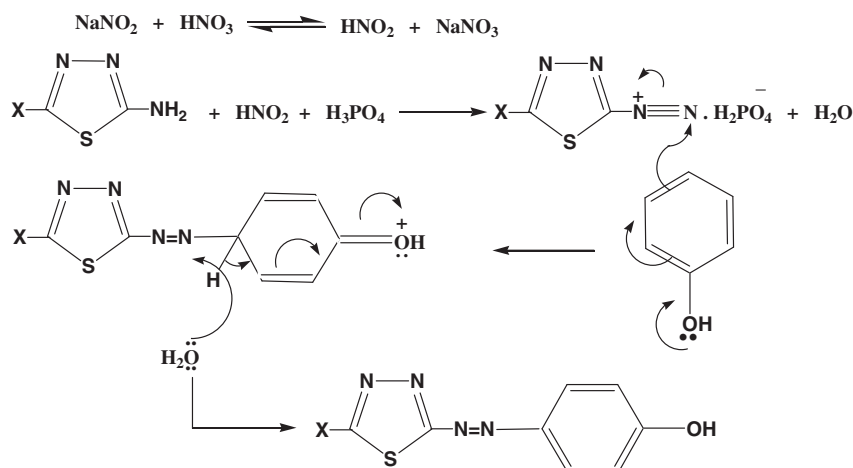
St., standard (Azithromycin).

of compounds 3(C)_n against *E. coli*, we observe that the antibacterial activity of these compounds increase when the chain of the alkyl group (CH₂)_n in the central part of the molecules increase. The derivative 3(B)₅ showed potent activity against *E. coli* (250.00%), whereas compounds 3(A)_{1–5} showed the same inhibition and good activity (159.09%) against *K. pneumonia*. Thus, it is concluded from the screening results that the most of bis-1,3,4-thiadiazole derivatives 3(A–D)_n have good antibacterial activity more than the standard (Azthromy-

cin) against *E. coli* and some of them against *K. pneumonia* and *S. aureus* also, all compounds 3(A–D)_n did not show any antibacterial activities against *P. aeruginosa* and *S. marscens* at a concentration of 300 µg/µL.

4. Conclusion

Bis-1,3,4-thiadiazole compounds containing the azo moiety was prepared and structurally characterized using spectro-



Scheme 3 The mechanism steps of formation of azo compounds **2(A–D)**.

scopic techniques. The synthetic route started from the cyclization reaction between thiosemicarbazide and appropriate carboxylic acids (nicotinic, isonicotinic, benzoic and cyclohexan carboxylic acid) in presence of POCl_3 followed by the diazotization reaction between the aminothiadiazole and phenol. The di azo compounds were prepared by etherification of azo compounds with dibromo or iodo alkane in alkali media. Bis-1,3,4-thiadiazole compounds containing azo moiety have been evaluated *in vitro* for their antimicrobial activities against several microbes like: *E. coli*, *K. pneumonia*, *P. aeruginosa*, *S. marcescens* and *S. aureus* and show that the compounds **3(B)_n**, **3(C)_n** and **3(D)_n** showed good activity against *E. coli*, while only the compounds **3(A)_n** showed good activity against *K. pneumonia*. Also we showed that some of the compounds **3(A–D)_n** have good activity against *S. aureus*, while all compounds **3(A–D)_n** did not show any antibacterial against *P. aeruginosa* and *S. marcescens*.

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