RESEARCH ARTICLE

Synthesis, Characterization and Antimicrobial Evaluation of Some New Azo Compounds Derived from 1, 3, 4-thiadiazole Ring

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ABSTRACT

New 1, 3, 4-Thiadiazole derivatives containing azo group were synthesized by the reaction of 1, 3, and 4-Thiadiazole derivatives prepared from benzoic acid thio-semicarbazide to give various derivatives of 1,3,4-Thiadiazole derivatives. The resulting compounds reacted with 1,2-dibromomethane in the presence of K_2CO_3 and acetone as solvent produce compounds. These compounds were characterized by melting point, Fourier-transform infrared (FT-IR), proton nuclear magnetic resonance (^{1}H-NMR) and Carbon-13 nuclear magnetic resonance (^{13}C-NMR) and evaluated their antibacterial activity *in-vitro* against four types of bacteria isolates two gram-negative (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and two gram-positive (*Escherichia coli* and *Pseudomonas aeruginosa*). Indeed, the synthesized compounds showed moderate to good activity against these types of bacteria.

Keywords: 1, 3, 4-thiadiazole, Antibacterial, Azo.

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INTRODUCTION

The first discovery of 1, 3, 4-Thidiazole was by Emil Fischer in 1882.[1] Thiadiazole is an aromatic five-membered heterocyclic ring, containing three heteroatoms sulfur atom and two nitrogen.[2] 1,3,4-Thiadiazole and their derivatives have various applications such as drugs, agriculture, photographic materials, dyes, etc.[3] In the last years, several types of research have been reported to synthesize novel derivatives of 1, 3, 4-thiadiazole for investigated their activity as antimicrobial agents.[4-10] The nucleus of the 1,3,4-thiadiazole and their derivatives have been infused, which offers antimicrobial activities is very important heterocyclic nuclei in medicinal.[11] Therefore, 3, 4-Thiadiazole and their derivatives have an important and wide range of biological activity in the pharmaceutical industry such as antibacterial, [12] anticancer, [13] anti-HIV, [14] antiviral, [15] anti-tubercular, [16] anti-inflammatory.[17] Looking at the importance and relevance of the 1, 3, 4-thiadiazol nucleus, we thought that we designed and synthesized some novel azo compounds containing bis-1, 3, 4-thiadiazole ring derived from benzoic acid derivatives in the same molecules moiety and screened them for possible antibacterial activity would be useful.

MATERIAL AND METHODS

Experimental

Pure starting materials from BDH and sigma were used for the preparation of synthesized compounds. All chemicals, solvents, and reagents were of synthetic grade and were buy it commercially, Stuart-SMP3 electronic system was used to measure melting points, the FT-IR spectrum was recorded by SHIMADZU (FT-IR 8400S), while Bruker (400 MHz) used for recorded ^{1}H and ^{13}C-NMR spectrums, DMSO-d_6 as a solvent and transcranial magnetic stimulation (TMS) as a reference, total leukocyte count (TLC) technique was used to ensure of completion of the reaction, the spots were visualized by using UV Cabinet for TLC.

Synthesis of Compounds (1-5) a

10 mmol, 5 mL of $POCl_3$ was added thoroughly and carefully to a mixture of 10 mmol from benzoic acid derivatives and (0.91 g, 10 mmol) from thio-semicarbazide, refluxed for 3 hours. After cooling down, the reaction mixture (25 mL) of distilling water was added dropwise and carefully with stirring and refluxed for 4 hours. The mixture cooled down and then neutralized with potassium hydroxide solution, and the obtained precipitate was filtered and washed with distilled water several times and dried. The product was recrystallized form ethanol. The completion of the reaction and purity of the obtained product was tested by TLC mobile phase (hexane: ethyl acetate) (7:3) percentage (V: V).

5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-amine (1a)

Pale beige, yield 89%, mp 215-217^{o}C, FTIR (cm^{-1}) 3272 and 3197 (NH_2), 3089(C-H, aromatic), 1633(C=N), 1581 and 1475 (C=C, aromatic).

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5-(4-bromophenyl)-1, 3, 4-thiadiazol-2-amine (2a)

White, yield 81%, mp 174–176°C, FTIR (cm^{-1}) 3277 and 3159 (NH_2), 3035 (C-H, aromatic), 1639(C=N), 1571 and 1460 (C=C, aromatic).

5-(3-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (3a)

Yellow, yield 89%, mp 234–236°C, FTIR (cm^{-1}) 3379 and 3280 (NH_2), 3074 (C-H, aromatic), 1620 (C=N), 1579 and 1423, 1531 and 1348 (NO_2), (C=C, aromatic).

5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (4a)

Yellow, yield 82%, mp 244–246°C, FTIR (cm^{-1}) 3377 and 3294 (NH_2), 3069(C-H, aromatic), 1620(C=N), 1604 and 1440, 1508 and 1342 (NO_2), (C=C, aromatic).

5-(3, 5-dinitrophenyl)-1, 3, 4-thiadiazol-2-amine (5a):

Dark yellow, yield 85%, mp 265–267°C, FTIR (cm^{-1}) 3360 and 3251 (NH_2), 3097 (C-H, aromatic), 1627(C=N), 1535 and 1350 (NO_2), 1593 and 1435 (C=C, aromatic).

Synthesis of Compounds (1-5) b

A 1.78 mmol from compounds (1a-5a) was dissolved in (8 mL) of 85% H_3PO_4 by heating with stirring. The solution was left to cool to 0°C at ice bath. A mixture of (1.87 mmol, 0.13 g in 2 mL of H_2O) sodium nitrate and 4 mL of conc. HNO_3 was added to the solution with vigorously stirring and kept temperature below 5°C during 10 minutes. Then a solution of β-naphthol (1.78 mmol, 0.17 g in 2 mL of ethanol) was added drop by drop with stirring. The mixture was poured onto (100 mL) of ice water. The obtained precipitate was filtered, and washed with cold water several times, and dried. The product was recrystallized from ethanol. The completion of the reaction and purity of the obtained product was tested by TLC mobile phase (hexane: ethyl acetate) 6:4% (V:V).

1-((5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol(1b)

Pale brow, yield 75%, mp 195–197°C, FTIR (cm^{-1}) 3421 (O-H), 3086 (Ar-CH), 1625 (C=N), 1496 (N=N), 1589 and 1433 (Ar, C=C); ^{1}H-NMR (DMSO- d6, 400MHz) 7.27- 8.41 (m, 10H, Ar), 9.07 (s, 1H, OH), ^{13}C-NMR (DMSO- d6, 125MHz) 114.53-151.79 (Ar-rings), 165.91 (C-OH), 179.58 and 164.36 (1, 3, 4-thiadiazole, C=N).

1-((5-(4-bromophenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol (2b)

Dark brown, yield 85%, mp 143–145°C, FTIR (cm^{-1}) 3394 (O-H), 3078 (Ar-CH), 1624 (C=N), 1500 (N=N), 7.01 and 8.41 (Ar, C=C). ^{1}H-NMR (DMSO- d6, 400MHz) 7.01- 8.41 (m, 10H, Ar), 9.83 (s, 1H, OH), ^{13}C-NMR (DMSO- d6, 125MHz) 125.84-137.25 (Ar-rings), 168.28 (C-OH), 177.08 and 162.02 (1, 3, 4-thiadiazole, C=N).

1-((5-(3-nitrophenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol (3b)

Red, yield 80%, mp 164–166°C, mp 253–255°C, FTIR (cm^{-1}) 3450 (O-H), 3066 (Ar-CH), 1627 (C=N), 1525 (N=N), 1591 and 1452 (Ar, C=C). ^{1}H-NMR (DMSO- d6, 400MHz) 7.02-8.13 (m, 10H, Ar), 8.47 (s, 1H, OH), ^{13}C-NMR (DMSO- d6, 125MHz) 126.71-139.45 (Ar-rings), 164.33 (C-OH), 179.56 and 142.27 (1, 3, 4-thiadiazole, C=N).

1-((5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol (4b)

Red, yield 88%, mp >300°C, FTIR (cm^{-1}) 3448 (O-H), 3066 (Ar-CH), 1625 (C=N), 1502 (N=N), 1597 and 1435 (Ar, C=C); ^{1}H-NMR (DMSO- d6, 400MHz) 7.00-8.07 (m, 10H, Ar), 8.47 (s, 1H, OH), ^{13}C-NMR (DMSO- d6, 125 MHz) 116.71-144.64 (Ar-rings), 166.24 (C-OH), 164.27 and 179.33 (1, 3, 4-thiadiazole, C=N).

1-((5-(3, 5-dinitrophenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol (5b)

Dark brown, yield 81%, mp 118–120°C, FTIR (cm^{-1}) 3356 (O-H), 3093 (Ar-CH), 1624 (C=N), 1492 (N=N), 1593 and 1492 (Ar, C=C); ^{1}H-NMR (DMSO- d6, 400MHz) 7.15-8.07 (m, 9H, Ar), 8.72 (s, 1H, OH), ^{13}C-NMR (DMSO- d6, 125MHz) 112.12-154.49 (Ar-rings), 160.46 (C-OH), 177.22 and 157, 11 (1, 3, 4-thiadiazole, C=N).

Synthesis of Compounds (1-5) c

They were synthesized by alkylation of dyes (a-c) using the reported method of Vyas and Shah.[18] A mixture 10 mmoles of compounds (1-5)b, 1, 2-dibromoethane (6 mmoles), and anhydrous potassium carbonate (15 mmoles) were added to dry acetone (10 mL). The reaction mixture was refluxed on a water bath for 24 hours. 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 minutes to remove unreacted azo dyes and was washed with water several times. The products obtained after filtration were finally crystallized using ethanol. The completion of the reaction and purity of the obtained product was evaluated by TLC mobile phase (hexane: ethyl acetate) (6:4) percentage (V: V).

1, 2-bis((1-((5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-yl) diazenyl)naphthalen-2-yl)oxy)ethane (1c)

Dark brown, yield 65%, mp 188-190°C, FTIR (cm^{-1}) 3059 (Ar-CH), 2947 and 2889 (aliph-CH), 1620(C=N), 1504(N=N), 1593 and 1469 (Ar, C=C), 1246 and 1076 (C-O-C); ^{1}H-NMR (DMSO-d6, 400MHz) 3.45 (s, 4H, CH_2), 7.41–7.90 (m, 20H, Ar); ^{13}C-NMR (DMSO-d6, 125MHz) 45.04 (CH_2), 114.53–144. 65 (Ar-rings), 165.91 (C-O), 164.36, and 179.58 (1, 3, 4-thiadiazole, C=N).

1, 2-bis((1-((5-(4-bromophenyl)-1, 3, 4-thiadiazol-2-yl) diazenyl)naphthalen-2-yl)oxy)ethane (2c)

Dark brown, yield 44%, mp 173-175°C, FTIR (cm^{-1}) 3082(Ar-CH), 2962 and 2889 (aliph-CH), 1616(C=N), 1500(N=N), 1589 and 1438 (Ar, C=C), 1246 and 1072 (C-O-C); ^{1}H-NMR (DMSO- d6, 400MHz) 3.38 (s, 4H, CH_2), 7.36-7.96 (m, 20H, Ar); ^{13}C-NMR (DMSO- d6, 125MHz) 64.33 (CH_2), 111.27-161.32 (Ar-rings), 166.11 (C-O), 131.57and 169.54 (1, 3, 4-thiadiazole, C=N).

1,2-bis((1-((5-(3-nitrophenyl)-1,3,4-thiadiazol-2-yl) diazenyl)naphthalen-2-yl)oxy)ethane (3c)

Dark brown, yield 70%, mp 248-250°C, FTIR (cm^{-1}) 3074 (Ar-CH), 2962 and 2858(aliph-CH), 1620(C=N), 1496 (N=N), 1593 and 1454 (Ar, C=C), 1246 and 1091 (C-O-C); ^{1}H-NMR (DMSO- d6, 400MHz) 3.40 (s, 4H, CH_2), 7.13–8.69 (m, 20H, Ar); ^{13}C-NMR (DMSO- d6, 125MHz) 62.88 (CH_2), 114.18-142.34(Ar-rings), 163.69(C-O), 155. 36and 175.94 (1,3,4-thiadiazole, C=N).

1,2-bis((1-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl) diazenyl)naphthalen-2-yl)oxy)ethane (4c)

Dark brown, yield 79%, mp 239-241°C, FTIR (cm^{-1}) 3070 (Ar-CH), 2939 and 2854 (aliph-CH), 1608(C=N), 1516 (N=N), 1585 and 1438 (Ar, C=C), 1249 and 1095 (C-O-C); ^{1}H-NMR (DMSO- d6, 400MHz) 3.31 (s, 4H, CH_2), 7.19 –8.30 (m, 20H, Ar); ^{13}C-NMR (DMSO- d6, 125MHz) 60.77 (CH_2), 116.05-148.14 (Ar-rings), 173.60 (C-O), 161.73 and 181.87 (1, 3, 4-thiadiazole, C=N).

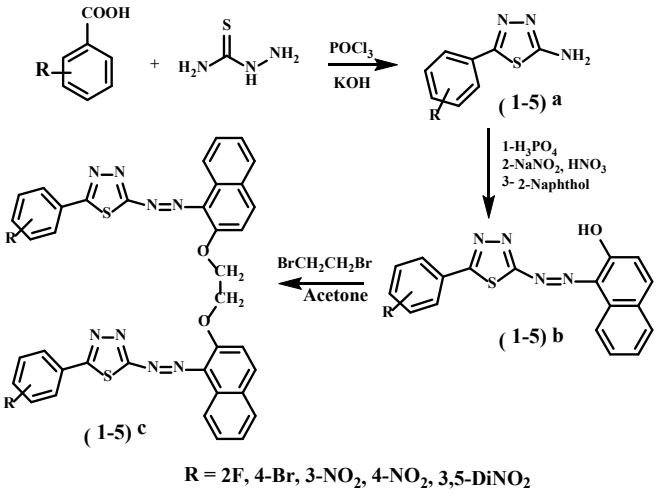
12-bis((1-((5-(3, 5-dinitrophenyl)-1, 3, 4-thiadiazol-2-yl) diazenyl)naphthalen-2-yl)oxy)ethane (5c)

Dark brown, yield 64%, mp 273-275°C, FTIR (cm^{-1}) 3089 (Ar-CH), 2939 and 2877(aliph-CH), 1608(C=N), 1500(N=N), 1543, 1454 (Ar, C=C), 1257 and 1083 (C-O-C); ^{1}H-NMR (DMSO-d6, 400MHz) 3.39 (s, 4H, CH_2), 7.25–9.13 (m, 18H, Ar); ^{13}C-NMR (DMSO- d6, 125MHz) 45.04 (CH_2), 115.31-152.77(Ar-rings), 169.66(C-O), 155.64 and 184.10 (1, 3, 4-thiadiazole, C=N).

RESULTS AND DISCUSSION

Experimental

The reaction steps for various title compounds were shown in Scheme 1, the starting material. Some derivatives compounds of 2-amino-5-(substituted-phenyl)-1,3,4-thiadiazole (1-5) a were prepared from the reaction of benzoic acid derivatives with thiosemicarbazide in presence of $POCl_3$.[19-21] FT-IR for these compounds showed two bands of stretching of NH_2 between (3391-3170) cm^{-1} and the stretching of C=N in (1614-1639) cm^{-1}.



Scheme 1: Synthesis of 1, 3, 4-Thiadiazole derivatives

1-((5-(substituted-phenyl)-1, 3, 4-thiadiazol-2-yl)diazenyl) naphthalen-2-ol (1-5)b derivatives were prepared by the reaction of 1,3,4-thiadiazole derivatives (1-5)a with H_3PO_4, HNO_3, $NaNO_2$ and β-naphthol by using ethanol as a solvent. All of these compounds showed hidden of stretch of N-H of NH_2 group of 1,3,4-Thiadiazole and showed broad band due to stretching of O-H (3450–3356 cm^{-1}), and stretching of N=N in range (1490-1525 cm^{-1})[22,23] showed the ^{1}H-NMR spectrum of compound number of peaks between δ (7.00–8.45), referred to aromatic protons and singlet peak between δ (9.83–8.47) accounted to OH, Condensation of azo compounds (1-5)b with 1, 2-dibromo in dry acetone in the presence of anhydrous K_2CO_3 gave di ethers.[18] The structure of compounds (1-5)c was identified by FT-IR, ^{1}H and ^{13}C-NMR.

Table 1: Physical characteristic of synthesized compounds.

No.	*R*	*Formula*	*M.wt*	*Color*	*M.P (°C)*	*Yield %*	R_f
1A	2-F	C8H6FN3S	195.22	Pale beige	215–217	89	0.52
2A	4-Br	C8H6BrN3S	256.13	White	174–176	81	0.51
3A	3-NO_2	C8H6N4O2S	222.23	Yellow	234–236	89	0.55
4A	4- NO_2	C8H6N4O2S	222.23	Yellow	244–246	82	0.45
5A	3, 5-di NO_2	C8H5N5O4S	267.23	Dark yellow	265–267	85	0.62
1B	2-F	$C_{38}H_{24}F_2N_8O_2S_2$	726.78	Dark red	188–190	65	0.56
2B	2-Br	$C_{38}H_{24}Br_2N_8O_2S_2$	848.59	Brown	173–175	44	0.61
3B	3-NO_2	$C_{38}H_{24}N_{10}O_6S_2$	780.79	Dark red	248–250	70	0.66
4B	4-NO_2	$C_{38}H_{24}N_{10}O_6S_2$	780.79	Dark brown	239–241	79	0.46
5B	3, 5-di NO_2	$C_{38}H_{22}N_{12}O_{10}S_2$	870.79	Dark brown	273–275	64	0.48
1C	2-F	C18H11FN4OS	350.37	Pale brow	219–221	75	0.60
2C	2-Br	C18H11BrN4OS	411.28	Dark brown	143–145	85	0.55
3C	3- NO_2	C18H11N5O3S	377.38	Red	164–166	80	0.45
4C	4-NO_2	C18H11N5O2S	377.38	Red	>300	88	0.48
5C	3, 5-di NO_2	C14H10N6O5S	422.38	Dark brown	118–120	81	0.40

Table 2: Antibacterial activity of synthesized compounds

Comp. No.	*Concentration mg/mL*	*Zone of inhibition (in mm)*			
		Gram-positive		*Gram-negative*	
		S. aureus	*S. epidermidis*	*P. aeruginosa*	*E. coli*
1C	100	23	24	0	26
	50	23	22	28	0
	25	23	19	15	-
	12.5	24	22	11	-
2C	100	24	24	-	25
	50	24	23	14	-
	25	24	20	13	-
	12.5	22	22	-	-
3C	100	23	23	-	29
	50	23	22	15	-
	25	22	22	13	-
	12.5	20	20	-	-
4C	100	23	23	-	29
	50	23	22	15	-
	25	22	22	13	-
	12.5	20	20	-	-
5C	100	23	28		
	50	23	24		
	25	22	22	11	-
	12.5	20	22	-	-
Clarithromycin	15	12	13	-	-
Ceftazidime	30	-	-	17	-
Ceftriaxone	30	-	-	-	12
Amikacin	30	18	21	-	-
Azetronam	30			-	12
Chloramphenicol	30	-	-	-	-
DMSO	-	-	-	-	-

The FTIR spectra of compounds (1-5)c showed the C–H stretching absorption band near (2980 and 2890 cm^{-1}) and C–O–C stretching band, asymmetrical and symmetrical near 1280 cm^{-1} and 1095 cm^{-1}, respectively.[24] shows the ^{1}H-NMR spectrum of compound singlet peak between δ (3.45-3.31) accounted to CH_2 and and number of peaks between δ (7.41-9.13) referred to aromatic protons, The physical properties of all compounds are listed in Table 1.

Antibacterial Activity

The treatment of infectious diseases is a major challenge due to several variables, including bacterial antibiotic resistance. The plant's biological impact the produced chemical was tested against Ge^{-ve} and Ge^{+ve} bacteria isolates. The listed results in table 2 showed the study of the antibacterial activity of some synthesized compounds in four concentrations (100, 50, 25, 12.5) mg/mL. They showed moderate to good activity as the antibacterial agents compared with standard antibiotic Ceftazidime, Ceftriaxone, Clarithromycin, Amikacin, Chloramphenicol, Azetronam. The antibacterial activity of the synthesized compounds was tested against two types of Ge^{+ve} bacteria isolates (*S. aureus* and *S. epidermidis*) and two types of Ge^{-ve} bacteria isolates (*P. aeruginosa* and *E. coli*). According to Table 2 all analogs showed good activity against (*S. aureus* and *S. epidermidis*) and the most active compounds were 2c, 3c, 4c, and 5c. While all analogs showed medium activity and, in some concentrations, did not show any activity against *P. aeruginosa* due to position and type of substituted group. All analogs especially 3c, 4c and 5c showed good activity and, in some concentrations, did not show any activity against *E. coli* due to position and type of substituted group.

CONCLUSION

In the present work, five target derivatives of azo compounds containing 1, 3, and 4-thiadiazole rings have been synthesized. All analogs were characterized through spectroscopic

techniques like FTIR, ^{1}H and ^{13}C NMR. All analogs have been evaluated for antibacterial activity against four types of bacteria and showed moderate to good activity against (*S. aureus* and *S. epidermidis*) and (*P.aeruginosa and E. coli*).

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