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SHORT COMMUNICATION

Cyclization and antimicrobial evolution of 1,3,4-oxadiazoles by carbohydrazide

Dinesh R. Godhani*, Vishal B. Mulani, Jignasu P. Mehta

Department of Chemistry (UGC NON-SAP & DST-FIST sponsored Department), Mahatma Gandhi Campus, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar 364002, India

*E-mail address: drgodhani@yahoo.com

ABSTRACT

A series of dihydropyrimidine substituted 1,3,4-oxadiazole derivatives was synthesized by cyclization of carbohydrazide by phosphoryl chloride and benzoic acid in acidic condition. The structures were perceived on the establishment of spectral tools and their purity by elemental analysis. Every compound was primary assessed for their *in vitro* antimicrobial activities against 5 bacterial strains *viz* [*Staphylococcus aureus* (MRSA; ATCC 43300), *Klebsiella pneumoniae* (ATCC 700603), *Escherichia coli* (ATCC 25922), *Acinetobacter baumannii* (ATCC 19606), *Pseudomonas aeruginosa* (ATCC 27853)] and 2 fungi Strains *viz.* [*Candida albicans* (ATCC 90028), *Cryptococcus neoformans var. grubii* (H99; ATCC 208821)]. Some compounds displayed significant antimicrobial activity, out of 15 compounds, 11 compounds indicated promising antifungal activities without any indications of human cells cytotoxic [Hk: Human Embryonic Kidney cells (ATCC CRL-1573)] and haemolytic activity [RBC (ARCBS 5400 00150)].

***Keywords*:** 1,3,4-oxadiazole, dihydropyrimidine, cytotoxicity, haemolysis, antimicrobial activity

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1. INTRODUCTION

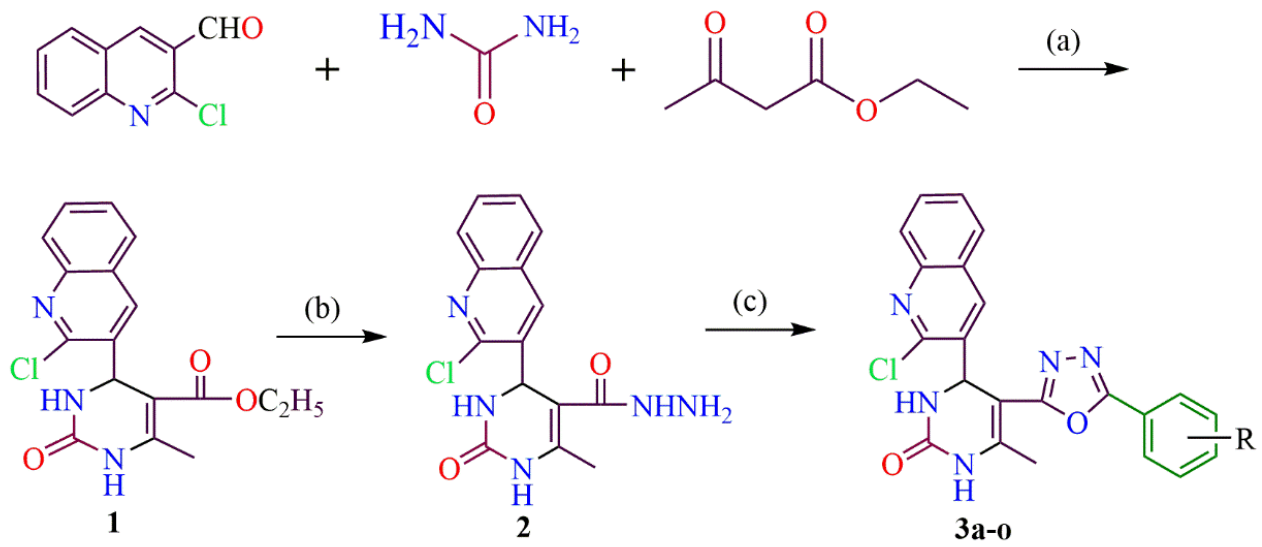
The boundless presentation of anti-microbials during the 1940s, start with penicillin [1, 2] and streptomycin [3], changed drug, giving compelling fixes to the most common illnesses of the time. Obstruction advancement confines the helpful life expectancy of anti-infection agents and results in the prerequisite for a continual production of new compounds [4, 5]. 1,3,4-Oxadiazole and its derivatives are an imperative type of compounds which possess industrial [6, 7], environmental [8] and biological activities, involving antidepressant [9], analgesic [10], antimicrobial [11], antiviral [12], antifungal [13, 14], anti-oxidant [15], antitubercular [16], anticonvulsant [17], anticancer [18], anti-inflammatory [19] and antiproliferative [20] activities. A search of the literature revealed that several published reports describe the route of cyclization of carbohydrazide to 1,3,4-oxadiazole nucleus, (Tokumaru *et al*.) [21] and (Godhani *et al*.) [22] explained the synthesis of such compounds by the cyclization reaction of carbohydrazide under acidic condition and examined the biological activity. Utilizing similar procedure and diverse approach, we have incorporated fifteen DHPM substituted 1,3,4-oxadiazole derivatives shaped by the reaction of carbohydrazide of dihydropyrimidine and benzoic acid under acidic condition. As outlined in **Scheme 1.** The compounds recommended thus were achieved in great segregated yields, utilizing straightforward strategies which did not require further cleaning for the fundamental items. In the expansion of our past work, we have created ionic liquid, for example, Butylbenzimidazolium tetrafluoroborate. The ionic liquids have been utilized as a green solvent for the synthesis of dihydropyrimidine. We in this report the combination of some new dihydropyrimidine substituted 1,3,4-oxadiazole derivatives and their antimicrobial, cytotoxic and haemolytic activities were likewise decided.

2. RESULTS AND DISCUSSION

2. 1. Chemistry

New dihydropyrimidine substituted 1,3,4-oxadiazole derivatives **(3a-o)** are set up according to standard conventions with minor alterations as displayed in **Scheme 1**. Biginelli reaction was transferred by solvent-free condition in presence of Ionic Liquid ([BBI][BF_4]). Hydrazinolysis of the ester in presence of hydrazine hydrate in 1,4-dioxane at 110 °C for 6 hours gave 4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide. Cyclization of carbohydrazide by benzoic acid derivatives in phosphoryl chloride afford 4-(2-chloroquinolin-3-yl)-6-methyl-5-(5-(substituted phenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one, (3a-o) derivatives in 61-78% yield. The structure and atom numbering of compound (3o) as an example is shown in **Figure 1.**

Spectral techniques *viz.* ^{1}H NMR, ^{13}C NMR, IR and Mass spectrometry were utilized for conceivable structure assurance of recently synthesized dihydropyrimidine substituted 1,3,4-oxadiazole derivatives **(3a-o)**. As a delegate model the ^{1}H NMR of 4-(2-chloroquinolin-3-yl)-6-methyl-5-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin- 2(1*H*)-one, (3a) is delineated here. The proton singlet at δ 2.54, 5.97, 6.26 and 8.05 ppm, due to presence of -CH_3 group, -C<u>H</u> of pyrimidine ring, -N<u>H</u>-C-Ph and –N<u>H</u>-C-CH_3, respectively. nine aromatic protons appeared as multiplet between δ 7.56-8.03 ppm. Appearance of characteristic peak in ^{13}C NMR spectra at δ 155.02, 51.38 and 16.38 ppm pointed out the presence of >C=O, -C<u>H</u> of pyrimidine ring, and -CH_3 group in the final compound respectively.



Where, R = **3a** -3-NO_2, **3b** -4-Cl, **3c** -4-OCH_3, **3d** -2-OH, **3e** -4-OH, **3f** -4-NO_2, **3g** -3-NH_2, **3h** -4-NH_2, **3i** -2-F, **3j** -4-F, **3k** -3-F, **3l** -2-Cl, **3m** -3-OH, **3n** -2-NO_2, **3o** -H,

Reagents and conditions: (a) ([BBI][BF_4]), 80 °C, 24 h; (b) NH_2NH_2, 1,4-Dioxane, Conc. HCl, reflux, 6 h; (c) Ar-COOH, $POCl_3$, reflux 8 h.

Scheme 1. Synthetic track for the preparation of title compounds (3a-o).

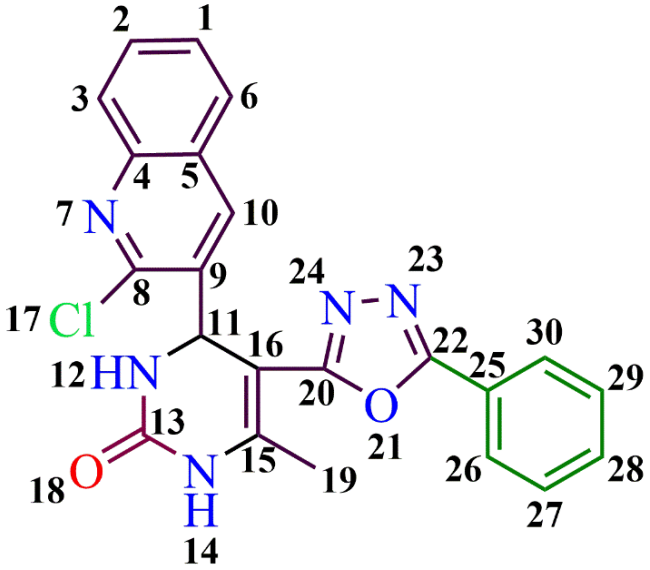


Figure 1. Molecule numbering of the final compound (3o).

The IR spectra of **3a** showed distinct stretching frequencies at 2943, 1643 cm^{-1} and 1257 cm^{-1} corresponding to -CH_3, >C=N and -C-O-C-, respectively. Molecular ion peak at *m/z* 462.85 [M+] in mass spectrometric data was in accordance with molecular weight of compound **3a**. Also, the basic affirmation of the remaining dihydropyrimidine substituted 1,3,4-oxadiazole derivatives **(3a-o)** was completed based on the above portrayal.

2. 2. Biological evaluation

2. 2. 1. Antimicrobial studies [23, 24]

The biological advancement of synthesized compounds was evaluated against varied bacterial and fungal strains by a standard broth-dilution technique. The active compounds were additionally screened for cytotoxicity against human embryonic kidney cell line, HEK293. The compounds were likewise screened for haemolysis of human blood cells. Fluconazole was utilized as a positive fungal inhibitor standard for fungi. Colistin was utilized as positive bacterial inhibitor guidelines for Gram-negative and Vancomycin for Gram-positive bacteria. Melittin and tamoxifen were utilized as a positive heamolytic and cytotoxicity standard, separately. The aftereffects of these examinations were denoted in **Table 1**. Compounds were considered to be active at a single concentration of 32 µg/mL, n = 2, where reproduces demonstrated hindrance of ≥ 30% and Z-Score ≥ 2.5.

Table 1. Percentage inhibition for compounds **3a-o** at 32µg/mL.

No.	-R	Antibacterial					Antifungal		Cytotoxicity	Haemolysis
		Sa	*Ec*	*Kp*	*Pa*	*Ab*	*Ca*	*Cn*	Hk, D_{Max}	RBC, D_{Max}
3a	-3-NO_2	-19.8; -20.0	-12.7; -3.5	16.8; 9.6	-3.1; 9.0	-9.4; 8.3	0.2; 2.0	119.7; 125.6	-4.5; 35.7	-1.1; -2.4
3b	-4-Cl	-12.3; -14.1	-11.3; -2.3	22.7; 9.4	2.3; 6.5	-10.8; 0.5	-0.7; 1.7	115.1; 123.6	30.5; 4.3	-0.3; 2.2
3c	-4-OCH_3	-20.5; -22.4	-14.4; -4.0	13.8; 8.9	-1.1; 3.0	-13.7; 4.2	-0.8; 2.3	116.3; 124.1	12.3; 21.6	-1.5; -2.6
3d	-2-OH	-13.0; -17.5	-12.5; -5.0	11.0; 14.5	-0.6; 3.1	-11.3; 3.4	-3.4; 0.6	120.9; 128.4	14.7; 38.5	-1.9; 2.6
3e	-4-OH	25.0; 27.2	-16.9; -9.7	-1.2; 3.7	12.8; 4.3	-14.5; -4.3	25.2; 6.2	91.3; 97.7	38.0; 5.9	2.4; 2.5
3f	-4-NO_2	-15.7; -17.7	-12.2; -9.7	10.6; 11.7	4.6; 5.8	-10.0; -6.0	-1.0; -4.0	-107.5; -122.1	NT	NT
3g	-3-NH_2	-10.4; -23.6	-11.6; -13.6	10.4; 11.0	3.3; 8.0	-8.7; 3.5	-6.4; -7.2	110.3; 116.0	34.3; 4.8	-2.6; 2.1
3h	-4-NH_2	-20.1; -9.6	-4.2; -6.3	2.6; 8.9	6.3; 9.3	-3.2; 3.0	-0.1; 7.3	-26.4; -46.1	NT	NT
3i	-2-F	-4.1; -9.3	-6.1; -7.2	15.9; 8.2	5.9; 6.4	-1.3; 2.2	4.0; 53.6	-22.5; -40.9	NT	NT
3j	-4-F	-17.6; 6.3	-10.4; -6.9	0.4; 20.0	-0.7; 5.1	-8.4; 1.4	53.8; 63.4	-65.9; -83.0	NT	NT
3k	-3-F	-8.9; -9.6	-1.0; -10.3	11.8; 14.0	0.6; 8.9	-9.8; 5.4	-1.9; 6.3	-41.6; 45.6	NT	NT
3l	-2-Cl	-3.7; -3.8	-1.3; -8.6	10.6; 9.2	3.0; 8.1	-7.4; 14.6	0.4; 30.1	-112.2; -99.0	NT	NT
3m	-3-OH	-0.3; 1.9	-1.1; -9.7	10.8; 22.0	6.8; 8.4	-10.8; 7.0	-0.4; 7.6	115.4; 122.8	4.1; 5.9	3.9; 4.3

3n	-2-NO_2	43.4; 45.6	-10.0; -2.8	11.3; 9.8	2.5; 9.8	-8.8; 8.7	14.7; 7.6	120.7; 129.2	2.5; 30.7	0.9; 3.9
3o	-H	-5.1; -9.7	-4.1; -9.5	12.1; 7.0	0.9; 1.7	-15.7; 2.0	0.7; 40.5	106.4; 110.2	18.1; 41.6	2.0; 2.9

Sa: *Staphylococcus aureus* (MRSA; ATCC 43300), *Ec*: *Escherichia coli* (ATCC 25922), *Kp*: *Klebsiella pneumoniae* (ATCC 700603), *Pa*: *Pseudomonas aeruginosa* (ATCC 27853), *Ab*: *Acinetobacter baumannii* (ATCC 19606), *Ca*: *Candida albicans* (ATCC 90028), *Cn*: *Cryptococcus neoformans* (ATCC 208821), Hk: Human Embryonic Kidney cells (ATCC CRL-1573), RBC: Human red blood cells (ARCBS 5400 00150), NT: Not Tested.

The results of the antimicrobial screening (at 32 μg/mL) revealed that compound **3a**, **3b, 3c, 3d, 3e, 3g, 3m, 3n** and **3o** had high activity against *Cryptococcus neoformans.* Compound **3n** is active against *Staphylococcus aureus*. Furthermore, compound **3i** and **3j** exhibited substantial activity against *Candida albicans*. No other necessary activity was detected for the other compounds that were tested at same concentration levels and with the equal microbial and fungous strains tested. All of the compounds that were tested confirmed to no mentionable cytotoxicity against the human embryonic kidney cell line, HK293 and no haemolytic activity observed against human whole blood cells.

3. EXPERIMENTAL

3. 1. Material and methods [24]

The starting materials were obtained from commercial providers and utilized with or without purification as required. Melting point was checked by an open capillary method on a 'Toshvin melting point' apparatus and are uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was utilized for purity checking and reaction monitoring. Flash chromatography with silica gel (Merck, 70-230 mesh and 230-400 mesh ASTH) was valuable when essential to isolate and refine the reaction products. ^{1}H NMR spectra were recorded on a Bruker Advance II 400 MHz and ^{13}C NMR spectra on Varian Mercury-400, 100 MHz in $CHCl_3$-d as a solvent and tetramethylsilane (TMS) as an internal standard. IR spectra was obtained from a Shimadzu Prestige-21 FT-IR spectrophotometer using ATR assembly. Mass spectra were acquired by Shimadzu LC-MS 2010 spectrometer. Elemental analysis (C, H, N) was completed by a Perkin-Elmer 2400 CHN analyser and found inside ±0.4% of theoretical values.

3. 2. Synthesis of ethyl 4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, (1) [25]

A mixture of 2-chloroquinoline-3-carbaldehyde (0.1mol), ethyl acetoacetate (0.1 mol) and urea (0.1 mol) were heated at 80 °C using Ionic Liquid ([BBI][BF_4]) (10 ml) in a RBF. The progress of the reaction was monitored by TLC. After 24 hr. the reaction mixture was permitted to cool at room temperature. Thus, obtained pale yellow colored solid mass was filtered, washed with hot water, dried and recrystallized from ethanol. Yield: 87.66%; m.p.: 292-294 °C

3. 3. General procedure for synthesis of 4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide, (2)

A mixture of compound **1** (0.05 mol) in 1,4-dioxane (50 mL) and hydrazine hydrate (85%) (0.05 mol) was added followed by the addition of a 2-3 drops of conc. HCl and stir for

6 h with reflux. After cooling, the reaction mixture was poured into chilled water and lite yellow colored solid mass was filtered washed with hot water, dried and recrystallized from methanol to obtain compound **2**. Yield: 89.13%; m.p.: 301-303 °C

3. 4. General procedure for synthesis of 4-(2-chloroquinolin-3-yl)-6-methyl-5-(5-aryl-4*H*-1,3,4-oxadiazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one, (3a–o)

To a solution of compound **2** (0.01 mol) and substituted benzoic acid (0.01 mol) in phosphoryl chloride (15 ml) were stirred and the mixture was refluxed for around 6-8 h. The mother liquor on neutralization with $NaHCO_3$ solution gave a solid precipitate, which was filtered and recrystallized from methanol to afford pure product. The TLC solvent system used was Benzene : Methanol : Chloroform (4:2:2).

3. 4. 1. 4-(2-chloroquinolin-3-yl)-6-methyl-5-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin- 2(1*H*)-one, (3a)

Dark yellow color powder, Yield 76%; mp 214-216 °C; IR (λ_{max}, cm^{-1}, KBr): 3192 (-N-H stretching), 3099 (-C-H- stretching, aromatic), 2985 (-C-H- stretching, H-C=C<), 2943 (-C-H stretching CH_3), 1705 (>C=O stretching), 1643 (>C=N- stretching), 1633 ((>C=C< stretching), 1564, 1384 (-N=O stretching, $-NO_2$), 1257 (-C-O-C- stretching), 752 (-C-Cl- stretching); ^{1}H NMR (400 MHz, $CHCl_3$-d, ppm): δ = 8.05 (s, 1H, –N<u>H</u>-C-CH_3), 7.56-8.03 (m, 9H, Ar-H), 6.26 (s, 1H, -N<u>H</u>-C-Ph), 5.97 (s, 1H, CH), 2.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CHCl_3$-d, ppm): δ = 164.60 (C, C-22), 159.65 (C, C-15), 155.02 (C, C-13), 154.86 (C, C-20), 149.19 (C, C-29), 148.86 (C, C-8), 145.24 (C, C-4), 135.66 (CH, C-10), 134.40 (CH, C-9), 131.59 (CH, C-26), 130.35 (CH, C-25), 130.10 (CH, C-2, C-5), 128.94 (CH, C-27), 128.67 (CH, C-6), 127.12 (CH, C-3), 125.52 (CH, C-1), 121.29 (CH, C-30), 119.84 (CH, C-28), 108.20 (C, C-16), 51.38 (CH, C-11), 16.38 (CH_3, C-19); TOF-MS (ESI+): m/z = 462.85 [M+]; Anal. Calcd. For $C_{22}H_{15}ClN_6O_4$: C, 57.09; H, 3.27; N, 18.16. Found: C, 56.23; H, 2.95; N, 17.97 %.

4. CONCLUSION

The cyclization of carbohydrazide to 1,3,4-oxadiazole derivatives with dihydropyrimidine skeleton was incorporated and assessed for their *in vitro* antimicrobial activities. Preliminary conclusions unveiled that some of the compounds displayed substantial antimicrobial activity. Compounds **3a**, **3b, 3c, 3d, 3e, 3g, 3m, 3n** and **3o** demonstrated the best inhibitory activity against *Candida albicans* and *Cryptococcus neoformans* fungi with no discernible cytotoxicity against Human Embryonic Kidney cells and haemolytic against whole blood. This exertion might be helpful to contend drug-resistant infections.

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