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Facile Synthesis of Some Novel 1, 3, 4-Oxadiazole Derivatives Associated with Pyrimidine Core Unit as a Anti-Microbial Agents

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Abstract

Aim: A new series of 2-(4-phenylpyrimidin-2-yl)-5-p-substituted-1, 3, 4-oxadiazole derivatives (8a-j) were synthesized after refluxing 4-phenylpyrimidine-2-carbohydrazide[6] with different aromatic/Heterocyclic carboxylic acids (7 a-j) in the presence of $POCl_3$. The chemical structures of these compounds were confirmed by various physico-chemical methods viz. IR, [1] H-NMR, EI-Mass, [13] C-NMR analysis. Newly synthesized compounds were screened in vitro for their antimicrobial activity against varieties of gram-positive and gram-negative bacterial strains and fungi strains. The compounds 8j, 8i and 8h shows highly significant antimicrobial activity as compared to the standard drug.

Materials and Methods: Melting points of the synthesized compounds were determined in Open-glass capillaries using GUNA melting point apparatus and are uncorrected. IR Absorption spectra were recorded in the 4000-400 cm^{-1} range on a Shimadzu FTIR-8400s Using KBr pellets, [1] H-NMR and [13] C-NMR were recorded on Bruker-NMR, 400 MHz Spectro photometer. EI-Mass spectra were recorded by Agilent-NMR, 400 MHz Spectro photometer. TLC was done on F254 grade silica-60 from SD Fine. Antimicrobial studies were done in the Microbiology Laboratory in S.K. University Anantapuramu.

Results and Discussion

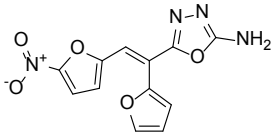
Chemistry: In the present work, 1, 3, 4-oxadiazole derivatives containing Pyrimidine nucleus unit8 (a-j) were synthesized and characterized on the basis of spectral (1) H NMR, (13) C-NMR, EI-Mass and IR) analyses. The synthesized compounds were evaluated for their antimicrobial activity against different bacteria and fungi strains. Synthetic chemistry involves conversion of corresponding aromatic acids to respective Methyl esters (5) and further converted to carbohydrazides (6) by refluxing with hydrazine hydrate. Various Para substituted carboxylic acids 7 (a-j) was refluxed in the presence of POCl3 and obtained a series of derivatives of 1, 3, 4-oxadiazole containing Pyrimidine core unit 8 (a-j).

Biology: Two gram negative and two gram positive bacterial strains were used for the evaluation of the antibacterial screening of the selected synthesized compounds. Ampicilin was used as the standard. Similarly, two fungi strains were used for the antifungal screening of the selected compounds. Flucanazole was used as the standard. The results were illustrated in the (Tables 1-3) respectively. The compounds 8j, 8i and 8h shows highly significant antimicrobial activity as compared to the standard drug. Rest of the compounds showed moderate inhibition on bacteria and fungi strains.

Conclusion: A new series of 2-(4-phenylpyrimidin-2-yl)-5-p-substituted-1, 3, 4-oxadiazole derivatives (8a-j) were synthesized. The synthesized compounds were also moderately active against different bacteria and fungi Strains. Among the selected compounds, 7h and 7i exhibited good antibacterial and antifungal agent in our study. These results indicated that substituted 1, 3,4oxadiazole with Pyrimidine core unit may be useful leads for Anti-microbial drug development in the future.

Keywords: 1, 3, 4-Oxadiazole; Pyrimidines; Cyclisation; Antibacterial and Antifungal activity

Table 1: Examples of 1, 3, 4-oxadiazole nucleus containing drugs.

Name	Structure	Medicinal use
Furamizole 5-[(E)-1-(furan-2-yl)-2-(5-nitrofuran-2-yl)ethenyl]-1,3,4-Oxadiazole-2-amine.		Anti-bacterial agent

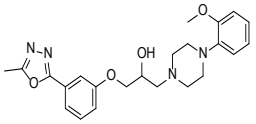
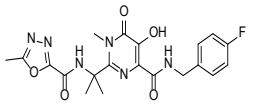
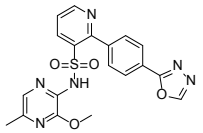
Nesapidil 1-[4-(2- Methoxy phenyl) piperazin-1-yl]-3-[3-(5-methyl-1,3,4- oxadiazol-2- yl)phenoxy]propan-2- ol		Anti-arrhythmic agent.
Raltegravir N-[2-[4-[(4-fluorophenyl)methylcarbamoyl[-5;hydroxyl-1-methyl-6-oxopyrimidin-2-yl]propan-2-yl]5-methyl-1,3,4-oxadiazole-2-carboxamide		Antiretroviral drug (Treatment of HIV infection)
Zibotentan N-(3-methoxy-5- methylpyrazin-2-yl)- 2-[4-(1,3,4-oxadiazol-2- yl)phenyl]pyridine-3- sulphonamide		Anti cancer agent

Table 2: Anti-bacterial activity of Novel 1, 3, 4-oxadiazole Pyrimidine derivatives 8(a-j).

Zone of inhibition measure in mm								
Synthesised Compounds	**Gram positive**				**Gram negative**			
	Bacillus sub tilis		***Staphylocouccus aurous***		***Klebsiella pneumonia***		***Escherichia coli***	
	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
8a	6	3	7.5	5	8	6	9.5	6
8b	8.5	6.5	9.0	6.5	10.15	8	11	8
8c	7.5	3.5	8	7	9.5	7	10.5	7.5
8d	10	8	11.1	9.5	12	11	13.5	11
8e	7	4.5	7	4.5	8.5	6.5	9	7
8f	9.5	7	9.5	7.5	12	10	12.5	10.5
8g	11	9.5	11.5	8.5	12.5	12	13	11.5
8h	11.5	9	12.5	11	14.5	11.5	15.5	12
8i	12.5	10	14.5	10.5	15	13.5	16.5	12.5
8j	13	10.5	15	11.5	16.5	14	17	13
Amoxicillin	15.9	12.5	17.3	14	17.6	14.5	19.5	15.5
Control **(DMSO)**	---	---	----	-----	----	-----	-----	-----

Table 3: Anti-fungal activity of Novel 1, 3, 4-oxadiazole Pyrimidine derivatives 7(a-j).

Zone of inhibition measure in mm				
Synthesised Compounds	***Candida albicans***		***Aspergillus flavus***	
	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
8a	6.5	4.5	7	4
8b	8.5	6.5	9.0	6.5
8c	7.5	3.5	8	7
8d	10	8	11.1	9.5
8e	8	5.5	7	3.5
8f	9.5	7	9.5	7.5
8g	11	9.5	11.5	8.5
8h	13	11.5	10.5	8
8i	14.5	12	12.5	9.5
8j	17.5	12.5	16	12
Flucanazole	21	16	18.5	14
Control (DMSO)	---	---	---	---

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Introduction

The development of new antimicrobial and cytotoxic agents is one of the fundamental goals in medicinal chemistry. In recent years, there has been a concerned search for the discovery and development of potent and selective cytotoxic and antimicrobial agents. N-heterocyclic ring systems are important for the drug design, among these Pyrimidine and 1,3,4-oxadiazole compounds are present in several classes of natural and synthetic biologically active compounds [1-7]. Oxadiazole (1) is five member cyclic compounds with one oxygen and two nitrogen atoms in the ring (Figure 1a-1d). 1, 3, 4-oxadiazoles have occupied unique place in the field of Medicinal chemistry due to their wide range of activities (2). The review of literature shows that 1, 3, 4-oxadiazole nucleus possess antimicrobial (3), antifungal (4), anti-inflammatory (5), anticonvulsant (6), antioxidant, Antihypertensive Activity (7-15), analgesic (7) and mutagenic activity (8).

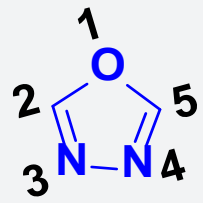
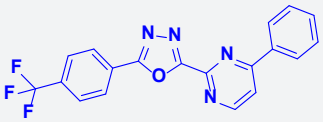
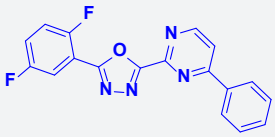


Figure 1a : structure of 1, 3, 4 oxadiazole.



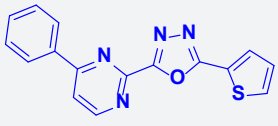
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (8h)

Figure 1b : 2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoro methyl) phenyl)-1, 3, 4-oxadiazole (8h).



2-(2, 5-difluorophenyl)-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8h)

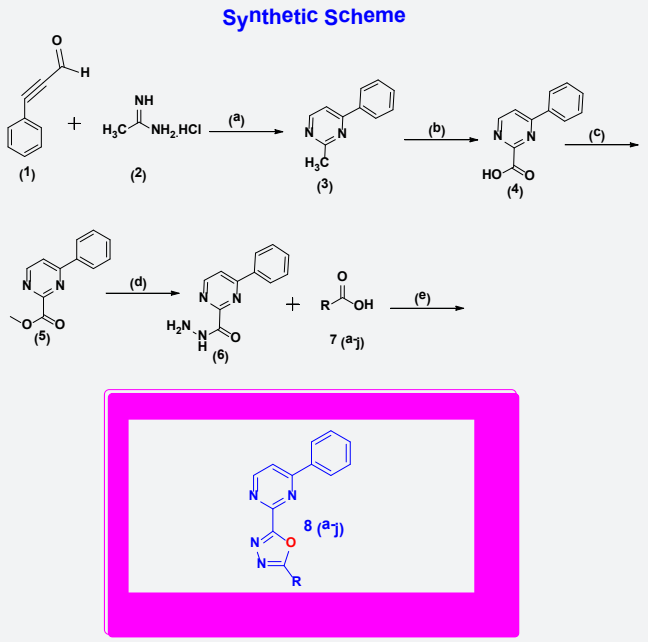
Figure 1c: 2-(2, 5-difluorophenyl)-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8i).



2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1, 3, 4-oxadiazole (8j)

Figure 1d : 2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1, 3, 4-oxadiazole (8j).

Number of drugs available in the market such as tiodazosin, nosapidil, furamizole are 1, 3, 4-oxadiazole derivatives (9). Apart from these biological activities, 1,3,4-oxadiazole derivatives were found to have some material applications in the field of liquid crystals and photosensitizer (10). Literature survey reveals that 1,3,4-oxadiazole derivatives posses a broad spectrum of biological activities (11-14). Antihypertensive Activity Consequently, they have attracted increasing attention in the field of drug discovery [8-10]. Attributable to such biological importance, Pyrimidine core structure derivatives have grown to be the synthetic goals of many organic and medicinal chemistry researchers.



R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 tri fluoro methoxy phenyl, -4 Tri fluoro phenyl, -4 Nitro phenyl, -2,5 di fluoro phenyl, Thiophene 2-yl, pyrazine-2-yl, iso nicotinic acids

Scheme 1: Synthetic path way for compounds 8a-8j.

Figure 1 : Reagents and Reaction conditions: (a) Microwave irradiation, Aceto nitrile, Na_2CO_3, 90°C, 1 hrs (b) SeO_2, Reflux, 16 hrs (c)Methanol, H_2SO_4, reflux 16 hrs (d) Hydrazine hydrate, Reflux, 10 hrs.
(e) $POCl_3$, Reflux, 6 hrs

Synthesis

Synthesis of 2-methyl-4-phenyl Pyrimidine (3)

A mixture of 3-phenylpropiolaldehyde (0.01 mol) and acetimidine hydro chloride (0.01 mol) was stirred in dry aceto nitrile (10 ml) and dry Na_2CO_3 (0.02mol) was added to it. The stirring was continued for 0.5 hr under Micro Wave conditions at 90°c .Reaction progress was monitored by TLC [11,12]. After completion of reaction cool to RT. Then concentrated under reduced pressure by using Rota evaporator & Purified by column chromatography(100-200 mesh size silica) with elution of 10% Ethyl acetate to get pure yellow solid yield:47 % mp: 130°c-132°c.

a. IR(KBr,cm^{-1}): 3100 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.);

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b. ^{1}H NMR (DMS0-d_6, ppm): 2.5(3H, S), 8.45(1H, d, J=7.4HZ), 7.8(1H, d, j=7.4HZ), 7.4-7.8(5H, m);

c. EI-Mass: 171 (M^+, +Ve mode)

Synthesis of 4-phenylpyrimidine-2-carboxylic acid (4)

A mixture of compound (3) (0.01 mol), selenium Di oxide (0.05 mol), and pyridine (10 ml) was refluxed for 2 hours. Reaction progress was monitored by TLC. After completion of compound 3, concentrated under reduced pressure, then added water (10 ml), acidified with Conc. HCl, white solid was formed, filter off, dried, to get 75 % yield. M.P: 187-189OC.

a. IR (KBr,cm^{-1}): 3100 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.),1720(C=O str.),3200(-OH Str.),1310(C-O str.);

b. ^{1}H NMR (DMS0-d_6, ppm):9.35(1H,d, j=8.3 HZ),8.55(^{1}H,d,j=8.3HZ),7.4-7.8(5H,m),10.5(-COOH);

c. EI-Mass: 199 (M+, -Ve mode)

Synthesis of methyl 4-phenylpyrimidine-2-carboxylate (5)

A mixture of compound (4) (0.05 mol, 10g), Sulphuric acid (catalytic), and Methanol (10 V, 100mL) was refluxed for 2 hours. Reaction progress was monitored by TLC. After completion of reaction concentrated under reduced pressure, then added Na_2CO_3 Solution (10 ml), white solid was formed, filter off, dried, to get 75 % yield.

a. IR (KBr, cm^{-1}): 3115(Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.), 1760(C=O str.), 1755(-Carbonyl Str.), 1310(C-O str.).

b. ^{1}H NMR (DMS0-d_6, ppm):9.45(1H, d, j=8.3 HZ), 8.65(1H, d,j=8.3HZ),7.4-7.8(5H,m),3.85(-O-CH_3);

c. EI-Mass: 215 (M+, +Ve mode)

Synthesis of methyl 4-phenylpyrimidine-2-carbohydrazide (5)

To a solution of compound (5) (0.05 mol, 10.8g),in ethyl alcohol (50 mL) was added with excess of 99% hydrazine hydrate and refluxed for 24 hr. Reaction mixture was concentrated and allowed to cool, separated crystals was filtered, dried and re-crystallized from minimum amount of ethyl alcohol [13-15]. The obtained yield is 75%.

a) IR (KBr, cm-1): 3320 (-N-H str.)3110 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.), 1690(C=O str.).

b) 1H NMR (DMS0-d6, ppm):9.45(1H, d, j=8.3 HZ), 8.65(1H, d,j=8.3HZ),7.4-7.8(5H,m),3.85(-O-CH3);

c) EI-Mass: 215 (M+, +Ve mode)

d) Synthesis of 2-phenyl-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8a),

e) 2-(4-phenylpyrimidin-2-yl)-5-p-tolyl-1, 3, 4-oxadiazole (8b),

f) 2-(4-methoxyphenyl)-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8c),

g) 2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethoxy) phenyl)-1, 3, 4-oxadiazole (8d),

h) 2-(4-phenylpyrimidin-2-yl)-5-(pyrazin-2-yl)-1, 3, 4-oxadiazole (8e),

i) 2-(4-nitrophenyl)-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8f),

j) 2-(4-phenylpyrimidin-2-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazole (8g),

k) 2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoro methyl) phenyl)-1, 3, 4-oxadiazole (8h),

l) 2-(2, 5-difluorophenyl)-5-(4-phenylpyrimidin-2-yl)-1, 3, 4-oxadiazole (8i),

m) 2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1, 3, 4-oxadiazole (8j)

To the equi molar mixture of compounds (6) and 7(a-j), catalytic amount of POCl3 was added and it was refluxed for 4-6 hrs. The reaction mixture was poured over crushed ice and neutralized by sodium carbonate solution. The precipitate formed was filtered and dried. The crude product was purified by the alcohol and DMF mixture.

a) IR (KBr, cm^{-1}): 1320 (-C-F str.)3110 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.), 1354 (C-O-C).

b) 1H NMR (DMS0-d_6, ppm):8.65(1H, d, j=7.3 HZ), 7.95(1H, d, j=7.3HZ),7.4-7.8(5H,m),7.85(2H, d, j=7.6HZ); 8.15(2H, d, j=7.6HZ);

c)^{13}C NMR (100 MHz; $CDCl_3$): δC 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65.

d) EI-Mass: 369 (M^+, +Ve mode)

e) IR (KBr, cm^{-1}): 1340 (-C-F str.), 3108 (Ar.C-H str.), 1620 (Ar.C-C str.), 1458 (C-N str.), 1350 (C-O-C).

f) $_1$H NMR (DMS0-d_6, ppm):8.65(1H, d, j=7.3 HZ), 7.95(1H, d, j=7.3HZ), 7.4-7.8(5H, m),7.55(1H, d, j=3.6HZ); 7.15(2H, d, j=7.6HZ); 7.35 (2H, d, j=7.6HZ).

g) ^{13}C NMR (100 MHz; $CDCl_3$): δC 125.5, 128.89, 130.55, 133.45,141,149, 155.45, 158.8, 162.34, 165.45.

h) EI-Mass: 335 (M^+, -Ve mode)

i) IR (KBr, cm^{-1}): 740 (-C-S-C str.), 3108 (Ar.C-H str.), 1620 (Ar.C-C str.), 1455 (C-N str.), 1350 (C-O-C).

j) ^{1}H NMR (DMS0-d_6, ppm):8.55(1H, d, j=7.3 HZ), 7.93(1H, d, j=7.3HZ), 7.4-7.8(5H,m),7.65(1H, d, j=7.6HZ); 7.15(1H, d, j=7.6HZ); 7.75 (1H, d, j=7.6HZ).

k) ^{13}C NMR (100 MHz; $CDCl_3$): δC 125.5, 128.89, 130.55, 133.45,141,149, 155.45, 158.8, 162.34, 165.45.

l) EI-Mass: 307 (M^+, +Ve mode)

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Biological Activity

Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia and Escherichia coli* (clinical isolate) bacterial strains by disc diffusion method (15, 16). A standard inoculums (1-2×107 c.f.u./ml 0.5 McFarland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6 mm in diameters were prepared from what man no. 1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. *Amoxicillin* (30 µg) was used as positive control and the disk poured in DMSO was used as negative control and the test compounds were dissolved in DMSO at concentration of 100 and 50 µg/ml. The plates were inverted and incubated for 24 h at 37°C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition of zone of measured and compared with controls. The bacterial zone of inhibition values are given in (Table 1). The order of activity was 8j>8i>8h>8g>8d>8f>8b>8c>8e>8a.

Antifungal studies

The newly prepared compounds were screened for their antifungal activity against Candida albicans and *Aspergillus flavus* in DMSO by agar diffusion method (17). Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH 5.7. Normal saline was used to make suspension of corresponding species. Twenty milli liters of agar media was poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h using an agar punch, wells were made and each well was labeled [16,17]. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The fungal activity of each compound was compared with *Flucanazole* as a standard drug. Inhibition zone were measured and compared with the controls. The fungal zone of inhibition values are given in (Tables 2 & 3).

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