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MICROWAVE INDUCED SYNTHESIS OF OXADIAZOLE

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Abstract: Novel 2-(4-Chloro-phenyl)-1-{2-[5-(substituted-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-ethanone derivatives were synthesized by converting carboxylic acid to acid chloride by treating with thionyl chloride in MDC to give reactive compound, this compound treated with hydrazine hydrate to give acid hydrazide**(2)** and with aromatic carboxylic acid to give 1,3,4-oxadiazole derivative compound **(3)**. Representative samples were screened for their anti-microbial activity against Yeast, Fungi, Gram positive and Gram negative organisms using disc diffusion method. The structures of all the molecules were confirmed by IR, ^{1}H, ^{13}C NMR and elemental analysis.

Keywords: 2-[2-(4-Chloro-phenyl)-acetyl]-benzoic acid, Aromatic acid, Hydrazine hydrate, Microwave.

Introduction:

The chemistry of heterocyclic compounds is an interesting field of study since a long time. Oxadiazoles have occupied a specific place in the field of medicinal chemistry due to their wide range of activities[I]. From the existing literature we can see that 1, 3, 4-Oxadiazole nucleus has been possessing antimicrobial[II], antifungal[III], anti-inflammatory[IV], anticonvulsant[V], antioxidant, analgesic[VI], antitubercular[VII] and mutagenic activity[VIII]. One pot synthesis of 1, 3, 4-oxadiazoles has been reported by the reaction of appropriate hydrazide and carboxylicacid[IX]. In Addition 1, 3, 4-oxadiazole have played a crucial role in the development of heterocyclic chemistry and they are also used extensively in medicinal synthesis[X],[XI].

Derivatives of Oxadiazole such as Tiodazosin, Nosapidil, and Furamizole[XII] are well known products in the market for their therapeutic uses.

Experimental:
Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Method A (Microwave Method):
2-[2-(4-Chloro-phenyl)-acetyl]-benzoic acid hydrazide (2):
Compound **(1)** (2.37 gm, 0.01 mole) and $SOCl_2$ (2.17gm 0.03 mole), MDC in 100 mL round bottom flask were stirred for 30 min at room temperature to obtained acid chloride of compound **(1)**. Excess of reagent and solvents were distilled off.
Acid chloride and excess of hydrazine hydrate in dry methanol were transferred in 100 mL round bottom flask and subjected for Microwave irradiation for 4-5mins. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, poured on crushed ice, On neutralization of the contents with sodium bicarbonate solution (20%) a solid mass separated out, which was filtered, washed with water ,dried and recrystallised from methanol to get **2**.
(Yield 75 %, m.p. 224-226°C).
IR (cm^{-1}): *v* 3350-3380 (NH-NH_2), 1680 (C=O), 1630 (NH-NH_2), 1600-1480(aromatic ring), 730-830 (disubstituted aromatic ring).
^{1}H NMR (500 MHz, DMSO-d6, ppm): 2.03 (s, 2H, NH_2), 3.82 (s, 2H, CH_2), 7.00 – 8.08 (m, 8H, ArH), 9.09 (s, 1H, NH).

2-(4-Chloro-phenyl)-1-{2-[5-(substituted-phenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-ethanone
3 a-g:
Equimolar mixture of compound **2** (0.01 mole), substituted aromatic acid (0.01 mole) and phosphorous oxychloride (5mL) was transferred in 100 mL round bottom flask and subjected to microwave irradiation. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20%) a solid mass separated out, which was filtered, washed with water and dried to yield **3 a-g**. The physical data of the compounds are given in **Table 1**.

Method B (Conventional):
Compound **2** (0.01 mole) was dissolved in phosphorous oxychloride (15mL) and to it was added substituted aromatic acid (0.01 mole). The reaction mixture, after refluxing for 6 hr, was cooled to room temperature and poured onto crushed ice. The product was isolated in a similar manner as described above to obtain the desired product.
Spectral Interpretation:
2-(4-Chloro-phenyl)-1-[2-(5-phenyl-[1, 3, 4] oxadiazol-2-yl)-phenyl]-ethanone 3a:
IR (cm-1): *v* (CH) 3040; *v* (CH) 2984; *v* (C=O) 1675; *v* (N-N=C) 1238; *v* (C-O-C) 1095.
1H NMR ð (ppm): 4.70 (s, 2H, CH_2); 7.24- 8.3 (m, 13H, Ar-H);
13 C NMR ð ppm: 50.2 (CH_2); 122-139 (ArC); 156-158 (O-C=N, Oxadiazole ring); 195.4 (C=O); MS: 374.5 (M+)
2-(4-Chloro-phenyl)-1-[2-(5-p-tolyl-[1, 3, 4] oxadiazol-2-yl)-phenyl]-ethanone 3b:
IR (cm-1): *v* (CH) 3048; *v* (C=O) 1665; *v* (C=O) 1690; *v* (N-N=C) 1245;
v (C-O-C) 1090.

1H NMR ð (ppm): 2.35 (s, 3H, CH_3), 4.78 (s, 2H, CH_2); 7.34- 8.40 (m, 12H, Ar-H);
13 C NMR ð ppm: 20.9 (CH_3); 54.2 (CH_2); 126-140 (ArC); 155-158 (O-C=N, Oxadiazole ring);
196.6 (C=O); MS: 388.5 (M+)

2-(4-Chloro-phenyl)-1-{2-[5-(4-nitro-phenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-ethanone 3e:

IR (cm-1): *v* (CH) 3060; *v* (C=O) 1680; *v* (NO_2) 1560-1340; *v* (N-N=C) 1230; *v* (C-O-C) 1085.
1H NMR ð (ppm): 4.79 (s, 2H, CH_2); 7.54- 8.65 (m, 12H, Ar-H);
13 CNMR ð ppm: 50.2 (CH_2); 127-145 (ArC); 156-159 (O-C=N, Oxadiazole ring); 195.4 (C=O); MS: 419.5 (M+)

1-{2-[5-(4-Hydroxy-phenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-2-phenyl-ethanone 3f:

IR (cm-1): *v* (OH) 3310; *v* (CH) 3010; *v* (C=O) 1670; *v* (N-N=C) 1242; *v* (C-O-C) 1090.
1H NMR ð (ppm): 4.81 (s, 2H, CH_2); 5.45 (s, 1H, OH); 7.50- 8.56 (m, 12H, Ar-H);
13 CNMR ð ppm: 50.2 (CH_2); 128-149 (ArC); 156-158 (O-C=N, Oxadiazole ring); 195.4 (C=O) MS: 390.5 (M+)

Antimicrobial and antifungal activities:

All the newly synthesized fused oxazoles were evaluated for their antibacterial activity against Yeast, Fungi, Gram positive and Gram negative organisms using disc diffusion method. The zone of inhibition was measured in mm and the activity was compared with standard drug. The results of antibacterial screening studies are reported in **Table-2**.

Conclusion:

Microwave irradiation for synthesis of the title compounds offers reduction in reaction time, operation simplicity, cleaner reaction, easy work up and improved yields. The procedure clearly highlights the advantages of microwave. The synthesized compounds **3a-g** showed convincing activity against Yeast, Fungi, Gram positive and Gram negative organisms. The data reported in this article may be helpful guide for the medical chemists who are working in this area.

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Table-1: Physical data of compounds 3a-g

Compound	Ar	Molecular Formula*	Molecular weight	Melting point (°C)	Yield (%)	
					MW	Conv.
3a	Phenyl	$C_{22}H_{15}O_2N_2Cl$	374.5	190	72	58
3b	4-methylphenyl	$C_{23}H_{17}O_2N_2Cl$	388.5	138	73	63
3c	2-methyl-3-nitrophenyl	$C_{23}H_{16}O_4N_3Cl$	433.5	176	77	62
3d	2-hydroxyphenyl	$C_{22}H_{15}O_2N_2Cl$	390.5	145	68	59
3e	4-nitrophenyl	$C_{22}H_{15}O_4N_3Cl$	419.5	180	78	62
3f	4-hydroxyphenyl	$C_{22}H_{15}O_2N_2Cl$	390.5	300	76	63
3g	2-methylphenyl	$C_{23}H_{17}O_2N_2Cl$	388.5	178	68	56

*Satisfactory C, H and N analysis were obtained for all the compounds.

Table-2: Antibacterial *in vitro* activity of compounds 3a-g

Compds	Inhibition Zone (mm) *						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.putide*	*B.subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.albicans*
3a	16	15	17	19	16	17	9
3b	17	16	19	20	18	10	10
3c	18	19	18	18	19	10	9
3d	19	18	17	19	20	9	9
3e	17	15	17	21	17	10	10
3f	16	17	17	21	19	10	9
3g	15	14	18	19	18	11	9
DMSO	0	0	0	0	0	0	0
Ampicilin®	24	20	19	22	24	14	14

E.coli. = Escherichia coli; P.putide = Pseudomonas putide; B. subtilis = Bacillus subtilis; S. lactis = Sterptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. albicans = Candida albicans.

The sensitivity of microorganisms to the tested compounds is identified in the following manner*;

Highly Sensitive = Inhibition zone: 15-20 mm

Moderately Sensitive = Inhibition zone: 10-15 mm

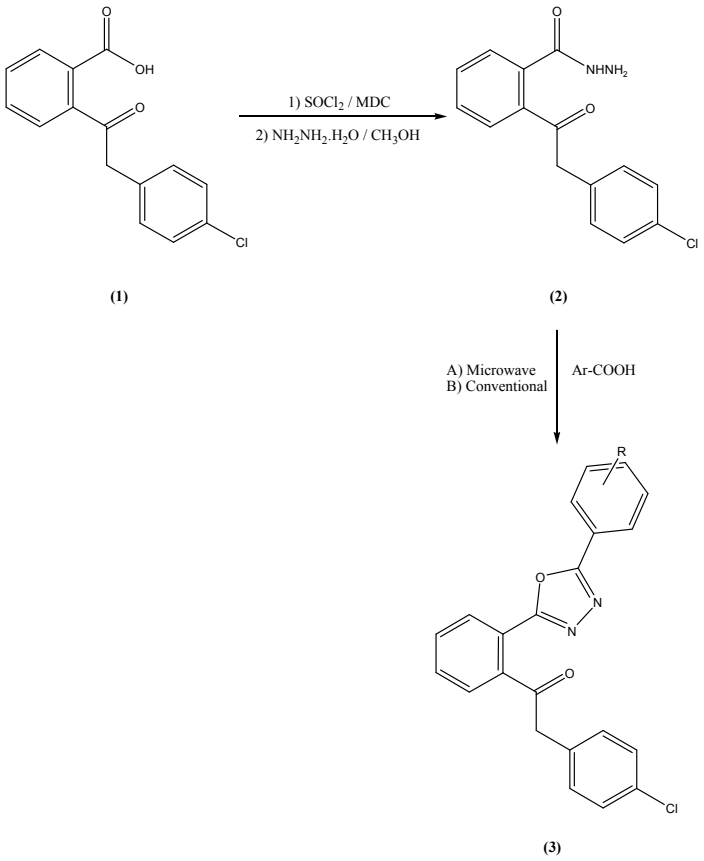
Slightly Sensitive = Inhibition zone: 5-10 mm

Not Sensitive = Inhibition zone: 0 mm

* Each result represents the average of triplicate readings.

* N.B. Concentration selected was 100 µg/ml and DMSO was used as the solvent**.**

Reaction Scheme



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