Synthesis and Antibacterial Activity of Novel Series of 2-(*p*-Tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)quinoline

Ratnadeep S. Joshi,[a] Priyanka G. Mandhane,[a] Wajid Khan,[b] and Charansingh H. Gill[a]*

[a]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India
[b]Department of Microbiology, Maulana Azad College, Aurangabad 431 210, India
*E-mail: chgill50@yahoo.com

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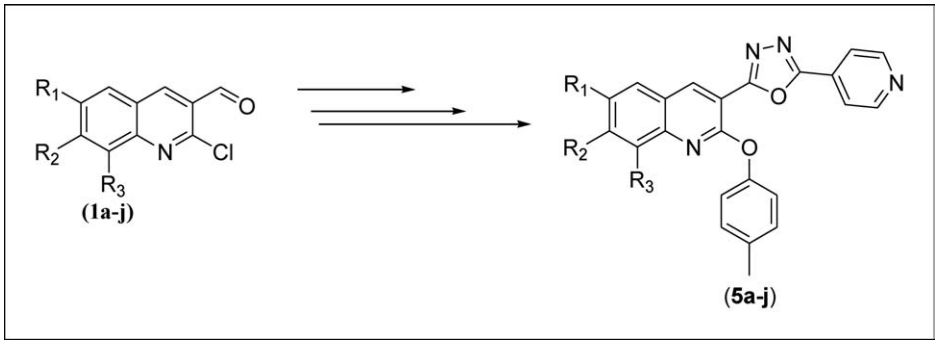

A new series of 2-(*p*-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)quinoline were synthesized from oxidative cyclization of *N′*-((2-(*p*-tolyloxy)quinoline-3-yl)methylene)isonicotinohydrazide in DMSO/I_2 at reflux condition for 3–4 h. The structures of the new compounds were confirmed by elemental analyses as well as IR, ^{1}H-NMR, and mass spectral data. All the synthesized compounds were screened for their antibacterial activities against various bacterial strains. Several of these compounds showed potential antibacterial activity.

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INTRODUCTION

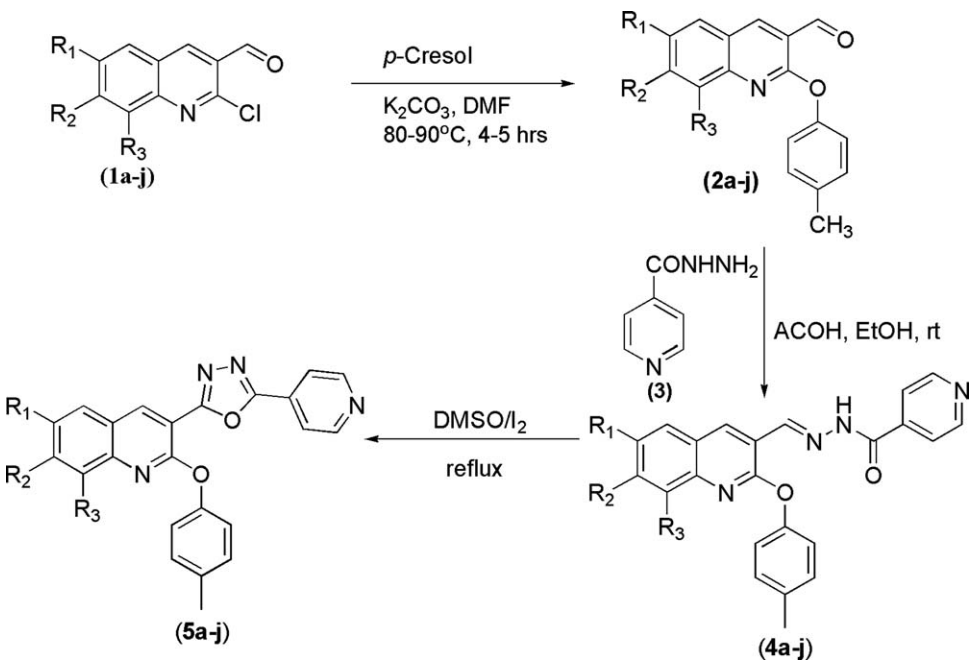
Quinoline ring systems represent a major class of heterocycles as they occur in various natural products especially in alkaloids [1]. It possesses diverse biological and physiological activities such as antimalarial [2], anti-inflammatory [3], antitumor [4], DNA binding capacity [5], and antibacterial properties [6]. Recently, quinoline has been used in the study of bio-organic and bio-organometallic processes [7]. There are many quinoline-based compounds which are known to exhibit anti-TB properties. Compound TMC207 [8] bearing a bulky biaryl side chain at position C3, is a highly potent anti-TB agent and is currently in phase II clinical trials. In particular, 2-chloroquinoline-3-carbaldehyde has been used as a key intermediate for the synthesis of variety of medicinally valuable compounds [9].

The substituted oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores. It also act as key elements with potential biological activities [10] such as pesticidal [11], antiperipheral vasomotility [12], CNS stimulant, antiinflammatory, hypotensive [13], insecticidal [14], bactericidal [15], hypoglycemic [16], analgesic, anticonvulsive, antiemetic, diuretic [17], muscle relaxant [18], and fungicidal activities [19].

There are several methods for the synthesis of substituted 1,3,4-oxadiazole. The classical synthetic routes to substituted 1,3,4-oxadiazoles involve ring-forming reactions. Widely used methods are cyclodehydration of 1,2-diacylhydrazines with various reagents such as thionyl chloride, phosphorus oxychloride, poly phosphoric acid (PPA), or sulfuric acid [20], oxidation of *N*-acylhydrazones with different oxidizing agents [21] and direct reaction of acyl chlorides or carboxylic acids with hydrazine or acid hydrazides [22]. Another convenient method of 1,3,4-oxadiazole synthesis is the thermal recyclization of *N*-acyltetrazoles, which are commonly generated *in situ* from appropriate *N*-unsubstituted tetrazoles and acyl chlorides [23]. Preparative methods *via* ring-metalated 1,3,4-oxadiazoles are much less common because of the opening of the heterocycles. Thus, the synthesis of the substituted 1,3,4-oxadiazoles *via* lithium derivative was described for the first time only several years ago [24].

In our continuous program in the search of new potent and safe synthesis of biologically active heterocycles [25,26], we have planned to synthesize some new series of various substituted 2-(*p*-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)quinoline by oxidative cyclisation of *N*-((2-(*p*-tolyloxy)quinoline-3-yl)methylene)isonicotinohydrazide using DMSO/I_2 and evaluating their antibacterial

Scheme 1



activity against the standard drug Streptomycin and Ampicillin.

RESULTS AND DISCUSSION

Chemistry. The synthetic work was carried out beginning from 2-chloro-3-formylquinoline (**1a–j**) according to **Scheme** 1. The reaction of 2-chloro-3-formylquinoline (**1a–j**) with *p*-cresol in presence of K_2CO_3/*N*,*N*-dimethylmethanamide (DMF) at 80–90°C for 4–5 h gave substituted 2-(*p*-tolyoxy)quinoline-3-carbaldehyde (**2a–j**). Further reaction of isonicotinohydrazide (**3**) with substituted 2-(*p*-tolyoxy)-quinoline-3-carbaldehyde (**2a–j**) gave corresponding *N*′-((2-(*p*-tolyloxy)quinoline-3-yl)methylene)isonicotinohydrazide (**4a–j**) in acetic acid in ethanol at room temperature, followed by the oxidative cyclisation of *N*′-((2-(*p*-tolyloxy)quinoline-3-yl)methylene)isonicotinohydrazide using DMSO and iodine at reflux condition gave our targeted product *i.e.*, substituted 2-(*p*-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl) (**5a–j**). All the synthesized compounds were characterized by their physical and spectral data (IR, ^{1}H-NMR, and Mass).

Spectral analysis. The structures of the synthesized compounds were confirmed by spectral analysis (IR, ^{1}H-NMR, and Mass). The IR spectrum of compound (**2a**) showed a peak at 1690 cm^{-1} due to C=O stretch. In ^{1}H-NMR spectrum, it exhibited two singlets, one at δ 2.41 due to —CH_3 protons and second at δ 10.65 due to —CHO proton. Mass spectrum was consistent with assigned structure showing (M+1) peak at $m/z = 264.1$. The structure of (**4a**) is interpreted from spectroscopic data, IR spectra of compound (**4a**) reveals absorption band in the region 1560 cm^{-1} corresponding to —C=N stretching at 1640 cm^{-1}.

The ^{1}H-NMR spectra of (**4a**) exhibits a sharp singlet at δ 2.01 for —CH_3 and one broad singlet at δ 10.50 of —NH. The pyridine ring protons appeared doublet at δ 8.92 and 8.75, respectively. C_4- proton of quinoline nuclei appears as a singlet at δ 8.33. All other aromatic protons arise at respective position. The IR spectrum of compound (**5a**) showed absorption peak at 1576 cm^{-1} due to C=N stretching vibrations. The absence of CO peak at 1640 cm^{-1} confirms the formation of oxadiazole ring, its ^{1}H-NMR spectrum revealed a multiplet at δ 7.02–8.98 due to quinoline and pyridine ring protons. The physical data are summarized in Table 1.

Antibacterial activity. The antibacterial activities of the synthesized compounds were determined by the well-diffusion method [27]. In this work, two Gram-positive bacteria, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 25923) and two Gram-negative bacteria, *Salmonella typhimurium* (ATCC 23564), *Pseudomonas aeruginosa* (ATCC 27853) were used to investigate the antibacterial activities. The bacterial liquid cultures were prepared in fusion broth for their activity tests. The compounds were dissolved in DMSO at concentration of 1 mg mL^{-1}. Antibacterial activity of DMSO against the test organisms was investigated, and was found to be nil. Molten nutrient agar (15 cm^3) kept at 45°C, was then poured into the Petri dishes and allowed to solidify. Ten millimeter diameter holes were

Table 1

Physical data of the compounds (**5a–j**).

Comp. No.	R_1	R_2	R_3	Yield (%)	M.P. (°C)
5a	H	H	H	68	121–124
5b	CH_3	H	H	72	135–136
5c	H	CH_3	H	67	127–129
5d	H	H	CH_3	74	140–142
5e	OCH_3	H	H	76	124–125
5f	H	OCH_3	H	64	130–131
5g	H	H	OCH_3	70	143–145
5h	OC_2H_5	H	H	73	147–149
5i	H	OC_2H_5H	H	69	141–142
5j	H	H	OC_2H_5	72	132–134

then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37°C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial activity was determined by measuring the diameter of inhibition zone and examining the minimal inhibitory concentration. Activity of each compound was compared with streptomycin and ampicillin as standards. The observed data of antibacterial activity of compounds and the standard drugs are given in Table 2. The compounds (**5c**), (**5d**), (**5i**), and (**5j**) show excellent antibacterial activity against Gram-positive bacterial strains. Likewise, compounds (**5a**), (**5b**), (**5f**), and (**5g**) showed excellent activity against Gram-negative bacterial strains.

CONCLUSION

In this report, we have synthesized novel series of 2-(*p*-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-quinoline from *N*′-((2-(*p*-tolyloxy) quinoline-3-yl)methylene)isonicotinohydrazide which shows potent antibacterial activity. Most of these compounds showed moderate antibacterial activity compared with commercially available drugs. Therefore, it becomes lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly holds a great promise toward pursuit to discover novel class of antibacterial agents. Further studies are being conducted to acquire more information about quantitative structure–activity relationships.

EXPERIMENTAL

Melting points were recorded in an open capillary in liquid paraffin bath and are uncorrected. The progress of reaction was monitored by thin layer chromatography using silica gel (Merck). IR spectra were recorded on a SHIMADZU–FT-IR spectrophotometer in KBr disc. ^{1}H-NMR spectra were recorded on BRUKER ADVANCE–II 400 NMR spectrophotometer in DMSO-d_6 as a solvent and tetramethyl silane (TMS) as an internal standard. Peak values are shown in δ ppm. Mass spectra were recorded on a PEP-SCIUX-APIQ pulsar (electron preionization) mass spectrometer. Elemental analyses were performed on Perkin-Elmer EAL-240 elemental analyzers.

General procedure for the synthesis of 2-(*p*-tolyloxy)-quinoline-3-carbaldehydes (2a-j). To the mixture of *p*-cresol (3.7 g, 0.034 mol) and K_2CO_3 (12.8 g, 0.093 mol) in DMF, compound **1a** (6 g, 0.031 mol) was added, and the reaction mixture was stirred at 80–90°C for 4–5 h. The completion of the reaction was monitored on TLC. After completion of the reaction, ice cold water (50 mL) was poured on the reaction mixture, and the solid thus obtained was filtered off and washed with water, further the compound was recrystallized in ethyl acetate.

2-(p-tolyloxy)quinoline-3-carbaldehyde (**2a**). **IR** (KBr, cm^{-1}): 1690 (C=O), 1610 (C=N), 1525 (C=C); **^{1}H-NMR**-(400 Hz, DMSO-d_6): δ 10.65 (s, 1H, —CHO), 8.72 (s, 1H, Ar-H), 7.89 (d, J = 8 Hz, 1H, Ar-H), 7.73 (d, J = 8 Hz, 1H, Ar-H), 7.70 (t, 1H, Ar-H), 7.45 (t, 1H, Ar-H), 7.27 (d, J = 8 Hz, 2H, Ar-H), 7.18 (d, J = 8 Hz, 2H, Ar-H), 2.41 (s, 3H, —CH_3); **ES-MS** (*m*/*z*): 264.4 (M+1).

Table 2

The minimum inhibitor concentrations of tested compounds (**5a–j**) in μg/mL.

Tested compounds	*B. subtili* ZI[a](MIC)[b]	*S. aureus* ZI[a](MIC)[b]	*S. typhi* ZI[a](MIC)[b]	*P. aeroginosa* ZI[a](MIC)[b]
5a	13.2 (15)	13.5 (15)	14.8 (10)	14.5 (10)
5b	13.8 (15)	13.3 (15)	15.1 (10)	14.9 (10)
5c	14.3 (10)	14.1 (10)	12.8 (15)	12.7 (15)
5d	15.1 (10)	14.7 (10)	13.5 (15)	13.4 (15)
5e	14.8 (10)	14.6 (10)	12.9 (15)	12.8 (15)
5f	13.1 (15)	13.6 (15)	14.2 (10)	14.0 (10)
5g	13.4 (15)	13.7 (15)	15.1 (10)	14.8 (10)
5h	13.1 (15)	13.2 (15)	11.1 (20)	10.4 (20)
5i	14.1 (10)	14.6 (10)	12.2 (15)	12.6 (15)
5j	15.6 (10)	15.3 (10)	11.7 (15)	11.2 (15)
Streptomycin	15.1 (10)	14.9 (10)	16.4 (5)	16.1 (5)
Ampicillin	14.3 (10)	14.7 (10)	16.3 (5)	15.9 (5)

[a] Zone of inhibition.
[b] Minimum inhibitory concentration in μg/mL.

General procedure for the synthesis of (*E*)-*N*′-((2-tolyloxy) quinoline-3-yl)methylene)isonicotinohydrazide (4a-j). An equimolar mixture of 2-chloro-3-formyl quinoline (**1a**) (0.004 mol) and isonicotinohydrazide (**3**) (0.004 mol) in 10 mL ethanol containing few drops of glacial acetic acid was stirred at room temperature. After completion of reaction (checked by TLC), the excess of solvent was removed on rotary evaporator to yield solid which was washed with petroleum ether followed by crystallization from ethanol.

(E)-N′-((2-tolyloxy) quinoline-3-yl) methylene)isonicotinohydrazide (**4a**). **IR** (KBr, cm^{-1}): 2980 (NH), 1560 (C=N), 1513 (C=C); **^{1}H-NMR**- (400 Hz, DMSO-d_6): δ 10.72 (s, 1H, —NH), 8.90 (s, 1H), 8.77 (d, J = 7.92 Hz, 3H, Ar-H), 7.75–7.80 (m, 4H, Ar-H), 7.26 (t, J = 10.94 Hz, 2H, Ar-H), 7.19 (dd, J = 8.21 and 4.24 Hz, 4H, Ar-H) 2.30 (s, 3H, Ar-CH_3), **ES-MS** (*m/z*): 383 (M+1); **Anal. Calcd**. $C_{23}H_{18}N_4O_2$ C, 72.24; H, 4.74; N, 14.65, found C, 72.22; H, 4.80; N, 14.56%.

(E)-N′-((2-tolyloxy)-6-ethoxyquinoline-3-yl)methylene)isonicotinohydrazide (**4h). IR** (KBr, cm^{-1}): 3009 (—NH), 1577 (C=N), 1510 (C=C); **^{1}H-NMR**- (400 Hz, DMSO-d_6): δ 10.79 (s, 1H, —NH), 8.92 (s, 1H), 8.73 (d, J = 8.21 Hz, 2H, Ar-H) 7.84–7.89 (dd, 4H, Ar-H), 7.21 (t, J = 11.30 Hz, 2H, Ar-H), 7.16 (dd, J = 8.44 and 4.66 Hz, 4H, Ar-H), 2.67 (s, 3H, Ar-CH_3), 1.41 (s, 3H, —CH_3); **ES-MS** (*m/z*): 427 (M+1); **Anal. Calcd**. $C_{25}H_{22}N_4O_3$ C, 70.41; H, 5.20; N, 13.14, found C, 70.43; H, 5.30; N, 13.21%.

General procedure for the synthesis of substituted 2-(*p*-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)quinoline (5a-j). (0.1 g, 0.00028 mol) of *N*′-((2-(*p*-tolyloxy)quinoline-3-yl)methylene)isonicotinohydrazide (**4a**) was dissolved in 10 mL of DMSO. To this reaction mixture, catalytic amount of iodine was added. The reaction mixture was heated in an oil bath for 3–4 h at 120°C and left for overnight. 10-mL ice cold water was slowly added to the flask and the separated product was filtered and washed with water. Further reaction mass washed with dil sodium thiosulphate solution for several times. It was again washed with water dried under vacuum. The residue was subjected to column chromatography (60–120 mesh size silica gel) eluted with hexane-ethyl acetate (80:20) to obtain the pure product. The compounds (**5a–j**) were prepared by following the above procedure and their percentage yield and physical constants were recorded in Table 1. Their structures have been confirmed by IR ^{1}H-NMR and mass spectra.

2-(p-tolyloxy)-3-(5-(pyridin-4-yl)-1,3,4 oxadiazol-2yl)quinoline (**5a**). **IR** (KBr, cm^{-1}): 2930 (C—H), 1577 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.73 (s, 1H), 8.69 (d, J = 8.9 Hz, 2H, Ar-H) 7.72–7.65 (m, 4H, Ar-H), 7.30 (t, J = 11.76 Hz, 2H, Ar-H), 7.12 (dd, J = 8.3, 3.92 Hz, 4H, Ar-H), 2.87 (s, 3H, Ar-CH_3); **ES-MS** (*m/z*): 381 (M+1); **Anal. Calcd**. $C_{23}H_{16}N_4O_2$ C, 72.62; H, 4.24; N, 14.73, found C, 72.59; H, 4.29; N, 14.71%.

2-(p-tolyloxy)-6-methyl-3-(5-(pyridin-4-yl)-1,3,4 oxadiazol-2yl)quinoline (**5b). IR** (KBr, cm^{-1}): 2945 (C–H), 1565 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.82 (s, 1H), 8.65 (d, J = 9.29 Hz, 2H, Ar-H), 7.67–7.62 (m, 3H, Ar-H), 7.21 (t, J = 12.23 Hz, 2H, Ar-H), 7.02 (dd, J = 8.43 and 4.12 Hz, 4H, Ar-H), 2.83 (s, 3H, Ar-CH_3); **ES-MS** (*m/z*): 395 (M+1); **Anal. Calcd**. $C_{24}H_{18}N_4O_2C$, 73.08; H, 4.60; N, 14.20, found C, 73.12; H, 4.67; N, 14.30%.

2-(p-tolyloxy)-7-methyl-3-(5-(pyridin-4-yl)-1,3,4- oxadiazol-2yl)quinoline (**5c**). **IR** (KBr, cm^{-1}): 2935 (C–H), 1555 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.70 (s, 1H), 8.62 (d, J = 10.12 Hz, 2H, Ar-H), 7.69–7.84 (m, 3H, Ar-H), 7.32 (t, J = 1.45 Hz, 2H, Ar-H), 7.10 (dd, J = 9.21 and 3.14 Hz, 4H, Ar-H), 2.65 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3); **ES-MS** (*m/z*): 395 (M+1); **Anal. Calcd**. $C_{24}H_{18}N_4O_2$ C, 73.08; H, 4.60; N, 14.20, found C, 73.10; H, 4.62; N, 14.23%.

2-(p-tolyloxy)-7-methoxy-3-(5-(pyridin-4-yl)-1,3,4- oxadiazol-2yl)quinoline (**5f**). **IR** (KBr, cm^{-1}): 2925 (C–H), 1570 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.85 (s, 1H), 8.76 (d, J = 9.2 Hz, 2H, Ar-H), 7.63–7.82 (m, 3H, Ar-H), 7.25 (t, J = 12 Hz, 2H, Ar-H), 7.08 (dd, J = 8 and 4.2 Hz, 4H, Ar-H), 3.82 (s, 3H, Ar-OCH_3), 2.93 (s, 3H, Ar-CH_3); **ES-MS** (*m/z*): 411 (M+1); **Anal. Calcd**. $C_{24}H_{18}N_4O_3$ C, 70.23; H, 4.42; N, 13.65, found C, 70.27; H, 4.47; N, 13.70%.

2-(p-tolyloxy)-6-methoxy-3-(5-(pyridin-4-yl)-1,3,4 oxadiazol-2yl)-quinoline (**5g). IR** (KBr, cm^{-1}): 2932 (C–H), 1562 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.80 (s, 1H), 8.66 (d, J = 8.6 Hz, 2H, Ar-H), 7.82–7.92 (m, 3H, Ar-H), 7.39 (t, J = 11.78 Hz, 2H, Ar-H), 7.21 (dd, J = 7.9 and 3.9 Hz, 4H, Ar-H) 3.64 (s, 3H, Ar-OCH_3), 2.02 (s, 3H, Ar-CH_3); **ES-MS** (*m/z*): 411 (M+1); **Anal. Calcd**. $C_{24}H_{18}N_4O_3$ C, 70.23; H, 4.42; N, 13.65, found C, 70.21; H, 4.46; N, 13.68%.

2-(p-tolyloxy)-6-ethoxy-3-(5-(pyridin-4-yl)-1,3,4 oxadiazol-2yl)-quinoline (**5h). IR** (KBr, cm^{-1}): 2950 (C–H), 1547 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.89 (s, 1H), 8.70 (d, J = 8.21 Hz, 2H, Ar-H), 7.71–7.75 (m, 3H, Ar-H), 7.34 (t, J = 12.17 Hz, 2H, Ar-H), 7.09 (dd, J = 9 and 4.34 Hz, 4H, Ar-H), 2.87 (s, 3H, Ar-CH_3), 1.43 (s, 3H, —CH_3); **ES-MS** (*m/z*): 425 (M+1); **Anal. Calcd**. $C_{25}H_{20}N_4O_3$ C, 70.74; H, 4.75; N, 13.20, found C, 70.80; H, 4.79; N, 13.18%.

2-(p-tolyloxy)-8-ethoxy-3-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2yl)-quinoline (**5j**). **IR** (KBr, cm^{-1}): 2954 (C–H), 1544 (C=N); **^{1}H-NMR** (400 Hz, DMSO-d_6): δ ppm 8.91 (s, 1H), 8.72 (d, J = 8.28 Hz, 2H, Ar-H), 7.74–7.78 (m, 3H, Ar-H), 7.38 (t, J = 11.92 Hz, 2H, Ar-H), 7.07 (dd, J = 8.98 and 4.31 Hz, 4H, Ar-H), 3.90 (q, 2H, —OCH_3), 2.67 (s, 3H, Ar-CH_3), 1.21 (s, 3H, —CH_3); **ES-MS** (*m/z*): 425 (M+1); **Anal. Calcd**. $C_{25}H_{20}N_4O_3$, C, 70.74; H, 4.75; N, 13.20, found C, 70.78; H, 4.80; N, 13.23%.

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