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Synthesis and Biological Properties of Some Novel 1,3,4-oxadiazole with Quinoline Moiety

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ABSTARCT

A series of novel hybrid 6-substituted-2-chloro-3- [5-(aryl substituted)-1,3,4-oxadiazol-2-yl]quinoline 7(a-l) derivatives have been synthesized. 6-substituted-2-hydroxy-quinoline-3-carboxylic acid 3(a-d) was used as the starting material and it was made to react with aromatic acid hydrazides 6(a-c) in presence of catalytic amount of Phosphoryl Chloride ($POCl_3$). All the newly synthesized derivatives have been characterized by Infra-Red (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), mass and elemental analysis. Further, selected synthesized scaffolds were screened in vitro antimicrobial activity. The newly synthesized compounds were showed significant antibacterial activity and antifungal activity compared to standard drugs chloramphenicol and nystatin respectively.

Keywords: 6-Substituted-2-Chloro-quinoline, 1,3,4-Oxadiazole, Antibacterial activity, Antifungal activity

INTRODUCTION

Oxadiazole is a heterocyclic aromatic compound containing one oxygen and two nitrogen atoms in a five membered ring. It occurs in various isomeric forms like 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known and more widely studied by researchers because of their many important chemical and biological properties [1]. Oxadiazole derivatives had been reported to exhibit several biological activities like antibacterial [2], antifungal [3], anti-HIV [4], antitubercular [5], veridical [6], antimalarial [7], genotoxic [8], insecticidal [9], herbicidal [10], analgesic [11], anti-inflammatory [12], muscle relaxants [13], anticonvulsant [14], sedative, hypnotic [15], anticancer [16] and lipid peroxidation inhibitor [17]. They have also attracted interest in medicinal chemistry as bioisosteres for carboxylic acids, esters and carboxamides [18]. Currently, drugs containing 1,3,4-oxadiazole moiety are used in the clinical medicines are, raltegravir, an antiretroviral drug, nesapidil, an antiarrythmic therapy, furamizole, a nitrofuran derivative that has strong antibacterial activity and Tiodazosin, an antihypertensive drug and their structures are given in Figure 1.

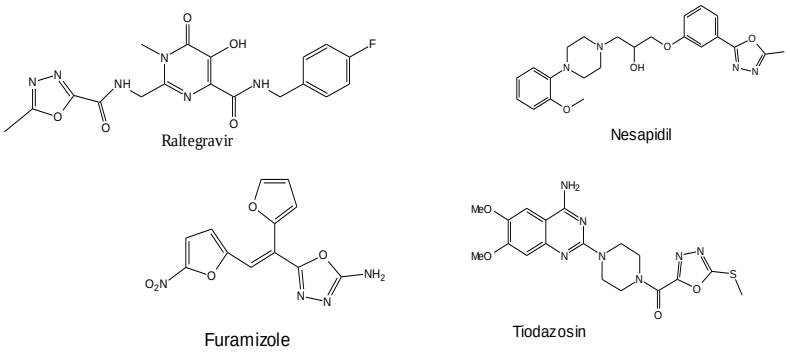


Figure 1: Commercially available drugs which contains 1,3,4-oxadiazole ring

The quinoline nucleus is an important heterocyclic structure found in many synthetic and naturally occurring products with a wide range of pharmacological activities such as antiviral [19], anti-HIV [20], anti-tubercular [21], analgesics [22], anticancer [23], antifungal [24], antibacterial [25], anti-obesity [26], anti-inflammatory [27], antifilarial [28] and antimalarial [29], this can be well illustrated by the large number of commercially available drugs.

MATERIALS AND METHODS

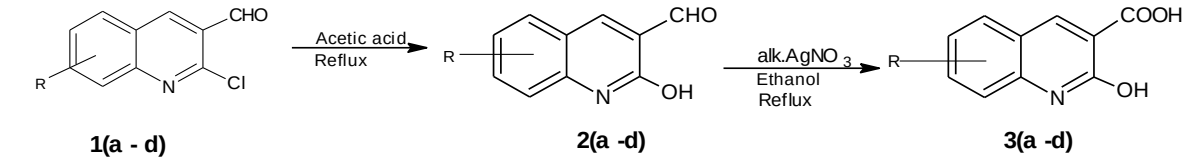
All chemicals used were obtained from commercial sources and were used without further purification. All yields refer to isolated products. The purity and completion of reaction was monitored by TLC on pre-coated silica gel plates (60F-254). Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu-IR470 spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker-Avance spectrometer (at 400 MHz) using Deuterated Dimethyl Sulfoxide (DMSO-d_6) as solvent and Tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per minute (ppm). The mass spectra were recorded on a Jeol GC mate Gas Chromatography-Mass Spectroscopy (GC-MS). Elemental analysis (C, H and N) of these compounds was carried out on a Carlo-Erba 1106 elemental analyzer. 6-Substituted-2-chloroquinoline-3-carbaldehyde, 1(a-d), was prepared by Vilsmeir-Haack reaction as reported in the literature and confirmed by the melting point [30]. 6-Substituted-2-hydroxyquinoline-3-carbaldehyde, 2(a-d), was prepared by a reported method in the literature and confirmed by the melting point [31]. 6-Substituted-2-hydroxyquinoline-3-carboxylic acid, 3(a-d), was prepared by a reported method in the literature and confirmed by the melting point [32].

General procedure for the synthesis of ethyl aromatic carboxylic acid esters, 5(a-c)

A mixture of 4-substituted-aromatic acids 4(a-c), ethyl alcohol (50 ml) and 3 ml of concentrated H_2SO_4 were refluxed for 4-6 h. Progress of the reaction was monitored by Thin Layer Chromatography (TLC). The mixture was poured to crushed ice; separated solid was filtered, dried and re-crystallized from minimum amount of ethyl alcohol. The compound was confirmed by the melting point coincide with the literature values.

General procedure for the synthesis of aromatic acid carbohydrazides, 6(a-c)

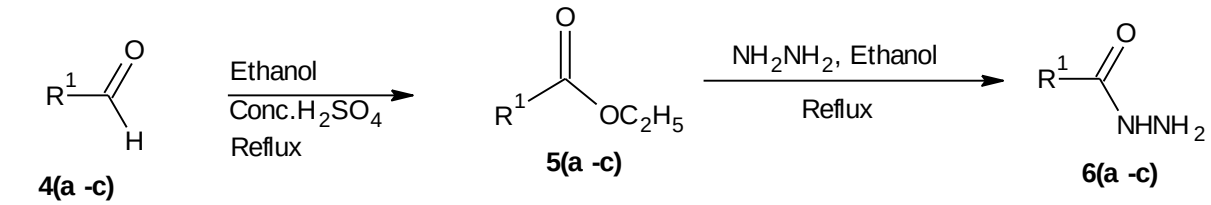
To a solution of ethyl aromatic acid esters, 5(a-c) in ethyl alcohol (50 ml) was added with excess of hydrazine hydrate and refluxed for 24 h. Progress of the reaction was monitored by TLC. Excess of solvent was removed by distillation under reduced pressure and allowed to cool, separated crystals was filtered, dried and re-crystallized from minimum amount of ethyl alcohol. The compound was confirmed by melting point as reported in the literature.



1(a - d) **2(a -d)** **3(a -d)**

R = H, CH_3,OCH_3, Cl

Scheme - I



4(a -c) **5(a -c)** **6(a -c)**

R^1 = -C_6H_5, p-Cl-C_6H_4, Nicotinoyl

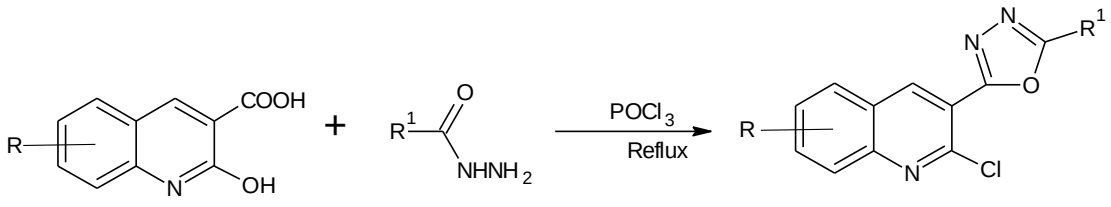
Scheme II

General procedure for the synthesis of 6-substituted-2-chloro-3-[5-(aryl substituted)-1,3,4-oxadiazol-2-yl]quinoline (7a-7l)

Equimolar mixture of 3(a-d) and 6(a-c) was refluxed in the presence of catalytic amount of $POCl_3$ for 3 h. The reaction mixture was cooled and poured to crushed ice followed by treatment with Na_2CO_3 to remove the un-reacted acid. Solid separated was filtered and recrystallized with alcohol+Dimethyl Formamide (DMF) mixture.

2-Chloro-3-[5-(phenyl)-1,3,4-oxadiazol-2-yl]quinoline, 7(a)

Yield-53%: Brown solid, MS (ES+) M+H: 308, mp. 198-200°C; Elemental analysis found: C, 66.34, H, 3.25, N, 13.65%. Calcd. for $C_{17}H_{10}ClON_3$: C, 66.31, H, 3.26, N, 13.67%. IR (KBr): 3420 (aromatic C-H), 1535 (C=C stretch), 1585 (C=N stretching). ^{1}H-NMR (DMSO-d6, 400 MHz): δ=7.22-7.48 (m, 5H, phenyl ring), δ=7.43-8.51(m, 5H, quinoline ring). ^{13}C-NMR (DMSO-d6): δ=125.95, 148.52, 129.11, 128.58, 123.15, 130.73, 129.60 (hetero aromatic carbon of quinoline ring nucleus), 127.25, 128.84, 131.14 (aromatic carbons of phenyl ring), 165.02, 156.18 (carbon of oxadiazole ring).



3(a -d) **6(a -d)** **7(a -d)**

Scheme III

6-Methyl-2-chloro-3-[5-(phenyl)-1,3,4-oxadiazol-2-yl]quinoline,7(d)

Yield-70%: Brown solid, mp. 260-261°C. MS (ES+) M+H: 322.5. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ=7.22-7.48 (m, 5H, phenyl ring), δ=2.5 (s, 3H,-CH3), δ=7.47-8.5 (m, 4H, quinoline ring). ^{13}C-NMR (DMSO-d6): δ=20.81 (carbon atom of the –CH3), 164.2, 165.03 (carbon atoms of the 1,3,4-oxadiazole ring), 126.4, 128.0, 131.2, 132.5, 136.2, 136.6, 143.7, 148.8 (carbon atoms of the quinoline ring), 124.2, 128.9, 129.3, 134.3 (carbon atoms of the phenyl ring). IR (KBr, cm^{-1}): 3410 (aromatic C-H), 1549 (C=C stretching), 1583 (C=N stretching). Elemental analysis calculated for $C_{18}H_{12}N_3OCl$: C, 67.18, H, 3.73, N, 13.06; found C, 67.17, H, 3.75, N, 13.08.

6-Methoxy-2-chloro-3- [5-(4-chloro phenyl)-1,3,4-oxadiazol-2-yl]quinoline, 7(h)

Yield-72%: Dark brown solid, mp. 269-271°C. MS (ES+) M+H: 373. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ=7.33-7.42 (m, 4H, p-chloro phenyl), δ3.9 (s, 3H, -OCH3), δ=6.98-8.44 (m, 4H, quinoline ring). ^{13}C-NMR (DMSO-d6): δ=55.81 (carbon atom of the –OCH3), 166.86 (carbon atom of the 1,3,4-oxadiazole ring), 105.6, 123.4, 129.3, 131.2, 131.9, 135.6, 141.4, 147.7, 157.4 (carbon atoms of the quinoline ring), 124.2, 128.9, 129.3, 134.3 (carbon atoms of the phenyl ring). IR (KBr, cm^{-1}): 3485 (aromatic), 1549 (C=C stretching), 1583 (C=N stretching). Elemental analysis calculated for $C_{18}H_{11}N_3O_2Cl_2$: C, 58.06, H, 2.95, N, 11.29; found C, 58.10, H, 2.94, N, 11.32.

RESULTS AND DISCUSSION

A new series of 2,5-disubstituted 1,3,4-oxadiazole derivatives incorporated with 6-substituted-2-chloroquinoline moiety was synthesized by the condensation of aromatic acid hydrazides and 6-substituted-2-hydroxy quinolinic acids in the presence of $POCl_3$. The physical data of the synthesized compounds 7(a-l) was collected and presented in Table 1. The percentage yield of all the synthesized compounds 7(a-l) was found to be in the range of 60%. The purity of the synthesized compounds was studied by TLC. The synthesized compounds were confirmed structurally by means of their FTIR, ^{1}H-NMR, ^{13}C-NMR ns mass spectra. The spectral and analytical data are in good agreement with their structure. In these compounds few were selected and evaluated for antibacterial and antifungal activities. The data of the microbial activities are presented in Tables 2 and 3 respectively.

Antibacterial activity

The antibacterial activity of the selected synthesized compounds was determined by well-diffusion method. In the present work, two Gram positive bacteria, *Bacillus subtilis*, *Staphylococcus aureus* and two Gram-negative bacteria, *Salmonella typhimurium*, *Pseudomonas aeruginosa* were used to investigate the antibacterial activity. Antibacterial activity was determined by measuring the diameter of inhibition zone and examining the Minimal Inhibitory Concentration (MIC). Activities of compounds were compared with Chloramphenicol as standard drug. The observed data of antibacterial activity of compounds is given in Table 2. The compounds 7a and 7h shows good activity against Gram-positive bacterial strains, 7d and 7i shows good activity against the Gram-negative bacterial strains.

Antifungal activity

The antifungal activity of the selected 1,3,4-oxadiazoles were assayed against fungal organisms *Aspergillus* and *Rhizopus*. The test organisms were grown for 48 h at 25°C in YPD Broth (1% yeast extract, 2% peptone and 2% dextrose) harvested by centrifugation and then washed with sterile water. The fungal activity was determined by using nystatin as standard and the compounds were showed good to moderate activity in which compound (7e) showed better activity. The observed data of antibacterial activity of compounds is given in Table 3.

Table 1: Physical data of compounds 7(a-l)

Compound	R	R^1	Molecular formula (Molecular weight)	Yield (%) Melting point (°C) Color	Elemental analysis found (Calculated) C, H, N
7a	H	C_6H_5	$C_{17}H_{10}ClON_3$ (307.5)	53 (198-200) Dark brown	66.34 3.25 13.65 (66.31) (3.26) (13.67)
7b	H	4-Cl	$C_{17}H_9Cl_2ON_3$ (342)	58 (257-260) Brown	59.64 2.63 12.28 (59.62) (2.61) (12.29)
7c	H	Nicotinoyl	$C_{16}H_9ClON_4$ (308.5)	54 (230-231) Brown	62.23 2.91 18.15 (62.25) (2.93) (18.17)
7d	CH_3	C_6H_5	$C_{18}H_{12}ClON_3$ (321.5)	60 (170-173) Brown	67.18 3.73 13.06 (67.19) (3.75) (13.08)
7e	CH_3	4-Cl	$C_{18}H_{11}Cl_2ON_3$ (356)	63 (234-236) Brown	60.67 3.08 11.79 (60.65) (3.07) (11.77)
7f	CH_3	Nicotinoyl	$C_{17}H_{11}ClON_4$ (322.5)	61 (267-269) Dark brown	63.25 3.41 17.36 (63.22) (3.39) (17.33)
7g	OCH_3	C_6H_5	$C_{18}H_{12}ClO_2N_3$ (337.5)	65 (189-191) Brown	64.00 3.25 12.44 (64.01) (3.26) (12.41)
7h	OCH_3	4-Cl	$C_{18}H_{11}Cl_2O_2N_3$ (372)	64 (273-274) Brown	58.06 2.95 11.29 (58.09) (2.97) (11.28)
7i	OCH_3	Nicotinoyl	$C_{17}H_{11}ClO_2N_4$ (338.5)	62 (280-283) Brown	60.26 3.24 16.54 (60.28) (3.25) (16.55)
7j	Cl	C_6H_5	$C_{17}H_9Cl_2ON_3$ (342)	58 (280-283) Red	59.64 2.63 12.28 (59.66) (2.65) (12.29)
7k	Cl	Cl	$C_{17}H_8Cl_3ON_3$ (376.5)	55 (> 300) Red	54.18 2.12 11.15 (54.19) (2.15) (11.18)
7l	Cl	Nicotinoyl	$C_{16}H_8Cl_2ON_4$ (343)	53 (> 300) Brown	55.97 2.33 16.32 (55.99) (2.36) (16.34)

Table 2: *In vitro* antibacterial activity of the selected compounds

Compounds	*Bacillus subtilis*, ZI[a],(MIC)[b]	Staphylococcus *aureus*, ZI[a], (MIC)[b]	*Salmonella typhi*, ZI[a], (MIC)[b]	*Pseudomonas aeruginosa*, ZI[a], (MIC)[b]
7a	15.1(10)	14.8(10)	11.5(20)	10.1(10)
7d	13.1(10)	13.2(10)	15.0(10)	14.8(10)
7h	14.7(10)	14.6(10)	12.2(15)	12.8(15)
7i	13.3(15)	13.8(15)	15.1(10)	14.9(10)
7j	13.4(15)	13.7(15)	11.7(15)	11.2(15)
Chloramphenicol	15.1(10)	14.9(10)	16.4(5)	16.1(5)

[a]Zone of Inhibition; [b]Minimum Inhibitor Concentration

Table 3: *In vitro* antifungal screening of the selected compounds

Compound	*Aspergillus niger*	*Rhizopus*
7a	13	13
7d	13	12
7e	7	15
7g	8	7
7i	12	8
Nystatin	14	16

CONCLUSION

In conclusion, a series of new 6-substituted-2-chloro-3-[5-(aryl substituted)-1,3,4-oxadiazol-2-yl]quinoline 7(a-l) were synthesized in good yield, characterized by different spectral techniques and their antimicrobial activities have been evaluated. Compounds 7a, 7h, 7d and 7i show good activity against different species of bacteria and fungi. Therefore, this work presents a new class of potent, wide spectrum antimicrobial activity of the compounds. The nature of functional group linkage and substituent on benzene ring are crucial for antimicrobial activities.

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