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Synthesis, Characterization and Biological Screening of Quinoline Linked Oxadiazole Derivatives as Potent Antibacterial Agents

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ABSTRACT: A series of ten derivatives of quinolin-8-yl[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]acetate was designed and derived through various steps. The structures of synthesized compounds were determined by IR, ^{1}H NMR and Mass spectroscopy analyses. The antibacterial strength of synthesized compounds was evaluated by using bacterial strains *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa* and Escherichia coli where the study data reveals that some of the compounds have good antibacterial potential.

Keywords: Quinoline; oxadiazole; acetamide and biological evaluation.

INTRODUCTION: Heterocyclic chemistry is an integral part of organic chemistry which covers more than half of the literature with numbers of novel heterocyclic compounds with different hetero atomic nucleus. The presence of nitrogen and oxygen heteroatom in five-member ring generates an important heterocyclic nucleus known as oxadiazole. This oxadiazole nucleus has diverse biological applications as antimicrobial[1-5], antioxidant[6-9], anticancer[10-12], anti-inflammatory[13], analgesic[14], anti-tubercular[15 & 16], anti-convulsant[17-18], Alzheimer[19], antiallergic[20] etc. In this work, we have generated series of compounds linked with 1,3,4-oxadiazole nucleus having antibacterial potential.

MATERIAL AND METHODS: In the preparation of derivatives laboratory and analytical grade chemicals were selected. The melting points of derivatives were measured by open capillary method and are uncorrected. To check the purity of compounds TLC method was elected where silica gel coated aluminIum plates (Merk) were used with appropriate mobile phase and obtaining spots were visualized in UV chamber. The Perkin-Elmer 237 spectrophotometer instrument was used where IR spectra was recorded by KBr pellet, Mass spectra was recorded on MS route JMS 600-H instrument and Bruker AM -400 instrument was used to record NMR spectra using DMSO as solvent and TMS as internal standards.

General Procedure for preparation of quinolin-8-yl[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]acetate:

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 (80 ml) and refluxed for 12 to 14 hours. The resulting reaction mass was then poured into crushed ice, stirred well and products were separated from reaction mass. The purification of products was 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 methyl alcohol (80 ml) and refluxed for 12 to 15 hours. 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.

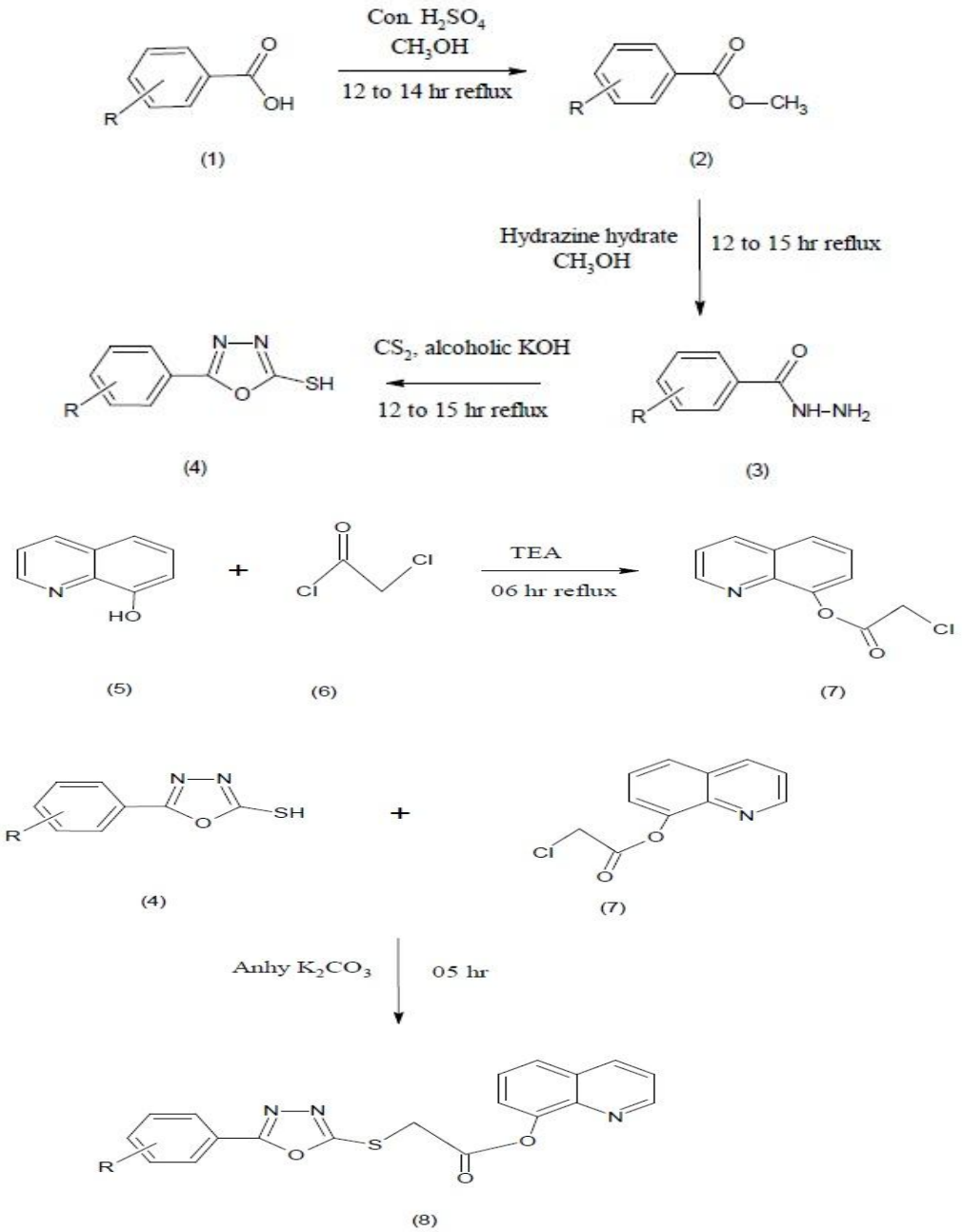
Step III: Synthesis of 5-aryl-1,3,4-oxadiazole-2-thiol (4) **-** To synthesize 5-aryl-1,3,4-oxadiazole-2-thiol, the mixture of aryl hydrazide (0.1 mol), CS_2 (0.1 mol) and alcoholic KOH (0.05 mol) were refluxed in methyl alcohol (80 ml) for 12 to 15 hours. The resulting mass was poured into crushed ice and 2N HCl was used to

neutralize 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.

Step IV: Synthesis of quinolin-8-yl chloroacetate (7) -The mixture of chloro acetyl chloride (0.1 mol), 2-4 drops of TEA and quiniol-8-ol (0.1 mol) in toluene (70 ml) was refluxed for 06 hours. The product was collected from the reaction mass by separation technique and washed by toluene (25 ml). The purification of product was done by ethyl alcohol. A TLC method was used to check the progress of reaction using toluene: acetone (8:2) as eluent.

Step V: Synthesis of quinolin-8-yl [(5-aryl-1,3,4-oxadiazol-2- yl)sulfanyl]acetate (8) -The mixture of 5-aryl-1,3,4-oxadiazole-2-thiol (0.1 mol), quinolin-8-yl chloroacetate (0.1 mol), anhydrous K_2CO_3 (0.2 mol) were taken in dry acetone (50 ml) and stirred for 05 hours. 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 using toluene: acetone (8:2) as eluent.

[Reaction Scheme]



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

RESULTS AND DISCUSSION:

Characterization:

8(a).Quinolin-8-yl {[5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 56%, m.p. 170-172˚ C, FT-IR (KBr): 659 (C-Br), 1141 (C-O-C), 1469 (-C=C-), 1568 (-C=N), 1769 (-C=O), 2916 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : 4.54 (s, 2H, -CH_2-), δ 7.21-7.25 (s. 2H, Ar-H), δ 7.35-7.39 (m, 2H, Ar-H), δ 7.46-7.47 (m, 1H, Ar-H), 7.63-7.65 (m, 1H, Ar-H), δ 7.91-7.95 (s, 2H, Ar-H), δ 7.99-8.01 (m, 1H, Ar-H), δ 8.39-8.41 (m, 1H, Ar-H), MS : m/z 443, Anal. Calcd for $C_{19}H_{12}BrN_3O_3S$: C-51.60, H-2.73, N-9.50, S-7.25 Anal. Found C-51.57, H-2.69, N-9.48, S-7.21%.

8(b). Quinolin-8-yl {[5-(4-flourophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 68%, m.p. 161-163˚ C, FT-IR (KBr): 1138 (C-O-C), 1374 (C-F), 1465 (-C=C-), 1595 (-C=N), 1764(-C=O), 2935 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : 4.77 (s, 2H, -CH_2-), δ 7.44-7.48 (s. 2H, Ar-H), δ 7.55-7.59 (m, 2H, Ar-H), δ 7.65-7.66 (m, 1H, Ar-H), 7.93-7.95 (m, 1H, Ar-H), δ 8.05-8.09 (s, 2H, Ar-H), δ 8.43-8.45 (m, 1H, Ar-H), δ 8.76-8.77 (m, 1H, Ar-H), MS : m/z 382, Anal. Calcd for $C_{19}H_{12}FN_3O_3S$: C-59.84, H-3.17, N-11.02, S-8.41 Anal. Found C-59.83, H-3.16, N-11.01, S-8.39%.

8(c). Quinolin-8-yl {[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 76%, m.p. 182-184˚ C, FT-IR (KBr): 1084 (C-O-C alkanyl), 1157 (C-O-C), 1473 (-C=C-), 1588 (-C=N), 1779(-C=O), 2921 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : δ 3.49 (s. 6H, -OCH_3), δ 3.56 (s, 3H, -OCH_3) 4.53 (s, 2H, -CH_2-), δ 7.19-7.23 (s. 2H, Ar-H), δ 7.43-7.47 (m, 2H, Ar-H), δ 7.59-7.61 (m, 1H, Ar-H), 7.88-7.90 (m, 1H, Ar-H), δ 8.13-8.15 (s, 2H, Ar-H), δ 8.39-8.41 (m, 1H, Ar-H), δ 8.62-8.64 (m, 1H, Ar-H), MS : m/z 455, Anal. Calcd for $C_{22}H_{19}N_3O_6S$: C-58.27, H-4.22, N-9.27, S-7.07 Anal. Found C-58.24, H-4.19, N-9.24, S-7.04%.

8(d). Quinolin-8-yl {[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 69%, m.p. 177-179˚ C, FT-IR (KBr): 1163 (C-O-C), 1482 (-C=C-), 1601 (-C=N), 1786(-C=O), 2898 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.37 (s, 2H, -CH_2-), δ 7.22-7.26 (s. 2H, Ar-H), δ 7.49-7.53(m, 2H, Ar-H), δ 7.64-7.68 (m, 1H, Ar-H), 7.93-7.97 (m, 1H, Ar-H), δ 8.19-8.21 (s, 2H, Ar-H), δ 8.45-8.47 (m, 1H, Ar-H), δ 8.69-8.71 (m, 1H, Ar-H), MS : m/z 409, Anal. Calcd for $C_{19}H_{12}N_4O_5S$: C-55.88, H-2.96, N-13.72, S-7.85 Anal. Found C-55.86, H-2.94, N-13.68, S-7.83%.

8(e). Quinolin-8-yl {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 69%, m.p. 183-185˚ C, FT-IR (KBr): 673(C-Br), 1157 (C-O-C), 1469 (-C=C-), 1608 (-C=N), 1698 (-C=O), 2893 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : 4.47 (s, 2H, -CH_2-), δ 7.13-7.17 (s. 2H, Ar-H), δ 7.32-7.36 (m, 2H, Ar-H), δ 7.48-7.50 (m, 1H, Ar-H), 7.67-7.69 (m, 1H, Ar-H), δ 7.99-8.01 (s, 2H, Ar-H), δ 8.12-8.14 (m, 1H, Ar-H), δ 8.45-8.47 (m, 1H, Ar-H), MS : m/z 443, Anal. Calcd for $C_{19}H_{12}BrN_3O_3S$: C-51.60, H-2.73, N-9.50, S-7.25 Anal. Found C-51.59, H-2.71, N-9.46, S-7.22%.

8(f). Quinolin-8-yl {[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 64%, m.p. 170-172˚ C, FT-IR (KBr): 659 (C-Cl), 1160 (C-O-C), 1463 (-C=C-), 1598 (-C=N), 1776 (-C=O), 2903 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : 4.38 (s, 2H, -CH_2-), δ 7.12-7.16 (s. 2H, Ar-H), δ 7.29-7.33 (m, 2H, Ar-H), δ 7.51-7.53 (m, 1H, Ar-H), 7.69-7.71 (m, 1H, Ar-H), δ 7.86-7.90 (s, 2H, Ar-H), δ 7.96-7.98 (m, 1H, Ar-H), δ 8.22-8.24 (m, 1H, Ar-H), MS : m/z 398, Anal. Calcd for $C_{19}H_{12}ClN_3O_3S$: C-57.36, H-3.04, N-10.56, S-8.06 Anal. Found C-57.33, H-3.01, N-10.52, S-8.02%.

8(g). Quinolin-8-yl {[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 73%, m.p. 176-178˚ C, FT-IR (KBr): 1182 (C-O-C), 1479 (-C=C-), 1609 (-C=N), 1798 (-C=O), 2872 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, -CH_3), δ 4.60 (s, 2H, -CH_2-), δ 7.04-7.08 (s. 2H, Ar-H), δ 7.23-7.27 (m, 2H, Ar-H), δ 7.57-7.59 (m, 1H, Ar-H), 7.73-7.76 (m, 1H, Ar-H), δ 7.89-7.93 (s, 2H, Ar-H), δ 8.04-8.06 (m, 1H, Ar-H), δ 8.43-8.45 (m, 1H, Ar-H), MS : m/z 378, Anal. Calcd for $C_{20}H_{15}N_3O_3S$: C-63.65, H-4.01, N-11.13, S-8.49 Anal. Found C-63.63, H-3.99, N-11.12, S-8.47%.

8(h). Quinolin-8-yl {[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 59%, m.p. 157-159˚ C, FT-IR (KBr): 1149 (C-O-C), 1456 (-C=C-), 1586 (-C=N), 1768 (-C=O), 2893 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6): 4.26 (s, 2H, -CH_2-), δ 7.18-7.22 (s. 2H, Ar-H), δ 7.33-7.37 (m, 2H, Ar-H), δ 7.56-7.58 (m, 1H, Ar-H), 7.67-7.71 (m, 1H, Ar-H), δ 7.82-7.86 (s, 2H, Ar-H), δ 7.99-8.03(m, 1H, Ar-H), δ 8.32-8.36 (m, 1H, Ar-H), MS : m/z 409, Anal. Calcd for $C_{19}H_{12}N_4O_5S$: C-55.88, H-2.96, N-13.72, S-7.85 Anal. Found C-55.85, H-2.92, N-13.71, S-7.81%.

8(i). Quinolin-8-yl {[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 72%, m.p. 181-183˚ C, FT-IR (KBr): 659 (C-Cl), 1178 (C-O-C), 1474 (-C=C-), 1583 (-C=N), 1772 (-C=O), 2843 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6) : 4.27 (s, 2H, -

CH_2-), δ 7.15-7.19 (s. 2H, Ar-H), δ 7.31-7.35 (m, 2H, Ar-H), δ 7.54-7.55 (m, 1H, Ar-H), δ 7.67-7.69 (m, 1H, Ar-H), δ 7.93-7.97 (s, 2H, Ar-H), δ 8.13-8.15 (m, 1H, Ar-H), δ 8.47-8.49 (m, 1H, Ar-H), MS : m/z 398, Anal. Calcd for $C_{19}H_{12}ClN_3O_3S$: C-57.36, H-3.04, N-10.56, S-8.06 Anal. Found C-57.35, H-3.03, N-10.53, S-8.04%.

8(j). Quinolin-8-yl {[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetate: Yield 58%, m.p. 164-166˚ C, FT-IR (KBr): 1196 (C-O-C), 1484 (-C=C-), 1602 (-C=N), 1787 (-C=O), 2891 (-CH_2-), ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, -CH_3), δ 4.51 (s, 2H, -CH_2-), δ 7.11-7.15 (s. 2H, Ar-H), δ 7.29-7.33 (m, 2H, Ar-H), δ 7.59-7.61 (m, 1H, Ar-H), δ 7.70-7.72 (m, 1H, Ar-H), δ 7.91-7.95 (s, 2H, Ar-H), δ 8.11-8.13 (m, 1H, Ar-H), δ 8.34-8.38 (m, 1H, Ar-H), MS : m/z 378, Anal. Calcd for $C_{20}H_{15}N_3O_3S$: C-63.65, H-4.01, N-11.13, S-8.49 Anal. Found C-63.61, H-3.97, N-11.10, S-8.45%.

Biological study: The antibacterial study of synthesized compounds was determined by efficient disc diffusion technique using *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and Escherichia coli bacterial strains in which DMSO was selected as solvent and nutrient agar as culture media. The study was carried out at different concentration and zone of inhibition was measured after 24 hours of incubation at 37° C. The effective antibacterial agent streptomycin was selected as reference in this study and the antibacterial data of synthesized compounds are mentioned in the following table.

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	9	>12.5	5	12.5	6	25	7	12.5
8b	8	12.5	11	>12.5	8	12.5	8	12.5
8c	8	25	16	50	8	25	7	25
8d	16	12.5	19	12.5	--	12.5	18	50
8e	8	12.5	--	--	8	12.5	31	100
8f	8	12.5	5	12.5	7	50	12	50
8g	13	25	9	12.5	16	12.5	14	12.5
8h	15	50	14	25	18	100	--	--
8i	10	>12.5	8	12.5	7	12.5	9	>12.5
8j	15	50	12	12.5	16	12.5	19	100
Reference drug	12	>12.5	13	>12.5	16	>12.5	13	>12.5

The antibacterial study data reveals that compounds 8a, 8b, 8f and 8i found to possess excellent antibacterial potential against all bacterial strains used for study compared to reference compound while rest of the compounds show moderate and poor activity. In this study compounds 8d, 8e and 8h found inactive against different bacterial strains.

CONCLUSION: The synthesized derivatives were prepared through various steps and different spectroscopy analyses support the structures of synthesized compounds. The biological potential of synthesized compounds was evaluated as potent antibacterial compounds.

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