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SYNTHESIS OF CERTAIN 1,3,4-OXADIAZOLES AS ANTIMICROBIAL AGENTS

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ABSTRACT

A new series of 1,3,4-Oxadiazoles (2a-j) were prepared by reacting methyl paraben hydrazide(1) with substituted aromatic acids in presence of phosphorous oxychloride. The structures of the newly synthesized compounds have been established on the basis of ^{1}H-NMR, IR and Mass spectral data. All the synthesized compounds have been evaluated for their *In-Vitro* growth inhibitory activity against several microbes like *E.coli, S.aureus, P.aeruginosa, B.subtilis* and fungi like *A.fumigatus* and *A.flavus*.

Keywords: 1,3,4-Oxadiazoles, Methyl paraben, Antibacterial activity, Antifungal activity.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen containing heterocycles with an oxygen atom are considered as an important class of compounds in medicinal chemistry because of their interesting diversified biological application. Oxadiazoles are used as scaffolds on which pharmacophores are arranged to provide potent and selective drugs. During the past years considerable evidences have also accumulated to demonstrate the efficacy of 1,3,4-Oxadiazoles including antibacterial [1], antitubercular [2], analgesic [3], anti-inflammatory [4], anticancer [5], antifungal [6],anticonvulsant [7], anti-HIV [8] etc.

Methyl paraben hydrazide [9] (1) was prepared by refluxing hydrazine hydrate and methyl paraben in alcohol medium. Methyl parabenhydrazide was condensed with various aromatic acids in presence of $POCl_3$ to yield the title compounds 1,3,4-Oxadiazole derivatives (2a-j). All the new compounds have been evaluated for their antibacterial and antifungal activities. The title compounds were characterized by spectral data. The reaction sequence leading into the formation of title compounds is given in Scheme 1.

MATERIALS AND METHODS

Melting points were determined in an open capillary tube and are uncorrected. The IR spectra were recorded by using Alpha Bruker IR spectrometer using a thin film on KBr pellet technique and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer. All spectra were obtained in $CDCl_3$ and DMSO. Chemical shift values are reported as values in ppm relative to TMS (δ=0) as internal standard. The mass spectra were recorded with ESI. The progress of each step was observed by TLC.

Synthesis of Methyl Paraben hydrazide (1)

To methyl paraben (0.1mol) in 30ml ethanol, hydrazine hydrate (0.1 mol) was added drop wise with stirring. The resulting mixture was refluxed for 6 hrs. Excess ethanol was distilled off and the content was allowed to cool. The white crystals which were separated, filtered, dried and recrystallized with ethanol. MP: 121ºC % Yield: 78%.

Synthesis of 1,3,4-Oxadiazoles (2a-j)

A solution of methyl parabenhydrazide (**1)** (0.01 mol) in phosphorous oxychloride (5 ml) and different

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substituted aromatic acids (0.01 mol) were added. The reaction mixture was refluxed for about 12-18hrs in an oil bath. The reaction mixture was cooled to room temperature and poured into crushed ice. On neutralization with 20% $NaHCO_3$ solution, a solid mass is separated out, which was filtered, washed with water and recrystallized from ethanol. The physical data of the compounds (2a-j) is given in table-1.

2a:IR(KBr,cm^{-1}) : 1167(C-O-C), 1549(C=C), 1609(C=N), 3062(C-H), 3454(OH).**^{1}H-NMR ($CDCl_3$) :**7.31-8.15 (m, Ar-H, 9H), 10.90 (s, OH, 1H). **MS (M/z):** 239(M^{+1}).

2b:IR(KBr,cm^{-1}): 724(C-Cl), 1077(C-O-C), 1545(C=C), 1599(C=N), 1348 & 1520(NO_2), 3093(C-H), 3471 (OH). **^{1}H-NMR ($CDCl_3$):** 8.20-8.43(m,Ar-H,7H), 8.92 (s,OH,1H). **MS (M/z):** 318(M^+) & 320 (M+2).

2c:IR(KBr,cm^{-1}): 1090(C-O-C), 1495(C=C), 1609(C=N), 3002(C-H), 3216(OH). **^{1}H-NMR ($CDCl_3$):** 3.88(s,OCH_3,3H), 7.08-8.11(m,Ar-H,8H), 10.20 (s, OH, 1H).**MS (M/z):** 269(M^{+1}).

2d:IR(KBr,cm^{-1}): 761(C-Cl), 1129(C-O-C), 1527(C=C), 1592(C=N), 3093(C-H), 3711(OH). **^{1}H-NMR ($CDCl_3$) :**7.41-8.13 (m, Ar-H, 8H), 10.70 (s, OH, 1H).

Scheme 1.

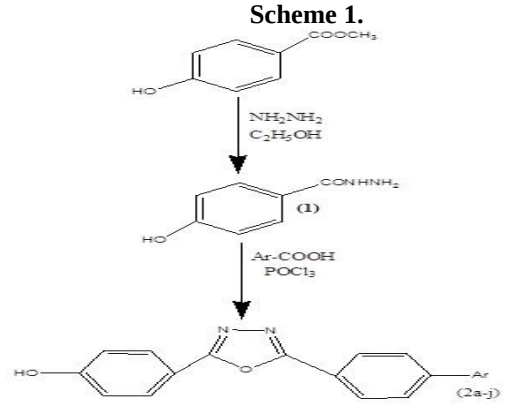

Table 1. Physical data of 1,3,4-Oxadiazole Derivatives (2a-j)

Comp	Ar-COOH	Molecular formula	Molecular weight	MP(°C)	Yield (%)
2a	C_6H_5	$C_{14}H_{10}N_2O_2$	238	82-84	60
2b	3-Cl,5-NO_2	$C_{14}H_8ClN_3O_4$	317	104-106	63
2c	4-OCH_3	$C_{15}H_{12}N_2O_3$	268	118-120	67
2d	4-Cl	$C_{14}H_9ClN_2O_2$	272	178-180	67
2e	4-OH	$C_{14}H_{10}N_2O_3$	254	124-126	61
2f	2-OH, 3,5-$(NO_2)_2$	$C_{14}H_8N_4O_7$	344	98-100	62
2g	2-Br	$C_{14}H_9BrN_2O_2$	316	163-165	61
2h	2,4-$(Cl)_2$	$C_{14}H_8Cl_2N_2O_2$	307	155-157	66
2i	2,4-$(OH)_2$	$C_{14}H_{10}N_2O_4$	238	144-146	61
2j	2-OH	$C_{14}H_{10}N_2O_3$	254	136-138	66

Table 2**. Antimicrobial data of 1,3,4-Oxadiazole Derivatives (2a-j)**

Comp	Diameter of zone of Inhibition (mm)					
	B.subtilis	***E.coli***	***P.aeruginosa***	***S.aureus***	***A.flavus***	***A.fumigatus***
2a	13	09	07	07	18	13
2b	08	08	08	08	12	07
2c	12	12	08	12	12	08
2d	13	12	16	10	18	08
2e	19	17	12	13	12	14
2f	16	11	13	12	13	10
2g	12	12	17	08	19	08
2h	11	09	10	10	15	08
2i	17	15	12	12	13	12
2j	19	17	13	10	14	14
Ciprofloxacin	24	23	24	23	-	-
Fluconazole	-	-	-	-	24	23
Control(DMF)	-	-	-	-	-	-

RESULTS AND DISCUSSION

Antimicrobial Activity

All the newly synthesized compounds (2a-j) have been screened for antibacterial and antifungal activities by Cup-Plate agar-diffusion method[10] by measuring the zone of inhibition in mm. Ciprofloxacin (100µg/ml) and Fluconazole (100µg/ml) were used as a standard drug for comparison of antibacterial and antifungal activity respectively. DMF was used as solvent control. The biological activity data of the compounds (2a-j) is given in table-2.

The IR spectrum of compound (2a) showed absorption band at 2950 –3100 cm^{-1} due to aliphatic C-H stretch. The absorption band for C=N was observed at 1609 cm^{-1}. The other prominent absorption band in IR spectrum were observed at 1549 (C=C) and 1167 (C-O-C) cm^{-1} and 3454(OH) cm^{-1}. The ^{1}H-NMR spectrum of compound (2a) showed a singlet at δ 10.90 corresponding to OH proton. A multiplet at δ 7.31-8.15 indicated the presence of aromatic protons. Further evidence for the formation of 1,3,4-oxadiazoles was obtained by recording the mass spectrum of the compound (2a). The mass spectrum of the compound showed molecular ion peak at 319 (M+1) m/z, in conformity with the molecular formula $C_{14}H_{10}N_2O_2$. All the above results are in agreement with the newly synthesized compounds, which are characterized by the spectral data.

CONCLUSION

In the antibacterial activity all the compounds showed moderate to good activity against *B.subtilis.* Some of the compounds showed moderate activity against *E.coli*, *P.aeruginosa.* The synthesized compounds showed weak to moderate activity against S.*aureus.* Compounds with electron donating group like OH showed significant activity against *B.subtilis.* The compounds with electron withdrawing group (-Cl, Br) showed moderate activity against *B.subtilis* and *S.aureus.* Compounds with electron donating group (-OH) showed moderate activity against *E.coli.* The rest of the compounds showed weak to moderate activity against *S.aureus.*

In the antifungal activity, all the compounds showed moderate to good activity against *A.flavus*and weak to moderate against *A.fumigatus.* The compounds with electron withdrawing group (-Cl, Br) showed significant activity against *A.flavus* and compounds with phenyl group also showed significant activity against *A.flavus.* The compounds with electron donating group (-OH) showed moderate activity against *A.fumigatus.*

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