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Synthesis and Biological Screening of Some Novel Oxadiazole Derivatives

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Abstract: A new class of 1,3,4-Oxadiazoles were prepared from acid hydrazide on treatment with aromatic aldehyde in presence of acetic acid to get hydrazones. Hydrazones on treatment with various chemicals & prepared 2-(biphenyl-4-yl)-5-phenyl-1,3,4-oxadiazole derivatives. The structures of these compounds have been elucidated by elemental and spectral (IR, ^{1}HNMR & Mass) analysis. Furthermore, compounds were screened for in vitro antimicrobial activity against the representative panel of gram positive and gram negative bacteria by disc diffusion method. The various compounds show potent inhibitory action against test organism.
Key words- 1,3,4-Oxadiazoles, antibacterial activity, Chloramine T.

Introduction

Now a day's many people died from bacterial infection. The resistance developed pathogens against from many marketed products. Five member Heterocyclic is the largest division of medicinal chemistry and is Importance of pharmacologically and industrially. Development of antibacterial molecules with structural characteristic, broad spectrum of activity against pathogen is needed. In the recent years man researchers have been paying to the synthesis of nitrogen based heterocyclic compounds because of their pharmacological significance[1].

A large number of heterocyclic compounds containing the 1,3,4-oxadiazoles are associated with various pharmacological properties. In the past years considerable evidence has been accumulated to demonstrate diverse pharmacologically properties. The majority of pharmaceutical and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial application ranging from reprography, Information storage, cosmetics and plastics are heterocyclic in nature. Oxadiazoles constitute an important class for new drug development in order to discover an effective compound against multi drug resistant microbial infection[2]. The available therapeutically medicine containing the 1, 3, 4-Oxadiazoles ring are associated with diverse pharmacological properties such as anti-inflammatory, antimicrobial, fungicidal and anti viral activity[3-6]. Substituted 1,3,4-oxadiazole have revealed antibacterial[7], antimycobacterail[8], anti fungal activity[9], anti-inflammatory activity[10], analgesic[11], anticonvulsant [12] and antidepressant activity[13]. Prompted by the observed

biological activities of the above mentioned derivatives and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized new 1,3,4-Oxadiazoles As a potential antimicrobial and Anti-Inflammatory agent.

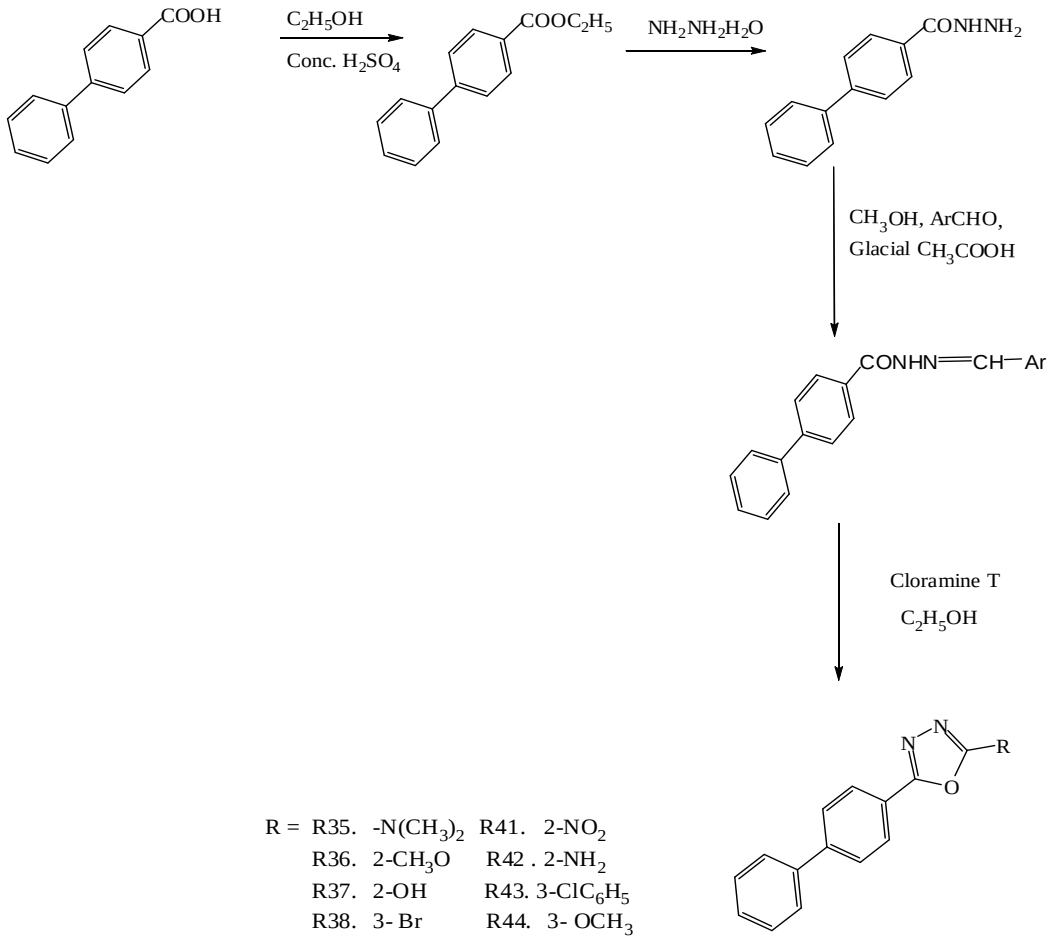
Experimental

The melting points were determined in open capillary tube and are uncorrected. Infra red spectra were recorded on Perkin Elmer spectrum spectrophotometer. ^{1}HNMR spectra were run on BRUCKER spectrometer (300MHz) using TMS as internal standard. The progress of the reaction was monitored by thin layer chromatography on TLC silica gel plates. The purity of synthesized compounds was as curtained by TLC on silica gel G in various solvent systems Toluene: Ethyl acetate: Formic acid (5:4:1) using Iodine vapors as detecting agents.

Chemistry

The preparation of target compounds is out lined in scheme. The Biphenyl 4- Carboxylic acid (I) was first reacted with ethanol in sulphuric acid yielded corresponding ethyl ester of Biphenyl 4- Carboxylic acid (II) in very good yield 80%. This ester was then converted almost quantitatively to the hydrazide (III) after treatment with hydrazine hydrate. Hydrazine hydrate react with aromatic aldehyde and glacial acetic acid converted to hydrazones. A mixture of biphenyl 4-carbohydrazide (0.001M) and chloramine T (0.001M) in ethanol (10 ml) was refluxed 5-7 hr. The reaction mixture was slowly poured over Crushed ice and kept overnight. The solid thus separated out was filtered, and recrystalysed from ethanol gives 2-(biphenyl-4-yl)-5-phenyl-1,3,4-oxadiazole derivatives (R35-R46).

Scheme



R = R35. -N(CH$_3$)$_2$ R41. 2-NO$_2$
R36. 2-CH$_3$O R42 . 2-NH$_2$
R37. 2-OH R43. 3-ClC$_6$H$_5$
R38. 3- Br R44. 3- OCH$_3$
R39. 4-OCH$_3$ R45. 4-NO$_2$
R40. 3-NH$_2$ R46. -C$_6$H$_5$

R35- 4-[5-(Biphenyl-4-yl)-1,3,4-oxadiazol-2-yl]-*N*,*N*-dimethylaniline
IR (γ max cm-^{1}): 1215 (C-O-C), 1621 (C=N), 2941 (Ar-CH), ^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 3.43 (s, 3H, N-CH_3), 7.25-7.99 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 341 (M^+).

R36- 2-(Biphenyl-4-yl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1211 (C-O-C), 1623 (C=N), 2937 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 3.80 (s, 3H, O-CH_3), 6.98-7.93 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 328 (M^+).

R37- 2-(5-(biphenyl-4-yl)-1,3,4-oxadiazol-2-yl)phenol
IR (γ max cm-^{1} 810 (Br), 1213 (C-O-C), 1626 (C=N), 2930 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.91-7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring) 9.81 (s, 1H, C-OH). MS: (m/z): 314 (M^+).

R38- 2-(biphenyl-4-yl)-5-(3-bromophenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 810 (Br), 1213 (C-O-C), 1626 (C=N), 2930 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.79-7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 378 (M^+).

R39- 2-(biphenyl-4-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1213 (C-O-C), 1626 (C=N), 2930 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 3.90 (s, 3H, Ar-OCH_3), 6.85 -7.96 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 328 (M^+).

R40- 2-[5-(biphenyl-4-yl)-1,3,4-oxadiazol-2-yl]aniline
IR (γ max cm-^{1}): 810 (Br), 1213 (C-O-C), 1626 (C=N), 2930 (Ar- CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.80 -7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 313 (M^+).

R41- 2-(biphenyl-4-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1410 (Ar-NO_2), 1213 (C-O-C), 1626 (C=N), 2930 (C-H).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.94-7.89 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 367 (M^+).

R42- 2-(biphenyl-4-yl)-5-(2-aminophenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1213 (C-O-C), 1260 (Ar-NH_2), 1628 (C=N), 2945 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 5.69 (s, 2H, NH_2), 6.25 -7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 313 (M^+).

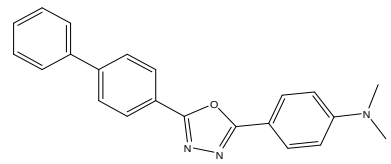
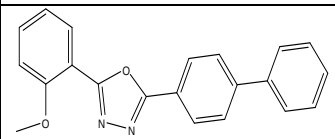
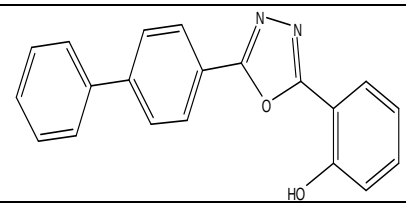
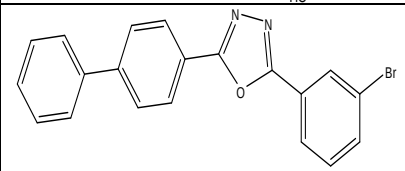
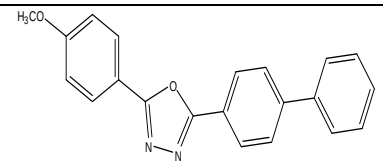
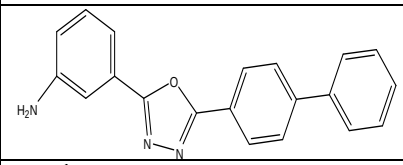
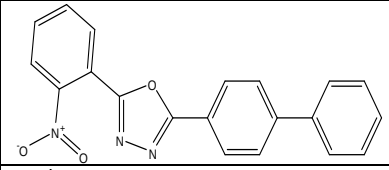
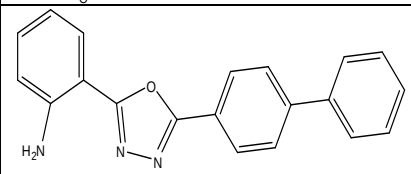
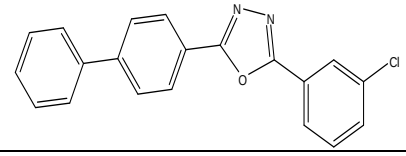
R43- 2-(biphenyl-4-yl)-5-(3-chlorophenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 760 (Ar-Cl), 1218 (C-O-C), 1636 (C=N), 2935 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 7.43-8.05 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 333 (M^+).

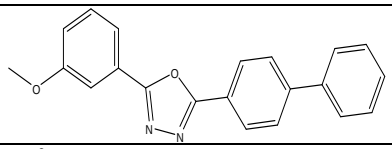
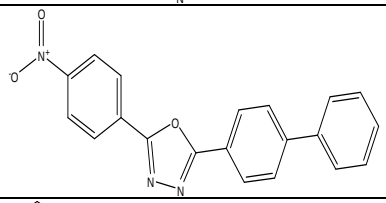
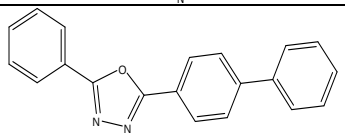
R44- 2-(biphenyl-4-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1213 (C-O-C), 1646 (C=N), 2945 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm 6.91-7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 328 (M^+).

R45- 2-(biphenyl-4-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1162 (Ar-NO_2), 1216 (C-O-C), 1628 (C=N), 2932 (Ar -CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.91-7.91 (m, 9H, Bi phenyl ring & m, 4H, Phenyl substituted ring). MS: (m/z): 343 (M^+)

R46- 2-(biphenyl-4-yl)-5-phenyl-1,3,4-oxadiazole
IR (γ max cm-^{1}): 1213 (C-O-C), 1629 (C=N), 2933 (Ar-CH).^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 6.88-7.81 (m, 9H, Bi phenyl ring & m, 5H, Phenyl substituted ring). MS: (m/z): 298 (M^+).

Table- 1 Analytical Data

S.N	Compd code	Compounds	Chemical Formula	Mole.Wt.	Yield %	M.P. (^{0}c)
1	R35		$C_{22}H_{19}N_3O$	341	59	111-113
2	R36		$C_{21}H_{16}N_2O_2$	328	62	132-134
3	R37		$C_{20}H_{14}N_2O_2$	314	50	115-117
4	R38		$C_{20}H_{13}BrN_2O$	377	48	124-126
5	R39		$C_{21}H_{16}N_2O_2$	328	65	120-122
6	R40		$C_{20}H_{15}N_3O$	313	61	126-128
7	R41		$C_{20}H_{13}N_3O_3$	343	55	119-121
8	R42		$C_{20}H_{15}N_3O$	313	59	112-114
9	R43		$C_{20}H_{13}ClN_2O$	332	63	109-111

10	R44		$C_{21}H_{16}N_2O_2$	328	59	123-125
11	R45		$C_{20}H_{13}N_3O_3$	343	62	116-118
12	R46		$C_{20}H_{14}N_2O$	298	60	105-107

Antimicrobial Activity-

The synthesized compounds were evaluated for their antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*); Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeroginosa*) were expressed as zone of inhibition values in mm[14, 15]. The zone of inhibition values were determined by cup plate agar diffusion method[16, 17]. Zone of inhibition values of the synthesized compounds and the standard drugs, Ofloxacin were compared at concentration of 100 µg/ml. The stock solutions of the compounds were prepared in dimethyl sulphoxide (DMSO) as solvent which was also used as control. The minimal inhibitory concentrations of the tested compounds are given table 2.

Table 2: In vitro antimicrobial activity of the titled compounds (R35-R46)

Compound	MIC in µg/ml and zone of inhibition			
	S.aureus	*B. subtilis*	*P. aeroginosa*	E.Coli
R35	21.45	20.94	21.42	21.44
R36	15.11	13.89	14.10	13.60
R37	20.21	20.90	19.42	20.15
R38	19.76	19.56	18.94	18.90
R39	15.45	16.54	16.10	18.38
R40	22.54	23.20	23.42	21.16
R41	24.23	24.65	24.76	23.98
R42	18.78	19.10	18.83	18.98
R43	19.80	19.94	20.76	19.68
R44	14.21	13.90	14.30	13.97
R45	23.07	23.95	22.96	23.40
R46	12.52	13.20	13.22	12.90
Ofloxacin	33.6	34.92	35.12	35.88

Results and Discussion

The results given in table 2 confirm that Oxadiazole derivatives are potential antimicrobial agents. The structures of compounds were confirmed by elemental analysis, IR spectra and ^{1}HNMR analysis. Analysis of structures and the activity displaced, some structure activity relationship can be extracted. This is proving by the fact that 2-(biphenyl-4-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole **(R41),**2-(biphenyl-4-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole **(R45)**, 2-[5-(biphenyl-4-yl)-1,3,4-oxadiazol-2-yl]aniline **(R40)**, 2-(5-(biphenyl-4-yl)-1,3,4-oxadiazol -2-yl)phenol **(R37)**, 2-(biphenyl-4-yl)-5-(3-chlorophenyl)-1,3,4-oxadiazole **(R43)** having electron withdrawing groups showed excellent antibacterial activity. It was noticed that the compounds having mild electron donating groups, 4-[5-(Biphenyl-4-yl)-1,3,4-oxadiazol-2-yl]-*N*,*N*-dimethylaniline **(R35)**, 2-(Biphenyl-4-yl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole **(R36)**, 2-(biphenyl-4-yl)-5-(3-bromophenyl)-1,3,4-oxadiazole **(R38)**, 2-(biphenyl-4-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole**(R39)**, 2-(biphenyl-4-yl)-5-(2-aminophenyl)-1,3,4-oxadi azole **(R42)**, compounds show moderate antibacterial activity where as compounds 2-(biphenyl-4-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole**(R44)**,2-(biphenyl-4-yl)-5-phenyl-1,3,4oxadiazole **(R46)** having p-phenyl group did not show appreciable antibacterial activity when compared with standard drug Ofloxacin. Therefore it May be concluded the presences of electron withdrawing groups on aromatic ring enhance the antimicrobial activity of Oxadiazole derivatives.

Conclusion

In conclusion, a series of substituted Oxadiazole derivatives have been synthesized and in their in vitro antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*); Gram-negative (*Escherichia coli* and *Pseudomonas aeroginosa*) bacteria. The minimal inhibitory concentrations (MIC) of all the compounds were determined by observing the zone of inhibition formed around the cup after 24 h of incubation. Oxadiazole as useful templates for further development through modification or derivitization to design more potent biologically active compounds .Various Oxadiazoles from biphenyl 4- carboxylic acid were prepared with the objective with of developing antimicrobial activity. Compounds were found to have excellent and moderate antibacterial activity.

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