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Synthesis, Characterization and Biological Screening of Oxadiazole Incorporated Acetamide Derivatives as Potent Antibacterial Agents

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ABSTRACT: A series of ten derivatives of 2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]-*N*-(2,4,6-tribromophenyl) acetamide was synthesized and the structure of synthesized compounds were determined by obtained IR, ^{1}H NMR and Mass spectroscopy data. To evaluate biological potential of synthesized compounds they were subjected for *invitro* antibacterial study against gram positive bacterial strains *Staphylococcus aureus, Bacillus subtilis* and gram negative bacterial strains *Pseudomonas aeruginosa, Escherichia coli* where antibacterial potential was shown by some compounds.

Keywords: 2,4,6-tribromo aniline; oxadiazole; acetamide and antibacterial study.

INTRODUCTION: The attraction of researchers in heterocyclic chemistry has expanded the boundaries of literature in the field with novel molecules having broad spectrum of biological activeness. Oxadiazole is one of the important class of heterocyclic chemistry with four possible isomers. Amongst these isomers an important isomer which have attracted researchers due to its biological activeness is 1,3,4-oxadiazole. The various biological potential of this 1,3,4-oxadiazole nucleus has gave numbers of compounds having potential as antimicrobial[1-6], anticancer[7-9], anti-HIV[10], anti-inflammatory[11-12], analgesic[13], antitubercular[14-16], antioxidant[17-19], antitumor[20], anticonvulsant[21], antidiabetic[22], antiviral[23] etc. The presence of 1,3,4-oxadiazole nucleus is found in many therapeutic agents like Furamizole, Raltegravir, Nesapidil etc.[24]

MATERIAL AND METHODS: All the synthesized compounds were prepared using analytical and laboratory grade chemicals. To monitor the reaction progress and purity of compounds a TLC technique was selected in which silica gel coated aluminium plates (E-Merk) and suitable eluents were used. The melting points of synthesized compounds were observed through open capillary method and they are uncorrected. The structure determination was achieved by various spectroscopy analyses where IR spectra was obtained with KBr and recorded on Perkin-Elmer 237 spectrophotometer. Mass spectra was recorded on M S route JMS 600-H and PMR analysis was carried out on Bruker AM -400 instrument using DMSO as solvent and TMS as internal standards.

General Reaction Scheme for Preparation of 2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]-*N*-(2,4,6-tribromophenyl)acetamide:

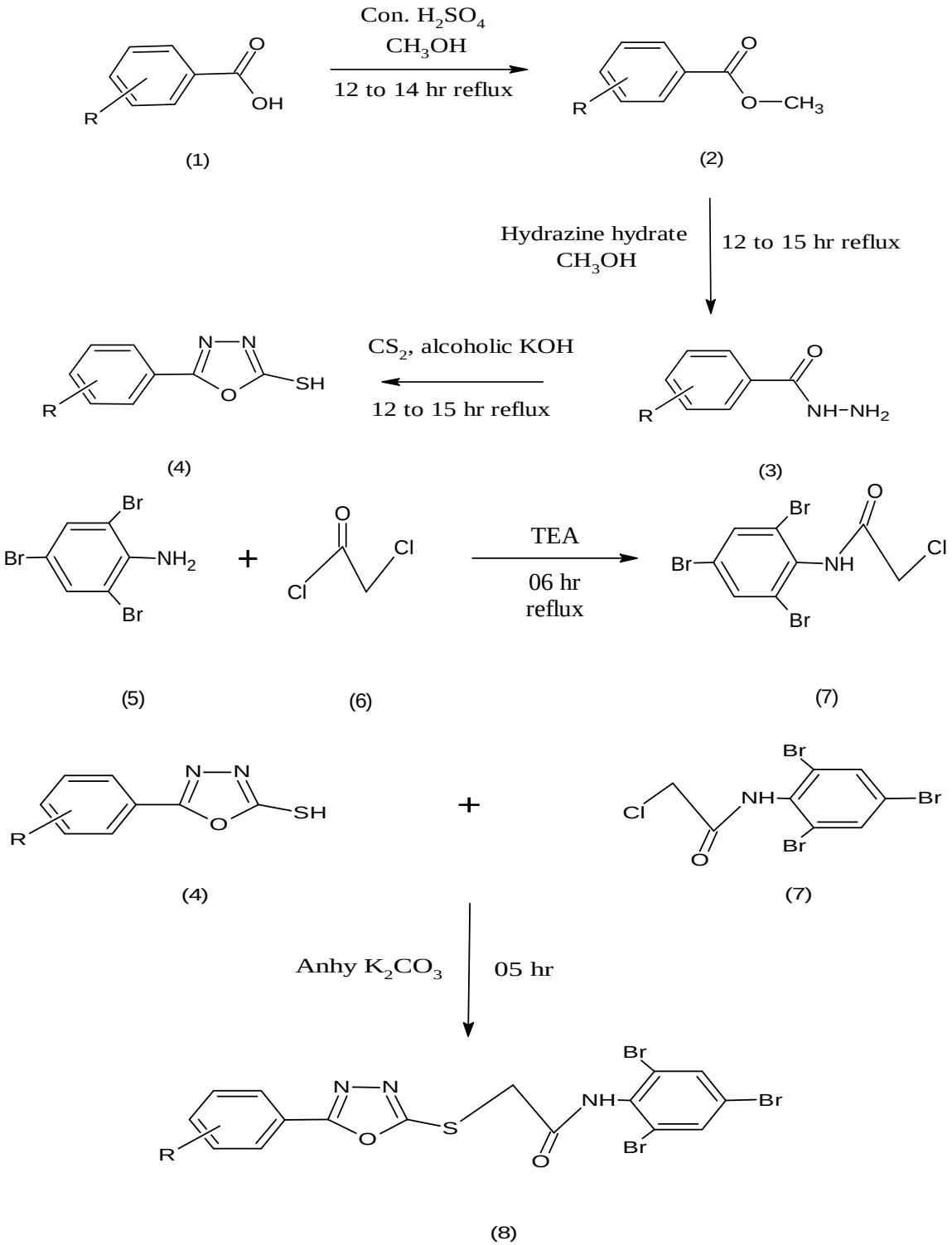
Step I: Synthesis of aryl enoate (2): In this step various substituted aromatic acid (0.1 mol) and concentrated H_2SO_4 (6.0 ml) were taken in methanol and refluxed for 12 to 14 hour. The resulting reaction mass was then poured into crushed ice, stirred well and products were separated from reaction mass. The purification of products were carried out in ethyl alcohol. A mixture of toluene: acetone (8:2) was used as eluent to check the progress of reaction by TLC method.

Step II: Synthesis of aryl hydrazide (3): In the synthesis of various substituted benzohydrazide, the mixture of aryl enoate (0.1 mol) and hydrazine hydrate (0.2 mol) were taken in (180 ml) methyl alcohol and refluxed for 12 to 15 hour, the reaction mass was then cooled, poured into crushed ice, stirred well and products were isolated from reaction mass. The products were recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC method with toluene: acetone (8:2) as eluent.

Step III: Synthesis of 5-aryl-1,3,4-oxadiazole-2-thiol (4): To synthesize 5-aryl-1,3,4-oxadiazole-2-thiol, the

mixture of aryl hydrazide (0.1 mol), CS_2 (0.1 mol) and alcoholic KOH (0.05 mol) were refluxed in methyl alcohol (120 ml) for 12 to 15 hour. The resulting mass was poured into crushed ice and 2N HCl was used to neutralise the mass. The mass was then filtered and washed by cold water to isolate the products. The products were recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent.

Reaction Scheme



Where R = (a) 4-F, (b) 2-CH_3, (c) 4-Br, (d) 3-NO_2, (e) 2-Cl, (f) 2-NO_2, (g) 3,4,5-OCH_3, (h) 4-CH_3, (i) 4-Cl, (j) 4-NO_2

Step IV: Synthesis of 2-chloro-N-(2,4,6-tribromophenyl)acetamide (7): The mixture of chloro acetyl chloride (0.1 mol), 2-4 drops of TEA and 2,4,6,-tri bromo aniline (0.1 mol) was taken in (150 ml) toluene, the reaction mass was then refluxed for 06 hour. The product was then isolated from reaction mixture and washed. The product was recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent.

Step V: 2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]-N-(2,4,6-tribromophenyl)acetamide (8): The mixture of 5-aryl-1,3,4-oxadiazole-2-thiol (0.1 mol), 2-chloro-*N*-(2,4,6-tribromophenyl)acetamide (0.1 mol) and anhydrous K_2CO_3 (0.2 mol) were taken in dry acetone (70 ml) and stirred for 05 hour. The reaction mixture was then poured into crushed ice, stirred well, filtered and washed by cold water. The products were recrystallized by ethyl alcohol. The progress of reaction was monitored by TLC method using toluene: acetone (8:2) as eluent.

RESULTS AND DISCUSSION:

Characterization:

8a: 2-{[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6- tribromophenyl)acetamide Yield 69%, m.p. 190-192˚ C, FT-IR (KBr): 1186 (C-O-C), 1367 (C-F), 1479 (-C=C-), 1608 (-C=N), 1674 (-C=O), 3007, (-CH_2-), 3228 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.36 (s, 2H, -CH_2-), δ 7.45-7.48 (m. 2H, Ar-H), δ 8.01 (m, 2H, Ar-H), δ 8.04-8.07 (m, 2H, Ar-H), δ 10.45 (s, 1H, -NH-); MS: m/z 568, Anal. Calcd for $C_{16}H_9Br_3FN_3O_2S$: C-33.95, H-1.60, N-7.42, S-5.66 Anal. Found C-33.91, H-1.58, N-7.38, S-5.64%.

8b: 2-{[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 60%, m.p. 170-172˚ C, FT-IR (KBr): 1289 (C-O-C), 1467 (-C=C-), 1659 (-C=N), 1691 (-C=O), 2844 (-CH_2-), 3283 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3) δ 4.64 (s, 2H, -CH_2-), δ 7.48-7.52 (m. 2H, Ar-H), δ 7.76-7.78 (m, 2H, Ar-H), δ 7.99-8.03 (m, 2H, Ar-H), δ 10.32 (s, 1H, -NH-); MS : m/z 564, Anal. Calcd for $C_{17}H_{12}Br_3N_3O_2S$: C-36.33, H-2.15, N-7.48, S-5.70 Anal. Found C-36.30, H-2.14, N-7.46, S-5.69%.

8c: 2-{[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 69%, m.p. 163-165˚ C, FT-IR (KBr): 581 (C-Br),1160 (C-O-C), 1456 (-C=C-), 1619 (-C=N), 1682 (-C=O), 2897, (-CH_2-), 3253 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.48 (s, 2H, -CH_2-), δ 7.26-7.30 (m. 2H, Ar-H), δ 7.73 (m, 2H, Ar-H), δ 7.92-7.96(m, 2H, Ar-H), δ 10.37 (s, 1H, -NH-); MS: m/z 628, Anal. Calcd for $C_{16}H_9Br_4N_3O_2S$: C-30.65, H-1.45, N-6.70, S-5.11 Anal. Found C-30.63, H-1.43, N-6.66, S-5.07%.

8d: 2-{[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 64%, m.p. 198-200 ˚ C, FT-IR (KBr): 1248 (C-O-C), 1462 (-C=C-), 1622 (-C=N), 1698 (-C=O), 2883, (-CH_2-), 3256 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.91 (s, 2H, -CH_2-), δ 7.56-7.60 (m. 2H, Ar-H), δ 7.82-7.84 (m, 2H, Ar-H), δ 8.03-8.07(m, 2H, Ar-H), δ 10.48 (s, 1H,-NH-); MS: m/z 595, Anal. Calcd for $C_{16}H_9Br_3N_4O_4S$: C-32.41, H-1.53, N-9.45, S-5.41 Anal. Found C-32.43, H-1.54, N-9.42, S-5.40%.

8e: 2-{[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 65%, m.p. 212-214˚ C, FT-IR (KBr) : 657 (C-Cl), 1198 (C-O-C), 1482 (-C=C-), 1624 (-C=N), 1691 (-C=O), 2906, (-CH_2-), 3226 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.28 (s, 2H, -CH_2-), δ 7.28-7.32 (m. 2H, Ar-H), δ 7.57 (m, 2H, Ar-H), δ 7.89-7.93 (m, 2H, Ar-H), δ 10.29 (s, 1H,-NH-); MS: m/z 584, Anal. Calcd for $C_{16}H_9Br_3ClN_3O_2S$: C-32.99, H-1.56, N-7.21, S-5.50 Anal. Found C-32.95, H-1.54, N-7.17, S-5.48%.

8f: 2-{[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 60%, m.p. 168-170 ˚ C, FT-IR (KBr): 1186 (C-O-C), 1473 (-C=C-), 1641 (-C=N), 1681 (-C=O), 2856 (-CH_2-), 3229 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 4.82 (s, 2H, -CH_2-), δ 7.43-7.47 (m. 2H, Ar-H), δ 7.69 (m, 2H, Ar-H), δ 7.91-7.95 (m, 2H, Ar-H), δ 10.34 (s, 1H,-NH-); MS: m/z 595, Anal. Calcd for $C_{16}H_9Br_3N_4O_4S$: C-32.41, H-1.53, N-9.45, S-5.41 Anal. Found C-32.38, H-1.52, N-9.44, S-5.38%.

8g: *N*-(2,4,6-tribromophenyl)-2-{[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide; Yield 72%, m.p. 219-221˚ C, FT-IR (KBr): 1080(C-O-C alkanyl), 1216 (C-O-C), 1471 (-C=C-), 1607 (-C=N), 1683 (-C=O), 2872 (-CH_2-), 3257 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 3.19 (s, 6H, -OCH_3), δ 3.36 (s, 3H, -OCH_3), δ 4.60 (s, 2H, -CH_2-), δ 7.54-7.58 (m. 2H, Ar-H), δ 7.88-7.90 (m, 2H, Ar-H), δ 10.19 (s, 1H, -NH-); MS : m/z 640, Anal. Calcd for $C_{19}H_{16}Br_3N_3O_5S$: C-35.76, H-2.53, N-6.59, S-5.02 Anal. Found C-35.72, H-2.51, N-6.57, S-4.99%.

8h: 2-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 71%, m.p. 196-198˚ C, FT-IR (KBr): 1238 (C-O-C), 1492 (-C=C-), 1632 (-C=N), 1697 (-C=O), 2856 (-CH_2-), 3208 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ

2.24(s, 3H, -CH_3) δ 4.70 (s, 2H, -CH_2-), δ 7.69-7.73 (m. 2H, Ar-H), δ 7.86 (m, 2H, Ar-H), δ 8.13-8.17(m, 2H, Ar-H), δ10.46 (s, 1H, -NH-); MS : m/z 564, Anal. Calcd for $C_{17}H_{12}Br_3N_3O_2S$: C-36.33, H-2.15, N-7.48, S-5.70 Anal. Found C-36.31, H-2.12, N-7.45, S-5.67%.

8i: 2-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide; Yield 72%, m.p. 244-246 ˚ C, FT-IR (KBr): 681 (C-Cl),1181 (C-O-C), 1467 (-C=C-), 1601 (-C=N), 1667 (-C=O), 2987, (-CH_2-), 3231 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.31 (s, 2H, -CH_2-), δ 7.39-7.43 (m. 2H, Ar-H), δ 7.85-7.87 (m, 2H, Ar-H), δ 8.00-8.04 (m, 2H, Ar-H), δ 10.37 (s,1H,-NH-); MS: m/z 584, Anal. Calcd for $C_{16}H_9Br_3ClN_3O_2S$: C-32.99, H-1.56, N-7.21, S-5.50 Anal. Found C-32.97, H-1.53, N-7.19, S-5.46%.

8j: 2-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(2,4,6-tribromophenyl)acetamide Yield 71%, m.p. 214-216˚ C, FT-IR (KBr): 1151 (C-O-C), 1448 (-C=C-), 1610 (-C=N), 1675 (-C=O), 2851, (-CH_2-), 3230 (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.29 (s, 2H, -CH_2-), δ 7.30-7.34 (m. 2H, Ar-H), δ 7.61 (m, 2H, Ar-H), δ 7.85-7.89 (m, 2H, Ar-H), δ 10.39 (s, 1H, -NH-); MS: m/z 595, Anal. Calcd for $C_{16}H_9Br_3N_4O_4S$: C-32.41, H-1.53, N-9.45, S-5.41 Anal. Found C-32.38, H-1.49, N-9.43, S-5.39%.

Biological Evaluation: The antibacterial potential of synthesized compounds was checked by disc diffusion method at different concentration using DMSO as solvent and nutrient agar as culture media in presence of gram positive bacterial strains *Staphylococcus aureus, Bacillus subtilis* and gram negative bacterial strains *Pseudomonas aeruginosa Escherichia coli*. The zone of inhibition was measured after 24 hour of incubation at 37 ˚C. The results of the study were compared with data of used reference streptomycin and are depicted in the following table 1.

In the antibacterial study of synthesized compounds it was found that compounds 8a, 8c, 8g and 8i found to possess excellent antibacterial strength against all used bacterial strains compared to reference antibacterial active compound taken for the study while rest of the compounds show moderate and poor activity. In this study compounds 8d, 8f and 8j found inactive against different bacterial strains.

Table 1: Antibacterial data of synthesized compounds.

Comp. Code	Gram Positive Bacteria				Gram Negative Bacteria			
	Staphylococcus aureus		*Bacillus subtilis*		*Pseudomonas aeruginosa*		*E. coli*	
	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)
8a	8	25	7	25	7	50	10	<100
8b	14	12.5	16	25	19	100	17	50
8c	9	12.5	10	12.5	12	25	11	12.5
8d	--	<100	--	>100	14	25	--	--
8e	15	25	7	12.5	19	>12.5	18	>12.5
8f	13	12.5	13	25	19	100	--	--
8g	11	50	8	25	7	50	11	<100
8h	13	>12.5	15	>12.5	18	12.5	16	12.5
8i	7	12.5	8	12.5	8	12.5	7	12.5
8j	--	<100	14	<100	18	>12.5	14	>12.5
Reference	12	>12.5	13	>12.5	16	>12.5	13	>12.5

CONCLUSION: In this study oxadiazole clubbed acetamide derivatives were synthesized and structures of these derivatives were determined by IR, ^{1}H NMR and Mass spectroscopy analyses. The antibacterial study of synthesized compounds reveals that some of compounds show high antibacterial strength compared to reference.

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