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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT

1,3,4-oxadiazoles are important because of its versatile biological actions. In the present study, several 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** have been synthesized by the condensation of 8-hydroxy quinoline acetyl hydrazide **(II)** with various aromatic acids in presence of phosphorus oxychloride. The structures of the newly synthesized compounds have been established on the basis of elemental analysis, UV, IR and 1H NMR spectral data. The synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50µg/ml) and Fluconazole (50µg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*.

KEYWORDS

1,3,4-oxadiazole, Ampicillin, Fluconazole, Antibacterial and Antifungal activity

RESUMO

Os compostos da classe 1,3,4-oxadiazol são importantes por causa de sua atividade biológica versátil. O presente trabalho descreve a síntese de vários derivados de 2-(quinolino-8-iloximetil)-5-aril-1,3,4-oxadiazol. As estruturas dos novos compostos foram estabelecidas através de técnicas de UV, IR e RMN. A atividade biológica dos novos compostos foi comprovada contra várias bactérias e fungos, i.e., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* e *A. fumigates* e comparada com compostos padrão como Ampicilina (50µg/ml) e Fluconazol (50µg/ml).

PALVRAS CHAVE: 1,3,4-oxadiazol, Ampicilina, Fluconazol, Atividade antibacteriana e antifúngica

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INTRODUCTION

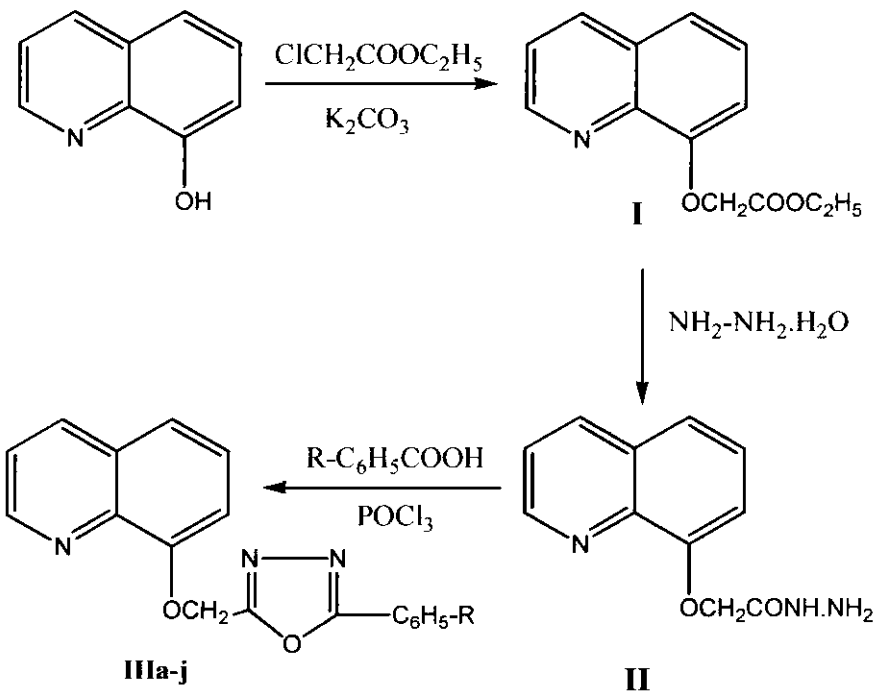
The compound 1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial[1], anti-HIV[1], antitubercular[2], antimalarial[3], analgesic[4], anti-inflammatory[5], anticonvulsant[6], hypoglycemic[7] and other biological properties such as genotoxic studies[8] and lipid peroxidation inhibitor[9]. The development of antifungal agents has lagged behind that of antibacterial agents[10-13]. This is a predictable consequence of the cellular structure of the organisms involved. This difficulty complicates experiments designed to evaluate the *in vitro* or *in vivo* properties of a potential antifungal agent. 1,3,4-Oxadiazoles show various biological activities and have been synthesized from different compounds. 1,3,4-oxadiazole is popularly known for its antimicrobial[14], anti-inflammatory[15], pesticidal[16] and antihypertensive[17] activities. It is well known that the synthesis of heterocyclic compounds tend to contain multi-structure in a molecule. In this study, it was planned to incorporate the oxadiazole ring system into quanoline ring.

The earliest evidence of successful chemotherapy is from ancient Peru, where the Indians used bark from the Cinchona tree to treat malaria. Modern chemotherapy has been dated to the work of Paul Ehrlich in Germany, who sought systematically to discover effective agents to treat trypanosomiasis and syphilis. Ehrlich postulated that it would be possible to find chemicals that were selectively toxic for parasites but not toxic to humans[18].

Progress in the development of novel antibacterial agents has been great, but the development of effective, nontoxic antifungal and antiviral agents has been slow. Amphotericin B, isolated in the1950s, remains an effective antifungal agent, although newer agents such as fluconazole[19] are now widely used. An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria (antibacterial activity), fungi (antifungal activity) and viruses (antiviral activity). Any attempt to discuss the chemotherapeutic properties[20] of heterocyclic compounds must, of necessity, be confined to a limited aspect of the subject.

EXPERIMENTAL

The protocol of compounds synthesized **(IIIa-j)** is given in Figure 1.



Compd.	R	Compd.	R
IIIa	4-Br	IIIf	4-OH
IIIb	4-NH_2	IIIg	3-Cl
IIIc	3-OCH_3	IIIh	4-Cl
IIId	3,4-OCH_3	IIIi	3-NO_2
IIIe	3,4-Cl	IIIj	2,4-OH

Figure 1. Schematic diagram for the synthesis of 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)**

The chemicals were supplied by E. Merck (Germany) and S.D Fine chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene-ethylacetate-formic acid (5:4:1) and benzene-methanol (8:2), the spots were located under iodine vapours and UV light. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). ^{1}H-NMR spectra were recorded or a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d_6/$CDCl_3$ and Mass spectra

under electron impact conditions (EI) were recorded at 70 ev ionizing voltage with a VG Prospec instrument and are presented as m/z. Microanalysis of the compounds was performed on a Perkin-Elmer model 240 analyzer.

Synthesis of Ethyl-2-(quanoline-8-yloxy)acetate (I):

A mixture of 8-hydroxy quanoline (0.01 mol) ethyl chloro acetate (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in dry acetone were refluxed on a water bath for 6hr and poured into ice-cold water. Solid product obtained was filtered and recrystallized from ethanol. Yield 76%.

Synthesis of 8-hydroxy quinoline acetyl hydrazide (II):

A mixture of compound 1(0.01 mol) hydrazine hydrate (99%, 0.07 mol) in methanol was refluxed for 5 hr. From the resultant mixture excess of ethanol was removed by distillation. On cooling, white needle crystals separates out. It was recrystallized with ethanol. The yield was 71%.

Synthesis of 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives (IIIa-j):

A mixture of compound 2 (0.01 mol) and various aromatic acid (0.01 mol) in $POCl_3$ were refluxed for 6 hr. The content was cooled and poured into ice-cold water, then neutralized with $NaHCO_3$ solution, until a solid was obtained. The solid separated by filtration and recrystallized with ethanol.

2-(quinoline-8-yloxymethyl)-5-(4-bromophenyl)-1,3,4-oxadiazole (IIIa): Yield: 66%; Mp. 135-137°C; R_f : 0.50 (toluene: ethylacetate: formic acid ; 5: 4: 1) FTIR (KBr, cm^{-1}) 3050 (C-H), 1578 (C=N), 1508 (C=C), 1206 (C-O-C), 575(C-Br); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ 7.5-8.5 (m,10H, Ar-H), 4.87 (s, 2H, OCH_2); MS: m/z 318(M^+); Anal. Calcd for $C_{18}H_{13}N_3O_2Br_1$: C,73.23; H, 5.04; N, 9.23. Found: C, 73.20; H, 5.02; N, 9.21.

2-(quinoline-8-yloxymethyl)-5-(4-aminophenyl)-1,3,4-oxadiazole (IIIb): Yield: 62%; Mp.190-192°C; R_f : 0.62 (toluene: ethylacetate: formic acid; 5: 4: 1); FTIR (KBr, cm^{-1}) 3550 (N-H), 1550 (C=N), 1480 (C=C), 1070 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.5-8.5 (m, 10H, Ar-H), 5.8 (s, 2H, NH_2), 4.8 (s, 2H, OCH_2); MS: m/z 318 (M^+); Anal. Calcd for $C_{18}H_{15}N_4O_2$: C, 68.05; H, 5.04; N, 13.05. Found: C, 68.02; H, 5.04; N, 13.01.

2-(quinoline-8-yloxymethyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (IIIc): Yield: 70%; Mp.170-171°C; R_f : 0.55 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3050 (C-H),1560 (C=N), 1580 (C=C), 1030 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.5-8.0 (m, 10H, Ar-H), 3.8(s, 2H, OCH_2), 2.9 (s, 3H, OCH_3); MS: m/z 335 (M^+); Anal. Calcd for $C_{19}H_{16}N_3O_3$: C, 72.23; H, 5.04; N, 10.23. Found: C, 72.20; H, 5.02; N, 10.21.

2-(quinoline-8-yloxymethyl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole (IIId): Yield: 75%; Mp.175-177°C; R_f : 0.62 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3040 (C-H), 1630 (C=N), 1450 (C=C), 1170 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 6.8-8.2 (m, 9H, Ar-H), 5.6 (s, 2H, OCH_2), 3.8 (s, 6H, OCH_3); MS: m/z 364 (M^+); Anal. Calcd for $C_{20}H_{18}N_3O_4$: C, 72.05; H, 5.61; N, 9.01. Found: C, 72.0; H, 5.60; N, 9.01.

2-(quinoline-8-yloxymethyl)-5-(3,4-dichlorophenyl)-1,3,4-oxadiazole (IIIe): Yield: 62%; Mp.156-157°C; R_f : 0.59 (toluene: ethylacetate: formic acid ; 5: 4: 1)FTIR (KBr, cm^{-1}) 3045 (C-H),1530 (C=N), 1550 (C=C), 1230 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.2-8.5 (m, 9H, Ar-H), 5.4 (s, 2H, OCH_2); MS: m/z 372(M^+), 373(M^++1) ; Anal. Calcd for $C_{18}H_{12}N_3O_2Cl_1$: C, 73.01; H, 6.32; N, 12.05. Found: C, 73.02; H, 6.34; N, 12.03.

2-(quinoline-8-yloxymethyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole (IIIf): Yield: 68%; Mp.195-197°C; R_f : 0.54 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3530 (O-H), 2925 (C-H),1638 (C=N),1454 (C=C), 1070 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.3-8.0 (m, 10H, Ar-H), 4.6(s, 1H, OH), 4.8 (s, 2H, OCH_2); MS: m/z 320 (M^+); Anal. Calcd for $C_{18}H_{14}N_3O_3$: C, 72.33; H, 8.01; N, 12.01. Found: C, 72.33; H, 8.01; N, 12.03.

2-(quinoline-8-yloxymethyl)-5-(3-chlorophenyl)-1,3,4-oxadiazole (IIIg): Yield: 60%; Mp.145-147°C; R_f : 0.58 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 2850 (C-H),1639 (C=N), 1458 (C=C), 1070 (C-O-C), 656 (C-Cl); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.0-8.2 (m, 10H, Ar-H), 5.1 (s, 1H, OH), 4.2 (s, 2H, OCH_2); MS: m/z 337(M^+), 338 (M^++1); Anal.Calcd for $C_{18}H_{13}N_3O_2Cl_1$: C, 74.01; H, 7.04; N, 9.33.Found: C, 74.02; H, 7.03; N, 9.32.

2-(quinoline-8-yloxymethyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (IIIh): Yield: 63%; Mp.155-156°C; R_f : 0.61 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3050 (C-H), 1539 (C=N), 1508 (C=C), 1090 (C-O-C), 650(C-Cl); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 6.9-8.4 (m, 10H, Ar-H), 4.6 (s, 2H, OCH_2); MS: m/z 338(M^+), 339(M^++1); Anal.Calcd for $C_{18}H_{13}N_3O_2Cl_1$: C, 73.01; H, 7.04; N, 8.33.Found: C, 73.02; H, 7.03; N, 8.32.

2-(quinoline-8-yloxymethyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole (IIIi): Yield: 66%; Mp.145-147°C; R_f : 0.62 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3020 (C-H), 1630 (C=N), 1554(C=C), 1170 (C-O-C), 1150 (N-=O); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.2-8.5 (m, 10H, Ar-H), 4.6 (s, 2H, OCH_2); MS: m/z 349(M^+); Anal. Calcd for $C_{18}H_{13}N_4O_4$: C, 70.13; H, 6.04; N, 9.16. Found: C, 70.12; H, 6.02; N, 9.13.

2-(quinoline-8-yloxymethyl)-5-(2,4-dihydroxyphenyl)-1,3,4-oxadiazole (IIIj): Yield: 72%; Mp.185-186°C; R_f : 0.56 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3450 (O-H), 1530 (C=N),1510 (C=C), 1205 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.0-8.1 (m, 9H, Ar-H), 5.5 (s, 2H, 2OH), 4.9 (s, 2H, OCH_2); MS: m/z 336(M^+); Anal. Calcd for $C_{18}H_{14}N_3O_4$: C, 71.13; H, 5.04; N, 9.16. Found: C, 71.12; H, 5.02; N, 9.13.

RESULTS AND DISCUSSION

Various 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** were synthesized and synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50μg/ml) and Fluconazole (50μg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*. Whereas remaining compounds have shown moderate antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa, A. flavus,* and *A. Fumigates* given in Table 1

Table 1: Antimicrobial activity of for 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives (IIIa-j)

Compd. no.	Zone of inhibition in mm					
	Antibacterial Activity			Antifungal Activity		
	SA	EC	PA	CA	AF	AFU
IIIa	15	14	12	10	20	18
IIIb	24	20	16	10	13	17
IIIc	15	10	17	20	15	18
IIId	17	20	23	22	20	12
IIIe	24	17	18	19	20	14
IIIf	23	11	10	16	13	23
IIIg	22	16	17	20	12	18
IIIh	17	15	18	20	18	10
IIIi	14	20	24	20	17	18
IIIj	19	20	24	10	16	15
Ampicillin	24	25	25	-	-	-
Fluconazole	-	-	-	17	16	17

Where SA-*S. aureus*, EC-*E. coli*, PA-*P. aeruginosa*, CA-*C. albicans*, AF-*A. flavus*, AFU-*A. fumigatus*

SCREENING FOR ANTIMICROBIAL ACTIVITY

The antimicrobial activity of all the newly synthesized compounds **(IIIa-j)** was determined by well plate method[21-22] in nutrient agar (Hi-Media) (antibacterial activity) and Sabouraud dextrose agar (SDA) (Hi- Media) (antifungal activity)[23-24]. The *in vitro* antimicrobial activity was carried out against 24h old cultures of bacterial and 72h old cultures of fungal strain. The bacterial and fungal strains for the study are listed in Table 1. The compounds were tested at a concentration of 100 µg/ml and solutions were prepared were prepared in dimethyl formamide (DMF). The petridishes used for antibacterial screening were incubated at 37±1° C for 24h, while those used for antifungal activity were incubated at 28°C for 48-72h. The results were compared to Ampicillin (50µg/ml) and Fluconazole (50µg/ml) for antibacterial and antifungal activity respectively by measuring zone of inhibition in mm. The antibacterial and antifungal screening results were presented in Table 1.

CONCLUSIONS

The entire study reveals that there is wide scope of modifications possible for 1,3,4-oxadiazole ring system. Oxadiazole ring system could be incorporated into many more ring systems which itself have their own activity and could lead to more potent and highly active compounds. Various 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** were synthesized and synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50µg/ml) and Fluconazole (50µg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*. Whereas remaining compounds have shown moderate antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa, A. flavus,* and *A. Fumigates* given in Table 1.

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