تم تدقيق البحث من قبل
الاستاذ:
بتاريخ:
وقد تم تصحيح كافة الاخطاء وكان البحث وفق متطلبات النشر
توقيع الاستاذ:

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES STUDY OF SOME AZO DERIVATIEVES OF AMINOTHIADIAZOLE DERIVED FROM NICOTINIC AND ISONICOTINIC ACIDS

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Abstract

In this study we synthesized the new compounds containing bis-1,3,4-thiadiazole $3(A\text{-}D)_n$ through many eaction steps (cyclization, diazotiazation and etherification respectively). The compounds have been characterized by melting point, FTIR and ^{1}HNMR data. All the synthesized compounds have been evaluated *in vitro* for their antimicrobial activities against several microbes like: Escherichia *coli*, Klebsiellia *pneumonia*, Pseudomonas *aerugenosa*, Serratia *marscens* and Staphylococcus *aureus* and the results showed that some of these compounds have very good antibacterial activity.

تحضير وتشخيص و دراسة الفعالية البايولوجية لبعض مشتقات الازو – امينو ثايادايازول المشتقة من حوامض النيكوتينك والايزونيكوتينك

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الخلاصة

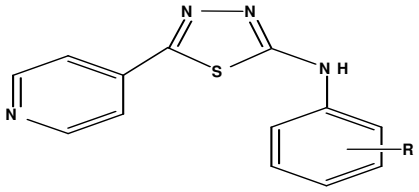
تم في هذه الدراسة تحضير مشتقات جديدة تحتوي على حلقتين من ٤،٣،١-ثايادايازول $(3A\text{-}D)_n$ وذلك بتطبيق عدة تفاعلات تضمنت (تفاعلات الغلق ، تفاعلات تحضير املاح الدايازونيوم وتفاعلات الايثرة على التوالي) . جميع المركبات شخصت بواسطة درجات انصهارها وطيف الاشعة تحت الحمراء FTIR وطيف الرنين النووي المغناطيسي ^{1}HNMR . فحصت الفعالية البايولوجية لجميع هذه المركبات خارج الجسم تجاه بعض انواع من البكتريا مثل Escherichia *coli*, Klebsiellia *pneumonia*, Pseudomonas *aerugenosa*, Serratia *marscens* and Staphylococcus *aureus* ووجد بان لهذه المركبات فعالية بايولوجية جيدة.

Introduction

Aminothiadiazoles have occupied an important place in drug industry. 1,3,4-Thiadiazole have wide applications in many fields. The uses were in the pharmaceutical area as antibacterial drugs [1]. 1,3,4-Thiadiazole ring systems have been incorporated in many substances with antibacterial, ameobicide, parasiticide and antifungal activity [2,3]. In addition, it was reported that 1,3,4-thaidiazoles exhibited various

of the N=C-S moiety [4]. It was also known 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 infection. For example, Sulfapyridine is a chemotherapeutic agent for the treatment of pneumococcal and other bacterial infections [5].

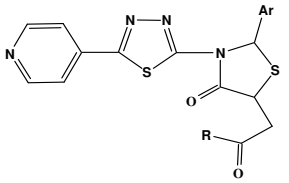
There are many interesting studies on the biological activity of 2-amino-1,3,4-thiadiazole. Shaharyar et al [6] found some derivatives of aminothiadiazole I.having good anticonvulsant activity in the range of 33-100% in comparison to phenytoin which completely inhibited the convulsions produced by electroconvulsometer in albino mice.



R = H , *O* -CH$_3$, *P* -CH$_3$, *O* -OCH$_3$, *P* -Cl

(I)

Ranjina et al [7], synthesized a number of derivatives of aminothiadiazole containing 4-pyridyl and oxothiazolidin moieties in the same molecules (II).



Ar = 4- $OCH_3C_6H_4$, 4-ClC_6H_4, 3,4,5-$OCH_3C_6H_2$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, C_6H_5, 2-Furyl, 4-$(CH_3)_2NHC_6H_4$, R= phthalimidoxy.

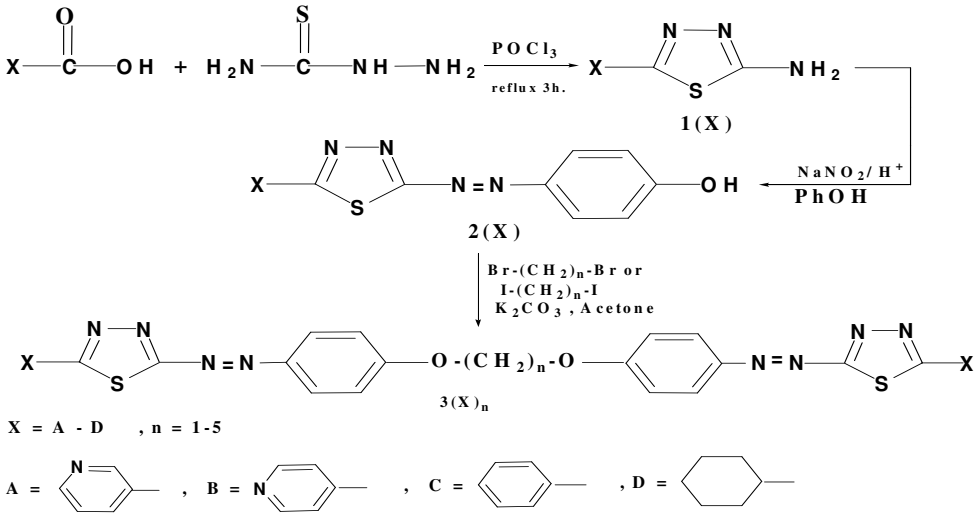
(II)

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 a 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 agent and we compared the biological activity results of these compounds with the analogous containing the same structural units except replacing the isonicotinic moieties with phenyl and cyclohexyl rings.

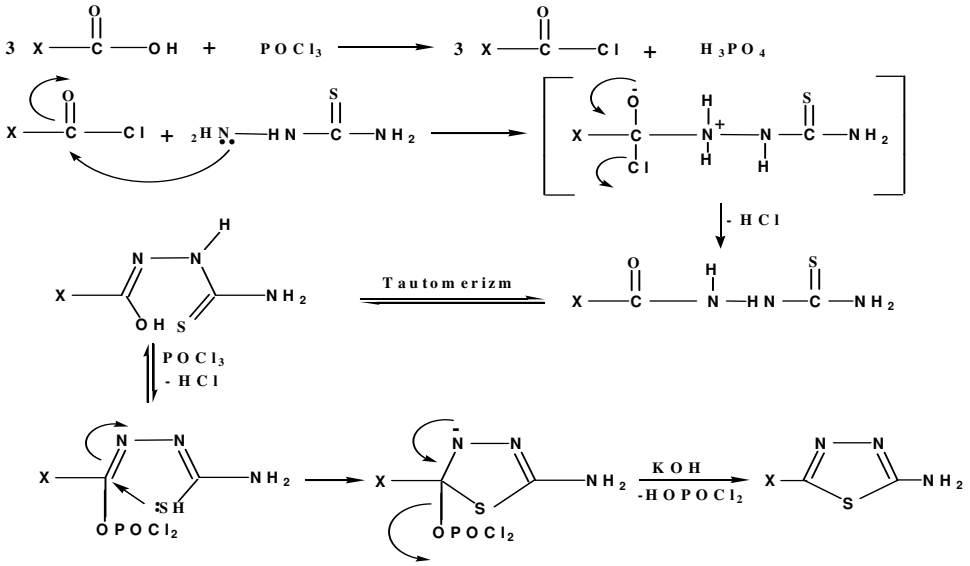
Result and Disccussion

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



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

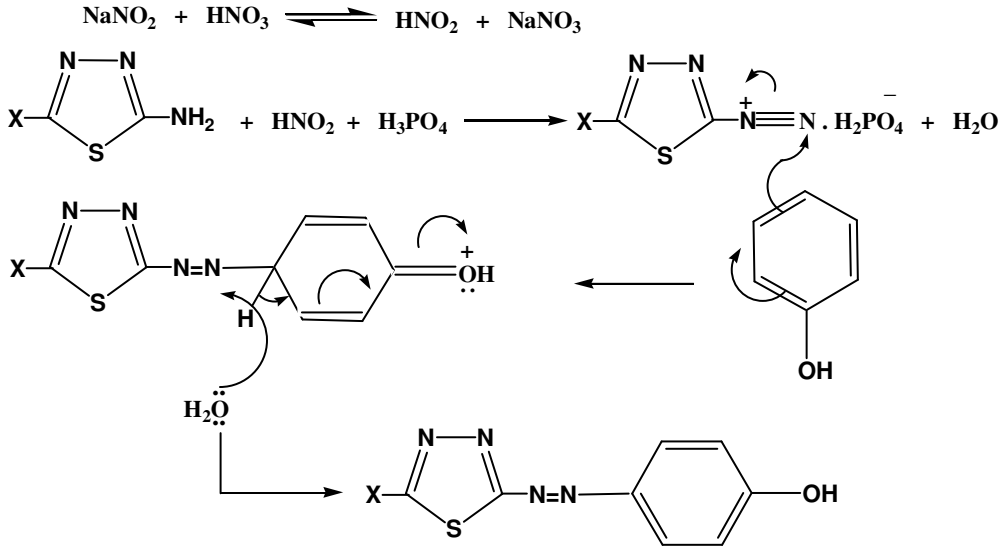
2-Amino-5-(substituted)-1,3,4-thiadiazole 1(A-D) were prepared in good yield by the reaction of the corresponding carboxylic acids with thiosemicarbazide in the presence of phosphorous oxychloride. The propose mechanism of this reaction is shown in (scheme 2)[8].



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

FTIR spectra of compounds 1(A-D) indicated the presence of a C=N bond (1631-1645 cm^{-1}) and two bands at (3320-3297 cm^{-1}) and (3168-3117 cm^{-1}) which could be attributed to asymmetric and symmetric stretching vibration of NH_2 group. The ^{1}HNMR spectra of these compounds showed a singlet at δ (6.9-7.7) ppm due to the NH_2 protons. (Figure 1). showed the ^{1}HNMR spectra of compounds 1(A), 1(C) and 1(D).

The azo compounds 2(A-D) were synthesized by diazotiazation of compounds 1(A-D) and coupling with phenol by following the method reported by Erlenmeyer and Ueberwasser [9]. This reaction may be outlined as follows in scheme 3 [10].



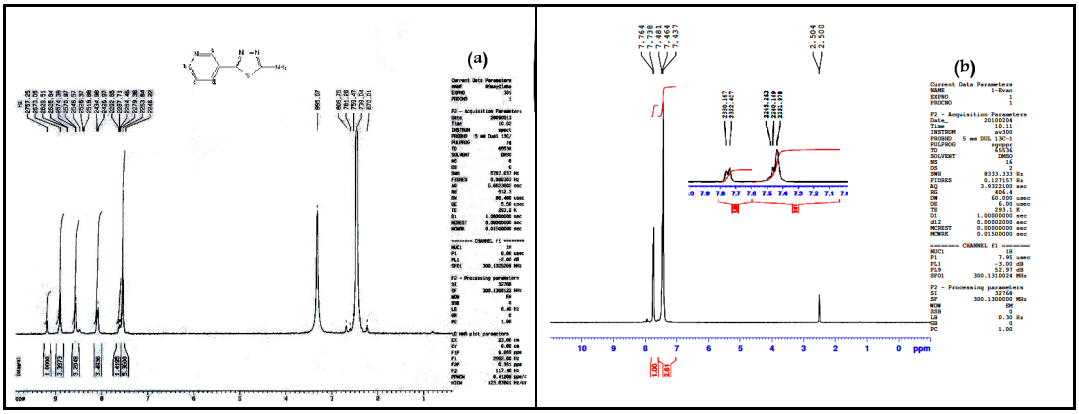
Scheme 3: The mechanism steps of formation of azo compounds 2(A-D).

The characteristic FTIR 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

(3550-3085 cm^{-1}) due to the intermolecular hydrogen bonded of phenolic O-H bond for compounds 2(A-D) [11]. It also shows a band at (1432-1397cm^{-1}) which is due to the N=N bond [12]. The ^{1}HNMR results of azo compounds 2(A-D) showed singlet peak at δ (8.49-8.59) that could be assigned to the protons of phenolic hydroxyl group. (Figure 2). showed the ^{1}HNMR spectra of compounds 2(A-D). Condensation of azo compounds 2(A-D) with α-ω di Bromo or di Iodo alkane in dry acetone in presence of anhydrous K_2CO_3 give di ethers, series $3(A-D)_n$. The FTIR spectra of compounds $3(A-D)_n$ showed the C-H stretching absorption band near (2919 and 2880cm^{-1}) and C-O-C stretching band, asymmetrical and symmetrical near 1267 cm^{-1} and 1024 cm^{-1} respectively. (Figure 3). showed the ^{1}HNMR spectrum of compound $3(A)_1$ as example for all compounds $3(A-D)_n$. The physical properties and FTIR spectral data of all compounds $3(A-D)_n$ are listed in Table(1).

Table 1: Physical properties and FTIR data of compounds $3(A-D)_n$

Comp. No.	Color	m.p °C	Yield %	υC-H Aliph.	υC-O-C Asym. & sym.
$3(A)_1$	Red	>300	٤٣	2920, 2877	1255, 1051
$3(A)_2$	Dark red	>300	٥٦	2929, 2871	1261, 1044
$3(A)_3$	Dark red	289-291	٤١	2919, 2866	1266, 1053
$3(A)_4$	Red	275-277	٣٩	2932, 2880	1257, 1047
$3(A)_5$	Dark red	281-283	٥٧	2927, 2858	1247, 1049
$3(B)_1$	Brown	>300	٣٣	2937, 2870	1247, 1046
$3(B)_2$	Brown	>300	٤٢	2941, 2866	1251, 1061
$3(B)_3$	Dark brown	>300	٥٢	2936, 2858	1259, 1043
$3(B)_4$	Brown	>300	٥٦	2932, 2867	1244, 1045
$3(B)_5$	Dark brown	285-288	٥٧	2928, 2856	1263, 1074
$3(C)_1$	Brown	>300	٣٧	2921, 2868	1266, 1081
$3(C)_2$	Brown	>300	٤٨	2935, 2855	1259, 1077
$3(C)_3$	Light brown	290-292	٣٣	2924, 2854	1248, 1070
$3(C)_4$	Dark brown	277-280	٣٢	2937, 2862	1242, 1060
$3(C)_5$	Brown	269-271	٤٨	2943, 2871	1249, 1071
$3(D)_1$	Deep orange	>300	٤٢	2929, 2854	1253, 1049
$3(D)_2$	Deep orange	288-289	٤٦	2934, 2859	1261, 1039
$3(D)_3$	Orange	238-240	٥٩	2941, 2844	1267, 1050
$3(D)_4$	Orange	200-202	٣٣	2929, 2852	1257, 1024
$3(D)_5$	Brown	194-197	٥٧	2931, 2857	1263, 1033



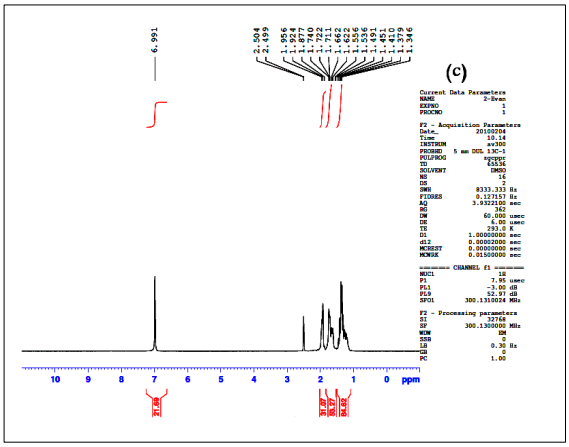


Figure 1: ^{1}HNMR spectra of compounds 1(A) (a), 1(C) (b) and 1(D) (c)

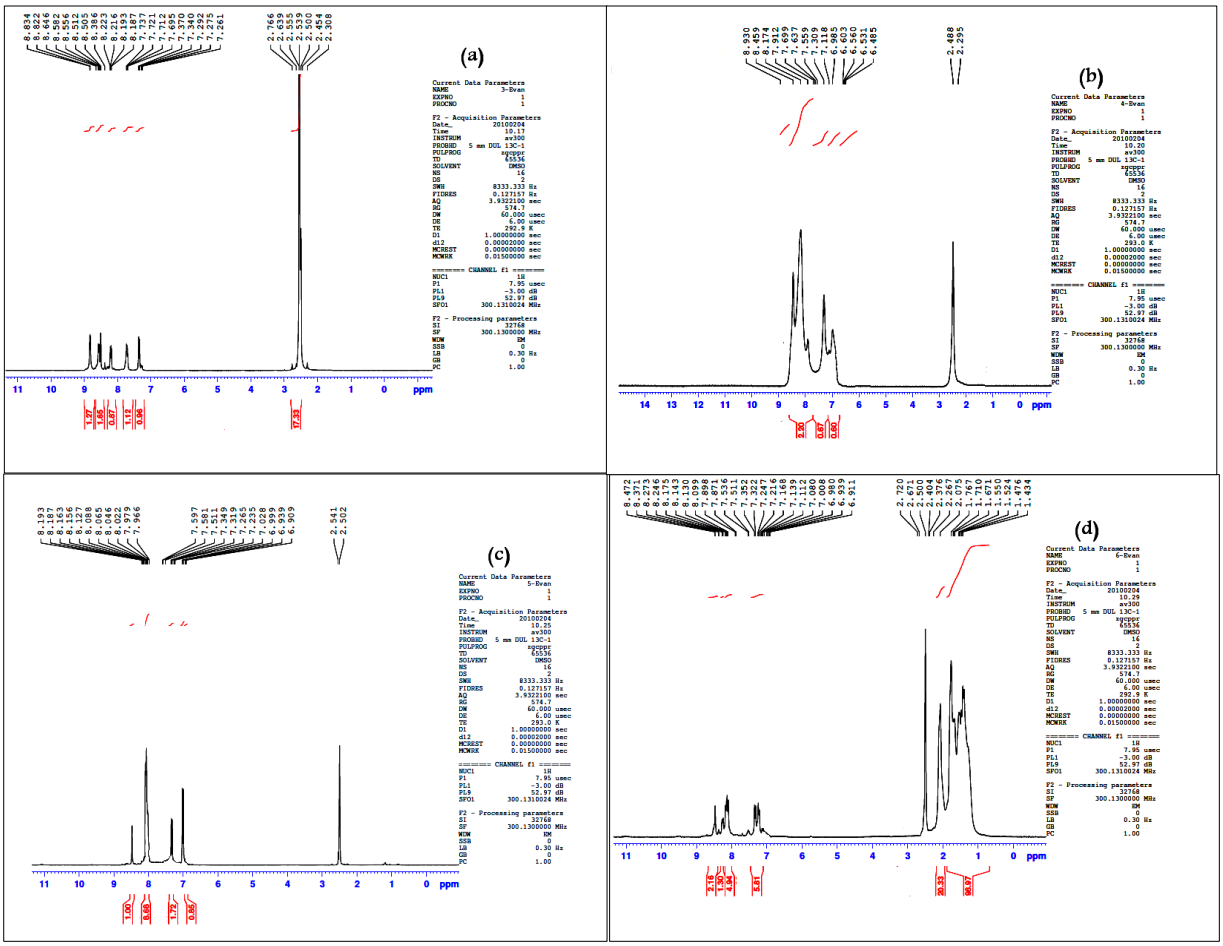


Figure 2: 1HNMR spectra of compounds 2(A) (a), 2(B) (b), 2(C) (c) and 2(D) (d)

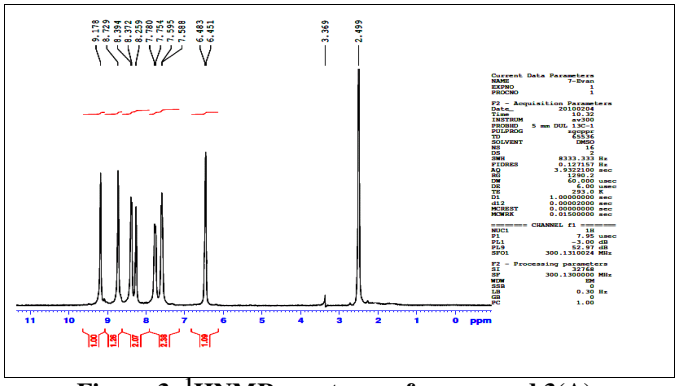


Figure 3: ^{1}HNMR spectrum of compound 3(A)$_1$

Biological Evaluation

All the synthesized compounds 3(A-D)$_n$ have been screened for antibacterial activities using cup-plate agar diffusion method [13] by measuring the inhibition zone in mm. Azthromycin (300 µg/µL) was used as a standard drug for antibacterial activity. The compounds were screened for antibacterial activity against Escherichia *coli*, Klebsiellia *pneumonia*, Pseudomonas *aerugenosa*, Serratia *marscens* 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 sterilized triangular loop. A stainless steel cylinder of 12 mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (300 µg/µL) were placed serially in cavities with the help of micropipette and allowed to diffuse for one hr. DMF was used as a solvent for all compounds (as a stock) then prepared the concentration (300 µg/µL) used sterile distilled water. These plates were incubated at 37°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).

Table 2: Antibacterial activities of compounds 3(A-D)$_n$

Comp. No.	Escherichia *coli*		Klebsiellia *pneumonia*		Pseudomonas *aerugenosa*		Serratia *marscens*		Staphylococcus *aureus*	
	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 (Azthromycin)

From the data of (inhibition zone %) of all compounds 3(A-D)$_n$ in table 2., we observed some important results: the first is 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. *marscens*. From the data of inhibition zone of compounds 3(C)$_n$ against E. *coli* in table 2, we observed that the antibacterial activity of these compounds increase when the chain of alkyl group $(CH_2)_n$ in the central of the molecules increase. The derivative 3(B)$_5$ showed potent activity against E. *coli* (250.00%), whereas compounds 3(A)$_{1-4}$ showed same inhibition and good activity (159.09%) against K. *pneumonia*. Thus, it is concluded from the screening results that the most of 1,3,4-thiadiazole derivatives 3(A-D)$_n$ have good antibacterial activity more than the standard (Azthromycin) against E. *coli*, K. *pneumonia* and S. *aureus* at a concentration of 300 µg/µL.

Experimental

All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on Electrothermal capillary apparatus and are uncorrected. The FTIR spectra were obtained using SHIMADZU model FTIR-8400S. ^{1}HNMR spectra were obtained on BRUKER model Ultra shield 300 MHz spectrophotometer in DMSO-d_6 solution with the TMS as internal standard. Note: in some ^{1}HNMR 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.

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

A mixture of corresponding carboxylic acid (10 mmoles), thiosemicarbazide (0.91 g, 10 mmoles) and phosphorous oxychloride (5mL) 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-Amino-5-(3-pyridyl)-1,3,4-thiadiazole (1A). This compound was obtained as pale yellow powder, yield (69%), mp >300°C; FTIR

(potassium bromide): 3308 and 3168 (NH_2), 1645 (C=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): 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, NH_2).

2-Amino-5-(4-pyridyl)-1,3,4-thiadiazole (1B). This compound was obtained as yellow powder, yield (74%), mp 239-240°C; FTIR (potassium bromide): 3297 and 3123 (NH_2), 1641 (C=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 8.70 (d, 2H, HC=N, pyridine), 7.85 (d, 2H, HC=C, pyridine), 7.75 (s, 2H, NH_2).

2-Amino-5-(4-phenyl)-1,3,4-thiadiazole (1C). This compound was obtained as off white powder, yield (82%), mp 220-222°C; FTIR (potassium bromide): 3320 and 3156 (NH_2), 1631 (C=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 7.47 – 7.78 (m, 5H, Ar-H), 7.43 (s, 2H, NH_2).

2-Amino-5-(4-cyclohexyl)-1,3,4-thiadiazole (1D). This compound was obtained as white powder, yield (91%), mp 238-240°C; FTIR (potassium bromide): 3302 and 3117 (NH_2), 1633 (C=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 6.99 (s, 2H, NH_2), 1.15- 1.99 (m, 11H, cyclohexyl).

General procedure for preparation of 2-(p-hydroxyphenyl-azo)-5-(substituted)-1,3,4-thiadiazole 2(A-D). Compounds 1(A-D) (1.78 mmoles) was dissolved by heating and stirring in (8mL) of 85% phosphoric acid. The solution was cooled to 0°C in an ice bath, and then concentrated nitric acid (4mL) and a solution of sodium nitrite (0.13 g, 1.87 mmoles) in (2mL) 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 mmoles) in (0.5mL) water was added dropwise with stirring. The mixture was poured into cold water (100mL). The precipitate solid was filtered, washed several times with water and recrystallized from ethanol.

2-(p-Hydroxyphenyl-azo)-5-(3-pyridyl)-1,3,4-thiadiazole 2(A). This compound was obtained as dark red powder, yield (71%), mp 246-248°C; FTIR (potassium bromide): 3450 – 3095 (broad O-H group), 1432 (N=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): 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-(p-Hydroxyphenyl-azo)-5-(4-pyridyl)-1,3,4-thiadiazole 2(B). This compound was obtained as dark brown powder, yield (77%), mp >300°C; FTIR (potassium bromide): 3431 – 3083 (broad O-H group), 1425 (N=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): 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-(p-Hydroxyphenyl-azo)-5-(phenyl)-1,3,4-thiadiazole 2(C). This compound was obtained as brown powder, yield (86%), mp 196-198°C; FTIR (potassium bromide): 3553-3112 (broad O-H group), 1417 (N=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): 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-(p-Hydroxyphenyl-azo)-5-(cyclohexyl)-1,3,4-thiadiazole 2(D). This compound was obtained as deep orange powder, yield (71%), mp 118-121°C; FTIR (potassium bromide): 3439-3097 (broad O-H group), 1397 (N=N) cm^{-1}; ^{1}HNMR (DMSO-d_6): 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).

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 of dyes 2(A-D) using the reported method of Vyas and Shah [14]**.** 2-(p-hydroxyphenyl-azo)-5-(substituted)-1,3,4-thiadiazole 2(A-D) (10 mmoles), appropriate 1,n di bromo or di iodo alkane (6 mmoles) and anhydrous potassium carbonate (15 mmoles) were added to dry acetone (10mL). 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 titurated 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 filtaration were finally crystallized using ethanol. The physical properties and FTIR spectral data of all compounds 3(A-D)$_n$ are listed in Table (1).

Methane – bis – α – ω - [2 - (p – alkoxyphenyl) – azo -) – 5 - (3 – pyridyl)] -1,3,4-thiadiazole 3(A)$_1$. ^{1}HNMR (DMSO-d_6): 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, CH_2)

Ethane – bis – α – ω - [2 - (p – alkoxyphenyl) – azo -) – 5 - (4 – pyridyl)] -1,3,4-thiadiazole 3(B)$_2$. ^{1}HNMR (DMSO-d_6): 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, CH_2).

Butane – bis – α – ω - [2 - (p – alkoxyphenyl) – azo -) – 5 - (phenyl)] -1,3,4-thiadiazole 3(C)$_4$. ^{1}HNMR (DMSO-d_6): 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, $OC\underline{H}_2CH_2$), 2.12 (m, 4H, $OCH_2C\underline{H}_2$).

Propane – bis – α – ω - [2 - (p – alkoxyphenyl) – azo -) – 5 - (cyclohexyl)] -1,3,4-thiadiazole 3(D)$_3$. ^{1}HNMR (DMSO-d_6): δ 8.21 (d, 4H, Ar-H), 7.34 (d, 4H, Ar-H), 4.21 (t, 4H, $OC\underline{H}_2$) 2.32- 1.09 (m, 24H, cyclohexyl and $OCH_2C\underline{H}_2CH_2O$).

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