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Research Article

Synthesis and antimicrobial activity of some new oxadiazole derivatives

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Abstract

The series of novel 1,3,4-oxadiazoles were synthesized from ethyl 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidin-5- carboxylate. Synthesized compounds were characterized by IR, ^{1}H NMR, and Mass spectral analysis and all the compounds are evaluated for their antimicrobial activities against different Gm (+ve) and Gm (-ve) bacteria. All the synthesized compounds has exhibited good antimicrobial activity against Gm (+ve) and Gm (-ve) bacteria like *Bacillus subtilis, Staphylococcus aureus* and *E.coli, Klebsiella pneumonia* at higher concentration (100µg).
Keywords: Oxadiazole; Dihydropyrimidine; Antibacterial activity.

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1. Introduction

1,3,4-oxadiazoles is a well known important heterocycle both in synthetic as well as medicinal chemistry due to its simple synthesis and a wide range of biological activities. The common synthetic method for these compounds is cyclodehydration of diacylhydrazines and their derivatives with dehydrants such as phosphorous oxychloride, trifluoroacetic anhydride, thionyl chloride polyphosphoric acid and also reaction between the properly substituted acid hydrazide, carbon disulfide.1,3,4 oxadiazole and their derivatives constitutes as important class of organic compounds which have attracted much attention due to diverse biological activity as antimicrobial[1], antibacterial[2], antifungal[3], antiviral[4], antituberculosis[5], antidiabetic[6], anticonvulsant[7], antioxidants[8], anti-inflammatory[9], anticancer[10] *etc.*,

2. Experimental

2.1. Materials and measurements

All chemicals used were of laboratory grade and used without further purification. Melting points of compounds were determined in open capillary tubes in a silicon oil bath using a Veego melting point apparatus and are uncorrected. Purity of compounds was monitored by TLC on silica F_{254} coated aluminum plates (Merck) as adsorbent and U.V. light and iodine as visualizing agents. ^{1}H spectra were recorded on Bruker (^{1}H NMR) using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard (Chemical shift in ppm). The High Resolution Mass Spectra were recorded on Waters QT micro-mass analyzer.

2.2. Synthesis

2.2.1 Step1: Synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidin-5- carboxylate:

A mixture of Anisaldehyde (0.05 mol), ethyl acetoacetate (0.05 mol), urea (0.05 mol) and add 10-15 ml of methanol and few drops of conc. H_2SO_4 to reflux for 90 min. Cool the reaction mixture and poured into crushed ice and scratching solid product obtained after filtration, dried and purified by recrystallized by using suitable solvent[11].

2.2.2 Step 2: Synthesis of carbohydrazide 3, 4-dihydropyrimidin-2(1H)-one:

Hydrazine hydrate (0.04 mol) was added to the solution of 3, 4-dihydropyrimidin-2(1*H*) - ones (0.01 mol) in DMF. The reaction mixture was heated under reflux for 28-30 hr, concentrated in vaccume, cooled and poured into ice cold water. The precipitate was obtained by filtration, dried and recrystallized by suitable solvent.

2.2.3 Step 3: Synthesis of Oxadiazole derivatives

Carbohydrazide derivative (0.005 mol) was dissolved in $POCl_3$ (2.5 ml) and different aromatic acid (0.005 mol) (Table 1) was added. The reaction mixture after refluxing for 8-10 hr was cooled to room temperature and poured into crushed ice. And neutralization of content with neutral 20% sodium bicarbonate solution, solid separated out was filtered, washed with water and dried. Then the resulting derivative was recrystallized by using suitable solvent.

Table 1: Various aromatic acids used for the Preparation of oxadiazole derivatives (3a-3e)

Compound	Various aromatic acid
3a	Benzoic acid
3b	4-chloro benzoic acid
3c	2-chloro benzoic acid
3d	4-amino benzoic acid
3e	Salicyclic acid

2.3. Characterization of synthesized compounds

2.3.1. 4-(4-methoxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5 carbohydrazide (1)

Color: Yellowish coloured solid. Yield 73.06%, m.p. 243-248 º C. IR (KBr cm ^{1}): 1693.5 (C=O), 3202.62 (N-H), 2848.86 (C-H); ^{1}H-NMR (DMSO-d_6): δ8.636 (s,1H,N-H), δ7.047-7.828(m,4H,Ar-H), δ3.337(s,1H,N-H), δ1.12(s,3H,CH_3), δ3.067(s,3H,OCH_3), δ2.041(s,1H,Ar-CH-), δ3.832 (d, 2H, NH_2), δ 6.73 (t, 3H, N-H).

2.3.2. 4-(4-methoxyphenyl)-6methyl 5-(5phenyl1, 3, 4-oxadiazole-2-yl)-3, 4dihydropyrimidin-2(1*H*) one (3a)

Color: Brown colored Amorphous solid. Yield 60.10%, m.p. 268-272 º C. IR (KBr, cm^{-1}): 1500.62 (C=N), 1629.85 (C=O), 1028.06 (C-O-C), 3437.15 (NH); ^{1}H-NMR (DMSO-d_6):δ8.320 (s, 1H, N-H), δ 7.52-7.95 (m, 9H,Ar-H),δ 3.778 (s, 1H, N-H), δ 3.49 (s, 3H, OCH_3,) δ1.2(s, 3H,CH_3), δ 2.33 (s, 1H, Ar-CH-). MS: m/z = 361.3 (M^+), 287.3, 134.3, 81.3

2.3.3. 5-[5-(4-chlor phenyl)-1, 3, 4-oxadiazol-2-yl] 4-(4-methoxyphenyl) 6-methyl-3,4dihydropyrimidin2 (1*H*) one (3b)

Color: Brownish colored solid. Yield 86.50%, m.p. 229-232 °C. IR (KBr, cm ^{1}): 1595.13 (C=N), 1004.91 (C-O-C), 1674.21 (C=O), 3385.07 (NH)

2.3.4. 5-[5-(2-chlorophenyl) 1, 3, 4 oxadiazol-2-yl] 4(4methoxy- phenyl) -6- methyl-3, 4-dihydropyrimidin 2(1*H*)-one (3c)

Color: Brownish colored solid. Yield 64.12%, m.p. 228-232 ºC. IR (KBr, cm ^{1}): 1600.92 (C=N), 1699.29 (C=O), 1028.06 (C-O-C),3387 (NH); ^{1}H-NMR (DMSO-d_6):δ 8.323 (s, 1H, N-H), δ 7.60-7.75 (m, 8H, Ar-H), δ 3.725 (s, 1H, N-H), δ 1.2 (s, 3H, CH_3) δ 3.332 (s, 1H, OCH_3), δ 2.3 (s, 1H, Ar-CH-). MS: m/z = 396.2 (M^+), 208.3, 151.2, 70.3

2.3.5. 5-[5-(4-aminophenyl)-1, 3, 4-oxadiazol-2-yl]-4-(4-methoxyphenyl)-6-methyl3, 4-dihydropyrimidin2 (1*H*)-one (3d)

Color: Brown colored solid. Yield 89.68%, m.p. 231-235 º C. IR (KBr, cm^{-1}): 1602.85 (C=N), 1602.85 (C=O), 1085.92(C-O-C), 3358.07 (NH); ^{1}H-NMR (DMSO-d_6):δ9.87(s,1H,N-H),δ7.80-7.89(m,9H,Ar-H),δ 3.778 (s, 1H, N-H), δ 1.2 (s, 3H, -CH_3), δ3.703 (s, 3H, OCH_3), δ 3.795 (s, 2H, -NH_2), δ 2.32 (s, 1H, Ar-CH-). MS: m/z = 374.3 (M^+), 325.3, 260.8, 159.0, 79.2.

2.3.2. 5-[5-(4-hydroxyphenyl)-1, 3, 4-oxadiazol-2-yl]-4-(4methoxyphenyl) 6-methyl-3, 4-dihydropyrimidin 2(1*H*) one 2(1*H*)-one (3e)

Color: Brown colored solid. Yield 66.30%, m.p. 233-238 º C. IR (KBr, cm^{-1}): 1500.62 (C=N), 1045.42 (C-O-C), 1612.49 (C=O),3425.58 (NH); ^{1}H-NMR (DMSO-d_6): δ 8.628 (s, 1H, N-H), δ 7.041-7.171(m, 8H, Ar-H),δ 3.686(s,1H,N-H),δ1.230(s,3H,CH_3)δ3.77(s,1H, OCH_3), δ 9.12 (s, 1H, Ar-OH), δ 2.034 (s, 1H, Ar-CH-). MS: m/z = 345.3 (M^+), 269.3, 225.2, 134.3.

2.4. Antimicrobial activity

Synthesized compounds were screened for antibacterial activity. The zones of inhibition of the microbial growth produced by different concentration of test compounds were measured in mm [12,13]. The zone of inhibition data of the newly synthesized compounds were tested for their antibacterial activity against four Gm (+) and Gm(-) microorganisms *viz. Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Escherichia coli* (MTCC 443)and *Klebsiella pneumoniae* at 50, 100 µg/ml concentration using streptomycin as a reference standard[14]. The plates were incubated at 37°Cfor 24 hours and the results were recorded.

3. Results and discussion

3.1. Chemistry

6-methyl-5-(5-substituted phenyl-1,3,4-oxadiazole -2-yl) 3-substituted 4-phenyl-3,4-dihydropyrimidin - 2(1*H*) -ones were synthesized by **Scheme I (figure 1).** Firstly, dihydropyrimidin-2(1*H*)-ones were synthesized from anisaldehyde, urea and ethylacetoacetate in presence of methanolic sulphuric acid through grinding method

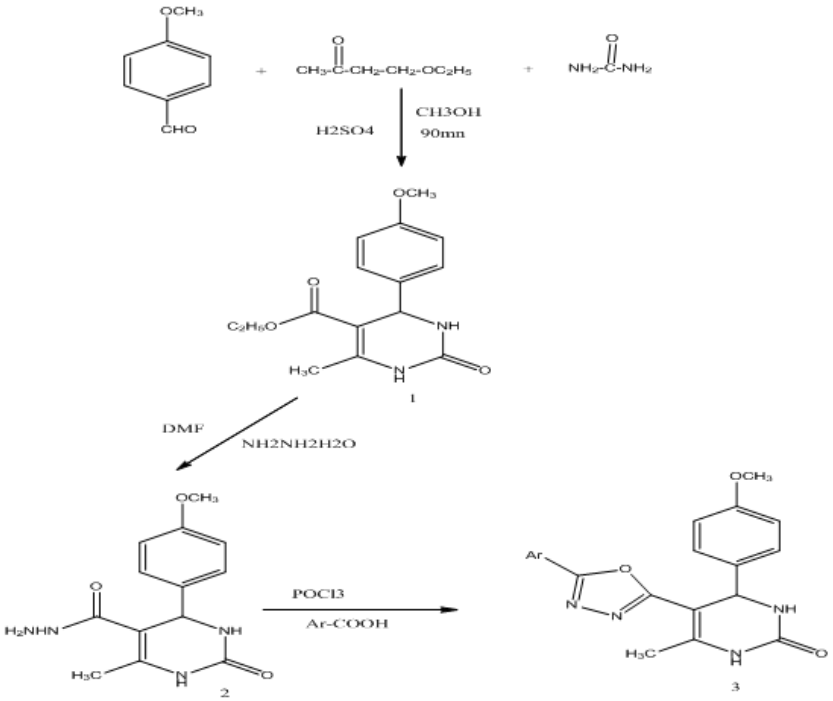
(biginelli reaction). Then, dihydropyrimidin-2(1*H*)-ones were converted to carbohydrazide 3,4-dihydropyrimidin-2(1*H*)-ones with hydrazine hydrate. These carbohydrazide 3,4-dihydropyrimidin-2(1*H*)-ones were cyclized to oxadiazoles with different aryl acids in presence of $POCl_3$**(3a-3e)**. Biginelli methodology does not have any enantiocontrol during formation of the new stereocenter. The yields of all synthesized compounds were found to be range between 41%-85%.

IR spectrum of intermediate (**1**) showed sharp peak at 2848.86 cm^{-1} to C-H stretching. IR spectrum of all compounds showed sharp peak at 2900-3000 cm^{-1} to C-H stretching for aromatic ring (phenyl). For oxadiazole moiety, absorbance bands appear at 1590-1660 cm^{-1} for C=N stretching and 1000-1200 cm-1 for C-O-C stretching. For compound **3b**, it shows peak at 752.24 cm^{-1} for C-Cl stretching. For compound **1**, it shows peak at 3358.07 cm^{-1} for free amino group. For the compound**3e**, it shows peak at 3425.58 cm^{-1} for O-H stretching.

The ^{1}H-NMR (DMSO-d6) spectra of intermediate (**1**) showed singlet δ 8.636 (s, 1H) for N-H, δ 3.337 (s, 1H) for N-H, δ 7.047-7.828 (m, 4H) for Ar-H, δ 1.12 (s, 3H) for -CH_3, δ 3.067 (s, 3H) for –OCH_3, δ 2.041 (s, 1H) for Ar-CH, δ 3.832 (d, 2H) for NH_2 and δ 6.73-6.75 (t, 3H) for N-H. The ^{1}H-NMR (DMSO-d6, δ ppm) spectra of all the compounds indicates aromatic multiplet δ 7.0-7.95 ppm. For the compound **3a**, ^{1}H-NMR values are δ 7.48-7.95 (m, 9H) for Ar-H, δ 8.320 (s, 1H) for N-H, δ 3.778 (s, 1H) for N-H, δ 3.49 (s, 3H) for –OCH_3, δ 1.2 (s, 3H) for –CH_3, δ 2.33 (s, 1H) for Ar-CH.

For the compound **3d,** ^{1}H-NMR value is δ 3.795 (s, 2H) for Ar-NH_2. For the compound **3e,** ^{1}H-NMR value is δ 9.12 for Ar-OH. Further, MASS spectra showed molecular ion peak at m/z [M+] 361.3, 396.2, 374.3 and 345.3 for the compounds **3a, 3c, 3d**and**3e,** respectively, which is in agreement with proposed molecular formula $C_{20}H_{18}N_4O_3$, $C_{20}H_{17}N_4O_3$, $C_{20}H_{19}N_5O_3$, $C_{20}H_{18}N_4O_4$.

Figure 1: Scheme-1



3.2. Antimicrobial activity

Synthesized compounds were screened for antibacterial activity at concentrations of 50, 100 µg using DMSO as control and streptomycin (10 µg) used as standard against gram(+ve) bacteria such as *Bacillus subtilis, Staphylococcus aureus* and gram (-ve) bacteria's such as *Escherichia coli, Klebsiella pneumoniae,* by using Disc diffusion method and the zone of inhibition was measured in mm. In case of gm +ve bacteria, Compounds **3a, 3b, 3c, 3d, 3e** and **1** showed good activity at 100 µg and moderate effect against *Bacillus subtilis* at concentration 100 µg. All the synthesized compounds showed less activity against *Staphylococcus aureus* at concentration 100 µg. In case of gm (–ve) bacteria, compounds **3a, 3b, 3c, 3d, 3e** and **1** showed good activity at concentration 100 µg against *Escherichia coli.* Compounds such as **3a, 3b, 3c, 3d, 3e** and **1** showed moderate activity against *Klebsiella pneumoniae* at concentration 100 µg.(Table 2)

Table 2: Antibacterial activity for substituted oxadiazole derivatives against gm (+) and gm (-) bacteria

SI. No.	Name of the compounds	Mean zone of inhibition (in mm)							
		gm (+) bacteria				gm (-) bacteria			
		Bacillus subtilis		*Staphylococcus aureus*		*Escherichia coli*		*Klebsiella pneumoniae*	
		50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
01	3a	8	9	-	7	7	10	6	7
02	3b	7	9	-	7	8	9	-	7
03	3c	7	10	-	7	6	10	-	7
04	3d	7	9	-	7	7	9	-	7
05	3e	7	9	-	7	7	8	-	7
06	1	7	8	-	7	7	9	-	7
07	STD (10 µg)	17		15		18		16	

4. Conclusion

In summary, we have synthesized a new series of 1,3,4-oxadiazoles derivatives and screened for their antimicrobial activity against few microorganisms. All the synthesized compounds has exhibited good antimicrobial activity against Gm (+ve) and Gm (-ve) bacteria like *Bacillus subtilis, Staphylococcus aureus* and *E.coli, Klebsiella pneumonia* at higher concentration (100µg). Dihydropyrimidone possess synergistic antibacterial activities at higher concentrations and therefore the newly synthesized 1, 3, 4-oxadiazole derivatives may serves as a lead molecule for further modification to obtain clinically useful novel entities in the new millennium.

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